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Impact of carrier surface modification and dosator capsule filling process on DPI performance of adhesive mixtures

Master Thesis

for obtaining the academic degree of

Diplom – Ingenieurin

in Chemical and Pharmaceutical Engineering

Submitted to the

Technical University Graz

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Graz, August 2014

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Acknowledgements

It is my pleasure to express my gratitude to all those who helped and supported me during my master thesis.

First, I want to thank Prof. Johannes Khinast for the opportunity to accomplish my master thesis under his supervision at the research center pharmaceutical engineering (RCPE).

I thank Marcos Llusa, PhD and Amrit Paudel, PhD for their support regarding scientific questions.

A special thank goes to my project colleague and dear friends Dr. Sarah Zellnitz and Mag. pharm. Verena Wahl for their scientific and team support during my master thesis at RCPE.

Further, I would like to thank Hartmuth Schröttner from the institute of electron microscopy and nanoanalysis for providing the SEM images.

Very special thanks goes to my beloved Josef, who supported me in many situations throughout the last years and who always believed in me.

Finally, I want to express my deepest gratitude to my family and my dear friends believing in me and supporting and of course for their everlasting encouragement and lifelong support for reaching my goals.

Abstract

In order to reach the deep lung, active pharmaceutical ingredient (API) particles have to exhibit an aerodynamic diameter of 1µm to 5µm. Particles of this size however are rather cohesive and have poor flow properties. This challenges reproducible dosing in dry powder inhalers (DPIs), which is carried out volumetrically. To still guarantee reproducible dosing carrier based formulations, where the small API particles are attached to larger carrier particles with adequate flowability, have been formulated. But in order to reach their target site, the deep lung, API particles must detach again from the carrier surface during inhalation. Therefore, the present study investigated the effect of carrier characteristics and dosator capsule filling operation on the in vitro deposition of mixtures containing salbutamol sulphate as a drug and lactose and mannitol as model carrier materials. The carrier surfaces of lactose and mannitol were modified via wet decantation. The impact of decantation process on the carriers was investigated by laser diffraction, density and flow measurements, gas adsorption and scanning electron microscopy. Differences in carrier type and untreated and decanted materials were identified. Adhesive carrier and API mixture (148.5:1.5) were prepared, mixture homogeneity was tested and subsequent the mixtures were filled into capsules at different process settings. Finally, the influence of the decantation process on the in vitro performance of the adhesive mixtures was tested with a next generation impactor (NGI) and Aerolizer® as inhalation device. For lactose the carrier decantation decreases the fine particle fraction (FPF) whereas, the latter of decanted mannitol carriers tends to increase at a low compression ratio.

Thus, in summary, the untreated lactose carrier particles blended with 1% salbutamol sulphate and a compression ratio of 1:2 proved to be the most efficient conditions first for accurate dosing (RSD < 0.8%) and second for a high fine particle fraction (14%).

Kurzfassung

Damit Wirkstoffpartikel bei der Inhalation über die Lunge aufgenommen werden können, müssen sie eine Partikelgröße zwischen 1µm und 5µm aufweisen. Partikel dieser Größe sind jedoch kohäsiv und fließen schlecht, was sich negativ auf die Reproduzierbarkeit der Dosierung, die meist volumetrisch erfolgt, auswirken kann. Um trotzdem eine gleichmäßige Dosierung sicher zu stellen, werden die Wirkstoffpartikel in einem Mischprozess auf ein gröberes Trägermaterial, welches gute Fließeigenschaften aufweist, aufgebracht. Damit der Wirkstoff die Lunge erreichen kann, muss er sich während der Inhalation wieder von der Trägeroberfläche ablösen. Deshalb ist das Ziel dieser Forschungsarbeit die Untersuchung verschiedener Träger (Laktose und Mannitol) vor und nach einer Modifizierung (Nass-Dekantation) der Trägeroberfläche. Der Einfluss der Dekantation auf die Trägeroberflächen wurde mittels Laserbeugung, Dichte- und Fließfähigkeitsmessungen, Gasadsorption sowie Rasterelektronenmikroskopie untersucht. Auf die Träger wurde Salbutamol Sulfat als Wirkstoff im Verhältnis 148.5:1.5 aufgebracht, die Mischungshomogenität bestimmt und die interaktiven Mischungen mit unterschiedlichen Prozesseinstellungen in Kapseln gefüllt. Schlussendlich wurde der Einfluss des Dekantation- und Kapsellfüllprozesses auf die lungengängige Dosis des Arzneistoffs, die sogenannte Fine Particle Fraction (FPF) mittels aufwändigen Impaktormessungen bestimmt. Bei Mischungen mit Laktose als Träger wurde die FPF nach der Dekantation verringert. Für Mannitol hingegen konnte eine Verbesserung der lungengängigen Dosis nach der Oberflächenmodifizierung festgestellt werden. Der Einfluss des Kapsellfüllprozesses war bei allen Mischungen zu sehen. Höhere Kompaktierung der Mischungen in den Kapseln führte zu geringeren FPFs.

Zusammengefasst kann gesagt werden, dass mit Mischungen aus Laktose ohne Oberflächenveränderung und geringer Kompaktierung während des Füllens die gleichmäßigste Dosierung und höchste lungengängige Dosis erreicht werden konnte.

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Abbreviations

ACI	Anderson cascade impactor
AoR	Angle of repose
API	Active pharmaceutical ingredient
BD	Bulk density
BET	Brunauer-Emmet-Teller
BJH	Barrett, Joynar and Halenda
CI	Carr`s compressibility index
CPH	Capsules per hour
CFC	Chlorofluorocarbons
CO2	Carbon dioxide
COPD	Chronically obstructive pulmonary disease
d	Particle diameter
d_{ae}	Aerodynamic diameter
d_n	Nozzle diameter
DPI	Dry powder inhaler
ED	Emitted dose
FPD	Fine particle dose
FPF	Fine particle fraction
g	Acceleration gravity
HFA	Hydrofluoroalkane
HPLC	High pressure liquid chromatography
k	Bolzmann constant
LH100	Lactohale 100
LH100_dec	Lactohale 100 decanted

MOC	Micro orifice collector
NGI	Next generation impactor
O_2	Oxygen
P160C	Pearlitol 160 C
P160C_dec	Pearlitol 160 C decanted
pMDI	pressurized Metered dose inhaler
R	Radius
RD	Recovered dose
r.H.	Relative humidity
RSD	Relative standard deviation
SSA	Specific surface area
SEM	Scanning electron microscopy
T	Absolute Temperature
TD	Tapped density
U	Velocity
U_{TS}	Settling velocity
U_0	Fluid velocity in nozzle
VdW	Van der Waals force
η	Viscosity
Π	Constant (3.1416)
ρ	Particle density
ρ_0	Unit density
ρ_a	Fluid (air) density

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1. Goals and Motivation

The lung offers a unique and challenging route of administration for the treatment of respiratory diseases such as asthma or chronically obstructive pulmonary disease (COPD), and cystic fibrosis [1]. Advances in drug formulation and inhalation device design are creating new opportunities for inhaled drug delivery as an alternative to oral and parenteral delivery methods [2]. Pulmonary drug delivery is gaining grounds in the local treatment of respiratory diseases as well as in the systemic application of highly potent, complex and low-dose active pharmaceutical ingredients (API). A high concentration of drug on the targeted site, the tissue of the lung is achieved with relatively low doses and in addition reducing adverse drug effects. These advantages can be attributed to the high absorption area in the alveolar region of the lungs and the circumvention of the first pass effect of the oral administration route [1], [3]. Other key features of respiratory drug delivery are the direct targeting of the drug, fast and predictable onset of action, and degradation within the gastrointestinal tract is avoided hence lower applied dosages minimize unwanted side effects and drug interactions [4]. All these factors result in less cost. Moreover, pulmonary administration means less physical stress for the patient compared to parenteral administration.

Nebulizers, pressurized metered-dose inhalers (pMDIs), and dry powder inhalers (DPIs) have each found a niche in the quest for optimal treatment of respiratory disease and convenient use [2]. However, a special focus is put on capsule-based DPIs as almost half of all marketed DPIs belong to this category. This can be related to the wide range of DPI advantages like better patient compliance, formulation stability and environmental sustainability, only to name a few [5]–[7]. In general DPIs can be categorized into two types [8], [9]: single-unit dose (capsules or disposable) and multiple-unit dose (pre-metered unit or reservoir). Pre-metered single-unit doses in capsules, are protected from environmental conditions until used, and ensure adequate control of dose uniformity [1]. Examples for capsule-based devices are the Rotahaler™ (Glaxo Smith Kline), the Handi-Haler™ (Boehringer-Ingelheim) as single unit-dose, and the Flowcaps® (Hovione) as novel multiple pre-metered unit-dose technology that comprises up to 20 capsules [10]–[12]. DPIs as a dosage form consist of a powder formulation in a device, which is designed to deliver an API to the respiratory tract. A lot of effort is put into research and development for novel DPI formulations and devices, searching ways to improve the efficiency of drug delivery [9]. The formulations used in DPIs typically consist of adhesive mixtures of the API attached

to the surface of coarse carrier particles, so called binary formulations. In order to reach the tiny airways of the deep lung the API particles have to exhibit an aerodynamic diameter of 1 – 5µm. Particles of this size are rather cohesive and show poor flow properties and difficult dosing [1]. Thus, to improve the flowability, dosing accuracy and minimizing dose variability of such powders carrier based formulations, are used [13]. During inhalation, the API detaches from the carrier to reach its target site, the deep lung. Therefore an aerodynamic diameter of <5µm is required, to avoid impaction and sedimentation in the upper respiratory tract together with the coarse carrier particles [14].

Especially with the increased recognition of the potential role of DPI systems for other low dose medications, DPIs could become the device category of choice for local and systemic drug delivery [10]. Several low-dose capsule filling systems are currently available. Filling principles can be divided into volumetric (e.g., the dosator nozzles, vacuum drum filler, vacuum dosator and tamp filler) and gravimetric (e.g., micro-dosing, not further illustrated here) or direct and indirect filling methods respectively. Capsule filling by nozzle dosators has been broadly investigated [15]–[18] and is an important technology applied in the pharmaceutical industry today. Especially in DPI filling the dosator principle plays an important role, as the doses need a controlled degree of compaction, to ensure the DPI can reliably turn the plug back into a powder for efficient dose delivery. Therefore, this research uses an indirect filling principle based on one of the most common volumetric techniques in standard doses, the dosator nozzle principle.

The key for the successful development of a DPI product is the preparation of particulate formulations that can provide reproducible and acceptable powder flowability, dosing efficacy and delivery of the drug particulates to the respiratory system. This controlled production of drug particles or carriers with optimal morphology, surfaces and structure is also called “particle engineering”. The main target is to incorporate special attributes into particles while taking into account the specifics of inhaler design and drug delivery requirements [19].

The present study investigates two carriers of different type and source (lactose and mannitol) as received and after engineering (wet decantation) and blended with spray dried API (salbutamol sulphate). After determining the mixture homogeneity the adhesive blend was filled into capsules for a single dose DPI (Aerolizer®) at different process settings. The

aerodynamic assessment of fine particles was carried out using Apparatus E (Next Generation Impactor (NGI), Copley Scientific, Nottingham, United Kingdom). With the present study (1) the effect of different types of carrier, (2) engineering of the carrier substances and (3) the effect of processing the adhesive mixtures at different settings in a low dose dosator capsule filling machine on the performance of the DPI was investigated.

2. The respiratory system

The respiratory system is made up of a gas-exchanging organ (the lungs) and a pump that ventilates it. The latter consists of (1) the chest wall, (2) the respiratory muscles, which increase and decrease the size of the thoracic cavity, (3) the areas in the brain that control the muscles, and (4) the tracts and nerves that connect the brain to the muscles. A normal human breathes 12 – 15 times a minute (at rest). About 500mL of air per breath, or 6–8 L/min, is inspired and expired. This air mixes with the gas in the alveoli, and, by simple diffusion oxygen (O2) enters the blood in the pulmonary capillaries, while carbon dioxide (CO2) enters the alveoli. In this manner, 250mL of O2 enters the body per minute and 200mL of CO2 is excreted [2] .

2.1. Anatomy of the airways

The respiratory system (Fig. 1 [20]) is divided into the upper and lower respiratory tract. The upper respiratory tract consists of the nose, pharynx, and larynx, whereas the lower respiratory tract consists of the trachea, bronchial tree, and lungs [2].

