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ORIGINAL ARTICLE

Influence of carrier surface fines on dry powder inhalation formulations

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Abstract

Background: The performance of carrier-based dry powder inhalation formulations strongly depends on particle interactions between the drug and the carrier. Among other factors like particle size and shape, surface properties of the interacting partners play a decisive role. This study aims at investigating the effect of carrier surface characteristics on the in vitro deposition of ordered mixtures containing salbutamol sulfate as a drug and lactose and mannitol as model carrier compounds. *Methods*: The wet decantation method was used to remove the carrier fines adhered to the carrier surface and to obtain smoother carrier surfaces. In vitro deposition was investigated using the Next Generation Impactor. *Results*: In comparison to the formulations containing untreated carriers, the removal of carrier fines by wet decantation leads to a reduced in vitro deposition. This is possibly caused by an increase in the surface smoothness and an increase in the number of high energetic spots.

Key words: *Dry powder inhaler; lactose; mannitol; salbutamol sulfate; surface modification; wet decantation*

Introduction

The origin of inhalation can be traced back to early civilization, since the respiratory tract is one of the oldest routes used for drug administration to treat local respiratory infections and diseases such as asthma and chronic obstructive pulmonary disease. Recently, the respiratory tract has attracted more attention as a route to deliver drugs as dry powder formulations to treat systemic and local diseases of the respiratory tract. Pulmonary delivery offers a number of advantages compared to other routes of drug administration, such as rapidity of action, directly targeting the lung, minimizing the dose required, avoiding the hepatic metabolism, and reducing the side effects. The preparation of dry powder formulation faces many challenges to provide a good formulation that offers a significant deposition of the drug deep in the lung. One of these challenges is achieving a controlled balance between the interparticulate forces in the powder mixture and the deagglomeration forces during inhalation. As the drug has to be attached to carrier particles in order to introduce sufficient flowability and uniformity of dosage[1], the attachment forces between the drug and the carrier have to be strong enough to maintain satisfactory blend homogeneity during handling and storage. On the other hand, it must be weak enough to yield efficient drug detachment from the carrier particles during inhalation. The dispersion and subsequent deposition of drug particles in the respiratory tract from dry powder inhalers (DPIs) are governed by the patient's inhalation flow rate, the design of the inhaler device, and the physicochemical properties of both the drug and the carrier particles[2].

Particle–particle interaction between drug and carrier particles is a surface phenomenon, mainly dependent upon the physicochemical properties of the interacting particles such as the particle size, shape, and, more importantly, surface texture as well as electrostatic properties and hygroscopicity. It is interesting to investigate the effect of the carrier surface smoothness and the role of carrier fines on the in vitro deposition of the dry powder inhalation formulations.

There are several studies aiming at altering the carrier surface by adding fine particles to the coarse carrier. This addition may lead to change in the adhesion forces between the drug and carrier particles. Iida[3] showed an

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increase in the in vitro deposition of formulations containing carrier particles layered by vegetable magnesium stearate using physical mixing. The added magnesium stearate is claimed to occupy of what are called high energetic spots on the coarse carrier surface, which is reflected in the in vitro deposition results. However, this hypothesis has not been supported by means able to quantify surface energy like, for example, inverse gas chromatography. Coverage of lactose with sucrose tristearate by mixing in a high-speed elliptical rotor mixer to increase carrier surface smoothness increased the in vitro deposition[4]. The coverage of surface depressions by added ternary material decreased the specific surface area available for drug attachment. This decreased the number of drug particles remaining in the carrier surface depressions and facilitated drug detachment. Processing of lactose using a high-speed elliptical rotor-type powder mixer resulted also in an increased fine particle fraction (FPF)[5]. Since smoothing of the carrier surface decreased drug particles attached to macro-depressions, the number of detached drug particles from the carrier particle was enhanced improving the in vitro deposition.

Increased FPF was also obtained with lactose coated by hydroxypropyl methyl cellulose (HPMC) in a Wurster fluidized bed coater[6]. Surface-coated lactose with an aqueous lactose solution containing HPMC contributed to the overall reduction of adhesion forces due to surface smoothing, resulting in an easier separation of drug particles from the lactose surface and a higher respirable fraction.

Chan[7] used spray drying to increase the carrier surface roughness and to decrease interparticle interaction, thereby improving the FPF. This is in contrast to the above finding, when increasing the smoothness resulted in an increase in FPF. Chan[7] showed an increase in micro roughness, which decreased the area of contact between drug and carrier particles and decreased the adhesion forces facilitating drug detachment during the inhalation process. Young[8] showed that the wetting of a lactose carrier using a water/ethanol (5:3) mixture with simultaneous continuous mixing introduced a smoothed carrier surface and increased the in vitro deposition. The removal of larger scale asperities with the preservation of nanoscale asperities on the carrier surface lead to limited drug–surface contact and improved drug liberation during aerosolization. Ferrari[9] modified the lactose surface rugosity by wetting the surface with an ethanol/water mixture in a high shear mixer designed for granulation to produce smoothed carrier surfaces that improved powder packing and flow properties. The following studies showed a reduction of carrier micro roughness followed by an increase in the area of contact and an increase in the adhesion forces between drug and the carrier and subsequently by a lower in vitro deposition. Recently, several studies showed that the removal of the carrier fines from the carrier surface by submersing the lactose carrier in 95% ethanol for 48 hours followed by subsequent filtration and drying in a vacuum oven at 70°C[10] lead to a decrease in the in vitro deposition. The removal of fine carrier particles from the carrier surface leads to an increase in smoothness. The decrease in the in vitro deposition was attributed to the presence of more high energy spots on the carrier surface that could be occupied with the added drug particles, which resulted in stronger adhesion forces between drug and carrier particles, although there was no experimental evidence given for the presence of high energy spots. Removal of carrier fines was also attained by a decantation process using lactose saturated absolute ethanol[11], which resulted in the decrease in the FPF.

Although the surface smoothing of lactose has been investigated by several authors, the impact of surface smoothness on the FPF is reported contradictorily. This might be due to the fact that carriers were subjected to various surface modifying procedures. Depending on the starting material, the same treatment intended to enhance smoothness may cause the decrease in the carrier 'micro roughness' of one carrier whereas it may cause the decrease in the carrier 'macro roughness' of another carrier. As the terms 'micro roughness' and 'macro roughness' refer to the roughness of the carrier surface in relation to the size of the drug particles adhered on it, the decrease in 'micro roughness' will decrease the contact area between the drug and the carrier, thereby decreasing interparticle interaction and enhancing drug detachment from the carrier upon inhalation, whereas the decrease of 'macro roughness' will increase the contact area between the drug and the carrier, thereby increasing interparticle interaction and decreasing drug detachment from the carrier upon inhalation. In this study, the term 'micro roughness' is used for the description of surfaces, where the distance between two peaks of the rough surface is smaller than the size of the drug particle resulting in the decrease in the contact area between drug and surface, whereas the term 'macro roughness' will be used if the distance between two peaks is of the same order as the size of the drug particle. The lack of knowledge about whether 'micro' or 'macro roughness' has been changed may be the major source of contradictory results in the literature. Another reason of contradiction might be the employment of drug particles obtained by comminution procedures, which differ between the studies described in the literature. Furthermore, there are differences between studies in relation to the means of quantifying smoothness and in relation to the techniques applied to determine interparticle interactions and related properties like drug

particle detachment. Finally, the lack of taking into account the impact of other factors except smoothness on interparticle interactions may be another cause of contradiction.

