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Alternative sugars as potential carriers for dry powder inhalations

Hartwig Steckel*, Nina Bolzen

Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University Kiel, Gutenbergstraße 76, Kiel 24118, Germany

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Abstract

Most dry powder inhaler (DPI) formulations rely on lactose monohydrate as a carrier in the drug powder blends. However, lactose cannot be used for compounds that interact with the reducing sugar function of the lactose, such as formoterol, budesonide or peptides and proteins. In this study, alternative carriers like mannitol, glucose, sorbitol, maltitol and xylitol have therefore been evaluated for their potential use in DPI formulations. Raw materials were characterised physico-chemically and blends with the model drug substance budesonide were tested with respect to the aerosolization behaviour of the powders.

It was found out that similarly to the problems known for lactose monohydrate, such as supplier variability, variability between different qualities of one supplier, the same difficulties apply to the alternative carriers investigated. Different sources and qualities of mannitol led to significant differences in the fine particle fraction (FPF), varying from 15 to 50% for two different qualities of mannitol. Similar observations were made for the other carrier materials studied. Also, the influence of conditioning the raw material at different relative humidity was found to have substantial influence on the performance of drug/carrier blends which is characterised by a strong decrease in the FPF. In summary, mannitol showed potential as a drug carrier to be used in DPIs whereas the more hygroscopic sugars only showed poor dispersibility.

Keywords: Dry powder inhaler; Carrier; Mannitol; Glucose; Particle size distribution

1. Introduction

Dry powder inhalers (DPIs) are so far being used for the local delivery of drugs to the lung, such as corticosteroids, β-agonists, anticholinergics and mast cell stabilisers, mainly for the treatment of asthma and COPD (Timsina et al., 1994). As the drug to be delivered to the lungs has to be micronised to penetrate the lung upon inhalation, current products for dry powder inhalations in most cases are carrier-based formulations to reduce drug agglomeration and to improve flowability and ex-device delivery of the powder (French et al., 1996). However, recent research was also focused on the delivery of systemically acting drugs via the pulmonary route (Ganderton, 1999). Especially dry powder inhalations are a promising application form for peptides and proteins for systemic delivery as they overcome the drawbacks of oral and invasive delivery forms, as enzymatic degradation in the GI-tract, low oral bioavailability, the need for i.m., s.c. or i.v. injection, etc. (Wall, 1995).

The carrier of choice for DPI products is currently lactose monohydrate (Lahrib et al., 1999). Nearly all DPI products already on the market or approaching

* Corresponding author. Tel.: +49-431-880-1333; fax: +49-431-880-1352.
E-mail address: steckel@pharmazie.uni-kiel.de (H. Steckel).

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the market are relying on lactose as a carrier material, with few exceptions present that contain glucose (Steckel, 2003). The advantages of lactose monohydrate are its well-investigated toxicity profile, its broad availability and the relatively low price. In addition, lactose crystals do have a smooth surface, a regular shape and show good flowability. In earlier studies, it could also be shown that the surface texture and the shape can be influenced by the manufacturing process or the crystallisation method (e.g., Zeng et al., 2001).

However, for some drugs, e.g., formoterol, or for specific applications, e.g., peptide or protein drugs, lactose monohydrate may not be the carrier of choice due to its reducing sugar function that may interact with functional groups of the drug or the protein, respectively (Patton and Platz, 1992). In addition, lactose monohydrate is produced from and with additives of bovine source so that the Transmissible Spongiform Encephalopathy (TSE) discussion is still an issue for this compound (EC Statement, 2002). Also, discussions regarding the endotoxin content and the necessity for a specification limit are ongoing (FDA draft guidance for industry, 1998). It is therefore reasonable to look for alternative carriers that still possess the positive aspects but overcome the above mentioned drawbacks of lactose monohydrate. It was the aim of this study to evaluate potential candidate carbohydrates as alternative carriers in dry powder inhalation products. Glucose monohydrate, mannitol and sorbitol received from different sources as well as maltitol and xylitol were selected for that purpose. Sieve fractions (32–125 μm) of the raw materials were prepared and the physico-chemical properties were analysed by scanning electron microscopy, differential scanning calorimetry (DSC) and laser diffraction. Finally, interactive mixtures of the sieve fractions with the model drug budesonide were manufactured and tested for their aerodynamic behaviour.

2. Materials and methods

2.1. Materials

The following carrier materials were selected for this study: glucose monohydrate (C*Dex, batch 0527/02001, Cerestar AG, Krefeld, Germany; Roferose ST, batch 638679, Roquette, Frankfurt, Germany), mannitol (Mannitol 25 and 60, batches 622441 and 641970, respectively, both from Roquette; Mannidex, batch 0527/16700, Cerestar AG), sorbitol (Neosorb P100T, batch 640343, Roquette; Sorbidex, batch 9043/16656, Cerestar AG); maltitol (Maltisorb 90, batch 638297, Roquette) and xylitol (Xylisorb 90, batch 642894, Roquette). Pharmatose 325 M (DMV International, Veghel, The Netherlands), batch 43439, was used as a reference carrier for the aerodynamic assessment of the blends. A laboratory batch of micronised budesonide (Lot. no. 19960411-577, AstraZeneca GmbH, Wedel, Germany) with a volume mean diameter (d_{50}) of 1.8 μm and a d_{90} of 3.6 μm was used as model drug. All reagents used were of analytical grade and supplied by Merck KGaA (Darmstadt, Germany).

