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Investigation of the triboelectric properties of pharmaceutical powders with special focus on inhalation powders for the application in Dry Powder Inhalers

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ABSTRACT

Active pharmaceutical ingredients (API) intended for pulmonary drug delivery need to reach the deeper lung, in order to cause the intended therapeutic effect. Therefore their aerodynamic diameter has to be between 0.5 µm and 5 µm leading in turn to poor flowability due to the small size of the particles and finally poor volumetric dosing. To ensure uniform dosage, adhesive mixtures of API particles in the size range of 0.5 µm – 5 µm and inert carrier particles in the size range of 50 µm – 200 µm, possessing an adequate fowability, are used in dry powder inhalers (DPI). However, API detachment from the carrier surface is crucial during inhalation or the release of the powder from the inhaler, respectively. Otherwise the API impacts in the mouth, throat and upper airways together with the carrier.

The performance of DPIs and adhesive mixtures are mainly governed by interparticle forces like Van der Waals and triboelectric forces. These forces on the one hand affect mixing homogeneity and hence dosing of the mixtures and on the other hand influence the very important detachment process of API from the carrier upon the release of the powder from the inhaler. Beyond this, triboelectric charge may cause difficulties in the production of adhesive mixtures like material loss and dust explosions. The tribo-charging of the electrically insulating powders during handling and application is strongly influenced by various particle, material and process characteristics and therefore difficult to control or predict. Especially the influences of particle characteristics like particle size, particle shape and particle surface roughness remained almost uninvestigated in the past.

Therefore the aim of the present work is to gain a deeper insight into these phenomena and to examine tribo-charging and evaluate possibilities to control tribo-charging by controlling the influencing factors. In addition to this, the influences of the tribo-charging behavior of different carrier powders and also adhesive mixtures on performance parameters like mixing homogeneity and lung deposition of the inhalation powder are investigated. As model API salbutamol sulphate and model carrier mannitol are used.

In the first part of the present work the focus lies on the investigation of tribo-charging during the preparation of the adhesive mixtures in a tumble blender. Hereby the factors particle size, particle surface roughness, carrier fines fraction, API content, mixing container size and material were investigated using statistical design of experiments. It was possible to show that tribo-charging in the tumble blending process strongly depends on the above mentioned process parameters and that it can be controlled by controlling them. Further these studies revealed that the charging behavior of the powder has a significant influence on the mixing homogeneity. In addition to these charging experiments, different discharge possibilities were developed and evaluated regarding their efficiency.

The second part of this work treats the application of the inhalation powder in DPIs. Therefore tribo-charging during aerosolization and release of the powder from a DPI is determined. In order to measure this tribo-charge a new open-end faraday cup measurement technique has been developed. The factors particle size, particle shape, particle surface roughness, carrier fines fraction, API content and aerosolization air flow rate were examined using statistical design of experiments. Significant tribo-charging was observed during the release process that was possible to control by adjusting the influencing process parameters. In the following assessment of the inhaler performance it was proven that the important inhaler performance parameters fine particle dose (FPD) and fine particle fraction (FPF) clearly correlated with the charging behavior of the carrier particles during aerosolization and release while the coefficient of variation of the released mass was not affected.

KURZFASSUNG

Für pharmazeutische Wirkstoffe die über die Lunge verabreicht werden, ist es von größter Wichtigkeit, dass sie die tieferen Bereiche der Lunge erreichen, um den gewünschten therapeutischen Effekt zu erzielen. Hierfür müssen sie einen aerodynamischen Durchmesser zwischen 0,5 µm und 5 µm aufweisen, was wiederum aufgrund der kleinen Partikelgröße zu einer sehr schlechten Fließfähigkeit und volumetrischen Dosierbarkeit des Pulvers führt. Um eine gleichmäßige Dosierbarkeit sicher zu stellen, verwendet man in Trockenpulverinhalatoren sogenannte interaktive Mischungen aus Wirkstoffpartikeln im Partikelgrößenbereich von 0,5 µm – 5 µm und inerte Trägerpartikel im Bereich von 50 µm – 200 µm, welche eine zufriedenstellende Fließfähigkeit aufweißen. Während der Inhalation bzw. der Abgabe des Pulvers aus dem Inhalator ist es wichtig, dass sich die Wirkstoffpartikel vom Träger lösen, da sonst der Wirkstoff gemeinsam mit dem Träger im Mund, Rachen und den oberen Atemwegen impaktiert.

Die Eigenschaften der interaktiven Mischungen und damit der therapeutische Erfolg der Trockenpulverinhalatoren hängen sehr stark von interpartikulären Kräften wie Van der Waals und elektrostatischen Kräften ab. Diese Kräfte beeinflussen einerseits die Mischhomogenität der interaktiven Mischung und dadurch auch die Dosierung und andererseits den sehr wichtigen Ablösungsprozess des Wirkstoffs vom Träger bei der Abgabe des Pulvers aus dem Inhalator. Darüber hinaus verursacht die elektrische Ladung einige Probleme bei der Herstellung der Mischungen wie Materialverluste und Staubexplosionen. Die triboelektrische Aufladung von elektrisch nicht leitenden Pulvern während der Erzeugung bzw. der Anwendung wird sehr stark von verschiedenen Partikel- und Materialeigenschaften sowie Prozessparametern beeinflusst und ist daher schwer vorherzusagen oder zu kontrollieren. Speziell der Einfluss von Partikelcharakteristiken wie Partikelgröße, Form und Oberflächenrauheit blieben in der Vergangenheit weitgehend unerforscht.

Aus diesem Grund ist das Ziel dieser Arbeit einen tieferen Einblick in diese Problematik zu bekommen und Möglichkeiten zu finden, die triboelektrische Aufladung durch Veränderung der Einflussgrößen zu kontrollieren und deren Praxisrelevanz zu beurteilen. Darüber hinaus soll der Einfluss des Aufladungsverhaltens verschiedener Trägerpartikel und interaktiver Mischungen auf deren Eigenschaften hinsichtlich Mischhomogenität, Fließfähigkeit und Lungengängigkeit untersucht werden. Als Modelarzneistoff wird Salbutamol Sulfat und als Träger Mannitol verwendet.

Der erste Teil dieser Arbeit beschäftigt sich mit der Entstehung von triboelektrischer Ladung bei der Herstellung der interaktiven Mischungen in einem Freifallmischer. Hierbei wurde der

Einfluss der Partikelgröße, der Oberflächenrauheit, des Träger Feinstanteils, des Wirkstoffanteils und der Mischbehältergröße und Material mittels eines statistischen Versuchsplans untersucht. Es konnte gezeigt werden, dass die Pulveraufladung im Mischprozess stark von den oben genannten Einflussgrößen abhängt und, dass sie sich dadurch kontrollieren lässt. Darüber hinaus zeigten diese Untersuchungen, dass die entstehende Aufladung einen signifikanten Einfluss auf die Mischhomogenität hat. Als Ergänzung zu diesen Aufladungsexperimenten wurden auch verschiedene Entladungsmöglichkeiten untersucht und hinsichtlich ihrer Effektivität beurteilt.

Der zweite Teil der Arbeit behandelt die Anwendung der interaktiven Mischungen in Trockenpulverinhalatoren. Zu diesem Zweck wurde die Aufladung des Pulvers während der Abgabe aus dem Inhalator gemessen. Um diese Aufladung messen zu können wurde eine neue open-end Faradaybecher Messtechnik entwickelt. Hier wurden die Einflussfaktoren Partikelgröße, Partikelform, Oberflächenrauheit, Träger Feinstanteil, Wirkstoffanteil und Volumenstrom des Aerosolisierungsluftstroms unter Verwendung eines statistischen Versuchsplans beleuchtet. Die Untersuchungen zeigten, dass während der Abgabe des Pulvers sehr hohe Aufladungen entstehen welche durch Variation der Einflussparameter kontrolliert werden können. Die nachfolgende Untersuchung der Inhalator- bzw. Aerosoleigenschaften zeigte eine eindeutige Abhängigkeit des lungengängigen Anteils des Pulvers von dem Aufladungsverhalten der Träger während der Abgabe aus dem Inhalator wohingegen die Gleichförmigkeit der abgegebenen Masse vom Ladungsverhalten unabhängig ist.

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1

Introduction into pulmonary drug delivery and tribo-charging

The application of pulmonary drugs has steadily increased in the last decades and is now a standard procedure for the treatment of respiratory diseases, such as bronchial asthma. Furthermore pulmonary drugs could also be used or are a desirable possibility for systemic drug delivery to the human body for the treatment of extrapulmonary diseases as well. An average human lung of a grown-up person offers approximately 100 m^2 surface and behaves like a highly permeable membrane [1]. Through the lung the drug is able to get directly into the blood stream without any detours over the digestive system and the liver.

The pulmonary route of administration has several advantages compared to other common forms of administration. In comparison to oral administration the onset of the action is much faster and only a fraction of the dose is needed to cause the same therapeutic effect, since the first-pass-effect in pulmonary administration is missing. This results in less cost. Moreover, pulmonary administration meansless physical stress for the patient compared to parenteral administration. The first-pass-effect is the loss or degradation of API through the gastrointestinal walls and the liver due to bio-transformation and extraction. Thereby the bioavailability of the drug is increased and the risk of an injury of the gastrointestinal tract and the liver by the API is overcome also.. The bioavailability characterizes the amount of API that actually reaches the blood stream to cause a therapeutic effect. Compared to parenteral administration pulmonary delivery is pain-free.. Last local treatment of the lung or parts of it is possible with lower API amounts and less side effects compared to systemic treatment.

1.1 Pulmonary drug delivery

Mainly three different types of inhaler devices have been established in the last years. These are nebulizers, metered dose inhalers (MDI), and dry powder inhalers (DPI). Nebulizers are used for the treatment of hospitalized or non-ambulatory patients because these inhalers are too big to be used as portable devices. The working principal is that the drug that is present in a solution or a suspension is converted into a spray by compressed air or ultrasound and then is inhaled. Metered dose inhalers use a propellant to aerosolize the active pharmaceutical ingredient (API). Nowadays hydrofluoroalkanes are used as propellant instead of chlorofluorocarbons. Although hydrofluoroalkanes are less environmentally harmful they still raise concerns. Another difficulty with MDIs is that the aerosol actuation has to be synchronized with the inspiration. Many patients stop inspiration due to the unpleasant feeling of the cool cloud in the throat or are simply not able to properly synchronize the two processes resulting in insufficient lung deposition and therapeutic effect.

A relatively new and promising inhaler technology are dry powder inhalers where the API is present as dry powder and the aerosolization is triggered just by human breath. Therefore no drug loss due to poorly coordinated inhalation and inhaler actuation is possible. Apart from that the propellant-free technology is environment-friendly.

Basically for every inhaler technology two main properties have to be guaranteed to achieve the desired therapeutic effect. The first one is a uniform dosage, which means that every actuation should release the same amount of API. The second one is a high respirable fraction of the inhalation powder that is able to deposit in the deeper parts of the lung. Deposition behavior in the lung is governed by three mechanisms, impaction, sedimentation and diffusion. Due to its inertia the aerosol particle is not able to follow the air stream and impacts on bifurcations of the the airways. Sedimentation is the mechanism of deposition when the particle settles in the airways forced by gravity. Diffusion is the main mechanism of deposition for particles with a diameter lower 1 μm that interact with gas molecules due to Brownian motion in the air.

API penetration in the deeper lung will only be achieved if the aerodynamic diameter of the API particles is below 5 μm [2]. Larger particles impact in the mouth, throat and the upper airways while particles smaller than 0,5 μm do not deposit and are exhaled again. Unfortunately powders of 0,5 μm to 5 μm in diameter are very cohesive resulting in poor flowability, poor dosing and insufficient aerolization after release from the inhaler which further cause a varying and low amount of API that reaches the deeper lung. Inadequate flowability and aerosolization are especially challenging in dry powder inhalers where dosing is performed volumetrically by free flowing of the powder into an orifice and aerosolization is conducted without propellant. One possibility to overcome the problem of poor flowability is to mix the fine API particles with larger carrier particles in the size range of 50 µm - 200 µm to generate so-called adhesive mixtures. The fine API sticks to the coarse carrier surface due to interparticle forces. As the size of the carrier ensures adequate flowability, the adhesive mixture can be dosed appropriately. As carrier materials usually sugars or sugar-alcohols like lactose, glucose or mannitol are used [3,4].

The positive effect of the adhesive mixtures on a uniform drug delivery to the lung is strongly governed by particle interactions between carrier and API which are mainly due to Van der Waals and electrostatic forces. On the one hand the interparticle forces have to be strong enough to form stable mixtures of API and carrier to guarantee adequate dosing. Since API as well as carriers are of electrical insulating material they accumulate high charge magnitudes during blending. That means sign and magnitude of the tribo-charge arising during the production of the adhesive mixtures in a tumble blender may strongly influence mixing homogeneity, the stability of the mixtures and thus dosage. On the other hand the interparticle forces have to be weak enough to allow API detachment from the carrier during inhalation or the release of the powder from the inhaler, respectively. Otherwise the API impacts in the mouth, throat and upper airways together with the carrier. In many DPI devices API detachment is realized or enhanced by high air velocities and shearing or impacting the inhalation powder particles to the inhaler material in cyclones or the like upon powder release from the inhaler. Especially this technique may result in the arising of high electrostatic or tribo-charge on the particles, influencing the particle detachment and also deposition behavior of the particles in the lung [5].

1.2 Tribo-charging

Tribo-charge arises when two unlike materials are brought into contact and are then separated. The detailed mechanisms of tribo-charging especially for insulating materials are up to now not completely clear and still under discussion. Basically the charging process can be explained in four steps.

In the first step the two materials come into contact and a potential difference arises between the two surfaces due to different surface workfunctions of the materials. The surface workfunction is material specific and depends on the Fermi level of the substance. Basically it is the energy that is needed to remove an electron out of the surface of the material and bring it in infinite distance. In the second step the potential difference is equalized by electron exchange between the surfaces in order to reach thermodynamic equilibrium. In the third step the contacting bodies are separated and the potential difference which was the driving force for charge exchange disappears. Thus the exchanged charges try to flow back. However often separation occurs fast and charge backflow is hindered by a weak electrical conductivity of the materials. As a result in step four there are two separated bodies each carrying a residual charge of the same magnitude but opposite polarity.

This contact and separation occurs many times in powder handling processes like mixing until the charge acquired on the surface of the contacting bodies reaches a level where in following contacts no further potential difference arises between the bodies because their Fermi level is equal. Therefore the driving force for charge exchange is no longer present and charge saturation is reached.

Theoretically sign and magnitude of the arising charge is mainly influenced by the surface workfunction of the contacting bodies or the potential difference between them, respectively. The higher the potential difference, the more charge is exchanged during contact. Whereby the contacting material with the lower workfunction (higher Fermi level) tends to release electrons and will thus charge positively in contact with a material with higher surface workfunction (lower Fermi level). In this way according to their surface workfunction materials can be listed in a so-called triboelectric series [6]. This triboelectric series can be used to make a rough prediction about the magnitude and polarity of tribo-charge that will arise on one material after the contact with another one.

In practice where not every particle – particle or particle – wall contact is equal the tribo-charge arising on a powder e.g. during mixing or any other powder handling process is influenced by many factors such as particle size and shape [7], surface roughness [8,9], nature and workfunctions [10,11], impurities [12–14], amorphicity [15], relative humidity [16] and the energy of contact [17,18]. This makes tribo-charging very complex and thus still very difficult to predict or control, especially when more than two different materials and various influencing factors are involved.

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2

Aim of the thesis

As mentioned in the introduction, the performance of DPIs is strongly influence by particle interactions between API and carrier that are further highly influence by triboelectric forces. Thus the tribo-charging behavior of the inhalation powder affects the usability of DPIs and their performance. Two processes where high tribo-charge magnitudes may arise on inhalation powder are the production of the adhesive mixtures in a tumble blender and the aerosolization and release process of the powder from the inhaler. Understanding how tribo-charging is influence by different factors opens up the possibility to control the charging process and thereby the DPI performance. The charge acquisition process, especially of electrical insulating materials, is very complex. The situation gets even more difficult when several influencing factors are involved. Correct, convincing and reproducible measurements are hard to perform and require a good practical and theoretical knowledge of triboelectrics. For these reasons the arising of triboelectric charge and its effects on powder properties are still widely uninvestigated.

Therefore the objective of this thesis is to investigate which factors and how they affect the emergence of tribo-charge on powders (adhesive mixtures) that are used in dry powder inhalers. As model substances mannitol is used as carrier material and salbutamol sulphate is used as the active pharmaceutical ingredient. To be application and practice oriented special attention is laid on the investigation of possible interactions between the influencing factors. Further the impact of the tribo-charge on powder properties like mixing homogeneity and inhaler performance is examined.

Chapter 2 gives a detailed review of the literature dealing with the phenomenon of tribo-charging, discusses various models for charge exchange and evaluates the impact of factors impacting charge uptake. An insight into charge measurement techniques and inhaler performance measurements is given. Further the techniques are evaluated with respect to their working principles, usability, restrictions and the correctness of their outputs.

Chapter 3 treats the tribo-charging of pharmaceutical powders in the mixing process and its influencing factors. Charge acquisition of the powder over mixing time is investigated to determine the time dependency of charge uptake.. Further statistical design of experiments is used to check the influence and interaction of the influencing factors particle size, mixing container size and carrier fines fraction. Further different discharge possibilities are examined and discussed. Three different possibilities for charge dissipation from charged insulating powders are treated and evaluated regarding to their efficiency.

Chapter 4 further treats the tribo-charge acquisition of powders during tumble blending and focuses on the influence of the particle surface roughness of surface modified carrier particles on charge uptake. Mixing experiments with pure carriers of different surface roughness and also ordered mixtures are performed. Additionally the effects of the arising charge on the mixing homogeneity are evaluated. Furthermore the flow characteristics of the modified carrier powders are assessed in inhaler studies by determining the uniformity of the released powder mass from the dry powder inhaler per actuation that is a measure of flowability. Finally correlations between the coefficient of variation of the released mass and the tribo-charging characteristics are checked.

Chapter 5 focuses on the application of ordered mixtures in dry powder inhalers and the arising of tribo-charge during aerosolization and release of the powder from the inhaler. An indirect charge measurement system using an open-end faraday cup is introduced. Statistical design of experiments is used to assess the significance of the influence and the interactions of the factors carrier particle size, fines fraction, aerosolization air flow rate and API content on the arising charge. Further long time actuation studies are used to check whether the tribo-charging behaviordepends on the number of consecutive actuations.

Chapter 6 further discusses tribo-charge acquisition during aerosolization and release of the inhalation powder from a DPI. Here the focus lies on the influence of the carrier particle characteristics surface roughness and shape on the charging behavior of pure carriers and ordered mixtures. Beyond that the measured tribo-charge is correlated with important inhaler properties like the coefficient of variation of the released mass, the fine particle dose and the fine particle fraction.

3

The impact of electrostatic charge in pharmaceutical powders with specific focus on inhalation-powders

The aim of this work is to give an overview about the literature available on the topic of electrostatic charge in pharmaceutical powders. The main focus is on powders used in dry powder inhaler devices. Pharmaceutical powders mainly consist of fine particles of electrical insulating materials. On the one hand, the insulating properties disfavor electrostatic charge dissipation. On the other hand small particle sizes in general result in high cohesive forces in relation to gravitational forces. For these reasons the powder may show very cohesive characteristics. In order to overcome the problems associated with cohesivity and deposit the active pharmaceutical ingredient in the deeper regions of the lung it is important to understand how electrostatic charge is acquired and by which factors acquisition is influenced. The work includes an overview about different operations in pharmaceutical process engineering in which charge may be introduced and the associated influencing process variables. Further more related topics like the utilization of electrostatic charge for improving lung deposition of powders intended for pulmonary drug delivery are reviewed. To complete the overview several static and dynamic measuring procedures for net charge and charge distribution are presented and compared.

3.1 Introduction

Drug delivery to the lungs has become more and more important in the last decades. Until now the pulmonary application of drugs has been mainly used for the treatment of respiratory diseases such as asthma. For the future it will be a preferable practice to use inhalation powders for systemic drug delivery as well [1]. That means that the drug is administered through the lung and is further carried from there into the systemic blood circulation. In this context it is a major advantage that the lung of grown-up humans has a surface of about 100 m^2 and works as a highly permeable membrane. If the active ingredient is intended to target the lung, pulmonary drug delivery has the advantages of lower drug doses and thus fewer side effects in comparison to systemic treatment. In addition to this the application is simple and pain-free and there are fewer problems of insufficient absorption and first-pass-effect. Also the onset of action is faster after pulmonary application compared to other administration forms.

Drug delivery to the lungs is carried out using nebulizers, metered dose inhalers (MDI) or dry powder inhalers (DPI). Nowadays mainly metered dose inhalers and dry powder inhalers are used. In these devices the drug becomes aerosolized and is then carried into the lungs by the human breath. To reach a satisfying treatment of diseases it is very important that each actuation of the inhaler reproducibly releases the prescribed dose. The dosage of the powders is based on the powder volume. To ensure reproducible dosing it is necessary that the powder shows adequate flow behavior.

In order to be deposited in the deeper lung, it is essential that the drug particles have an aerodynamic diameter between 0.5 μm and 5 μm [2]. Smaller particles will be exhaled while larger particles will impact in the mouth or throat due to their inertia. Because of their low particle mass, such fine powders are very cohesive. Cohesivity emerges because of interparticle interactions which impede flowability. Interactions mainly arise through Van der Waals and electrostatic forces.

To overcome the problems of dosing and to ensure deposition of the active ingredient in the deeper regions of the lung, there are mainly two possibilities. The first one is to attach small drug particles on larger carrier particles. As carrier materials lactose, glucose or mannitol are used [3,4]. The diameter of these carrier particles is between 50 μm and 200 μm, ensuring adequate flowability of the powder. To reach the deeper parts of the lung, the small drug particles have to detach from the carrier particles, which impact in the mouth or throat. The second possibility is to form larger agglomerates, so called soft pellets, out of fine drug particles in order to overcome the flowability problem. These soft pellets also have to disperse when they are released from the inhaler, to ensure drug deposition in the deeper lung. Drug detachment / dispersion are strongly influenced by interparticle interactions between the drug and the carrier caused mainly by Van der Waals and electrostatic forces.

A new approach of formulation, which is still under investigation, is to cover the active ingredient particles with nanoparticles, which work as spacers between drug particles thereby reducing cohesive behavior [5,6]. As already mentioned before the performance of these inhalates is strongly dependent on interparticle forces such as Van der Waals and electrostatic forces.

The deposition of the drug particles in the lung is influenced by different mechanisms. The main mechanisms are impaction, sedimentation, Brownian diffusion and electrostatic deposition [7]. Impaction is caused by the inertia of particles, that are not able to follow the air-stream at bifurcations of the airways due to their mass and thus impact on the walls of the airways. Sedimentation means the settling of particles forced by gravity. Diffusion occurs in the deep alveolar regions of the lung where particles smaller than 1 μm get in interaction with gas molecules and are deposited by chance on the alveolar walls. Electrostatic forces have been shown to influence the deposition in the lung, and can be divided into two different categories: space charge and image charge forces. Space charge seems to be more important in the upper region of the respiratory tract, especially when the aerosol cloud is dense, while the image charge forces are dominant in the alveolar region [8]. Similar results have also been reported with nebulizers. These studies suggested that the deposition in the lung could be improved by taking advantage of the electrostatic charges present on the particles [9][10]. In addition to this clinical studies supported this statement [11–13].

Last but not least, electrostatic charge on pharmaceutical powders has a strong impact on material loss during manufacturing of the inhalate and upon actuation of the inhaler. Especially in the mixing process charged particles tend to adhere on the walls of the mixing vessel. In addition to this charged drug may also adhere to the inhaler material and thus influence the released dose.

Summarizing, manufacturing of an inhalate, dosing, the mass and the reproducibility of the mass of drug released from the inhaler as well as the deposition of the drug particles in the lung are affected by electrostatic charges present on the powder. Therefore it is a very important factor in handling pharmaceutical powders, which, in comparison to other influencing factors, is widely uninvestigated.

3.2 Arise of electrostatic charge on pharmaceutical powders and influencing variables

3.2.1 Causes for the arise of electrostatic charge

Mostly, pharmaceutical powders are composed of fine particles of insulating material which are in contact with each other or with the surfaces of different devices surrounding the powder. These contacts cause, that electrons may be donated or accepted during various processes. Electron exchange occurs because of surface potential differences between the contacting bodies. These potential differences are mainly caused by different contact materials, but may also be influenced by different particles size, surface roughness, etc. The difference of surface potential is compensated by exchanging charges. If the separation of the bodies occurs fast enough the charge backflow is disabled and the contacting bodies remain charged.

The phenomenon of contact charging has been observed for the first time in the late 19th century in pharmaceutical sciences and it further was assumed that it must have a strong impact on interparticle forces [14–17]. This is obvious because opposite charged particles tend to attract each other and thus cohesion increases thereby decreasing flowability. In early studies it was found out that electrostatic charges are generated when materials, of which at least one is insulating, are brought into contact and then are separated again [18]. Only if at least one of the contacting bodies is an electrical insulator real charge accumulation can occur. An electrical conducting material would dissipate the contact charge immediately. The transferred charge is equal but opposite in the contacting bodies.

In fact contact charging can be classified into three categories according to the contacting materials. These are metal-metal contact, metal-insulator contact and insulator-insulator contact [19]. As above-mentioned pharmaceutical powders mainly are electrical insulators, so only the last two categories are relevant. The models to describe the charging process of the insulator-insulator contact are similar to those of metal-insulator contacts, but the movement of electrons or ions in the insulating body is much more restricted. In the charging process of the metal-insulator category three different proceedings can be distinguished [19]. These are electron transfer where the charging occurs by a flow of electrons [20], ion transfer where ions are exchanged by diffusion [18,21–23]and material transfer where material is rubbed off one contacting body and adheres on the other one [24]. Normally the charging process is a combination of these three proceedings. To describe the charging processes of pharmaceutical powders usually the electron transfer model is used because it provides a good understandable description of a charging process driven by a surface potential difference.

One of the most common ideas to describe the charging process is the simple capacitor or condenser model where it is assumed that the accumulation of charge on the surface of the contacting particles is analogous to the build-up of charge on a capacitor as shown in figure 3.1 [25]. Matsusyama commented that this model had a severe disadvantage because only charge generation and no charge relaxation was minded. He pointed out that the potential difference between the surfaces might increase very fast during separation causing gas discharge and thus charge relaxation during the separation process. This objection is valid because charge relaxation always occurs during separation either in the form of charge backflow, gas discharge or both proceedings. This is caused by the fact that the driving force for the initial charge exchange (surface potential difference) is eliminated during the separation step. Therefore Matsusyama and Yamamoto [26] proposed a charge relaxation model referring to this problem. Anyway the simple condenser model is still a good approach to the very complex phenomenon of triboelectrification and has therefore been used in many studies [27–33].

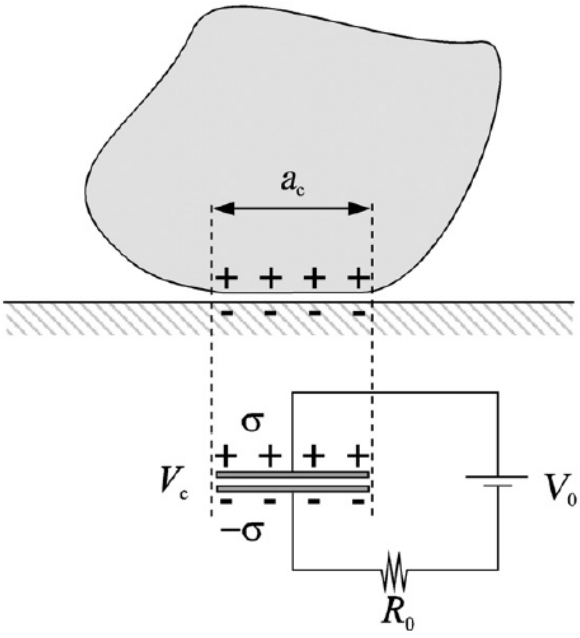

Figure 3.1: Capacitor model of contact charging [25]

A different concept of how the exchange of electrons occurs was introduced by Yu and Watson [34]. They presented a two-step-model for the arising and accumulation of contact charge of the metal-insulator contact. It was assumed that charge transfer was not accomplished during the contact, but during separation. The idea of this model is that, when the materials are brought into contact new interface states are created and these become populated by electrons from one or both contacting bodies. During the separation, before the interface states are eliminated, all of the electrons from those interface states are transferred to either the metal or the insulator [34]. This two-step-model provides a good possibility to describe the arising of charge in particle contact where the charge exchange takes place during separation. However the easier and more frequently applied idea or model is that charge is exchanged when the contact is formed, in order to compensate the surface potential difference between the contacting bodies. When separation occurs, the backflow of the charge is hindered due to the poor surface conductivity of the contacting materials and therefore the charge remains on the contacting bodies.

As above-mentioned triboelectrical charging proceeds in almost every powder handling process. One of the most important processes in powder handling, in which electrostatic charge arises is mixing. The phenomenon of tribo-charging can cause problems or can even be useful. The effect that two different contacting materials will charge oppositely can be used to improve the mixing homogeneity of mixtures of two different materials. This is because particles of the same material will repel and particles of unlike materials will attract each other. Thus, the two components to be mixed will be uniformly distributed. Linsenbuehler and Wirth used this effect to prepare ordered mixtures. Ordered mixtures are blends of particles with different particle sizes or materials in which particles of one component adhere to the surface of the particles of the other component and in which the particle interactions are among others controlled by electrostatic forces [35]. In their studies Linsenbuehler and Wirth dispersed and stirred different pharmaceutical powders in a non-conducting liquid to charge the particles. As the non-conducting liquid they used liquid nitrogen. As shown in figure 3.2 they found out that the arising charge on the surface of the powder approaches a constant value after a certain time of mixing. This is because no charge exchange occurs over a certain level of accumulated charge on the particles since potential difference is equalized. The arising of charge in powder mixing processes and its possible utilization had also been investigated by Huber [36] and Wirth and Linsenbuehler [37] before. This is a very new and promising technique to either improve the mixing uniformity or to carry out controlled coating of larger particles with smaller ones (see also section 3.3).

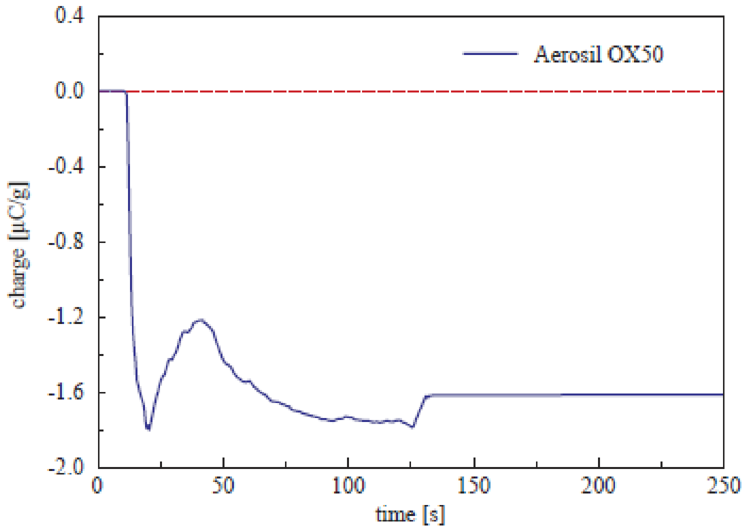

Figure 3.2: Electrostatic charge of Aerosil OX50® during dispersing [35]

In addition to the mixing process also in filling, transport and release from the inhaler the powder might become charged by getting into contact with different materials. To investigate these processes Rowley [38] invented a cyclone charger with removable wall materials (see also section 3.2.2.1). This device provides a good means to check the influence of contacting materials with which the powder may come into contact during the above mentioned processes.

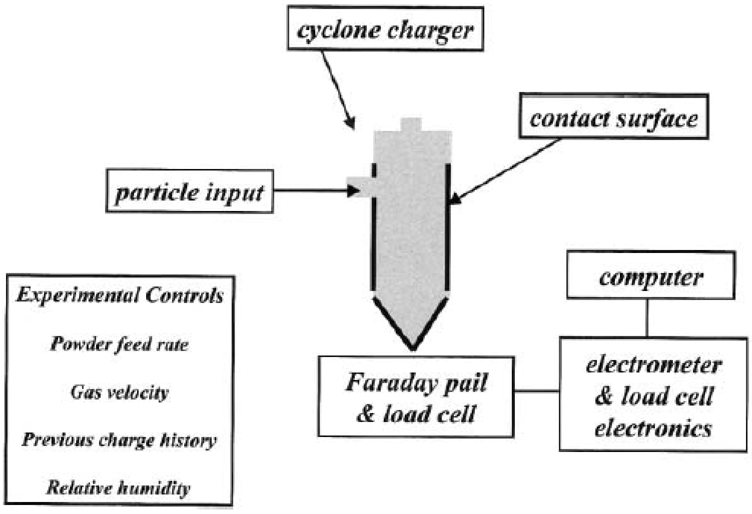

Figure 3.3: Sketch of a cyclone charger setup [38]

Charge does not only arise in handling the powders, but also during the manufacturing processes of the particles such as spray-drying. It was observed that a lactose solution became charged negatively when leaving the spraying nozzle [39]. However, after collecting the powder from the spray-dryer the powder showed strong positive charge. This might be because the powder got into contact with the glass walls of the spray-dryer and thus became positively charged leaving behind the negative charge on the walls. It is common knowledge, that lactose powder becomes positively charged in contact with glass. (see also section 3.2.2.3)

To further study powder charging in transport, Chow et al. [40] conducted tapping experiments for lactose filled in gelatine capsules. They detected a significant increase in charge from 100 taps onwards. Tapping or shaking studies are commonly used and provide a good approach to investigate the proceedings, which occur during transport of capsules or multi dose inhalers. Under this topic it would be nice to see how many taps are required to reach saturation and how high saturation charge is. Another interesting aspect would be the influence of the capsule material and the usage of an ordered mixture. Because of the dependence on the interactions between the different compounds the net charge of the powder may be increased or even equalized.