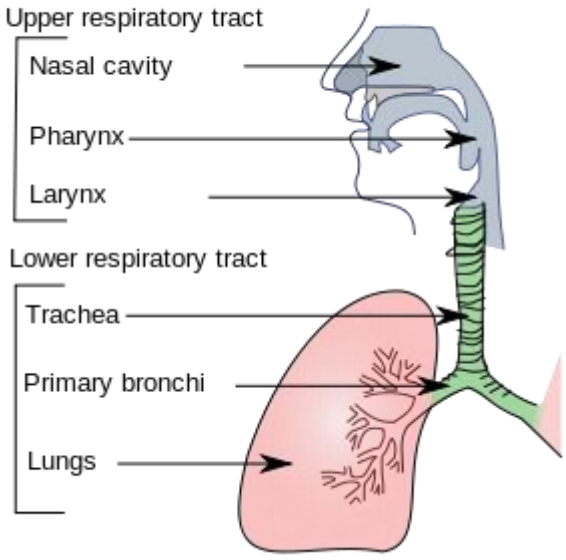

Figure 1: The respiratory tract

The structure of the airways is often described as a pulmonary tree. The tree trunk is analogous to the trachea of the airways that bifurcates to form main bronchi. The latter divides to form smaller bronchi, which lead to individual lung lobes (three lobes on the right

side and two on the left side). Inside each lobe, the bronchi are further divided to form new generations of smaller caliber airways, the bronchioles. This process continues through the terminal bronchioles (the smallest airway not involved with an alveolus), the respiratory bronchioles (which exhibit alveoli protruding from their walls), and alveolar ducts and terminates in the alveolar sacs [21].

Weibel describes the classic model of the airways, where each airway divides to form two smaller "daughter" airways (Fig. 2 [22]). As a result, the number of airways at each generation is double that of the previous generation. The model proposes the existence of 24 airway generations in total, with the trachea being generation 0 and the alveolar sacs being generation 23. This means that between the trachea and the alveolar sacs, the airways divide 23 times. The diameter of the branch decrease with increasing generation. The first generation (main bronchi) has a diameter of 12mm, whereas the smallest bronchi only have 0.41mm. This permits adequate penetration of air to the lower airways for a given expansion of the lungs [21]. The surface area of all the branches of one generation is compared to the previous generation initially about the same or slightly decreased, when the transition of the trachea into the main bronchi and further into the lobar is considered. From the lobar, the surface area increases strongly, so that the total area at the level of the human alveolus is in the order of 140m². Consequently, the velocity of airflow decreases from the upper to the lower respiratory tract. This phenomenon is essential for the understanding of the deposition of inhaled drug particles [23].

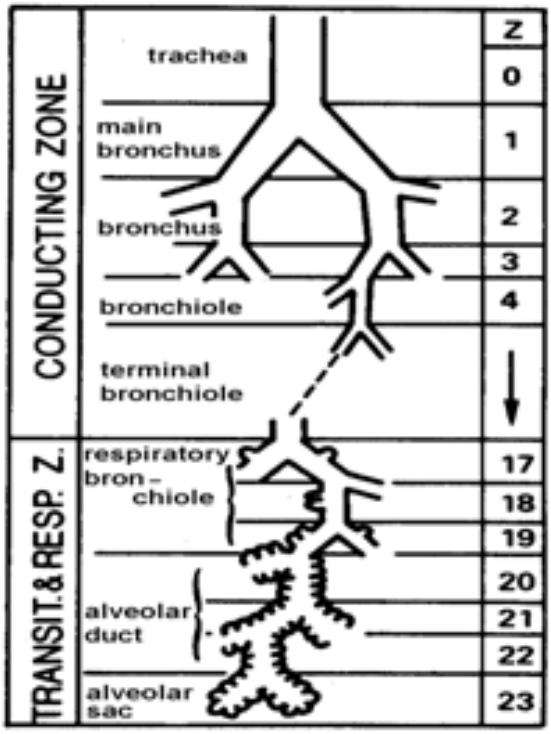

Figure 2: Model of the aiways according to Weibel

2.2. Zones of the airways

The different zones of the airways, conducting and respiratory zones, possess different physiological functions and are distinguished by their roles in the exchange of gases [21].

2.2.1. Conducting Zone

The conducting region essentially consists of the nasal cavity, nasopharynx, bronchi, and bronchioles. Airways distal to the bronchioles and the alveoli constitute the respiratory region, where rapid solute exchange takes place. According to Weibel's tracheobronchial classification (Fig. 2 [22]), the conducting airways comprise the first 16 generations (from the traches to the terminal bronchioles) and are not participating in gas exchange. The conducting airways perform two functions: gas buffering and humidification. This region is also the principal site of airway obstruction in obstructive lung diseases, such as asthma [21].

2.2.2. Respiratory Zone

The respiratory zone or exchange zone includes airways involved with gas exchange and comprises respiratory bronchioles, alveolar ducts, and alveolar sacs (generations 17 – 23). It allows the body to trade waste carbon dioxide (CO_2) for fresh oxygen. Along with the conducting zone, which draws air into the bronchial passages, it is part of the lower airway. The alveoli act as the primary gas-exchange units of the lung, especially as the gas–blood barrier between the alveolar space and the pulmonary capillaries is extremely thin, allowing rapid gas exchange. Beside the main role as gas exchange organ the lung and airways have further functionality in the acid-base balance, the endocrine system and in metabolism [21].

2.3. Particle deposition in the respiratory tract

The therapeutic effect of aerosols depends on the dose deposited and its distribution in the lung. API penetration in the deeper lung will only be achieved if the aerodynamic diameter (d_{ae}) of the API particles is below 5µm. Larger particles impact in the mouth, throat and the upper airways, while particles smaller than 0.5µm do not deposit and are exhaled again [24]. The aerodynamic diameter is the diameter of a sphere with unit density (ρ=1) that has the same settling velocity in still air as the particle in consideration. This independent variable incorporates the effect of geometric diameters and density, given in the following Equation:

$$d_{ae} = d. \sqrt{\frac{\rho}{\rho_0}}$$

Equation 1: Aerodynamic diameter

where *d* is the actual diameter of the sphere, ρ is the density of the spherical particle and ρo is unit density. For non spherical particles correction for shape factors are introduced [25], [26] .

2.4. Deposition mechanism

There are three main mechanism (Fig. 3 [25]), which cause particle deposition in the lungs. Impaction and sedimentation, which are directly related to the particle size, and diffusion also called brownian motion, which is inversely related to the particle size [19], [23], [25].

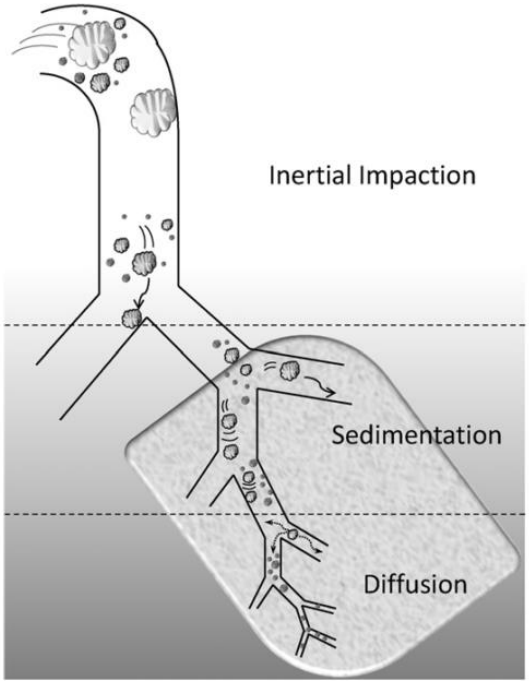

Figure 3: Particle deposition mechanism

2.4.1. Inertial impaction

When airborne particles possess enough momentum to keep its trajectory and therefore do not follow the airstream when the latter changes direction, inertial impaction on the walls of the airways occurs. The bigger and denser a particle the higher is its inertia [25].
The dimensionless Stokes`s number (Stk) describes the probability of a particle to deposit in the airways via impaction, according to Eq. (2):

$$Stk = \frac{\rho . d^2 . U}{18 . \eta . R}$$

Equation 2: Stoke`s number

where ρ_p is the particle density, *d* the particle diameter, *U* is the air velocity, η the air viscosity and *R* is the airways radius. Considering the bifurcal structure of the lung, large particles which travel with higher velocities are more likely to impact in upper airways [25].

2.4.2. Sedimentation

During sedimentation, particles settle due to gravity. This time dependent process follows the Stoke`s law, which assumes that the relative velocity between the surface of a particle and the airstream is zero. Considering spheres with densities of 1 - 40µm, Stoke`s law can predict the terminal settling velocity, U_{ts}, see Eq. (3):

$$U_{ts} = \frac{(\rho - \rho_a).d^2.g}{18.\eta}$$

Equation 3: Settling velocity

where ρ_a is the density of the air ($\rho_p > \rho_a$) and *g* is the gravitational acceleration . For particles smaller than 1µm [26] and Reynoldsnumber (Re) much bigger than 1, a slip correction factor, Cunningham factor (Cc), Eq. (4), should be added to Stokes`s law because this particles settle faster than predicted:

$$C_c = 1 + Kn.[A_1 + A_2 + \exp(-\frac{A_3}{Kn})]$$

Equation 4: Cunningham factor

where *Kn* is the Knudsen number and A_1,A_2,A_3 are constants.

The stokes`s equation considers particles as spheres, Re much smaller than 1 and that the particles density is greater than the density of the air. Therefore, this equation assumes laminar flow within the airways, as defined by the Re Eq. (5):

$$Re = \rho_a.U.d/\eta$$

Equation 5: Reynolds number

Care should be taken to note that the density in Eq. 5 refers to the density of the air not of the particles. Re is a dimensionless number that indicates if the flow of a fluid is completely steady (laminar flow) or steady on average but with small unsteady changes (turbulent flow). The human respiratory system between the trachea and the terminal bronchioles exhibits a laminar airflow (Re of 0.01 – 2). The airflow through an impactor has a Re of 0.1 – 20. The Stokes laminar flow represents an aerodynamic diameter related to particle deposition by sedimentation and Brownian diffusion. However, at Re >1 and increasing airflow, deposition by impaction represents the major deposition mechanism at upper airways. Therefore the use of Stokes flow in the aerodynamic assessment of aerosol at high airflow rates is considered to lead to systematic errors [26].
The Re is very high in upper airways and quite low in the deep lung. At high Re numbers inertial flow becomes turbulent, whereas it is lamina at low Re values. Thus, it is reasonable to expect that turbulence is present in the upper airways and trachea (extrathoracic airways). The turbulence might be still present in the first few generations of the lung. However, under these regions laminar flow is considered [27].

2.4.3. Diffusion

Very small particles (< 1µm) undergo a random motion, also known as brownian motion. The latter is correlated to the particle size according to Stoke`s- Einstein equation Eq. (6):

$$Dif = \frac{k.T.C_c}{3\pi.\eta.d}$$

Equation 6: Diffusion coefficient

where Dif is the diffusion coefficient, k the Boltzmann's constant and T the absolute temperature (T) in Kelvin. The Dif increases with decreasing particle size. Therefore, diffusion becomes more important for small particles and a correction factor is needed.
The geometry of the respiratory system is highly complex, varies greatly from individual to individual and is not known in detail. Therefore, it is not possible to specify the detailed fluid dynamics in the respiratory tract with great accuracy. However, a number of useful information about the general nature of the fluid dynamics can be provided [27].

3. Pulmonary drug delivery

As already mentioned, pulmonary drug delivery is a common route of administration for the treatment of respiratory diseases such as asthma or chronically obstructive pulmonary disease (COPD), and cystic fibrosis [1]. As the lung provides an enormous surface area and a relatively low enzymatic, controlled environment for systemic absorption of medications [24], it is the ideal target for the local treatment of respiratory diseases. Another advantage compared to oral administered drugs is that the first pass effect is missing, the onset of action is much faster and only a fraction of the oral dose is needed to cause a therapeutic effect. Inhalation therapy can have either a local, or a systemic effect. The local therapeutic effect is used for respiratory disease (Asthma; COPD) and pulmonary hypertension, without the inefficiencies and unwanted effects of systemic delivery. Systemic administration includes the treatment of migraine, parkinson`s disease or diabetes mellitus where the drug is absorbed and a systematic therapeutic effect is reached. Airway geometry, humidity and clearance, as well as lung disease influence the therapeutic effectiveness of inhaled medications [2].

3.1. Inhalation devices

The development of an inhalation therapy depends not only on the API and the formulation, but also on a well-designed delivery system (device). Drug-device combinations must aerosolize the drug in appropriate particle size distribution and concentration to ensure particle deposition in the desired region of the lung [28]. The inhalation devices can be divided into three different categories: nebulizers, pressurized metered dose inhalers (pMDI) and dry powder inhalers (DPI). Formulations used in nebulizers and pMDIs are liquid whereas solid formulations are used in DPIs [29], [30].

3.1.1. Nebulizers

A nebulizer uses compressed air to generate a fine aerosol mist that can be inhaled via tidal breathing. It delivers the drug dose slowly over a number of inhalations. This can be very helpful if the patient is medicated with a bronchodilator and the airways are not completely opened. There are two types of nebulizers, jet and ultrasonic nebulizers. The jet nebulizer

(Fig. 4 [20]) works on the Bernoulli principle where compressed gas (air or oxygen) passes through an orifice creating a low pressure area at the outlet of the adjacent liquid feed tube. Based on that, the drug solution is drawn up from the reservoir and scattered into droplets in the gas stream. The ultrasonic nebulizer uses a piezoelectric crystal vibrating at high frequency (1 - 3 MHz). The higher the frequency the smaller are the droplets produced.

Figure 4: Nebulizer

An advantage of nebulizers is that it is the only practical means of treating very young children, because no specific inhalation technique or coordination is needed. Due to their larger size and suitability for all patients, nebulizers are commonly used in hospital treatment. However, it is the least portable type of inhalation device. Another disadvantage is that the treatment is time consuming, relatively expensive due to drug wastage and it has a poor delivery efficiency [29].

