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Fundamental Investigations on Hard Capsule Manufacturing from Synthetic Material for Application in Dry Powder Inhalers

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Kurzzusammenfassung

Hartkapseln für den Gebrauch in pharmazeutischen Anwendungen oder in Nahrungsergänzungsmittel werden gegenwärtig aus Gelatine oder Hydroxypropylmethylcellulose (HPMC) hergestellt. Diese Art des Dosierens eines pharmazeutischen Wirkstoffes (WS) bietet vielversprechende Möglichkeiten. Aus diesem Grund werden derlei Kapseln in sogenannten Trockenpulverinhalatoren (DPI) verwendet, um verschiedenste Atemwegerkrankungen zu behandeln. Mittlerweile hat sich dadurch eine probate Möglichkeit entwickelt, einen Wirkstoff direkt in die Lungen und der zu behandelnden Stelle zu bringen. Allerdings gibt es an der Kapsel nach wie vor unzählige Faktoren, wie beispielsweise die Stabilität, die Durchlässigkeit von Luftfeuchtigkeit oder Sauerstoff, die Kapseloberfläche und ihren Einfluss auf den Wirkstoff und seine Freisetzung, sowie die Reaktivität zwischen Wirkstoff und Kapselwand, welche die Gesamtleistung massiv beeinflussen.

Diese Arbeit hatte zum Ziel eine potentielle Anwendbarkeit synthetischer Polymere als DPI Kapseln zu überprüfen. Verschiedene handelsübliche und technische Polymere wurden zunächst in einem Thermoformprozess ohne Zugabe von Additiven zu rechteckigen Filmen geformt, welche dann bei unterschiedlichen Luftfeuchtigkeitsbedingungen gelagert wurden. Handelsübliche Kapseln tendieren bei solchem Vorgehen zu einer Verhaltensveränderung, die weitgehende Folgen für die Eigenschaften einer Kapsel und daraus resultierend auf die Wirksamkeit eines Medikamentes haben kann. Nicht so die verwendeten Polymere. Eine gravimetrische Analyse ergab keinerlei signifikante Veränderungen. Der Zugtest ergab nur wenig informative Resultate, da eine Homogenität der Filme nur bedingt erreicht wurde und die Standardabweichung hohe Differenzen aufwies. Lediglich die Polymere ABS und PBT schienen von diesen Umständen unbeeindruckt zu bleiben. Die Verhaltensevaluierung der Polymere unter Krafteinfluss bei sich ändernder Temperatur gestaltete sich wesentlich spannender. Temperaturänderungen innerhalb der relevanten Bereiche hatten große Auswirkungen auf die Stoßkraft der Thermoplasten. So konnte beispielsweise bestätigt werden, dass eine ansteigende Temperatur die Molekülketten eines Polymers mehr mobilisiert, mit dem Effekt einer sich verbessernden Dehnbarkeit und abnehmender Sprödigkeit. Zudem wurden bei diesem Test die Auswirkung von Substituenten in der Polymerkette, sowie die Konzentration der Substituenten festgestellt. Es fiel auf, dass ein Anstieg der Substituentenkonzentration eine gleichzeitige Verringerung der mechanischen

Stabilität nach sich zog. Abgeschlossen wurde der analytische Teil der Arbeit mit der Evaluierung der Wirkstofffreisetzung. Als WS diente in diesem Zusammenhang eine Formulierung mit 10% Salbutamolsulfat (SS) auf Laktose als Trägermaterial. Die Analyse wurde neben den Polymerfilmen auch an gängigen Kapseln durchgeführt. Zudem wurde in einer Nebenstudie das unterschiedliche Verhalten von sprühgetrocknetem und mikronisiertem WS untersucht. Die Ergebnisse zeigten, dass die Filme aus Polymeren grundsätzlich viel weniger WS auf ihrer Oberfläche zurück behielten als die gängigen Kapseln aus Gelatine, wodurch eine generelle Verbesserung der Wirkstoffversorgung gewährleistet wurde. Zudem zeigte sich die mikronisierte Pulverformulierung als weniger anhaftend.

In Summe ließ sich feststellen, dass Polymere grundsätzlich Gelatine und HPMC als Kapselmaterialien für DPIs ersetzen können. Allerdings sind für einen letztendlichen Erfolg weitere Tests und Analysen unumgänglich.

Abstract

Hard capsules designed for pharmaceutical application or food supplements are generally made from gelatin or hydroxypropyl methylcellulose (HPMC) and they offer promising possibilities for delivering active pharmaceutical ingredients (API) via the oral or pulmonary route[1]. Therefore, capsules are used in dry powder inhaler systems (DPI), which became an auspicious method for the treatment of respiratory diseases via direct delivery of the API to the targeted regions in the lungs. However, both capsule materials reveal some polymer characteristics limiting the performance of the powder blend. Stability issues, moisture effects, water and oxygen effects, surface impact on the powder retention, and reactivity properties between shell wall and API are only a few of them.

On this ground, this thesis aimed to evaluate a potential applicability of synthetic polymers for capsule type metered dose packaging for DPIs. A mix of classical commodity thermoplastics and engineering thermoplastics were thermoformed without any additives into rectangular films. These films were then stored at different relevant levels of relative humidity. Common capsule materials tend to change their properties with changing humidity, and consequently change the head space humidity affecting the capsule properties, API and formulation performance negatively. Noticeable effects of that sort were not observed after gravitational analysis of polymer films, which were stored at different humidity due to the inert nature. The results from engineering stress test revealed a low level of homogeneity with large deviation of the film thickness and were, for this reason, less informative. Only ABS and PBT seemed not to be swayed by this circumstance. Temperature variations within the relevant temperature range had strong effects on the impact force on the thermoplastic materials. With this method it was confirmed that increasing temperatures affect the mobility of the molecular chains of a polymer, making them more ductile and less brittle. Additionally, this analysis showed the effect of additional substituents and their concentration in the polymer backbone, meaning a decreased mechanical strength of the material. The analytical part was finished by determining the powder retention of a 10% salbutamol sulfate (SS) lactose carrierblendon polymer films as well as in common gelatin and HPMC capsules. Thus, a side study evaluated the difference of spray-dried and micronized powder formulations. First, it was found that polymer films have much lower powder residues remaining on their surface after inhalation than capsules from gelatin.

Therefore, it was concluded that the performance of the entire DPI system can be improved by the use of polymer capsules. Second, it was observed that micronized powder particles seem to have fewer tendencies to remain on the film surface than its spray-dried counterpart.

In summary, it can be said that thermoplastic polymers have to be considered as a potential replacement of the commonly used gelatin and HPMC capsule materials for DPIs. However, further optimization, testing and analysis are inevitable for the final success.

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1. Introduction

Respiratory diseases like Chronic obstructive pulmonary disease (COPD) are one of the major health burden due to their high prevalence for morbidity and mortality worldwide. Between 1970 and 2002 the death rates doubled and it is expected that this disease become the third leading cause of death on the globe by 2020.[2] COPD manifests itself by persistent respiratory symptoms and airflow limitations, which are caused by significant exposure to harmful particles or gases, smoking tobacco and eventually also e-cigarettes, environmental influences coming from fuels and air pollution, and due to genetic abnormalities or abnormal lung development[3].For this reason significant efforts are being made by medical and pharmaceutical scientists to reduce disease progression and improve or at least maintain the lung function in COPD patients. The available pharmacotherapies today able to prevent or minimize exacerbation, which is a step in the right direction.[2]

Among the different currently available ways of treatment there is one method that gained recognition of countless researchers. This method is based on the use of micronized drug attached to carrier particles, which upon inhalation through a device creates a fine aerosol of the drug, which is inhaled by the patients. Inhalation of drugs in aerosol shape provides selective and direct delivery to the lung and as such a fast onset of the desired drug action. Furthermore, inhalation therapy is non-invasive and painless therapy.[4]The supply of drugs can be tailored according the situation: for immediate symptom relieve metered dose inhalers (MDI) are more appropriate to provide short-acting inhaled agents, as they are more independent from the patient's inhalation capacity. In contrast to these, the DPI systems are more appropriate for the preventive treatment strategy with long-acting therapeutic inhaled agents. Thus, DPIs offer greater convenience and are an essential part of managing respiratory diseses.[2] In summary, the use of inhalation systems offers the chance to alleviate patients suffering in a way that they have to go to hospital for example every third week instead of every third day[5].

However, economical reasons might presume a huge drawback for the treatment of respiratory disease treatment, mainly driven by the complexity of the devices, the mode of packaging (e.g. blister, reservoir) and the related costs. Even though

capsule materials used for DPI capsules, usually pharmaceutical quality gelatin or HPMC are considered most cost effective, there might still be room for further cost saving by the use of thermoplastic materials.[1] Furthermore, convenience and the ability of patients to use the device in the correct way are other reasons that affect the treatment[4]. Especially the latter seems to be a major factor that negatively influences the therapeutic outcomes of a highly effective therapy. Patients often have difficulties in the correct use, either coming from confusing and inadequate training on the device, a combination of disease treatment with different inhalers, or from functional problems like device activation and inhalation coordination, missing grip strength, inappropriate time of breath holding, limited inspiratory flow rates, insufficient shaking of the inhaler before use or simply due to stress in acute situations.[6,7]

This study aimed to evaluate a possible application of synthetic polymers as a container for metered doses in the field of DPIs. As a non-industrial funded project, dozens of European companies manufacturing or selling potentially suitable polymers were contacted with an enquiry for already available and free polymer samples. The received materials were tested for their suitability to be used for pharmaceutical inhalation products. Polymer films with capsule-like thickness were manufactured by a recently developed thermal process, followed by common analysis of mechanical, physical and chemical behavior. Analysis included a test on the influence of relative humidity, determination of engineering stress and mechanical properties under different environmental conditions, and an evaluation of powder adhesion on the surface mimicking retention on the potential capsule shell walls. From the received results correlating inferences were drawn about the suitability of the available polymers as capsule materials.

The present study also offers fundamental explanations on the inhalation system, consisting of inhaler, powder formulation and capsule. The aim was to provide an adequate foundation on important backgrounds of DPIs. Additionally, polymers, their properties and possibilities of processing are illustrated in a few pages to get the reader well prepared for the remarks on the practical work.

2. Dry Powder Inhalation

2.1 Inhalers

2.1.1Development of Dry Powder Inhalers

Inhalation of medicines as the therapy to treat a variety of disease conditions including pulmonary diseases seems to be as old as mankind itself. In the ancient world it was a common practice to inhale vapors for medicinal and psychosocial purposes, but the knowledge and development of this therapy was suppressed and forbidden when Christianity rose up[7]. It was not until the 19th century, however, that this method and its benefits was recognized again and developments were encouraged, but it took another century that scientists came up with the pressurized MDIs in the middle of last century[7]. MDIs were used to treat diseases like asthma, but came under scrutiny since they contain environmentally damaging chlorofluorocarbon (CFC) propellants. The Kyoto protocol stated the stepwise elimination of CFCs from inhalations system and fostered the development of propellant-free DPIs as alternative devices.[8]

Over the years companies developed and launched several DPI systems like *Spinhaler*® from *Fisons Ltd.*, *Rotahaler/Rotacaps*® and *Diskhaler/Diskus* from *GlaxoSmithKline plc.*, *Foradil*® *Aerolizer*® made by *Novartis/Schering-Plough*, *HandiHaler*® manufactured by *Boehringer Ingelheim Pharma GmbH & Co. KG/Pfizer Pharma GmbH* and *Turbuhaler*® from *AstraZeneca GmbH*. Though the principle behind all of these is the same, there is one distinction that divides the inhalers into two groups. That is on the one hand the group of unit-dose devices, where the drug is metered and released from individual dose unit like foil-foil blister or capsules from gelatin or cellulose, and on the other hand the multi-dose device group, which contains a reservoir of active agent from where doses are metered out[9]. An additional distinction is that the majority of DPI inhalers on the market are ‘passive’ inhalers. These inhalers are activated by the energy necessary for drug dispersion and inhalation provided by patients breathing. Obviously, this could be limited for patients in the case of a sudden attack where the patient is not able to provide the required respiration energy by himself. This is supposed by be overcome by devices where energy is provided actively to release the drug particles by the inhaler itself to substitute or at least reduce the respiration force of the patient[9] (Figure 1).

A short overview of currently used inhalers is given in Table 1, including some characteristic facts from the devices. Herein however, only unit dose inhalers will be explained in more detail, since this thesis aimed to investigate new capsule materials for these.