The aim of this study is to alter surface smoothness by another improved decantation process using a new sequence of organic solvents. First absolute ethanol was directly used without sugar saturations, in order to remove the carrier fines, and then dichloromethane was used at the last step to prevent solid bridging between the coarse carrier particles.

Furthermore, this study aims to alter the surface characteristics of mannitol as an alternative carrier rather than lactose, since lactose has several disadvantages like its ability to reduce the amino groups of peptides and proteins. As surface modification of mannitol has not been described in the literature before, this study focuses on this issue.

Materials and methods

Materials

Mannitol (Pearlitol160c) was supplied kindly by Roquette GmbH (Lestrem, France), lactose (InhaLac120) was supplied kindly by Meggle GmbH (Wasserburg, Germany). Salbutamol sulfate was kindly supplied by Lindopharm (Hilden, Germany). Absolute ethanol, methanol, and acetonitrile (HPLC grade) were purchased from VWR International GmbH (Darmstadt, Germany). Dichloromethane was purchased from KMF Laborchemie Handles GmbH (Lohmar, Germany). Acetic acid was purchased from Mallinckrodt Baker B.V. (Deventer, Holland).

Preparation of coarse carrier

The sieved fractions (112–140 μm) of coarse carrier comprising lactose and mannitol was obtained by sieving a quantity of the powder sequentially through test sieves with an aperture width of 112 and 140 μm, using a sieve shaker AS 200 control (Retsch GmbH & Co. KG, Haan, Germany) for 20 minutes at an amplitude of 1.5 mm. The sieved carriers were placed over silica gel in a desiccator until further required.

Wet decantation process

The carrier sieve fractions were decanted with absolute ethanol for five and nine times, respectively. Finally, the powders were washed with dichloromethane in which the solubility of lactose and mannitol is negligible, in order to prevent solid bridging. Mannitol (60 g; 112–140 μm fraction) was washed with absolute ethanol to remove the fine particles, the mixture was stirred to make a homogenous suspension and then allowed to settle for 10 minutes at ambient conditions. The cloudy supernatant fluid was decanted and replaced by 60 mL dichloromethane (CH_2Cl_2) in the final washing step. Again the powder was allowed to settle for 10 minutes at ambient conditions. The cloudy supernatant was decanted. During the removal of the supernatant, special care was taken to ensure minimum disturbance of the lower part of the suspension. The powder sample was left for 2–4 days under the fume hood to dry, and sieved through 112 and 140 μm sieves. The same steps were applied to lactose.

Micronization of salbutamol sulfate

Salbutamol sulfate was milled by using an air jet mill (50AS, Hosokawa Alpine AG, Augsburg, Germany). The injection pressure was set to 3 bar, the milling pressure to 2 bar, and the feeding rate was adjusted to approximately 1 g/min. Micronized salbutamol sulfate was placed over silica gel in desiccators until further required.

Preparation of ordered mixtures

Blends of salbutamol sulfate (X_{50} = 2.03 ± 0.03 μm) with coarse lactose or coarse mannitol (112–140 μm) were prepared in a ratio of 1:99 (w/w) in 8 g batches in a stainless steel mixing container using a tumbling mixer (Turbula T2C, WA Bachofen AG, Basel, Switzerland) for 90 minutes, a standard mixing speed of 42 rpm was used. Micronized salbutamol sulfate was blended with lactose or mannitol in a sandwich method. Briefly, an amount of the carrier, equivalent to about half the total mass of the carrier was used to 'sandwich' the drug in the blend. To minimize the effects of tribocharge, a stainless steel container of 5.2 cm diameter and 3.2 cm height was used. The sample was then stored in a vacuum desiccator over silica gel at least 24 hours to allow the electrostatic charge decay. Three mixtures of each composition have been prepared.

Determination of blend uniformity

The blend uniformity was determined by taking 12 samples with a special sample taker. Each sample was dissolved in acetate buffer of pH 3 in a 50 mL graduated cylinder. The amount of salbutamol sulfate in each sample was analyzed using high-performance liquid chromatography (HPLC). Mean and relative SD of the samples were calculated to assess the homogeneity of the different blends.

Determination of surface fines

The percentage of the fine particles that can be removed by compressed air was determined using air jet sieving (A200, Alpine AG, Augsburg, Germany). Carrier (30 g)

was sieved using a 63 μm sieve by subjecting the carrier powder to an air pressure of 1500, 2000, 2500, 3000, 3500, and 4000 Pa, at 5, 10, 15, 25, 45, 60, 120, 180, 240, and 300 seconds. The carrier samples were weighed after finishing the sieving process and the percentage of fines was calculated as follows:

$$\text{Percentage of carrier fines} = 100 - ([\text{mass of carrier after sieving}/\text{mass of start carrier}] \times 100). \quad (1)$$

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was carried out using a differential scanning calorimeter (DSC30, Mettler-Toledo GmbH, Schwerzenbach, Switzerland) calibrated with indium. Small amounts (3 mg) of the carriers were crimp-sealed in aluminum pans with pierced lids. One pan was then placed in the sample chamber and an empty matched aluminum pan was used as the reference for all measurements. The experiments were performed in the range from 0°C to 300°C under nitrogen flow of 50 mL/min. The scanning rate was adjusted to 10°C/min. The onset temperatures and heat of enthalpy (ΔH) for each peak was determined from the normalized DSC thermogram. Each experiment was carried out in duplicate. The second time measuring is shown in the graphs.

X-ray diffractometry

Powder X-ray diffraction patterns of samples were obtained using the Miniflex diffractometer (Rigaku Corporation, Tokyo, Japan) with a Cu–Kα radiation (λ = 1.5406Å) as the source of radiation. The diffractometer was operated at the voltage of 30 kV and the current of 10 mA. Each sample was placed in the cavity of an aluminum sample holder. All samples were measured in the 2θ angle range between 5° and 40° with a step size of 0.02°. All samples were analyzed in triplicate. The second time measuring is shown in the graphs.

Water vapor sorption

Sorption/desorption profiles were determined using water vapor sorption. The gravimetric studies were undertaken in a temperature- and humidity-controlled system (SPS11, Projekt Messtechnik, Ulm, Germany). Approximately 3 g of samples were loaded. The relative humidity (RH) was first set to 0% and then raised in steps of 10% to 90% and one step further to 95%. Subsequently, the RH was decreased from 95% to 90% then to 0% in the same way. This cycle was repeated once more. The equilibrium condition was set to 0.01% mass change per 60 minutes, which had to be reached before the program moved to the next humidity step. The temperature was set to 25°C. Samples were weighed in time intervals of 6 minutes.

Laser diffractometry

The particle size distributions of the micronized drug and the excipients were determined with a Sympatec HELOS laser diffraction spectrometer equipped with a RODOS dry powder dispersing system (Sympatec GmbH, D-Clausthal-Zellerfeld, Germany). The samples were fed to the dispersing air stream using a funnel connected to the injector of the RODOS. All calculations were made using the Fraunhofer theory. All data given represent the average values of at least 10 determinations at the dispersing pressure of 2.5 bar.

