ORIGINAL ARTICLE

An Investigation into Alternative Sugars as Potential Carriers for a Dry Powder Formulation of Budesonide and Formoterol

Ali Nokhodchi, Mohammed N. Momin, Azher Iqbal

Medway School of Pharmacy, Universities of Kent and Greenwich, Kent, UK

ABSTRACT

Delivery of two drugs in one dry powder inhaler (DPI) is expected to play an increasing and more effective role in the management of asthma and chronic obstructive pulmonary disease. In this study we investigated five sugars as possible carriers of both budesonide, an anti-inflammatory glucocorticoid, and formoterol, a long-acting $\beta_2$ agonist, in one DPI formulation. Most DPI formulations utilise lactose as a carrier in the drug-carrier blends; however, it cannot be used for compounds that react with its reducing group, such as budesonide, formoterol, or peptide/protein-based drugs. Therefore, alternative carriers such as sorbitol, mannitol, dextrose and xylitol were selected for this study in addition to lactose, which was used as a reference. A formulation comprising 5% w/w budesonide and 0.3% w/w formoterol was prepared with each sugar. The carriers were sieved to obtain 63-90 µm fractions and physicochemically characterised via true density, powder flow, particle size and surface morphology analyses. The dispersion and deaggregation of the two drugs from the five formulations were assessed after aerosolisation at 58-68 L min$^{-1}$ via a device-metered Airmax inhaler into a Multi-Stage Liquid Impinger. The findings show that the deposition efficiencies of the five formulations were influenced by the particle size distribution, surface morphology and flowability of the respective carriers, and that mannitol showed the greatest potential as an alternative carrier to lactose. Mannitol produced the highest fine particle fraction values of 72.4% and 27.5% for budesonide and formoterol, respectively, and this performance was largely attributable to the relatively high percentage of fine particles (< 10.50 µm) compared to the other carriers. Biomed. Int. 2011; 2: 43-54. ©2011 Biomedicine International, Inc.

Key words: Dry powder inhaler, carrier, fine particle fraction, particle size distribution

INTRODUCTION

Asthma, which is estimated to affect 300 million people of all ages and all ethnic backgrounds, is optimally treated via pulmonary drug delivery. Advantages of inhalation therapy include drug delivery directly to the site of action, minimisation of the dose required, lower incidence of adverse effects, and avoidance of drug metabolism via the gastrointestinal tract and liver. Inhaled $\beta_2$-adrenoreceptor agonists ($\beta_2$ agonists) and corticosteroids are the cornerstone in the management of asthma and chronic obstructive pulmonary disease. Budesonide is an anti-inflammatory glucocorticoid used for treating not only asthma but also allergic rhinitis and Crohn’s disease. In the UK it is available for the management of asthma in dry powder inhaler (DPI) form (Budelin Novoliser; Meda and Plumicort Turbuhaler; AstraZeneca), as a pMDI (Plumicort; AstraZeneca), and as a nebulized suspension (Plumicort Repsules; AstraZeneca) (BNF 60, 2010). Budesonide
consists of an epimeric mixture of the α- and β-propyl forms of 16α,17α-butyldenedioxy-11β,21-dihydroxy-pregna-1,4-diene-3,20-dione; both epimers have similar anti-inflammatory potency.\textsuperscript{3}

Formoterol (previously known as eformoterol in the UK) is a potent long-acting selective β\textsubscript{2} agonist formulated as the fumarate. Its bronchodilatory effects last for 12 h compared to 4 h for the short-acting β\textsubscript{2} agonist salbutamol. In the UK formoterol is licensed for short-term symptom relief and for the prevention of exercise-induced bronchospasm, and is marketed as the pMDI Atimos Modulite\textsuperscript{\textregistered} (Chiesi S.p.A) and the DPIs Foradil\textsuperscript{\textregistered} (Novartis AG) and Oxis\textsuperscript{\textregistered} (AstraZeneca) (BNF 60, 2010). Structurally, formoterol is a phenylethylamine derivative with one phenolic hydroxyl and one secondary amino group, and is widely marketed as a racemate of the RR+SS enantiomers.\textsuperscript{5} The β\textsubscript{2} agonist activity resides in the RR-enantiomer whilst the SS form is essentially inactive.\textsuperscript{6}