3. Methods

3.1. Fractionation/conditioning

All raw materials were sieved on a laboratory sieve shaker (Retsch GmbH & Co. KG, Haan, Germany) using 125 and 32 μm analytical sieves. The intermediate fractions were then conditioned on trays at 45 and 75% relative humidity, respectively, and 20 °C for at least 24 h prior to further use. The trays were stored in desiccators conditioned with saturated salt solutions of NaBr (45%) and NaCl (75%) or water (100%).

3.2. Particle size analysis

The volume particle size distribution of the conditioned carbohydrates was measured in a cuvette with a Sympatec HELOS laser diffractometer (Sympatec AG, Clausthal-Zellerfeld, Germany) in carbohydrate saturated miglyol oil as dispersion medium.

3.3. Preparation of powder blends

The carbohydrate compound and budesonide were sieved through a 250 μm mesh and weighed into the stainless steel mixing vessel (corresponding to 25% of the vessel volume) using the sandwich method. The vessel was fixed in a Turbula blender T2C (Bachofen, Switzerland), mixing time was 30 min at

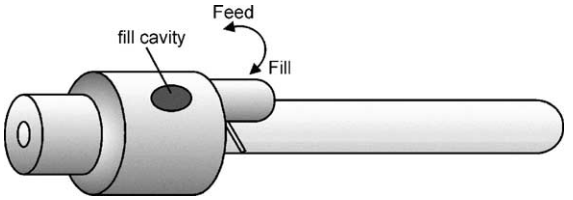

Fig. 1. Application system connected to the multistage liquid impinger for the aerodynamic size distribution measurement.

90 rpm. Batches containing an additional fine component (either 10% (w/w) sieve fraction <32 μm or 0.5% (w/w) Aerosil®) were prepared by pre-mixing the coarse carrier and the fine additive for 10 min, sieving through a 250 μm screen and then final mixing with the drug substance (1% w/w) as described above. Batch size was 25 g for all batches. All blends were prepared in duplicate.

3.4. Blend homogeneity

The powder blends were sampled randomly by taking 10 samples directly from the mixing vessel. The powder was dissolved in a mixture of methanol/water 75% v/v and analysed by reversed phase high performance liquid chromatography (HPLC). The relative standard deviation (RSD) of the average content was used as a measure for the homogeneity of the powder mixture. Batches were accepted and used for aerodynamic testing when the RSD of the average content was below 3%.

3.5. Aerodynamic properties

The fine particle fraction (FPF) (fraction of particles <5 μm), mass median aerodynamic diameter and geometric standard deviation were determined using a Multi-Stage-Liquid-Impinger (Ph. Eur. 2002) with glass throat and a laboratory steel applicator instead of an inhalation device. Measurements were performed at a pressure drop of 4 kPa across the applicator corresponding to a flow rate of 80 l/min through the applicator. Twenty microlitres of a methanol/water mixture (75% v/v) were used as collection fluid in the impinger stages.

The application system (Fig. 1) was used to eliminate the influence of a specific device. Briefly, the device consists of a stainless steel tube with an inner diameter of 5 mm and a total length of 170 mm. The applicator is tightly connected to the glass inlet of the impinger by a rubber adapter. For the delivery of the powder into the nearly laminar airflow in the tube, powder is weighed into the cavity and released into the impinger by rotating the inner part of the applicator. The powder is transferred into the stainless steel tubing and entrained by the air. All impinger tests were done in triplicate for both batches ($n = 6$ for each formulation); error bars given in the figures indicate the standard deviation of the tests.

3.6. HPLC

All budesonide samples were analysed by a validated HPLC method using a Gynkotec high precision pump, model 300 (Gynkotec, Munich, Germany), a Shimadzu UV-detector, a Shimadzu Integrator C-R6A (Shimadzu, Tokyo, Japan) and a Kontron 360 Autosampler (Kontron Instruments, Milan, Italy). A LiChroCART 125-4 was used as reversed phase stationary phase and an acetonitrile:water mixture of 45:55 parts (v/v) was used as mobile phase. UV-detection was carried out a wavelength of 246 nm. The system was calibrated in a concentration range of 1–20 μg/ml budesonide using an external standard.

3.7. Scanning electron microscopy

SEM pictures of the carrier materials (sieve fractions) were made by means of a Philips XL 20 (Philips, Eindhoven, Netherlands). The samples were prepared on conductive, double-sided adhesive tape and sputter-coated with gold under an argon atmosphere at 50 mPa under-pressure with a sputter coater SCD 005 (Bal-Tec AG, Balzers, Liechtenstein).