Particle morphology

The particle morphology of lactose, mannitol, and salbutamol sulfate was examined by using scanning electron microscopy (SEM; LEO VP 1430, LEO Electron Microscopy Ltd., Cambridge, England), operated by using an electron beam at an acceleration voltage of 19 kV and a working distance of approximately 18 mm. Samples (≈0.5 mg) were mounted via a graphite tape to an aluminum stub. After stripping off the upper side of the adhesive, a small amount of particles was scattered on the stub and dispersed by tapping lightly on the edge of the stub with a spatula to break agglomerates or by using an air stream. The particles were then coated with ~15–20 nm of gold with an Agar manual sputter coater (Agar Scientific Ltd., Stansted, Essex, England), using an electrical potential of 1.5 kV and 20 mA. Photomicrographs of several different areas of the powder on each stub were taken randomly. Representative areas of stub were photographed with different magnification power.

Surface area measurement

The surface areas of carrier and drug particles were measured by nitrogen adsorption. Prior to surface area measurement, known masses of the samples were accurately weighed into sample tubes and outgassed overnight at 40°C using vacuum for mannitol and at 50°C using a continuous N_2 flow for lactose to remove any adsorbed gases from the surfaces of the particles. This difference of preparation temperatures between the two carriers is due to the sensitivity of each carrier and relies on preliminary experiments. Samples were prepared for 24 hours, the sample tubes were then connected to a surface area apparatus. The specific surface carrier area (m^2/g) was obtained by Brunauer, Emmett,

and Teller (BET) nitrogen adsorption measurements using a Micromeritics Tristar 3000 (Micromeritics GmbH, Moenchengladbach, Germany) using multipoint analysis. Each sample was measured in triplicate and the mean and SD were calculated.

In vitro deposition by Next Generation Impactor

The aerodynamic particle size distribution analysis of aerosolized salbutamol sulfate was carried out using a Next Generation Impactor (Copley Scientific Limited, Nottingham, UK). Methodology followed that of the European Pharmacopoeia. The adhesive mixtures were filled into Novolizer® cartridges (Viatris GmbH & Co. KG, Frankfurt, Germany) and dosing was performed with the built-in metering system. The aerosolization was done at 79.3 L/min. The impactor plates were coated with a viscous solution of the emulgator polyoxyethylene-20-cetylether (0.25%) in glycerol anhydride (4.75%) and isopropanol HPLC grade (95%). A specified volume [2 mL for stages 2–7 and 4 mL for stage 1 and the micro-orifice collector (MOC)] of this solution was distributed on each collection plate to provide a thick film. The plates were left to dry under ambient conditions for at least 2 hours prior to each analysis. The preseparator was coated with 7.5 mL acetate buffer. The impactor was assembled and the Novolizer® was then fitted into the molded rubber mouthpiece attached to the throat of the impactor. The TPK Copley pump (Copley Scientific Limited), which was connected to the outlet of the apparatus, was switched on and allowed to run for 3 seconds prior to the release of the dose. The pump was then allowed to run for another 3 seconds at 79.3 L/min, 50 doses were released in this way. The impactor was dismantled and the individual plates as well as the MOC were carefully washed with acetate buffer pH 3. The inhaler mouthpiece, the throat and the preseparator were washed into volumetric flasks of 100 mL, and the washing solution was made up to a set volume with the same solvent (acetate buffer, pH 3). The concentration of salbutamol sulfate in each of the samples was analyzed by HPLC. The particles of less than 5 μm were expected to be deposited in the lung after inhalation. The ratio of the mass of drug particles less than 5 μm and the emitted dose is defined as the FPF, which is used to describe the respirable fraction of DPI formulations.

HPLC analysis of salbutamol sulfate

Salbutamol sulfate was analyzed by HPLC (Shimadzu C-R4AX CHROMATPAC, Kyoto, Japan) employing a 15 cm × 4.6 mm internal diameter reversed phase column packed with 5 μm C-18 Nucleosil HD RP 18 MN 250/4 (Macherey-Nagel GmbH & Co. KG, Dueren, Germany) and a mobile phase mixture of 50% acetonitrile and 50% acetate buffer (2.5 g glacial acetic acid (100%) in 1000 mL distilled water), adjusted to pH 3.0. The 50:50 ratio mobile phase was running at a flow rate of 0.52 mL/min. The HPLC system consisted of a pump (LC 6A, Shimadzu, Duisburg, Germany), a multiple wavelength detector (SPD-6AV), and an auto sampler (SIL-6B). The UV/VIS detector was operated at a wavelength of 276 nm and the injection volume was 10 μL.

Statistical tests

The in vitro deposition data were examined for statistically significant differences by using the single variance analysis (ANOVA) test. A P-value of <0.05 was considered significant.

Results and discussion

In DPI formulation an ideal carrier should have suitable surface characteristics. This means a surface on which the adhesion forces between carrier and drug are strong enough for drug particles to be attached to the carrier, yet such that a large proportion of the emitted drug can subsequently detach from the carrier on inhalation. In this study, the carrier surface was modified by wet decantation. Lactose and mannitol were chosen for wet decantation, they possess significant concentrations of fine carrier particles. Air jet sieving was performed in order to quantify the amount of fines being detached from the coarse carrier by compressed air. The sieved fraction (112–140 μm) of lactose and mannitol were subjected to wet decantation to remove the fine particles associated with these carriers. The decantation process was carried out for five and nine times, respectively, with absolute ethanol. Finally, the last decantation cycle was performed using dichloromethane. The use of absolute ethanol in the wet decantation process was intended, since lactose and mannitol are slightly soluble in absolute ethanol, which is expected to remove the carrier fines. Furthermore, the use of dichloromethane in the last step of the wet decantation process was intended, because the solubility of lactose and mannitol in dichloromethane is negligible, thus it is used to prevent solid bridge formation between the coarse carrier particles.

The treated and the untreated samples were characterized by DSC, X-ray powder diffraction (XRPD), and water vapor sorption in order to investigate whether there is any influence of the decantation process on the crystallinity of the carriers. Their particle sizes and morphology were investigated by laser diffraction and SEM, respectively. The impact of the decantation process on the surface properties of the carriers was investigated by gas adsorption according to BET and water vapor sorption.

Finally, the influence of decantation on the in vitro deposition of the ordered mixtures consisting of salbutamol sulfate and the modified carriers was examined.

Determination of surface fines

The air jet sieve method was used in this study to get an idea about the amount of fine carrier particles present on the coarse carrier surface. Carrier powders (112–140 μm) were sieved through a 63 mesh wire screen at an air pressure of 1500, 2000, 2500, 3000, 3500, and 4000 Pa, respectively. The amount of carrier fines that has been removed from the carrier surface was assessed after the sieving. Figure 1 shows the percent of fines that have been detached at different compressed air pressures and sieving times. The increase in the compressed air pressure and the elongation of the sieving time lead to an increase in the percent of surface fines detached from the coarse carrier particles. Mannitol contains more fines at the coarse carrier surface or the fines are bound more loosely in comparison to lactose. Mannitol shows the removal of fines up to 13%, whereas lactose shows about 5% at the maximum compressed air pressure applied (4000 Pa). This method of using the air jet sieving assesses whether the carrier contains fines at all, that possibly could be removed by wet decantation.