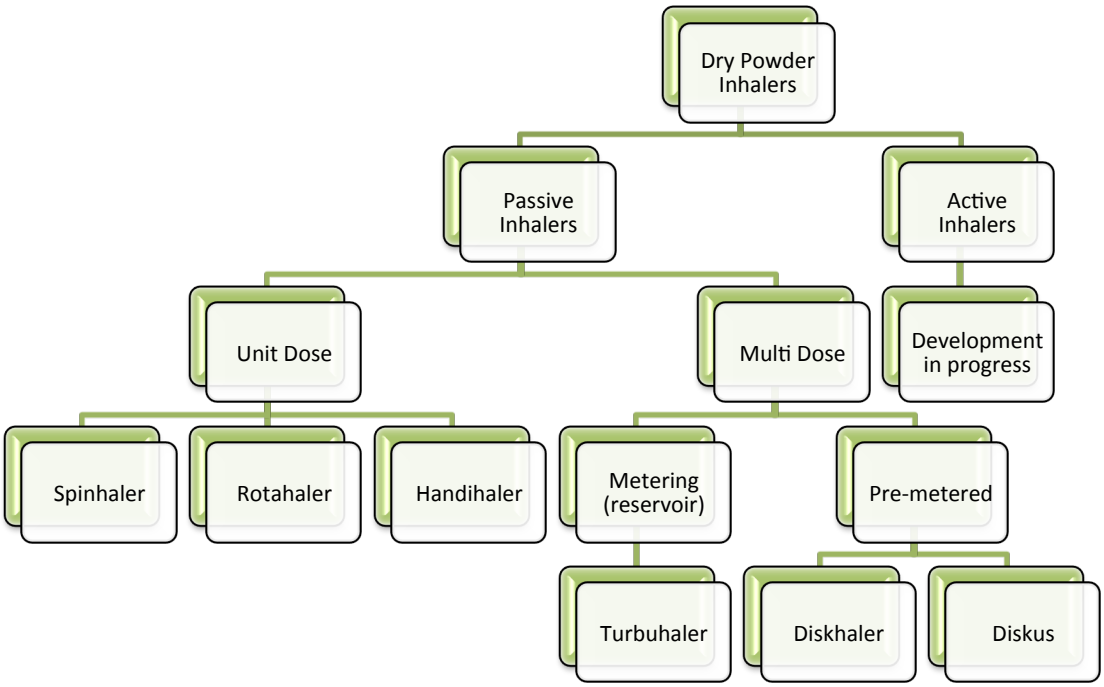


Figure 1: Development tree of dry powder inhalers[8]

Device	Formulation storage	Number of delivered dose	Constant perform. flow rate in L/min	Nominal dose delivered	Easy to use / Drawback
Spinhaler®	Capsule	1	30 – 60	<50%	No / Capsule insertion

Rotahaler	Capsule	1	30 – 90	60%	No / Capsule insertion
HandiHaler	Capsule	1	30 – 60	58%	No / Capsule insertion, but better than other unit-dose devices
Diskhaler	Blister disk	4 or 8	30 – 60	50 – 70%	Acceptable / problems with drug load
Diskus	Blister strip	60	30 – 90	87 – 93%	Yes / most accepted device
Turbuhaler	Reservoir	200	40 - 60	40 – 58%	Acceptable / easier than Diskhaler

Table 1: Overview on different DPI designs and the impact of critical factors on their performance: formulation dosage, flow rate, drug release and easiness of use[9–14]

2.1.2Unit-Dose Inhalers

The principle of the single-dose capsule based DPIs is that they contain a metered dose within a single drug-containing capsule. Upon activation the capsule is opened within the inhaler and the patient inhales the powder. The empty capsule has to be removed afterwards and a new capsule is inserted.[9]

Beneath others, *Fision Ltd.* was one of the companies to manufacture capsules for inhalation purpose and they came up with an own DPI device called *Spinhaler*®[15]. This inhaler is equipped with a small plastic rotor on which a capsule holder is placed. After piercing the capsule, air is drawn through the mouthpiece and the rotor starts characteristic whirling motion in the device, which is conveyed to the capsule and the drug it contains. As a result from that the powder inside the capsule gets fluidized and is dispensed from the chamber through two holes in the side walls which were pierced by needles directly before use.[16]

The piercing method described before is probably the most common method to open the capsule in an inhalation device, but several other techniques are already available. One of these different techniques was realized by *GlaxoSmithKline plc.*, who came up with a product pair known as *Rotahaler*® and *Rotacaps*®[9]*.* Instead of piercing the capsules for content release, the capsules are opened by shear force generated by a twist motion of the inhaler. This basically means that the device is filled vertically with a capsule, which is fixed on the one half while the other half extends into the dispersing chamber. Due to the twist the capsule is exposed to shear forces along the horizontal axis with the support of an integrated plastic bar until it divides into the two pieces and allowing the powder to be dispersed in an air flow.[17] Again, a motion is generated by the human airstream causing the capsule to move arbitrarily through the dispersing chamber and ensuring an effective release of the drug. Instead of the shear mechanism also a sharp blade can be implemented into the device to cut the capsule and allow powder release. An additionally integrated mesh assures powder dispersion and prevents undesired fragments of the capsules being released into the airways and lungs.[18]

The two unit-dose devices mentioned above describe the state of the art of commercialized DPIs today. They were developed approximately 50 years ago and constantly improved. For example, the design of these two devices largely became out of fashion and newer ones relieved them, though the principle is still the same.

Boehringer Ingelheim Pharma GmbH & Co. KG/Pfizer Pharma GmbH for example developed an inhaler called HandiHaler®, where the capsule is pierced to reveal its content at given air stream. The benefit and thus the reason for realization of this method is hidden in the inner design of the device since the required air flow rate of 20 L/min is pretty low.[10,19]

2.2Powder Formulation for DPI

In the same way as the DPI design influences the performance and drug delivery, also the powder formulation that is inhaled can totally change the emitted dose. Typically, the formulation consists of a drug that was blended with an excipient, mostly lactose or glucose, which has the task to support the metering process and provide higher dose uniformity. Moreover, these carrier materials provide a pleasant taste and sensation in the patients mouth, indicating that inhalation and drug delivery was successful.[9,12,20]

However, the properties of the powder play an important role. In general, it is mandatory that a dispersion of formulation is conducted from a static powder bed upon inspiratory airflow, which creates shear and turbulence. This process that was previously denoted as de-agglomeration depends on the compound properties, including crystallinity, hygroscopicity, particle size and fine particle fraction, morphology, and interacting forces. Unfortunately, these properties can have a wide range of variability, thus evaluation and optimization of them are mandatory in development and manufacturing process to provide better performance.[9,21]

The importance of solid-state knowledge is derived from the fact that materials, in the present case the micronized drug powder, have the ability to exist in different forms though it has the same molecule formula, a phenomenon that is declared as polymorphism. It was reported that almost one third of all drugs display polymorphism. Its evaluation is important since the different polymorphs are not equivalent to each other. For example, they differ in energy states, thus in properties such as stability, solubility, density, hygroscopicity, and melting point. Generally, the most stable representative is the one with highest density, highest melting point, and lowest solubility. Moreover, this stable form is usually used in development due to its reduced risk of transformation during processing or storage. Anyway, polymorphism

offers the advantageous possibility to derive drugs that are less susceptible to transformation upon external impacts such as temperature or moisture. Moreover, the solid-state behavior is regarded in the design process of a formulation since it is relevant for the particle shape and thus the aerodynamic diameter. Best performances to some reason were obtained at aerodynamic diameter range of 1-5μm. The problem with particles larger than the given range is early deposition in the oral cavity or pharynx, while smaller particles suffer from the disadvantage of slow settling and deposition due to Brownian motion. Further, the smaller the particles, the larger the total surface and the higher the potential for charging and moisture uptake. This reveals the importance of surface morphology, which determines the rate of drug deposition in the lungs by particle size on the one hand, and interacting forces on the other hand. Between the single particles a phalanx of interacting forces is present that has to be overcome during inhalation process. First force is some mechanical interlocking that avoids dispersion of the particles due to its roughness, second comes capillary force that is introduced by the presence of moisture, then electrostatic interaction coming from different circumstances, and finally weak van der Waals forces. Finding an adequate adjustment and interaction of these forces can be very useful to provide high performance.[21]

2.3 Hard Capsules for Primary Packaging of API

The last missing piece in the puzzle of inhalation system is the drug-containing capsule, which is inserted in the unit-dose device[22].The main task of the hard capsule is to protect the metered content from any external impacts that occur during filling, packaging, shipping and storage. Due to that a certain mechanical strength is asked from the shell material to give the capsule a consistent shape and avoid deformation upon force impact. More, the encapsulated drug is usually very sensitive to humidity and quite often it has a predominant hygroscopic nature.[21] For this reason the capsule should have the ability to suppress water vapor transmission as good as possible, though the material might have hydrophilic behavior. In the same way as diffusion has to be suppressed, also gas permeability should be avoided, since undesired chemical reactions can come up due to the presence of oxygen for example. This can be fulfilled by a homogeneous, smooth film surface that lacks of fine pores and defects, which would allow the gas to easily pass through.[23]

Additionally, the capsule can challenge the performance characteristics insofar that the drug delivery to some degree depends also on inner surface characteristics, lubrication, and the specific opening performance[24]. However, the essential issues can be tailored during the overall manufacturing process[25]. The following explanations highlight the current state of the art of capsule manufacturing for DPIs, including benefits, but also difficulties and challenges of current materials.

2.3.1Materials for Hard Capsules

Over the past decade, several polymers were introduced in the development and supply of pharmaceuticals, mainly for solid oral dosage forms. Especially proteins, polysaccharides and lipids gained a lot of interest and were successfully used for tablet and capsule formulations. Since then, gelatin, corn, collagen, starch, cellulose, waxes, oils and other bioproducts were commercially used for capsules, supplements, tablets, coatings and more. Among these materials, gelatin and the cellulose derivative hydroxyl propylated methyl cellulose (HPMC) became the most popular material for capsule manufacturing since their properties in film formation, mechanical strength, the behavior as gas and water barrier, the availability of raw material, and their biodegradability turned out to be highly suitable and an alternative to gelatin.[26]

Historically, the first patent for a gelatin capsule was applied in the mid 19th century by the pharmacist Joseph Gérard Auguste Dublanc and his student François Achille Barnabé Mothès[27]. It was also in that time when Jules César Lehuby produced the two-piece capsule, consisting of the two sections cap and body that fit together, the first time. The Frenchman used silver-coated metal pins, which he dipped into a gelatin solution and then let them for drying[27]. This process of dip-coating was improved over the years and is currently still used in industry[28].

Beyond the good stability and barrier behavior of gelatin, itis favored in manufacturing due to its easy processability slightly above ambient temperature and fast formation of homogeneous films, which is an essential factor. However, gelatin provides several problems and disadvantages. Among others these drawbacks include property changing external impacts, such as elevated temperatures together with high relative humidity, which potentially results in cross-linking reaction that

affects the capsule shell and as a result from that also the drug inside[29]. But the largest problem in the use of gelatin is the chemically bound water content of approximately 15% that is necessary for the film as plasticizer. On the one hand, the presence of free water is absolutely undesired since it affects the drug inside the capsule, causing for example an agglomerated, sticky powder that result in a significant decrease of drug delivery. But on the other hand the plasticizing water is mandatory, because of its positive impact on the properties, as for example lowering the brittleness or increasing mechanical stability[22,30]. Finally, gelatin is a product that is usually obtained from animal origin, which is prohibited in several religious cultures and refused by vegetarians[26].

Especially the last named drawback from gelatin as capsule shell encouraged scientists to find gelatin free alternatives for capsule manufacturing and they came up with pure HPMC capsules and HPMC capsules that were blended with either carrageenan or gellan gum as answers[24]. Under the premise that storing conditions, meaning moisture level and temperature of the surrounding environment, have the identical level, HPMC has the big advantage of exhibiting moisture content of maximally 9%, which is significantly lower than in gelatin capsules that contain the mentioned 15%. This is a main issue that makes HPMC more suitable for water-sensitive drugs. Even under low moisture conditions the cellulose derivative maintains its mechanical integrity and it does not become brittle, which is a major difference to gelatin. Generally, HPMC has physical properties that are tolerant to a wide range of different environmental conditions and it provides more chemical stability and compatibility with a large variety of active agents[29,31]. And finally, the manufacturing process of HPMC capsules requires conditions that are close to those from gelatin capsule formation. For this reason it is possible to maintain the same equipment for this process[32]. Beside these benefits, there is one thing that has to be considered during manufacturing: the influence of substituents. HPMC is substituted with methoxy and hydroxypropoxy groups, which have different hydrophobicity, hence the polymer can differ in solubility[33]. Also the film formation can be tailored for example by an increased amount of hydroxypropoxy substituents, which results in a decreased temperature for the onset of gelation[34]. Moreover, it was reported that capsules from different manufacturers always differ in properties, since capsule shell and its physicochemical properties are sensitive to any changes in manufacturing conditions, such as gelling temperature, mixing, gelling time, and drying process[31].

What is also affected is the quality of the capsule, to be precisely, mechanical stability, a key factor for the processability of the final product on filling machines[35], and stability in terms of oxygen and water vapor permeability[36].

Undoubtedly, gelatin and HPMC capsules possess beneficial quality properties. Nevertheless, one challenging issue, namely the effect of surface properties of formulation and shell material on the physical properties of the formulation during inhalation, remains. This effect, which is commonly evaluated as powder retention, has its origin in so-called adhesion force between the formulation particles and the capsule surface and depends on several factors. From physical point of view, van der Waals forces, electrostatic forces and capillary forces are predominant during adhesion of particles to surfaces. Furthermore, roughness of the wall, shape and surface of particles, initial applied load, contact time, temperature and cohesive strength of particle and wall surface affect the adhesion of particles to a surface, and in the same manner the opposite way, the removal from the surface.[37]

Except for the roughness, all factors describe formulation dependent issues, which were already explained. The roughness on the other hand represents a performance influencing factor that is assigned to the capsule. The different inner capsule shell morphologies can be related to the manufacturing process. Due to shrinkage of the capsule films on the mold pins during the drying process adhesion force, in the present case adhesion of the film increases, hampering the capsule ejection. However, when the process comes to the point where the capsules are stripped of the mold pins the degree of adhesion results in a rough surface, which is depicted as mountain and valley structure. The problem with that is that drug particles become entrapped or lodged within this structure and the inhalation efficiency decreases significantly.[38]

Fortunately, this adhesion force between capsule shell and the mold pins and therefore the surface roughness can be easily reduced by the use of hydrophobic lubricants, which are usually stearates. In practice the mold pins are covered by lubricants before they are immersed into the dipping pan with the capsule material. According to the level respectively the amount of lubricant on the pin the mountain and valley structure of the surface changes. With increasing amount of lubricant the surface becomes smoother, less rough and more homogeneous, because adhesion during removal decreases. And as a result, formulation particles have less

possibilities to get entrapped.[38] Nevertheless, the amount of lubricant has to remain within reasonable boarders to avoid any negative affection of the drug formulation.