3.8. Differential scanning calorimetry

DSC scans were taken for all the raw and the conditioned materials used in the study by means of a power compensated differential scanning calorimetry (DSC 7, Perkin-Elmer, USA). The samples were investigated using non-hermetically sealed/open pans in a temperature range of 20–260 °C with a scanning rate of 10 °C/min. The instrument was calibrated with indium. The sample weight was approximately 2.2 mg.

4. Results and discussion

4.1. Particle size distribution and appearance of the carriers

Recent studies on carrier materials used for dry powder inhalations have indicated that amorphous parts can be present even on the surface of crystallised and non-milled lactose. Therefore, conditioning of the lactose at elevated relative humidity, e.g., at 45 or 75% RH for at least 24 h, seems appropriate to bring the amorphous parts to re-crystallisation (Steckel, 2002). Accordingly, the investigated alternative carrier materials have also been conditioned at 45 and 75% RH, respectively, and the changes in particle size distribution, thermal behaviour and visual appearance have been observed. The results of the particle size distribution measurements after the fractionation step are outlined in Table 1. It has to be noted that the fractionation process, even if standardised, does not result in similar size distributions of the sieve fractions. Mannitol that has been sieved according to the described process shows an x_{50} of 63 μm with 10% of the particles being smaller than 19 μm for the Roquette quality and an x_{50} of 47 μm and 10% smaller than 8 μm for the Cerestar quality. In both sieve fractions, particles that are distinctly higher than the mesh size of the used sieve can be detected (x_{90} of 255 and 226 μm, respectively). This indicates that the mannitol particles are not spherical or equi-dimensional in shape but slightly elongated. These differences in the particle size distributions of materials from different suppliers could also be observed for the two sorbitol and dextrose qualities used: The Neosorb quality has an x_{50} of 75 μm whereas the Sorbidex quality shows an x_{50} of 118 μm and a considerable amount of particles >125 μm. Similarly, the C*Dex glucose quality has a lower x_{50} (85 μm) than the Roferose quality (x_{50}: 118 μm). For the xylitol and the maltitol, only material from one supplier was used in this study. The size distributions of these two sugar alcohols also differ significantly. One mannitol quality, Mannitol 25, was used and recrystallised as received without any further classification because the raw material had already a suitable size distribution with 90% of particles <65 μm.

It can also be concluded from the data shown in Table 1 that the conditioning process at the higher relative humidity (75%) led to a distinct particle growth indicating that small particles become attached to the surfaces of the larger particles. However, a change in the thermal behaviour of the powders could not be observed as exemplarily shown for sorbitol powders in Fig. 2. The results from the size distribution measurements indicate that it will most probably not be possible to use a carrier substance coming from two different sources, even if the raw material is further processed by conditioning and classification. This is

Table 1
Volume particle size distributions (±S.D.) of the used carriers after conditioning at 45 and 75% RH and sieving

	x_{10} (μm)	x_{50} (μm)	x_{85} (μm)	x_{90} (μm)	x_{99} (μm)
Mannitol 60 (45%)	18.8 ± 0.8	62.6 ± 1.3	118.8 ± 2.1	138.7 ± 2.8	255.0 ± 1.6
Mannitol 60 (75%)	15.3 ± 0.4	66.3 ± 1.6	127.1 ± 0.2	145.6 ± 1.0	247.4 ± 3.7
Mannitol 25 (45%)[a]	3.9 ± 0.2	20.3 ± 1.1	53.4 ± 2.2	64.8 ± 2.5	156.2 ± 0.4
Mannidex (45%)	7.8 ± 0.3	47.4 ± 0.4	102.1 ± 0.1	119.5 ± 1.0	225.5 ± 0.8
Mannidex (75%)	15.7 ± 0.3	58.1 ± 0.5	113.6 ± 1.4	131.2 ± 2.1	236.5 ± 2.0
Neosorb P100T (45%)	29.8 ± 0.6	75.5 ± 1.3	117.2 ± 1.5	127.5 ± 0.5	174.4 ± 0.8
Sorbidex (45%)	28.5 ± 0.5	117.8 ± 1.0	169.9 ± 1.8	184.0 ± 2.4	246.6 ± 1.5
Sorbidex (75%)	47.3 ± 0.6	124.6 ± 0.8	175.0 ± 2.0	190.5 ± 2.2	258.5 ± 0.7
Roferose ST (45%)	42.6 ± 0.1	118.4 ± 0.3	189.3 ± 0.2	208.6 ± 0.4	319.3 ± 1.5
C*Dex (45%)	23.0 ± 0.3	85.6 ± 0.4	142.4 ± 0.4	158.2 ± 1.0	237.1 ± 0.6
C*Dex (75%)	23.1 ± 0.3	85.2 ± 1.2	146.4 ± 2.0	164.3 ± 0.2	245.0 ± 0.5
Xylisorb 90 (45%)[b]	25.0 ± 1.8	77.5 ± 0.1	126.8 ± 0.8	139.5 ± 0.9	194.5 ± 1.3
Maltisorb 90 (45%)[a,b]	4.9 ± 0.2	37.7 ± 0.1	95.3 ± 0.3	115.8 ± 0.2	146.6 ± 0.9

[a] Non-sieved raw material.
[b] Conditioning at 75% RH led to visually detectable, sticky agglomerates.

