Carrier-free Formulation of Dry Powder Inhalates

Nanoparticle coating of drug microparticles

Viktoriya Mykhaylova[1], Karin Dresely[1], Fabian Klar[1], Nora Anne Urbanetz[2]

[1] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany
[2] Research Center Pharmaceutical Engineering GmbH, Graz, Austria

Corresponding author: Prof. Dr. Nora Anne Urbanetz, Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 21 A, 8010 Graz, Austria; e-mail: nora.urbanetz@tugraz.at

ABSTRACT

The present study aims at evaluating the suitability of nanoparticle covered drug microparticles as an alternative to conventional carrier based formulations for pulmonary drug delivery. Colloidal silicon dioxide was used as model nanoparticle, lactose as model drug. The influence of the nanoparticle to microparticle ratio and the preparation procedure were evaluated. In comparison to nanoparticle free formulations nanoparticle covered lactose particles showed enhanced flowability, single dose uniformity and respirable fraction. However, there is an optimum amount of nanoparticles and further increasing it leads to a deterioration of these characteristics. Furthermore, with respect to the mode of preparation, mixtures prepared by electrostatically supported mixing, meaning that the dispersion of the nano- and microparticulate fraction is assisted by triboelectric charging of these fractions prior to the mixing procedure, are superior to those prepared by conventional mixing using a tumble mixer in terms of flowability, single dose uniformity and respirable fraction.

ZUSAMMENFASSUNG

Trägerfreie Formulierungen von Pulverinhalaten/ Mit Nanopartikeln umhüllte Wirkstoffmikropartikel
Ziel der vorliegenden Studie ist es, die Eignung von mit Nanopartikeln beschichteten Wirkstoffmikropartikeln für die pulmonale Anwendung als Alternative zu konventionellen Carrier-basierten Formulierungen zu untersuchen. Kolloidale Kieselsäure wurde als Modellsubstanz für die Nanopartikel, Laktose als Modell für den Wirkstoff verwandt. Der Einfluss des Nanopartikel-Mikropartikel-Verhältnisses und des Herstellungsverfahrens wurde untersucht. Im Vergleich zu reiner Laktose zeigten die mit Nanopartikeln beschichteten Laktosepartikel eine verbesserte Fließfähigkeit, Gleichförmigkeit der abgegebenen Masse und eine *in vitro* bestimmte, erhöhte Lungengängigkeit. Nichtsdestotrotz gibt es ein Optimum des Nanopartikelgehalts, und eine weitere Erhöhung des Nanopartikelgehalts führt wiederum zu einer Verschlechterung dieser Eigenschaften. Weiterhin wurde gefunden, dass Mischungen, bei denen durch gezielte tribolektrische Aufladung die Dispergierung der nano- und mikropartikulären Fraktion vor dem eigentlichen Mischvorgang der beiden Komponenten gefördert wurde, hinsichtlich Fließfähigkeit, Gleichförmigkeit der abgegebenen Masse und Lungengängigkeit anderen Mischungen überlegen waren, die durch einen konventionellen Mischprozess in einem Freifallmischer erzeugt wurden.

1. Introduction

Drug formulations specifically designed for administration to the respiratory tract include pressurized metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulizers. The efficacy of pharmaceutical inhalers, especially of dry powder inhalers, is reliant on the particle size of the drug influencing the amount of active ingredient reaching the respiratory tract. Also, good flowability has a decisive influence on the uniformity of dosage. To ensure a sufficient amount of active ingredient delivered to the respiratory tract, the aerodynamic size distribution of particles discharged by DPIs should range between 1 µm and 5 µm.

Micronized powders are characterized by cohesiveness and poor flowability. This effect decreases the single dose uniformity and the amount of active ingredient reaching the respiratory tract varies. To enhance flowability, coarse carriers with the diameter ranging between 50 µm and 200 µm on which the drug particles are adhered may be used for DPIs [1]. The coarse carrier, because of its large size and non-cohesiveness is usually used to ensure flowability and the reproducibility of dosing. Also an additional third fraction, such as carrier fines and also other additives, like magnesium stearate, may be used [2, 3]. The desired effect of adding the carrier fines or additives is the occupation of high energy sites on the carrier sur-

KEY WORDS

- Dry powder inhaler
- Flowability
- Interparticle force
- Microparticle
- Nanoparticle
- Pulmonary drug delivery

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face by carrier fines or additives leading to the adhesion of the drug particles on sites of lower energy. Consequently, interactive forces between the coarse carrier and the active ingredient are reduced and the detachment of the drug from the carrier upon inhalation is increased.

