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Research paper

Adhesion forces in interactive mixtures for dry powder inhalers – Evaluation of a new measuring method

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Abstract

Dry powder inhalers mostly contain carrier based formulations where micronized drug particles are adhered to coarse carrier particles. The performance of the dry powder inhaler depends on the inhaler device, the inhalation manoeuvre and the formulation. The most important factor influencing the behaviour of the formulation is the adhesion force acting between the active ingredient and the carrier particles, which can be measured using different methods, for example the centrifuge technique or atomic force microscopy. In this study the tensile strength method, usually applied to determine cohesion forces between powder particles of one material, is optimized for adhesion force measurements between powder particles of unlike materials. Adhesion force measurements between the carrier materials lactose or mannitol and the drug substance salbutamol sulphate using the tensile strength method and the atomic force microscopy show higher values with increasing relative humidity. Consequently, the fine particle fraction determined using the Next Generation Impactor decreases with increasing relative humidity as a result of the enhanced interparticle interactions.

Keywords: Adhesion forces; Atomic force microscopy; Dry powder inhalers; Interparticle interactions; Tensile strength measurements

1. Introduction

Application of active ingredients to the deeper part of the lungs requires particle sizes between 1 and 5 μm. Therefore a micronization of the active ingredient is needed. The micronization causes particles of high surface area, which can form a cohesive system where the particles adhere to each other. The flowability and dispersion properties of these systems are poor, causing problems during dosage form manufacturing and application. Because of these problems dry powder inhalers very often contain interactive mixtures consisting of a coarse carrier material and the micronized active ingredient. The most common carrier material is α-lactose-monohydrate. Alternative materials like mannitol and trehalose are also under investigation [1].

During the mixing process formation of the interactive mixture depends on two forces: The above mentioned cohesion forces between the drug particles and the adhesion forces of the active ingredient to the carrier particles. Only if the adhesion force between the two substances is high enough the mixing process will be complete and no agglomerates of the active will be left. On the other hand the redispersion of the drug affecting the performance of a dry powder inhaler is influenced by three factors: The inhaler device, the inhalation manoeuvre of the patient and the formulation. These factors determine the fine particle fraction which is that part of the active supposed to

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reach the deeper part of the lungs. The fine particle fraction can be determined by one of the impactors described in the European Pharmacopoeia [2], for example the Next Generation Impactor (NGI).

With respect to the formulation several parameters are discussed that are relevant for the performance of a dry powder inhalate, like carrier rugosity and active carrier sites. Those can be manipulated for example by adding fines of the carrier material or other materials [3,4]. Manipulations of the carrier material cause changes of the adhesion force between carrier and active ingredient. The adhesion forces should not be too high so that the detachment of the drug particles during inhalation is possible and impaction of the active together with the carrier in the upper airways is avoided. Therefore the adhesion force is a key parameter for the behaviour of the interactive mixture.

Different methods are described for the measurement of interparticle interactions e.g. the centrifuge technique where particles of an interactive mixture are adhered to a disc in a special device rotating in a centrifuge. The amount of detached particles depending on the centrifugation speed is determined [5]. The adhesion force is calculated from the centrifugation speed. Another method which is used in this study is the atomic force microscopy (AFM). This method, which was first used as an excellent tool for high resolution imaging of surface topography, became important for sensitive adhesion force measurements. The method enables the user to measure the adhesion force of a single particle on a given substrate. This is also called colloid probe technique and is used to understand surface forces in different areas of interest [6]. For both methods the correlation between the adhesion force obtained and the fine particle fraction of the respective interactive mixtures was investigated and the usefulness of the methods to support the development process of dry powder inhalers was evaluated [7–9].

Another method to determine interparticle forces is the tensile strength method where the forces acting between two powder layers are measured. The method is mostly used for the determination of cohesion forces between like materials for example to evaluate the influence of porosity of powder bed [10], relative humidity [11] or flow conditioners [12] and rarely used for the determination of forces between unlike materials [13]. For the cohesion force measurements the powder layers are formed during the measurement by dipping the measuring device covered with a sticky agent in a loose powder bed. After a determined contact time it is removed and the force acting between the two powder layers, the one sticking to the measuring device and the one left behind in the powder bed, is measured. For the adhesion force measurements the two powder layers are prepared prior to the measurement by fixing one of them on the measuring device, the other one on a second disc which is in parallel to the measuring device. The powder layers are brought into contact and separated again after a given contact time.