In June 2007, AstraZeneca launched Symbicort\textsuperscript{\textregistered}, a fixed-dose combination of budesonide and formoterol. This product was developed in response to one of the most common problems in long-term asthma control, which is poor compliance with inhaled corticosteroid (ICS) therapy. This results in inadequate treatment of airway inflammation, and as a consequence many patients overuse their short-acting β\textsubscript{2} agonist (SABA) reliever. Over-reliance on a SABA is a key risk factor for severe exacerbations in asthma.\textsuperscript{7} The budesonide/formoterol combination DPI reduces the exacerbation risk and increases the chances of controlling asthma more often, more quickly and at a lower dose of ICS than is seen with ICS therapy alone.\textsuperscript{8}

Efficient drug delivery to the lungs through dry powder inhalers (DPIs) is dependent on several factors including inhaler device, formulation, and inhalation manoeuvre. Preparing ideal DPI formulations requires control overall formulation characteristics at particulate and bulk level to ensure drug delivery to lower airway regions.\textsuperscript{9,10} In DPI formulations, it is customary to blend micronized drug particles (less than 5 µm) with larger carrier particles to address flowability and dose variability issues.\textsuperscript{11,12} DPI formulations usually incorporate at least one other component as a carrier to facilitate aerosolisation of the active agent, lactose being the most common. This sugar has been employed owing primarily to its long history of use and consequently well-established stability and safety profile. Particles of lactose can also be produced with predetermined properties such as a smooth surface and good flow properties.\textsuperscript{13} However, the use of lactose has some disadvantages, notably its incompatibility with drugs (such as formoterol, budesonide and peptides) that have primary amine moieties.\textsuperscript{13} Furthermore, lactose can be produced with traces (proteins) of its bovine source, so it carries a theoretical risk of transmissible spongiform encephalopathy (TSE).\textsuperscript{14} In the previous study only one drug (budesonide) was used,\textsuperscript{15} whereas in the present study an attempt was made to find an alternative carrier for binary mixtures of two drugs (budesonide and formoterol). Therefore, the aim of this study was to build upon the research conducted by Steckel and Bolzen,\textsuperscript{15} and to explore the feasibility of attaching both budesonide and formoterol to one non-lactose carrier such as sorbitol, mannitol, dextrose, or xylitol to produce a single efficient combination DPI formulation. The current carrier of choice, lactose, was also employed and used as reference.

MATERIALS AND METHODS

Micronised budesonide (IVAX Pharmaceuticals Ireland), formoterol fumarate dehydrate (AstraZeneca UK LTD), lactose (Borculo Domo Ingredients), mannitol, sorbitol, dextrose
and xylitol were obtained from Roquette (France). All other used chemicals were of analytical grade.

**Sievimg**

In order to obtain carrier particles in the 63-90 µm range, the carrier powders were first passed through a nest of sieves using a mechanical sieve shaker (Endecotts, UK). Approximately 100 g of the carrier was added to the top sieve before the nest was secured in the sieve shaker and shaken for 5 min, after which the powder that had collected in the 63 µm pan was transferred to a glass container and labelled. The rest of the sieves were emptied and the whole process was repeated until approximately 20 g of sieved material had been obtained. The sieved powders were then used throughout the rest of the study.

**True density measurement**

The true density of each carrier was measured using an Ultrapycnometer 1000 (Quantachrome Instruments, USA). This instrument calculates the true density from the displacement of helium gas by the volume of material of known mass. The true density data reported in the present study are the means and standard deviations of three determinations.

**Powder flow assessment**

Carr’s Index (CI) was employed to give an indication of flowability of each tested powder. A 10 ml measuring cylinder was filled with the powder and after the volume was recorded (bulk volume) the cylinder was tapped 100 times and the new volume was recorded (tap volume). A preliminary experiment showed that 100 taps is enough to achieve the maximum reduction in the volume of the powder bed. The CI was then calculated using the following equation:\(^{16,17}\)

\[
CI = \left(\frac{\text{Tapped density} \times \text{Bulk density}}{\text{Tapped density}}\right) \times 100
\]

**Particle size analysis**

Carrier particle sizes were measured using a laser diffraction particle size analyser (Sympatec, GmbH) consisting of a HELOS/KF laser diffraction sensor, a RODOS dry dispersing unit, and a VIBRI vibratory feeder. Approximately 10 g of the carrier was transferred to the funnel of the VIBRI feeder, and then a reference measurement was conducted before the test measurement was performed. The volume mean diameter (VMD) and other particle size parameters (D\(_{10}\%), D\(_{50}\%) and D\(_{90}\%) and span value were calculated automatically using the software provided.