3.1.1. Pressurized Metered dose Inhaler (pMDI)

The pMDI or in the US called MDI device consists of a canister, actuator (Fig. 5 [29]), and sometimes a spacer as special adjustment (Fig. 6 [29]). The canister itself consists of a metering dose valve with an actuating system. The formulation resides within the canister and is either solubilized or suspended in the propellants, namely chlorofluorocarbons - CFC (obsolet because of the chlorine effect on ozon) and more recently hydrofluoroalkanes (HFA-134a and HFA-227), and the local concentration of drug in the canister determines the therapeutic dose. Actuation of the device releases a single metered dose of liquid propellant that contains the medication. The volatile propellant breaks up into droplets,

which evaporate and create an aerosol containing micronized drug that is inhaled into the lung. pMDIs deliver only small amounts (maximum dose of 5mg) of the drug dose to the lungs. Typically, 10 - 20% of the emitted dose deposits in the deep lung. The high velocity (<30m/s) and the large particles result in a deposition of 50 - 80% of the aerosol in the oropharyngeal region. The device is compact and portable, but some co-ordination between actuation and inhalation is required by the patient for correct dosage. An assortment of different spacer tubes (Fig. 6) can help to overcome the coordination issues and the deposition of particles in the oropharyngeal region [29], [31].

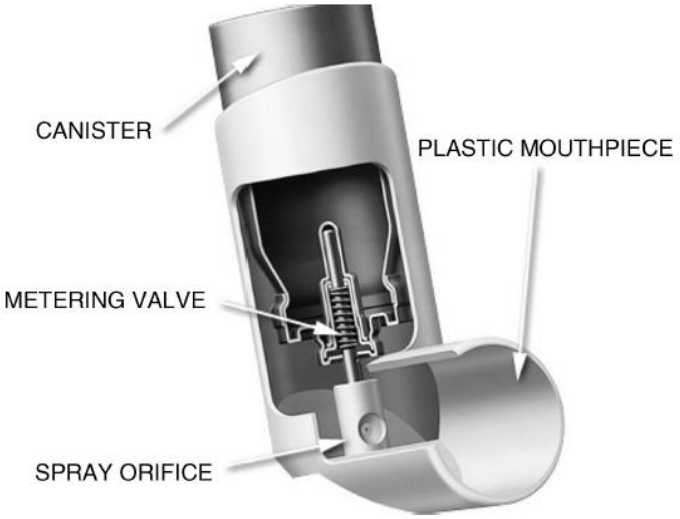

Figure 5: pressurized Metered Dose Inhaler (pMDI)

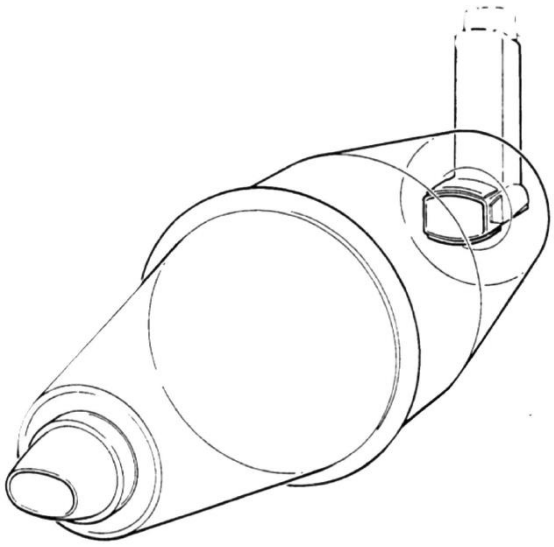

Figure 6: Schematic presentation of a pMDI with spacer

3.1.2. Dry Powder Inhaler (DPI)

DPIs were designed to eliminate first, the coordination difficulties associated with the pMDI and second, the urgency to eliminate CFC-containing pMDIs. DPIs are the most recent type to appear on the inhaler market and there is a wide range of DPI devices available. From single-dose devices (Fig. 7 [29]) where the capsule is loaded by the patient and thrown after each use (e.g. Aerolizer, Cylohaler, Rotahaler), to multiunit dose devices, where the drug is provided in a blister pack (e.g. Diskhaler) or on a strip which moves through the inhaler (e.g. Diskus) and the reservoir-type (bulk powder) systems (e.g. Turbuhaler), which also contain multiple doses but in a single area. They all are compact, easy to use and portable systems [29]. DPIs are breath-actuated systems, which means that the respirable dose depends on the respirable flow rate of the patient. Approximately 12 – 40% of the emitted dose is delivered to the lungs with 20 – 25% of the drug being retained within the device. Inefficient drug deposition and therefore ineffective pulmonary delivery with DPIs can be caused by insufficient detachment of the fine drug particles from coarser carrier particles, due to temperature and humidity issues and respiratory effort. Thus, dispersion of the powder into respirable particles depends on the creation of turbulent airflow in the powder container. The turbulent airstream causes the aggregates to break up into particles small enough to be carried into the lower airways and also to separate drug from the carrier. Each DPI has a different airflow resistance that governs the required inspiratory effort. The higher the resistance of the device, the more difficult it is to generate an inspiratory flow great enough to achieve the maximum dose from the inhaler [29].

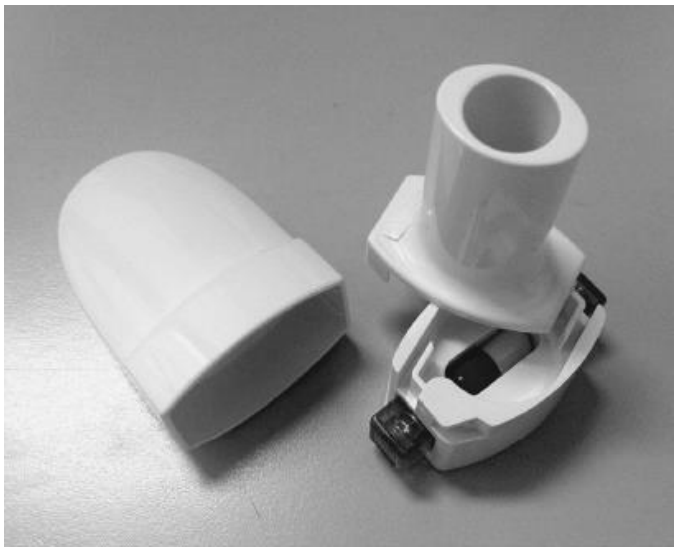

Figure 7: Dry Powder Inhaler (DPI), Platiape, IT

3.1.3. DPI formulation

A successful formulation relies on a combination of factors including formulation composition, container closure system and delivery device. The challenge is that the formulation should ensure a consistent and controllable delivery of drug particles. Research efforts continue to focus on improving inhalation drug delivery through formulation science, e.g. drug particle engineering, new excipient, process technology, delivery devices, container closure systems, etc. There is still room for improvements in the current state of the art inhalation formulation [30].

3.1.3.1. Carrier free technology

A new trend in pulmonary drug delivery is to administer the API alone, as single compound. Therefore special production techniques like spray drying, supercritical fluid processing [32] and sono-crystallization have found to be suitable to endow the API with the aerodynamic characteristics [1]. In the challenging task of dosing pure API into the lungs, still a lot of work has to be done. Nevertheless, the two main formulation for DPIs are the carrier based- and the agglomerate technology [30].

3.1.3.2. Carrier technology

APIs intended for pulmonary drug delivery need to reach the deeper lung, in order to cause a therapeutic effect. Therefore, their aerodynamic diameter has to be between 0.5 µm and 5 µm leading to poor flowability due to the small size of the particles. This poor flow behavior and the very low doses needed in inhalation therapy lead to poor volumetric dosing. To ensure uniform dosage, which is related to an adequate powder flow, and to a certain bulk volume, adhesive binary mixtures (Fig. 8 [30]) of API particles (0.5 µm – 5µm) and inert carrier particles (50 µm – 200 µm) and adhesive ternary mixtures with API, fines and carrier are used in dry powder inhalers [1]. As carrier materials usually sugars or sugar-alcohols like lactose, glucose or mannitol are used [33]. Alpha lactose monohydrate is the powder mainly used as carrier. There are many pharmaceutical grades of lactose, which differ in physical properties and flow characteristics, as sieved, milled, spray dried or crystalline powders of α-lactose and β-lactose are available and used. Microscopically α-lactose monohydrate has tomahawk shaped crystals. The advantages of lactose are the known

toxicity profile, low cost, low hygroscopicity as well as smooth surfaces and regular shape, which lead to good flowability [34]–[36]. Several researchers have investigated the use of lactose in dry powder inhalers [11], [37], [38]. However, lactose cannot be used for substances that interact with the reducing sugar function of the lactose, like formoterol or budenosid. Here mannitol would be one of the alternative carrier material of choice [33].

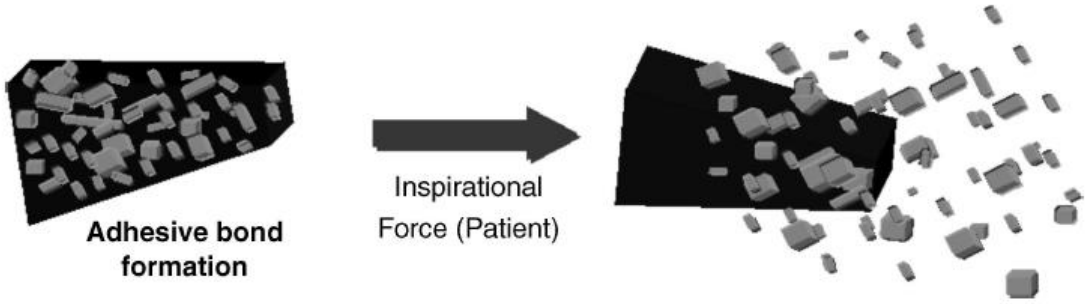

Figure 8: DPI - Carrier based system

3.1.3.3. Agglomerate technology

Agglomerate based formulations (Fig. 9 [30]) contain spheronized aggregates with many micronized particles of suitable size for inhalation. They have good flow and metering properties since the agglomerate size is relatively large and the breakup of the powder relies on inspirational energy. Astra Zeneca`s Turbuhaler formulations for example use this technology. When formulation size becomes lower than 100 µm the agglomerates become too small to maintain good flowability. Thus low dose formulations are agglomerated as binary systems containing drug and micronized excipients [30].

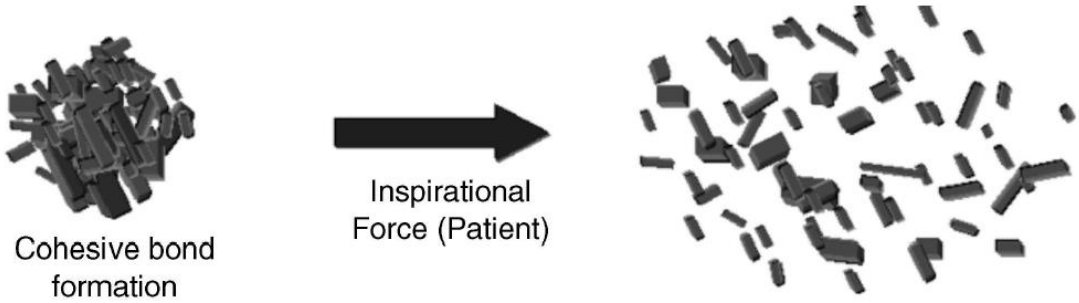

Figure 9: DPI - Agglomerate Formation and Dispersion

3.1.4. Interparticulate interactions in DPI formulations

The main challenge with the efficiency of dry powder inhalers are strong interparticulate forces that act between the cohesive drug particles or drug and carrier/excipient particles. Thus, the performance of the DPIs and adhesive mixtures strongly depends on the interparticulate forces. These forces, namely van der Waals (VdW), electrostatic and capillary forces affect on the one hand mixing homogeneity and hence dosing of the mixtures and on the other hand the very important detachment process of API from the carrier upon the release of the powder from the inhaler. Van der Waals forces are present when particles are sufficiently close (0.2 – 1.0nm) to each other and when the particles are smaller than 20µm [39]. Physicochemical characteristics like surface roughness and energy, chemical structure and deformation of the particles can change the van der Waals forces. Further, particle size and shape play a crucial role. Electrostatic forces occur by tribo-electric charging or by potential differences when the particles with different work function come into contact. Due to the resulting coulomb attraction, the powder gets charged and consequently adhesive. Capillary forces result from fluid condensation in the gaps between particles, which are in narrow contact. Further liquid bridges between particles are formed [1]. All these forces have to be strong enough, to keep the formulation stable during transport, handling and dosing and they need to be low enough, that drug detachment during inhalation can take place. Drug particles that are not detached during inhalation will impact together with the coarse carrier in the mouth or the upper airways and will not reach their target site, the bronchiolar region of the lung. [40], [41], [42].

3.2. Engineered formulations

According to literature one major factor influencing interparticle interactions is the carrier surface topography [40]. Therefore different techniques to modify or engineer the surface topography of commonly used carrier particles, like lactose or mannitol, were performed by several research groups with the main goal to increase drug detachment from the carrier particles.