The aim of the first part of this study is to further adapt the tensile strength method to determine adhesion forces between unlike materials. Therefore an optimization of the experimental setup and especially the measuring device was necessary. In the second part the ability of the method to determine different adhesion forces was investigated and the results obtained are compared to the results of the measurements obtained using the atomic force microscope. Furthermore, these results are discussed with respect to the fine particle fraction determined using the next generation impactor. As model drug substance the β_2-sympathomimeticum salbutamol sulphate was used in combination with the common carrier material α-lactose monohydrate and the alternative carrier material mannitol. Measurements were carried out at different relative humidities.

2. Materials and methods

2.1. Materials

α-Lactose-monohydrate (InhaLac®70) ($x_{10} = 92.25$ μm, $x_{50} = 189.76$ μm, $x_{90} = 310.25$ μm) was given by Meggle AG, D-Wasserburg, Mannitol (Pearlitol SD 200) ($x_{10} = 16.49$ μm, $x_{50} = 141.57$ μm, $x_{90} = 264.34$ μm) by Roquette, F-Lestrem. Salbutamol sulphate was received from Stada, D-Bad Vilbel. It is micronized using an Air Jet Mill 50 AS (Hosokawa Alpine, D-Augsburg). The obtained powder exhibits a particle size distribution of $x_{10} = 0.67$ μm, $x_{50} = 2.05$ μm and $x_{90} = 5.68$ μm. Particle size distributions are determined using laser diffraction (see Section 2.2.5).

2.2. Methods

2.2.1. Determination of tensile strength

The powder layer on the upper disc is prepared by placing a double-sided tape (Plano GmbH, D-Wetzlar) onto the surface of the measuring device and dipping it into a powder bed. Loose particles are removed with a brush. This is repeated several times. Finally the surface is cleared from loosely adhered particles using compressed air at a pressure of 5 bar.

The powder layer on the lower disc is prepared by placing a double sided tape onto a metal disc, pouring a powder layer of 0.3 mm height on it and loading this with a 500 g weight for about 30 s. Loose powder is removed and the load is applied again. Unfixed powder particles are removed using compressed air at a pressure of 5 bar before performing the measurement.

The measuring device consists of aluminum. The diameter of the disc is 40 mm. It hangs on a sphere of steel with a diameter of 10 mm which is connected to the balance by a rod.

The measurements are performed using a tensiometer K100 (Kruess GmbH, D-Hamburg) with two fixed powder layers, one on the measuring device and one on the disc located on the table of the tensiometer (Fig. 1). The load

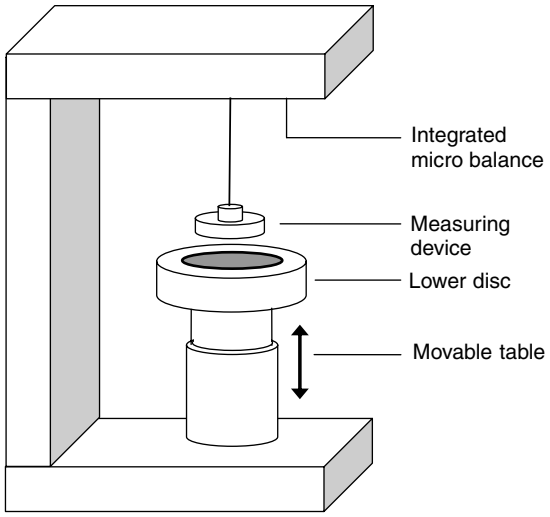

Fig. 1. Scheme of the modified tensiometer.

of the balance is recorded permanently. During the measurement the two powder layers are approaching each other with a rate of 6 mm/min moving the table of the tensiometer upwards. Contact of the two layers causes a decrease of the load of the balance. Once this decrease exceeds 0.1 g (detection point) the table is still moved upwards two more millimeters to ensure a satisfactory contact between the two powder layers. The system remains in this position for 30 s before the table moves down again at a rate of 3 mm/min stopping 1 mm above the detection point. There, the measurement starts with a measuring rate of 0.5 mm/min. The time of measurement is 300 s maximally. Once the measurement has started, 20 values per second will be acquired by the software. The value of the adhesion force is the difference between the maximum of the curve minus the endpoint (Fig. 2). Since during all measurements the area is kept constant the value is not expressed by tensile strength (N/m^2) but only in force (N). The measurements are repeated 3–18 times.