Goal of this study is the evaluation of a DPI formulation approach, designed to work without coarse carriers using drugs coated with particles in the nanometer range. The formulations consist of the drug having a particle size between 1 µm and 5 µm and nanoparticles. The nanoparticles, placed on the surface of the drug particles, act as spacers between the drug particles, thereby decreasing the interparticle forces [4, 17]. The mixtures show improved flowability, reproducibility of dosing and improved respirable fraction of the drug particles without the use of coarse carrier particles. To prove the viability of this concept, a model was chosen consisting of spray dried lactose as the model substance for the active ingredient and colloidal silicon dioxide (Aerosil® R972) [5] as the model substance for the nanoparticles covering the lactose particles. Lactose was chosen as model drug for reasons of economy. Furthermore, it has to be pointed out that Aerosil R972 is not approved for pulmonary delivery and has to be replaced by a physiologically inert compound when application to humans is intended. Mixtures consisting of microparticles and different concentrations of nanoparticles (w/w) were prepared by conventional mixing using a Turbula® shaker mixer or by electrostatically supported mixing [6] using the high speed homogenator Ultra-Turrax®. The Turbula blender mixes the particle fractions in a three dimensional movement of the mixing container producing directly the nanoparticle coated lactose [7]. For the efficient distribution of the nanoparticles on the surface of the microparticles electrostatically supported mixing was introduced. Electrostatically supported mixing is performed by triboelectric charging of the particles during the dispersion of the powder in liquid nitrogen using the high speed homogenator Ultra-Turrax [8]. Triboelectric charging improves the dispersion, especially of the nanoparticles, before the subsequent attachment of the nanoparticles on the microparticle surface.

The charge acquired depends, among other factors, on the work function of the material [9]. The work function is the energy that an electron requires to leave the particle. So different materials with different work functions will be charged differently. If now oppositely charged particles are mixed, they will attract each other. So, during the mixing not only dispersion and charging of the particles take place, but also attraction between unlike charged particles which promotes the targeted placing of Aerosil R972 nanoparticles on the lactose microparticles. Therefore a dispersion of the nanoparticles in liquid nitrogen was prepared, and to that the microparticulate lactose was added. After the evaporation of the nitrogen the dry powder mixture was obtained.

The amount of active ingredient presumably reaching the respiratory tract was determined by measuring the fine particle fraction *in vitro* using the Next Generation Impactor (NGI). Different methods to characterize the flowability of the mixtures by measuring the angle of repose, flow rate and ring sheer testing were evaluated in order to obtain a measure for the uniformity of dosage [10]. Finally the different mixtures were investigated by scanning electron microscopy.

2. Material and methods

2.1 Materials

Spray dried lactose was kindly provided by Molkerei Meggle Wasserburg GmbH & Co. KG (Wasserburg, Germany). The median particle diameter of the spray dried lactose $x_{50} = 8.37$ µm was measured using laser diffractometry. Colloidal silicon dioxide (Aerosil R972) with the median diameter of the primary particles $x_{50} = 0.016$ µm [11] was provided by Degussa AG (Duesseldorf, Germany) and liquid nitrogen 5.0 by Linde AG (Munich, Germany). All other chemicals were purchased from Merck KGaA (Darmstadt, Germany).

2.2 Methods

Mixing – Different mixtures of spray dried lactose and 0 %, 0.5 %, 2.5 % and 12.5 % Aerosil R972 (batches weight 200 g) were prepared by mixing the components 90 min in a glass vial using a Turbula shaker mixer (T2C, Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland) at 65 rpm. In order to keep the preparation conditions similar for all samples, the sample containing 0 % Aerosil R972 was treated in the mixer under the same conditions as the mixtures containing 0.5 %, 2.5 % and 12.5 % Aerosil R972. Powder mixtures of above mentioned concentrations were prepared in triplicate and stored in a desiccator until further required.