**Preparation of formulations**

Batches (10 g) of each formulation consisting of 5% w/w budesonide and 0.3% w/w formoterol were prepared by accurately weighing 500 mg of budesonide, 30 mg of formoterol and 9.47 g of the carrier into separate weighing boats. The contents of the weighing boats were placed in an aluminium tin and mixed for 20 min using a Turbula® T2C shaker (Willy A. Bachofen AG) to produce homogenous blends. This shaker uses inversionsal motion in addition to rotational and translation motion leading to more efficient mixing. After mixing, the formulations were transferred to sealable glass containers and labelled.

**Scanning electron microscopy**
In order to investigate the effect of carrier morphology on DPI formulation efficiency, the drugs, carriers and five formulations were examined with a scanning electron microscope (Stereoscan 360, Cambridge Instruments, UK) operating at 20 kV. The samples were sputter coated with gold before examination at magnifications of 100, 250, 1000 and 3000.

**Budesonide high performance liquid chromatography**

A suitable budesonide HPLC assay for this study was developed by a slight modification of a method previously developed by IVAX Pharmaceuticals Ireland. The method employed as the mobile phase a 64:36 mixture of phosphate buffer, adjusted to pH 3.2 with orthophosphoric acid (containing 1 ml/L of diethylamine), and acetonitrile. The mobile phase was degassed for 30 min by using the degassing function on an ultrasonic cleaner (Copley Scientific, UK). The phosphate buffer solution was prepared by dissolving 7.2 g of sodium dihydrogen phosphate in 2 L of water. The flow rate of the mobile phase was 2.0 ml/min, injection volume was 50 µl and budesonide was detected by absorbance at 240 nm. The retention time for budesonide epimer B was 9 min and for epimer A was 10 min. The HPLC system comprised a Waters™ 600 Controller with pump, a Waters™ 717 plus Autosampler, a Waters™ 486 tunable absorbance detector, and a Jones Chromatography column block heater. The column, 250 × 4.6 mm Nucleosil® 120-5C18, was heated to 40º C.

**Formoterol high performance liquid chromatography**

A purpose-designed formoterol HPLC method was also developed on the basis of previous methods. The HPLC system comprised a Varian ProStar 210 solvent delivery module, a Varian ProStar 410 Autosampler and a Varian ProStar 370 electrochemical detector. The detector settings included the following: working electrode potential, 0.65V; guard cell potential, 0.70V; range select; nano Amps; range 50 nano Amps; temperature, 30ºC; offset, 20%, and filter, 0.1 s. The chromatographic conditions consisted of the following: column (housed in the detector), 3.9 × 300 mm Waters™ µBondapak C18; mobile phase, potassium dihydrogen phosphate buffer and acetonitrile (81:19); flow rate, 1.5 ml/min; injection volume, 10 microlitres; injector wash, methanol; and sample solvent, methanol. The retention time for formoterol was between 4 and 6 min.

The phosphate buffer to be mixed with acetonitrile for the mobile phase was prepared by dissolving 6.7 g of HPLC grade potassium dihydrogen orthophosphate and 0.2 g of electrophoresis grade EDTA in 2000 ml of in-house purified water. The pH of the resultant solution was adjusted to 5.6 by the dropwise addition of 2M sodium hydroxide with magnetic stirring.

**Multi-stage liquid impinger studies**

These studies involved an experimental set-up of a critical flow controller (Copley Scientific, UK) interposed between a five-stage liquid impinger fitted with an induction port, mouthpiece adapter (all Copley Scientific, UK) for the DPI, and a vacuum pump (Copley Scientific, UK). The process involved 20 actuations from a formulation-loaded Airmax inhaler at a flow rate of 58-68 L/min, generating a pressure drop of 4 kPa. Critical (sonic) flow was monitored and maintained throughout the experiment. Prior to use the MSLI was prepared by filling stages 1 to 4 with 20 ml of analytical reagent grade methanol, inserting a 70 mm glass microfiber filter (Whatman) into stage 5, and sealing the connection between the impinger and the induction port airtight using Parafilm®. The mouthpiece adapter plus the inhaler in the actuated position were connected to the MSLI before the test flow duration in seconds was set on the flow controller and activated. After each actuation the device was removed from the adapter, closed and re-actuated before...
being re-attached to the MSLI via the adapter for another run. After 20 actuations, the impinger was disconnected from the flow controller and the inhaler removed from the mouthpiece adapter. The induction port and the mouthpiece adapter were carefully rinsed with methanol contained in a wash bottle over a funnel collecting into a 100 ml volumetric flask. This was repeated until no powder particles were visible on either the induction port or the adapter. Stage 5 was unclipped from the impinger, and using a pair of tweezers the filter was carefully removed and transferred to a 50 ml beaker where it was immersed in methanol. The beaker was sonicated for 1 min using the sonicator function of an ultrasonic cleaner (Copley Scientific, UK), after which the contents were poured via a funnel into a volumetric flask. The metal grill on which the filter sat, the rubber washer and the bottom surface of the impinger were also rinsed into the flask in order to recover as much budesonide and formoterol as possible. The contents of stages 2 to 4 were carefully swirled three times in both clockwise and anti-clockwise directions and inverted, ensuring no liquid transfer took place between the various stages, before being poured into separate flasks. Each stage was then cleaned three times with approximately 20 ml methanol, and the powder that had deposited in the impinger neck leading into stage 2 was washed into stage 2 and collected.