2.2.2. Determination of adhesion forces using atomic force microscopy (AFM)

The probes are prepared by sticking a particle of the drug substance to the cantilever using a micromanipulator

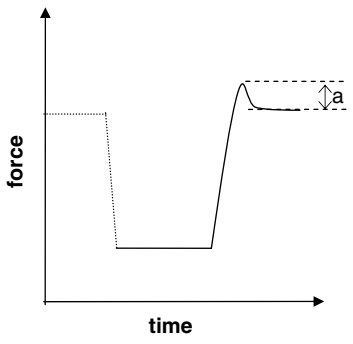

Fig. 2. Scheme of the measuring curve for adhesion force measurements using the tensile strength method.

(MMO-203, Narishige, Japan). The cantilever is first dipped into a two component epoxy adhesive (UHU GmbH, D-Bühl) and afterwards moved to collect a particle from the glass plate. The presence of the particle on the cantilever is verified using a light microscope (Axiotech Vario, Carl-Zeiss AG, D-Oberkochen) before measuring the adhesion forces and checked again after the experiment using a low-voltage field emission electron microscope (LEO 1530 Gemini, Carl Zeiss NTS GmbH, D-Oberkochen) to ensure that the particle is still there.

Preparation of the crystal planes is performed by crystallization of a 10% solution of the carrier material on a silicon waver. Once the crystallite is dry, a metal plate is sticked to the upper side of the crystal with glue. Finally, the silicon waver is removed resulting in a smooth and flat surface.

All measurements are performed using an atomic force microscope (Multimode, Nanoscope IIIa Controller, Digital Instruments, USA-Santa Barbara, equipped with software version 5.12r5, J-Scanner) standing on an active vibration isolation (Table Stable Ltd., CH-Zwillikon). To choose a measurement site images of 10×10 μm are taken in contact mode applying constant force at a velocity of 2 Hz using a V-shaped silicon nitride cantilever (NP-S, Veeco, USA-Santa Barbara) with $K = 0.12$ N/m nominal spring constant. The roughness of the surface is described by the root mean square value (R_q) [14]. For the force distance curves only squares with a R_q smaller than 3 nm are taken.

The force distance curves are taken as force volume plots with 32×32 measurements on a square of 8×8 μm at a velocity of 5 Hz maintaining a constant load during the measurements using a rectangular silicon dioxide cantilever (210 μm long, 52.5 μm width, $K = 0.68$ N/m). The adhesion force is calculated using a self-written software evaluating the cantilever deflection, which can be converted into force by using Hooke's law if the spring constant of the cantilever is known. To calibrate the spring constants of the cantilevers with particles the method described by Torii [15] is used. The spring constant of the reference cantilever needed is determined using the thermal noise method [16].

For the force-distance curves the cantilever is located in a humidity cell. The relative humidity is controlled by mixing two air streams (0 % and 100% relative humidity) using a mass flow controller (GFC, Aalborg, USA-Orangeburg). Temperature and relative humidity are monitored permanently (SHT 15, Sensirion, Switzerland). Further details of the humidity cell are described by Farshchi-Tabrizi [17]. Before the measurement the system is equilibrated for 15 min at the defined relative humidity.

2.2.3. Aerodynamic assessment of fine particles

The aerodynamic assessment of fine particles is performed using the next generation impactor (NGI) (Copley Scientific, Nottingham, UK). Before the measurements the small cups of the NGI are coated with 1 mL coating agent

(solution of 5% of a mixture of glycerol and polyoxyethylene-20-cetylether (95:5) in isopropanol), the large cups with 2 mL. The preseparator is filled with 15 mL diluted acetic acid. The measurements are performed according to the European Pharmacopoeia [2] using 79.3 L/min flow rate of and 3 s calculated opening time. The flow rate is measured with an electronic digital flowmeter (Model DFM, Copley Scientific). Pumps (Typ SHC P3, Typ HC P3) and the critical flow controller (Model TPK) are also from Copley Scientific. The interactive mixture is filled in the powder container of a Novolizer® (Sofotec, D-Frankfurt) which is fixed to the throat of the impactor by a suitable adapter.