Another way to prepare the interactive mixtures is electrostatically supported mixing. At the beginning of the experiment the nanoparticle fraction was suspended in liquid nitrogen. The nanoparticle dispersion was stirred at 8200 rpm with a high-speed homogenator (IKA-Ultra-Turrax T25 basic, IKA®-Werke GmbH & Co. KG, Staufen, Germany). Due to the intensive contact between the particles and the homogenator triboelectric charging of particles takes place [12]. Liquid nitrogen is an electrically non-conducting fluid. Therefore the nanoparticles are able to retain their charge. After the charge measured by an electrometer (Keithley 6514, Keithley Instruments GmbH, Germering, Germany) had reached a plateau microparticles were given to the nanoparticle suspension. At that point not only charging and dispersion of like charged particles, but also attraction and charge diffusion between unlike charged micro- and nanoparticles and therefore the coating of microparticles with nanoparticles take place. After the evaporation of nitrogen the dry powder mixture is obtained. Mixtures of spray dried lactose and 0 %, 0.5 %, 2.5 % and 12.5 % Aerosil R972 (batches of approximately 2 g) were prepared by electrostatically supported mixing. Powder mixtures of the above mentioned concentration were produced in triplicate and stored in a desiccator until further required.

Ring shear tester – In order to measure the flow properties of the fine-grained solids a ring shear tester type RST-01.pc (Dietmar Schulze, Schuettgutmesstechnik, Wolfenbuettel, Germany) was used. The aim of a shear test is to measure the yield limit of a consolidated powder [13]. Flowability ff_c is defined as the ratio of the consolidation stress δ_1 to the unconfined yield strength δ_c ($ff_c = \delta_1/\delta_c$). ff_c is dependent on the consolidation stress δ_1, therefore on the stress level at which it is measured. At the beginning of the measurement during the pre-shear step the consolidation of the powder with the vertical normal load of 4 000 Pa takes place. For the construction of the yield limit during the second shear step the same powder blend is sheared under different normal loads of 800, 1600, 2400, 3200 Pa. The ff_c of the powder can then be calculated with the help of the yield limit and Mohr's circles. During one run approximately 120 g of each powder blend was used.

Angle of repose – All measurements were carried out using the equipment as described in the German Industry Norm DIN 53916: "Surface active agents – Powders and granules – Measurement of the angle of repose; Proceeding according to Pfrengle".

For the measurements of the angle of repose of the powders showing poor flow properties a stirring device was used. During the test the powder flows out of the funnel and settles as a cone on a plastic plate of 100 mm diameter. 100 ml of each mixture were tested. The angle of repose is the angle between the sloping surface of the sample pile and the horizontal. A free flowable powder, forming a relatively flat pile has a low angle of repose. A poorly flowable powder with a relatively tall pile has a higher angle of repose.

Flow rate – This conventional method is used for the characterisation of the dynamical flow behaviour of the powder. Here the time which 100 ml of the powder need to pass the outlet of the funnel is determined. All measurements were carried out using the funnel described in the Monograph "Flow behaviour" of the European Pharmacopoeia, 6th edition. The diameter of the outlet orifice is 10 ± 0.01 mm.

Uniformity of dosage – Measurements were performed using the experimental setup described under section aerodynamic assessment of fine particles in the monograph "Preparations for inhalation: aerodynamic assessment of fine particles" of the European Pharmacopoeia, 6th edition. The multiple-unit reservoir containing the mixture was weighed before and after each dose discharge. Forty samples of each mixture were discharged. The mass of each dose was calculated by subtracting the weight of the multi dose reservoir before discharge from the weight after discharge.

Aerodynamic assessment of the fine particles – The aerodynamic assessment was carried out according to the monograph "Preparations for inhalation: aerodynamic assessment of fine particles" of the European Pharmacopoeia, 6th edition, using apparatus E, a high-performance, particle-classifying cascade impactor, called the Next Generation Impactor (NGI). The collection cups of stage 1 and the micro orifice collector were coated with 2 ml of a mixture consisting of isopropanol 95 %, glycerol anhydrous 4.75 % and polyoxyethylene 20 cetyl ether (Brij® 58), the collection cups of the stages 2 – 7 with 1 ml respectively. Isopropanol was allowed to evaporate. Approximately 0.5 g powder per batch was filled in the reservoir of the Novolizer® DPI (Meda Pharma GmbH & Co. KG, Bad Homburg, Germany). Sixty-five doses were dispensed per test run. Each dose was released into the impactor at a flow rate of 79.3 l/min, corresponding to a pressure drop of 4 kPa over the device. The NGI was then dismantled and the weight gain on each of the stages was determined gravimetrically. The fine particle fractions (FPF) were calculated as percentage of the mass of particles smaller than 5 µm and the total mass of particles recoverd in the impactor.

Scanning electron microscope (SEM) – The samples were fixed on a double-sided electroconductive adhesive tape and sputter-coated with gold during 180 s in an argon atmosphere using the Agar Sputter Coater B7340 (Agar Scientific Ltd., Essex, United Kingdom). The scanning electron micrographs were taken using a LEO VP 1430 (Carl Zeiss NTS GmbH, Oberkochen, Germany) at 20 kV voltage under vacuum.

