A Novel Moisture Protective Film Forming Oil-in-Water Pickering Emulsion

Dissertation
der Mathematisch-Naturwissenschaftlichen Fakultät
der Eberhard Karls Universität Tübingen
zur Erlangung des Grades eines
Doktors der Naturwissenschaften
(Dr. rer. nat)

vorgelegt von

Ahmad Ghoniem

aus Tripolis, Libyen

Tübingen
2017

Gedruckt mit Genehmigung der Mathematisch-Naturwissenschaftlichen Fakultät der Eberhard Karls Universität Tübingen.

Tag der Mündlichen Qualifikation:	31 07 2017
Dekan:	Prof. Dr. Wolfgang Rosenstiel
Erster Berichterstatter:	Prof. Dr. Rolf Daniels
Zweiter Berichterstatter:	Prof. Dr. Martin Wahl

Affidavit

Sehr geehrte Damen und Herren,

hiermit erkläre ich, dass ich die beigefügte Dissertation selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel genutzt habe. Alle wörtlich oder inhaltlich übernommenen Stellen habe ich als solche gekennzeichnet.

Ich versichere außerdem, dass ich die beigefügte Dissertation nur in diesem und keinem anderen Promotionsverfahren eingereicht habe und, dass diesem Promotionsverfahren keine endgültig gescheiterten Promotionsverfahren vorausgegangen sind.

For My Belief
For Humanity
For My Family
For Myself

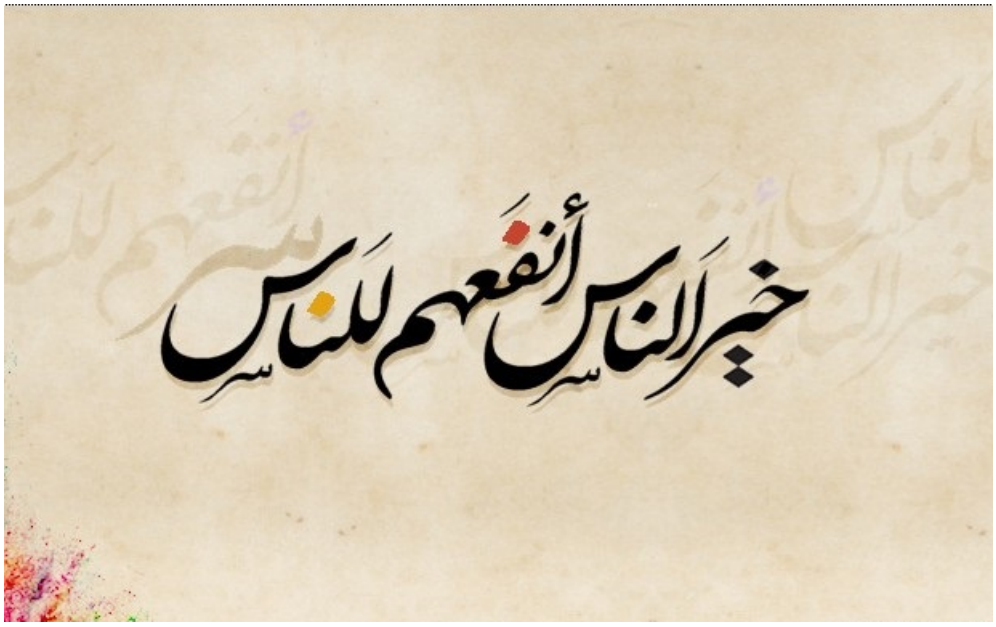
Motivation

I would like to quickly mention my personal motivation behind this almost 5 year work:

First, it is my belief that has made me endure hard moments in a foreign country, away from home, my home country, Cairo, Egypt and above all, away from my beloved ones. For my belief have I worked harder than my own definition of hard, giving me the strength and power to give that last bit over and over again, until success has been witnessed and the defined goal reached. My perspective and philosophy in life is – amongst others – driven by Prophet Mohammad's saying (*Hadeeth*), peace and blessings be upon him: "The most beloved people to Allah are those who are most beneficial to the people". I believe, this is one of the best deeds a human could ever do, and hence I have kept on trying more and more, wishing to contribute as little as with this doctoral thesis to a development in technology and medicine, serving humanity. I would hereby like to quickly mention that no race, sex, nationality or religion is - to me - superior over the other. My main motive was to serve humanity in its basic sense of definition.

For my family, especially my parents who have always believed in me and in my capabilities have I made it through the years, trying to spend as much time as possible with them in my free time, whereas a PhD student is known to have little free time - there is always that little more that could be done to improve one's own project.

For myself and my technical, scientific, academic, and personal distinction have I worked on myself on various levels to be the person I am today; and yet, there is a lot to be done.



Hadeeth by Prophet Muhammad, peace be upon him. It translates: "The most beloved people to Allah are those who are most beneficial to the people"

Acknowledgements

Without the support of various people, would this research work in its current form and state never be published. I would like to hereby acknowledge the people and parties involved.

First, I would like to thank my family for their endless support and constant motivation, even if it sometimes seemed a bit distressing; may God give you health and long years to live to keep on nagging me forward. My father, Dr. Abdelwahab Ghoniem, who pushed me to go for a PhD project abroad, in Germany, to him I owe this. My mother, Teti Moussa, who kept telling me to lessen work a bit and enjoy life more, to her I owe many happy moments; to her we - as a family - owe the outcome we have reached today and to her father, Prof. Dr. Ahmed Moussa, after whom I have been named, we owe the great opportunity of a unique relationship, as Egyptians, to Germany as a country and culture. My sister, Dr. Shada Ghoniem (Judy) who has prayed a lot for me and my wellbeing, who has endless time to listen over a long distance to my problems and challenges, to her I owe a big thank you for being there, always. And my brother, Dr. Youssef Ghoniem, who has taught me to take things less serious, to him I owe the capability laughing about things that sometimes bother. To my sister and brother in law, Dr. Amira Awad and Dr. Ayman El Shentenawy, to my nephews, Omar, Ahmad, Yassin, and to my niece, Amina, thank you for making life more beautiful.

My friends, who have visited me, allowed me to visit, called, sent messages, asked directly or indirectly, the closer and the less close ones, to you I owe a big thank you for making life joyful and fun. But also thanks for your support in times of need. And because you are so many, I will mention the ones who were there over the years of this doctoral research, being more or less directly involved:

Dr. Karim Hegazy, thanks for being there for almost 27 years now. In the past years you have made so multiple visits to Tübingen, Germany, a city you never really liked but visited for the sake of seeing me.

Dr. Ahmad Abdelazeem, thanks for being there from the beginning of the Egyptian revolution in 2011, and for being a great host for me and my friends and even their friends in Munich.

To Dr. Noran Azmy, my ex-fiancee, thanks for supporting me, even after our engagement was over; you always believed in me in a rare way, and I wish I could ever return your support to me the way you deserve it. You are the reason why I started using Latex for my dissertation; thanks for all the London visits, where you took the time to help me finish this thesis.

Ahmad Allam, a friend who never failed to be there, one who has always an ear and good ideas to move forward.

Omar El Maghraby, a friend who sometimes forgets details, but never gave me a feeling of forgetting true friendship and brotherhood, thanks to you for being more than a friend.

Amira Mundinger, my best female friend, the most fun girl, mother and probably wife out there on the planet, I will always love you as my 6 weeks younger sister and will always be there for you, no matter what.

A big thanks as well to my good friends including Amr Khairy, Omar El Bassiouny, Mahmoud El Assy, and many other valuable and dear people whether from school time (Deutsche Evangelische Oberschule, Kairo), university time (German University in Cairo, faculties of Pharmacy and Engineering) or along the journey of my personal and academic life - the people whom I have not mentioned here, but who were part of my journey.

Thanks to the newcomers of Germany, the Syrian refugees, in particular the ones of Lörrach. You taught me that so many other things matter other than the things I thought mattered most. You taught me a lot about priorities, and with you I spent an amazing time along my first job at Glatt GmbH in Binzen, Germany, as well as along the time of finalizing this doctoral thesis. It is true that because of the valuable time spent with you have I found less time to finish this thesis, but I do not regret one

single moment spent with all of you: Mohamad Salem, Thaer Zen-Al-Arab, Al-Rifaie family, Zahra family, Ali family, Khaled Debsi, and many many more, to you I owe a big thank you for indirectly contributing to my personal development and for motivating me to finish up my studies as soon as possible.

A great person I am glad to have gotten to meet through my life is my "Doktorvater", a German word for "PhD supervisor". But in fact, this word has a deeper meaning than just a supervisor, because it includes the word "father" in it: Prof. Dr. Daniels, my Doktorvater, a person I at the beginning did not understand well, but by time got to see more and more of his soul. Prof. Daniels, I thank you for so many things: I thank you for giving me this opportunity to come to your research group and learn. I thank you for letting me learn without you being a micromanager; you just gave me the opportunity to sometimes fail but stand up again, watching with lots of patience. Thank you for letting me have the opportunity to travel to lots of different places, attend symposia, workshops, and learn, just learn. Prof. Daniels, to you I would like to mention that part of my motivation along my PhD time was to meet your demands, who were always subtle but to the point. And above all, I thank you for the fatherly advices and chats we sometimes had in your office or along the corridor. Thank you.

Prof. Wahl, my co-supervisor, our statistics expert, as well as the expert for so many other things including electronics, cameras, and grill. Prof. Wahl, it was a great pleasure to work with you during the 5 years of my stay in Tübingen, knowing that one could knock at your door at any time, not only when it is related to science, but even on a personal level. The scientific discussions were always fruitful and inspiring. Thank you.

Klaus Weyhing, not only the technical expert, but also the "google" of our lab. Ask Klaus anything, and he always has an answer, even if it is a "I dont know, but let's try".Even when you had no time, Klaus, you always created time to be there and help. I could not even name all the various topics we have discussed, whether scientific, social, religious, political, cultural, historic, and many more. Your smile in the lab surely made time pass by more nicely, your motivation helped moving forward. Thank you.

Martina Brenn and Irina Eck, thanks to both of you for your constant support, whether on a personal level or for the students laboratory classes. Lots of things were made easier by you, giving a feeling of relief that there was someone to rely on when it comes to topics I had no clue about. Thank you.

My PhD colleagues, whom I will write dedicated thank you letters in person, to you I would like to say thanks for being not only colleagues or friends, but part of family in Germany. Dr. Dominique Lunter, Dr. Christoph Rott, Dr. Korbinian Schneider, Dr Kathrin Spielberger, Dr. Nelli Peters, Dr. Katrin Müllers, Dr. Michael Rottke, Dr. Philipe Metzger, Dr. Angelika Ellermann as well as the hopefully soon to be graduated PhD students, Ayse Bildir, Anna Färber, Isabell Steinbrenner, Rouven Heck, Kashif Ghaffar, Pavel Shubin, Markus Armbruster, Markus Schmidberger, thank you all for the beautiful years we spent together, especially during Mensa time, at the coffee room, or just making lots of fun in the lab.

In short, there are so many people and circumstances where as little as words of acknowledgement do not fully describe the extent of credit deserved.

I am grateful for this opportunity I had and I am aware that without all of you, this would have not been what it is today, in its current shape and form.

Parts of this doctoral thesis have already been published in the following events:

- A. Ghoniem, R. Daniels "Novel moisture protective film coatings from o/w Pickering emulsions depending on different lipophilic phases"; DPhG Annual Meeting (German Pharmaceutical Association): Scientific poster, Freiburg, Germany, October 2013.

- A. Ghoniem, R. Daniels "Novel moisture protective film coatings from o/w Pickering emulsions (II) Mechanisms Underlying Water vapor permeability"; 9th World Meeting of the APV (International Association for Pharmaceutical Technology): Scientific poster, Lissabon, Portugal, April 2014.

- A. Ghoniem, R. Daniels "Novel moisture protective film coatings from o/w Pickering emulsions (III) Dynamic Vapor Sorption Studies"; Annual Meeting & Exposition of the AAPS (American Association of Pharmaceutical Sciences): Scientific poster, San Diego, USA, November 2014.

Special Note: In this doctoral thesis, brands protected by law were not labeled by special labels.

Abstract

Deutsch / German: In dieser Doktorarbeit wurde eine innovative Formulierung entwickelt, die als Überzug zu Tabletten und / oder Pellets zum Schutz vor Feuchtigkeit dient. Sie basiert auf eine feststoffstabilisierte, filmbildende Öl-in-Wasser Emulsion, eine sogenannte Pickering Emulsion. Pulverisiertes $CaCO_3$ mit bestimmten geometrischen und Partikelgrößenanforderungen (100 - 300nm, rund) dient als Feststoff, welches – zusammen mit Stearinsäure – die Phasengrenze stabilisiert. Für die Innenphase wurden 6 Lipide als Kandidaten gewählt, namentlich Mittelkettige Triglyceride (MCT), Sonnenblumenöl (SFO), Isopropylmyristat (IPM), Rizinusöl (CO), dünn- und dickflüssiges Paraffin (PPL und PSL). Die Verwendung jedes der Lipide ergab bei gleichen Verhältnissen der Einzelkomponenten eine stabile O/W Emulsion, wobei bei mehr als 25% Ölkomponente in der Endformulierung instabile Emulsionen oder welche mit W/O Charakter herauskamen; das optimale Öl-zu-$CaCO_3$ Verhältnis lag bei 4 : 1 oder 4 : 1.5, um die Stabilität der Emulsion zu gewährleisten. Die filmbildende Komponente ist HPMC.

Um die Funktionalität dieser Formulierung bezüglich ihrer erzielten niedrigen Wasserdampfpermeabilität zu untersuchen, wurden mehrere Experimente an der getrockneten Formulierung (also an freien Filmen) durchgeführt: eine Kombination dieser zeigte, dass Wasserdampf nicht nur durch die HPMC Matrix, sondern auch durch die Lipidphase diffundiert. Außerdem weisten raster-elektronenmikroskopische Aufnahmen der freien Filme Emulsionsstrukturen auf; der Film ist somit eine getrocknete Emulsion, in der die Lipidphase – umgeben von dem Feststoffemulgator – in einer HPMC Matrix immobilisiert ist.

Der sogenannte Wasserdampfpermeabilitätswert (WVP-Wert) wurde an freien Filmen ermittelt und dient als Funktionalitätsparameter dieser Formulierung bezüglich des erzielten Feuchtigkeitsschutzes. Die Ergebnisse zeigen, dass der WVP-Wert vor allem eine Funktion der Lipidphase ist,

deren Viskosität und Polarität eine wesentliche Rolle spielen. Weiterhin spielt die innere Morphologie des Films eine Rolle; das Vermögen des Filmes die Lipidphase zu halten kann sich sowohl positiv als auch negativ auf den WVP-Wert auswirken. Die Reihenfolge der WVP-Werte lautet PSL < PPL < SFO < CO < MCT < IPM. Der WVP-Wert eines Benchmarks, Eudragit E PO, ist mit dem WVP-Wert von SFO haltigen Emulsionen vergleichbar – ein Indiz für den Erfolg der Funktionalität dieser innovativen Formulierung.

Desweiteren wurden Emulsionen auf inerte Pellets in einem Wirbelschichtverfahren überzogen, um die Prozessparameter und die genaue Formulierung festzulegen, die den Emulsionscharakter des Überzugs gewährleisten. Somit ist nicht nur der freie Film, sondern auch der Überzug eine getrocknete Emulsion, die in Wasser schnell wiederhergestellt werden kann und dabei die Freisetzung des Kerns nicht beeinträchtigt wird.

Als Mittel zum Zweck wurden hygroskopische Tabletten produziert, um diese in einem weiteren Schritt zu überziehen. Analog zum Wasserdampfpermeabilitätsversuch wurde hier über die Massenzunahme der Tabletten bei standarisierten Bedingungen (33% rF und 75% rF) der sogenannte Wasserdampfaufnahmewert (WVU-Wert) der Tabletten ermittelt. Unter den verschiedenen zur Verfgung stehenden Emulsionsrezepturen, wurde die SFO haltige Rezeptur aus galenischen und funktionellen Gründen zur Weiterverarbeitung ausgesucht. Diese Rezeptur enthielt 15% SFO und ein Öl-zu-$CaCO_3$-zu HPMC Verhältnis von 4 : 1.5 : 1.5. Tabletten, die mit dieser Emulsion überzogen wurden, zeigten, dass das Öl in den Kern diffundierte und somit die Wasserdampf-Aufnahmekapazität der Tabletten beeinträchtigt wurde. Um dies zu verhindern, und um einen wissenschaftlich-gerechten Benchmark machen zu können, wurde ein HPMC Vor-Überzug lediglich als mechanische Barriere eingesetzt, bevor die Emulsion aufgetragen wurde. Das Endresultat ergab, dass der Emulsionsüberzug aus SFO haltiger filmbildender Pickering Emulsion einen zum Eudragit E PO vergleichbaren WVU-Wert ergibt: beide Formulierungen verhindern ca. 50% Wasserdampfaufnahme innerhalb der ersten 24 Stunden im Vergleich zu un-überzogenen Tabletten.

English: A novel film-forming oil-in-water Pickering emulsions formulation has been developed in this doctoral thesis, serving the protection of moisutre sensitive pellets or tablets. Nano-sized $CaCO_3$ with a specific geometric shape and particle size (100 - 300nm, round) is the particulate emulsifier, which – together with stearic acid – stabilizes the phase boundary. The inner phase is of one of 6 lipids, namely medium chain triglycerides (MCT), sunflower oil (SFO), isopropylmyristate (IPM), castor oil (CO), heavy and light liquid paraffin (PPL, PSL). Including any of those lipids – at equal ratios of the components – resulted in a stable o/w emulsions; a lipid concentration of 25% or more resulted in unstable emulsions. The optimal ratio of oil:$CaCO_3$ is$4 : 1$ or $4 : 1.5$. HPMC is the film-forming component.

Experiments on dried formulation (free films) were performed, aiming to assess the desired decrease in water vapor permeability (WVP). A combination of the experiments showed that water vapor diffuses not only through the HPMC matrix, but also through the lipid phase. Furthermore, scanning-electron microscopic (SEM) images showed that the free films were dried emulsions, where the lipid droplets are embedded in the HPMC matrix.

The so-called WVP-value – attained on free films – is the (main) functionality parameter of the formulation's moisture protective ability (MPA). Results show that WVP is a function of lipid viscosity and polarity. Moreover, WVP is affected by free film morphology; a film's ability to hold the lipid immobilised can have positive or negative results on the WVP. The order of WVP – depending on the lipid phase – is PSL $<$ PPL $<$ SFO $<$ CO $<$ MCT $<$ IPM. Eudragit E PO, a benchmark, has a WVP-value close to emulsions containing SFO – an indication for the successful MPA of the novel formulation.

The emulsion was also coated onto inert pellets using a fluid bed device, in order to develop the process parameters that allow emulsion character preservation. Hence, not only free films, but also the film coat is a dried emulsion, which is reconstituted back to an emulsion – once dispersed in water – without prolonging the release of the inner core.

As a means to an end, hygroscopic tablets have been produced and coated by the emulsion. Similar to the WVP-value, the WVU-value was assessed

for tablets stored under defined conditions (33% rF und 75% rF). The emulsion used for tablet coating was the one containing SFO for galenic and functional reasons. The formulation contained 15% SFO and an oil-to-$CaCO_3$-to HPMC ratio of $4 : 1.5 : 1.5$.

Tablets coated by this formulation showed that oil diffused into the tablet core, reducing the core's capacity to absorb water vapor. In order to overcome this and in order to scientifically assess the novel formulation's MPA, a seal coat was applied (HPMC) serving as a mechanical barrier to the uptake of oil by the core. On top, the novel formulation was then applied. The end result showed that the novel formulation decreased water vapor uptake by 50% within the first 24 hours, compared to HPMC coated tablets, a result that is similar to the benchmark, Eudragit E PO.

Contents

Chapter 1

Introduction

1.1 Overview

This doctoral thesis presents a novel moisture protective film-coating concept that is applied to solid dosage forms (tablets, pellets), decreasing water vapor permeability into the core. Chapter 1 introduces the topic as follows: in Section 1.2, the necessity to develop this formulation and the justification of it being on the basis of an oil-in-water emulsion is presented. Afterwards, some scientific background information to various aspects involved in this research are reviewed and discussed (Section 1.3). In Section 1.4, the layout of the practical work and results of this thesis is presented describing the structure of Chapters 2 - 4.

Starting Chapter 2, this thesis offers materials (Chapter 2), methods (Chapter 3) and results (Chapter 4) for the production and characterization of the novel formulation, discusses the factors affecting and the mechanisms governing it and investigates its aptness for film coating. Finally, tablets coated by the novel formulation are benchmarked to tablets coated by marketed products, allowing an objective evaluation of the novel formulation's moisture protective ability.

Chapter 5 summarizes the doctoral thesis; Chapter 6 contains some extra background information, that might be revised when needed and referred to.

1.2 Objective

The aim of this doctoral thesis was to develop an alternative and novel moisture protective concept on the basis of oil-in-water (o/w) Pickering emulsions. The formulation's moisture protective ability (MPA) is to be benchmarked to a moisture protective marketed product for objective assessment. The first questions that would cross the mind of a scientist getting to know about a new system and / or application

is "why", "what is the benefit" and "why this and not that". So, in order to follow the rationale behind this research, some aspects are considered and discussed here: the first one deals with the pharmaceutical industry, its market(s), its needs and its drivers; this part generally and shortly reviews the continuous need for innovation in the pharmaceutical market and mentions my motivation to this work. It partially answers the "why" and justifies the word "alternative" of the statement above. The remaining aspects are solely scientific ones: pharmaceutical instabilities particularly moisture induced ones are presented, strategies for moisture protection are reviewed and emulsion dosage forms are discussed. Last but not least, the necessity to develop this particular formulation is justified, by integrating the previous introductory topics. In short, the rationale behind this work including the choice of the topic and the formulation is justified here. Chapter 4 (Results and Discussion) then proves the statement and answers the "what is the benefit" question.

(1) Market Needs and Motivation The pharmaceutical industry is constantly craving for innovative solutions that contribute to the success rate of new drugs' bringing to the market. The economic and technological competition is increasing for all pharmaceutical playmakers. Originator companies face the challenges of a low success rate of new chemical entities (NCEs) and the high R&D costs of new pharmaceutical products; new drug discovery followed by new drug development become tighter with increasing R&D costs. Generic companies face the challenge of high competition and price beat downs as well as patent circumvention aspects: they are always searching for alternative solutions. Pharmaceutical service companies (e.g. excipient vendors) fight to achieve or keep a competitive advantage and are thus obliged to constantly offer novel excipient solutions. Hence, one thing is for sure: novel and alternative solutions are persistently needed.

As a scientist in pharmaceutical technology, I constantly crave for innovation and alternatives, aiming to widen the spectrum of choices and applications and finally contribute to improving the lives of humanity. The following work has been inspired by this thought, amongst others.

(2) API Instabilities This doctoral research deals with developing a novel film-forming concept meant for moisture protection. "Why researching in moisture protection?" and "why protection particularly by coating?" are justified questions that are answered as follows: Active pharmaceutical ingredients (APIs) are demanded to be efficient, non-toxic and physico-chemically stable. Before a new product is

approved for market entry, its stability is necessarily investigated and guaranteed for a defined period of time. The instability of a product is usually overcome by technological means; else, uncured instabilities might affect a medicine's shelf life and eventually negatively affect its lifecycle on the market.

There are numerous types and causes of instabilities that might result from any of the components of the final product (API(s), excipient(s) or the combination of components (formulation)). They may be physical, chemical and/ or microbiological. Furthermore, they may arise at all stages along the supply chain: the raw materials and their supply, handling and storage, the manufacturing processes and steps, the products (intermediate and final ones), the transportation and distribution of the final product, the storage conditions on the shelf (final sales channel), and finally the handling steps at the end user level. As part of good manufacturing practice (GMP), the manufacturing steps are developed and predefined to be reproductive and protective, allowing the control of instability causes. Yet, once the final product leaves the pharmaceutical plant, controlling becomes hard and this is where environmental factors come mostly into play; products might be sensitive to light, oxygen, or moisture. Focusing on the latter, the World Health Organization (WHO) has conducted a study in 1986 stating that 110 out of 296 drugs (mostly essential ones) are shown to be degradable under moist conditions [42]. Moreover, Rosenberg et al. reported that out of 300 prescription oral solid dosage form medications, 146 were moisture sensitive [45]. Not all the just mentioned references (studies and articles) are peer-reviewed publications, but still usefully indicate the amount of moisture sensitive APIs out there on the market. In turn, this information shows the existing need to moisture protection: various chemical moieties and nuclei are known to be sensitive to moisture, which are found in many therapeutic categories. If unprotected, (pseudo-)polymorphs of altered solubility behavior may form or API degradation to inactive or even toxic degradation products may result. Hence, moisture sensitive product protection is inevitable [64].

There are several ways to prevent moisture uptake by a product. Packaging (1st form) offers great protection on the one hand, but is costly on the other. Furthermore, depending on the target market and group, packaging might be somewhat inefficient; some target groups (e.g. elder people, U.S. market) prefer pill boxes, where multiple pills are collectively packed together. Opening and closing the box at every dose may expose the finished product to moisture. Some boxes contain a desiccant in the cap; yet their capacity to moisture absorption is limited, their toxicity is not negligible and their application is not always feasible. For example, so-called dossett boxes are

preferred dose organizers among patients with multiple chronic diseases or at clinical trials. Those boxes are usually filled on a daily or weekly or even monthly base and contain all products sufficient for the defined period of time. Moisture sensitive drugs are thus exposed to humidity and prone to degradation if unprotected. Coating of moisture sensitive products is usually the method of choice in that case and can still be combined with proper packaging and storing conditions. Furthermore, coating of tablets, pellets or granules has additional advantages; palatability enhancement, coloring for marketing purposes and controlled release profiles can be combined with moisture protection if needed. However, for moisture protective purposes a coating is usually applied for that sole sake without the intention to alter the release profile. And this is where the challenge lies: moisture protection (no or low water permeability) shall be achieved while an immediate release (i.e. fast dissolution) of the drug is guaranteed. Low moisture permeability could easily be achieved by coating highly hydrophobic material onto solid dosage forms; but once ingested orally, the gastric fluid would not interact with the highly hydrophobic coat material leading to a delayed dissolution.

Marketed products achieve moisture protection and immediate release simultaneously as follows: they contain a polymer that is water insoluble at neutral pH and dissolves pH dependently (e.g. Eudragit E PO), or they contain a water soluble barrier forming substance that assures fast dissolution, but a water repellent substance is incorporated to reduce the permeability (e.g. Opadry 200: PVA based; Seppifilm LP: HPMC based including stearic acid). In such marketed products, one often finds minerals and additional inorganic material incorporated (e.g. talc and color pigments) that enhance moisture protection by serving as mechanical barrier to moisture. Polymeric coatings are usually synthetic or semi-synthetic and are composed mostly of the film-forming polymer; allergic or toxic reactions to polymers and synthetic materials might occur or incompatibilities with other substances might result [61]. In looking for an alternative coat system, emulsions seemed to be a valuable candidate. Reasons for that are discussed in the next paragraph.

Please note, that details on moisture instability, its causes and types are presented in Section 1.3.1. Furthermore, more background information regarding moisture protective formulations is provided under Section 1.3.4.

(3) Emulsions In this doctoral research, the novel concept used for moisture protection is based on an emulsion. An important question at this stage would be

"why use emulsions for that purpose?" and a simple answer would be "because - theoretically- they fulfill all requirements and demands to serve as an alternative novel moisture protective formulation".

Emulsions are widely spread formulations with many advantages and are used for various applications. The physico-chemical laws governing their stability are well understood. Focusing on Pickering emulsions (solid stabilized emulsions), their stability is advantageous compared to surfactant stabilized ones. Furthermore, their surfactant free nature reduces the risk of irritancy or even toxic reactions. Moreover, previous research has shown they can be sprayed, dried to granules and redispersed to their original form again. Those aspects are very promising for the purpose of this research and are exactly what is needed for moisture protection: o/w Pickering emulsions that can be dried to give granules [35, 37] are expected to become dried onto solid dosage forms surfaces to form a film coat (aim of this research). Besides, their oily component is water repellant and thus expected to be of low moisture permeability. Further, dried emulsions (coming originally from o/w emulsions) are water dispersible and thus believed to provide the core with an immediate release profile.

These previous aspects have been considered theoretically only. So the aim of this doctoral thesis was to investigate the previous aspects practically. In particular it was the aim to develop a film-forming oil-in-water Pickering emulsion for moisture protective purposes having a low water vapor permeability, be coatable onto solid dosage forms and not delay the dissolution of the core. And since the market is craving for innovation and alternative systems, and since moisture protection is inevitable for pharmaceutical stability of moisture sensitive products, the following research has begun.

Please note that more detailed information on emulsion background is provided under Section 1.3.3.

1.3 Background

In this section, background information to aspects discussed in this doctoral research are provided. This sub-chapter is structured as follows: first, in Section 1.3.1, background information regarding moisture instability is provided; this part includes information regarding the source(s) of moisture, types of water found in solids, the potential drawbacks of moisture interaction with solid dosage forms and also some approaches to reduce this. Following that, in Section 1.3.2, background information of pharmaceutical coating is presented, including the devices used for that matter. In

this part, the mechanism of water vapor permeability (WVP) is presented and some important equation derivation shown. Later, in Section 1.3.3, general information about emulsions is provided, with a special focus on Pickering emulsions. Last, in Section 1.3.4, several moisture protective formulations from the market are presented. This part also includes a short review on lipid-based and / or lipid-containing coatings found on the market.

1.3.1 Moisture and its Impacts on Solid Dosage Forms

There are many solid pharmaceutical dosage forms that exhibit undesirable changes when exposed to a moist environment before being administered. The moisture sensitive component can be the active pharmaceutical ingredient (API) itself, or any incorporated excipient. The first important aspect in the context of moisture sensitivity is the source of water. Generally speaking, there are two ways for water to be present in a solid formulation. The first is the intrinsic route: here, water is already present in the product as (for example) a result of hygroscopic and / or hydrophilic materials used in the formulation. During drug product manufacturing humid environments may exacerbate this phenomenon. Modern manufacturing plants allow humidity control of the production rooms and hence reduce the humidity level of the finished product. The second possibility is the extrinsic route; in that case, a moisture sensitive finished product with controlled humidity level is produced, but interacts with humidity during its shelf life or at the patient level.

But not all water negatively affects the dosage form leading to instability. In other words, there are different types of water in a solid. Zografi describes 2 main water types in the presence of solids: “bound” and “solvent-like”, where the latter is usually the cause of instabilities [65]. Zografi also distinguishes between water interaction with crystal solids and amorphous substances, where the latter is of focus in the context of this research (polymeric films are usually amorphous). Furthermore, water can interact with solids in many different forms, including adsorption to the surface (as mono- or multilayers), condensation as capillary water into micropores, hydrate crystal formation, deliquescence and / or even absorption into the bulk phase of amorphous solids [65]. It is worth mentioning at this stage, that not all forms of interaction are considered here, but only the pharmaceutically significant ones.

In general, moisture may negatively affect any kind of substance, which may undergo any physical and / or chemical modification or even react with another substance in presence of “solvent-like” (available) water. The resulting modifications may diminish the effect of a substance, lead to alteration of its effect or even result

in a new substance with harmful outcome. The changes may be physical, including for example recrystallization, formation of (pseudo-)polymorphs and hence solubility modifications. They may also be chemical: depending on the chemical nature of the moisture sensitive substance, different types of chemical instabilities may occur. Hydrolysis is the most common instability type of pharmaceutical substances involving water and it may affect various functional groups. The latter include amides and esters, which are found for example in barbiturates and β -lactams [64].

Having presented the causes of moisture presence in a solid dosage form and its possible effects, the third and last important aspect in this context is the ways to control humidity permeability. Aluminum blisters as primary packaging material are used because of their almost diminished moisture permeability. Single tablet blisters protect from moisture only as long as they are unopened. Tablets collectively packed in HDPE boxes usually contain a desiccant in the box cover; every time the box is opened and moisture enters, the desiccant may absorb it up to its maximum limit. Any further moisture is exposed to the tablet cores. A third option is to render the formulation itself moisture absorbing: some tablet formulations contain a hygroscopic substance such as mesoporous silica gel, which acts as a scavenger to moisture [28]. Once moisture reaches the inner of a solid dosage form, the scavenging substance absorbs it, leaving no free ("solvent-like") water. Last but not least, coating is a very effective way to protect from moisture permeation. It requires an additional manufacturing step, but protects each individual dose. The necessary background information to coating is discussed in Section 1.3.2, particularly to moisture protective one.

There are different methods to quantify water in solids, including gravimetric and non-gravimetric ones. The former include thermal-gravimetric analysis (TGA) techniques and loss-on-drying (LOD) usually by Infrared (IR) as an energy source. The latter include Karl-Fischer titration, nuclear magnetic resonance (NMR), differential scanning calorimetric (DSC) analysis and others. Water activity is also a common method to obtain correlating results for the amount of free water in a solid. One important aspect is important to mention here: the abovementioned methods differ in the data they provide the analysts with. Some methods quantify the absolute water amount in a solid (including or excluding crystal water), others relate more to the free water available. Regardless, those methods are not presented further in this doctoral research; yet, relevant methods and quantifications of moisture passing through a film coat or residing in it are described in Section 1.3.2.4.

1.3.2 Coating Basics and Film Coat Formation

Coating of pharmaceutical solid dosage forms is a well-studied process involved in the manufacturing of various products. It may be used to improve aesthetic feelings and palatability, for drug layering and for functionalization as well as protection. In I.2 it has been mentioned that coating is an efficient option to protect pharmaceutical dosage forms from moisture.

There are mainly two device types for coating of solids depending on their size and weight-to-volume ratio. Heavier products (e.g. tablets) are usually coated in a drum or pan coater. Fluid bed coating is typically the process of choice for smaller products like pellets and minitablets (e.g. bottom spray process). Figure 1.1 illustrate both processes, respectively. In both cases, the uncoated products are moved (rotated or fluidized), a coating fluid is sprayed via an atomization nozzle onto the cores, and dry and warm air is introduced to the system allowing the production of coated dosage forms.

There are numerous factors contributing to the success of a coating process: while developing one, it is the aim to find the proper balance between all those parameters. Spray rate, inlet air temperature, velocity and amount, atomization pressure (affecting the droplet sizes of the coating fluid) and some others are set in such a way as to avoid two undesired extremes: if a process is too dry (e.g. as a result of too high temperatures, too slow spraying, too small droplets, etc.), more of spray drying of the coating fluid occurs, leaving fines of the polymeric substance side by side to the uncoated cores; if a process is too wet (e.g. as a result of the opposite), over wetting occurs, leading to more of a granulation process and the cores tend to form twins or agglomerates. A proper coating process can be summarized as follows: the coating fluid (composed of a dispersant and the coating materials) needs to spread on the moving (rotating or fluidizing) cores of the solid dosage form; the droplet size of the coating fluid is a function of the atomization pressure and spraying rate; the dispersant is allowed to dry (role of the drying air) leaving the polymeric material for film formation. These steps are repeated until the desired coating level is achieved. The next sub-chapters present in more details some aspects involved in coating.

1.3.2.1 The Film-Forming Substance, its Solubility and the Coating Fluid Dispersant

In general, there are two dispersant types for coating fluids: aqueous based and organic ones. At the same time, a polymeric system may contain a polymer in a

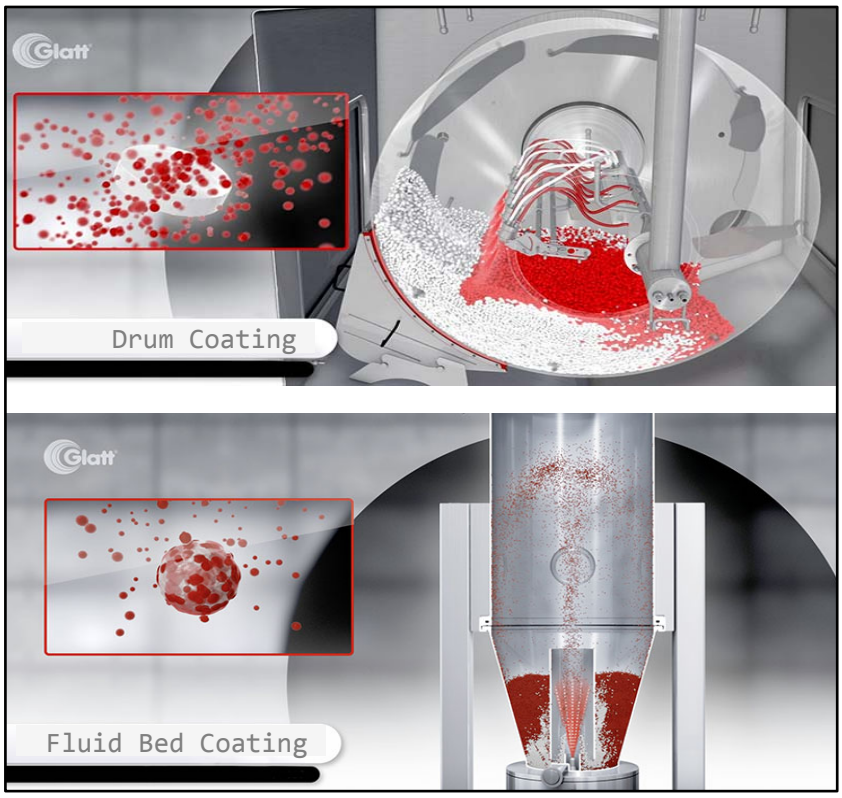


Figure 1.1: Coating Processes - Typical Devices. Source: www.glatt.com; with permission from Glatt.

suspended or dissolved way depending on the solubility of the polymer in the dispersant. In the pharmaceutical industry, many polymers used for (especially) controlled release purposes are hydrophobic. Therefore, organic based coatings had evolved in times, where environmental aspects were not been considered much. Nowadays, organic based coating processes need special care: organic solvents exhibit a much lower ignition temperature than water and are thus prone to explosion at milder conditions; devices intended for organic solvent handling must be explosion-proof to assure personnel safety. Organic solvents may not be eliminated freely to the environment because of their hazardous nature; special treatment must be performed before their outburst is allowed. Moreover, the organic solvents are per se extremely expensive leading often to the necessity to recycle them for future use. Such processes need special accessories capable of performing the aspired recycling. Hence, from an economic perspective, processes involving organic solvents are expensive to run (high operational cost) and require special investments (high acquisition cost). Furthermore, the final products need to be investigated for residual solvents.

One would not find a reason to chose an organic based system over an aqueous

one, except for the following reasons: the polymeric substances are water insoluble and a polymeric coating solution is preferred. The reasoning behind this statement is discussed below. Another reason for the privilege of an organic based coating over an aqueous based one is the latter being harmful to the product (e.g. in case of moisture sensitivity). Yet, processes involving moisture sensitive products can be coated for moisture protection in an aqueous based system, if special care is accounted for; details on that are discussed below.

1.3.2.2 Film Formation Mechanisms

Generally, coating fluids may exist in two forms as follows: the polymer may be dissolved or suspended in the coating fluid depending on its solubility in the latter. This information is important for the mechanism of film formation: suspended (undissolved) polymer particles exist in a rubber-like state in the coating fluid and likewise when sprayed onto the core of the pharmaceutical dosage form. Hence, once the (usually aqueous based) dispersant evaporates, a polymeric film is allowed to form only under the following conditions: the polymeric substance can only form an intact film if its energetic state is sufficiently high allowing the stiff polymer clusters to become flexible enough to coalesce. This is achieved at temperatures above the glass transition temperature (Tg) of the polymer, and occurs at a so-called Minimum-Film-Forming-Temperature (MFT). At its distinct MFT, a polymer dispersion becomes rubbery enough to coalesce and integrate to an intact film, when the dispersant evaporates. It is worth mentioning that an MFT of a polymer is usually above its Tg; yet, no literature has been found presenting the previous statement as a general rule. Regardless, Figure 1.2 illustrates the mechanism of film formation from a suspension. Furthermore, Figure 1.3-a illustrates the previous statements, by showing a coated latex aqueous dispersion of Eudragit L 30 D on top of a tablet surface; here the MFT of the polymer has not been reached and the polymers have not formed an intact film, consequently. So, coating must take place at temperatures high enough to assure intact film formation. Yet, at temperatures highly above the MFT (but still lower than temperatures for undesired spray drying occurrence), the polymer might become rubbery. Consequently, tackiness is promoted and twin formation is enhanced. Hence, when coating polymers from a suspension, information on the polymer's MFT and Tg must be pre-determined or provided. Controlling the temperature is crucial in order to guarantee the success of coating from (aqueous) suspensions. It is worth mentioning that most polymeric suspensions are of aqueous nature, since no sense is found for organic based ones.

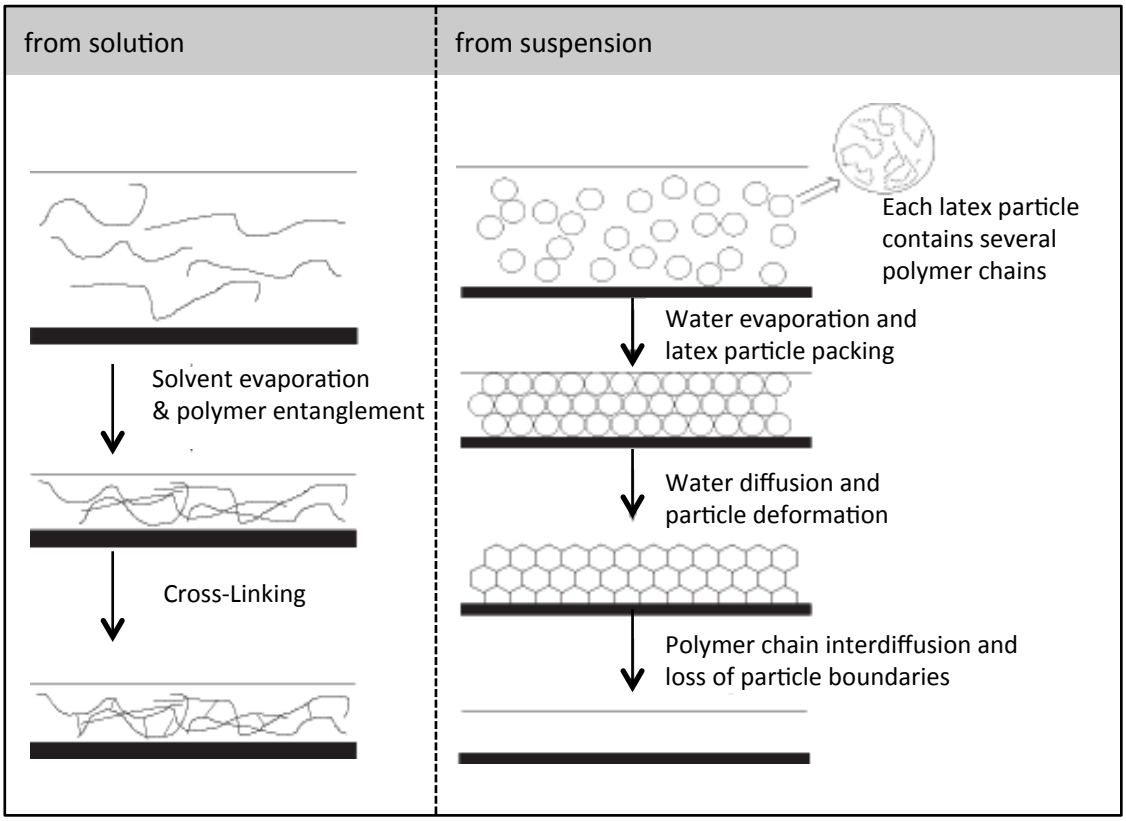


Figure 1.2: Film Formation from Solution or Suspension.
Source: http://www.industrialpaintquality.com/education/inthecan/vs03.html.
Shown: Film formation on solid surface, depending on dispersion type.

As opposed to polymeric suspensions, coating fluids of polymeric solutions (whether aqueous or organic) contain polymer chains that are flexibly surrounded by solvate molecules. Once the coating fluid droplets reach the surface of the pharmaceutical dosage forms' surface and the solvent evaporates, the polymeric chains are flexible enough, allowing their close proximity and hence the formation of intact films. Coating of polymers from a dissolved state is thus somewhat simpler and requires less attention.

The previous reasons present the motives of some formulators preferring polymeric solutions over suspensions. And since most functional pharmaceutical polymers are water insoluble, organic coating became more popular by time. Yet, its previously mentioned disadvantages (environmental and economic) limited its use. Besides, aqueous polymeric suspensions can easily be coated onto solid dosage forms, if the process parameters are well understood.

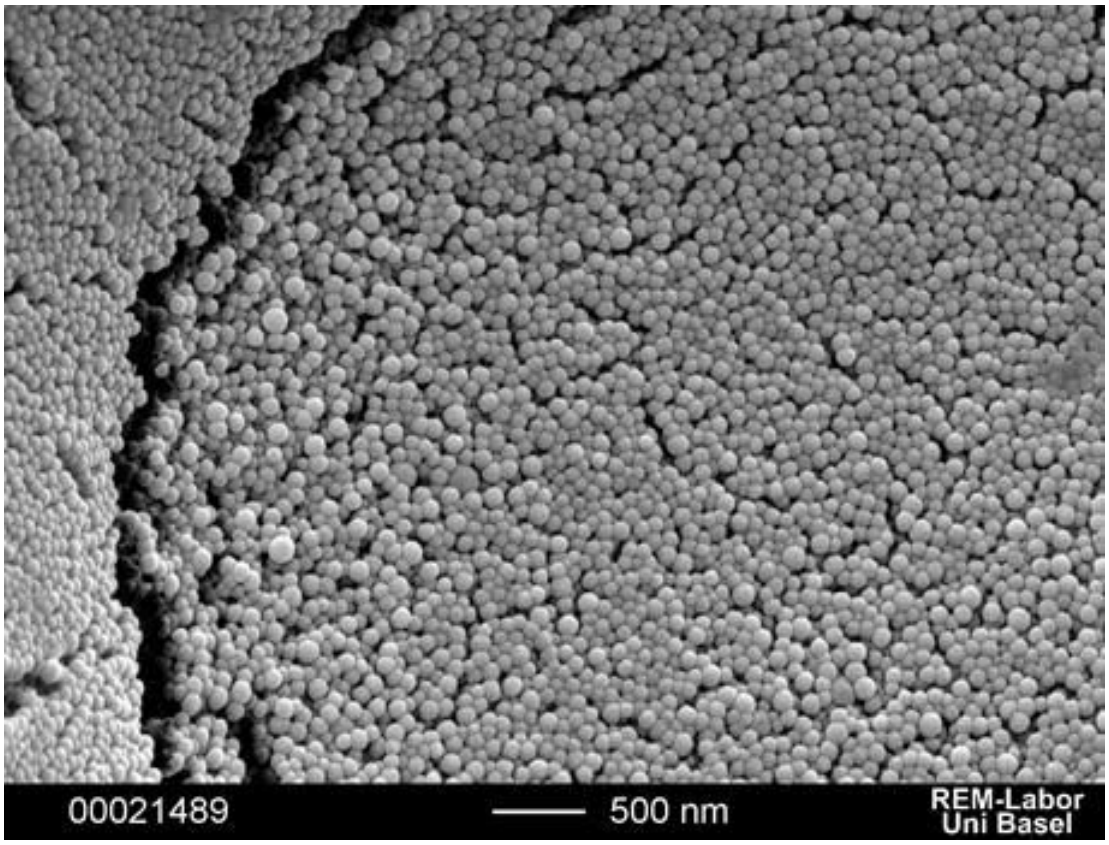


Figure 1.3: Uncured Film Coat From Dispersion.
Source: Glatt Pharmaceutical Services, Glatt GmbH - Internal projects (with permission from Glatt). Image taken by University of Basel, Switzerland. Coat: Eudragit L 30 D film coat.

1.3.2.3 Special Care for Moisture Protective Coating

In general, when performing coating of moisture protective formulations, two main aspects are tactically considered and designed: the coating process and the moisture protective formulation. The former is discussed here (Section 1.3.2.3) and the latter is discussed under Section 1.3.4. The previous aspects under Section 1.3.2 have presented some general background information on pharmaceutical coating. Now, contextual knowledge on coating for moisture protective purposes is discussed.

Coating processes involving moisture-sensitive substances require special care, especially when the coating fluid is aqueous based. Once coating occurs and evaporation of the aqueous dispersant takes place, the humidity level inside the coating chamber (in the coating pan or in the fluidized bed coater) is raised; it shall not exceed a critical value, where degradation of the moisture sensitive substance might occur. Depending on the kinetics of the degradation reaction, the coating process duration might be sufficient to result in degraded substances already at time zero of the shelf life (end of manufacturing steps). But what is even more critical is the process itself delivering a finished (coated) product that contains residual moisture as a result of uncontrolled humidity in the coating chamber. In that case, the final moisture protective coat will indeed impair extrinsic moisture permeability to the dosage form (fulfilling its purpose), but will also keep any residual moisture inside the dosage form. And if this trapped water is unbound (solvent-like water), moisture sensitive substances will degrade. In short, aqueous coating of moisture sensitive substances is to be processed with caution regarding humidity level in the coating chamber: harmonic adjustment of spray rate, atomization pressure, inlet air temperature and the remaining process parameters may keep the coating process relatively dry.

In summary, when applying aqueous coating to moisture sensitive substances, balanced process parameters assuring low humidity levels in the coating chambers are to be aspired; the process is to be adjusted to avoid undesired moisture uptake during this manufacturing step.

For the sake of mentioning alternatives, it is worth citing other techniques involving moisture sensitive substance coating: powder layering, hot-melt coating and super-critical coating can also be applied here, amongst other [15]; however, details are not contained in this research.

1.3.2.4 Moisture Protective Ability Characterization

As previously presented, pharmaceutical moisture protection can take place by several means, including packaging and coating. In this sub-section, the focus is on characterizing moisture protective formulations intended for coating. They are not characterized in their liquid state, but in their dried state, as films (edible / free films or film coats; details will follow below).

1.3.2.4.1 Introducing MPA: Terminology Definitions Before the moisture protective ability (MPA) characterization may be presented, it is important to define the following terms:

Moisture Vapor Transmission Rate; Water Vapor Permeability: Moisture vapor transmission rate (MVTR) and water vapor permeability (WVP), are gravimetric measures of the passage of water vapor through a substance, here a free film (see Section 3.1.2.3.1). For WVP, there is also a more *general* definition, as will be presented below (see "WVP in its Broad Sense and WVP Derivation").

Water Vapor Solubility: Water vapor solubility (WVS) describes the equilibrium amount of water vapor sorbed by a substance at defined environmental conditions, e.g. as a function of steady state relative vapor pressure and temperature (see Section 3.1.2.4).

Water Vapor Uptake: water vapor uptake (WVU) describes gravimetically the amount of water vapor which is accumulated in a substance (e.g. a tablet) while storing under certain (environmental) conditions for a certain time (see Section 3.2.2).

Moisture Protective Ability: Moisture protective ability (MPA) of a substance (e.g. a formulation, free film, film coat) is the collective ability – of any measure – to protect another substance, Substance X (e.g. an active pharmaceutical ingredient, API) generally from any harmful effects of water vapor; the harmful effects are usually caused by the reach of water vapor to that Substance X. Thus, the protection may be measured generally as a decreased water permeability and / or uptake, gravimetically, or by the extent of a chemical degradation (e.g. hydrolysis) of that substance, Substance X.

Substance X: Substance X is any test substance that is chosen to assess the MPA of a formulation. Substance X can be a moisture sensitive substance (Option A) that degrades when exposed to humidity over time (chemical change, e.g. hydrolysis) or that experiences a physical change (e.g. polymorphic change). It can also be a hygroscopic substance (Option B) that absorbs water vapor in presence of the latter and increases in weight; MPA characterization takes place indirectly via the

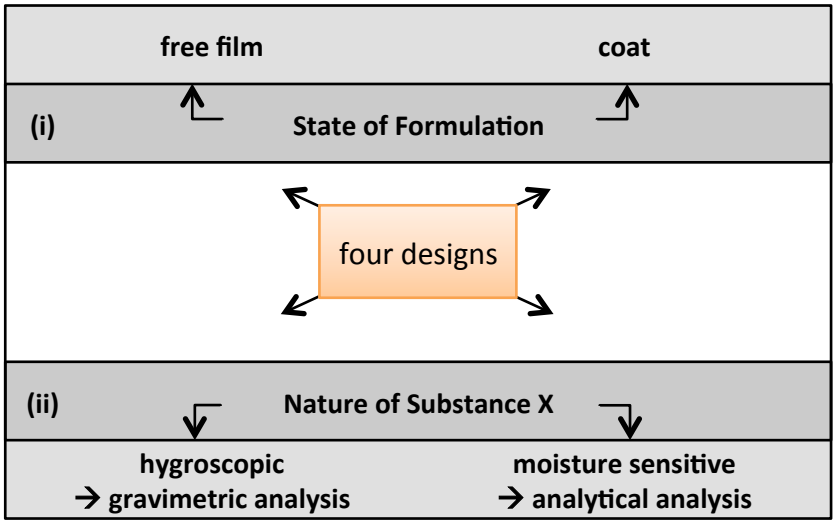


Figure 1.4: Overview of All Possible Experimental Designs – Depending on State of Formulation and Nature of Substance X.

characterization of Substance X (whether as Option A or B), and the experimental design for MPA measurement depends on the nature of Substance X (as will be presented shortly).

Option A vs. B; Option 1 vs. 2 In general, there are four combinations, depending on the nature of Substance X (being hygroscopic or moisture degrading) and on the form of the formulation in the test (being a free film or in its coated form). Each option has some advantages and disadvantages for the overall assessment of a formulation's MPA, as shown in Figure 1.4.

MPA Characterization of a formulation: Integrating all the abovementioned terms leads to the following: in the context of this doctoral thesis, a new formulation has been developed and its MPA assessed. Speaking of MPA characterization of a novel formulation that is initially liquid, this liquid formulation needs to be transformed into a solid (for MPA characterization). This solid is either a free film (produced by drying the liquid formulation; Option 1) or a film coat (achieved by coating the liquid formulation onto solid cores; Option 2). In both cases, MPA assessment takes place by observing changes to Substance X, i.e. MPA assessment can only be done if Substance X is included in the experimental design. The practical and mathematical methodologies will be shown below. More details to these terms are elaborately presented in the Annex Chapter (see Chapter 6).

1.3.2.4.2 Details to MPA Characterization As just mentioned, MPA assessment takes place by observing changes on Substance X and by measuring the abovementioned terms (MVTR, WVP, WVS, WVU; equations are presented below). Generally speaking, MPA assessment takes place by storing samples under certain environmental conditions (e.g. constant relative humidity and temperature) and measuring the changes periodically over time. The test model depends on the nature of Substance X, being (a) moisture sensitive, or (b) hygroscopic. In case Substance X is moisture sensitive (Option A), then the methodology applied to assess MPA is rather analytical, measuring the harmful effect of water vapor on Substance X. In case Substance X is hygroscopic (Option B), then the methodology applied to assess MPA is by measuring the (gravimetric) amount of permeated water vapor. It is worth mentioning that several options, test models and methods may be applied to assess a formulation's MPA, but on reviewing scientific literature[1] regarding pharmaceutical moisture protective formulations, most formulations were assessed gravimetrically (by WVP tests). Only a few research groups measure MPA of a moisture protective formulation analytically (where Substance X is a moisture sensitive substance). Therefore, in the context of this doctoral thesis, the focus is made on Substance X being hygroscopic in nature (not moisture sensitive). The formulation's MPA is assessed on free films (Option 1) and on film coats (Option 2). In the following, details on the methodologies, the terms and mathematical calculations serving that purpose are described.

Practical Methodologies and Mathematical Calculations: In the following, the abovementioned terms WVP, WVS and WVU are mathematically presented and their practical methods described. Furthermore, it is mentioned which of the abovementioned options apply to the test model (Substance X being moisture sensitive or hygroscopic; the formulation being a free film or a film coat).

– **Water Vapor Permeability (WVP):** WVP, in a practical / experimental sense[2], is defined as the amount of water vapor permeating at a unit time, unit area and unit film thickness. So-called WVP-tests performed (usually on free films, and not film coats, and on X being hygroscopic, not moisture sensitive) yield WVP-values. Typical tests are described in details below. So-called WVP-tests performed provide WVP-values. The tests are usually performed on free films (Option 1), and not film coats, and on Substance X being hygroscopic (Option B), not moisture

[1] see below: "Literature Review: Methodologies Used by Other Scientists"

[2] WVP has also a non mathematical definition: it is the "act of water vapor permeation through a barrier substance", as presented later.

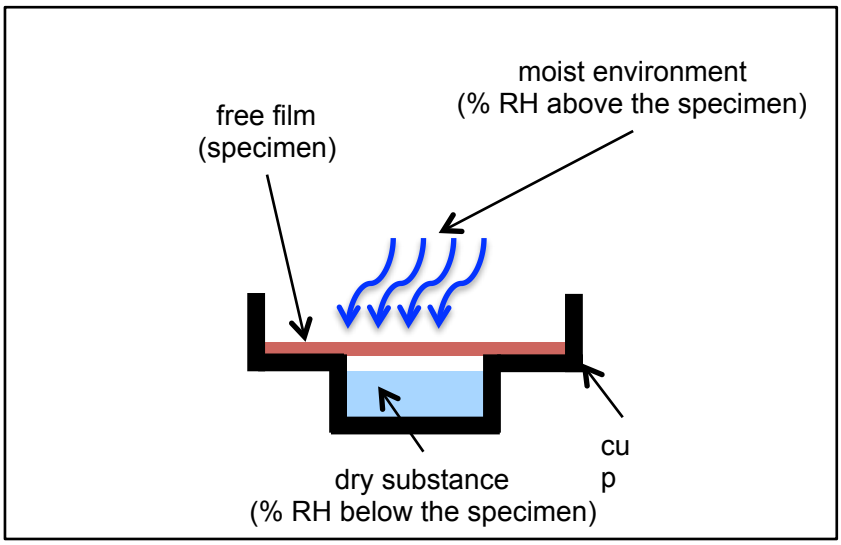


Figure 1.5: Cup Method (Schematic Drawing).

sensitive. The most common test is the so-called cup method. Figure 1.5 illustrates one of the constellations available for this method: a cup containing a hygroscopic material capable of absorbing moisture and gaining in weight is separated from a moist environment by a film membrane (the dried formulation). Below the latter, air is dry (at least at the beginning of the test). Over time, weight gain of the entire cup is measured and WVP-value calculated. And since the entire cup is weighed, the amount of weight gain (corresponding to moisture) reflects the sum of both, permeated moisture through the film and moisture residing in the film. Details to the mathematical calculation of the WVP-value are shown below (see under WVP in its Broad Sense and WVP Derivation - Figure 1.6 (below), and see under Section III.1.2.3 and in Chapter IV).

– **Water Vapor Uptake (WVU)** In general, the WVU-value is very similar to the WVP-value: instead of using the formulation in its free film form (as in case of WVP-tests), coated solid dosage forms containing a hygroscopic substance are tested by the so-called water vapor uptake (WVU) tests (Option 2: free film; Option B: Substance X being hygroscopic). In other words, the WVU-test includes coated tablets that contain a hygroscopic substance, and – periodically over time the weight gain is measured and the WVU-value calculated (see Section III.2.2). And since the entire tablet is weighed, the amount of weight gain (corresponding to moisture) reflects the sum of both, permeated moisture through the film and moisture residing in the film.

In short, the previous approaches where Substance X is hygroscopic provide

gravimetric data, quantifying the amount of moisture passing through and / or residing in a film. Details to the mathematical equations for WVU-value calculation are presented in Chapter III and IV.

– **Water Vapor Solubility (WVS)** The term - in this context - is defined as the capacity of dried formulations (whether as free films or as film coats) to comprise water vapor. In other words, it is the maximum amount of a permeant (water vapor) that can reside in the barrier membrane and hence, it is a static value (unlike WVP-values). Please note that WVS is not necessarily the absolutely maximum amount of a film's capacity to water; it can also be related to conditional cases (e.g. WVS of a film at a certain environmental relative humidity, % RH). At this stage, it is worth mentioning that WVS is a general term used for any amount of water vapor residing in a film. WVS has various forms for its calculation, which are described in detail under Section 4.1.2.2.1 (Table 4.13). Here, in Chapter 1, WVS is a general term used to describe the amount of water vapor residing in a film. Furthermore, in avoiding confusion, it is worth mentioning that WVS-tests are not related to Substance X; the tests do not necessarily include Substance X, but include at least a film.

It has been mentioned above, that WVP- and WVU- values reflect the sum of both, permeated moisture through the film and moisture residing in the film. This explains the significance of WVS-values; they contribute to the overall understanding of a formulation's MPA, by answering questions to the hygroscopicity of the barrier membrane itself. Especially the gravimetric tests performed on free films described above (WVP-tests) require further investigations, providing data on a film's WVS. The following reasons explain why: assuming the investigation of two moisture protective formulations having the exact same (quantified) WVP-value, their MPA can still differ significantly. For example, Formulation 1 with a low WVS-value (or any other value representing WVS) has less capacity to water vapor than Formulation 2 having a high WVS-value. Formulation 1 could for example be less hygroscopic than Formulation 2 and hence allow more moisture to pass / permeate. Yet, the measured WVP-value is equal in both cases, representing the total amount of weight gain (for moisture inside the film and moisture passing through it). Their MPA would then be different. WVS can be assessed by various techniques, mostly gravimetric ones. For example, absolute film solubility to water vapor could also be obtained by exposing the film samples to a maximum relative humidity (100 % RH) and by gravimetric or analytical means the water content assessed (water uptake studies [13, 12]. A similar but yet different approach is the following: Mwesigwa et al. have assessed moisture

solubility in polymeric films by the so-called dynamic vapor sorption (DVS) technique [38]. Mwesigwa calculated a film's solubility to water vapor from its sorption-desorption studies. The same technique is also expected to work for the weight gain of standardized films that are exposed to a certain relative humidity. In that case, WVS-values or EMC-values (equilibrium moisture content; explained under Section 4.1.2.2.1) would result, depending on their degree of dryness. A third approach described in literature is performed by Tongdeesoontorn; this research group assesses absolute water solubility in edible films by soaking the latter in water for a certain period of time and via the weight difference- absolute water uptake (solubility) is calculated (S-value). This can only be performed, if the film is (absolutely) insoluble in water; otherwise, film material would dissolve "away", leading to confusing results. One could argue here, whether all just-described techniques result in the same quantified value for water residing in a film. This is indeed prone to negotiation, and is not part of this doctoral research. Yet, any value representing WVS of standardized films would contribute to the overall understanding of a film's MPA. Moreover, there are surely non-gravimetric methods capable of answering the question to WVS; they are, yet, not considered in the context of this doctoral research. Details to the mathematical equations for WVS-value calculation are presented in Chapter III and IV.

– **WVP in its Broad Sense and WVP Derivation** Water vapor permeability (WVP) is a complex term of various definitions. One has to distinguish between two meanings for WVP here: a practical / experimental one (that has been described above), and a general (progress-related) one. WVP, in a practical / experimental sense, has been defined above (it is the amount of water vapor permeating at a unit time, unit area and unit film thickness). But there is also "WVP" in a broad sense; it is not the quantified value for water vapor permeation (as the WVP-value), but rather the stepwise process of water vapor permeation through a barrier membrane; WVP - according to its broad definition - applies to free films and film coats, and does not depend on the nature of Substance X (being hygroscopic or moisture sensitive); in short, it defines the act of water vapor permeation through a film reaching the "other side".

– **WVP Mechanism, WVP Derivation, WVS Significance** Protecting Substance X with a moisture protective formulation does not guarantee a lifelong protection; as long as the polymeric film is pore-free and its affinity to water is above

zero[3], then moisture can always permeate through it and / or reside in it. Hence, moisture protection is more of a delay to the possible harm affecting Substance X that might result from water vapor permeability. Water vapor passes a film in a three-step mechanism: it first adsorbs to the film surface, diffuses through the film and completely or partially desorbs on the other side. The more hydrophilic the film is, the higher its WVS and the higher the permeability. This process of WVP (both, in its broad sense and experimentally) is a function of both, moisture's solubility and its diffusivity in the film (Figure 1.6 – Equation IV). Equation IV of Figure 1.6 is widely found in literature, describing the factors contributing to WVP: the solubility, S, is a measure of the amount of penetrant sorbed by the polymer; the diffusivity, D, represents the ability of the permeant to move within the polymer. It clearly relates WVP to its contributing factors. In short, the solubility and diffusivity of moisture in a barrier membrane are dependent on the barrier's affinity to moisture (hydrophilic vs. hydrophobic), its density and geometric packing configuration, amongst others. Here, the difference between water vapor permeability, WVP, and water vapor sorption, WVS, appears better: WVP of a barrier membrane (either free film or film coat) is dependent on the WVS of moisture *in* the film. The higher a film's WVS, the higher its WVP at constant diffusivity, D. But the opposite is not necessarily true: a high WVP does not necessarily result from (only) a high WVS of a film, as WVP also depends on D.

WVP being a product of moisture's solubility and its diffusivity has now described (some of) the factors affecting it. In other words, this definition is valid for the step-wise progress of moisture permeation through a barrier membrane (in its broad sense), and it also describes the experimental term (mathematical derivation, experimental definition) as shown now. Thinking back of the practical definition - the experimental aspect of WVP -, WVP quantification can mathematically be derived as shown in Figure 1.6: The P-coefficient is derived from Fick's first law of diffusion (Equation I in Figure 1.6) and Henry's gas law (Equation II in Figure 1.6). Using Equation II of the figure for the concentration term, c, of Equation I results in Equation III.a. The latter can be re-structured to result in Equation III.b, which is equivalent to Equation IV. Equation IV includes a P-term (Permeability). This derivation is found often in literature (e.g. [53]). If Equation IV of Figure 1.6 is slightly modified and restructured, it gives Equation V as follows (Figure 1.7): the Flux, J, representing the

[3]Polymeric films having absolutely no affinity to water are expected to result in no or very low dissolution rates (an undesired property for moisture protective and immediate release coating formulation).

amount of substance diffusing per unit area of the barrier membrane and unit time is rewritten to be the weight gain (resulting from moisture) per unit area and unit time; the film thickness, l, is replaced by the film weight (for the lack of inaccurate film thickness measurement, film weight may be used as a measure for film thickness, assuming a linear relationship between both); the delta partial pressure term, $p_a - p_b$, found in Equation III.b, is considered to be constant for a given relative humidity gradient above and below the barrier film and hence Equation V results. Equation III.c of Figure 1.7 illustrates the intermediate step from Equation III.b to Equation V of Figure 1.6. Some scientists use Equation III.b of Figure 1.6 or Equation III.c of Figure 1.7 (e.g. [43]), while others use Equation IV of Figure 1.6 (e.g. [38]) to quantify WVP. A detailed review on the different approaches, equations and their results is explained below (see sub-section titled "Literature Review: Methodologies Used by Other Scientists" later in this chapter). In this doctoral research, Equation V of Figure 1.6 is used to determine WVP-value (see Equations of Chapter 3 and Chapter 4). Here, and before continuing with the background information, the following is important: all, the P-value described in Equation IV, the WVP-value calculated in Equation III.b, and the WVP-value found in Equation V (all found in Figure 1.6), describe the same term. Values for WVP calculated by Equations III.b and IV are expected to be equal, but different from the value obtained from Equation V. This is so, because the partial pressure term, found in Equation III.b is not accounted for in Equation V (as seen in the intermediate Equation III.c); it is considered to be constant as long as sink conditions apply. However, results from all those equations do certainly correlate.

Above, it has been mentioned that tests for WVP include ones performed on free films or film coats. It has also been mentioned above that - in order to obtain WVP-values -, tests are performed on free films using the gravimetric methods (to our knowledge). Looking at the just presented equations in Figure 1.7, all the equations require information on the amount of moisture permeating through the film. This is why we believe that WVP-tests aiming to calculate WVP-values use Substance X being hygroscopic substances (and not moisture sensitive); the results are gravimetric (and not analytical).