3.2.2 Influencing variables

The sign and amount of transferred charge depend on many factors such as particle size and shape [41], surface roughness [42,43], nature and work functions [14], impurities [44–46], amorphicity [47], contact material [48], relative humidity [49] and the energy of contact [50][51]. The most important factors will be discussed in the following chapters.

3.2.2.1 Workfunction

The tendency of an insulator getting charged positively or negatively in contact with another insulator can be evaluated using the ‘triboelectric series’, in which insulators are ranked in an order such that a material higher up the series will always charge positively when brought into contact with a material lower down [19]. This is because materials higher up in this series have a lower work function than those lower down and thus tend to release electrons and accumulate positive charge. Furthermore the amount of transferred charge is all the more, the larger the gap in the series between the contacting bodies. However, this series is just empirical, not quantitative and not always correct.

In order to improve the utility of the series Diaz and Felix-Navarro [52] created a semi-quantitative triboelectric series. They combined four qualitative series from literature reports into one big series and further merged these series with quantitative results for similar materials in other studies. The qualitative series they used were published by Coehn [53], Hersh and Montgomery [54], Henniker [55] and Adams [56]. The quantitative data were obtained from Lowell and Akande [57], Akande and Adedoyin [58], Lowell and Brown [59] Charlson et al. [60], Wåhlin and Bäckström [61]. This semi-quantitative series can be very useful to estimate the relative charging capacity of many polymeric materials because it contains qualitative as well as quantitative information about charging behavior of a wide range of polymers. Even though the combined series showed good correlations with experimental data, there is still no theoretical background which approves the series.

To measure and examine the impact of contact material on the arising of charge in different powder handling processes a cyclone charger with removable cyclone-walls can be used [38]. Figure 3.3 shows a sketch of this experimental set-up. In his study Rowley determined the influence of different wall materials on the charging process for a defined particle size fraction. He figured out that the α-lactose monohydrate powder became negatively charged in contact with stainless steel and positively charged in contact with PVC. This indicates that the metal tends to release electrons in contact with the powder. Concluding it was approved that the contact material has an important effect on the polarity and magnitude of the charge. These results are in agreement with the papers of Elajnaf et al. [48], Engers et al. [62] and Zhu et al. [63] who performed mixing studies to investigate these effects.

As the material of the contact surface seems to influence the contact charge, also surface contamination with particles has to have effects. Eilbeck et al. [45] studied the role of adhered particles as contact surface contaminants on the electrical charging of size fractioned lactose in a cyclone. He found out that a decrease in the net electronegative charge due to adhered lactose particles to the cyclone wall occurred. This is obvious because the lactose particles in the air stream came into contact with adhered lactose instead of the cyclone wall.

3.2.2.2 Mechanical factors

Ireland [25] developed a model to indentify mechanical factors that influence the accumulation of triboelectric charge on a continuous flow of particles in contact with a flat surface. He used a simple capacitor model for charge accumulation, coupled with an equally simple surface coverage model in the case of rolling particles. Concluding he made three important statements. First, particles with irregular geometry accumulate more charge when sliding than rolling. This was due to the greater average contact area for the sliding contact than of the rolling contact. The same effect can be observed on regular shaped particles but it has less impact on the amount of charge because the reduction of contact area from the sliding to the rolling contact is less when regular shaped particles are treated. Secondly, continuous contact transfers more charge than bouncing contact. This was only partly due to the greater total time in contact. There appeared to be some sort of mechanism that limited the charge on bouncing particles, presumably gas discharge and other mechanisms like separation discharge. These discharge proceedings may also occur in continuous contact but are much stronger when particles are bouncing. And thirdly, that charge transfer increases with normal force in a manner consistent with the expected increase in contact area. One important parameter he neglected is that a temperature increase caused through sliding or rubbing contact may reduce the surface workfunction and enforce the agility of the electrons leading to an enhanced electron release.

3.2.2.3 Mixing ratio

Another parameter affecting the acquisition of charge is the mixing ratio of two different compounds in the treated blend [64]. To investigate this phenomenon Murtomaa and Laine carried out charging experiments by sliding mixtures of lactose and glucose through a glass pipe into a faraday cup where the charge on the powder was measured. Lactose and glucose are widely used excipients in the pharmaceutical industry. They noticed that pure glucose became positively charged, but as soon as lactose was introduced, the accumulated net charge on the powder mixture became negative. The mixture charged negatively if the amount of lactose was between 20 and 40 wt%, but became again positively charged when the amount of lactose increased further. Pure lactose accumulated also positive charge. He concluded that both, lactose and glucose became positively charged in contact with the glass pipe, but in contact with each other lactose became charged positively and glucose negatively. This means that both excipients have a lower surface work function than glass and that glucose has a higher than lactose. However it is not clearly explained why this phenomenon arises. The net charge of the lactose-glucose contact is neutral and the glass pipe can only give positive charge to both materials. Therefore the whole net charge normally can only be positive. Maybe some dynamic charge transfer effects are the explanation for these results.

Similar experiments were carried out by Engers et al. [65]. They evaluated the influence of the concentration of pseudoephedrine hydrochloride in dicalcium phosphate dehydrate and acetaminophen in microcrystalline cellulose on the surface net charge when mixing the powders in a blender. They also noticed a strong dependence of the net charge on the mixing ratio but no change of the sign was detected. This could be because the potential difference between the two substances was not large enough to bring about this change.

Elajnaf et al. [48] also investigated the interactions between active ingredient, excipient and mixing vessel material. Such studies are very helpful to evaluate the influence of the drug on the charging behavior of the excipient in an ordered mixture. He showed that e.g. salbutamol sulphate strongly alters the charging characteristics of lactose powder.

3.2.2.4 Relative humidity

Since moisture has a strong effect on the electrical conductivity of the surface of particles, the relative humidity is an important influencing parameter of charging processes of powders.

Therefore Rowley and Mackin [66] extended their cyclone charger experiments about the consideration of relative humidity. These factor was also checked by Elajnaf et al. [48] and Zhu et al. [63]. Zhu et al. and Rowley and Mackin showed that the magnitude of the arising net charge decreases with increasing relative humidity. These results can be explained by two mechanisms. The first one is that moisture in the air increases the conductivity of the air and thus enforces gas discharge. The second one is that the surface conductivity of the contacting bodies is increased by adsorbed water and therefore the charge backflow during the separation of the bodies is enhanced.

Kwok and Chan [67] partly approved this consideration. They measured the electrostatic charge of an aerosol released from a Pulmicort® and a Bricanyl® inhaler device at different RH-levels using an ELPI. The charge of the aerosol released from the Bricanyl® followed the above mentioned trend and decreased with increasing relative humidity. In contrast to this the Pulmicort® aerosol reached a minimum charge level at a relative humidity of 40%RH and charge increased at lower and higher RH-levels. This was explained by differences in hygroscopicity and other physiochemical factors between the two drugs.

A very interesting effect can be seen in the results of Elajnaf et al. [48] who reported a change of the sign of the net charge of pure lactose and also of a lactose / salbutamol sulphate mixture in contact with stainless steel and acetal, respectively when the relative humidity was increased. This effect occurred when the relative humidity was increased over 60%RH. For the mixture this proceeding might be explained by different moisture sorption behavior of the components in combination with opposite charging properties. But for pure lactose the magnitude of the net charge can only approach or theoretically reach the zero level when increasing the relative humidity.

Relative humidity experiments from a different point of view were performed by Eilbeck et al. [45]. He studied the role of adhered moisture as contact surface contaminant on the electrical charging of size fractioned lactose in a cyclone. He observed a decrease in the net charge when increasing the relative humidity in the cyclone from 2 % to 100 % because of increased electrical surface conductivity and therefore enhanced charge relaxation.

Electrostatic charge and relative humidity further influence the fine particle fraction and the emitted dose of a DPI. Zhu et al. [68] examined this by actuating a dry powder inhaler device and releasing the dose into a Twin Stage Impinger (see section 3.6) at different relative humidities. They concluded that adhesion forces decrease with increasing RH initially, and then increase with further increasing of RH. At the low RH range, the decrease of the adhesion forces was probably due to the reduction in the electrostatic forces arising from the dissipation of electrostatic charges associated with the increase of moisture content. At the high RH range, the increase in the adhesion force with RH was the result of liquid bridge forces. One interesting result mentioned in their paper is that the emitted dose increased with an increase of the relative humidity from 20 %RH to 75 %RH while the fine particle fraction (aerodynamic diameter smaller than 6,4 µm) only increased up to a relative humidity level of 43 %RH and then further decreased. Considering these results it can be assessed that the fine particle fraction seems to be more sensitive to liquid bridge forces than the emitted dose. This is obvious because of the higher force to mass ratio of the fine particles adhered to the carrier surface.

Similar results were published by Young et al. [69]. They investigated the aerosolisation and electrostatic properties of a salbutamol and α-lactose monohydrate mixture actuated from a DPI. Using an NGI and ELPI they detected an increasing fine particle fraction aerosol performance when increasing the relative humidity from 0%RH to 60%RH before it decreases at 60%RH. They also concluded that the aerosol performance is dependent on both electrostatic and capillary forces.

In contrast to this Adi et al. [70] came to the conclusion that the aerosolisation of a powder is not affected by electrostatic charge. They charged mannitol powder to different magnitudes of charge by tumbling it inside containers of different materials and then dispersed it from an Aerolizer®. Irrespective to the charge level they measured similar fine particle fraction, emitted dose and device retention for the different samples. Normally the charge should have an affect. Maybe the powder got discharge during transport and filling into the inhaler device.

3.2.2.5 Amorphicity

The amorphicity of the treated particles is also an important factor, which influences the charging behaviour of pharmaceutical powders [8]. Actually the amorphicity just influences the surface workfunction but should anyway be mentioned as a separate influencing factor. This phenomenon could be of interest if spray or freeze dried materials are used. Spray as well as freeze drying procedures may have an impact on crystal properties. If metastable or amorphous products are generated a change of amorphicity can even occur immediately after the drying process. Different structure types of the same substance may show completely different charging behaviour. Murtomaa et al. investigated this factor on different types of lactose powder actuated from DPIs. In their studies they figured out that powders with a higher amorphous content showed a higher specific charge after actuation. This was attributed to the larger specific surface of the amorphous powder. This aspect should be looked at very carefully because the specific surface area of amorphous powders may also be smaller than the one of crystalline powders. Another explanation for the higher specific charge of amorphous powders reported by

Murtomaa et al. may be the higher softness of amorphous materials compared to crystalline ones resulting in a larger contact area of the amorphous materials. The dependence of the charge acquired on the contact area will be discussed in the following section.

3.2.2.6 Particle size and roughness

To examine the impact of the particle size on the arising of charge Rowley [38] extended his cyclone charger experiments. The experimental set-up has already been described in section 3.2.2.1. In this study he varied the particle size fraction used and found out that the amount of specific charge is inversely related to the particle size fraction. He commented that this is because of the higher number of particle-wall contacts of the finer powder. Furthermore the larger specific surface of the smaller particle size fractions might be responsible for this phenomenon. His results were also approved by Zhu et al. [63].

Also the surface roughness as it influences the contacting area has to be mentioned as an influencing variable in the charging process [42,43].

3.2.2.7 Energy of contact / mixing speed

As Watanabe et al. [50,51] suggested the impact velocity also influences the impact charge. He investigated the arising of charge in single particle impacts under consideration of different impact velocities and angles. Watanabe et al. found out that the amount of charge is related to the normal component of the impact velocity. In fact the amount of arising charge is a function of the contact area which is in a linear relationship to the normal component of the impact velocity. They further determined an equilibrium initial charge, where no charge transfer takes place at the impact of the particle due to equalized surface potential of the contacting bodies. The relationship of impact velocity and contact charge is illustrated in figure 3.4. The results of Wantanabe are in agreement with former studies of Matsusaka et al. [71] who performed similar experiments with 30 mm rubber balls.

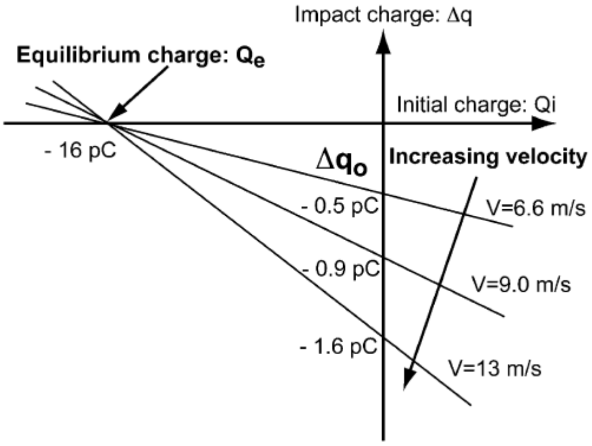

Figure 3.4: Relationship between impact velocity and impact charge [51]

The contact energy as a function of the rotation speed of a mixer was also investigated by Zhu et al. [63]. He came to the conclusion that the saturation charge in his experiments was not influenced by the rotation speed. This is because the rotation speed of the mixer only influences the frequency of particle contacts. Thus the required time to reach saturation increases with decreasing rotation speed, but the total amount of saturated charge is defined by the surface potential difference of the contacting bodies and therefore cannot be influenced by the rotation speed. These results are in agreement with the blender studies performed by Engers et al. [62].

Energy of contact can also be a function of the airflow rate through a DPI. This was shown by Chow et al. [40]. They found out that the charge carried by the powder after release from the inhaler increased with increasing airflow rate. Actually the magnitude of the charge is not influenced by the airflow rate but by the air velocity through the inhaler and thus by the impact velocity of the particles. In practice airflow rate is limited by the human breathing capability and thus cannot be influenced. One possibility to control the air velocity is maybe via the design of the inhaler. However it should not be forgotten that a certain air velocity is required to aerosolize the powder.

3.2.2.8 Charge dissipation

Engers et al. [62] compared two different possibilities of charge dissipation from powders after blending. He checked the effectiveness of equipment grounding and hold time after processing. Hold time means the time the powder is kept in the mixing container after stopping the mixing process, while in equipment grounding the blender shell is in continuous contact with a conductive grounding brush during rotation. It has been shown that hold time after processing was the most effective option of managing charge, while the use of 'grounding straps' during blending to dissipate charge were less effective. The big problem in charge dissipation of insulating powders by grounding the mixing vessel is that the surface conductivity of the powder is very low, so that praktically no charge conduction to the grounded vessel occurs and only a small amount of the powder is in physical contact with the surface of the vessel. The dissipation effect of hold time also depends on the conductivity of the powder and the container. This effect would be enhanced if the container is open and grounded.

3.3 Utilization of electrostatic charge

In most powder handling processes electrostatic charge is annoying because of its negative influences on various processes as mentioned above, but in some cases it can be beneficial. For example it can be used to improve the homogeneity of mixtures in a suspension and to produce homogeneous coating of coarse particles with fine-grained particles (ordered mixtures) in order to improve e.g. flow behavior [5,6,35,72,73]. This is possible, because the components of the mixture may be charged oppositely, leading to enhanced dispersion of like charged particles and to selective attraction of unlike charged particles in the mixture.

Particle charging can be performed either by tribo-charging or contact charging with an electrode [5]. Contact charging can also be performed in special charger devices such as the boxercharger used by Vercoulen et al. [74]. This device was developed by Prof. Senichi Masuda at Tokio University [75]. Detailed information about the boxercharger can be found in another work of Vercoulen et al. [76]. Tribo-charging has the advantages of higher efficiency in the sense that higher surface charge per particle can be reached and that it needs less experimental effort than contact charging. On the other hand it has the disadvantage that the polarity depends on the used materials and cannot be controlled [73]. Tribo-charge normally is generated by stirring the particles in a non conductive liquid using a high shear agitator. One possibility to prepare mixtures using tribo-charging is to stir the components separately and bring them together after charging. The other possibility is to stir them together where mixing and charging is performed at the same time. The advantage of separate charging is that the generation of the charge can be controlled easier but the process is more complicated and takes more time. If only one substance is treated electrostatic charge can also be used to stabilize dispersions. Depended on relevant process parameters like temperature of the liquid, surface charge density, the radius and the density of the particles stable dispersions can be generated. Werth conducted experimental and theoretical studies on the behavior of electrically charged nanoparticles suspended in liquid nitrogen. He summarized that it is possible to reach a stable cluster size in a dispersion containing charged nanoparticles.

Coagulation behavior of powders was also studied by Vercoulen et al. [77]. He presented a theoretical coagulation model for aerosols. However no comparison to practical data was done and therefore no qualitative statement can be given.

Another area of application in the pharmaceutical technology where the effect of oppositely charged particles can be used is the very new technique of dry powder coating of e.g. tablets [78–81]. The principle of this dry powder coating is that fine coating particles adhere at the surface of the substrate to be coated due to electrostatic forces. The coating film is then generated by increasing the temperature and melting the adhered particles in order to form a uniform film. The advantage of this technique is that the fine particles uniformly cover the substrate without the use of any solvent or water. Therefore the process gets cheaper and faster because less process steps are required and the evaporation of solvents is missing. In addition to this no problems or interactions between solvent or water and drug formulation can occur. Many different procedures and techniques can be used to perform dry powder coating, but as this topic is not within the main focus of this work it should not be discussed further. A related application to pharmaceutical dry powder coating can also be found in the car painting sector where charged paint particles are used to form a uniform paint film on the car body with out any liquid expedients [82].

The most important utilization with respect to the topic of this paper was mentioned by Telko et al. [83]. He suggested that the polarity and magnitude of the charge on DPI aerosols can be controlled by the choice of the lactose type, capsule material and inhaler device, which could be exploited for targeting different lung physiologies. He checked the influence of these factors by actuating the powder from a DPI to an ELPI (see section 3.7) to determine how the charge is distributed over the different particle size fractions. He came to the very interesting result that different lactose types (sieved or milled lactose) and different capsule sizes and materials lead to a totally different distribution of sign and magnitude of charge. Therefore he suggested that this effect could be utilized to influence the lung deposition of the powder. This would be a desirable improvement for the technique of powder inhalation, but there is still a long way to go, as far as not all influencing variables on the arising of charge and their interactions are completely investigated. Further more the influence of electrostatic charge, carried by aerosol particles, on the deposition behavior in the lung is not fully understood so far.

3.4 Net charge measurement

3.4.1 Static charge measurement

Interparticulate collisions as well as particle collisions with different surfaces lead to a net charge on a powder sample that may be electropositive, electronegative or even neutral and is often a complex bipolar system [84]. Net charge means the sum of electrostatic charges which is carried by a powder sample. The most common method to measure a charge on a powder is to transfer it to a known capacitor and to measure the voltage developed [85]. This may be done by pouring the charged powder into a Faraday pail.

A Faraday pail is a very simple construction which is used by many scientists for net charge measuring. The pail consists of two cups of conducting material e.g. metal which are placed into each other and separated from each other by an insulating material such as Teflon™. The outer cup (protection cup) is grounded and works as a shield to protect the inner cup (measuring cup) from external influences. When a charged powder is poured into the inner cup, its charge induces a charge of the same magnitude but opposite sign in the conducting material of the cup. The charge of the powder can be measured between the inner cup and the ground using an electrometer with known capacitor. Fig. 5 shows the model of a Faraday cup.

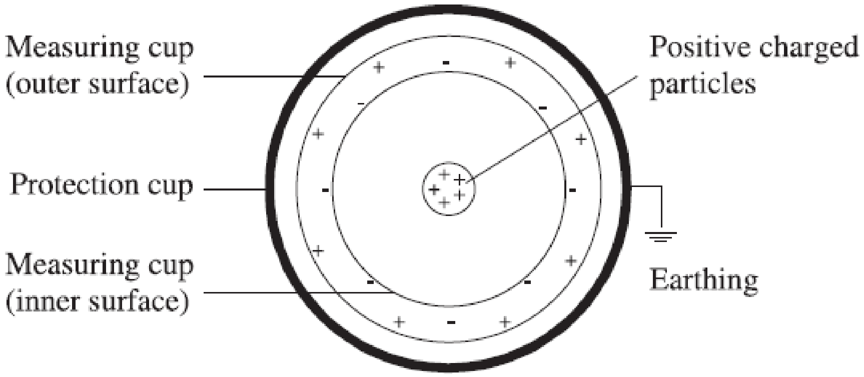

Figure 3.5: Faraday cup [5]

The Faraday cup is often used when charging caused by mixing has to be determined. In static charge measurement the powder is mixed externally in a blender and then poured into the faraday cup [48,62,63,65].The Faraday cup measurement system is a very sensitive device and therefore many factors have to be minded if correct and reproducible data have to be obtained. Before starting the experiment the powder samples should be stored in grounded conductive containers under controlled relative humidity for at least 48 hours in order to discharge the powder and to equilibrate it at a defined RH. When using an external mixer it is important that the mixing container is well cleaned before every experiment. Prior to each measurement the inner wall should be washed with deionized water, scrubbed, rinsed with pure ethanol and then blown dry using compressed air in order to ensure cleanness and charge removal Zhu et al. [63]. After cleaning, the mixing vessels should also be stored under the same conditions as the powder. When the mixing process is finished, the powder can be poured carefully into the measuring cup and after a few seconds a constant reading can be taken from the electrometer. If conductive mixing vessels are used it should be minded that the charge will dissipate when touching the vessel. Care must also be taken on the fact that the measurement system may be influenced by the electrostatic field of the body of persons being present close to it. One possibility to overcome this obstacle is to ground these persons by metal bracelets connected to earth. The whole procedure should be performed accurately but immediately after the charging event because charge will dissipate to the atmosphere.

The Faraday cup can also be used in other ways. One possibility to use the cup was invented by Murtomaa and Laine. He constructed a combination of the cup and an angular pipe, where the powder slides through the pipe into the Faraday cup. This construction was used to analyze the charging behaviour of the sliding powder [64]. This is a good technique to investigate tribo-charging of free flowing powders. As mentioned for the mixing containers, the pipe should also be cleaned well prior to each experiment.

Murtomaa didn’t clean the pipe between each measurement. Therefore he obtained different charge data for the first slide and the following ones due to adhered powder on the inner pipe surface. He found out that after a few slides without cleaning a saturated charge value is reached. He always performed sliding until saturation was reached and only then started data acquisition. This is a good technique to gain practically relevant data.

3.4.2 Dynamic charge measurement

A Faraday cup can also be used for dynamic charge measurements. It can be applied to investigate the charging of particles in a cyclone by putting the cup around the collecting vessel and performing real time data logging [38,39,45,66]. This technique provides good means to investigate the influence of contact material, surface contaminations and airflow rate on the charging process under realistic conditions. However, one thing has to be pointed out, namely that the strong electrostatic field of the cyclone must have an effect on the sensitive measurement in the Faraday cup. To perform undisturbed measurements the cup has to be sealed very well from external influences. Another problem is the adherence of the treated powder to the inner walls of the cyclone necessitating cleaning the inner walls if contact charging with the wall material is investigated. In order to obtain reproducible data it has to be ensured that the powder is discharged directly before entering the cyclone charger. This is also important if the charging behavior of the powder in contact with a defined material is of interest and the feed pipe to the cyclone is of a different material.

To perform dynamic measurements in mixing processes it is possible to put a glass cup in which mixing takes place directly into the inner measuring cup. Huber and Wirth [5] as well as Linsenbuehler and Wirth [72] used this experimental setup for measuring the charge of particles suspended and stirred in liquid nitrogen. Charge data is logged continuously as shown in Fig. 2. In this experimental setup only the charge arising from the contact between the powder and the earthed agitator is measured. This is because the powder inside the Faraday cup is neutral. If e.g. a powder is stirred inside the cup in liquid nitrogen in a glass container by an insulated agitator no charge will be measured because the whole system is neutral.

Further on, the Faraday cup can be modified to an open-end Faraday cup as shown in Fig. 6. The working principle of this cup is the same as in the normal one but it has two open ends, so that air can be sucked through. This modification is often used to measure charge carried by aerosols after the release from the inhaler. There are two operating possibilities of the open-end Faraday cup. The first one is to put the inhaler into the cup, suck the powder out of the inhaler and measure the left-behind charge on the inhaler [40]. This is possible because the charge left behind has the same magnitude but opposite polarity as the charge carried by the aerosol.

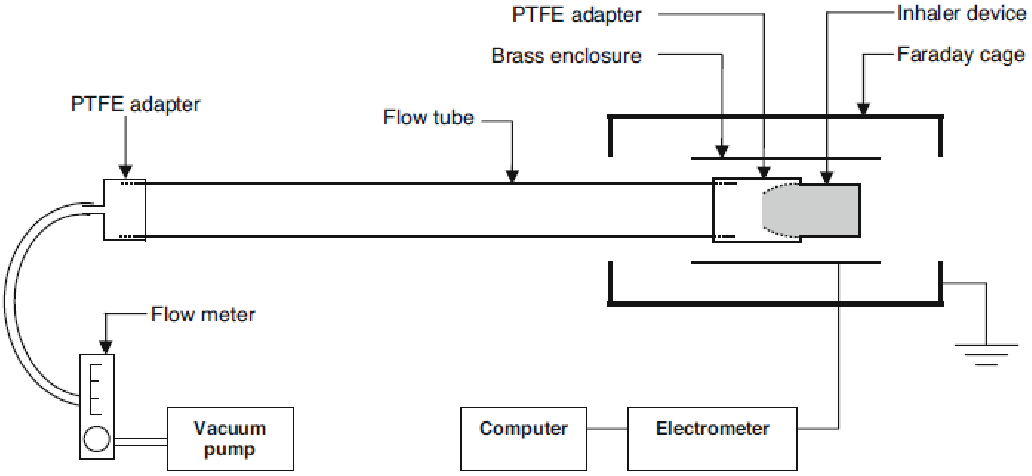

Figure 3.6: Open-end Faraday cup [40]

The second possibility is to situate the inhaler outside the cup, suck the aerosol through the cup, whereby the particles are caught in the cup by a filter, and charge is measured directly. Murtomaa et al. [8] used this technique to determine the emerging electrostatic charge of lactose of different particle morphologies and amorphous contents when actuated from two different dry powder inhalers. Also in the car painting industry open-end Faraday cups are used to measure the charge of paint particles.

Comparing the two operating possibilities of the open-end Faraday, the advantage of the first possibility is that no problems can occur due to very fine particles which do not get caught in the filter and are therefore not measured. Thus this measurement possibility might be a little bit more precise. On the other hand the second possibility might be easier to perform because no manipulations on the inhaler inside the measuring cup, which can result in disturbance of the measurement, have to be carried out.

For understanding in detail the charging of a particle collective, it is necessary to investigate the charge of single particles. Matsusyama therefore shot single particles against an insulated target plate and measured the left-behind charge on the plate [26]. Similar single impact studies were also carried out by several other scientists [31–33,71,86–92].

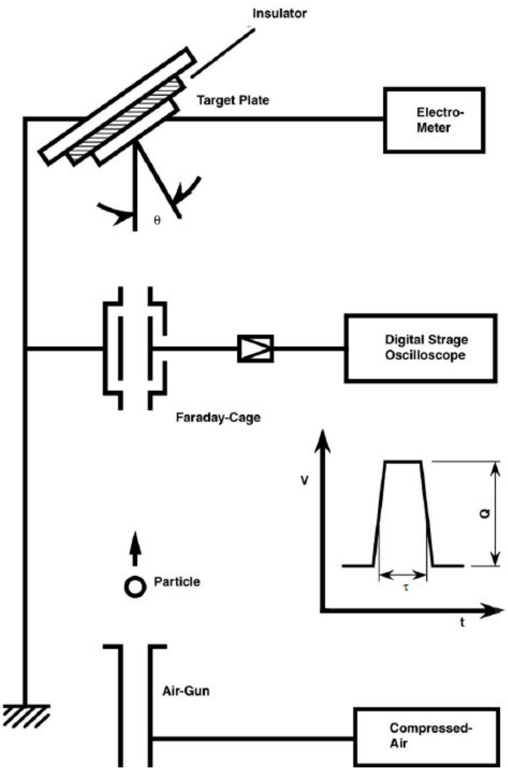

Figure 3.7: Schematic illustration of the single impact experimental set-up [26]

The charging process of particle collectives e.g. in a mixer results often in a very complex and bipolar system because the particles get in contact with each other, with the agitator and the mixing vessel. For these reasons the single impact studies are very important in order to understand the underlying mechanisms of triboelectrification in particle impacts in a very controlled environment. The measuring set-up for these experiments can be very simple as shown in Fig. 7 In this experimental set-up it is possible to control the contact area due to particle deformation and the contact separation process by controlling impact velocity and angle. By measuring the charge carried by the particles before impact the effect of initial charge can be studied. This is interesting because the amount of initial charge strongly influences the quantity of charge that is transferred during the impact (see also section 3.2.2.7).

3.5 Charge distribution measurement

As mentioned in section 3.4.1 tribo-charging may cause a complex bipolar system, so it might be of interest to measure a charge distribution. One simple possibility was introduced by Vercoulen et al. [93]. The method he used is based on the work of Gajewski and Szaynok [94] and Gajewski [95]. The working principle of the device invented by Vercoulen is that a charge is induced in a conducting ring when a charged particle moves through it and is further explained by Vercoulen [96]. He used a measuring ring electrode which was surrounded by a grounded copper tube and placed inside a grounded metal box to minimize the noise generated by external disturbance. When an aerosol moves through the electrode the induced charge can be measured. By plotting the number of the single charge peaks over the magnitude of the charge a kind of charge distribution can be constructed, which is illustrated in figure 3.8. Here it should be remarked that when this set-up is used it has to be ensured that just single particles cross the measuring zone in order to prevent superposition of signals. Anyway it is a simple method to measure charge on particles without any contact and therefore without destroying the particles.

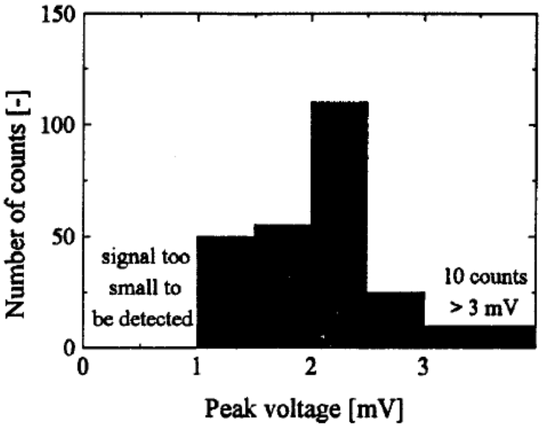

Figure 3.8: Number of charge peaks over their magnitude [96]

To improve the reliability of this technique it is possible to use more than one ring electrode. This was reported by Rossner [97] who measured particle concentrations. He used three rings in a row and correlated the signals. This is a good possibility to enhance the reliability of the results since each particle is measured three times and the signal can be correlated or the measurement value can be evaluated by its standard deviation. In previous studies Vercoulen et al. [98,99] also used two electrodes. However they utilized them in a different way. He mounted them in a defined distance to each other to determine the particle velocity for investigations of the contact energy. This is a common and proved way to determine velocities in every field of technical engineering.

A similar procedure for aerosol charge measurements was used by Murtomaa et al [100]. He measured the charge carried by particles after the release from a dry powder inhaler. His measurement system consisted of three conducting grids through which the charged aerosol passed. The grids were mounted parallel to each other whereby the outer grids were earthed to protect the inner measuring grid from external influences. In the same way as in the work of Vercoulen [96] a charge is induced in the inner grid when charged particles pass through it. This signal is detected by an electrometer and logged on a PC at 2 ms intervals. Thus it is possible to gain a charge distribution over time. However using this technique provides no charge distribution over particle number, size or mass. Thus the received information is not very convincing or useful for the pharmaceutical engineering. But it can be used to determine whether the drug and the additives are released separately or together which has important consequences on a proper function of the inhaler device and the therapeutic effect. Care must be taken when analyzing the measurement signals because signal disturbances may arise due to particle impacts and particles adhered to the grids.

3.6 Investigation of the lung deposition of the powder

The deposition of particles in the lung should be mentioned in this work because it is strongly related to electrostatic charge carried by the particles. Improved particle deposition, due to electrical charge, was first suggested by Wilson [101]. Since then, the impact of particle-charge on the deposition of particles within the respiratory system has been studied theoretically in physical lung models by Yu [102] and Hashish [103], experimentally in animals by Longley [104], Fraser [105], Ferin et al. [106], Vincent [107] and in man by Melandri et al. [108,109], Prodi and Mullerony [110]. The animal studies showed that charge carried by inhaled particles enhances the retention of the particles in the lung considerably. Also clinical measurements on human volunteers confirmed that the deposition of particles can be significantly increased by charging the particles.

In addition to this Bailey [111] pointed out that charge on an aerosol particle may affect its behaviour in three ways: (1) it will be deflected by an electric field; (2) coagulation and interaction with other particles is altered; (3) particles are attracted to neutral surfaces by image forces. Since negligible electric fields exist within the air spaces of the respiratory system, which will act as a Faraday cage, the first consideration does not apply. The second factor may be important for dense aerosols. The third factor is significant when charged particles are close to the walls of the airways which is the case in the deeper regions of the lung.

Bailey [111] suggested a mathematical model of the human lung for the deposition of charged particles together with complementary clinical studies. It was demonstrated that electrical charge is important for the deposition when particles with a diameter of about 1 μm are considered. This is because electrostatic forces have a stronger impact on particles with low mass due to a high force to mass ratio.

An additional study of the same author also deals with the enhancement of particle deposition within the respiratory system and selectively targeting of certain regions of the lung. This is possible because a certain amount of charge will cause a deposition in a predefined region of the lung. Bailey et al. [112] assessed that the charge level can be increased by a corona or induction charging to levels where a significant increase in the deposition of inhaled particles occurs. This could be utilized to control the drug delivery or to enhance the trapping of pollutant particles in the upper airways [112]. However other parameters such as breathing flow rate, breath-holding pause and particle size also strongly influence this procedure. So the combination of all these factors has to be controlled to effectively control the lung deposition.