2.3.2 Manufacturing Process of Hard Capsules

No matter if the capsule is based on gelatin or HPMC, the process of manufacturing is the same. All cases use a dipping process, which is a continuous process, to receive the desired product. Figure 2illustrates the whole procedure[28].

In the case of gelatin manufacturing, a group of stainless steel mold pins is dipped into the so-called 'dip pan', which is a temperature controlled reservoir that contains an aqueous solution of the polymer. Gelation is initiated by the temperature difference between the hot gelatin solution, which usually is maintained at approximately 50°C, on the one hand, and the stainless steel pins held at ambient temperature on the other hand. According to the desired size of the capsule, the pins remain in dipping position for several seconds, whereby the larger capsules require 'longer' dipping time[1,28].

HPMC gelation can be initiated the same way; however, it requires small amounts of additional additives like carrageenan and potassium chloride as gelling agent and gelling promoter to initiate chemical gelling. The reason is that HPMC gels at temperatures above 60°C, but somehow it does not at temperatures below that[36]. Nevertheless, after a few modifications on the molding machine HPMC capsule manufacturing is also possible without the use of gelling agents. But therefore, hot pins dip into the cold HPMC solution to reach the higher temperature to induce thermal gelation of the HPMC. This is possible due to an increase of solution viscosity, caused by a raise of temperature. However, these pins require some heat panel to maintain their temperature and avoid liquefying the polymer again[32,39].

Anyway, after sufficient time the pins are withdrawn from the solution whilst at the same time they rotate to allow uniform polymer distribution. In the next step the films are dried in a series of drying chamber to remove water and finally, the capsules are removed from the pins by striping them off. This is generally supported by a small amount of external lubricants, which enable an easier ejection of the pins due to reduced friction between equipment surface and shell material. Lubrication in this case is known as wall friction, not to confuse with internal friction that is used

between powders to improve for example its flowability[40]. It was found that hydrophobic stearates, such as magnesium stearate, calcium stearate, and stearic acid are the most effective external lubricants. Despite the supporting issue of lubricants, the amount should be kept within reasonable limits, because impacts on the active agent and thus on drug delivery performance cannot be excluded. The bodies are then cut to the desired length and joined together[1,28].

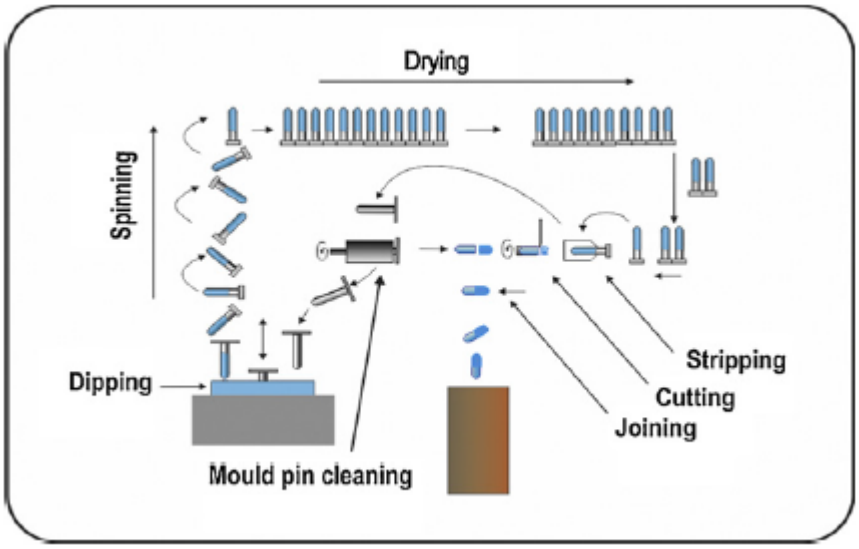


Figure 2: Continuous dipping process for capsule manufacturing (from Qualicaps Europe)[28]

2.3.3 Current Capsule Products

Gelatin capsules are well-known and extensively studied medical supply applications that are used now for more than 80 years. However, animal diseases like bovine spongiform encephalopathy, and religious and dietary issues led to the introduction and development of HPMC as shell material, which already gained a high quality level in the more recent past.[24,32,41]

Few manufacturers and their commercialized products are listed in Table 2. The question of property impact on the capsule was already described before, but the remaining questionable issue between the trade products is whether gelling agents like carrageenan or gellan gum, and gelling promoters such as potassium acetate or potassium chloride were used during capsule manufacture, since performance properties are also influenced by these compounds.[24,32,41]

Capsule Brand	Company	Polymer	Gelling agent
Quali-V®	Shionogi Qualicaps	HPMC	Carrageenan
Vcaps® Plus	Capsugel	HPMC	None
Vcaps®	Capsugel	HPMC	Gellan gum
VegiCaps®	G S Technologies Inc.	HPMC	None
Embo Caps® Vg	Suheung Capsule Co., Ltd	HPMC	Pectin and glycerin
Capstech's HPMC Capsule	Baotou Capstech Co., Ltd	HPMC	None
Natural Plant Capsule	Zhejiang LinFeng Capsules Co., Ltd	HPMC	Carrageenan
Quali-G™	Shionogi Qualicaps	Gelatin	None
G-Caps®	GoCaps GmbH	Gelatin	None

Table 2: List of commercialized capsules with their manufacturing companies, polymer, and gelling agent

2.4 Dry Powder Inhalation – Summary

Dry powder inhalation has become a promising method for the treatment of pulmonary diseases and is therefore favorably used. However, the system has a complex nature coming from three differently acting issues, namely the inhalation device, the drug formulation and the metered dose capsule.

The development of DPIs began with the advancement of MDIs, since the latter contained environmentally harmful compounds. Over the years, companies came up with several different breath-activated devices, which differed in design, dosing method and performance. However, the overall goal was and is still to deliver as much drug as possible into the airways and thus achieve better effects against COPD. This is dependent of several different factors, from which flow rate and the connected dose delivery, inner design of the inhaler and appropriate training for enhancing the sense of easiness, were mentioned as representative factors that concern the device itself.

The delivery performance of drug formulation strongly depends on the size and shape of the particles and the forces acting between them. However, the perfect interaction, if that even exists, between all factors is not that easy and therefore, carrier systems like lactose are added to improve physical and chemical stability of the drug and enhance dispersing and metering properties of the formulation. By that way it is possible to administer even very small doses of only a few micrograms.[21]

And finally, the capsule has the main task to protect the drug from external impacts such as humidity, gas, and forces. Additionally, they should be inert on the inner side against the drug, which means that interactions between powder and wall should be avoided in any way. However, this is not always that easy, since adhesion between capsule and mold pin results in problematic surface morphology that results in increasing powder retention. Gelatin was the first material that fulfilled most of the requirements, unfortunately its animal origin turned out to be problematic for religious and dietary purpose. As a consequence of this companies used HPMC as the vegetarian alternative. Apart from this the cellulose derivative offered the possibility to maintain the manufacturing principles from gelatin.

3. Polymers and their Processing Methods

3.1 Numerical Definitions of Polymers

Polymers define themselves via different factors. This is caused by the fact that they do not have fixed molecular weights like organics and inorganics, instead the molecular weight of polymers depend on the number of repeating units in the chain. The number of repeating units is a statistical representative that is generally known as degree of polymerization, which is defined as

$$Degreeofpolymerization = \frac{averagemolecularweightofpolymer}{molecularweightofrepeatingunit}$$

Eq. 1: Degree of polymerization

Something like an ideal polymer, where each chain has exactly the same degree of polymerization, hardly exists since the chain length in a polymer varies considerably. Some had early termination, thus they are short, and some are longer than the average. This obviously influences also the average molecular weight and reveals some molecular weight distribution as shown in Figure 3.[42]

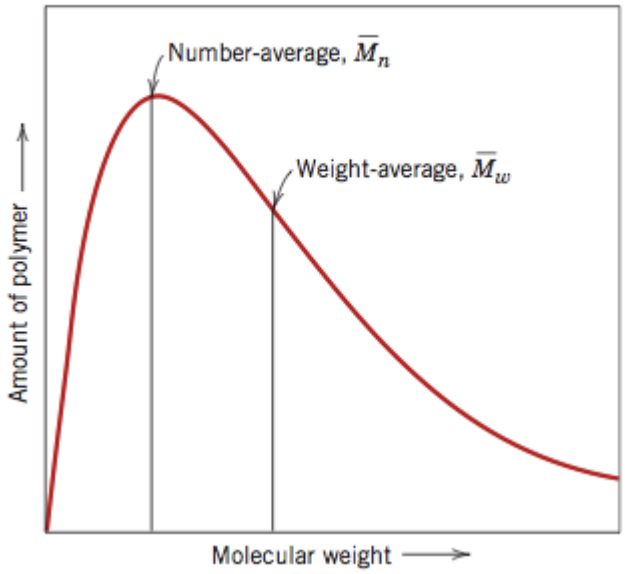


Figure 3: Distribution of molecular weights for polymers[43]

The average molecular weight can be defined in two ways. First, the *weight average molecular weight* $\overline{M_w}$ can be determined when the chains are divided into series of size ranges, followed by the evaluation of the number fraction of chains within a certain range. This is expressed as

$$\overline{M_w} = \sum f_i M_i$$

Eq. 2: Weight average molecular weight

with M_i representing the molecular weight within a size range *i,* and f_i as the weight of the polymer with chains in that range.[42,43]

For calculating the *number average molecular weight* $\overline{M_n}$ it is the number fraction of chains within the size range, rather than the weight fraction, that is required, given by

$$\overline{M_n} = \sum x_i M_i$$

Eq. 3: Number average molecular weight

Again, M_i represents the molecular weight within a size range *i,* but x_i represents the fraction of the total number of chains within each range.[42,43]

3.2 Generals Classification of Polymers

Among the definitions of polymers, there is also a distinction of amorphous polymers, crystalline polymers and semi-crystalline polymers[44,45]. This distinction is in fact important because it determines the thermal conductivity of the material, which is important for the manufacturing processes.

An amorphous polymer can be characterized via its stiffness, meaning the resistance to deformation. Regarding for example the modulus of elasticity as a function of temperature reveals that with increasing temperature stiffness, and thus the modulus of elasticity, decreases. This behavior is depicted in Figure 4. Further, one can observe different phases, the glassy state where polymers behave like glass, the

rubbery phase where certain mobility of the chain parts can be identified and obviously the liquid phase[46]. In another explanation amorphous compounds are described as hard, rigid glasses below the glass transition temperature. Exceeding this characteristic temperature makes the polymer soft and enables the possibility to form the material into desired shapes[47].

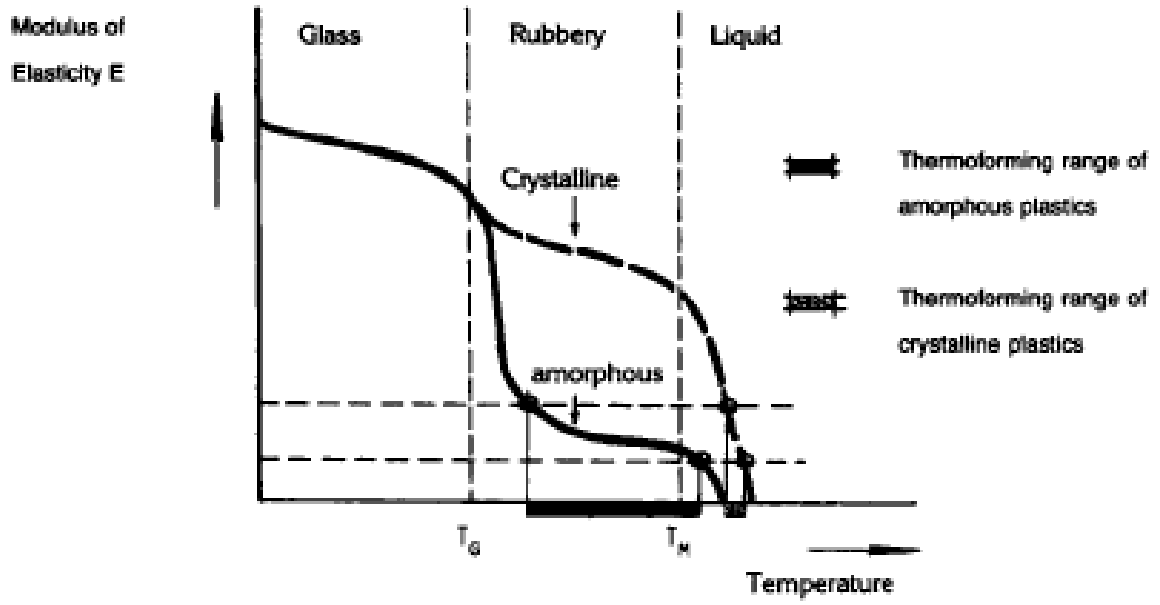


Figure 4: Modulus of elasticity as a function of temperature reveals the different behavior of amorphous and crystalline polymers by thermal impact[46]

Crystalline polymers on the other side are strongly shaped by a regular chain structure. Although there is not something like a perfect crystal and thus, amorphous phases are always occurring in crystalline polymers, there are remarkable differences. Recall the previously mentioned modulus of elasticity as a function of temperature: quite different than before the chains in a crystal are densely packed and they strongly interact with each other. And, even more important, they do not pass something like a rubbery state when heated since the chains remain immobile until they reach the melting point[46]. It is also said that crystalline polymers become less rigid above their glass transition but they will not flow before temperature exceeds the melting point of the crystals. This confirms that the properties, especially the thermal ones, of the material are strongly affected by a degree of crystallinity[47].

