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Investigation into Alternative Sugars as Potential Carriers for Dry Powder Formulation of Budesonide

Mohammed-Nurul Momin, Atoosa Hedayati and Ali Nokhodchi*

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

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ABSTRACT

Introduction: Dry powder inhaler (DPI) formulations are so far being used for pulmonary drug delivery, mainly for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Currently most of DPI formulations rely on lactose as a carrier in the drug powder blend. However, due to reducing sugar function of lactose which makes it incompatible with some drugs such as budesonide, it is realistic to investigate for alternative sugars that would overcome the concerned drawback but still have the positive aspects of lactose. ***Methods:*** The study was conducted by characterizing carriers for their physico-chemical properties and preparing drug/carrier blends with concentration of 5% and 10% drug with the carrier. The mixing uniformity (homogeneity) of Budesonide in the blends was analyzed using spectrophotometer. The blend was then filled into NB7/2 Airmax inhaler device and the deposition profiles of the drug were determined using multi stage liquid impinger (MSLI) after aerosolization at 4 kPa via the inhaler. The morphology of the carriers conducted using the scanning electron microscope. ***Results:*** The results determined that the mean fine particle fraction (FPF) of 5% and 10% blends of mannitol was 61%, possibly due to fine elongated particles. Dextrose exhibited excellent flowability. Scanning electron microscope illustrated mannitol with fine elongated particles and dextrose presenting larger and coarse particles. It was found out that type of carriers, particle size distribution, and morphology would influence the FPF of budesonide. ***Conclusion:*** It may be concluded that mannitol could be suitable as a carrier on the basis of its pharmaceutical performance and successful achievement of FPF whereas the more hygroscopic sugars such as sorbitol or xylitol showed poor dispersibility leading to lower FPF.

Introduction

Over the past decades, inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases, such as asthma or chronic obstructive pulmonary disease. As therapeutic agents are delivered directly to the lungs, the inhaled route offers a more rapid onset of action, allows smaller doses to be used and has a better efficacy to safety ratio compared to systemic therapy. Bronchodilators and inhaled corticosteroids have become the pharmacological mainstay of management programs, treating the symptoms of disease and the underlying inflammatory processes, respectively (Byron and Patton 1994; COPD Guidelines Group of the Standards of Care Committee of the BTS 1997; British Thoracic Society 1997; G.K. Crompton *et al*. 2007).

It is believed that the maximum particle size (aerodynamic diameter) for deposition in the central airways is approximately 5 m, but only 2–3 m for peripheral/deep lung (alveolar) deposition (Newman and Clarke 1983; Gonda 1990; Zanen *et al*. 1992; Timsina *et al*. 1994). Particles larger than this will be cleared off by the lung's defenses, whereas particles <0.5 m will be exhaled.

Although only 5–30% of the total aerosol dose delivered is deposited in the lower respiratory tract (Dolovich 1995), doses required to achieve a therapeutic effect are normally only one tenth to one fifth compared to an oral dose. Since portal circulation as well as first pass effect can be avoided, undesirable systemic side effects can be minimized compared to oral drug administration.

***Corresponding author:** Ali Nokhodchi (PhD), Tel.: +44 (0) 1634 20 2947, Fax: +98 411 3367929, E-mail**:** a.nokhodchi@kent.ac.uk

Most notably, DPIs are activated by the patient's inspiratory airflow; therefore, they no longer need to co-ordinate activation of the inhaler with inspiration (Borgstrom *et al*. 1996). They are environmentally friendly, easy to use and deliver more drugs to the lungs (O'Connor 2004; Agertoft *et al*. 1999; Lipworth and Clark 1997).

Since, almost all micronized active ingredient exhibit strong interparticulate cohesion, leading to poor powder flow properties, a larger carrier is used to enhance the flowability (Zeng *et al*. 2001; Parry-Billings *et al*. 2000; Brinley *et al*. 1995; Podczeck 1997).

During the development of dry powder inhalers, the adhesion between the drug and carrier must be taken into account. This is because, on one hand, the adhesion between the drug and carrier has to be strong enough so that the blend is stable. But on the other hand this adhesion must be weak enough so that the drugs get separated from the carrier (Frijlink and Boer 2004; Ganderton and Kassem 1992).

Inadequate drug/carrier separation is one of the main explanations for the low deposition efficiency encountered with DPIs (Zeng *et al*. 2000).

Currently most of the dry powder inhaler products that are already on the market or entering the market are using lactose as a carrier (Steckel 2003). Lactose had long been used as an excipient in oral dosage form before being used in DPIs. It has an established safety and stability profile, manufacturing process with tight controls over purity and physical properties, and is readily available and inexpensive.