Crystallization of lactose particles from different media and under different crystallization conditions is one of the main investigated particle engineering methods [36], [41], [43]–[45]. Furthermore, particle smoothing by coating lactose particles with aqueous lactose solutions was one engineering attempt that lead to differences in the surface topography [46], [47]. Another technology to remove fines and therefore smoothen the surface of particles is the

decantation. Here the carrier material gets dispersed in a dispersion media, which is eliminated subsequently [48]. More recently spray drying was described to be a suitable method to generate mannitol particles with modified surface roughness [49]–[51]. Other techniques use the effect of mechanical stress on lactose surface properties, like wet smoothing in a high shear mixer [52], particle smoothing with a high speed mixer in the presence of a small amount of wetting solvent [53], surface processing with a high speed elliptical-rotor type powder mixer [54] as well as milling lactose with various mill speeds to avoid batch to batch variability and to make the carrier particle surface homogenous [38]. However, in many cases not only the surface topography but also other properties affecting interparticle interactions, like particle size or shape of the carrier particles, were altered.

4. Low dose capsule filling for DPIs

In the pharmaceutical industry a wide range of capsule filling systems, which employ different technologies and principles are used today. Hard capsules can be filled in several ways from manual preparation in the lab to fully automated industrial production. Although capsule-filling machines may vary widely in their engineering design the major difference between them is the dosing technique. The most common classification found in literature is direct and indirect filling methods [55]. Therein all unit operations that dose directly in the capsule are direct methods (Auger filling principle and gravimetric/volumetric vibration assisted filling) and machines that implement dosing techniques out of the capsule before filling are considered indirect methods (Dosing disc or tamp filling as well as drum filling and dosator nozzle principles). Indirect filling methods use some sort of dosing chamber to fix the volume of powder for the capsule filling. The major challenge for these systems is that although doses are specified by weight these filling systems work on volumetric basis.

The current trend in pharmaceutical industry is to manufacture small doses (< 50mg) of pure potent API for early research clinical trials using drug in capsule approach and for inhalation purpose (DPI) for the treatment of respiratory disease or if the API is not readily absorbed orally [6]. This low doses lead to challenges during manufacturing but can be successfully manufactured using modern capsule filling technologies [18], [56]–[58]. Most of the high output low-dose systems are operated on volumetric basis.

4.1. Direct filling

4.1.1. Auger filling

This principle is based on a semi-automatic and automatic equipment, where the powder in a hopper is filled into the capsules continuously by a rotating auger in conjunction with a stirrer. The empty capsule bodies are placed beneath the auger by a rotating turntable. The dosed weight is dependent on the auger speed, the twist angle of the auger and the time the capsule body spends under the hopper outlet. Fill weight is also dependent on the powder density, which evolves from initial bulk density in the auger until reaching steady state [55]. Mettler Toledo is producing the *Quantos MicroDosing System*™, which uses the above described Auger filling principle (Mettler Toledo, Greifensee, Switzerland).

4.1.2. Vibration assisted filling

In this dosing principle, the capsule body is filled directly through a mesh, which is connected to a vibration plate. This vibration assists powder flow and therefor dosing ("pepper shaker principle"). In addition, the equipment includes a microbalance, a load cell or a capacitance system to control fill weight, even for very low doses (i.e. MG2 Microdose, Capsugel Xcelodose®S, 3P Innovation Fill2weight). These machines are of special interest for research purposes and clinical trials batches and allow the filling of several hundred capsules per hour with doses in the range between 0.1mg and 100mg.

4.2. Indirect filling

4.2.1. Tamp Filling

In Dosing Discs or Tamp Filling machines, the powder is in a cylindrical powder bowl that contains a removal dosing disk with six dosing holes bored through it. The powder bowl rotates 360 degrees stopping at six stations with matching dosing bores. The material is fed from a hopper, to a dosing cone, which helps to distribute the powder horizontally into the powder bowl. As the dosing disk rotates, the first bore is partially filled with powder and then is tapped by a pin or tamping fingers. This process of partially filling and tamping is repeated until the last hole is reached. Afterwards excess powder is scraped off, the dosating disk positions the plug of powder over a capsule body and rejects it into the capsule. The fill weight can be controlled by the thickness of the dosing-disc, the powder bed depth and the tamping pressure. The tamping pins are spring loaded in lab and medium scale or have a cushion of compressed air at industrial scale to minimize the tamping force to keep the plug density low [55], [59]. Tamping machines like the Bosch GKF 2500 (Robert Bosch GmbH Germany) adjusted with up to 18 tamping fingers (industrial scale) and can produce up to 150.000 capsules per hour. Other manufacturers of the tamping mechanism are IMA (Italy), Romaco (Italy), and Harro Höfliger (Germany).

4.2.2. Dosator nozzle filling

In dosator nozzle machines, the dosator moves into the powder bed and collects the desired volume of powder from the powder layer. The cylindrical volume (dosing chamber) is determined by dosing chamber length (bordered by a movable piston) and dosator diameter

(Fig. 10). After collecting the powder (without piston compaction) the dosator nozzle is lifted from the powder bed and moved towards the empty capsule body into which the dose is ejected. Due to the working principle, the powder has to be retained in the dosing chamber, while this section is in motion. For the retention of the powder in the nozzle during transfer, the powder must be able to form an arch. Therefore, the requirements for powders and granules to be used in dosator nozzle machines vary significantly from those used in tamping pin machines. The powder is fed form a dosing hopper. Fill weight of capsules is controlled by adjusting the dosing chamber as well as varying the powder bed height. Compared to Tamp-filling, the Dosator Nozzle System allows a wide range of fill weights by simple adjustment of the piston position for the choice of nozzle. High-end continuous dosator machines like the Planeta 100 with two dosing units and 16 dosators mounted on each of them (MG2, Pianoro, Bologna, Italy) offers very accurate low dose capsule filling at an industrial output up to 100.000 capsules per hour. A further development in dosator nozzle design is the vacuum operated system that implements a static piston with a porous plate at its product touching end. The powder is sucked into the nozzle by vacuum and ejected into the capsule by reversal of the airflow. Therefore, the nozzle does not contain any moving parts, resulting in less demand for lubrication and less densified powder plugs and consequently very small doses can be filled. Romaco (Italy) produces the Macofar series and Harro Höfliger (Germany) offers vacuum assisted dosator nozzles which are able to dose 10 – 600mg with an maximum output of 4500 capsules per hour, especially for low doses [55].

Figure 10: Low dose dosator, piston and spring.

In the present study adhesive powder mixtures were filled into Coni-Snap hard gelatin size 3 capsules by a lab-scale dosator nozzle capsule filling machine (Labby, MG2, Bologna, Fig. 11), with special low dose adjustment. In this system, filling of inhalation powders with smaller nozzles was made possible by introducing special features to the equipment (MG2),

which can be seen in Fig. 12. The nozzle cleaning unit removes adhering powder from the outer wall or around the nozzle tip to minimize weight variability. Moreover, the stabilizing blades keep the powder layer as smooth and homogenous as possible (Fig. 12). Furthermore, no compaction step is performed in low-dose capsule filling for inhalation administration to avoid the formation of hard powder plugs.

Figure 11: Labby, R&D dosator capsule filler

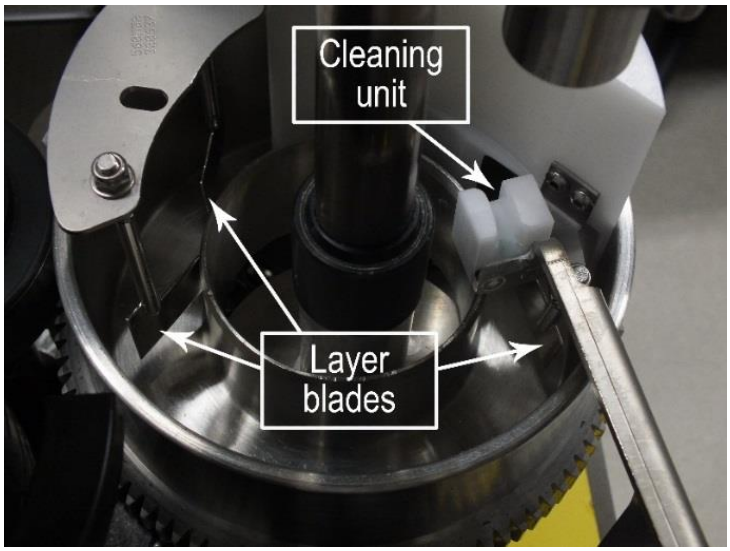

Figure 12: Special adjustments for low dose capsule filling

5. Aerodynamic assessment for inhalation products

The main instruments for the aerodynamic assessment are impactors and impingers. The difference between impactors and impingers is the surface where the particles are collected. In impactors, the particles impact on a dry surface and in impingers particles deposit on a liquid surface. Both are built based on the concept of general inertial impaction. The main instruments used today are the cascade impactors, namely Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI) [60] and therefore the impingers (twin impinger, and the multi stage liquid impinger) as well as the Marple Miller Impactor are only mentioned but not described in this section.

An impactor consists of one or more stages where the aerosol stream passes through. Larger particles will follow inertia and deposit and smaller particles will follow the air stream through the impactor to the next impaction stage. A cascade impactor can measure the aerodynamic particle size, the API dose per stage and the entire dose. The entrance to the impactor is a right-angled introduction port, which mimes the throat, where the inhaler is connected via a mouthpiece adapter. Once the aerosol is discharges from the inhaler it is streaming through the impactor driven by a vacuum pump [26].

By analyzing the amount of drug deposited on the various stages, it is possible to calculate the Emitted Dose (ED), the Fine Particle dose (FPD) and Fine Particle Fraction (FPF) of the active drug particles collected. The ED gives the amount of active found in the whole impactor (mouthpiece adaptor, introduction port, pre-separator, impaction stages). FDP divided by ED gives the FPF. So, the FPF gives the percentage of API particles that are detached from the carrier during inhalation and that have an aerodynamic particle size smaller than 5µm and thus are able to reach the deep lung related to the total amount of API particles that leave the inhaler. Therefore, the FPF may be defined as the main parameter describing the performance or efficiency of a DPI carrier system. Additionally the recovered dose (RD) where the amount of salbutamol sulphate recovered in all the stages, the pre-separator, the mouthpiece and induction port and the inhaler were summed up, can be determined according European Pharmacopoeia (preparations for inhalation: aerodynamic assessment of fine particles, Ph. Eur., 7.0).

The efficiency of particle impact on the collection plate of the impactor is defined as the ratio of particle stopping distance at the average nozzle exit velocity (U) to the nozzle radius (Eq. 7).

$$Stk = \frac{\rho_p . d^2 . U_0 . C_c}{9 . \eta . D_n}$$

Equation 7: Stoke`s equation

Where ρ is the particle density, d the particle diameter, U_0 the fluid velocity to the nozzle, C_c the Cunningham correction factor, η the dynamic viscosity and D_n the diameter of the nozzle. It is assumed that the particle density is higher than the density of the air, that the particles are spherical and that laminar flow is present. A particle will impact if the Stokes number is larger than approximately unity, which translates to a need for longer relaxation times. All particles larger than the stages cut-off diameter will impact, smaller ones will follow the airflow through successive stages. The cut-off diameter has to be regularly calibrated as nozzle and plates can corrode due to time and usage [26].

5.1. Andersen cascade impactor (ACI)

The AIC (Fig. 13 [61]) is an eight-stage impactor that measures particle size distribution generated by MDIs and DPIs according to European and United States Pharmacopoeias. The apparatus can be operated at various flow rates and offers a detailed determination of particle size distribution. The standard ACI uses 28.3 L/min but many times it is necessary to work above this limit (60 L/min and a 90L/min). Impactor versions with some adjustments concerning the stages are available. The standard version of the ACI can be used to test pMDI. For testing DPIs a pre-separator is interposed between the introduction port and stage 0 [26]. However, when testing DPIs a number of additional factors have to be taken into account.

Figure 13: Anderson cascade impactor (ACI)

5.2. Next Generation Impactor (NGI)

Figure 14: Next generation impactor (NGI)

The NGI (Fig.14 [61]) has seven stages and operates at flow rates between 30 and 100 L/min. It works with cut-off diameters in the 0.5 – 5 micron range. At a volumetric flow rate of 60 L/min, the cut-off points for stages 1 to 7 are 8.06, 4.46, 2.82, 1.66, 0.94, 0.55 and 0.34 microns respectively. It spans a cut size (D_{50}) range from 0.54 - 11.7μm aerodynamic diameter at 30 L/min and 0.24 - 6.12μm at 100 L/min. The air flow passes through the impactor and particle separation and sizing is achieved by successively increasing the velocity of the airstream. Also the NGI requires the use of a pre-separator when used with DPIs in order to catch large non-inhalable particles. An enormous advantage of the NGI is that particles deposit on collection cups that are held in a tray. The latter is removed from the impactor as a single unit, very easy to operate and minimizes the risk of inter-stage losses and particle carryover. Above every tear shaped collecting tray is a circular nozzle assembly (stage) (Fig. 12) with progressively reducing jet diameters [61]. This eliminates the risk associated with removable nozzles being replaced at the wrong position. Another unique feature is a micro-orifice collector (MOC) that captures in a collection cup extremely small particles normally collected on the final filter in other impactors. The particles captured in the MOC cup can be analyzed in the same manner as the particles collected in the other impactor stage cups [62].