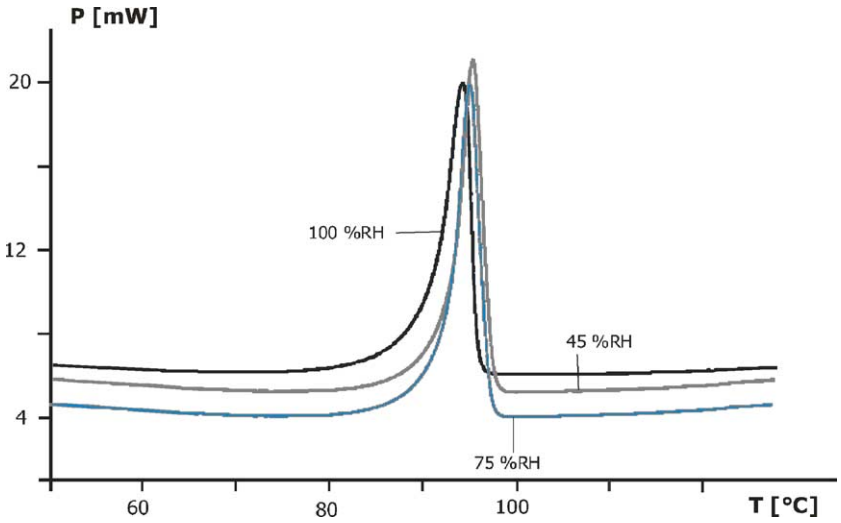

Fig. 2. DSC scan of sorbitol powders after conditioning at 45, 75 and 100% RH, respectively.

further supported by the SEM photographs which clearly show that, besides the crystal size and size distribution of the carbohydrates, also the shape and the surface morphology is different between carriers derived from different sources. Comparing, e.g., the Mannidex mannitol quality which shows a kind of lamellar-structured crystal with the Mannitol 60 quality, substantiates this observation. Also, crystal surface and shape of material coming from the same supplier can differ slightly as can be seen from the Mannitol 60 and Mannitol 25 photographs. The sorbitol qualities analysed show the similar rough and sponge-like surface whereas the glucose, the maltitol and the xylitol exhibit relatively smooth surfaces.

4.2. Aerodynamic assessment of the powder blends

Blends with budesonide and all carriers under investigation were produced and analysed in the multistage liquid impinger. The results of the impinger analysis are given as mass fraction of drug $<5\,\mu m$, both calculated on the delivered (without considering the drug left in the applicator) and on the total dose (including the fraction retained in the applicator). As can be seen from Figs. 3–6, the retention of drug in the applicator is very small indicating that all powders are well entrained into the air-stream upon delivery.

The highest potential as alternative carrier substance might be attributed to mannitol because it is a well known excipient widely used in pharmaceutical sciences with an established toxicity profile, even though there are some reports that high doses of mannitol increase mucus secretion and mucociliary clearance (Daviskas et al., 1999). The FPFs of budesonide/mannitol blends are summarised in Fig. 4. Similarly to experiences made with lactose monohydrate, the fine (milled) quality of mannitol performs best in the impinger test giving a fraction $<5\,\mu m$ as high as 50% of the total dose. The other two qualities (classified Mannitol 60 and M-Dex) also indicated suitability for a use in dry powder inhalations with FPFs in the range of 20% of the delivered dose for the M60 quality and 15% for the M-Dex quality; the retention was in both cases negligible. With both qualities mixtures with 10% fines content (sieve fraction $< 32\,\mu m$) were manufactured and analysed to elaborate whether the FPF can be boosted as known for lactose formulations by the addition of a fine powdered material. In case of the M60 mannitol quality, no effect on the FPF and the retention could be observed whereas the FPF could be increased to 22% by adding 10% of the fine material to the M-Dex mannitol. This different behaviour can be attributed to the different surface texture of the mannitol qualities: the M60 quality consists of relatively smooth surfaces with only few clefts and hollows. A certain amount of fine particles is also visible from the SEM photographs (Fig. 2). Accord-