Regardless of the equation used for WVP, after all, WVP-value of free films is a material property and enables the comparison of different edible film materials regardless of their thickness. It is obtained at a constant relative humidity and temperature and is valid for pore-free films (moisture permeation through porous films would take place via the least resistant route, the pores). WVP (as opposed to WVS) is a kinetic

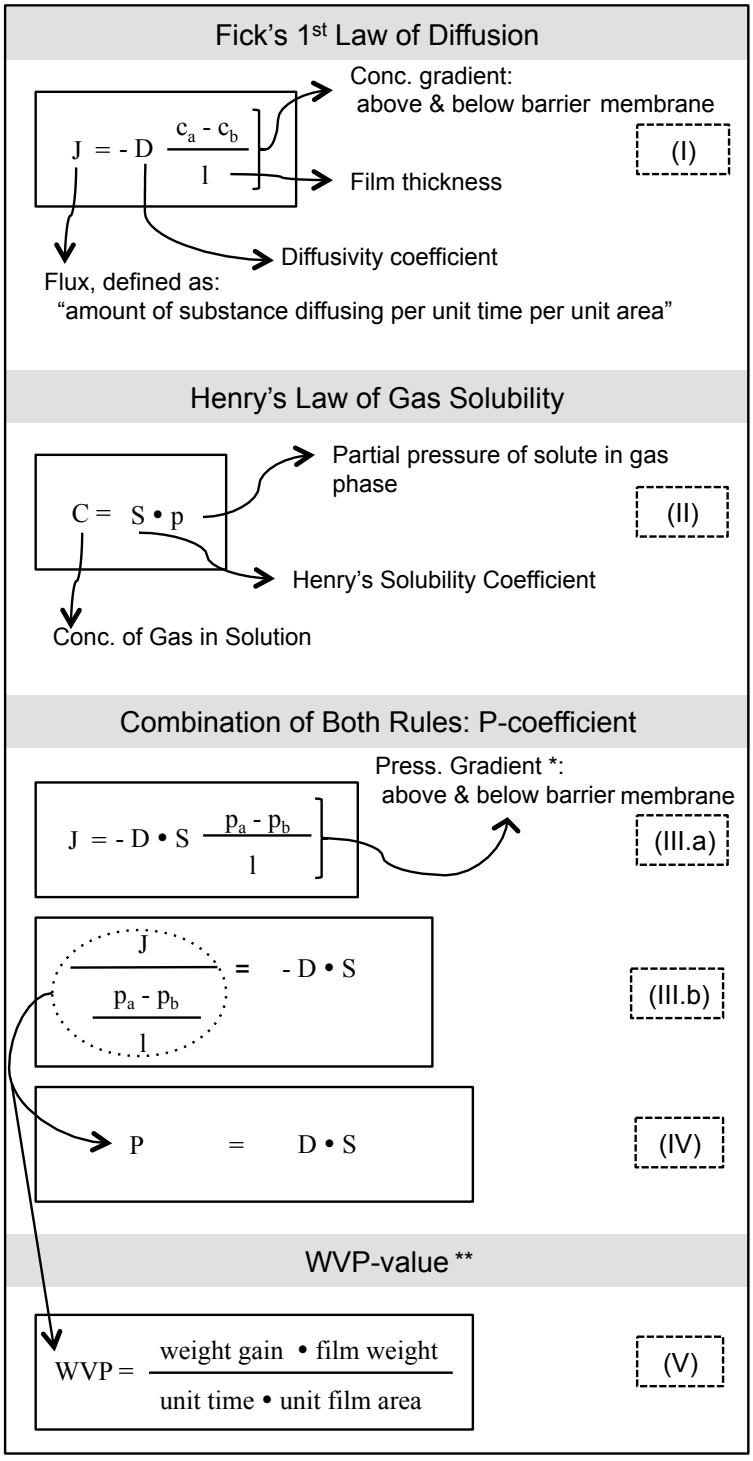


Figure 1.6: Derivation of Permeability Value(s) - Part 1. *Pressure gradient is equivalent to difference of relative humidity above and below the barrier film. **Derivation of Equation (V) from Equation III.b: see Figure 1.7. Parameter units are not relevant at this stage; units may be used individually.

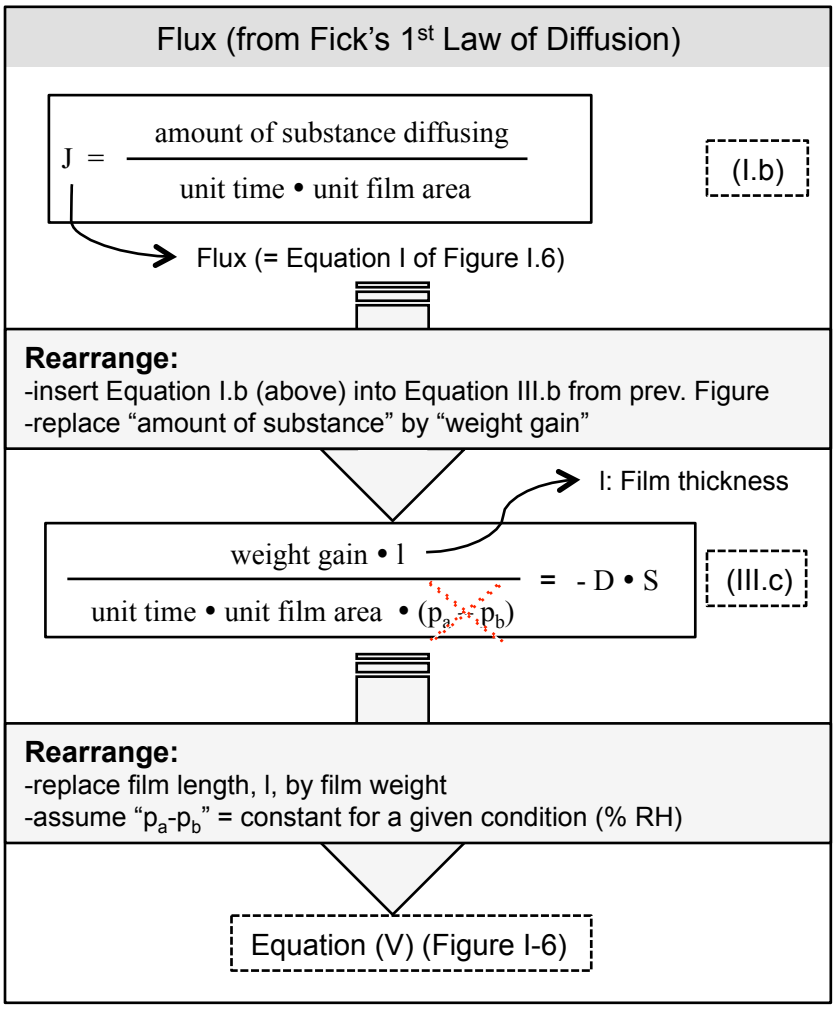


Figure 1.7: Derivation of Permeability Value(s) - Part 2

value that defines the overall moisture permeation rate of a substance under kinetic conditions (while moisture permeation takes place). In other words, the lower the WVP value of a substance, the higher its moisture protective ability is expected to be. The last statement is, however, not always valid of course, as previously presented under the WVS-term definition.

– **Lack of MPA-value** Note, as previously described, MPA is a general term describing the collective ability of a formulation, free film or film coat, to prevent moisture reach / uptake to / by a "Substance X", protecting the latter from water vapor. The broad term "MPA" - to us - includes any mechanism or approach to reduce water vapor permeability (WVP) through a film, water vapor solubility (WVS) and diffusivity, D, of water vapor in the moisture protective film, water vapor uptake (WVU) by a core (e.g. tablet) coated by the film. Hence, – to us – there is no mathematical value for MPA; it is rather a collective assessment of the various values described above, that indicate a formulation's MPA.

Summary of MPA Considerations Being aware of the complexity and confusing nature of the previous information, here a short summary: Tests containing Substance X of the *hygroscopic nature* provide gravimetric data that enable the quantification of moisture permeation and / or uptake by the film. Cup methods use free film as the barrier membranes and result in the so-called WVP-value, which can be calculated by several equations (as shown in Figure 1.6). Film coats protecting Substance X of the same nature provide also gravimetric data, but WVP-values are not provided; calculating the latter would require film coat thickness or weight characterization, which is not (always) feasible to assess for film coats. Yet, tests on film coats provide WVU-values, which are comparable to WVP-values and simulate the real application of the formulation in its coated form. In both cases, gravimetric data from WVP-tests do not unleash moisture distribution. However, WVS-tests can assist in answering such questions, because they assess a film's extent of hygroscopicity.

On the other hand, tests performed on Substance X being of the *moisture degrading nature* provide data on a true formulation's MPA; the extent of moisture-caused harm affecting this substance can be quantified. The results are, however, valid only for *this particular* substance. Furthermore, no (direct) quantification on the amount of moisture uptake is provided here, and thus - unfortunately - no WVP-values can be calculated.

Until here, all aspects have been presented in a theoretical manner. Those aspects have been concluded from various peer-reviewed studies, that we have studied in the

context of this research. Those aspects are our own subjective assessment. The coming sub-section summarizes the most relevant aspects coming from those studies; the findings support the abovementioned theoretical statements.

Literature Review: Methodologies Used by Other Scientists Ideally, a true formulation's MPA is obtained by combination of all the previously mentioned experimental models; the result would be the amount of moisture that has permeated through the film and the extent of degradation that has occurred at is consequence. In reviewing pharmaceutical literature regarding moisture protective formulations for coating purposes, several interesting studies have been found: most scientific groups settle for one experimental model or at most a combination of two. In other words, in our literature review, we have found no research group publishing formulations' MPA by performing tests of the four abovementioned constellations. Furthermore, the investigation is usually performed as a comparative study, including several formulations that are competed. In that case, it is usually sufficient to compare the different formulations' MPA by one or two experimental models, because the test substance is constant (i.e. Substance X being the same in all cases).

The following sub-section serves two purposes: it presents a detailed review of the different approaches for WVP calculation; it also presents various results of scientific groups in that context. Here the a summary of the most relevant ones:

For example, Rachtanapun et al. and Bilbao-Sainz et al. have quantified WVP by gravimetric means only (weight gain due to moisture uptake) using Equation III.b of Figure 1.6 or Equation III.c of Figure 1.7 [43, 5]. In fact, in our literature review, most of the studies assessing a formulation's MPA and a free film's WVP had only performed gravimetric tests; even companies, such as Evonik and BASF, mostly use published data of the gravimetric type, to assess the MPA of a (novel) formulation [22, 59]. It is worth mentioning again, that - when using Equation III.b of Figure 1.6 (or Equation III.c of Figure 1.7) to empirically obtain WVP of a film - the film's *own* contribution to WVP (the film's *own* affinity to water vapor – characterized by its WVS – and its *diffusivity* to water vapor) are not assessed for reasons described earlier in detail; using those equations rather quantifies the amount of vapor permeating *through* the film.

Some scientists measure the film's *own* affinity to water vapor (characterized by its WVS) by measuring the extent of hygroscopicity of a free film as the *only* quantitative measure for a formulation's MPA. Bley et al. have assessed the water content of several dried formulations, studied their glass transition temperature and performed

sorption-desorption studies using the DVS technique [12]. The group has *not* performed any quantitative measure for the amount of moisture *permeating through* the film in this paper. In our opinion, it is surely valuable information to quantify the amount of moisture residing in the polymer itself, and moisture's diffusivity in it. Yet for moisture protective purposes, it is more or at least equally relevant to quantify the amount of moisture permeating through a polymer, and reaching the "other side".

Mwesigwa et al. performed WVP calculation by a completely different means; the group used Equation IV of Figure 1.6 directly for WVP calculation [38]. They calculated a film's solubility to water vapor from its sorption-desorption studies, analyzed the diffusion coefficient mathematically from the linear portion of the sorption isotherm (where Henry's law is assumed to apply) and hence calculated WVP. In doing so, Mwesigwa et al. gained information about the formulations' WVS and WVP, and thus its MPA.

Most scientific literature was found doing gravimetric assessment of formulations' MPA performed on free films; no moisture sensitive API was included and no coating performed. Yet, we have found two exceptional previously referred-to research groups: Bley et al. and Mwesigwa et al. [13, 38]: what makes both research groups so interesting is that both have assessed and compared the moisture protective abilities of marketed products; both have included a moisture sensitive pharmaceutical drug and performed coating studies. First, a quick overview of the complete work is given as follows: Bley et al. have used dynamic scanning calorimetry (DSC) and dynamic vapor sorption (DVS) techniques, as well as water uptake studies on free films; the findings collectively unleashed the factors contributing to water vapor permeation [12]. As previously mentioned, they did not assess a free film's WVP-value as such, but settled for the hygroscopicity of the free film, amongst others, which is an insufficient approach in our opinion. Yet, in another paper, this research group has also conducted tests on coated tablets containing moisture sensitive allicin [13]. Mwesigwa et al. have also assessed the moisture protective abilities of marketed formulations as free and as coated films. As previously mentioned, they have calculated WVP for free films using Equation IV of Figure 1.6; their model drug was acetylsalicylic acid [38].

Starting with the results for free films (not coated formulations): Bley et al. have found that the investigated marketed formulations possess different WVS values; their behavior in humid conditions varied strongly, their glass transition temperature reduce in presence of water, amongst others [12]. Mwesigwa et al. have included the same marketed products as Bley et al. They have found that a formulation obtaining a high permeability-value could have a low WVS-value; in other words, the trend

of three dried formulation's sorptivity to water vapor did not go in line with their WVP trend. Hence, a moisture protective barrier membrane having high moisture sorption does not necessarily mean the film is of low moisture protective abilities; yet, such finding is indicative. After all, they have found Eudragit E PO to be the least permeable formulation on the market [38].

Please note that - to us and by just looking at the published data regarding free films (and not coats) - Mwesigwa et al. have made a more thorough assessment of the products' MPA and have more looked at the overall picture, assessing the formulation's MPA; Bley et al. have more assessed the interaction of a free film with humidity and its behavior in moist conditions. Yet, this is a personal judgment based on a subjective opinion about the significance of results.

Beside the free film assessment, both research groups have performed studies on tablets containing a moisture sensitive drug that degrades in moist conditions. Both groups have quantified the product (or its degradation products) analytically, in order to state the formulations' best MPA (lowest harm to the model drug). The interesting result is controversial: Bley et al. have found that coated marketed moisture protective formulations reduced allicin degradation in tablets compared to uncoated ones, Eudragit E PO being the best in that [13]. Mwesigwa et al. have found that uncoated aspirin tablets showed the least degradation compared to 3 marketed coated formulations [38]: a formulation showing the least permeability (WVP of free film) did indeed reduce the amount of water vapor sorbed most (WVU of coated tablets), but, in fact, it protected least from moisture as a coat (most degradation of acetylsalicylic acid in the tablets). This unexpected result was not attributed to a moist coating process (that could have caused acetylsalicylic acid degradation), but rather to the altered adhesion of the film on the tablet surface as a result of moisture exposure. The claimed poor adhesion of the film coats to the tablet surface in combination with aggregation of water in the coating resulted in moisture-rich zones between the coat and the tablet surface. They concluded that the validity and usefulness of currently available moisture barrier coating systems is questionable.

From both studies, one can conclude several aspects: assessing moisture protective formulations on free films provides insufficient data on the moisture protective ability assessment of a formulation and might lead to biased results; tests on coated formulations are inevitable; moisture sensitive substances included in MPA assessment provide data that are valid for this particular substance only; both research groups have used the exact same marketed products and yet have come up with totally contradicting results. In short, multiple factors contribute to the overall MPA

assessment, as seen from those two research groups. Hence, the important results, the most important findings to us were considered in this doctoral research and have inspired us.

As mentioned above, a true formulation's MPA is ideally obtained by combination of all the previously mentioned experimental models. But due to the lack of time and resources, this doctoral research has included various experimental models in assessing our novel formulation's MPA, aiming to reduce any bias of results. In doing so, we have decided to settle for gravimetric trials, and did not include any moisture sensitive drug in our research.

Lastly, it is notable that three pharmaceutically accepted marketed products are included in many research groups, when it comes to moisture protection: Opadry by Colorcon, Eudragit E PO by Evonik, Seppifilm by Seppic. HPMC is often included, as well, as a film with relatively poor MPA. In Section 1.3.4, strategies for formulation design of moisture protective formulations are presented and more details on those products presented together with some other marketed moisture protective products.

1.3.3 Emulsions

1.3.3.1 Emulsions in General: Definition and Overview

According to IUPAC (International Union of Pure and Applied Chemistry), emulsions are dispersions of at least two immiscible fluid components [17]. Typically, one phase – e.g. a lipophilic one – is dispersed in a continuous outer phase, which may be oily or aqueous. In case the latter is the outer phase, the emulsion is of the oil-in-water (o/w) type. Emulsification is an energy consuming process, in which the inner phase is actively divided into small droplets, while it is homogenously distributed into the outer phase. This in turn causes a massive increase in the interfacial area between both phases, which results in an increase in interfacial energy according to Equation 1.1. The resulting emulsions are thermodynamically unstable systems. Each component tends to minimize its interfacial surface area and - without emulsifiers at the interface - immediate phase separation would occur. Emulsifiers are substances that allocate to the phase boundary, stabilizing the emulsion by reducing the interfacial tension, decreasing the rate of agglomeration, coalescence or both.

In general, there are 4 types of emulsifiers, which are categorized according to the stabilizing mechanism [40]. The first group includes the most common emulsifiers; they are small molecular weight surfactants that prevent coalescence by reducing the

surface free energy of the inner phase and by forming an interfacial film. Examples include sodium dodecyl sulfate. Group 2 includes high molecular weight polymers, which are amphiphilic and thus localize at the phase boundary; they mainly stabilize emulsions by steric hindrance and increased viscosity, thereby decreasing sedimentation or floating velocities according to stoke's law (Equation 1.2). Some cellulose derivatives are examples for this group [62]. Schubert et al. describe stability supporting substances, which either modify or enhance an emulsifier by - for example - electrostatic means (Group 3) [50]. Last but not least, small colloidal solid particles may also stabilize emulsions by only steric hindrance. As opposed to Group 2 emulsifiers, those particles are not necessarily polymeric in nature and do not obtain any surface-active property. Emulsions stabilized by the fourth group are called Pickering emulsions and are discussed in more detail below (Section 1.3.3.3).

$$\Delta E = \gamma \times \Delta A \tag{1.1}$$

Surface Energy

ΔE = surface energy
γ = surface tension
ΔA = surface area

$$\nu = \frac{2r^2 \times g \times \Delta\rho}{9\eta} \tag{1.2}$$

Stoke's Law

ν = sedimentation velocity
r = particle radius
g = gravitational constant
ρ = density
η = viscosity

1.3.3.2 Emulsion Instability Forms and Classical Stabilization Techniques

As previously mentioned, liquid in liquid two-phase systems without an emulsifier are unstable as a result of immediate phase separation. Yet, even with an emulsifier emulsions tend to destabilize, because of their thermodynamic instability. During storage different instability forms might occur as depicted in Figure 1.8. The first step to instability is the emulsion droplets moving within the outer phase and coming closer

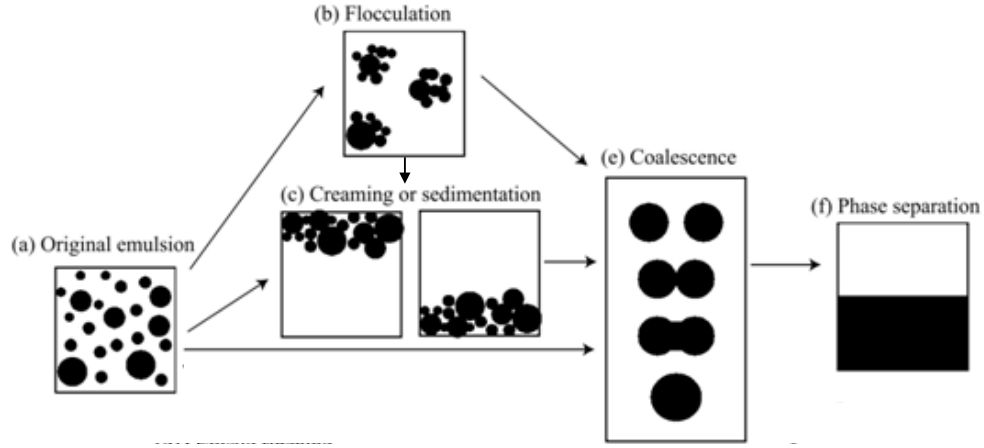


Figure 1.8: Emulsion Instability Steps and Forms.
Source: https://isalama.wordpress.com/article/corrosion-inhibitors-in-the-oilfield-3uf3kbfllnswt-4/; modified copy.

together. The velocity at which inner phase droplets (oil in case of o/w emulsions) move within the outer phase is a function of the density difference of the inner and outer phase, the droplets' diameter and the viscosity of the outer medium (Equation 1.2). Once the droplets are aggregated (flocculated), their state is energetically more stable than individually dispersed small droplets; reduced surface area is linked to reduced surface free energy. Flocculated droplets tend to float (cream) or sediment even faster than individual droplets; creaming or sedimentation depends on difference in density between the outer and inner phase. The seemingly phase separated emulsion can still be reversed into its original state by simple shaking; the inner phase still retains its droplet character without having fused into bigger droplets. However, once the droplets unite to bigger ones (coalescence followed by phase separation), emulsion's physical state changes irreversibly; droplet size distribution (DSD) measurements show a shift towards increased droplet sizes. It is worth mentioning, that the reversible flotation (or sedimentation) step might end up with phase separation as well, since the individual droplets are in a state of high proximity with enhanced tendency to fuse. According to Jafari et al., there is an increased collision frequency, which may lead to a higher probability of fusion [33].

In order to prolong the stabilization time the very initial step of emulsion instability -the droplet migration- is to be minimized and slowed down: higher viscosity, smaller droplets and smaller density differences reduce droplet migration velocity (Equation 1.2). In literature, several other techniques are described as well that are used to stabilize emulsions; those are not discussed in detail in this doctoral thesis.

1.3.3.3 Pickering Emulsions

A Pickering emulsion (PE) is an emulsion stabilized by a colloidal solid particles. The stabilizing mechanism differs greatly from surfactants' stabilizing one: the latter stabilize emulsions mainly by reducing the surface tension of each phase, thus reducing the surface free energy. By contrast, colloidal solid particles show no surface-active properties despite their affinity to the phase boundary; they rather stabilize the phase boundary by a simple mechanical barrier functioning. In other words, the surface energy is not reduced as a result of lowering the surface tension of both phases. Furthermore, as opposed to surfactants, solid particles are not in equilibrium with the environmental bulk; the former constantly adsorb and desorb to and from the inner phase boundary, whereas solid particles almost irreversibly allocate to the phase boundary and remain unchanged [8]. This gives Pickering emulsions a stability advantage over surfactant-stabilized emulsions.

The aforementioned binding energy of the solid particles to the phase boundary is described and quantified by Equation 1.3. The solid barrier stability is directly related to the energy required to desorb the colloidal particles from the phase boundary; this energy is a function of the interfacial tension between both phases, the particles' radius and their wettability [56, 8, 7]. Thus, the higher the binding ability of the solid emulsifier the more stable the formulation. High binding ability of the solid particles is achieved only if some prerequisites are fulfilled. Those include wettability of the solid particles by both phases, as well as considerations regarding solids' particle size and the interfacial tension. Those parameters are found in Equation 1.3. The following sub-points discuss those.

$$E = \pi \times r^2 \times \gamma_{OW} \times (1 + \cos\theta)^2 \tag{1.3}$$

Surface Energy

E = adsorption energy
r = pigment radius
γ = interfacial tension
θ = contact angle

Wettability of the Particles Solid particulate emulsifiers must exhibit similar affinities to both phases. Solid particles demonstrating a significantly higher affinity to one of both phases over the other are preferentially located in that particular phase

rather than at the interface. In turn, this would result in unstable emulsions. Particle wettability by a fluid is a measure of their affinity to that fluid (phase) and is typically illustrated by a droplet on a solid surface; the so-called contact (wetting) angle can be measured for example by a modification of the well-established Wilhelmy-Plate method. The unmodified method is usually used to measure surface tensions [16].

Speaking of Pickering emulsions, the wettability of the solid emulsifier by either phase plays a significant role in the emulsion phase formation, as seen in Figure 1.9: particles in water and showing contact angles close or equal to 180° are mostly lipophilic, whereas contact angles close to 0° are seen for hydrophilic particles as a result of complete spreading over the particle's surface. Hence, particles showing intermediate contact angles are wetted by both phases and thus are suitable for Pickering emulsion stabilization (Figure 1.9). This statement is even seen by pure mathematical means: cos(0°) and cos(180°) result in 1 and -1, respectively, whereas cos(90°) equals 0; in the former cases the energy term is reduced, whereas in the latter case, the term is maximized. Analogous to the Bancroft rule [46], emulsion phase is dictated by the particles' preferred wetting phase; the outer phase is that one that spreads better on the emulsifier. Consequently, particles (in water and) showing a wetting angle $> 90\,^{\circ}$ are likely to result in w/o emulsions as a result of poor aqueous wettability, whereas particles showing a wetting angle $< 90\,^{\circ}$ are likely to result in o/w emulsions. Hence, the further away the wetting angle from 90 °, the less stable the Pickering emulsions [52].

Typical solid particles used as emulsifiers include titanium dioxide and zinc oxide [35, 54], colloidal silica [24] and $CaCO_3$. The latter's particulate emulsification abilities have been described by Tambe and Sharma [56]. The resulting decane in water (o/w) emulsion's stability was a function of added stearic acid concentration; increasing the latter results in low stability emulsions, until at certain amounts a stable water in decane (w/o) emulsion is produced. Binks et al. [6] describe a similar phenomenon: keeping the interfacial tension and particle size constant but varying the wetting angle of silica (particulate emulsifier) results in variable emulsion stability; the most stable product is observed for wetting angles of about 90 °.

Daniels et al. [32] have measured the wettability angles for different $CaCO_3$ grades. It has been found that crude (unmodified, uncoated) $CaCO_3$ exhibits a contact angle to water of about $68\,^{\circ} \pm 5$, whereas lipophilized $CaCO_3$ (by stearic acid coating) exhibits a contact angle to water of about $128\,^{\circ} \pm 2$. A feasibility experiment showed the following: 20% oil (medium-chain triglycerides), 75% water and 5% $CaCO_3$ (of either $CaCO_3$ grade) has been chosen as a prototype formulation and emulsified by

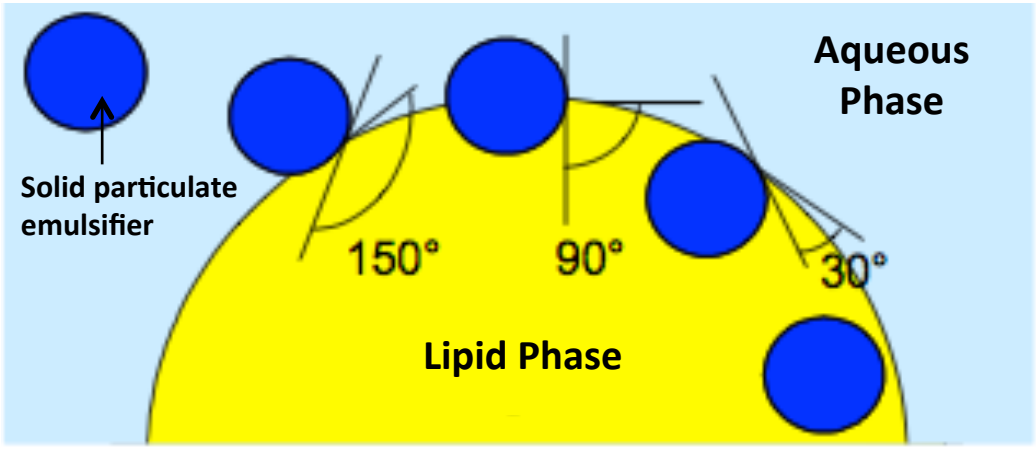


Figure 1.9: Effect of Contact Angle on Wettability. Source: Kannen et al. [35]; modified copy.

a laboratory scale UltraTurrax. Both $CaCO_3$ types did not stabilize emulsions well and the products separated within a few days. The crude $CaCO_3$ type was chosen for the following experiment: the same prototype formulation was produced, but different concentrations of stearic acid were added to (dissolved in) the oil phase before emulsification took place. More stable emulsions were produced (compared to emulsions containing either $CaCO_3$ grade); 2% stearic acid has been found to stabilize emulsions most. It is believed that stearic acid supports the localization of $CaCO_3$ at the phase boundary, stabilizing the oil to water interface. Stearic acid probably adjusts the wettability of crude $CaCO_3$, by increasing its contact angle to values close to 90°.

Size of the Particles According to Equation 1.3, the particle size (radius) affects the adsorption energy and thus emulsion stability. However, this equation is valid only for particles smaller than 1 μm, where gravity effects do not apply; particles above 1 μm in size are affected by gravitational forces and Equation 1.3 loses its validity. Binks et al. [11] have investigated the effect of particle radius on adsorption energy. Hypothetically, the greater the particle size the more stable the emulsions; adsorption energy increases exponentially with particle radius (Equation 1.3). Binks theoretically calculated the aforementioned relationship for particles ranging 0.1 to 100 nm. Particles of about 0.5 nm or smaller are expected to weakly stabilize emulsions; their size is comparable to classical surfactant emulsifiers, where - similarly to surfactants – particles would not reside in the interface of both phases. Instead, they would rather be in equilibrium with the particles in the bulk (desorption-adsorption-equilibrium). The reduced emulsion stability by such small particles is a result of lack

of surface tension reduction (as opposed to surfactants), and their insufficient phase boundary stabilization due to the small particles. According to Binks et al. [9], particles above 500 nm also stabilize emulsions insufficiently. This finding is contradictory to Equation 1.3 at a first sight. Yet, the equation is valid for individual particles and does not account for aggregated ones. Integrating both seemingly controverting findings, the following can be stated: On the one hand, particles must be big enough to remain at phase boundary without equilibrating from and to the phase boundary. On the other hand, for sufficient emulsions stabilization, the phase boundary must be "covered" by enough particles, that extend over the entire phase boundary to form a full shield around it. The latter is achieved mainly by quantitative means; the smaller the particles the more individual ones participating in the overall protection. In sum, a balanced particle size range must be achieved to fulfill the aforementioned balance: Particles ranging from 100 nm 500 nm are considered qualified for Pickering emulsion stabilization.

For the sake of this doctoral thesis, the following measurement findings are relevant: Daniels et al. [32] have investigated the particle size of one (of several available) $CaCO_3$ batch; it has an average particle sizes of about 247 $\pm$ 1 nm. This batch was for crude $CaCO_3$, not for the lipophilized one from above. Other available batches had not been investigated prior to this doctoral research.

Interfacial Tension From Equation 1.3, the interfacial between the aqueous and the lipid phase plays a role in the stabilizing mechanism of Pickering emulsions by affecting the adsorption energy.

Lipid phases with a low interfacial tension with water result in high contact angles of the particulate emulsifiers. As previously shown, this preferentially results in water-in-oil emulsions. This finding has been shown and theoretically calculated by Binks et al. [7] as follows: medium hydrophobicity silica particulates result in emulsions of the o/w type with non polar oils, and in w/o emulsions if the oil is more polar.

The previous findings lead to the conclusion that a defined particulate emulsifier with a specified hydrophobicity results in different emulsion types, depending on the polarity of oil and its consequent interfacial tension toward water. Hence, low interfacial tension between a lipid and water preferentially results in more hydrophobic surface properties compared to high interfacial tensions.

Apart from that, it has been shown by Binks et al. [10] that the order of emulsion manufacturing affects the final emulsion type: particles in water showed smaller contact angles when they were initially dispersed in water compared to being initially

dispersed in lipids. Hence, adding the lipid phase to the aqueous phase in the former case resulted in o/w emulsions. The opposite was shown to be true, for particles initially dispersed in lipids.

Further Stabilization Mechanisms Apart from the previous stabilizing mechanisms, the solid particles at the phase boundary may also interact together to form a 3D network resulting in an increased viscosity of the continuous phase. This in turn reduces the collision frequency and consequently enhances emulsion stability [31, 58, 57].

Other Potential Risk Factors for Pickering Emulsion Stabilization Ellermann 2015 [21] described several stabilizing mechanisms of dispersions including stabilization by surface charge or by steric hindrance; the aim was to prevent closeness of the dispersed particles / droplets followed by sedimentation / fusion (coalescence) and phase separation. In literature, it is described that suspensions may be stabilized with a relatively high surface charge that prevents the closeness of dispersed particles and hence no or low sedimentation. For emulsion droplets, the same consideration may apply; however these considerations apply for the entire inner phase droplet, which is composed of the lipid droplet surrounded by emulsifier particles; it does neither apply to the single emulsifying particle (e.g. $CaCO_3$), nor to the individual lipid droplet. For the lipid droplet, a zeta potential high in magnitude may be beneficial to avoid closeness of the individual droplets [4]. But for the particulate emulsifier, it is important to notice that the zeta potential may not exceed a certain value; in that case the particles would not get close enough to form a protective shield, and would rather repel each other [14]. Particles should have a rather medium valued zeta potential in the range of 20 to 30 mV [35]. Particulate emulsifiers zeta potential has been measured for Eusolex T-2000 (a titanium dioxide powder): it values approximately 28 mV [35] and it has shown good emulsion stabilization properties. Daniels et al. have measured a zeta potential for nano sized $CaCO_3$ in the range of 15 mV [32]. The research group has also found that pH changes of the outer phase, electrolytes addition, combination of (functional) polymers dispersions and any substance addition that may alter surface charge can result in zeta potential changes of the entire inner phase (lipid plus emulsifier); this may cause instabilities of the final product and hence, caution must be taken when incorporating any further material

[4] Some scientific groups claim to have obtained stable Pickering emulsions even on adding high concentrations of electrolytes to the aqueous phase. This has not been further examined in this literature review.

to the already stable Pickering emulsion, as Ellermann [21] has described. Sudden flocculation and emulsion instability may result.

1.3.3.4 Dried Emulsions

Pickering emulsions of the oil-in-water type can be transferred into solid (dosage) forms to serve various purposes. Möllgaard [37] has developed an o/w Pickering emulsion with HPMC in the aqueous phase, which has been dried by spray drying to serve as a topical sun screen. Kannen and Ellermann [35, 21] have developed similar Pickering emulsion formulations, which - by spray granulation – have been dried to serve as lipid based oral drug delivery systems with or without controlled release profiles. Other drying techniques may be applied as well, such as rota-drying, freeze-drying and spray-drying [41, 1, 37, 3, 27]. Their review is not relevant to this research.

Because the film-forming emulsions developed by Möllgaard, Kannen and Ellermann [37, 35, 21] are similar to the emulsion developed in this doctoral research, a greater focus is set on them: a remarkable aspect is the lipophilic phase of the emulsion not solidifying at room temperature on drying, but remaining in a liquid state of matter. Hence, valid questions are "how is the film formed?" and "how is the liquid lipid immobilized in the film?". The first question is simply answered as follows: a film-forming excipient that is added to the outer phase of the original (un-dried) Pickering emulsion is responsible for film formation on drying. The film-forming agent may be dissolved or suspended in the outer (aqueous) emulsion phase. Water-soluble candidates include gelatin [1], povidon [63], HPMC [37] and others; water-insoluble candidates include ethylcellulose. Regardless of the solubility of the film-forming agent, on drying a film is formed as described under Section 1.3.2.1 and Section 1.3.2.2. Coming to the second question, the following is valid: to the moment of starting this doctoral research, we had no scientific information on the inner morphology of those dried emulsions. We believe, the inner lipophilic phase is immobilized in an outer polymer matrix composed of the film-forming agent; the latter mechanically prevents coalescence by immobilization of the individual oil droplets. And because the (un-dried) emulsions were Pickering emulsions, the particulate emulsifier is expected to support stability on drying and to enhance coalescence prevention. Yet, no detailed information or microscopic image has been found for that matter. Furthermore, a highly interesting result for those emulsions is emulsion character preservation and stability of the dried products; Möllgaard has shown that the dried formulations preserve emulsion character in the solid state, by reconstituting

the dried Pickering emulsion in water; the latter shows similar drop size distributions to the original formulation [37]. In turn, this indicates two important aspects: first, the drying process itself (e.g. the atomization step in the case of spray-drying or granulation) has obviously retained the emulsion droplets intact without destroying them, and second, this finding per se implies the presence of individually existing oil droplets. Furthermore, Möllgaard has found that the dried Pickering emulsion is stable over a period of 6 months. The previous open questions have been captured and partially answered in this doctoral research (see Section 4.1.2.1.3).

1.3.4 Moisture Protective Formulations and Lipid-based Coatings

In this section different formulations are presented and discussed. Those are mainly divided into the following paragraphs: first, moisture protective formulations from the market are presented, which are mostly non lipid-based. Following that, various lipid-containing and lipid-based formulations meant for coating are presented. Those include some designed for moisture protections and others designed for other purposes. In the last, paragraph, the idea and rationale behind the particular choice of developing a Pickering emulsion for moisture protection is discussed.

Marketed Moisture Protective Formulations There are quiet a few different marketed polymeric products claiming taste masking and moisture protection. They are typically applied to solid cores using a fluid bed or pan coater and require no hot-melting module (as will be shown for lipid coatings in the next paragraph). Those products are mainly based on methacrylate copolymers (e.g. Eudragit E PO by Evonik; Kollicoat Smartseal by BASF), polyvinyl alcohol polymers (e.g. Opadry 200 by Colorcon), or cellulose-derivatives (e.g HPMC mixed with stearic acid as in Seppifilm LP by Seppic; cellulose copolymers with additional waxes as in Aqualon by Ashland). For marketing purposes, those companies offer different forms of the same basic formulation, covering a wide range of palatability and handling; products are in different colors and appearance, but also in various forms of handling (ready mix powder, ready mix dispersions, etc.). However, the competition lies mainly in achieving low moisture permeability simultaneous to immediate release profiles at the lowest coating quantity. Here is where Equation IV of Figure 1.6 comes into play: the formulation must form an intact film on the pellet or tablet surface, be pore-free and thus restrict free moisture passage. In this way, moisture can pass only by diffusion through the polymer to reach the inner core (diffusivity rules discussed in Section

1.3.2.4 apply; adsorption, diffusion, desorption). Furthermore, the less polar the substances used in the formulation, the lower the solubility for water in the film and the less the permeability. At the same time, if substances become too lipophilic, their dissolution becomes impaired and the release profile consequently altered. Therefore, it is crucial to find a reasonable balance.

Methacrylate copolymer-based formulations used for moisture protection include a dimethyl-amino group, making them insoluble in water at any pH above 5; in acidic media (pH < 5), their amino group becomes protonated and thus the polymers become water soluble. This characteristic gives them their taste masking and moisture protective abilities without delaying the API release. The remaining formulations, which are based on water-soluble polymers (PVA or cellulose), mainly outbalance their hydrophilicity (high affinity to water) and their moisture protection (low permeability). The former property allows immediate release profiles that are pH independent (fast disintegration), while the latter is achieved by incorporation of hydrophobic excipients (e.g. stearic acid or waxes added to cellulose-based formulations), as discussed in the next sub-section.

Lipid-based Coatings In general, it is believed that lipid incorporation into film coating formulations enhances the moisture protective ability of a film coat: Rajabi-Siahboomi et al. show that HPMC free films containing stearic acid are approximately 30% less permeable to water vapor compared to crude HPMC free films (at certain conditions) [44].

Not only lipid-containing products but also lipid based ones are used for moisture protection, amongst others. But before presenting this, the term "Lipids" needs to be introduced, because of its extendible nature. "Lipids" is a general term used for mostly hydrophobic substances, including fatty acids, triglycerides (oils and fats), waxes and others. They differ strongly in their melting points: waxes and saturated triglycerides (fats) are rather solid at room temperature as opposed to unsaturated triglycerides (oils), a fact that needs to be considered as seen below.

Coating of lipid-based substances is found on the market as well as in literature. Most such marketed products are used for the food industry rather than the pharmaceutical one. Several fruits, vegetables and dairy products are coated by natural and / or synthetic lipids, which serve a functional or protective purpose. Coatings for moisture-protective barriers are mostly applied as liquefied fats (hot-melt coating), which solidify on the surface of the cores [49, 47]. Gaudy et al. on the other hand have coated a Trilaurin organic solution, probably aiming to eliminate the melting step as

well [26]. In the pharmaceutical industry, lipid-based coatings are not widespread and when applied usually found for taste masking and moisture protection purposes or controlled release reasons. Now the type and state of matter of the lipid at room temperature matters most: hot-melt coating is often necessary, in order to liquefy the coat formulation for the coating process. Gattefoss (France) has a pair of products that are applied by this technology. They contain a mixture of mono-, di- and tri-glycerides, which are esterified with behenic acid (Compritol 888 ATO), or with stearic and palmitic acids (Precirol ATO 5) [23]. The first is used for taste masking, whereas the second for controlled release coatings. However, hot-melt coating cannot always be applied (e.g. in case of temperature sensitivity of the core or lack of the technology). Hence, alternative systems are inevitable. For example, Seppic S.A. (F-Paris) markets 2 products that require no hot-melt coating: film coats of the product Seppifilm SN are polymer-based (Schellack and PVP) with solid lipid incorporation (acetylated monoglyceride); the coat is applied as an organic solution. Seppifilm LP 010 is a powder ready mix based on HPMC and MCC and contains stearic acid; the product needs to be suspended in water before coating. Both products claim moisture protection. Now since aqueous coating processes are more conventional and typical (compared to organic coating and hot-melt ones), and since purely lipid-based coatings usually result in controlled release (an undesired property in case of moisture protection) the following is valid: a coating fluid containing dispersed lipids overcomes the first challenge (no hot-melt or organic coating needed) and if designed properly overcomes the second challenge as well (no controlled release). Starting with the first challenge, Schaal et al. have developed an aqueous based triglyceride-nanodispersion with a lipid that usually has a melting point above room temperature. By crystallizing modifications, he has rendered the lipid in a supercooled melting state of matter, and the molten lipid has been processed to an “oil” in water emulsion using a high-pressure emulsification device. The final formulation is a fluid, that can be sprayed / coated onto solid cores; it thus requires no hot-melt coating. Schaal et al. have compared their formulation to Seppifilm LP 010 and have obtained a similar behavior in moist conditions as well as a similar release profile [49].

If, however, as opposed to above, the incorporated lipid is a liquid at room temperature (e.g. oils and unsaturated fatty acids), special attention is required: the lipid in the final film coat must be immobilized by a solid polymer in a matrix like structure (e.g. dried emulsions), or shielded by a solid carrier (e.g. mesoporous silica products) in order to keep them in a solid-like state. An example for that is presented as follows: Hernandes et al., Baldwin et al. and Garcia et al. have used aqueous emulsions

[4, 30, 25]. Garcia et al. use sunflower oil (liquid at room temperature) as a preferred lipid over waxes (high melting point), in order to avoid using hot-melt techniques and exposure of the cores to high temperatures. So, both previously mentioned approaches (by Schaal et al. and by Garcia et al.) include a liquid coating fluid that requires no hot-melt technology. Yet, the main difference lies in the state of the lipid at room temperature: Schaal's formulation includes a lipid that solidifies at room temperature over time, while Garcia's formulation includes an emulsified liquid lipid that stays as such. This distinction is extremely important in this research, since all used lipids in this thesis are liquid at room temperature. In that context, it is worth mentioning, that the immobilization of the liquid lipid in the coat and its migration risk (leaving the film) are important aspects to consider. Garcia declares the latter being dependent on the final concentration of the oil in the formulation / film. Those aspects are well considered in this doctoral research.

Oil in Water Pickering Emulsions For Moisture-Protection Above, it has been presented, that formulations for moisture protection can be based on polymers (with or without a lipid component) and based on lipids. It has also been presented, that moisture protective coatings are usually aspired to render the cores unchanged with respect to their disintegration and drug release. Furthermore, some (purely) lipid-based formulations intended for coating need to be liquefied for atomization - a property achieved by melting, and hence hot-melt coating technology is applied. Alternatively, solid or liquid lipid components can be incorporated (emulsified or suspended) in a liquid and hence coated onto cores. The liquid may be aqueous or organic, while the former has shown several advantages over the latter, as previously discussed (see Section 1.3.2.1). All of these aspects have been presented above and are basis for the next point.

Those aspects, considerations and demands - when integrated together with aspects and findings previously presented above - make Pickering emulsions of the oil-in-water type interesting formulations regarding that matter: Pickering emulsions are well understood (dosage) forms showing a profound stability; they are surfactant free and hence safe for oral use; they can be dried giving a solid (dosage) form; they contain a lipid, which is water repelling and thus their dried form are expected to have low water vapor permeability (WVP); they are aqueous based and hence require no organic coating; once dried, they are re-dispersible to their original form, but their dispersing rate is undefined, yet. The only thing missing is their film-forming activity, which is expected to be possible if a film-forming agent is added to them.

Those reasons make oil-in-water Pickering emulsions interesting formulations for moisture protection.

Therefore, the central aim of this doctoral thesis is to develop novel formulations in form of o/w Pickering emulsions, that are film-forming, moisture protective, coatable, and of no modifying nature to the disintegration property of the coated cores.

In Section 1.4, the overall layout of this doctoral research is presented.

1.4 Thesis Layout

Figure 1.10 illustrates the general structure of this doctoral thesis. The methods and results of doctoral research are divided into three main stages, namely Stage 1 to Stage 3. Each Stage is again divided into two sub-stages (e.g. Stage 1.1 and 1.2). The reader finds those stages in both, Chapter 3 and Chapter 4. In Chapter 3, one finds the methods related to each stage / sub-stage, while Chapter 4 includes the results to those methods. By the term "information" used in the following text, methods and / or results are meant.

Stage 1 is "Everything about the Formulation(s)": Information related to the formulation production and its characterization are collectively described, presented and discussed in this stage. It contains Stage 1.1, which includes information for the production and characterization of the formulations; it also includes Stage 1.2, which includes information regarding the formulations' investigation with respect to water vapor permeability (WVP). In a feedback loop, formulation development is achieved by reaching the lowest WVP-value, amongst others.

Stage 2 is "Everything about the tablets": It includes information regarding tablets formulation and production. Stage 2.1 has information regarding the production and characterization of tablets; Stage 2.2 includes information regarding the tablets' behavior in moist conditions. Results of this stage set a reference to the water vapor uptake (WVU-values) of the uncoated tablets.

Stage 3 is "Everything about the coated tablets": Formulations described in Stage 1 are coated to tablets presented in Stage 2. Stage 3.1 includes information regarding the feasibility of coating the formulations developed in Stage 1. Its aim is to develop suitable coating process parameters. In Stage 3.2, the main aim is to assess the formulation's moisture protective ability in its coated form, by performing water vapor uptake (WVU) tests.

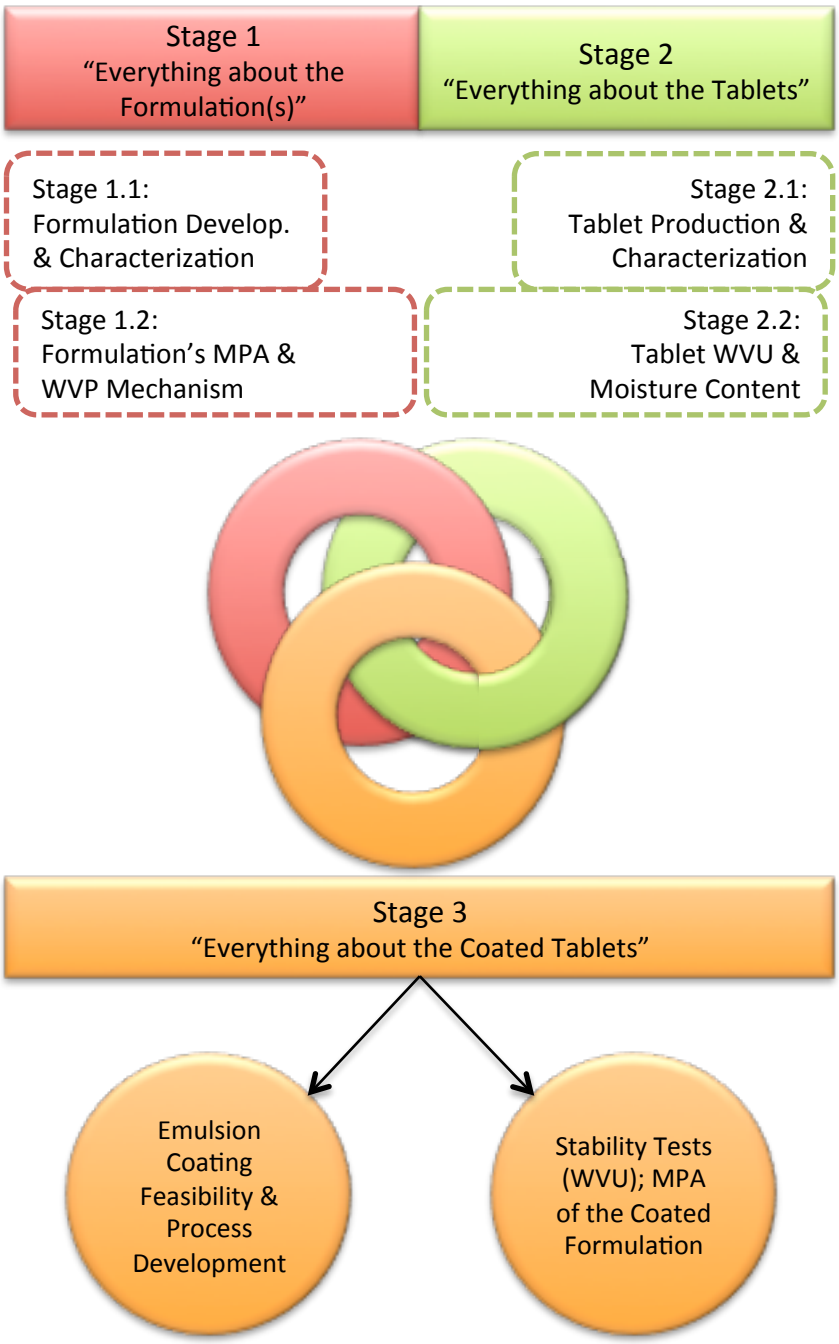


Figure 1.10: Structural Layout of this Doctoral Thesis.

Chapter 2

Material

This chapter presents all materials and devices used in this doctoral thesis.

Substance *	Abbreviation**	Trade Name (Description)	Provider
Castor oil (CO)	(CO)	Refined castor oil Ph.Eur. 7.0	Caeolo (Ceasar & Loretz GmbH)
Nano-sized $CaCO_3$	($CaCO_3$)	Gefälltes $CaCO_3$ (Different batches & specifications)	Fels GmbH - Germany
Isopropylmyristate	(IPM)	Isopropylmyristate Ph.Eur. 7.0	Caeolo (Ceasar & Loretz GmbH)
Hydroxypropyl-methylcellulose	(HPMC)	Pharmacoat® 606	Shin-Etsu Chemical Co. Ltd.
Medium chain triglycerides	(MCT	Tegosoft CT	Evonik Industries
Light liquid parrafin	(PPL***)	Pionier 2076 P	Hansen & Rosenthal KG
(Heavy) liquid Paraffin	(PSL***)	Pionier 2071 P	Hansen & Rosenthal KG
Purified water		See Table II - 3	
Sunflower oil	(SFO)	Refined sunflower oil Ph.Eur. 7.0	Caeolo (Ceasar & Loretz GmbH)

Table 2.1: Emulsion Materials. List of all components used for emulsion production. Related methods are presented in Chapter III Section 1 (III.1) * All listed materials are compliant with European Pharmacopoeia (8.0). ** Abbreviations between brackets listed in the second column of the table are found throughout this doctoral thesis. *** Light liquid paraffin and (heavy) liquid paraffin are abbreviated as PPL and PSL, respectively. The abbreviation PPL is for the latin name "paraffin perliquidum" and the abbreviation PSL is for the latin name "paraffin subliquidum".

Substance *	Trade Name **	Provider
Anhydrous silicon dioxide (fumed silica)	Aerosil® 200 Pharma	Evonik Industries
Spray-dried α lactose monohydrate	FlowLac® 100	Meggle Pharma
Colloidal hydrated silicon dioxide (silica gel)	Syloid® AL 1 FP	Grace
Microcrystalline cellulose	Vivapur® 112	JRS Pharma
Talc (Mg-Silicate)	MicroTalc Pharm 8®	Mondo Minerals B.V.
Magnesium stearate	Magnesium Stearate Pharma	Wiga Pharma GmbH

Table 2.2: Tablets Materials. List of all components used for tablet production. Related methods are presented in Section 3.2 * All listed materials are compliant with European Pharmacopoeia (8.0). ** Trade names listed in the second column of the table are referred to throughout this doctoral thesis.

Substance *	Trade Name (Abbreviation) ** / Description	Provider
Basic Butylated Methacrylate Copolymer	Eudragit® E PO (EPO)	Evonik Industries
Magnesium chloride hexahydrate	Magnesium chloride hexahydrate, Ph.Eur. ($MgCl_2$)	Carl Roth GmbH + Co. KG
Malachite green oxalate ***	Malachite green oxalate	VWR Prolab
Potassium chloride	Potassium chloride, Ph.Eur. (KCl)	Caelo (Ceasar & Loretz GmbH)
Purified water	Obtained by reverse osmosis device	Elga Lab Water (ELGA Purelab Option Q (Option Q 7)
Silica gel ***	Silica gel orange globules (1-3 mm diameter)	Carl Roth GmbH + Co. KG
Sodium nitrite	Sodium nitrite salt, Ph.Eur. ($NaNO_2$)	Merck-Schuchardt
Sudan Red ***	Sudan III Red	Aefa Aesar GmbH + Co. KG
Homoeopathic pellets	Globuli sacchari, size 3 (sucrose pellets)	Pharm-a-spheres, Hanns. G. Werner GmbH + Co. KG
Stearic acid	Stearic acid, Ph.Eur. micronized	Caelo (Ceasar & Loretz GmbH)
Sodium laurylsulphate	Texapon® K12	Cognis Deutschland GmbH + Co. KG

Table 2.3: Other Materials. List of all components used for random experiments. Related methods are presented throughout Chapter III. * / *** All listed materials are compliant with European Pharmacopoeia (8.0) or the German Homoeopathic Pharmacopoia (HAB), except the substances with *** (Malachite Green Oxalate, Silica gel and Sudan Red). ** Abbreviations in brackets found in the second column of the table are referred to throughout this doctoral thesis.

Item	Description	Provider
PTFE Filter	Polytetrafluoroethylene membrane filter 25 mm diameter; 0.1 mm thickness	Sartorius AG
Vial	HPLC glass vial (2mL)	Macherey-Nagel

Table 2.4: Disposable Materials. List of disposable components used for water vapor permeability (WVP) tests. Related methods are presented in Section 3.1.2.3.

Device / Technique	Model Type	Company	Auxiliary (A) / Software (S)
Briquette milling	Stada Allzweck Type TG 2	Erweka GmbH	Motor: Erweka AR 400 Type UG, Erweka Gerätebau (A)
Dissolution apparatus (Monograph 2.9.3, Ph.Eur. 8.0)	Erweka ZT2	Erweka-Apparatebau-GmbH	n.a.
Dynamic vapor sorption (DVS)	DVS 1/2	Surface Measurement Systems Ltd.	DVSWin. 2.06 (S)
Fluidized bed coater (FBC)	Hüttlin Kugelcoater HKC - 05 TJ	Hüttlin Coating Technik GmbH (now Bosch AG)	Two 3-component nozzles & Turbojet® fluid bed distributor plate (A)
Interfacial & surface tension measurement (Ring method)	Lauda TD 1C	Lauda	n.a.
Laser diffraction particle sizing technique (LDPST)	Detector: MasterSizer 2000, APA 2000 Dispersion Unit: Hydro 2000S	Malvern Instruments	Master Sizer 2000, Version 5.22 (S)
Optical / Fluorescence microscope	Carl Zeiss ApoTome Axio Imager.Z1	Carl Zeiss	AxioVs 40 V4.8.2.0 (S)
Pan coater	8 L cupper pan, revolving by rotary motor (see auxiliary)	Erweka GmbH	Motor: Erweka AR 400 Type UG, Erweka Gerätebau (A)
Peristaltic pump	Watson Marlow 520 S	Watson Marlow Bredel Pumps	Tube: Watson Marlow Pumpsil, 3.2 mm inner diameter & 2-component nozzle (A)
Pipette	Eppendorf Research Plus (10 - 100 µL; 100-1000 µL)	Eppendorf	n.a.

Table 2.5: Devices (1 of 2).

Device / Technique	Model Type	Company	Auxiliary (A) / Software (S)
Rheometer	Anton Paar Physica MCR 501	Anton Paar	Cone: 0.997 ° (A); Rheoplus/32 V3.40 (S)
Rotary tablet press	Kilian Type RL-H; 3x bi-concave punch, radius 7 mm	Kilian	Built-in strain gages for pressing force determination (A) and Messfix vers. 2.3 March 1992, by Reinhard Herzog Unternehmensberatung (S)
Single punch tablet press	Korsch Type EK0; 1x bi-planar punch, radius 17 mm	Korsch	
LabMixer	Somakon Type: MPL USA	Somakon Vertieb e.K.	0.5 L container & several tools for shearing force exertion (A)
Tablet hardness tester (Monograph 2.9.8, Ph.Eur. 8.0)	Pharma Test PTB 111 E P	Pharma Test	n.a.
Turbula Mixer	Turbula Type T2C	System Schatz, Willy Bachofen Maschinenfabrik Basel	Turbula glas __ L (volume) 0.5 L ??
UltraTurrax	UltraTurrax® T25	IKA® - Jauke & Kunkel GmbH & Co. KG	Dispersing shaft with 18 mm stator diameter (A)

Table 2.6: Devices (2 of 2).

Weighing Balance	Model Type	Company	Readability; Repeatability
Laboratory balance	Sartorius LE16001S	Sartorius	0.1 g; 0.1g
Analytical balance	Sartorius CP224S	Sartorius	0.1 mg; ≤ 0.1 mg
Micro balance	Mettler Toldeo DeltaRange®, XP205DR	Mettler Toledo	0.1 / 0.01 mg; ± 0.015 / 0.06 mg

Table 2.7: List of Balances. Depending on the experiment (desired readability), different balances are used.

Chapter 3

Methods

This chapter deals with all the methods used in this doctoral thesis. The methods and techniques are divided according to the sections earlier described in Section 1.4.

3.1 Methods of Stage 1: Formulation Development

In this section, all methods related to formulation development, the benchmarking to marketed products and the mechanism of water vapor permeability are illustrated (Stage 1). The stage is divided into two sub-stages: in Section 3.1.1 (Methods of Stage 1.1), all methods related to the emulsions in the liquid form are described, including the characterization of the different emulsion components, the emulsion production and its characterization. Furthermore, the production of some marketed formulations for moisture protection is described. In Section 3.1.2 (Stage 1.2), the methods related to the aforementioned formulations in the dried state (free films) are discussed, where the focus lies on both, assessing the moisture protective ability of different films, and understanding the mechanism governing it.

3.1.1 Emulsion Production and Characterization (Methods of Stage 1.1)

3.1.1.1 Emulsion Material Characterization

3.1.1.1.1 $CaCO_3$ Characterization Scanning electron microscopic images have been made as follows [1] the powder is suspended in de-ionized water followed by a sonication step in a water bath for 1 minute. A drop of the suspension is finely spread on glass slides covered with Aluminum foil and allowed to dry in a desiccator.

[1] SEM images were taken by Dr. Salma Tammam at the Youssef Jameel Science and Technology Research Center (STRC) at the American University in Cairo (AUC), Cairo, Egypt.

There, in a sputter disposition process the dried material is covered typically with gold particles before its characterization by scanning electron microscopy. The SEM Device is a field emission scanning electron microscope (LEO SUPRA 55, Carl Zeiss, Reutlingen, Germany).

3.1.1.1.2 Physicochemical Characterization of Crude Lipids

Density The density of the different lipids is measured using an interfacial and surface tension measurement device (Table 2.5) according to the principles of Archimedes. A standardized glass body of defined volume and mass is first dipped into purified water (density = 999 mg/ml) for calibration. The glass body is then dipped into different lipids and the density is obtained. The density measurement is needed for the interfacial tension calculation.

Surface tension and Interfacial Tension The interfacial tension of different lipids to water is measured using interfacial and surface tension measurement device (Table 2.5) using the ring method. The device is calibrated and prepared according to the manual provided by the supplier. The surface tension of water is measured prior to each measurement to assure proper calibration of the device and that the glass ware is free of any surface tension modifying agent. Only if the surface tension of water is found to be between 71 - 73 mN/m the measurement may start. Otherwise, the glassware is rinsed with purified water and the measurement repeated. The following dimensions are applied: radius, R, of ring = 9.55 mm; radius, r, of wire r = 0.20 mm. All measurements are performed at room temperature and in triplicates.

Viscosity Viscosity of different lipids is measured using a rheometer (Table 2.6). The temperature is set to 26 °C, the cones radius equals 50 mm with an angle of 0.997°. Approximately 2 mL of the lipid is poured centrally onto the plate, after which the cone is driven down to a gap width valuing 50μm; any squeezed sample is dipped away with a napkin before the measurement starts. The shear rate is adjusted to $50s^{-1}$, and each measurement lasts 120 seconds, where 20 measures are obtained for each. All lipids are measured in triplicates and the average viscosity is calculated accordingly.

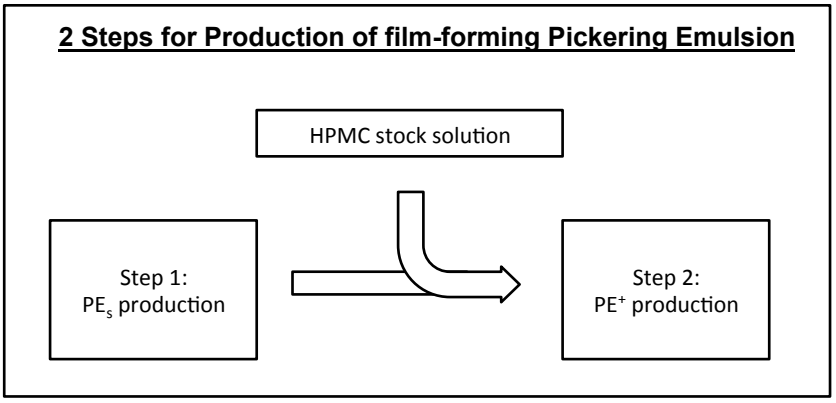


Figure 3.1: Emulsion Production - Broad Overview.

3.1.1.2 Pickering Emulsions

Figure 3.1 gives an overview of the two steps involved in producing the final product, a film-forming Pickering emulsion containing HPMC as the film-forming agent (PE^+). In general, a stock Pickering emulsion (PE_s) is first produced using one of two devices as described in Section 3.1.1.2.1 (Figure 3.3) where the different process parameters will be described in detail. The different components of the emulsions and their concentrations are described in Figure 3.3 and in Table 3.1, respectively. In a second step, PE_s is further processed to give the final HPMC containing Pickering emulsion (PE^+), as described in Section 3.1.1.2.2 (Figure 3.4). The lipophilic phase (LP) is sometimes stained with approximately 50 mg/L of an oil soluble dye (Sudan III Red) according to the need, in order to aid visualizing the emulsification process, the stability test results, the coating process or the resulting film coats.

At this stage it is worth defining two terms: in Chapter 1, the broad term for fats has been defined and it has been mentioned to include several subgroups. In the context of this doctoral thesis, a lipid refers to (liquid) triglycerides (oils such as MCT, SFO, CO), lipid esters (IPM), or hydrocarbons (PPL and PSL). All three groups are referred to in their crude state, without any additives. Once stearic acid is added to any of the just mentioned lipids, the resulting solution is then called a lipophilic phase (LP). Emulsions produced in this doctoral research are produced from lipophilic phases (LPs) and purified water.

3.1.1.2.1 Stock Pickering Emulsion (PE_s) Production Figure 3.2 illustrates the production steps of the stock Pickering emulsion PE_s. Stearic acid is added to the lipid and dissolved at 50 °C in a beaker while stirring gently to avoid air bubbles giving the lipophilic phase (LP); the LP is then cooled to room temperature (a). In parallel,

$CaCO_3$ is homogenously dispersed in water (=1.5*LP quantity) for 5 minutes using the same device where emulsification will take place (Ultra-Turrax or Lab Mixer) (b). The LP is then added to the aqueous phase in a stepwise manner (c) and emulsification takes place in one of the aforementioned devices (d). The process parameters and duration for emulsification depend on the device used for that purpose, which in turn depends on the scale of production: final products (PE^+) aimed at 100 or 200 g are performed using the Ultra-Turrax, whereas final products ranging from 250 g to 500 g are produced using the LabMixer. The ratios and concentrations for producing PE_s are described in Table 3.1. In general, the amount of water used for producing PE_s values 1.5 times the quantity of the LP used. The final formulation is diluted with either pure water or with an HPMC stock solution (12.5 % or 16 % w/w) and then pure water depending on the aim of the experiment. Details on that are explained in later contexts.

Table 3.1 illustrates the different emulsion ratios investigated throughout the doctoral research. All ratios listed in this are performed using medium chain triglycerides (MCT) as the lipid. Only promising ratios are further investigated using each of the other five lipids at a time. An example below illustrates the absolute quantities of each component.

Example: The following illustrates the absolute amounts of each emulsion component used for producing a stock Pickering emulsion (PE_s). The example is presented for the most concentrated product in the thesis: in order to produce 100 g (PE_s, with 30 % LP and a LP to $CaCO_3$ ratio of 4:1, the total amount of each component would be as follows: 30 g lipid, 7.5 g $CaCO_3$ (= 30 /4), 45 g water (=30*1.5) and 0.15 g stearic acid (=2 % of $CaCO_3$). It is worth mentioning that for PE_s production all substances are weighed 10 % in excess to account for any losses during production. The above-mentioned production steps to produce PE_s apply. Pure water is then added to the produced stock Pickering emulsion to a final weight of 100 g, if no further additives are required. In case a film-forming product is wished for, the addition of the latter is described in Section 3.1.1.2.2. Please note that the amount of stearic acid is so little that its percentage in the final product is neglected.

Emulsification using the Ultraturrax Small scale PE_s (maximum 110 g) is performed using the Ultraturrax. The beaker used has volume of 150 ml, where the formulations fills a maximum of two thirds of its volume, in order to assure proper homogenization. This method is mainly used for developing new formulations, where formulation stability is often unknown. Thus, the outcome is further investigated

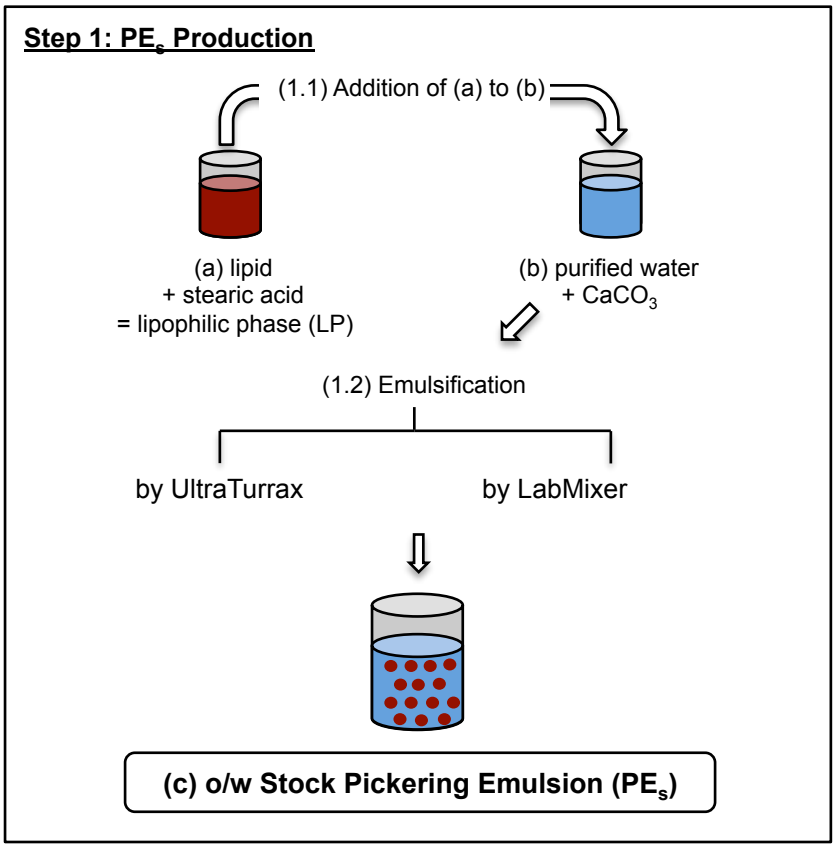


Figure 3.2: Stock Pickering Emulsion (PE_s) Production Step 1.

macroscopically, in order to assess preliminary stability results. Both, the first step of homogenously dispersing $CaCO_3$ in water and the second step of emulsification take place at 9500 rpm for 5 minutes each. Promising formulations are produced using the LabMixer for bigger scale.

Emulsification using the Lab Mixer Large scale PE_s (maximum 250 g) are produced using a Lab Mixer, in the same manner as described above. Table 3.2 summarizes the steps, process parameters and duration of emulsification using a Lab-Mixer. $CaCO_3$ is dispersed in purified water for 5 minutes as described above. The LP is slowly added in 2 steps to the aqueous phase, where emulsification takes place for 5 minutes each at 850 rpm. When all LP is added, further mixing occurs for 20 minutes at 2500 rpm. The scraper is turned on during the whole emulsification process, to assure proper mixing of the bulk.

3.1.1.2.2 HPMC containing Pickering Emulsion (PE^+) Production For the final film-forming Pickering emulsion (PE^+), a concentrated HPMC stock solu-

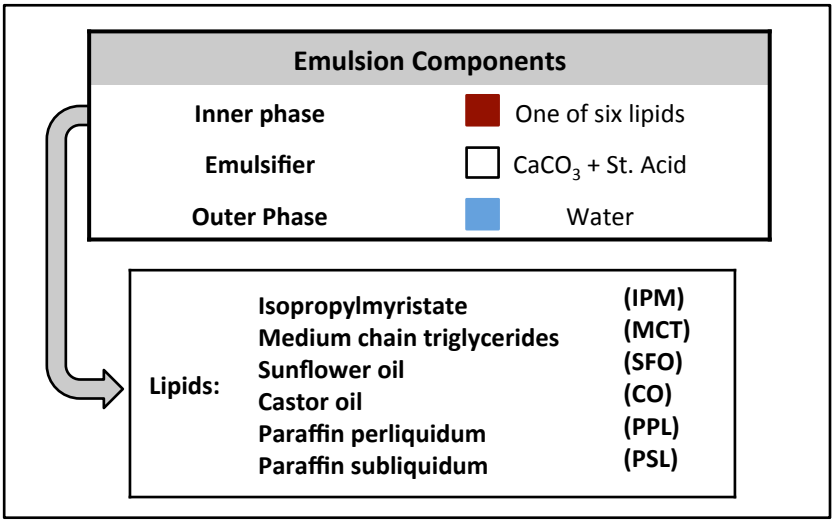


Figure 3.3: PE_s **Emulsion Components**.