Another computer model to simulate the lung deposition was introduced by Balachandran et al. [113]. His model takes into account gravitational sedimentation, Brownian diffusion, inertial impaction and electrostatic forces (space charge and image charge force). In his experiments deposition efficiencies were defined as the number of particles deposited in a section of a tube divided by the number of particles entering the section. The total deposition efficiency in each generation of the respiratory tract was calculated as the sum of the five deposition efficiencies mentioned above. The mathematical expressions used for the calculation of the different deposition efficiencies were taken from literature [114–120]. In agreement with Bailey he concluded that the particle deposition in the lung can be controlled by the charge carried by the particles. He determined particles of a diameter smaller than 2,5 μm to be influenced by electrostatic charge with respect to lung deposition. Actually the limiting factor to influence the deposition of particles is not the diameter but the magnitude of charge carried and the charge to mass ratio, respectively. So the main questions of substance are which amount of charge can be generated in an inhalation device and how can it be influenced and controlled. These issues are not fully understood until now and have to be further investigated.

To perform in vitro studies of lung deposition several impactor or impinger devices can be used. The basic working principle of these devices is that the aerosol is sucked through the device whereby the particles impact/impinge on different stages according to their aerodynamic diameter. After accomplishing the experiment the whole delivered dose and the fine particle fraction, which is able to enter the deeper regions of the lung, can be determined. The most commonly used devices are the Next Generation Impactor (NGI), the Anderson Cascade Impactor (ACI), the Twin Stage Impinger (TSI) and the Multistage Liquid Impinger (MSLI). To properly simulate a human breath the total amount of air sucked through the impinger should be 4 l [121]. The air flow rate is defined by a pressure drop of 4 kPa over the inhaler device.

3.7 Simultaneous measuring of charge and mass/size distribution on pharmaceutical powders

As Carter et al. [84] and Telko et al. [83] assessed, charge separation may occur between different size factions, i. e. different size fractions may carry charges of different magnitude and when mixtures of two components are used also a different sign of charge may occur. This is because different size fractions may have different mixing ratios of the components. For this reason it might be of interest to examine how the charge is distributed over particle size or mass of a powder. Therefore different devices and measurement principles to measure a charge distribution have been developed.

One possibility is to provide an optical image analysis and a mapping of charge distribution using an electrostatic probe [122]. Carter et al. modified the stage of a metallurgical microscope and designed an apparatus in which the samples under investigation are placed on a rotating polished stainless steel table and scanned with a capacitive electrostatic microprobe. Capacitive probes have been shown earlier to be very useful for identifying charge distribution in planar polymers [123] and particulate systems [124]. In Carters device a video camera was used to display the image and further analysis was performed with the VIDS V software. Superimposition of the optical profile with the 2-D charge contour map was realized. In addition, Mathematica provided a means of producing a 3-D charge distribution map of the charged particles. So briefly speaking an electrostatic probe and a video camera is incrementally moved over a powder and afterwards both recordings are combined leading to a charge distribution over the considered particles. However no charge distribution over particle size can be obtained.

Another important device for charge measurement and for relating the electrostatic charge to the aerodynamic diameter of powder particles is the Electrical Low Pressure Impactor (ELPI) which is schematically illustrated in figure 3.9. The ELPI is built up of several impaction stages with different cut off diameters similar to the Anderson Cascade Impactor. The difference is that every stage is connected to an electrometer to measure the electrical charge distribution over the aerodynamic particle size and the temporal trend of the deposited charge on the stages. An additional ability of the ELPI is to charge particles in a preceding corona charge if desired.

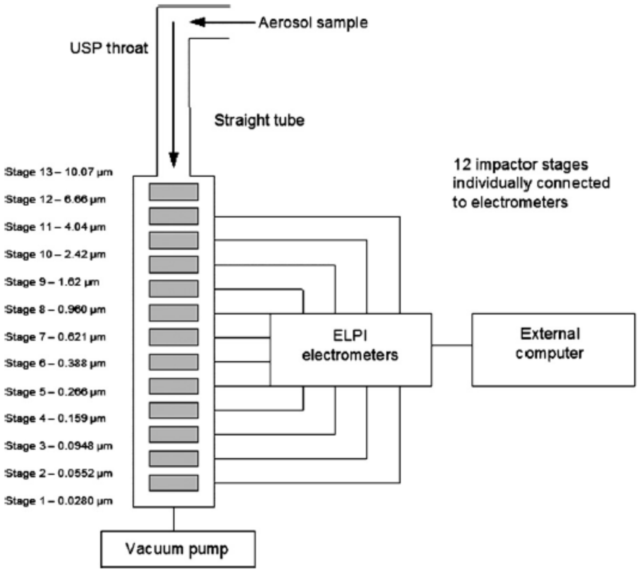

Figure 3.9: Schematic diagram of an ELPI [67]

Kwok used the ELPI in many different studies to investigate the effect of different inhaler devices [125], spacers [126] and moisture [127] [67] on the electrostatic charge properties of metered dose inhaler (MDI) aerosols. In his work dating from 2005 he showed that different MDI inhaler devices can lead to a completely different charge distribution over the particle size fraction. For example the Intal® and Tilade® aerosol showed positive charge on the fine fractions and a shift to negative charge on the coarser fractions whilst the Ventolin® aerosol became charged in the opposite way. This is because different active pharmaceutical ingredients are used in the MDIs.

Kwok et al. [126] investigated the influence of a spacer on the charge carried by aerosols after release from a MDI. Therefore he mounted a spacer between the MDI and the ELPI and noticed a significant alteration of the charge due to interaction between the aerosol and the spacer. This is obvious and could be utilized to generate a defined charged aerosol in order to influence lung deposition.

It has already been noted in this work, that moisture alters the charging behavior of DPIs. The same applies to MDIs as shown by Kwok et al. [67]. Even though the altering effect is different it should not be further discussed in this paper.

As the ELPI is not regularly used in pharmaceutical aerosol work Telko et al. [83] performed a comparison between an ELPI and an ACI to validate the results obtained with the ELPI. When an ELPI is used there are two major obstacles to overcome. The first one is that the ELPI operates at 30 L/min whereas inhalers typically are tested at various air flow rates ranging between 30 L/min and 60 L/min. The second one is that the ELPI has no pre-separator to remove larger particle agglomerates. Telko designed a device where the DPI is connected to the mouthpiece and standard USP induction port, which is connected to the ACI pre-separator. After the pre-separator the 60 L/min airstream is divided into two tubes connected to an ELPI and an ACI, each connected to a vacuum pump operated at 30 L/min. Thus it was possible to test both devices under equal conditions. He came to the conclusion that the result from both units are in good correlation with each other. He further pointed out that one major advantage of the ELPI is its ability to provide temporal deposition data across the stages. This data could be used to check inhaler devices, formulation emission and deposition behavior from a temporal perspective.

A further evaluation of the ELPI was done by Marjamäki et al. [128]. They compared the charge distribution of an aerosol obtained from the ELPI with the results from a SMPS (Scanning Mobility Particle Sizer, TSI Inc.) and found out that they are in good agreement. The measurement principle of the SMPS utilizes the electrical mobility of a charged particle in an electrical field. Also the charging efficiency of the corona charger was checked and it was found out that it showed good conformity with the manufacturer's specifications for particles less than 2 µm in diameter but the performance was lower than the specification for lager particles because of the high material loss in the charger [128].

Glover and Chan [129] applied the ELPI to characterize the charging properties of MDI aerosols. Figure 3.10 shows the results of these studies which are typical outcomes of an ELPI or eNGI. The eNGI is also a device to measure charge distributions over particle size and will be discussed later. The numbers in Fig 10 correspond to the different stages of the ELPI. However it is not clearly explained why different size faction (=stages) carried charge of opposite sign. As long as only one powder material is treated no change in the sign is possible. Maybe there were some interactions with the propellant that resulted in this phenomenon.

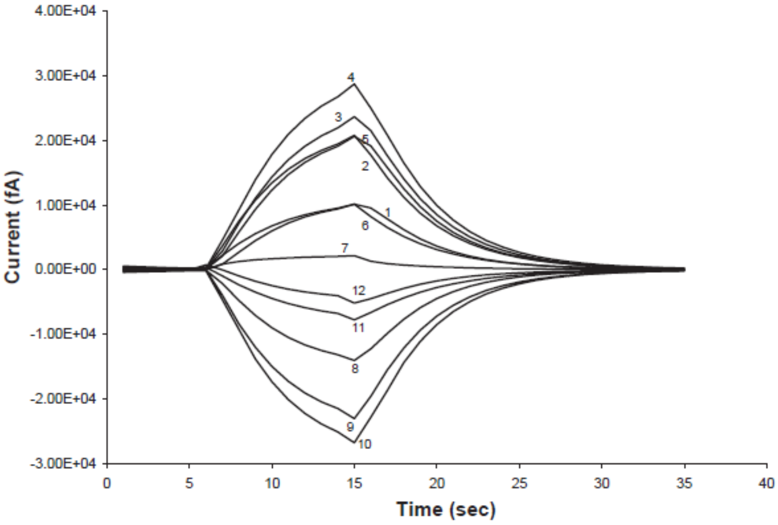

Figure 3.10: Charge profile of a typical actuation from a MDI [129]

In addition to the ELPI the electrical Next Generation Impactor (eNGI) is another possibility to simultaneously perform charge and mass distribution measurements. This device is a modification of the normal NGI. Hoe et al. [130] evaluated the performance of the eNGI with reference to particle size distribution measurements with the NGI and with reference to charge distribution measurements with the ELPI. The results from eNGI showed good correlation with the output of the two other devices if commercial drug-only DPI products were considered. Carrier based formulations were not investigated. Furthermore, the eNGI has been demonstrated as an apparatus capable of the measurement at a range of flow rates, which is relevant for DPI formulations since different DPIs should be checked at different air flow rates. The NGI apparatus already has a pre-separator unit for the fractioning of particle agglomerates and coarse carrier particles from multi component formulations. With modification of this pre-separator, the eNGI could also be used to study carrier-drug formulations in the future [130].

Another modified measurement device was introduced by Zhu et al. [68]. They utilized a modified Twin Stage Impinger to perform simultaneous charge and aerodynamic diameter distribution measurements. They mounted two electrodes, which were connected to an electrometer, under each stage of the impinger. When charged particles deposited on the stages they induced the same magnitude of charge at these electrodes. This device was evaluated in comparison to a faraday cage system and showed good agreement. Further the modification of the TSI did not seem to affect the particle deposition [68].

3.8 Conclusion

It has been shown that electrostatic charge on pharmaceutical powders can be a nuisance or even, if well understood and controlled, a good instrument to manipulate the characteristics of a powder. This review illustrates that nowadays there are many possibilities and techniques to investigate this phenomenon. As it can be seen in this work, sometimes simple modifications on existing techniques or devices can lead to new and precious information. Thus many important data concerning different powder handling processes have been provided. However there is still a lot of work to do, to improve the understanding of the often complex charging behavior of powders and its influencing factors. For the future it would be preferable to get a better insight into this new and interesting field of research in order to minimize its negative aspects and optimally utilize its positive means of application.

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4

Factors affecting tribo-charging during mixing

The aim of this work is to improve the understanding of how triboelectric charge arises on pharmaceutical powders and of how it can be influenced and controlled especially with respect to dry powder inhaler development. In the present work the triboelectric properties of mannitol are examined because very few literature treating this new alternative carrier material for dry powder inhalers is available. To study the very complex triboelectric charging process in a simple and controlled way mixing studies are carried out. The powder samples are blended in polypropylene and stainless steel mixing containers for defined durations using a tumble blender (T2F Turbula®, Willy A. Bachofen AG - Maschinenfabrik, Switzerland) and then poured into a Faraday cup where charge measurement is performed. Several influencing factors like mixing time, particle size, mixing container size and the addition of a fines fraction to the powder are studied. In contrast to other published literature the present work focuses on the new alternative carrier material mannitol and uses statistical tools like design of experiments (DOE) to check the significance of the influence of factors and also the interactions between the influencing factors. The study reveals a direct relationship between the arising charge and the container size as well as the fines fraction and an indirect relationship between the arising charge and the particle size. Further also three different charge dissipation scenarios are investigated. It is shown that charge dissipation to the atmosphere is negligible within on hour. Keeping the powder inside the mixing container allowing charge dissipation via the container walls is more effective. Additional grounding of the mixing container does not result in a significant enhancement of the dissipation process. This is because charge transport from the powder bulk to the mixing container walls is limited.

4.1 Introduction

Drug delivery to the lungs via Dry Powder Inhalers (DPIs) has become more and more important in the last decades. In order to be deposited in the deeper lung, it is essential that the drug particles of DPIs have an aerodynamic diameter between 0.5 µm and 5 µm [1]. Unfortunately such fine powders are very cohesive resulting in poor flowability and dosing behavior. One possibility to improve these properties is to mix the small drug particles with larger carrier particles. These carrier particles are usually made of lactose or glucose and have a particle size between 50 µm and 200 µm. An alternative carrier material which is still under investigation is mannitol [2]. Mixing, flowability, dosage uniformity as well as the very important drug detachment of the active from the carrier surface of ordered mixtures upon inhalation are governed by the interparticle interaction between drug and carrier which mainly arises through Van der Waals and electrostatic forces. This may result in various problems with respect to mixing homogeneity, dosing and lung deposition. Nevertheless charging of particles may also be exploited to enhance mixing uniformity of powder blends or may be advantageously used for dry powder coating of tablets for example [3,4]. In addition to this the triboelectric charge carried by aerosolized powders may influence the release of the formulation from the inhaler and the deposition behavior of the particles in the throat and lung [5]. Telko et al. mentioned that a controlled electrostatic charge on inhalation powders could be exploited for targeting different lung physiologies.

Electrostatic charge is generated when two different materials are brought into contact and then separated [6]. Since drug as well as carrier particles consist of insulating material, they are unable to dissipate and therefore accumulate charge in any process where the powder comes into contact with surfaces. In which way sign and magnitude of the charge is influenced is still poorly understood and therefore difficult to predict. This problem gets even more complex when two or more materials and more than one varying influencing factor is involved. Especially the arising of charge in metal / insulator contact and insulator / insulator contact is very complex [7]. Unfortunately particularly this case appears in many pharmaceutical processes and also in DPI-technology. Different models to describe charge generation and accumulation like the ion transfer model [8], the surface state model (electron transfer model) of Castle and Schein [9] and the two step model (electron transfer model) of Yu and Watson [7] have been presented. Further Diaz and Felix-Navarro [10] presented a semi-quantitative triboelectric series to estimate how different materials will charge when they are brought into contact. Nevertheless only a small number of scientists published literature dealing with electrostatic charge on pharmaceutical powders until now.

As mentioned above the sign and magnitude of the arising charge depend on many factors such as particle size and shape [11], surface roughness [12,13], nature and work functions [14], impurities [15–17], amorphicity [18], contact material [19], relative humidity [20] and the energy of contact [21,22]. A summary of these influences can be found at Karner and Urbanetz [23].

The best way to get reproducible basic data concerning the complex arising of electrostatic charge is to focus on a simple and controlled process. Maybe the most important and common powder handling process in pharmaceutical industry is mixing. Therefore the present work focuses on the arising of triboelectric charge in the powder mixing process and the factors impacting charge acquisition of mannitol as carrier for DPI´s.

Naturally, mixing studies have been performed before by other scientists like Elajnaf et al. [19], Engers et al. [24,25] and Zhu et al. [26]. Elajnaf et al. [19] laid their attention on the dependence of the electrostatic charge on different mixing container materials and blends of different APIs and α-lactose monohydrate. They further tested the influence of relative humidity.

Engers et al. [24] first measured the arising netcharge in a tumble-blender for different size fractions of dicalcium phosphate dihydrate. Then they checked the efficacy of hold time after mixing and equipment grounding for charge dissipation using different grades and size fractions of microcrystalline cellulose and binary mixtures of API and excipient. Engers et al. [25] tried to correlate the triboelectric charging data of mixtures of different APIs with their dielectric properties.

Zhu et al. [26] measured the arising netcharge in stainless steel containers mounted on a tumble blender and a horizontally oscillating blender for adipic acid, glycine and MCC as a function of the mixing time. They further checked the influence of the particle size fraction, the mixing speed and the relative humidity.

Beside the above mentioned investigations on mixing there is more literature available concerning the electrostatic charging behavior of pharmaceutical powders when subjected to other unit operations. But these shall not be mentioned here because this work focuses on the mixing process.

It has to be pointed out that most of the above mentioned publications just focused on the influencing factors one by one and in doing so neglect that there might be interactions among them. For this reason the present paper utilizes statistical tools like design of experiments (DOE) in order to check the significance of the factors and interactions of more than one factor.

Since triboelectric studies dealing with lactose have already been carried out in the past by Carter et al. [11], Eilbeck et al. [15,16], Murtomaa and Laine, [27], Rowley, [28], Murtomaa et al. [18], Murtomaa et al. [29,30], Elajnaf et al. [19], Telko et al. [5] and Chow et al. [31] and not much literature regarding the electrostatic properties of mannitol is available the focus of the present work lies on the charging behavior of this alternative carrier material. The authors are aware that there is also literature available dealing with the electrostatic properties of mannitol [32,33]. Therefore the focus of this work was laid on other factors and investigation principles.

In this study three important factors are chosen to be analyzed using statistical design of experiments (DOE), first the particle size as it had shown to have a strong impact on the arising of charge in other materials in previous studies [26,28]. As the second factor the size of the mixing container is chosen because the area of the inner surface of the container and also the filler loading might influence the charge exchanged between the powder and the vessel. The third influencing factor is the amount of mannitol fines (the percentage of a 0 µm – 40 µm mannitol fraction) in a blend with coarser mannitol particles. This is relevant for the DPI technology because it is a common practice to add carrier fines to a DPI formulation in order to increase the respirable fraction [34]. Further also detailed studies on the influence of the mixing time and the particle size are performed. All measurements are carried out in polypropylene and stainless steel mixing containers using a tumble blender (T2F Turbula®, Willy A. Bachofen AG - Maschinenfabrik, Switzerland). In addition to the charging experiments also charge dissipation of charged powders in stainless steel containers are checked. Three scenarios are tested. Charge dissipation to the atmosphere is checked by leaving the charged powder in the faraday cup. Charge backflow to the mixing container is tested by leaving the powder in the mixing container after blending. And further the possibility to enhance this charge backflow by grounding the mixing containers is checked.

Although mannitol is an alternative to lactose in this paper just the properties of mannitol are investigated and no quantitative comparisons between mannitol and lactose are carried out. This is because comparisons between substances are difficult due to probable differences of other influencing factors like particle roughness, particle shape and amorphicity of both substances as well as the relative humidity of the surrounding environment beside the factors under investigation. For the same reasons also no quantitative comparisons to results reported in literature dealing with mannitol are undertaken. Only slight divergences in the particle properties or measurement principles can generate big differences in the results since the electrostatic charging process is extremely sensitive to a multitude of factors.

4.2 Materials and Methods

4.2.1 Materials

Crystalline mannitol was donated by Roquette Frères (160C, Roquette Frères, Lestrem, France). As mixing containers 60 ml and 125 ml polypropylene jars are used. The 60 ml jar has an internal diameter of approximately 38 mm and an inner height of 53 mm. The 125 ml jar has an internal diameter of approximately 50 mm and an inner height of 64 mm. Further also stainless steel containers are used. Unfortunately they were not available in the same size as the polypropylene containers. Consequently the difference in size was balanced by adjusting the sample size for the stainless steel containers. Containers with a volume of 25 ml (inner diameter: 31 mm; inner height: 33 mm) and 75 ml (inner diameter: 49 mm; inner height: 40 mm) are used.

For conditioning, the powder samples are stored inside a climate box (see section 4.2.2). The constant relative humidity inside this box is generated using saturated salt solution of potassium carbonate (43 % at room temperature; [35]).

4.2.2 Sample preparation

Mannitol is size fractionated by sieving. It is mechanically sieved into size fractions of 0 µm – 40 µm, 40 µm – 63 µm, 63 µm-80 µm, 80 µm-100 µm, 100 µm-125 µm, 125 µm-160 µm using a sieve shaker (Analysette®, Fritsch, Germany).

In order to gain correct and reproducible experimental results it is of main importance that the powder samples are electrically discharged and equilibrated at a defined and constant relative humidity before performing the experiments. This is carried out by storing the powder samples in thin layers in earthed metal containers inside a climate box (proprietary construction) at constant relative humidity for at least 72 hours. Sample size was set to 10 g for the polypropylene containers and 5 g for the stainless steel containers.

Discharging the insulating polypropylene mixing containers is difficult but important for correct measurement results. Therefore the containers are rinsed with deionized water first and then with ethanol to remove charges from their surface. After drying they are also stored open inside the climate box on an earthed metal plate for 72 hours. Even though the charge transport on the surface of the polypropylene is very slow this should remove the residual charge from the containers. After this procedure the containers are only handled extreme carefully wearing insulating gloves and just as much as necessary. Prior control measurements to approve the correctness of this procedure revealed that the maximum residual charge in the mixing container that is taken up by the powder is lower than 0.5 nC (See also section 4.2.3). This is first of all lower than every measured effect and in addition to this every sample (measurement cycle) will carry approximately the same error charge. So the arising error is systematic and is therefore irrelevant since only effects and not the exact charge magnitude is of interest.

For the electrical conducting stainless steel containers the discharging procedure is much easier. They are also rinsed with deionized water and ethanol, dried and subsequently placed on the earthed metal plate inside the climate box. To prevent interactions with the operator and charge dissipation through the conducting container walls, the outer container wall is coated with electrically insulating material.

4.2.3 Charge measurements

Charge measurement is performed using a Faraday cup (proprietary construction) connected to a high resistance electrometer (Keithley 6517 B, Keithley Instruments, USA). The cup consists of two cups of stainless steel which are placed into each other and separated from each other by a thick-walled jar made of Teflon™. The outer cup (protection cup) is grounded and works as a shield to protect the inner cup (measuring cup) from external influences. When a charged powder is poured into the inner cup, its charge induces a charge with the same magnitude but opposite sign in the conducting material of the cup. Thus the charge of the powder can be calculated by measuring the voltage between the inner cup and the ground using an electrometer with known capacitor. Figure 4.1 shows an illustration of the used Faraday cup.

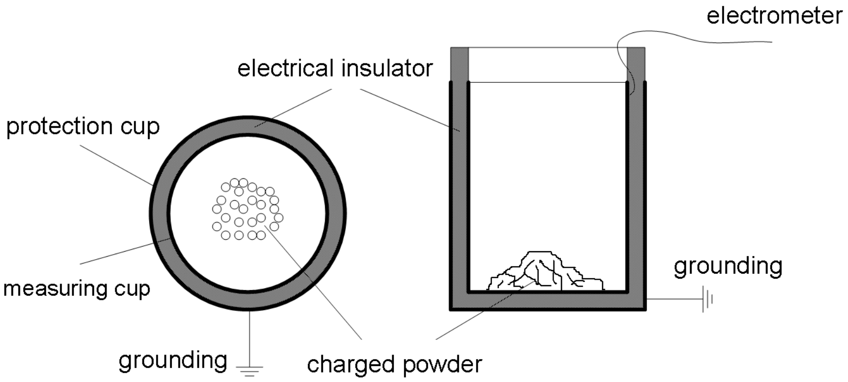


Figure 4.1: Illustration of the Faraday cup

Prior to each measurement the powder samples are conditioned as described above. After conditioning the samples are filled into the polypropylene mixing containers and closed airtight. Afterwards the containers are taken out of the climate box, mounted on a tumble blender (T2F Turbula®, Willy A. Bachofen AG - Maschinenfabrik, Switzerland) and blended for a defined duration with 60 rpm. Subsequent to mixing the samples are taken back into the climate box where charge measurement is performed. The samples in the stainless steel containers are treated in the same way with one difference. It is not necessary to transfer the samples from the storage containers to the mixing containers. The samples are directly stored in the stainless steel mixing containers during conditioning. Before and after charge measuring the inner Faraday cup is weighed to calculate the powder mass poured into the cup and the mass-specific netcharge carried by the powder.

As mentioned under section 4.2.2 the error that is caused by residual charge on the polypropylene mixing containers was investigated in prior studies. These were performed by treating the samples in the same way as in the effective experiment except blending. That means the discharged powder was filled into the mixing containers. Then they were closed, taken out of the climate box, taken back into the box and then the powder charge was measured. The results of this prior experiment are not shown in this work but concluding they revealed that the arising error charge on the powder through this procedure is firstly lower than 0.5 nC and secondly systematic. Therefore this influence is neglected in the following investigations.

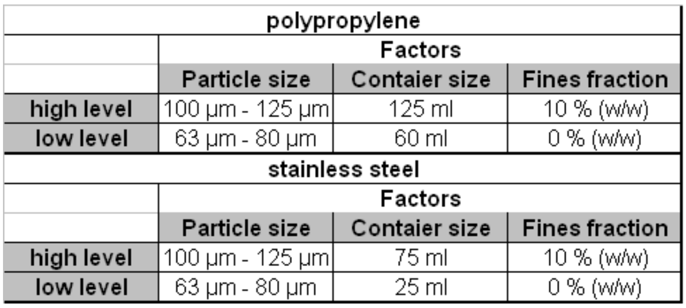
4.2.3.1 Mixing time dependent specific netcharge measurements

It is important to understand the arising of charge over mixing time for the determination of the mixing duration after which charge saturation is reached. These experiments are performed because this information is the prerequisite for the following investigations where charge saturation is desired. The study of the dependence of the netcharge on the mixing time is carried out by blending the samples for predetermined periods of time followed by the charge measurement. The investigated intervals are 5 min, 10 min, 20 min and 30 min. For these time dependence studies the size fractions 63 µm - 80 µm and 100 µm - 125 µm are chosen. These two size fractions are chosen because they appear in adequate quantity in the raw material. Further the particle size difference of the fraction seems to be big enough to result in a different charging behavior. Tumbling speed is set to 60 rpm. The 125 ml polypropylene and 75 ml stainless steel mixing vessels are used and every data point is reproduced in triplicate.

4.2.3.2 Statistical design of experiments (DOE)

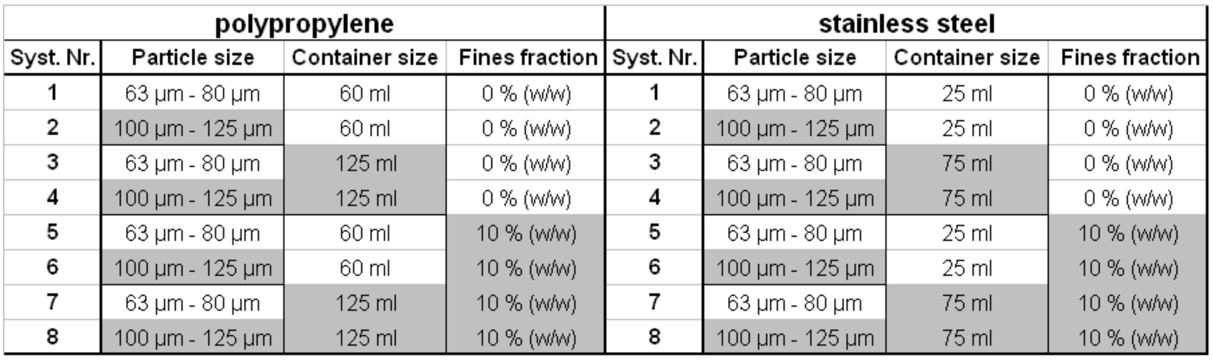
To investigate the significance of influences and interactions of more than one factors statistical design of experiments (DOE) is used. Three influencing factors on two levels are checked. As mentioned in the introduction the factors studied are the particle size, the mixing container size and the presence and amount of fines in a blend with coarser mannitol particles. For every factor a high and low level are defined. These levels are 63 µm-80 µm and 100 µm-125 µm fractions for the particle size. Container size levels are defined with 60 ml and 125 ml for polypropylene and 25 ml and 75 ml for stainless steel. For the exact dimensions see section 4.2.1. Amount of fines means, that a defined percentage of a fraction between 0 µm – 40 µm is added to the fractions 63 µm – 80 µm and 100 µm -125 µm. The two levels for the fines fraction are set to 0 % (w/w) and 10 % (w/w) in order to be practice-oriented [34]. Table 4.1 summarizes the factors and levels. Further table 4.2 shows the combinations of factors and levels for the experiment. These combinations are executed randomized and repeated twice. The analysis of the DOE results is conducted using statistical software (Statistica 8, Statsoft®, USA). Analysis are performed using ANOVA-test including 2-way interactions on a significance level of 95%.

Table 4.1: Factors and levels of the statistical design of experiments (DOE)



polypropylene			
	Factors		
	Particle size	Contaier size	Fines fraction
high level	100 µm - 125 µm	125 ml	10 % (w/w)
low level	63 µm - 80 µm	60 ml	0 % (w/w)
stainless steel			
	Factors		
	Particle size	Contaier size	Fines fraction
high level	100 µm - 125 µm	75 ml	10 % (w/w)
low level	63 µm - 80 µm	25 ml	0 % (w/w)

Table 4.2: Experimental design with all factors and levels



polypropylene				stainless steel			
Syst. Nr.	Particle size	Container size	Fines fraction	Syst. Nr.	Particle size	Container size	Fines fraction
1	63 µm - 80 µm	60 ml	0 % (w/w)	1	63 µm - 80 µm	25 ml	0 % (w/w)
2	100 µm - 125 µm	60 ml	0 % (w/w)	2	100 µm - 125 µm	25 ml	0 % (w/w)
3	63 µm - 80 µm	125 ml	0 % (w/w)	3	63 µm - 80 µm	75 ml	0 % (w/w)
4	100 µm - 125 µm	125 ml	0 % (w/w)	4	100 µm - 125 µm	75 ml	0 % (w/w)
5	63 µm - 80 µm	60 ml	10 % (w/w)	5	63 µm - 80 µm	25 ml	10 % (w/w)
6	100 µm - 125 µm	60 ml	10 % (w/w)	6	100 µm - 125 µm	25 ml	10 % (w/w)
7	63 µm - 80 µm	125 ml	10 % (w/w)	7	63 µm - 80 µm	75 ml	10 % (w/w)
8	100 µm - 125 µm	125 ml	10 % (w/w)	8	100 µm - 125 µm	75 ml	10 % (w/w)

Other factors that are kept constant through out all experiments are the relative humidity at 43% RH, the mixing speed at 60 rpm, mixing time at 20 min (see section 4.3.1), sample size with 10 g for polypropylene containers and 5 g for stainless steel containers. This is essential to generate reproducible experimental data.

4.2.3.3 Detailed investigation of the influence of the particle size

To further investigate the impact of the particle size on the specific netcharge all size fractions 0 µm - 40µm, 63 µm-80 µm, 80 µm-100 µm and 100 µm-125 µm are treated. Charging (mixing) was carried out in the 125 ml polypropylene and 75 ml stainless steel containers. The other constant factors are the same as described under section 4.2.3.2.

4.2.3.4 Charge dissipation studies

In this section three different charge dissipation scenarios are checked regarding to their efficacy. Firstly the dissipation to the surrounding atmosphere is investigated. This is performed by pouring the powder into the completely shielded faraday cup, leaving it there for one hour and measuring the charge after this time. Inside the faraday cup the only possibility for the charge to dissipate is to the atmosphere. Secondly charge dissipation by charge backflow to the mixing container is verified. This is realized by leaving the powder inside the mixing container for one hour and putting the container on an insulating plate. Last but not least the possibility to enhance the charge backflow to the mixing container by putting the container on a grounded metal plate is checked. Prior to this one hour discharge procedure the powder samples are charge by tumbling them for 20 minutes in the 75 ml stainless steel containers at 60 rpm. The whole procedure is performed for 5 g and 10 g samples of the 63 µm – 80 µm size fraction of the mannitol powder.

4.3 Experimental results and discussion

4.3.1 Dependence of the specific netcharge on the mixing time

As already mentioned, preliminary studies on the dependence of the specific netcharge on the mixing time and the particle size are carried out in order to prove that charge saturation occurs and to find out how long it takes until charging comes to an end and saturation is reached.

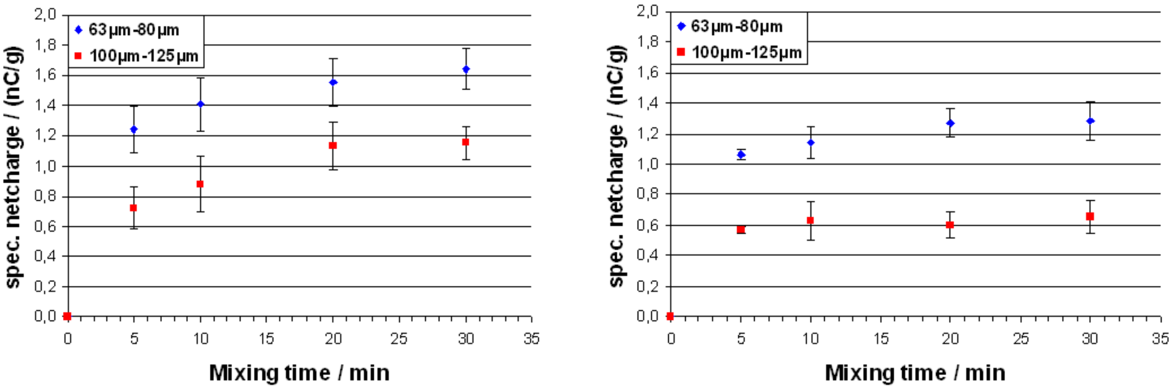


Figure 4.2: Dependence of the specific netcharge on the mixing time; 63 µm – 80 µm and 100 µm – 125 µm size fraction, 5 g samples mixed in 75 ml stainless steel containers (left) and 10 g samples mixed in 125 ml polypropylene containers (right); (mean and 95 % CI of n=3)

This charge saturation occurs because no further charge exchange between the contacting bodies takes place. This happens when the driving force of charge exchange, the surface potential difference between the contacting bodies, is equalized by the charge acquired by the particle surface or the inner container wall, respectively. For detailed discussion see also section 4.3.2.