All six volumetric flasks were made up to the mark and the contents thoroughly shaken before being transferred to HPLC vials for budesonide and formoterol assays. The whole procedure was repeated twice for each formulation and the loading chamber of the inhaler was thoroughly cleaned before a new formulation was introduced. Using the straight line equations obtained from the calibration curves, the concentration of drug in each stage was determined before the fine particle dose (FPD, µg) and fine particle fraction (FPF, %) were calculated.

RESULTS AND DISCUSSION

According to Table 1 the true density of the five carriers ranged from 1.50 to 1.56 g/cm³. Mannitol had the lowest true density of 1.50 g/cm³, and dextrose had the highest true density of 1.56 g/cm³. It has been shown that the tapped density of a powder has a significant influence on the aerosolisation performance, FPF values being improved as the tapped density is lowered. The tapped densities of the carriers (Table 1), established during the powder flow assessment, was highest for dextrose and lowest for sorbitol and mannitol. These changes in the tapped density might affect the FPF, as discussed below.

<table>
<thead>
<tr>
<th>Carrier</th>
<th>True density (g/cm³)</th>
<th>Tapped density (g/cm³)</th>
<th>Carr's Index (%)</th>
<th>Q10% (µm)</th>
<th>Q50% (µm)</th>
<th>Q90% (µm)</th>
<th>Span</th>
<th>Q&gt;10 µm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>1.55 ± 0.006</td>
<td>0.64</td>
<td>22.2±0.7</td>
<td>16</td>
<td>50</td>
<td>95</td>
<td>1.58</td>
<td>5.46</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>1.51 ± 0.003</td>
<td>0.57</td>
<td>16.9±1.0</td>
<td>21</td>
<td>55</td>
<td>92</td>
<td>1.29</td>
<td>5.06</td>
</tr>
<tr>
<td>Mannitol</td>
<td>1.50 ± 0.003</td>
<td>0.59</td>
<td>13.7±1.7</td>
<td>4</td>
<td>32</td>
<td>80</td>
<td>2.36</td>
<td>22.11</td>
</tr>
<tr>
<td>Dextrose</td>
<td>1.56 ± 0.009</td>
<td>0.80</td>
<td>36.4±1.6</td>
<td>40</td>
<td>80</td>
<td>135</td>
<td>1.19</td>
<td>1.83</td>
</tr>
<tr>
<td>Xylitol</td>
<td>1.54 ± 0.002</td>
<td>0.66</td>
<td>41.2±1.6</td>
<td>14</td>
<td>45</td>
<td>92</td>
<td>1.73</td>
<td>6.45</td>
</tr>
</tbody>
</table>

A critical factor affecting DPI performance is powder flow because the carrier-drug complexes must be transported through the mouth. The five carriers differed in properties known to affect particle flow such as particle size, particle shape, and surface roughness, so it is unsurprising that markedly different carrier flowabilities resulted. In this study,
powder flow was assessed via the simple Carr’s Index (CI) method. This involved determining the bulk density, which takes macroscopic inter-particle space and the tapped density of each powder into account. A CI of less than 25 is usually indicative of good flow characteristics, whereas a CI over 40 represents extremely poor powder flowability. Smaller particles with high surface area do not flow as well as larger particles. The greater the surface area, the more dominant such surface interactions as friction and cohesion/adhesion that interfere with flow, so an increase in CI is proportional to the adhesion and friction properties of the powder, and powder flow properties deteriorate nearly exponentially with decreasing particle size. However, particle surface irregularities increase the tendency for mechanical interlocking and inter-particle friction, and thus impede free powder flow. Therefore, depending on the surface geometry of particles, different powders will exhibit different sensitivities to particle size effects. With reference to Table 1 it is clear that mannitol, despite its small particle size (mean particle size 32 µm), achieved the best flowability with a mean CI of 13.7%. This could be due to its morphology and or surface smoothness. Despite having large particles, the dextrose and xylitol carriers showed the two highest CI values of 36.38% and 41.24%, respectively, and this could be due to the angular shapes of these particles, which can cause interlocking between particles and hence lead to poor flow. Lactose and sorbitol demonstrated good flow properties with CIs of 23.06% and 16.95%, respectively, and this was expected owing to their large median particle size.