The dose of active ingredient on the stages is determined by HPLC (see Section 2.2.7). The fine particle dose is calculated as the dose of active ingredient exhibiting an aerodynamic diameter of <5 μm by addition of the doses of active on stages 3–7 plus the part of active <5 μm on stage 2 obtained by interpolation. The fine particle fraction is defined as the fine particle dose divided by the whole dose of active found in the impactor.

2.2.4. Micronization of salbutamol sulphate

Salbutamol sulphate is micronized using the Air Jet Mill 50 AS (Hosokawa Alpine, D-Augsburg). The feeding rate is adjusted to 1 g/min, the injection pressure to 4 bar and the milling pressure to 2 bar.

2.2.5. Particle size analysis by laser diffraction

Particle size distributions are determined using the laser diffractometer Helos H1402/KF-Magic using the dry disperser Rodos (Sympatec, D-Clausthal-Zellerfeld) with a pressure of 2.0 bar and the measuring range of 0.25/0.45–87.5 μm and 0.5/4.5–875 μm.

2.2.6. Preparation and storage of interactive mixtures

Interactive mixtures are prepared using a carrier to drug ratio of 99:1. Half of the carrier material is weighed into a stainless steal vessel, then salbutamol sulphate is added and finally, the second half of the carrier material. The powder is mixed in a turbula mixer (T2C, Bachofen AG, CH-Basel) at 65 rpm for 90 min and allowed to settle for 2 h before further treatment. First the mixing uniformity of the mixture is determined using 12 samples of about 50 mg mass. The content of the active ingredient is analyzed by HPLC. For the aerodynamic assessment of fine particles, only interactive mixtures with mixing uniformity of <5 % standard deviation are used.

The mixtures are filled into the powder container of the inhaler and stored at defined relative humidities for one week over silica gel (approximately 10% rh), in an environmental chamber at 45% rh, 21 °C and over a saturated solution of sodium chloride in a chamber at 75% rh.

2.2.7. Analysis of the samples by HPLC

Each powder collected on the stages of the NGI is dissolved in 20.0 mL diluted acetic acid (pH 3), the preseparator is washed with 50.0 mL diluted acetic acid (pH 3). Samples are examined using a high liquid pressure chromatograph (LC 6A, Shimadzu, D-Duisburg) with an autoinjector (SIL-6B, Shimadzu) and a column Nucleodur C 18, 5 μm, 250/4 with precolumn (Macherey u. Nagel, D-Düren). The temperature of the column oven (Thermasphere TS-430, Phenomenex, D-Aschaffenburg) is adjusted to 35 °C. Detection of the active is performed using a UV/Vis detector (SPD-6AV, Shimadzu) at 276 nm wavelength. Integration of the curves is carried out using an integrator (C-R4AX Chromatopac, Shimadzu). The mobile phase is a mixture of A (acetonitrile) and B (2.5 g acetic acid 100% in 1000 mL distilled water, pH 3) in the ratio 52:48. The flow rate is set to 0.45 mL/min. Before the measurements, linearity and calibration curve are determined using three solutions of known concentration. Every sample is analyzed four times.

3. Results and discussion

3.1. Development of tensile strength measurements for the determination of adhesion forces

Tensile strength measurements are mostly used for cohesion force measurements of solids and powders. The experimental setup for tensile strength measurements of powders is comparable to the one for surface tension measurements of liquids. However, the Wilhelmy plate used for surface tension measurements of liquids is replaced by a measuring device coated with an adhesive surface. It is dipped into a loose powder bed. Powder particles stick to the surface. Raising the device again, the powder particles sticking to the surface will be removed from the powder bed and thereby separated from the powder particles left behind in the powder bed. The force detected at the moment of separation of the powder layers is the cohesion force.

In this study the method is optimized for the measurement of adhesion forces between unlike materials. The setup for adhesion force measurements is different from cohesion force measurements, where a sticky surface is dipped into a loose powder bed. It works with two fixed powder layers, one on the measuring device also called upper disc, and one on a lower disc. The powder layer on the measuring device is brought in contact with the powder layer on the lower disc by moving the lower disc upwards until it touches the upper disc. The force required to separate the two powder layers by moving the lower disc downwards again is the adhesion force.