Laser diffraction (LD) – The particle size distribution was determined using a Sympatec Helos H1402 & Rodos Laser diffractometer (Sympatec GmbH, Clausthal-Zellerfeld, Germany). The powders were dispersed by compressed air of 2 bar.

Statistical method of calculation – The statistical analysis of the experimental data was carried out using the two-sample two-tailed t-test. The two-sample (independent groups) t-test was used to determine whether the unknown means of two populations were different from each other based on independent samples from each population. In cases, where the preliminary F-test for equality of variances indicated that the variances of the two groups were significantly different, a two-sample t-test was performed that does not assume equal variances. If the two-sample means were sufficiently different from each other, then the population means were declared to be significantly different. The statistical probability $^*p$-value was < 0.05.

3. Results and Discussion

For the measurement of the flow behaviour different tests were carried out. Most of them except for the uniformity of dosing, which may be taken as a measure for flowability as well, were done only with the powders treated by Turbula mixing, because they require a minimum of 100 ml of each mixture which exceeds by far the batch size obtainable by electrostatically supported mixing. Firstly, the ring shear tester was used. It enables time consolidation measurements and also measurements for low consolidation stresses [14]. A characteristic of flowability is the relationship of the consolidation stress to the yield strength. This is called the ff_c value. The greater the ff_c value, the better the material flows [15].

The average of the ff_c values obtained by three measurements is shown in Fig. 1. The spray dried lactose with 0 % Aerosil R972 treated by Turbula mixing shows the lowest ff_c value indicating poor flowability. This means a cohesive behaviour. The mixtures of spray dried lactose containing 0.5 %, 2.5 % or 12.5 % nanoparticles behave differently. The mixtures show higher ff_c values than the pure spray dried lactose. This means an improvement of the flow properties obtained by coating the lactose particles with nanoparticles of Aerosil R972. The cohesive properties of the microparticles are reduced and the flowability is enhanced. The mixture with 0.5 % possesses the highest ff_c value of all mixtures, further increasing the amount of Aerosil R972 from 0.5 % to 2.5 % and 12.5 % results in a decrease of the ff_c value again. The possible reasons for this decrease will be discussed below. Summarizing, ring shear testing allows not only to differentiate between pure spray dried lactose and mixtures containing Aerosil R972, but also to rate the improvement of the flow behaviour in the order 12.5 % < 2.5 % < 0.5 % Aerosil R972.

In flow rate tests the time which is needed to release 100 ml of the powder through the outlet of a funnel was measured. While the determination of the flow rate for spray dried lactose containing no Aerosil R972 was not

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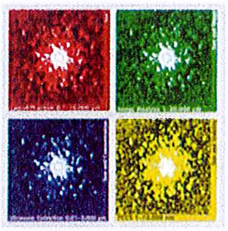

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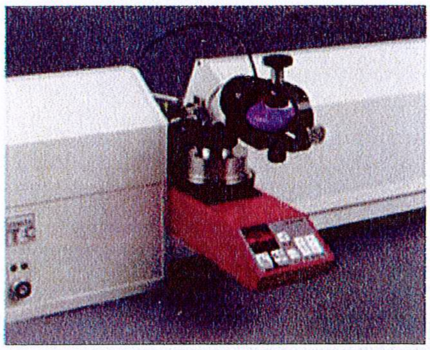

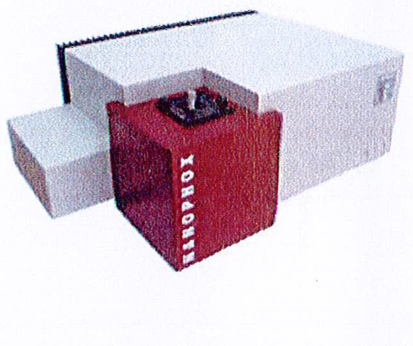

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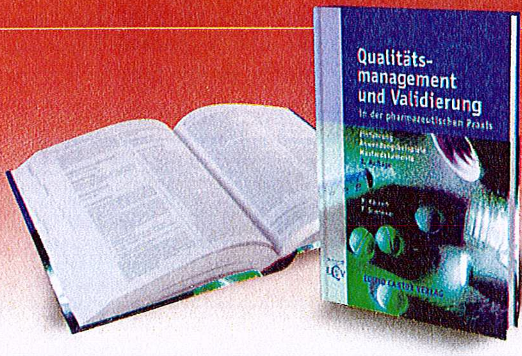