Even though lactose is a carrier of choice for dry powder formulation but it cannot be used for some drugs such as formoterol, protein, and peptides. Because its reducing sugar function prevents its use with the mentioned drug, it may interact with the functional group of the drug (Patton and Platz 1992). As a result of reducing sugar function of lactose, it is realistic to investigate for alternative sugar/carrier that would overcome the concerned drawbacks but still have the positive aspects of lactose. In addition, various studies have shown that changing the carrier can influence fine particle delivery and, therefore, formulation performance, as such a change will also lead to different levels of drug-carrier adhesion (Smyth and Hickey 2005).

Materials and methods

Budesonide (Batch number 02020204, Secor) as supplied by IVAX UK LTD. The following carrier materials were selected for this study and they all were supplied by Roquette UK LTD: Dextrose (Dextrose Monohydrate ST,), Maltitol (Maltisorb P90), Mannitol (Pearlitol 25C), sorbitol (Nesosorb P100T) and Xylitol (Xylisorb 90).

Flowability measurement

Carr's indices were determined using a Tapped density tester (JV 1000, Copley Scientific). The method involved measuring tap density and bulk density and Carr's indices were worked out using the formula:

CI = [(Tapped density – Bulk density)/Tapped density] x 100

True density measurements

True density of all the carriers was measured by using Ultrapycnometer 1000, (Quantachrome instruments, USA). This involved displacement of helium gas caused by the volume of known mass of material. The measurements were carried out at room temperature and the samples were run in triplicates.

Particle size analysis

The particle size of each carriers/sugars, the blends and the drug itself were monitored by using laser scattering particles size distribution analyser (HELOS Sympatec GmbH). A small of each sample (about 5 g) was analysed in the range of 0.1 to 500 μm. The instrument consisted of a laser sensor HELOS and a RODOS dry-powder air-dispersion system. An expanded laser beam was passed through each powder that was being drawn through a measuring zone. Since different size particles diffract the light at different angles, a computer algorithm interpreted the diffraction pattern of particle size distribution. A total of 16 analyses (one active drug budesonide, five carriers, five 5% blends, five 10% blends) were carried out but only one analysis is shown in this report for the sake of simplicity.

Scanning electron microscope (SEM)

The morphology of the carriers was conducted using a scanning electron microscope (Stereoscan 360, Cambridge instruments, UK) operating at 20 kV. The samples were sputter coated with gold before examination. The micrographs were taken at different magnifications.

Preparation of powder mixture

Preparing the blends involved using Budesonide in conjunction with the sugar using a turbula blender, (Bachofen, Switzerland) gear 3 apparatus. This apparatus allowed manufacturing a homogenous powder for the use with DPIs. Two sets of blends were produced, 5% (1 g of Bedesonide and 19 g of sugar) and 10% (1 g of Budesonide and 9 g of sugar). For the 5% blend, 1 g of Budesonide was weighed accurately using a weighing boat. The sugar was sieved through a 90 m to 63 m mesh sieve, and 19 g of the sugar was weighed using a weighing boat. Approximately 4.8 g of the sugar and 0.25 g of Budesonide was transferred from the weighing

boat into the aluminium container. The mixture containing the sugar and Budesonide was mixed for 1 minute using a spatula. An additional set of the same quantity mixture was added and mixed for a minute. This step was repeated for a further 2 attempts until all the quantity was occupied. The container was then transferred into the turbula for 20 minutes to allow mixing, and finally transferred into a plastic sealable container and labelled.

Homogeneity testing

Homogeneity testing was undertaken to investigate the homogenous content of Budesonide by selecting 10 random samples, each of 20 mg from different settings in the powder bed. The powder was dissolved in 100 ml of 50-60 ºC distilled water and analysed using spectrophotometer (Ultra-violet- 160A, Shimadzu, Japan) at a wavelength of 240 nm. The Standard deviation of the average content and co-efficient of variation (%) was used as a measure for the homogeneity of the powder mixture.

Device filling

Once the blend was found to be homogeneous in Budesonide distribution, it was filled into NB7/2 (small dose cup) multi-dose dry powder inhaler to give not less than 50 actuations from each device. Each actuation delivering a nominal dose of 100 g Budesonide (based on 2 mg mass delivery) for 5% blend and 200 g Budesonide for 10% blend. The device was stored under laboratory conditions before aerodynamic particle size distribution testing. Following completion, the blend was disposed off safely thoroughly to avoid any further contaminant with other sugars.