Figure 1: An example of particle size distribution and cumulative undersize for sorbitol carrier.

The particle sizes of the five carriers were measured via laser diffraction, and the particle size and cumulative undersize distributions are presented in Table 1. As expected, all five carriers demonstrated unimodal distributions since they were all sieved to obtain 63-90 µm fractions prior to use. An example is shown in Figure 1. However, differences were observed in the span and median ($D_{50\%}$) values, which could influence their respective FPF
The span value, calculated via $(D_{90\%}-D_{10\%})/D_{50\%}$ and representing the breadth of the particle distribution, was highest for mannitol (2.36) and lowest for dextrose (1.19). The relatively high mannitol span value is due to the presence of fines (< 10.5 µm) in this sample in spite of the mechanical sieving. Therefore, mannitol demonstrated higher polydispersity than dextrose, whose particle sizes were more closely centred around the median value of 80 µm, which was the highest median value obtained. In contrast, mannitol had the lowest median value of 32 µm. Although particle size is the single most important design variable in a DPI formulation, the most efficient size range of carrier particles remains unclear. However, previous work has shown that as particle size decreases the FPF measured by cascade impaction is increased. While small particles are expected to be more difficult to disperse owing to increased cohesiveness, increasing the inhaler dispersion efficiency and air flow improves carrier drug de-agglomeration leading to an increased FPF. An additional important factor, which could explain the relatively high FPF of mannitol, is the amount of fines, defined as particles less than 10.50 µm, attached to the surfaces of large carrier particles. Although they were sieved in the same manner, great differences in the amounts of fines present in the sugar powders resulted.

For example, 22.11% of the mannitol carrier was sized below 10.50 µm, which was more than three times that of its nearest rival, xylitol, which had a fines value of 6.45%. The addition of fine lactose particles to blends containing coarser lactose particles have been shown to increase the dispersion and FPF of salbutamol sulphate, and in the case of salmeterol xinafoate, the FPF decreased significantly as fine lactose particles (< 5 µm) were removed, and the degree of dispersion became independent of the volume mean diameter.
It is clear from the SEM images of the carriers (Figure 2) and the formulations (Figure 3) that they all exhibited diverse morphologies and the degree of budesonide and formoterol attachment varied considerably. For example, the lactose, sorbitol, dextrose and xylitol carriers exhibited large coarse irregular shapes (Figures 2c, 2d, 2f and 2g), whereas mannitol, in addition to being considerably smaller in size, showed irregular coarse shapes with some degree of elongation (Figure 2e). A similar study by Tee et al.\textsuperscript{26} showed that mannitol was more elongated than sorbitol and lactose. In addition, they described lactose as being tomahawk-shaped and sorbitol particles more symmetrical and rounder than either mannitol or lactose. Tajber et al.\textsuperscript{27} in a physicochemical characterisation study of budesonide and formoterol described their micronized budesonide material as being composed of rough, irregularly shaped particles typical of milled crystalline material, and formoterol fumarate dihydrate as crystalline, i.e. having a geometric or multi-faceted regular shape, with a well-defined peak pattern. To some extent, these observations can also be applied to the SEM images of the two drugs shown in Figures 2a and 2b. With regard to the formulations (drug-carrier mixtures) at high magnification (Figure 3), all show successful budesonide and formoterol attachment, though to varying degrees. For example, the carrier particles in the lactose and xylitol formulations show the lowest amount of drug attachment, as relatively large areas of the particles seem bare of both drugs. This can be clearly seen in the high magnification images shown in Figure 3a and 3e. On the other hand, the dextrose carrier particles displayed the best drug attachment both in terms of number of drug particles and of coverage uniformity. The sorbitol and mannitol formulation images revealed intermediate drug attachment with good coverage. Interestingly, the sorbitol carrier particle surfaces seemed to be covered with needle-like structures, which overlapped each other in a haphazard manner, thereby presenting large
number of small pores and crevices into which the drugs may have deposited. This can be clearly seen in Figure 3b.