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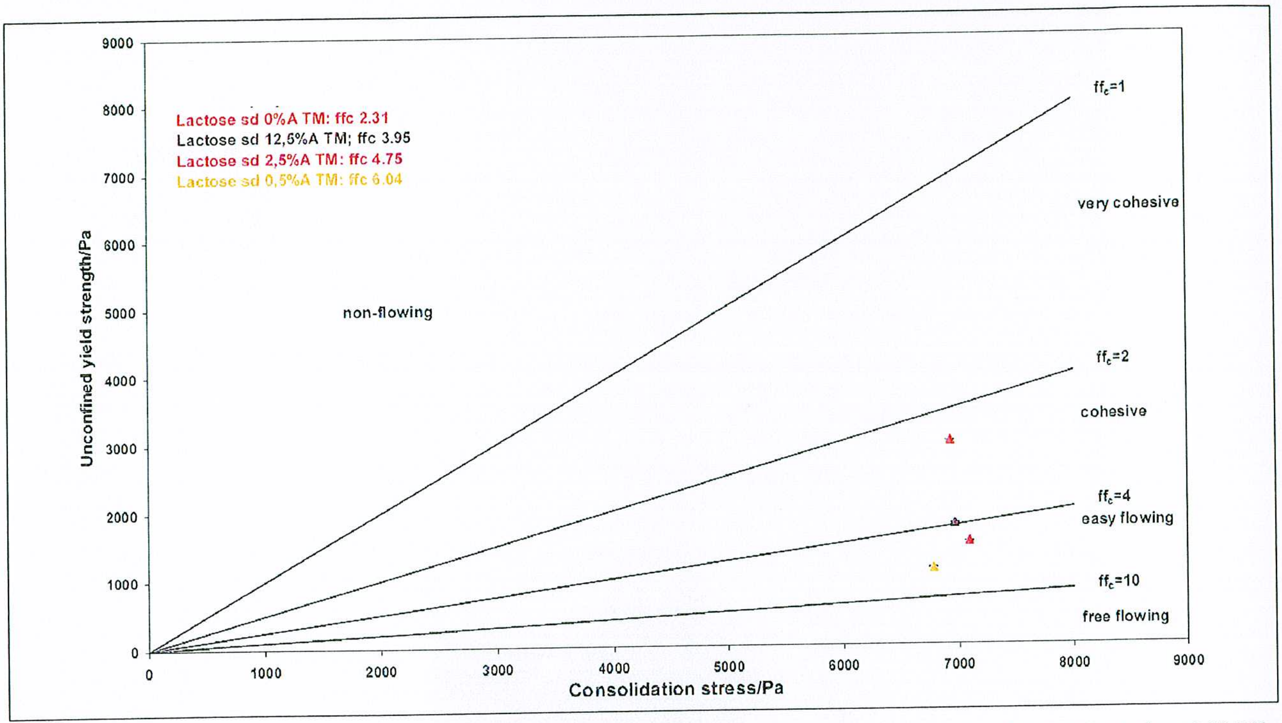

Fig. 1: Mean ± S.D. of the ff_c-values of n = 3 samples of spray dried lactose and mixtures containing 0 %, 0.5 %, 2.5 % and 12.5 % Aerosil R972 (A) prepared by Turbula mixing (TM).

possible due to its very poor flow properties, the determination of the angle of repose of mixtures of spray dried lactose and 0 % 0.5 % 2.5 % and 12.5 % Aerosil R972 respectively, was possible. The results of the flow rate measurements are in good accordance with the results which were determined by measuring the angle of repose. Fig. 2 represents the results of the performed experiments. The data obtained by the measurements of the flow rate and angle of repose support the statement that mixing of the spray dried lactose with 0.5 % Aerosil R972 leads to the best flowability ($^*p < 0.05$). In comparison to mixtures containing 0.5 % Aerosil R972, mixtures containing 2.5 % exhibit a lower flowing rate, which deteriorates even more for the mixtures containing 12.5 %. However, mixtures containing 2.5 % and 12.5 % Aerosil R972 do not differ significantly ($^*p < 0.05$) with respect to their angle of repose which is indicative for the lower sensitivity of the angle of repose to changes of flowability.