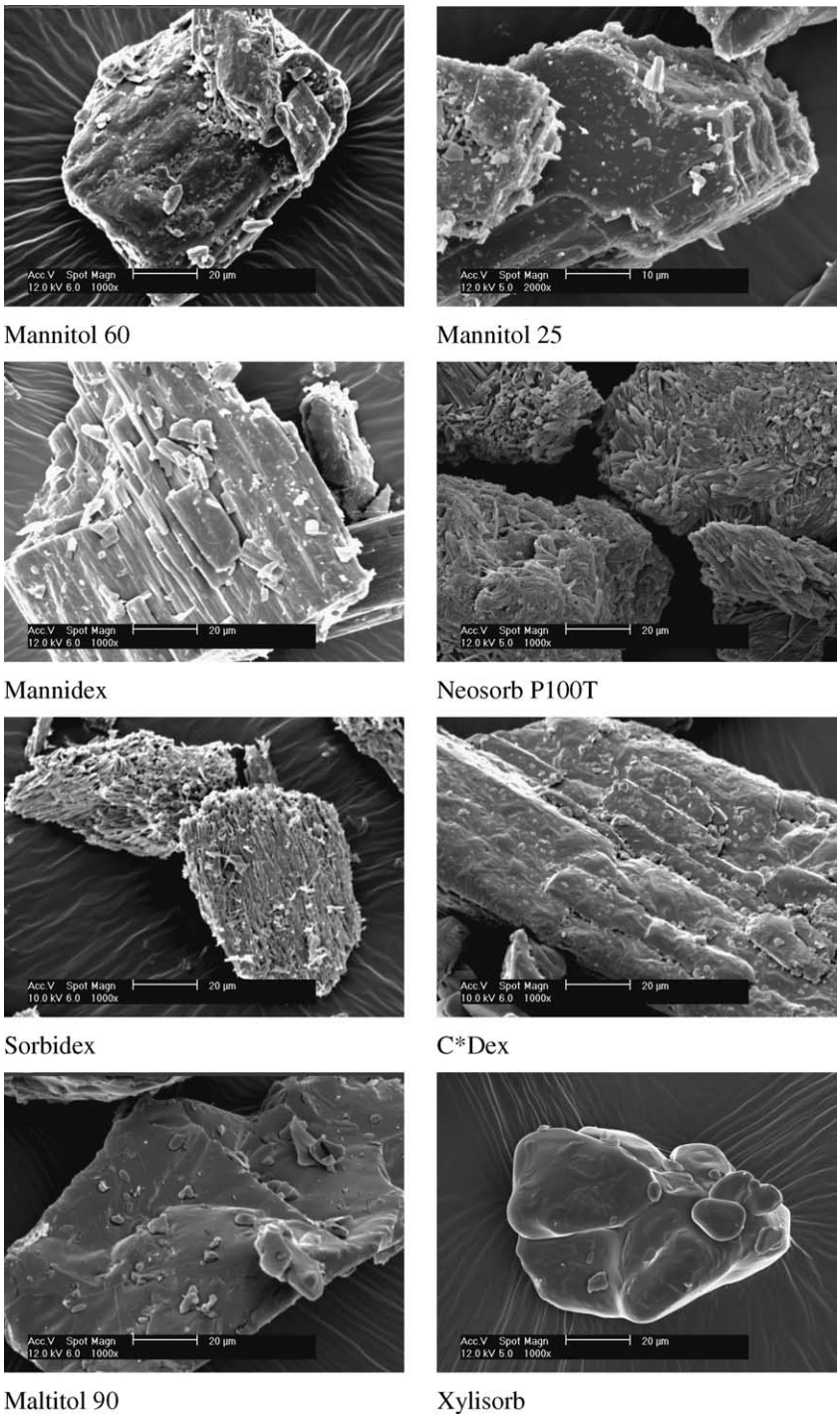

Fig. 3. SEM photographs of sieved and conditioned sugar carriers.

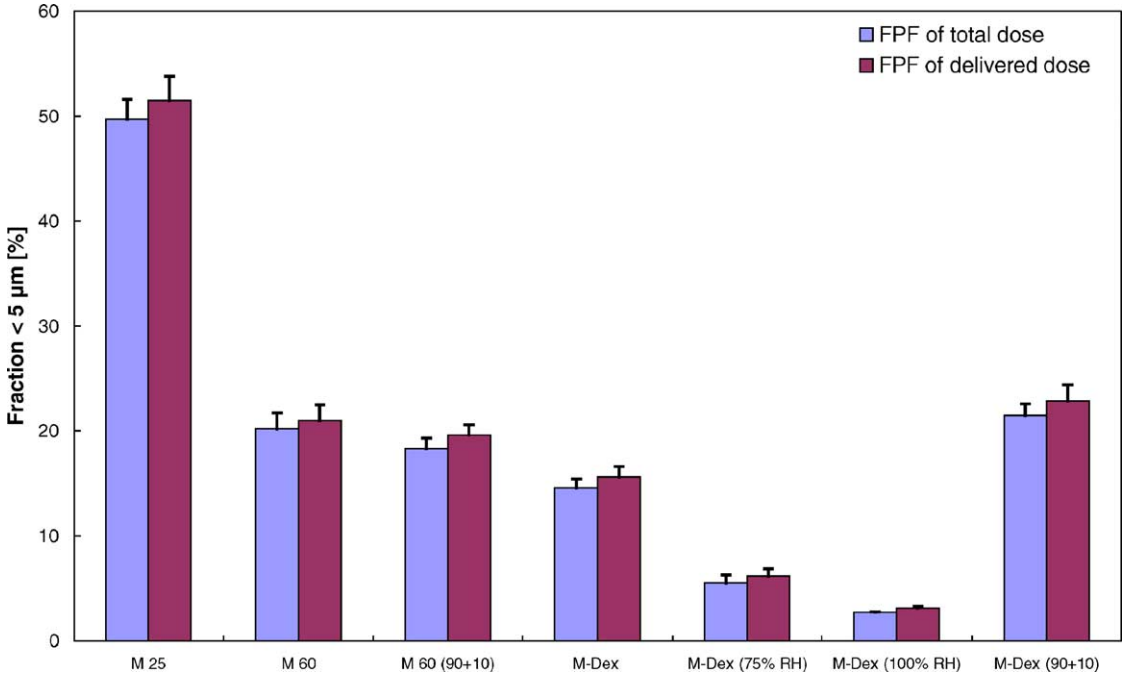

Fig. 4. Budesonide deposition of mannitol blends in the multistage liquid impinger.