In figure 4.2 it can be seen that the magnitude of the saturation netcharge acquired by the 63 µm – 80 µm fraction is significantly higher than that arising on the 100 µm – 125 µm fraction. This applies for samples treated in stainless steel as well as polypropylene containers. The effect will be further investigated and explained in the following sections. Further it can be seen that both fractions reach a higher netcharge in the stainless steel containers than in the polypropylene containers. This is because of the different surface workfunctions of the container materials and thus a different potential difference between the contacting bodies. Further also the ratio of sample mass to mixing container volume is slightly lower in the stainless steel container. This is also a possible explanation for the higher arising netcharge. For further discussions on the influence of the mixing container size see section 4.3.2.

To further analyze the time profile of the arising charge the data points (mean values) shown in figure 4.2 were fitted to a mathematic function. Using these function the asymptotic charge maxima (infinite mixing time) and the characteristic mixing times until 50 % and 90 % of the asymptotic maximum is reached were calculated. Table 4.3 displays the equations and results of these considerations.

Table 4.3: Mathematic curve fit of the dependence of the specific netcharge on the mixing time; 63 µm – 80 µm and 100 µm – 125 µm size fractions mixed in 75 ml stainless steel containers and 125 ml polypropylene containers

	stainless steel		**polypropylene**	
	63µm-80µm	**100µm-125µm**	**63µm-80µm**	**100µm-125µm**
equation	Q=a-b*c^t	Q=a-b*c^t	Q=a*(1-exp(-b*x))	Q=a*(1-b^t)
a	1,57636	1,15102	1,25183	0,63029
b	1,57164	1,14089	0,35346	0,63051
c	0,75088	0,84166	-	-
R^2	0,99315	0,99136	0,9935	0,99519
asymptotic maximum	1,576 nC/g	1,151 nC/g	1,252 nC/g	0,63 nC/g
t_{50}	2 min 26 s	3 min 58 s	1 min 58 s	1 min 34 s
t_{90}	8 min 2 s	13 min 19 s	6 min 34 s	4 min 59 s

It can be concluded that saturation is reached faster in the polypropylene containers. Comparing the two size fractions no statement to their dynamic charging behavior can be made. In the case of the stainless steel mixing containers the 100 µm – 125 µm fraction requires more time to reach 90 % of the asymptotic maximum than the 63 µm – 80 µm fraction, whereas in the polypropylene mixing containers the 100 µm – 125 µm fraction shows a t_{90} of just approximately five minutes. Such a fast arising of charge was also observed by Zhu et al. [26] who performed mixing studies with other substances than mannitol. However it can be summarized that there is no significant increase in the magnitude of the netcharge (experimental data) between 10 minutes and 20 minutes. This is true for both fractions and both container materials. This was also proved by the mathematical curve fit considerations Therefore for all following experiments the mixing time was fixed at 20 minutes.

4.3.2 Statistical design of experiments (DOE)

Out of the coefficient of determination and the mean square residuals (polypropylene: R^2 = 0.97188; MSresidual = 0.007722 and stainless steel: R^2 = 0.95945; MSresidual = 0.012425) it can be seen that the model fits the data points satisfying. This is also proofed in figure 4.4 and figure 4.6 where the observed vs. predicted values of the statistical model are illustrated.

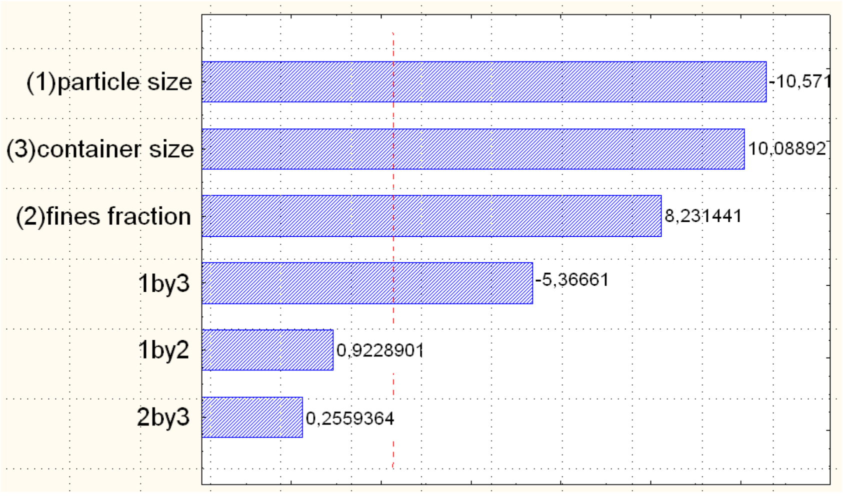


Figure 4.3: Effect-plot of the DOE studies in polypropylene mixing containers with significance limit p=0.05 (dotted line)

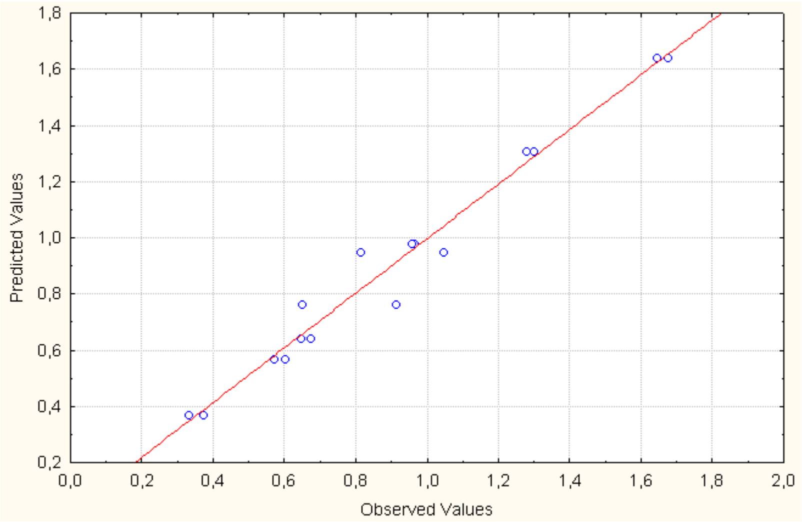
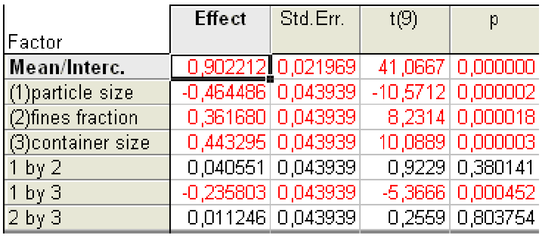


Figure 4.4: Observed vs. predicted values of the statistical model of the DOE for polypropylene mixing containers

Table 4.4: Statistical data and effect estimates of the DOE studies in polypropylene mixing containers (coefficient of determination $R^2 = 0.97188$; mean square residual = 0.007722)



Factor	Effect	Std.Err.	t(9)	p
Mean/Interc.	0,902212	0,021969	41,0667	0,000000
(1)particle size	-0,464486	0,043939	-10,5712	0,000002
(2)fines fraction	0,361680	0,043939	8,2314	0,000018
(3)container size	0,443295	0,043939	10,0889	0,000003
1 by 2	0,040551	0,043939	0,9229	0,380141
1 by 3	-0,235803	0,043939	-5,3666	0,000452
2 by 3	0,011246	0,043939	0,2559	0,803754

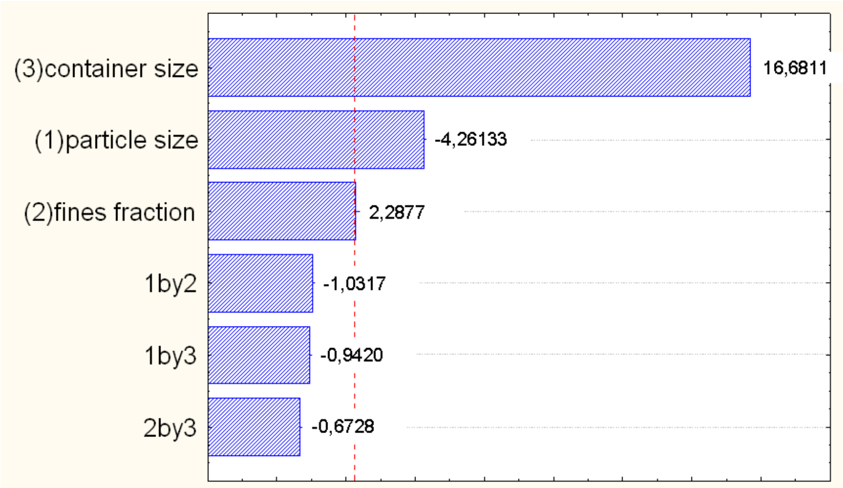


Figure 4.5: Effect-plot of the DOE studies in stainless steel mixing containers with significance limit p=0.05 (red line)

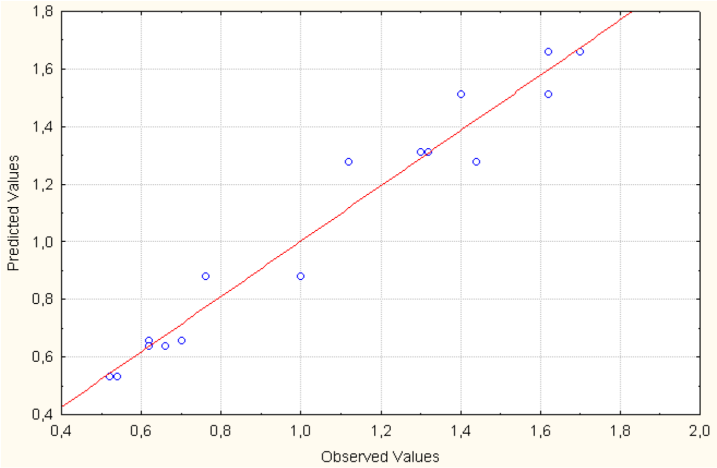
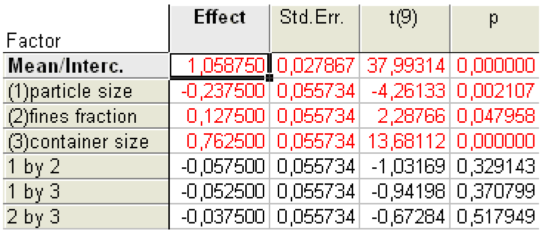


Figure 4.6: Observed vs. predicted values of the statistical model of the DOE for stainless steel mixing containers

Table 4.5: Statistical data and effect estimates of the DOE studies in stainless steel mixing containers (coefficient of determination $R^2 = 0.95945$; mean square residual = 0.012425)



Factor	Effect	Std.Err.	t(9)	p
Mean/Interc.	1,058750	0,027867	37,99314	0,000000
(1)particle size	-0,237500	0,055734	-4,26133	0,002107
(2)fines fraction	0,127500	0,055734	2,28766	0,047958
(3)container size	0,762500	0,055734	13,68112	0,000000
1 by 2	-0,057500	0,055734	-1,03169	0,329143
1 by 3	-0,052500	0,055734	-0,94198	0,370799
2 by 3	-0,037500	0,055734	-0,67284	0,517949

The DOE-studies reveal a significant impact of the particle size, the container size and the addition of a 0 µm – 40 µm fraction (fines fraction) to the 63 µm – 80 µm and the 100 µm – 125 µm powder fraction in the mixing process for both mixing container materials. In addition to this an interaction between the particle size and the container size is detected in the polypropylene mixing containers. The statistical parameters and the corresponding effect-plots are presented in table 4.4, table 4.5, figure 4.3 and figure 4.5. The reasons for the interaction will be discussed later. First the arising effects shall be discussed. The netcharge shows an indirect relationship to the particle size and a direct relationship to the container size and the addition of 10% (w/w) 0 µm – 40 µm fraction to the 63 µm – 80 µm and 100 µm – 125 µm fractions. In order to understand this phenomenon, it has to be explained how and why charging occurs. First of all it has to be pointed out that the charging process in insulator-insulator contacts and metal-insulator contacts is not yet understood completely. However in a very simplified way it works as shown in figure 4.7.

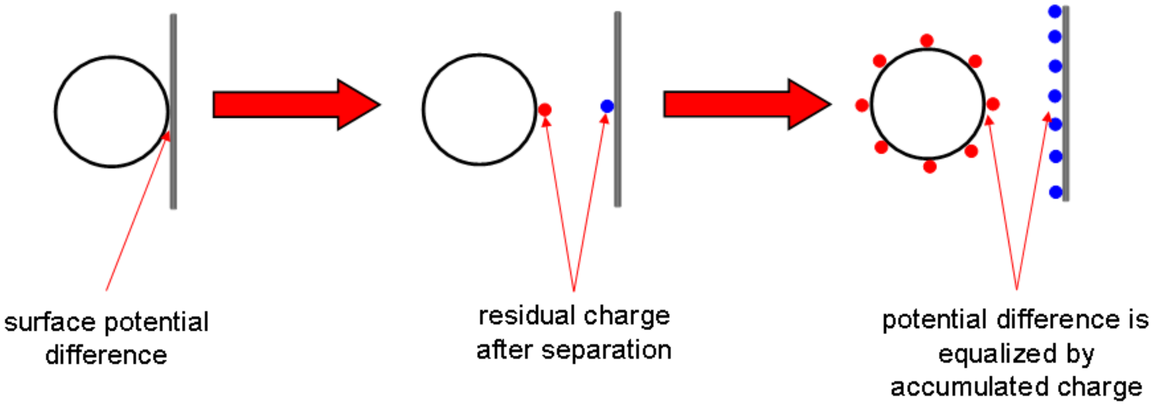


Figure 4.7: Simplified illustration of the arising and accumulation of electrostatic charge between particle and container wall

When the particle contacts the container wall, a potential difference arises because of the different surface workfunctions of the materials. This potential difference is reduced by charge exchange between the contacting bodies in order to approach thermodynamic equilibrium. When the contacting bodies are separated fast enough the charge backflow is hindered and both bodies keep a residual charge of opposite sign. This contact and separation occurs many times in the mixing process until the number of the charges acquired is such that the potential difference diminishes. This is the point when charge saturation is reached. Therefore saturation depends on the surface area of the powder as well as on the inner surface area of the container wall.

As mentioned above the netcharge shows an indirect relationship to the particle size meaning that the arising netcharge gets higher the lower the particle size is. This effect is mainly attributed to the larger specific surface area and thus the larger absolute surface area of the 63 µm - 80 µm fraction compared to the 100 µm – 125 µm fraction. This leads to the ability of the 63 µm – 80 µm fraction to take up more charges until saturation of the powder surface is reached and therefore to a higher saturation charge.

Further the netcharge indicates a direct relationship to the size of the used mixing container. The netcharge increases with the size of the mixing vessel. This effect can be explained by the larger surface area of the inner container wall of the larger container leading to the fact that the container is able to take up more charge from or to give more charge to the powder until the surface potential of the contacting bodies is equalized.

The addition of 10 % (w/w) of the 0 µm – 40 µm fraction to the 63 µm – 80 µm and 100 µm – 125 µm fractions also leads to an increase of the netcharge in comparison to the pure 63 µm – 80 µm and 100 µm – 125 µm fractions. The strong increase in the netcharge suggests that the 0 µm – 40 µm particles adhered to the 63 µm – 80 µm and 100 µm – 125 µm particles lead to an enhancement of the surface roughness of the coarse particles and an enlargement of the specific surface of the entire powder.

The interaction between the particle size and the size of the polypropylene containers is illustrated in the 3D-plot in figure 4.8. The term "interaction" in this context means, that the effect of one factor, namely the particle size, depends on the level of another factor, in the present case the container size. The interaction is indicated by the curved non-linear area boundaries, which are illustrated through different color codes, of the magnitude of the netcharge in figure 4.8.

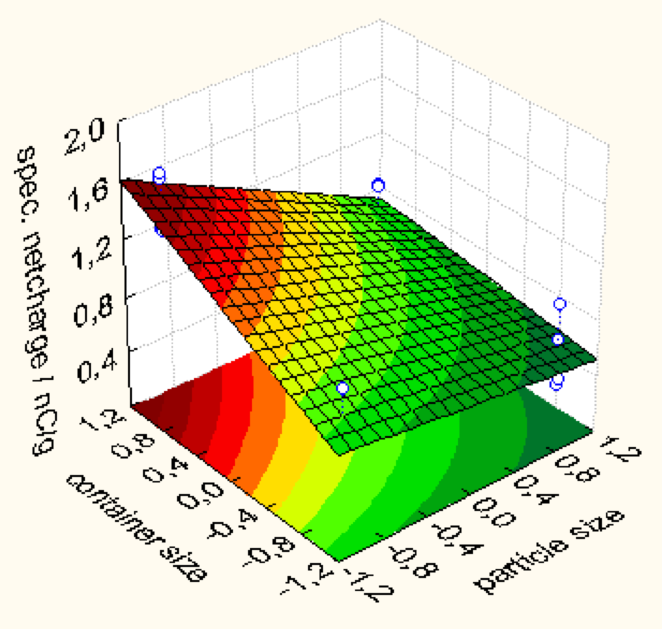


Figure 4.8: Specific netcharge plotted versus polypropylene container size and particle size (results out of DOE-studies; the scaling with -1.2 and 1.2 indicates the low and high level of each factor)

In fact the interaction appears in the way that the increase of the specific netcharge, when changing from 60 ml vessels to 125 ml vessels, was much stronger for the 63 µm – 80 µm fraction than for the 100 µm – 125 µm fraction. Or vice versa the difference in the arising charge between 63 µm – 80 µm powder and 100 µm – 125 µm powder was much greater in the 125 ml vessel than in the 60 ml vessel. Table 4.6 captures this interaction quantitatively.

Table 4.6: Specific net charge for 63 µm -80 µm fraction and 100 µm – 125 µm fraction in the 60 ml and 125 ml polypropylene mixing containers

	60 ml	125 ml	ΔQ
63 µm – 80 µm	0.66 nC/g	1.29 nC/g	0.63 nC/g
100 µm – 125 µm	0.35 nC/g	0.58 nC/g	0.24 nC/g

As discussed above there are two limitations for the arising saturation netcharge. These are the surface area of the powder and the surface area of the inner container wall.

The fact that the netcharge increases when changing from small to large mixing containers suggests that the netcharge acquired by the powder is restricted by the limited surface area of the small container. However if this is the one and only limitation, both fractions, the 63 µm – 80 µm fraction and the 100 µm – 125 µm fraction, should show the same electrostatic charge magnitude irrespective of the particle size and equal to the maximum charge the container is able to release or take up. However this is not the case. That means in this case both important areas have an influence on the arising charge in an interactive way. The higher number of charges the bigger container is able to release or take up is stronger accepted by the 63 µm – 80 µm fraction and its larger surface area.

4.3.3 Detailed investigation of the influence of the particle size

Since the particle size is one of the most important factors and also easily controllable an extended investigation of its effect on the arising netcharge was carried out. The results are illustrated in figure 4.9. It can be seen that the magnitude of charge increases as expected when particle size decreases.

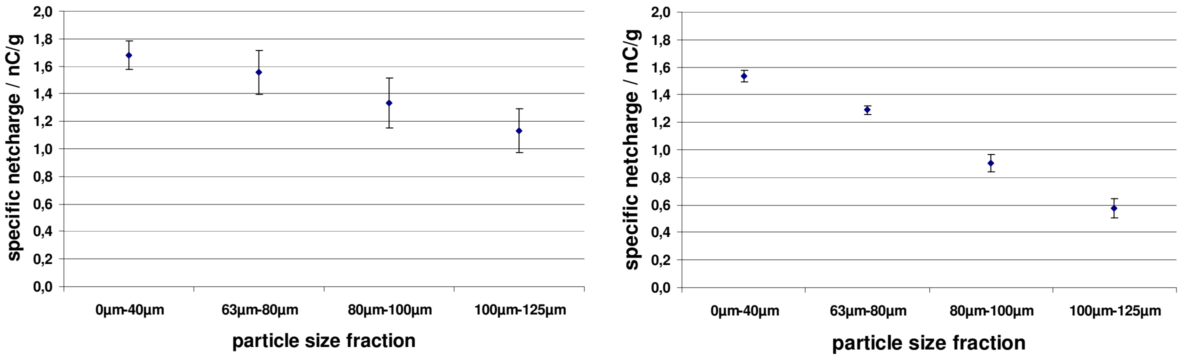


Figure 4.9: Specific netcharge arising on different particle size fractions, 5 g samples mixed in 75 ml stainless steel (left) and 10 g samples mixed in 125 ml polypropylene (right) mixing containers (mean and 95 % CI of n=3)

The explanation for this is the higher specific surface of the finer fractions. However the arising netcharge is not only influenced by powder properties like the specific surface of the powder but also by other factors like interaction between the particles and between the particles and the mixing container. This can be seen when comparing the netcharge arising on the pure 0 µm – 40 µm fraction with the charge arising on the mixture of a 63 µm – 80 µm fraction with only 10 % (w/w) of 0 µm – 40 µm fraction that is used in the DOE studies. The mixtures reached an equal or even higher netcharge magnitude after tumble blending although the pure 0 µm – 40 µm fraction has a larger specific surface area. This can be explained by the fact that the pure 0 µm – 40 µm fraction was observed to form agglomerates and to adhere to the inner container surface thus reducing the possibilty of particle – wall contacts. That means that only considering particle properties and neglecting particle interactions may be misleading when investigating the impact on triboelectric charge.

4.3.4 Charge dissipation studies

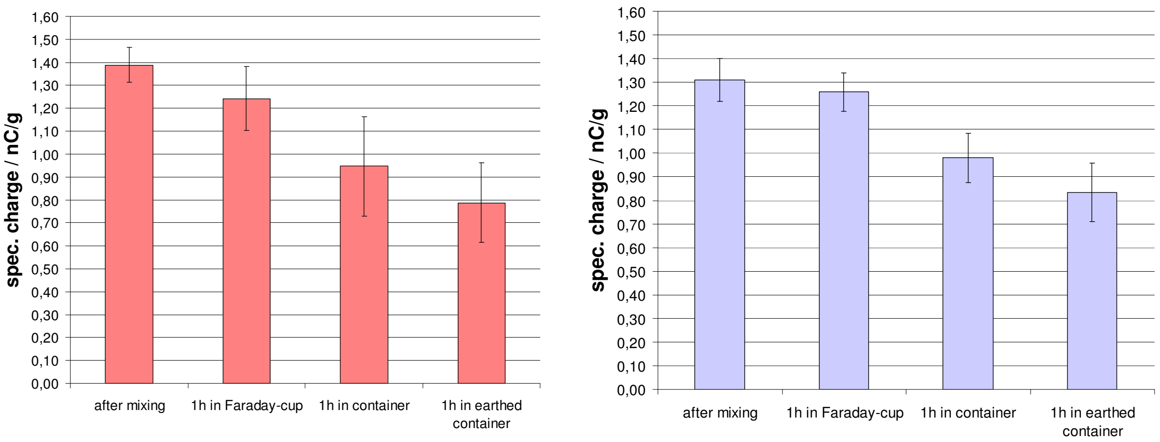


Figure 4.10: Specific netcharge on the 5 g (left) and 10 g (right) samples directly after mixing and after the charge dissipation treatments for one hour (mean and 95 % CI of n=3) performed in 75 ml stainless steel mixing containers

Studies on the charge decay were performed after mixing samples of 5 g and 10 g of the 63 µm – 80 µm size fraction of the mannitol powder in stainless steel containers. Figure 4.10 shows that no significant charge dissipation occurs within one hour when the powder is left in a Faraday-cup. This is because in this experimental setup charge may not be dissipated by contact with the walls of the Faraday-cup but only by contact with the surrounding gas atmosphere. For this discharge method more discharge time would be necessary. In contrast leaving the powder in the mixing container for one hour results in a significant reduction of the netcharge. Grounding the mixing containers does not result in a significant additional reduction of the netcharge. Therefore it can be concluded that charge transport from the inner of the insulating powder bulk by surface conduction is the limitation for charge dissipation. That means that grounding the mixing container is no option to enhance the discharge process of insulating powders, especially when larger amounts of powder are used. The only possibility to improve this process would be to insert grounded electrodes directly into the powder bulk, which means grounding the particles themselves. This should result in a charge reduction since the electrostatic charge on the powder is removed from the particle surface without the need of any charge transport trough the insulating powder. Another option is to enlarge the contact area between powder and grounded electrode by spreading the powder in thin layers on a grounded metal plate. However this is not suitable in practice for larger amounts of powder.

4.4 Conclusion

It is shown that the magnitude of triboelectric charge accumulating on powders in the mixing process can be targeted by controlling the influencing factors. First it is demonstrated that charge saturation occurs in the mixing process.

Further on statistical DOE studies are carried out to investigate the influence and interactions of three factors. It is figured out that particle size, mixing container size and the presence and amount of fine particles (0 µm – 40 µm) present in blends with coarser particle fractions have a significant influence on the charging process. An indirect relationship between netcharge and particle size and a direct relationship between netcharge and container size and the amount of fines is detected. In addition to these significant effects, an interaction between the particle size and the container size is found in the studies using polypropylene mixing containers.

Detailed studies of a wider range of particle sizes prove that the magnitude of the charge increases continuously when decreasing the particle size. Nevertheless, it is also shown that not only the particle size or the specific surface, respectively of the powder but also other powder properties like agglomeration and affinity of the powder to stick to the container walls may influence the charging process, when coming down to very fine particle sizes.

Discharge studies show that different charge dissipation scenarios can result in strongly different residual charge magnitudes after one hour discharge time. Further it is observed that grounding the mixing container does not significantly enhance the discharge process because of the limitation of the charge transport out of the powder bulk.

All in all it was possible to generate important data to get an idea how the tribo-charging process can be partly controlled. Anyway there is still a long way to go to improve the understanding of this important phenomenon. For the future it would be desirable to understand the triboelectrification in a way that it is possible to design drugs, manufacturing processes and inhaler devices that generate no or controllable charging.

4.5 References

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5

Impact of carrier surface roughness on tribo-charging during mixing and mixing homogeneity

For active pharmaceutical ingredients (API) delivered to the lung it is of main importance that they reach the deeper lung, in order to cause the intended therapeutic effect. To obtain inhalable powders that on the one hand are small enough to travel along the tiny airways finally reaching their target site and on the other hand show sufficient flowability, so-called adhesive mixtures are used. They consist of API particles in the size range of 0.5 µm - 5 µm and carrier particles in the size range of 50 µm - 200 µm, that, due to the size of the carrier, exhibit adequate flowability. However, when administered to the patient, the API has to separate from the carrier surface in order to be able to penetrate the deep lung. The performance of dry powder inhalers (DPIs) and adhesive mixtures are mainly governed by interparticle forces like Van der Waals and triboelectric forces. Carrier surface roughness modification is a new method to alter the contact area and thus the Van der Waals forces between API and carrier. Unfortunately the tribo-charging during handling, especially during the generation of the adhesive mixtures in a tumble blender, is strongly influenced by particle characteristics like particle surface roughness. Thus the mixing quality and stability and thereby the usability of the powder mixture might be additionally influenced by tribo-charging. Therefore the aim of the present work is to investigate whether tribo-charging during the mixing process is influenced by the carrier particle surface roughness. Further the influence of tribo-charging on mixing homogeneity is assessed. Netcharge measurements are performed using a faraday cup. As model API and carrier salbutamol sulphate and spray dried mannitol, respectively are used. It is shown that the carrier particle characteristics impact tribo-charging of the pure carriers in a tumble blender. This influence is not observed for the adhesive mixtures of carrier and API. Nevertheless the homogeneity of the adhesive mixtures is still influenced by the charging of the carriers.

5.1 Introduction

For active pharmaceutical ingredients (API) delivered to the lung it is of main importance that they reach the deeper lung, in order to cause the intended therapeutic effect. In order to penetrate the deeper lung, it is essential that the API particles of dry powder inhalers (DPI) have an aerodynamic diameter between 0.5 µm and 5 µm [1]. Unfortunately such fine powders are very cohesive resulting in poor flowability and dosing since the dosing in DPIs is performed by letting the powder flow from a reservoir into well defined orifices. One possibility to improve the flow properties is to mix the small API particles with larger carrier particles to get so-called adhesive mixtures. The carrier particles are made of e.g. lactose, glucose or mannitol and have to have an adequate size (50 µm - 200 µm) to ensure good flowability of the mixtures. The performance of these mixtures depends on the inter-particle forces between the drug and the carrier that on the one hand must be strong enough to ensure mixing homogeneity and stability of the mixtures during powder handling and dosing, but on the other hand weak enough to allow the detachment of the API particles from the carriers during inhalation in order to ensure lung penetration.

Interactions between particles are mainly governed by inter-particle forces like Van der Waals and triboelectric forces. Van der Waals forces in turn depend on the contact area between the API and carrier particles. One approach to alter this contact area is to modify the carrier particles with respect to surface roughness. From literature it can be taken that the surface roughness of mannitol carrier particles may be modified by spray drying at different drying conditions e.g. different air outlet temperatures and spraying flowrates [2].

However controlling triboelectric forces is difficult and complex. Triboelectric charge is generated when two different materials get into contact and then separate [3]. When they get into contact a potential difference arises between them due to different surface workfunctions of the materials. This potential difference is equalized by charge exchange between the two surfaces. When separation occurs the potential difference is eliminated and the exchanged charges try to flow back. However separation normally occurs fast and charge backflow is hindered by a weak electrical conductivity. Therefore both contacting bodies keep a residual charge after separation. Since drug as well as carrier particles consist of insulating material, they are unable to dissipate and therefore accumulate charge after each contact in any process where the powder comes in contact with other particles or surfaces. In which way sign and magnitude of the charge is influenced is still poorly understood and therefore difficult to predict. This problem gets even more complex when two or more materials and more than one influencing factors are involved. Especially tribo-charging in metal / insulator contact and insulator / insulator contact is very complex [4]. Unfortunately particularly this case appears in many pharmaceutical processes and also in DPI-technology.

The adhesive mixtures used in DPIs are usually produced by tumble blending. To gain a high mixing homogeneity and stable mixtures it is very important that the API particles make close contact with the carrier particles and are able to attach at their surface. Long mixing durations are used and intended to generate homogenous mixtures. However, the longer electrically insulating powders are tumbled the higher the number of particle-particle and particle-wall contacts will be. In this process step interparticle forces like tribo-electric forces may strongly govern the API attachment and thereby the mixing homogeneity. Further also the adhesion forces between the API and the carrier remaining after charge dissipation (mainly Van der Waals force) and thereby the stability of the mixtures is influenced by the charge that has been present during mixing. This is because higher tribo-charge during mixing can lead to stronger adhesion between the particles, closer contact between them and thereby stronger remaining forces after charge dissipation. Depending on magnitude and polarity, tribo-charge may result in weak or strong, attractive or repulsive forces between API and carrier during mixing. Unfortunately tribo-charging of powder and powder blends is pretty hard to predict since there are many impacting factors.

Sign and magnitude of the arising charge depends on for example particle size and shape [5], surface roughness [6,7], nature and work functions [8], impurities [9–11], amorphicity [12], contact material [13,14], relative humidity [15] and the energy of contact [16,17]. A summary of these factors and how they impact tribo-charging can be found at Karner and Urbanetz [18]. Considering these factors it can be seen that by altering the contact area between API and carrier by modification of carrier properties like surface roughness and thereby specific surface area also the triboelectric charging behavior of the powder might be influenced.

For this reason the aim of the present work is to study the triboelectric charging of surface modified spray dried mannitol carrier powders (Littringer et al. [2]). The tribo-charge arising during the tumble blending process on pure carriers and also adhesive mixtures with the API salbutamol sulphate is investigated. Further the influence of the arising tribo-charge on the mixing homogeneity is examined. In addition to mixing studies also the flowability and dosing behavior of the modified carriers are analyzed by measuring the uniformity of the released mass from a common DPI device (Novolizer®).

5.2 Materials and Methods

5.2.1 Materials

Two mannitol samples of different surface roughness were prepared on a pilot-scale co-current spray dryer with a diameter of 2.7 m and an overall height of 3.7 m (proprietary construction, Prof. Walzel, Department of Biochemical- and Chemical Engineering, TU Dortmund, Germany). A rotary atomizer was used for spray generation and was operated at 8100 rpm. The set-up of the spray dryer and the generation of particles of different surface roughness are described in detail by Littringer et al. [2]. Briefly samples of different surface roughness were prepared from aqueous mannitol solutions (15 % [w/w]). Drying conditions are given in Table 5.1.

Table 5.1: Drying conditions

	Gas-Heater temperature [°C]	Outlettemperature [°C]	Flow rate [l/h]
smooth	170	81	10
rough	170	71	20

As active pharmaceutical ingredient (API) micronized salbutamol sulphate (USP25 quality) was used. Salbutamol sulphate was purchased from Selectchemie AG (Selectchemie AG, Switzerland) and micronized using an air jet mill (Alpine 50 AS, Hosokawa, Germany). The injection pressure was 6.0 bar and the milling pressure was 2.0 bar. A feed rate of 1 g/min was used. The particle size distribution of the API was analyzed using laser diffraction (HELOS/KR, Sympatec GmbH, Germany). A dispersion pressure of 4 bar was applied. After milling the API showed the characteristic diameters $x_{10,3}$ = 0.46 µm, $x_{50,3}$ = 1.69 µm, $x_{90,3}$ = 5,65 µm.

As mixing containers closable stainless steel vessels with a volume of 75 ml were used. They had an inner diameter of 49 mm and inner height of 40 mm.

For conditioning, the powder samples were stored inside a climate box (see section 5.2.2). The constant relative humidity inside this box was generated using a saturated salt solution of potassium carbonate (43 % at room temperature; [19]).

5.2.2 Sample preparation

A 63 µm – 125 µm size fraction of both mannitol carrier types was obtained by mechanical sieving using a sieve shaker (Analysette®, Fritsch, Germany).