Determination of the extent of crystallinity by differential scanning calorimetry

The extent of crystallinity was examined using a differential scanning calorimeter. It is known from the literature[12] that lactose may have a small part of the amorphous form at the carrier surface, which may recrystallize during the decantation process by the effect of the organic solvents that were used in this process. Untreated as well as treated mannitol show only one endothermic melting peak between 165°C and 166°C (Figure 2b). The enthalpy of fusion of treated mannitol (298.84–304.54 J/g) does not significantly exceed the enthalpy of fusion of untreated mannitol (285.90–300.42 J/g). All lactose samples exhibit complex thermoanalytical transitions because of several crystalline as well as amorphous forms of lactose. As shown in Figure 3a, α-lactose monohydrate becomes anhydrous at 146–147°C. Anhydrous α-lactose has a melting point of 217°C whereas the endothermic peak at approximately 223°C is the melting endotherm of β-lactose dehydrate. The value for the enthalpy of dehydration ranges from 149.84 to 153.51 J/g, which is similar to the value reported in the literature. Interestingly, there was no evidence of any crystallization exotherm, indicating that the amorphous part of the material, if there was any before decantation, has already recrystallized before the DSC measurements. However, amorphous character in highly crystalline solids might be difficult to detect using traditional analytical techniques such as DSC, where the limit of detection is 5–10%[12].

Determination of the extent of crystallinity by X-ray diffractometry

The XRPD is a widely employed analytical technique for both qualitative and quantitive characterization

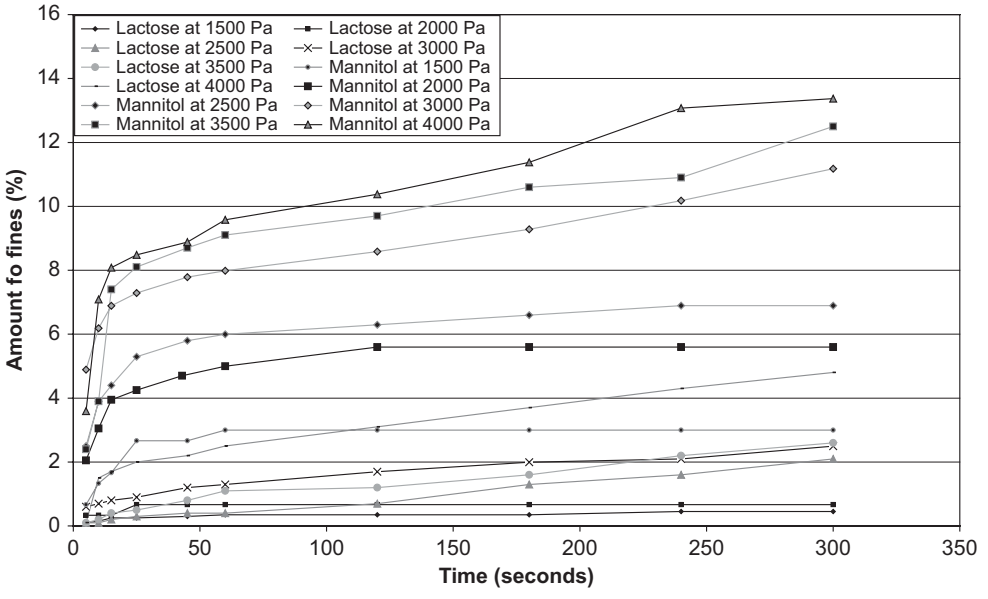

Figure 1. The percent of fine carrier particles removed from the carrier surface of lactose and mannitol determined using air jet sieving at different air pressures and for different periods of time.

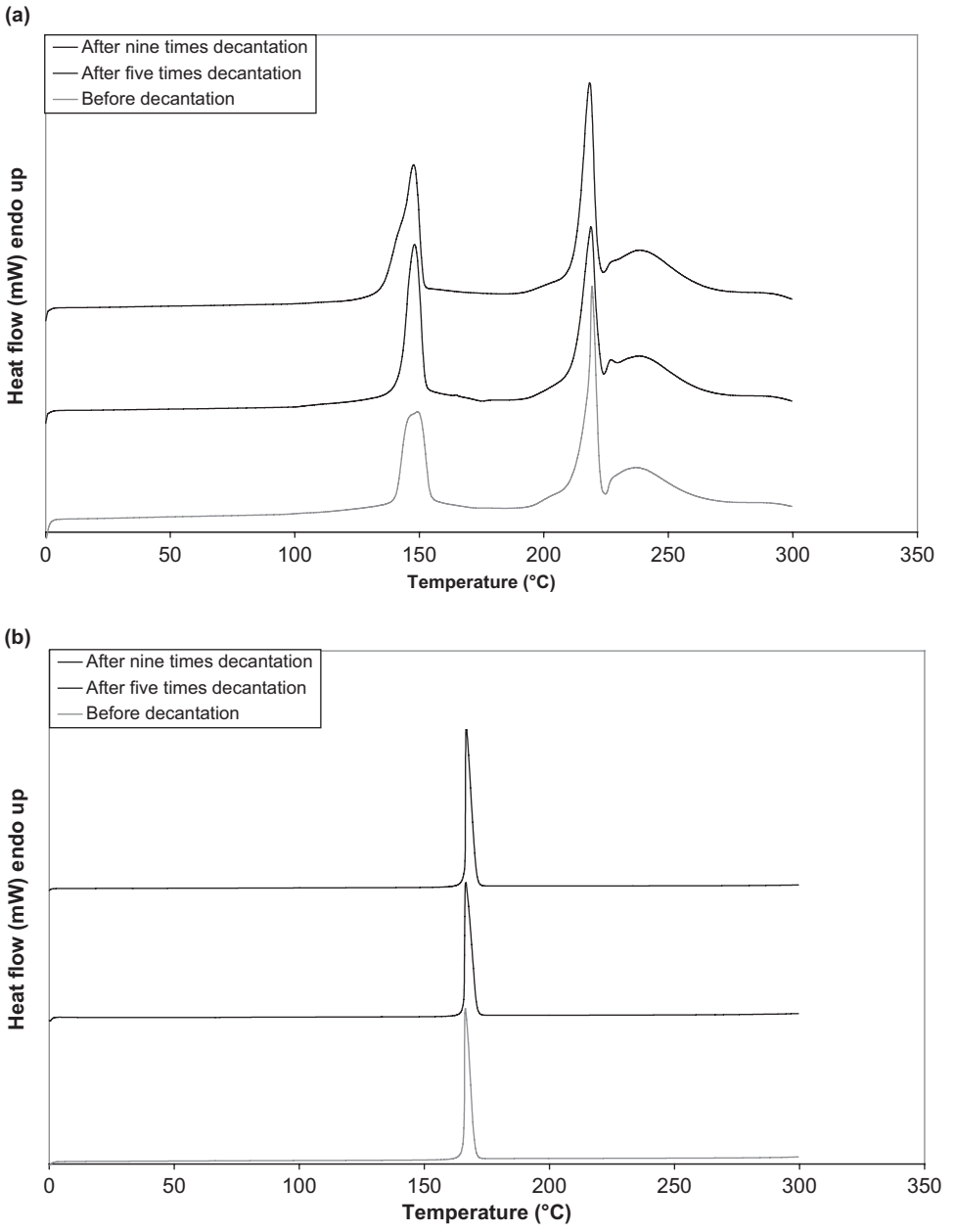

Figure 2. DSC thermograms of lactose (a) and mannitol (b) carriers before and after the decantation process.

purposes of drugs at the particulate level. The X-ray diffractograms of untreated and treated lactose and mannitol carriers show characteristic sharp peaks as indication of crystallinity and the absence of a broad, amorphous halo peak (Figure 3). From the diffractograms shown in Figure 3, it can be concluded that lactose and mannitol carriers were not affected by the decantation process in terms of crystallinity when compared to the 'as supplied' starting material. Generally, X-ray is better at detecting a small amount of crystalline material of an amorphous sample than it is at detecting a small amount of the amorphous form in a crystalline sample. Water vapor sorption is the next choice to detect crystallinity after the wet decantation process.