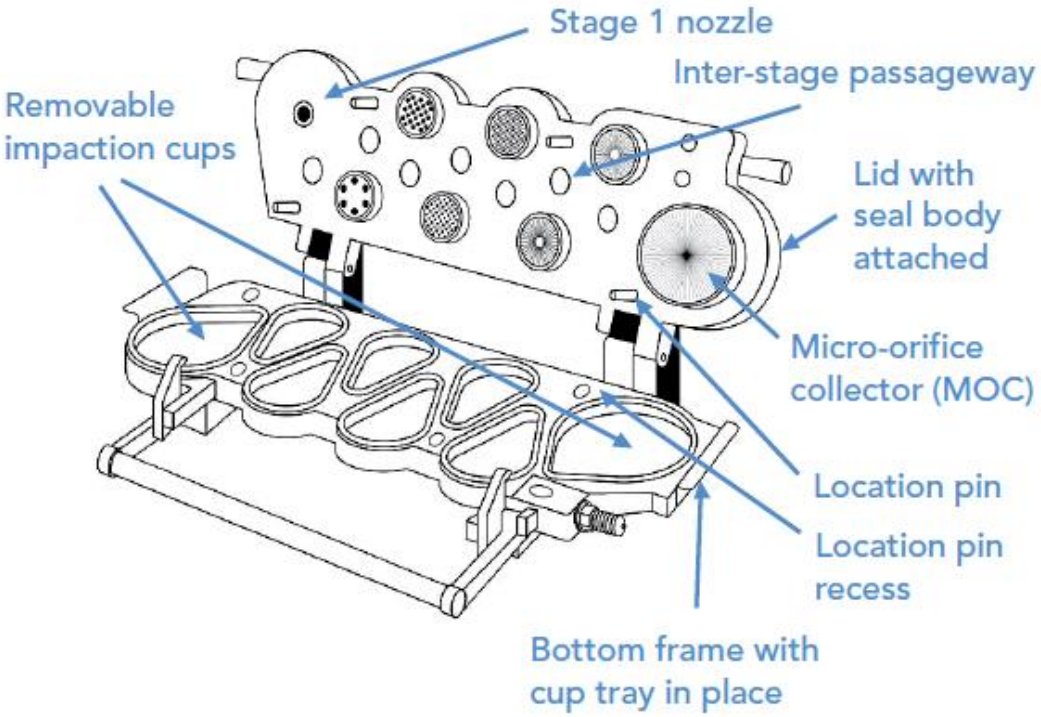

Figure 15: NGI - collecting trays and above the nozzles

The impactor itself comprises just three main parts (see Fig. 15 [61]):

1. The cup tray containing the eight collection cups used to collect the samples prior to analysis.
2. The bottom frame used to support the cup tray.
3. The lid containing the inter-stage passageways and the seal body, which holds the nozzles in place.

In the present study (see chapter 6) the aerodynamic assessment of fine particles was carried out using Apparatus E (Next Generation Impactor (NGI), Copley Scientific, Nottingham, United Kingdom).

6. Results and Discussion

Impact of carrier surface modification and dosator capsule filling process on DPI performance of adhesive mixtures

To be submitted to the Journal of Aerosol Science

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Abstract

This study aims to investigate the effect of carrier characteristics and dosator capsule filling operation on the in vitro deposition of mixtures containing salbutamol sulphate as a drug and lactose and mannitol as model carrier materials. The carrier surfaces of lactose and mannitol were modified via wet decantation. The impact of decantation process on the carriers was investigated by laser diffraction, density and flow measurements, gas adsorption and scanning electron microscopy. Differences in carrier type and untreated and decanted materials were identified. Adhesive carrier and active pharmaceutical ingredient (API) mixture (98.5:1.5) were prepared, mixture homogeneity was tested and subsequent the mixtures were filled into capsules at different process settings. Finally, the influence of the decantation process on the in vitro performance of the adhesive mixtures was tested with a next generation impactor and Aerolizer as inhalation device. For lactose the carrier decantation decreases the fine particle fraction (FPF) whereas, the latter of decanted mannitol carriers at a low compression ratio tends to increase.

Thus, in summary, the untreated lactose carrier particles blended with 1% salbutamol sulphate and a compression ratio of 1:2 proved to be the most efficient conditions first for accurate dosing (RSD < 0.8%) and second for a high fine particle fraction (14%).

Keywords: dry powder inhalers (DPI), powder aerosols; carrier decantation; fine particle fraction, dosator capsule filling

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NOTE: Eva Faulhammer, Verena Wahl and Sarah Zellnitz contributed equally to this work.

6.1. Introduction

The lung offers a unique and challenging route of administration for the treatment of respiratory diseases such as asthma or chronically obstructive pulmonary disease (COPD), and cystic fibrosis (Daniher & Zhu, 2008a). Advances in drug formulation and inhalation device design are creating new opportunities for inhaled drug delivery as an alternative to oral and parenteral delivery methods (Traini, 2013). Pulmonary drug delivery is gaining grounds in the local treatment of respiratory diseases as well as in the targeted systemic application of highly potent, complex and low-dose active pharmaceutical ingredients (API).

Nebulizers, pressurized metered-dose inhalers (pMDIs), and dry powder inhalers (DPIs) are the devices available for drug delivery to the lung. However, a special focus is put on capsule-based dry powder inhalers (DPIs) as almost half of all marketed DPIs belong to this category. This can be related to the wide range of DPI advantages like better patient compliance, formulation stability and environmental sustainability, only to name a few (Ashurst, Malton, Prime, & Sumby, 2000; S.P. Newman & Busse, 2002; Smith & Parry-Billings, 2003). Examples for capsule-based devices are the Rotahaler™ (Glaxo Smith Kline) and Handi-Haler™ (Boehringer-Ingelheim), which are both single unit-dose devices (Islam & Gladki, 2008; Stephen P Newman, 2004; Steckel, Markefka, TeWierik, & Kammelar, 2004). DPIs as a dosage form consist of a powder formulation in a device, which is designed to deliver an active ingredient to the respiratory tract. A lot of effort is put into research and development of novel DPI formulations and devices, searching ways to improve the efficiency of drug delivery (Islam & Cleary, 2012). In order to reach their target size the tiny airways of the lung, API particles have to exhibit an aerodynamic diameter of 1–5 µm. Particles of this size are rather cohesive and show poor flow properties and difficult dosing (Daniher and Zhu, 2008). Thus, to improve the flowability, dosing accuracy and minimizing dose variability of such powder carrier based formulations, are used (M. D. Jones & Price, 2006). These carrier based formulations consist of adhesive mixtures of the active pharmaceutical ingredient (API) attached to the surface of coarser carrier particles, also called binary formulations. During inhalation it is important that the API detaches again from the carrier to reach its target site, the deep lung. Otherwise the API will impact in the upper respiratory tract together with the coarse carrier particles (Alagusundaram et al., 2010).

The key for the successful development of a DPI product is the preparation of particulate formulations that can provide reproducible and acceptable powder flowability, dosing efficacy and delivery of the drug particulates to the respiratory system. This controlled production of drug particles or carriers with optimal morphology, surfaces and structure is also called “particle engineering”(Chew & Chan, 2002). The main target is to incorporate special attributes into particles while taking into account the specifics of inhaler design and drug delivery requirements (Pilcer & Amighi, 2010). With the increased recognition of the potential role of DPI systems for low dose medications, DPIs could become the device category of choice for local and systemic drug delivery (Stephen P Newman, 2004).

Most of the existing low-dose applications for filling capsules are based on the direct filling principle with gravimetric techniques. Therefore, this research uses an indirect filling principle based on one of the most common volumetric techniques in standard doses, the dosator nozzle principle. Especially in DPI filling the dosator principle plays an important role, as the doses need a controlled degree of compaction, to ensure the DPI can reliably turn the plug back into a powder for efficient dose delivery.

The present study investigates two carriers of different type and source (lactose and mannitol) (1) as received and (2) after engineering (wet decantation) and blended with spray dried API (salbutamol sulphate). After determining the mixing homogeneity the adhesive blend was filled into capsules for a single dose DPI (Aerolizer®) at different process settings. The aerodynamic assessment of fine particles was carried out using Apparatus E (Next Generation Impactor (NGI), Copley Scientific, Nottingham, United Kingdom). With the present study (1) the effect of different types of carrier, (2) engineering of the carrier substances and (3) the effect of processing the adhesive mixtures at different settings in a low dose dosator capsule filling machine on the performance of the DPI was investigated.

6.2. Experimental

6.2.1. Materials

The used carrier substances were a sieved α-lactose monohydrate excipient (Lactohale 100) supplied by DFE Pharma (Goch, Germany) and crystalline mannitol (Pearlitol 160 C) from Roquette (Freres, Lestrem, France). The carrier materials were used as received.

Salbutamol sulphate (USP25 quality) was purchased from Selectchemie (Zuerich, Switzerland) and used as model API after spray drying.
Ethanol absolute, for the decantation of the carriers was obtained from Sigma Aldrich (Munich, Germany).

6.2.2. Particle Engineering

6.2.2.1. Spray drying

Salbutamol sulphate was spray dried using a Nano Spray Dryer B-90 (Buechi Labortechnik AG, Flawil, Switzerland) equipped with the long version of the drying chamber. To form particles in the size range of 1µm - 5µm a sprayhead mesh of 7µm was chosen and a feed concentration of 7.5% (Littringer, Zellnitz, et al., 2013). The flow rate was set to 110 L/min and the spraying intensity was set to 30%. Aqueous salbutamol sulphate solutions used for spray drying were prepared with purified water (TKA Micro Pure UV ultrapure water system, TKA Wasseraufbereitunssysteme GmbH, Niederelbert, Germany) equipped with a capsule filter (0.2µm).

6.2.2.2. Decantation

Fine compound particles were removed from the carrier substances by wet decantation. The material was decanted with absolute ethanol (99%) for various numbers of times. Ethanol absolute was added to the carrier, the mixture was vigorously mixed to create a homogenous suspension and then allowed to settle for appropriate minutes at ambient conditions. The cloudy supernatant fluid was decanted and replaced. During the removal of the supernatant, special care was taken to ensure minimum disturbance of the lower part of the suspension. The powder sample was left for 2 – 4 days under the fume hood to dry and afterwards stored in desiccators on silica.

6.2.3. Powder Characterization

Particle size, density, flow behavior and surface characteristics were investigated and each measurement was done in triplicate (n=3).

6.2.3.1. Particle size characterization

HELOS (HELOS/KR, Sympatec GmbH, Clausthal-Zellerfeld, Germany) was used to measure particle size distribution via the principle of laser light diffraction. A dry dispersing system Rodos=L, Sympatec) and a vibrating chute (Vibri, Sympatec) were used for powder dispersion. A dispersion pressure of 2.5 bar was applied. The typical sampling time was 30 seconds. Evaluation of the data was performed using the software Windox 5 (Sympatec).

6.2.3.2. Bulk density, tap density and true density

The bulk (BD) and tapped densities (TD) were analyzed (Pharmatest PT-TD200) via a standardized method described in the United States Pharmacopeia (USP 2011, <616>). A certain mass of powder was filled into the cylinder and the level was recorded. The tapped density was attained after mechanically tapping the powder sample. To obtain the true density or pycnometric density, a helium pycnometer (AccuPyc II 1340, Micromeritics, Norcross, USA) was used. Measurements were performed after drying the powders.

6.2.3.3. Powder flow indicators

Carr`s Compressibility Index (CI) (Carr, 1965) is a density-based index assessed according to Pharmacopoeia 2011 (Method <616>). CI indicates how a powder changes its density upon tapping. Large changes indicate poor flowability.
Angle of Repose (AoR) was determined by using a glass funnel described in the pharmacopoeia (USP 2007, 1174).

6.2.3.4. Residual moisture content

The residual moisture content of the carriers before and after decantation was determined using Karl-Fischer Titration (Titroline 7500 KF, SI Analytics, Mainz, Germany). The powders were directly added to the titrator cell. To enhance their solubility, a methanol/formamide mixture (1:1 ratio) was used to determine the moisture content.

6.2.3.5. Specific surface area (SSA)

The specific surface of the two carriers before and after treatment was investigated using the Micromeritics Tristar II 3020 (Norcross,USA). The samples were degassed for two days at 60°C at the Micromeritics VacPrep 061 degas unit (Norcross,USA). The measurements were performed using nitrogen gas. Brunauer, Emmett, and Teller (BET) adsorption theory was used to calculate the specific surface areas, using a pressure range of 0.05 – 0.30 normalized to the saturation pressure of the adsorbate.

The method of Barrett, Joyner, and Halenda (BJH) was used for calculating pore size distributions from experimental isotherms using the Kelvin model of pore filling. It applies to the mesopore and small macropore size range.