Sample size for the mixing experiments (pure carriers and adhesive mixtures) was set to 5 g. For the preparation of the adhesive mixtures the micronized salbutamol sulphate was first passed through a 250 µm sieve to remove large agglomerates. After this procedure mannitol and salbutamol sulphate were weighed into stainless steel containers using the sandwich methode. The ratio of API and carrier was 1/40.

To gain accurate and reproducible experimental results it is of main importance that the powder samples are electrically discharged and equilibrated at a defined and constant relative humidity before performing the experiments. This was carried out by storing the powder samples in thin layers in earthed stainless steel containers inside a climate box (proprietary construction) at constant relative humidity for at least 72 hours. These stainless steel containers that were used as mixing containers later on, were previously rinsed with deionized water and ethanol and dried using oil-free compressed air.

5.2.3 Carrier particle characterization

At the beginning the particle size distribution (PSD) of the size fractionated powder was checked to ensure that the yield fraction is between 63 µm and 125 µm. The particle size distribution was determined using laser diffraction in the dry state (Helos with Rodos dry dispersing unit, Sympatec GmbH, Clausthal- Zellerfeld, Germany). A dispersion pressure of 1 bar was applied.

To evaluate the roughness of the two powder samples the particles were examined using a scanning electron microscope (SEM) (Zeiss Ultra 55, Zeiss, Oberkochen, Germany) operating at 5 kV.

Specific surface area was measured via nitrogen gas adsorption (ASAP 2000, Micromeritics GmbH, US). Samples were degassed for at least 24 h at 30 °C prior to analysis. Surface area was calculated according to the Brunauer–Emmet–Teller equation from 8 relative pressure values ranging from 0.05 to 0.30 of the desorption line.

Bulk and tapped density measurements were performed according to the European Pharmacopoeia (bulk density and tapped density of powder, Ph. Eur. 7.0) using method 1.

The density of each powder was determined by Helium pycnometry (Accu-PycII1340, Micromeritics, Germany). Powder samples were dried in an oven for 1.5 h at 95 °C and then cooled down to room temperature in a desiccator filled with silica gel prior to the measurements.

To ensure that the carrier particles do not break during sieving and mixing strength tests were performed. Therefore each powder was pictured before and after sieving and mixing with a light microscope (Leica 4000, Leica Microsystems Inc., USA) and also analyzed using SEM (Zeiss Ultra 55, Zeiss Oberkochen, Germany) operating at 5 kV to assess whether particle breakage occurred.

5.2.4 Electrostatic charge measurement

Charge measurement was performed using a Faraday cup (proprietary construction) connected to a high resistance electrometer (Keithley 6517 B, Keithley Instruments, USA). The cup consists of two cups of stainless steel which are placed into each other and separated from each other by a thick-walled jar made of Teflon™. The outer cup (protection cup) is grounded and works as a shield to protect the inner cup (measuring cup) from external influences. When a charged powder is poured into the inner cup, its charge induces a charge with the same magnitude but opposite polarity in the conducting material of the cup. Thus the charge of the powder can be calculated by measuring the voltage between the inner cup and the ground using an electrometer with known capacitor. Figure 5.1 shows an illustration of the used Faraday cup.

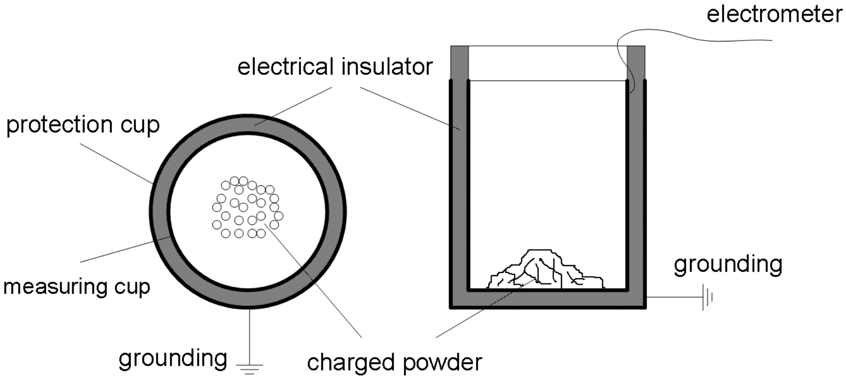

Figure 5.1: Illustration of the Faraday cup

Prior to each measurement the powder samples were conditioned as described above. After conditioning the storage/mixing containers were closed airtight. Afterwards the containers were taken out of the climate box, mounted on a tumble blender (T2F Turbula®, Willy A. Bachofen AG - Maschinenfabrik, Switzerland) and blended for 20 minutes at 60 rpm. Subsequent to mixing the samples were taken back into the climate box where charge measurement was performed by pouring the powder into the measuring cup. Before and after charge measuring the inner Faraday cup was weighed to calculate the powder mass poured into the cup and the mass-specific netcharge carried by the powder.

5.2.5 Mixing uniformity

To evaluate possible correlations between the arising tribo-charge during mixing and the resulting mixing quality of the adhesive mixtures, their mixing uniformity was determined. Therefore, subsequent to the tribo-charge measurements of the adhesive mixtures 10 samples in a range of 10 mg to 20 mg were taken out of the Faraday Cup. Three samples were taken from the top, four from the middle and three from the bottom. Each of these 10 samples was dissolved in 10 ml deionized water with a pH of 3 (generated with acetic acid) and analyzed using a HPLC device (HP1090, Aglient technologies, Germany).

5.2.6 Flowability

The flowability was evaluated by filling the different carrier powders into dry powder inhalers (Novolizer©, MEDA Pharma GmbH & Co. KG, Germany), actuating the devices and determining the released mass per actuation and the uniformity of the released masses. The dosage in such dry powder inhalers is carried out volumetrically just forced by gravity. Therefore the uniformity of the released mass from the inhaler is a good indicator for the flow behavior of the powder. The measuring setup consisted of a vacuum pump (SV1025, Busch, Chevenez, Switzerland), a connection tube, a mouthpiece for the inhaler and filter paper (Type A/E, 47 mm, PALL GmbH, Dreireich, Germany). An illustration of this setup is shown in Figure 5.2. The released mass was determined by weighing the inhaler before and after each actuation. This procedure was repeated 49 times for each powder type. This procedure was performed in triplicate. The air flow rate through the inhaler was set to 78,2 l/min which corresponds to a pressure drop of 4 kPa across the inhaler. Suction time was set to 3 seconds to ensure that the total volume of air sucked through the inhaler is 4 l.

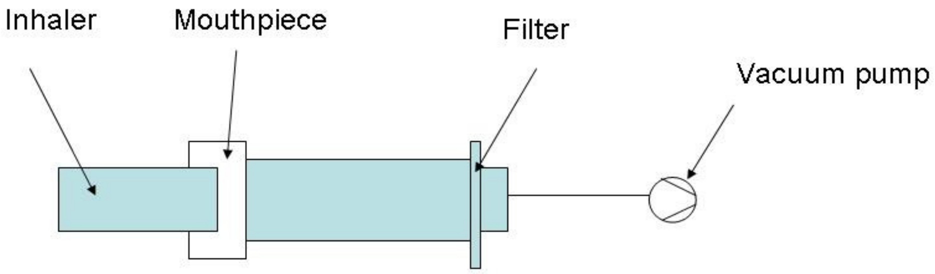

Figure 5.2: Experimental Set up, Flowability

5.3 Experimental results and discussion

5.3.1 Carrier particle characterization

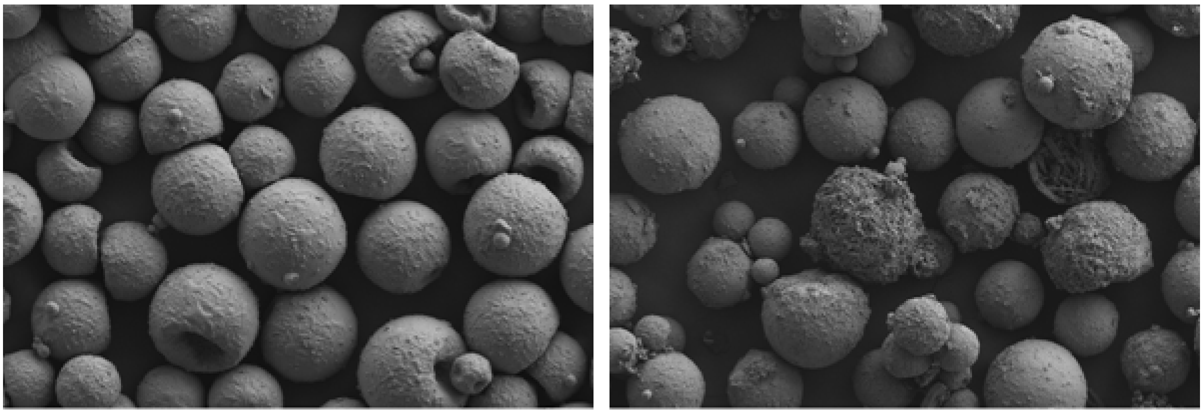

Figure 5.3: Scanning electron micrograph of the smooth (left) and the rough (right) powder

The SEM images shown in figure 5.3 reveal that the two mannitol samples exhibit different surface roughnesses. While the particles on the left hand side have a uniformly smooth surface, at least some of the particles on the right hand side show a higher surface roughness. Therefore in the following sections the samples will be termed “smooth” and “rough”.

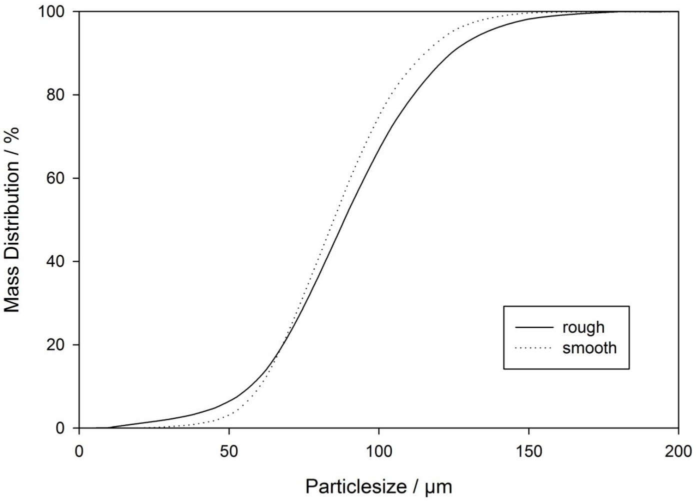

Figure 5.4: Particle size distribution of the rough and the smooth powder determined by laser diffraction (mean of n=3)

The particle size distributions of the smooth and the rough carriers were determined to ensure that both samples are similar and in the desired size range. Figure 5.4 and table 5.2 confirm that the samples are in the size range suitable for carriers in DPIs (50 µm – 200 µm) and that their PSDs do not differ from each other significantly.

Table 5.2: Characteristic diameters of the PSD (mean ± SD of n=3)

	smooth	rough
X_{10} [µm]	59,5±0,156	56,32±0,243
X_{50} [µm]	84,85±0,155	88,39±0,325
X_{90} [µm]	117,27±0,550	124,34±0,454

Examination of the bulk and tapped density revealed a higher bulk as well as tapped density of the smooth powder. This is not unexpected since nicely smooth particles may exhibit a closer packing of spheres than rough ones. This is on the one hand caused by mechanical interlocking of the rough particles and on the other hand by the fact that any roughness leaves more space for air within the powder bulk than a smooth surface. Also differences in the particle density are conceivable. Therefore the particle density was measured by Helium pycnometry.

Table 5.3: Bulk and tapped density

	Bulk density [g/ml]	Tapped density [g/ml]
smooth	0.496	0.588
rough	0.403	0.484

Surprisingly also the measurement of the particle density by helium pycnometry revealed a difference between rough and smooth powder. In contrast to the bulk and tapped density the smooth powder showed a lower particle density of 1.3386±0.0005 g/cm^3 than the rough powder that had a higher one of 1.4903±0.0018 g/cm^3. This value is very close to the true density of Mannitol with 1.514 g/cm^3 [20]. This suggests that the Helium permeated into the particles. This is supported by the findings of Littringer et al. [21] who mentioned that such spray dried particles are of porous nature and might have a partly permeable shell. Littringer et al. [22] further performed mercury intrusion porosimetry measurements and showed that particles with less surface roughness have a higher particle density. This would be a further explanation for the findings in the bulk and tapped density measurements.

The surface area measurements revealed a specific surface area of 0.5930±0.007 m^2/g for the rough powder and 0.3868±0.0046 m^2/g for the smooth powder. As expected the rough powder shows a higher specific surface. However, as mentioned above these results should be treated with caution since the particles might be porous and have a partly permeable shell.

The validation of the particle strength approved that the particles do not break during sieving and mixing.

5.3.2 Electrostatic charge of pure mannitol in stainless steel

The charging experiments of the pure mannitol carriers in stainless steel mixing containers showed a specific charge of 0.05±0.009 nC/g for the smooth powder and of 0.25±0.0189 nC/g for the rough one. Here the rough powder exhibited a significantly higher tribo-charge that can also be seen in figure 5.5.

One explanation for this is the specific surface area of the powders. Even though the specific surface measurements are not completely reliable, a rougher surface of particles of the same size, has to result in a larger specific surface area. This larger surface area enables the powder to take up more tribo-charge until the surface is charge saturated [23].

A second reason for the different charging behavior might be a different rolling behavior of the particles or different powder-bed movement of the rough and smooth powder in the mixing containers. Smooth particle are able to gently roll over each other and the container wall while the rough particles might more tend to interlock to each other and the wall resulting in more sliding and falling movement of the powder. A sliding powder movement would result in more friction which strongly enhances tribo-charging. If kind of a falling powder movement occurs due to interlocking the increased impact velocity of the particle on the wall might enhance tribo-charging. As Watanabe et al. [16,17] suggested the impact energy that arises between particle and wall may strongly influence the arising tribo-charge.

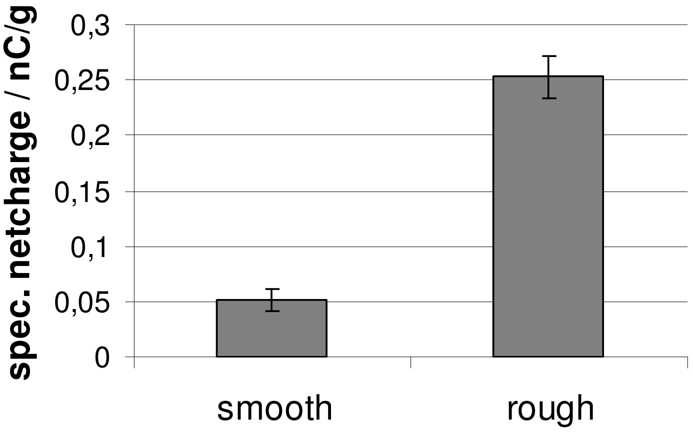

Figure 5.5: Net-charge of the carriers acquired during mixing (mean ± SD of n=3)

5.3.3 Flowability

The uniformity of the released mass was determined by actuating the Novolizer® 50 times and measuring the weight loss of the inhaler device after each actuation. This was repeated three times. The standard deviation of the released mass of the 50 actuations and the mean standard deviation of the three cycles was calculated and used as a measure of the uniformity of the released mass or the powder flowability, respectively.

In table 5.4 where the results are shown, it can be seen that the smooth carrier powder show a lower mean standard deviation of the released mass of 1.09 mg compared to 1.23 mg for the rough carriers.

Table 5.4: Standard deviation of the released mass of 3 independent cycles (n = 50)

	cycle 1	cycle 2	cycle 3	mean
smooth	1,35 mg	1,02 mg	0,72 mg	1,09 mg
rough	1,15 mg	1,31 mg	1,23 mg	1,23 mg

If these mean standard deviations are taken as a measure of the uniformity of the released mass or the powder flowability, respectively, the smooth carriers show a better uniformity of the released mass and thus flow behavior. Nevertheless looking at the standard deviations of the released mass of the single cycles the difference between rough and smooth is not significant. This can also be seen in figure 5.6 where the mean standard deviations of the three cycles and its standard deviation are illustrated. Despite the different charging behavior of the carrier powders during mixing, tribo-charge does not influence the dosing behavior of pure carriers. This is because obviously to less powder movement takes place during dosing that would cause significant tribo-charging that further would influence the flow behavior during dosing. Also the roughness differences of the carrier particles do not seem to influence the flowability in a mechanical way.

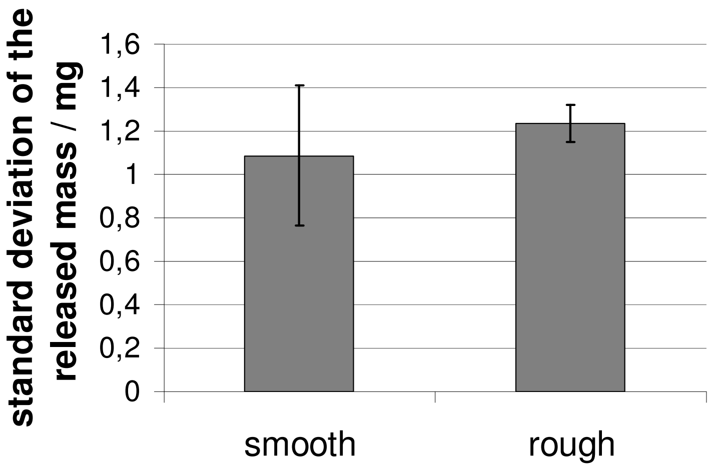

Figure 5.6: Standard deviation of 50 released masses (mean ± SD of n=3)

5.3.4 Electrostatic charge of the adhesive mixtures in stainless steel

To include the possible interactions between carrier and active pharmaceutical ingredient with respect to tribo-charging, mixing studies with adhesive mixtures of salbutamol sulphate and mannitol in stainless steel vessels were performed.

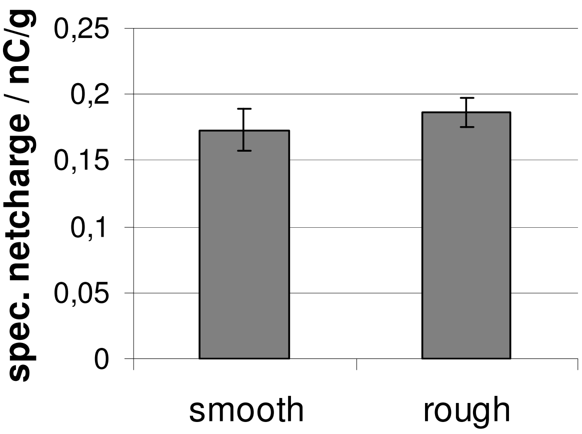

Figure 5.7: Net-charge of the adhesive mixtures acquired during mixing (mean ± SD of n=3)

As can be seen in figure 5.7 the netcharge arising on the adhesive mixtures containing the rough and smooth carriers do not differ significantly. Both lie in the range of 0.2 nC/g. This means the presence of the API adherent to the carrier surface superimposed the impact of the carrier particle characteristic surface roughness. Taking into consideration that the carrier surface is covered by API particles that will get into contact with each other and the mixing container wall instead of the carrier particle itself and that will govern the charging behavior, these findings are not surprising. That means by the coverage of the carries by the API particles, new particles with similar surface roughness that is independent on the surface roughness of the original carrier particles are generated. This finally results in the almost identical charging behavior of the adhesive mixtures.

5.3.5 Mixing uniformity

Subsequently to mixing and charge measurement three different mixtures containing the smooth or the rough carriers respectively where analyzed regarding mixing homogeneity by drawing ten samples from each mixture. Table 5.5 shows the standard deviation of the API content of the ten samples and the mean standard deviation of the three mixtures. It can be seen that the mixtures containing the rough carrier have a higher mean standard deviation of 0.80 mg/g compared to the mixtures containing the smooth carriers with a mean standard deviation 0.45 mg/g. These results indicate a better mixing quality / uniformity of the mixtures containing the smooth carriers, although the difference is not highly significant as can be seen in figure 5.8. Correlating this with the charge measurement results shown in figure 5.5 (pure carriers), it is found that the adhesive mixtures containing the carriers with the lower charging tendency achieve better mixing uniformity irrespective of the fact that the netcharge acquired by the adhesive mixtures is equal.

It is believed that this occurred because at the beginning of the mixing process carrier and API are separate. After a certain time of mixing the API completely covers the carrier, resulting in this above mentioned new particles with similar surface roughness and further almost equal netcharge magnitude. However the mixing uniformity depends also on the first minutes of mixing where the two components first come into contact. In this process particle interactions or inter particle forces between carrier and API particles have a strong influence on API attachment to the carrier surface. And here the charging behaviour of the pure carrier particles impacts the mixing results. Adi et al. [14] and Elajnaf et al. [13] already showed that mannitol as well as salbutamol suphate charge negatively in stainless steel mixing containers. In this case higher tribo-charge on the carriers would result in repulsive forces between API and carrier. This would further result in less intense contacts or lower contact areas between API and carrier during mixing and thus less strong remaining adhesion forces (mainly Van der Waals Forces) between them after mixing. This would be a reason for unstable mixtures and the resulting lower mixing homogeneity.

Table 5.5: Standard deviation of the API content of 10 samples taken from 3 independent adhesive mixtures

	mixture 1	mixture 2	mixture 3	mean
smooth	0.51 mg/g	0.47 mg/g	0.30 mg/g	0.45 mg/g
rough	0.93 mg/g	0.38 mg/g	0.89 mg/g	0.80 mg/g

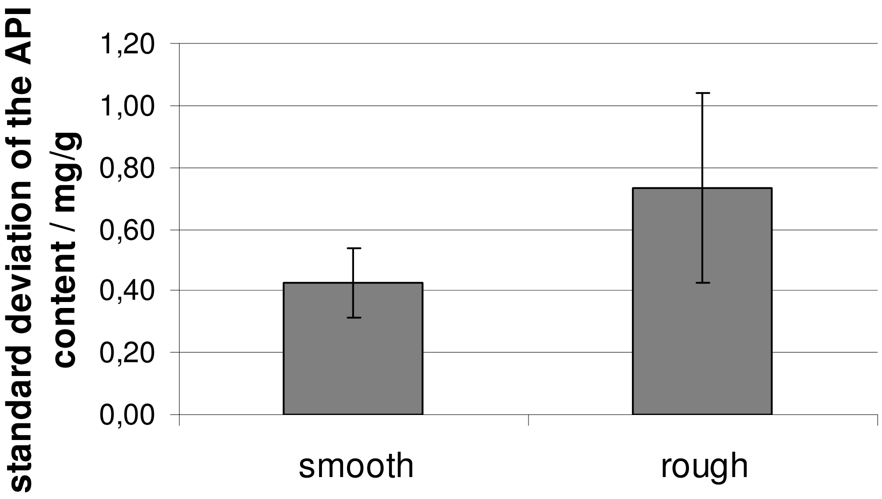

Figure 5.8: Standard deviation of the API content of 10 samples (mean ± SD of n=3)

5.4 Conclusion

It was possible to prove that surface modifications (surface roughness) of the carrier particles through spray drying result in different charging behavior of the carriers in a standard tumble blending process in stainless steel containers. The rougher carrier particles charged significantly higher. This was attributed to a different contact behavior, contact area between particles as well as particle and mixing container wall and charge saturation behavior of the powder due to the different surface properties of the smooth and rough carrier particles. Further it was demonstrated that this different charging behavior is not appearing in the case of adhesive mixtures. The influence of the carrier surface roughness on tribocharging is compensated by the presence of the API that completely covered the carrier surface resulting in almost equal netcharge magnitudes of the different adhesive mixtures.

Despite the same charge uptake of the two different adhesive mixtures they showed differences in the mixing homogeneity. The mixtures containing the rougher carriers which showed the higher charge uptake in the pure carrier studies had a lower mixing homogeneity. This was explained by the fact that carrier and API are separated at the beginning of the mixing process and that in this early stage of the mixing process the interparticle forces between carrier and API, that strongly affect mixing quality, are influenced by electrostatic charge and thus by the charging behavior of the carriers. In this case the homopolar charging of API and carrier in the stainless steel vessels resulted in repulsive forces between the two pharmaceutical ingredients and finally lower mixing homogeneity.

The assessment of the dosing behavior of the carriers in the inhaler did not reveal a difference between the smooth and rough carrier products. This is because to less powder movement takes place during dosing that would cause a diverse tribo-charging that further would influence the flow behavior during dosing. Also mechanical influences through the roughness differences seem to be neglectable.

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6

Factors affecting tribo-charging during aerosolization and release form DPIs

Inhalation powders may be charged by triboelectrification upon aerosolization and release of the powder from the inhaler device due to frequent contacts and high impact velocities between the particles and the inhaler material. This is particularly challenging in dry powder inhaler (DPI) technology where usually adhesive mixtures of carrier particles in the size range of 50 µm – 200 µm and active pharmaceutical ingredient (API) particles in the size range of 0.5 µm – 5 µm are used. In these adhesive mixtures it is crucial that the API particles adhere to the coarser carrier particles to ensure good flowability and dosing behavior. However during aerosolization the API particles should detach from the carriers in order to reach the deeper lung. This means that the performance of such adhesive mixtures used in DPI devices is strongly affected by inter-particle forces which are further affected by electrostatic charge. Sign and magnitude of the arising charge is on the one hand influenced by the contacting material, relative humidity and impact velocity and on the other hand by particle characteristics like particle size, particle shape and surface roughness.

For these reasons the aim of this work is to investigate which factors actually influence the charging process during powder aerosolization and release from the inhaler and how it can be controlled. In the present study the influence and interactions of four practice-relevant factors is checked using statistical design of experiments. These are the carrier particles size, the aerosolization air flow rate, the API content in the adhesive mixtures and the addition of carrier fines <40 µm. The experiments are performed using the Novolizer® as DPI device. Electrostatic charge measurements are conducted using an open-end faraday cup. The study revealed that the netcharge increases with an increasing amount of carrier fines and an increasing air flow rate.

Further the netcharge decreases with increasing particle size and the presence of API. Finally investigations on the dependence of tribo-charging on the number of actuations of the device revealed that the netcharge arising on adhesive mixtures released in 50 consecutive doses from the DPI is almost the same for each dose at an air flow rate of 60 l/min whereas at 90 l/min there is a noticeable trend of decreasing netcharge over the number of actuations.

6.1 Introduction

Drug delivery to the lungs via Dry Powder Inhalers (DPIs) has become more and more important in the last decades. In order to be deposited in the deeper lung, it is essential that the active pharmaceutical ingredient (API) particles of DPIs have an aerodynamic diameter between 0.5 µm and 5 µm [1]. Unfortunately such fine powders are very cohesive resulting in poor flowability and dosing behavior. One possibility to improve these properties is to mix the small API particles with larger carrier particles (adhesive mixtures). These carrier particles are usually made of lactose or glucose and have particle sizes between 50 µm and 200 µm [2–4]. An alternative carrier material which is still under investigation is mannitol [3]. Mixing, flowability as well as the very important drug detachment of the active from the carrier surface of adhesive mixtures upon inhalation are governed by the interparticle interactions which mainly arise through Van der Waals and electrostatic forces. In addition to this the triboelectric charge carried by aerosolized powders may influence the release of the formulation from the inhaler and the deposition behavior of the particles in the throat and lung [5].

Electrostatic charge is generated when two different materials are brought into contact and then are separated [6]. Since drug as well as carrier particles consist of insulating material, they are unable to dissipate and therefore accumulate charge in any process where the powder comes into contact with surfaces. In which way sign and magnitude of the charge is influenced is still poorly understood and therefore difficult to predict. This problem gets even more complex when two or more materials and more than one influencing factors are involved. Furthermore the arising of charge in metal / insulator contact and insulator / insulator contact is very complex [7]. Unfortunately, this phenomenon appears in many pharmaceutical processes and also in DPI-technology. Different models to describe charge generation and accumulation like the ion transfer model [8], the surface state model (electron transfer model) of Castle and Schein [9] and the two step model (electron transfer model) of Yu and Watson [7] have been presented. Further Diaz and Felix-Navarro [10] presented a semi-quantitative triboelectric series to estimate how different materials will charge when they are brought into contact.

As mentioned above the sign and magnitude of the arising charge depend on many factors such as particle size and shape [11], surface roughness [12,13], nature and work functions [14], impurities [15–17], amorphicity [18], contact material [19,20], relative humidity [21] and the energy of contact [22,23]. A summary of these influences can be found at Karner and Urbanetz [24].

Especially during aerosolization and release from a DPI device a high number of contacts among inhalation powder particles and between particles and inhaler device may be observed. In addition to this, depending on the DPI device, very high impact and shear velocities may occur. The high air and contact velocities are intended to detach the API particles from the carrier particles. However, these contacts may result in very high charge magnitudes arising on the inhalation powder. As mentioned above this charge affects the interaction between the components of the adhesive mixtures, the dosage uniformity and also the deposition behavior of the particles in the lung. This makes triboelectric charge one of the main influencing factors on the performance and usability of DPIs. To optimize the performance and to extend the applicability of DPIs it is very important to understand which and how factors significantly influence the arising charge.

A number of scientists already performed charge measurements on pharmaceutical aerosols using different measurement techniques. Early studies in this field were performed by Murtomaa et al. [25] who used an electrical conducting grid to measure the charge carried by aerosols. More modern devices are the electrical next generation impactor (eNGI) and the electrical low pressure impactor (ELPI). These techniques were frequently used by several scientists like Young et al. [26], Telko et al. [5] and Hoe et al. [27–30]. Another simple instrument to measure the netcharge present on aerosols is the open-end faraday cup that has been used by Murtomaa et al. [31] and Chow et al. [32]. Beside the above mentioned investigations there is more literature available dealing with charge measurements on aerosols. However, these papers will not be discussed in the present work, because they do not treat the charging process of carrier-based DPI formulations as they are used in the present study particularly. Even though already several work has been done to investigate how the arising tribo-charge of pharmaceutical aerosols can be influenced there are still many uninvestigated factors and interactions in this research area.

Therefore the aim of the present work is to investigate the influence of four practice-oriented influencing factors on the charging behavior of adhesive mixtures of mannitol (carrier) and salbutamol sulphate (API). As mentioned above mannitol is a new alternative carrier material of which not many experimental data concerning its triboelectric behavior is available. The factors possibly impacting tribo-charging and investigated in the present work are the carrier particle size, the addition of carrier fines <40 µm, the aerosolization air flow rate and the presence of API in the adhesive mixtures. The factor particle size is chosen because in earlier mixing studies it was shown to have a strong impact on the charging behavior of the powder [33–35]. The investigation of the influence of the carrier fines is relevant for the DPI technology because it is a common practice to add carrier fines to a DPI formulation in order to increase the respirable fraction [36]. In prior inhaler studies performed by Guenette et al. [37] the influence of carrier fines on the behavior of the drug powder formulations was investigated. They observed that the presence of fines had a positive effect on the released fine particle dose but a negative influence on the formulation stability and flowability of the adhesive mixtures. For this reason it would be interesting to determine how the arsing tribo-charge is influenced by the presence of fines and if there is a correlation between the charge and the powder behavior.

In most of theses studies carrier fines with particle diameters <10 µm were used. However the carrier fines fraction used in the present study was <40 µm as this fraction may be adequately separated from the coarse fraction by mechanical sieving. Although some of the particles of this fines fraction is too large and may therefore not adhere to the surface of the coarse carrier particles, still there should be a sufficient number of very fine particles sticking on the surface allowing to investigate the impact of adherent carrier fines on the electrostatic behavior. The air flow rate is included in the studies because it was shown to influence the arising charge during single particle impacts on plates [23,38] and also metered dose inhalers [39]. Furthermore Heng et al. [40] showed that the aerosolization air flow rate strongly influenced the performance of DPIs like fine particle fraction, throat deposition, inhaler- and capsule-retention. The influence of the presence of API is also interesting due to the surface potential difference between API and carrier.

In order to thoroughly investigate the phenomenon of tribo-charging statistical design of experiments (DOE) is used to check the influence and the interaction between the factors possibly impacting tribo-charging. As usually more than one factors influence the performance of DPIs in an interactive way it is crucial to have a close look on the interactions of factors in order to be able to efficiently improve the performance of dry powder inhalers and the related drug formulations. Therefore it is key to understand how influencing factors interact in order to find the perfect combination of factors thereby maximizing the therapeutic effect with DPIs.

The above mentioned work of Telko et al. [5] focused on the arsing of charge in capsule inhalers. In their conclusion they mentioned that for the future it would be important to investigate the arising of tribo-charge in DPIs with reservoirs since this type of inhalers is more common. Therefore in the present work the inhalation powder is released from a commonly used DPI device with reservoir, the Novolizer®. Also not much data concerning the characteristics of this inhaler type is available. Netcharge measurement is performed using the above mentioned open-end faraday cup technique.

6.2 Materials and Methods

6.2.1 Materials

Crystalline mannitol was donated by Roquette Frères (160C, Roquette Frères, France). This mannitol was size fractioned by sieving. It was mechanically sieved into size fractions of <40 µm, 40 µm – 63 µm, 63 µm - 80 µm, 80 µm - 100 µm, 100 µm - 125 µm, 125 µm - 160 µm using a sieve shaker (Analysette®, Fritsch, Germany). Only the fractions <40 µm, 63 µm – 80 µm and 100 µm – 125 µm were used for the further experiments. Particle size distributions of these sieve fractions were determined by laser diffraction (HELOS/KR, Sympatec GmbH, Germany) using a dry dispersion unit (Rodos/L, Sympatec GmbH, Germany). The software Windox 5 (Sympatec GmbH, Germany) was used to evaluate the measurement data. The sieve fractions showed the following characteristic parameters of the size distribution: <40 µm fraction: $x_{10,3}$ = 33.7 µm, $x_{50,3}$ = 48.1 µm, $x_{90,3}$ = 58.9 µm; 63 µm – 80 µm fraction: $x_{10,3}$ = 62.8 µm, $x_{50,3}$ = 94.8 µm, $x_{90,3}$ = 142.7 µm and 100 µm – 125 µm fraction: $x_{10,3}$ = 82.5 µm, $x_{50,3}$ = 136.4 µm, $x_{90,3}$ = 175.2 µm. The fact that the particle diameters measured by laser diffraction are higher than the mesh size of the sieves is caused by the elongated shape of the mannitol particles (see figure 6.1). However there is still a significant size difference between the fractions.