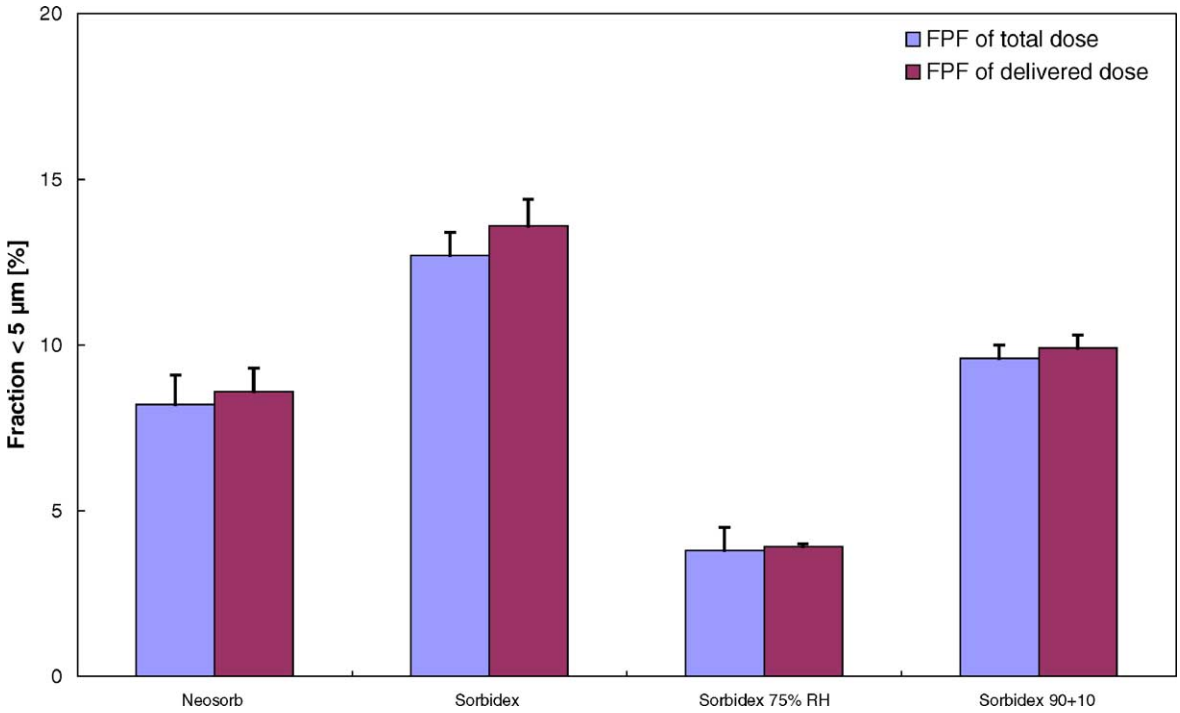

Fig. 5. Budesonide deposition of sorbitol blends in the multistage liquid impinger.

