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International Journal of Pharmaceutics 208 (2000) 111–123

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

The use of different sugars as fine and coarse carriers for aerosolised salbutamol sulphate

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Received 9 June 2000; received in revised form 15 August 2000; accepted 15 August 2000

Abstract

The aim of this study was to investigate the dispersion and deaggregation of a model drug, salbutamol sulphate (SS), using lactose, mannitol or sorbitol as coarse and fine carriers. Binary and tertiary formulations containing micronised salbutamol sulphate (SS) and sieved (63–90 μm) coarse sugar crystals or salbutamol sulphate (SS) with a mixture of coarse and fine sugar particles were prepared. Factorial design was employed to investigate the effects of three variables, i.e. the chemical entity of the coarse sugar carrier, the chemical entity of the fine sugar and the concentration of fine sugar, on the dispersion and deaggregation of salbutamol sulphate after aerosolisation at 60 l/min via a Rotahaler® into a twin stage liquid impinger (TSI). The binary formulations containing the different sugar entities produced differences in the fine (<6.4 μm) particle fraction (FPF) of SS in a decreasing order of mannitol > sorbitol > lactose, but failed to produce efficient dispersion of SS since the FPF was $<10\%$. Adding fine sugar particles and increasing their concentration to the binary mixtures generally resulted in an increase in the FPF of salbutamol sulphate. The chemical nature of the fine carriers was found to play a less important role in determining respirable fraction of the drug than the coarse carriers. In conclusion, other sugars such as mannitol or sorbitol, besides lactose, may be employed as coarse and/or fine carriers for incorporation into dry powder aerosol formulations to increase FPF. © 2000 Published by Elsevier Science B.V.

Keywords: Dry powder inhalers; Salbutamol sulphate; Lactose; Mannitol; Sorbitol

1. Introduction

Pulmonary delivery of pharmacological agents from dry powder inhalers (DPI) is dependent on the design of the DPI, the formulation and the inhalation manoeuvres of the patient. The aerodynamic diameter of drug particles should ideally be between 1 and 5 μm for deep lung penetration (Newman and Clarke, 1983; Gonda, 1990; Zanen et al., 1992; Timsina et al., 1994), but these particles are characteristically cohesive with poor flow and entrainment properties (Byron, 1986). One of the approaches employed to overcome these prob-

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0378-5173/00/$ - see front matter © 2000 Published by Elsevier Science B.V.

PII: S0378-5173(00)00553-6

lems involves blending the drug with a coarser carrier, typically lactose (Ganderton and Kassem, 1992). However, the fraction of deeply inspirable drug particles from most carrier-based DPI formulations at present is considered relatively low since only $\sim 10\%$ total dose can be delivered to the lower airways, the site of action for most aerosolised drugs. Various attempts to improve the delivery efficiency of drug particles to the lung have been made including: the design of novel inhaler devices (Brindley et al., 1995), the production of smooth carrier particles (Ganderton and Kassem, 1992), the use of lactose particles of different surface morphologies (Kawashima et al., 1998a; Zeng et al., 2000), the mixing of different grades of lactose carriers (Karhu et al., 2000), the utilisation other carrier excipient such as mannitol and Avicel (Broadhead et al., 1996), or the adding ternary materials to the blends (Ganderton and Kassem, 1992; Staniforth, 1996). Reducing the carrier particle size has also been exploited in an attempt to improve in vitro drug deposition (French et al., 1996; Steckel and Müller, 1997; Srichana et al., 1998a). Other attempts to improve drug dispersion included the surface modification of the hydrophobic drug particles with hydrophilic particles (Kawashima et al., 1998b,c), micronisation of drug particles by supercritical carbon dioxide (Steckel et al., 1997) and the incorporation of drugs into microspheres (Philip et al., 1997). A more practical approach, which might be employed industrially to improve drug delivery efficiency from DPI, might involve manipulation of the powder formulation. Such an approach could include the addition of fine particles of a third component or micronised lactose carrier to powder formulations (Zeng et al., 1996a,b; Lucas et al., 1998). The use of fine carrier particles to improve drug delivery might be considered to be preferential to the use of ternary materials, since the latter may require additional toxicological testing.