Aerodynamic particle size distribution

Aerodynamic particle size distribution of Budesonide was measured after firing 10 actuations into a multistage liquid impinger (MSLI) at a flow rate *ca*. 60–70 L min^{-1} that generated a pressure drop of 4 kPa across the device. Sonic flow was monitored and maintained throughout. The drug deposited in each stage of the MSLI was then recovered and quantified using a calibration curve generated by spectrophotometer.

Deposition of Budesonide from each formulation was determined twice and a variety of parameters were used to characterise the deposition profiles of the drug. The recovered dose (RD) was the sum of the drug recovered from the induction port (throat) and all five stages of the impinger. Fine particle dose (FPD) was the sum of the amount of drug recovered from stages three, four and five and the fine particle fraction (FPF) was calculated as the ratio of FPD to RD.

Results and discussion

Micromeritic properties

The Carr's index is frequently used as an indication of flowability of powder was measured for all carriers and formulation blends and the results are listed in Table 1. True density was also determined and included in Table 1.

Table 1. Flow behaviour and True density of different carriers used in DPI formulations

Carriers	Carr's Index (%)	True density(g/cm^3)
Sorbitol	20.68 ± 2.80	1.601 ± 0.010
Dextrose	22.80 ± 4.59	1.586 ± 0.011
Mannitol	36.92 ± 4.17	1.551 ± 0.002
Xylitol	46.94 ± 2.26	1.562 ± 0.003
Maltitol	39.38 ± 3.43	1.652 ± 0.005

Flowability is an important factor for the drug and carrier to be attached together and further transported from the mouth, down the trachea and into the lower airways to be deposited to demonstrate its pharmacological effect (Momin *et al*. 2010). According to Table 1, Pure sorbitol with the Carr's index value of 20.68% illustrated fair flowability, and a similar study involving sorbitol closer to sphericity in shape exhibited better flowability than mannitol and lactose (Tee *et al*. 2000). Xylitol with the Carr's index value of 46.94% appears to be the worse carrier, in terms of flowability.

Budesonide-Dextrose monohydrate tends to have an excellent flowability, with the Carr's index value of 15.4%, out of the entire 5% blends, whereas Budesonide-Maltitol tends to have a very poor flowability with the Carr's index value of 37.4%. The same blend, i.e. budesonide-dextrose monohydrate has again excellent flowability, with the Carr's index value of 13.48%, out of all the 10% blends. However, budesonide-mannitol tends to be the worse blend with the Carr's index value of 38.38% in terms of flowability. Although, a high FPF is expected for Dextrose monohydrate carrier formulation blends from the flowability data, the deposition results showed that mannitol formulation blends showed higher FPF (better aerosolization performance) than formulation blends containing Dextrose monohydrate (Table 2).

Table 2. Flow behaviour and True density of various formulations blends containing Budesonide

Carrier-drug formulation blend	Carr's Index (%)	True density (g/cm^3)
5% blends		
Sorbitol	25.20 ± 2.28	1.569 ± 0.012
Dextrose	15.40 ± 1.52	1.555 ± 0.005
Mannitol	32.60 ± 2.97	1.571 ± 0.008
Xylitol	18.30 ± 3.45	1.569 ± 0.004
Maltitol	37.40 ± 1.95	1.650 ± 0.010
10% blends		
Sorbitol	24.36 ± 3.09	1.514 ± 0.004
Dextrose	13.48 ± 0.44	1.553 ± 0.003
Mannitol	38.38 ± 2.15	1.550 ± 0.004
Xylitol	23.52 ± 1.87	1.534 ± 0.004
Maltitol	35.80 ± 5.49	1.622 ± 0.013

This indicated that any relationship between flowability of carrier and FPF values could not be established. Similar conclusion was reported (Kaialy *et al*. 2010) when mannitol with different flowabilities was produced by crystallization techniques using different combinations of organic solvents.

Homogeneity results

All mixtures were found to be homogenous with a coefficient of variation in Budesonide content of <8.83% (n=10).

Particle size analysis

The particle size distribution of various carriers and blends was determined by laser diffraction. The particle size distribution and cumulative undersize are presented in Figure 1 for sorbitol.

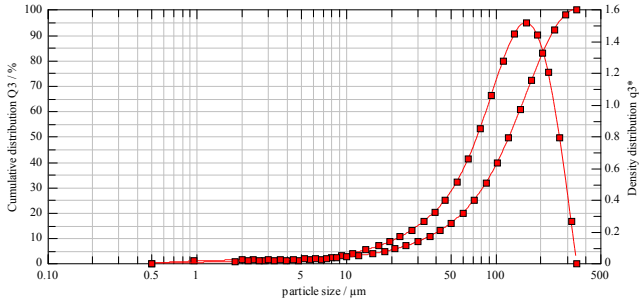

Fig. 1. Particle size distribution of Sorbitol.