Determination of the extent of crystallinity by water vapor sorption

Lactose and mannitol are nonhygroscopic carriers and show an increase in the mass with increase in RH (Figures 4 and 5). Buckton[13] used the water vapor sorption to assess the amorphous content of lactose by using the mass loss at 60% RH as indication of the conversion of the amorphous form to crystalline α-lactose monohydrate by the expulsion of water.

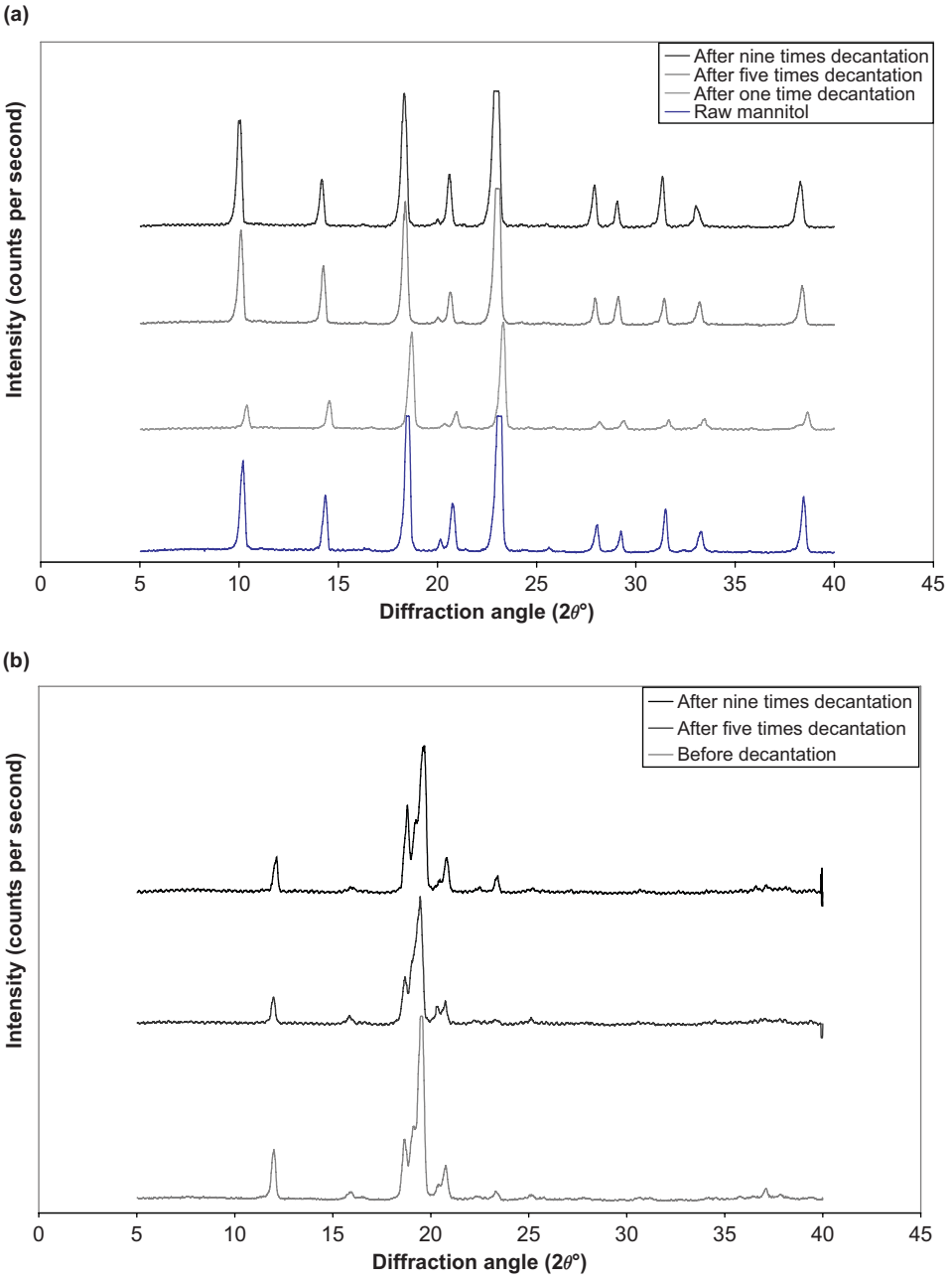

Figure 3. X-ray diffractograms of lactose carriers (a) and mannitol (b) carriers before and after the decantation process.

Untreated as well as nine times treated lactose used in this study shows an increase in the mass with the increase in the RH followed by a decrease in the carrier mass with the decrease in the RH in the first sorption cycle. The sorption behavior of the second cycle is similar. The absence of the mass loss at 60% RH in the first cycle and the similarity of the sorption behavior in the second cycle assure that there is no amorphous part in this lactose even after nine times decantation. Similarly, mannitol shows a sorption behavior of a crystalline carrier with no amorphous content.

Determination of the particle size distribution by laser diffraction

To investigate the effect of the decantation process on the particle size of lactose and mannitol carriers, laser diffraction analysis was carried out. The mean particle diameter of the carriers after the smoothing process is shown in Table 1. The size distribution of the carrier particles is not changed markedly, which indicates that the decantation process has no major influence on the particle size distribution. There is no decrease in the particle size indicating that ethanol did not solubilize the coarse carrier particles.