However, the majority of previous studies have focused on lactose-based formulations. Lactose was chosen originally as the carrier for dry powder aerosols largely because it is a safe pharmaceutical excipient, readily available, physico-chemically stable and compatible with the majority of small molecular weight drugs. There are many other pharmaceutical excipients, particularly some sugars, that also meet the criteria required for incorporation as a suitable carrier in dry powder aerosols. Surprisingly, little work has been published detailing the merits, or otherwise, of sugars other than lactose which is by no means the ideal carrier for all drugs. For example, lactose is a reducing sugar and will not provide an appropriate excipient for some drugs such as proteins or peptides. Thus, it is pertinent to study the potential application of other sugar entities as carriers for dry powder for inhalation. Therefore, it was the aim of the present study to investigate the dispersion and deaggregation of a model drug, salbutamol sulphate, from formulations containing mixtures of different sugars as the coarse and fine carriers. The carriers that were selected were lactose, mannitol and sorbitol. Mannitol was chosen since it has been employed widely in the pharmaceutical industry, particularly as a stabilising agent for proteins and peptides. Sorbitol, although a stereo-isomer of mannitol, has different physical properties, including greater hygroscopicity compared with mannitol. It was thought therefore that sorbitol, mannitol and lactose would provide ideal samples to compare the effects of different physical properties on drug dispersion. A 3^3-factorial design was employed such that all possible combinations between the drug and carriers were included in the studies.

2. Materials and methods

2.1. Materials

Micronised salbutamol sulphate (Allchem International, Maidenhead, UK), regular grade α-lactose monohydrate (batch no. 812701) (Borculo, Holland), mannitol (batch no. 9769463497) (Sigma, Poole, UK) and sorbitol (batch no. 38676245) (Fisons Scientific Equipment, Loughborough, UK) were obtained from the suppliers indicated. The Rotahaler® and clear hard gelatin capsules (size 3) were obtained from Allen and Hanbury's, UK and Capsugel, Bornem, Belgium, respectively. Chemical and solvents used were *p*-

hydroxybenzoic acid ethyl ester (ethyl paraben) (Sigma, Poole, UK), methanol (HPLC grade) (BDH Laboratory Supplies, Poole, UK) and distilled water (MilliQ grade) (Millipore, Watford, UK).

2.2. Preparation of coarse and fine sugar carrier particles and micronised salbutamol sulphate

The sieved fraction (63–90 μm) of coarse sugar carrier (CC), comprising lactose (CL), mannitol (CM) or sorbitol (CS), was obtained by sieving 100 g of the sugar particles sequentially through test sieves with an aperture width of 90 and 63 μm using an air-jet sieve (Alpine, Augsburg, Germany) for 15 min. Those particles retained by the 63-μm sieve comprised the coarse carriers. Fine sugar particles (FC) of lactose (FL), mannitol (FM) and sorbitol (FS) were prepared by collecting the particles which passed through the 63-μm sieve (i.e. < 63 μm) and passing them through a jet mill (JM-80; M&M Fryma, UK) until more than 70% particles were less than 10 μm, as characterised using laser diffraction (Malvern Instruments, Malvern, UK). Micronised salbutamol sulphate (SS) as obtained from the supplier was re-micronised following a similar procedure. All the powders were stored in glass containers, which were placed in a desiccator at room temperature over silica gel until further required.

2.3. Experimental design

Different dry powder formulations were produced by altering three factors, namely, the type of the coarse carrier, the type of fine carrier and the ratio of the coarse to the fine carrier. Each factor had three levels and thus a total of 27 ($3 \times 3 \times 3$) combinations are possible (Table 1). Only three combinations are possible for formula-

Table 1
Salbutamol sulphate (SS) was incorporated with coarse carrier (CC) alone to form binary mixtures or with CC containing fine carrier (FC) in different ratios to form 21 different dry powder formulations[a]