LP: $CaCO_3$	Ratio	Lipid*	$CaCO_3$	St. A.	Water
		Group (a)			
2:1	2	10 %	5 %	2 % of $CaCO_3$	Ad 100 %
3:1	3	15 %	5 %		
4:1	4	20 %	5 %		
5:1	5	25 %	5 %		
6:1	6	30 %	5 %		
		Group (b)			
4:2	2	20 %	10 %	2 % of $CaCO_3$	Ad 100 %
4:1.5	2.67	20 %	7.5 %		
4:1	4	20 %	5 %		
4:0.5	8	20 %	2.5 %		
		Group (c)			
4:1	4	15 %	3.75 %	2 % of $CaCO_3$	Ad 100 %
	4	20 %	5 %		
	4	25 %	6.25 %		
	4	30 %	7.5 %		

Table 3.1: Emulsion Components Ratios.Group a) constant $CaCO_3$ at varying oil concentrations, Group b)constant oil concentration at varying $CaCO_3$ concentrations; Group c) constant oil-to-$CaCO_3$ ratio, at different concentrations of both. Lipid*: all emulsions ratios are performed with medium chain triglycerides (MCT) as the lipid.

	Steps	RPMs	Duration	Scraper
a	$CaCO_3$ dispersion in purified water	850	5 min	On
b	Addition of ½ LP amount	850	5 min	On
c	Addition of remaining LP	850	5 min	On
d	Complete Formulation	2500	10 min	On

Table 3.2: Process Parameters for PE_s Production in LabMixer.

Promising PE_s ratios (PE_s Code)	LP:CaCO3:HPMC	PE^+ Code
LP-15%_4:1	15 % LP 3.75 % $CaCO_3$ 3. 75 % HPMC	LP-15%_4:1:1
LP-20%_4:1	20 % LP 5 % $CaCO_3$ 5 % HPMC	LP-20%_4:1:1
LP-15%_4:1.5	15 % LP 5.625 % $CaCO_3$ 5.625 % HPMC	LP-15%_4:1.5:1.5
LP-20%_4:1.5	20 % LP 7.5 % $CaCO_3$ 7.5 % HPMC	LP-20%_4:1.5:1.5

Table 3.3: HPMC Containing Pickering Emulsions (PE^+) - Emulsion Codes and Components Ratios.

tion (12.5 % or 16 % or 18 % w/w; HPMCs-12.5% or HPMCs-16%, HPMCs-18% respectively) is added to promising stock Pickering emulsion (PE_s), stirred gently with a laboratory spoon and diluted with purified water to the desired concentration (Figure 3.4). Promising PE_s are those Pickering emulsions that show emulsion characteristics and meet the demands described in Chapter 4. Table 3.3 summarizes the ratio of LP to $CaCO_3$ to HPMC in the final formulation PE^+. An example below illustrates the absolute quantities of each component used. Please note that stearic acids quantity in the final product is negligible and thus not accounted for in the components ratio of the final emulsion.

The following example illustrates the absolute quantities used for producing an HPMC containing Pickering emulsion (PE^+). Producing 100 g PE^+ with the code

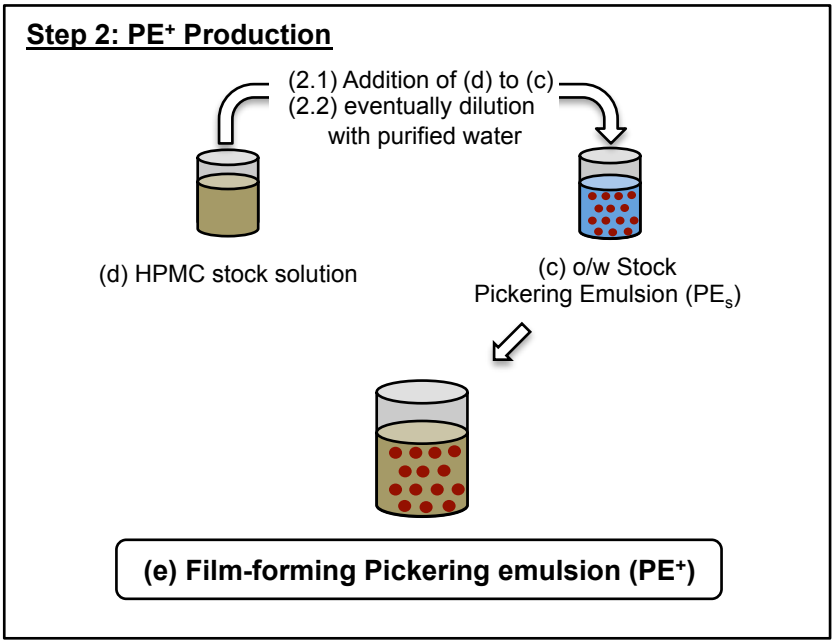


Figure 3.4: HPMC containing Pickering Emulsion (PE^+) Production - Step 2.

$MCT-20\%\_4:1.5:1.5$ requires the following absolute quantities for each component: PE_s is first produced with 20 g MCT that are emulsified by 7.5 g $CaCO_3$ (and 0.15g stearic acid) in 30 g water (=1.5 x LP quantity). A concentrated HPMC stock solution (e.g. 41.67 g $HPMC_{s-18\%}$) is added to PE_s and stirred gently using a laboratory spoon. Pure water is added to a final weight of 100 g. The order of steps from above applies. The codes presented in Table 3.3 suggest the LP of the emulsion, its percentage, and the ratio LP to $CaCO_3$ to HPMC. For example $MCT-20\%\_4:1:1$ means that the HPMC containing Pickering emulsion (PE^+) consists of 20 % MCT as the lipid (+ 0.1 g stearic acid = 20 % LP), 5 % $CaCO_3$ and 5 % HPMC (LP:$CaCO_3$:HPMC ratio = 4:1:1). An emulsion containing the general formula $LP-15\%_4:1:1$means that the same concept applies for any of the aforementioned LPs mentioned in Figure 3.3. Stearic acids quantity in the final product is negligible and thus not explicitly mentioned in the emulsion code.

3.1.1.3 Emulsion Characterization

3.1.1.3.1 Phase Testing

Phase Testing by Dye Test 1 g of emulsion was added to a microscopic slide and a few crystals of both oil- soluble Sudan-III-Red and water-soluble Malachite

Green were added each at a time. Subsequently, the specimen was observed under the microscope and assessed for its background color. Coloring of the continuous phase stains the entire emulsion: a green stain indicates an o/w emulsion, a red one a w/o type.

Phase Testing by Fluorescence Only emulsions with a stained LP (by fluorescing Sudan-III-Red) are investigated under fluorescing light in the microscope. This experiment serves as a means to visualize the LP drops. In Section 3.1.1.3.2, the preparation of the emulsion samples for microscopic imaging is described.

3.1.1.3.2 Microscopic Imaging Samples from PE_s are diluted with purified water and added gently to a microscopic slide. Microscopic images are taken using an optical / fluorescence microscope (Table 2.5) with transmitted light. Oil droplets are visualized with transmitted light and under fluorescence light using 10 x and 20 x magnifications.

3.1.1.3.3 Droplet Size Measurement (Monograph 2.9.31, Ph.Eur. 8.0) Laser diffraction technique is used to measure the droplet size distributions of the samples (Mastersizer 2000, Malvern Instruments Ltd., UK-Worcestershire). The background noise is eliminated prior to sample measuring, where purified water serves as a blank. In general, samples (PE_s and / or PE^+) are diluted with purified water (1:10) in a beaker, stirred gently using a spatula and then added to the dispersion unit to an obscuration level of maximum 20 %. The container is already filled with purified water. While measuring, the sample is stirred at 1750 rpm and consequently it circulates from the container to the measuring unit. Inside the sample container, the samples are hit by a laser beam and diffraction occurs for detection. The software (Table 2.5) uses the principles of Fraunhofer to convert the laser diffraction pattern to a drop size distribution. Considered results comprise the following: d10, d50 and d90 values, where 10 %, 50 % and 90 % of the total sample drops are smaller or equal to the resulting drop size. Other samples measured by this technique need prior preparations before measurement. Aside PE_s or PE^+ samples, re-dispersed free-films of the dried emulsion (PE^+-FF; see Section 3.1.2.2), or pellets coated with the emulsion (see Section 3.3.1.2) may also be measured using this technique (as discussed later). Regardless of the sample type, each formulation batch is considered an individual entity. Most formulations have been produced at least thrice (n 3). For those, out of each batch, at least 3 aliquots have been chosen randomly for measurement, and

each aliquot has been measured thrice by the Master Sizer software (Table 2.5) for a best fit. The resulting best fits of each aliquot have been averaged, and those averages considered as one measurement (for this one batch). The final drop size distribution for a certain emulsion type (e.g. MCT − 20%_4 : 1 : 1) is presented as the average of the averages; the deviation is measured as the standard deviation. However, due to shortage of material, some formulations have been produced only twice (CO − 20%_4 : 1) or even once (PSL − 20%_4 : 1). For those, from each produced batch at least 3 aliquots have been measured in the same manner as described above. The final results are presented as follows: for (CO − 20%_4 : 1) (n = 2) the average of both batches has been calculated and the deviation calculated as the span. As for PSL − 20%_4 : 1 (n = 1) the (single) result has been calculated by taking the average of the 3 aliquot results for the one batch produced. No deviation is shown here.

3.1.1.3.4 Emulsion Stability Test PE_s and PE^+ are tested for their stability over time by storing them at room temperature in glass bottles with screw caps. No special treatment is applied to the stored emulsions. At specified time intervals emulsions are vigorously shaken in case of sedimentation and are then visually observed. For big scale emulsions (produced by the LabMixer), samples are measured for drop size distribution in the Master Sizer (Table 2.5) at specified time intervals according to Section 3.1.1.3.3.

3.1.1.4 Other Marketed Formulations Production

3.1.1.4.1 Eudragit E PO Aqueous Dispersion Production The preparation is a modification to the production steps obtained from Evonik [22]. First, 1 % SDS is added to purified water and homogenized for 5 minutes at 8000 rpm using a high shear homogenizer (UltraTurrax, IKA, D-Staufen). Afterwards, 1.5 % stearic acid is added and homogenized for 15 minutes, followed by the addition of 10 % Eudragit E PO and homogenization for at least 25 minutes. Talcum, suggested by Evonik, is left out purposely and is replaced by purified water. The final aqueous dispersion (EPOaq-d) is used for free film production (see Section 3.1.2.1) or coating (Section 3.3.1.1).

3.1.1.4.2 HPMC Stock Solution Production Purified water is heated in a beaker to 60 °C and the HPMC powder is added in a stepwise manner while stirring vigorously to avoid agglomeration of the powder on the surface. After complete addition of the powder, the stirrer speed is reduced to moderate levels, to avoid

Film-forming Formulation	Drying Temperature [°C]
PE⁺ (all formulations)	45
Eudragit EPO®	55
HPMC stock solution	45

Table 3.4: Drying Temperatures for various Film-Forming Formulations.

excessive air bubbles in the solution. The heating plate is turned off and the solution is stirred over night and allowed to cool to room temperature. Any evaporated water is added the next day to give the final aqueous stock solution of HPMC (HPMCs). Concentrations used in the context of this research include 12.5 %, 16 %, and 18 % w/w. HPMC stock solutions are used for PE^+ production, free film production and coating of tablets.

3.1.2 Mechanism of Water Vapor Permeability (Methods of Stage 1.2)

3.1.2.1 Free Film Production and Characterization

Free films are prepared using a motorized, heatable film-forming device [29], where film-forming samples (any of the PE^+ formulations, aqueous dispersionof E PO, 12.5 % HPMC) are casted into a movable metal reservoir (17 x 4 cm, gap width: 0.8 mm, 0.6 mm or 0.4 mm) onto Teflon plates (17 x 34 cm) (Figure 3.5). While moving with a constant speed of 2.5 mm/s, the liquid formulation is dragged onto the Teflon sheet, leaving a fluid film behind. The film is dried for 1 h at different temperatures, depending on the film-forming formulation used (Table 3.4) and subsequently at room temperature for additional 24 h. It is then withdrawn from the Teflon plate and assessed visually at this stage. A micrometer screw gauge is used to approximate the final film thickness.

3.1.2.2 Dispersion of Free Films

Free films of the dried Pickering emulsion (PE^+-FF) are cut into pieces of approximately 2 cm2 and added to 10 ml purified water. After 2 hours, the resulting aqueous dispersion of the free film is measured by laser diffraction for drop size distribution (Section 3.1.1.3.3). Results are compared to the respective crude emulsion drop size distribution findings before drying.

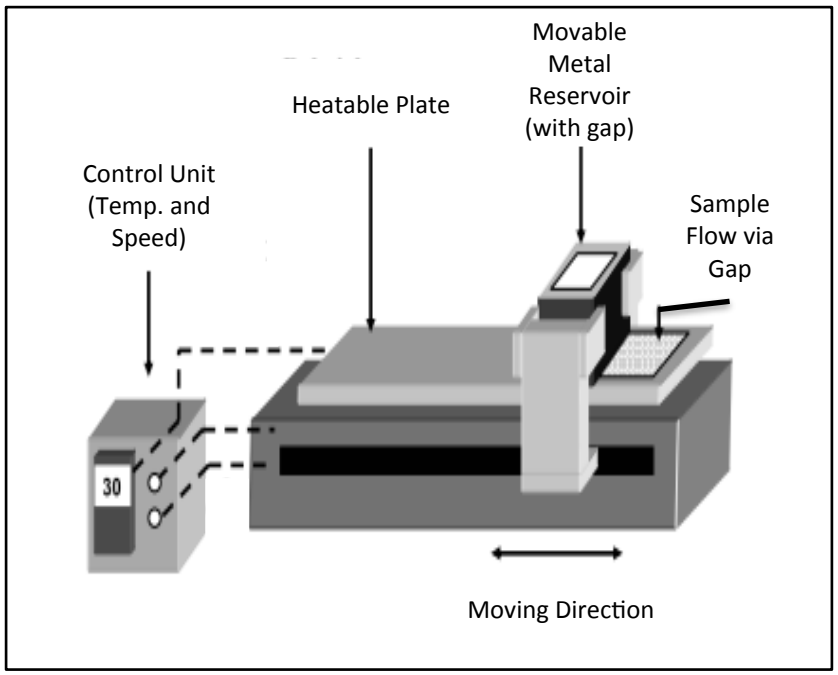


Figure 3.5: Schematic Drawing of Film-Forming Device.Schematic drawing is copied and modified from doctoral thesis of Dr. Grützmann, (Grützmann et al. [29]).

3.1.2.3 Water Vapor Permeability (WVP) Tests

Figure 3.6 illustrates water vapor permeability (WVP) testing across barrier membranes using a modified dry cup method [2]. Approximately 1 g desiccant (silica gel globules; Table 2.3) are filled in 2 mL glass vials (cups) with 8 mm diameter opening and dried at 130 °C for at least 90 minutes. The cups - now containing activated (dried) silica gel globules - are immediately covered with the already prepared barrier membranes (see Section 3.1.2.3.1 or Section 3.1.2.3.2), their plastic screw ring are added (circular perforated plastic caps; perforation diameter = 5 mm) and sealed cautiously (see Section 3.1.2.3.3). Samples also include vials having no barrier membrane (negative control) or a reference membrane (reference control). Regardless of the sample type, the full weight of each vial is then obtained and the cups are immediately placed in different controlled humidity chambers at room temperature. Table 3.5 shows the various conditioning agents providing constant relative humidity levels (% RH). The weight gain is obtained every 24 hours for at least 4 days and weight gain after 72 hours serves as a measure for the WVP value, where sink conditions of the activated silica globules still apply. WVP is calculated according to Equation 3.3 and Equation 3.1 or Equation 3.2 depending on the barrier membrane (for details

about the derivations of the equations and barrier membranes: see below). MVTR has the units [mg/d], and is calculated as follows: after 72 hours the cumulative weight gain is divided by 72 h and multiplied by 24 h, to assess the average weight gain per day (derivations of the just mentioned equations will be discussed shortly.

For free films barrier samples, moisture vapor transmission rate (MVTR) alone does not suffice to compare the different samples, because they differ in their film thicknesses or composition; WVP calculations standardizes the different film thicknesses, by dividing MVTR by the reciprocal of the film widths per effective unit surface area (unit area) or by the reciprocal of the film weight per effective unit surface area (unit area). In this doctoral thesis, film weights are used instead of film thicknesses for the lack of accurate experimental determination of the latter. The effective unit area values 19.1 mm^2 and is defined by the inner opening diameter of the cap (5 mm). All weights in this experiment are obtained using a micro balance (Table 2.7). Those include the weights of the separating membrane (as discussed below), the full weights of the vials at different time intervals, and any other weight needed for the calculation depending on the experiment.

General Note on Equations found in this Doctoral Thesis Please note, some equations found in Chapter 1 are presented in this chapter and in Chapter 4 again, for the sake of completion in a certain context. Some equations are restructured and presented differently.

For example, Equation 3.1 is equivalent to Equation IV of Figure 1.6, differing just in the mode of presenting; its derivation has been presented in Chapter 1. It is also equivalent to Equation 4.2 in Chapter 4. All these equations are used for quantifying WVP when the barrier membrane is a free film.

Equation 3.2 is almost equivalent to Equation 3.1, differing only in the following: the weight of the free film, m_{FF}, is replaced by the lipid volume, V_{lipid}. The latter is calculated from the lipid loading weight per PTFE (in mg) and the density of the lipid (in mg/mm^3). Details on PTFE filter loading by a lipid is presented under Section 3.1.2.3.2. Equation 3.2 is also equivalent to Equation 4.9 in Chapter 4, and both are used to quantify WVP when the barrier membrane is a PTFE filter loaded with a lipid.

Equation 3.4 is equivalent to Equation 4.7 and both are used to quantify a free film's affinity to moisture, represented by the WVS-value.

RH [%]	Conditioning Agent
33 %	Saturated solution of $MgCl_2$*$6H_2O$
65 %	Saturated solution of $NaNO_2$
75 %	Saturated solution of NaCl
85 %	Saturated solution of KCL
100 %	Purified Water

Table 3.5: Conditioning Agents For Adjusting Relative Humidity Conditions.

Other equations are presented in the context of their experimental design (e.g. Equation 3.5). As for the barrier membrane types, details on them are discussed next.

Barrier Membrane Types Depending on the barrier membrane, water vapor permeability (WVP) tests are performed in two variations: The membrane is either a free film (a dried formulation of PE^+, EPO, HPMCs-12.5%) or a polytetraflouroethylene (PTFE) filter loaded with different lipids. The preparation of either follows below. Depending on the barrier membrane, WVP calculation differs slightly (Equation 3.1 for free films or Equation 3.2 for PTFE filters loaded with different lipids).

3.1.2.3.1 Free Films as Barrier Membranes Free films (FF) are produced according to Section 3.1.2.1, as described above. FF sheets or pieces showing holes or any obvious defects are excluded at this stage. FF thickness is approximated using a micrometer screw gauge resulting in film thicknesses; the resulting thickness depends on the gap width and the formulation used while producing the film sheets (see 4.1.2.1.1, Figure 4.10). The choice of the gap width depends on the experimental design. Regardless, circular film pieces (PE^+-FF, EPO-FF, HPMC-FF) are punched out of the FF sheets using a hole punch (8 mm diameter) and subsequently weighed individually. Each circular FF piece is laid gently on the opening of the cup, serving as the membrane barrier as described above. The sealing step is discussed below (Section 3.1.2.3.3).

$$WVP = \frac{MVTR}{(m_{FF}/A)^{-1}} \tag{3.1}$$

WVP-Value (for Free Films)

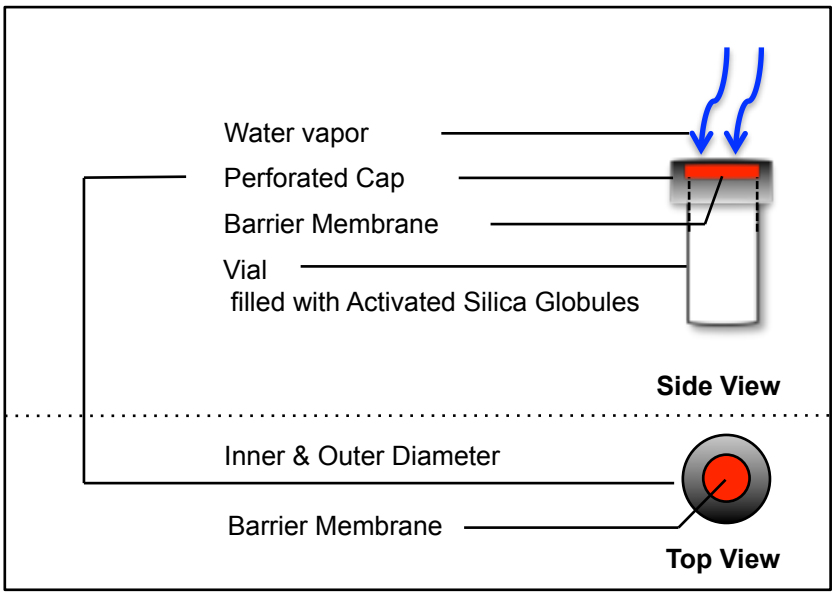


Figure 3.6: Schematic Drawing of HPLC Vial for WVP Test.

WVP = water vapor permeability $[mg^2/(d \times mm^2)]$
$MVTR$ = moisture vapor transmission rate $[mg/d]$
m_{FF} = weight of free film $[mg]$
A = active surface area $[mm^2]$

$$WVP = \frac{MVTR}{(V_{lipid}/A)^{-1}} \tag{3.2}$$

WVP-value Calculation (for PTFE-F)

WVP = water vapor permeability $[mg \times mm/d]$
$MVTR$ = moisture vapor transmission rate $[mg/d]$
V_{Lipid} = lipid volume $[mm^3]$
A = active surface area $[mm^2]$

$$MVTR = \frac{\Delta m}{t} \tag{3.3}$$

MVTR-value

$MVTR$ = moisture vapor transmission rate $[mg/d]$
Δm = weight gain $[mg]$
t = unit time $[d]$

3.1.2.3.2 PTFE Filters as Barrier Membranes

LP:	LP Polarity:	LP-Petrol Ether Mixture	LP-Isopropanol Mixture
CO	High	2 phases	ok*
MCT		ok	ok*
SFO		ok*	ok
IPM		ok*	ok
PPL		ok*	ok
PSL	Low	ok*	2 phases

Table 3.6: Mixture of Lipids and Organic Solvent (OS). *: Mixture chosen for PTFE Filter loading.

(a): Loading and Preparation for WVP-tests In order to investigate the WVP across the lipid exclusively, the latter need to be loaded onto inert carriers, which do not uptake water vapor. Polytetraflouroethylene filters (PTFE-F) (Table 2.4) are chosen for that matter. Loading them with different lipids takes place as follows: for each lipid, a mixture of it with a suitable volatile organic solvent is first prepared in a ratio 1+2 or 1+3 (lipid + org. solvent), shaken gently and left to stand for three minutes. Organic solvents chosen for that matter include the less polar petrol ether and the more polar isopropanol. Only mixtures showing a homogenous blend with no phase separation are selected for PTFE loading (Table 3.6). The chosen mixtures have lower viscosities than the crude lipids and thus complete wetting of the filter and loading into its tight pores is supported. Different amounts of the mixture are added to the PTFE-F by an Eppendorf Pipette (Table 2.5) in a stepwise manner and the loaded PTFE-F are left to dry. Loading steps and amounts vary from $40\mu L$ to $120\mu L$ depending on the experiment as discussed below (Section b: Loading Amount Validation)). In order to assure homogenous loading of the PTFE-F, each is weighed individually before and after loading to obtain the exact amount of lipid per PTFE-F. Loaded PTFE-F are not punched out (as with free films), but are used in one piece to cover the vials containing activated silica gel globules; each PTFE-F is positioned centrally above the opening, serving as the barrier membrane, as discussed above. The sealing step is discussed below (Section 3.1.2.3.3).

(b): Validation of Loading Amount In order to assure complete filling of the pores and since the porosity of the cylindrical filters is unknown, the following theoretical scenario is considered: Assuming a 100% porosity, the total loading volume for the lipid in the filter is approximately 1 mm^3 (25 mm diameter, 0.2 mm thickness or height). Thus, the lipid amount per filter may not exceed $100ml$ (= approximately

PTFE loaded with Lipophilic Phase Mixture (1+3) or (1+2)	Volume added to the PTFE Filter [µL]	Visual Assessment
	< 40	No wetting
	40 - 120 *	Wetting
	> 120	Greasy Filter

Table 3.7: Lipid-Organic Solvent (lipid-OS) Quantity Assessment. *: Range for PTFE loading; maximum lipid-organic solvent mixtured added at a time = 60 μ L.

$100\mu L$), but is certainly less due to the porosity of the filter ($< 100\%$). This piece of information indicates a theoretical maximum value for the absorbing capacity of the filter [20]. Practically, different amounts of lipid mixtures (Table 3.7) are loaded to the filter, whereas the maximum quantity loaded at a time is $60\mu L$. Any further quantity is added in a second step. Hereafter, the organic solvent (OS) is left to dry for 30 minutes and the loaded filters are visually assessed: filters surrounded by excessive lipid (loading $> 120\mu L$ lipid-OS mixture) are excluded, since the absorbing capacity of the filters is exceeded. Similarly, incompletely wetted filters (loading $< 40\mu L$) are excluded. Thus, the suitable loading amount ranges from $40\mu L$ lipid-OS to maximum $120\mu L$, where the exact amount of loading depends on the experiment, as discussed under Section 4.1.2.2.3. Steps and precautions discussed above do apply, where the highest amount of mixture added at a time equals $60\mu L$; the lipid-OS mixture is then left to dry before a further addition is performed.

(c): Calculating the Lipid Volume The lipid volume, V_{lipid}, found in Equation 3.2 is calculated as follows: from the loading amount per PTFE filter (in mg) presented above, the lipid volume (in mm^3) is calculated via the density of the lipid. The latter's determination has been presented in Section 3.1.1.1.2.

3.1.2.3.3 The Sealing Step The cup, being covered by either barrier membrane (FF or loaded PTFE-F), is sealed with the perforated cap in a crucial step, which is handled quickly on the one hand but carefully on the other. The following aspects describe the reasons and steps regarding that matter: quick sealing prevents unaccounted and undesired weight gain of the activated silica, thereby preventing a decrease in its water vapor uptake capacity. At the same time, the sealing step needs great attention and must be performed sensibly; loose attaching of the cap would cause undesired water vapor permeation through the edges of the cap, whereas too tight twisting and thus squeeze of either barrier membrane would lead to unwanted internal lipophilic phase escape or even destruction of the barrier membrane. Once

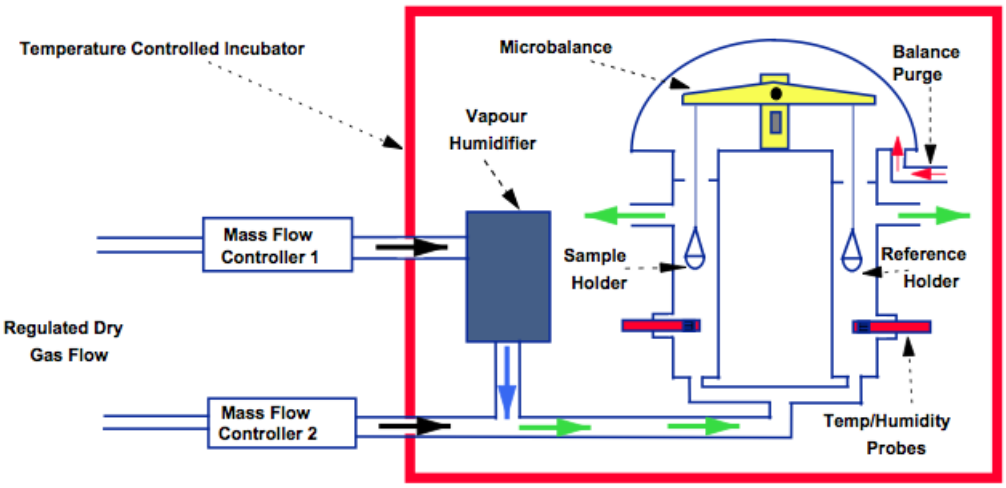


Figure 3.7: Schematic Drawing of DVS Device. Source: Device Manual [55].

sealed well, cups are positioned in the different humidity chambers as described above. Any weight gain results only from water vapor permeation via the opening of the cap. The effective surface area for diffusion via the barrier membrane is thus defined by the perforation diameter in the cap (diameter = 5 mm) and values 19.1 mm^2, as described above.

3.1.2.4 DVS Measurement

Dynamic vapor sorption (DVS) is a method used to gravimetrically characterize samples for their behavior at different moisture levels. The automated gravimetric dynamic vapor sorption (DVS) analyzer (Table 2.5) has two moisture chambers, where the different moisture levels are adjusted automatically according to a programmed experimental design. Each chamber has a hung quartz basket, while the latter are connected to the each other via an accurate microbalance (minimum sample weight: $1mg$; readability: $0.1\mu g$). One chamber is for the sample, while the other serves as a reference. Figure 3.7 illustrates the schematic drawing of the device.

The software (Table 2.5) allows pre-designing the program for incremental moisture levels [% RH], durations and / or accuracy of weight change detection. The chosen design depends on the sample types (free films, crude lipids or other materials) (see Section 3.1.2.4.1 and Section 3.1.2.4.2). Regardless of the sample type, samples have been exposed to a moisture level of 30 % RH before the pre-defined % RH levels have started. Thus, samples have been standardized for their equilibrium moisture content prior to each measurement. By that, the sample weight obtained at the end

of the 30 % RH stage is considered the starting weight. At the end of each humidity level stage the so-called water vapor sorption (WVS) value is calculated according to Equation 3.4 (equivalent to Equation 4.7). Measured samples include free films (FF) of the different formulations (PE^{+}-FF, EPO-FF, HPMC-FF), Batch 1 $CaCO_3$ (crude powder) and the different lipids used for emulsion production. The preparation of the samples and the designed programs are described below (see Section 3.1.2.4.1 and Section 3.1.2.4.2).

$$WVS = \frac{m_x - m_0}{m_{30}} \tag{3.4}$$

WVS-value

WVS = water vapor sorption [%]
m_x = equilibrium weight of sample at any defined % RH
m_{30} = equilibrium weight of sample at 30 % RH

3.1.2.4.1 DVS Measurements for Free Films and $CaCO_3$ Circular pieces of the free film (FF) are punched out using a punch hole (5 mm diameter) and added to the quartz basket. The starting target humidity level is set at 30 % RH and the moisture level is incrementally raised by 10 % at a time, until it reaches 100 %. The minimum duration of each moisture level is set at 10 minutes and it is automatically switched to the next level if the mass variation versus time dm/dt is smaller than 0.01 mg/min. Otherwise, the humidity level lasts for maximum 100 minutes. Desorption takes place in the reverse order under the same conditions. Of the three runs for each FF, at least one is run a full cycle (adsorption and desorption). As for $CaCO_3$ measurement, the powder is directly added to the quartz basket, without any further sample preparation. The program run for the FF samples (described above) is used for $CaCO_3$ samples.

It is worth mentioning that unlike all other experiments in this experiment, free films from only one independently produced formulation were taken for the lack of sufficient material; minimum 2 separate circular pieces were taken from the dried free film and run in an independent experimental run.

3.1.2.4.2 DVS Measurement for Crude Materials Different crude lipids used in the emulsion formulation are subjected to different moisture levels using the DVS device described above. Approximately 80 mg lipid is added via an Eppendorf pipette

(Table 2.5) to the quartz basket. The program is set as follows: the initial moisture level is set at 30 % RH and lasts exactly 15 minutes before the moisture level is increased to 90 % RH. During those 15 minutes, the different lipids are pre-treated equally for standardization. Hereafter, the lipid are exposed to 90 % RH, and the device holds this moisture level as long as mass variation versus time dm/dt is larger than 0.005 mg/min or for maximum 100 minutes.

3.2 Methods of Stage 2: Tablets

In this section all methods related to the hygroscopic cores (the Syloid Tablets) are described. This includes methods related to material characterization, tablet production and instrumentation, and tablet characterization (Section 3.2.1). In Section 3.2.2, methods related to the behavior of Syloid Tablets in moist environments are discussed, aiming to investigate and assess their aptness for coating and their degree of hygroscopicity.

3.2.1 Tablet Production and Characterization (Methods of Stage 2.1)

3.2.1.1 Tablet Production

From powder to tablets, four main steps are involved, as seen in Figure 3.8. First the powder is mixed in a stepwise manner, to give the final powder mix ("Tablet Formulation"). Secondly, in the briquetting process, lose tablets are formed from the Tablet Formulation using as single punch press to give "Briquettes". Afterwards, Briquettes are milled by a briquette-milling device (Table 2.5) to give "Granules" of the powder mix (3rd step). The latter are immediately added to the rotary tableting press for the last step, the tableting, to give the "Tablets". In this research, the final tablets are called "Syloid Tablets". The briquetting and subsequent sieving steps are necessary for two reasons: briquetting reduces the bulk volume of the powder and once sieved, the briquettes give Granules. The particle size of the Granules is more uniform compared to the unprocessed powder components, therefore improving the flowability of the latter, which in turn shows in the (improved) mass uniformity of the final tablets. Without the briquetting process, the powder separates in the feeder enormously as a result of the enormous difference in particle size of the powder. Tableting takes place at highly fluctuating compression force, which affects mass uniformity and hardness immensely. Therefore, in the context of this research, briquetting has shown to be inevitable to enable uniform tableting of small tablets and to improve flowability.

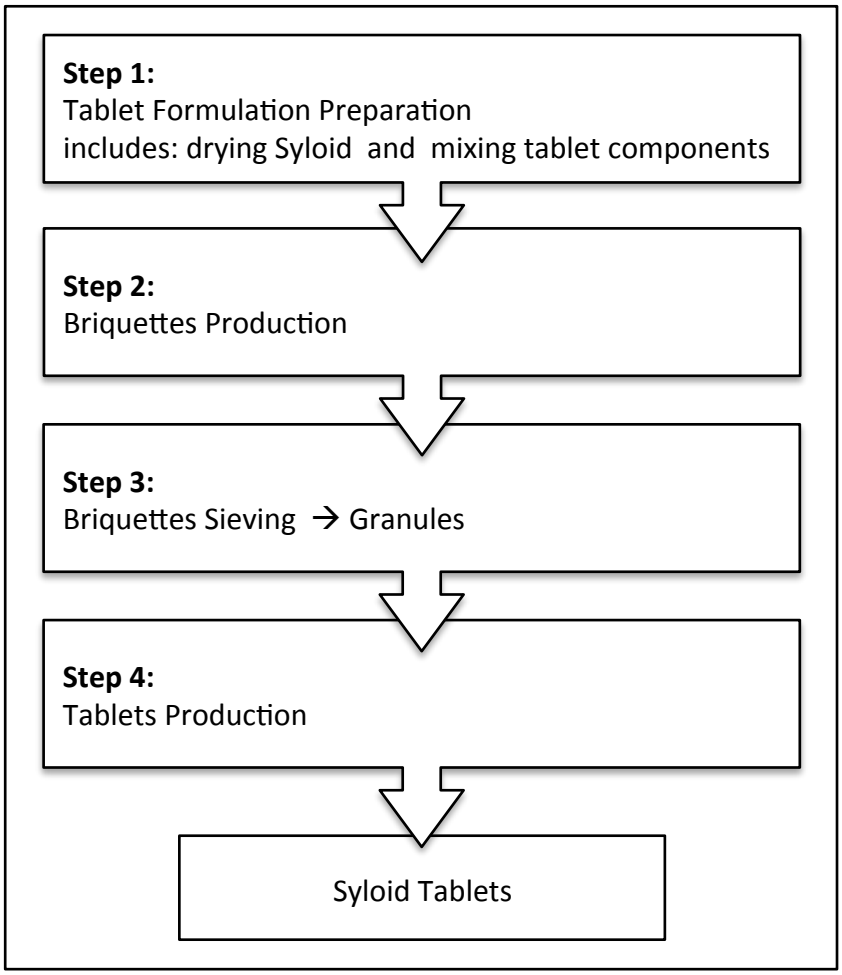


Figure 3.8: From Powder to Tablet Overview of Production Steps.

However, despite briquetting, Granule flowability is suboptimal, leading to mild fluctuations of the compression force. This effect can be reduced as will be discussed later (see below: Tableting (4th Step)). Since the whole process (from "Tablet Formulation" to "Syloid Tablets") takes place in a room without special humidity control, the following precautions are considered during the process, in order to avoid excessive moisture uptake of the (very hygroscopic) Tablet Formulation, the powder is added to the feeder of the single punch press (during briquetting) in two steps, the relative humidity and temperature in the room are constantly monitored using a hygrometer (Testo 625, Testo AG), and samples from the Tablet Formulation are weighed before briquetting and after tableting to measure the percent weight gain of the powder (Tablet Formulation) during the whole process. All materials used for tablet production are listed in Table 2.2. All devices used for tablet production are listed in Table 2.5 and Table 2.6.

Trade Name	Component	Concentration in Final Blend
Syloid® AL 1 FP	Silica Gel	30 %
Vivapur® 112	Microcrystalline Cellulose	58 %
FlowLac® 100	Lactose	10 %
Aerosil® 200 Pharma	Fumed Silica	1 %
MicroTalc Pharma 8	Talc	0.5 %
Magnesiumstearate Pharma	Magnesium stearate	0.5 %

Table 3.8: List of Tablet Components.

1st Step: Tablet Formulation Preparation Tablet components and their different concentrations in the pre-mixture are listed in Table 3.8. First, Syloid AL 1-FP (SAF) is dried for at least 90 minutes at 130 °C. In parallel, Vivapur 112 and FlowLac 100 are filled into a glass jar under reduced moisture in a controlled chamber having maximum 20 % RH. The components are mixed for 15 minutes in the Turbula Mixer ("Mixture A"). SAF – once dried– is added immediately to Mixture A and mixing takes place for 15 minutes ("Mixture B"). Mixture B is sieved through a sieve with mesh size 0.8 mm under reduced moisture in a controlled chamber having maximum 20 % RH. MikroTalc Pharm 8, Magnesium Stearate Pharma and finally Aerosil 200 Pharma are added via a small sieve to Mixture B and the formulation is mixed for 15 minutes ("Tablet Formulation"). The Tablet Formulation is kept in the glass jar of the Turbula Mixer sealed and protected from moisture, until briquetting starts.

2nd Step: Briquetting In the context of this thesis, briquetting refers to the formation of lose tablets, that are pressed using an instrumented single punch tablet press. The die and biplanar, circular punch diameters amount 17 mm, giving biplanar disc shaped tablets. Compression takes place at speed 5 (speed of motor), and the compression force ranges from 20 to 25 kN. Each single briquette weighs approximately 750 mg. Produced briquettes are immediately stored in a dry chamber, before the next step is preceded with.

3rd Step: Milling Briquettes are milled twice to give "Granules" using a briquette-milling device. Granules are collected and immediately transferred to the hopper of rotary tablet press for tableting.

4th Step: Tableting For each batch, Granules are filled into the feeder of the rotary tablet press followed by immediate covering of the feeder, in order to reduce the Granules' exposure to moist environments. Die and punch diameter value 7 mm and compression force is set to maximum 14 kN. Due to the relatively bad flowability of the Granules, the compression force might vary significantly during the course of tableting. In order to maintain a relatively narrow compression force range, the Granules in the feeder are manually mixed with a spatula every few minutes and – by instant monitoring – the compression force is controlled. In 5-minute cycles, an average compression force is measured from the individual compression forces of each tablet produced during this interval. Those tablets are collected in a glass jar, stored dry and labeled accordingly (sub-batch$_1$, sub-batch$_n$). Tableting goes on for another cycle until the next sub-batch is produced. From each sub-batch, 3 tablets are chosen randomly for weight and hardness measurements (Section 3.2.1.2.1 and Section 3.2.1.2.2). After the last sub-batch is produced, all tablets are collectively stored dry for at least 1 hour before any further investigation may start. Figure 3.9 illustrates the aforementioned procedure. In case the tablets' behavior in moisture conditions (WVU-test) is tested for tablets from different sub-batches, tablets are randomly chosen from the respective sub-batches before all sub-batches are mixed to one batch. Tableting process parameters are set to produce tablets weighing around 160 mg; however, each tablet batch might differ slightly in the average weight of tablets, which is mentioned with the results of the respective experiment (see Section 4.2.1 and Section 4.3.2). In Section 4.2.1, the average results for compression force, tablets weight and hardness is presented for each tablet batch. Furthermore, results of a representative batch are shown to elaborate some challenges of tablet production.

3.2.1.2 Tablet Characterization

The following characterization experiments are performed with produced tablets that come from different sources (batches or sub-batches): mass uniformity and hardness testing take place for tablets randomly chosen from each sub-batch, while disintegration testing takes place for tablets randomly chosen from the whole batch, after it has been stored dry for at least 1 hour.

3.2.1.2.1 Mass uniformity For each produced tablet batch there are (at least) 15 sub-batches. From each sub-batch, 3 tablets are randomly chosen and weighed individually using the analytical balance (Table 2.7). The total 45 tablets (3 x 15) are assessed for mass uniformity as follows: the average tablet weight is calculated and

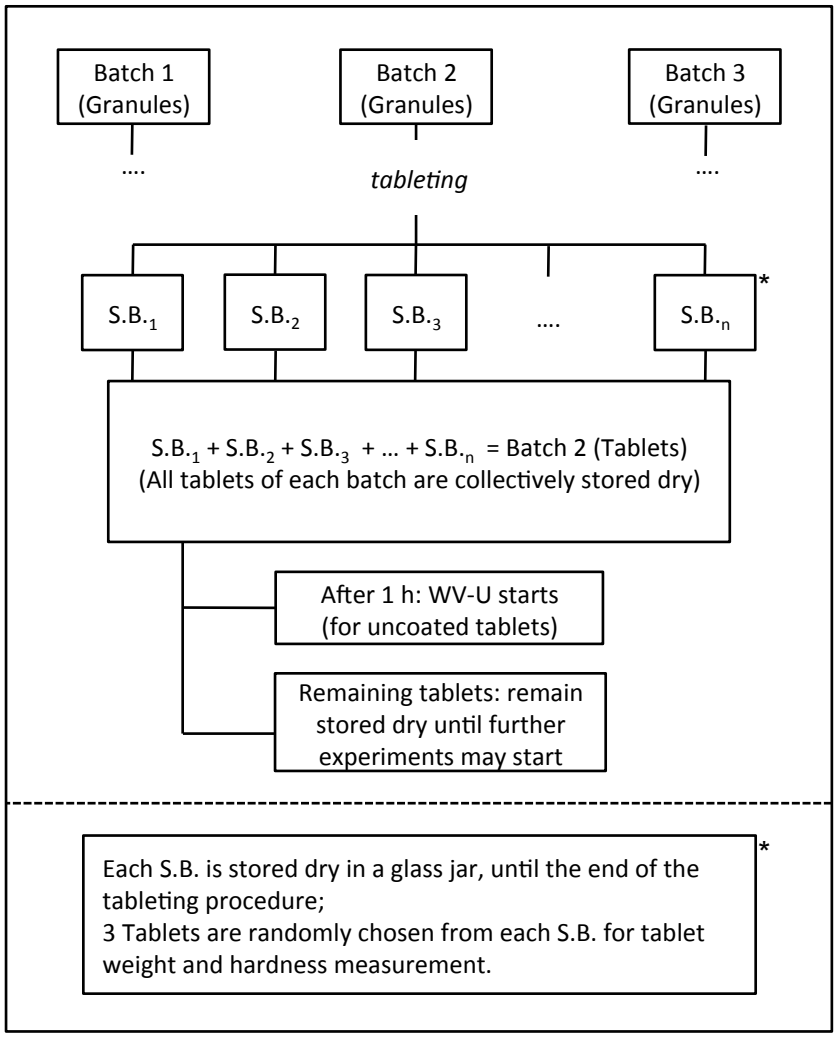


Figure 3.9: Tablet Production: Sub-Batches and Batches. S.B.: sub-batch This scheme exemplary shows the production of Syloid Tablets. Procedure is shown in detail for Batch 2 tablets. The same procedure applies to Batch 1 and Batch 3 tablets.

the deviation of each from the calculated average is assessed. Maximum two tablets are allowed to deviate more than 7.5% from the average and no tablet is allowed to deviate more than 15% from the average. The limits are based on European Pharmacopoeia standards (Ph.Eur. 2.4 or 9.5 Uniformity of mass of single dose preparations). The mean and the standard deviation are calculated for each tablet production batch.

3.2.1.2.2 Hardness Each single tablet weighed under Section 3.2.1.2.1 is measured for hardness using the tablet hardness tester and is correlated to its weigh (Ph.Eur. 2.9.8 Resistance to crushing of tablets). The mean and the standard deviation are calculated for each tablet production batch.

3.2.1.2.3 Disintegration Disintegration time of (uncoated) Syloid Tablets is examined according to European Pharmacopeia (Ph.Eur. 2.9.1 Disintegration of tablets and capsules). Immersion fluid is purified water. The experiment takes place for tablets that are randomly chosen from the (overall) tablet batch (and not from each sub-batch).

3.2.2 Water Vapor Uptake (WVU) of Uncoated Tablets (Methods of Stage 2.2)

3.2.2.1 Tablet Choice and Preparation

In this Section 3.2.1.2 it has been described that Syloid Tablets are stored for 1 hour before they are further investigated. Afterwards, water vapor uptake (WVU) tests of uncoated tablets start, which include uncoated tablets that are intact and halved. First, at least triplicate pairs of intact tablets are randomly chosen and individually added to pre-labeled weighing dishes. The total weight (weighing dish and tablet pairs) is assessed and the samples are instantly placed in the respective desiccators or humidity chambers (dry, 33 % RH, 75 % RH). Tablets to be halved are randomly chosen, halved by a scalpel and the above-mentioned steps apply. Time zero is the time the samples are placed in the desiccators or humidity chamber. Weight change of intact and halved tablets is measured periodically every 24 hours for four days. Water vapor uptake (WVU) is calculated according to Equation 3.5, which applies also to coated tablets and is presented again in Stage 3 (Equation 3.7). Both equations include the terms m_t and m_0, which describe the weight of each tablet pair at the measuring time t and time zero, respectively. All weight measurements

are performed using the micro-balance (Table 2.7). The duration and order of steps between tablet choice and actual beginning of the WVU test is crucial. Precautions regarding that matter are described in 3.2.2.2. In order to avoid confusion, it is worth mentioning that all tablets are still uncoated at this stage. Nevertheless, the same method is applied to coated tablets (3.3.2). The remaining bulk of tablets is kept in the aforementioned dry desiccator until further experiments (e.g. coating) may start, as can be seen in Figure 3.14.

$$WVU = \frac{m_t - m_0}{m_0} \tag{3.5}$$

WVU-value

WVU = water vapor uptake [%]
m_t = weight of tablet at time t
m_0 = weight of tablet at time 0

3.2.2.2 Precautions

The time between the random choice of tablets for the stability tests and the actual start of the WVU-test (t_0) is critical, since the Syloid Tablets are extremely hygroscopic (Section 3.2.1.1); any unaccounted moisture uptake might cause misleading results. Hence, the following precautions are taken to avoid any unconsidered moisture uptake: first, all weighing dishes are already labeled and weighed (tare weight) before the samples are added. Second, intact tablets are randomly chosen from the dry desiccator in which all uncoated tablets are contained. The Syloid Tablets are immediately placed in their corresponding weighing dishes and the total weight is measured instantly. Afterwards, the weighing dishes are abruptly placed into the different desiccators. Third, tablets to be halved are chosen randomly as well and the previous steps are repeated. All those steps are performed within a few minutes, in order to avoid unconsidered moisture uptake. The stability test described in Section 3.2.2.1 may begin.

3.3 Methods of Stage 3: Coating and Stability Tests

In this section all methods related to coating pellets and tablets are described (Stage 3). The section is divided into two sub-sections: in Section 3.3.1 (Stage 3.1), all

methods related to coating process parameters development are described, where methods are developed with the main aim of maintaining emulsion character while coating. In Section 3.3.2 (Stage 3.2), methods related to the functionality of the novel formulation regarding its moisture protective ability and its benchmarking to marketed products are described.

3.3.1 Development of Coating Process Parameters and Characterization of Coated Products (Methods of Stage 3.1)

3.3.1.1 Emulsion Coating

Three individual experiments are involved in defining and developing the critical process parameters for coating of film-forming o/w Pickering emulsions (PE^+), as illustrated in Figure 3.10. Each single experiment serves as a prerequisite for conducting the consecutive one, as will be discussed in detail in each paragraph. First, "Emulsion Sprayability" is performed, where the effect of atomization on emulsion character is being tested in order to assure preservation of the physical form of the emulsion. In a second experiment, emulsions are being coated onto inert sucrose pellets using a fluidized bed coater (FBC) (Table 2.5), in order to test real coating conditions using minimal amounts of emulsion. Furthermore, coated sucrose pellets are later used for further investigations regarding emulsion character preservation in the coat. Both previous experiments provide necessary findings, that are adopted in the third investigate; Syloid Tablets are coated in a pan coater (Table 2.5) under reduced humidity. Those coated tablets are then used for the stability test in 3.3.2.

3.3.1.1.1 Emulsion Sprayability (Experiment One) Figure 3.11 illustrates the experimental design to test emulsion sprayability; preservation of emulsion character is investigated using a 3-component nozzle (Table 2.5) by spraying PE^+ into a beaker filled with 20 ml purified water at a constant microclimate (0.2 bar) and varying atomization pressures (0.3, 0.5, and 0.7 bar). Spraying occurs at a constant pumping rate of 1.5 rpm using a peristaltic pump (Table 2.5). The dispersion is measured by laser diffraction particle sizing technique (Section 3.1.1.3.3) and the resulting particle size distribution is compared to the one of the original emulsion. The findings of this experiment reveal the atomization pressure, at which spraying of PE^+ occurs while its emulsion character is preserved (see Section 4.3.1.1); those findings are used in all further coating procedures for PE^+ coating. The prototype film-forming Pickering emulsion (PE^+) is used for this investigate ($MCT - 20\%\_4 : 1 : 1$).

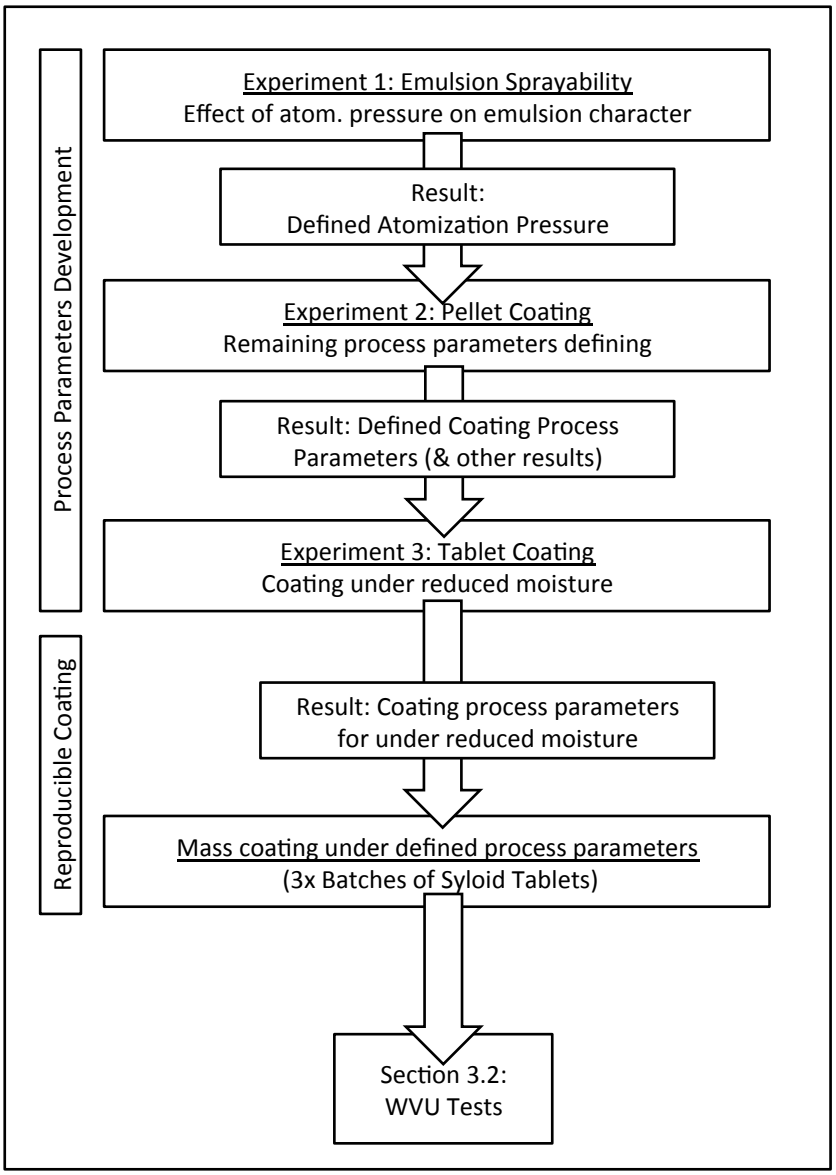


Figure 3.10: Overview of Coating Experiments.

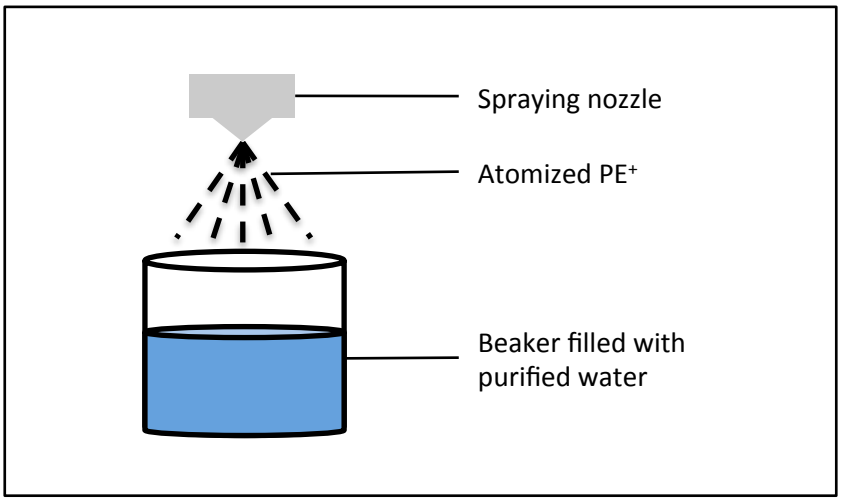


Figure 3.11: Schematic Drawing of Sprayability Experiment.

3.3.1.1.2 Pellet Coating: A Trial and Error Approach (Experiment Two) 300 g inert sucrose pellets (1.7 2.0 mm) are loaded into the laboratory-scale fluid bed coater (Table 2.5). Pellets are pre-heated at 50 °C for 5 minutes before their coating by 100 g PE^+ starts. The prototype PE^+ ($MCT - 20\%\_4 : 1 : 1$) is chosen for the development of the process parameters, and is later substituted by $MCT - 15\%\_4 : 1.5 : 1.5$ for optimization (see Table 4.9).

The air velocity is not measured; instead, it is indirectly set by the maximum power of the machine. The latter is fixed at 95% to assure sufficient fluidization of pellets. The atomizing pressure is set at 0.3 bar and the microclimate at 0.2 bar (Section 4.3.1.1). A systematic trial and error approach is applied, in order to develop the remaining process parameters, which are believed to be the critical ones during the coating process. Those include mainly the spraying rate and the inlet temperature. Their ranges are limited according to theoretical expectations, as illustrated in Figure 3.12. Both, the inlet temperature and spraying rate are aimed to be within an optimal range, in order to assure a successful coating process; the rate of PE^+ spraying, spreading onto the cores' surface and its proper drying are considered for that purpose. A drying temperature below or above the optimal range might result in wet processes or spray drying, respectively. Similarly, spraying rates below or above the optimum range might result in too slow processes or incomplete drying, respectively. Table 3.9 summarizes the altered process parameters of the seven different coating trials performed, by which the critical process parameters have been developed and defined. Coated pellets are visually assessed, where process parameters leading to tackiness, oiliness or any obvious defect in coatings are altered

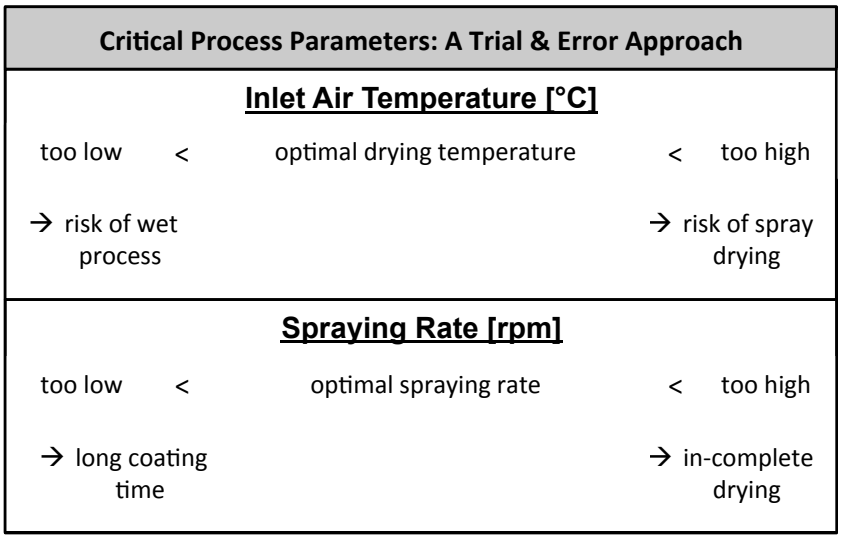


Figure 3.12: Hypothetical Process Parameter Limits Risk Assessment.

Trial #	Inlet Air Temperature [°C]	Spraying Rate [rpm]
Trial 1	40 °C	0.5
Trial 2	55 °C	0.5
Trial 3	70 °C	0.5
Trial 4	55 °C	1.5
Trial 5	55 °C	3.0
Trial 6	70 °C	3.0
Trial 7	70 °C	1.5

Table 3.9: Overview of Performed Trials. (Trial and Error Approach for Process Parameter Development).

and excluded. Hence, each trial has provided findings that have been considered in the next trial and the rationale behind the trials and their outcome will be discussed in Section 4.3.1.2.1. The final coat level is assessed according to Equation 3.6. The pellets weight before and after coating is calculated from the average weight of 3 weights (150 pellets total), where each measurement comprises 50 pellets.

$$\text{Coat Level} = \frac{m_c - m_u}{m_u} \tag{3.6}$$

Coat Level

m_c = weight of coated tablets
m_u = weight of uncoated tablets

3.3.1.1.3 Tablet Coating (Experiment Three) The process of Syloid Tablets coating is technically not feasible using the Hüttlin Kugelcoater HKC 05 TJ (Table 2.5), since the latters power does not suffice to fluidize tablets. Furthermore, Syloid Tablets are extremely hygroscopic by nature (see Section 4.2.2) and need very dry coating conditions to prevent excessive weight gain during coating. The moisture content of the drying air of the Hüttlin Kugelcoater HKC 05 TJ can neither be varied nor be measured to meet the coating process demands of Syloid Tablets. For the two previous reasons, Syloid Tablets are coated in a pan coater (Table 2.5). Figure 3.13 illustrates the experimental design for coating tablets in a coating pan assuring high drying temperature and low moisture drying air. The latter is part of the infrastructure of the laboratory (Pharmaceutical Technology Department at the University of Tübingen, Germany) and is provided at a pressure valuing 8 bars. It has a temperature of 20 °C, and its moisture content is not measured directly but known to be low. Before this compressed air is used as the drying process air, it is adjusted as follows: reduced to 1 - 1.5 bar by a pressure controlling valve, the drying air circulates through a coiled copper pipe having a diameter of 1 cm, which is inserted in a water bath at 70 - 80 °C for heating. The heated air, now at 60 - 70 °C and a humidity below 5 % RH is directed via flexible plastic pipe (diameter 6 cm) into the coating pan. Respecting the findings of the previous two experiments (see Section 4.3.1.1 and Section 4.3.1.2) the process parameters for coating Syloid Tablets in the coating pan are set as follows: 200 to 300 g Syloid Tablets are preheated in the coating pan at a relatively low rpm (25 % of maximum rotating speed), avoiding excessive mechanical stress on the Syloid Tablets. After 30 minutes, one hundred pre-heated tablets (10 x 10) are weighed to assess the average weight of the pre-heated tablets. This value serves as a reference for calculating the average amount of coat per tablet (Equation 3.6: wbefore coating). Furthermore, pre-heated tablets are chosen as the reference tablets in WVU testing (see Section III.3.2). Afterwards, the rotary motor speed is increased to 50 % of its maximum power and spraying of the coating fluid (PE^+, EPOaq-d or HPMCs-12.5%) is started; the coating fluid is delivered to the spraying nozzle by a peristaltic pump (Table 2.5). Depending on the coating fluid (PE^+, EPOaq.dis or HPMCs-12.5%) different process parameters have been applied (Table 3.10). Once coating starts, the air temperature (measured near the spraying spot) drops to approximately 50 60 °C, and the relative humidity is measured at maximum 15 % RH. Both parameters are manually measured every 5 minutes by placing a thermo-/hygrometer (Testo 625, Testo AG) right behind the spraying nozzle and at the surface of the tablet bed. Every 50 g of coating fluid

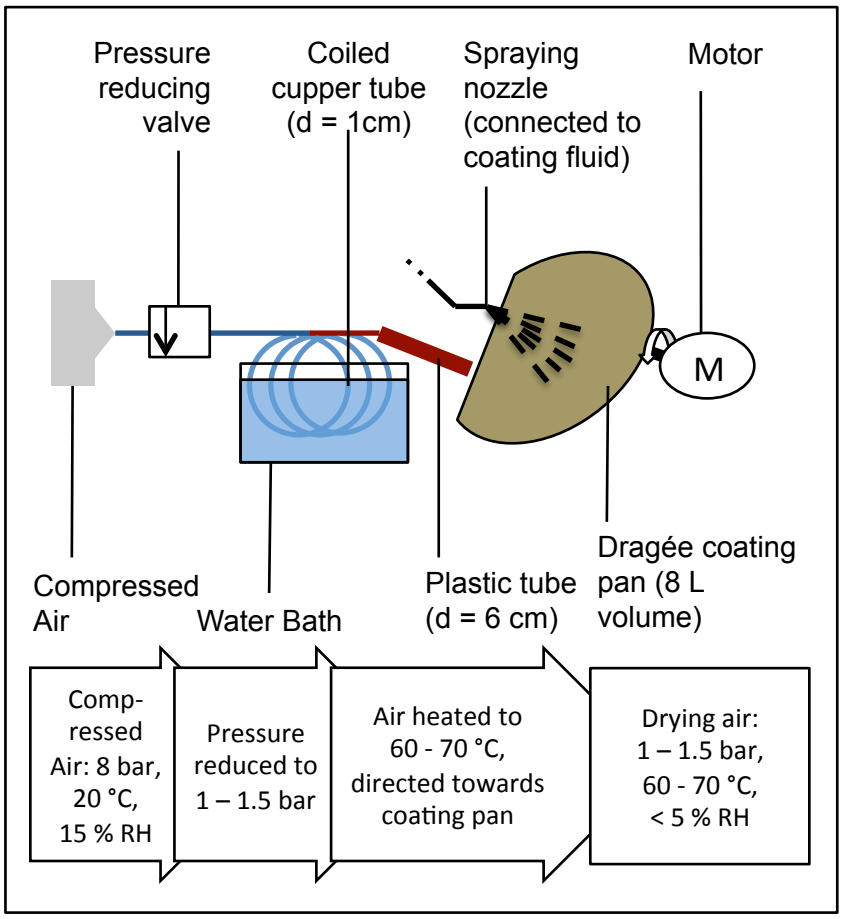


Figure 3.13: Schematic Drawing of Pan Coating. Key: d: diameter

spraying, spraying is paused for two minutes and fifty tablets (5 x 10) are weighed to calculate and control the amount of coating per tablet (Equation 3.6: wafter coating). As long as the desired coating level is not reached, the tablets are returned to the coating pan and coating is continued. When the desired average amount of coating per tablet is reached, coating is stopped and tablets are further post-dried for ten minutes. Afterwards, tablets are stored for one hour in a dry desiccator before 100 tablets (10 x 10) are weighed and the final coat level assessed according to (Equation 3.6: wafter coating). Tablet weight before and after coating is calculated from the average of 100 tablets (10x10) for each. Regardless of the coating fluid, all coating quantities are aimed to be equal, in order to standardize the conditions among the different batches and coatings.

After the coating level has been assessed, any further investigations may take place then (see below). In case a second coat is desired, tablets with a first coat (pre-coated Tablets) are stored for at least 1 day in a dry desiccator before the second

Process Paramaters for Coating Syloid® Tablets in the Dragée Pan	
Syloid Tablet Quantity:	200 – 300 g Tablets
Dragée Pan Rotation Speed:	Intermediate (50 % of maximum speed)
Drying Air:	1 - 1.5 bar 65 °C – 70 °C
Atomization Pressure:	0.3 bar for PE^+ 1 bar for $EPO_{aq.-disp}$ or $HPMC_{s-12.5\%}$
Spraying Rate:	0.8 rpm for PE^+ 3.5 rpm for $EPO_{aq.-disp}$ or $HPMC_{s-12.5\%}$

Table 3.10: Summary of Coating Process Parameters (Pan Coating).

coat is applied. Pre-coated tablets are heated for 30 minutes at 60 - 70 °C prior to the application of the second coat. The same steps and conditions described above apply. Figure 3.14 illustrates the above-mentioned steps.

3.3.1.2 Characterization of Coated Pellets: Emulsion Character Preservation

Inert sucrose pellets coated with PE^+ are chosen to characterize if the emulsion character is preserved in the coat. Coated Syloid Tablets are not chosen for that purpose, because the components of the Syloid Tablets are not water-soluble. Consequently, the analysis of the PE^+ coated Syloid Tablets is expected to have been less reliable compared to PE^+ coated water-soluble sucrose pellets.

Coated and uncoated pellets (2 g) are dispersed in 30 g water and shaken gently using a laboratory shaker with orbital motion (KL-2, Edmund-Bühler Gerätebau, DE-Tübingen) until no agglomerates could be seen visually. After at least 30 minutes, the droplet size distribution of the dispersion is measured according to Section 3.1.1.3.3. The results are compared to drop size distribution of the unprocessed emulsion.

3.3.1.3 Characterization of Coated Tablets: Disintegration Time

Disintegration time of (coated) Syloid Tablets is measured as described under Section 3.2.1.2.3. Samples include Syloid Tablets coated with PE^+, EPO or HPMC as well as HPMC pre-coated tablets further coated with PE^+ or EPO. Immersion medium

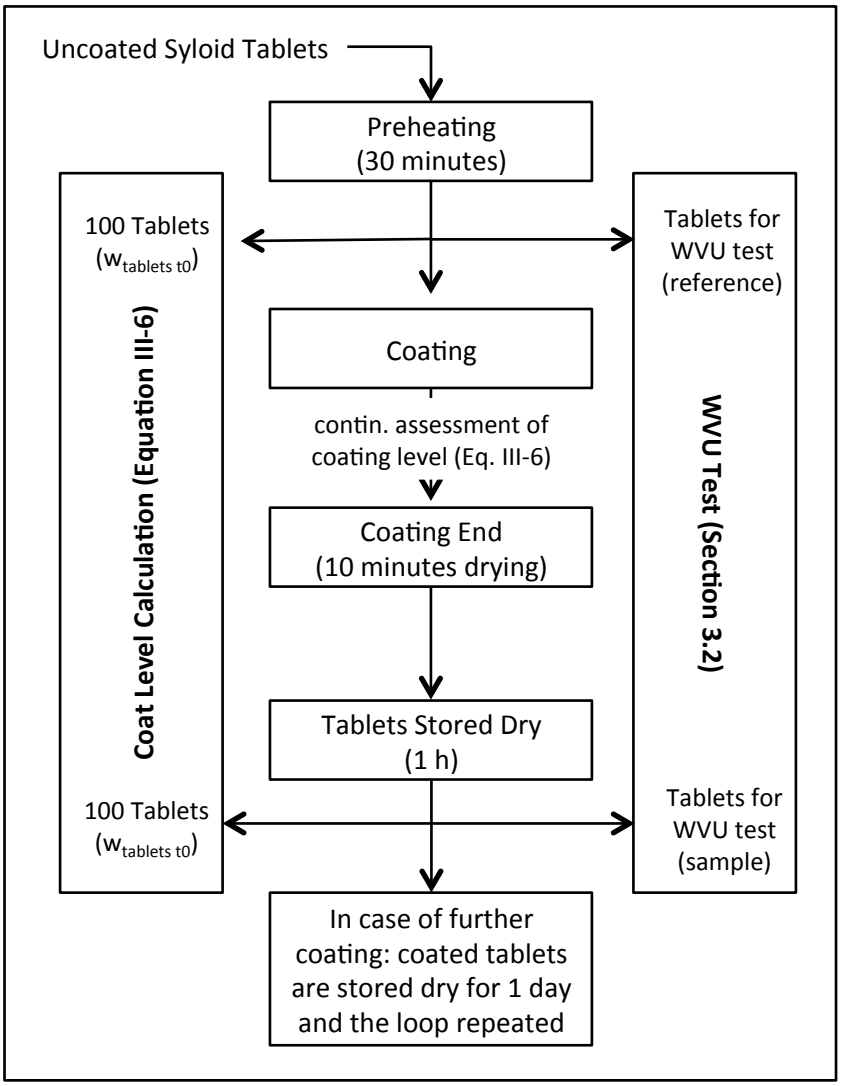


Figure 3.14: Pan Coating Steps Coating of Syloid Tablets

is purified water in case of HPMC and PE^+ coated tablets, and 0.1 M HCl in case of EPO coated tablets.