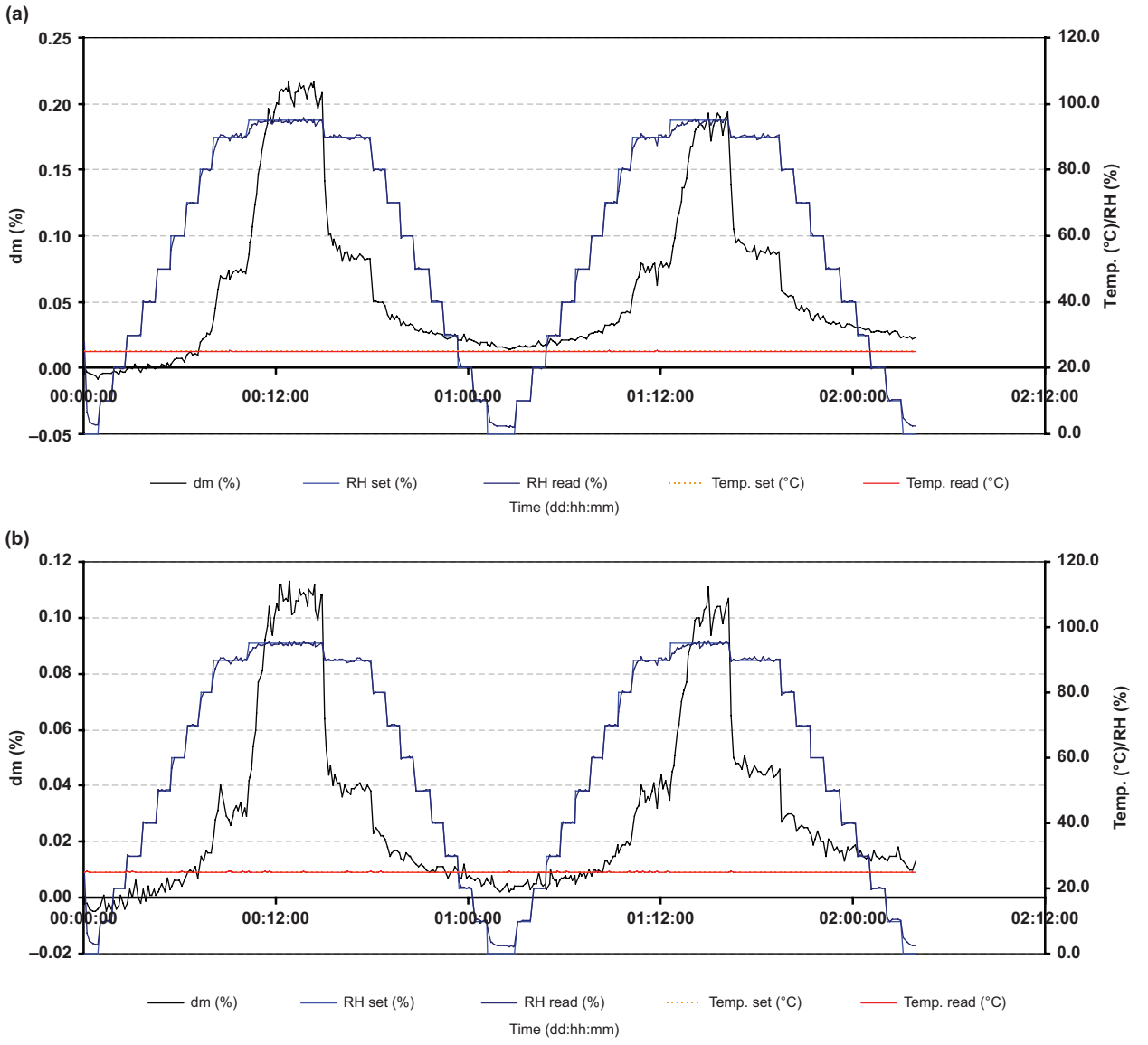

Figure 4. Water vapor sorption of lactose before decantation (a) and after nine times decantation (b).

There is also no increase in the particle size indicating that dichloromethane inhibited solid bridging efficiently.

Determination of the particle shape and the surface characteristics by scanning electron microscopy

The particle morphology of lactose and mannitol carriers was examined by using a scanning electron microscope. Several photomicrographs were produced by scanning fields, selected randomly at several magnifications. According to Figure 6, lactose after nine times decantation shows a smoother surface with less fines in comparison to lactose before decantation, whereas mannitol still has fines even after nine times decantation frequency. However, the possibility of investigating the whole carrier sample by using SEM cannot be attained. Scanning electron micrographs capture just a few particles of the whole bulk and do not provide representative information about the whole number of particles and how they will appear. This clarifies why the resultant micrographs before and after decantation may give a rough idea about the effect of decantation, but it is not a powerful tool to indicate the success of the applied decantation process.

Determination of surface area by BET measurements

Figure 7 shows the specific surface area of treated and untreated lactose, treated and untreated mannitol, respectively. From this diagram, it is obvious that decantation decreases the specific surface area of the carriers. This is attributed to the removal of fine particles from the surface of the coarse carrier. The extent to which this occurs

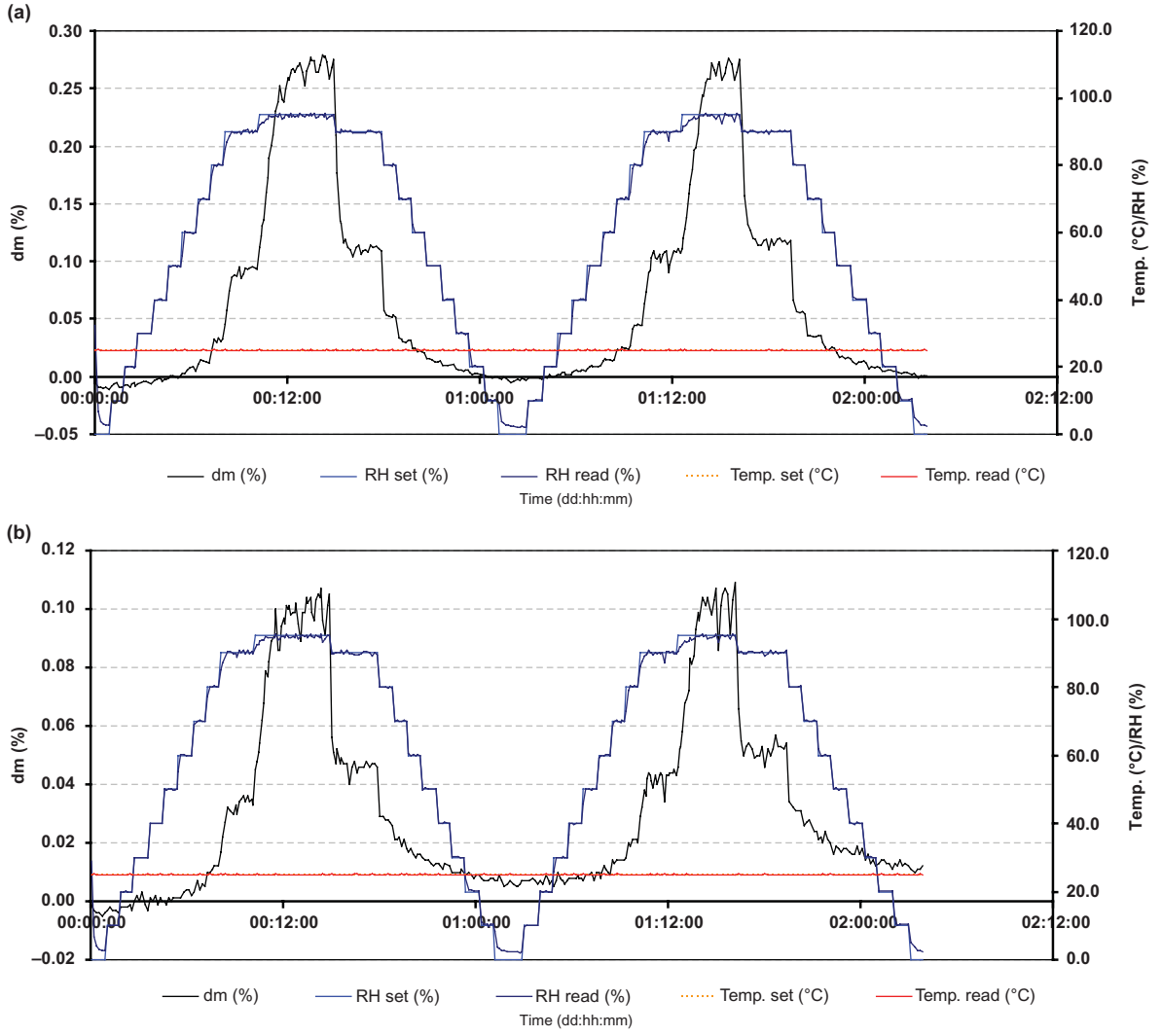

Figure 5. Water vapor sorption of mannitol before decantation (a) and after nine times decantation (b).