These explanations reveal two important and for polymers characteristic temperature values: the glass transition temperature T_g, representing the phase transition from glass to rubber, and the melting temperature T_m, that obviously represents the transition from rubber to melt. Now, knowing these two temperatures, one can simplify the distinction between amorphous and crystalline. While the first has a T_g, the other does not, but of course it is not as simple as that. The degree of crystallinity of polymers reaches top values of 90 % which means that 'crystalline' polymers are more like semi-crystalline materials. And thus, also the 'crystalline' representatives show slight signs of a glass transition.[46]

So far, polymers were mainly distinguished upon their thermal behavior. Other explanations define polymers as either linear or branched compounds, meaning whether one monomer follows the other in a linear manner, or whether side chains, cross-links or even networks occur (Figure 5), which have distinct effects on the properties[42]. However, a better way to describe polymers is the following classification in the three major categories.

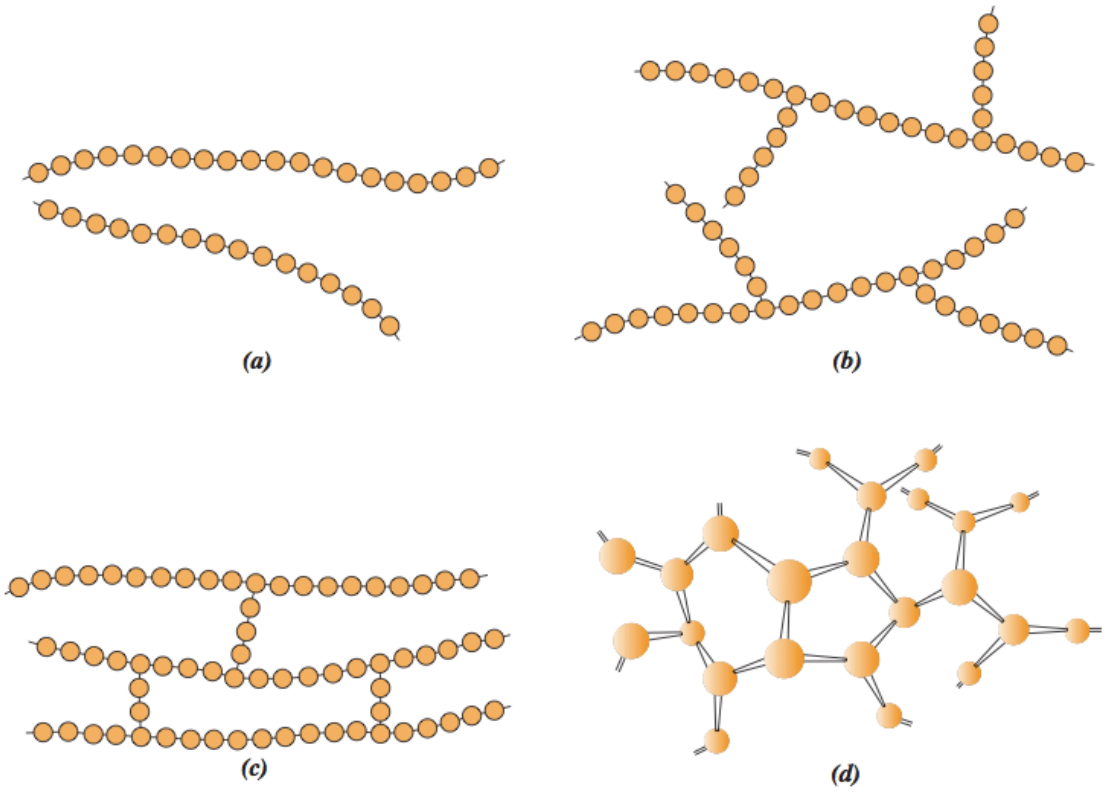


Figure 5: Arrangement of repeating units in polymers. Representing the four possibilities of a (a) linear, (b) branched, (c) cross-linked, and (d) network polymer[43]

The first important class is named thermosetting materials or simply thermosets. These materials are linear or branched, and in either way they have long molecular chains that are strongly cross-linked revealing highly stable network[42]. This network is induced by external impacts such as hear or UV light, where the chains perform irreversible cross-linking to result in permanent shape of the polymer. It is hardened, cured, or as the name tells us, it is set[47].

The second class to mention is thermoplastics polymers, which can be amorphous as well as crystalline[42]. These compounds do also have the ability to get heated and shaped but different to thermosets they do not set or cure. The reason therefore is that polymer chains of thermoplastics are not physically connected in a strong network like the thermosets. What happens upon heating is that the chains soften to a mobile, flowable state where they are formed into desired shapes and upon cooling, thermoplastics become hard and hold their shape. What is also important in this context is that this process of heating, forming and cooling of thermoplastics can be repeated several times.[47]

And finally, the third class is the one that includes elastomeric materials. As the name already reveals, these materials impress with soft and flexible shape, elastic behavior respectively. Elastomers are often described as rubberlike polymers with glass transition below room temperature and they have the ability to deform reversibly until a certain point.[47]

3.3 Processing of Polymers

Knowing the general properties of polymers, and especially the facts of its thermal behavior, is of high interest in the considerations of polymer processing, because it determines the choice of the required process. Injection molding, extrusion, thermoforming and other temperature-dependent processes are rapid and versatile techniques, which are used in industry to manufacture films, fibers, and other shapes of polymers.[42]

Extrusion is probably the most widely applied technique in manufacturing of thermoplastics. Beside the possibility of continuous forming, extrusion provides also the possibility of excellent mixing of polymer with different additives that might be

required to change the compound behavior. Good mixing and also transportation of polymer through the application is provided by screw mechanisms with different heating zones. Very often, the extruder is connected with the proper application for injection molding, another method that is commonly used in industry. The hot extrudate is forced into a closed die with certain shape. The polymer is then allowed to cool and solidify again to remain in the given shape.[42]

Another method to form polymers is given by thermoforming process. This process is possible only for thermoplastic materials since these are the ones that can be heated and formed several times. During thermoforming polymer sheets are heated and then formed by the use of matching dies, vacuum or air pressure.[42]

Beside the explained methods, there are more ways to thermally process polymers like calendaring, spinning, compression molding, reaction injection molding, and so on. Very recently, vacuum compression molding (VCM) was introduced as a new cost-efficient and fast alternative method of polymer processing.[48]

3.4 Polymers and their Application in Pharmacy

The applications of polymers in our daily life are countless. Food packaging, smart phone covers, vehicles are only a few, and among these also pharmaceutical applications are found. Especially the physical, chemical, and the material specific properties are the reason why synthetic polymers found their way into the scope of biomedicine. Drug delivery devices, vascular stents, sutures, clot removal devices, use for aneurysm or ductus arteriosus occlusion, and orthodontic therapy were reported as fields where synthetic polymers are applicable. Table 3 shows a few selected polymers that are already applied in the medical field.[49]

Interestingly, synthetic polymers such as polyethylene, polycarbonate, polyester, polyethylene terephthalate, and others are already known to suit for manufacturing capsules for inhalation devices. A mixture of high density polyethylene, ethylene-vinyl acetate and synthetic zeolite was even patented by a group of scientists from Boehringer Ingelheim Pharma GmbH& Co. KG (Ingelheim/Rhein, Germany). They found that the use of a synthetic polymer based capsule increased the in-use stability, meaning the period from capsule removal from secondary packaging until

inhalation maneuver, of a formulation from 1 day in conventional capsules to at least 9 days. During this time frame the capsule has enough stability for sufficient protection of the API against external impacts before it properties start to worsen.[50]

Beside the good protective properties of polymer capsules, there are other aspects that militate for the use of synthetic compounds for this purpose. Previously, it was explained that the surface morphology of common gelatin and HPMC capsules exhibits strong impact on the inhalation performance and for this reason utilization of lubricants is recommended. Anyway, roughness evaluations with atomic force microscopy (AFM) have shown a roughness R_a of approximately 40nm at very low lubrication level[38]. In contrast to that, examples of untreated polymer films were found in literature, which all revealed lower R_a values even without lubrication. The 'worst' result was found for LDPE with R_a around 30nm[51]. Even better values were found by two other scientific groups, which examined PA films respectively films out of thermoplastic polyurethane (TPU). Both materials had a roughness below 5 nm[52,53]. But regardless of the material, a smooth surface was ascribed to all of them in untreated state. However, in a further sense this would mean that the powder retention can be reduced by a polymer capsule if the roughness is assumed to be the only influencing factor.

Another thinkable advantage of synthetic polymers against currently used capsule materials might be the lower water solubility of the polymers. This hypothesis would mean that polymer capsules would not dissolve when they are poured in water with the purpose of purification after manufacturing process or sterilization before filling process. Furthermore, this would offer the possibility to increase the amount of lubricant during the manufacturing process, since its residues could be removed easily.

Polymer	Full name	Application
HDPE	High density Poly(ethylene)	Packaging, catheters, graft
LDPE	Low density Poly(ethylene)	Packaging
PA	Poly(amide)	Nylon; suture material, for ligament and tendon repair, balloon of catheters,…
PC	Poly(carbonate)	Stable polyester for dialysis membrane and containers
PEG	Poly(ethylene glycol)	Antifouling coating on catheters, hydrogel,
PET	Poly(ethylene terphthalate)	Stable polyester for membrans, grafts, surgical meshes, ligament and tendon repair
PVA	Poly(vinyl alcohol)	Antifouling coating, vitreous body replacement
PVC	Poly(vinyl chloride)	Tubings, blood bags
PMMA	Poly(methyl methacrylate)	Bone cement, intraocular lens, dialysis membrane

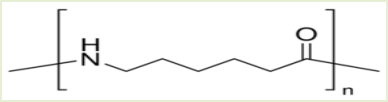
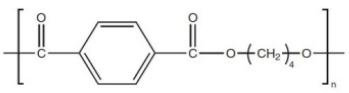
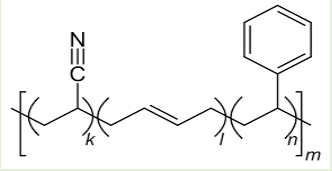
Table 3: Selective list of synthetic polymers in biomedical applications developed by different groups and pooled in one report[49]

4. Materials and Methods

4.1 Polymers

Though it seems that the currently used materials gelatin and HPMC are satisfyingly applicable for capsules in terms of properties, economical reasons remain as open question. To evaluate potential substitutes in this non-industrial funded project dozens of European companies manufacturing or selling potentially suitable polymers were contacted with an enquiry for already available and free polymer samples.

Generally, the type of polymer was not fixed in any matter and the requirements were reduced to a minimum. The only request was that the compound is already confirmed and allowed for food contact, since it was expected that such materials could be applied in the capsule chain and thus, in pharmaceutical issues more easily. Few companies replied on the enquiry, only fewer had really sent polymers. All polymers that were used in the current study are listed in Table 4.

Company	Polymer	Trade-Name	Structure
Lanxess GmbH	Polyamide (Nylon) PA6	Durethan	
Lanxess GmbH	Poly(butylene terephthalate) PBT	Pocan	
INEOS GmbH	Acrylonitrile butadiene styrene ABS	Novodur	

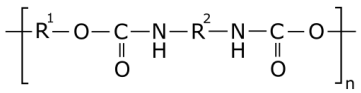
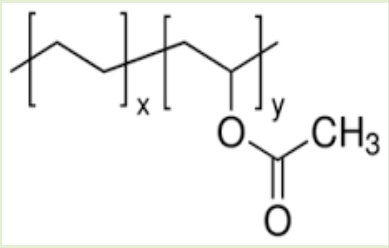
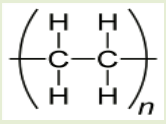
Covestro AG	Thermoplastic Polyurethane TPU	Desmopan	
Versalis S.p.A.	Ethylvinylacetate 6 EVA6	Greenflex	
Versalis S.p.A.	Ethylvinylacetate 9 EVA9	Greenflex	
Versalis S.p.A.	Low-density Polyethylene LD-PE	Pharmalene	

Table 4: Polymers that were used for the current aim

The choice of polymers for the experimental part was limited to some extent, but fortunately the given proposal offered a good mix of classical commodity thermoplastics and engineering thermoplastics.