3.3.2 Water Vapor Uptake (WVU) of coated Tablets Functionality and Stability Tests (Methods of Stage 3.2)

For each coated tablet batch undergoing WVU testing, an internal reference is chosen and subjected to the same conditions as the sample. Depending on the experimental design, the internal reference may be uncoated tablets, or HPMC coated tablets that have been stored dry until the day of coating. In either case, the internal reference tablets are randomly chosen from the preheated ones prior to coating (as described in Section 3.3.1.1.3 and as shown in Figure 3.14), immediately weighed on respective weighing dishes and placed in a dry desiccator for the next 2-3 hours until the coating process is finished. Hereby, unconsidered moisture uptake by the internal reference tablets is avoided. After coating has finished, coated tablets are stored dry (1 h) before tablets are randomly chosen for WVU testing. Tablets are prepared in the same manner as described in Section 3.2.2.1. The same precautions described in Section 3.2.2.2 apply here as well, whether for intact or halved coated tablets. The weighing dishes are placed in a dry desiccator and in humid ones containing 33 % RH and 75 % RH; t0 is the time, where all weighing dishes are added to the desiccators; weight gain is measured every 24 hours for at least four days (Equation 3.7). This equation applies to uncoated tablets as well and has been previously presented in Stage 2 (Equation 3.5).

$$WVU = \frac{m_t - m_0}{m_0} \tag{3.7}$$

WVU-value

WVU = water vapor uptake [%]
m_t = weight of tablet at time t
m_0 = weight of tablet at time 0

Chapter 4

Results and Discussion

This chapter presents all results obtained throughout this doctoral research and discusses each. The topics are divided into three stages (Stage 1 - 3), where each is divided into two sub-stages. Stage 1 (Section 4.1) deals with results related to formulation development, Stage 2 (Section 4.2) with results related to Syloid Tablets and Stage 3 (Section 4.3) with results related to coating processes and stability tests. At the end of each section the findings are discussed, summarized and interrelated.

4.1 Stage 1: Formulation Development

In this section, all results related to the emulsion development are presented and discussed. Those results are subdivided as follows: in Section 4.1.1 (Stage 1.1), all results related to the Pickering emulsion production and characterization are described, where the emulsion is in its crude (liquid) form and is not dried yet (as in Stage 1.2). Main topics covered include emulsion starting material characterization and final formulation reproducibility and stability investigations. In Section 4.1.2, results are presented for emulsions and other formulations being in the dried state (free films). Main topics include free film characterization and moisture protective ability (MPA) quantification of the novel formulation; great emphasis is laid on the mechanism governing water vapor permeability and the factors affecting it. Furthermore, the novel formulation's MPA is benchmarked to marketed products claiming moisture protection.

4.1.1 Emulsion Production and Characterization

4.1.1.1 Emulsion Material Characterization

4.1.1.1.1 Physico-chemical Properties of Crude Lipids

Viscosity The dynamic viscosity results of the six different lipids contained in this thesis are depicted in Figure 4.1. The viscosities are ascendingly ordered as follows:

$$\text{IPM} < \text{MCT} < \text{PPL} < \text{SFO} < \text{PSL} < \text{CO},$$

where all viscosities vary significantly ($p = 0.05$). It is worth mentioning that CO has by far the highest viscosity of all, at least five times higher than any other lipid.

Interfacial Tension (Polarity) The interfacial tension serves as an indirect measure for the polarity of substances when measured against water. Figure 4.2 depicts the values, where the interfacial tension is in the order

$$\text{PSL} > \text{PPL} > \text{IPM} > \text{SFO} > \text{MCT} > \text{CO},$$

where all values vary significantly ($p = 0.05$). As expected, the lowest interfacial tension and thus highest polarity is found to be for Castor Oil (CO). This is due to the fact that CO contains hydroxy fatty acid. The two types of paraffins used are found to have the highest interfacial tension towards water, and thus the lowest polarity. This is expected as well, since Paraffins are composed of mostly saturated hydrocarbons. The more viscous (heavy) liquid paraffin (PSL, for paraffin subliquidum) has been found to be slightly lower in polarity when compared to the less viscous light liquid paraffin (PPL, for paraffin perliquidum). This could be explained by the relatively short duration of measurement; the water-lipid interface has probably not equilibrated within the course of the measurement [48]. The remaining lipids are found to have polarities ranging between Paraffins (most apolar) and CO (most polar).

Justification of Lipid Choice Chapter 1 has discussed the derivation of the permeability equation (Equation IV in Figure 1.6), which results in the multiplication of the permeant's solubility, S, with its diffusivity, D, in the barrier membrane. According to this equation, keeping both, S and D, low results in a low permeability. This in turn explains the rationale behind choosing the above-mentioned lipids as components for the novel formulation: by varying the permeants' polarities and viscosities, water vapor permeability (WVP) might be varied; this is later investigated in Section 4.1.2.2.

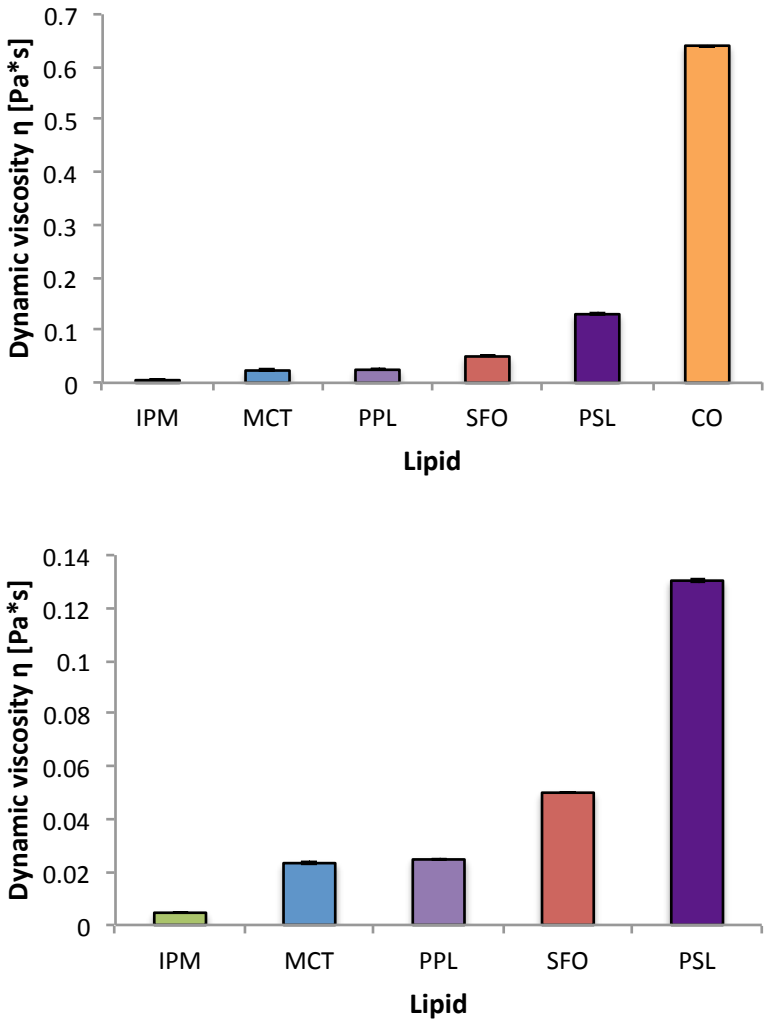


Figure 4.1: Dynamic Viscosities of Lipids – upper image: all lipids; – lower image: all lipids except CO. $n = 3$, Error bars: standard deviation. Statistics: $p = 0.05$; ANOVA and Newmann-Keuls tests.

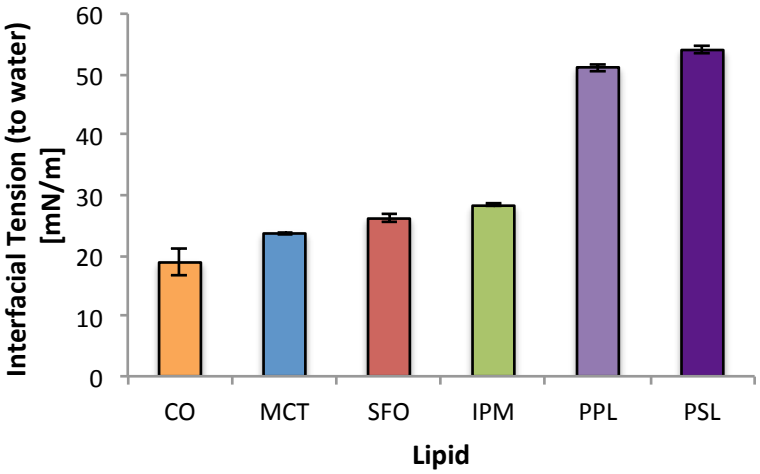


Figure 4.2: Interfacial Tension of Lipids. $n = 3$: Error bars: standard deviation Statistics: $p = 0.05$; ANOVA and Newmann-Keuls tests.

The six different lipids contained in this research have been characterized regarding their viscosity and polarity (indirectly via the interfacial tension to water). Plotting the viscosity against the polarity of each lipid in an arbitrary scale results in the 2×2 matrix shown in Figure 4.3. The 6 lipids can be divided into a total of 2×2 categories, two for high versus low viscosity (y-axis) of varying polarity, and two for high versus low polarity (x-axis) of varying viscosity. Above the dashed line are three lipids of a relatively high viscosity in the order CO > PSL > SFO, which differ in their polarity in the order CO > SFO > PSL. Below the dashed line are the remaining three lipids of a relatively low viscosity in the order PPS > MCT > IPM, which differ in their polarity in the order MCT > IPM > PPL. Similarly, the solid line divides the same lipids into high and low polarities of varying viscosities. The overall order of both polarity and viscosity is shown in the matrix image.

The figure illustrates the reason for choosing those particular lipids: The six lipids used in this thesis cover a wide spectrum of physic-chemical properties. High and low viscosity lipids, each of high and low polarities are chosen, aiming to scientifically clarify the factors contributing to water vapor permeability. In other words, the entire spectrum of lipid physico-chemical properties is covered, where for each of the four options (high/high, high/low, low/high and low/low) there is at least one representing lipid.

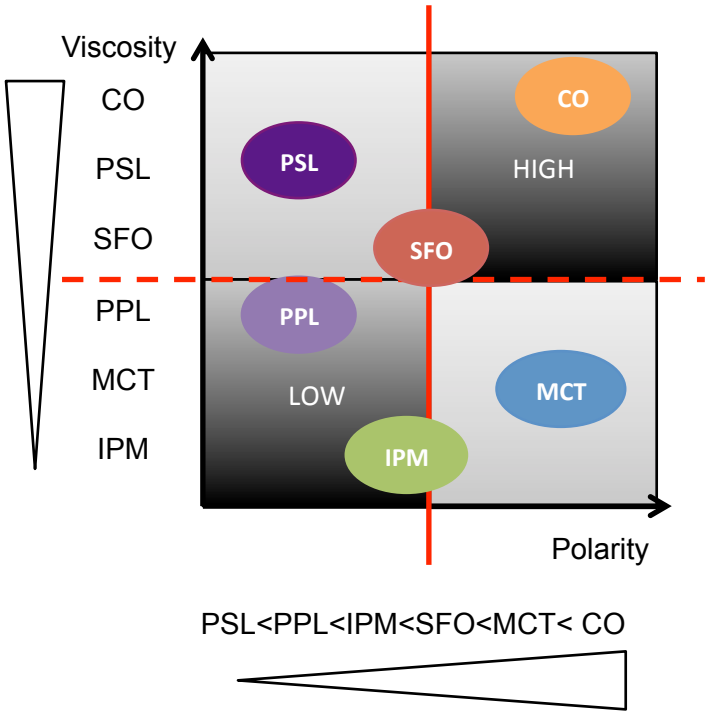


Figure 4.3: 2×2 **Matrix and Classification of Lipids: Polarity vs. Viscosity.** Arbitrary scale.

$CaCO_3$ Batch	Surface Area [m^2/g]
Batch 1	17.8
Batch 2	3.6
Batch 3	n.a.

Table 4.1: Particle Surface Area of $CaCO_3$

4.1.1.1.2 $CaCO_3$ Characterization

Fels GmbH, Germany, has provided us with 3 different batches of $CaCO_3$ (Batch 1, 2 and 3). The specific surface has been determined for the samples of each batch [32].

Table 4.1 shows the specific surface area results for Batch 1 and 2. Batch 1 $CaCO_3$ has a significantly higher surface area per unit weight compared to Batch 2 powder. This finding suggests either a higher porosity and / or smaller particle size.

Furthermore, scanning electron microscope (SEM) images have been performed and the resulting images (Figure 4.4*a-c*) confirm the latter suggestion; Batch 1 $CaCO_3$ has particle sizes up to 100 nm, whereas Batches 2 and 3 $CaCO_3$ have bigger particle sizes with diameters up to 2 μm. Furthermore, the figure shows that Batch 1 $CaCO_3$

particles are spherical, whereas Batches 2 and 3 $CaCO_3$ are needle shaped.

4.1.1.2 Formulation Demands: Choice of Emulsion Components and Ratios

In general, the formulation is developed to meet some demands: first, a stable Pickering emulsion using $CaCO_3$ (and stearic acid) as a particulate emulsifier is to be achieved. The aptness of $CaCO_3$ is investigated in Section 4.1.1.2.1. Second, since the novel formulation aims to have moisture protective properties once dried (Section 4.1.2), it is hypothesized that a high quantity of the inner lipid in the final formulation is beneficial, because the lipid per se is the water-repellent component. Therefore, Section 4.1.1.2.2 presents results of the effect of different formulation ratios on emulsion stability. Additionally, low-polarity lipids are expected to result in low moisture permeability and hence, the effect of different lipids is investigated on emulsion stability (Section 4.1.1.2.3) and on water vapor permeability (Section 4.1.2.2.2 and Section 4.1.2.2.3).

In Chapter 1 the advantages of aqueous coatings over organic ones have been discussed. The novel formulation is therefore designed to be of the oil in water type and hence, it is comparable to aqueous dispersion coatings. In order to form a film coat onto moisture sensitive cores (Stage 3), a film-forming agent is a crucial component of the final formulation. Its quantity is aspired to be sufficient to provide intact films (Section 4.1.1.2.4).

Furthermore, it is worth mentioning at this stage, that the duration of the coating process is intended to be short, in order to prevent excessive moisture uptake while the outer aqueous phase of the emulsion is dried and the film formed on the pellet or tablet surface. Therefore, the aqueous phase is desired to be of low quantity, to meet the previous demand. The previous demands favor high quantities of all emulsion components (emulsifier, lipid, film-forming agent) except for the aqueous phase. However, the final viscosity of the formulation limits the quantities of each component for galenic reasons; high quantities of either may result in high viscosity formulations, which in turn may lead to blocking of the nozzle while spraying.

Table 4.2 summarizes the demands on the formulation components. The following results describe the effect of each on the formulation with respect to emulsion phase, emulsion stability, and viscosity. The effect of different formulations on water vapor permeability is discussed in Stage 1.2 (Section 4.1.2).

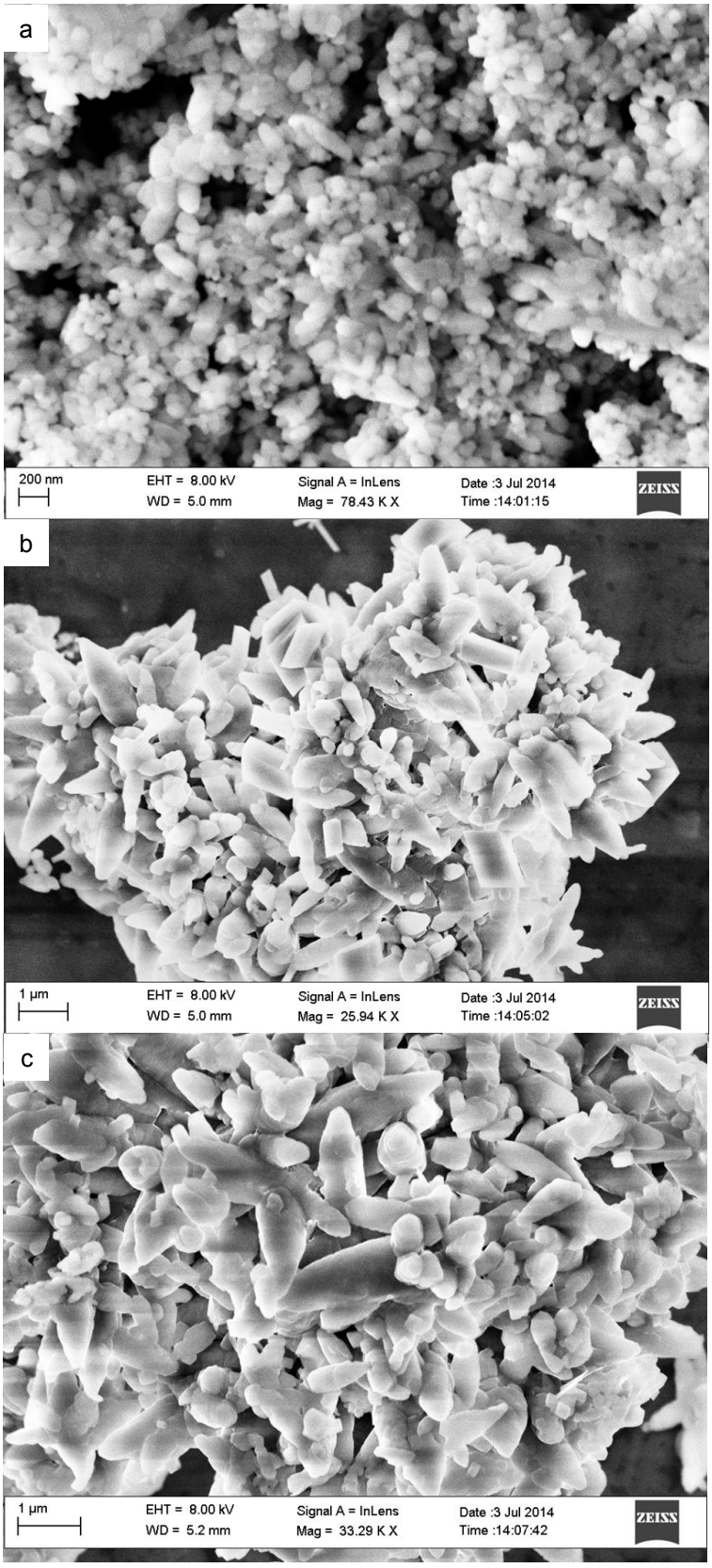


Figure 4.4: SEM Images of $CaCO_3$ Batches. Batch 1 $CaCO_3$; b) Batch 2 $CaCO_3$; c) Batch 3 $CaCO_3$. Images at different magnifications.

Demands on Formulation				
Component & its Demands		Expected Advantage		Limitation
$CaCO_3$*	↑ quantity	↑	Emulsion stability	Components quantities may limit final formulation viscosity
lipid	↑ quantity & ↓ polarity	↓	WVP	
Film-forming agent	Aqueous solubility; ↑ quantity	Aqueous coating Intact film;		
	↓ quantity	↓	WVP	
Water (outer phase)	↓ quantity	↓	coating duration exposure to moisture	

Table 4.2: Overview of Demands on Final Emulsion (PE^+). *Stearic acid quantity is dictated by $CaCO_3$ quantity; both together are considered the final emulsifier and are responsible for emulsion stability.

4.1.1.2.1 Choice of $CaCO_3$ Batch

Previous findings have shown that stable Pickering emulsions can be produced by emulsifying 20% MCT in water using an UltraTurrax. The formulation consists of 5% nano-sized $CaCO_3$ and 0.1% stearic acid as the particulate emulsifiers [32]. In order to investigate the aptness of the different $CaCO_3$ batches for that purpose, the same formulation ratios have been adopted and $CaCO_3$ from Batches 1, 2 and 3 have been used as the emulsifier, each at a time. The resulting products have been assessed visually and by a dye test according to Section 3.1.1.3.1.

Table 4.3 summarizes the outcome and Figure 4.5 depicts it: only Batch 1 $CaCO_3$ is capable of forming an emulsion. Formulations produced with Batch 2 or 3 $CaCO_3$ give unstable products, where a creamy and very viscous mass is surrounded by water (Figure 4.5*b*). It is suggested from this finding and from previous findings (Section 4.1.1.1.2) that $CaCO_3$ geometry plays a significant role in stabilizing the oil-water interface. Batch 1 $CaCO_3$ particles are spherical and smaller in size compared to Batches 2 and 3 $CaCO_3$. Therefore, it is believed that the geometry of the particulate emulsifier greatly contributes in stabilizing the oil droplets and preventing coalescence. Furthermore, by looking at Equation 1.3, it becomes obvious that Batch

$CaCO_3$ Batch Used	Visual Assessment of the Product	Emulsion Phase Type
Batch 1	Milky (Fig. IV-7 left)	o/w
Batch 2	Creamy mass in water	not applicable
Batch 3	(Fig. IV-7 right)	not applicable

Table 4.3: $CaCO_3$ Aptness for PE_s Stabilisation. Prototype formulation: $MCT - 20\%\_4 : 1$ (i.e.: 20% MCT, 5% $CaCO_3$, 0.1% Stearic acid, in water)

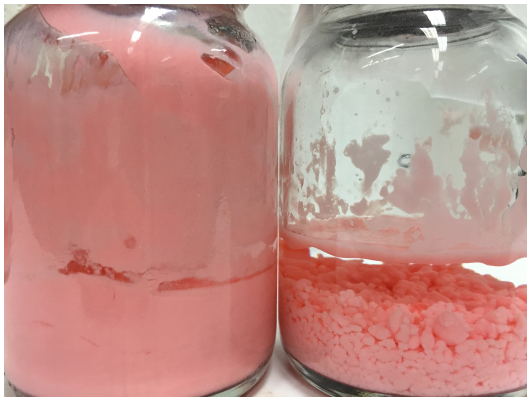


Figure 4.5: Macroscopic Image of PE_S. left: PE_s produced with Batch 1 $CaCO_3$; right: PE_s produced with Batch 2 $CaCO_3$; PE_s produced with Batch 3 $CaCO_3$ has the same macroscopic appearance as the ones produced by Batch 2 $CaCO_3$. PE_s: $MCT - 20\%\_4 : 1$.

2 or 3 $CaCO_3$ is not expected to be capable of stabilizing Pickering emulsions; as presented in Chapter 1.3.3.3, particulate emulsifiers size must be in the range of $100\ nm - 500\ nm$. Figure 4.4 clearly shows that $CaCO_3$ particles from Batch 2 and 3 are above 1 μm. $CaCO_3$ particles from Batch 1 are much smaller and in the nano-range. Horst et. al have confirmed that [32] (see Section 1.3.3.3).

Hence, all further emulsions in the context of this doctoral thesis are produced with Batch 1 $CaCO_3$.

4.1.1.2.2 Choice of Emulsion Ratios

In Section 4.1.1.2.1 it has been shown that only Batch 1 $CaCO_3$ is suitable for producing stable Pickering emulsions. The formulation consists of 20 % MCT in water that are emulsified by 5 % nano-sized $CaCO_3$ and 0.1 % stearic acid. Horst et al. state that stearic acid amounts 2 % of the $CaCO_3$ quantity used and, thus, stearic acid quantity is directly linked to the $CaCO_3$ ratio in the emulsion [32]. This finding

LP: $CaCO_3$	Ratio	Lipid*	$CaCO_3$	St. A.	Water	Phase Type
			Group (a)			
2:1	2	10 %	5 %	2 % of $CaCO_3$	Ad 100 %	o/w
3:1	3	15 %	5 %			o/w
4:1	4	20 %	5 %			o/w
5:1	5	25 %	5 %			o/w
6:1	6	30 %	5 %			unst.
			Group (b)			
4:2	2	20 %	10 %	2 % of $CaCO_3$	Ad 100 %	o/w
4:1.5	2.67	20 %	7.5 %			o/w
4:1	4	20 %	5 %			o/w
4:0.5	8	20 %	2.5 %			broken
			Group (c)			
4:1	4	15 %	3.75 %	2 % of $CaCO_3$	Ad 100 %	o/w
	4	20 %	5 %			o/w
	4	25 %	6.25 %			o/w
	4	30 %	7.5 %			unst.

Table 4.4: Overview of Formulation Ratios. Group (a) constant $CaCO_3$ at varying oil concentrations; Group (b) constant oil concentration at varying $CaCO_3$ concentrations; Group (c) constant oil-to-$CaCO_3$ ratio, at different concentrations of both. *Lipid: all emulsions ratios are performed with medium chain triglycerides (MCT) as the lipid.

is adopted and not altered throughout this doctoral thesis; any change in the amount of $CaCO_3$ results directly in a change in the stearic acid amount, correspondingly.

The aim of the following experiment is to systematically vary emulsion component ratios in order to investigate the latters effect on emulsion phase and emulsion stability. All formulations are produced using Batch 1 $CaCO_3$. The products are visually assessed, categorizing them into emulsions (milky appearance) versus unstable formulations. At this stage milky formulations are considered emulsions and are further investigated for emulsion phase by the tests described under Section 3.1.1.3. Furthermore, they are categorized according to their consistency; liquid formulations are pourable and thus considered to have a reasonable viscosity, whereas semi-solid ones are considered too viscous.

In Group (a) of the tablets, the quantity of $CaCO_3$ in the final emulsion has been held constant at 5%, while the amount of MCT has been incrementally raised from 10% to 30%, in order investigate the maximum capability of $CaCO_3$ to emulsify oil.

The results show that for 5% $CaCO_3$ the maximum amount of oil emulsified is 25%, where the emulsion is still of the oil in water type. However, emulsions produced with 25% oil are not pourable and thus believed to be too viscous to be sprayed and coated in a further step.

In Group (b) of the table, the quantity of oil in the final emulsion is kept constant at 20%, while the amount of $CaCO_3$ is incrementally raised from 2.5% up to 10%. This investigate serves two purposes: on the one hand it proposes the minimum amount of $CaCO_3$ needed to emulsify 20% oil. On the other hand, it suggests the lowest ratio of oil to $CaCO_3$ that can be used, regardless of the oil quantity, while producing emulsions of reasonable viscosity. The results show that a high ratio of oil to $CaCO_3$ ($4 : 0.5$; ratio $= 8$) results in unstable emulsions that break on standing, which is probably due to the lack of enough emulsifier to entrap all oil droplets. On the other hand, a low oil to $CaCO_3$ ratio ($4 : 2$) results in emulsions of the desired phase type (oil in water), which are however very viscous and not pourable.

In Group (c), the ratio of oil to $CaCO_3$ is kept constant at $4 : 1$, while the concentration of the oil and thus $CaCO_3$ in the final formulation is incrementally raised from 15% to 30% and 3.75% to 7.5%, respectively. The results show that up to 25% oil and 6.25%, a stable emulsion can be formed. However, such concentrated emulsions have the drawback of being too viscous fur spraying and coating in a further step.

Summarizing the results lead to the following conclusions: $CaCO_3$ stabilizes MCT up to a maximum concentration of 25%, provided the ratio of oil to $CaCO_3$ is at most 5 to 1 (Table 4.4 a and c). Higher ratio emulsions ($> 5 : 1$) contain too little $CaCO_3$ to account for the total quantity of oil in the formulation, leading to unstable products. Oil concentrations above 25% could be emulsified using a suitable (high enough) amount of emulsifier; however, the formulation would be too viscous to be produced using conventional high shear devices and the viscosity would be too high for further spraying (Table 4.4c). Therefore it is suggested that oil concentrations of 15% or 20% present a good compromise between high oil quantities and reasonable viscosities. The $CaCO_3$ quantity may not be less than a quarter of the oil amount (oil: $CaCO_3$ 4:1) and may not be too high for viscosity reasons (Table 4.4b). Consequently, emulsions with certain criteria are selected for further investigations. Table 4.5 presents the ratios and names of the products that are further investigated. It shows that emulsions comprising 20% or 15% lipophilic phase are chosen for further development. The oil to $CaCO_3$ ratio is selected to be either $4 : 1$ or $4 : 1.5$. Abbreviations presented in Table 4.5 under “Coding” will be used throughout the dissertation. This emulsion code

Used LP	LP: $CaCO_3$	Conc. Oil	Conc. $CaCO_3$	Conc. St. Acid	Coding*
e.g. MCT	4:1	15 %	3.75 %	2 % of $CaCO_3$	LP-15%_4:1
		20 %	5 %		LP-20%_4:1
	4:1.5	15 %	5.625 %		LP-15%_4:1.5
		20 %	7.5 %		LP-20%_4:1.5

Table 4.5: Promising PE_S Ratios. PE^+ ratios used for further investigations. *Coding: those emulsion codes are used throughout this doctoral thesis.

Used LP	Emulsion Code	Result	
		Appearance	Phase Type
MCT	MCT-20%-4:1	Milky	o/w
IPM	IPM-20%-4:1	Milky	o/w
CO	CO-20%-4:1	Milky	o/w
SFO	SFO-20%-4:1	Milky	o/w
PPL	PPL-20%-4:1	Milky	o/w
PSL	PSL-20%-4:1	Milky	o/w

Table 4.6: PE_S from different LPs

suggests the lipid of the emulsion, its percentage, and the ratio lipid to $CaCO_3$. For example $MCT - 20\%\_4:1$ would mean the stock Pickering emulsion (PE_s) consists of 20% MCT as the lipophilic phase and 5% $CaCO_3$ (Lipid:$CaCO_3$ ratio = 4 : 1).

4.1.1.2.3 Effect of Different Lipids on Pickering Emulsion

According to the demands on the final formulation mentioned in Section 4.1.1.2 different lipids are believed to result in different moisture barrier properties of the dried formulation. Therefore, lipid with a wide spectrum of physico-chemical properties (mainly viscosity and polarity) have been chosen (Section 4.1.1.1.1).

The effect of the different lipids on emulsion stability and emulsion phase is examined here, where the emulsion phase depending on the different lipids is presented in Table 4.6. The findings described here are for stock Pickering emulsions with a Lipid:$CaCO_3$ ratio valuing 4 : 1, where the lipid concentration comprises 20% (general emulsion code: $LP - 20\%\_4:1$).

The results show that all lipids give creamy products that are macroscopically stable on standing for at least four weeks. Furthermore, all products are emulsions of the oil in water type. Thus, all formulations consisting of one of the six different lipids emulsified by Batch 1 $CaCO_3$ may be further investigated.

4.1.1.2.4 Choice of Film-Forming Agent and its Concentration in the Final Formulation

The demands on the formulation described in Section 4.1.1.2 pronounce the necessity to include a film-forming agent in the final formulation, because the latter is aimed to coat moisture-sensitive cores. Since the stock Pickering emulsion (PE_s) is of the oil in water type, the film-forming agent is chosen to be water-soluble; water-insoluble polymers might have been more favorable than water soluble ones with respect to moisture protection and could be aqueous dispersed (suspended) in the outer emulsion phase. However, they are intentionally excluded from my research for four reasons: First, water-insoluble polymer coats might alter the disintegration of solid cores and hence the dissolution profile an undesired property in the context of moisture protection. Second, formulations including a water-insoluble polymer and showing low moisture permeability are complex to interpret; moisture protection could be attributed to either solely the polymer, to the formulation or probably- to a synergistic effect of both. In other words, the novel formulations intrinsic moisture protective ability is to of main focus. Second, Ellerman et al. [21] report that a number of polymers show incompatibilities when added to stable Pickering emulsions, leading to unstable formulations (as discussed under Section 1.3.3.3).

Last, for reasons mentioned under Section 1.3.2.2, film forming agents dissolved in the coating fluid (here o/w emulsion) are easier to coat; the film-forming polymer coming from a solution are usually less sensitive to process parameters and no curing is usually needed. All previous aspects have been reason enough to choose a water-soluble polymer as the film-forming agent of the novel formulation. Hydroxypropyl methyl cellulose (HPMC) is chosen for this purpose.

Other demands on the film-forming agent apart from being water-soluble are as follows: the polymer is expected to form intact films and to have a relatively low viscosity. The latter is aspired, because the final formulation is going to be sprayed in a later stage. Last but not least, the film-forming agent shall be applied in a lowest possible concentration, in order to avoid undesired moisture permeability by it and thus to correctly assess the moisture protective ability of the novel formulation.

Choice of HPMC Grade Two candidates are chosen at this stage: HPMC 603 and HPMC 606, where both are of the substitution type 2910. HPMC 603 solutions have lower viscosity than HPMC 606 solutions of the same concentration. To our knowledge HPMC 603 has the lowest available viscosity HPMC supplied on the

PE_s	HPMC Quantity	HPMC 603	HPMC 606
MCT-20%_4:1	1 %	not intact	not intact
	2 %	not intact	not intact
	3 %	not intact	not intact
	4 %	not intact	intact
	5 %	not intact	intact

Table 4.7: Free Film Characterization - Effect of HPMC

market. On the other hand, HPMC 606 has longer chain polymers and its solutions are expected to form more intact films at similar concentrations. In order to find a suitable concentration of the HPMC in the final formulation and to choose one of the above-mentioned HPMC grades, HPMC is added at different concentration (1 % - 5 %) to the prototype, stock PE_s ($MCT - 20\%\_4:1$) and free films (FFs) have been produced. FFs are visually assessed for cracks and for film intactness. The results reveal the following: HPMC 603 forms free films with cracks at all concentrations. On the other hand, HPMC 606 forms intact free films at already 4 % of the final formulation (Table 4.7). Therefore, HPMC 606 is more preferable and is further investigated.

Choice of HPMC Concentration In a second investigate, the promising PE_s ratios presented in Table 4.5 are further examined by producing PE^+ with HPMC concentrations in the final formulation equal to the $CaCO_3$ concentration of each formulation (Table 4.8). The findings reveal that a minimum concentration of 5 % HPMC in the final formulation is required to form intact free films. However, its maximum concentration values 7.5 %. Consequently, formulations with 15 % LP and a ratio LP:$CaCO_3$:HPMC 4 : 1 : 1 are excluded from further investigations, due to insufficient HPMC quantity in the final product. Table 4.9 lists the emulsion codes that will be further examined. PE^+ ratios presented in this table will be further investigated and referred to throughout the dissertation.

4.1.1.3 Emulsion Characterization

After the principal formulation has been developed, its components chosen and their concentrations determined, the next step has been to characterize both, the stock Pickering emulsion (PE_s) and the film-forming Pickering emulsion containing HPMC (PE^+). Both, PE_s and PE^+ have been produced with different lipids at different concentrations for each component. Each of those products has been characterized

Promising PE_s ratios (PE_s Code)	LP:$CaCO_3$:HPMC (PE^+ code)	PE^+ Code	Free Film Intact-ness
LP-15%_4:1	15 % LP 3.75 % $CaCO_3$ 3. 75 % HPMC	LP-15%_4:1:1	not intact
LP-20%_4:1	20 % LP 5 % $CaCO_3$ 5 % HPMC	LP-20%_4:1:1	intact
LP-15%_4:1.5	15 % LP 5.625 % $CaCO_3$ 5.625 % HPMC	LP-15%_4:1.5:1.5	intact
LP-20%_4:1.5	20 % LP 7.5 % $CaCO_3$ 7.5 % HPMC	LP-20%_4:1.5:1.5	intact

Table 4.8: Promising PE^+ Ratios and their FF Intactness

PE^+ Code	LP:$CaCO_3$:HPMC
LP-20%_4:1:1	20 % LP 5 % $CaCO_3$ 5 % HPMC
LP-20%_4:1.5:1.5	20 % LP 7.5 % $CaCO_3$ 7.5 % HPMC
LP-15%_4:1.5:1.5	15 % LP 5.625 % $CaCO_3$ 5.625 % HPMC

Table 4.9: Summary of Stable PE^+ Ratios.

by optical and fluorescence microscopy. It is worth mentioning that emulsion phase has already been characterized (Table 4.4), but the microscopic images have been used as an additional confirmation of the findings. Furthermore, all products have been subjected to laser diffraction particle sizing technique for drop size distributions (DSD). DSD results have been used to investigate several effects on the emulsion product, which are going to be mentioned in detail in Section 4.1.1.3.2; DSD results mainly serve as a good assessment of the emulsion production process, whether for PE_s or PE^+.

4.1.1.3.1 Microscopic Imaging

Microscopic images are taken to confirm the emulsion phase. Only emulsions containing Sudan III are subject to fluorescence imaging. Figure 4.6*a* shows droplets surrounded by an outer phase and that all droplets are much smaller than 100 μm. Furthermore, it shows that the drops tend to form agglomerates. Figure 4.6*b* shows the emulsion drops under a 20× magnification. Emulsion drop size ranges from < 20 μm up to approximately 50 μm. Figure 4.6*c* shows the exact same position of the specimen shown in (b) after being excited with fluorescence light. It can be seen that the individual drops (inner phase) fluoresce under the microscope. This finding confirms that oil is the inner phase and is surrounded by water.

4.1.1.3.2 Drop Size Measurement

In general, drop size distribution (DSD) results serve two main purposes: First, the results assess each emulsion product (components, ratios) for its reproducibility and stability over time. Second it enables the comparison among products composed of different components and ratios. Horst et. al have previously produced Pickering emulsions comprising 20% MCT as the lipid, 5% $CaCO_3$ (from Batch 1 $CaCO_3$) and 2% stearic acid ($MCT - 20\%\_4 : 1 : 1$) [32]. The emulsion has been produced using an UltraTurrax for 5 minutes at 8000 rpm.The emulsion's DSD has been measured, setting a reference DSD for this doctoral thesis (Table 4.10). However, in this research some modifications in the formulation components, ratios and emulsification procedure have been made and the results investigated regarding DSD. In the following, each sub-section discusses the aim of its investigate and findings. Please note that all quantities, in n, shown under each finding are for independently produced emulsions; from each emulsion at least three aliquots were taken for a triplicate measurement in

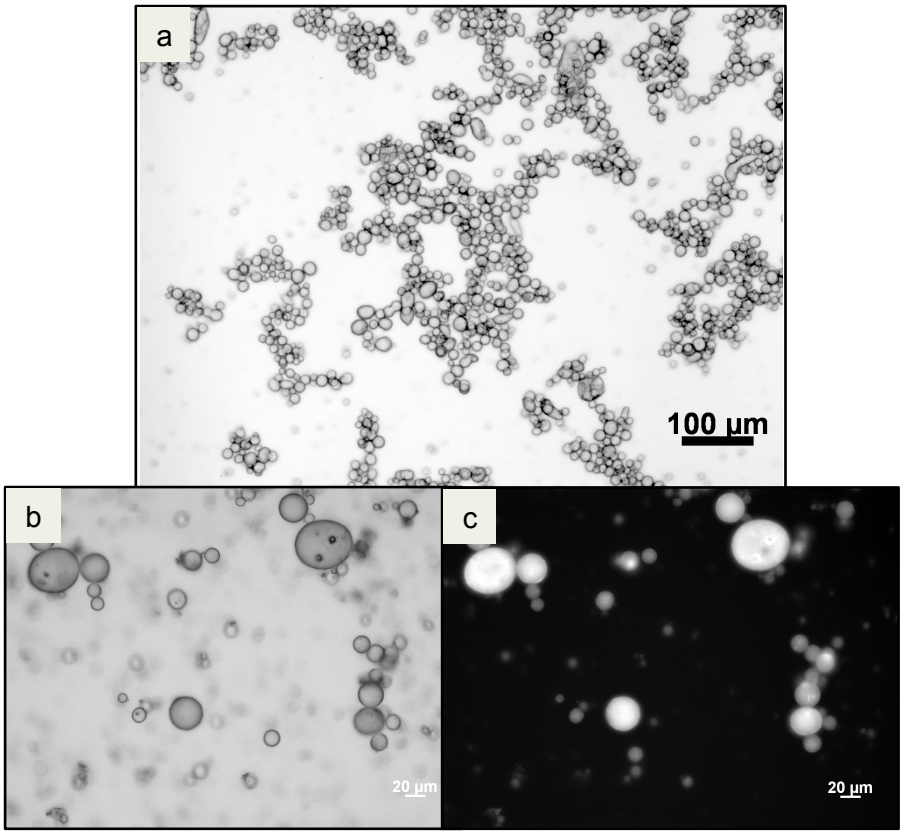


Figure 4.6: Microscopic Images. a) transmitting light, 10 x magnification, b) flourescence light, 20 x magnification; c) same spot as in b), flourescence light, 20 x magnificaiton. PE_s is $MCT - 20\%\_4 : 1 : 1$.

Emulsification Device	d10 [µm]	d50 [µm]	d90 [µm]
UltraTurrax (Reference)	12 ± 2	20 ± 2	40 ± 5
UltraTurrax	8.3 ± 2.2	20.1 ± 2.0 *	43.4 ± 5.9
LabMixer	7.8 ± 0.5	17.0 ± 0.3 *	38.6 ± 3.5

Table 4.10: Drop Size Distribution (DSD) - Effect of Emulsification Device. Result: "UltraTurrax (Reference)" is the reference DSD performed by Horst et al. [32]. Lower two rows are results of this doctoral thesis; DSD of "n" independently produced emulsions. n=7 for Ultraturrax; n=7 for LabMixer. Measurement immediately after production (0D). Average d10, d50 and d90, error: standard deviation. Statistics: p = 0.01; unpaired t-test: * significantly different.

the device. For example, $n = 7$ means 7 independent emulsions were produced and a total of at least 21 aliquots were measured.

Effect of Emulsification Device on Drop Size Distribution This experiment investigates the effect of different devices used in the production of stock Pickering emulsion (PE_s). In Section 3.1.1.2.1 two devices have been mentioned for PE_s production (the UltraTurrax and the LabMixer). Table 4.10 sets a reference for the drop size distribution (DSD) results obtained using an UltraTurrax; the result labeled "UltraTurrax (Reference)" is the reference DSD performed by Horst et al. [32]. Hence, the aim here is to produce prototype stock Pickering emulsions ($MCT - 20\%\_4 : 1$) showing a similar DSD as shown in this table using both devices.

Table 4.10 presents the drop size distributions for prototype PE_s ($MCT - 20\%\_4 : 1$) produced by both devices. The findings show that formulations produced by the LabMixer are comparable.

In turn, there is no major difference in the properties between formulations produced by either device. The LabMixer provides a successful upscale for PE_s, whereas both devices may be used to obtain reproducible products.

Effect of HPMC Addition on Drop Size Distribution This experiment investigates the effect of HPMC addition on drop size distribution (DSD). Comparing PE_s and PE^+ prototype emulsions ($MCT - 20\%\_4 : 1$ vs. $MCT - 20\%\_4 : 1 : 1$) regarding their DSD (Figure 4.7) reveals the following: HPMC containing Pickering emulsions (PE^+) have similar $d10$ and $d50$ values compared to stock Pickering emulsions (PE_s). An unpaired t-test has shown no significant difference between the 2

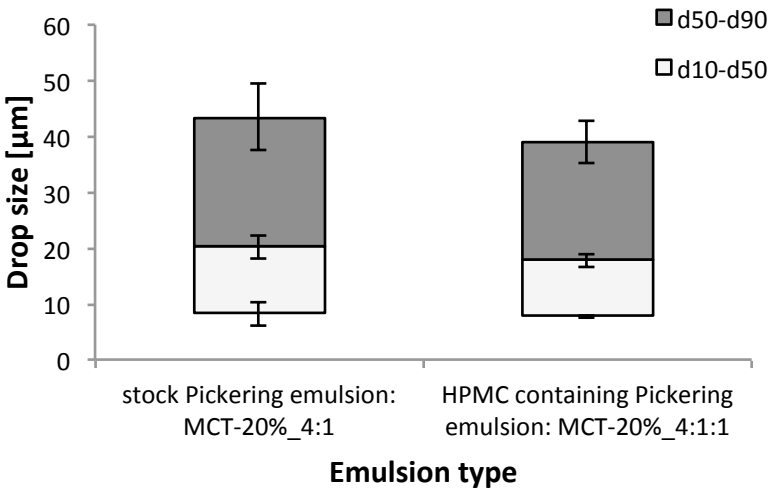


Figure 4.7: Drop Size Distribution - PE_S vs. PE_S. Result: DSD of "n" independently produced emulsions. n=7 for stock Pickering emulsion (PE_s); n=5 for HPMC containing Pickering emulsion (PE^+). Measurement immediately after production (0D). Average d10, d50 and d90, error bars: standard deviation. PE_s was produced using an UltraTurrax; for HPMC addition see III.1.1.2.2. Statistics: p = 0.01; unpaired t-test.

groups ($p = 0.01$).

Since both, PE_s and PE^+ have quite similar drop sizes, emulsion character of the formulation is mostly – if not exclusively – attributed to $CaCO_3$ (and not to HPMC). HPMC is known to have surface-active properties [18], but does not greatly contribute to the emulsification of the novel formulation.

This finding demonstrates the necessity of adding HPMC stock solution by gentle stirring to the final PE_s, instead of incorporating it in the emulsification step: in order to prevent emulsification by HPMC, the latter has been added via its stock solution, followed by gentle stirring (Section 3.1.1.2.2). By that, it is assured that HPMC does not greatly reduce PE_s drop sizes and thus it is assured that emulsion character of the formulation is exclusively attributed to $CaCO_3$ (and not to HPMC).

Effect of Different Emulsion Ratios on Drop Size Distribution This investigate examines the effect of different emulsion ratios on drop size distribution (DSD) of stock Pickering emulsion (PE_s). PE_s presented in Table 4.9 are chosen for that purpose; they comprise different ratios of LP:$CaCO_3$. Figure 4.8 shows the following: $LP-20\%\_4:1.5$ has an obviously smaller DSD compared to both, the prototype emulsion ($LP-20\%\_4:1$) and to $LP-15\%\_4:1.5$. This can be

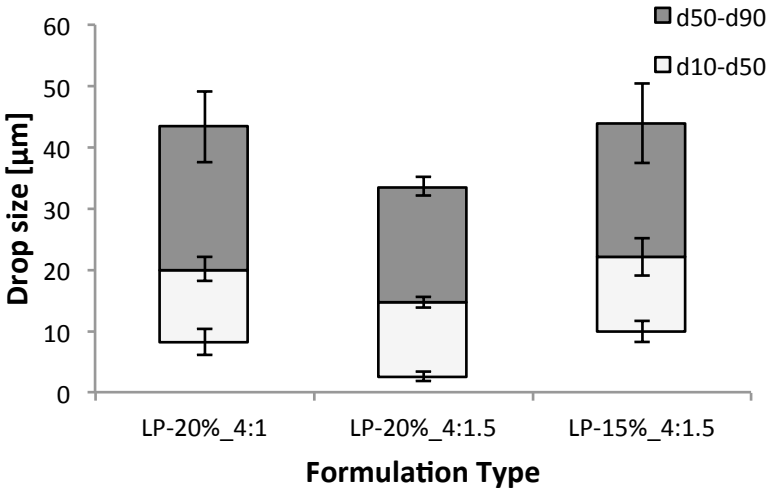


Figure 4.8: Drop Size Distribution - Effect of PE_S Components Ratio. Result: DSD of "n" independently produced emulsions. n=7 for $LP-20\%\_4:1$ (LP=MCT); n=2 for $LP-20\%\_4:1.5$ (LP=MCT); n=3 for $LP-15\%\_4:1.5$ (LP=SFO). Measurement immediately after production (0D). Average d10, d50 and d90, Error bars: standard deviation for n≥3; error bars: span for n=2. All PE_s produced using an UltraTurrax.

explained by the following: $LP-20\%\_4:1.5$ is the most concentrated PE_s among the invesitaged ones here, comprising the least amount of water. This in turn results in the highest viscosity (shown in its relatively least pourability after production compared to the other two emulsions). A high viscosity causes a high energy input into the emulsion, which is a result of the relatively longer retention time in the gap of the UltraTurrax because of the high viscosity (compared to low viscosity formulations). Thus, the duration of shear energy input is elongated leading to smaller drop sizes. This phenomenon has been described by arch group of Prof. Schuchmann (Karlsruhe Institite of Technology) [36].

$LP-15\%\_4:1.5$ has a comparable DSD to the prototype emulsion ($LP-20\%\_4:1$). The former's higher amount of $CaCO_3$ is compensated by a lower lipid concentration (15% Lipid), which in total results in an even less concentrated PE_s compared to the prototype emulsion. Hence, it is of similar viscosity and consequently of similar DSD. The above-mentioned findings suggest that the emulsion concentration and consequently its viscosity affect the DSD of produced stock Pickering emulsions.

Effect of Different Lipids on Drop Size Distribution It has previously been shown that emulsifying any of the six different lipids used in this doctoral research

result in Pickering emulsions of the oil in water type (Table 4.6). The following experiment compares the drop size distributions (DSD) of six different stock Pickering emulsion (PE_s) formulations, each consisting of one of the six lipids. All formulations consist of 20% lipid, 5% $CaCO_3$ and 0.1% stearic acid ($LP - 20\%\_4 : 1$).

Figure 4.9 illustrates that formulations prepared with almost all lipids (MCT, PSL, PPL, SFO, IPM) show DSDs of the same range, the smallest being around $10\mu m$ and the largest around $60\mu m$, where the d50 is in the range of $23\mu m$; PE_s prepared with CO show obviously smaller d10 values, and also obviously larger d50 and d90 values. This is mainly attributable to the following two aspects: first, it is an effect of the comparably very high viscosity of CO (Figure 4.1). The UltraTurrax reaches its upper process limits when emulsifying PE_s prepared with CO, because the very viscous mass is barely mixed homogeneously during the procedure (indicated by the inhomogenous distribution of colorant while emulsifying). This in turn results in bigger drop sizes (d50 and d90). On the other hand, a little percentage is emulsified quiet well, resulting in the smallest d10 values among the sample series. This is probably due to a phenomenon described above; the energy densities are distributed differently among the emulsion formulation as a result of their variable viscosities. Second, Schulz describes the low stability of Pickering emulsions containing CO as their lipid; the author relates the observed instability to the relatively high polarity of CO, where the particulate emulsifier is not sufficiently located in the lipid-water interface and hence cannot stabilize it properly [51]. The theoretical background to this aspect is described under Section 1.3.3.3. In conclusion, the above-mentioned findings suggest that lipid viscosity is directly related to PE_s viscosity, which then affect the DSD of PE_s.

Effect of Time on Drop Size Distribution (Pickering Emulsion Stability) Emulsions are known to be thermodynamically and physically unstable and tend to agglomerate (reversibly) or even coalesce (irreversibly).

Taking the prototype stock Pickering emulsion as an example ($MCT - 20\%\_4 : 1$), it has been observed that - on standing for a few days - the formulation separates into two phases: an upper aqueous phase and a lower lipophilic one. This can be explained as follows: the inner lipid phase of the novel formulation tends to sediment rather than float, because the apparent density of the individual drops is higher than the continuous aqueous phase; the lipid (of lower density than water) is surrounded and encapsulated by $CaCO_3$ solid particles (particulate emulsifier), which together have a higher apparent density than water. Furthermore, as seen under the microscope

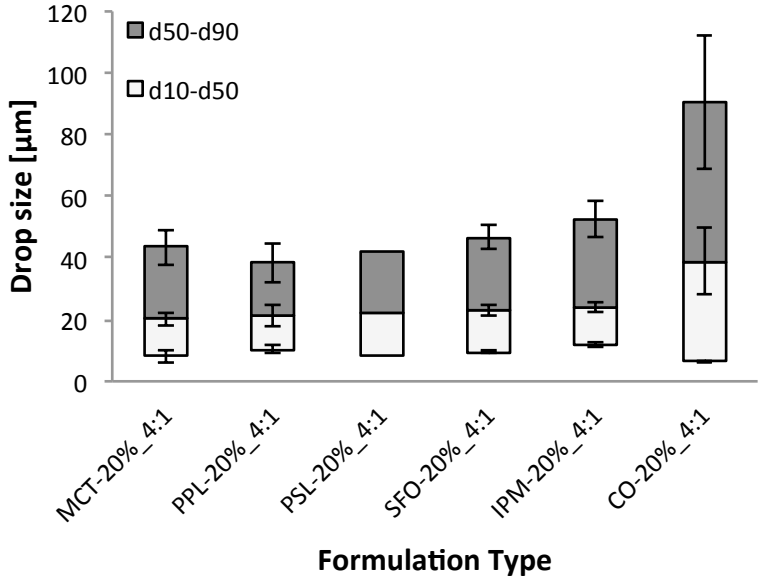


Figure 4.9: Drop Size Distribution Effect of Lipid. Result: DSD of "n" independently produced emulsions. n=7 for MCT − 20%_4 : 1; n=6 for PPL − 20%_4 : 1; n=1 for PSL − 20%_4 : 1; n=5 for SFO − 20%_4 : 1; n=3 for IPM − 20%_4 : 1; n=2 for CO − 20%_4 : 1. Measurement immediately after production (0D). Average d10, d50 and d90, Error bars: standard deviation for n3; error bars: span for n=2; no error bars for n=1. All PE_s produced using an UltraTurrax.

(Figure 4.6a) the inner phase has a tendency to agglomerate, which may cause an even higher affinity to sedimentation. However, on slightly vigorous shaking, the product reverses to its original macroscopic appearance.

This phenomenon has been observed for almost all stock Pickering emulsions (PE_s), that have been stored at room temperature for a few days and produced by the LabMixer[1].

On the other hand, HPMC containing Pickering emulsions (PE^+) have shown a similar but less pronounced outcome. For the above-mentioned reasons, the following experiment is designed to answer two main aspects: first, it investigates the physical stability of the Pickering emulsions, by relating the effect of sedimentation to the drop size distribution over time. Moreover, it examines the effect of HPMC on the stability of the formulation, by comparing the drop size growth of PE_s to PE^+. For that purpose, one batch of PE_s and its respective PE^+ ($MCT-20\%\_4:1$ and $MCT-20\%\_4:1:1$, respectively) have been measured for their DSD at three different times after vigorous shaking prior to measurement: the day of production (0D), after 2 weeks (14D) and after cumulatively 3 weeks (21D). On each of those days, a total of 9 aliquots have been measured for each sample from 3 different spots (top, middle, bottom; 3 aliquots from each spot). In the meantime, the products have been stored at room temperature in sealed glass bottles. Table 4.11 shows that both, PE_s and PE^+ experience an upward shift in their DSDs over time, indicating a mild tendency of emulsion drops to coalesce. Nevertheless, comparing both emulsion types together, the following is detected: First, PE^+ has already smaller drop sizes at the day of production than PE_s, which can again be explained by shearing the biggest drops of PE_s while adding the very viscous HPMC stock solution to it (see above: Subsection "*Effect of HPMC Addition on Drop Size Distribution*"). Furthermore, an average rise in the PE_s d90 value of approximately 10 μm in three weeks is observed, whereas the corresponding value for PE^+ grows in average about 6 μm only. This fact can be explained by Equation 4.1[2]: PE^+ is more viscous than PE_s, due to the presence of HPMC in the continuous phase. According to Stoke's law (Equation 4.1), a high viscosity, η, may decrease the sedimentation rate, ν. In summary, the sedimentation observed for both PE_s and PE^+ on standing is reversible and has no major effect on drop size distribution for at least 3 weeks storage at room temperature. In order to keep emulsion character preserved most, PE_s produced by the LabMixer

[1]Note: products obtained by the UltraTurrax are usually consumed for other investigates on the same day of production and therefore, no stability tests has been made for emulsions produced by the UltraTurrax.

[2]Equation 4.1 is equivalent to Equation 1.2

Emulsion Type	Day	d10 [µm]	d50 [µm]	d90 [µm]
PE_s: MCT-20%_4:1	0D	7.6 ± 0.3	16.9 ± 1.4	39.0 ± 5.3
	14D	7.1 ± 0.2	16.4 ± 0.5	46.3 ± 2.0
	21D	7.6 ± 0.5	17.5 ± 0.9	49.18 ± 5.0
PE^+: MCT-20%:4:1:1	0D	6.7 ± 0.2	14.4 ± 0.2	33.0 ± 0.2
	14D	7.1 ± 0.1	16.4 ± 0.2	39.1 ± 1.0
	21D	7.2 ± 0.1	16.4 ± 0.3	39.3 ± 4.3

Table 4.11: Drop Size Distribution - Emulsion Stability. Result: DSD of "n" independently produced emulsions. n=1 for PE_s and PE^+. Measurement immediately after production (0D), 14 days later (14D), 21 days later (21D). Average d10, d50 and d90, error: standard deviation of three spots: top, middle, bottom.

are further processed to the more viscous (and thus more stable) PE^+ immediately after production. The products are consumed within three weeks and during this period they are stored conventionally at room temperature without further storage precautions.

$$\nu = \frac{2r^2 \times g \times \Delta\rho}{9\eta} \tag{4.1}$$

Stoke's Law

ν = sedimentation velocity
r = particle radius
g = gravitational constant
ρ = density
η = viscosity

4.1.2 Dried Formulations and the Mechanism of Water Vapor Permeability

Previously, under Section 4.1.1 (Stage 1.1), results for experiments have been shown, where the formulations were investigated in their liquid form. Under this Section (Stage 1.2), all results are shown for experiments, where the starting material was a dried formulation. First, in Section 4.1.2.1, the free films characterization results are shown. Afterwards, in Section 4.1.2.2, the moisture protective ability (MPA) of the formulations is presented, which is considered on of the most important results of this doctoral thesis.

4.1.2.1 Free Film Characterization

4.1.2.1.1 Free Film Widths

Free films were produced by film casting, as previously described in Section 3.1.2.1. In general, a wide range of free film (FF) widths can be achieved, depending on the choice of the metal reservoir, since the latter is available at various gap widths (Section 3.1.2.1). However, the production of FFs with comparable film widths has been a challenge for FFs from different formulations. The latter include all the different PE^+ formulations with different emulsion ratios and / or components, EPOaq-d and HPMCs-12.5%. Figure 4.10a illustrates the resulting free film width ranges for each formulation type.

Starting with both, EPO-FFs and HPMC-FFs, the following is seen: both formulations have been produced from a metal reservoir with 0.8 mm gap width and have resulted in free films approximately ranging from $0.08 - 0.21$ mm and $0.14 - 0.16$ mm, respectively. Comparing them to PE^+-FFs, it is noticeable that FFs from emulsion formulations (PE^+) are wide-ranged and can be much thicker. Depending on the formulations LP, components ratio and the gap width of the metal reservoir, PE^+-FFs vary from $0.15 - 0.75$ mm (wide range!). Most PE^+-FFs produced from a metal reservoir with 0.8 mm gap width vary from $0.3 - 0.55$ mm (Figure 4.10: dark blue). Rarely, PE^+-FFs' thickness reaches 0.75 mm (Figure 4.10: dark blue dashed). This wide variation is attributed to the variety of PE^+ formulations available in this research; the novel formulation varies in its compositions (different LPs) and / or component ratio (Table 4.9). For example, formulations differing only in their LP component (e.g. CO vs. MCT) but having the same formulation ratio have shown different film widths. PE^+ films produced from a metal reservoir with only 0.6 mm gap width results in FF widths ranging from $0.15 - 0.3$ mm, but are not reproducible. The viscous formulations remain in the metal reservoir and do not pass the narrow gap. Hence, producing PE^+-FF from even narrower gap widths (e.g. 0.4 mm) has not been feasible. The previous phenomenon can be explained as follows: first, PE^+ is a lot more viscous (less pourable) than the other formulations, which results in a higher surface tension. In turn, this causes less spreading on the Teflon plate and consequently thicker films. Second, depending on the components ratio, PE^+ formulations contain at least 22.5 % film-forming material, whereas both HPMCs-12.5% and EPOaq-d contain 12.5 % each (Figure 4.10b). Consequently, the same amount of film forming formulation results in a thicker film for PE^+. In conclusion, FFs from different formulations vary strongly in their film widths and the latter strongly

depends on the formulation: formulation components (PE^+ and its variable LPs vs. HPMCs-12.5% vs. EPOaq-d) and formulation ratio (% film-forming substances) affect film thickness, by affecting formulation viscosity and spreading on Teflon. In turn, it has been technically not feasible to produce films with comparable widths.

4.1.2.1.2 Visual Observations on Free Films

Free Films (FF) from EPOaq.-d and from HPMCs-12.5% are opaque. HPMC-FFs and EPO-FFs are flexible at the first day after drying for 24 hours, but soon change: HPMC-FFs become hard and less flexible, but do not break easily, whereas EPO-FFs become brittle and break easily. Therefore, both film types are further processed for water vapor permeability (WVP) test preparation within the first few days after drying. PE^+-FFs remain soft even after weeks of production. However, a shiny oil layer is observed on the surface of most FFs that have been dried from formulations having the general formula $LP - 20\%\_4 : 1 : 1$ (20% LP, 5% $CaCO_3$, 5% HPMC). Visually, it is obvious that some FFs show this phenomenon more than others. Placing the different PE^+-FFs (from the different PE^+ formulations) on a filter paper for several days reveals the following: FFs containing CO, PSL or IPM as their lipid are more shiny and leave a bigger oil spot behind compared to FFs from other formulations (MCT, SFO, PPL). FFs from formulations with less lipid concentration and a higher $CaCO_3$ and HPMC ratio to lipid (e.g. $MCT - 15\%\_4 : 1.5 : 1.5$) have shown less greasiness (smaller oil spot on tissue) compared to the previously discussed FFs (e.g. $MCT - 20\%\_4 : 1 : 1$). The previous findings indicate that some lipid is released from the formulation on drying. More $CaCO_3$ and HPMC can decrease this phenomenon, by better encapsulating and immobilizing the emulsion drops within, as seen for $MCT - 15\%\_4 : 1.5 : 1.5$. However, a detailed study (quantification) has not been performed at this stage.

The aforementioned results are more supported after considering results presented in Section 4.1.2.1.3. Figure 4.12 summarizes both results together.

4.1.2.1.3 Emulsion Re-constitution - Free Film Dispersion

The aim of this experiment is to investigate the preservation of emulsion character in the free films (dried state), by dispersing the latter in water. Hereby, the dried emulsion (the free film) is reconstituted in water, assessed macro- and microscopically and its drop size distribution (DSD) measured as presented in Section 3.1.2.2.

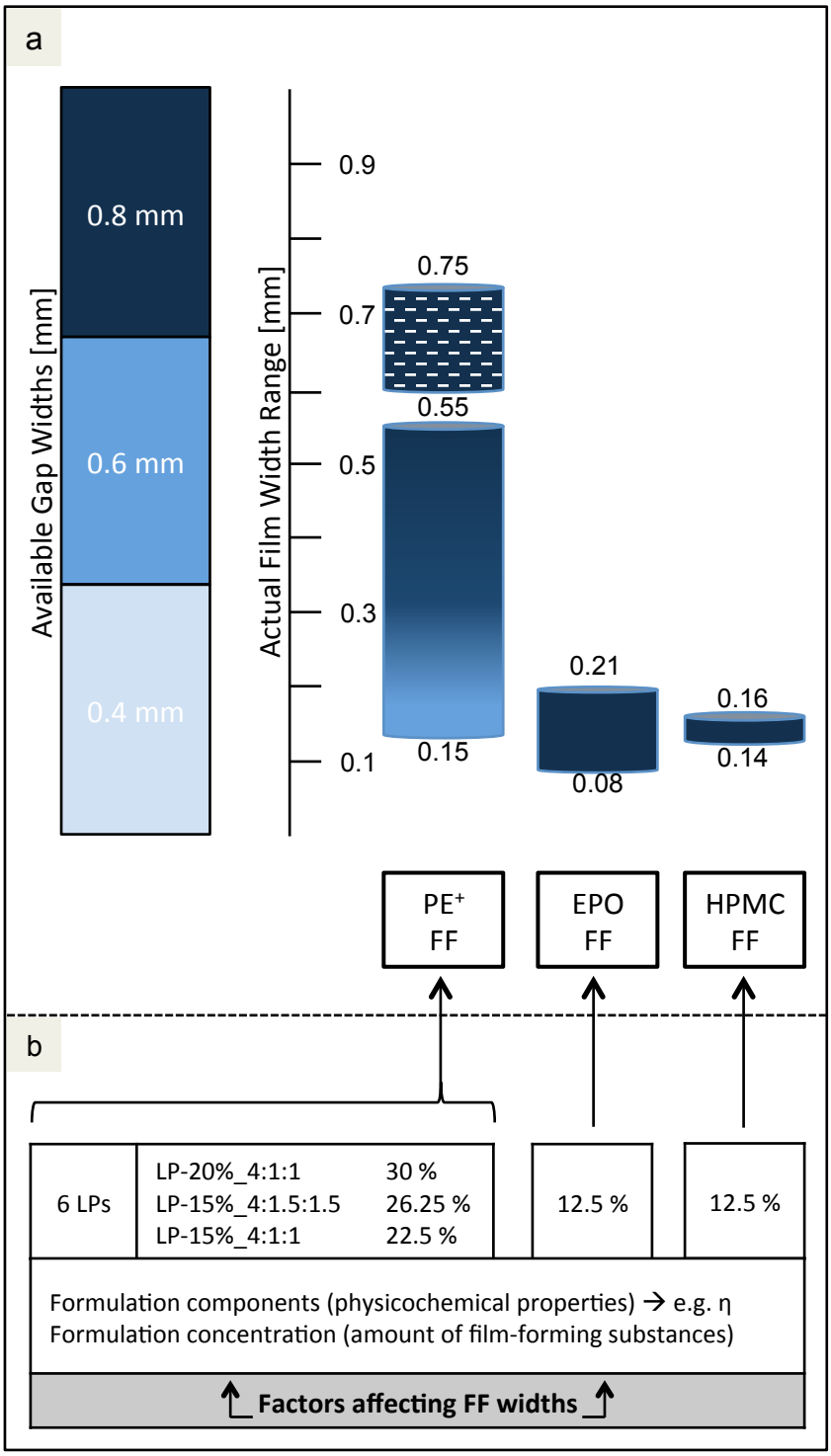


Figure 4.10: FF Characterization – Correlation of Gap With to FF Thickness. * % w/w describes the percentage of components forming the free film.

Samples include free films (FFs) of PE^+ formulations having the same components ratio, but differ in their components (lipids). Macroscopically the FF-dispersion is turbid; microscopically, the dispersion shows drops dispersed in an outer phase and is comparable to the image shown in Figure 4.6. Figure 4.11 summarizes the results of the DSD of the dispersed FFs. It compares all aqueous dispersions of free film formulations (re-FF) to their original stock Pickering emulsions (PE_s); the latter have been previously presented and discussed in Figure 4.9.

In Figure 4.11 it is shown that all free film dispersions (re-FFs) show a DSD result, which per se indicates that a reconstituted emulsion is present. This in turn indicates emulsion character preservation in the dried state.

The following paragraphs discuss the variation among the different series: Free film dispersions of $MCT-20\%\_4:1$ and $PSL-20\%\_4:1$ show DSDs in the range of the DSD of their respective PE_s. The biggest difference is observed for re-constituted emulsions from $SFO-20\%\_4:1$; the d90-value is clearly higher than the crude emulsion, but the d10 and d50-values remain almost unchanged. A similar phenomenon is observed with CO and PPL formulations. That can be explained by the tackiness of the free films, which is believed to be related to the viscosity of the lipid component; more viscous lipids form more tacky FFs. Dispersing the latter according to Section 3.1.2.2 in water is obviously not completed after 2 hours (indicated by the presence of emulsion lumps in the dispersion). Hence, the detector perceives information on bigger particles that are actually undispersed lumps of tacky FF pieces. Despite PSL's highly viscous nature (as shown in Figure 4.1), its FFs (PSL-FFs) do not show this phenomenon. However, PSL-FF has been produced only once; a solid statement is hard to make here. Furthermore, it has been the youngest free film in this research, and, therefore, is not comparable to other free films at this stage; aging effects are thus not considered.