Formulation no.	Formulation code	Experimental setting		
		CC:FC:SS ratio	Type of FC	Type of CC
1	L0	67.5:0:1	No FC	CL
2	Ll1	66.5:1:1	FL	CL
3	Ll2	64.5:3:1	FL	CL
4	Lm1	66.5:1:1	FM	CL
5	Lm2	64.5:3:1	FM	CL
6	Ls1	66.5:1:1	FS	CL
7	Ls2	64.5:3:1	FS	CL
8	M0	67.5:0:1	No FC	CM
9	Ml1	66.5:1:1	FL	CM
10	Ml2	64.5:3:1	FL	CM
11	Mm1	66.5:1:1	FM	CM
12	Mm2	64.5:3:1	FM	CM
13	Ms1	66.5:1:1	FS	CM
14	Ms2	64.5:3:1	FS	CM
15	S0	67.5:0:1	No FC	CS
16	Sl1	66.5:1:1	FL	CS
17	Sl2	64.5:3:1	FL	CS
18	Sm1	66.5:1:1	FM	CS
19	Sm2	64.5:3:1	FM	CS
20	Ss1	66.5:1:1	FS	CS
21	Ss2	64.5:3:1	FS	CS

[a] CL, CM and CS represent coarse lactose, coarse mannitol and coarse sorbitol, respectively, while FL, FM and FS represent fine lactose, fine mannitol and fine sorbitol, respectively.

tions with a ratio of coarse to fine carrier of 67.5:0 and this resulted in a total of 21 possible formulations. A total of 18 combinations ($2 \times 3 \times 3$) are composed of three components, i.e. the drug, coarse and fine carrier, and are termed ternary interactive mixtures. The three combinations containing the coarse carrier and the drug only (without added fine carrier) were defined as binary interactive mixtures (Table 1). In all the combinations, the ratio of salbutamol sulphate to the excipient was kept constant at 1:67.5, w/w.

2.4. Preparation of dry powder formulations

All powder mixing was performed using a Turbula® mixer (Glen Creston, Stanmore, UK). The three components of each formulation were blended using the sequences of addition reported by Zeng et al. (1996a). In preparing formulations containing CC:FC:SS of 64.5:3:1, 0.215 g fine sugar was first mixed with 4.633 g coarse sugar by mean of geometric dilution to disperse the cohesive fine sugar in a 20-ml glass container (25-mm i.d. × 50-mm height) followed by a 30-min mixing process using a Turbula® mixer at 136 rpm to form an ordered mixture (Hersey, 1975). The resultant mixtures were then blended with 0.072 g salbutamol sulphate for a further 30 min under similar conditions (Tee et al., 1998). The amounts of each component employed to produce formulations CC:FC:SS and CC:SS were in the ratio 66.5:1:1 and 67.5:1, respectively, being 4.776: 0.072:0.072 and 4.848:0.072 g, respectively.

Homogeneity of the mixtures was evaluated by removing six randomly selected samples, each weighing 32 ± 2 mg, for assay of salbutamol sulphate content. This weight was selected since it was the amount of powder formulation in each capsule. The degree of homogeneity was expressed in terms of coefficient of variation (CV) in salbutamol sulphate content. Blended powders with a CV less than 6% were considered to be satisfactorily mixed.

All blended powders containing salbutamol sulphate were filled in hard gelatin capsules (size 3) manually such that each capsule contained 32 ± 2 mg of the powder.

2.5. Particle size distribution measurement by laser diffraction

Particles size analysis was performed by suspending ~ 5 mg of powder in chloroform containing a few drops of Span 85 which was pre-saturated with the powder under investigation. The suspension was sonicated in a water bath (Model F5100b; Decon Laboratories, Hove, UK) for 1 min. The particle size of the sample was measured by laser diffraction (Malvern Instruments, Malvern, UK) using a 63-mm focal length lens at an obscuration of ~ 0.165 and fitting the data to an independent model. Each sample was measured at least six times. Particle size distributions were expressed in terms of volume median diameter (VMD) and geometric standard deviation (GSD). The percentage of fine particles (< 10 and < 5 μm) contained in each powder was also determined.

2.6. Measurement of particle shape factor by microscopic image analysis

The elongation ratio and roundness value of coarse sugar carriers were determined using image analysis software (designed in-house at King's College London) installed on an Archimedes computer, which was attached to an optical microscope (Nikon Labophot, Japan) via a miniature video camera. A total of 500 particles were analysed using the well-accepted shape factors of roundness and elongation ratio, which were defined as follows:

$$\text{Roundness} = \frac{\text{Perimeter}^2}{4 \times \pi \times \text{area}} \quad (1)$$

$$\text{Elongation ratio} = \frac{\text{Maximum Feret diameter}}{\text{Minimum Feret diameter}} \quad (2)$$

Measurements on each batch of sugar were carried out on at least three samples.