The measurements are performed using a modified tensiometer (Fig. 1). During the measurement the load of the measuring device is recorded. A scheme of the resulting curve is shown in Fig. 2. The load of the measuring device is recorded as a function of the separation distance between upper and lower disc or time, which, at a given separation rate, can easily be converted into each other. The adhesion force is the value of line (a) which is the difference of the maximum load minus the weight of the measuring device.

In order to determine the maximum accurately, continuous reading of the data is required. Therefore a special software is developed in collaboration with Kruess AG, Hamburg, which provides a scanning rate of 20 values per second.

3.1.1. Design of the measuring device

The challenges of the development of the measuring device are on the one hand to provide a contact area sufficiently high to permit quantifying adhesion forces and on the other hand to guarantee that both discs are in parallel to each other at the moment of detachment in order to ensure that all contact sites separate simultaneously.

The first measuring device was a square disc with a fixed and stiff connection to the balance (Fig. 3a). This connection caused problems during the adjustment of the measuring device with the lower disc which resulted in canting of the device coming in contact with the lower disc. This phenomenon could not be avoided using a round disc either. The next idea was to design a measuring device adjusting itself to the lower disc at the moment of contact. Therefore a suspension with a ball located in the body of a round disc was developed (Fig. 3b). But the contact area and therefore the friction between the ball and the body was not high enough to keep the device parallel to the surface below at the moment of separation. Finally a device with a larger ball fulfils the requirements (Fig. 3c). At the moment of contact between the two surfaces the upper surface is adjusted to the one below and during separation friction keeps both discs parallel. This leads to the separation of all contact sites simultaneously.

3.1.2. Selection of separation rate

To get an idea of the dependency of the separation rate on the adhesion forces an experiment using plain discs without adhered powder layers is performed (Fig. 4).

The pronounced increase of adhesion force with increasing scanning rate up to 5 mm/min might be due to the vacuum arising by separating two smooth surfaces from each other. There might not be enough time for the air to stream into the gap between the two discs sufficiently fast as the separation rate is increased. The reason for the decrease of the adhesion force at 10 mm/min rate may be caused by the limited number of data acquired by the software. As 20 values are acquired by the software per second, the number of data points used to generate the curve depends on the separation rate. Simply speaking: the lower the separation rate the more data points are available to plot the curve. If now the separation rate becomes too high, the maximum adhesion force may lay in between two data points.

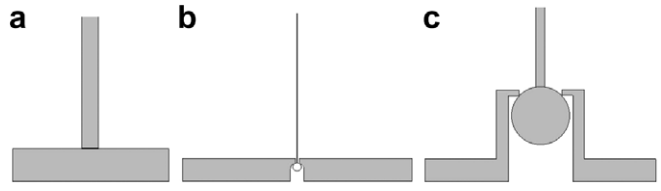

Fig. 3. Measuring devices for adhesion force measurements using the tensile strength method.

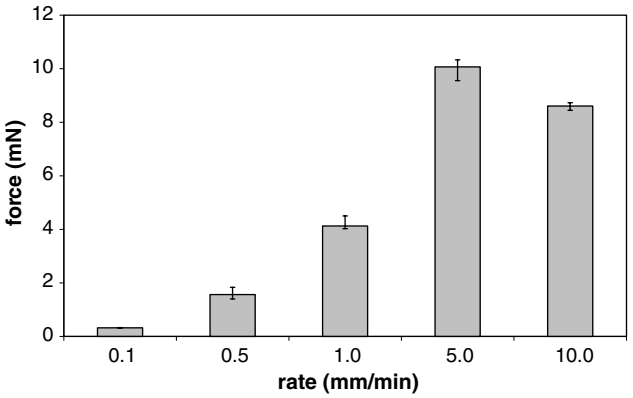

Fig. 4. Dependence of the adhesion force between upper and lower disc without powder layers on the separation rate using tensile strength measurements, median, error bars = 25% and 75% quantile, $n = 6$.