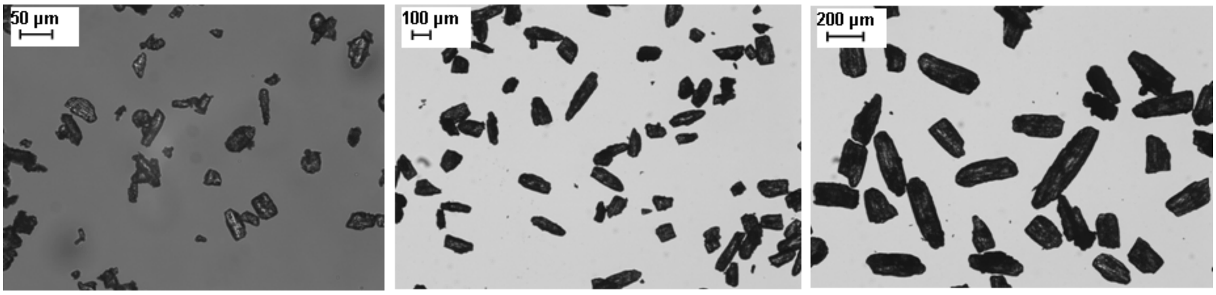

Figure 6.1: Light microscopy images of the mannitol fractions <40 µm (left), 63 µm – 80 µm (middle), 100 µm – 125 µm (right)

As active pharmaceutical ingredient (API) micronized salbutamol sulphate (USP25 quality) was used. Salbutamol sulphate was purchased from Selectchemie AG (Selectchemie AG, Switzerland) and micronized using an air jet mill (Alpine 50 AS, Hosokawa, Germany). The injection pressure was 6.0 bar and the milling pressure was 2.0 bar. A feed rate of 1 g/min was used. The particle size distribution of the API was also analyzed using the above mentioned laser diffraction technique. The micronized material showed a median particle diameter of 1.69 µm ($x_{10,3}$ = 0.46 µm, $x_{50,3}$ = 1.69 µm, $x_{90,3}$ = 5,65 µm).

For the preparation of the inhalation powder blends 75 ml stainless steel mixing containers were used. The containers had an inner diameter of 49 mm and an inner height of 40 mm.

As dry powder inhaler device a Novolizer® (MEDA Pharma GmbH & Co. KG, Germany) was used. Three different Novolizer® devices were used alternately. The Novolizer® is made of polycarbonate. Unfortunately almost no data about the triboelectric properties of this material is reported in literature. One of the few citations can be found in the triboelectric series of Diaz and Felix-Navarro [10]. Its workfunction is in the range of polyethylene and polypropylene.

6.2.2 Sample preparation

To check the influence and interactions of different factors on the arising charge on inhalation powder during aerosolization and release from a dry powder inhaler (DPI) eight different inhalation powder blends with different compositions were used. The respective batch compositions are shown in table 6.1. For the blends the 63 µm – 80 µm and the 100 µm – 125 µm fractions of the mannitol powder were used because the yield of these fractions when fractionating the mannitol mentioned above were reasonably high and their particle size was in the range of commonly used carrier particles. Further also the <40 µm mannitol fraction was used as carrier fines. The blends were prepared by tumbling the powder mixtures in stainless steel containers for 90 minutes at 60 rpm using a tumble blender (T2F Turbula®, Willy A. Bachofen AG - Maschinenfabrik, Switzerland).

Table 6.1: Compositions of the inhalation powder blends in grams (63µm-80µm mannitol, 100µm-125µm mannitol, 0µm-40µm mannitol (fines) and salbutamol sulphate (API)); "C" stands for pure mannitol carrier and "OM" stands for adhesive mixture of carier and API

	C1	C2	C3	C4	OM1	OM2	OM3	OM4
Ingredient	1/g	1/g	1/g	1/g	1/g	1/g	1/g	1/g
63µm-80µm	10		9		10		9	
100µm-125µm		10		9		10		9
Fines			1	1			1	1
API					0,25	0,25	0,25	0,25

In order to gain correct and reproducible experimental results it is of main importance that the powder samples are electrically discharged and equilibrated at a defined and constant relative humidity before performing the experiments. Therefore the powder samples were spread in thin layers on earthed aluminum foils and conditioned for 24 hours. This is a standard procedure for discharging insulating powders as reported in literature [32]. The storage time of 24 hours is adequate for powder discharge since the powder was spread in thin layers and thereby had a large contact area to the grounded metal. The procedure of discharging insulating powder by grounding was validated in prior studies [33] (results not shown here). The discharge and conditioning procedure was performed inside a walk-in environmental chamber (proprietary construction) at constant relative humidity of 43±2 %RH and temperature 22±2 °C. All parts of the Novolizer® were first rinsed with deionized water, then with ethanol and in the end once again with ultrapure water. After washing, the inhalers were dried using compressed air and were also stored inside the environmental chamber on an earthed metal plate for at least 24 hours. After discharge and conditioning the samples were carefully poured from the aluminium foils directly into the reservoir of the Novolizer®. After filling the reservoirs, the Novolizer® was assembled and kept inside the environmental chamber for another two hours prior the experiment.

6.2.3 Charge measurement

Charge measurement was also performed inside the walk-in environmental chamber (same conditions as mentioned above) using an open-end faraday cup (proprietary construction) connected to a high resistance electrometer (Keithley 6517 B, Keithley Instruments, USA). Figure 6.2 shows an illustration of the experimental setup. The setup consists of an inhaler that is placed inside the open-end faraday cup and is connected to an 80 cm long PVC-pipe through a mouthpiece. On the other end of the pipe there is a filter to collect the aerosolized inhalation powder. Behind the filter there is a flow control device (TPK, Copley Scientific, United Kingdom) and a vacuum pump (SV 1025C 000 IKXX, Busch, Switzerland).

The principle of the charge measurement procedure is that the inhalation powder is aerosolized and sucked out of the inhaler by the airflow generated by the vacuum pump. The powder is sucked through the PVC-pipe away from the faraday cup and gets caught in the filter. It is very important that the charged powder is carried far enough away from the measuring faraday cup. This is the reason why the PVC-pipe is installed between the inhaler and the filter where the powder is caught. If the powder would be caught close to the faraday cup the tribo-charge present on the powder would distort the charge measurement procedure by electrostatic induction in the faraday cup that works as follows.

When the powder is sucked out of the inhaler it gets into contact with the material of the inhaler and thereby takes up triboelectric charge. The same magnitude of charge but with opposite polarity is left behind in the inhaler. This left behind charge in the inhaler induces a charge with the same magnitude but opposite polarity in the electrically conducting material of the inner faraday cup (measuring cup). The outer faraday cup (protection cup) is grounded and works as a shield to protect the inner cup and thereby the whole measurement from disturbing external influences. The two cups are made of copper and are divided by an electrically insulating material (Teflon™).

The cups are connected to a high resistance electrometer that is able to measure the voltage or charge, respectively between the measuring cup and the protection cup (ground) which in fact is the triboelectric netcharge carried by the aerosolized inhalation powder. The electrometer is further connected to a measurement computer for data acquisition. The same measurement principle was also used by Chow et al. [32]. The flow control device on the one hand controls the air flow rate through the system by a valve. On the other hand it controls the total amount of air that is sucked through the inhaler by controlling the suction time.

The actual measurement procedure was as follows: The Novolizer® was mounted to the mouth piece and actuated. Then it was inserted into the faraday cup. The electrometer was turned on two hours before measurement to minimize variation of the measurement signal. The vacuum pump was switched on half an hour before measurement to ensure a constant air flow rate. The charge measurement was started by adjusting the electrometer at zero and initiating the aerosolization by actuating the flow control device (opens the valve for defined duration).

The first stable charge signal was taken as the netcharge carried by the powder. The mass specific netcharge was calculated by dividing this netcharge by the released powder mass. The released powder mass was determined by weighing the Novolizer® before and after actuations. These masses were not determined after each single actuation. This would induce too much disturbance in the very sensitive charge measurement process. The released mass was measured after 50 actuations, the arithmetic mean value of this mass was calculated and used to determine the mass specific netcharge.

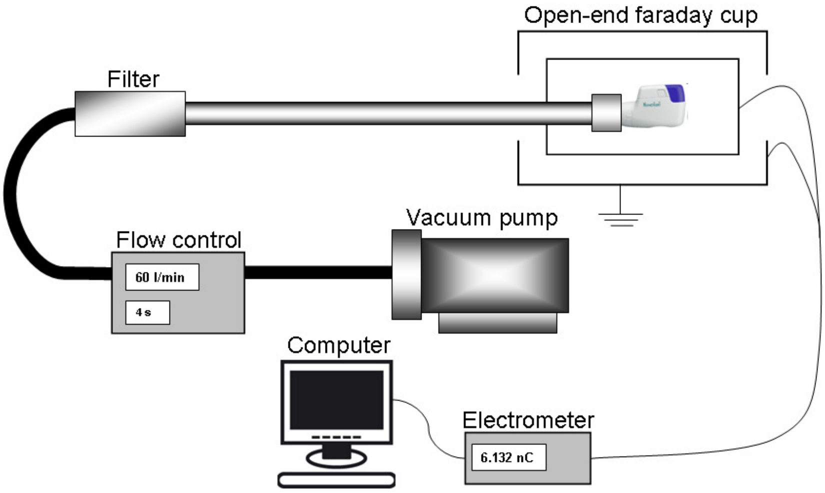

Figure 6.2: Schematic illustration of the experimental measurement setup

6.2.4 Statistical design of experiments (DOE)

The DOE-studies were used to check the influence and interactions of different factors on the arising charge on inhalation powders during aerosolization and release from a DPI (Novolizer®). First the factors particle size, fines fraction (amount of carrier fines <40 µm) and air flow rate were checked for pure mannitol powder (carrier). Each factor was checked on two levels. Therefore a high and low level for the factors had to be defined. The defined levels were the 63 µm – 80 µm and the 100 µm – 125 µm fraction of the mannitol powder for the particle size, 0 %(w/w) and 10 %(w/w) for the amount of carrier fines (<40 µm fraction of mannitol) and 60 l/min and 90 l/min for the air flow rate. That means for these experiments the powder blends C1, C2, C3 and C4 (see table 6.1) were used and were sucked out of the inhaler with 60 l/min and 90 l/min air flow rate. Table 6.3 summarizes the factors and levels. Further table 6.2 shows the combinations of factors and levels for the experimental design for these carrier only DOE-studies.

Table 6.2: Factors and levels of the statistical design of experiments (DOE with three factors on two levels)

	Factors		
	Particle size	**Fines fraction**	**Flow rate**
high level	100 µm - 125 µm	10 % (w/w)	90 l/min
low level	63 µm - 80 µm	0 % (w/w)	60 l/min

Table 6.3: Experimental design with all factors and levels (DOE with three factors on two levels)

Syst. Nr.	Particle size	Fines fraction	Flow rate
1	63µm-80µm	0 % (w/w)	60 l/min
2	100µm-125µm	0 % (w/w)	60 l/min
3	63µm-80µm	10 % (w/w)	60 l/min
4	100µm-125µm	10 % (w/w)	60 l/min
5	63µm-80µm	0 % (w/w)	90 l/min
6	100µm-125µm	0 % (w/w)	90 l/min
7	63µm-80µm	10 % (w/w)	90 l/min
8	100µm-125µm	10 % (w/w)	90 l/min

After the studies treating the pure mannitol carrier particles the investigations were extended for the consideration of the API content: an experimental design with the factors particle size, fines fraction, air flow rate and API content was designed. The two levels for the API content were 0 %(w/w) and 2.44 %(w/w) respectively a mixing ratio of 1/40 (mass salbutamol sulphate / mass mannitol). For these experiments all mixtures listed in table 6.1 were used. They were dispersed from the inhaler at 60 l/min and 90 l/min air flow rate. Therefore the experimental design looked as shown in table 6.5. In addition table 6.4 summarizes the factors and levels.

Table 6.4: Factors and levels of the statistical design of experiments (DOE with four factors on two levels)

	Factors			
	Particle size	Fines fraction	Flow rate	API / mannitol ratio
high level	100 µm - 125 µm	10 % (w/w)	90 l/min	1/40
low level	63 µm - 80 µm	0 % (w/w)	60 l/min	0

Table 6.5: Experimental design with all factors and levels (DOE with four factors on two levels)

Syst. Nr.	Particle Size	Fines Fraction	Flow Rate	API / mannitol ratio
1	63µm-80µm	0 % (w/w)	60 l/min	0
2	100µm-125µm	0 % (w/w)	60 l/min	0
3	63µm-80µm	10 % (w/w)	60 l/min	0
4	100µm-125µm	10 % (w/w)	60 l/min	0
5	63µm-80µm	0 % (w/w)	90 l/min	0
6	100µm-125µm	0 % (w/w)	90 l/min	0
7	63µm-80µm	10 % (w/w)	90 l/min	0
8	100µm-125µm	10 % (w/w)	90 l/min	0
9	63µm-80µm	0 % (w/w)	60 l/min	1/40
10	100µm-125µm	0 % (w/w)	60 l/min	1/40
11	63µm-80µm	10 % (w/w)	60 l/min	1/40
12	100µm-125µm	10 % (w/w)	60 l/min	1/40
13	63µm-80µm	0 % (w/w)	90 l/min	1/40
14	100µm-125µm	0 % (w/w)	90 l/min	1/40
15	63µm-80µm	10 % (w/w)	90 l/min	1/40
16	100µm-125µm	10 % (w/w)	90 l/min	1/40

Generally the suction time was set to 4 seconds for 60 l/min and 2.7 seconds for 90 l/min for all performed experiments to reach a total air volume that is sucked through the inhaler of 4 liters. This is important to be consistent with the guidelines of the European Pharmacopoeia (powders for inhalation, Ph. Eur., 7.0). All combinations of the experimental designs were executed randomized and repeated twice. Each data point is the mean value of 50 actuations. The analysis of all DOE results was conducted using statistical software (Statistica 8, Statsoft®, USA). Analysis are performed using ANOVA-test on a significance level of 95%.

6.2.5 Long time actuation studies

In these investigations the four different adhesive mixtures (OM1, OM2, OM3, OM4) shown in table 6.1 were treated. Each adhesive mixture was dispersed 50 times from the same inhaler device consecutively. This was done in triplicate using three different Novolizer® devices. The whole procedure was conducted at an air flow rate of 60 l/min and 90 l/min. Suction time was adjusted as described under section 6.2.4.

6.3 Experimental results and discussion

6.3.1 Evaluating the impact of three factors on tribo-charging of mannitol

Studies with the DPI carrier mannitol revealed that particle size of the carrier, the addition of carrier fines and the airflow rate significantly impact the netcharge acquired by mannitol powder when it is aerosolized in and released from a common DPI device (Novolizer®). The effect plot of the DOE is illustrated in figure 6.6. The strongest effect is observed with the air flow rate. Increasing the air flow rate through the inhaler from 60 l/min to 90 l/min results in a very strong increase of the triboelectric netcharge carried by the powder. This is attributed to the higher impact and shear velocity of particle-particle and particle-wall contacts at higher airflow rates. This effect has also been reported in literature by Watanabe et al. [23] and Matsusyama and Yamamoto [38] who investigated single particle impacts on plates. The increase of the netcharge with the flow rate was also observed by Hoe et al. [39] who investigated the charge arising on metered dose inhaler aerosols using an electrical next generation impactor (eNGI). Also De Boer et al. [41] hypothesized that tribo-charge increases with higher flow rates.

The second strongest effect is the effect of adding a mannitol fines fraction <40 μm to carrier particles with 63 μm - 80 μm and 100 μm - 125 μm in size. The addition of these carrier fines results in an increase of the arising netcharge during aerosolization and release of the powder from the DPI. Interestingly Bennet et al. [42] observed the inverse effect when adding lactose carrier fines to coarser carrier particles. They investigated the charging behavior of lactose carriers in a stainless steel cyclone charger and noticed a reduction of the netcharge caused by the addition of the fines. In the present study an increase of the netcharge might be caused on the one hand by the increase of the specific surface of the powder and on the other hand by the increase of the number of particles per volume. The increase of the specific surface area of the powder enhances the ability of the powder to take up charge. This effect was also reported by Karner and Urbanetz [33] who investigated the influence of the particle size on the arising tribo-charge in a tumble blending process. The increased number of particles per volume further enhances the probability of particle-particle and particle-wall contacts. Further as De Boer [41] mentioned the fine carriers, in the present case <40 μm, would have a longer residence time in the inhaler device which would also lead to a stronger charge accumulation. The inverse effect reported by Bennet et al. [42] might have been observed because, as the authors reported, fines adhered to and covered the walls of the cyclone and thus reduced the number of possible particle-wall contacts. However in the present study deposition of particles on the inhaler walls was negligible. It might be possible that the lower particle adhesion to the inhaler walls observed in the present study was due to the fact that the fines used in this study were <40 µm and in the work of Bennet et al. <10 µm. Since finer particles are more adhesive this could be an explanation for the observed inverse effects. However we believe that it is because of the different flow conditions in the Novolizer® compared to a cyclone charger preventing increased particle adhesion. Nevertheless it will be shown that the particle deposition has still a slight impact on some interactions of the influencing factors and also the long time usage of the inhaler devices that will be discussed later.

The third significant factor is particle size. Tribo-charge increases with decreasing particle size. This can also be explained by the impact of the larger specific surface area and the higher number of particles per volume as discussed above. Furthermore the higher charge carried by the 63 µm – 80 µm fraction compared to the 100 µm – 125 µm may also be attributed to the longer residence time of the finer powder fraction in the device as reported by De Boer et al. [41]. However as De Boer et al. mentioned the impact of the residence time does not appear significantly but at particle sizes <75 µm.

In addition to these significant effects three statistically significant interactions between the factors were detected. The addition of the mannitol fraction <40 µm has a stronger impact on the arising netcharge at lower flow rates. This can be seen in table 6.6 that summarizes the mean netcharge differences between the samples containing fines and the sample without carrier fines. The interaction is also illustrated in figure 6.3.

Table 6.6: Mean netcharge differences between the samples containing fines (C3, C4) and the sample without carrier fines (C1, C2)

	60 l/min / nC/g	90 l/min / nC/g
ΔQ(C3 - C1)	987	402
ΔQ(C4 - C2)	272	175

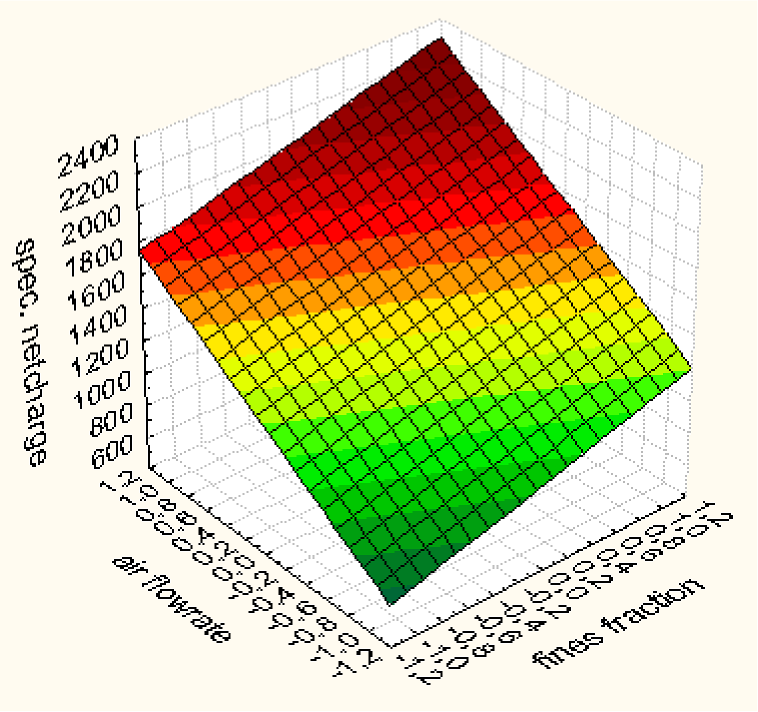

Figure 6.3: Specific netcharge plotted versus air flow rate and fines fraction (results out of DOE-studies; the scaling with -1.2 and 1.2 indicates the low and high level of each factor)

An explanation is that at higher flow rates the charge acquired by the powder is higher. Although the deposition of particles on the inhaler walls was negligible, as mentioned above, the deposition of the carrier fines was slightly higher at high airflow rates due to the higher charge levels. This was observed in practice when disassembling and cleaning the inhaler after the experiments. By this deposition of the fine particles on the inhaler material the influence of the larger specific surface and the higher number of particles per volume, that is caused by the addition of carrier fines <40 µm, is weakened, because the number of possible particle – wall contacts is reduced by the particles adhered to the inhaler. A second explanation is a charge saturation of the inhaler wall that will be explained below in the discussion of the interaction between air flow rate and particle size.

The influence of the particle size is also stronger at lower flow rates. This means that the range between the netcharge arising on the 63 µm - 80 µm carrier particles and the 100 µm - 125 µm particles is greater at 60 l/min flow rate than at 90 l/min flow rate. This can be seen in table 6.7 and graphically in figure 6.4.

Table 6.7: Mean netcharge differences between the samples containing 63 µm – 80 µm carriers (C1, C3) and the sample containing 100 µm – 125 µm carriers (C2, C4)

	60 l/min / nC/g	90 l/min / nC/g
ΔQ(C1 - C2)	223	111
ΔQ(C3 - C4)	938	338

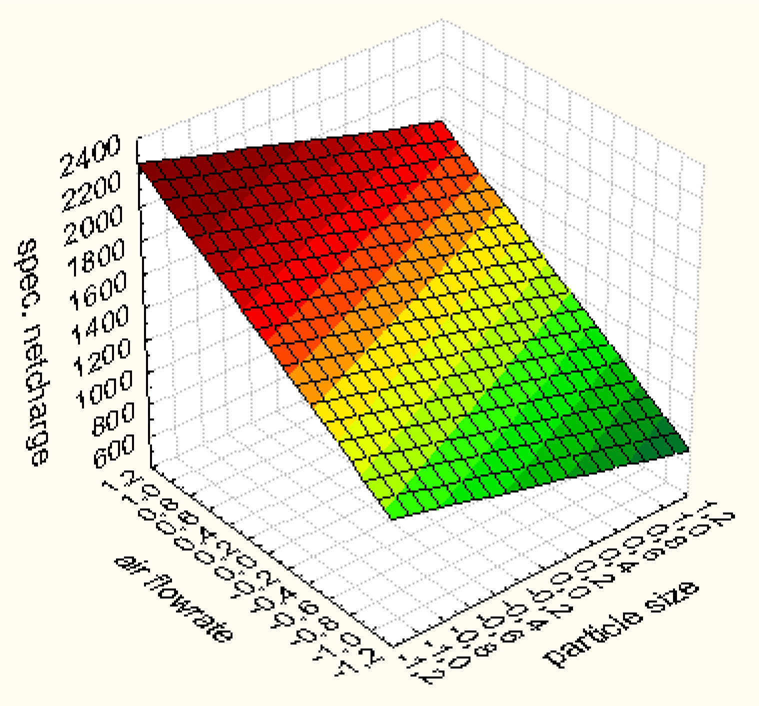

Figure 6.4: Specific netcharge plotted versus air flow rate and particle size (results out of DOE-studies; the scaling with -1.2 and 1.2 indicates the low and high level of each factor)

It is possible that a kind of charge saturation of the inhaler wall caused this interaction. Depending on the surface potential difference between the contacting bodies and their surface area each contacting body (e.g. the inhaler wall) can take up or release a certain magnitude of charge [33]. If now in the case of 90 l/min air flow rate the saturation charge of the inhaler wall is approached or exceeded for the 63 µm - 80 µm fraction the difference between the charges carried by the two different fractions is reduced.

The interaction between the particle size and the addition of a fraction <40 µm appears in the way, that the addition of the fraction <40 µm enhances the influence of the carrier particle size fraction (63 µm - 80 µm and 100 µm - 125 µm). That means that the difference between the netcharges carried by the 63 µm - 80 µm carrier particles and the 100 µm - 125 µm carrier particles is greater when a fraction <40 µm is added to the 63 µm - 80 µm and 100 µm - 125 µm fractions. This is illustrated in figure 6.5.

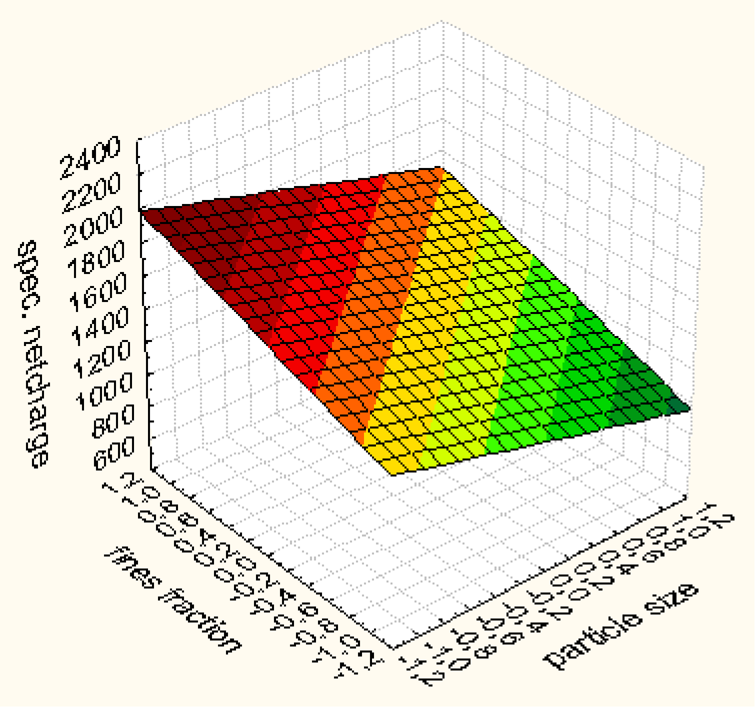

Figure 6.5: Specific netcharge plotted versus fines fraction and particle size (results out of DOE-studies; the scaling with -1.2 and 1.2 indicates the low and high level of each factor)

This fact can also be seen in table 6.7 where C1 and C2 are the mixtures without carrier fines and C3 and C4 the mixtures containing carrier fines <40 µm. So there must be a different particle interaction between the carrier fines and the 63 µm – 80 µm carrier fraction than between carrier fines and 100 µm – 125 µm carrier fraction. It seems that the carrier fines adhered less strongly to 63 µm – 80 µm carriers resulting in more free fine particles and thereby a higher charging tendency of this powder blend. This is possibly the result of the low particle size difference between the fraction 63 µm – 80 µm and the carrier fines <40 µm.

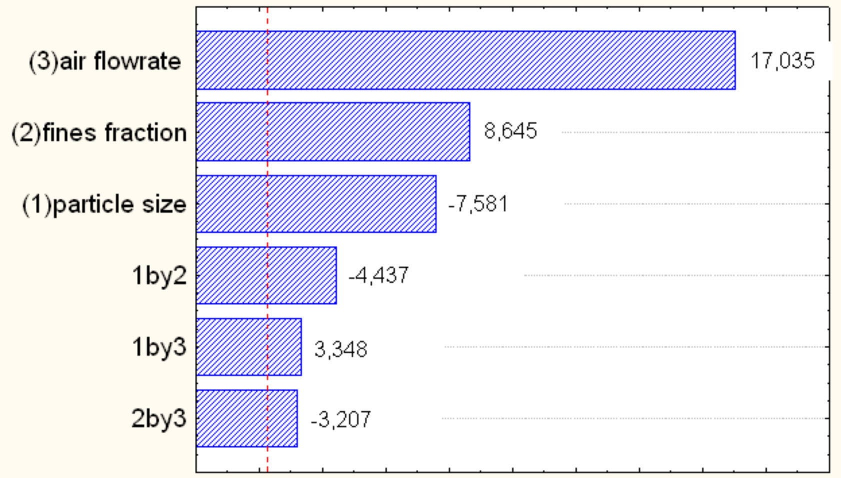

Figure 6.6: Effect-plot of the DOE-studies performed with pure mannitol carrier treating three factors with significance limit p=0.05 (dotted line)

6.3.2 Evaluating the impact of four factors on tribo-charging of adhesive mixtures

To extend the investigations reported in section 6.3.1 the influence of four factors on the tribo-charging of adhesive mixtures consisting of mannitol and salbutamol sulphate was evaluated using DOE. In addition to the factors particle size, fines fraction and air flow rate the API content of the adhesive mixtures was included in the studies. The effect estimation plot of these studies is shown in figure 6.8. Also in the case of the adhesive mixtures it is confirmed that all factors checked have a statistically significant influence on the arising netcharge during aerosolization and release of inhalation powder from the device. Similar to the pure carrier-studies a direct relationship between the netcharge carried by the inhalation powder and the air flow rate and the addition of a fraction <40 μm to the coarser 63 μm - 80 μm and 100 μm - 125 μm carrier particle fractions was found. Further, an indirect relationship between the netcharge and the carrier particle size was observed again. However the addition of API caused a reduction of the netcharge of the adhesive mixtures compared to the pure carriers. This can be seen in figure 6.8 that shows the negative effect of the API-content.

This charge reduction can be attributed to the potential difference (different workfunction of the materials) between mannitol and salbutamol sulphate. This obviously results in a reduction of the netcharge of the blend. Furthermore the different charging behavior leads to stronger interparticle force between unlike particles than between like particles. This means that the API particles exhibit an affinity to the coarse carrier particles (63 μm - 80 μm and 100 μm - 125 μm fraction) as well as the carrier fines fraction (<40 μm) leading to the formation of a particle layer around the coarse carrier that may incorporate also the carrier fines (<40 μm). Furthermore the formation of agglomerates of the API particles and the <40 μm carrier particles is enhanced. These processes additionally lead to a reduction of the number of free single particles and thus the possible number of particle-particle and particle-wall contacts. As discussed in section 6.3.1 this further reduces the arising netcharge and also weakens the influence of the factors particle size, carrier fines fraction and to a minor extent also the airflow rate.

The decreased effect of particle size in the adhesive mixtures (figure 6.8) with respect to the effect of particle size in pure mannitol samples (figure 6.6) might be explained as follows: Due to opposite charging API fines firmly attach to the carrier surface. As the specific surface area of the 100 μm – 125 μm fraction is lower, the number of the API layers covering the carrier particles is higher. Taking into account that the interparticle forces between the carrier and the first API-layer is highest and further taking into account that the interparticle forces between the API layers decrease from the inner layers to the outer ones, the API particles of the outer layers on the 100 µm – 125 µm carriers are less strongly attached than the ones on the 63 µm – 80 µm fraction. This in turn causes more API particles to detach from the 100 µm – 125 µm carrier fraction than from the 63 µm - 80 µm carrier fraction upon aerosolization, which increase the over all specific surface area. In essence, the presence of the API particles increases the overall specific surface area of the 100 µm – 125 µm fraction more than the over all specific surface area of the 63 µm – 80 µm fraction. This is why the impact of the particle size of the carrier is less significant in the adhesive mixtures.

Further also the influence of the carrier fines was weakened through the presence of the API. This also manifests itself in a significant interaction between the two factors. This is illustrated in figure 6.7 and can also be seen in figure 6.8. In this case the interaction cannot be displayed numerically because there are too many influences and interactions to summarize the results through the comparison of two averaged charge values as it was done above in table 6.7. The reduction of the influence of the fines fraction was attributed to the above mentioned adhesion between the API and the carrier fines. Where the presence of the API enhances the formation of agglomerates and thereby reduces the number of free fine particles.

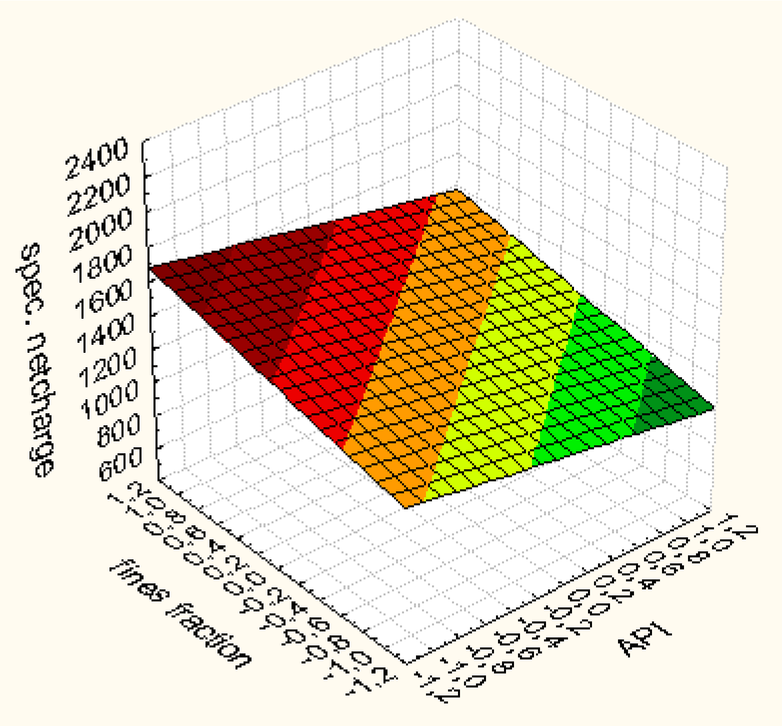

Figure 6.7: Specific netcharge plotted versus fines fraction and API content (results out of DOE-studies; the scaling with -1.2 and 1.2 indicates the low and high level of each factor)

The second significant interaction in this study is between the particle size and fines fraction. This has been found for the pure carriers as well. For the interpretation of the interaction the reader may wish to refer to section 6.3.1. The significance of the interaction is lower compared to the pure carriers, which is due to the fact that the influence of the fines fraction is generally weakened by the presence of the API as discussed above.