2.7. Qualitative analysis of surface texture by scanning electron microscopy

The particle surface topography and texture of

the coarse and fine sugar carriers were assessed qualitatively using scanning electron microscopy (Philip SEM 501B scanning electron microscope, Eindhoven, Holland). The sample powder was dispersed on a conductive, double-sided, adhesive tape on an aluminium sample stub. The particles were then coated with ~ 15–20 nm gold using a sputter coater (Polaron E5100, Polaron Equipment, Watford, UK) using an electrical potential of 2.0 kV, 20 mA. Several photomicrographs were produced by viewing fields, selected randomly, at several magnifications (Philips SEM501B scanning electron microscope, Eindhoven, The Netherlands).

2.8. HPLC analysis of salbutamol sulphate

Salbutamol sulphate was analysed using a validated HPLC assay employing a 15-cm × 4.6-mm i.d. column packed with 5 μm C-18 (Hypersil, Phenomenax, UK) and a mobile phase comprising a mixture of 0.125% w/v 1-heptane sulfonic acid aqueous solution combined with methanol in the ratio of 50:50 v/v. The analysis was carried out using a flow rate of 0.8 ml/min, incorporating *p*-hydroxybenzoic acid ethyl ester (2.5 μg/ml) as the internal standard and monitoring the eluant at λ_{max} of 238 nm. The retention times for salbutamol sulphate and the internal standard were 2.67 and 6.92 min, respectively. For all assays, samples were analysed in duplicate. Calibration plots of salbutamol sulphate were linear over the range of 1–20 μg/ml with $R^2 = 0.9999$. For assay validation, replicate analysis ($n = 5$) of salbutamol sulphate standard solutions (2, 8 and 15 μg/ml) was performed and the mean percentage recovery of salbutamol sulphate was found to be 100.6 ± 1.0, 99.6 ± 0.9 and 99.8 ± 0.4%, respectively.

2.9. In vitro deposition test of salbutamol sulphate

In vitro deposition of salbutamol sulphate from dry powder formulations was determined using a twin stage impinger (TSI, Apparatus A; British Pharmacopoeia, 2000). Each deposition experiment involved the aerosolisation of five capsules, each containing a nominal dose of 32 ± 2 mg powder, equivalent to 480 ± 29 μg salbutamol sulphate, at 60 l/min, via a Rotahaler®. The inhaler device, capsule shells and the mouthpiece adaptor were rinsed five times with mobile phase containing internal standard. The same procedure was repeated for the upper stage (stage 1) and lower stage (stage 2) of the TSI. All samples were sonicated in a sonic water bath for 5 min before analysing the concentration of salbutamol sulphate using the HPLC method described above. Deposition of salbutamol sulphate was determined a total of five times from each formulation.

The amount (μg) of salbutamol sulphate per capsule that deposited in the lower stage of the TSI after aerosolisation at 60 l/min (effective cut-off diameter (ECD) < 6.4 μm) (Hallworth and Westmoreland, 1987) was considered to be the fine particle dose (FPD). The recovered dose (RD) was defined as the total quantity of drug recovered per capsule after each actuation, while the emitted dose (ED) was that emitted from the inhaler device into the TSI. Percentage emission was calculated as the percentage of emitted dose to total recovered dose. Fine particle fraction (FPF) was the ratio of FPD to RD, while dispersibility was the percentage of FPD to ED.

3. Results

3.1. Morphology of the carriers and the drug

Fig. 1 shows the SE micrographs of the three coarse sugar carriers. The coarse lactose exhibited a tomahawk shape, typical of α-lactose monohydrate grown to maturity. Mannitol particles appeared to be slightly more elongated with more surface asperities than lactose. The sorbitol particles were more symmetrical (Fig. 1) and clearly rounder (Table 2) than either mannitol or lactose. Interestingly, many small pores were evident on the surface of the coarse sorbitol, and these may have been formed during the hydration and dehydration process since sorbitol is highly hygroscopic and easily loses its water of crystallisation (Nash, 2000).