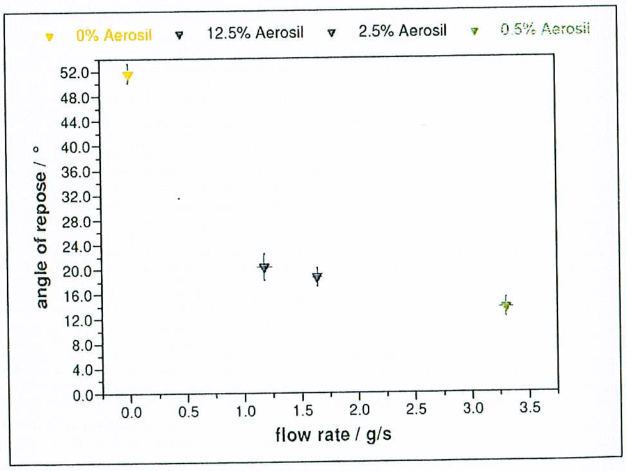

Fig. 2: Mean ± S.D. of the angle of repose and flow rate values of n = 3 samples of mixtures containing spray dried lactose and 0 %, 0.5 %, 2.5 % and 12.5 % Aerosil R972 prepared by Turbula mixing.

Uniformity of dosage is a functional factor for the performance of any multidose dry powder inhaler [16] and a measure for flowability as well. Mixtures of spray dried lactose containing 0 % 0.5 %, 2.5 % and 12.5 % Aerosil R972 which were prepared by conventional and electrostatically supported mixing demonstrate different single dose uniformity. The relative standard deviation can be used as a measure for the uniformity of dosage. A high relative standard deviation means poor uniformity of dosage whereas a low relative standard deviation means a good uniformity of dosage. Uniformity of dosage was investigated by discharging the powder 40 times using a Novolizer DPI. The relative standard deviation of the mass of the 40 discharged doses was calculated. This procedure was performed in triplicate. The mean of the obtained relative standard deviations is plotted in Fig. 3. The uniformity of dosage of spray

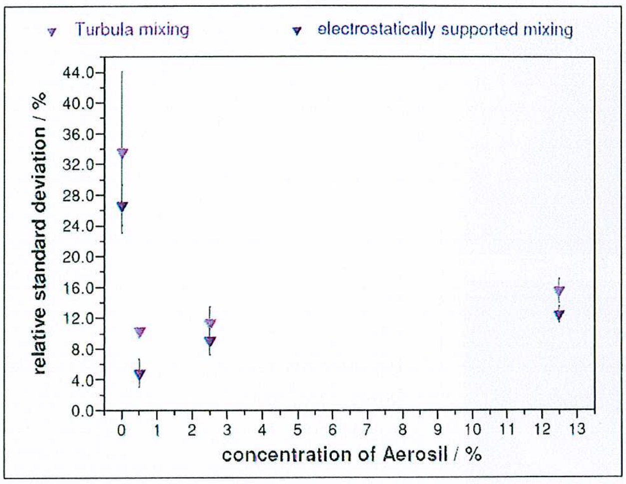

Fig. 3: ***Mean ± S.D. of the relative standard deviation of the mass of 40 doses of n = 3 samples of mixtures containing spray dried lactose and 0 %, 0.5 %, 2.5 % and 12.5 % Aerosil R972 prepared by Turbula mixing or electrostatically supported mixing released from a Novolizer dry powder inhaler.***

dried lactose treated by conventional and electrostatically supported mixing is poor and the relative standard deviation is high. The nanoparticle coated systems display a significantly lower relative standard deviation ($^*p < 0.05$), which indicates an enhanced uniformity of dosage due to the decrease of cohesiveness of the particles. Having a closer look at the mixtures prepared by conventional mixing, the relative standard deviation seems to increase with the amount of Aerosil R972 present in the order 0.5 % < 2.5 % < 12.5 %. However, the difference between the mixtures containing 0.5 % and 2.5 % Aerosil R972 is not significant ($^*p < 0.05$). The effect of the addition of nanoparticles on the uniformity of dosage is in good accordance with the results obtained by flowability measurements using the ring shear tester and with measurements of the powder flow rate and angle of repose. Especially noteworthy is, that the mixture with 0.5 % Aerosil R972 prepared by electrostatically supported mixing displays an even lower standard deviation in comparison to the one prepared by conventional mixing. This phenomenon might be explained by the fact, that the thorough dispersion and charging of the Aerosil R972 in the liquid nitrogen by the shear forces of the high-speed homogenator led to a more homogeneous distribution of the nanoparticles on the lactose surface during the subsequent mixing of Aerosil R972 and lactose particles. This finally caused a more pronounced