Table 1. Laser diffraction analysis of the carrier particle size distribution before and after the wet decantation process ($n = 10$, mean ± SD).

Substance	X_{50} (µm)	X_{10} (µm)	X_{90} (µm)
Lactose before decantation	130.12 ± 3.97	92.40 ± 3.35	178.14 ± 2.48
Lactose after five times decantation	133.95 ± 1.76	93.24 ± 1.70	184.26 ± 3.23
Lactose after nine times decantation	136.76 ± 1.00	91.42 ± 2.07	193.29 ± 1.15
Mannitol before decantation	156.06 ± 2.32	63.15 ± 11.66	247.67 ± 5.17
Mannitol after five times decantation	156.49 ± 6.56	69.27 ± 5.41	262.00 ± 3.91
Mannitol after nine times decantation	155.70 ± 5.23	56.50 ± 4.54	269.48 ± 1.23

depends on the frequency of the wet decantation method applied.

Investigation of surface characteristics by water vapor sorption

The water vapor sorption plots (Figure 8) show that untreated carrier particles are taking up more water than the treated carriers. The lower lines are the adsorption responses and the upper lines are the desorption responses. The adsorption response is due to the building up of a few layers of water molecules on the surface. The maximum weight gain for untreated lactose is 0.21% and for untreated mannitol 0.28%. The water vapor sorption isotherm of treated lactose shows a decrease in water uptake by the increase in

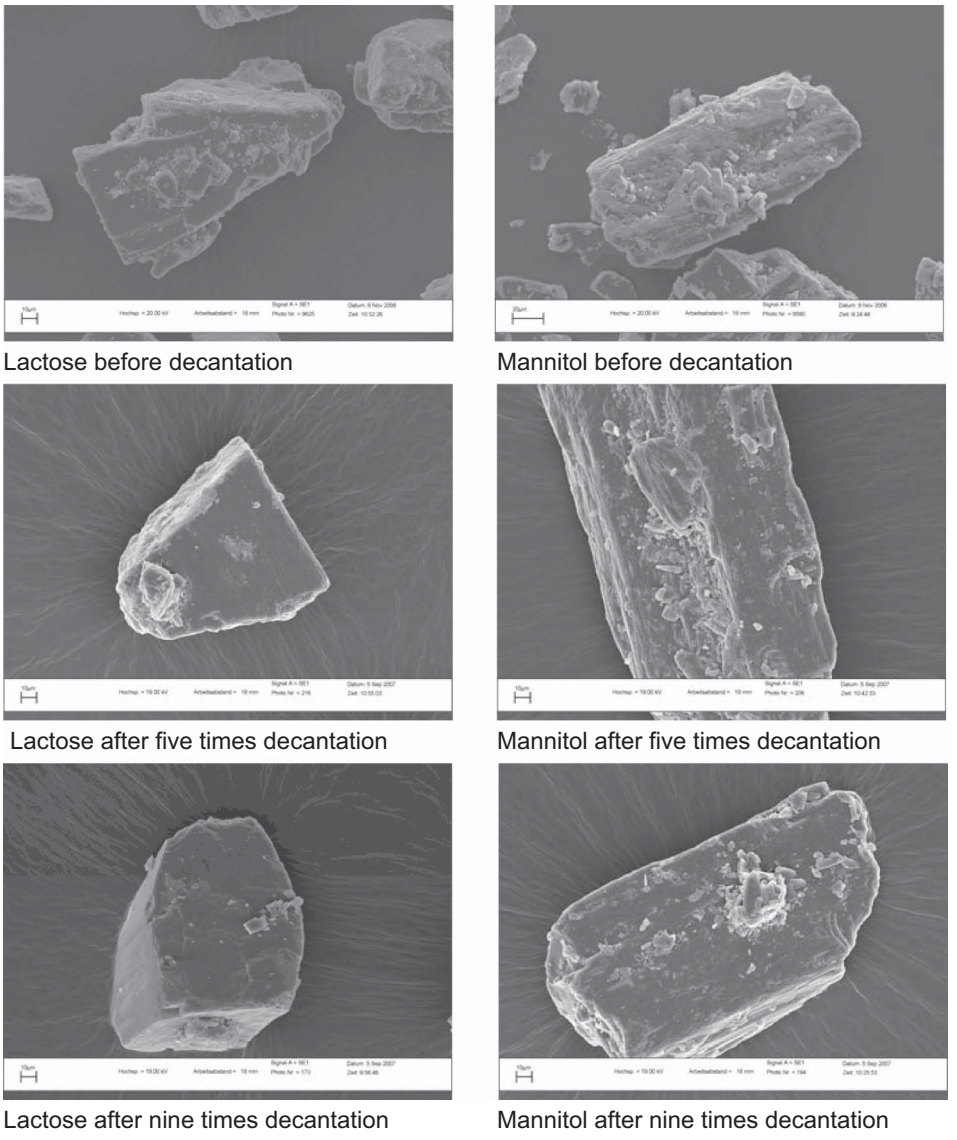

Figure 6. Scanning electron micrographs of lactose and mannitol before and after wet decantation.

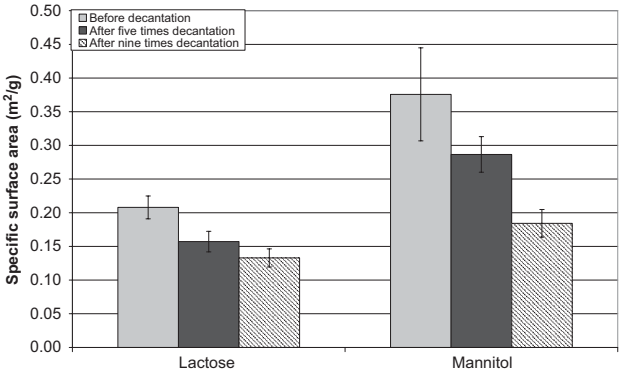

Figure 7. Specific surface area of lactose and mannitol before and after decantation ($n = 3$, mean ± SD).

the decantation frequency in comparison to the untreated lactose. This can be explained by the part of fine carrier particles that has been removed from the carrier surface by wet decantation leading to a decrease in the surface area and subsequent decrease in water sorption. The water vapor sorption of treated mannitol shows a decrease in water sorption after five times decantation. Nine times decantation does not further reduce the water sorption. The results of water vapor sorption of lactose are in agreement with the results of the BET measurements, where the decrease in surface area due to the removal of fines is accompanied with a decrease in water uptake after five and nine times decantation, respectively. Furthermore, mannitol water sorption is decreased up to five times decantation. However, after nine times decantation mannitol water