The results for other sugars, drug (budesonide) and the blends are not shown for simplicity. The mean particle size and the associated spans are outlined in Table 3. The span for each sugars were calculated according to the following formula: Span = (X90 – X10)/X50

Table 3. Span and mean particle size of various carriers, blends and the drug

Material	$X_{90\%}$	$X_{50\%}$	$X_{10\%}$	Span	Volume mean diameter (µm)
Sorbitol	237.79	123.55	36.00	1.63	130
Dextrose	297.28	198.11	88.00	1.06	200
Mannitol	99.41	28.21	5.50	3.33	28
Xylitol	243.41	121.74	24.00	1.80	130
Maltitol	119.56	37.74	5.50	3.02	37
Budesonide	3.80	2.00	0.50	1.15	2.8

Generally, particle size is an important determinant of in vitro aerosol performance for dry powder inhalers (Louey *et al*. 2004). The smaller the particle size the higher the fine particle fraction. In addition, previous studies have also shown that as the particle size of powders is decreased, the fine particle fraction measured by cascade impaction is increased (Chew *et al*. 1999, 2000). While particles of small size are expected to be more difficult to disperse into aerosols due to increased cohesion (Zimon 1969), increasing the inhaler dispersion efficiency and airflow improve deagglomeration, leading to a larger fine particle fraction (Chew *et al*. 2000). Particle is also known to affect deposition of dry powder inhaler in the lungs as well as therapeutic response (Zanen *et al*. 1994, 1995). According to table 3, it is clear that Dextrose exhibits the narrowest particle size distribution with the span value of 1.06. This means that most of the particle sizes are in the similar range i.e 200 µm. Mannitol has the widest particle size distribution with the span value of 3.33. Budesonide, the drug, has the span value of 1.15 and the volume mean diameter of 2.8 µm.

Morphology of the carriers and the drug

The principle aim of this study has been to find a sugar other than lactose which can be used with Budesonide (drug) in DPI formulation as a carrier and the drug deposition of which will result in high fine particle fraction (FPF) or high fine particle dose (FPD).

In order to investigate the effect of morphology of the carriers on efficiency of DPI formulation, SEM of the carriers and their formulation blends were taken at different magnifications and the results are shown in Figure 2.

It is clear from the morphologies of the sugars, they all exhibited diverse images which may have resulted in changes to their performances for inhalation. Dextrose, sorbitol and xylitol exhibited large coarse irregular shapes (Figure 2). Mannitol and maltitol both illustrated small irregular coarse shape, although some degree of elongated particles existed for mannitol. A similar study showed that mannitol was more elongated in comparison to lactose and sorbitol (Tee *et al*. 2000).

The elongated shape for mannitol may have therefore partly contributed to the high FPF, since incorporating carrier particles has been reported to promote higher FPF or FPD (Xeng 1997). Budesonide presented with extreme small agglomerate particles shaped like flakes (Figure 2).

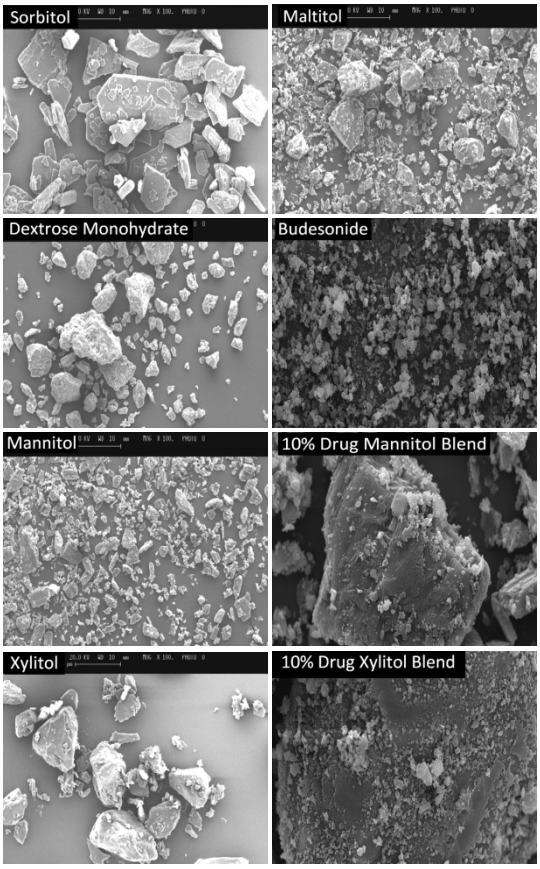

Fig. 2. Morphology of the sugars and Budesonide.