6.2.3.6. Scanning electron microscopy (SEM)

Carrier material, API and adhesive mixture morphology was examined before and after decantation using a scanning electron microscope (SEM) (Zeiss Ultra 55, Zeiss, Oberkochen/Germany) operating at 5 kV. The carrier particles had been sputtered with gold–palladium prior to analysis.

6.2.4. Blend preparation

Four adhesive mixtures of 1% API were prepared: Therefore 148.5g of carrier (untreated and decanted Lactohale 100 and Pearlitol 160C) and the calculated amount of salbutamol sulphate (1.5g) were weighed into plastic vessels (filling volume approximately 40%) using the sandwich method. The vessel were then fixed in a Turbula blender TC2 (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland) and mixed for 60 minutes at 62rpm. The blends were stored in a desiccator over silica gel before investigated.

Homogeneity of each blend was determined by taking 10 samples of about 150 mg from the powder blends via a spatula. Samples were dissolved in 20ml of buffer (water adjusted by acetic acid to pH 3) and subsequently analyzed for salbutamol sulphate concentration by reversed phase high performance liquid chromatography. The blend homogeneity was expressed as the coefficient of variation of the drug content of n=10 sample and under 5% for all blends tested.

6.2.5. Capsule filling

The four mixtures were filled into Coni-Snap hard gelatin capsules of size 3 (0.3 mL) supplied by Capsugel with a low dose dosator nozzle capsule filling machine (Labby, MG2, Bologna, Italy) with a target weight of approximately 20mg. This is a research and development machine based on the same principle as industrial capsule filling machines but has only one dosator nozzle and a maximum production speed of 3000 capsules per hour (cph). For details, see Faulhammer et al. 2014 (Faulhammer, Fink, et al., 2014; Faulhammer, Llusa, et al., 2014).

The capsules were filled with a 3.4mm dosator nozzle with an output rate of 2500 cph, one dosing chamber length (2.5mm) and two powder bed heights (5mm and 10mm). Therefor we filled at two compression ratios of the powder bed height and dosing chamber length (1:2 and 1:4). Before the experiments were conducted, a smooth powder layer was created. Next, the dosator was mounted and feeding was optimized to match the amount of powder collected by the nozzle. The powder layer height was measured with a venier caliper. To ensure that the filling operation runs in a steady state condition the first capsules were sampled after 5minutes. The whole study was performed under humidity and temperature controlled conditions to avoid moisture uptake

6.2.6. Analysis of capsule weight and weight uniformity

Due to a relatively high weight of empty capsules and their variability, using a precise scale and knowing the exact weight of every empty capsule body was required. Therefore, each empty capsule shell was assigned a number and, subsequently, the weight was recorded with the Denver SI-234A (reproducibility 0.1mg) analytical scale. The filled, numbered capsules were weighed again on the Denver SI-234A analytical scale. To obtain the capsule fill weight, the weight of the empty, numbered capsules was subtracted from the gross weight (capsule shell and powder). Furthermore, visual examination of the powder plugs was performed. The capsules were stored in a desiccator over silica gel before further investigated.

6.2.7. HPLC method

Salbutamol sulfate samples were analyzed by HPLC on a Waters 2695 (Milford, USA) HPLC system equipped with an autosampler and a Waters 2996 photodiode array detector. UV-detection was performed at 276nm. Mobile phase consisted of 60% A: 5 mM

hexanesulfonic acid sodium salt in water + 1% acetic acid and 40% B: methanol. Analysis has been carried out under isocratic elution conditions with a flow rate of 1ml/min. A Phenomenex Luna C18 5µm 100 A column (150mm x 4.6mm, 5micron), was used as stationary phase. Column temperature was set to 30°C and an aliquot of 50µl of sample solution was injected into the HPLC system. Each sample was analyzed two times. Linearity of the method was confirmed between 2.6µg/ml and 70.5µg/ml.

6.2.8. Aerodynamic assessment

The aerodynamic assessment of fine particles was performed using the Next Generation Impactor (NGI) (Copley Scientific, Nottingham, United Kingdom). Methodology followed that of the European Pharmacopoeia (preparations for inhalation: aerodynamic assessment of fine particles, Ph. Eur., 7.0). Prior to each experiment the small cups of the impactor were coated with 2ml, the large cups with 4ml of coating agent (solution of 5% of a mixture of glycerol and polyoxyethylene-20-cetylether (95:5) in isopropanol) and the pre-separator was filled with 10ml of buffer (diluted acetic acid, pH = 3). The inhalation device used for these experiments was the Aerolizer®. As this type of inhaler is a low resistance inhaler and the pressure drop of 4.0kPa could not be achieved a flow rate of 100 l/min was adjusted. During the experiments the solenoid valve of the critical flow controller (TPK, Copley Scientific, Nottingham,United Kingdom) was kept open 2.4seconds so that 4l of air were sucked (SV1040, Busch, Chevenez, Switzerland) through the apparatus. Additionally a leak test was performed prior to each experiment. Within 60s, the pressure of the closed NGI must not increase by more than 2.0kPa. Then a capsule was placed in the compartment in base of the inhaler and by pushing two buttons inwards on base of the inhaler the capsule was pierced so that the powder could be released. For each adhesive mixture three or six capsules were discharged into the impactor directly after each other. The active on the cups was then dissolved in 10ml of buffer. The induction port together with the mouthpiece was also rinsed with 10ml of buffer and the pre-separator with 50ml. Moreover the inhalation device was rinsed with 10ml buffer too. The amount of salbutamol sulphate in each compartment, the pre-separator, the introduction port plus the mouthpiece and the inhaler was subsequently determined via HPLC. According to the European Pharmacopoeia the fine particle dose (FPD), the emitted dose (ED) and the fine particle fraction (FPF) were calculated. FPD gives the amount of API exhibiting an aerodynamic diameter of < 5µm and the ED the amount of active found in the whole impactor (mouthpiece adaptor, introduction port, pre-separator, impaction stages). FDP divided by ED gives the FPF. Additionally the recovered dose (RD)

where the amount of salbutamol sulphate recovered in all the stages, the pre-separator, the mouthpiece and induction port and the inhaler were summed up, was determined. Each blend was tested in triplicate.

6.3. Results and discussion

In the following section Lactohale 100 will further be called LH100 and the decanted Lactohale 100, LH100_dec. Pearlitol 160C will be indicated as P160C and the decanted one, as P160C_dec.

6.3.1. Particle characterization

Table 1: Particle size distribution and particle surface

	x_{10} [µm]	x_{50} [µm]	x_{90} [µm]	SPAN [$(x_{90}-x_{10})/x_{50}$]	SSA [m^2/g]
Salbutamol sulphate	0.51 (+/- 0.018)	3.04 (+/- 0.124)	5.81 (+/- 0.28)	1.74	n.a.
LH 100	68.83 (+/- 0.45)	138.37 (+/- 0.37)	219.32 (+/- 3.2)	1.09	0.221 (+/- 0.018)
LH100_dec	64.06 (+/- 1.32)	138.37 (+/- 1.5)	225.67 (+/- 1.4)	1.17	0.244 (+/- 0.009)
P160C	10.93 (+/- 0.24)	81.45 (+/- 0.49)	237.59 (+/- 1.63)	2.78	0.218 (+/- 0.002)
P160C_dec	14.55 (+/- 0.18)	89.72 (+/- 1.23)	240.49 (+/- 3.08)	2.52	0.151 (+/- 0.004)

To investigate the effect of the carrier decantation on the particle size of lactose and mannitol laser diffraction was carried out. Table 1 shows the particle size distribution and surface area of the inhalation carriers. According to the powder fineness classification in the USP 2011 <811>, Lactohale 100 and is a fine powder, whereas mannitol can be classified as very fine in terms of particle size. For lactose the x_{10} and x_{90} are decreasing whereas the x_{50} is surprisingly exactly the same than before decantation. The span of the particle size distribution remained practically unaffected. In the case of mannitol an overall increase in particle size and decrease in span can be observed.

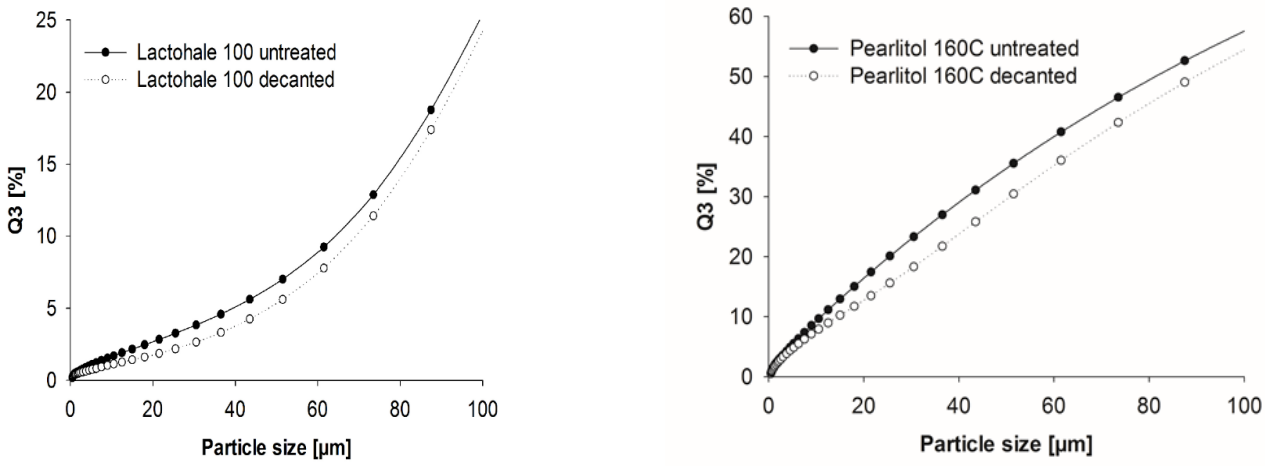

Figure 16: Particle size distribution of untreated and decanted carrier material

Figure 16 shows that the Q3 distribution of LH100_dec is decreasing. Upon closer investigation it can be seen that particle fraction < 100µm is decreasing, but no significant reduction in the fine particle fraction < 10µm can be observed. According to published data it was assumed that the particle size is not changing during decantation (Islam, Stewart, Larson, & Hartley, 2004), which was also identified in our study. In the Q3 distribution x_{10} is decreasing, which indicated the decrease of small particles, while x_{50} and x_{90} remain constant.

For mannitol the same effect on Q3 distribution after the decantation was observed. However, the overall particle size is increasing after the decantation process. The span of the particle size was also found to be increased. It was observed that the resolution in the fine particle fraction region (here: < 10µm) was not high enough to determine differences in the generated Q3 distributions before and after decantation. This is due to the higher polydispersity of the mannitol carrier material compared with the lactose carrier. Generally, narrower size distributions have better possibilities to show tiny differences in particle size than wide classes (Labiris & Dolovich, 2003). Overall the decantation process had no major influence on the PSD.

Thus, the removal of small particles can be observed by the decreasing specific surface area for mannitol (Table 1, Figure 17). In contrast to the major decrease of the specific surface area of mannitol the one of lactose does not change significantly. Indeed, pore size and surface even get a little higher after decantation. Also mannitol showed bigger pores after decantation and it was seen that the increase in pore size was bigger for mannitol. In general the pore size of lactose was smaller than the one for mannitol. Therefore, it can be stated that

the surface area, determined via gas adsorption is not the suitable indicator fur the successfulness of decantation process for lactose.

The water content of the samples remained almost unchanged after the decantation process. Lactose has a residual moisture content of 4.6% whereas mannitol has less than 0.1%.

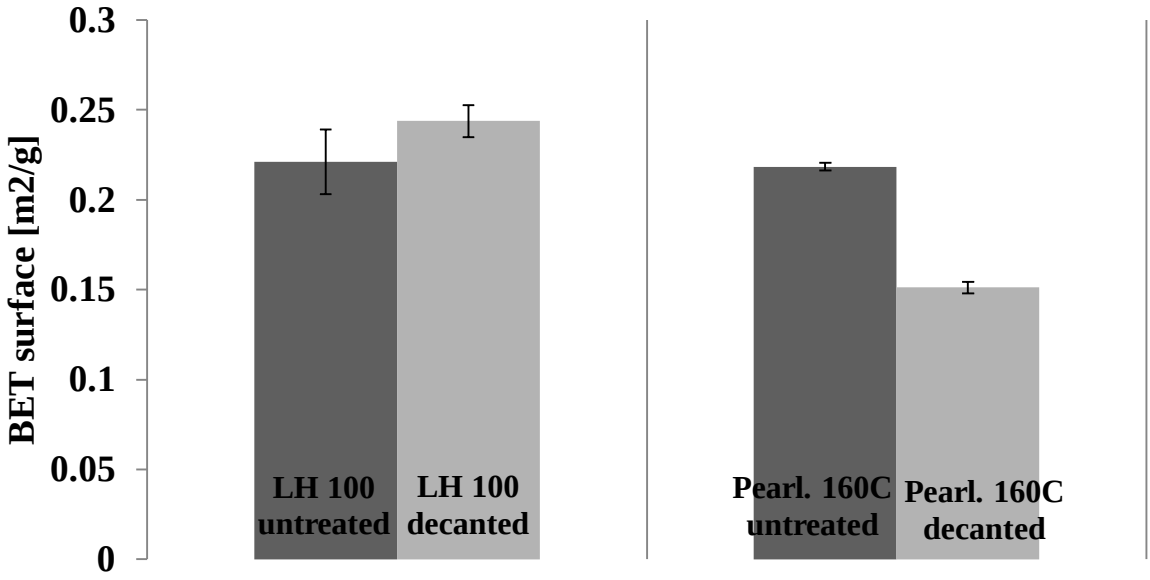

Figure 17: Specific surface of the carrier material before and after decantation

Table 2 presents the density and flowability of the untreated and decanted inhalation carriers investigated. Lactose showed no difference in BD after the treatment. However, the TD decreases with the reduction of fines. Mannitol shows exactly the opposite behavior. The BD increased whereas the TD was unaffected by the decantation. The true density decreased for decanted lactose and mannitol, thus mannitol shows a bigger density decrease. According to the parameters CI and AoR the lactose has a fair to good flowability before and after decantation. For mannitol the flowability could be increased from poor to passable with the removal of fines, which is indicated by the major increase of CI and decrease for the AoR.