The first two polymers from Table 4, PA6 and PBT, are more on the engineering side with high-performance properties. PBT can be described as a crystalline polymer with fast crystallization rate, what is very interesting in terms of fast molding process. Furthermore, the polymer is known to have low moisture absorption, and resistance against solvents and loss of mechanical behavior at elevated temperatures. Polyamides such as PA6 are also crystalline materials with good solvent resistance, toughness, and fatigue resistance as the key features. But compared to PBT, they can be influenced and change their properties in the presence of water, since it acts as plasticizer on the one hand, and on the other hand it decreases rigidity and strength, while at the same time the ductility increases.[47]

First member of the commodity thermoplastics is ABS. As its name already reveals, it is a ter-polymer that is made from acrylonitrile, butadiene, and styrene monomers. Thus, the ratio of the three components affects the properties of the polymer to some degree. But anyway, impact strength and chemical resistance are usually high for ABS. In this particular case, it is notable that the delivered form of ABS is already used in medical applications like insulin pens and inhaler housings.[47]

It might be that PE is the most well known plastic in the world. Different types of polymerization reaction lead to different forms of PE in terms of structure and density. But anyway, PE is described as a crystalline thermoplastic with good toughness, almost zero moisture absorption, admirable resistance and among others, it can be easily processed[47]. Easy processability is applied for example with incorporation of different substituents in the polymer backbone. Vinyl acetate for instance can be introduced by copolymerization reaction, what yields in a copolymer with different physical properties. First effect is a reduction of crystallinity, second is a change in solubility, and third is a higher glass transition temperature of the copolymer when the content of vinyl acetate increases[54].

The last missing polymer has something special. Generally, a urea resin belongs to the group of thermosets, and as it was mentioned above, thermosets undergo cross-linking when heated once, and hence it would be more difficult to process the material[47]. However, the reaction between di-isocyanate and diols somehow results in thermoplastic polyurethane (TPU). This polymer possesses the same properties as common thermoplastics when it comes to multiple heating, forming and cooling cycles. Besides that, the resistance against chemicals and the elasticity are other remarkable properties of TPU.[55]

4.2 Polymer Film Manufacturing

The recently developed VCM tool was used as cost and time efficient method to produce polymer films that are suitable for a comparison to the shell wall of a DPI capsule. The tool has a cylindrical design and consists of five parts (Figure 6):

1) Main body
2) Base plate
3) Lid
4) Piston
5) Separation foils

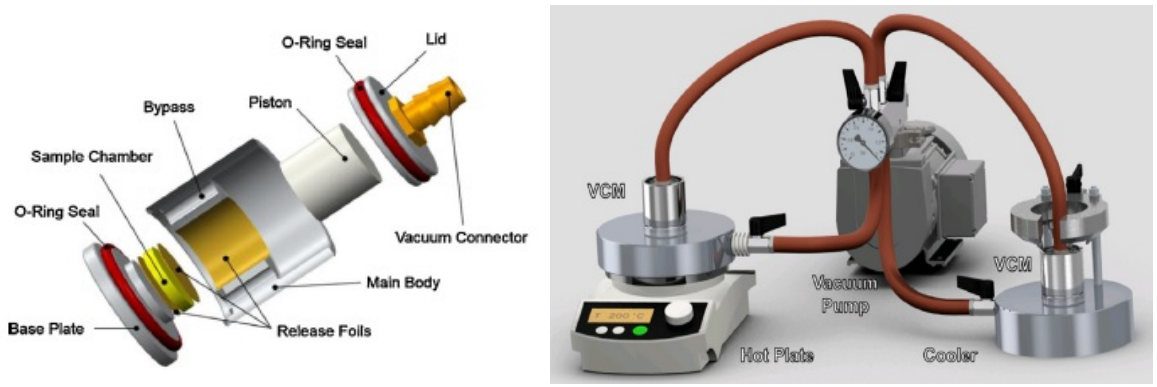


Figure 6: Left: 3D view of the VCM tool, right: complete assembly of the VCM application including hot plate, vacuum pump and cooling part[48]

O-ring seals on both ends achieve a gas-tight closure. The tool is assembled and equipped with special separation foils that should help to avoid sticky polymer residues on the housing material. In the next step powdery material is loaded into the sample chamber, and then followed by another foil and the piston. Thickness of the final product is strongly affected by the filling weight. After filling, the tool is closed with the lid and set under vacuum, which causes some compressive force on the material and thus, compacting. These low-pressure conditions have the additional benefit to remove moisture and avoid bubble-formation and air enclosure in the sample. Additionally, the VCM tool is put on a hot plate, from which heat is transferred across the base plate to the sample. As a result, the polymer changes from solid crystals into some viscoelastic state that allows the material to form a homogeneous film. Allowing the assemble to cool down results in a re-solidification of the polymer in a given geometrical shape (Figure 7)[48].

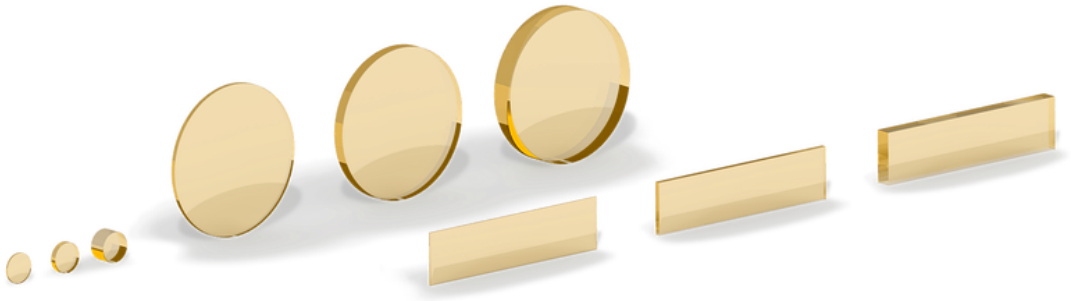


Figure 7: possible shapes of the VCM products: round shaped films with possible diameters of 5 – 25mm, and rectangular films with the size of 10 x 40mm[56]

Polymers in powdery form are more desirable, however, the companies provide the polymers in granular shape, which is not advantageous at all, because it is more time consuming and the film homogeneity is less. Good pulverization of the granules was achieved with cryogenic grinding, a process, where materials are cooled continuously with liquid nitrogen to -196°C, making them more brittle and facilitating impact ball milling[57]. The grinding was performed in 6 cycles à 3:30 minutes with Cryomill (Retsch GmbH, Haan, Germany) at a motion frequency of 15Hz, resulting in sufficiently milled powder.

Several pretests were necessary to find satisfying conditions for the mold work. The challenge was to find a good homogeneity, which is required from the films for several purposes. Additionally, the thickness of the films should be in accordance with that of a capsule, which have shell walls of 100µm[58], or at least close to it. To achieve these goals, an acceptable synergy between polymer mass, temperature and exposure time has to be found. The used settings for molding with VCM bar tool and VCM disk tool (MeltPrep GmbH, Graz, Austria) are listed in Table 5.

Polymer	**Time**	**Temperature**	**Mass disk tool ⌀ = 25 mm**	**Mass bar tool 10 x 40 mm**
	[min]	[°C]	[mg]	[mg]
PA6	45	250	100	85
PBT	45	250	100	85
ABS	45	250	100	85

TPU	25	190	100	65
EVA6	20	150	125	100
EVA9	20	150	125	100
LD-PE	20	150	125	100

Table 5: Settings for film formation with VCM tools from MeltPrep

For the experimental analysis the films were then retreated. The bars were cut to a size of 5 x 30 mm, because of some irregularities that occurred occasionally. For analysis of powder retention a molded film was thought to be more favored than a flat film since formulation loss due to motion before the actual removing is undesired. Thus, the disk films were molded with the VCM disk tool and with the help of holey disks and a suitable pistil.

4.3Relative Humidity Analysis

External impacts such as moisture can affect the capsule and the drug formulation in a negative manner. For this reason, a gravitational analysis was performed, which should reveal whether the polymers do absorb moisture from the environment or not. Therefore, three desiccators were used as conditioning cabinets, from whom each accommodated a saturated salt solution that is required to adjust the surrounding humidity to a desired value[59].NaCl (purity ≥99%) and $MgCl_2$ (purity ≥98,5%) from Carl Roth GmbH (Karlsruhe, Germany), and $LiBr_2$ (purity ≥99%) purchased from Sigma Aldrich (St. Louis, Missouri, USA) were used to adjust the humidity. The conditions were controlled with the, analogous, Klimatherm hygrometer (TFA Dostmann GmbH & Co. KG, Wertheim-Reicholzheim, Germany). Previously prepared bar films were divided between the desiccators and then stored at the prepared conditions for one week.

4.4Train Test

Stability of the capsule shell wall is one of those factors that influence the supply chain of drug formulation. This is why an analysis of mechanical properties of the films is mandatory. Normal mechanical testing specifies the parameters modulus of

elasticity, yield strength, and tensile strength in stress-strain test. With this method the sensitivity of polymers to the rate of deformation, also called strain rate, to temperature, and to the chemical nature of the environment, the influence of moisture, oxygen, and other chemicals respectively, is evaluated.[43]

For any disadvantageous reasons this essential testing method was not available for the present work. But fortunately, as the proverb has it: necessity is the mother of invention.

Stress-strain testing, also known as tensile testing or tension test is based on a rather simple principle. Specimens of usually rectangular geometry are fixed between two grip areas and then force is applied, what brings the film in tension. By that, the strength of a material is determined together with its elongation, and the break or rupture point. The results are visualized in graphs of stress or applied force against strain or change in length.[60]

To maintain the important mechanical analysis a very simple, method was developed by the author of this thesis. The testing application, which was named ‘Train-Tester’, after its inventor on the one hand and on the other hand after the meaning of the German one-on-one translation of the name, ‘Zug-Test’, which actually describes the principle of the test, consists of two double-layered metal plates and a tension belt, which is normally used to fix cargo. The belt was in contact with one of the metal plates, and the two metal plates were connected with the polymer film. Screw clamps were used to fix one metal plate and the tension mechanism of the belt. For better comprehension, Figure 8 shows the assembly of the application.

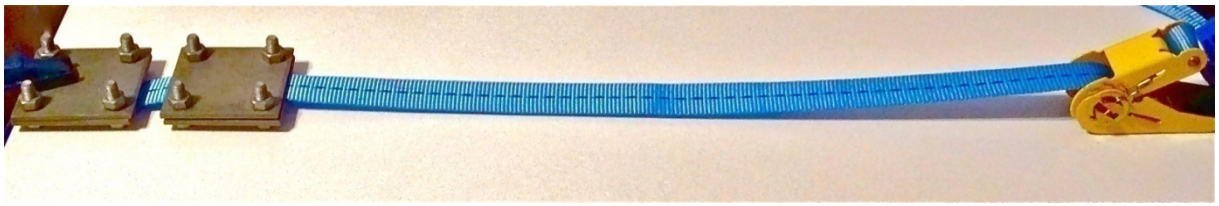


Figure 8: Train-Tester for evaluation of engineering stress

Although modulus of elasticity cannot be evaluated due to a missing force output, the Train-Tester is able to determine any changes in elasticity, because it reveals the possible length of a polymer film with the size of 5 x 30 mm to be elongated under stress until it breaks. From mathematical point of view, the effect of the force impact can be described as engineering stress *e* with the formula

$$e = \frac{\Delta l}{l_0}$$

Eq. 4: Engineering stress

where l_0 describes the original distance between the two fixing areas and Δl the change in length after a force was applied[42].

Furthermore, the percent elongation of a polymer film, calculated by

$$\%\, Elongation = \frac{l_f - l_0}{l_0} \times 100$$

Eq. 5: Percentual elongation of polymer films

with l_f as the distance between the fixing areas after break, allows better sample comparison[42].

At the beginning of this section the effect of moisture on the mechanical properties of capsules was explained. Thus, to prove a potential affection the bar films that were previously stored in desiccators at certain relative humidity were tested with Train-Tester to proof any salience as a result from environmental conditions.

4.5 Rheological Analysis

Beside moisture, oxygen, and other chemicals, temperature is another factor that can influence the mechanical properties of polymer films. Generally, an increasing temperature simultaneously results in decreasing of characteristic mechanical coefficients such as modulus of elasticity, yield strength, and tensile strength[42,46].

For the analysis of mechanical properties as a function of temperature a Physica MCR 300 rheometer (Anton Paar GmbH, Graz, Austria) equipped with a temperature unit was used with aD-CP/PP measuring system (d = 0,6mm). With this method, the force impact on a disk film with a thickness of at least 300µm was analyzed. The

measurement was performed at four different temperatures, 10°C, 20°C, 30°C, and 40°C respectively, to demonstrate the effect of increasing temperatures on the mechanical properties of polymers. For each specimen, the time setting was 100 measuring points with measurement duration of 2s. Additionally, the films were allowed to get used to each temperature step for 300s.

4.6 Powder Retention

Analyses of powder retention on the capsule shell wall are often used in developing a DPI system, because this reveals important information on the overall performance of the system. Low retention values already indicate good fine particle release rate from the capsule. Unfortunately, this depends on many factors, such as shell surface, lubricants, and others. Also differently manufactured powder formulations have shown different retentions.[24]

For this performance evaluation two different powder formulations for inhalation application were used. SS lactose carrierblend, manufactured once with spray-drying method, and once by micronization, resulting in formulations with 10% API on the carrier was chosen as active agent for the analysis. A mass of 5 – 6 mg was loaded on molded disk films, which were then put on a shaker for 20 minutes to obtain formulation distribution over the molded area. The simulation of drug release during inhalation situation was then accomplished with the help of a vacuum pump and a powder trap made from a plastic bottle filled with water.