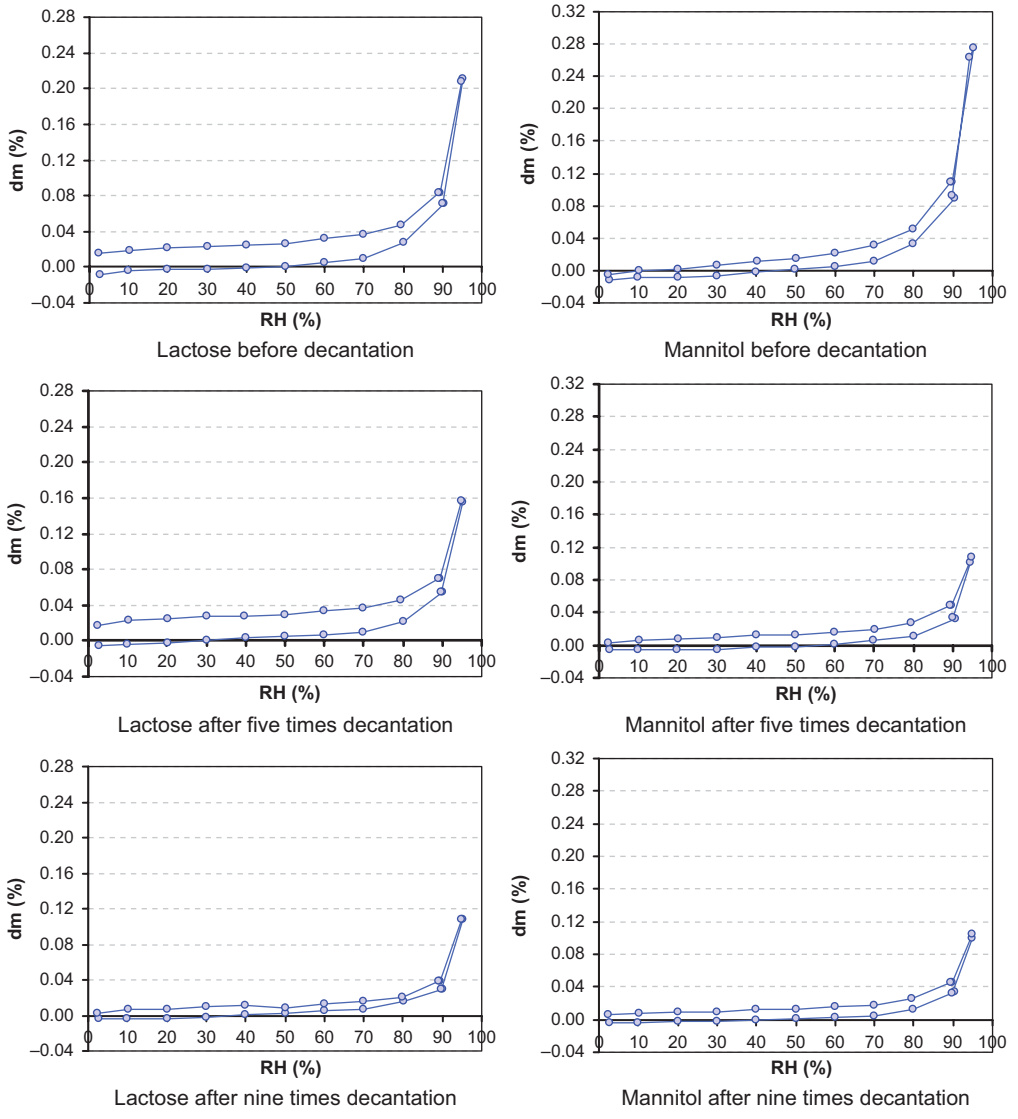

Figure 8. Water vapor sorption isotherms of lactose and mannitol before and after decantation.

sorption is not significantly decreased, although the specific surface area is markedly decreased. Nevertheless, it has to be kept in mind that water vapor sorption may give a rough idea about the surface area of a powder, but is not solely reliant on it. This may cause the above-mentioned deviation of the results.

In vitro deposition test

In vitro deposition was estimated by aerodynamic assessment of fine particles using the Next Generation Impactor. In this study, the FPF of salbutamol sulfate was calculated. The formulations containing lactose or mannitol and micronized salbutamol sulfate show an acceptable degree of homogeneity with the mean drug content across all blends being within 100.0% ± 5.0% of the theoretical value and each blend exhibiting a coefficient of variation below 5% (n = 12). This suggests that the overall process of mixing, sampling, and analyzing is accurate and reproducible. The FPF of salbutamol sulfate using untreated lactose and mannitol as carriers is higher than that of the modified carriers (Figure 9). The FPF is significantly reduced after five times decantation (ANOVA, $P < 0.05$) and it is significantly reduced after nine times decantation in comparison to five times decantation. This change in FPF can be explained as follows: Removing the fine particles from the coarse carrier surface will lead to free high energetic sites on the carrier surface that can be occupied with micronized drug. This provides more adhesion between the fine drug and the coarse carrier, which leads to difficulties in separation of these fine drug particles from the coarse carrier upon aerosolization. Additionally, the increase in surface smoothness of the coarse carrier

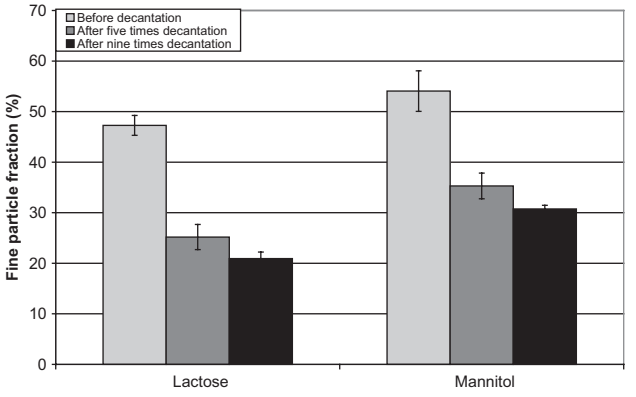

Figure 9. Fine particle fraction of mixtures of salbutamol sulfate with lactose and mannitol before and after five and nine times wet decantation ($n = 3$, mean ± SD).

caused by the removal of carrier fines after decantation thereby decreasing the surface micro roughness will provide a smooth surface of the carrier to be contacted with the fine drug, which results in an increase in the area of contact in comparison to a rough surface and consequently in higher adhesion forces between the drug and the smoothed carrier particle. This results in difficult detachment of drug particles from the carrier particles upon inhalation. The results of this study demonstrate the importance of adhered carrier fines on the coarse carrier surface. The results with lactose are in agreement with the results of Islam[11] who reported that ordered mixtures with treated lactose showed a decline of the FPF in comparison to untreated lactose. The mechanism of action is also valid for the newly introduced mannitol carrier.

Conclusion

This study introduces an improved decantation process with a new sequence of solvents, which is a valuable method of removing the fine carrier particles from coarse lactose and mannitol carrier surfaces without solid bridge formation. Lactose and mannitol show successful removal of surface fines by decantation in comparison to 'as supplied' starting carrier materials. The increased frequency of the decantation process results in a decrease in the specific surface area due to removal of fines from the particle surface. The engineering of lactose and mannitol carrier surfaces using this improved decantation process for carrier fines removal resulted in a significant decrease in the FPF when compared with the 'as supplied' starting materials. This decrease of the FPF might be explained by two possible mechanisms: The first one is that the removal of fine particles leads to provide more high energetic spots at the carrier surface that can be occupied with the added drug. This occupation results in higher adhesion forces between drug and carrier particle and reduced FPF. The second mechanism is that the removal of carrier fines from the carrier surface leads to an increase in the surface smoothness by decreasing the micro roughness caused by the carrier fines, which possibly results in the increase of the contact area and the formation of stronger adhesion forces between the carrier surface and the drug particle. These strong adhesion forces result in difficulties of drug particle detachment from the carrier particles during inhalation process and subsequently in a low FPF.

***Declaration of interest*:** The authors report no conflicts of interest.

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