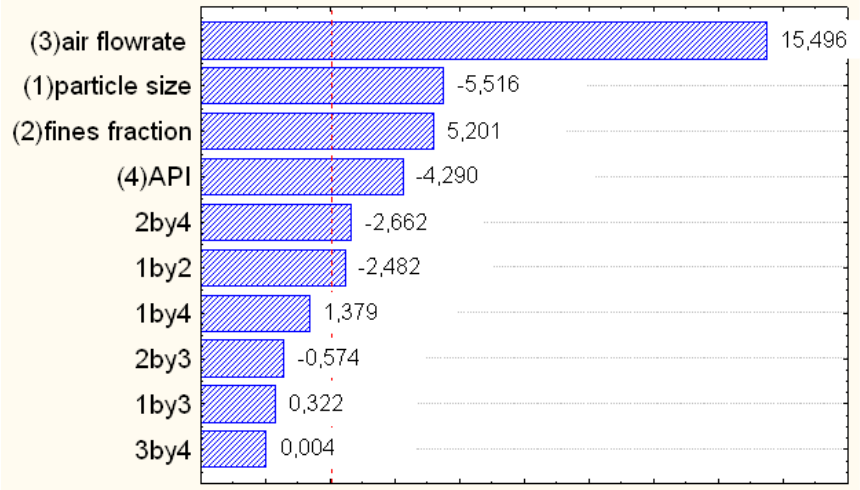

Figure 6.8: Effect-plot of the DOE-studies performed with adhesive mixtures of mannitol and salbutamol sulphate treating four factors with significance limit p=0.05 (dotted line)

In contrast to the pure carriers the interaction of the aerosolization air flow rate and the carrier particle size as well as the interaction of the aerosolization air flow rate and the carrier fines is not significant. This occurred because of the general reduction of the significance of the influence of the factors carrier particle size and fines fraction through the presence of the API.

6.3.3 Evaluating the impact of consecutive releases on tribo-charging of adhesive mixtures

The figures 6.9 – 6.12 show the netcharge arising on the different powder blends during each actuation when the same inhaler device is used for 50 consecutive actuations. At the air flow rate of 60 l/min the netcharge arising on adhesive mixtures released in 50 consecutive doses from the DPI is almost the same for each dose. In contrast to this at 90 l/min air flow rate there is a noticeable trend of decreasing netcharge over the number of actuations. This phenomenon may be attributed to the diminishing driving force of charge transfer from the increasingly charged inhaler-wall to the powder. Since the inhaler is made of electrically insulating polycarbonate charge dissipation between the single actuations may be incomplete. Therefore a residual charge may remain on the inhaler surface. Thus the driving force for charge exchange or charging of the powder respectively might be reduced. However, a plateau is reached where charging and subsequent charge dissipation become equal. The effect of incomplete charge dissipation is more pronounced at 90 l/min as the charge exchanged is higher in this case.

Beside incomplete charge dissipation, particles increasingly tend to stick to the walls of the inhaler as the netcharge carried by the inhaler-wall becomes higher. This in turn further may reduce the number of particle-wall contacts also resulting in a decrease of the netcharge over the number of actuations.

The reasons for the noticeably higher netcharge emerging on the mixtures OM2 and OM4 (based on 100 µm – 125 µm) upon the first two actuations at 90 l/min are not fully understood. A possible explanation might be non-uniformity of the released mass.

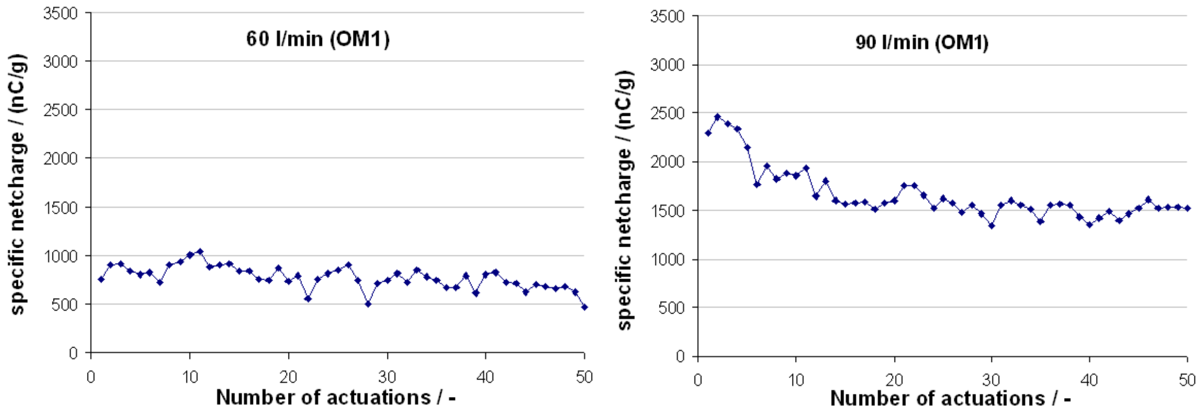

Figure 6.9: Specific netcharge of OM1 over 50 actuations at 60 l/min and 90 l/min air flow rate (mean of n=3)

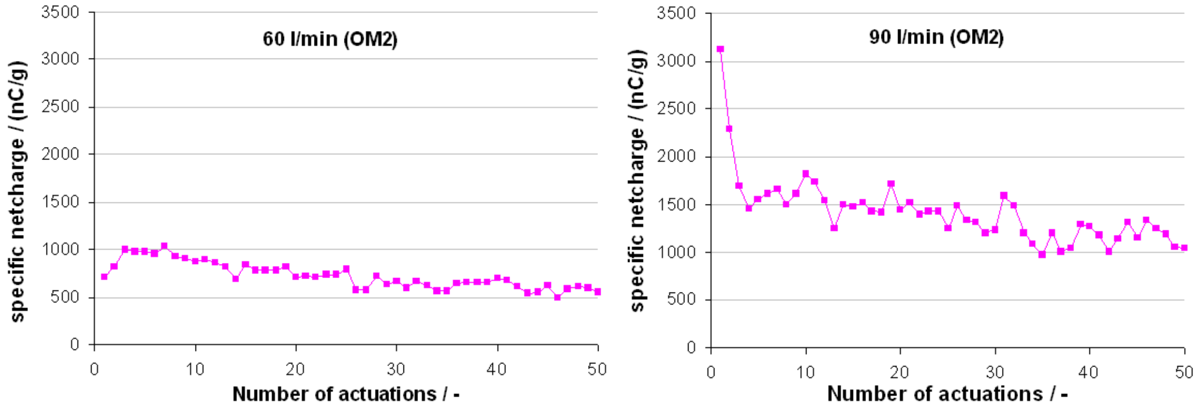

Figure 6.10: Specific netcharge of OM2 over 50 actuations at 60 l/min and 90 l/min air flow rate (mean of n=3)

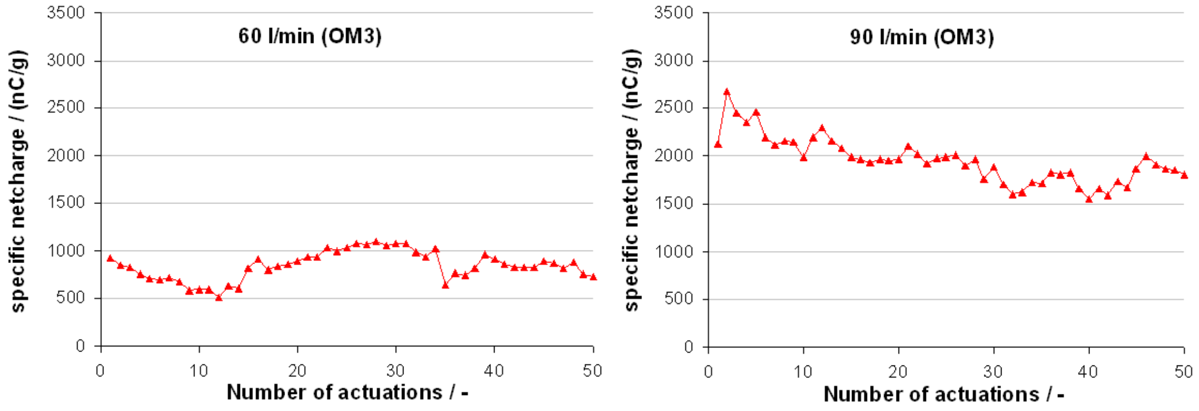

Figure 6.11: Specific netcharge of OM3 over 50 actuations at 60 l/min and 90 l/min air flow rate (mean of n=3)

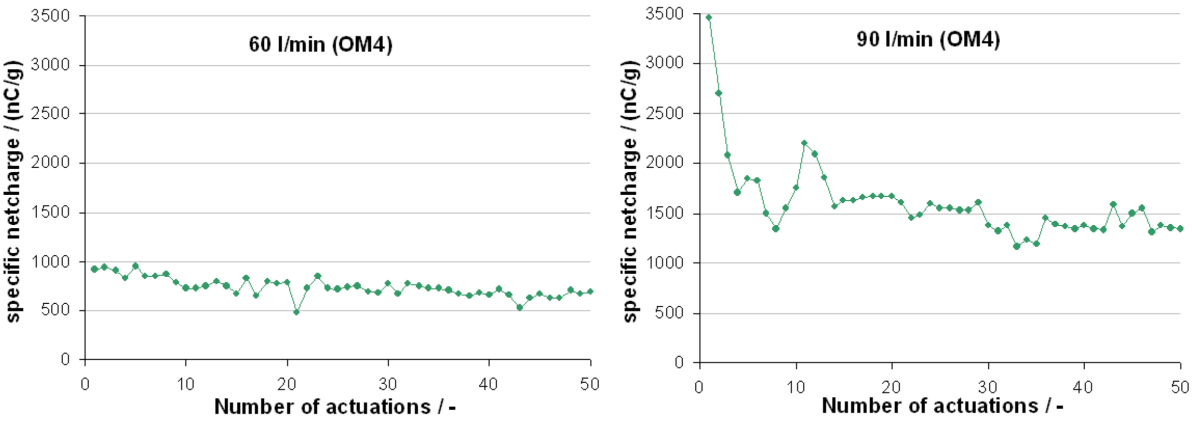

Figure 6.12: Specific netcharge of OM4 over 50 actuations at 60 l/min and 90 l/min air flow rate (mean of n=3)

6.4 Conclusion

Relevant data concerning the triboelectric behavior of the alternative carrier material mannitol have been generated. Tribo-charge arising on adhesive mixtures upon the release from a common DPI device can be influenced by controlling relevant parameters. It has been figured out that the factors particle size, presence of carrier fines <40 µm, presence of API and aerosolization air flow rate significantly impact the magnitude of charge. The netcharge increases with increasing amount of carrier fines as well as increasing air flow rate. Further the netcharge decreases with increasing particle size and the presence of API. This means that tribo-charging may be minimized when using coarse carrier particles, a low fines fraction and a low aerosolization air flow rate. However it has to be considered that too low air flow rates may reduce drug–carrier detachment finally reducing the amount of drug reaching the target site, the deep parts of the lungs. For this reason it will be important to correlate the tribo-charge with the inhaler performance attributes like the fine particle fraction (FPF) which is the fraction of the drug that is able to travel along the tiny airways finally reaching the target site. In addition to the significant impact of the single factors also interactions have been proven. In the additional “long time actuation studies” it has been shown that the charging behavior depends on the number of actuations at higher air flow rates. At an air flow rate of 60 l/min the netcharge arising on adhesive mixtures released in 50 consecutive doses from the DPI is almost the same for each dose. In contrast to this at 90 l/min air flow rate there is a noticeable trend of decreasing netcharge over the number of actuations.

6.5 References

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7

Impact of carrier surface roughness and shape on tribo-charging during aerosolization and DPI performance

For active pharmaceutical ingredients (API) delivered to the lung it is of main importance that they reach the deeper lung, in order to cause the intended therapeutic effect. To ensure lung deposition and uniform dosage, adhesive mixtures of API particles in the size range of 0.5 µm – 5 µm and inert carrier particles in the size range of 50 µm – 200 µm are used in dry powder inhalers (DPI). The performance of DPIs and adhesive mixtures are mainly governed by interparticle forces like Van der Waals and tribo-electric forces between the active and the carrier as well as between the particles of the adhesive mixture and between adhesive mixture particles and inhaler wall. The arising tribo-charge on the mixtures during handling is influenced by various particle and material characteristics. For adequate inhaler performance especially the charge arising on the powder during the release from the inhaler is of interest. Therefore the aim of this work is to investigate how tribo-charging during aerosolization and release of the powder from a common DPI (Novolizer®) is affected by the carrier particle characteristics of surface roughness and shape and how the accumulated charge further influences the inhaler performance. Tribo-charge measurement of the pure carriers and the adhesive mixtures was performed using an open-end faraday cup. As model API and carrier salbutamol sulphate and spray dried mannitol were used. It was possible to show that tribo-charging during aerosolization is significantly influenced by the above mentioned particle characteristics. Further it was shown that this charge has also significant effects on important performance properties of the DPI like coefficient of variation of the released mass, fine particle dose and fine particle fraction.

7.1 Introduction

For active pharmaceutical ingredients (API) delivered to the lung it is of main importance that they reach the deeper lung, in order to cause the intended therapeutic effect. In order to travel along the tiny airways finally reaching the deep lung, it is essential that the API particles of dry powder inhalers (DPI) have an aerodynamic diameter between 0.5 µm and 5 µm [1]. Unfortunately such fine powders are very cohesive resulting in poor flowability and dosing behavior since the dosing in DPIs is performed by flowing of the powder from a reservoir into well defined orifices. One possibility to improve the flow properties is to attach the small API particles on the surface of larger carrier particles by a simple mixing procedure to get so-called adhesive mixtures. These carrier particles are made of for example lactose, glucose or mannitol and have to have an adequate size (50 µm - 200 µm) to ensure good flowability of the mixtures. The usability of these mixtures depends on the inter-particle interactions between the drug and the carrier that on the one hand must be strong enough to ensure mixing homogeneity and stability of the mixtures during powder handling, transport, storing and dosing, but on the other hand weak enough to allow the detachment of the API particles from the carriers during inhalation.

The interactions between the particles are mainly governed by inter-particle forces like Van der Waals and triboelectric forces and the contact area between the particles. One approach to alter this contact area is to tailor carrier particles with defined shape and surface roughness. This is possible by spray drying mannitol carrier particles at different drying conditions e.g. different air outlet temperatures [2].

Controlling the triboelectric forces is a little bit more complex. Triboelectric charge is generated when two different materials are brought into contact and then are separated [3]. Since drug as well as carrier particles consist of insulating material, they are unable to dissipate and therefore accumulate charge after each contact in any process where the powder comes into contact with surfaces. In which way sign and magnitude of the charge are influenced is still poorly understood and therefore difficult to predict. This problem gets even more complex when two or more materials and more than one influencing factors are involved. Especially the arising of charge in metal / insulator contact and insulator / insulator contact is very complex [4]. Unfortunately particularly this case appears in many pharmaceutical processes and also in DPI-technology.

During aerosolization and release from a DPI device a high number of contacts among inhalation powder particles and between particles and inhaler device may be observed. In addition to this, depending on the DPI device, very high impact and shear velocities may occur. The high air and contact velocities are intended to detach the API particles from the carrier particles. However, these contacts may result in very high charge magnitudes arising on the inhalation powder.

Sign and magnitude of the arising charge depend on many factors such as particle size and shape [5], surface roughness [6,7], nature and work functions [8], impurities [9–11], amorphicity [12], contact material [13,14], relative humidity [15] and the energy of contact [16,17]. A summary of these influences can be found at Karner and Urbanetz [18].

Considering these influencing factors it can be seen that by altering the contact area between API and carrier by modification of carrier properties like particle shape and surface roughness also the triboelectric charging behavior of the powder might be influenced and thereby additional interparticle forces might be caused.It is important to investigate if carrier particle modification e.g. via spray drying alters the triboelectric charging characteristics of the inhalation powder and if the resulting powder properties and inhaler performance like dosage uniformity and fine particle fraction (FPF) are further affected by this tribo- charge as it is supposed in literature [19].

For these reasons the aim of the present work is to study the tribo-electric charging behavior of adhesive mixtures as well as of the pure carriers based on five surface modified carrier powders spray dried by Littringer et al. [2]. The modified carrier particles differ in particle surface roughness but also in shape. The netcharge arising on the pure carriers and adhesive mixtures during aerosolization and release form a common dry powder inhaler device (Novolizer®) is measured using an open-end faraday cup. Furthermore the influence of the tribo-charge on the inhaler performance (described in Littringer et al. [20]) is investigated and evaluated.

7.2 Materials and Methods

7.2.1 Materials

The mannitol samples of different surface roughness were prepared on a pilot-scale co-current spray dryer with a diameter of 2.7 m and an overall height of 3.7 m (proprietary construction of the research group of Prof. Walzel, Department of Biochemical- and Chemical Engineering, TU Dortmund, Germany). A rotary atomizer was used for spray generation (operated at 7200 rpm). The set-up of the spray dryer and the generation of particles of different surface roughness are described in detail by Littringer et al. [2]. Briefly samples of different surface roughness were prepared from aqueous mannitol solutions (15 % [w/w]) with a feed rate of 10 l/h. Five powder samples with different surface roughness were produced by spray drying at predetermined outlet temperatures between 67 °C and 102 °C. According to the outlet temperature the samples were named M67, M80, M84, M92 and M102.

Micronized salbutamol sulphate (USP25 quality, Selectchemie, Switzerland; $x_{3.10}$ = 0.46µm±0.00 µm, $x_{3.50}$ = 1.69±0.01 µm, $x_{3.90}$ = 5.65±0.05 µm) was used as model API for the adhesive mixtures. For the preparation of the adhesive mixtures stainless steel mixing containers with an inner diameter of 32 mm and an inner height of 45 mm were used.

As dry powder inhaler device a Novolizer® (MEDA Pharma GmbH & Co. KG, Germany) was used. In fact three different Novolizer® devices were used alternately.

7.2.2 Sample preparation

The adhesive mixtures of mannitol and salbutamol sulphate were prepared by tumbling the powder mixtures in stainless steel containers for 90 minutes at 62 rpm using a tumble blender (T2F Turbula®, Willy A. Bachofen AG - Maschinenfabrik, Switzerland). A 0.1 g of salbutamol sulphate and 4.0 g of the carrier (drug content of 2.4 % (w/w)) were weighed into the mixing vessels using the sandwich method.

In order to gain correct and reproducible experimental results especially with respect to the triboelectric powder properties it is of main importance that the powder samples are electrically discharged and equilibrated at a defined and constant relative humidity before performing the experiments. Therefore the powder samples were spread in thin layers on earthed aluminum foils and stored for 24 hours. This is a standard procedure for discharging insulating powders as reported in literature [21]. The storage time of 24 hours is adequate for powder discharge since the powder was spread in thin layers and thereby had a large contact area to the grounded metal. The procedure of discharging insulating powder by grounding was validated in prior studies [22]. This procedure was performed inside a walk-in environmental chamber at the constant relative humidity of 43±2 %RH and temperature of 22±2 °C.

All parts of the Novolizer® were first rinsed with deionized water, then with ethanol and finally once again with ultrapure water. After washing, the inhalers were dried using compressed air and were also stored inside the environmental chamber on an earthed stainless steel plate for at least 24 hours. After discharge and conditioning the samples were gently poured from the aluminum foils directly into the reservoir of the Novolizer®. After filling the reservoirs, the Novolizer® was assembled and kept inside the environmental chamber for another two hours prior to the experiment.

7.2.3 Particle characterization of the carriers

The carrier particles were characterized with respect to their particle size distribution, specific surface area, surface roughness, particle shape, surface topography, powder density, bulk and tapped density, powder crystallinity and particle stability during inhalation. For detailed insight into the used methods and all characterizations that were performed see Littringer et al. [20].

7.2.4 DPI performance characteristics

In order to assess the behavior of the adhesive mixtures during dosing, aerosolization and inhalation crucial properties regarding these processes were measured by Littringer et al. [20]. These were the metering reproducibility of the adhesive mixtures and the fine particle fraction (FPF) and fine particle dose (FPD). Metering reproducibility is assessed by actuating the inhaler and determining the released mass by weighing the inhaler before and after actuation. The standard deviation of the released mass can then be taken as a measure of metering reproducibility. Details are reported in Littringer et al. [20]. FPD and FPF are determined according to the European Pharmacopoeia using the Next Generation Impactor (assessment of fine particles, Ph. Eur., 7.0). Details are described in Littringer et al. [20].

7.2.5 Charge measurement

Since electrostatic charge is very sensitive to humidity the charge measurement was also performed inside the walk-in environmental chamber (same conditions as mentioned above in section sample preparation) using an open-end faraday cup (proprietary construction) connected to a high resistance electrometer (Keithley 6517 B, Keithley Instruments, USA). Figure 7.1 shows an illustration of the experimental setup. The setup consists of an inhaler that is placed inside the open-end faraday cup and is connected to an 80 cm long PVC-pipe through a mouthpiece. On the other end of the pipe there is a filter to collect the aerosolized inhalation powder. Behind the filter there is a flow control device (TPK, Copley Scientific, United Kingdom) and a vacuum pump (SV 1025C 000 IKXX, Busch, Switzerland).

The principle of the charge measurement procedure is that the inhalation powder is aerosolized and sucked out of the inhaler by the airflow generated by the vacuum pump. The powder is sucked through the PVC-pipe away from the faraday cup and gets caught in the filter. It is very important that the charged powder is carried far enough away from the measuring faraday cup. This is the reason why the PVC-pipe is installed between the inhaler and the filter where the powder is caught.

When the powder is sucked out of the inhaler it gets into contact with the material of the inhaler and thereby takes up triboelectric charge. The same magnitude of charge but with opposite polarity is left behind in the inhaler. This left behind charge in the inhaler induces a charge with the same magnitude but opposite polarity in the electrically conducting material of the inner faraday cup (measuring cup). The outer faraday cup (protection cup) is grounded and works as a shield to protect the inner cup and thereby the whole measurement from disturbing external influences. The two cups are made of copper and are divided by an electrically insulating material (Teflon™).

The cups are connected to a high resistance electrometer that is able to measure the voltage or charge, respectively between the measuring cup and the protection cup (ground) which in fact is the triboelectric netcharge carried by the aerosolized inhalation powder. The electrometer is further connected to a computer for data acquisition. The same measurement principle was also used by Chow et al. [21]. A flow control device on the one hand controls the air flow rate through the system by a valve. On the other hand it controls the total amount of air that is sucked through the inhaler by controlling the suction time.

For all inhaler testing experiments (charge measurement, delivered dose, fine particle assessment, …) the air flow rate was adjusted to 78.2 l/min. Suction time was set to 3.1 s to get a total air volume sucked through the inhaler of approximately 4 l.

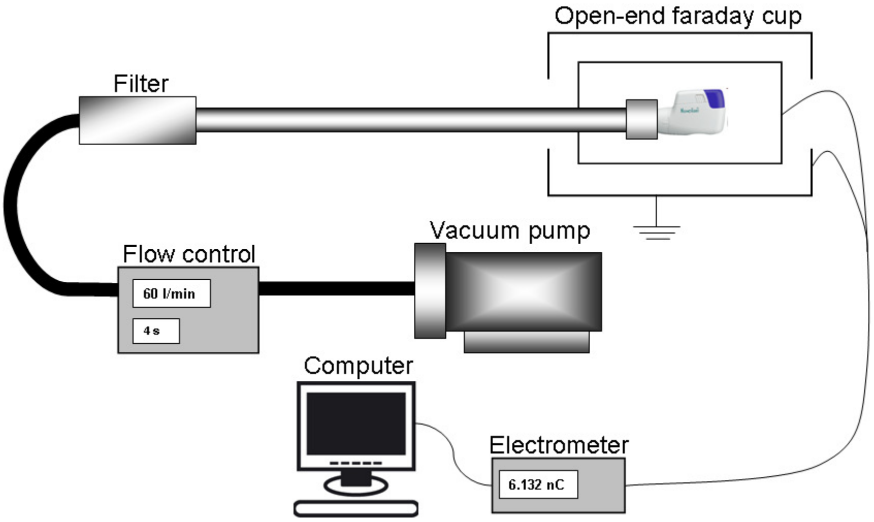


Figure 7.1: Schematic illustration of the experimental measurement setup

The actual measurement procedure was as follows: The Novolizer® was mounted to the mouth piece and actuated. Then it was inserted into the faraday cup. The electrometer was turned on two hours before measurement to minimize variability of the measurement signal. The vacuum pump was switched on half an hour before measurement to ensure a constant air flow rate. The charge measurement was started by adjusting the electrometer at zero and initiating the aerosolization by actuating the flow control device (opens the valve for predetermined duration).

The first stable charge signal was taken as the netcharge carried by the powder. The mass specific netcharge was calculated by dividing this netcharge by the released powder mass. The released powder mass was determined by weighing the Novolizer® before and after actuations. These masses were not determined after each single actuation. This would induce too much disturbance in the very sensitive charge measurement process. The released mass was measured after 20 actuations and by dividing this mass by 20 the mass released per actuation was calculated and further used to calculate the mass specific netcharge. This procedure of 20 actuations was repeated three times. Afterwards the mean value of the netcharge and the coefficient of variation were calculated.

7.3 Experimental results and discussion

7.3.1 Particle characterization of the carriers

7.3.1.1 Surface topography

The SEM micrographs in figure 7.2 show that spray drying of mannitol at different outlet temperatures leads to the formation of particles of different surface roughness. At 67 °C outlet temperature (M67), the carrier surface consists of rod shaped crystals of approximately 3 µm in length. At intermediate temperatures (M84) the particle surface gets smoother, due to smudging of the single crystals at the surface. At higher temperatures (M102), the surface roughness increases again, due to the presence of smaller, single crystals at the particle surface [2].

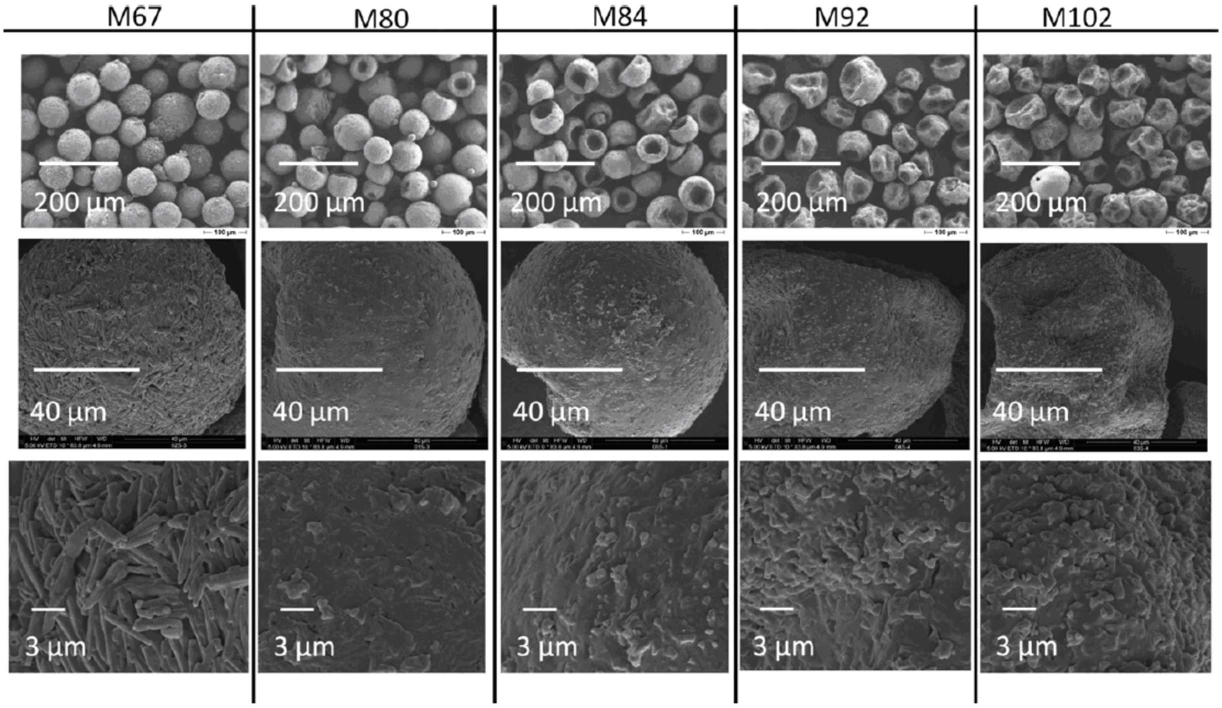
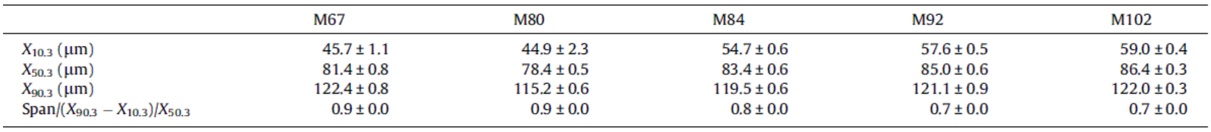


Figure 7.2: SEM micrographs of the spray dried carrier particles (taken from Littringer et al. [2])

7.3.1.2 Particle size distribution

Table 7.1 shows that the five carrier types have a median particle diameter of approximately 80 µm to 85 µm. Further all products have a narrow particle size distribution shown by a span-value $[(x_{90,3} - x_{10,3})/x_{50,3}]$ lower than 1 [2].

Table 7.1: Significant particle diameters (mean ± SD, n = 3) of the carrier particles (taken from Littringer et al. [2])



	M67	M80	M84	M92	M102
$X_{10.3}$ (µm)	45.7 ± 1.1	44.9 ± 2.3	54.7 ± 0.6	57.6 ± 0.5	59.0 ± 0.4
$X_{50.3}$ (µm)	81.4 ± 0.8	78.4 ± 0.5	83.4 ± 0.6	85.0 ± 0.6	86.4 ± 0.3
$X_{90.3}$ (µm)	122.4 ± 0.8	115.2 ± 0.6	119.5 ± 0.6	121.1 ± 0.9	122.0 ± 0.3
Span/$(X_{90.3} - X_{10.3})/X_{50.3}$	0.9 ± 0.0	0.9 ± 0.0	0.8 ± 0.0	0.7 ± 0.0	0.7 ± 0.0

7.3.2 Charge measurement of the pure carriers

To get a basic idea how the particle characteristics influence the charging behavior of the inhalation powder (without the influence of the API) during the aerosolization process samples of the pure carrier were dispensed from the Novolizer® and charge was measured. The results of these charge measurements can be seen in figure 7.3.

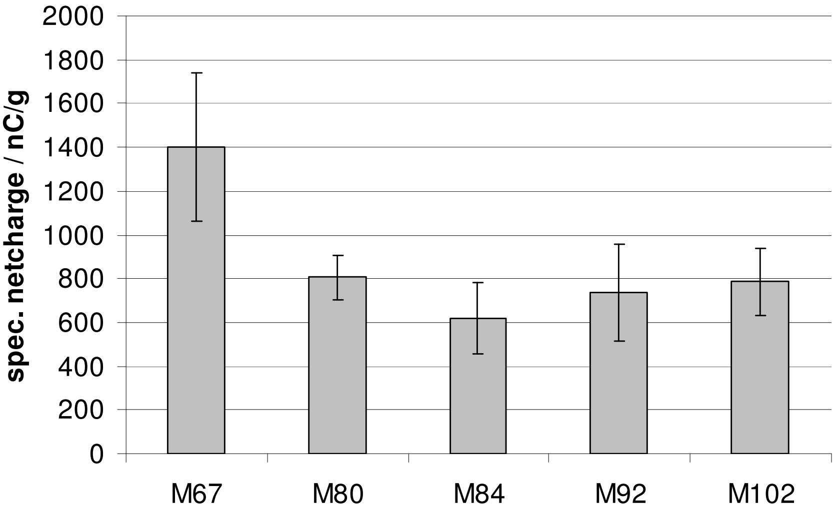


Figure 7.3: Specific netcharge of the pure carriers M67, M80, M84, M92, M102 acquired during aerosolization and release from the Novolizer® (mean ± SD, n = 3)

It can be seen that the different surface properties and shape of the carriers lead to a different tribo-charging behavior. Carriers spray dried at low outlet temperature (M67) acquired a significantly higher charge than the other samples. The charge differences between the other carriers M80 to M102 are not significant. A discussion of these results will follow in section 7.3.4.

7.3.3 Charge measurement of the adhesive mixtures

In figure 7.4 it is clearly evident that also the tribo-charging of adhesive mixtures containing the different carriers during aerosolization and release form the inhaler device is influenced by the carrier particle properties. Similar to the pure carrier studies also in these measurements the mixture containing the carrier spray dried at low outlet temperature (M67) reached the highest charge. However the mixtures containing M80 and M84 show only a slightly lower charge compared to M67. And further the mixtures with M92 and M102 have a significantly lower charge than M67, M80 and M84.

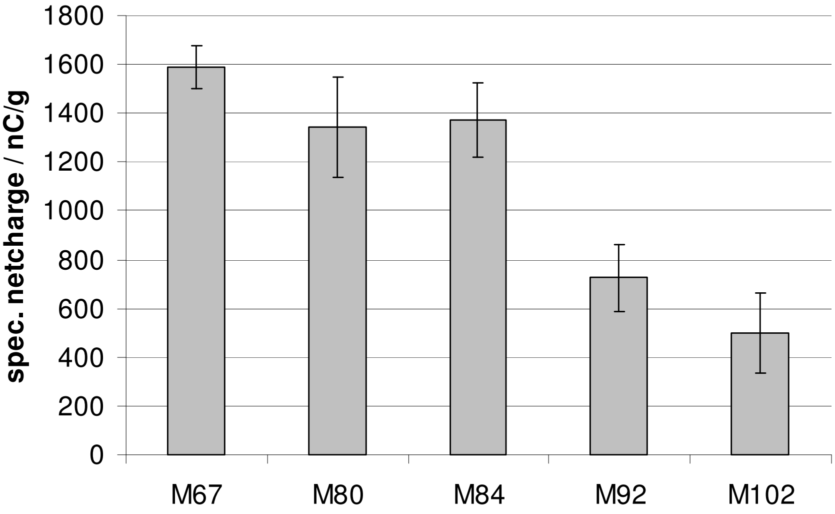


Figure 7.4: Specific netcharge of the adhesive mixtures containing the carriers M67, M80, M84, M92, M102 acquired during aerosolization and release from the Novolizer® (mean ± SD, n = 3)

Comparing figure 7.3 and figure 7.4 it is apparent that the pure carrier M67 and its mixtures as well as the pure carriers M92 and M102 and their mixtures carry charges almost in the same range. Whereas the mixtures with M80 and M84 took up significantly higher charge than the pure carriers M80 and M84. The discussion of these results will be given in section 7.3.4.