The remaining amount of API was determined with a PE 950 UV/Vis Spectrometer (Perkin Elmer, Waltham, Massachusetts, USA). Therefore, the films were put in 10mL SS dissolving methanol for 2 minutes under stirring. The films were then removed and the solutions were analyzed with the spectrometer. A calibration curve, prepared from a 1 g/L stock solution was used to obtain the concentration of remaining SS in methanol. Besides the quantitative evaluation of the powder retention, a Leica DM4000 microscope equipped with a Leica DFC320 camera (Leica Camera AG, Wetzlar, Germany) served as visualization method of the powder retention by showing the blank polymer films before powder load, and after ‘inhalation’

5. Results and Discussion

5.1 Manufactured Polymer Films

Vacuum compression molding, a very recently developed thermoforming process for polymers, was the method of manufacturing for the present topic. The resulting films made with VCM disk tool and VCM bar tool were characterized by means of their thickness, as shown in Table 6.

Polymer	Thickness disk tool ⌀ = 25 mm		Thickness bar tool 5 x 30 mm	
	Mean	RSD	Mean	RSD
	µm	µm	µm	µm
PA6	222.6	12.3	216.7	16.4
PBT	197.4	8.0	209.3	20.9
ABS	266.8	11.3	218.3	25.7
TPU	205.0	51.4	211.9	31.9
EVA6	275.6	3.2	233.1	25.6
EVA9	284.2	7.8	247.3	22.2
LD-PE	273.0	3.1	308.0	22.4

Table 6: Mean thickness from manufactured films correlated to the RSD

These results show that the desired goal of preparing films with thicknesses of 100µm, which corresponds to literally claimed capsule thickness[58], had not succeeded. Fortunately, the film thickness can be neglected for the scope of the present work, because its potential influence on the behavior of a complete DPI system was not part of the work. However, the results confirm the importance of the material load for this process. It was said before that the thickness of the films increases with the amount of polymer. Comparing the material load listed in Table 5 with the thickness of the films presented in Table 6 approve the trend that the products show indeed this alternating shape, but only under the premise that the difference of the materials and their specific properties is excluded for this purpose.

For the film formation it was expected that the cryo-milled polymer powder will be poured into the tool, will then be thermoformed and result in an equally shaped film of certain thickness. This assumption was based on basic knowledge of polymer behavior under thermal impact. Polymers usually maintain their molecular chain structure even under heat. Indeed, macromolecules start oscillation, they become mobile at elevated temperatures and at certain temperature they become a viscous melt. This specific temperature is called glass transition temperature (T_g). Exceeding T_g results in a realignment of the polymer chains, from a randomly coiled order to a more ordered, straight form. As a result, the molecules can slide against each other due to some degree of flowability.[61] Applying this to the present issue it would logically mean that the molecular chains of the particles would align in a viscoelastic flow with equal height, which is maintained even after cooling and reformation of the mobile chains in static, coiled, and cured position as a homogeneous film. However, regarding the RSD values reveals that the thickness of the films was far from any consistency. The lowest RSD value was achieved for PA6 with a RSD of 16µm, which still means that the thickness difference of the 9 films that were prepared in the same way is, on average, as much as 32µm. This is too much in deviation, regarding what was published earlier as scientists found that different thicknesses of polymer films have significant influence on the compound characteristics and its properties such as the modulus of elasticity[62]. Generally, the obtained results of the single films were extremely ambivalent. Apart from deviations among each other, even some films showed exorbitantly large thickness deviation on its few millimeters. The worst result was observed in a film of EVA9, which had a RSD of 47µm, meaning a difference of approximately 90µm over 30mm length. This was, however, an exception, since the majority of the produced films had an acceptable variance up to 10µm. Nevertheless, among the tested polymers, RSD was only of limited suitability.

However, as the available VCM tools were not blessed with the best quality and as tool optimization was not possible, the reason for the overall variability can be ascribed to some extent to the milling process, but mainly explained by the polymer morphology. Polymers generally become brittle when they are cooled[61]. Besides, it was found during experiments that polymer films of PBT, PA6, and ABS are more stable, thus brittle, than the other four materials, which had more elastic behavior. Based on these two facts one can assume that granules of ABS for example exhibit

even more brittleness than EVA, when they get cooled for the cryo-milling process. For this reason, it seems reasonable that ABS results in a finer powder than LDPE when they are milled at the same settings and as a consequence, ABS can form more homogeneous films. Figure 9 presents three of the samples after cryo-milling. It can be seen that the size of the particles differs significantly according to the given argumentation. Anyway, different processing profile of a polymer in powdery and granular form was examined during the first trials. It was found that granules hardly melt in the same time as powders do due to the reduced surface area for heat transfer and as a result the resulting films lack of homogeneity. The same principle can be attributed to the melting of granular and powdery thermoplastics, because total flowability of the powder is already succeeded while the core of a granule has not even started to change the molecular chain alignment. This chain alignment occurs due to a loss of secondary forces, van der Waals forces to be exact, which is caused by heat and results in chain movement against each other and thus in increased distance between the molecular chains.[42,63]

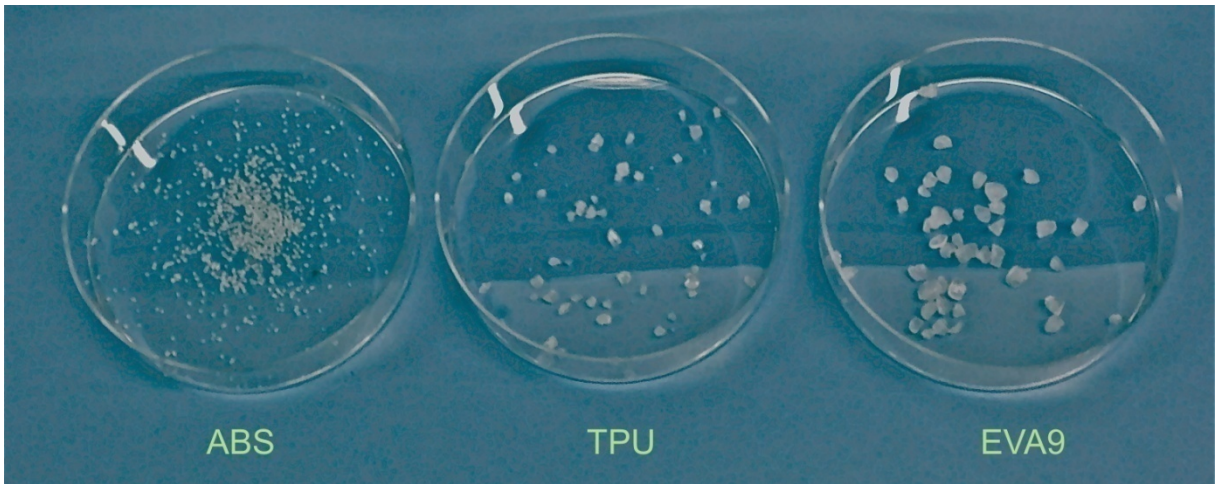


Figure 9: Polymers revealed different powder particle size after cryo-milling with the same settings

Despite the claimed challenges of film manufacturing, VCM proved to be a very versatile tool for fast screening of new materials, here with focus on polymers suitable for the manufacturing of DPI capsules. Nevertheless, a few things have to be

considered. Beside the load also the shape of the applied material plays an important role.

5.2 Environmental Impact on Films

The effect of moisture/relative humidity (RH) on the properties of capsules was reported earlier. In general, capsules made from gelatin have a basic water content of 12 – 16%, those from HPMC contain 4 – 6% moisture at storage conditions between 15-25°C and 35-60% RH. For this reasons studies were performed under similar conditions for the polymer films.

The conditions presented in Table 7 were those that were achieved from each saturated salt solution. For unknown reason, the humidity values did not match those revealed from literature[64]. Anyway, a sufficiently broad distribution was given to observe potential changes on the film properties.

Salt	Temperature [°C]	Humidity [%]
NaCl	25	60
$MgCl_2$	25	42
$LiBr_2$	25	<20

Table 7: Mean storing conditions monitored over one week

From every polymer, nine films were manufactured, which were divided equally among the desiccators after weighing them. After one week, the films were weighed again, once directly after taking them out from the conditioning cabinet, and once after wiping them with cellulose. The latter step was done due to a specific background. It was reported that polymers absorb water vapor due to Fickian diffusion into polymers. Furthermore, it was claimed that moisture will condense and form some mixture of liquid and vaporized water, once it has entered the polymer matrix. The total amount of this entering water refers to absorbed moisture, which remains in free volume and is free to move, or in other words, stays as ‘unbound’ water liquid or vapor. From the total volume of absorbed water only a small amount forms hydrogen bonds in the polymer matrix or is trapped due to physical or chemical

interactions. The majority, in terms of numbers 90%, of the absorbed moisture remains as unbound water.[65] However, as this generally confirms that moisture absorption is present in the bulk, it was assumed that water can equally absorb or condense on the film surface. Anyway, by wiping the films of it was proved whether any unbound water could be removed. The results are shown in Table 8 by means of the weight.

	Weight [mg]					
	Start	‚Wet'	‚Dry'	Start	‚Wet'	‚Dry'
Polymer	**PBT**			**PA6**		
NaCl	35.2	35.2	35.1	29.6	29.9	29.9
$MgCl_2$	31.0	31.1	31.0	31.8	31.7	31.7
$LiBr_2$	31.4	31.5	31.4	33.5	32.7	32.7
Polymer	ABS			TPU		
NaCl	26.7	26.7	26.7	32.7	32.7	32.6
$MgCl_2$	28.7	28.7	28.6	31.0	30.9	31.0
$LiBr_2$	28.0	27.9	28.0	31.4	31.2	31.3
Polymer	**EVA6**			**EVA9**		
NaCl	28.5	28.6	28.4	31.8	31.7	31.7
$MgCl_2$	27.7	27.9	27.8	29.8	29.7	29.7
$LiBr_2$	26.8	26.8	26.8	31.2	31.2	31.2
Polymer	**LDPE**					
NaCl	42.1	42.1	42.1			
$MgCl_2$	38.5	38.3	38.3			
$LiBr_2$	42.7	42.6	42.6			

Table 8: Weighed masses of the polymer films before RH storage, directly after removal from RH storage, and after wiping with cellulose

In principle, the data shows positive results. It seems that without one exception, all seven materials did not absorb water from the simulated environment. Differences were observed only slightly from the value after the comma, moreover one was the most occurring discrepancy. It was thought that this could be attributed to the allowable tolerance of the balance hence it was neglected. However, these results were interpreted as success, since water vapor transmission was not observed, which by implication suggests that even hydrophilic APIs would be protected from

moisture and do not interact with the material and transform or agglomerate. In addition to that significant changes of melt rheology and phase behavior that provide a plasticization effect, which changes modulus of elasticity and thermal transition, or simply the mechanical properties[66], are not expected. The reason for these circumstances was attributed to the VCM processing, which includes the continuous use of vacuum to remove moisture during manufacture and avoids oxygen inclusion into the films.

Nevertheless, the performed analysis was only of gravimetrical nature, hence additional in-depth material tests in this section will be required to confirm the results. Besides, the used balance might have not been the best choice for this analysis due to the limited accuracy in the low milligram region. This assumption is based on results from previous research on the effect of absorbed moisture on polymers. It was found that pure, granular PA6 for example gains around 5% weight when stored for one week at 70% relative humidity[67], and it seems reasonable that the results would be even lower after thermoforming. Even lower values were obtained by another group, which observed a weight gain of not even 0.1% for a thin polymer film after one week[65]. By this, it is shown that changes in weight refer to low amounts, and for this reason it is advisable to perform such analysis with precision balances.

Further aspects, or eventually different results, could be revealed by other analysis techniques. What would be interesting for further analysis for example is an infrared (IR) spectroscopy analysis, in advance and after storage, to visualize spectral changes that might be caused by the presence of moisture. Furthermore, the porosity of the polymer films and the surface area would be of interest in this context. Therefore, gas adsorption analysis would be an appropriate technique, because characteristic factors such as density, porosity, pore volume, and pore size distribution are gained[68]. These in turn provide an imagination of moisture uptake from the surroundings.

5.3 Strain Test of Polymer Films

The results from humidity tests allow some prediction of a moisture independent impact on the mechanical analysis. As it seems that the samples did not gain moisture weight from the surrounding environment, the assumption appears to be

reasonable that the engineering stress, which describes the strain force until the break from the view of mechanical properties, should be the same across all moisture ranges for the films of each polymer. The determination of the engineering stress was conducted for the case that one of the used polymers favorably absorbs moisture from the environment, simulated by the use of saturated salt solutions, and changes its behavior. This evaluation was performed by a rather simple apparatus, which was developed by the author to overcome problems with internal resources. The results from engineering stress are presented in Table 9 and Table 10.

The results confirmed only for PBT and ABS the expected moisture independent mechanical properties of the films. Moreover, the films from these two polymers show almost identical behavior at any time. Furthermore, it can be seen from the results that PBT and ABS films break at relatively low mechanical stress, which indicates that both polymers exhibit lower mechanical resistance behavior. This was consistent with the observation from the cryo-milling, where these polymers resulted in finer powder particles than those with higher ductility.