Table 2: Densities and flow properties of investigated powders (CI ≤ 10: excellent flow, CI= 11-15: good flow, CI= 16-20: fair flow, CI=21-25: passable flow, CI= 26-31: poor flow, CI= 32-37: very poor flow, CI ≥ 38: very, very poor flow; AoR=25-30: excellent flow, AoR= 31-35: good; AoR=36-40: fair; AoR=41-45: passable, AoR=46-55: poor, AoR=56-65: very poor:, AoR>65:very very poor).

	BD [g/ml]	TD [g/ml]	True density [g/cm³]	CI	AoR [°]
Salbutamol sulphate	n.a.	n.a.	1.2812 (+/- 0.082)	n.a.	n.a.
LH 100	0.69	0.86	1.5450 (+/- 0.044)	18.9	37.7

LH100_dec	0.68	0.82	1.5389 (+/- 0.0033)	17.5	34.2
P160C	0.59	0.86	1.5108 (+/- 0.0033)	31.7	47.0
P160C_dec	0.63	0.85	1.4891 (+/- 0.0092)	25.4	40.7

6.3.2. Investigations on particle morphology by Scanning Electron Microscopy

The particle morphology was examined by using scanning electron microscopy (SEM). It has to be mentioned that SEM images only capture a few particles and do not provide representative information about the whole bulk. However, it gives a rough idea about the decantation and blending effect.

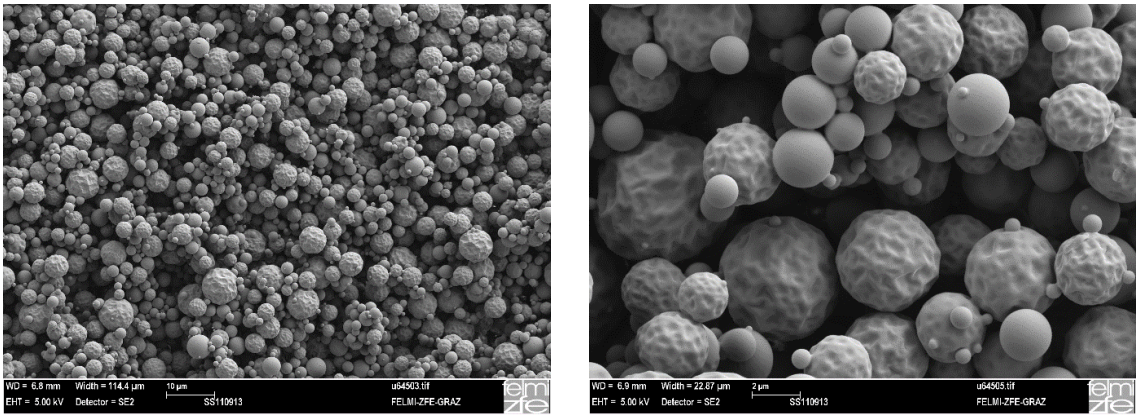

Figure 18: SEM images (width 114.4µm/left and 22.87µm/right) of spray dried salbutamol sulphate

Figure 18 shows SEM images of the spray dried salbutamol sulphate particles at two different magnifications. The images display that spray drying led to spherically shaped particles with a particle size suitable for inhalation. Compared to small API particles with a smooth surface larger API particles show corrugated surfaces.

The different surface topography could be explained by the drying history of the droplets. Littringer et. al proposed that due to the evaporation of water on the droplet surface during the drying process the concentration of API on the surface increases until shell formation takes place. Inside the shell water is trapped, vaporization continues and a pressure arises that consequently leads to particle inflation. Due to sufficient mechanical stability of the

shell of smaller particles they remain spherical whereas the shell of the larger particles will collapse after inflation, leading to corrugated particles (E. M. Littringer et al., 2013a; E.M. Littringer et al., 2013b).

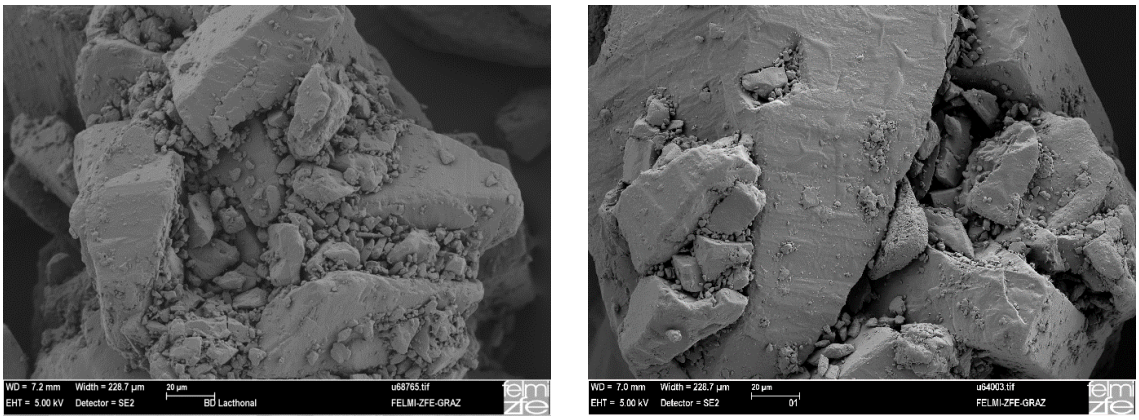

Figure 19: SEM images (width 228.7µm) of LH100 (left) and LH100_dec (right) carrier material

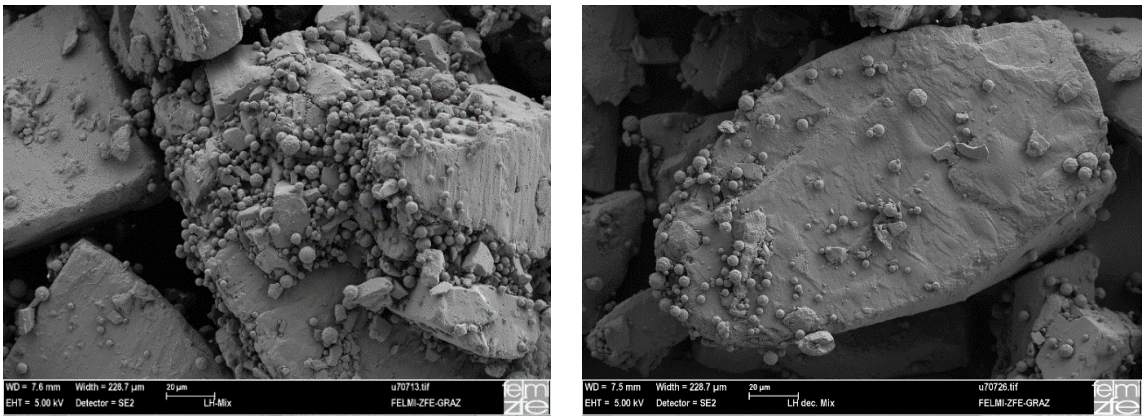

Figure 20: SEM images (width 228.7µm) of LH100 (left) and LH100_dec (right) and API

SEM images of untreated and decanted carrier particles were taken to evaluate the efficiency of the decantation process. In Fig. 19 lactose carrier particles before (left) and after (right) decantation indicate that with the decantation process a reduction of fines on the surface of lactose particles was achieved. Further it was observed that the surface of the lactose appeared smoother after decantation.

Figure 20 shows adhesive mixtures of untreated (left) and decanted lactose (right) with salbutamol sulphate. It is evident that more API particles adhere to the surface of untreated lactose. This can be explained by the higher fraction of fines and thus bigger and more porous surface of the latter, where API particles tend to adhere. By contrast the binding affinity of API particles onto the smooth surfaces of decanted lactose particles is much lower (Fig. 20 right).

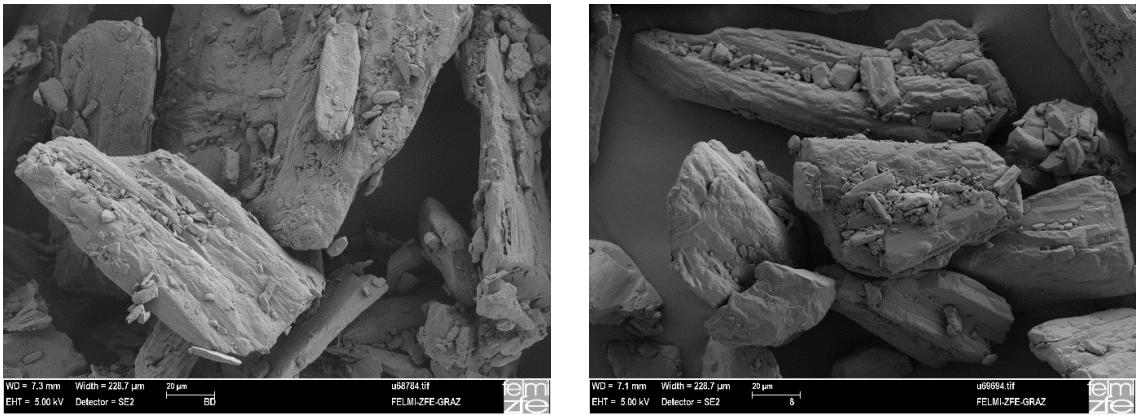

Figure 21: SEM images (width 228.7µm) of P160C (left) and P160C_dec (right) carrier material

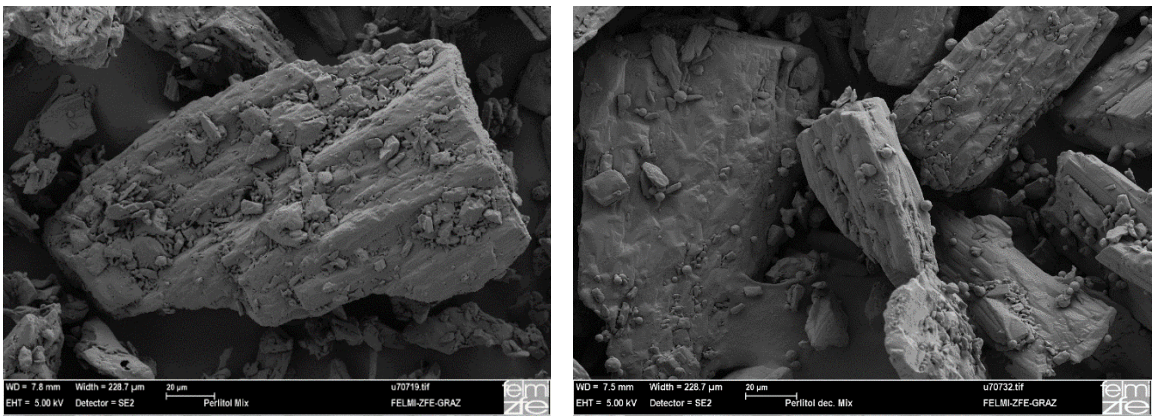

Figure 22: SEM images (width 228.7µm) of P160C (left) and P160C-dec (right) and API

In Fig. 21 mannitol carrier particles before (left) and after (right) decantation are shown. The visible effect of the decantation process is less pronounced compared to the lactose carrier particles. Nevertheless, a reductions in particle size occurred as already discussed.

The adhesive mixtures of untreated (left) and decanted (right) mannitol with salbutamol sulphate are shown in Fig. 22. SEM images of adhesive mixtures with untreated mannitol show hardly any API on the surface of the carrier particles although the mixing homogeneity indicated that the API is distributed well on the carrier surface. It seems that the surface topography has changed and appears somehow "coated". This can probably be explained by the fusion of API particles with the carrier surface. As the authors are well aware that spray dried salbutamol recrystallizes at 60% relative humidity (r.H.) and 25°C room temperature (Gorny, Jakobs, Mykhaylova, & Urbanetz, 2007; Littringer, Zellnitz, et al., 2013) all samples were prepared under same temperature and humidity controlled conditions and the same day. So, the observed phenomenon cannot be related to humidity or temperature issues. To verify the blending process of untreated mannitol and API, the procedure was repeated 3 times.