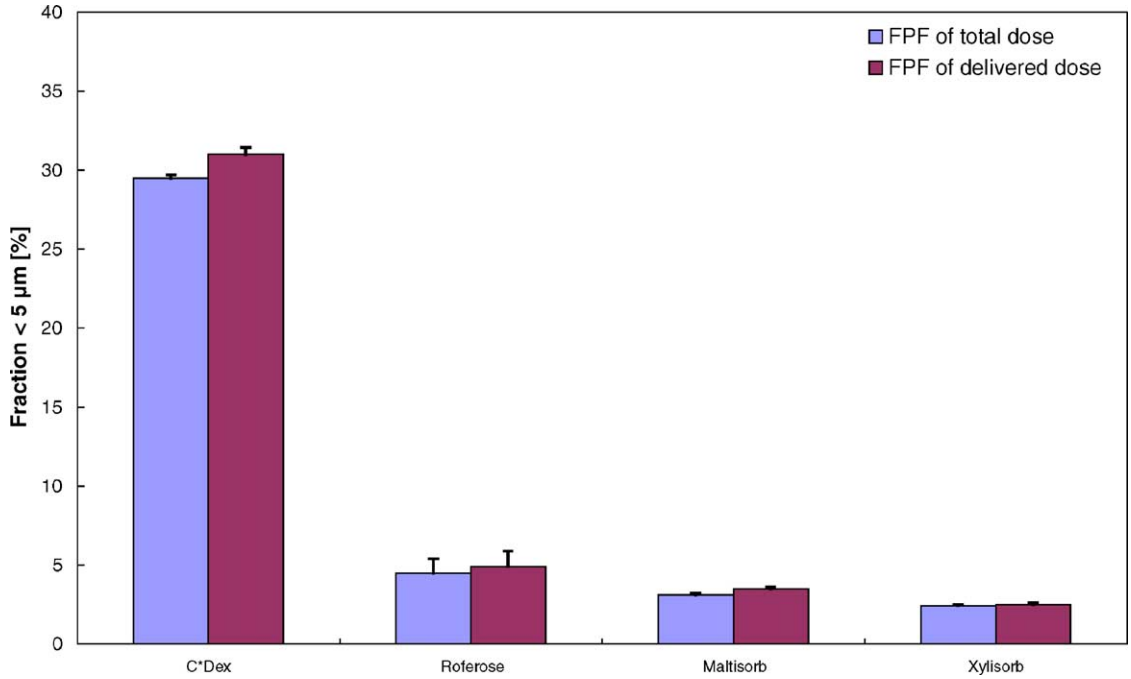

Fig. 6. Deposition of budesonide blends with other carriers in the multistage liquid impinger.

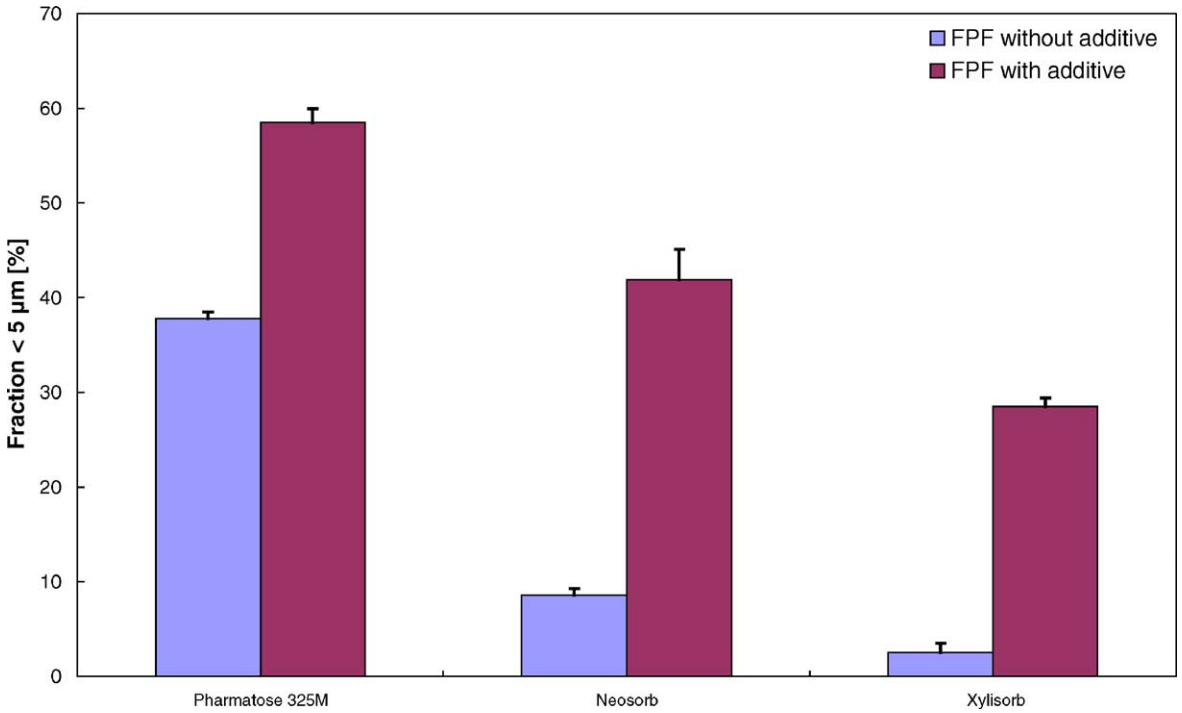

Fig. 7. Influence of the nano-particulate additive Aerosil on the aerosolisation properties of drug/carrier blends (FPF of delivered dose).

ing to the 'hot spot theory' established for lactose in interactive powder mixtures (Staniforth, 1996; Lucas et al., 1999) a smooth surface is preferable to a rough surface with respect to delivery of adhered drug particles. An addition of fines does in such cases not necessarily improve the efficiency of the powder blend. On the other hand, the M-Dex mannitol shows a very rough and splitted surface with a lot of irregularities where the micronised drug is captured. When this mannitol quality is pre-blended with 10% of fine material the irregularities are covered by the fine mannitol particles leading to less adhesion of the drug particles. These can then be delivered more easily during the inhalation process (Fig. 4). The results obtained for the batches that have been conditioned at different relative humidity indicate in addition that the conditioning of the mannitol should not be done at relative humidity as high as 75%. Obviously, water is adsorbed onto the surface of the mannitol resulting in particle growth during the conditioning cycle and possibly in a water layer on the crystal surface of the mannitol particles which in turn increase the adhesion of drug particles. Accordingly, the FPF is dramatically reduced when the powder conditioned at 75% RH and 100% RH is used for the preparation of the blends (Fig. 4).