For the remaining polymers, no clear trend was observable from the engineering stress test. From the film formation and the resulting occurrence it was expected that PA6 would reveal similar results during stress as PBT and ABS. The reason for this was that PA6 films felt similar in the hands, it seemed that they have comparable hardness and stability. On the other hand, it was reported earlier that especially PA6 is predestinated of being strongly affected upon moisture impact[69]. No clear tendency towards one direction was observed during the analysis and it remains unclear whether PA6 states itself as candidate for DPI capsules. For the two representatives of EVA it was thought that the impact of moisture will result in more elasticity and thus in increasing engineering stress resistance. To confirm this theory, EVA films should have a higher degree of brittleness when they are exposed to an environment with low RH. LDPE and TPU were also ascribed to behave similarly. Indeed, none of these expectations were undoubtedly confirmed or denied. But, it was found that mechanical properties of polyurethanes on the one hand are influenced by moisture, while PE on the other hand is rather resistant against moisture absorption[69,70]. The latter can certainly be expected also from both EVA polymers, since they are a derivative from PEs.

Based on the results from engineering stress test it can be assumed that ABS and PBT are potential materials for capsule formation. Both provide a stable shell and are seemingly unaffected by moisture. The latter is questionable for the remaining five polymers from the obtained results. Taking into account the relatively large variation of the film thickness additional studies would be required to evaluate the impact of the film thickness on water uptake and mechanical stress behavior. Other limitations of our studies are the use of a single polymer batch and the milling process leading to different milled particle sizes. It was extensively described before that especially the less brittle polymers ended up in less fine particles and thus the thermoforming process was quite challenging. However, it still remains unclear after this mechanical analysis is a clearly visible trend that allows a limitation of the used materials.

#	RH	Polymer	L_0	ΔL	e	Polymer	L_0	ΔL	e
	salt		mm	mm			mm	mm	
1	NaCl	**PBT**	43	12	0.28	**PA**	43	51	1.19
2			44	11	0.25		44	12	0.27
3			45	9	0.20		45	37	0.82
4	$MgCl_2$		43	8	0.19		43	19	0.44
5			42	10	0.24		43	57	1.33
6			43	11	0.26		43	49	1.14
7	$LiBr_2$		43	10	0.23		44	14	0.32
8			41	11	0.27		42	13	0.31
9			42	8	0.19		46	33	0.72
1	NaCl	**ABS**	42	6	0.14	**TPU**	42	50	1.19
2			42	7	0.17		43	87	2.02
3			44	7	0.16		40	85	2.13
4	$MgCl_2$		43	8	0.19		42	70	1.67
5			43	7	0.16		41	94	2.29
6			44	7	0.16		41	91	2.22
7	$LiBr_2$		42	6	0.14		44	70	1.59
8			43	5	0.12		41	66	1.61
9			44	11	0.25		40	75	1.88

1	NaCl	**EVA 6**	41	89	2.17	**EVA 9**	41	63	1.54
2			40	74	1.85		42	90	2.14
3			40	73	1.83		40	95	2.38
4	$MgCl_2$		43	72	1.67		41	77	1.88
5			42	66	1.57		40	72	1.80
6			40	93	2.33		40	111	2.78
7	$LiBr_2$		41	69	1.68		44	87	1.98
8			41	64	1.56		40	86	2.15
9			42	79	1.88		38	66	1.74

Table 9: Engineering stress results from Train Test I

#	RH	Polymer	L_0	ΔL	e
	salt		mm	mm	
1	NaCl	**LD-PE**	43	29	0.67
2			41	82	2.00
3			41	24	0.59
4	$MgCl_2$		40	18	0.45
5			37	66	1.78
6			41	34	0.83
7	$LiBr_2$		45	67	1.49
8			41	51	1.24
9			40	28	0.70

Table 10: Engineering stress results from Train Test II

5.4 Force Impact on Polymer Films

Determining the force impact of a ball-shaped piston on a polymer film reveals mechanical properties of a material as a function of force against distance. An additional temperature gradient provides a distinct imagination on changing behavior with increasing temperature influence.

The results of the analysis are depicted in Figure 10, which shows the graphs of each polymer film. It can be seen that increasing temperature results in softening of the

polymer films and thus, they lose mechanical strength. This is confirmed by only comparing the progress of the force impact at the lowest temperature with that of a higher temperature: the higher the temperature, the lower the required force. What is also interesting from the graphs is the progress of the curves. PBT, PA6, and ABS have a rather steep curve, which is an indicator for high stiffness and brittleness[63]. Opposite behavior is regarded from TPU, LDPE, and both EVA derivatives, which all have comparably less steep curves and thus, they have lower stability and brittleness, but higher ductility.

The trend of decreasing force for mechanical deformation with increasing temperature can be discerned more accurately from Table 11. It can be noted that the slope of the linear parts of each graph generally becomes less steep when temperature rises by 10°C. The only exception, for some reason, is ABS, which reveals the inverse behavior, meaning that force requirements increase with temperature.

However, the impact test coincidentally unfolded another result that was actually not planed. It was written in the explanations on the polymer material, that an incorporation of substituents into the main polymer chain can have enormous impact on the properties of the material. More precisely, PE gets less strong with vinyl acetate substituents in the backbone, whereby a larger amount of VA means less elasticity. Indeed, comparing the slope of LDPE, EVA6, and EVA9 reveals that it becomes less when the content increases, a fact that was reported elsewhere[54].

The verification of the mechanical properties of the polymer films was finalized in this study by the force impact analysis with a rheometer. While the engineering stress test did not reveal sufficiently notable results for a material limitation, the impression changed now. It was claimed earlier in this thesis that mechanical stability is an important factor for capsules. First, it has shape affective tasks, but the main requirement of stability is mainly important during the filling process, where capsules are opened and closed, and it is important for the moment when the capsule is pierced open to reveals the encapsulated powder formulation.

For this reason, TPU can be put aside as the first material, because of the comparably low slope and high elasticity. It is assumed that TPU is too soft to get opened adequately by piercing. According to the author's opinion, also the EVA

derivatives would be excluded from further use as capsule material, if LDPE was available. The reason is argued to be the same as for TPU, thus the slope values speak for themselves that LDPE is tougher than EVA. Besides, PE is a common material that is used as packaging material for foods and more, and therefore the permission to use it as capsule material in DPI might be easier to achieve.

For the three DPI capsule candidates PBT, PA6 and ABS no distinct exclusion of one participant is possible after all mechanical analysis. Even though it seems that PA6 is less strong than the others, the open question remains whether the strength of PBT and ABS is maybe too high for the use as capsule. However, the most potential is assumed to belong to ABS because of its possibilities in copolymerization. Due to the fact of consisting of three components, the properties of ABS can be directed during manufacture and thus, it can fulfill manifold challenges according to specific requirements.

Apart from these assumptions, further tests are mandatory to evaluate the suitability of LDPE and ABS as capsule materials. However, one method of manufacturing would also be worth to consider: blending. Blends are typically mixtures between two or more components, for example elastic EVA and brittle PBT, which aim to combine benefits from both sides. In this way it is thinkable that a capsule provides enough stability, but it is not too strong. A combination of two materials can also be manufactured as double-layer, if one material is for example forbidden in the contact with active agents and thus, only useable as outer layer of a capsule.

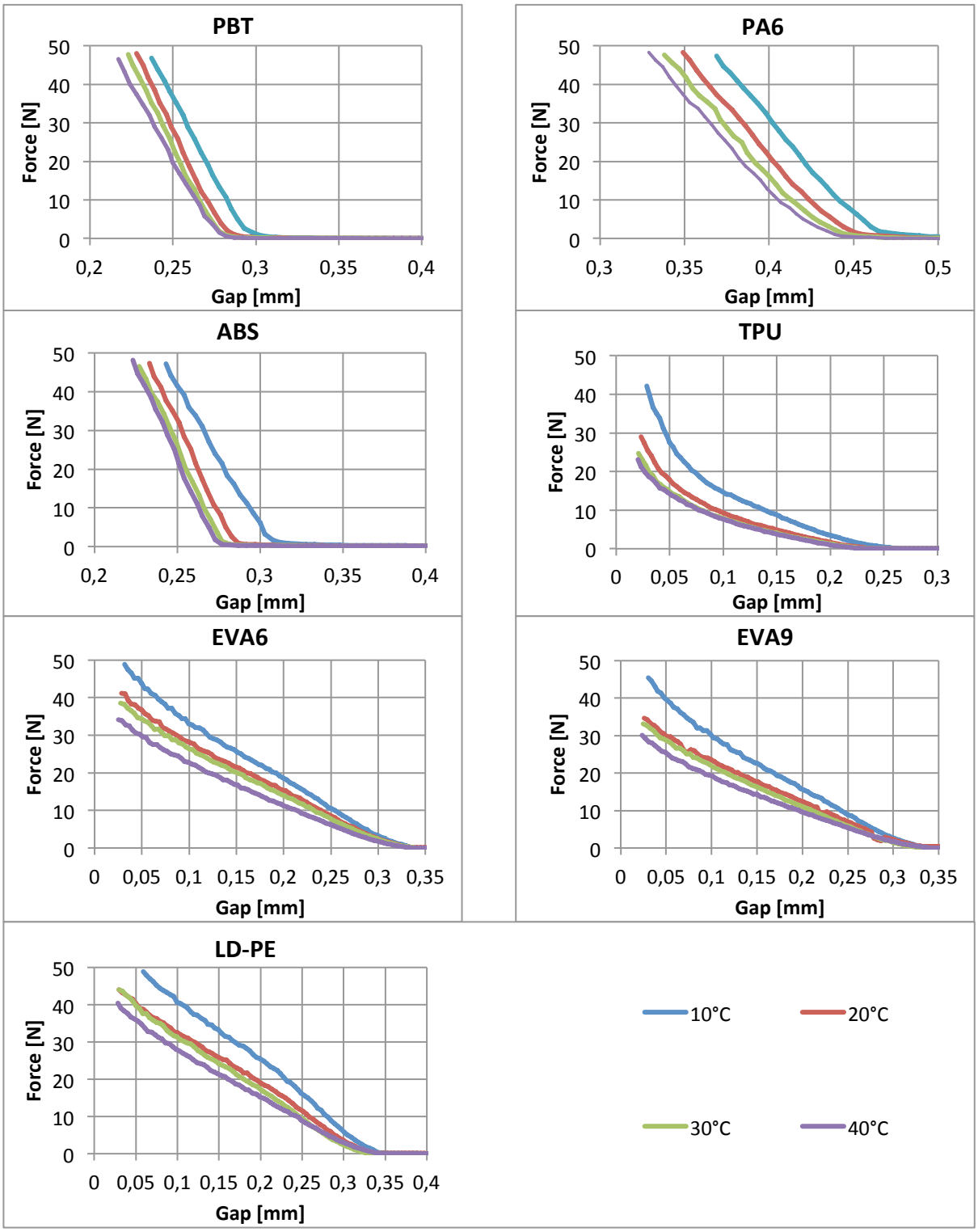


Figure 10: Force impact measurement results with respect of a temperature gradient

Polymer	Slope			
	10°C	20°C	30°C	40°C
PBT	-821.4	-903.5	-882.2	-777.4
PA	-510.6	-503.5	-499.5	-485.9
ABS	-728.5	-921.9	-940.6	-964.4
TPU	-113.4	-74.8	-64.9	-65.8
EVA6	-149.8	-129.1	-122.5	-105.5
EVA9	-134.2	-107.5	-103.6	-87.0
LDPE	-166.2	-142.9	-147.7	-123.3

Table 11: Depiction of the slope to show the trend of decreasing force with increasing temperature

5.5 Powder Retention on Polymer Films

Evaluation of the powder retention is of crucial importance for the performance of a new DPI component. For fast screening, light microscopy is an appropriate method for this purpose. Figure 11 and Figure 12 represent the assessment of powder retention of micronized API on the tested polymers ABS and TPU. The pictures are expressed in tenfold magnitude of the original. In both cases, obviously, API remained on the film surface after the simulation of an inhalation situation, created by a vacuum pump. Even though this method cannot determine the exact amount, it evidently states remaining API.