At a flow rate of 58-68 L/min, generating a pressure drop of 4 kPa across the device-metered DPI, each of the five formulations was evaluated by cascade impaction to determine the formulation efficiency via FPF values. The Airmax inhaler was manufactured to actuate exactly 2 mg of the powder formulation it contained, which equates to a dose of 100 µg budesonide and 6 µg formoterol. It is clear from Figure 4 that mannitol had the greatest mean budesonide and formoterol FPF values of 72.44%, and 27.49%, respectively. In a similar study by Steckel and Bolzen,15 mannitol produced the highest budesonide FPF value when evaluated against glucose, sorbitol, maltitol and xylitol. The next best carrier differed between the two drugs, for example, the second best budesonide and formoterol carriers were sorbitol with values of 54.57%, and xylitol with 24.45%.

Figure 4: Fine particle fraction (FPF) obtained for budesonide and formoterol in the presence of different carriers.

The relatively high performance of mannitol as a carrier of both drugs compared to the other carriers is most probably due to the large number of fines present in the formulation. High energy active sites are known to exist on the surface of coarse carrier particles,28 and according to the ‘hot spot theory’ established for lactose powder mixtures,29 a smooth surface is preferred to a rough surface for the delivery of an adhering drug.30 The presence of fine particles saturates these active sites, which would otherwise bind the drug strongly. Therefore, more drugs adhere to passive (lower energy) sites and this allows the drug to be more easily deaggregated during inhalation, leading to enhanced FPF.28 In addition, the fine particles cover the surface irregularities on carrier particles making them smoother.35

Mannitol and sorbitol are stereoisomers with different physical characteristics, and when they were used as coarse carriers in the formulations, different in vitro depositions resulted. The lower FPF values of sorbitol can be attributed to a lower percentage of fines in the formulation, but also to the rough and pitted surface morphology displayed in Figure 3b, which can lead to the strong adhesion of drug particles in the surface irregularities. The percentages of the budesonide and formoterol doses depositing in the induction port and each MSLI stage are displayed in Table 2. It is clear that the amount of budesonide in the
induction port, which is designed to mimic the mouth and the top section of the throat, is lowest for mannitol and highest for xylitol with mean values of 15.7% and 26.1%, respectively. For formoterol, minimal deposition was achieved again by mannitol with a mean value of 47.8%, whereas dextrose deposited 62.1%. The induction port is the location where the carrier particles are expected to impact and deposit prior to drug detachment and entrainment in the airstream. Therefore, high budesonide and formoterol deposition in the induction port is indicative of strong drug-carrier adhesion. If the cohesive forces acting on the formulation are too strong, the shear airflow during inhalation may not be sufficient to separate the drug from the carrier particles, leading to low deposition efficiency. Other factors that may have contributed to the performance of mannitol are its elongated shape and lower hygroscopicity compared to the other carriers. Although the elongation ratios of the five carriers were not assessed in this study, the slight elongation of the mannitol carrier particles is a visual observation from SEM images such as Figure 2e. Previous studies with lactose have suggested that the more elongated carrier particles would be more aerodynamic and would increase the respirable fraction of salbutamol sulphate.

A recent study by Kaialy et al., which investigated the use of engineered mannitol carrier particles with the drug salbutamol sulphate, revealed that the FPF was considerably better when engineered mannitol particles were used as the carrier in formulations instead of commercial mannitol. Given such information, this approach, i.e. the use of engineered mannitol crystals, is an avenue that should be explored with budesonide and formoterol for future work.

**CONCLUSIONS**

This study evaluated four non-lactose sugars for their potential as a carrier of the pulmonary drugs, budesonide and formoterol, in one DPI formulation, and mannitol proved to be the most promising candidate. Not only did it result in the highest FPF values for both drugs, but its established toxicity profile, sweet after-taste, and the fact that it is a widely used pharmaceutical excipient, also make it an attractive alternative carrier to lactose. In addition, its lower hygroscopicity than the other alternative carriers makes it more favourable from a pharmaceutical stability viewpoint. Its performance can largely be attributed to the high percentage of fines in the formulations, and therefore a repeat of this study is recommended in which the number of fine particles in all the formulations is
somehow standardised to allow other variables known to affect deposition efficiency to be evaluated.

REFERENCES