7.3.4 Correlation of the charge measurements with the particle characteristics

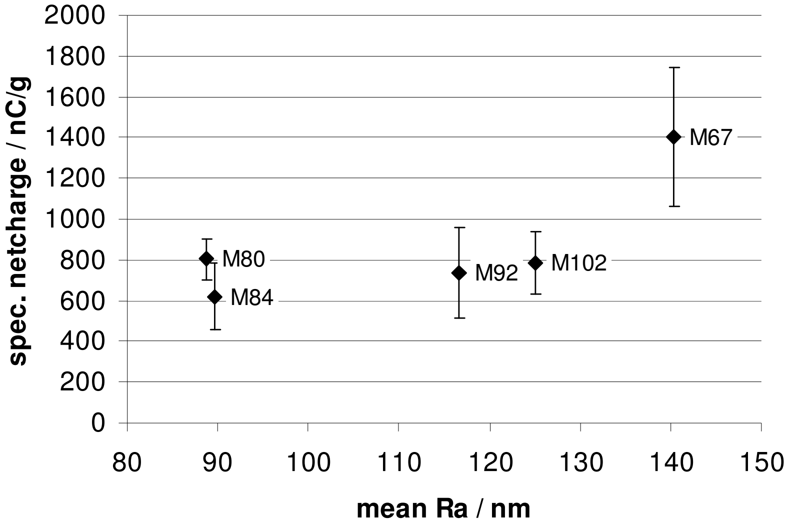


Figure 7.5: Specific netcharge carried by the pure carriers plotted versus the mean Ra value of the carriers (mean ± SD, n = 3)

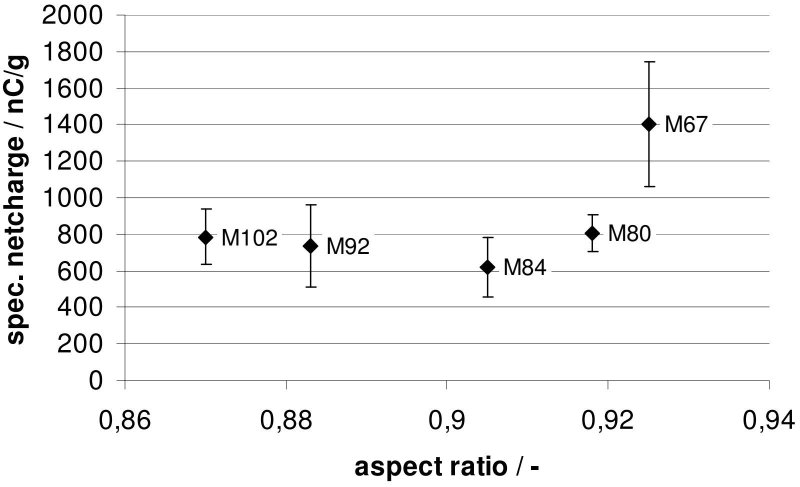


Figure 7.6: Specific netcharge carried by the pure carriers plotted versus the aspect ratio of the carriers (mean ± SD, n = 3)

In Figures 7.5 the specific netcharge carried by the pure carriers is plotted versus the mean Ra value, that is a measure for surface roughness and that is defined as the average roughness integrated over the particle surface. In figure 7.6 the specific netcharge carried by the pure carriers is plotted versus the aspect ratio. Relatively weak correlations between the netcharge and the two particle characteristics can be observed. The coefficient of correlation between the roughness and the netcharge was calculated with 0.7408 and between aspect ratio and netcharge with 0.5511. The impact of surface roughness and the aspect ratio on tribo-charging can be explained as follows. First the aspect ratio is a measure for the sphericity of the particles. When looking at the SEM-images in figure 7.2, it can be seen that the sphericity decreases and the waviness of the particles increases with increasing drying outlet temperature. This is especially true for M92 and M102. Particles of M67 are nicely spherical. This applies more or less also to M80 and M84, whereas particles of M92 and M102 look shriveled. That means that an increase in sphericity and a decrease of waviness causes the tribo-charge to increase. This behavior may be attributed to two facts. First for the spherical particles the probability of particle-wall contacts is similar at each point of the particle surface leading to a uniform charge distribution over the whole particle surface. In contrast the shriveled particles may not contact the inhaler wall but at their edges leading to a charge saturation on these edges (unless the charge is distributed over the whole particle surface area as a result of surface conductivity). Thus the edges do not take up further charge. Consequently the overall charge of the shriveled particles is lower than for the spherical ones.

The second explanation is that the non-spherically shaped particles might have a lower residence time inside the cyclone of the Novolizer® and thereby less time for charge uptake. The residence time of the particles directly correlates with their aerodynamic diameter. The lower the aerodynamic diameter the lower is the residence time within the inhaler [20]. The aerodynamic diameter of a particle is defined as the diameter of a hypothetical sphere of density 1 g/cm^3 having the same terminal settling velocity in calm air as the particle under investigation, regardless of its geometric size, shape and true density. The settling velocity of a particle depends on three forces, the weight force, the lift force and the drag force. The lift force can be neglected since the density of air is low. The weight force is the same for all mannitol particles considered in the present study since they have the same weight due to the fact that the droplet size generated by the spray dryer was the same for all particles under investigation and the particle size of the spray dried products is similar. The drag force is mainly affected by the cross section area and the drag coefficient of the particles. The cross section area of the different carrier particles does not differ much, but the drag coefficient of the irregular shaped particles (M102) should be higher than that of the nicely spherical shaped ones (M67). That results in a higher drag force, further in a lower settling velocity, further in a lower aerodynamic diameter and in the end in a lower residence time of the shriveled particles. In addition to a different aerodynamic diameter also a diverse rolling or bouncing behavior of the particles in the inhaler-cyclone might result in diverse residence times of the different powder types. While the more spherically shaped particles are able to roll over the blades in the inhaler-cyclone the shriveled particles with their edges more bounce off the blades into the main air stream. This would also increase the probability of the shriveled particles to be taken out of the inhaler and thereby shorten the residence time.

Regarding surface roughness, in theory an increase in surface roughness would result in a lower charging in the inhaler due to a lower contact area (particle – inhaler) and charge saturation on the peaks of the rough particles as described above for the waviness. Apparently this is not the case in the present study as tribo-charge is highest for the powder with the highest roughness (M67) (figure 7.5). An explanation might be that higher roughness results in a larger specific surface area which may take up more charges before saturation is reached [22] if surface conductivity is sufficient.

In the case of the adhesive mixtures of carrier and API there is no correlation of the netcharge with the Ra value of the carrier (figure 7.7). A coefficient of correlation of -0.1746 was calculated. This is probably due to the presence of the drug particles on the carrier surface which gives the surface of the particles of the adhesive mixture a similar roughness independent of the carrier surface roughness. Consequently the charge acquisition of particles of the adhesive mixture is similar and not dependent on the surface roughness of the carrier. It is likely that the API particles completely covered the surface of the carriers resulting in the fact that during release of the powder from the inhaler primarily just the API comes into contact with the inhaler and not the carrier. Thereby the influence of the surface roughness of the carrier is compensated and thus the influence of the aspect ratio becomes more important and its correlation to the netcharge gets clear (figure 7.8). An almost linear relationship with a regression coefficient of 0.9492 and a correlation coefficient of 0.9743 was observed.

Compared to this the correlation of the aspect ratio and the specific netcharge carried by the pure carriers is rather weak (Figure 7.6). This is due to the fact that besides the aspect ratio also the surface roughness that decreases from M67 to M84 impacts tribo-charging. Vice versa the correlation of the surface roughness and the specific netcharge carried by the pure carriers is rather weak (Figure 7.5), because besides the surface roughness the aspect ratio impacts tribo-charging.

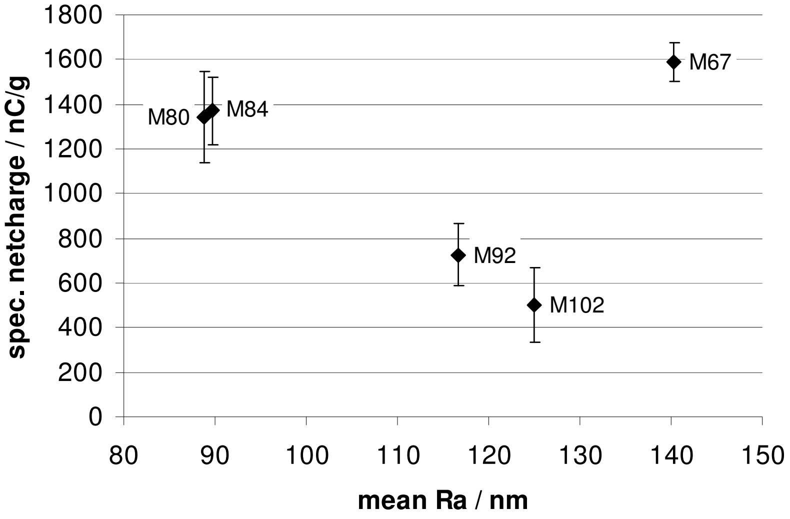


Figure 7.7: Specific netcharge carried by the adhesive mixtures plotted versus the mean Ra value of the carriers (mean ± SD, n = 3)

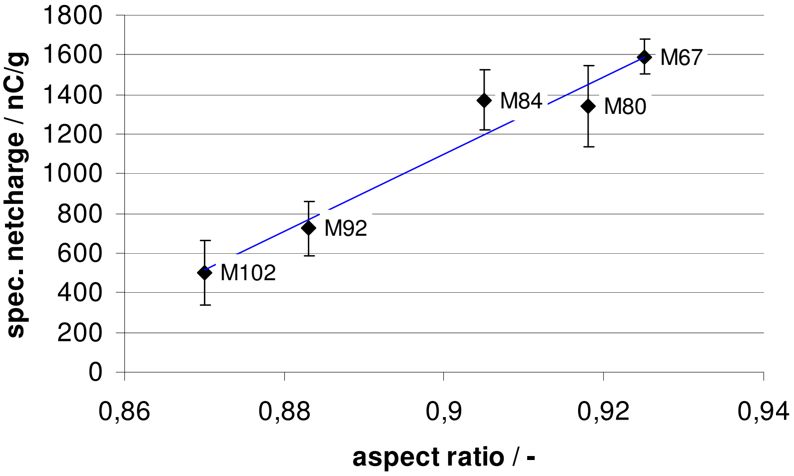


Figure 7.8: Specific netcharge carried by the adhesive mixtures plotted versus the aspect ratio of the carriers (mean ± SD, n = 3)

7.3.5 Correlation of the charge measurements with the inhaler performance

7.3.5.1 Aerodynamic properties of the adhesive mixtures (FPD, FPF)

In figure 7.9 and figure 7.10 a strong correlation between the FPD as well as the FPF and the specific netcharge of the pure carriers is observable. An almost linear relationship between FPD (coefficient of regression 0.9699; coefficient of correlation 0.9848) and FPF (coefficient of regression 0.9938; coefficient of correlation 0.9969) and the charging tendency of the pure carriers can be observed. Mixtures containing the carriers with the stronger charging tendency showed a higher FPD and FPF. This was explained by two facts.

First, it is likely that the carrier with the stronger charging tendency during release form the inhaler also exhibits a similar charging behavior during mixing and production of the adhesive mixtures. Adi et al. [14] and Elajnaf et al. [13] already showed that mannitol as well as salbutamol suphate charge negatively in stainless steel mixing containers. In this case higher tribo-charge on the carriers would result in repulsive forces between API and carrier. This would further result in less intensive contacts or lower contact areas between API and carrier during mixing and thus less strong remaining adhesion forces (Van der Waals Forces) between them after charge dissipation [23]. This results in higher FPD and FPF. So the correlation of the FPF is actually a correlation to the tribo-charging of the carrier during mixing rather than a correlation to the tribo-charging of the carrier during aerosolization. However as the tribo-charging behavior of the carrier during aerosolization and mixing seems to be similar, a correlation between the FPF and the tribo-charge acquired by the carrier during aerosolization is found.

Further, if the API detaches from the carriers during release from the inhaler a higher charge uptake of the separated carriers during this release process would also enhance repulsive forces between API and carrier when the two materials charge in the same polarity and thus hinders reattachment.

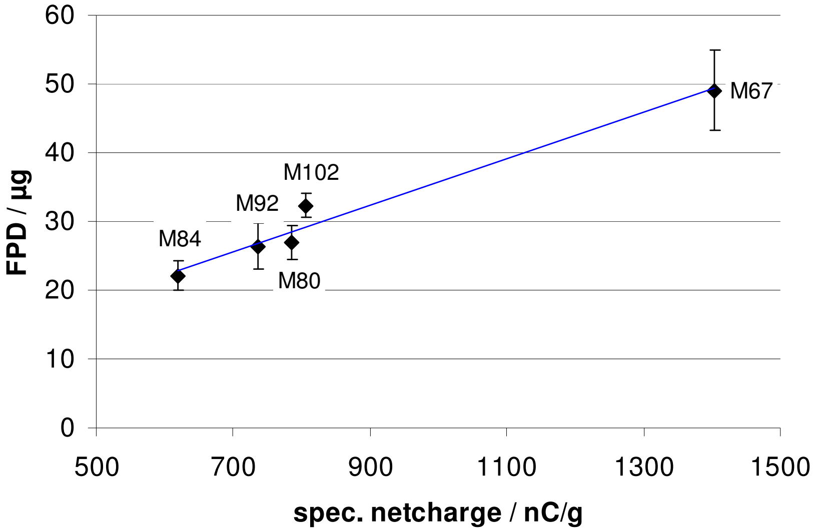


Figure 7.9: Fine particle dose of the adhesive mixtures (mean ± SD, n = 3) plotted versus the specific netcharge of the pure carriers

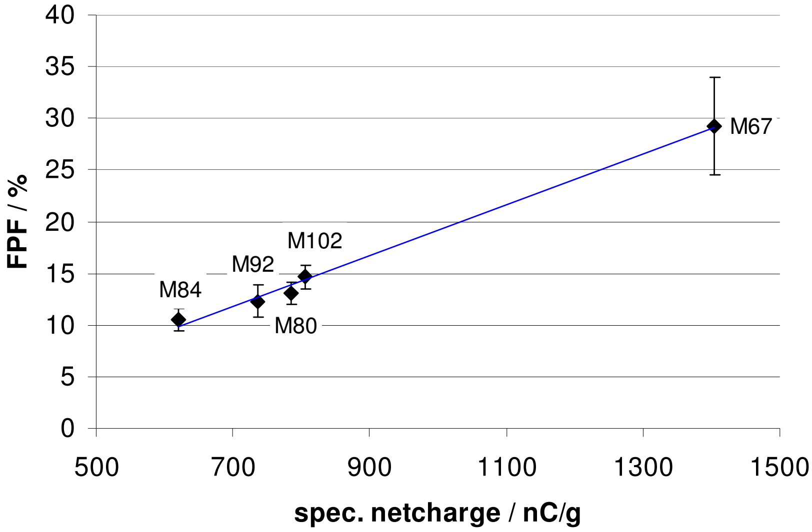


Figure 7.10: Fine particle fraction of the adhesive mixtures (mean ± SD, n = 3) plotted versus the specific netcharge of the pure carriers

In contrast the FPD and FPF did not show a strong correlation to the charge measured for the adhesive mixtures. For both FPD and FPF correlation coefficients in the range of 0.55 where calculated.

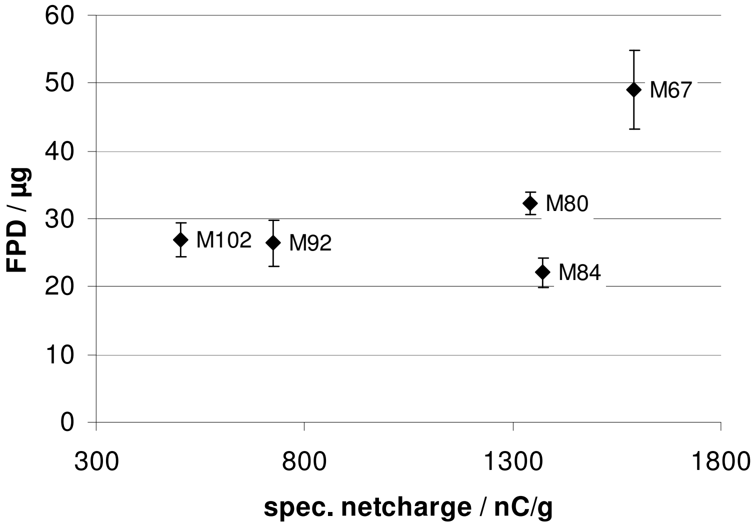


Figure 7.11: Fine particle dose of the adhesive mixtures (mean ± SD, n = 3) plotted versus the specific netcharge of the adhesive mixtures

The fact that the FPD and FPF of the adhesive mixtures correlates with the tribo-charge of the pure carriers is a quite interesting fact. The charge measured for the adhesive mixtures mainly result from API to inhaler contacts. But it seems that the FPF, which is a function of the detachment behavior of API and carrier, more depends on the charging behavior of the carrier particles and thus on the interparticle forces between the API and the carrier which is displayed by the tribo-charge studies of the pure carrier.

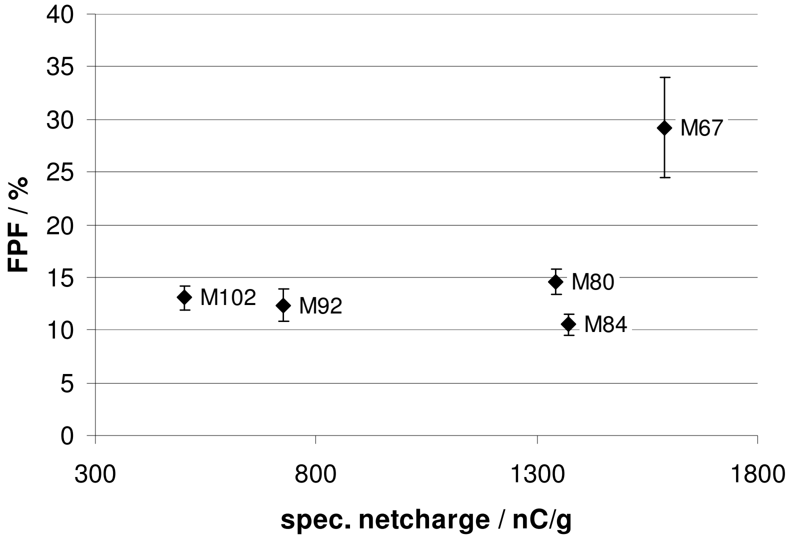


Figure 7.12: Fine particle fraction of the adhesive mixtures (mean ± SD, n = 3) plotted verses the specific netcharge of the adhesive mixtures

7.3.5.2 Coefficient of the variation of the metered mass of the adhesive mixtures

In figure 7.13 it can be seen that the coefficient of variation of the metered mass of the different adhesive mixtures do not differ significantly. Despite the different charging behavior of the carrier powders during aerosolization, tribo-charge does not influence the dosing behavior of the adhesive mixtures.

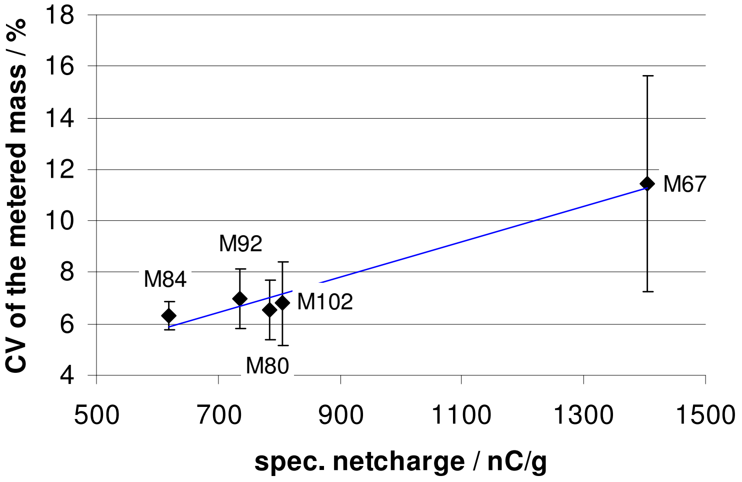


Figure 7.13: Coefficient of variation of the metered mass of the adhesive mixtures (mean ± SD, n = 3) plotted versus the specific netcharge of the pure carriers

In figure 7.14, where the coefficient of variation of the released mass of the adhesive mixtures is plotted versus the netcharge arising on the adhesive mixtures during aerosolization, also no significant correlation can be found.

One reason for the lack of correlation between the coefficient of variation and the netcharge of the pure carriers and the adhesive mixtures would be that there is not much powder movement involved during dosing that could be the cause of significant tribo-charging. Also the roughness differences of the carrier particles do not seem to influence the flowability from a mechanical point of view. This is also not surprising since the carrier is completely covered by the API, as mentioned above.

Further also the different charging behavior of the carriers during mixing (mentioned in section 7.3.5.1) that impacts the remaining adhesion forces between the particles after charge dissipation apparently only influences the forces between API and carrier and not the flow behavior of the adhesive mixture.

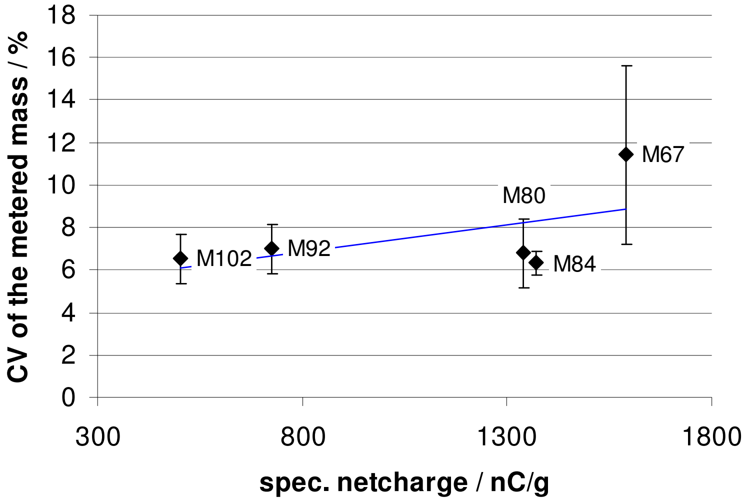


Figure 7.14: Coefficient of variation of the metered mass of the adhesive mixtures (mean ± SD, n = 3) plotted versus the specific netcharge of the adhesive mixtures

7.4 Conclusion

In this study it was possible to prove that surface modifications of the carrier particles by spray drying result in different charging behavior of the carriers and their adhesive mixtures upon release from a commercially available inhaler.

In the case of the pure carriers tribo-charge uptake is governed by an interaction of the influencing factors surface roughness and particle shape. The accumulated charge increases with increasing surface roughness and increasing sphericity (aspect ratio).

As for the adhesive mixtures surface roughness is determined by the presence of the drug on the carrier surface and therefore is almost the same for all adhesive mixtures under investigation, charge uptake is mainly governed by the sphericity of the carriers. This is supported by an almost linear correlation between the netcharge and the aspect ratio of the carriers. Also in this case charge increases with increasing aspect ratio.

Assessing the inhaler performance shows that the FPF and FPD of the adhesive mixtures are in an almost perfect correlation with the netcharge measured for the pure carriers. The FPF and FPD increase with increasing charge. This effect was attributed to repulsive forces between API and carrier during the preparation of the adhesive mixtures. In fact, it is likely that the carrier with the stronger charging tendency during release form the inhaler also exhibited a similar charging behavior during mixing and preparation of the adhesive mixtures. Since API and carrier both charge negatively during mixing, higher tribo-charge on the carriers would result in repulsive forces between API and carrier. This would further result in less intensive contacts or lower contact areas between API and carrier during mixing and thus less strong remaining adhesion forces (Van der Waals Forces) between them after charge dissipation.

As the coefficient of variation of the metered mass is similar for all mixtures under investigation no correlation between the coefficient of variation and the tribo-charging can be found. It is likely that the metered mass is independent of the charging behavior of the powder because tribo-charging occurs during aerosolization and release of the powder from the inhaler but not during metering where less powder movement is involved.

For future work it will be important to further investigate this observed effect of higher FPF and FPD at higher charge levels. It would be interesting and important to understand these interactions in detail and to exploit them for optimization of dry powder inhaler performance.

7.5 References

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8

Summary, conclusion and outlook

In this work novel data and important information concerning the triboelectric charging of pharmaceutical powders with special focus on powders used for pulmonary drug delivery using dry powder inhalers has been achieved. Tribo-charging has been shown to be controllable in common pharmaceutical processes and applications by controlling the influencing factors. In addition to the general perceptions regarding tribo-charging in powder handling processes also essential data concerning charge dissipation from insulating powders have been obtained and triboelectric data of the new alternative carrier material mannitol have been gained. Further a correlation between tribo-charging and the performance of the dry powder inhalate has been demonstrated.

8.1 Summary

The charging behavior of different pure mannitol carriers and also adhesive mixtures of API (salbutamol sulphate) and carrier in a ratio of 1/40 was investigated first in the mixing process and further also during aerosolization and release of the powder from a dry powder inhaler device. In both processes the influence of different particle characteristics and process parameters on tribo-charging was investigated. Following the effects of the arising tribo-charge on mixing quality parameters and inhaler performance were examined. Summarizing the following facts could be established:

In the first mixing studies where only pure carriers were treated it was proved that charge saturation occurs after a certain mixing time. The time until saturation is reached and the saturation charge level depends on particle characteristics and the mixing container material. This is because charge saturation is a function of the potential difference between the contacting materials and the surface area of the contacting bodies. The higher the potential difference, the more charge is exchanged between the bodies in the contact step. Further the larger the surface area of the contacting bodies, the more charge can be accumulated on their surface until the charge density on the surface reaches a level where the potential difference is equalized, no further charge exchange takes place and charge saturation is reached.

The DOE studies concerning the mixing process of pure carriers revealed that tribo-charging is proportional to the mixing container size and the amount of carrier fines and indirectly proportional to the particle size. This means that tribo-charging in the mixing process increases with decreasing particle size, increasing container size and increasing amount of carrier fines. This was confirmed for polypropylene as well as stainless steel mixing vessels. These findings can also be attributed to the above mentioned influence of the surface area of the contacting bodies which in this case was a function of the mixing container size and obviously also the carrier particle size and the amount carrier fines.

The DOE further showed a significant interaction between the factors container size and particle size. The influence of the factor particle size is stronger in large mixing containers and vice versa the charge difference between the smaller and larger mixing container is more pronounced for particles of low size. That means in this case the surface area of the inner mixing container wall and the surface area of the powder have an influence on the arising charge in an interactive way. It was concluded, that the higher number of charges the bigger container is able to release or take up is stronger accepted by the powder of smaller particle size and its larger surface area.

The evaluation of three different discharge scenarios for pure carriers in stainless steel containers showed that first, no significant charge dissipation to the atmosphere occurs within one hour. Furthermore, it was shown that storing the charged powder in the stainless steel mixing container for one hour after mixing results in a significant reduction of tribo-charge. In case of storing the powder in the stainless steel container it was observed that grounding the mixing container does not bring about an improvement of the charge dissipation. This suggests that the limitation for charge dissipation is not the charge transport away from the mixing container but the charge transport out of the powder bulk through the electrically insulating material just by surface conduction.

The mixing studies focusing on the influence of the carrier particle surface roughness on tribo-charging in the tumble blending process in stainless steel containers revealed that carrier particles with a higher roughness charge significantly higher. This was attributed to the higher specific surface area of the rough carriers and the above explained influence of the surface area of the contacting bodies. However this was not observed in the case of adhesive mixtures of carrier and API. The influence of the carrier surface roughness on the arising charge is compensated by the presence of the API. Through the complete coverage of the carries by the API particles, new particle with similar surface roughness that is independent of the surface roughness of the original carrier particles are generated. Despite this the mixing homogeneity still showed a dependence on the charging behavior of the pure carrier particles. The mixtures containing the rougher carriers which showed the higher charge uptake in the pure carrier studies exhibited a lower mixing homogeneity. It is believed that this occurred because at the beginning of the mixing process carrier and API are separate. After a longer time of mixing the API completely covers the carrier, resulting in this above mentioned new particles with similar surface roughness. However the mixing uniformity depends also on the first minutes of mixing where the two different substances first come into contact. And here the charging behaviour of the pure carrier particles impacts the mixing results. The assessment of the dosing behavior of the pure carriers in the inhaler did not reveal a difference between the smooth and rough carrier products. Dosage in the inhaler is independent of the charging behavior of the carriers in the mixing process.

Charge measurements on pure mannitol carriers after dispersion from the Novolizer® showed that the arising netcharge magnitude is in a direct relation to the air flow rate and the carrier fines and indirectly proportional to the particle size. That means tribo-charging during aerosolization increases with increasing aerosolization air flow rate, increasing amount of carrier fines and decreasing particle size.

The DOE for the pure carrier inhaler studies revealed several interactions between the influencing factors. One interaction was observed between the amount of carrier fines and the air flow rate. The addition of carrier fines has a stronger impact on tribo-charging at lower flow rates. Further also the interaction between the particle size and the flow rate causes that the dependence of the netcharge on the particles size is stronger at lower flow rates. The third interaction was observed between the factors particle size and amount of carrier fines. The influence of the particles size on tribocharging is enhanced by the addition of fines.

Charge measurements on the adhesive mixtures after release from the Novolizer® proved the influence of the prior checked factors airflow rate, carrier fines and carrier particle size. Beyond that an indirect relation between API content and netcharge was determined. So in the present case the addition of API causes a reduction of tribo-charging during aerosolization.

With respect to the adhesive mixture inhaler studies the DOE only revealed one significant interaction between the API content and the amount of carrier fines. The influence of the fines on the netcharge is weakened by the presence of the API.

The detailed investigations of the impact of consecutive actuations on tribo-charging showed a dependence on the number of prior actuations in the case of 90 l/min air flow rate. In fact the netcharge arising on the inhalation powder upon actuation and release from the inhaler decreases in consecutive actuations and approaches a constant value after about 40 actuations. At 60 l/min air flow rate no such dependence was found and the tribo-charge arising in consecutive actuations is relatively constant.

In the additional inhaler charge measurements the dependence of tribo-charging on the carrier particle shape and surface roughness was proven. The initially performed pure carrier studies revealed that the charging of the pure carrier powder in this case depends on an interactive influence of particle shape and surface roughness. An increasing charging tendency with increasing aspect ratio (sphericity) and increasing surface roughness was observed. However the influence of the surface roughness is not clearly visible and strongly superimposed by the influence of the particle shape.

Further the influence of carrier particle shape and surface roughness on the tribo-charging of adhesive mixtures was demonstrated. Compared to the pure carriers, in the case of the adhesive mixtures the influence of the carrier surface roughness is weakened by the presence of the API, thus the influence of the particle shape is more pronounced. An almost linearly increasing netcharge with increasing aspect ratio of the carriers was observed.

Assessing the inhaler performance good correlations between the charging behavior of the pure carrier powder and the inhaler performance were demonstrated. It was shown that the coefficient of variation of the metered mass of the adhesive mixtures increases with increasing charging tendency of the carrier powder. Additionally it was possible to demonstrate that also the important inhaler performance parameters fine particle dose (FPD) and fine particle fraction (FPF) depend on the charging behavior of the carriers. An almost linearly increasing FPD and FPF with increasing charging tendency of the mannitol carrier particles were observed.

8.2 Conclusions and outlook

The fact that tribo-charging of powders or powder mixtures can be influenced or controlled opens up new possibilities. On the one hand the knowledge gained by the present work can be used to reduce tribo-charging where it is disturbing or hazardous. On the other hand controlled tribo-charging can be used to tailor certain powder properties. For example in powder mixing it can be used to generate stable adhesive mixtures of two particulate materials. This is especially true if API and carrier could be charged with unlike polarity. The findings of the discharge studies cleared out some misunderstandings concerning electrical discharge of insulating powders and may help to find or improve charge dissipation possibilities after powder processing. The insights gained in the inhaler studies are particularly interesting since the manipulation of particle – particle and particle - inhaler interactions caused by tribo-charge is an opportunity to enhance inhaler performance and extend their applicability. Knowing how certain factors influence the charging behavior and what interactions appear it is possible to develop API - carrier combinations with optimal performance. By choosing the appropriate inhaler material and design further improvement can be achieved.

Certainly further studies are required to completely understand the very complex tribo-charging process. Especially tribo-charging at insulator – insulator contact needs further attention since this form of charging appears in many processes and causes great problems. Up to now it is not clear how this insulator charging occurs in detail. In this field theoretical and basic studies have to be performed to understand how insulator charging works to get a comprehensive knowledge of all relevant factors. Further practice related application studies have to be done to prove the basic findings and to examine interactions between the influences which can have a great impact on the charging behavior and also offer additional opportunities for tribo-charge control. Beside the idea of preventing powder charging, the focus in this field of investigations should also be laid on the improvement of charge dissipation from insulating powders after powder processing. Despite all good knowledge of how tribo-charge can be controlled it will not be possible to completely eliminate it in any process. Therefore the improvement of charge dissipation from larger amounts of charged insulating powder will be one of the greatest challenges but also opportunities for improvement of powder handling technology. Last but not least another very desirable possibility beside preventing and reducing tribo-charge is to use its positive aspects to design powder mixtures with defined charging behavior to get powders or powder mixtures with tailored characteristics and properties.

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