Unlike CO-FFs, PPL-FFs and SFO-FFs (which all show an increased DSD, as discussed above), reconstituted IPM-FFs show smaller drop sizes compared to their mother formulation (IPM-PE_s). Considering the results from Section 4.1.2.1.2, the following could be a possible explanation: similar to CO-FFs and PSL-FFs, IPM-FFs liberate some of its biggest IPM-drops onto its surface, which results in the aforementioned shininess of the films (Section 4.1.2.1.2). However, unlike CO-FFs and PPL-FFs (which have tacky films), IPM-FFs are not tacky at all (IPM is the least viscous lipid in the series); their FFs reconstitute in water quickly, leaving no visual agglomerates and hence, no agglomerates are detected. Therefore, re-constituting IPM-FFs show no increased drop sizes. The liberated lipid droplets float on the

surface of the re-constituted free film dispersion, coalesce to a lipid film and are thereby not detected by the laser beam. Only the smaller drops are measured. Figure 4.12 summarizes the aforementioned results.

In conclusion, the d10 and d50 values of reconstituted PE^{+}-FFs show results that are similar to-, or at least in the range of their mother formulations. Only the d90 value is increased for some formulations, which is likely related to the tackiness of the free films, resulting from the effect of both, lipid viscosity and aging. Yet, and most importantly, these results indicate emulsion character preservation in the dried state.

In Chapter 1, several research groups have been presented, where Pickering emulsions have been dried by different mechanisms (Section 1.3.3.4); however, the internal morphology of those dried formulations have not been revealed. Figure 4.13 is a scanning electron microscopic image of the inner morphology of dried emulsions: it clearly offers a further proof for the preservation of emulsion character in the dried state. The image shows a cross-sectional cut of a free film piece that exposes the inner morphology of dried emulsions: HPMC forms a matrix or sponge like structure, immobilizing the individual oil drops (encapsulated by $CaCO_3$) within. Ellermann et al. and Möllgaard et al. have shown that emulsion character is preserved in the dried state as well [21, 37].

4.1.2.2 Moisture Protective Ability (MPA) of Pickering Emulsion Free Films

Chapter 1 has discussed the derivation of the permeability equation (Figure 1.6 Equation IV), which shows the proportionality of the permeability, P, to both, the permeants solubility, S, and its diffusivity, D, in the barrier membrane. According to the equation, keeping both, S and D, low results in low permeability. In Section 4.1.1.1.1, the choice of the 6 lipids has been justified, by illustrating the wide spectrum of physico-chemical properties covered by them. In other words, the components of the novel formulation are chosen in a way, as to include a wide spectrum of polarity (high and low) and viscosity (high and low), where the latter directly affects the permeates diffusivity (see later: Equation 4.8). Hence, varying the diffusivity, D and the solubility, S, enables the investigation of the effect of the physico-chemical properties on the permeability, P.

In this Section, the central aim is to assess the moisture protective ability (MPA) for the novel formulations, and to benchmark its moisture permeation to marketed products. For this purpose, two main experiments (see below) were performed, where each is applied to one of two possible barrier membranes; the barrier membrane may

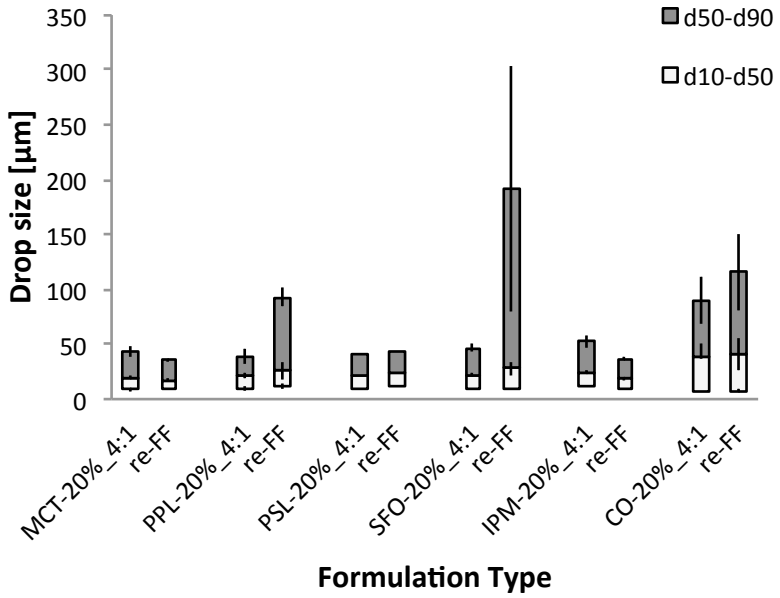


Figure 4.11: DSD of FF Dispersions - Reconstituted Emulsions. Result: DSD of "n" independently produced emulsions. n=7 for $MCT-20\%\_4:1$; n=6 for $PPS-20\%\_4:1$, n=1 for $PSL-20\%\_4:1$; n=5 for $SFO-20\%\_4:1$; n=3 for $IPM-20\%\_4:1$; n=2 for $CO-20\%\_4:1$. n=2 for all re-FFs (i.e. each FF-dispersion from two different free film pieces); exception: re-FF for PSL-FFs. Error bars: standard deviation for $n \geq 3$; error bars: span for n=2; no error bars for n=1. All PE_s results previously presented in Figure 4.9.

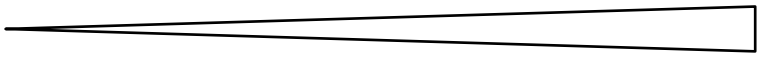
Emulsion Ratio →		LP-20%_4:1:1					
Lipid →		IPM	MCT	PPL	SFO	PSL	CO
FF Charact.	Greasy?	yes	no	yes	no	yes	yes
	Size of oil spot:	big	small	med.	small	biggest	biggest
Reconst. FF	Δ drop size distr.	↓	-	↑	↑↑	-	↑
	Tackiness	no	no	no	yes	yes	yes
Viscosity							

Figure 4.12: Correlation of Lipid viscosity to FF Oiliness to Reconstitution Properties.

be either a free film (dried formulation) or a crude material (LP). Both are discussed throughout the MPA investigate (Table 4.12). The findings of both investigates together with (some) results from Section 4.1.1 unleash the various factors contributing to the MPA and the mechanism governing moisture permeation through the dried formulations.

The two main experiments discussed here are Water Vapor Permeability (WVP) and Dynamic Vapor Sorption (DVS). The main difference lies in the information provided by each experiment: WVP tests (Section 4.1.2.2.2 and Section 4.1.2.2.3) provide information about the rate of vapor transmission through the barrier film (WVP-value). Water vapor is absorbed by activated silica gel, which is separated from moisture by the barrier membrane. On the other hand, DVS tests (Section 4.1.2.2.4 and Section 4.1.2.2.5) provide information about the equilibrium amount of sorbed water vapor (WVS-value) by the barrier film itself. In other words, a WVP test describes water permeability through the barrier membrane before the dynamic equilibrium has been reached, and thus is considered a kinetic experiment. A DVS measurement rather provides information on the barrier membranes own affinity to moisture, and thus evaluates it at equilibrium (steady state) and hence is considered a static experiment. Moreover, DVS results deliver information on the sorption

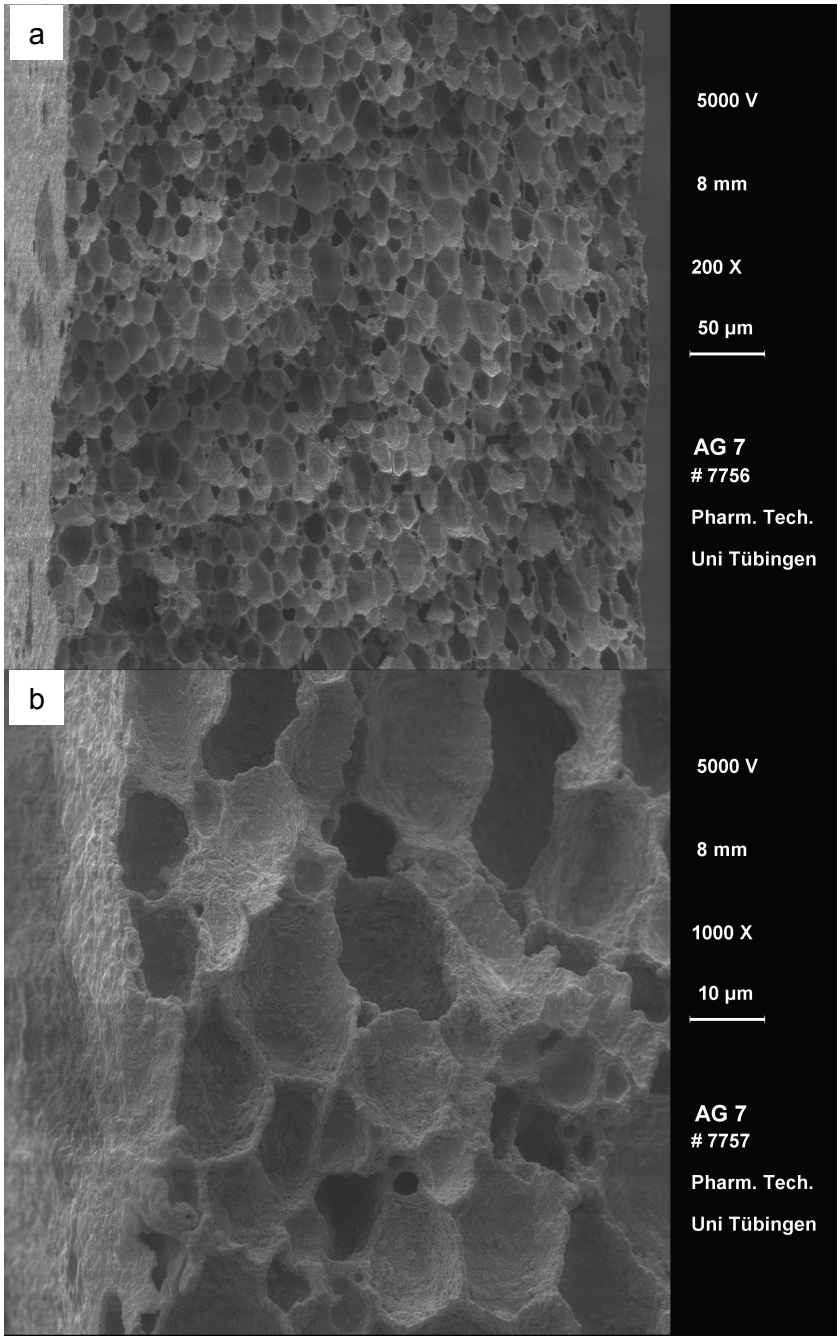


Figure 4.13: SEM Image of Cross-Sectional Cut of PE$^+$-FF. Cross-sectional cut for PPL – 20%_4 : 1 free film. a) 200x magnification; b) 1000x magnification.

WVP test → WVP-value	DVS test → WVS-value
• Dynamic • Before equilibrium • Water vapor permeating through the sample	• Static • At equilibrium • Water vapor sorbed to the sample

Table 4.12: Overview of Experiments for MPA Assessment. Overview of MPA experiments, elaborating the factors affecting moisture protection and its mechanism. Samples were either free films or crude materials (e.g. crude lipids).

isotherms of the samples measured. In summary, WVP-tests provide information on the overall WVP of a film sample, while DVS-tests provide information on its affinity to water vapor, which contributes to the overall permeability. Thus, having obtained both parameters, information on the diffusivity of water vapor through the film can be provided. Table 4.12 summarizes the previous aspects in an overview.

4.1.2.2.1 Theoretical Background Considerations and Calculations

Throughout this doctoral research both, WVP and DVS results have been empirically obtained by measuring weight gains (Equation 4.2 and Equation 4.7). Before presenting their results (Section 4.1.2.2.2 Section 4.1.2.2.5), some theoretical considerations and justifications are presented here.

It is worth mentioning that in Section 3.1.2.3 and in Section 3.1.2.4 the equations for WVP calculation and WVS have been previously shown (Equation 3.1, Equation 3.2, Equation 3.4; derivations and rearrangements have been presented in Chapter 1, amongst others). However, the equations are presented in the following paragraphs again for the sake of comparison to other similar calculations.

The WVP-value (Result of WVP-tests) The WVP-value is calculated from the experimental weight gain of silica over time, which corresponds to the amount of permeated moisture through the barrier membrane (Equation 4.2[3]). The WVP-value is not exactly equivalent to the P-coefficient presented in Equation 4.4[4]. The

[3]Equation 4.2 is equivalent to Equation V in Figure 1.6 (see Section 1.3.2.4 for its derivation); it is also equivalent to Equation 3.1 (see Section 3.1.2.3.1)

[4]Equation 4.4 is equivalent to Equation IV in Figure 1.6. Units for P depend on its calculation according to literature.

latter is derived from Henry's and Fick's laws (as described in Chapter 1) and requires information on the permeate's diffusivity through- and solubility in the barrier membrane. The derivation of both equations and their correlation is presented under Section 1.3.2.4.

The WVP-value is very similar to the P-coefficient found in Equation 4.4, but is gravimetrically assessed as discussed in Chapter 1. In literature, some scientists use Equation 4.3[5] to quantify WVP [34]. This calculation is derived similarly to the derivation of Equation 4.4 as presented in Figure 1.6. However, Equation 4.3 includes parameters for the pressure drop across the barrier membrane as opposed to the latter. The pressure drop, Δp, is equivalent to the relative humidity difference above and below the barrier film; we consider it to be constant for a specified humidity level in the experiment as long as sink conditions apply, and hence we do not include it in our calculations. WVP-values obtained empirically in this research (Equation 4.2) correlate with the P-coefficient from Equation 4.4. This in turn means that variable water vapor diffusivity of and solubility in the barrier membrane directly affect WVP-value. In order to obtain the latter, WVP-tests are performed. Equation 4.2 is used for calculating WVP through free films; WVP for PTFE loaded filters (see Section 4.1.2.2.3, Equation 4.9) is calculated according to a slight modification of Equation 4.2.

$$WVP = \frac{MVTR}{(m_{FF}/A)^{-1}} = \frac{\Delta m \times m_{FF}}{t \times A} \tag{4.2}$$

WVP-value Calculation (for FFs)

WVP = water vapor permeability $[mg^2/(d \times mm^2)]$
$MVTR$ = moisture vapor transmission rate $[mg/d]$
Δm = weight gain due to water vapor $[mg]$
m_{FF} = free film weight $[mg]$
t = unit time $[d]$
A = unit film area $[mm^2]$

$$WVP = \frac{\Delta m \times d_{FF}}{t \times A \times \Delta p} \tag{4.3}$$

WVP-value Calculation (According to Literature)

[5]Equation 4.3 is equivalent to Equation III.b in Figure 1.6, which is also equivalent to Equation III.c in Figure 1.7.

WVP = water vapor permeability $[mg/(d \times mm \times mmHg)]$
Δm = weight gain due to water vapor $[mg]$
d_{FF} = free film thickness $[mm]$
t = unit time in days
A = unit film area $[mm^2]$
Δp = pressure drop across the barrier membrane $[mmHg]$

$$P = D \times S \tag{4.4}$$

Permeability Coefficient Calculation

P = permeability coefficient
D = diffusivity
S = solubility

The WVS-value (the result of DVS-tests)— and its Distinction from EMC In Chapter 1, water vapor sorption (WVS) has been defined and its significance to the overall understanding of a formulation's moisture protective ability (MPA) stated. WVS is a general term used for the amount of a permeant (water vapor) residing in a barrier film. In literature three similar values are described in the context of WVS, DVS-techniques and solubility of water vapor in a film. We will call those three terms as follows: the S-value, the WVS-value and the EMC-value. In this doctoral research, we are mostly concerned with the WVS-value; similar to the WVP-value, the WVS-value has been empirically obtained via the samples weight changes in the dynamic vapor sorption (DVS) device (Table 2.5). But before its practical and mathematical background is explained and its correlation to the S-value (found in Equation 4.4) presented, the difference between the three values is presented; how either one could possibly be assessed using a DVS device is also mentioned. The first and most common value in this context is the EMC-value (equilibrium moisture content), and it is usually obtained by the DVS technique. Here, the DVS experiment is designed as follows: the sample is pre-dried to 0 % RH and EMC at any given relative humidity is equivalent to the weight gain compared to the pre-dried sample (Equation 4.5). To our knowledge, the EMC-value is not necessarily equivalent to the absolute solubility of water in a sample, because the EMC value is assessed at any given humidity level. Hence, the amount of a samples water uptake at e.g. 75 % RH would not be equivalent to the absolute and maximum amount possible at higher humidity levels (e.g. 100 % RH). Yet, as mentioned in Chapter 1 (Section 1.3.2.4)

Mwesigwa et al. have used the DVS-technique to obtain the S-coefficient[6] found in Equation 4.4 by simply obtaining the EMC-value of free films at various % RH levels. The solubility-coefficient was then calculated as an average of the different values obtained for the EMC-values [38].

The second value in this context is the S-value. It is very similar to the just presented EMC-value but differs in the target % RH level. The question now would be, which of both is equivalent to the S-coefficient found in Equation 4.4. It depends on whether the S-coefficient of Equation 4.4 is defined as the absolute maximum amount a film can hold (i.e. its absolute solubility for water vapor) or if it is defined only as an equilibrium amount at a given % RH level. As discussed in Chapter 1 (Section 1.3.2.4), Henry's law correlates the solubility of a gas in a solvent to the gas's partial pressure. Hence, the definition of the S-value rather correlates to the second option. Yet, in order to distinguish both options and because the term solubility suggests either option, we prefer to separate both values. In doing so, we relate the S-value term to the absolute maximum amount of water vapor a barrier film can accommodate. In that case and applying the equation to free film samples, S would describe the absolute solubility of water vapor in the film (at a 100 % RH) and hence, WVP would be obtained at 100 % RH. To our knowledge, no scientific work has been performed using the DVS technique to assess the absolute solubility, S, of water vapor in free films. In other words, we have found no literature describing the absolutely maximum uptake of water by film samples. However, we believe that the latter could be obtained by the DVS technique as follows: the equilibrium weight gain of the sample at 100 % RH would need to be measured, and compared to the completely pre-dried sample (at 0 % RH) (Equation 4.6). However, in that case any surface adsorption of water vapor is assumed to be negligible. Furthermore, this solubility value could still be less in magnitude than the actual and absolute solubility of water in the film. For example, Tongdeesoontorn et al. [60] assess absolute water solubility in edible films by soaking the latter in water for a certain period of time and via the weight difference absolute water uptake (solubility) is calculated. This and similar approaches are not possible with PE^{+}-FFs, since the latter are partially water soluble (the HPMC component is an unlimited swellable one) and partially water dispersible (the emulsion droplets); hence, the film would not remain intact in water and waters solubility in PE^{+}-FFs could not be obtained alike. Therefore, we do not obtain the absolute water solubility in free films. Instead, we determine free

[6]The S-coefficient found in Equation 4.4 is not necessarily equal to the S-value found in Equation 4.6.

films affinity to water (vapor) by performing DVS tests and calculating WVS-values, which is described as follows.

In short, we believe the EMC-value and the S-value can both be used for the S-coefficient of Equation 4.4 and hence for WVP calculation according to this equation; the resulting P-coefficient (WVP-value) would apply then for a certain % RH level, depending on the experimental design.

The third and for this doctoral research relevant value is the WVS one. In Section 3.1.2, it is described that the samples have been standardized (pre-treated) at 30 % RH and not completely dried at 0 % RH (due to time limitations), which is the main difference to the EMC-value and S-value. Similar to the WVP-value, the WVS-value is gravimetrically obtained as follows: the weight gain at different relative humidity levels is obtained and the WVS-value calculated according to Equation 4.7 [7]. Please note that the WVS-value obtained by the DVS technique cannot be equivalent to the S-value found in Equation 4.4, because the former does not indicate an absolute amount of water vapor residing in a film sample, but rather a relative one. Yet, it is believed to correlate with it. For that purpose, the following assumption is made: the higher the films solubility to water, the higher its affinity to water vapor and the higher the film sorbs water vapor. The latter shows in higher WVS-values. It is worth mentioning again that having both, the WVP-value and WVS-value of a sample, information on water vapors diffusivity through it can be concluded. As just mentioned, the WVS-value obtained by the DVS technique is not equivalent to the S-value found in Equation 4.4; in fact, this limitation does not negatively affect our calculations for WVP for the following reason: in this doctoral research, the WVS-value is not part of the WVP calculation, but is only a means to unleash a formulations MPA, as described in Chapter 1 (Section 1.3.2.4). Table 4.13 summarizes the above-mentioned ideas and correlations.

MVTR-value vs. WVP-value Previously, it has been discussed that it is technically not feasible to form reproducible films of comparable widths (Section 4.1.2.1.1). This technical drawback has made moisture vapor transmission rate (MVTR) (Equation 3.3) an insufficient parameter to compare the different formulations with respect to their moisture protective ability. MVTR does not consider the film width in its calculation. On the other hand, the water vapor permeability (WVP) value accounts for the barrier quantity (width or weight), in multiplying MVTR by the latter

[7] Equation 4.7 is equivalent to Equation 3.4.

(Equation 4.2). Hence, WVP is the parameter of choice when comparing different formulations with unequal barrier widths (as presented in Section 3.1.2.3).

Film Weight vs. Film Widths In preparation to the WVP test circular film pieces are punched out of the free film sheets (Section 3.1.2.3.1). Those barrier membranes need to be individually quantified for each sample / vial, being part of the denominator of the WVP value (Equation 4.2). Accurate and precise film width results can be obtained by a micrometer screw gauge only if the barrier membrane is tightly screwed, increasing the risk of its destroy. Therefore, film pieces are weighed, rather than measured for their widths.

$$EMC = \frac{m_x - m_0}{m_0} \times 100\ \% \tag{4.5}$$

EMC-value

EMC = equilibrium moisture content [%]
m_x = equilibrium weight of sample at any defined % RH
m_0 = equilibrium weight of sample at 0 % RH

$$S = \frac{m_{100} - m_0}{m_0} \times 100\ \% \tag{4.6}$$

S-value

S = S-value [%]
m_{100} = equilibrium weight of sample at 100 % RH
m_0 = equilibrium weight of sample at 0 % RH

$$WVS = \frac{m_x - m_0}{m_{30}} \times 100\ \% \tag{4.7}$$

WVS-value

WVS = water vapor sorption [%]
m_x = equilibrium weight of sample at any given % RH
m_{30} = equilibrium weight of sample at 30 % RH

	EMC-value	S-value	WVS-value
Equation:	Equation IV-5	Equation IV-6	Equation IV-7
Description:	Relative % weight gain at: any % RH, compared to the weight of the sample at: 0 % RH	100 % RH, 0 % RH	any % RH, any % RH
Conditions:	All measurements obtained at equilibrium conditions		
Reference Weight:	Equilibrium sample weight at: 0 % RH (dry)	0 % RH (dry)	any RH%
Sample Weight:	Equilibrium sample weight at: any RH %	100 RH %	any RH %

Table 4.13: Overview of WVS - Its Three Values.

From Theory to Practice - Introducing the Practical Results Now that the theoretical and calculation backgrounds are discussed the following paragraphs deal with the results of the moisture protective ability (MPA) of free films; two main experiments are performed, namely WVP and DVS tests. Each experiment is first performed with free films and then with crude material, as will be discussed in detail under each paragraph. Furthermore, for either experiment, first the prototype formulation is investigated ($MCT - 20\%\_4 : 1 : 1$) and then compared to different formulations. After all results are presented, findings from individual experiments will be summarized and discussed to give the final statement suggesting the novel formulations mechanism of moisture protection and the different effects contributing to it.

4.1.2.2.2 Water Vapor Permeability (WVP) Tests - Free Films

WVP is tested for two sample types: first, it is being applied to different dried formulations (free films), in order to directly assess their moisture protective ability (Section 4.1.2.2.2). In Section 4.1.2.2.3, it is applied to inert carriers polytetraflouroethylene filters (PTFE-F) loaded with different lipophilic phases, in order to assess the WVP-value for the crude LPs.

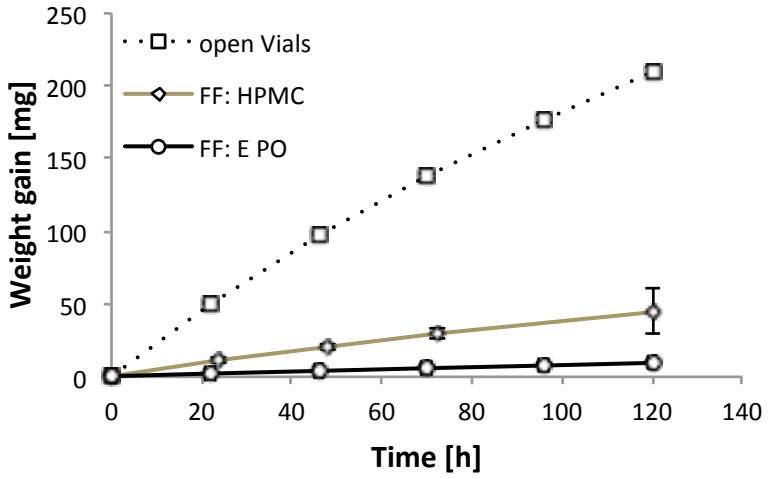


Figure 4.14: Weight Gain vs. Time (Reference Samples). Result: average weight gain of 3 vials per sample type (n=3) (presented for one exemplary experiment). Conditions: 75 % RH; Error bars: standard deviation. Investigated sample types: see legend.

Setting a Reference: Eudragit E PO and HPMC Free Films Figure 4.14 shows the weight gain over time of activated (dried) silica being unprotected, protected with dried Eudragit E PO (EPO) and HPMC free films. Furthermore, Figure 4.15 shows the WVP values for both dried formulations at various % RH levels. Those findings serve solely as a reference for results shown later; their discussion is presented below when needed under different paragraphs.

Moisture Protective Ability (MPA) of the Novel Formulation Figure 4.16 shows the weight gain of activated (dried) silica protected with dried novel formulation compared to unprotected samples . The findings show, the novel formulation has reduced water vapor uptake by 90% within the first four days, compared to the unprotected vials containing activated silica gel. This finding per se indicates that the formulation has moisture protective abilities; its weight gain reduction is in the range as shown for EPO and HPMC free films, as shown in the figure. The findings in Figure 4.16 set the basis for all further experiments and justify the calculation of WVP after 72 hours (Section 3.1.2.3): in order to calculate WVP, sink conditions for the moisture sorbent (activated silica gel) must apply. Else, WVP may not be considered to be solely dependent on the formulation but would rather be a function of both, the dried formulation and the absorbent's capacity to bind water vapor. Therefore, the calculation for WVP must take place during the first four days (96 hours), where

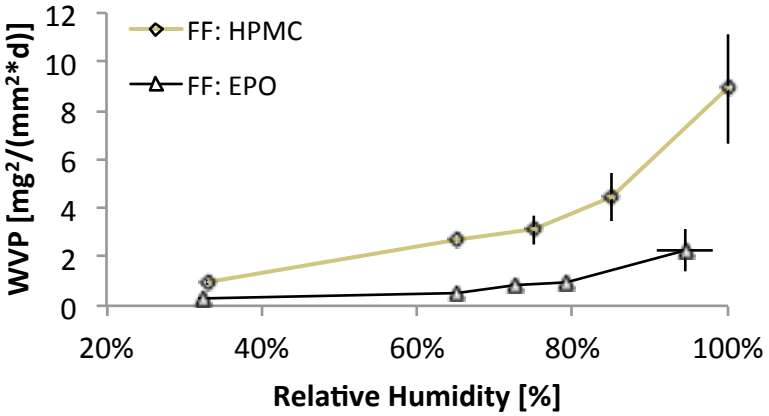


Figure 4.15: WVP vs. Relative Humidity (Reference Samples). Result: Average WVP of 2 experiments with at least 3 vials for each sample type per experiment (n=2 experiments) - after 72 hours at the different denoted % RH conditions (x-axis). Note: repeated experiment for each sample type is performed with same (un-fresh) formulation. Error bars: span. Investigated sample types: see legend.

the capacity of activated silica gel has not exceeded 10% of its maximum. Hence, the 72-hour measurement has been chosen to calculate WVP values.

It is worth mentioning here that the tested films contained no visually detected pores; in case a tested free film contained any visually detected pores, the sample (test vial sealed with that film) has been declared as defect and – on WVP testing – it showed no reduction in weight gain compared to open vials. This finding indicates per se that the films are pore free.

Effect of Film Widths and Possible Routes of WVP The aim of this investigate is to test the effect of different film widths on moisture vapor transmission rate (MVTR) and water vapor permeability (WVP). Different film widths of the novel formulation ($MCT - 20\%\_4 : 1 : 1$) have been produced and classified into 5 categories (Table 4.14). The average film weight per unit area has been plotted against their corresponding MVTR, as seen in Figure 4.17. The figure shows that MVTR is inversely proportional to the film weight per unit area, which correlates directly with the film width (Table 4.14). This indicates the films are homogenous. suggests that water vapor diffuses through PE^{+}-FF.

Now since the free films are homogenous, the question about water permeability mechanism through the free films arises. In order to follow the thought stream here, it is important to revise previously presented findings and integrate them together:

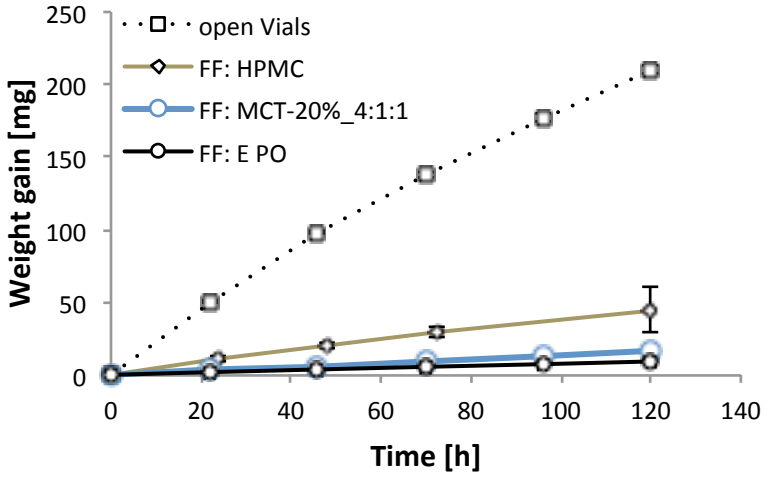


Figure 4.16: Weight Gain vs. Time. Results. Result: average weight gain of 3 vials per sample type (n=3) (presented for one exemplary experiment). Conditions: 75 % RH; Free films of: $MCT-20\%\_4:1:1$; EPO; HPMC. Results for open vials, EPO- and HPMC-FFs previously shown in Figure 4.16. Error bars: standard deviation. Investigated sample types: see legend.

first, it has just been shown that free films are homogenous. Second, it has been previously presented that free films show moisture protection (see Figure 4.14), but at the same time do not completely constrain water permeability; in other words, water *does* permeate through the film. Third, in Section 4.1.2.1.3, it has been found that the dried novel formulation preserves emulsion character, where the lipid droplets are immobilized in the HPMC matrix (Figure 4.13). Fourth, it is assumed that the films are pore-free (as mentioned above) and hence water vapor permeates through the film by diffusion[8].

Thus, two scenarios are possible for the route of moisture diffusion as illustrated in Figure 4.18. The first possible route (Route 1) depicts water vapor migrating only through the HPMC matrix and the $CaCO_3$ / Ca-stearate phase boundary, "avoiding" any lipid droplets. In other words, water vapor dissolves in the HPMC matrix only, diffuses through it without permeating through the lipid droplets (first hypothesis). The second possible scenario depicts water vapor permeating through the HPMC matrix and the lipid droplets; in that case, water vapor is dissolved in the HPMC matrix, partitions into the lipid phase, moving between both phases alternatingly. These routes show some resemblance to drug permeation through the skin, where

[8]Visually, the tested films contained no pores; tested films that contained any visually detected pores showed no reduction in weight gain compared to open vials (compare to Figure 4.14).

Film Widths [mm] (approximation)	Average Film Weight / unit area [mg / mm²]
0.15	0.40 ± 0.01
0.22	0.61 ± 0.00
0.23	0.66 ± 0.02
0.49	1.37 ± 0.04
0.53	1.39 ± 0.14

Table 4.14: Free Film Width Categorization.

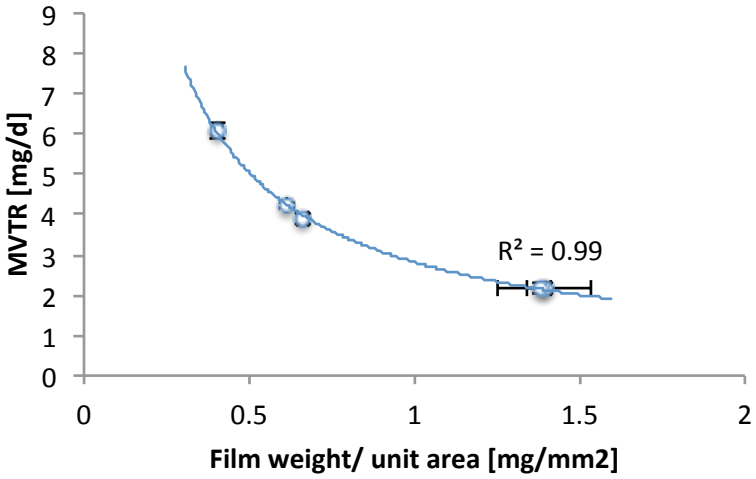


Figure 4.17: MVTR vs. Film Weight per Unit Area. Result: average MVTR of 4 vials (for one sample type) (n=4) – after 72 hours; results from several independent experiments. Conditions: 75 % RH. Error bars: standard deviation. Curve fit: polygon curse (power law). Sample type: Free film of MCT – 20%_4 : 1 : 1.

substances may diffuse intercellularly (here: via the HPMC matrix) or transcellularly (here: via the lipid phase) [19]. In order to validate that hypothesis, further experiments are designed to investigate that matter, which are going to be discussed later (Section 4.1.2.2.2 and Section 4.1.2.2.3).

Effect of Different Humidity Conditions on WVP This experiment investigates the behavior of WVP with increasing moisture levels. It is worth reminding, that all investigates discussed under Section 4.1.2.2.2 have been performed at only 75 % RH (as stated with each experiment), except for this one: free films (FFs) from different dried formulation (EPO-FF, HPMC-FF and MCT – 20%_4 : 1 : 1-FF) have been investigated at 33 % RH, 65 % RH, 75 % RH, 85 % RH and 100 % RH and the WVP-value for each moisture condition plotted against the corresponding

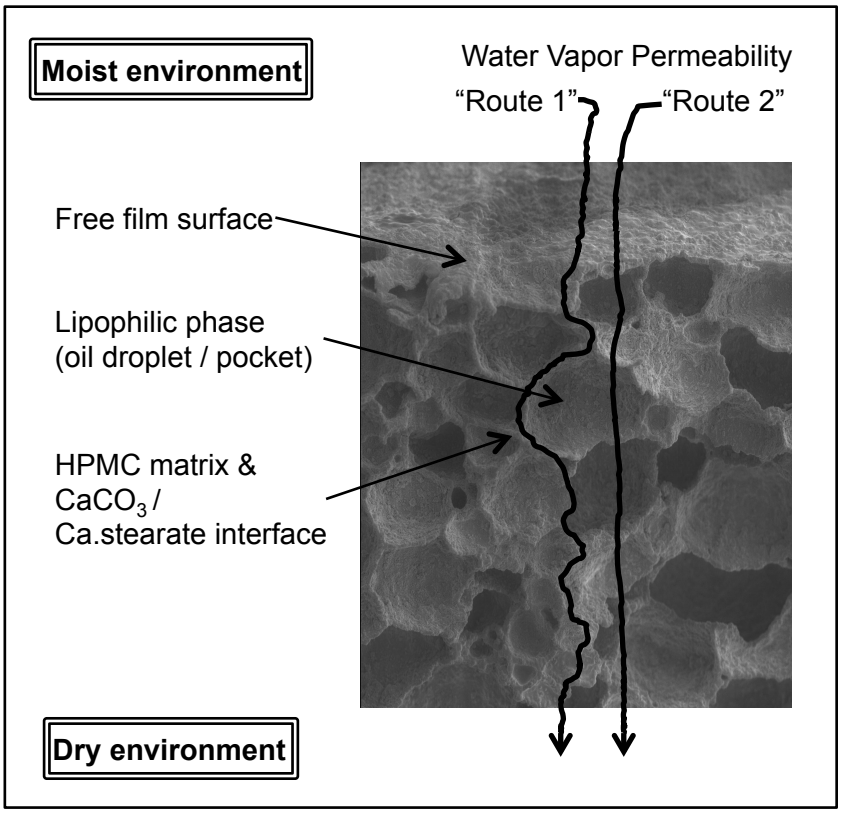


Figure 4.18: Possible WVP Routes through PE$^+$-FF. Cross-sectional cut for exemplary PE$^+$-FF.

relative humidity value (Figure 4.19). Figure 4.19 shows the following: for all dried formulations (FF: EPO, HPMC, MCT − 20%_4 : 1 : 1) increasing the moisture conditions results in an over-proportional increase in WVP-value. This finding can be explained by the following: the dried formulations contain water-soluble substances (e.g. HPMC) that are capable of swelling and thus at high moisture levels absorb moisture disproportionately. This phenomenon leads to more permeable free films and thus permeability is increased exponentially at higher % RH. In literature it is often described how water acts as a plasticizer for HPMC polymeric films, contributing to its increased flexibility and, consequently, permeability [65, 12, 13]. This finding supports the above-mentioned statements.

Comparing the findings for each formulation, the following is shown: at all relative humidity levels, WVP is highest for HPMC-FF and lowest for EPO-FF. This finding as such proves that the moisture protective ability (MPA) of the dried emulsions is not solely attributable to the HPMC matrix; the immobilized lipid droplets contribute to the effect positively. Had the MPA of dried PE^+ been solely attributable to the HPMC polymer, then PE^+-FFs permeability would have been expected to be almost equal to HPMC-FFs one. In a later experiment (Section 4.1.2.2.5), dried formulations are further investigated, in order to examine their own interaction with moisture regardless of their permeability and to further examine the previous hypothesis.

WVP of Different Formulation Ratios on WVP In Section 4.1.1.3.2 (Figure 4.8) it has been discussed that different emulsion ratios are selected for further investigation. This experiment examines the effect of different emulsion ratios on WVP for formulations consisting of MCT as the lipid. Figure 4.20 shows that WVP of both tested emulsion ratios are in the range of the propotype emulsion (MCT − 20%_4 : 1 : 1). The different ratios of Lipid to $CaCO_3$ to HPMC does obviously not affect WVP. Please note, due to lack of material, not all emulsion ratios could have been independently produced more than twice.

Effect of Different Lipophilic Phases on WVP Previous findings have shown the effect of different formulation variation for emulsions containing MCT as the lipid phase. In this coming experiment, the effect of different lipids on WVP is investigated and the results benchmarked to EPO-FF and HPMC-FF: please note that WVP-value results for all, EPO-, HPMC- and MCT − 20%_4 : 1 : 1 free films have been previously shown in Figure 4.19 when stored at 75 % RH, amongst others.

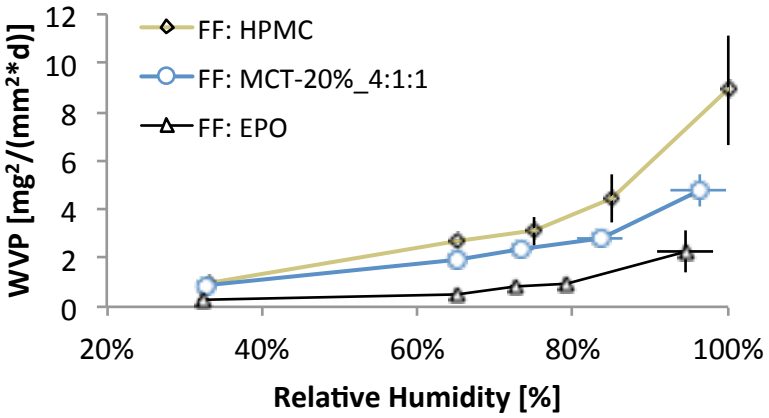


Figure 4.19: WVP vs. Relative Humidity. Result: Average WVP of at least 2 experiments with 3 vials for each sample type per experiment (n=2 experiments for HPMC trials and for EPO; n≥3 experiments for MCT − 20%_4 : 1 : 1) - after 72 hours of storage at the different denoted % RH conditions (x-axis). Error bars: standard deviation for n≥3 or span for n=2 experiments. Investigated sample types: MCT − 20%_4 : 1 : 1: results from 2 independent formulations; EPO and HPMC: each results from 1 independent formulation. Note: results for EPO- and HPMC-FFs previously shown in Figure 4.15.

In this following investigate, formulations produced independently were investigated as follows.

Before presenting the results, please note that –due to lack of $CaCO_3$ – not all formulations were produced at least three times independently, and hence no statistical test was made here. Yet, the trend among the various formulations shows the following: Figure 4.21 shows that WVP is a function of the formulation. Looking first at both marketed products, EPO-FF and HPMC-FF, have rather low and very high WVP, respectively. HPMC is a water-soluble polymer and thus is highly permeable to water vapor. Eudragit EPO consists mainly of the hydrophobic methacrylate copolymer, which is based on dimethylaminoethyl, butyl, and methyl remainders.

Focusing on PE^+-FFs only, it is noticeable that WVP is a function of the lipid in the formulation. In general, WVP of different formulations can be as high as HPMC-FF and as low as EPO-FF. The highest WVP is for emulsions containing IPM as the lipid, and decreases in the order IPM > MCT > CO > SFO > PPL > PSL. Comparing the trend of WVP with the polarity trend in Section 4.1.1 (Figure 4.1 and Figure 4.2), the following is noticeable: most formulations have WVP-values that go in line with their polarity trend; both paraffins (PPL and PSL) have the lowest polarity

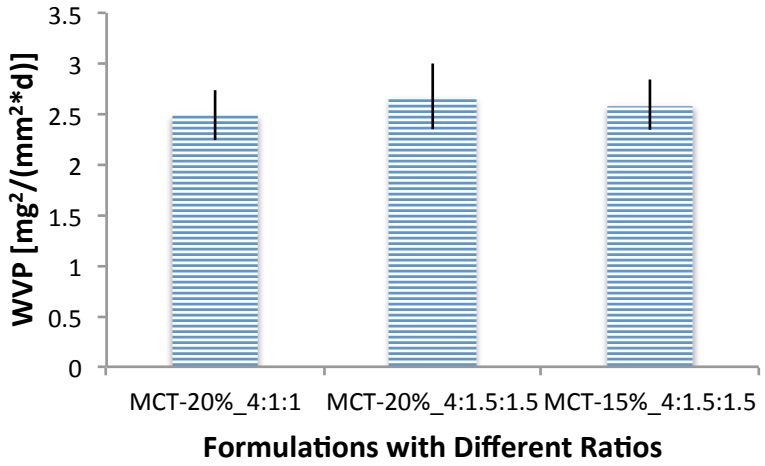


Figure 4.20: WVP Dependence on PE$^+$-Ratio. Result: average WVP-value of "n" independently produced emulsions (sample types) from several experiments, each including at least 3 vials per sample type per experiment – after 72 hours of storage. Note: each "n" is one independently produced emulsion that may be included in several independent experiments for WVP. Quantity of independently produced sample types (FFs) used for the experiments: n=8 from 10 independent experiments for $MCT-20\%\_4:1:1$; n=2 from 2 independent experiments for each, $MCT-15\%\_4:1:1$ and $MCT-15\%\_4:1.5:1.5$. Samples are free films of the denoted formulation code. Conditions: 75 % RH. Error bars: standard deviation for n$\geq$3; span for n=2.

and their formulations show the lowest WVP; SFO has an intermediate polarity and SFO-FF shows an intermediate WVP; MCT has a relatively high polarity and its formulation shows a relatively high WVP.

However, two formulations do not match the orders: CO has the highest polarity of all lipids, whereas CO-FF has an intermediate WVP. Similarly, IPM has an intermediate polarity, but its dried formulation (IPM-FF) has the highest WVP, one that is comparable to HPMC-FF. This switch in trends between polarity of lipids and WVP for CO-FF and IPM-FF indicates that WVP does not solely depend on the polarity; not all high polarity lipids result in high WVP free films. A possible explanation to this finding lies in the viscosity factor of the lipids. According to Equation 4.8, the diffusivity of a substance is inversely proportional to the viscosity of the medium. Applying that to this experiment, water vapor diffuses through the free films, which contain different lipids of different polarities and viscosities (Equation 4.4). A permeable substance (here lipid) having a high viscosity, leads to a low diffusivity of the permeant (here moisture) and thus decreases WVP according to Equation 4.8. The previous explanation is supported by the following: PSL and PPL (as crude lipids) have similar polarity values, but differ in their viscosities by a factor 5:1 (PSL:PPL). WVP of PSL-FF is approximately 30% lower than PPL-FF permeability; the value for PSL-FF does not even fall in the error margin of PPL-FFs, which suggests a significant difference among both groups. Had the viscosity no effect on WVP, then PSL- and PPL-FF would have been equal in their WVP-value. In short, it is suggested that the viscosity of the lipid also contributes to the overall water vapor permeation mechanism through PE^{+}-FFs.

An additional hypothesis is made at this stage: since WVP is a function of the lipid, then water vapor must be surely passing through it. Therefore, it is suggested that water vapor permeates through both, the HPMC matrix *and* the lipid. By that, Route 1 for WVP described above is unlikely and Route 2 is more probable (see above: "*Effect of Film Widths*" – Figure 4.18). In order to further investigate the previous two suggestions, the crude lipids are investigated for their WVP in the following experiment (see below: Section 4.1.2.2.3).

But before going on with further investigates and before the results for this experiment end, it is worth mentioning that WVP *itself* of the free films is determined and unleashed by *this* experiment; the WVP-value for free films ends here. All further experiments (from Section 4.1.2.2.3 until Section 4.1.2.2.5) are mainly performed to clarify the *mechanism* of WVP and to unleash the *factors* affecting it. The different factors are then collected and finally discussed in Section 4.1.2.2.6.

$$D = \frac{k_B \times T}{6\pi \times \eta \times r} \tag{4.8}$$

Einstein Stokes Equation

D = diffusivity
k_B = Boltzmann constant
T = absolute temperature
η = dynamic viscosity
r = particle radius

4.1.2.2.3 WVP Tests for the Lipophilic Phases - Lipid-Loaded PTFE Filters

As previously discussed, in this research WVP is tested for two sample types: in Section 4.1.2.2.2 it has been tested for different free films, in order to directly assess their moisture protective ability (MPA). In the second step (here), it is applied to inert carriers, namely PTFE-Filters (PTFE-F) loaded with different lipids, in order to asses the WVP-value for the crude lipids.

In order to follow the rationale of this experiment, two previous findings are shortly reviewed: in Section 4.1.2.1.3, dried PE^+ formulations have been found to compose an HPMC matrix backbone that immobilizes oil droplets in between. In Section 4.1.2.2.2, it has been found that WVP is (amongst others) a function of the physicochemical properties of the lipids. Together, the findings have led to the following hypotheses: water vapor is believed to diffuse through both, the HPMC matrix *and* the lipid droplets and both, lipid *polarity* and *viscosity* affect WVP. In order to validate both postulates, WVP through the *crude lipids* has been investigated by loading hydrophobic porous filters (PTFE) with different lipids. The loaded filters serve as the barrier membranes for WVP tests (Section 3.1.2.3.2). The main advantage of this experiment lies in the morphological resemblance to the free film model of the novel formulations: the filter material represents the HPMC matrix of the free films, and the lipid loaded pores are comparable to the lipid droplets of the dried emulsions. However, a hydrophobic material backbone is deliberately chosen to depict the hydrophilic HPMC matrix, assuming the former is completely water resistant; any moisture permeation is possible only through the pores of the filter, whether loaded or not. This isolates the effect of the lipids, excluding any additional effect of the HPMC matrix on WVP.

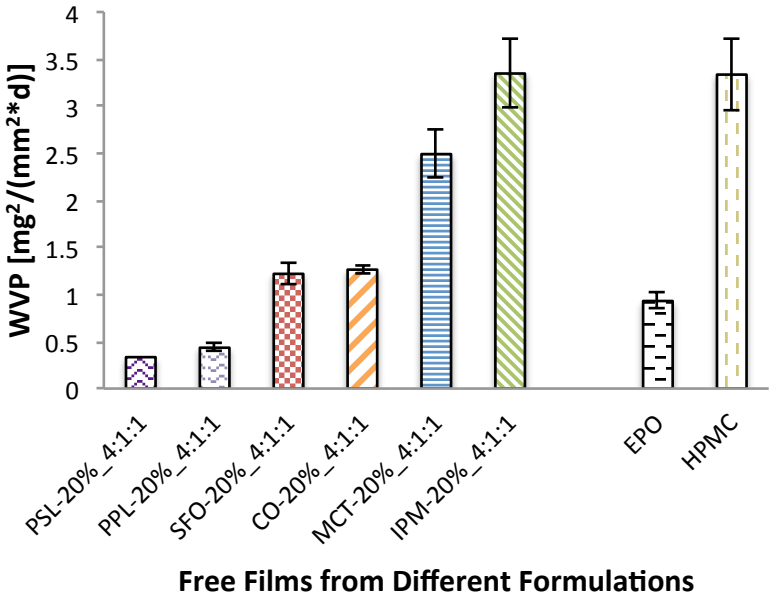


Figure 4.21: WVP Dependence on Lipids (for FFs). Results: average WVP-value of "n" independently produced emulsions or other formulations (sample types) from several experiments, each including at least 3 vials per sample type per experiment – after 72 hours of storage. Note: each "n" is one independently produced emulsion / formulation that may be included in several independent experiments for WVP. Not all experiments contain fresh formulations. Quantity of independently produced sample types (FFs) used for the experiments: n=8 from 10 independent experiments for $MCT-20\%\_4:1:1$; n=3 from 4 independent experiments for $PPL-20\%\_4:1:1$; n=1 from 1 experiment for $PSL-20\%\_4:1:1$; n=4 from 6 independent experiments for $SFO-20\%\_4:1:1$; n=2 from 2 independent experiments for $IPM-20\%\_4:1$; n=2 from 3 independent experiments for $CO-20\%\_4:1:1$; n = 4 from 4 independent experiments for EPO; n=2 from 3 independent experiments for HPMC. All sample types are free films of the denoted formulation code. Conditions: 75 % RH. Error bars: standard deviation for $n \geq 3$; span for n=2; no error bars for n=1.

The WVP-value for PTFE-F is calculated similarly to the calculations for FFs (Section 4.1.2.2.2). However, here MVTR for each sample is standardized to the volume of the lipid in the filter, rather than the weight of the free film (as in Equation 4.2). The volume is calculated via the density of the Lipid (Equation 4.9[9]).

$$WVP = \frac{MVTR}{(V_{lipid}/A)^{-1}} = \frac{MVTR \times V_{Lipid}}{A} \tag{4.9}$$

WVP-value Calculation (for PTFE-F)

WVP = water vapor permeability $[mg \times mm/d]$
$MVTR$ = moisture vapor transmission rate $[mg/d]$
V_{Lipid} = lipid volume $[mm^3]$
A = active surface area $[mm^2]$

Validation of Aptness of PTFE Filter Figure 4.22 plots the weight gain over time for vials covered with unloaded PTFE filters and compares it to vials without a barrier membrane. It shows that unloaded PTFE filters do not decrease moisture uptake by the activated silica gel. This finding sets a basis for the remaining experiments: any decrease in moisture uptake by loaded PTFE filters will not be attributable to the filter itself but rather to the loading. Hence, PTFE filters are suitable for this investigation.

Effect of different loading amounts on WVP Figure 4.23 depicts seven loading amount levels for PTFE filter loading by MCT. The figure shows the lipid loading amount dependence on the lipid-organic solvent (Lipid-OS) mixture loading amount: the more mixture of the Lipid-OS mixture added to the filter, the higher the loading of the filters. The latter is indirectly calculated from the weight gain of the PTFE filters before and after loading (Section 3.1.2.3.2). All filters with different loading amounts of MCT are investigated for their moisture permeation. Figure 4.24 shows an inversely proportional correlation between the weight gain and the loading quantity per filter. This finding is similar to the previously shown results for the free films (Figure 4.17); weight gain (and thus WVP) is inversely proportional to the MCT quantity per PTFE filter, which correlates directly with the loading amount. Hence, it suggests that water vapor diffuses through MCT.

[9]Equation 4.9 is equivalent to Equation 3.2.

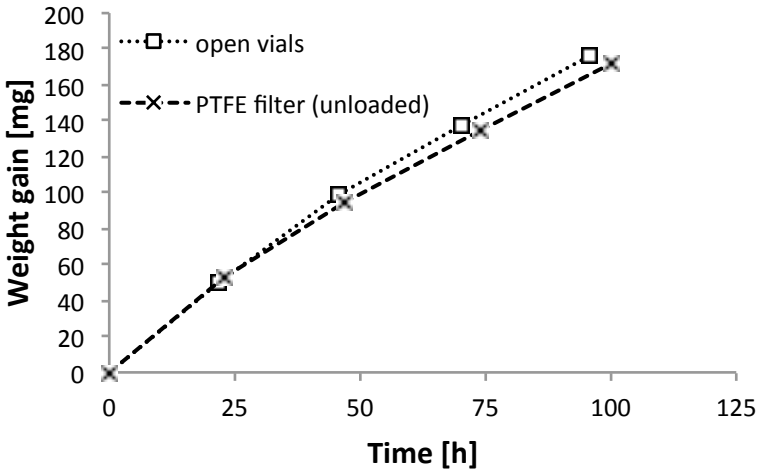


Figure 4.22: Weight gain vs. Time. Result: average weight gain of 3 vials (n=3) per sample type (presented for one exemplary experiment). Conditions: 75 % RH. Error bars: standard deviation. Investigated sample types: see legend.

On another note, this finding is also a proof for the capability of water vapor to diffuse through lipids, since WVP is a function of the lipid quantity per PTFE filter. Thereby, this finding further supports the hypothesis that WVP occurs via the lipid, and not only via the HPMC matrix.

This experiment has provided first results on the moisture protective ability of a crude lipid (here: MCT).

Effect of different % RH conditions on WVP This experiment investigates the effect of different humidity conditions on WVP through a crude lipid (here: MCT). For this purpose, PTFE filters have been almost equally loaded with an average loading amount of 18.2 mg MCT ±6 %.

Previously, it has been shown, that WVP of free films increases exponentially with increasing moisture conditions (Figure 4.19); Figure 4.25 shows a rather linear relationship between WVP of crude MCT and % RH. This finding can be explained by the following: as opposed to dried formulations (PE^{+}-FFs), MCT - as a crude oil - is not capable of swelling and thus, its permeability to water vapor does not increase exponentially at higher % RH conditions.

Effect of different Lipids on WVP The aim of this experiment is to examine the effect of crude lipids on WVP and to further compare the trend to the WVP trend of dried Pickering emulsions seen in Figure 4.21. Figure 4.26 (upper image) shows

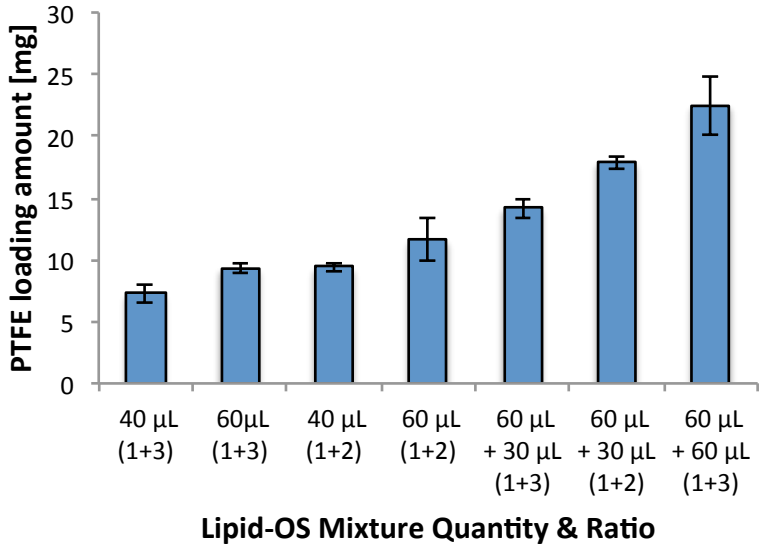


Figure 4.23: (explanation: see text). Result: Average loading amount of 3 PTFE filters (n=3). Error bars: standard deviation. Explanation of naming: e.g."$40\mu L$" means $40\mu L$ of the lipid-OS mixture are added to the PTFE Filter at once; further portions added to the PTFE Filter are denoted by a "+"sign, followed by the quantity; ratio of mixture components is presented in brackets (lipid + organic solvent).

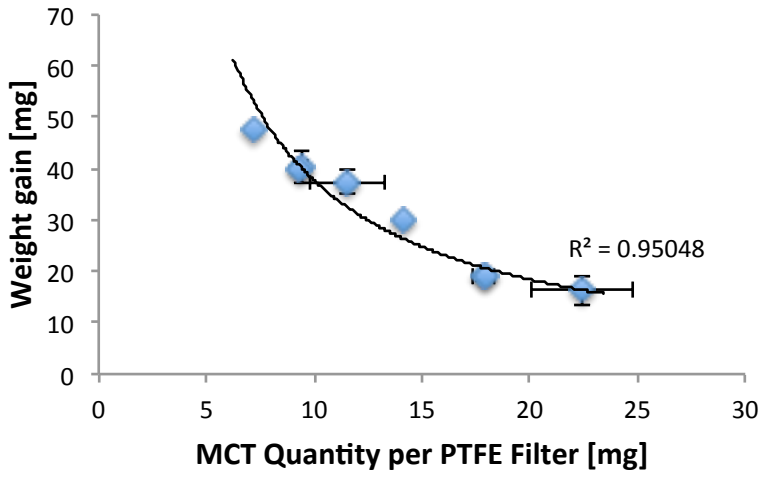


Figure 4.24: Weight Gain vs. MCT Loading Quantity. Result: Average weight gain of 3 independently loaded PTFE-Filters (n=3) for each category - after 72 hours. Conditions: 75 % RH. Error bars: standard deviation. Curve fit: polygon curse (power law). Loaded lipid: MCT. Categoization of x-axis: see Figure 4.23.

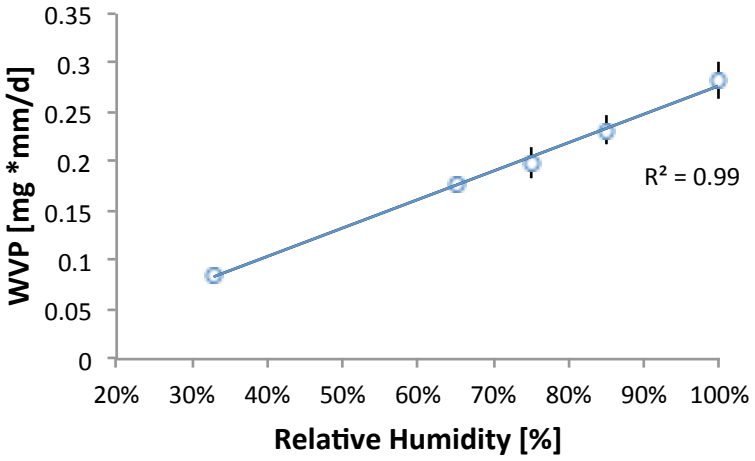


Figure 4.25: WVP vs. Relative Humidity. Result: Average WVP of 3 independently loaded PTFE-Filters (n=3) - after 72 hours of storage at the different denoted % RH conditions (x-axis). Loaded lipid: MCT.

the following: WVP of crude lipids is a function of the lipid and goes in the same order as previously shown for dried PE^+-FF: IPM > MCT > CO > SFO > PPL ≥ PSL (after 72 hours); all values vary significantly (p = 0.05), except PPL and PSL loaded PTFE filters: no significant difference between both groups. This latter fact is probably due to the low resolution of the experiment after 72 hours, as indicated by Figure 4.26 (lower image): it is shown that PPL and PSL differ greatly in their weight gain after more than just 72 hours, where the resolution shows better.

Coming back to the trend described above: the fact – that WVP of crude lipids is a function of the lipid – per se proves the previously mentioned hypothesis stated under Section 4.1.2.2.2 (see before: "Effect of different Lipids on WVP"): WVP is not only dependent on polarity, but also on viscosity of the lipids: high polarity CO does not show the highest WVP (because of its high viscosity), and IPM - being of intermediate polarity - shows the highest WVP (because of its low viscosity); PPL – being of lower viscosity but equal polarity when compared to PSL - shows higher weight gains (Figure 4.26 –lower image).

On further investigation of the mechanism governing water vapor permeation through the dried PE^+formulations and the crude lipids, dynamic vapor sorption (DVS) tests have been performed and their results are discussed next.

4.1.2.2.4 DVS Tests for Crude Material: $CaCO_3$ and Crude Lipids

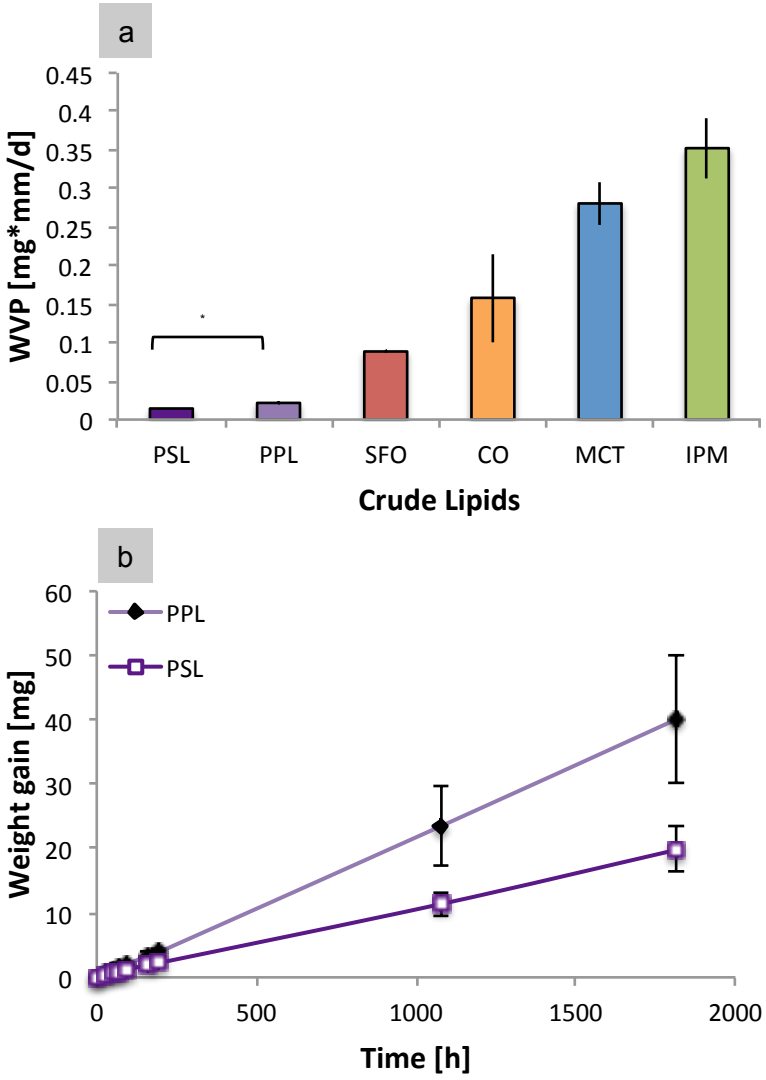


Figure 4.26: WVP Dependence on Crude Lipids. a: Result: average WVP of 3 independently loaded PTFE-Filters (n=3) for each sample type (lipid) at equal average lipid loading per PTFE-Filter (18.5 mg ± 1.1 mg) – after 72 hours. Conditions: 75 % RH; Error bars: standard deviation. Exact loading of each individual PTFE-Filter is considered in the calculation. Statistics: p = 0.05; ANOVA and Newmann-Keuls tests; Key: * no significant difference (remaining samples vary significantly). b: Result: average weight gain for PPL and PSL loaded PTFE-Filters only (n=3), after various durations. Conditions: 75 % RH; Error bars: standard deviation.

Similar to the WVP-tests, DVS-tests are performed for different sample types: first, crude materials (lipids and $CaCO_3$) are being examined by the DVS technique (this section). In the next section (Section 4.1.2.2.5), different free film formulations are investigated by the DVS-technique.

It is worth mentioning again, that the DVS-tests present information on the affinity of the samples to water vapor, reflected in the water vapor sorption (WVS) value. Hence, having both, the WVP-value (Section 4.1.2.2.2 or Section 4.1.2.2.3) and WVS-value of a sample, information on water vapors diffusivity through it can be concluded. Further details on the theoretical background and basics for calculation have been discussed in Chapter 1 and previously in this chapter (see Section 4.1.2.2 and under the different paragraphs in Section 4.1.2.2.1).

DVS for $CaCO_3$ Batch 1 $CaCO_3$[10] has been investigated by the DVS technique to assess its WVS-value. Because all investigated dried Pickering emulsions investigated by the DVS technology contain theoretically the same quantity of $CaCO_3$ in the free films (17% = 1/6), $CaCO_3$'s WVS-value does not account for any difference in the WVS-values among the free films.

The results show, compared to its equilibrium weight at 30 % RH, $CaCO_3$ shows an approximate increase by $0.35\% \pm 0.1\%, 0.52\% \pm 0.1\%$ and $0.89 \pm 0.2\%$ in weight at 70%, 80% and 90 % RH, respectively.

DVS for Crude Lipids The crude lipids have been examined for their equilibrium % weight gain at 70 % RH and their WVS-value calculated in comparison to their initial equilibrium weight at 30 % RH. The results are depicted in Figure 4.27. The figure shows that the lowest % weight gain (WVS-value) is for PSL and PPL, whereas the highest for CO. The trend of the WVS-values for the crude lipids goes in line with their polarities for almost all lipids (Figure 4.2): PSL and PPL < SFO $\leq$ IPM < MCT < CO. As for PPL and PSL, their absolute weight gains are lower than the detection limit of the balance in the DVS device and hence no statement is made with respect to a possible difference among both groups. Yet, their WVS-values are almost zero and hence their affinity to water vapor is equally small, explained by their very low polarity (see Section 4.1.1.1.1). The remaining values vary significantly among each other ($p = 0.05$), except SFO and IPM; no significant difference between those 2 groups is observed.

[10]For details on the various batches of $CaCO_3$ see 4.1.1.2.1.

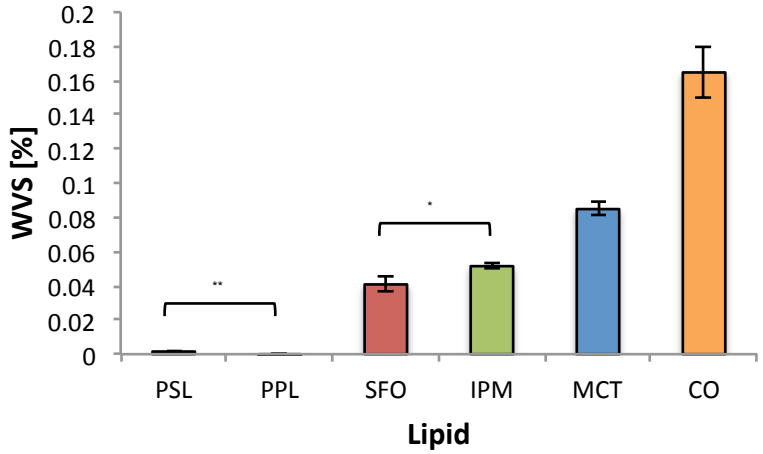


Figure 4.27: WVS Dependence on Crude Lipids. Result: average equilibrium WVS-value of 3 independent lipid samples (n=3). Conditions: 70% RH, constant temperature at 25 °C. Error bars: standard deviation. Statistics: p = 0.05; ANOVA and Newmann-Keuls tests; Key: * no significant difference; ** results below detection limit of device.

Coming back to the overall trend observed among the different lipids, this results goes in line with the expectation, since low polarity lipids are more likely to uptake less water vapor compared to high polarity ones and hence results in lower WVS-value (compare results to Figure 4.2).

4.1.2.2.5 DVS Tests for Free Films

As previously discussed, DVS-tests are performed for two sample types: in Section 4.1.2.2.4 it has been tested for different crude materials; in the second step (here), it is applied to different free films (PE^{+}-FF, HPMC-FF, EPO-FF). In both cases, the test is performed in order to assess the samples' affinity to water vapor.

Before going on with the results for the second sample type, it is worth mentioning that, - unlike in all previous experiments - in this experiment, results shown under this Section are from only *one* independently produced formulation for the lack of sufficient material ($CaCO_3$) (see Section 3.1.2.4.1). This surely makes the following statements less general and maybe even less reliable, but, yet, indicative enough to the overall understanding of the trend and mechanism governing WVP[11].

[11]Results for only one independently produced formulation are shown in Figure 4.28 and in Figure 4.29.