Summarizing the results obtained by flowability and single dose uniformity measurements, it is concluded that flowability and dosing of mixtures consisting of spray dried lactose and 0.5 % of Aerosil R972 are superior to pure spray dried lactose and mixtures containing higher amounts of Aerosil R972, namely 2.5 % and 12.5 %. Adding the nanoparticles to the spray dried lactose apparently causes an enhancement of the roughness of surface thereby decreasing the interaction between the particles and enhancing flowability and dosing. However, exceeding the optimum amount of 0.5 % of nanoparticles may cause mechanical interlocking by the excess of nanoparticles forming large agglomerates on the lactose surface. This deterioration manifests itself in the decrease of flowability and uniformity of dosing of mixtures containing 2.5 % and 12.5 % of Aerosil R972 in comparison to mixtures containing only 0.5 % of nanoparticles. These assumptions will be supported by scanning electron micrographs discussed below. Furthermore, it has to be pointed out, that the uniformity of dosage of mixtures prepared by electrostatically supported mixing is superior compared to conventionally prepared mixtures containing the same amount of Aerosil R972, most remarkably in case of the 0.5 % Aerosil R972. This might be explained by the fact that electrostatically supported mixing enhances the dispersion of the nanoparticles during the mixing process before being attached to the microparticles. Thereby agglomerates are destroyed leading to a homogeneous distribution of the nanoparticles on the microparticles surface.

Finally, comparing the different methods applied to determine flowability it has to be mentioned, that two of them, namely ring shear testing and powder flow rate measurements are appropriate to differentiate between all powders prepared by conventional mixing under investigation. According these measurements, flowability decreases in the order 0.5 % > 2.5 % > 12.5 % Aerosil R972. The poorest flowability was found for nanoparticle-free spray dried lactose. Nevertheless, all other flowability measuring techniques identified mixtures containing 0.5 % Aerosil R972 to exhibit the highest flowability, at least.

In order to better understand the initial improvement of the uniformity of dosing when adding 0.5 % of Aerosil R972, and the subsequent deterioration when further increasing the amount of Aerosil R972 from 0.5 % to 2.5 % and 12.5 %, SEM pictures of spray dried lactose mixed with 0 %, 0.5 %, 2.5 % and 12.5 % were taken. They are shown in Fig. 4 for samples prepared by electrostatically supported mixing. The addition of 0.5 % Aerosil R972 to spray dried lactose enhances the surface roughness of the lactose particles. This is likely to prevent the lactose particle getting into close contact thereby decreasing particle-particle-interactions between them and increasing the uniformity of dosing. Further increasing the amount of Aerosil R972 from 0.5 % to 2.5 % and 12.5 % leads to a higher load of the nanoparticles on the lactose surface making the lactose surface look somewhat hairy. These hairs probably may increase the risk for mechanical interlocking between the lactose particles finally decreasing the uniformity of dosing again.

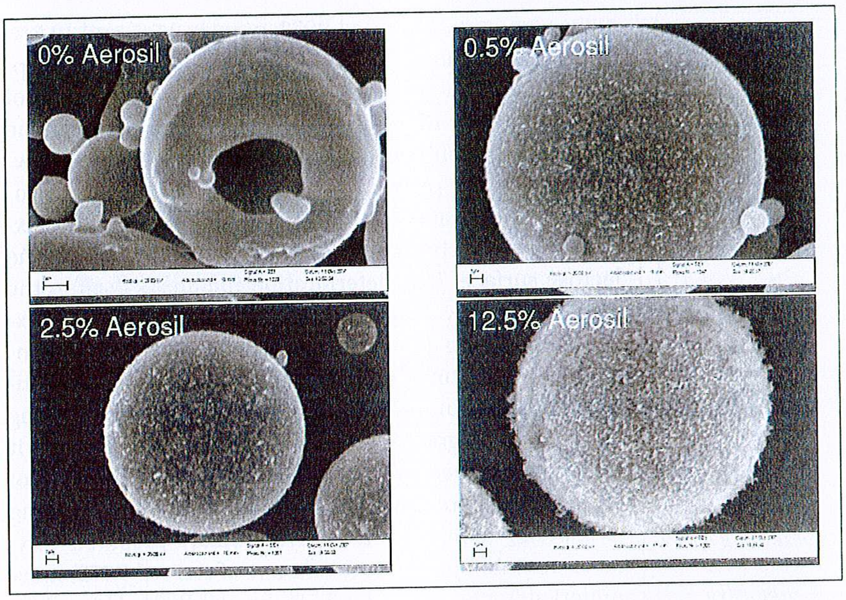

Fig. 4: Scanning electron micrographs (magnification: 4000 ×) of mixtures containing spray dried lactose and 0 %, 0.5 %, 2.5 % and 12.5 % Aerosil R972 prepared by electrostatically supported mixing.