In order to evaluate whether the increase of the determined adhesion force with increasing separation rate is relevant to adhesion force measurements between two powder layers, experiments are carried out using lactose as model carrier particles, fixed on the lower disc, and micronized lactose as model drug particles, fixed on the upper disc. It is expected that the dependence of the adhesion force on the separation rate is less pronounced using powder surfaces because the access of air is facilitated by the pores of the two powder layers. Experiments at velocities between 0.1 and 1.0 mm/min confirm the expectation (Fig. 5). There is no influence of the separation rate detectable. However, at very low rates, the maximum of the curve is not clearly detectable. This might be caused by a successive separation of the contact sites between the powder layers. This gradual separation results in an only weakly pronounced maximum covering a wider distance and therefore longer duration. This improves when using higher velocities. As a compromise between the difficulties to detect the maximum and

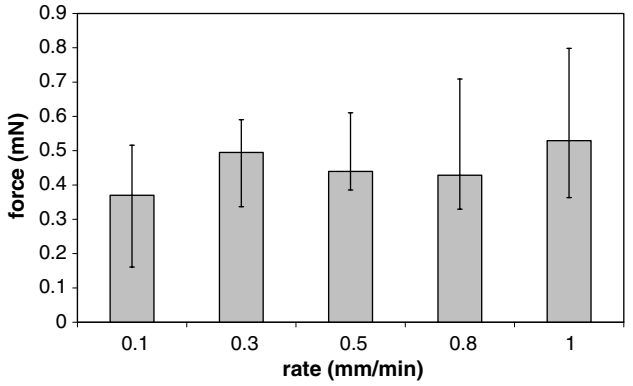

Fig. 5. Dependence of the adhesion force between lactose on the lower disc and micronized lactose as model drug substance on the upper disc on the separation rate using tensile strength measurements, median, error bars = 25% and 75% quantile, $n = 18$.

the risk of recording forces due to the above described vacuum, all further experiments are performed at 0.5 mm/min.

3.1.3. Influence of the preparation of the powder layer on the measuring device

In former studies aiming to detect cohesion forces, mostly vaseline was used as an adhesive. But using vaseline provokes problems regarding the preparation of the powder layers. Due to the thickness and viscosity of the adhesive layer, immersion of the adhered particles into the adhesive and enclosure of the particles by the adhesive may occur. This applies especially for fine powders whereas coarse particles should be proud of the adhesive layer. Therefore the influence of the preparation of the powder layer of micronized lactose on the upper disc is investigated. It is decided to use a double faced adhesive tape. First a tape with a thickness of about 190 μm was used. Micronized lactose was used to prepare the powder layer on the upper disc, coarse lactose for the lower disc. The detected adhesion force was unexpectedly high. Adding additional powder layers by dipping the upper disc into a powder bed repeatedly resulted in a decrease of the adhesive forces until a plateau was reached (Fig. 6).

In order to eliminate the risk of measuring the adhesion force exerted by the adhesive tape, especially when the number of adhered powder layers is low, another adhesive tape with a thickness of 110 μm normally used for SEM was tried. With this tape the influence of the loading on the adhesion force disappears (data not shown).

3.2. Suitability of the tensile strength measurement for the determination of adhesion forces depending on the relative humidity

In this section the suitability of the method for detecting differences in adhesion forces due to variable environmental conditions is investigated measuring the adhesion force between salbutamol sulphate as active ingredient and lactose or mannitol as carrier materials at different relative humidities. The obtained results are compared to adhesion forces obtained by AFM measurements and are discussed with respect to the fine particle fraction of the respective interactive mixtures obtained by aerodynamic assessment of fine particles using the NGI.

3.2.1. Aerodynamic assessment of fine particles

The fine particle fraction of interactive mixtures consisting of lactose or mannitol and salbutamol sulphate is determined after storage at three different relative humidites (10%, 45% and 75%) (Fig. 7).

The fine particle fraction decreases with increasing relative humidity. The difference between the two lower humidities (10% rh, 45% rh) is smaller in comparison to the higher relative humidity (75% rh). The higher humidity probably causes adsorption of considerable amounts of water resulting in the interaction between the adsorption layers on the particles' surfaces which is higher than between the dry surfaces. The dependence of the delivered dose on storage conditions and the following decrease of the fine particle fraction was shown in earlier publications [18].