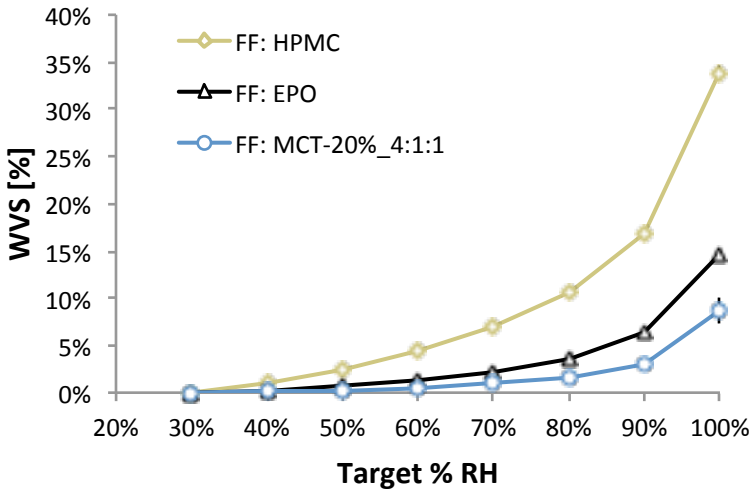


Figure 4.28: WVS vs. Relative Humidity (Sorption Isotherm). Results: average WVS-value of "n" independently run experiments, for only 1 independently produced and dried formulation of each sample type, each at various humidity conditions (x-axis). Number of experiments, "n": for $MCT-20\%\_4:1:1$-FF n=3; for EPO-FF and HPMC-FF n=2. Conditions: constant temperature at 25 °C. Error bars: standard deviation for n=3; span for n=2.

Now, coming back to the results and assuming the results are indicative enough, the following is shown: Figure 4.28 depicts the sorption isotherms for HPMC-, EPO- and $MCT-20\%\_4:1:1$-FF. The findings show an exponential behavior of the free films with increasing moisture levels. This finding supports the hypothesis previously mentioned under Section 4.1.2.2.2: free films of different formulations (e.g. dried Pickering emulsion) contain substances capable of swelling at high moisture levels. Thus, increasing the humidity level results in an overproportional increase in the WVS-value, as seen in Figure 4.28. Similar to the results discussed under Section 4.1.2.2.2, at higher % RH levels there is more water solubilized in the films (Henry's law); this water - usually in its free, unbound and thus "harmful" form - acts as a plasticizer to the polymeric film, thereby making it more flexible [38, 12]. It is obvious from Figure 4.28 that the same statement applies to HPMC- and EPO-FFs.

Furthermore, and still assuming the results are indicative enough (despite the fact that only *one* independently produced formulation per sample type has been investigated), the following is shown: the WVS-value of each dried formulation at 70 % RH (compared to its equilibrium weight at 30 % RH) is depicted in Figure 4.29. The figure shows that HPMC-FF has the highest % weight gain (WVS-value), followed by dried EPO formulations. All WVS-values for the dried Pickering emulsion

formulations are lower compared to EPO. Without considering previous findings, the results found here indicate that PE^+-FFs are of lower affinity to water vapor compared to EPO-FFs, which could be interpreted in favor of PE^+-FFs: lower affinity to water vapor is expected to result in lower permeability, according to Equation 4.4. However, considering the result trends shown in Figure 4.19 (where the *WVP*-values for the different free films is shown), it is obvious that the result trends of Figure 4.29 (*WVS*-values for the different free films) do not go in line with the former: the *WVP*-value for EPO-FF has been shown to be *lower* than the corresponding one for dried Pickering emulsion formulation $MCT - 20\%\_4 : 1 : 1$ at all moisture levels. Assuming that EPO-FF's values are reference values, then the question would be "why does PE^+-FFs have lower *WVS*-values, but higher *WVP*-values?". This switch in trends can be explained by the following: PE^+-FFs of e.g. $MCT - 20\%\_4 : 1 : 1$ contain approximately 67% MCT (= 4/6 of the film weight), 17% HPMC (=1/6th of the film weight) and 1/6th $CaCO_3$. The low amount of water vapor dissolving into the free film arises probably from the relatively low and almost only contributing component capable of interacting with water vapor, namely HPMC; $CaCO_3$ quantity in the free films is almost only 16% and can gain in weight up to a maximum of 1% of its own weight; weight gain effects from lipids - which comprise the major component of dry films - are also almost negligible (as seen in Figure 4.27). Consequently, as just mentioned, it is almost only HPMC that contributes to the *WVS*-value of PE^+-FFs - its quantity is relatively low and hence the low WVS-value of all PE^+-FFs. But the *WVP*-value of $MCT - 20\%\_4 : 1 : 1$ is higher than EPO-FFs and that is obviously because the HPMC greatly contributes to *WVP*, especially at high moisture levels (as shown in Figure 4.19 and Figure 4.28). Bley et al. describe a similar behavior [12]. Furthermore, according to Equation 4.4, the diffusivity of water vapor in the free films must surely be playing a role, as well, and is likely higher in PE^+-FFs compared to EPO-FFs. In short, the *WVS*-value of e.g. $MCT - 20\%\_4 : 1 : 1$ is mainly affected by the high lipid quantity, which results in low water vapor uptake, whereas its *WVP* is mostly affected by the HPMC component, which is even more permeable at higher % RH levels and by the consequent diffusivity. At last, this finding supports a statement mentioned in Chapter 1 (under Section 1.3.2.4): barrier membranes having a high water capacity (moisture solubility) do not necessarily have the highest permeability to water vapor. Therefore, for MPA assessment of formulations, different results from different experiments contribute to the overall picture in a puzzle-like manner.

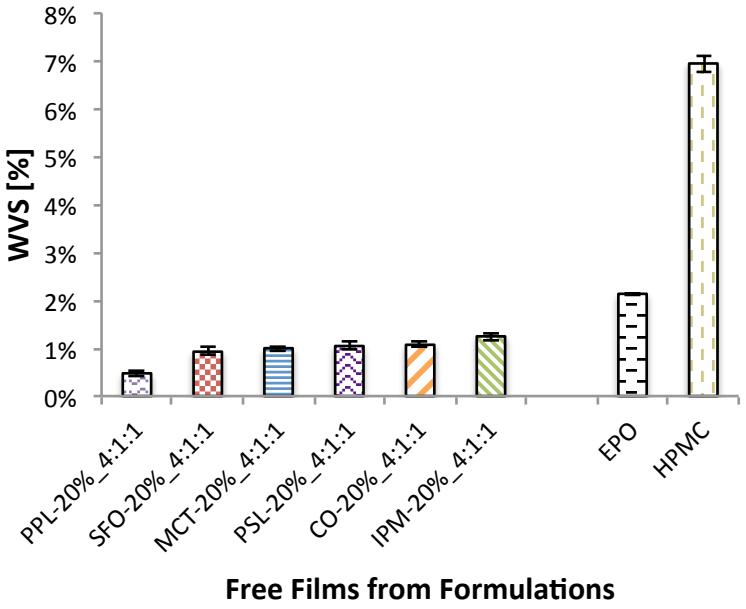


Figure 4.29: WVS-values for different Dried Formulations. Results: average WVS-value (at equilibrium moisture) of "n" independently run experiments, for only 1 independently produced and dried formulation sample. Number of experiments, n: n = 3 for all PE^{+}-FFs; n=2 for EPO- and HPMC-FF. Conditions: 70 % RH; constant temperature at 25 °C. Error bars: standard deviation for n=3; span for n=2.

In fact, the previous paragraph on the possible explanation to the trend flip between EPO-FFs and PE^+-FFs in terms of WVS- and WVP-values could also be interpreted from a different perspective, as follows: Figure 4.30 shows the "Expected" WVS-values for PE^+-FFs versus the "Actual" ones; the term expected relies on the formulations' components ratio before drying, and once dried, it is assumed that the free films are completely dry (no more water available). So, all PE^+-FFs are assumed to contain exact and equal quantities of each component (2/3rd lipid, 1/6th HPMC, 1/6th $CaCO_3$) and from the WVS-value of HPMC, of $CaCO_3$ and of each lipid (presented above in Section 4.1.2.2.4) the expected WVS-value is calculated for conditions applying at 70 % RH [12]. This calculation is not very accurate, since it uses for each component its average weight gains; however, it serves as a good estimate for the expected WVS-values of PE^+-FFs. The results show that all PE^+-FFs absorb less or equal water vapor (lower WVS-value) than expected by calculation. This per se raises attention to two aspects: first, the previous explanation to the trend flip between EPO-FFs and PE^+-FFs in terms of WVS- and WVP-values could be inaccurate, and in that case, the difference between EPO-FFs' and PE^+-FFs' WVS-values becomes smaller; hence the interpretation may differ. Second and more importantly, the findings of Figure 4.30 indicate that a further factor contributes to the abovementioned results of PE^+-FFs. For that purpose, a closer look is taken on PE^+-FFs' actual WVS-values only, as depicted in Figure 4.31.

Now the focus on the WVS-values among the 6 different PE^+-FFs is made: their WVS-values have been shown in Figures IV-29 and 30, but for better visualization Figure 4.31 focuses on the trend of WVS-values among the dried Pickering emulsion formulations only. Before the results are presented and discussed, it is worth mentioning that no statistical test has been performed here as all results arise from only 1 independently formed emulsion. Now therefore, the results can be interpreted by two different approaches, depending on the reliability of the results. The first approach considers the samples mostly belonging to 3 populations only: without performing statistical tests, it is obvious that SFO-, MCT-, PSL- and CO-FFs have almost equal WVS-values and thus belong to the middle population; PPL-FFs have the lowest WVS-values, and IPM-FFs having the highest WVS-values. Assuming this is true

[12] Exemplary calculation of "Expected" WVS Value for $MCT-20\%\_4:1:1$: e.g. at 70 % RH, HPMC and $CaCO_3$ gain an average of 8% and 0.35% in weight, respectively; MCT for example gains 0.1% in weight when exposed to 70 % RH; assuming a free film weight of 7.5 mg (composed of 2/3rd lipid = 5 mg; 1/6th HPMC and 1/6th $CaCO_3$ = 1.25 mg, each), then the final weight of the film sample after exposure to humidity is calculated to be 7.59 mg, equivalent to 1.27% weight gain.

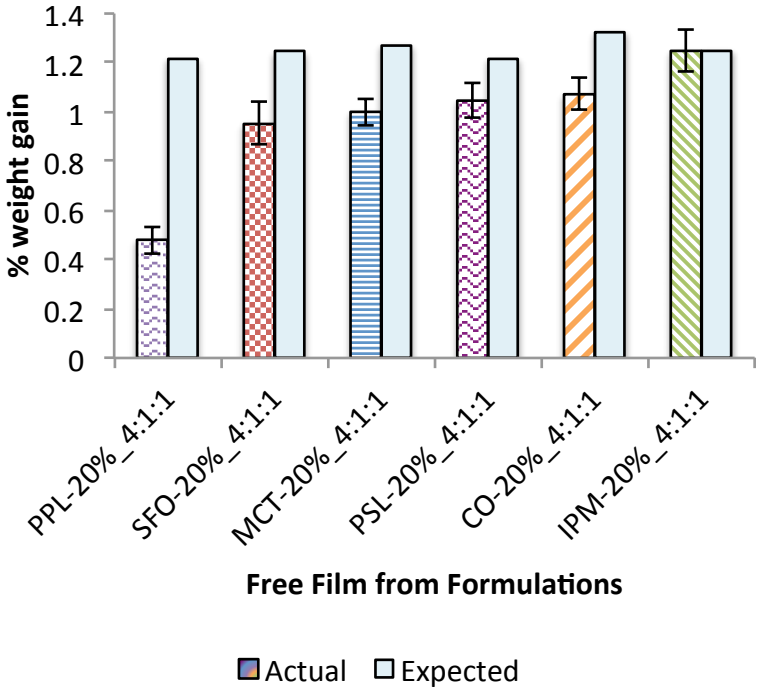


Figure 4.30: Actual vs. Expected WVS-values for PE^{+}-FFs. For "Actual" results: see caption under Figure 4.29; for "Expected" results: calculation explained in text.

and significantly valid, the question would be about the lack of significant variation among the samples of the middle population, unlike seen for previous experiments. The answer would lie in the equal composition of all PE^+-FFs: 1/3rd of all dried PE^+-FFs is HPMC, which contributes most to their WVS-value, whereas the only variable component among the free films is the lipid; the latter has a very low contribution to the WVS-value (because all lipids absorb very little water vapor, maximum 0.18% of their own weight, as seen in Figure 4.27). Hence, WVS-values of PE^+-FFs is mainly attributable to the HPMC component and hence no major difference is observed for the WVS-values.

The second approach assumes a statistical test would result in a significant difference among the samples; in that case, WVS-values for the PE^+-FFs is a function of the lipid component, where lipid water vapor uptake significantly contributes to the overall WVS-value of each PE^+-FF. WVS-value order is then PPL < SFO < MCT < PSL < CO < IPM.

Now regardless of the statistics and the two approaches presented above, both approaches to results' explanation go in line with the following findings: Comparing this trend with the trend for *polarity* and WVS-values of the *crude lipids* (Figure 4.2 and Figure 4.27, respectively), a mismatch is obvious, unexpectedly. Previously, it has been shown that the *polarity* and WVS-values of the *crude lipids* follow almost the same trend (Section 4.1.2.2.4); high polarity lipids (e.g. CO, MCT) have the highest WVS-values and low polarity lipids (e.g. PSL, PPL) have the lowest WVS-value (Figure 4.2 and Figure 4.27). The WVS-values for PE^+-FFs have been expected to follow the same trend of both, since the WVS-value is an equilibrium value, mostly being a function of the affinity of any sample to water vapor. Yet, there is a mismatch being observed, mainly for three formulations: first, PE^+-FFs containing IPM as their lipid have the highest WVS-value, whereas IPM's polarity is rather intermediate (Figure 4.2). Second, PE^+-FFs containing CO as their lipid have the second highest WVS-value (2nd approach) or belongs to the intermediate population (1st approach), whereas CO's polarity is highest among the lipids. Last, PE^+-FFs containing PSL as their lipid have the third highest WVS-value (2nd approach) or belongs to the intermediate population (1st approach), whereas PSL's polarity is lowest among all lipids (Figure 4.2).

Hence, a third factor aside polarity and viscosity is suggested to affect the trend of the WVS-value results for PE^+-FFs. It is believed that the *lipid holding ability* by the free films plays a role in the overall results. For that purpose, a closer look to a previously mentioned result is made: under Section 4.1.2.1, it has been mentioned

that some dried Pickering emulsions are more greasy than others (Section 4.1.2.1.2). Now at this stage of the discussion this phenomenon is believed to affect WVP- and WVS values as follows: greasy PE^+-FFs are a result of lipid escape from the dried formulation, a phenomenon described by Garcia et. al [25]. It is believed that some lipid droplets make it to the surface of the film and thus leave some empty pockets behind. This greasiness could not be quantified, but it was observed most for PE^+-FFs containing CO and PSL as their lipids. The commonality between both lipids is their high viscosity, which might lead to a difficult emulsification process while producing highly viscous lipids have been observed to result in emulsions with bigger droplet sizes compared to less viscous ones (Section 4.1.1.3.2). The former might cause a certain kind of instability in the dried state, one that has not been studied in the context of this research. In addition to PSL and CO containing PE^+-FFs, greasy ones have been also observed for PE^+-FFs containing IPM as their lipid, which is the least viscous lipid in this research. But the effect here is different compared to PSL and CO emulsions; IPM's very low viscosity might exacerbate its migration from the inner FF position to the surface. Yet, the greasiness of PE^+-FFs containing IPM as their lipid has been moderate compared to the previous two formulations. In short, the PE^+-FFs containing CO, PSL or IPM as their lipids are the ones showing a mismatch in the WVS-value trend compared to the WVS-value trend of the crude lipids and their polarities and the reason to that is believed to be correlated to as so-called lipid holding capacity of the dried formulation; the reasons behind the low lipid holding capacity of PE^+-FFs containing CO and PSL is most likely related to their high viscosity, and the rather low viscosity of IPM is believed to result in a similar phenomenon.

Now the question is "how exactly is lipid migration and consequent greasiness affecting WVS-values? And how would lipid migration even affect the previously shown WVP-values of PE^+-FFs?". In general, lipid escape and consequent greasiness are believed to affect WVP- and WVS-values for PE^+-FFs as follows: WVP-value of PE^+-FFs is expected to be decreased for greasy free films (CO-FFs, PSL-FFs, IPM-FFs), because the existence of a lipid film (as a result of lipid migration) on the upper surface may reduce moisture interaction with the free film (please note: water vapor interaction and consequent permeability through the free film may only occur from the upper side, as seen in Figure 3.6). However, WVP includes also the effect of lipid viscosity, which complicates data evaluation. The additive effect of all parameters contributing to WVP will be presented in Section 4.1.2.2.6. Focusing on lipid migrations effect on WVS-value, the latter is oppositely affected by greasiness;

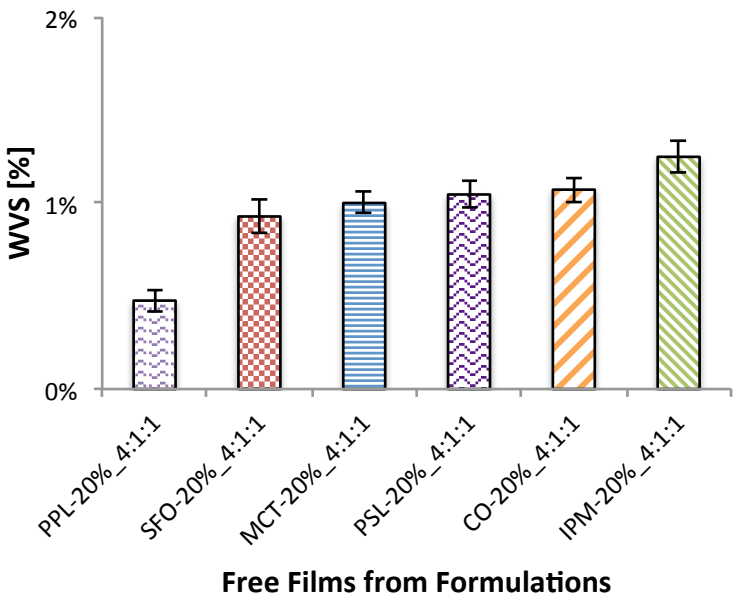


Figure 4.31: WVS Dependence on PE$^+$-FFs with different lipids. Results: Average WVS-value (at equilibrium moisture) of 3 experimental runs for only 1 independently produced and dried formulation sample. Conditions: 70 % RH; constant temperature at 25 °C. Error bars: standard deviation for n=3. (Note: in this experiment only, n = number of independent experimental runs, where all runs were made for only 1 independent formulation due to lack of material). Results are previously shown in Figure 4.29 and in Figure 4.30.

since moisture reaches the samples in the DVS device from both sides, so a greasy upper surface is not enough to reduce moisture interaction with the free film. The upper surface might have reduced ability to interact with moisture, which would eventually lead to a false reduced WVS-value, but the lower surface counteracts that effect; the latter consists mainly of an HPMC matrix with less lipid available (due to the escape phenomenon) and thus, moisture is expected to interact with the film more easily. Applying the previous concept to the three mismatched formulations, the following is obvious: dried formulations consisting of SFO, MCT or PPL have WVS-values that go in line with the expectation, where their polarity is reflected in the WVS-value trend. Their viscosities are in a moderate range (SFO > MCT > PPL) and their free films show the least greasiness. In turn, oil escape is not distinctive, and thus moisture-to-FF interaction is undisturbed by surface lipids. On the other hand, dried formulations containing IPM, CO or PSL show a moderate to high greasiness resulting from lipid escape. Lipid escape to the upper surface renders the lower part of the free film with a higher HPMC ratio than initially present, leading to higher moisture-to-FF interaction, which shows in unexpected higher WVS-values for the FFs of those formulations. The effect of the above-mentioned lipid-escape on the WVP-value of all dried formulation in discussed in the next sub-section (Section 4.1.2.2.6).

One last aspect is mentioned here for the sake of completion: lipid escape is expected to contribute to the lower actual WVS-value compared to the expected one (Figure 4.30). In other words, the observed mismatch between polarity and WVS-values for crude lipids on the one hand and PE^+-FFs' WVS-value on the other (described above) may be also caused by lipid migration. Yet, the results, do not necessarily go in line with each other: if the just mentioned correlation is solely true, then "Expected" versus "Actual" WVS-values for PE^+-FFs would have been largest for the most greasy films, namely PE^+-FFs containing PSL, CO and IPM as their lipid phase. Figure 4.30, however, does not show this; the largest difference is for PE^+-FFs containing PPL as their lipid. Since the calculation behind the values shown in Figure 4.30 are obtained from average WVS-values for each component, no reliable statement can be made here.

4.1.2.2.6 Discussion: Factors Affecting WVP

In this sub-section, the factors affecting WVP of novel film-forming Pickering emulsions (PE^+) are summarized and discussed. This paragraph does not provide

new results, but rather integrates results from Sections 4.1.1 and 4.1.2 regarding WVP.

Figure 4.17 has shown an inversely proportional relationship between MVTR and film thickness, indicating the homogeneity of the film along its own thickness, independent of the film thickness. Since this is valid and assuming the film is pore-free and hence water vapor permeability takes place by *diffusion*, then equation Equation 4.4 applies to WVP through PE^+-FFs. As discussed in Chapter 1, permeability, P is a function of both, diffusivity and solubility of the permeate through the membrane (Equation 4.4). WVS-value and WVP-value empirically obtained throughout this doctoral research correlate with the permeability, P and solubility, S, respectively. Hence, having information on both parameters enables concluding information regarding the diffusivit, D, of the membrane. Furthermore, the polarity and viscosity results of the crude lipids (discussed under Section 4.1.1.1.1) present information on the membrane's solubility, S, and diffusivity, D, respectively. It is worth mentioning again that the viscosity of a substance is linked to its diffusivity, D, according to Equation 4.8. All the previous parameters together with some results of the different investigates from Sections 4.1.1 and 4.1.2 contribute in a puzzle like structure to the clarification process of the routes of WVP, the mechanism governing it and the factors affecting it.

Routes of WVP The inner morphology of the dried PE^+ has been seen in Figure 4.13 and emulsion character has been found to be preserved in the dried state (PE^+-FFs) as discussed in Section 4.1.2.1.3. Water vapor is found to permeate through the individual lipid pockets and not only via the hydrophilic HPMC matrix. Those statements are supported by the following previously discussed results: in Figure 4.21, WVP has been found to be a function of the different lipids and in Figure 4.26 water vapor has been found to permeate through the crude lipids. Hence, WVP only though the hydrophilic matrix as described by Garcia [Garcia et al I have it!] is not correct.

WVP for One Model Lipid (Mechanism and Factors - Part a) Free films from formulations with three different emulsion components ratios have been investigated for their WVP. The latter has been found to be independent on the components ratios (Figure 4.20). MCT has been the model lipid. Hence, any of the different PE^+ formulations shown in Table 4.9 has been chosen according to the need, without risking an altered WVP.

WVP for Different Lipids (Mechanism and Factors - Part b) The factors affecting WVP are concluded from the comparison of the result trend from 6 different experiments. The experiments include: crude lipids viscosity and polarity (Section 4.1.1.1.1 including Figure 4.1 and Figure 4.2), WVP of PE^+-FFs (Figure 4.21) and of PTFE filters loaded with different lipids (Figure 4.26), DVS results for PE^+-FFs from different lipids (Figure 4.31) and for the different crude lipids (Figure 4.26). Figure 4.32 summarizes all the trends of all 6 experiments. Details on the results are presented and discussed under each paragraph. Here, only the interrelated results and their effect on WVP are highlighted as follows: At first, it is important to recognize that WVP is a function of the lipid. On further correlating all the results, three main effects are believed to contribute to that finding. The affinity of the lipid to water vapor is the first one, which correlates to the solubility term of Equation 4.4. The second factor is the viscosity of the lipid, which affects the diffusivity term of the same equation. The last factor is the lipid holding ability of the emulsion, which affects the morphology of the free films and the interaction of moisture with the film. The resulting WVP-values, WVS-values and hence moisture protective ability (MPA) of a dried formulation is an additive effect of all three factors.

Starting with formulations containing CO, the following is revealed: CO has the highest polarity of all lipids, and also the highest viscosity. Its high polarity results in a high affinity for moisture (high WVS-value), which per se favors a high permeability. However, its high viscosity results in a low diffusivity, which in turn favors a low permeability. The additive effect of both, results in an intermediate permeability (Figure 4.21). CO-FFs are greasy, indicating a low oil holding ability of the FF. The crude emulsion (PE_s) has already had big droplet sizes resulting from its high viscosity (Figure 4.9). Greasiness of the free films is believed to contribute to a reduced permeability (low WVP for CO-FF), but favors a higher moisture-to-FF interaction leading to relatively high WVS-values for the reasons mentioned under Section 4.1.2.2.5.

IPM has an intermediate polarity (favoring an intermediate permeability,) but the lowest viscosity. The additive effect of both factors results in a high permeability (Figure 4.21: WVP Dependence on Lipids (for FFs). In the hypothetical case of absolutely no greasiness, PE^+-FFs containing IPM as their lipid are expected to show an intermediate WVS-value, mainly due to the intermediate polarity (IPM-FFs are expected to uptake low amounts of water vapor and thus to have a lower DVS-value for its FFs). However, IPM-FFs show some greasiness, resulting in an increased WVS-value for reasons mentioned under Section 4.1.2.2.5. Furthermore, its very low

viscosity does not hinder moisture permeation to the film and thus supports moisture uptake by the film. One would expect now that IPM-FFs greasiness would reduce its WVP, because of a potentially reduced moisture-to-FF interaction on the greasy (upper) side. Yet, IPM-FFs slight greasiness is not a much compared to CO-FFs or PSL-FFs one; the lipid spots on the free film surface are likely insufficient to form a complete barrier. Besides, IPMs low viscosity enhances the diffusivity of moisture. Both reasons explain why the WVP of IPM free films is not affected by IPMs escape.

PSL has a low polarity and a high viscosity. Both factors favor a low permeability for the free films, which results in a low permeability, as seen in Figure 4.21. However, PSL-FFs WVS-value has been expected to be much lower (PSL being so hydrophobic does not uptake much water vapor; its FF is expected to behave similarly). However, the PSL escape for its FFs leaves the HPMC matrix without much lipids behind, which results in an increased moisture-to-FF interaction (from the lower side).

The remaining three lipids behave according to the expectations: MCT is a rather polar oil, has a relatively low viscosity and its FFs are not greasy. Hence, its affinity to water vapor is rather high, its diffusivity similarly high and its FFs hold MCT well. All three qualities favor a relatively high permeability. SFO and PPL are low polarity lipids, which favor low permeability. Their viscosities are relatively high, which also favors a low permeability. Their FFs are of low greasiness, which does not enhance moisture-to-FF interaction. The observed surface lipid (FF greasiness) for formulations containing MCT, SFO or PPL does not impede moisture-to-FF interaction on the upper surface, because the observed lipid escape is rather little.

Summarizing the previous results, the following can be concluded: lipids with a low polarity are generally favorable for low WVP. Lipids with too high or too low viscosities tend to form unstable dried Pickering emulsions; lipid escape is enhanced, leading to altered moisture-to-FF interaction. Figure 4.33 illustrates a prediction scheme for WVP based on the three factors described above and hence illustrates the risk of

4.1.2.3 Summary

Methods and results of Section 4.1 deal with all experiments and findings related to the Pickering emulsion formulation development and its water vapor permeability (WVP).

Horst et. al [32] have shown that $CaCO_3$ and stearic acid are suitable in stabilizing Pickering emulsions . In this doctoral thesis, the main aim has been to develop this formulation or a modification based on it, in order to obtain moisture protective

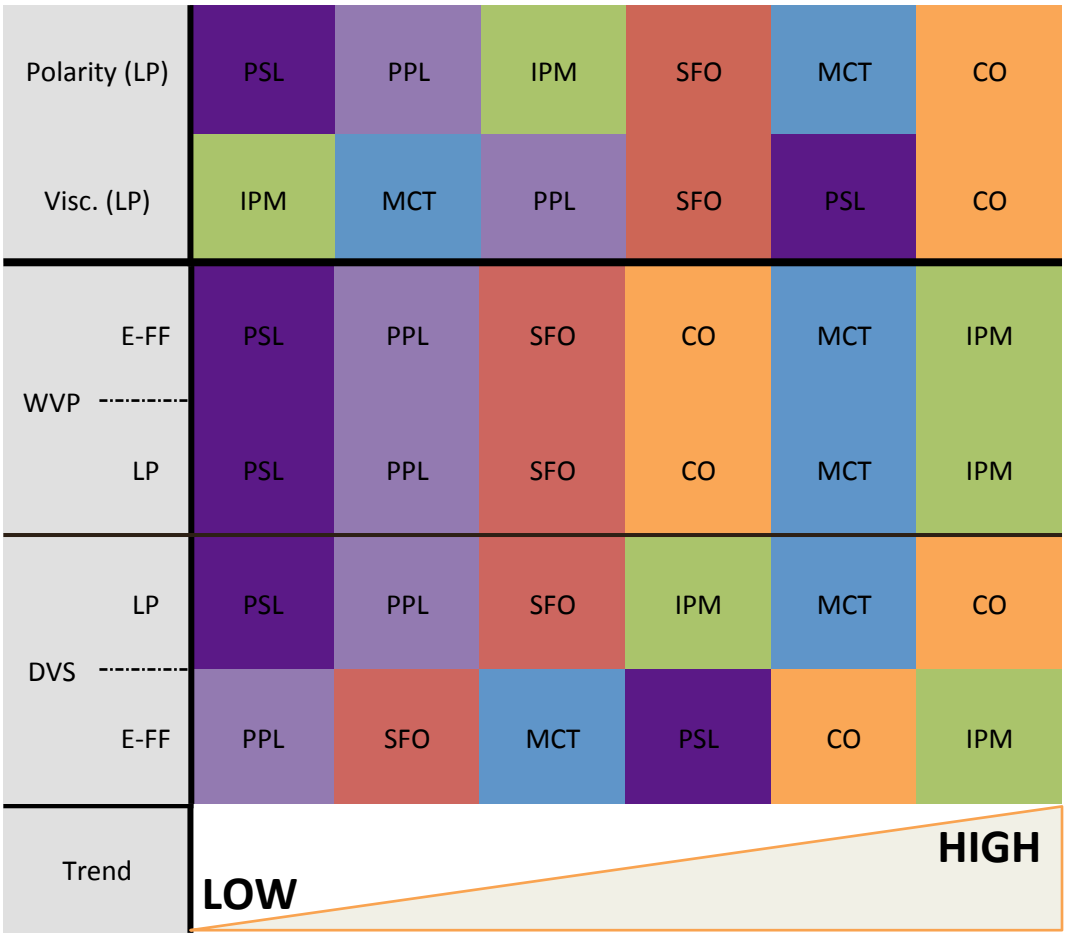


Figure 4.32: Moisture Protective Ability of PE^{+}-FFs containing different Lipids. Overview of Resulting Trend for each Experiment. Figure 4.29 is a collection of all trend (order) of LPs from 6 previously presented figures. Arbitrary scale

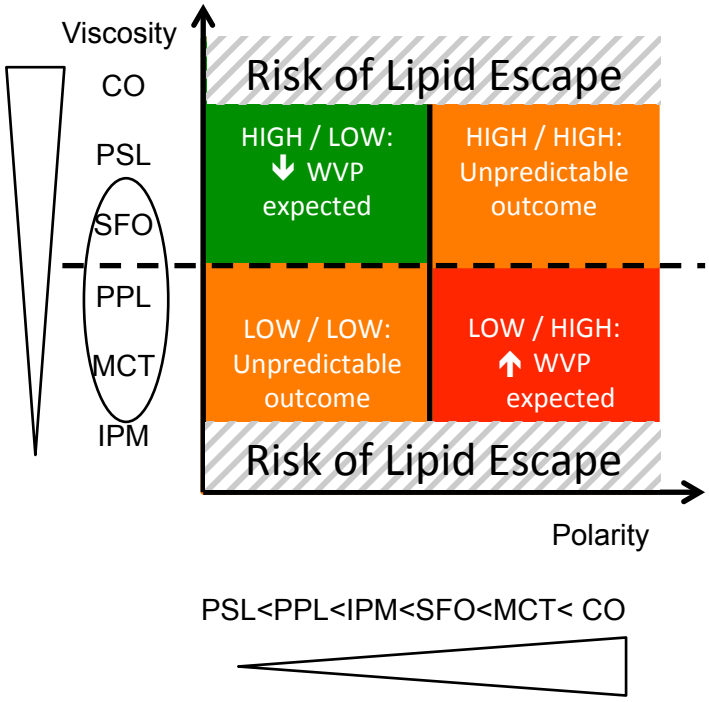


Figure 4.33: Risk Assessment. 2 × 2 Matrix Key: Green: high viscosity / low polarity = low WVP expected; Red: low viscosity / high polarity = high WVP expected; Orange: high/high or low/low viscosity and polarity = unpredictable outcome additive effect of polarity and viscosity. Risk definition: unexpected MPA for PE^+-FFs containing very high or very low viscosity lipids. The previous findings lead to the choice of film-forming Pickering emulsions containing SFO or MCT as a lipid for further investigation. MCT-PE^+ is chosen for the development of coating process parameters and SFO-PE^+ is chosen for coating of tablets as will be discussed in Section 4.3.

abilities (MPA). For that matter, some demands have been presented in Chapter 1 and in Section 4.1.1.2. Accordingly, from 3 different $CaCO_3$ types provided by the vendor, Batch 1 $CaCO_3$ has been found to be the only one stabilizing the emulsion. This $CaCO_3$ type has been used for the remaining emulsion formulations. In a further step, various emulsion ratios have been investigated to assess the suitable emulsion components ratios that give stable emulsions (Table 4.4). Promising ratios have been further investigated using different lipids as the inner phase. All PE^+ formulations containing either lipid give emulsions of the oil in water type. Drop size distribution (DSD) tests have been performed to assess various effects on emulsion reproducibility and stability. It has been shown that all PE^+ formulations can equally be produced by either an UltraTurrax or a LabMixer, resulting in formulations with different DSDs. The resulting DSD depends strongly on the lipid in use, its viscosity and polarity, as discussed under Section 4.1.1.3.2. The various formulations, including film-forming Pickering emulsions and other marketed products have been dried to form free films for further investigation (Section 4.1.2). Free films have been characterized for their film width and morphology; PE^+-FFs have been to be somewhat greasy, likely as a result of lipid migration. This latter phenomenon mentioned under Section 4.1.2.1.2 has been correlated with results under Section 4.1.2.2. Starting Section 4.1.2.2 various results from different experiments have been presented; all thos results are aiming to unleash the moisture protective ability (MPA) mainly of PE^+-FFs, and have served in benchmarking them to marketed products. The findings have shown that dried PE^+ formulations protect from moisture and that their MPA is a function of the lipid in use; lipid polarity, viscosity and film morphology contribute to the overall MPA. Details on the mechanism and its contributing factors are summarized under Section 4.1.2.2.6. Last but not least, it has been shown that dried PE^+-FFs are dried emulsions, preserving emulsion character in the dried state.

4.2 Results of Section 4.2: Tablets

In Results of Section 4.1, the results for the formulation development and moisture protective abilities of film-forming Pickering emulsion formulation have been presented and the different factors affecting each discussed. In order to assess the moisture protective ability of coated Pickering emulsions, the novel formulation is sprayed onto moisture sensitive cores and the latter subjected to stability tests (Section 4.3). For that purpose, hygroscopic tablets have been produced, and their aptness for moisture uptake investigated (Section 4.2). In other words, tablets have been produced as

a means to an end. Several demands on the tablets formulation have been considered and the formulation has been developed accordingly: the tablets are expected to be uniform in mass, mechanically stable to withstand further coating and to be moisture sensitive. The latter property is of highest priority for the above-mentioned reasons. Therefore, the formulation components shown in Table 3.8 have been chosen. Particularly Syloid AL 1 FP (SAF) has been chosen for its high water absorptive capacity and hygroscopicity [Ref. Grace]. SAF can be regarded as the moisture sensitive ingredient of the Syloid Tablets. Furthermore, Vivapur 112 has been chosen as a binder, since it is a pre-dried form of microcrystalline cellulose (MCC), which is considered to be more hygroscopic than a conventional MCC type. In the following, results for the production and characterization of three batches are presented (Section 4.2.1) and the cores tested for the extent of moisture uptake (Section 4.2.2).

4.2.1 Tablet Production (Section 4.2.1)

4.2.1.1 Tablet Production Results (For All Batches)

At first, the production results for all produced tablet batches (Batches 1-3) are shown (Section 4.2.1.1). Afterwards, an example shown below illustrates some detailed results of one batch and exemplifies the challenges of Syloid Tablet production (Section 4.2.1.2).

In the context of this doctoral research, all produced and examined tablets are manufactured over three individual tablet batches. The tablet batches are equal in composition and manufacturing steps, but differ slightly in their tablet characteristics. The average results of each parameter are presented in Figure 4.34 for each batch. The average compression force for each batch is determined from the compression forces for each sub-batch, as will be discussed in the example below. Therefore, the error bars in the figure are somewhat high.

Figure 4.34-a shows no significant difference between all three batches regarding the compression force, which in turn demonstrates the reproducibility of the production process ($p = 0.05$, ANOVA test). Tablets from all three batches are produced at approximately 13 kN, and weigh around 165 mg (Figure 4.34a, b). However, it is noticeable that the deviation for each batch is relatively high: the compression force varies in Batch 3 up to 22% (in Batch 1 and 2 it is almost 10%), which in turn directly affects tablet hardness (hardness deviation: 23 - 28%). This occurrence can be explained as follows: the unprocessed tablet components suffer from a very poor flowability, which could be visually observed; the crude (un-briquetted) powder

mix remains in the feeder with completely no flowability. This challenge has been circumvented by the briquetting process, which is believed to improve flowability by decreasing the tap volume of the tablet components and decrease the particle size distribution (Section 3.2.1.1). Thus, the Granules' flowability is improved enormously compared to the crude powder mix. However, they are manually mixed every couple of minutes to avoid segregation of the Granules in the feeder. Yet, Granules do not homogenously fill the tablet press dies, which in turn results in a relatively high variation among the tablets' weight, compression force and hardness. In spite of this variation, each tablet batch has been uniform in mass (Section 3.2.1.2.1) according to Ph.Eur 8.0. An example below illustrates the various results and measures obtained for the production of one batch. The example serves to illustrate the reasons behind the above-mentioned variation.

Please note that in the case of a statistically significant difference among the batches with respect to tablets' weight and / or hardness does not affect the results of the upcoming WVU-tests (see Section 4.2.2), since each single tablet sets its own reference regarding its weight gain or loss or dry conditions, respectively – details on that will be discussed later.

Uncoated Tablets' Disintegration From each tablet batch, Syloid tablets were tested for their disintegration time. Uncoated Syloid Tablets disintegrate within two minutes completely. Results for coated ones are shown in Section 4.3.1.3.3.

4.2.1.2 Example: Tablet Production Results For One Batch

The following subsection presents an example from Batch 3 Syloid Tablet production. Messfix vers. 2.3 March 1992 (Table 2.6) is the in-process control software that measures the compression force for each single tablet. After a definable time interval it calculates the average compression force for all measured tablets that have been produced within that specified time interval. The settings have been defined to obtain 15 measurements for the whole batch, dividing the latter into 15 sub-batches. Each of those sub-batches contains approximately 6 % of the total tablets of the whole batch (= 1/15). Figure 4.35-a plots the average compression forces (for each sub-batch) obtained throughout the whole process. From each sub-batch, 3 tablets have been chosen randomly, labeled and weighed individually. Furthermore, the exact same tablets have been tested for hardness. Thus, 45 tablets (= 15*3) have been assessed for mass uniformity (Figure 4.35-b), and hardness (Figure 4.35-c).

The results show the following: Figure 4.35-a shows a high fluctuation in the compression force throughout the whole production process. In spite of the briquetting step (III-2.1.1), the briquettes (Granules) suffer from poor flowability, which in turn shows in the high deviation among the tablets: poor flowability leads to unequal die filling, which directly affects the tablet weight. However, despite the variation in tablets weight, they are conforming to pharmacopeia demands (Figure 4.35-b). Correlating the weight of each tablet to its hardness (Figure 4.36), the following gets obvious: variation in tablet weight is the main cause of the variation in the remaining two parameters (compression force and tablet hardness). A high die filling amount results in a higher compressed tablet compared to a low die filling amount; in turn this directly shows in the hardness of the tablets. The figure shows that tablets having a higher weight are harder than lower weight ones. Hence, this finding proves the above-mentioned hypothesis regarding the poor flowability being the main cause of the tablets deviation. Figure 4.37 summarizes the above-mentioned statements.

The above-mentioned tests have been performed likewise for each of the three Syloid Tablet production batches, assuring that all sub-batches are in the range of pharmacopeia demands. Nevertheless, in this research, the tablets are mainly produced to serve as hygroscopic cores for coating. Therefore, it has been important to assure that the compression force and hardness deviations among the sub-batches show no significant effect on the moisture affinity of the produced tablets. For that purpose, tablets from different sub-batches (sub-batch 1: high compression force, sub-batch 8: intermediate compression force, sub-batch 10: low compression force) have been chosen and subjected to moisture uptake (Section 4.2.2). The findings are shown and discussed in details in Section 4.2.2.2. However, it is mentioned here beforehand that tablets from different sub-batches of varying compression and hardness show no significant difference in their water vapor uptake (WVU) (see Section 4.2.2.3). This result has been important to allow integrating all the sub-batches (of different average compression forces) into one batch.

As mentioned above, please note again that any statistically significant difference among the batches and / or sub-batches with respect to tablets' weight and / or hardness does not affect the results of the upcoming WVU-tests (see Section 4.2.2), since each single tablet sets its own reference regarding its weight gain or loss or dry conditions, respectively – details on that will be discussed later.

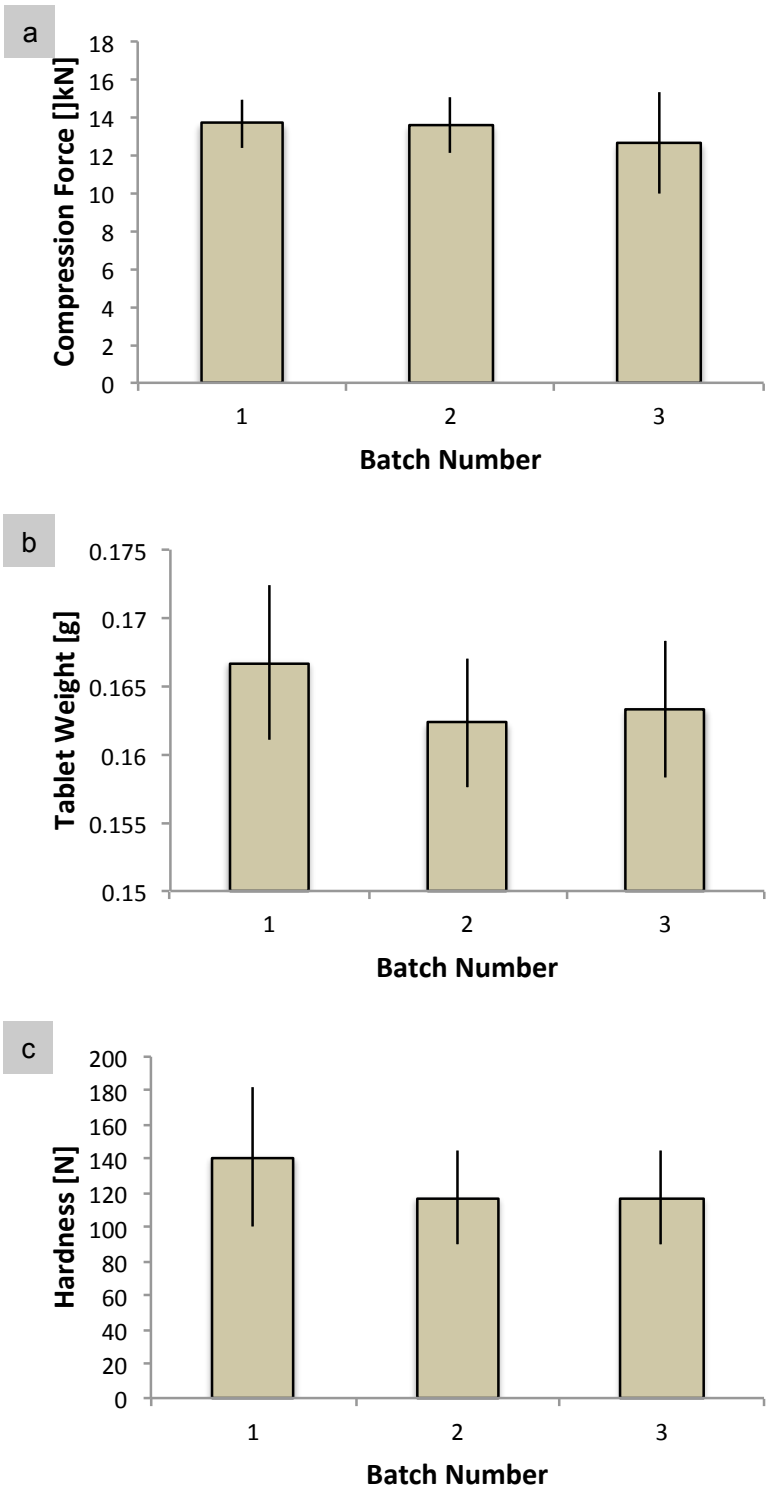


Figure 4.34: Average Compression Force, Weight and Hardness for each Tablet Batch. a: Average compression force; b- Average tablet weight, c- Average tablet hardness; average shown for each batch (n=3 independent batches). Error bars: standard deviation. Statistics for (a): $p = 0.05$, ANOVA.

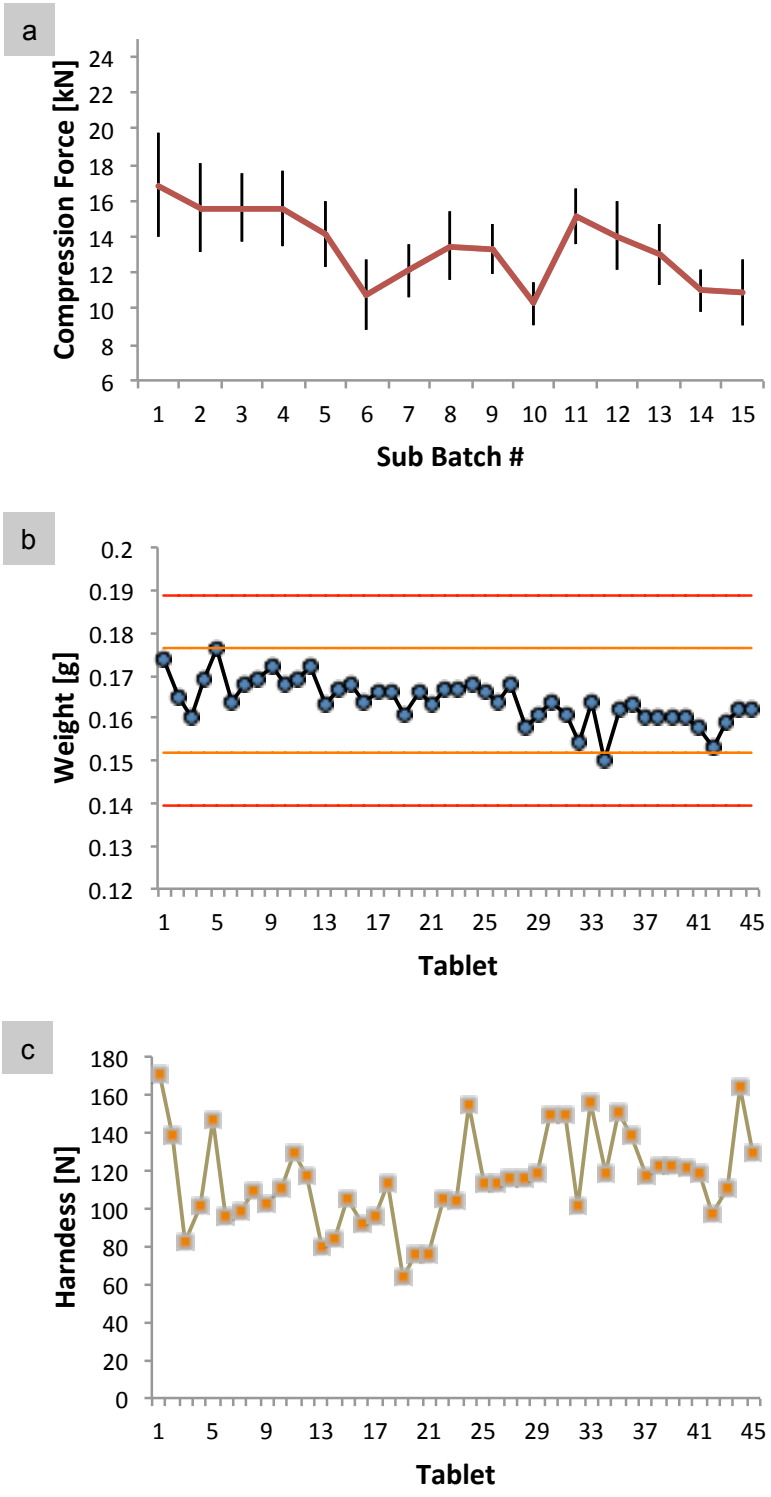


Figure 4.35: Exemplary Results for One Tablet Batch (Batch 3). In-Process Compression Force, Tablet Weight and Hardness. a: Average Compression force per sub-batch; b- Tablet weight with upper and lower limits according to Ph.Eur. 7.0 (±7.5% and ±15% from average tablet weight), c- Tablet hardness. Error bars shown in a): standard deviation.

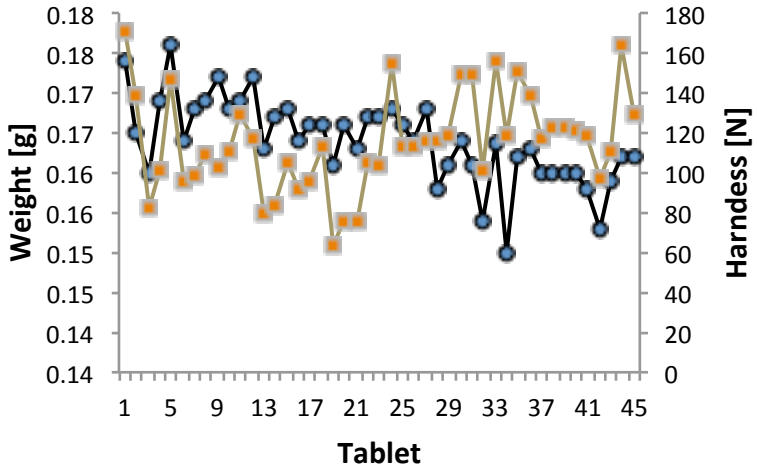


Figure 4.36: Tablet Weight and Tablet Hardness Correlation.

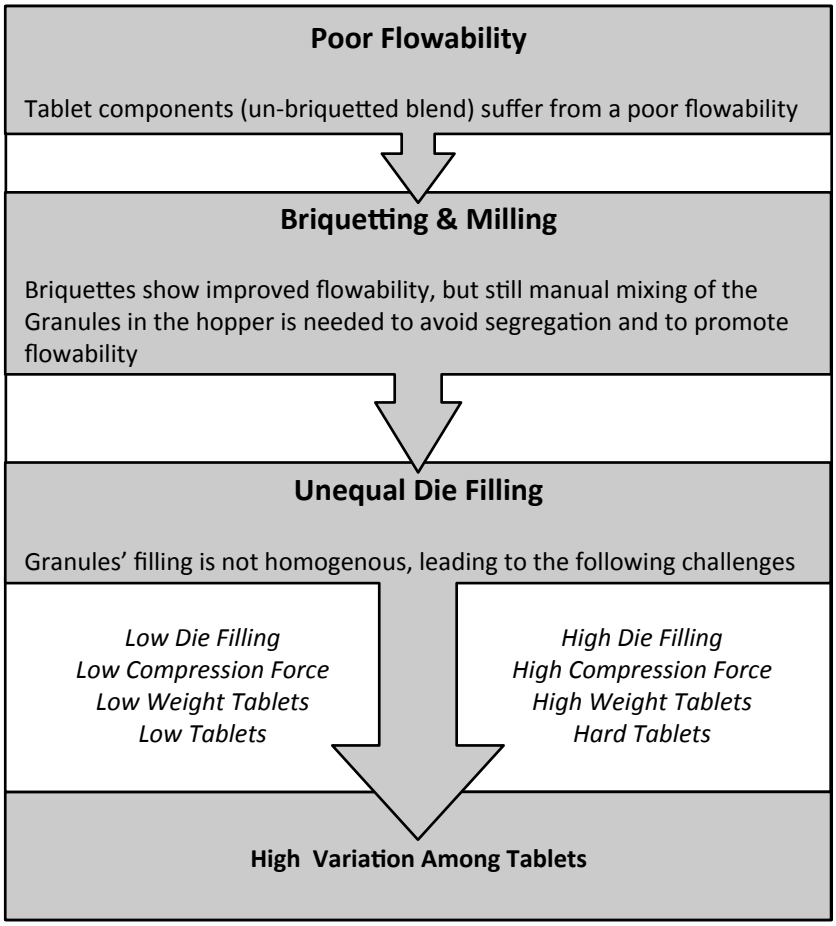


Figure 4.37: Explanation of Tablet Variation.

4.2.2 Water Vapor Uptake (WVU) Tests for uncoated Syloid Tablets (Section 4.2.2)

In Section 4.2.2, the production and characterization results of Syloid Tablets have been presented. Here, in Section 4.2.2, tablets are further characterized, by assessing their extent of moisture sensitivity. It is worth mentioning that – at this stage – no coating has taken place, yet. Depending on the experimental design, from each batch (or sub-batch) tablets are randomly chosen and stored intact and halved in a humid environment and in a dry desiccator (Section 3.2.2.1). Storing tablets in a controlled *humidity chamber* and assessing their water vapor uptake (WVU) serves mainly two purposes: first, WVU of uncoated Syloid Tablets is a measure for reproducibility among the tablets batches. Second, hygroscopicity of the produced tablets and thus their ability to uptake water vapor when stored at elevated humidity levels is being investigated. In other words, WVU tests set a reference for uncoated Syloid Tablets' WVU capacity. Storing the uncoated tablets in a *dry* desiccator and assessing their WVU serves a different purpose; it investigates whether the tablets have taken up (unintended) moisture during the tableting process. In that case the WVU is negative and refers to water vapor loss (negative WVU value). Both experiments are necessary, since both provide important measures for the aptness of the produced tablets for the stability tests discussed in Section 4.3.2. Regardless of their storing conditions, intact and halved tablets are expected to show similar WVU values.

Tablets are usually randomly chosen from the total batch, which presents the sum of all sub-batches mixed together. In Section 4.2.2.3, it is being tested, whether any unintended fluctuation in tableting compression force (see Section 3.2.1.2) affects water vapor uptake of the tablets. For that purpose tablets are randomly chosen from the respective sub-batches, after they have been stored dry for 1 hour (Section 3.2.2.1).

4.2.2.1 Syloid Tablets Stored in Dry Desiccators

Table 4.15 illustrates the negative WVU-value (% weight loss) of uncoated tablets stored dry for 24 hours. The intact ones lose approximately 1% of their weight, due to the presence of some humidity. The halved tablets give up more humidity than the intact ones (roughly 2%); yet there is no significant difference among the two sample types (unpaired t-test, $p = 0.05$). However, obviously the halved tablets have a bigger negative WVU-value, which is probably due to the following: halved tablets contain a bigger exposed surface area and thus interact with the environment faster

Tablet Type	Negative WVU value (% weight loss)
intact	-1.08 % ± 0.28
halved	-1.75 % ± 0.99

Table 4.15: WVU-value for Uncoated Tablets Stored Dry. Tablets stored dry for 24 hours; n=3 (3 independent batches). Error: standard deviation. Statistics: $p = 0.05$, unpaired t-test.

compared to intact ones. It is worth mentioning, that uncoated tablets in this context are included in this WVU test only 1 hour after tableting. During that time interval, they have been collected and stored dry. But since the tableting blend is extremely hygroscopic and since tableting takes place in a room without controlled humidity, controlling their moisture uptake during the tableting process has not been possible. Hence, the negative WVU value presented in the table is believed to be a result of unintended moisture uptake during the tableting process.

The values shown in the table are average values from all three WVU tests performed on random Syloid Tablets from all three batches (Batches 1-3). Those batches have been produced on different days and thus at different humidity conditions in the tableting room. In order to minimize the batch-to-batch residual moisture variation, after this experiment the uncoated tablet have been stored dry for at least 24 hours and then preheated for 30 minutes before coating starts (Section 3.3.1.1.3). Results regarding that matter are presented and discussed in Section 4.3.2.1.2.

4.2.2.2 Syloid Tablets Stored at Humid Conditions

Figure 4.38 depicts the water vapor uptake (WVU) - as % weight gain - for intact and halved Syloid Tablets over time at 33 % RH and 75 % RH. The results show that - regardless of the moisture level (33 % RH or 75 % RH) - all tablets from all batches reach a plateau after one day. This finding sets a basis for all remaining WVU tests; in advance it is mentioned here, that uncoated and coated tablets are compared after 1 day in the stability tests, as will be shown in Section 4.3.

Focusing on the weight gain after 1 day, the findings show that Syloid Tablets from all tablet batches (Batch 1, 2 and 3) experience an average increase in weight ranging from 5 - 6% and 9-11% when exposed to 33 % RH and 75 % RH, respectively (Figure 4.39). Comparing the intact to the halved tablets, it is noticeable that halved tablets unexpectedly absorb slightly less moisture than the intact ones; however, the difference is not statistically significant ($p = 0.05$, unpaired t-test).

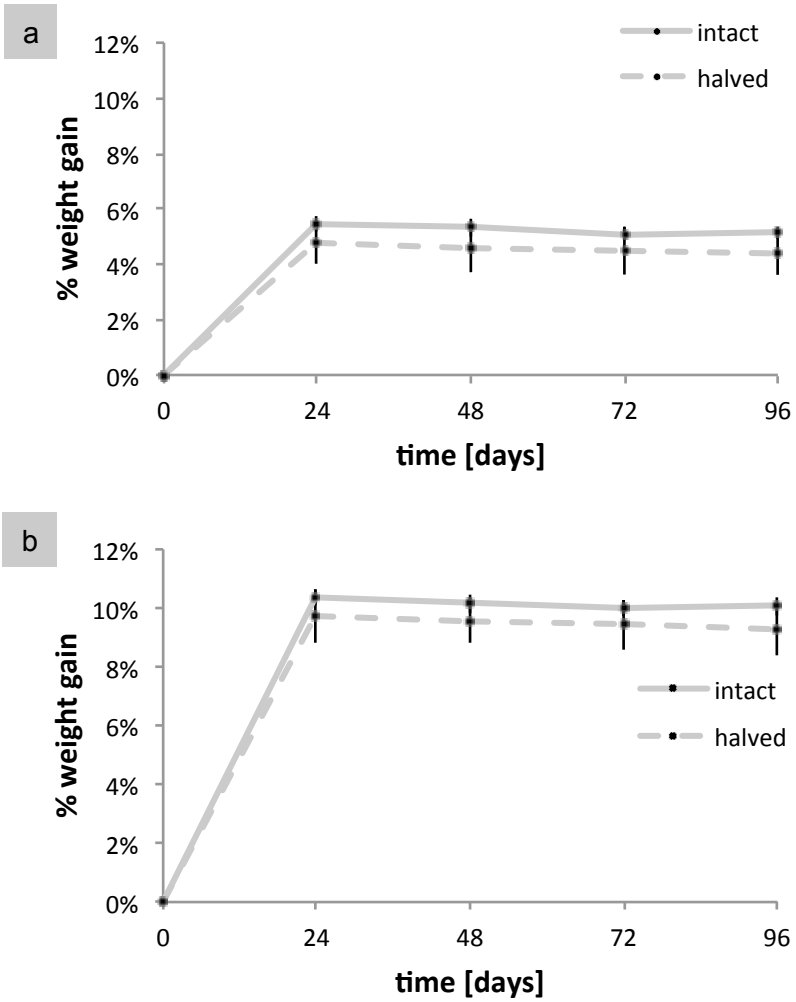


Figure 4.38: WVU vs. Time at Different Humidity Levels. Result: average WVU value from 3 independent batches (n=3). Conditions and Key: storage of sample at a) 33 % RH; b) 75 % RH. Error bars: standard deviation.

It is worth noting that the values shown in Figure 4.38 and in Figure 4.39 are average values from all three WVU tests performed on random Syloid Tablets from all three batches (Batches 1-3). As previously mentioned under Section 4.2.2.1, those batches have been produced on different days and thus at different humidity conditions in the tableting room. In order to minimize the batch-to-batch residual moisture variation, after this experiment the uncoated tablet have been stored dry for at least 24 hours and then preheated for 30 minutes before coating starts (Section 3.3.1.1.3).

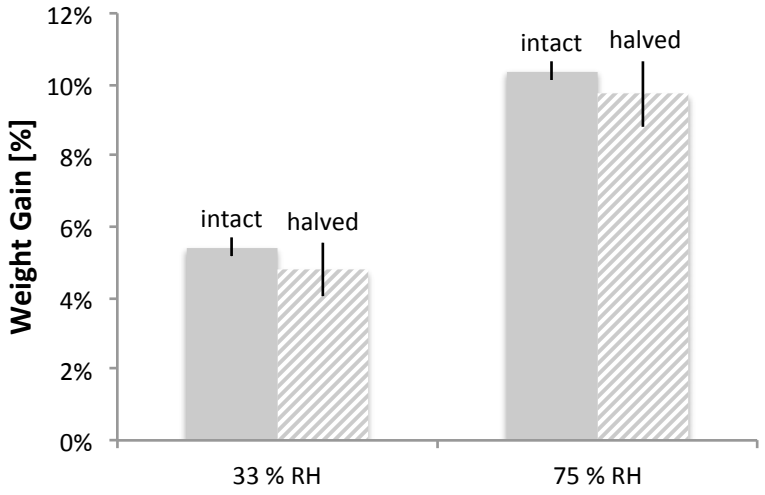


Figure 4.39: WVU-value After 1 Day. Result: Average WVU value from 3 independent batches (n=3). Error bars: standard deviation. Statistics: $p = 0.05$, unpaired t-test.

4.2.2.3 Effect of Compression Force on Hygroscopicity

In Section 4.2.1 the challenges in Syloid Tablet production have been discussed, where poor flowability of the Granules has shown to result in a high fluctuation of the compression force (see Figure 4.35 and Figure 4.37). The aim of this experiment has been to assure that no major difference in WVU of (uncoated) tablets with different hardness profiles is observed. Therefore, it has been important to investigate the effect of the compression force on the extent of moisture uptake of the tablets. For that purpose, three sub-batches from Batch 3 have been chosen to include tablets compressed highly, moderately and with a low compression force, at 16.88 ± 2.9 kN, 13.48 ± 1.9 kN and 10.3 ± 1.23 kN, respectively.

The results of average WVU-values of each sub-batch are depicted in Figure 4.40: it shows no major difference among the tablets of variable compression force. High compression force tablets (Sub-Batch 1) show the same weight gain compared to medium compression force ones (Sub-Batch 8). Low compression force tablets (Sub-Batch 10) show a slightly higher moisture uptake, which could be attributable to the less packed density of the tablets. However, the difference is negligible.

This finding has been necessary to allow mixing of all sub-batches into one batch.

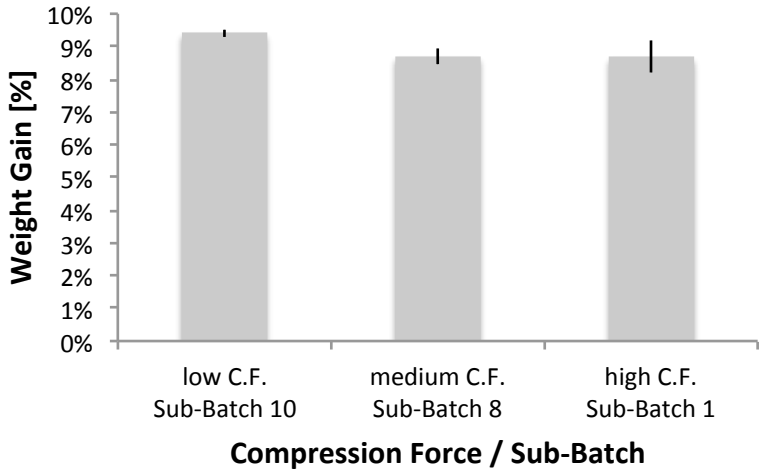


Figure 4.40: Effect of Compression Force on WVU. Samples from 3 independent sub-batches (n=3) from Batch 3. Condition: Tablets stored for 1 day at 75 % RH. Error bars: standard deviation. C.F.: Compression force.

4.2.3 Summary

Methods and results of Section 4.2 deal with all experiments and findings related to Syloid Tablets.

In this research, tablets are mainly produced as a means to an end: the tablet cores are intended to be coated by the novel formulation developed in Section 4.1 and other marketed moisture protective ones. Thereby, a benchmark of the formers moisture protective ability (MPA) to the latter is possible. For that purpose a tablet formulation has been chosen as to give hygroscopic tablet cores (Table 3.8). The resulting tablets (named Syloid Tablets) contain 30% Syloid AL -1 FP (SAF), which is the main hygroscopic substance. The tablet components have been prepared and mixed as to avoid any (excessive) moisture uptake during the course of tableting; steps and precautions regarding that matter are presented under Section 3.2.1. Without briquetting, tablet components suffer from an entire lack of flowability; the powder bulk remains almost completely in the hopper of the tablet press. Therefore, a briquetting step has been inevitable, leading to a somewhat improved but yet poor flowability. The milled briquettes (Granules) are manually mixed in the hopper to avoid segregation and to promote flowability. Still, the somewhat inconsistent tablet flowability results in a high variation of die filling in the tablet press. The latter causes a somewhat high tablet-to-tablet deviation regarding tablet weight, compression force, and hardness. Figure 4.36 supports this statement, by depicting the correlation of tablet

weight to tablet hardness. Yet, produced tablets are conforming to pharmacopeia demands (mass uniformity).

In Stage 2.2, water vapor uptake (WVU) tests have been performed on uncoated tablets. Despite the lack of humidity control during tableting, different tablet batches have shown to be almost equally hygroscopic after tableting. The amount of water vapor absorbed depends on the surrounding humidity level: at 33 % RH and 75 % RH Syloid Tablets absorb water vapor equivalent to $5.5 \pm 0.5\%$ and $9 \pm 1\%$ of their own weight, respectively. WVU capacity is independent on tablet hardness. The water absorbing capacity is reached after one day (Figure 4.38). Therefore, in Section 4.3.2 coated and uncoated tablets are assessed and compared after 24 hours.

Despite the relatively equal hygroscopic nature of the tablets among the different batches, before the tablets have been coated (Section 4.3.2), they were stored in a dry desiccator for 24 hours; this followed by a preheating step at 50 °C for 30 minutes in the pan coater (Table 2.5) has been capable of removing some residual moisture of the tablets. This step serves the purpose of standardizing the tablets extent of hygroscopicity.

4.3 Coated Cores

This sub-chapter presents the results of coating novel moisture protective PE^+ onto inert pellets and Syloid Tablets. In Section 4.3.1, the process parameters and findings are presented, describing the feasibility of coating PE^+ onto different cores. Emulsion character preservation in the coat is focused on in this section. In Section 4.3.2, moisture protective ability of the novel formulation is investigated and benchmarked to conventional products from the market.

4.3.1 Coating Process Parameters Development and Characterization of Coated Cores

4.3.1.1 Atomization Pressure / Emulsion Sprayability

The novel formulation developed throughout this doctoral research is a Pickering emulsion from the oil in water type. Its emulsion character preservation in the dried state has been presented in Section 4.1.2.1.3. Yet, atomization of it might cause any destruction of the emulsion droplets. The following experiment is designed to investigate emulsion character preservation while spraying. From literature it is known that - at a constant spraying rate - high spraying pressure results in more atomization of the sprayed fluid by a nozzle, which shows in smaller droplets (Figure 4.41). To

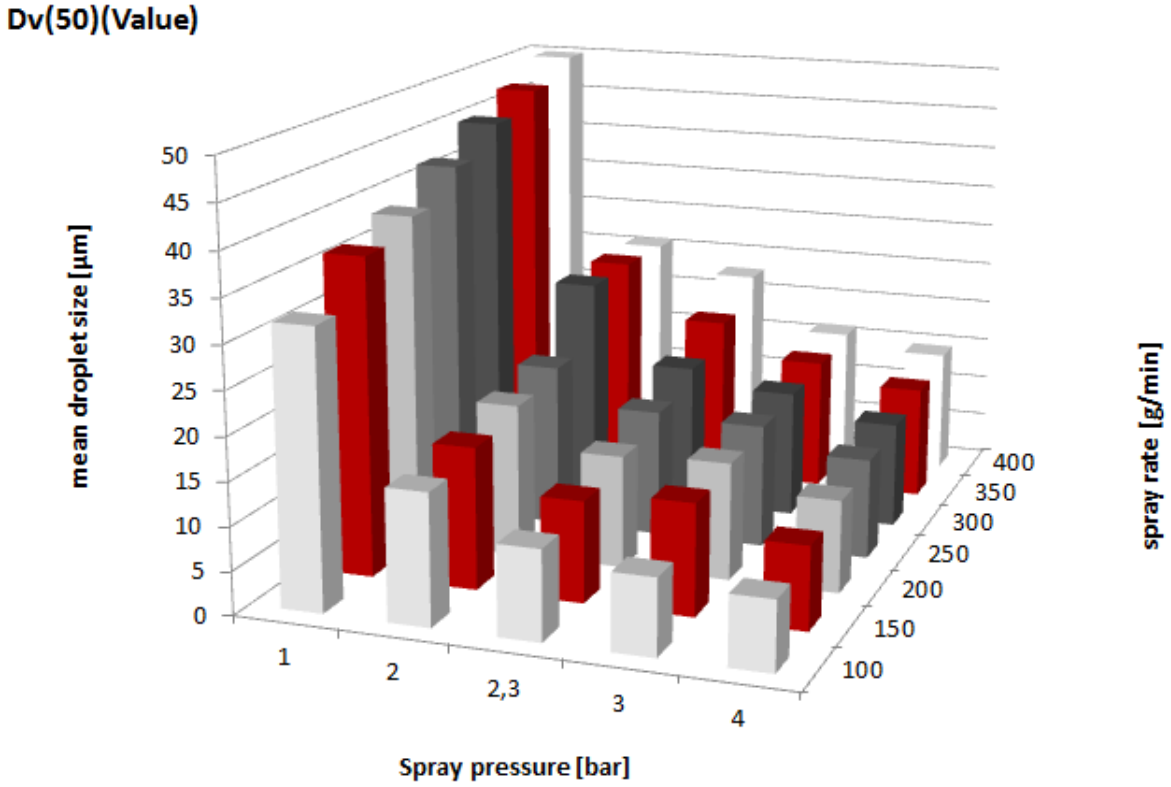


Figure 4.41: Effect of Spraying Rate and Atomization Pressure on DSD of Sprayed Coating Fluid. Source: Glatt Pharmaceutical Services, Glatt GmbH - Internal Projects: with permission from Glatt: data generated by laser diffraction (Malvern).

our knowledge there is no data about the effect of atomization pressure on emulsion character preservation and consequently on its drop size distribution (DSD). Yet, it has been hypothesized that the effect could be negative on the formulation; high atomization pressures will still lead to small formulation droplets, but might destroy emulsion character (e.g. inner phase droplet coalescence due to high shear forces). Hence, at a constant spraying rate the effect of different atomization pressure values on DSD of emulsions has been studied (Method described in Section 3.3.1.1.1).