Aerodynamic assessment

Effect of carriers on Fine Particle Fraction of budesonide samples

The fine particle fraction of each blends were measured and the results are presented in Figure 3.

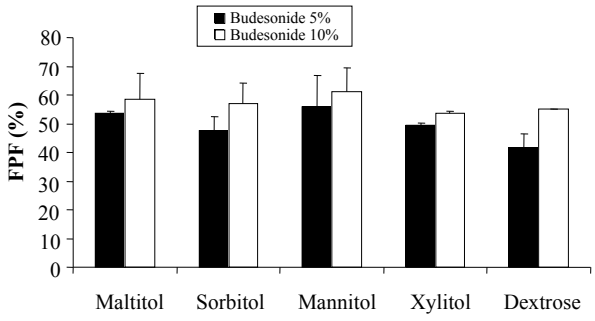

Fig. 3. Represent the average Fine Particle Fraction of 5% and 10% blends of budesonide containing various sugars

Several parameters can be measured when assessing the aerodynamic behaviour of a powder by means of Multi Stage Liquid Impinger (MSLI) (Luca *et al*. 1998). This apparatus was used for the aerodynamic assessment of fine particles. The amount of the powder deposited in different stages (Induction Port to stage 5) of MSLI was measured and the FPF of each blend was calculated as mass fraction of drug less than 5µm. The average values for FPF of 5% blends ranges from 41.5% to 55.75% in which the 41.5% represent budesonide- Dextrose Monohydrate and 55.75% represent mannitol blend respectively.

The figure shows that the 10% formulation blends tend to be slightly higher than in 5% blend. Mannitol blend with the FPF value of 61% appears to be the highest one. Taking into account mannitol being a known excipient widely used in pharmaceutical industry with an established toxicity profile (Daviskas 1999), therefore it may be used as an alternative carrier for drug delivery. Xylitol blend appears to have the lowest FPF with the value of 53.5%.

Low FPF can be resulted from combined effect of the device, the inhalation flow rate and the formulation (Timsina *et al*. 1994). In the current study, the flow rate of 60 l/min was conducted. More recent Pharmacopoeias (European Pharmacopoeia 1999, British Pharmacopoeia 2000) require that the aerodynamic particle size distribution of aerosols be measured under a flow rate achievable at a pressure drop of 4 kPa across the inhaler device, which represents the inhalation effort of an average asthmatic patient (Snel *et al*. 1999). In addition, the low FPF of Budesonide can also be attributable to the sub-optimal formulations since these binary mixtures consisted of micronized drug particles adhered directly to the coarse carrier particles. The direct interaction between the drug and coarse carrier will result in strong adhesion forces and therefore a higher detachment force is required to detach the drug particles from the carrier particles before they can be entrained into the air stream (Visser 1989) .The relatively high FPF of budesonide from the 10% formulation containing mannitol as compared with the other carriers such as sorbitol, may have been partly due to the elongated shape of the mannitol. Previous studies have been shown that elongated shape of carrier improves pulmonary drug delivery (Zeng 1997; Zeng *et al*. 2000; Podczeck 1998). The blends with sorbitol as a carrier generally resulted in smaller FPF as compared to the mannitol in both ratios i.e. 5% and 10%. This could be due to the fact that sorbitol exhibit rough and irregular shapes. This behaviour can be attributed to the strong adhesion of drug particles into the surface irregularities of the carrier.

Conclusion

Several parameters alter the formulation performance. Type of carriers, source of materials, surface texture of materials, particle size distribution etc. The experimental

results confirmed that interactions of drug-carrier are depending on the drug and the carrier whose role is paramount in adhesion phenomena. Also for one drug, the influence of carrier is very important. If the drug is changed, the influence of carriers also changed. The study of different carriers has to be in relation to one drug. Generalisation of the performance of one carrier of dry powder formulation to different drug is not possible.
In the current study, various sugars were evaluated for their potential use in dry powder formulations. Mannitol seems to be the highest potential as alternative carrier for dry powder formulation of Budesonide. It produced the highest fine particle fractions and it is well known excipient widely used in pharmaceutical sciences with an established toxicity profile. The more hygroscopic sugars such as xylitol, sorbitol, and maltitol were not able to generate suitable amount of fine particle fractions. However, the difficulties arising from their hygroscopicity can be investigated in an additional study whether the efficiency of powder blends could be improved by adding hydrophobic excipient.

Ethical issues

None to be declared.

Conflict of interests

Authors declare no conflict of interest.

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