The blends with sorbitol as a carrier generally resulted in smaller FPFs as compared to the mannitol (Fig. 5). With the Neosorb powder approximately 8% of drug particles were found to be $<5\,\mu m$ and with the Sorbidex powder the FPF was 13%. Considering the rough and irregular surface of the sorbitol powders (Fig. 3) this behaviour can be attributed to the strong adhesion of drug particles into the surface irregularities. However, a pre-mixture with fine sorbitol powder did not improve the dispersibility of the blend (Fig. 5, Sorbidex 90 + 10). Also, conditioning the sorbitol at high relative humidity (75% RH) led to a significant ($P = 0.01$) decrease of the FPF from 13 to 3.5%. The same arguments as already made for the mannitol powders apply: water is adsorbed onto the surface and gives a thin water layer on the surface. The effect of increasing drug-to-carrier adhesion seems to be more pronounced with sorbitol as carrier which might be due to the fact that sorbitol is more hygroscopic than mannitol (Moraly et al., 2001).

Large differences with respect to efficiency were also detected with glucose, maltitol and xylitol as a carrier. The C*Dex glucose quality delivered approximately 30% of drug particles $<5\,\mu m$ compared to a FPF of only 4% with the Roferose quality. Also, the classified maltitol and xylitol qualities used in this study proved to be unsuitable for the delivery of budesonide in the selected formulation approach by inhalation (Fig. 6).

A major problem with the sugar alcohols used in this study, especially with the more hygroscopic substances sorbitol, maltitol and xylitol, seemed to be their sensitivity to humidity. It should therefore be investigated in an additional study whether the efficiency of powder blends with these sugars could be improved by adding hydrophobic Aerosil® as shown earlier for

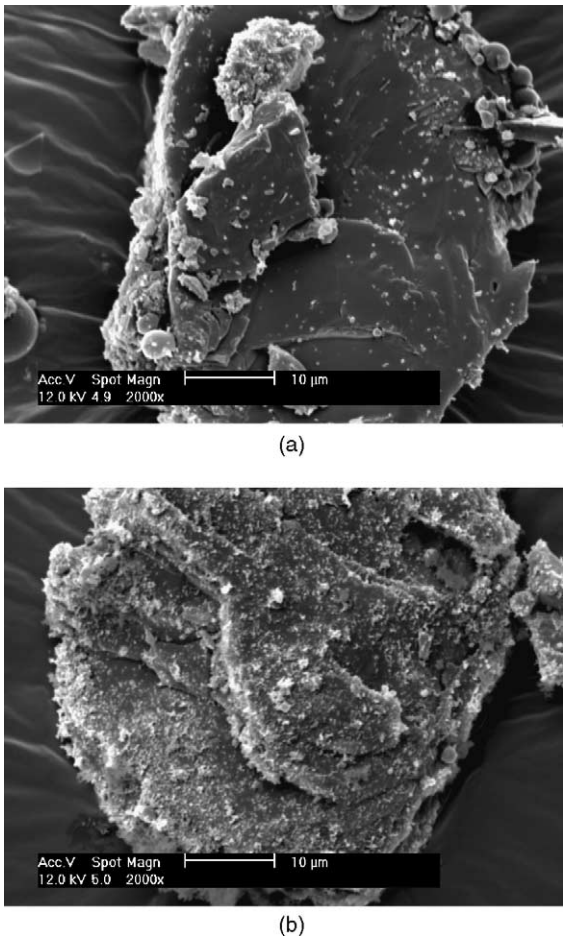

Fig. 8. SEM photographs of an interactive powder mixture containing (a) 1% (w/w) budesonide and (b) 1% (w/w) budesonide plus 2% (w/w) Aerosil.

lactose (Steckel and Bolzen, 2003). The results obtained by the addition of 2% of Aerosil® R972, shown in Fig. 7, prove this concept: the FPFs can be increased from 8 to 42% and from 3 to 29% when sorbitol and xylitol are used as a carrier, respectively. As comparator a formulation with standard inhalation grade lactose has been analysed accordingly, indicating that the FPF can be increased with lactose as well. The effect of Aerosil® in the powder blend is twofold: firstly, the surface of the crystals is covered by the nano-sized silica particles (Fig. 8) which reduces the contact area of drug and carrier and secondly, the drug particles themselves are covered with the nano-sized Aerosil® particles which result in reduced cohesion forces and, hence, in better dispersibility.

5. Conclusions

Several sugar alcohols were evaluated for their potential use in dry powder inhalation formulations. Mannitol proved to be the most promising candidate for this application, although the same difficulties as already known for lactose, like dependence on particle size distribution of the material, source of the material, surface texture of the material, etc. arise. The more hygroscopic sugar alcohols sorbitol, xylitol and maltitol were not able to generate suitable amounts of fine particles in a drug/carrier mixture. However, the difficulties arising from their hygroscopicity can be overcome by adding an ultrafine hydrophobic excipient to the powder blend.

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