Figure 4.42 proves the hypothesis right: it shows that emulsions atomized at 0.3 bar have drop sizes comparable to the crude emulsion ($MCT - 20\%\_4 : 1$). However, higher atomization (0.5 and 0.7 bar) results in a shift to bigger drop sizes. This phenomenon can be explained as follows: each atomized droplet is a sample of the emulsions; in other words, each atomized droplet consists of an outer aqueous and an

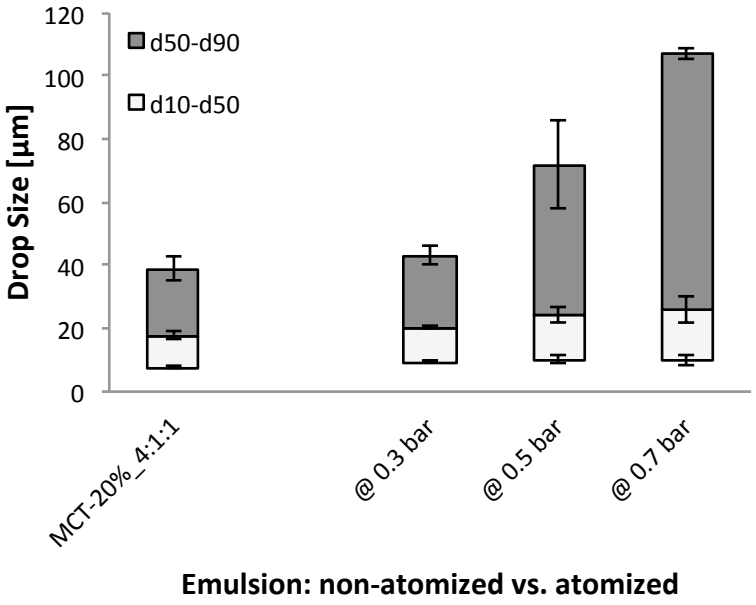


Figure 4.42: Effect of Atomization Pressure on Emulsion DSD. Result: DSD of "n" independently produced emulsions or independently atomized PE^{+}s. n=7 for $MCT-20\%\_4:1:1$ (Prototype emulsion, previously presented in Figure 4.7); n=3 for all atomized emulsions at different atomization pressures; Error bars: standard deviation.

internal lipophilic phase. Since higher atomization pressure leads to smaller atomization droplets, the atomization droplet size may not be smaller than the lipid droplet size during the atomization process. Once the atomization droplets are small enough (as a result of high atomization pressure), the internal lipid droplets are exposed to high shear forces at the nozzle edge, which results in the destruction of the lipid water interface. Hence, with increasing atomization pressures, very small atomization droplets are formed, exposing the emulsion droplets to high shear forces; this destroys the emulsion character and the lipid phase unites consequently. In turn, this shows in the droplet size distribution findings. Previously it has been mentioned that emulsion character must be preserved at all experimental stages. Therefore, atomization of emulsions takes place at 0.3 bar, in order to preserve emulsion character during the coating process.

4.3.1.2 Coating of Inert Sucrose Pellets

4.3.1.2.1 Coating Process Parameters Development: A Trial and Error Approach

Coating inert sucrose pellets in the fluidized bed coater serves two main purposes. First, Syloid AL- 1 FP (SAF) has been a limited resource, which limits the amount of tablets produced during this research, whereas inert sucrose pellets are sufficiently available. Therefore, in order to develop the critical process parameters for coating of PE^+ (except atomization pressure, which has been determined in Section 4.3.1.1 and is set at 0.3 bar) inert sucrose pellets offer a suitable alternative to tablets; they are typically coated in a fluidized bed coater (and not in a pan coater). Furthermore, sucrose pellets are unlike Syloid Tablets completely soluble in water. Hence, coated sucrose pellets are fundamental for investigating the coat regarding emulsion character preservation. The latter is a useful property needed in the next experiment (Section 4.3.1.2.2).

In Section 3.3.1.1.2, a trial and error approach has been described, by which the process parameters for coating of PE^+ onto inert sucrose pellets have been developed and set. In all trials, 100 g PE^+ have been coated onto 200 g pellets and the fluidization power has been held constant at 95 % of the total machine power. However, it is hypothesized that both, inlet drying air temperature and spraying rate, are the critical process parameters of PE^+ coating. Hence, both have been systematically altered to develop a successful coating process of PE^+ onto the pellets. Figure 4.43 illustrates the steps of process parameter development and rational of each, which have suggested the final process parameters (Table 4.16).

At the beginning the effect of drying temperature on coating procedure has been investigated, while keeping the spraying rate low and constant (Trial 1 to Trial 3). The spraying rate has been adjusted via the spraying pump's power, the latter being set during those three trials at 0.5 rpm, which is considered an extremely low one. Consequently, the coating process lasts for a relatively long time, which might exert excessive mechanical stress on the cores. On the other hand, a low spraying rate assures slow spraying, which avoids consequent tackiness. Since HPMC polymer solutions for film coatings are known to form intact films at a drying temperature approximating 40 °C, in a first trial (Trial 1), the drying temperature has been set to 40 °C; lower drying temperatures are not considered, since they are expected to result in wet coating processes. Yet, Trial 1 has shown a wet coating process, which is probably attributable to insufficient drying. Thus, in the second trial (Trial 2) the temperature has been raised to 55 °C while keeping the spraying rate unchanged. Thereby, the wetness of the process has been overcome. On further investigating the effect of the drying air temperature on the coating process, the drying temperature

has been raised to 70 °C (Trial 3). Here, the formed film has become scaly; this is explained by the additive effect of both, a very low spraying rate (0.5 rpm) and relatively high drying temperature (70 °C), which results in a combination of coating and spray drying. Here, the atomized droplets are sprayed at a low rate and are partially dried immediately before even reaching the surface of the coat resulting in the observed flakes. In order to overcome the observed flakes phenomenon and to accelerate the relatively slow coating processes of the first three trials, the spraying rate has been raised to 1.5 rpm and the drying temperature set to 55 °C (Trial 4). Here, the process has been dry (not wet) and the flakes have been successfully reversed. However, to further accelerate the coating process, the spraying rate has been raised again to be 3.0 rpm (Trial 5). This has resulted in an extremely wet process, where some pellets have partially dissolved into the coating fluid and united to form one bulk of a mass. Raising the drying temperature to 70 °C (Trial 6) has not compensated the high spraying rate and the occurrence observed in Trial 5 has remained. In Trial 7, the temperature has been kept at 70 °C but the spraying rate has been reversed to 1.5 rpm. Here, the coating procedure has been successful, resulting in pellets similar to the ones produced in Trial 4.

In end, process parameters of Trials 4 and 7 only have provided successfully coated pellets, which are summarized in Table 4.16: 50 70 °C is a suitable drying temperature range for coating PE^+ onto inert sucrose pellets. The spraying rate seems to be dependent on the drying temperature and is expected to also depend on the cores' quantity and the coating device. Still, coating PE^+ is feasible using conventional coating devices at typical process parameters and does not require extraordinary technical adjustments. And because the following results build up on each other, here a take-away message from this finding: PE^+ coating is feasible at conventional process parameters using conventional coating devices; the drying temperature and the spraying rate seem, however, to be the critical process parameters.

It is worth mentioning that all previous trials (Trial 1 to Trial 7) have been performed with $MCT - 20\%\_4 : 1 : 1$ as the coating fluid. Visually, the resulting coated pellets have been relatively greasy and shiny, regardless of the process parameters. This so-called "free lipid phenomenon" can be explained by the following: pellets are constantly subjected to mechanical stress during the coating process, which probably exerts a shear force onto the emulsion droplets within the coat. That leads to an undesired but ongoing mobilization of MCT within the HPMC matrix resulting in free lipid on the coat surface. Hence, it has been hypothesized that a higher quantity of the film-forming agent (HPMC) and a higher $CaCO_3$ to lipid ratio might result in

Coating of Sucrose Pellets in Fluidized Bed Coater	
Pellet Quantity	200 g
Coating Fluid Quantity (PE^{+})	100 g
Fluidization Power	95 % of total machine power
Drying Temperature Range	55 °C – 70 °C
Pump Speed*	0.5 - 1.5 rpm

Table 4.16: Final Process Parameters. Coating of Pellets in Fluid Bed Coater. *Pump speed dictates spraying rate.

a greater mechanical stability of the emulsion droplets towards the pellets' exposure to mechanical stress during the coating process. In Table 4.9, all formulation component ratios that give stable emulsions have been presented and in Section 4.1.2.2.2 (Figure 4.20) it has been found that water vapor permeability (WVP) is independent on emulsion component ratios. Therefore, adopting the coating process parameters from Trial 4 (Figure 4.43) $MCT - 15\%\_4 : 1.5 : 1.5$ has been chosen as the coating fluid for that purpose. This emulsion component ratio has a lower lipid concentration (15% instead of 20%) and a higher $CaCO_3$ and HPMC to lipid ratio compared to the prototype emulsion ($MCT - 20\%\_4 : 1 : 1$). The final coating quantity on the pellets has been held constant (as % weight gain of pellets) and the final products have been visually assessed for greasiness. Pellets coated with $MCT - 15\%\_4 : 1.5 : 1.5$ show a significant reduction in the previously observed greasiness and thus the hypothesis has been confirmed. According to this finding, emulsion formulations comprising 15% lipid and a lipid to $CaCO_3$ to HPMC ratio of 4:1.5:1.5 provide the least greasy coating (by limiting the free lipid quantity). Hence, this emulsion ratio is chosen for further investigation in (Section 4.3.1.3). However, some mild lipid escape is still observed, especially when the coated pellets are rubbed and dabbed by a tissue; the latter gets stained red by the lipid coloring dye, Sudan red. And because the following results build up on each other, here a take-away message from this finding: emulsion ratios with a higher $CaCO_3$ and HPMC to lipid ratio provide less greasy coatings.

4.3.1.2.2 Emulsion Character Preservation

During this research, it has been important to assure emulsion character preservation at all stages. In Section 4.1.2.1.3 it has been shown that free films are dried emulsions, and in Section 4.3.1.1 it has been shown that atomization at 0.3 bar maintains emulsion character. Last but not least, it is crucial to assure that emulsion character is preserved in the coat as well. For that purpose, sucrose pellets coated

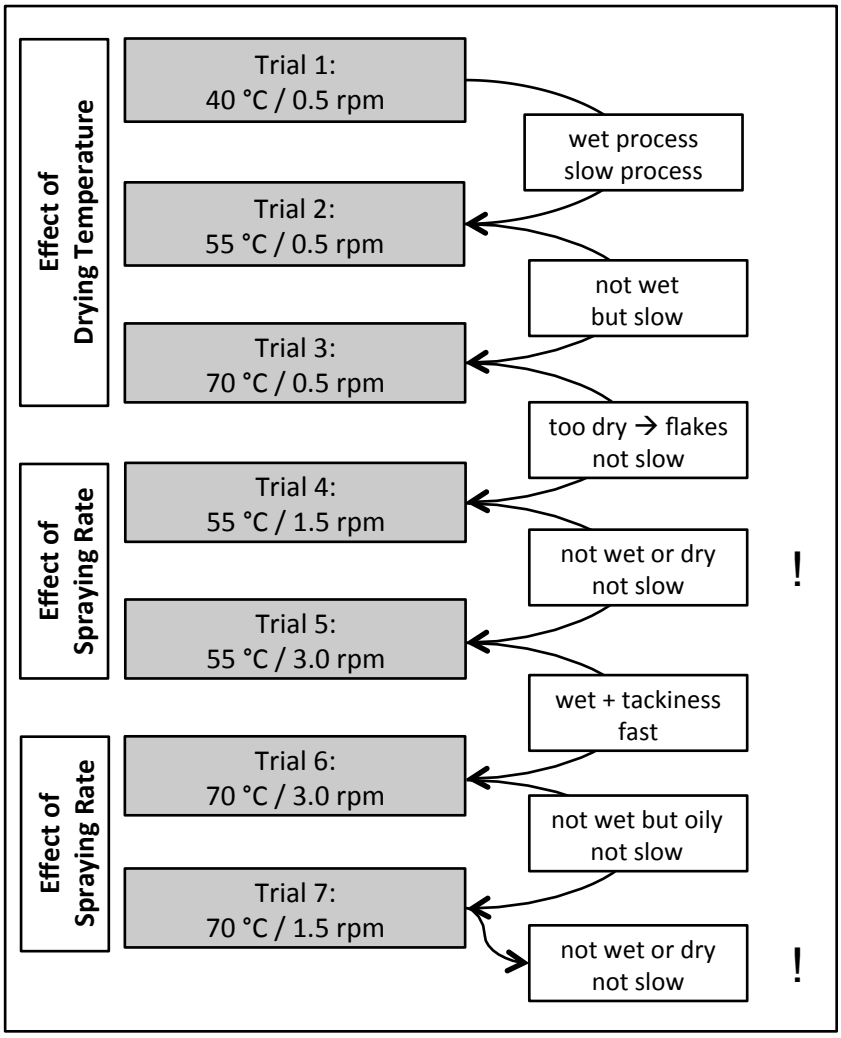


Figure 4.43: Process Parameter Finding by Trial and Error

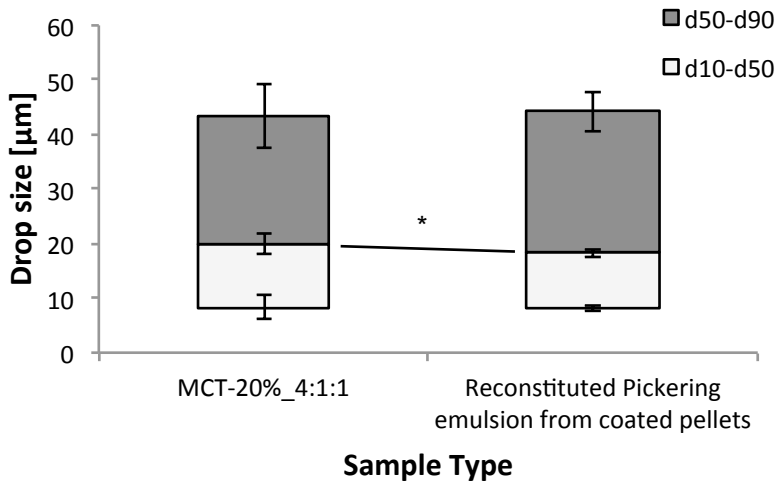


Figure 4.44: DSD of Reconstituted Pickering Emulsion in Comparison to the Uncoated One. Result: DSD of "n" independently produced emulsions or its reconstitution. n=8 for $MCT-20\%\_4:1:1$ (previously shown in Figure 4.7); n=3 for reconstituted Pickering emulsion from coated pellets. Key: * significant difference. Error bars: standard deviation. Statistics: $p = 0.05$, unpaired t-test.

with $MCT-20\%\_4:1:1$ have been completely dissolved in water and the drop size distribution (DSD) measured as described in Section 3.3.1.2. Figure 4.44 shows that DSD of the reconstituted emulsion is similar to the formulations DSD before coating: an unpaired t-test has shown only significant difference between the 2 groups for the d50 value ($p = 0.05$).

Furthermore, aqueous solutions of the inert (uncoated) sucrose pellets have been subjected to the same measurement; no drops or particles have been detected. The previous finding elaborates the necessity to use a completely water-soluble core. In other words, this finding proves that the above-mentioned DSD of the reconstituted dispersion is solely attributable to the coating and not the core. Hence, both findings demonstrate emulsion character preservation within the coat.

Moreover, Figure 4.45 shows a scanning electron microscopic image of a cross-sectional cut of coated pellets. The coat shows a great resemblance to Figure 4.13, which verifies the previous finding. Thereby, during this research it has been shown that emulsion character is preserved at all stages; similar to free films, the final film coat is a dried emulsion as well.

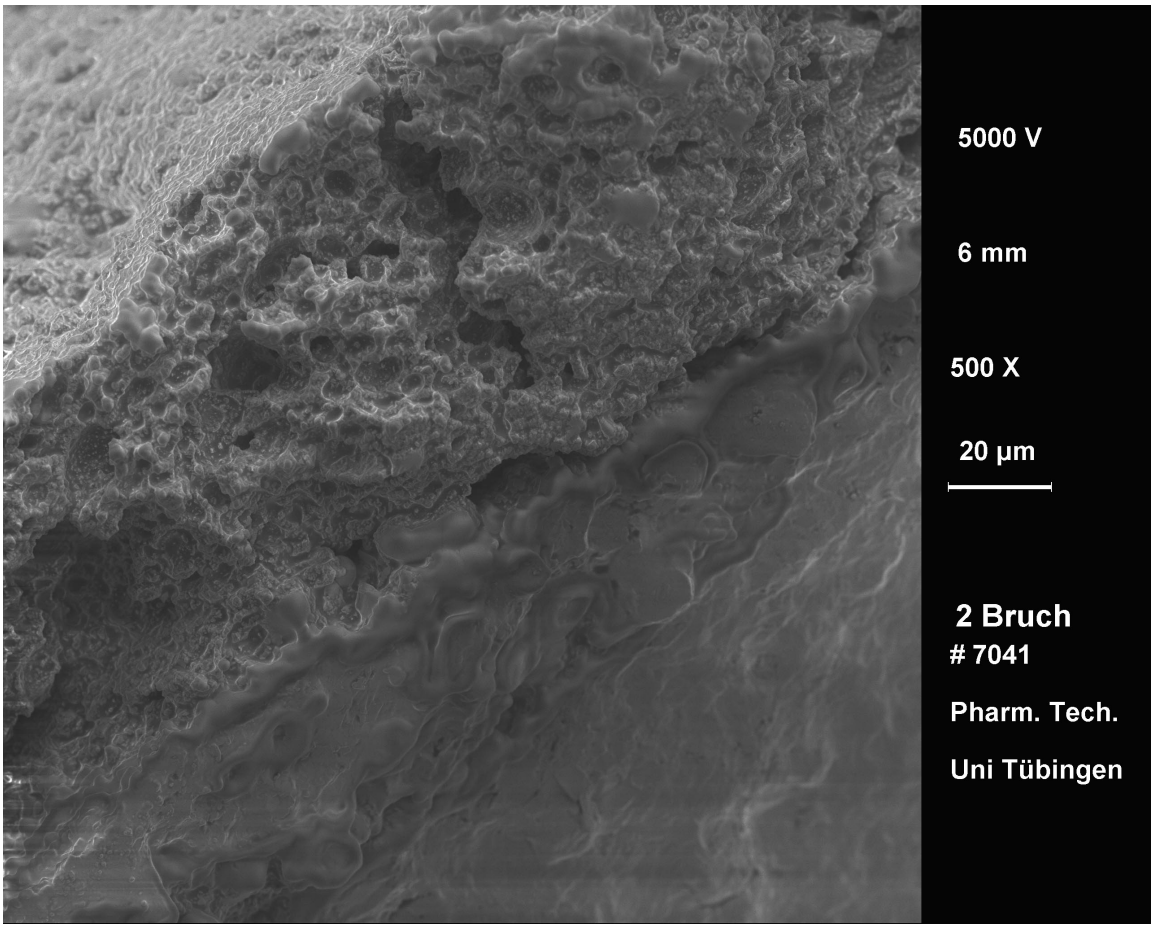


Figure 4.45: SEM Image from Coated Pellets. Cross-Sectional Cut.

Amount of Film-Forming Components	
$HPMC_{s\text{-}12.5\%}$:	12.5 % film-forming components (solids)
$EPO_{aq\text{-}d}$:	12.5 % film-forming components (solids)
SFO-15%_4:1.5:1.5 :	26.25 % film-forming components (15 % sunflower oil + 11.25 % solids)

Table 4.17: Coating Fluids.

4.3.1.3 Coating of Syloid Tablets

In Section 4.3.1.2.1 pellet coating in a fluidized bed coater (FBC) has been described, where process parameters for PE^+ coating onto pellets have been developed in a trial and error approach. Table 4.16 summarizes the process parameter ranges obtained there. Coating Syloid Tablets is technically not achievable in the FBC, for two previously mentioned reasons (Section 3.3.1.1.3). First, tablets are too heavy for fluidization, which practically impairs their homogenous coating using our FBC. Second, humidity detection and thus control is technically not feasible using our FBC, since the coating chamber is fully protected and thus inaccessible. For those two reasons, Syloid Tablets have been coated using coating pan, as discussed in Section 3.3.1.1.3. The final process parameters chosen are summarized in Table 3.10. Some parameters depend on the used coating formulation as seen in the table. The exact amount of film-forming components per coating fluid is summarized in Table 4.17. It is worth mentioning that $SFO - 15\%\_4 : 1.5 : 1.5$ has been the Pickering emulsion of choice for coating Syloid Tablets. Formulations containing SFO as their lipid have shown a superior combination of demands on galenic and functional levels, as previously discussed in Section 4.1.2.2.6.

4.3.1.3.1 Characterization of Coated Syloid Tablets (without a pre-coat)

Table 4.18 summarizes the quantity of coat per Syloid Tablet for all formulations and shows that different coating batches have been coated with almost the same amount of coat per tablet.

EPO, HPMC and PE^+ coated Syloid Tablets have appeared normal and have shown no visual imperfections or obvious defects; the coats have appeared homogenous and intact when visually assessed. However, it has been noticeable that Syloid Tablets coated with PE^+ show absolutely no greasiness and unlike the coated pellets

Coating Fluid:	% weight gain	
$HPMC_{s\text{-}12.5\%}$:	9.00 %	± 2.11
$EPO_{aq\text{-}d}$:	9.38 %	± 1.38
SFO-15%_4:1.5:1.5:	11.02 %	± 1.48

Table 4.18: Average Coat Quantity per Tablet. Coat quantity as % weight gain (no pre-coat). n=6 for HPMC coat; n=2 for EPO und SFO coatings. Error bars: standard deviation for n=6; span for n=2.

when rubbed with tissues no lipid escape from the coat is observed. Even the previously discussed pellets (that were coated with the Pickering emulsion containing SFO (and not MCT) as their lipid – (Section 4.3.1.2)), showed some greasiness, which in turn excludes the possibility that SFO coats are less or not greasy compared to MCT ones.

Investigating the lack of greasiness more, a cross-sectional cut of Syloid Tablets reveals the following: the interior of uncoated, HPMC and Eudragit coated Syloid Tablets are brightly white, whereas PE^+ coated ones show a yellowish tinge. The latter finding indicates the entrance of lipid into the tablet core. Furthermore, Syloid Tablets coated with a red stained SFO (by oil-soluble Sudan-III) show red spots inside their cores or even an entire reddish coloration of the inner core, which supports the above-mentioned statement. It is obvious, that during the coating procedure, free lipid has been available for the core surface and consequently is sucked by capillary forces; this phenomenon is called wicking effect. Figure 4.46 shows the images for uncoated Syloid tablets, tablets coated with EPO and with $SFO - 15\%\_4 : 1.5 : 1.5$, all being coated with the quantity described in Table 4.18.

At this stage, two important aspects are worth analysis: first, it is crucial to understand the reason behind the (obviously excessive) availability of oil from the coat. Second, it is similarly important to investigate the effect of lipid uptake by the core on the moisture protective ability of the coat. Starting with the first aspect, in Section 4.3.1.2.1 it has been shown that coating formulations with a higher Lipid:$CaCO_3$:HPMC ratio (4:1.5:1.5 instead of 4:1:1) result in almost no greasy coating due to a better stabilization of the lipid inside the HPMC matrix (less greasy coated pellets). Hence, it has been expected that no free lipid is available in the first place for the Syloid Tablets to absorb it. Yet, the above-mentioned findings have shown that Syloid Tablets have taken up some lipid, in spite of the higher anticipated PE^+ stability during coating.

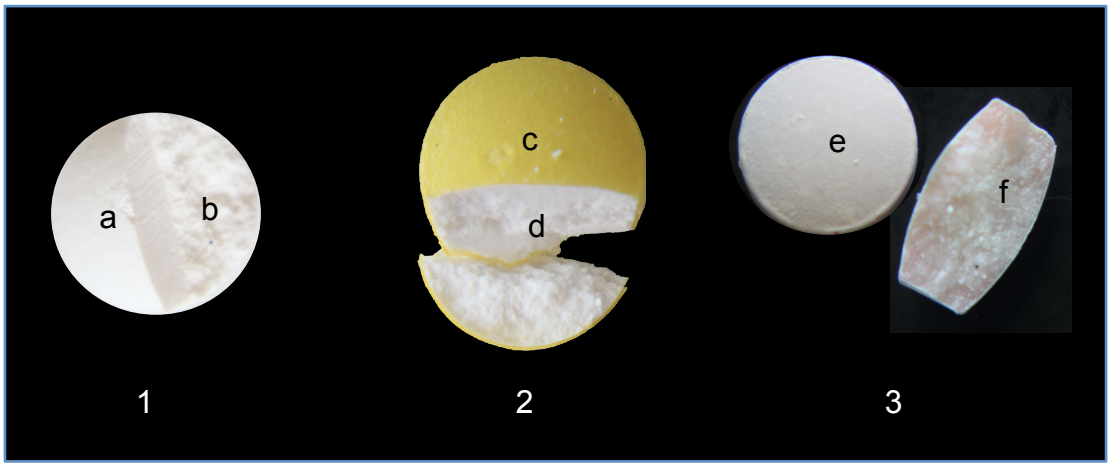


Figure 4.46: Macroscopic Imaging of Syloid Tablets (no pre-coat) Key: 1: uncoated Syloid tablet: a - outer surface, b - inner core 2: Syloid tablet coated with EPO: c - film coat, d - inner core 3: Syloid tablet coated with SFO – 15%_4 : 1.5 : 1.5: e - film coat, f – inner core

The explanation is binary: on the one hand, Syloid is known to have a very high absorbing capacity for oils [28] and by capillary forces at the tablet surface (duct effect), available oil is sucked from the coat into the core. Thus, compared to sucrose the absorbing capacity of Syloid to oils is much more pronounced and hence more lipid can be absorbed by the latter versus the former. Consequently, Syloid Tablets present a sub-optimal core for PE^+ coating. On the other hand, the coating pan used in this research has a rough surface and the cores are consequently subjected to a higher mechanical stress compared to the pellets coated in the FBC. Therefore, the impaction forces constantly destroy the coat, the lipid-water interface is thus partially damaged and free lipid is available at and to the tablet surface for uptake by the core. In order to overcome the above-mentioned effect, a non-moisture protective pre-coat is designed to be applied to the Syloid Tablets, serving as a mechanical barrier to free lipid. For that purpose HPMC coated tablets have been chosen to be further coated with each, Eudragit and PE^+. HPMC's suitability as a pre-coat has been validated after some considerations have been taken into account; in Section 4.3.2.2.2 it is shown that HPMC pre-coated Tablets' WVU capacity is only slightly less compared to uncoated ones. A detailed discussion regarding that matter is presented there.

4.3.1.3.2 Characterization of Coated Syloid Tablets (with a pre-coat)

HPMC pre-coated tablets have been further coated by each EPO and SFO – 15%_4 : 1.5 : 1.5 and Table 4.19 summarizes the average quantity of coat per tablet. In fact,

Coating Fluid:	% weight gain	
$HPMC_{s\text{-}12.5\%}$:	9.00 %	± 2.11
$EPO_{aq\text{-}d}$:	9.02 %	± 1.53
SFO-15%_4:1.5:1.5:	8.23 %	± 2.24
-- dabbed:	7.57 %	± 3.2

Table 4.19: Average Coat Quantity per Tablet. Coat quantity as % weight gain (with pre-coat). n=6 for HPMC coat; n=3 for EPO and SFO coatings. Error bars: standard deviation.

the pre-coat is mainly designed for PE^+ coating, in order to serve as a mechanical barrier to free emulsion entry (Section 4.3.1.3.1). However, in order to be able to compare PE^+ coated tablets to Eudragit coated ones, the conditions must be similar. Therefore, Eudragit coating has been applied to HPMC pre-coated tablets as well.

Table 4.19 shows that uncoated Syloid Tablets have increased in their weight by 9% due to HPMC coating. The resulting HPMC pre-coated tablets have increased in their weight by 9.02% and by 8.23% when further coated by EPOaq.-d and $SFO-15\%\_4:1.5:1.5$, respectively. The findings show no remarkable difference in the final quantity of coat per tablet between EPO and PE^+ coated ones. HPMC pre-coated Syloid Tablets that are further coated with EPO appear similar to the ones without a pre-coat; the coat seems intact and lacks any obvious defects. A cross-sectional cut shows a brightly white core (Figure 4.47). HPMC pre-coated tablets coated by $SFO-15\%\_4:1.5:1.5$ are somewhat greasy (especially after rubbing by hand), unlike the ones without a pre-coat. A cross-sectional cut shows a relatively brightly white core, with mild oil spurs at the tablet edges, compared to tablets without a pre-coat (Figure 4.47). These findings indicate that the pre-coat has successfully reduced the quantity of lipid entrance into the tablet core, by functioning as a mechanical barrier on the tablet surface; free lipid now enters the tablet core only at the tablet edges, where the HPMC pre-coat is relatively thin compared to the remaining tablet surface. However, release of free lipid from the coat during the coating process is inevitable, since its main cause (the mechanical stress during the coating process) still remains. The oily tablets have been dabbed by a tissue until all free lipid has been removed from the tablet surface. The final quantity of coat per table equals 7.57% (Table 4.19), which in turn means that free lipid amounts only 6% of the total coat quantity calculated before dabbing. In Section 4.3.2.2.2, the moisture protective ability of both, PE^+ and Eudragit is investigated, where each formulation is coated onto HPMC pre-coated Syloid Tablets.

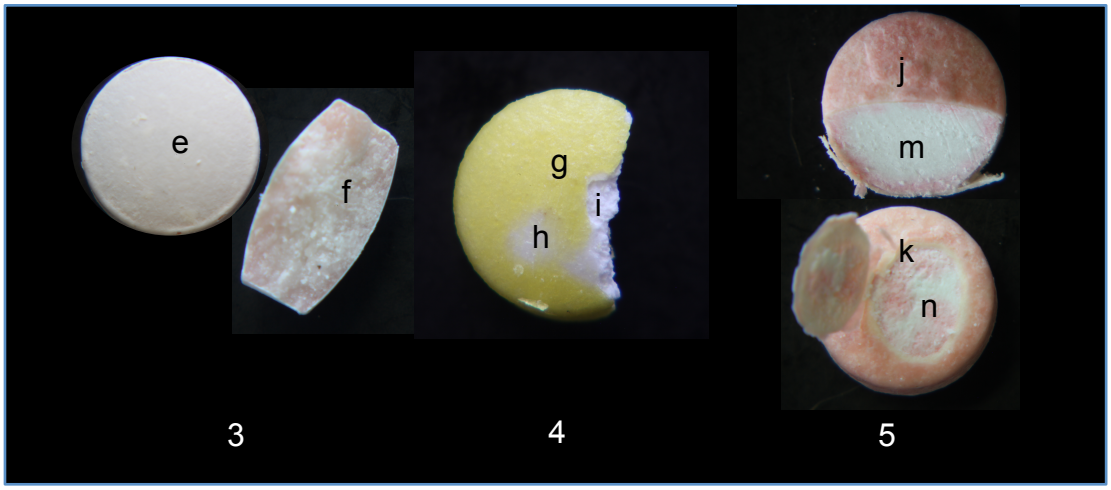


Figure 4.47: Macroscopic Imaging of Syloid Tablets (with pre-coat). 3: Syloid tablet coated with SFO – 15%_4 : 1.5 : 1.5: e - film coat, f – inner core (see Figure 4.46) 4: Syloid tablet coated with HPMC then EPO: g - outer surface (2nd coat), h - 1st coat (HPMC), i: inner core 5: Syloid tablet coated with HPMC then with SFO – 15%_4 : 1.5 : 1.5: j – outer surface (2nd coat), k – 1st coat (HPMC), m: inner core, n: oil spots.

4.3.1.3.3 Coated Tablets' Disintegration

Under Section 4.2.1.1 it has been presented that uncoated tablets disintegrate within two minutes. Syloid Tablets coated with PE^+ disintegrate within less than 5 minutes in purified water. Eudragit E PO coated tablets disintegrate within 5 minutes in 0.1 M HCl. Secondarily coated tablets with each formulation disintegrate within ten to fifteen minutes; HPMC pre-coat delays the release compared to the non-pre-coated ones. Yet, all tablets are released in less than 60 minutes and are considered immediate release ones.

4.3.2 WVU tests of Coated Syloid Tablets

Results found in Section 4.3.2 include the following samples: uncoated Syloid Tablets, Syloid Tablets coated with HPMC, EPO, or PE^+, as well as tablets coated with an HPMC pre-coat followed by EPO- or PE^+-coating are investigated; all those samples are stored intact and halved. The investigating conditions are either dry or humid. Details for each of those investigates are described under the following sub-chapters (Section 4.3.2.1 and Section 4.3.2.2); Table 4.20 illustrates an overview. Please note beforehand that some samples required a pre-coat for reasons described throughout

the stream of thoughts found below; the prerequisites for and validation of that pre-coat are described and discussed below.

4.3.2.1 Coated Tablets Stored Dry

As previously mentioned in Section 4.2.2, storing the uncoated Syloid Tablets in a dry desiccator and assessing their WVU value represents the unintended amount of moisture uptake during the tableting process.

WVU tests for *coated* Syloid Tablets stored in a dry desiccator serve a slightly different purpose: the WVU-values obtained here indicate the amount of absorbed moisture during the coating process, where ideally no moisture uptake by the tablets is desired. However, in practice the tablet cores always absorb some moisture during the coating process and hence, the following results are expected: intact-coated tablets are supposed to show a WVU value equal or close to zero, since any absorbed moisture is expected to remain in the tablet shielded by the coat; halved-coated tablets are supposed to show a more negative WVU value than intact-coated one's, since the effect of the coat is compensated by halving the tablets: the inner surface of halved-coated tablets is exposed and any moisture absorbed during the coating process is typically desorbed from the tablet core. Table 4.20 illustrates the above-mentioned idea and compares it to WVU values expected for tablets stored in humid conditions (Section 4.3.2.2).

4.3.2.1.1 Coated Syloid Tablets Stored in Dry Desiccators

In this research, all coating fluids are water-based, which might lead to a relatively humid environment inside the coating pan during the coating process. Since Syloid Tablets are extremely hygroscopic (Section 4.2.2.2), special caution of the humidity level in the coating chamber is required.

In Section 3.3.1.1.3, it has been described that the drying temperature is set at 60 - 70 °C to keep the relative humidity as low as possible (5 % RH); once coating starts, the measured relative humidity reaches a value up to 15 % RH as a result of aqueous coating (Section 3.3.1.1.3). So, due to the increased risk of water vapor uptake (WVU) by the Syloid Tablets during the coating process itself, both intact and halved tablets of each coating batch are stored at dry conditions immediately after coating. Uncoated tablets are also included in this investigate, setting a reference for this experiment. Figure 4.48 shows the average % weight change of Syloid Tablets

of different batches when stored dry for 1 day; the samples include both, intact and halved tablets.

Uncoated Tablets (previously presented under Section 4.2.2.1) Results for uncoated Syloid Tablets shown in Figure 4.48 have been previously shown in Section 4.2.2.1, but are included here again for a better comparison: there, it was shown that those uncoated tablets have been investigated only 1 hour after tableting and yet contain moisture equivalent to roughly 1 - 2% of their weight. This amount represented the residual moisture inside the tablets, which is believed to be absorbed during the tableting process. Since tableting takes place in a room without humidity control, reducing this moisture content has not been possible. Furthermore, all Syloid Tablets intended for coating come from different tablet batches, which might contain variable amounts of residual moisture. Hence, in order to standardize (and minimize) their humidity content, uncoated tablets have been stored dry until the coating experiment took place and further preheated for 30 minutes before coating starts (Section 3.3.1.1.3).

Coated Tablets Similar to uncoated tablets, HPMC coated tablets contain some residual moisture, as well. However, the amount of residual moisture is slightly less compared to uncoated ones, but more compared to tablets coated by other formulations: emulsion coated tablets contain less residual moisture compared to both, uncoated and HPMC coated tablets; intact EPO coated tablets show a slight increase in their weight (positive WVU value), whereas the halved ones show a slight decrease. Thus, from this finding it is suggested that the coating process in the case of EPO coating results in the least residual moisture compared to HPMC and emulsion coating. Regardless, the findings indicate that the coating process does not cause any excessive moisture uptake of the Syloid Tablets during coating compared to the initial uncoated Syloid Tablets. In other words, the coating process has been relatively dry, despite coating of aqueous formulations.

4.3.2.1.2 HPMC Coated Tablets: Effect of Preheating

In Sections 4.3.1.3.1 and 4.3.1.3.2 it has been mentioned that HPMC pre-coated tablets have been further coated by EPO or PE^{+}. In order to assure the highest water absorbing capacity of HPMC pre-coated Syloid Tablets, the latter have been preheated before the second coat is applied. Figure 4.49 shows that HPMC coated

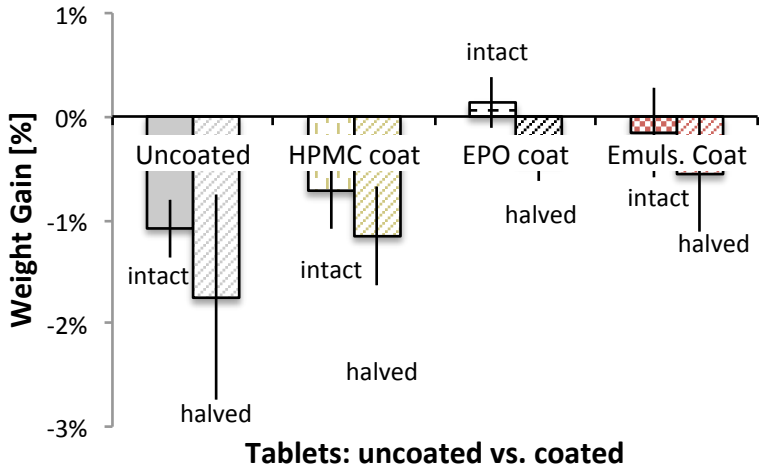


Figure 4.48: Tablets Stored Dry (no precoat; no preheat). Result: Average % weight gain from "n" independent experiments, each with at least 3 tablet pairs per sample type – after 24 hours. Sample types: n=3 for uncoated tablets, n=3 for EPO coated tablets, n=3 for SFO − 15%_4 : 1.5 : 1.5coated tablets, n=6 for HPMC coated tablets; each sample type included two arms: intact and halved tablets. Conditions: samples types stored dry. Error bars: standard deviation.

Syloid Tablets that have been preheated contain almost no residual moisture compared to non preheated ones. In end, preheating reverses any residual moisture of HPMC coated tablets and regains the maximum water vapor absorbing capacity. And because the following results build up on each other, here a take-away message from this finding: preheating HPMC coated Tablets reduces residual moisture from the HPMC coated tablet core.

4.3.2.2 Coated Syloid Tablets Stored at Humid Conditions

Here in Section 4.3.2.2, the findings of the stability tests are discussed. Firstly, the results for Syloid Tablets that are coated with different coating formulations are presented. Secondly, the results for the investigate of HPMC pre-coated Syloid Tablets that contain different second coatings are shown. In general, coated Syloid Tablets that are stored in humid conditions are expected to experience less water vapor uptake (WVU) when compared to their reference ones (e.g. uncoated or HPMC pre-coated). However, once the coated tablets are halved the internal hygroscopic core is exposed to the moist environment, where the former interacts with the latter faster and thus the coats effect is counteracted. Therefore, both intact and halved tablets for each batch are subjected to the same humidity level and the results are

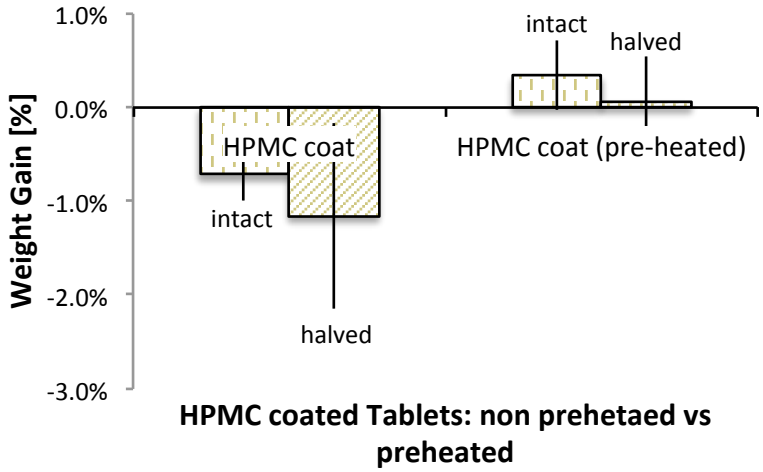


Figure 4.49: Effect of Preheating – Removal of Residual Moisture. Result: Average % weight gain from "n" independent experiments, each with at least 3 tablet pairs per sample type – after 24 hours. Sample types: n=6 for both, HPMC coated tablets and pre-heated ones; each sample type included two arms: intact and halved tablets. Conditions: samples types stored dry. Error bars: standard deviation.

coupled together. The reference tablets intact and halved are exposed to the same conditions as well. In Section 4.2.2 the amount of WVU by uncoated tablets at different humidity conditions has been discussed. Their maximum amount of WVU is reached after 1 day and therefore all coming investigates are presented accordingly (after 1 day). It is expected that intact-coated tablets experience a lower WVU value than their reference counteracts, whereas halved coated ones are expected to equal WVU value compared to their reference. Table 4.20 illustrates the above-mentioned idea and compares it to WVU values expected for dry conditions (Section 4.3.2.1)

4.3.2.2.1 WVU Syloid Tablets (no pre-coat)

Figure 4.50 illustrates the % weight gain of uncoated and coated Syloid Tablets at 33 % RH after one day. As previously shown, uncoated tablets experience a weight gain of almost 5.5% when stored at 33 % RH (Section 4.2.2.2). This value serves as a reference for all coated tablets in this context, by defining the maximum water vapor uptake (WVU) for non pre-coated Syloid Tablets. All batches of coated Syloid Tablets presented in Figure 4.50 contain almost an equal amount of coat per tablet, which is summarized in Table 4.18. Hence, any difference in moisture uptake of coated tablets is mainly a function of the coat itself and not its quantity.

Storage Condition	Tablet Type	Tablet form	Purpose (P) of Test / Expectation (E) of Test
Dry	Uncoated	intact & halved	P1: Info about residual moisture of tablets resulting from tableting process
			E1: No difference between intact and halved tablets; WVU value ≤ 0 (*[1])
	Coated	intact	P2: Info about intactness of coat
			E2: WVU value = 0 (zero)
		halved	P3: Info about residual moisture of tablets resulting from coating process
			E3: WVU value ≤ 0 (similar to uncoated tablets; *[1])
Moist	Uncoated	intact & halved	P4: WVU capacity of Syloid Tablets
			E4: WVU > 0 (*[2])
	Coated	intact	P5: Info about MPA of coat
			E5: 0 < WVU < WVU of uncoated tablets (*[2] in E4)
		halved	P6: Info about max WVU
			E6: WVU = WVU of uncoated tablets (*[2]in E4)

Table 4.20: Overview of WVU-Tests – Purpose and Expectation of Resulting WVU-Values. Table shows rationale of investigate and the theoretically expected WVU for coated and uncoated tablets at different storage conditions.

HPMC coated Tablets Starting with HPMC coated tablets the findings reveal that they experience an average weight gain of approximately 4.1%, which is almost 25% less than the uncoated ones. HPMC coated tablets that are halved absorb almost the same quantity of water vapor compared to the intact ones. The previous findings suggest the following: on the one hand, HPMC coating does reduce water vapor permeability to a certain extent, but compared to marketed products its moisture protective ability (MPA) is insufficient. Thus, it does not offer a satisfying moisture protective coating. On the other hand, halved HPMC coated tablets do not absorb as much water vapor as the uncoated tablets, which is an unexpected finding. An important question at this stage would be "why not?": the fact that halved HPMC coated tablets do not absorb as much water vapor as the uncoated Syloid tablets indicates that Syloid Tablets' water absorbing capacity has been reduced by the coating process. Now the explanation to this phenomenon could be as follows: from Section 4.3.2.1.1 it is known that HPMC coated tablets contain the highest amount of residual moisture among the coated batches (Figure 4.48) and obviously this reduces the water absorbing capacity of Syloid Tablets. In conclusion, the reduced moisture uptake of intact Syloid Tablets coated with HPMC is attributable to an additive effect of both, the HPMC coat per se (that successfully reduces water vapor permeability) and the reduced moisture absorbing capacity resulting from residual moisture in the tablets. The point that the HPMC coating process per se render the Syloid Tablets with reduced water absorbing capacity is supported by the following two reasons: the residual moisture is reversed by preheating (as shown in Section 4.3.2.1.2) and the water absorbing capacity of Syloid is almost fully regained (as will be shown in Section 4.3.2.2.2; see sub-chapter *Consideration One*). In other words, preheated HPMC tablets absorb more water compared to non pre-heated ones, because preheated HPMC coated tablets are more dry than non preheated ones.

EPO Coated Tablets (that are not pre-coated) EPO coated tablets show an almost 60% less water vapor uptake compared to uncoated tablets after 1 day. Halved tablets coated with EPO experience almost the same weight gain as uncoated ones, which goes in line with the expectation. EPO coating successfully protects Syloid Tablets from moisture uptake without reducing their moisture absorbing capacity.

PE$^+$ Coated Tablets (that are not pre-coated) Looking at Pickering emulsion coated tablets, at a first glance the results seem satisfactory: intact tablets ex-

perience almost 3.2 % weight gain, which is almost 40% less than uncoated ones. Without considering the halved tablets, this finding suggests that emulsion coating has moisture protective abilities (MPA) comparable to EPO coating. However, unlike expected the halved tablets experience the same amount of % weight gain compared to the intact ones. Even after a total of 48 hours (one more day) % weight gain does not rise, which suggests that the maximum uptake of PE^+ coated tablets has already been reached after 1 day. This phenomenon can be explained as follows: in Section 4.3.1.3.1 it is described that tablets coated with PE^+ have absorbed free lipid (SFO) into the core. This occurrence has obviously affected the cores, by reducing their moisture absorbing capacity. Syloid now filled with free lipid has a lower capability for moisture uptake, which falsifies the results. The total reduction in moisture uptake of intact PE^+ coated tablets is now attributable to the following additive effects: the coating process itself has left the tablets with some residual moisture, reducing its water vapor absorption capacity (see above: as in the case of HPMC coated tablets); it is a result of the reduced capacity to moisture uptake due to lipid uptake by Syloid.

It is worth mentioning that in Figure 4.50 both, EPO- and PE^+-coated tablet batches represent only one example of two similar experiments. On repeating the experiments the findings have endured and hence this model (coating of non pre-coated Syloid Tablets) has not been further investigated.

4.3.2.2.2 WVU Syloid Tablets (with HPMC pre-coat)

In Section 4.3.2.2.1 it has been shown that free lipid uptake by the tablet core affects the capacity of Syloid Tablets to absorb water vapor and thus the results have been misleading. Aiming to overcome the aforementioned deceive HPMC pre-coated Tablets have been further coated with each, EPO or PE^+. It is worth mentioning again that the pre-coat is not intended for EPO coating, but has yet been used in order to assure similar conditions. Instead the pre-coat is mainly useful and hence designed for PE^+ coating, since free lipid (in case of PE^+ coating) has been almost entirely banned from entering the cores. The latter has shown in the visual assessment of the secondary coated tablets: the greasiness of HPMC pre-coated tablets further coated with PE^+ indicates the aforementioned aspect (Section 4.3.1.3.2).

The pre-coat has thus fulfilled its main purpose to serve as a mechanical barrier to free lipid from uptake by the tablet core and its effect on water vapor uptake will be discussed in this sub-section (see later The Final Results).

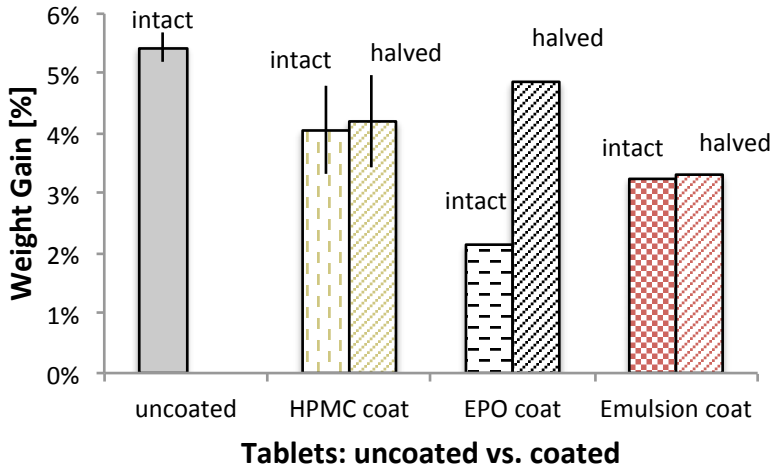


Figure 4.50: WVU of Coated Tablets Stored in Humid Conditions (no pre-coat). Result: Average % weight gain from "n" independent experiments, each with at least 3 tablet pairs per sample type – after 24 hours. Sample types: n=3 for uncoated tablets, n=6 for HPMC coated tablets, n=1 (exemplary) for SFO coated and EPO coated tablets; each sample type included two arms: intact and halved tablets. Conditions: tablets stored at 33 % RH. Error bars: standard deviation for $n \geq 3$; no error bars for n=1.

Nevertheless, a second demand has been also a requirement to qualify HPMC as a suitable pre-coat: the latter is expected to have no moisture protective abilities (MPA), in order to avoid falsification of results. In other words, any major reduction in WVU of HPMC pre-coated tablets that are further coated by a second coating (PE^+ or E PO) shall be attributable only to the latter, when compared with tablets that are not further coated.

In order to assess the MPA of the second coat without falsifying the results, the following two considerations are crucial to consider while approving HPMC coating as a suitable pre-coat:

Consideration 1: Validation of the HPMC Pre-Coat – Effect of Pre-heating In order to validate HPMC as a suitable pre-coat, two previous findings for HPMC coating are considered: first, HPMC coated Syloid Tablets contain the highest residual moisture, compared to Eudragit and PE^+ coating (approximately 0.7%; Figure 4.48). Heating HPMC coated tablets reduces the residual moisture (Section 4.3.2.1.2); preheated HPMC coated tablets show no negative WVU value when stored in a dry desiccator for one day (Figure 4.49), indicating that "no more moisture is inside" the tablets. Second, Figure 4.50 shows that - after 1 day at 33

% RH - HPMC coating reduces moisture uptake by 25% compared to uncoated ones. As previously discussed, this finding is attributable to the additive effect of HPMC coat's moisture protective ability together with the fact that the HPMC coating process per se has rendered the tablet's water vapor absorbing capacity reduced (see Section 4.3.2.2.1). In order to investigate these hypotheses, both findings are integrated and the following investigate is performed: preheated HPMC coated tablets are stored at different humidity levels and compared to both, HPMC coated tablets that are not preheated and to uncoated tablets.

Figure 4.51 shows that preheating HPMC coated tablets increases their water absorbing capacity to an average 90% (instead of 75%) of the uncoated ones at 33 % RH; the HPMC coat now reduces the absorbed water vapor by only 10% instead of 25% (at 33 % RH). In other words, preheated HPMC coated tablets have a higher WVU capacity than non-preheated ones. This finding indicates the following: compared to non preheated ones, preheated HPMC coated tablets contain less residual moisture, which leads to a regain of Syloid Tablets' moisture absorbing capacity. Consequently, WVU of preheated tablets coated with HPMC is reduced (compared to uncoated tablets) solely as a result of the HPMC coat.

As previously mentioned, the HPMC pre-coat has been aimed to only serve as a mechanical barrier to lipid entry, without obtaining any moisture protective ability, a property that is desired but not achieved. And because the following results build up on each other, here a take-away message from this finding: preheating HPMC coated tablets not only reduces Syloid Tablets' residual moisture but also regains most of their WVU capacity; consequently, preheated HPMC coated tablets show a higher WVU compared to non-preheated ones. Yet, HPMC's moisture protective ability (MPA) is significant and must be considered, since their tablets' WVU is not as high as uncoated ones. This effect is suboptimal, but inevitable.

Consideration 2: HPMC's Moisture Protective Ability as a Function of its Quantity per Tablet – A New Internal Reference Given the previous findings, it is now known that HPMC coat does have moisture protective abilities, a property that is undesired, but inevitable (Consideration 1). If all HPMC pre-coated tablet batches would have been coated with the exact same HPMC quantity, then no further considerations would have been needed. However, for technical reasons HPMC's quantity per tablet batch has not been well controlled, leading to a somewhat high relative standard deviation among the batches (23%); Table 4.18 has shown that the average quantity of HPMC coat per Syloid Tablet equals $9.00\% \pm 2.11\%$, which

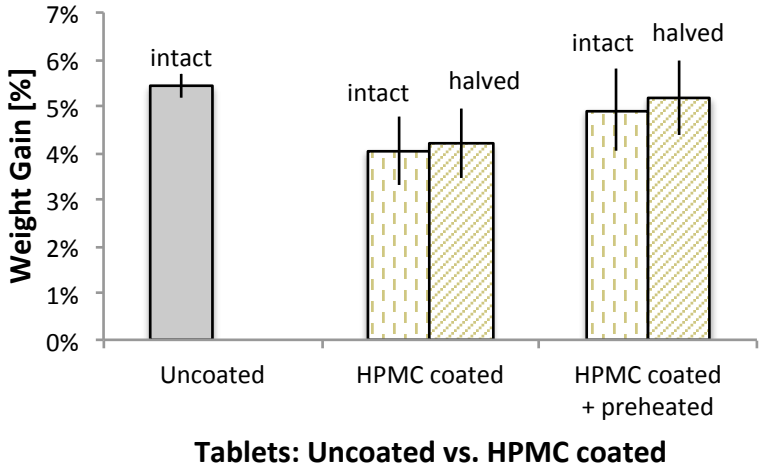


Figure 4.51: WVU of HPMC Coated Tablets Stored in Humid Conditions Effect of Pre-Heating. Result: Average % weight gain from "n" independent experiments, each with at least 3 tablet pairs per sample type – after 24 hours. Sample types: n=3 for uncoated tablets, n=6 for HPMC coated tablets and pre-heated ones; each sample type included two arms: intact and halved tablets. Conditions: tabets stored at 33 % RH. Error bars: standard deviation.

is calculated as an average of 6 individual HPMC coated tablet batches ($n = 6$; coat quantity for each batch is shown in Table 4.21).

As seen in Table 4.21, some batches are coated with a relatively low, others with a comparatively high HPMC quantity. Therefore, it is important to assess the effect of HPMC coating quantity per tablet on WVU of HPMC coated Syloid Tablets. Figure 4.52 exemplary shows % weight gain for three (out of a total six) batches depending on HPMC's quantity per tablet. The example includes the batch coated with the lowest, the highest and the intermediate average HPMC quantity per tablet (Batches 1 – 3).

The figure shows that an HPMC coated tablet batch containing a low HPMC quantity per tablet (Batch 1) experiences an average weight gain of 5.6% when stored at 33 % RH for 1 day. The amount of water absorbed is comparable to uncoated tablets absorbed amount (Figure 4.51). The higher the HPMC coating quantity, the lower the WVU: Batch 2 HPMC coated tablets contain 8.42% HPMC per tablet and increase by 4.20% in their weight; Batch 3 HPMC coated tablets contain 13.00% HPMC per tablet and increase by 3.77% in their weight when stored at 33 % RH for 1 day. As shown in Figure 4.51 those three batches together with 3 other batches experience an average % weight gain of 4.05% when stored at 33 % RH for 1 day.

Batch Name	HPMC Quantity per Syloid Tablet	
Batch 1	7.14 %	Average of all Batches: 9.00 % ± 2.11
Batch 2	8.42 %	
Batch 3	13.00 %	
Batch 4	7.67 %	
Batch 5	8.35 %	
Batch 6	9.43 %	

Table 4.21: Average Coat Quantity per Tablet for each HPMC Coated Tablets Batch. Coat quantity as % weight gain.

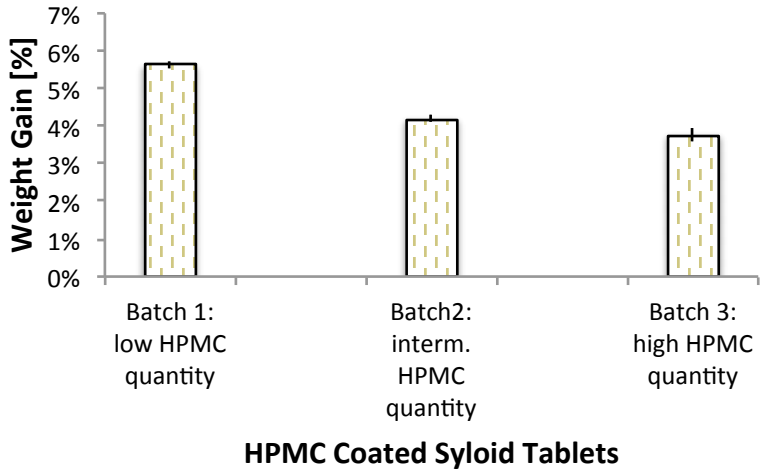


Figure 4.52: Effect of HPMC Coating Quantity on WVU of Syloid Tablets. Result: Average weight gain of three tablet pairs from one tablet batch and one experimental run (n=1) – after 24 hours. Conditions: tablets stored at 33 % RH. Error bars: Standard deviation (of triplicate tablet pairs' % weight gain, investigated in same experimental run). Note: Results shown here are for intact tablets.

The previous findings prove that water vapor permeability through HPMC coated tablets is a function of the HPMC coat quantity – a result that *must* be considered when using HPMC coated tablets for further coating by Eudragit or PE^{+}. Hence, it is necessary to include each HPMC coated tablet batch as a reference to the secondly coated batch. In other words, the average % weight gain shown in Figure 4.51 is scientifically insufficient to be included as the reference value for secondarily coated tablets.

And because the following results build up on each other, here a take-away message from this finding: each HPMC coated tablets batch is used as an internal reference to its own further coated batch after the tablets are preheated.

Example In assessing the moisture protective ability (MPA) of each second coating, Eudragit and PE^+, both previously discussed considerations have been taken into account (Consideration 1 and 2). Figure 4.53 illustrates one example of three coating batches performed for each, Eudragit and PE^+ coating. Both formulations are coated onto preheated HPMC coated Syloid Tablets (Consideration 1), where the latter serve as the internal reference (Consideration 2).

Starting with both HPMC coated batches, the following is seen: HPMC pre-coated tablets from Batch 1 experience different % weight gain compared to Batch 2 (Figure 4.53). These findings are previously shown in Consideration Two (see above), where % weight gain of (preheated) HPMC coated tablets is a function of the coats quantity. It is worth mentioning that Batch 1 and Batch 2 HPMC pre-coated tablets in Figure 4.53 are the same ones shown in Figure 4.52.

Next, the most important result in this context is that the pre-coat has indeed fulfilled its purpose, which can be seen when focusing on PE^+ coated tablets. The previously shown results seen in Section 4.3.2.2.1 (Figure 4.50) are improved: HPMC has successfully reduced free LP uptake by the Syloid Tablets, compared to non pre-coated Syloid Tablets coated with PE^+. As previously shown, in case of PE^+ coating onto Syloid Tablets without a pre-coat (Figure 4.50), halved tablets absorb almost the same quantity of water vapor (3.3%) compared to intact ones (3.2%). On the other hand, PE^+ coating onto HPMC pre-coated Syloid Tablets (Figure 4.53) shows that halved tablets absorb significantly more water vapor (3.44%) compared to intact ones (2.28%) of the same batch. Hence, these findings confirm that HPMCs pre-coat functionality has successfully reversed the negative effect of free LP.

Now that the results are evaluable, the model can be further investigated. Comparing both, intact Eudragit and emulsion coated tablets, at a first glance it seems that the emulsion coat reduces moisture uptake more than Eudragit coating; Eudragit coated tablets gain weight by 2.9% while emulsion coated ones by only 2.3%. However, relating % weight gain of each secondly coated batch to its own pre-coated one (internal reference) shows that both formulations are quiet comparable: an average 2.9 % weight gain divided by an average 5.6% (for Batch 1 HPMC pre-coated tablets) equals 52% relative weight gain. Similarly, emulsion-coating results in 55% relative weight gain.

Hence, this example illustrates the necessity to compare each coated batch to its pre-coated one, in order to assess the moisture protective ability of the second coat solely; HPMCs contribution to the moisture protection is thus excluded. Had the HPMC coat absolutely no moisture protective ability, would this calculation be

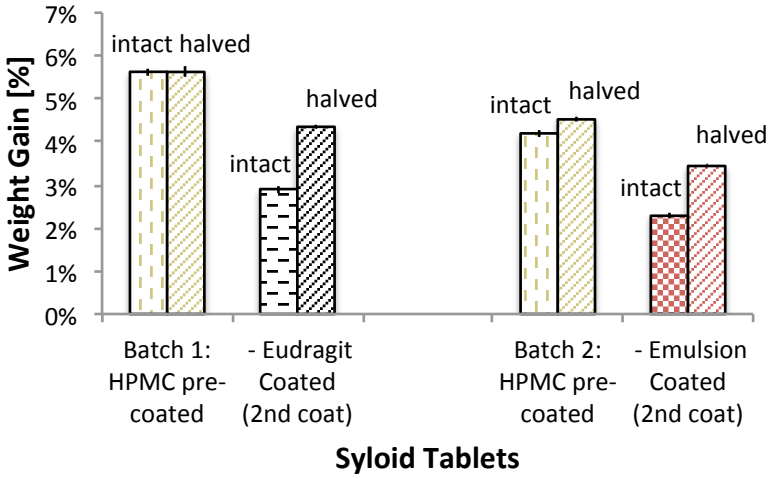


Figure 4.53: WVU of Secondarily Coated Tablets Compared to Internal Reference. Result: Average % weight gain of 3 tablet pairs from one tablet batch and one experimental run (n=1) – after 24 hours. Conditions: tablets stored at 33 % RH. Error bars: Standard deviation (of triplicate tablet pairs' % weight gain, investigated in same experimental run.

redundant. Similarly, had all HPMC coated batches an equal coat quantity per tablet, had this calculation been simplified.

Last but not least, focusing on the halved secondly coated tablets in comparison to the intact ones of the same batch the following is revealed: both, Eudragit and PE^+ secondly coated halved tablets absorb less water vapor compared to their internal references. For example, halved Eudragit coated tablets experience 4.35 % weight gain, whereas Batch 1 HPMC pre-coated tablets experience 5.62%. The same applies to emulsion coated tablets. This finding can be explained by the suboptimal coating process, where Syloid Tablets absorb some water vapor during the coating process, despite the relatively dry process (Figure 4.48). Section 4.3.2.1.1 confirms this finding: both, coated Eudragit and PE^+ results contain some residual moisture. The coating process is thus prone to optimization, aiming to reduce the moisture uptake by the tablet cores during the process. Suggestions regarding that matter are discussed in Section 4.3.2.2.3.

The Final Result - Novel Pickering Emulsions Moisture Protective Ability compared to Eudragit From the example described above, it is concluded that the relative weight gain of PE^+ and Eudragit coated tablets is a crucial parameter to compare both. Figure 4.54 illustrates the relative weight gain of PE^+

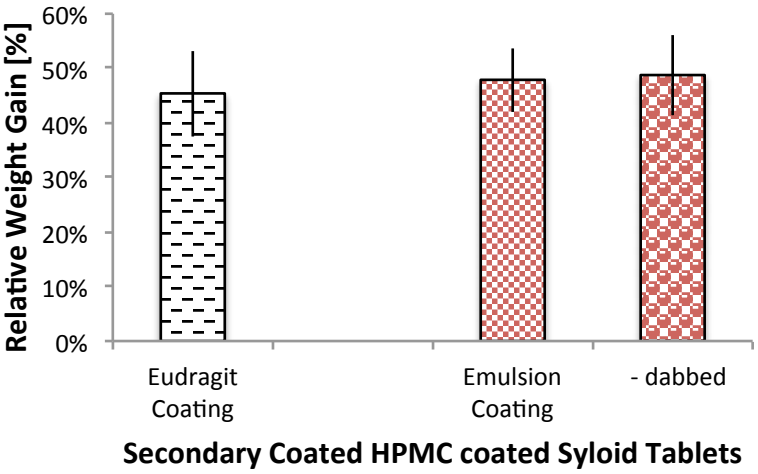


Figure 4.54: Moisture Protective Ability of PE$^+$ Benchmarked to Eudragit E PO. Result: Average % weight gain from all three independent experiments – after 24 hours Conditions: tablets stored at 33 % RH. Error bars: Standard deviation.

coated tablets compared to Eudragit coated ones, which is calculated as an average from three batches for each. The findings show that both formulations have similar moisture protective abilities. The amount of coat per tablet is similar for both. Furthermore, PE$^+$ coated tablets have been dabbed with a tissue, in order to remove any excessive oil from the tablet surface. The dabbed tablets absorb slightly -but insignificantly- more water vapor. This proves moisture protection of PE$^+$ coated tablets is attributable to the coat itself, and not a result of the free lipid available on the tablet surface.

4.3.2.2.3 Suggestions to Reduce Moisture During Coating

In Section 4.3.2.1 it has been shown that HPMC and PE$^+$ coated tablets contain higher residual moisture compared to Eudragit coated ones. The following explanation is based on a hypothesis that is not investigated during this research: it is believed that the viscosity of the formulation might affect the amount of moisture entering inside the tablet during the coating process. As opposed to EPOaq.-d, both HPMCs-12.5% and PE$^+$ are comparably viscous. Reducing the viscosity (by aqueous dilution) would elongate the coating process time but would lead to a reduction in the residual moisture of HPMC and PE$^+$ coated tablets. In general, atomized formulation drops reach the tablets surface, where the dispersant (water) is dried by mass (heat) transfer. The film polymers are left to form the film. Viscous coatings

show less spreading compared to non-viscous ones. Hence, the transfer of water from a highly viscous drop is expected to take more time than from less viscous ones. In turn, when a next drop reaches the tablet surface, remaining water is trapped behind the new drop leading to residual moisture inside the tablet. Residual moisture decreases the water absorbing capacity of Syloid, which in turn affects the results in different ways. For one, it might misrepresent the moisture protective ability of the coat, by falsely reducing it. Moreover, for the previously mentioned reason, halved coated tablets show less water uptake, which distorts the results as well. However, the above-mentioned hypothesis has not been examined during this doctoral thesis.