3.2.2. Determination of adhesion forces using atomic force microscopy (AFM)

Measurements of adhesion forces between the active and the carrier material are also performed as force volume plots with 1024 different contact sites on a square of 8×8 μm at three different relative humidities. In order to decrease the scatter of the measurements caused by the surface roughness of the untreated carrier materials and resulting in varying contact areas at each contact site, the measurements are carried out by tipping one particle of the active ingredient stuck to the cantilever onto a crystallized and therefore flat and smooth surface of the carrier material. However, this implies a change of the properties of the carrier in comparison to the material which is used for the preparation of the respective interactive mixture. Furthermore, it has to be kept in mind that atomic force

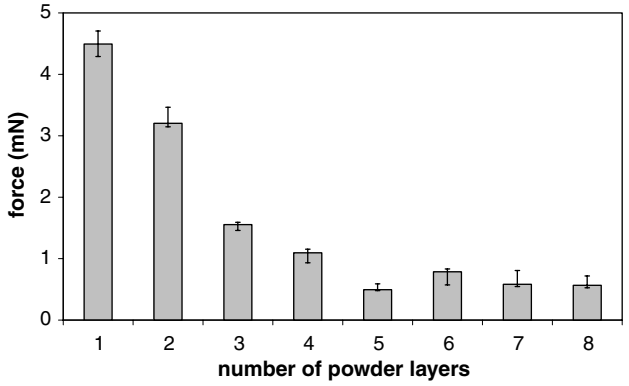

Fig. 6. Dependence of the adhesion force of the powder layers added on the upper disc determined by tensile strength experiments, using coarse lactose on the lower disc and micronized lactose as model drug substance on the upper disc, median, error bars = 25% and 75% quantile, $n \geqslant 3$.

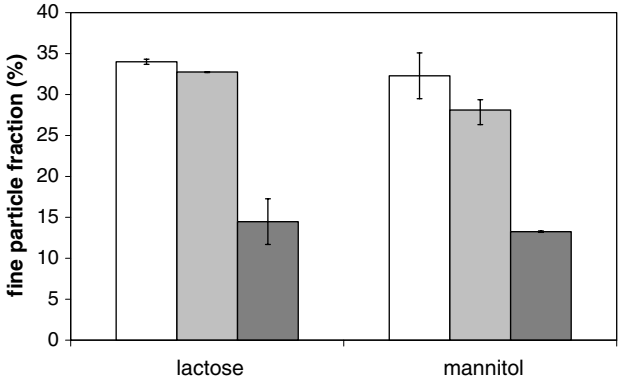

Fig. 7. Fine particle fraction of interactive mixtures of salbutamol sulphate and lactose or mannitol as carrier material after storage for 3 months at different relative humidities (□, 10% rh; ■, 45% rh; ■, 75% rh), mean, SD, $n = 3$.

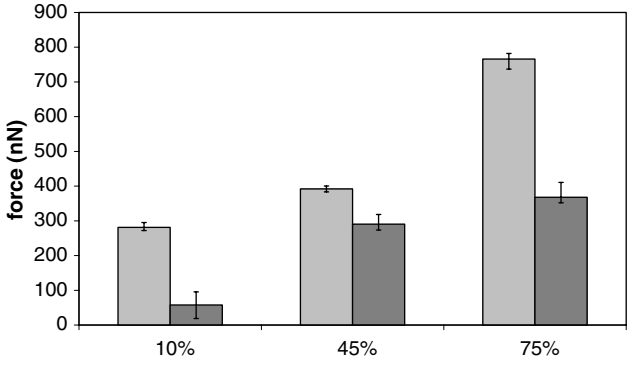

Fig. 8. Adhesion force measured by atomic force microscopy experiments between micronized salbutamol sulphate glued to the cantilever against crystallisates of lactose (■) or mannitol (■), median, error bars = 25% and 75% quantile of force volume measurements using a single tip.

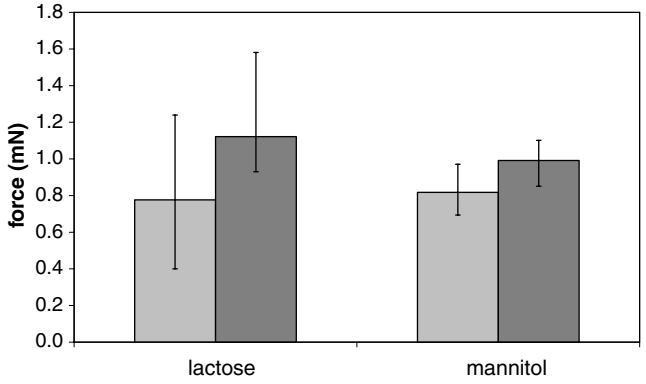

Fig. 9. Adhesion force measured by tensile strength experiments between lactose or mannitol at the lower disc and micronized salbutamol sulphate at the upper disc at two different relative humidities (■, 30% rh; ■, 75% rh), median, error bars = 25% and 75% quantile, $n = 12$.