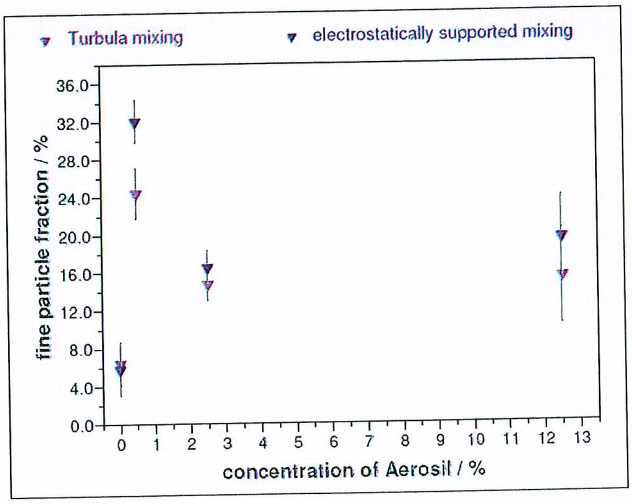

Fig. 5: Mean ± S.D. of the fine particle fraction of n = 3 samples of mixtures containing spray dried lactose and 0 %, 0.5 %, 2.5 % and 12.5 % Aerosil R972 prepared by Turbula mixing or electrostatically supported mixing.

The FPF of spray dried lactose samples without nanoparticles treated by conventional and electrostatically supported mixing are low (Fig. 5). This is caused by the strong interactions between the lactose particles. In contrast, the mixtures containing Aerosil R972 show a significantly higher FPF ($^{*}p < 0.05$), indicating the decrease of the interparticle interactions. The best results were obtained by the mixture containing 0.5 % Aerosil R972 produced by electrostatically supported mixing. These results are in a good accordance with the results of the uniformity of dosing supporting the assumption that electrostatically supported mixing enhances the dispersion of the nanoparticles leading to their homogeneous distribution on the microparticles and resulting in the most efficient reduction of the interparticle interaction. All other mixtures containing 2.5 % and 12.5 % of Aerosil R972 display a significantly ($^{*}p < 0.05$) lower FPF than the samples containing 0.5 % Aerosil R972 – irrespective of whether they have been prepared by electrostatically supported or conventional mixing. These results correspond with the results of the reproducibility of the single dose, where also significant differences between the results of the mixtures with 0.5 % Aerosil R972 and mixtures with higher nanoparticle concentrations are detected. The only difference between the results obtained for the FPF and the uniformity of dosage is found for the samples containing 2.5 % Aerosil R972 prepared by conventional mixing. In case of the FPF a significant difference is found between the samples containing 2.5 % Aerosil R972 and samples containing 0.5 % Aerosil R972, whereas in case of the uniformity of dosage the difference was not significant. The differences in results may be due to the simple fact that the forces acting on the particles during the measurements are different.

Generally, the results obtained from the measurements of the FPF support the results obtained by the investigations regarding the uniformity of dosage and the data obtained by the measurements of the ff_c, angle of repose and flow rate.

4. Conclusion

Summarizing, coating of the model drug particles lactose with model nanoparticles Aerosil R972 is a technology offering the possibility to increase the flowability, the dose uniformity and the fine particle fraction, which is supposed to represent the amount of particles reaching the deeper part of the lungs. The concentration of the nanoparticles plays an important role in the improvement of the flowability, uniformity of dosage and fine particle fraction, low concentrations (0.5 %) leading to a reduction of interparticle interaction, whereas further increasing the nanoparticle concentration (2.5 % and 12.5 %) may cause mechanical interlocking leading to the deterioration of the flowability, uniformity of dosage and fine particle fraction again. It seems that in this case the amount of nanoparticles possesses the ability to increase the surface roughness of the microparticle decreasing the interparticle interactions on the one hand, but also does not lead to mechanical interlocking between the Aerosil R972 particles on the other hand. Comparing conventional and electrostatically supported mixing, electrostatically supported mixing is more efficient with respect to the increase of the fine particle fraction and the uniformity of dosage possibly due to a more efficient dispersion of the nanoparticles finally leading to a more efficient and homogeneous distribution of the nanoparticles over the lactose surface.

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