4.3.3 Summary

Section 4.3 integrates results from both previous sections. It mainly deals with coating of the formulation (from Section 4.1) onto the developed and produced hygroscopic tablets (from Section 4.2). In Section 4.3, pellets and tablets are coated with different formulations using a fluid bed coater (FBC) and a drum coater, respectively. First, the process parameters for coating Pickering emulsions onto pellets have been developed in a trial and error approach, until suitable process parameter ranges have been found. Coating of Pickering emulsions onto different cores requires no special technical adjustments or coating devices. The process parameter ranges are typical (Section 4.3.1.2.1). However, in order to preserve emulsion character while coating, the atomization pressure may not exceed 0.3 bars (Section 4.3.1.1); higher atomization pressure is found to cause emulsion drop destruction leading to increased d90 values (Figure 4.42). Coated pellets have shown to be somewhat greasy. The greasiness can be reduced by increasing the emulsifier to lipid ratio, as shown in Section 4.3.1.2.1. Pellets coated with $LP-15\%\_4:1.5:1.5$ have shown almost no oiliness compared to pellets coated with $LP-20\%\_4:1:1$. Yet, regardless of the emulsion components ratio, the coat is found to be a dried emulsion, where a dispersion of the emulsion coated pellets have shown the exact same droplet size as the crude emulsion (Figure 4.44). The coating process parameters ranges developed for pellet coating in a FBC (Section 4.3.1.2) have been adapted to coating Syloid Tablets using a drum coater (Section 4.3.1.3). The drying temperature has been set to the highest acceptable limit (70 °C), in order to assure the lowest possible moisture level during coating ($\leq$ 15 % RH). Nevertheless, coated tablets contain some residual moisture, which is most pronounced for the coatings in the order HPMC > PE^+ > EPO (Figure 4.48). It is believed that a more viscous coating formulation results in a higher moisture uptake by the tablet cores as a result of more localized moisture (Section 4.3.2.2.3).

Coated PE^+ tablets (without a precoat) have not been evaluated for the following reasons: the drum coater exerts a relatively high mechanical stress on the formed coat leading to undesired destruction of some oil droplets. Free lipid (the resulting exposed oil droplets) is absorbed by the tablet core, leading to misleading results. In order to avoid the aforementioned matter, HPMC coated tablets have been chosen to be further coated. HPMC serves mainly as a mechanical barrier to free lipid absorption by the tablet core. However, two considerations must be taken into account in avoiding false results: HPMC coated tablets need to be preheated before the second coat is applied, since the former contain some residual moisture that might negatively affect the results. Moreover, HPMC has some moisture protective ability, and the extent of moisture protection is a function of the coat quantity. Thus, each HPMC coated batches serves as internal reference for its secondarily coated batch.

Coating HPMC coated tablets with PE^+ has resulted in almost 50% less moisture uptake compared to HPMC coated tablets. The results are comparable to marketed products such as Eudragit E PO at equal coat quantities. In end, $SFO - 15\%\_4 : 1.5 : 1.5$ has moisture protective abilities comparable to Eudragit E PO.

Chapter 5

Summary

In this doctoral thesis, a novel formulation has been developed for moisture protective purposes. The formulation is a film-forming oil-in-water Pickering emulsion (PE^+). The rationale behind this choice is described as follows: Generally speaking, alternative systems have always been needed in the pharmaceutical industry at all levels, for example in order to circumvent patent issues, amongst others. Speaking of moisture protection, the latter can be achieved by several mechanisms, whereas coating (of tablets or pellets) is often regarded as the most convenient. Aqueous coating is advantageous over organic ones, for reasons mentioned in Chapter I (e.g. environmental, economic and safety reasons). When performing coating for moisture protective reasons several demands must be met, in order to guarantee a successful coat. Over the shelf, moisture permeation shall be as slow as possible (low water vapor permeability), protecting the moisture sensitive component from the environment; the latter is often achieved by incorporation of hydrophobic components into the formulation. However, once ingested, immediate release of the active ingredient must be guaranteed. As with all film coats, the film must be flexible, intact, stable and safe. Pickering emulsions seem to fulfill those demands, if the above challenges are to be considered on a galenic level as well as on a process level.

Starting with the galenic challenges (Stage 1.1: see Section 4.1.1), at the beginning of this doctoral research, dried emulsions seemed to meet the various demands for moisture protective film coats. Especially Pickering emulsions – the emulsions that are stabilized by particulate substances – show an advanced stability over conventional (surfactant stabilized) emulsions. The Pickering emulsions are known to be suitable for drying, resulting in dried emulsions, which - once redispersed in water - give Pickering emulsions, again. The idea was then to develop a stable film-forming Pickering emulsion suitable for spraying (coating) onto tablets or pellets, forming a film coat. From previous research it was known that nano-sized $CaCO_3$ is a suitable

particulate emulsifier resulting - at certain concentrations - in oil-in-water Pickering emulsions; stearic acid is added (2% of $CaCO_3$ concentration) to the lipid phase, supporting the localization of $CaCO_3$ at the oil-to-water phase boundary and hereby stabilizing the oil to water interface. Stearic acid probably adjusts the wettability of crude $CaCO_3$, by increasing its wetting angle to values close to 90°, as described under Section 1.3.3.3 [32]. It was shown that a formulation with 20% oil (medium-chain triglycerides), 75% water and 5% $CaCO_3$ and 2% stearic acid (the latter being relative to the $CaCO_3$ quantity) resulted in a stable oil-in-water Pickering emulsion.

Furthermore, $CaCO_3$ is a soluble in acidic media, which is believed to have a positive effect on the coat release once ingested; the film coat (made up of the Pickering emulsion) is then believed to dissolve away from the core quickly.

For moisture protective film coating reasons, the choice of the prototype emulsion took place in a systematic manner as follows: first, the $CaCO_3$ suitable for emulsification needed to be identified; it was found that not any $CaCO_3$ powder allows stable emulsion production; of 3 different $CaCO_3$ batches, only one showed stable emulsion production, probably for geometric and particle size reasons, allowing the particles to stabilize the water-to-lipid interface (Section 4.1.1.2.1). Hence, all further emulsions in the context of this doctoral thesis are produced with this so-called Batch 1 $CaCO_3$. In order to reach a high moisture protective ability (MPA) of the formulation, several demands had to be met on a formulation level (Table 4.2), for example, a low polarity lipid was expected to result in a low water vapor permeability (WVP). Hence, 6 lipids were chosen as lipid candidates for the formulation. The lipids were medium-chain triglycerides (MCT), sunflower oil (SFO), castor oil (CO), isopropylmyristate (IPM), paraffin subliquidum (PSL) and paraffin perliquidum (PPL), all with varying polarities and viscosities. Each lipid was assessed for its polarity and viscosity (Section 4.1.1.1.1, Figure 4.3). MCT was chosen as an exemplary lipid for component ratio modifications of the emulsion; several lipid concentrations as well as $CaCO_3$ concentrations were systematically investigated, assessing the phase type and the stability of the resulting formulation; not all lipids and / or $CaCO_3$ concentrations resulted in stable oil-in-water Pickering emulsions (Section 4.1.1.2.2): lipid concentrations of 15 or 20%, as well as a lipid-to-$CaCO_3$ ratio of 4 : 1 or 4 : 1.5 resulted in positive results (Table 4.5). Hereby, 4 formulation ratios were shown to result in stable stock Pickering emulsions (PE_s). The other 5 lipids were also incorporated into the formulation, one at a time, resulting in oil-in-water emulsions as well Table (4.6). The film-forming property was achieved by HPMC 606 with at least 4% of the final formulation. The resulting film-forming Pickering emulsion (PE^+). However, when the

latter was allowed to dry to free films, only 3 of the 4 formulation ratios resulted in intact films (Table 4.8). Hence, as seen in Table 4.9, 3 formulation ratio types were identified for further research. Before continuing with the moisture protective assessment (MPA) of the formulations, it is worth mentioning that emulsion stability was mainly assessed macroscopically, microscopically and by droplet size measurement, whether at time zero or at specified time intervals (Section 4.1.1.3). The galenic development was hereby finalized and various formulations were dried to free films for MPA assessment; the aim was to reach the highest MPA and to be competitive to marketed products claiming moisture protection. Among the various methods to assess a MPA of a formulation, to us, the most feasible constellation of tests has been the following: gravimetric tests performed on cup methods and as coated films seemed to be most significant and universal. A modified cup method performed on free films allows assessment of the WVP-values of several formulations; further studies allow the assessment of water vapor sorption (WVS-) values of the free films. Background information to the mentioned parameters are mentioned in Chapter 1 (Section 1.3.2.4) and in Chapter 4 (Section 4.1.2.2.2). From the various tests performed the following results are collected in a puzzle-like manner as described now: performed on free films with MCT as an exemplary lipid, water vapor seems to migrate through a dried Pickering emulsion film by diffusion as with conventional films (Figure 4.17). Moisture diffusion does not take place via the HPMC backbone matrix only (as could have been expected), but also via the lipid component / droplets, that are immobilized by the $CaCO_3$ emulsifier and the HPMC matrix (as seen in Figure 4.13). This was proven by the experiment showing that water vapor migrated through crude lipids loaded into the pores of PTFE-filter (Section 4.1.2.2.3), amongst others. $CaCO_3$ and lipid ratio variation seem to have no major effect on WVP (Figure 4.20). Comparing the results for free films containing variable lipids, the following was seen: WVP through free films is not only a function of the polarity but also of the viscosity of the lipid incorporated in the formulation. For example, higher polarity lipids expected to result in higher WVP can show lower WVP results as a result of the high viscosity of that lipid (e.g. castor oil, CO, containing emulsions), where the viscosity compensates the polarity according to Equation 4.4. Figure 4.31 summarizes shows the results of the WVP of dried emulsions containing different lipids. WVP tests allow the assessment of the quantity of moisture going through the film as well as the amount of moisture residing in the film. The latter can be identified by dynamic vapor sorption (DVS) tests, resulting in the so-called water vapor sorption (WVS-) value. Since all free films of the comparative study included the same formulation ratio (5% HPMC, 20% lipid

and 5% $CaCO_3$), the trend of WVS-values was expected to follow the polarity trend of the lipids (high polarity lipid formulations would have a higher affinity to water vapor and hence have higher vapor residing in them). However, this expectation was not met and, instead, another factor played a significant role: free film morphology as a result of lipid escape from the dried Pickering emulsions altered the film behavior in that sense (Section 4.1.2.2.5 and Section 4.1.2.2.6). Figure 4.32 summarizes the collection of the results of all experiments serving MPA assessment. After the detailed review of the trends of the various results (Figure 4.32), it was suggested that lipid escape is expected to be highest for very high or very low viscosity lipids (Figure 4.33). In summary to the MPA of dried Pickering emulsions, a low WVP-value is surely advantageous and is expected to be achieved by incorporating a lipid of high viscosity and low polarity (Figure 4.33); the viscosity may however not exceed an optimal range, in order to avoid its escape from the dried film. Last but not least regarding the MPA of dried Pickering emulsions, it is worth mentioning that emulsions containing sunflower oil showed low WVP-values as low as Eudragit E PO; emulsions containing either paraffin showed even lower WVP than Eudragit E PO.

Apart from the MPA assessment, emulsion re-dispersability in water and emulsion character preservation in the dried state needed to be guaranteed (Section 4.1.2.1.3). All dried PE^+ formulations (free films) were shown to result in oil-in-water emulsions after the addition to water, which was measured by droplet size measurement after dispersion in water. Furthermore, Figure 4.13 shows a scanning electron microscopic image of a cross-sectional cut of a dried emulsion free film, where droplet like structures could be identified, supporting the previous statement. The previous results were mostly on a galenic level and its effect on the functionality of the dried formulation with respect to moisture protection. The challenge on a process level was discussed in Stage 3.1 (Section 4.3.1) and is summarized later.

In Stage 2, tablet cores (named Syloid Tablets in this doctoral research) were produced for coating by various moisture protective film coating formulations. The tablets were produced to serve the main purpose of being hygroscopic, in order to assess the moisture protective ability of the aforementioned formulations. As a means to an end, a hygroscopic formulation based on dried silica was pre-assessed for its hygroscopicity. Once approved, tablets were produced and characterized. Despite some challenges in flowability of powder / granules during tableting, tablets met the demands of the European Pharmacopoeia for mass uniformity. Water vapor uptake (WVU-) tests were performed for uncoated tablets, where the weight gain over time was measured at specified time intervals for tablets stored at various humidity

conditions (dry, 33% RH, 75% RH). The results showed that uncoated tablets had residual moisture of 1 - 2%, and they increased in weight by 5 - 6% and 9 - 10% when stored at 33% RH and 75% RH, respectively. The maximum uptake of water vapor was reached already after 24 hours, setting a fundament for further studies in terms of the experimental duration; yet, the studies took place for 4 days, assuring that no further weight gain was observed indeed.

In the last stage of this doctoral thesis (Stage 3), the main aim was to coat the produced Syloid Tablets with the novel formulation, being one of the experiments for the moisture protective ability (MPA) assessment of the latter and its benchmark to marketed products. After showing that emulsion character preservation is guaranteed in the free film form, it had to be guaranteed in the coat as well. And in order to do so, as mentioned at the beginning of this chapter, challenges on a process level had to be faced: for one, the emulsion character may not be destroyed due to spraying at high atomization pressures; secondly, the hygroscopic tablet are not allowed to uptake excessive moisture during the coating process itself, decreasing their moisture uptake capacity. Starting with the first challenge, emulsion character preservation was shown to be preserved during the spraying process, as long as the atomization pressure did not exceed an optimal value ($\leq$ 0.3 bar). In the coat itself, emulsion character preservation was proven by coating inert sucrose pellets followed by their re-dispersion in water and measuring the resulting droplet size distribution. Comparing the latter to the droplet size distribution of the crude emulsion before coating (PE^+), it was shown that both results were almost identical (Figure 4.44). Furthermore, a scanning electron microscopic image of a cross-sectional cut of a coated pellet showed emulsion like structure in the film coat, supporting the previous result (Figure 4.45). Hence, emulsion character was shown to be preserved during the process itself and in the final coat: free films as well as film coats of the novel formulation, PE^+, are dried emulsions. Continuing with the second mentioned challenge, the main coating process parameter ranges allowing emulsion character preservation during coating were developed by coating the aforementioned inert sucrose pellets: the optimal inlet air temperature range was found to be 50 - 70 °C, the spraying rate at 0.5 - 1.5 rpm. Those were the process parameter ranges that resulted in coated pellets that were macroscopically with intact film coats, as well as resulting pellets that showed no tackiness, no flacks of dried film pieces, nor were too wet and oily. Yet, some oiliness of the film coat was observed for coating of the prototype that included 20% lipid (MCT in that case) and a ratio of oil-to-$CaCO_3$-to-HPMC of 4:1:1. The oiliness expected as a result of oil migration from the HPMC Matrix to the surface due to mechanical

stress during the coating process was found to be least for alternative formulation components ratio: formulations containing 15% oil and a ratio of oil-to-$CaCO_3$-to-HPMC of 4:1.5:1.5 were advantageous and hence chosen for further experiments, as shown below for tablet coating. Before even assessing the MPA of the formulation, the previous results per se are valuable for the following reason: the results show that Pickering emulsions can be coated onto solid cores (here pellets) using conventional coating devices and process parameters, while retaining emulsion character during the coating process as well as in the final coat.

Previously (in Stage 2.2: see Section 4.2.2), the novel formulations MPA has been defined for it being in a free film form. Now, for the MPA assessment of the novel formulation as a coat, Syloid Tablets were coated and water vapor uptake (WVU-) tests run. The coating process of the Syloid Tablets respected the previously developed process parameter ranges for pellet coating. Since the Syloid Tablets are extremely hygroscopic, their water absorbing capacity was not allowed to be decreased during the coating process, or otherwise the WVU-value results comparison to the uncoated reference would have been misleading. So, the Syloid tablets were shown to retain their hygroscopicity and moisture uptake capacity during the process if two conditions are met: first, prior to the coating process (start of spraying the coating fluid), the tablets must be preheated for almost 30 minutes to give up any unintended absorbed humidity during tableting itself or storage (from the time of Syloid Tablet production until coating); as previously mentioned, the produced Syloid Tablets have shown to have a residual moisture of 1 - 2% after tableting, which was removed by the preheating step (see Section 4.3.2.1.2). Furthermore, because the novel formulation and the marketed moisture protective formulation benchmarks are of aqueous nature, undesired water uptake during the coating process itself was expected to take place if the drying capacity of the coating process is not adjusted; hence, in order to assure the absence of this undesired aspect, the process parameters were set to include relatively high inlet air temperatures and hence low relative humidity levels during the coating process: the inlet air temperature was chosen to be at the upper end of the previously developed inlet air temperature range (70 °C) (see Table 3.10). Last but not least, it is worth mentioning, that the formulation of choice for tablet coating was the one containing SFO as its lipid, since it has shown a superior combination of demands on galenic and functional levels, as previously discussed in Section 4.1.2.2.6. Syloid Tablets coated by the PE^+ were quickly identified as unsuitable for MPA assessment of the novel formulation, since the hygroscopic component of the tablets (namely Syloid) has absorbed some free lipid, altering the moisture protective ability

of the tablet cores. This so-called wicking effect has probably taken place by lipid escape from the emulsion during the mechanically stressful coating process in the pan. Figure IV-46 shows the images for uncoated Syloid tablets, tablets coated with E PO and with SFO − 15%_4 : 1.5 : 1.5, all being coated with a comparable quantity. This challenge has been overcome by a mechanical shield between the emulsion coat and the crude tablet surface, by an HPMC pre-coat at defined quantities. Those pre-coated tablets have been validated and standardized for their moisture absorbing capacity, as described under Sections IV.3.1.3.2, IV.3.2.2.1 and IV.3.2.2.2. The precoated tablets were further coated with the novel formulation and its benchmark at comparable coating quantities and subjected to WVU-tests. Figure IV-54 shows that the novel formulation has a comparable moisture protective ability (MPA) compared to its benchmark Eudragit E PO: both formulations show a reduction in weight gain by approximately 50% relative to the uncoated tablets.

This doctoral research has hereby offered a successful novel moisture protective formulation, that surely has great potential to make it to the market, if some challenges on a galenic as well as process levels are optimized.

Chapter 6

Annex

This chapter includes further information, that are believed to be important background information for this doctoral thesis.

6.1 Moisture Protective Ability Characterization

This section includes more information than previously presented regarding the moisture protective ability characterization of a formulation claiming moisture protection. The information presented below, have been partially demonstrated before, under Section 1.3.2.4:

As previously presented, pharmaceutical moisture protection can take place by several means, including packaging and coating. In this sub-section, the focus is on characterizing moisture protective formulations intended for coating. They are not characterized in their liquid state, but in their dried state, as films (edible / free films or film coats; details will follow below).

Ahead, please note that the coming text is more of a review to current research groups performing moisture protective ability (MPA) assessment of various moisture protective formulations. Until the end of the sub-section "Summary of MPA Considerations", all the important aspects are discussed theoretically. Starting the sub-section titled "Literature Review: Methodologies Used by Other Scientists", the theoretically presented aspects are supported by findings from various peer-reviewed studies. After all, the theoretical aspects to consider are collected from those various peer-reviewed studies and their significance presented subjectively.

Terminology Definitions - Moisture Protective Ability (MPA) - 1st Term So, first, and before going into details about the different methods and approaches of moisture protection characterization, four main terms need to be defined

upfront (Figure 6.1). We consider the moisture protective ability (MPA; 1st term) of a formulation or film to be the collective ability of this formulation or film to prevent moisture uptake by a "Substance X", protecting the latter from water vapor. The broad term "MPA" - to us - includes any mechanism or approach to reduce water vapor permeability (WVP; 2nd term) and water vapor uptake (WVU; 3rd term); water vapor solubility (WVS, 4th term) and the diffusivity (D) of water vapor in the moisture protective film are considered accordingly. Before continuing with their definitions, Substance X, can be a moisture sensitive substance (Option A) that degrades when exposed to humidity over time (chemical change, e.g. hydrolysis) or that experiences a physical change (e.g. polymorphic change). It can also be a hygroscopic substance (Option B) that absorbs water vapor in presence of the latter and increases in weight; MPA characterization takes place indirectly via the characterization of Substance X (whether as Option A or B), and the experimental design depends on its nature (as will be presented shortly). Furthermore and as mentioned above, a coating formulation's MPA is assessed for the formulation being in its dried film state; the film is in a free-film form (edible film; Option 1) or in a coated form (Option 2). More details on Substance X and the film state will follow below.

Going on with our definition of MPA, it is worth mentioning that - again, to us - regardless of what exactly is happening with moisture, as long as Substance X is not "harmed", it does not really matter where "the" moisture is localized; in other words, if moisture is rejected by the moisture protective formulation or if the latter absorbs it and keeps it away from Substance X, the most important factor here is the protection of X.

Terminology Definitions - Water Vapor Permeability (WVP) – 2nd Term Water vapor permeability (WVP; 2nd term), it is a complex term of various definitions. We have to distinguish between two meanings for WVP here: a practical / experimental one, and a general (progress-related) one. WVP, in a practical / experimental sense, is defined as the amount of water vapor permeating at a unit time, unit area and unit film thickness. So-called WVP-tests performed (usually on free films, and not film coats, and on X being hygroscopic, not moisture sensitive) yield WVP-values. Typical tests are described in details below. WVP in a broad sense is not the quantified value for water vapor permeation (as the WVP-value), but rather the stepwise process of water vapor permeation through a barrier membrane; WVP - according to its broad definition - applies to free films and film coats, and does not depend on the nature of Substance X (being hygroscopic or moisture sensitive);

in short, it defines the act of water vapor permeation through a film reaching the "other side".

A detailed definition of it, its significance, methods of assessment and calculation will follow below. But at this stage, the important point is the following: to us, WVP (especially in its broad sense) differs from the MPA term, in that the latter is the overall protective ability (or approach) of a formulation to reduce WVP (in its broad sense), whereas the former (in its practical sense) is mostly a quantification of the amount of moisture passing the formulation being usually a free film. Before going on with further definitions, please note that depending on the experimental design WVP-test results can also include the amount of moisture residing in the dried formulation (and not just passing it); details on that will follow below.

Before conducting any of the various experiments assessing a formulation's MPA found in literature, the main question is "what is the aspired result and data of a designed experiment?". Depending on the answer, the experiment is designed, Substance X is chosen (Option A or B) and the film state is chosen (Option 1 or 2), as follows: Starting with Substance X, tests performed on X being a moisture sensitive substance (which degrades by moisture) characterize a formulation's MPA indirectly by providing data on the extent of harm affecting X. As mentioned above, in that case, X would be a moisture sensitive substance undergoing a chemical change (e.g. hydrolysis) in presence of moisture; X itself and / or its degradation product are quantified analytically. X could also be a substance undergoing a polymorphic change with different solubility; X's chemical bonds nature has remained in that case. Yet, in both cases (both = Option A), the tests do not (directly) quantify the amount of moisture passing the film. So, to quantify the amount of moisture passing through a moisture protective barrier, gravimetric techniques are typical, amongst others (e.g. WVP tests). Those require Substance X being of a (highly) hygroscopic nature (Option B).

On reviewing scientific literature regarding pharmaceutical moisture protective formulations, most formulations were assessed gravimetrically (by WVP tests). Only a few research groups measure MPA of a moisture protective formulation analytically (where Substance X is a moisture sensitive substance). However, several other tests can also be performed for the same purpose (e.g. X-Ray, FTIR, etc.) [38].

Regardless of the test substance (X being hygroscopic or moisture sensitive), the following is valid for the film state: broadly, two main experiment types exist depending on the state of the formulation. The first one includes investigation of the dried moisture protective formulation being a free film (not coated onto solids, Option 1)

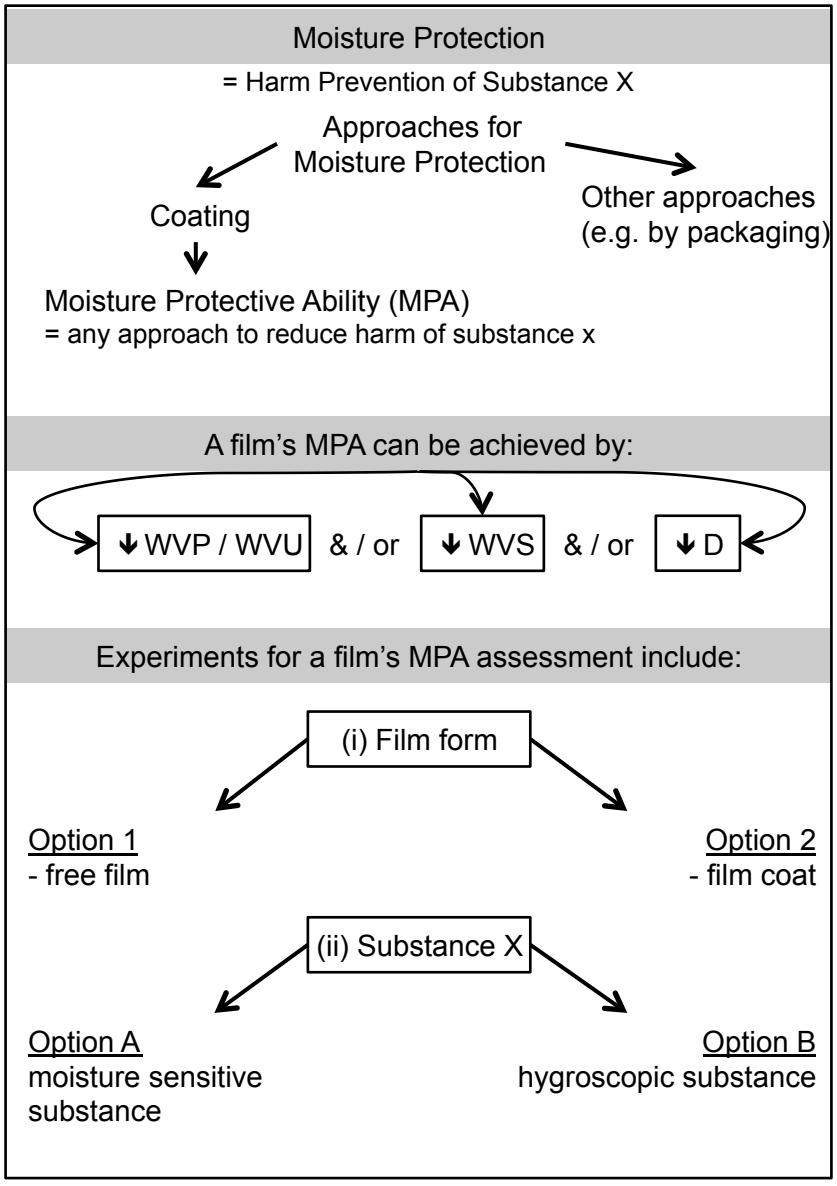


Figure 6.1: Overview of Terms and Definitions.

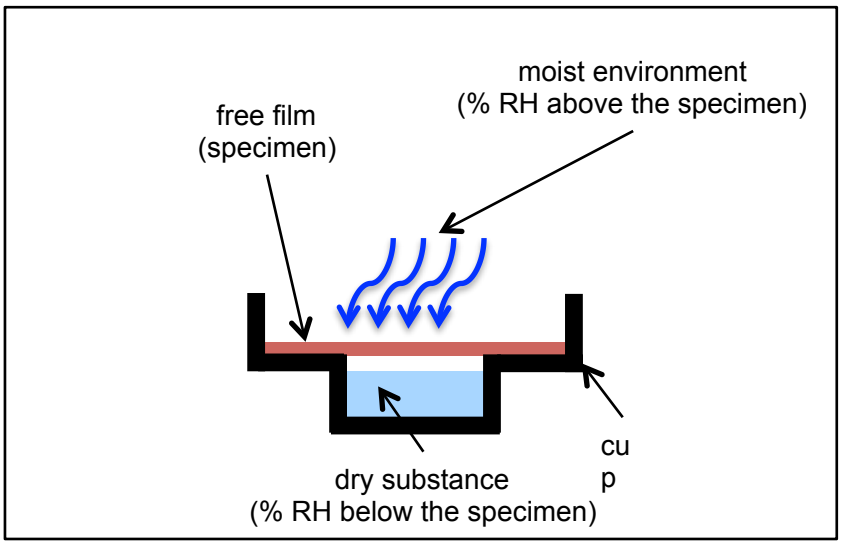


Figure 6.2: Cup Method (Schematic Drawing).

that separates surrounding moisture from Substance X. The so-called cup method (or modifications of it) are typical here [2]. The second test type includes coating a solid formulation, and testing the coated form (Option 2).

Water Vapor Permeability (WVP) Tests Now, one of the different combinations of the binary options (film and Substance X) are shortly presented: usually, free film (Option 1) tests (e.g cup method) are performed on Substance X being hygroscopic (Option B). In that case, our research group names the tests "WVP tests". Figure 6.2 illustrates one of the constellations available for this method: a cup containing a hygroscopic material capable of absorbing moisture and gaining in weight is separated from a moist environment by a film membrane. Below the latter, air is dry (at least at the beginning of the test). Over time, weight gain of the entire cup is measured and WVP-value calculated. For the complexity of this calculation, its details are shown below (see under WVP in its Broad Sense and WVP Derivation - Figure 6.3 (below), and see under Section III.1.2.3). And since the entire cup is weighed, the amount of weight gain (corresponding to moisture) reflects the sum of both, permeated moisture through the film and moisture residing in the film (as mentioned above; under WVP Term definition).

Terminology Definitions - Water Vapor Uptake (WVU) - 3rd Term Instead of using the formulation in its free film form, coated solid dosage forms containing a hygroscopic substance are tested by the so-called water vapor uptake (WVU; 3rd

term) tests (Option 2: film coat; Option B: Substance X being hygroscopic). WVP in its broad sense still applies (water vapor permeates through the film, resides in it and / or reaches the core), but is called "WVU". The terminological variation is useful, in order to distinguish the two resulting values (coming from WVP- vs. WVU-tests): the "WVU-value" as a term has resulted. It is analogous to the WVP-value, but differs in that it applies to coated tablets or pellets (see Section III.2.2). In short, the previous approaches - where Substance X is hygroscopic - provide gravimetric data, quantifying the amount of moisture passing through and / or residing in a film. Please note, however, the same experimental methods (cup-method or coated tablets) can be applied to tests including Substance X being moisture sensitive (Option A for Substance X); analytical data are provided in this case. In fact, it is uncommon for methods including free films (e.g. cup methods), but typical for coated forms. Pros and cons of each test type (free film vs. coated film; gravimetric vs. analytical) are discussed later under this sub-section (Section 1.3.2.4).

Terminology Definitions - Water Vapor Sorption (WVS) - 4th Term Now, and before integrating the previous aspects, another term is worth defining: water vapor sorption (WVS; 4th term). The term in this context is defined as the capacity of dried formulations (whether as free films or as film coats) to comprise water vapor. In other words, it is the maximum amount of a permeant (water vapor) that can reside in the barrier membrane and hence, it is a static value (unlike WVP-values). Please note that WVS is not necessarily the absolutely maximum amount of a film's capacity to water; it can also be related to conditional cases (e.g. WVS of a film at a certain environmental relative humidity, % RH). At this stage, it is worth mentioning that WVS is a general term used for any amount of water vapor residing in a film. In Chapter 1, WVS is a general term used for three experimentally obtained values (WVS-value, EMC-value, S-value) that slightly differ among each other. They are described in detail under Section 4.1.2.2.1 (Table 4.13). Furthermore, in avoiding confusion, it is worth mentioning that WVS-tests are not related to Substance X; the tests do not necessarily include Substance X, but include at least a film.

WVS results contribute to the overall understanding of a formulation's MPA: they answer questions to the hygroscopicity of the barrier membrane itself. Especially the gravimetric tests performed on free films described above (WVP-tests) require further investigations, providing data on a film's WVS. The following reasons explain why: assuming the investigation of two moisture protective formulations having the exact same (quantified) WVP-value, their MPA can still differ significantly. For example,

Formulation 1 with a low WVS-value (or any other value representing WVS) has less capacity to water vapor than Formulation 2 having a high WVS-value. Formulation 1 could for example be less hygroscopic than Formulation 2 and hence allow more moisture to pass / permeate. Yet, the measured WVP-value is equal in both cases, representing the total amount of weight gain (for moisture inside the film and moisture passing through it). Their MPA would then be different.

WVS can be assessed by various techniques, mostly gravimetric ones. For example, absolute film solubility to water vapor could also be obtained by exposing the film samples to a maximum relative humidity (100 % RH) and by gravimetric or analytical means the water content assessed (water uptake studies [13, 12]. A similar but yet different approach is the following: Mwesigwa et al. have assessed moisture solubility in polymeric films by the so-called dynamic vapor sorption (DVS) technique [38]. Mwesigwa calculated a film's solubility to water vapor from its sorption-desorption studies. The same technique is also expected to work for the weight gain of standardized films that are exposed to a certain relative humidity. In that case, WVS-values or EMC-values (equilibrium moisture content; explained under Section 4.1.2.2.1) would result, depending on their degree of dryness. A third approach described in literature is performed by Tongdeesoontorn; this research group assesses absolute water solubility in edible films by soaking the latter in water for a certain period of time and - via the weight difference – absolute water uptake (solubility) is calculated (S-value). This can only be performed, if the film is (absolutely) insoluble in water; otherwise, film material would dissolve "away", leading to confusing results.

One could argue here, whether all just-described techniques result in the same quantified value for water residing in a film. This is indeed prone to negotiation, and is not part of this doctoral research. Yet, any value representing WVS of standardized films would contribute to the overall understanding of a film's MPA. Moreover, there are surely non-gravimetric methods capable of answering the question to WVS; they are, yet, not considered in the context of this doctoral research.

WVP in its Broad Sense and WVP-Value Derivation Until now, several terms including the WVP-term have been defined. The latter has been presented in its broad and its experimental sense, but its calculation has not been presented, yet; the cup-method was described quickly and it is captured here again. So, coming back to WVP, in fact, it is a complex term and as previously mentioned its definition in the experimental context of this doctoral research is defined as the amount of water vapor permeating through a unit time, unit area and unit film thickness (WVP-value); in

its broad sense, it is the ability of a moisture protective formulation to allow moisture passing. Now, in order to understand moisture protection and water vapor permeability (WVP), the following aspects need to be considered; both perspectives (the experimental and the broad definition) of WVP are integrated as follows: protecting Substance X with a moisture protective formulation does not guarantee a lifelong protection; as long as the polymeric film is pore-free and its affinity to water is above zero [1], then moisture can always permeate through it and / or reside in it. Hence, moisture protection is more of a delay to the possible harm affecting Substance X that might result from water vapor permeability. Water vapor passes a film in a three-step mechanism: it first adsorbs to the film surface, diffuses through the film and completely or partially desorbs on the other side. The more hydrophilic the film is, the higher its WVS and the higher the permeability. This process of WVP (both, in its broad sense and experimentally) is a function of both, moisture's solubility and its diffusivity in the film (Figure 6.3 – Equation IV). Equation IV of Figure 6.3 is widely found in literature, describing the factors contributing to WVP: the solubility, S, is a measure of the amount of penetrant sorbed by the polymer; the diffusivity, D, represents the ability of the permeant to move within the polymer. It clearly relates WVP to its contributing factors. In short, the solubility and diffusivity of moisture in a barrier membrane are dependent on the barrier's affinity to moisture (hydrophilic vs. hydrophobic), its density and geometric packing configuration, amongst others. Here, the difference between water vapor permeability, WVP, and water vapor sorption, WVS, appears better: WVP of a barrier membrane (either free film or film coat) is dependent on the WVS of moisture *in* the film. The higher a film's WVS, the higher its WVP at constant diffusivity, D. But the opposite is not necessarily true: a high WVP does not necessarily result from (only) a high WVS of a film, as WVP also depends on D.

WVP being a product of moisture's solubility and its diffusivity has now described (some of) the factors affecting it. In other words, this definition is valid for the stepwise progress of moisture permeation through a barrier membrane (in its broad sense), and it also describes the experimental term (mathematical derivation, experimental definition) as shown now. Thinking back of the practical definition - the experimental aspect of WVP -, WVP quantification can mathematically be derived as shown in Figure 6.3: The P-coefficient is derived from Fick's first law of diffusion (Equation I

[1]Polymeric films having absolutely no affinity to water are expected to result in no or very low dissolution rates (an undesired property for moisture protective and immediate release coating formulation).

in Figure 6.3) and Henry's gas law (Equation II in Figure 6.3). Using Equation II of the figure for the concentration term, c, of Equation I results in Equation III.a. The latter can be re-structured to result in Equation III.b, which is equivalent to Equation IV. Equation IV includes a P-term (Permeability). This derivation is found often in literature (e.g. [53]). If Equation IV of Figure 6.3 is slightly modified and restructured, it gives Equation V as follows (Figure 6.4): the Flux, J, representing the amount of substance diffusing per unit area of the barrier membrane and unit time is rewritten to be the weight gain (resulting from moisture) per unit area and unit time; the film thickness, l, is replaced by the film weight (for the lack of inaccurate film thickness measurement, film weight may be used as a measure for film thickness, assuming a linear relationship between both); the delta partial pressure term, $p_a - p_b$, found in Equation III.b, is considered to be constant for a given relative humidity gradient above and below the barrier film and hence Equation V results. Equation III.c of Figure 6.4 illustrates the intermediate step from Equation III.b to Equation V of Figure 6.3. Some scientists use Equation III.b of Figure 1.6 or Equation III.c of Figure 6.4 (e.g. [43]), while others use Equation IV of Figure 6.3 (e.g. [38]) to quantify WVP. A detailed review on the different approaches, equations and their results is explained below (see sub-section titled "Literature Review: Methodologies Used by Other Scientists" later in this chapter). In this doctoral research, Equation V of Figure 6.3 is used to determine WVP-value (see Equations of Chapter 3 and Chapter 4). Here, and before continuing with the background information, the following is important: all, the P-value described in Equation IV, the WVP-value calculated in Equation III.b, and the WVP-value found in Equation V (all found in Figure 6.3), describe the same term. Values for WVP calculated by Equations III.b and IV are expected to be equal, but different from the value obtained from Equation V. This is so, because the partial pressure term, found in Equation III.b is not accounted for in Equation V (as seen in the intermediate Equation III.c); it is considered to be constant as long as sink conditions apply. However, results from all those equations do certainly correlate.

Above, it has been mentioned that tests for WVP include ones performed on free films or film coats. It has also been mentioned above that - in order to obtain WVP-values -, tests are performed on free films using the gravimetric methods (to our knowledge). Looking at the just presented equations in Figure 6.4, all the equations require information on the amount of moisture permeating through the film. This is why we believe that WVP-tests aiming to calculate WVP-values use Substance X

being hygroscopic substances (and not moisture sensitive); the results are gravimetric (and not analytical).

Regardless of the equation used for WVP, after all, WVP-value of free films is a material property and enables the comparison of different edible film materials regardless of their thickness. It is obtained at a constant relative humidity and temperature and is valid for pore-free films (moisture permeation through porous films would take place via the least resistant route, the pores). WVP (as opposed to WVS) is a kinetic value that defines the overall moisture permeation rate of a substance under kinetic conditions (while moisture permeation takes place). In other words, the lower the WVP value of a substance, the higher its moisture protective ability is expected to be. The last statement is, however, not always valid of course, as previously presented under the WVS-term definition.

Pros and Cons of Either Option - Moisture Sensitive vs. Hygroscopic Substance (Option A vs. B) and Free film vs. Film Coat (Option 1 vs. 2) Until here, various random options to assess WVP and WVS have been presented, and some terms defined. At this stage the different experiments and their possible outcomes are presented. Depending on the model and experimental design and constellation, different results may arise. In general, there are four combinations, depending on the nature of Substance X (being hygroscopic or moisture degrading) and on the form of the formulation in the test (being a free film or in its coated form). Each option has some advantages and disadvantages for the overall assessment of a formulation's MPA, as shown in Figure 6.5.

Pros and Cons of Either Option - The Film being a Free-Film or a Coat (Option 1 vs. 2) A major advantage of free film assessments over coated formulations is the lack of coating process contribution. When coated formulations (on solids containing a hygroscopic or moisture sensitive substance) are tested for moisture's effect, the coating process itself may have affected the results, especially in case of aqueous coating (see Section 1.3.2.3). Yet, if special care is taken while coating (by adjusting the process parameters), the results are indeed valuable. Another advantage of free film characterization over coated ones is the former test being faster and less effortful. However, free films of the formulations may behave differently than their coated form and hence, the result may be of less real simulation. Moisture protective formulations in their coated form require a solid to be coated on. Depending on the nature of the solid core, the latter may contain either a moisture

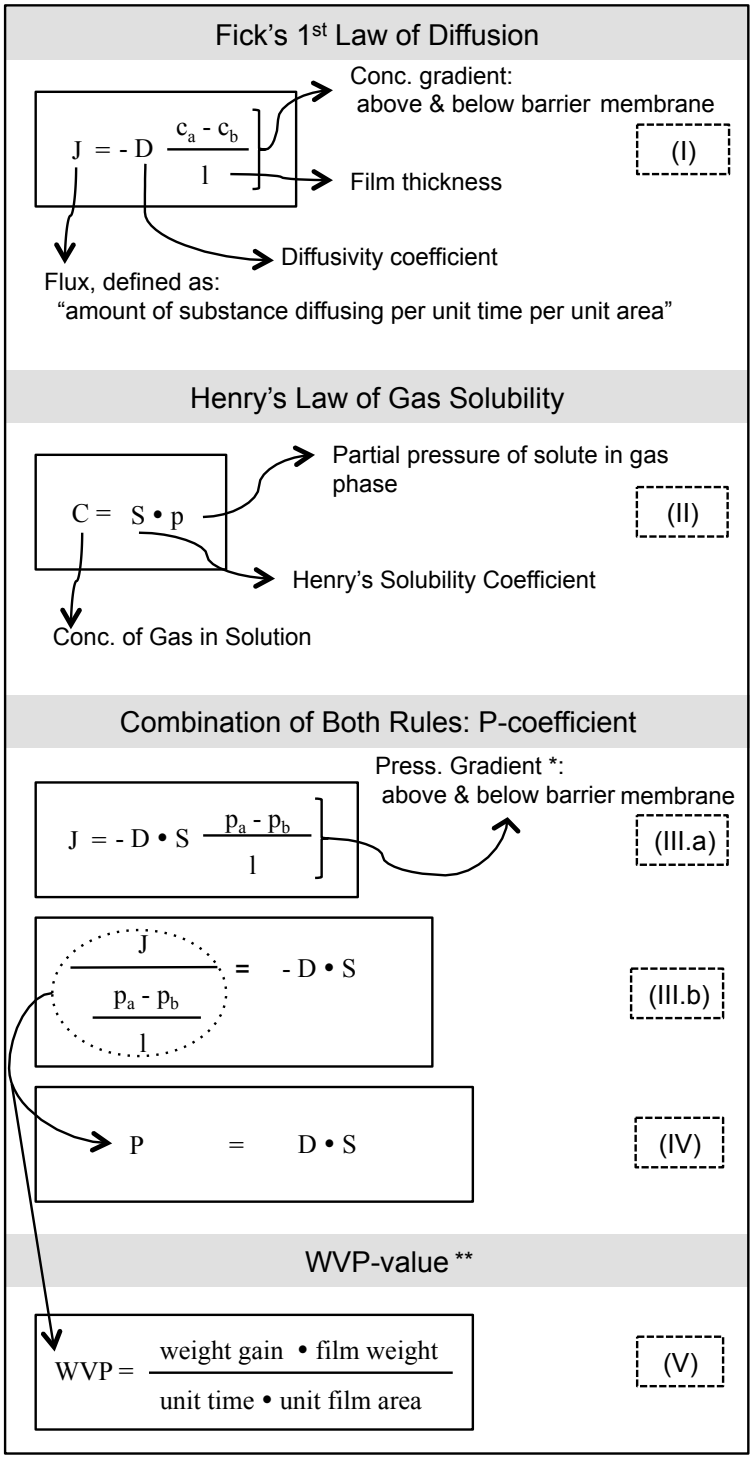


Figure 6.3: Derivation of Permeability Value(s) - Part 1. * Pressure gradient is equivalent to difference of relative humidity above and below the barrier film. ** Derivation of Equation (V) from Equation III.b: see Figure 6.4 Parameter units are not relevant at this stage; units may be used individually.

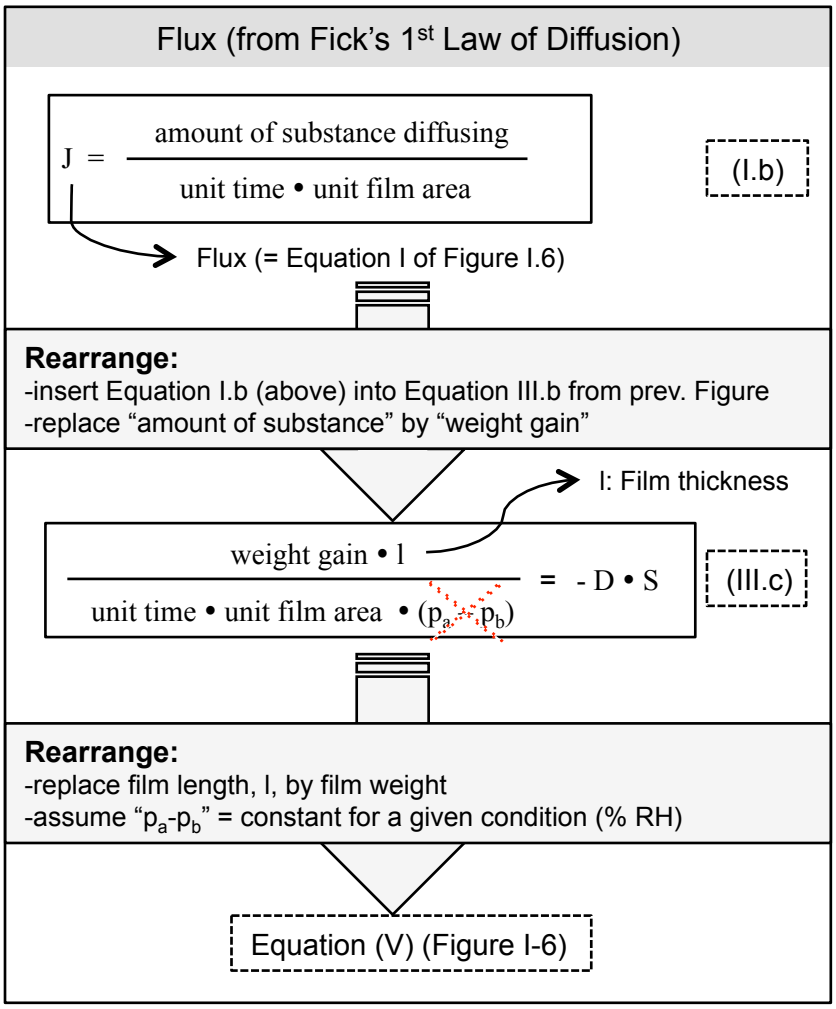


Figure 6.4: Derivation of Permeability Value(s) - Part 2

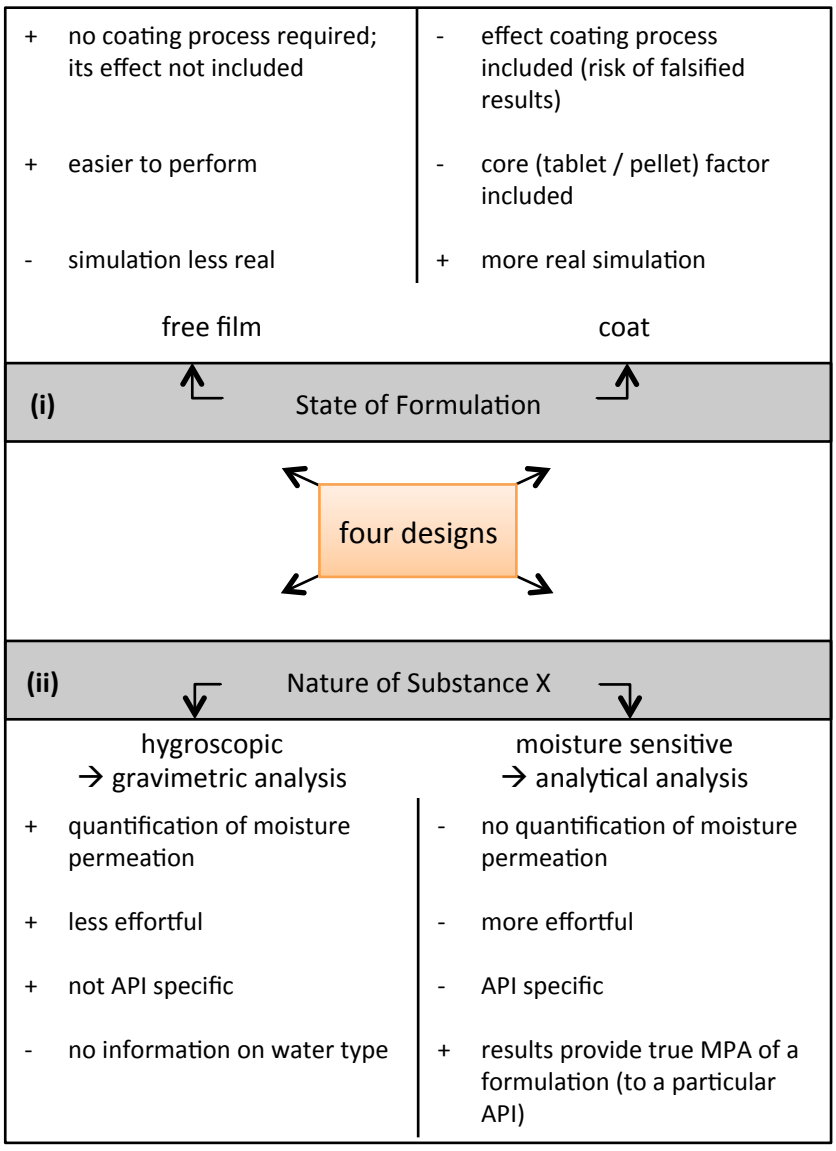


Figure 6.5: Overview of All Possible Experimental Designs – Depending on State of Formulation and Nature of Substance X. Key: +: advantage; - : disadvantage

sensitive substance or a hygroscopic one. Mwesigwa et al. have found that the extent of hygroscopicity may affect the water vapor permeation rate [39]. Moreover, it is expected that several factors and characteristics of the solid core itself, may affect the results; in case of tablets for example, their surface roughness, their hardness and their components, may have an impact on the results. In general, tests on free films are easier and faster to perform compared to ones requiring a coating step; however, the results are somewhat limited.

Pros and Cons of Either Option - Substance X being Hygroscopic or Moisture-Sensitive (Option A vs. B) Depending on the nature of the test substance (Substance X), MPA is assessed gravimetrically or analytically (as described above). The most typical experiment in the context of MPA assessment is the above-mentioned cup method (or a modification of it; details on this experiment are described in Section III.1.2.3) performed on free films (and not coated solids). The (modified) cup method is usually performed to gravimetrically assess the amount of moisture permeating through a dried formulation. In that case, Substance X is hygroscopic and not (necessarily) moisture sensitive. The gravimetric assessment is way easier and faster than the analytical one and - as mentioned before - quantifies the amount of moisture permeating through the film. Apart from the previous advantage(s), the major value of using hygroscopic test substances over moisture sensitive ones is at the same time the drawback of using the latter: obtained gravimetric results (in case of hygroscopic substances) are not specific to a certain moisture sensitive substance. Assuming a moisture protective formulation protecting two different moisture sensitive drugs and also assuming that the permeated moisture is available as solvent-like water (capable of causing harm), the following outcomes may show: Drug 1 can degrade strongly (depending on its degradation rate) and result in a "new" molecule (e.g. hydrolyzed products); Drug 2 might dissolve in the permeated moisture (deliquescence), and its crystal form change. Chemically speaking, drug 2 has remained (no alteration of chemical bonds), where its solubility might have changed, but its therapeutic effect remained. From this example, the following becomes obvious: assessing a formulation's MPA based on analytical (non-gravimetric) methods of moisture sensitive substances might be misleading. It is surely helpful for comparative studies, but it does neither provide absolute values, nor generally valid ones. As opposed to the previous argument, this one is advantageous and valuable in case of analytical assessments versus gravimetric ones: the observed weight gain in case of the latter does not suggest moisture's distribution. In other words,

gravimetric quantification of the moisture amount does not necessarily unleash its location and potential harm. Weight gain (in case of cup methods or coated solids) can be resulting from moisture residing in the free film itself or from true permeation through it and hence its probable damaging power is unknown. For example, in the case of the cup method, two films of equally resulting WVP-values must not necessarily comply in their true amount of moisture permeation through the film. Similarly, WVU-values of coated tablets reflect the total amount of moisture absorbed. This moisture may have localized in the core, the coat or both. Hence, the quantified weight gain is not directly indicating the extent of harm that could result from moisture uptake. This uncertainty can be overcome by the following methods: in case of free film tests (e.g. cup methods), calculated WVP-values alone are not sufficient to assess a formulation's MPA, again, because they are derived from the total weight gain measured, which includes the amount of water vapor residing in the free film. WVS-values are inevitable here; they characterize the crude film's hygroscopicity and both results together unleash the potential harm of permeated water vapor. In case of tests performed on coated formulations, analytical testing to moisture sensitive substances (and not hygroscopic ones) provide data on the real damage occurring to the substance and hence indirectly the true "amount" of moisture passing the film (reaching the core and exerting the damage). This leaves no room to speculations about the location of moisture. Moreover, the occurred damage(s) must have taken place from solvent-like water reaching the core (and not residing in the film); this data further elaborates the type of water inside the core. In short, the advantage of using moisture sensitive substances include the true assessment of a formulation's MPA, that is yet, and unfortunately- valid for this substance only; other cores containing other moisture sensitive substances may behave differently if coated with the same set of formulation(s).

Pros and Cons of Either Option - The Complexity of Combining the Options The previous discussion does not aim to point to one experiment being favorable over the other. On the contrary, the aim of the previous discussion is to present the various possibilities and the complexity of assessing a formulation's true MPA; one experiment does usually not suffice to answer all valid questions in this context. Hence, the previous text presented a collection of experiments that need to be performed to be able to make a true and unbiased statement. It also showed that MPA assessment could be presented with much unintended obliviousness if the previous aspects were not considered or even deliberate favoritism.

Summary of MPA Considerations Being aware of the complexity and confusing nature of the previous information, here a short summary: Tests containing Substance X of the hygroscopic nature provide gravimetric data that enable the quantification of moisture permeation and / or uptake by the film. Cup methods use free film as the barrier membranes and result in the so-called WVP-value, which can be calculated by several equations (as shown in Figure 1.6). Film coats protecting Substance X of the same nature provide also gravimetric data, but WVP-values are not provided; calculating the latter would require film coat thickness or weight characterization, which is not (always) feasible to assess for film coats. Yet, tests on film coats provide WVU-values, which are comparable to WVP-values and simulate the real application of the formulation in its coated form. In both cases, gravimetric data from WVP-tests do not unleash moisture distribution. However, WVS-tests can assist in answering such questions, because they assess a film's extent of hygroscopicity.

On the other hand, tests performed on Substance X being of the moisture degrading nature provide data on a true formulation's MPA; the extent of moisture-caused harm affecting this substance can be quantified. The results are, however, valid only for this particular substance. Furthermore, no (direct) quantification on the amount of moisture uptake is provided here, and thus unfortunately no WVP-values can be calculated.

Until here, all aspects have been presented in a theoretical manner. Those aspects have been concluded from various peer-reviewed studies, that we have studied in the context of this research. Those aspects are our own subjective assessment. Subsection "Literature Review: Methodologies Used by Other Scientists" under Section 1.3.2.4 summarizes the most relevant aspects coming from those studies; the findings support the abovementioned theoretical statements.

Bibliography

[1] Iman Saad Ahmed and Mona Hassan Aboul-Einien. In vitro and in vivo evaluation of a fast-disintegrating lyophilized dry emulsion tablet containing griseofulvin. *European Journal of Pharmaceutical Sciences*, 32(1):58–68, 2007.

[2] American Society for Testing and Materials. ASTM E96/E96M-10 Standard Test Methods for Water Vapor Transmission. Technical report, American Society for Testing and Materials, 2010.

[3] In-hwan Baek, Jung-Soo Kim, Eun-Sol Ha, Gwang-Ho Choo, Wonkyung Cho, Sung-Joo Hwang, and Min-Soo Kim. Oral absorption of a valsartan-loaded spray-dried emulsion based on hydroxypropylmethyl cellulose. *International Journal of Biological Macromolecules*, 69:222–228, 2014.

[4] E.A. Baldwin, M.O. Nisperos, and R.A. Hagenmaier, R.D. Baker. Use of lipids in coatings for food products. *Food Technology*, 51(6):56 – 64, 1997.

[5] Cristina Bilbao-Sáinz, Roberto J. Avena-Bustillos, Delilah F. Wood, Tina G. Williams, and Tara H. Mchugh. Composite edible films based on hydroxypropyl methylcellulose reinforced with microcrystalline cellulose nanoparticles. *Journal of Agricultural and Food Chemistry*, 58(6):3753–3760, 2010.

[6] B P Binks and S O Lumsdon. Catastrophic Phase Inversion of Water-in-Oil Emulsions Stabilized by Hydrophobic Silica. *Langmuir*, 16(6):2539–2547, 2000.

[7] B P Binks and S O Lumsdon. Effects of oil type and aqueous phase composition on oil-water mixtures containing particles of intermediate hydrophobicity. *Phys. Chem. Chem. Phys.*, 2(13):2959–2967, 2000.

[8] B P Binks and S O Lumsdon. Influence of Particle Wettability on the Type and Stability of Surfactant-Free Emulsions. *Langmuir*, 16(23):8622 – 8631, 2000.

[9] B P Binks and S O Lumsdon. Pickering Emulsions Stabilized by Monodisperse Latex Particles: Effects of Particle Size. *Langmuir*, 17(15):4540–4547, 2001.

[10] B P Binks and J A Rodrigues. Types of Phase Inversion of Silica Particle Stabilized Emulsions Containing Triglyceride Oil. *Langmuir*, 19(12):4905–4912, 2003.

[11] Bernard P Binks and John H Clint. Particles as surfactantssimilarities and differences. *Current Opinion in Colloid & Interface Science*, 7(1-2):21–41, 2002.

[12] O. Bley, J. Siepmann, and R. Bodmeier. Characterization of Moisture-Protective Polymer Coatings Using Differential Scanning Calorimetry and Dynamic Vapor Sorption. *Journal of pharmaceutical sciences*, 98(2):651–64, 2009.

[13] O. Bley, J. Siepmann, and R. Bodmeier. Protection of moisture-sensitive drugs with aqueous polymer coatings: Importance of coating and curing conditions. *International Journal of Pharmaceutics*, 378(1-2):59–65, 2009.

[14] Stefan A F Bon and Patrick J Colver. Pickering miniemulsion polymerization using laponite clay as a stabilizer. *Langmuir*, 23(16):8316–8322, 2007.

[15] Sagarika Bose and Robin H Bogner. Solventless Pharmaceutical Coating Processes: A Review. *Pharmaceutical Development and Technology: A Review*, 12(2):115–131, 2007.

[16] J Burri and S Hartland. Eine Methode zur Bestimmung von Ober- und Grenzflächenspannungen unter Benutzung einer Wilhelmy-Platte. *Colloid and Polymer Science*, 255(7):675–681, 1977.

[17] Robert L Burwell. Manual of Symbols and Terminology for Physicochemical Quantities and Units, Appendix II: Definitions, Terminology and Symbols in Colloid and Surface Chemistry. *Pure and Applied Chemistry*, 46:71–90, 1976.

[18] Rolf Daniels and Albert Barta. Pharmacopoeial cellulose ethers as oil-in-water emulsifiers. 1. interfacial properties. *European journal of pharmaceutics and biopharmaceutics*, 40(3):128–133, 1994.

[19] Nava Dayan. Pathways for Skin Penetration. *Cosmetics & Toiletries*, 120(6):67–76, 2005.

[20] Carsten Döhling. *Systematische Untersuchungen zum Hygienerisiko nicht konservierter Cremes*. PhD thesis, Eberhard Karls Universität Tübingen, 2011.

[21] Angelika Ellermann. *Pickering-Emulsionen als Basis Lipid-basierter oraler Drug Delivery Systeme mit veränderter Wirkstofffreisetzung*. PhD thesis, Eberhard Karls Universität Tübingen, 2015.

[22] Evonik Industries. EUDRAGIT ® E PO Protective Coating with Talc as Anti-Tacking Agent.

[23] Nabil Farah, Philippe Barthelemy, and Joseph Joachim. Method for preparing a pharmaceutical composition with modified release of the active principle, comprising a matrix. Patent-Nr. US 6194005, 2003.

[24] Justyna Frelichowska, Marie-Alexandrine Bolzinger, Jocelyne Pelletier, Jean-Pierre Valour, and Yves Chevalier. Topical delivery of lipophilic drugs from o/w Pickering emulsions. *International Journal of Pharmaceutics*, 371(12):56–63, 2009.

[25] M A Garcia, M N Martino, and N E Zaritzky. Lipid Addition to Improve Barrier Properties of Edible Starch-based Films and Coatings. *Journal of Food Science*, 65(6):941–947, 2000.

[26] D. Gaudy, M. M. Miracy De Albuquerque, C. Dudu, M. Jacob, and A. Puech. Controlled drug release from spheronized microgranules by lipid coating. *Pharma Sciences*, 2(6):475–480, 1992.

[27] Adem Gharsallaoui, Rémi Saurel, Odile Chambin, Eliane Cases, Andrée Voilley, and Philippe Cayot. Utilisation of pectin coating to enhance spray-dry stability of pea protein-stabilised oil-in-water emulsions. *Food Chemistry*, 122(2):447–454, 2010.

[28] Grace. Syloid Silica - Excipients for Pharmaceutical Applications.

[29] Ronny Grützmann. *Zum Mechanismus der Anionenwirkung auf die Permeabilität kationischer Polymethacrylatüberzüge*. PhD thesis, Eberhard-Karls-Universität Tübingen, 2005.

[30] E. Hernandez. Edible Coatings form Lipids and Resins. In J.M. Krochta, E.A. Baldwin, and M.O. Nisperos-Carriedo, editors, *Edible coatings and films to improve food quality*, chapter 10. Technomic Publishing Company, Inc., Lancaster, 1994.

[31] Tommy S. Horozov and Bernard P. Binks. Particle-Stabilized Emulsions: A Bilayer or a Bridging Monolayer? *Angewandte Chemie, International Edition*, 45(5):773–776, 2006.

[32] Annina Horst and Rolf Daniels. Unpublished Data on Oil-in-Water Pickering Emulsions Using CaCO3 as the Particulate Emulsifier, 2010.

[33] Seid Mahdi Jafari, Elham Assadpoor, Yinghe He, and Bhesh Bhandari. Recoalescence of emulsion droplets during high-energy emulsification. *Food Hydrocolloids*, 22(7):1191–1202, 2008.

[34] Keith Johnson, Royal Hathaway, Pauline Leung, and Robert Franz. Effect of triacetin and polyethylene glycol 400 on some physical properties of hydroxypropyl methylcellulose free films. *International Journal of Pharmaceutics*, 73(3):197–208, 1991.

[35] Barbara Kannen. *Herstellung und Charakterisierung fester Darreichungsformen unter Verwendung von Pickering-Emulsionen als Drug Delivery Systeme.* PhD thesis, Eberhard Karls Universität Tübingen, 2010.

[36] Karsten Köhler and Prof. Ing. Heike P Schuchmann. Tropfenaufbruch und Energiedichtekonzept beim mechanischen Emulgieren. In Karsten Köhler and Heike P. Prof. Dr.-Ing. Schuchmann, editors, *Emulgiertechnik: Grundlagen, Verfahren und Anwendungen*, chapter 7, pages 133 – 163. Behr's Verlag DE, 2012.

[37] Svenja Lena Möllgaard. *Entwicklung und Charakterisierung von sprühgetrockneten Lichtschutzformulierungen unter Verwendung polymer- und feststoffstabilisierter O / W-Emulsionen.* PhD thesis, Technische Universität Carolo-Wilhelmina zu Braunschweig, 2006.

[38] Enosh Mwesigwa, Abdul W. Basit, and Graham Buckton. Moisture Sorption and Permeability Characteristics of Polymer. *Journal of pharmaceutical sciences*, 97(10):4433–4445, 2008.

[39] Enosh Mwesigwa, Graham Buckton, and Abdul W. Basit. The Hygroscopicity of Moisture Barrier Film Coatings. *Drug Development and Industrial Pharmacy*, 31(10):959–968, 2005.

[40] Drew Myers. *Surfaces, Interfaces and Colloids Principles and Applications, Second Edition by D. Myers, Wiley-VCH, New York, 1999*, volume 51. Wiley-VCH, second edition, 2000.

[41] Scott L Myers and Merrick L Shively. Solid-State Emulsions: The Effects of Maltodextrin on Microcrystalline Aging. *Pharmaceutical Research*, 10(9):1389–1391, 1993.

[42] World Health Organisation. Accelerated Stability Studies of Widely Used Pharmaceutical Substances Under Simulated Tropical Conditions (WHO/Pharm/86.529) - Unpublished. Technical report, World Health Organisation, 1986.

[43] Pornchai Rachtanapun and Wirongrong Tongdeesoontorn. Moisture sorption isotherms and water vapour permeability of carboxymethyl cellulose from papaya peel/cornflour blended films. *Asian Journal of Food and Agro-Industry*, 2(04):948–957, 2009.

[44] Ali R Rajabi-Siahboomi, Marina Levina, Sampada B. Upadhye, and Jason Teckoe. Excipient Selection in Oral Solid Dosage Formulations Containing Moisture Sensitive Drugs. In Ajit S. Narang and Said HS Boddu, editors, *Excipient Application in Formulation Design and Drug Delivery*, chapter 13, pages 385 – 422. Springer, 2015.

[45] Jack M Rosenberg, S Schilit, and J Nathan. Which oral solid medications should be protected from light and/or moisture?, 2008.

[46] Eli Ruckenstein. Microemulsions, Macroemulsions, and the Bancroft Rule. *Langmuir*, 12(26):6351–6353, 1996.

[47] Guilbert S. Technology and Application of Edible Protective Films. In *Mathliouthi M. (Ed.) Food Packaging and Preservation: Theory and Practice.*, chapter 19. Blackie Academic & Professional, London, 1986.

[48] Snežana Savić, Christian Weber, Miroslav M. Savić, and Christel Müller-Goymann. Natural surfactant-based topical vehicles for two model drugs: Influence of different lipophilic excipients on in vitro/in vivo skin performance. *International Journal of Pharmaceutics*, 381(2):220–230, 2009.

[49] Gernot Schaal. *Untersuchungen einer Befilmungsmöglichkeit fester Arzneiformen mit modifizierten Triglycerid-Dispersionen.* PhD thesis, Friedrich-Schiller-Universität Jena, 2003.

[50] H. Schubert and H. Armbruster. Principles of formation and stability of emulsions. *Chemie Ingenieur technik*, 61(9):701 – 711, 1989.

[51] Michaela Schulz. *Entwicklung tensidfreier Submikron-Emulsionen mit Methylhydroxypropylcellulose als Polymeremulgatoren*. PhD thesis, Universität Regensburg, 1996.

[52] Spomenka Simovic and Clive A Prestidge. Nanoparticles of Varying Hydrophobicity at the Emulsion Droplet-Water Interface: Adsorption and Coalescence Stability. *Langmuir*, 20(19):8357–8365, 2004.

[53] Valentina Siracusa. Food packaging permeability behaviour: A report. *International Journal of Polymer Science*, 2012, 2012.

[54] S Stiller, H Gers-Barlag, M Lergenmueller, F Pflücker, J Schulz, K P Wittern, and R Daniels. Investigation of the stability in emulsions stabilized with different surface modified titanium dioxides. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 232(23):261–267, 2004.

[55] Surface Measurement Systems. DVS User Guide/Manual Version 9.0 July 2003 1 (by Surface Measurement Systems, Ltd.), 2003.

[56] David E Tambe and Mukul M Sharma. Factors Controlling the Stability of Colloid-Stabilized Emulsions. *Journal of Colloid and Interface Science*, 157(1):244–253, 1993.

[57] Prachi Thareja and Sachin Velankar. Particle-induced bridging in immiscible polymer blends. *Rheologica Acta*, 46(3):405–412, 2007.

[58] J Thieme, S Abend, and G Lagaly. Aggregation in Pickering emulsions. *Colloid and Polymer Science*, 277(2):257–260, 1999.

[59] Cech Thorsten. Kollicoat ® Smartseal 30 D, 2010.

[60] Pornchai Tongdeesoontorn, Wirongrong; Mauer, Lisa J; Wongruong, Sasitorn; Rachtanapun. Water vapour permeability and sorption isotherms of cassava starch based films blended with gelatin and carboxymethyl cellulose. *Asian Journal of Food and Agro-Industry*, 2(04):501–514, 2009.

[61] Jennifer Walsh, Anne Cram, Katharina Woertz, Joerg Breitkreutz, Gesine Winzenburg, Roy Turner, and Catherine Tuleu. Playing hide and seek with poorly tasting paediatric medicines: Do not forget the excipients. *Advanced Drug Delivery Reviews*, 73:14–33, 2014.

[62] C. Wollenweber, A.V. Makievski, R. Miller, and R. Daniels. Adsorption of hydroxypropyl methylcellulose at the liquid/liquid interface and the effect on emulsion stability. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 172(1-3):91–101, 2000.

[63] Tao Yi, Jiangling Wan, Huibi Xu, and Xiangliang Yang. A new solid self-microemulsifying formulation prepared by spray-drying to improve the oral bioavailability of poorly water soluble drugs. *European Journal of Pharmaceutics and Biopharmaceutics*, 70(2):439–444, 2008.

[64] Sumie Yoshioka and Valentino J. Stella. *Stability of Drugs and Dosage Forms*. Kluwer Academic Publisher, New York, 2002.

[65] George Zografi. States of water associated with solids. *Drug Development and Industrial Pharmacy*, 14(14):1905–1926, 1988.