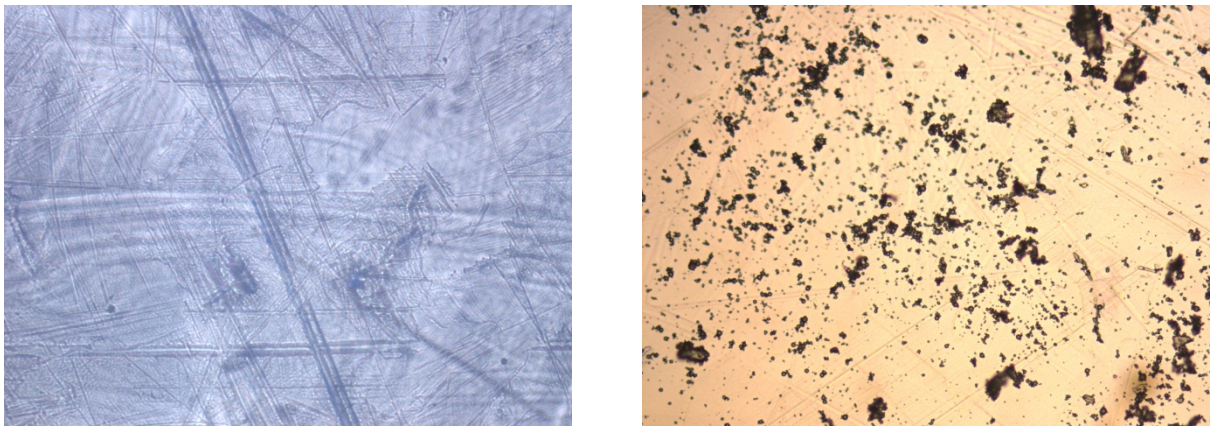


Figure 11: Illustration of powder retention on the example TPU – before load (left) and after 'inhalation' (right)

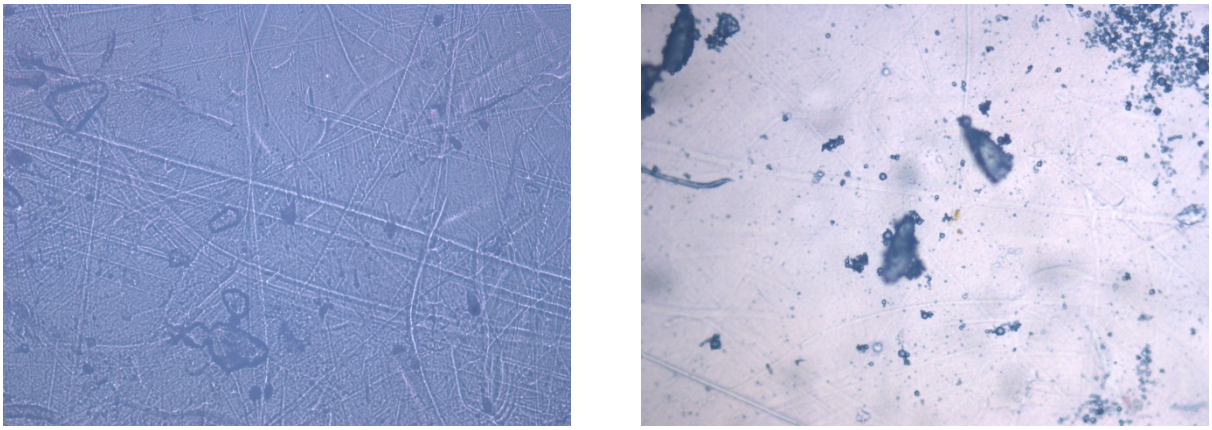


Figure 12: Illustration of powder retention on the example ABS – before load (left) and after 'inhalation' (right)

More accuracy is given by the determination of the concentration of a solution, containing the dissolved API that was left on the film surface. The calibration curve, depicted in Figure 13, and its linear equation were used for the calculation of the concentration of SS, micronized as well as spray-dried, in 10mL MeOH. The wavelength of absorption for SS is 278nm.

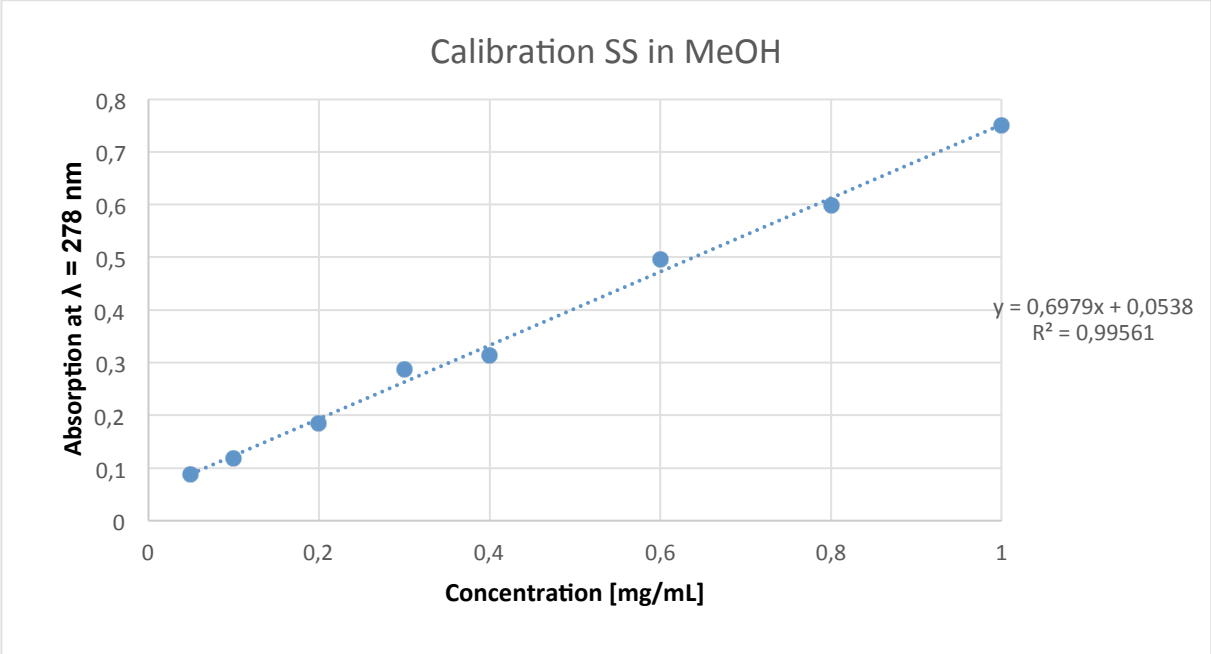


Figure 13: Calibration of 10% SS on lactose carrier, dissolved in MeOH

		spray-dried			micronized		
Sample		A	B	C	D	E	F
Lamda 278	nm	0.81	0.53	0.43	0.31	0.41	0.37
Concentration	mg/mL	1.09	0.69	0.53	0.37	0.51	0.46
Rem. API	mg	10.88	6.86	5.34	3.73	5.06	4.58
Load API	mg	26.10	26.00	26.20	25.80	25.50	25.30
Powder Ret.	**%**	**41.67**	**26.40**	**20.40**	**14.46**	**19.84**	**18.11**

Table 12: Powder retention of spray-dried and micronized 10% SS from gelatin capsules

		PBT	PA6	ABS	TPU	EVA6	EVA9	LDPE
Lamda 278	nm	0.12	0.07	0.08	0.14	0.10	0.12	0.11
Concentration	mg/mL	0.10	0.02	0.04	0.13	0.06	0.09	0.09
Rem. API	mg	0.99	0.22	0.42	1.28	0.63	0.90	0.88
Load API	mg	5.90	5.50	5.70	5.60	5.70	5.80	5.30
Powder Ret.	**%**	**16.75**	**4.07**	**7.30**	**22.93**	**11.05**	**15.46**	**16.62**

Table 13: Powder retention of spray-dried 10% SS on polymer films

		PBT	PA6	ABS	TPU	EVA6	EVA9	LDPE
Lamda 278	nm	0.10	0.09	0.08	0.12	0.11	0.09	0.10
Concentration	mg/mL	0.07	0.06	0.04	0.09	0.08	0.05	0.07
Rem. API	mg	0.67	0.57	0.42	0.89	0.80	0.52	0.66
Load API	mg	5.90	5.40	6.30	5.10	6.20	5.40	6.30
Powder Ret.	**%**	**11.31**	**10.47**	**6.72**	**17.50**	**12.89**	**9.59**	**10.43**

Table 14: Powder retention of micronized 10% SS on polymer films

Comparing the two different methods that were used for the manufacture of the SS formulations reveal that micronized powders provide better results in terms of powder retention than the spray-dried ones. Each formulation method per se has its benefits and drawbacks, however, micronized particles, manufactured by opposing jets of compressed air that force particles to collide with each other, are reported to yield in better performance than spray-dried particles, which are provided by transforming a solution or suspension into a fine powder due to droplet formation and fast solvent

evaporation[71]. This was confirmed in five out of seven cases, however, PA6 behaved differently, and EVA6 was slightly better with the spray-dried formulation.

What can also be observed from the results is that all polymer films, no matter of the powder formulation, performed better then already available gelatin capsules. Admittedly, this conclusion has to be treated with caution. Capsule manufacturers generally use lubricants during the formation, which helps to strip the capsules from the mold pin. This is possible, because lubricants lower the inevitably occurring degree of adhesion that would be responsible for rough shell surface and therefore, for a 'mountain-valley-surface' that would entrap or lodge API particles during inhalation.[38] On the other side, high residuals of lubricant are also accountable for creating sticky agglomerates that would equally influence the powder retention in a negative way. However, such lubricants were not used during manufacturing of the polymer films and the magnificent thermoforming application VCM obviously provides films with smooth surface with no or even less irregularities, thus this was assigned to be the main reason for this delightful result.

The results regarded during the mechanical analysis did not reveal a positive or negative difference between the three mechanically tough materials PBT, PA6, and ABS. Now, as the results from powder retention are available, ABS can be declared out of the tested as the best polymer for an application as DPI capsule, since less than 10% of the powder formulation loaded on the film remained. Besides, the study ultimately unfolds that TPU is useless as capsule shell, at least as inner shell wall if the capsule was prepared as blend or double-layer. From the three ductile polymers none of them was able to emphasize itself in positive or negative manner. All three were in the same range in terms of powder retention. But, taking the mechanical analysis into account, LDPE would be suggested from the author's side.

Anyway, the experiment states that the remaining powder fraction after a simulated inhalation is significantly lower with synthetic polymers as capsule shell wall than with commonly used capsules. Nevertheless, these results have to be considered with caution, since removal of API was done directly from the capsules on the one hand, and from a plane polymer film with a small deepening on the other hand. What remains unclear in this case is, whether the retention would change, if the polymer materials were also molded as a capsule. This becomes the question of interest for further investigations on this topic.

6. Conclusion

The development of dry powder inhaler systems (DPI) gained enormous interest over the past years in the pharmaceutical and medical sector with the aim to treat diseases of the airways. Companies from all over the world came up with different devices and inhalation systems, from which each has its benefits and drawbacks.

The performance of dry powder inhalation systems is of crucial importance for the treatment of pulmonary diseases. However, it was shown that the total performance is the sum of multiple smaller factors that define the success of disease treatment. This begins with the inhaler device, its dosing method, and its design, which affect the drug delivery to a large extent. Thus, appropriate training on the application is mandatory. Next in the list of influencing factors is the design of the powder formulation. It was mentioned that specific properties such as crystallinity, hygroscopicity, particle size, internal forces, and more affect the de-agglomeration upon inspiratory airflow and therefore, the drug delivery. Within this context it was said that carrier systems like lactose are often used to improve specific properties of the drug transport. And finally, the capsule was denoted as the last factor that affects the performance. Explanations were made on the currently used materials and methods. Additionally, the main task of a capsule was highlighted as well as associated problems with gelatin and HPMC as shell material.

The goal of this thesis was to make a first step to identify the use of thermoplastic materials as an alternative to gelatin and HPMC as shell material for a capsule to be used for DPI products. For this purpose, seven materials were examined on their suitability as capsule materials. The recently developed method of vacuum compression molding (VCM), a fast and simple method for material screening, was used for manufacturing films, which were the base for analysis. During this process it was found that different particle sizes of the polymers significantly affect the resulting films in terms of thickness and homogeneity. The different size distribution was assigned to the specific material properties, since all of them were milled at the same conditions. The resistance of the polymer films to relative humidity was tested, revealing at first view that all materials did not absorb water from the environment.

Mechanical analysis was performed by monitoring the engineering stress of rectangular films stored at different humidity. However, it was found for PBT and ABS only that both maintain their strength upon humidity impact. The other polymers did not reveal any significant tendency, which was attributed to the challenging film formation. Therefore, the force impact was tested to demonstrate strength and elasticity behavior of polymers at different temperatures. The results clearly demonstrate the difference between brittle and ductile materials and the effect of increasing temperature. Based on these facts it was concluded that TPU is ruled out because of its ductility. Furthermore, it was claimed that LDPE is more favored compared to EVA due to higher stability. The three brittle polymers did not reveal significant differences in the mechanical testing. This was then achieved by evaluation of the powder retention. Based on the results, ABS is the best compound that can be used for DPI capsules. Moreover, it was demonstrated that polymer films generally have lower powder retention than common capsules made from gelatin.

The presented results provide evidence that the use of polymer materials as capsule materials for inhalation products provide an opportunity for development and advancement of DPI systems. Even though the scope of analysis was limited, the polymers tested showed favorable performance behaviors. Of course, a lot of work is still remaining, nevertheless, polymers as capsule materials are a possibility for the future and therefore, investigations in this sector should maintain.

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Appendix

List of Abbreviations

ABS	Acrylonitrile Butadiene Styrene
API	Active Pharmaceutical Ingredient
CFC	Chloro Fluoro Carbon
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry Powder Inhaler
EVA	Ethylvinylacetate
HDPE	High Density Polyethylene
HPMC	Hydroxypropylmethylcellulose
LDPE	Low Density Polyethylene
MDI	Metered Dose Inhaler
PA	Poly(amide)
PBT	Poly(butylenes terephthalate)
PC	Poly(carbonate)
PEG	Poly(ethylene glycol)
PET	Poly(ethylene terphthalate)
PMMA	Poly(methyl methacrylate)
PVA	Poly(vinyl alcohol)
PVC	Poly(vinyl chloride)
RH	Relative Humidity
RSD	Relative Standard Deviation
SS	Salbutamol Sulfate
T_g	Glass Transition Temperature
T_m	Melting Temperature
TPU	Thermoplastic Poly(urethane)
VCM	Vacuum Compression Molding

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List of Equations

Eq. 1: Degree of polymerization

Eq. 2: Weight average molecular weight

Eq. 3: Number average molecular weight

Eq. 4: Engineering stress

Eq. 5: Percentual elongation of polymer films

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