microscopy measures the forces between one single drug particle and a limited section of the carrier's whole surface available for the adhesion of the drug. Additionally, the contact area is predetermined by the shape and the orientation of the particle glued to the cantilever and the carrier surface selected for the measurement. Even the repetition of the measurement using several different drug particles glued to the cantilever gives a limited number of contact areas and interparticle forces eventually occurring between the drug and the carrier in an interactive mixture.

Nevertheless, Fig. 8 shows that the difference of the adhesion forces at different relative humidities is detectable. The adhesion force between the active ingredient and the carrier material obtained by atomic force microscopy increases with higher humidity in accordance with the results of the NGI measurements where the fine particle fraction is higher at the lower relative humidity. Increasing adhesion forces with increasing humidity and the ability of atomic force microscopy to detect differences between the adhesion force were also demonstrated by Price et al. [19].

3.2.3. Determination of the adhesion force using tensile strength measurements

Similarly, tensile strength measurements are carried out at a lower (30% rh) and a higher (75% rh) relative humidity. Untreated carrier material is fixed on the lower disc and micronized salbutamol sulphate on the upper disc.

In accordance with the results obtained by AFM the median of the adhesion force increases with increasing relative humidity (Fig. 9). However, the high scatter of the obtained adhesion forces complicates the interpretation and is a drawback of this method. The highly scattered values are probably caused by slight changes of the position of the upper disc relative to the lower disc differing from one determination to the other and causing differences in the total contact area between the two powder layers fixed on the lower and the upper disc. In contrast to the experiments by AFM, tensile strength measurements rely on the examination of a particle collective, so they are expected to be more representative in this point. The optimization of the experimental setup using crystallized surfaces as it was performed with the AFM measurements was not possible because the preparation of flat and smooth surfaces is very limited. Obtainable flat and smooth areas usually do not exceed 1 cm^2.

3.3. Comparison of the adhesion forces obtained by tensile strength measurements and atomic force microscopy and the fine particle dose determined by aerodynamic assessment of fine particles

The preparation of interactive mixtures by simply mixing the particles of the active and the carrier leads to the formation of contact sites between the two components due to adsorption of the fines to the surface. The formation of these contact sites is driven by short range forces as well as long range forces. The magnitude of the adhesion forces depends on various properties of the particles being in contact like surface roughness and surface energy distribution.

However, adhesion forces are dependent on the amount of fines which is present in the carrier material and which might be introduced by grinding of the material during the mixing procedure also. Furthermore, the particle size of the active might be altered due to grinding. And finally, the fine particle dose is not only dependent on interparticle interactions but also on other factors like drag forces exerted by the inhaled air stream and the performance of the device. Obviously, all these factors are not taken into account when determining adhesion forces between the drug and the carrier by tensile strength measurements or atomic force microscopy.

Furthermore, the sample preparation and the experimental setup required for experiments by tensile strength measurements or atomic force microscopy may create contact sites between the drug and the carrier which may differ significantly from those which would have occurred when preparing an interactive mixture by mixing the drug and the carrier in a mixer. Therefore it has to be kept in mind

that the adhesion forces determined by tensile strength measurements or atomic force microscopy may not reflect the adhesion forces present in an interactive mixture of the respective components exactly. This is especially true if interparticle forces are mainly based on forces requiring a certain position or orientation of the particles towards each other like specific interactions between functional groups on the interacting particles' surfaces. This orientation is easily ensured in a mixing process whereas the positions of the drug and the carrier particles are fixed by the experimental setup when performing tensile strength measurement or experiments by atomic force microscopy.

However, the decrease of the fine particle dose with increasing relative humidity which has been found by the aerodynamic assessment of fine particles and which is supposed to be caused by increasing adhesion forces between the drug and the carrier is verified by atomic force microscopy as well as by tensile strength measurements, although the latter one suffers from a high scatter of the measured values. The optimization and further evaluation of the potential of this method will be subject of future work.

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