Again mixing homogeneity was promising but the resulting SEM images all showed the same carrier surface appearance. Surprisingly, SEM images of decanted mannitol particles blended with API (Fig. 22) right show that some spherical API particles are present on the carrier's surface. However, it seems that the API particles again tend to fuse on the carrier surface. A possible explanation could be a change in the crystalline surface structure (polymorphism) of mannitol during the decantation process. This surface changes could increase the adhesion tendency of the API to the carrier. Kailay et al. could see in their research that after particle engineering via crystallization different polymorphs were present depending on the anti solvent (Kaialy, Martin, Ticehurst, Momin, & Nokhodchi, 2010a).

6.3.3. Capsule filling

Table 3: Low dose capsule filling of adhesive mixtures at a filling speed of 2500 cph

Dosator diameter [mm]	Dosing chamber length [mm]	Powder layer height [mm]	Compression ratio	Fill weight [mg] (and RSD) LH100+ API	Fill weight [mg] and (RSD) LH100_dec + API	Fill weight [mg] (and RSD) P160C + API	Fill weight [mg] (and RSD) P160C_dec + API
3.4	2.5	5	1:2	23.8 (0.8%)	23.5 (1.3%)	20.8 (2.0%)	17.1 (4.2%)
3.4	2.5	10	1:4	24.5 (2.2%)	24.3 (1.2%)	28.8 (1.6%)	25.9 (3.1%)

Table 3 shows the different process settings during capsule filling, the fill weight and the corresponding weight variability (RSD) of capsules filled with the 4 adhesive mixtures. All of them were easy to handle during the entire process. Comparing the adhesive mixtures of untreated and decanted lactose no big changes of fill weight and weight variability were observed. Further, the higher compression ratio of 1:4 did not lead to higher fill weights due to the low compressibility of LH100. In both cases the fill weight increased by under 1mg.
For untreated and decanted mannitol different behavior during processing was noted. Compared to lactose, creating the layer and adjusting machine parameters took significantly longer. Furthermore, the powder layer was more uneven, the surface appeared to crack

easily. All these factors can be related to the smaller particle size and therefore more cohesiveness and harder powder feed and lead to an overall higher weight variability than for lactose. The adhesive mixtures of decanted mannitol show a major decrease in fill weight and increase in weight variability of the latter. This can be explained due to the bigger reduction of fines compared to lactose. When the dosator dips into the powder bed and collects coarse particles with less fine content (1) small interparticulate wholes are not filled by smaller particles and (2) bigger particles are less compressible and therefore the weight reduction can be explained.

Furthermore, the capsule fill weight of mannitol is much more affected by the depth of powder layer than the fill weight of lactose. In experiments with deeper powder layers, much heavier capsules are produced, due to higher compression of the powder inside the dosing cylinder.

As desired, hard plugs were never formed, not even at the high compression ratio of 1:4 between the dosing chamber length and powder layer depth. The reason may be low powder cohesiveness and the lack of piston compaction during the filling. This is also supported by literature (Jolliffe and Newton, 1983; Jones, 2001). A visual examination of the filled capsules indicated that no powder plug formation occurred for all mixtures when filling was performed at a 1:2 compression ratio. Weak plugs were formed, in all experiments with 1:4 compression ratios at low filling speeds. Therefore the capsules were manipulated before insertion into the Aerolizer (shaken in hands) and before adapted to the mouthpiece.

6.3.4. Aerodynamic assessment

In the present study, the FPF of salbutamol sulphate was calculated and chosen as parameter to compare the performance of the different carrier types and different blends among each other. In vitro deposition was determined using the next generation impactor (NGI). For NGI experiments of adhesive mixtures with untreated and decanted lactose 3 capsules were used. In the case of mannitol mixtures, the amount of salbutamol sulphate recovered in the different NGI stages from 3 capsules was too low to be quantified. Therefore 6 capsules were used for the mannitol mixtures. Consequently, as a percentage value the FPF suits best for comparing the performance of the different carrier types among each other.

Moreover, the relationship between surface characteristics, carrier type, compression ratio and FPF will be discussed in the following section.

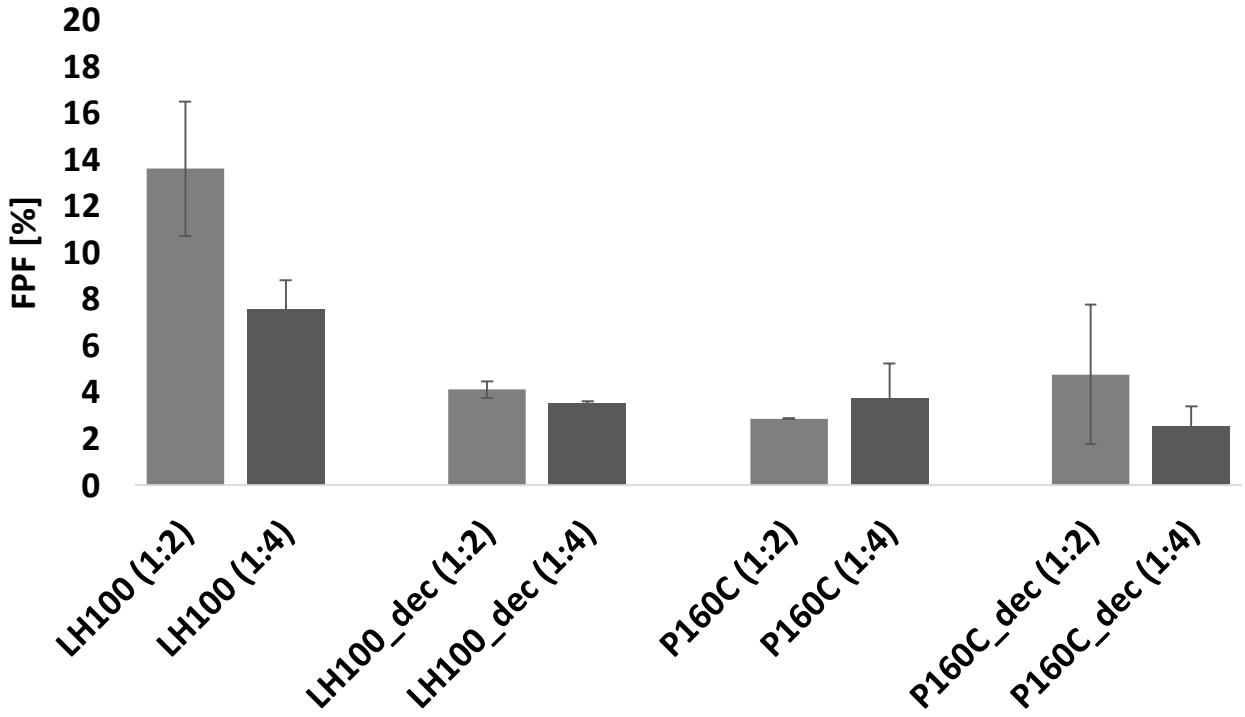

Figure 23: FPF of the four adhesive mixtures filled into capsules with a 1:2 and 1:4 compression ratio

Figure 23 displays the FPFs of mixtures containing untreated and decanted carrier (lactose and mannitol) and API. Results show that the FPF obtained for adhesive mixtures containing untreated lactose exhibits the highest FPF. All the other mixtures show significantly lower FPFs.

The FPF of decanted lactose decreases by more than half compared to the FPF of untreated lactose. This can be explained by the smoother surface of the decanted particles where less API particles adhered, which could already be seen on the SEM images. All in all the decantation process did not lead to higher FPF of lactose, which is in agreement of the findings of other research groups. Boshhiha et al. stated that due to reduction of the fine particles from the coarse carrier (lactose and mannitol) surface free high energetic sites on the carrier surface that can be occupied with API are present. This causes greater adhesion between drug and carrier, and therefore difficulties in separation of the API from the carrier. Moreover, the smoother surfaces of the carrier after decantation provides a good contact area for the fine drug, which also results in higher adhesion forces between the drug and the smoothed carrier particle. This further leads to insufficient detachment of drug particles from the carrier particles upon inhalation (Boshhiha & Urbanetz, 2009; Islam et al., 2004).

For all adhesive lactose mixtures, independent from decantation, an increase in compression ratio lead to a decrease in FPF, which means that first, the weak plug was not turned back

into a powder and therefore no efficient dose delivery was achieved and second that interparticulate forces between particles were not overcome and no deaggregation occurred, which is one of the most important functions of a DPI (Daniher & Zhu, 2008).

For mannitol we achieved overall relatively low FPFs, but the decantation led to an increase in the FPF for capsules filled with decanted ones and a compression ratio of 1:2, although not significantly. Other studies show a decrease of FPF after engineering the mannitol particles via decantation (Boshhiha & Urbanetz, 2009). Kaialy et al. could see a considerable increase of FPF when recrystallizing the mannitol (Kaialy, Martin, Ticehurst, Momin, & Nokhodchi, 2010a; Kaialy, Momin, Ticehurst, Murphy, & Nokhodchi, 2010b), where the particles were after treatment more elongated and had a smoother surface than the commercial one.

Untreated mannitol and API blends were unaffected from compression during filling. Whereas for P160C_dec a major decrease of FPF with a 1:4 compression ratio was observed. It can be concluded that for lactose the carrier decantation decreases the FPF whereas, the FPF of decanted mannitol carriers at a compression ratio of 1:4 remains the same and even tends to increase at a compression ratio of 1:2. For spray dried salbutamol sulphate untreated lactose carrier particles and a compression ratio of 1:2 proved to be the most efficient conditions first for accurate dosing (lowest RSD) and second for a high fine particle fraction.

6.4. Conclusions

In the present study one standard and one alternative carrier of different type and source (lactose and mannitol) were investigated as received and after decantation regarding their physicochemical properties, blended with API (spray dried salbutamol sulphate) and filled into capsules at different process settings. Finally the FPF of all adhesive mixtures was determined.

Overall it can be said that mannitol and lactose behaved rather different and show frequently opposite behavior. The decantation did not affect the particle size, bulk density and the surface of lactose, whereas an increase concerning the before mentioned attributes could be observed for mannitol.
Further, decantation of the lactose carrier particles decreased the FPF whereas decantation of the mannitol carrier particles tends to increase the FPF. For lactose contradictory findings concerning the effect of decantation on the FPF are reported in literature (Boshhiha & Urbanetz, 2009) as besides the surface topography also particle size and shape might be altered and also the used API particle affects the FPF. Less data are available for mannitol but Boshhiha et al. reported that the FPF increases after decantation (Boshhiha & Urbanetz, 2009). The same trend was observed in the present study. The different behavior of lactose and mannitol was not surprising as the SEM images already revealed a lower amount of API and a different distribution of the API on the surface of mannitol compared to the adhesive mixtures with lactose.

During capsule filling different behavior of carrier type during processing was noted. The decantation had no influence on the processing in the capsule filling machine. Higher compression ratios led to lower FPFs. This is not surprisingly as weak plug formation occurred in all experiments at the higher compression ratio of 1:4.

Summing up, the blend of untreated lactose carrier and a low compression ratio showed the most accurate filling and lead to the highest FPFs (14%) of spray dried salbutamol sulphate and thus is the most suitable carrier for salbutamol sulphate of the carriers investigated in the present study.

Acknowledgements

The authors would like to thank Thomas Wutscher for his scientific support and Hartmuth Schröttner for providing the SEM images.

Further the authors thank Roquette Fre`res (Lestrem, France) for providing mannitol and DFE Pharma (Goch, Germany) for providing the lactose.

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7. Conclusions and Outlook

In the present study one standard and one alternative carrier of different type and source (lactose and mannitol) were investigated as received and after decantation regarding their physicochemical properties, blended with API (spray dried salbutamol sulphate) and filled into capsules at different process settings. Finally, the FPF of all adhesive mixtures was determined.

Overall, it can be said that mannitol and lactose behaved rather different and show frequently opposite behavior. The decantation did not affect the particle size, bulk density and the surface of lactose, whereas an increase concerning the before mentioned attributes could be observed for mannitol. Further, decantation of the lactose carrier particles decreased the FPF whereas decantation of the mannitol carrier particles tends to increase the FPF. For lactose contradictory findings concerning the effect of decantation on the FPF are reported in literature (Boshhiha & Urbanetz, 2009) as besides the surface topography also particle size and shape might be altered and also the used API particle affects the FPF. Less data are available for mannitol but Boshhiha et al. reported that the FPF increases after decantation (Boshhiha & Urbanetz, 2009). The same trend was observed in the present study. The different behavior of lactose and mannitol was not surprising as the SEM images already revealed a lower amount of API and a different distribution of the API on the surface of mannitol compared to the adhesive mixtures with lactose.

During capsule filling different behavior of carrier type during processing was noted. The decantation had no influence on the processing in the capsule filling machine. Higher compression ratios led to lower FPFs. This is not surprisingly as weak plug formation occurred in all experiments at the higher compression ratio of 1:4.

Summing up, the blend of untreated lactose carrier and a low compression ratio showed the most accurate filling and lead to the highest FPFs (14%) of spray dried salbutamol sulphate and thus is the most suitable carrier for salbutamol sulphate of the carriers investigated in the present study. Due to the fact that lactose was already extensivly investiagted by different research groups, it is planned to conduct further studies with other types of mannitol as alternative carrier and blend it with spray dried salbutamol sulphate to see what happens with the API on the mannitol surface.

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