Different values of the roundness and elongation ratio were obtained for the three coarse

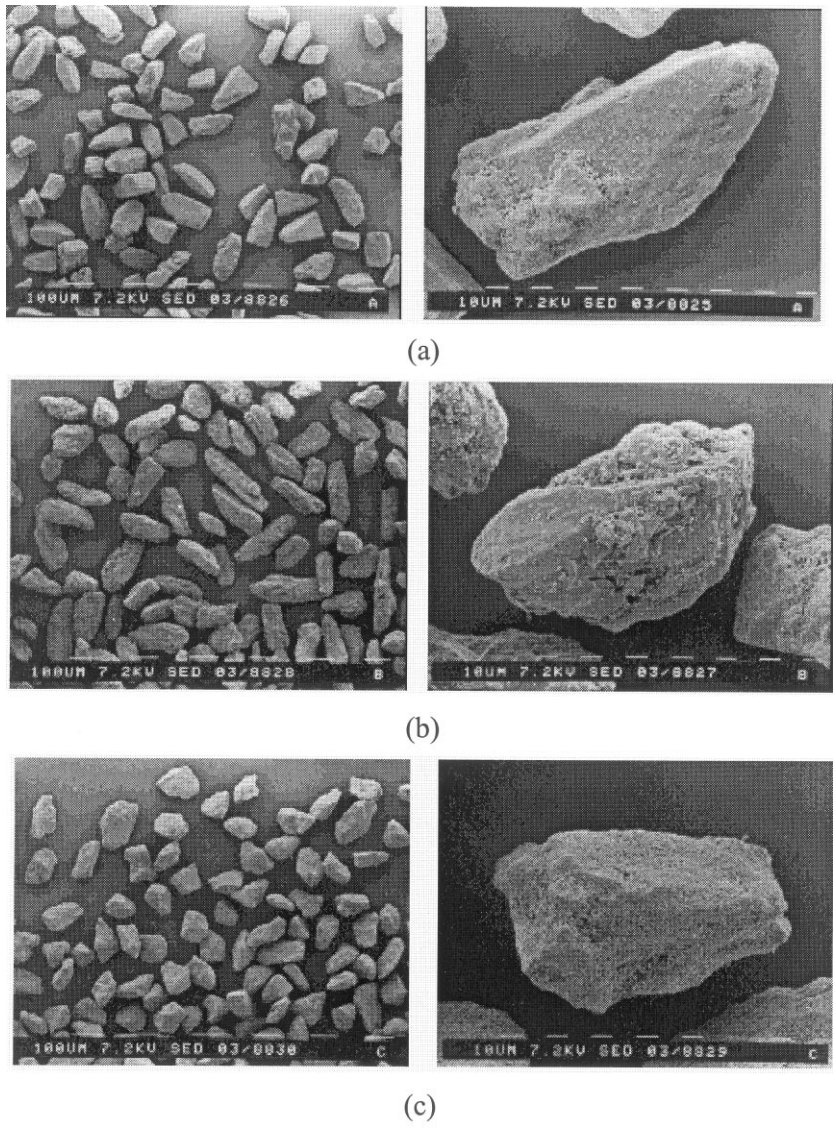

Fig. 1. Scanning electron micrographs showing particle morphology of (a) coarse α-lactose monohydrate, (b) coarse mannitol and (c) coarse sorbitol.

carriers (Table 2). Roundness, as defined in Eq. (1), is a factor which combines both geometric shape and surface smoothness. A sphere, converted to a circle by image analysis, with surface asperities below the level of detection will have a roundness value of 1. A sphere with rough surfaces or particles of any other shape will possess roundness value >1. A higher value of a particle roundness is indicative of the particles having either a more irregular shape or a rougher surface. The elongation ratio is defined as the length expressed as a function of the width (Eq. (2)) and hence, spheres and perfect cubes have a ratio of 1.0. The higher the elongation ratio the more elongated and/or irregular the shape. Thus, the coarse mannitol employed in this study was more elongated than the coarse lactose, which was in turn more elongated than the sorbitol. Such dif-

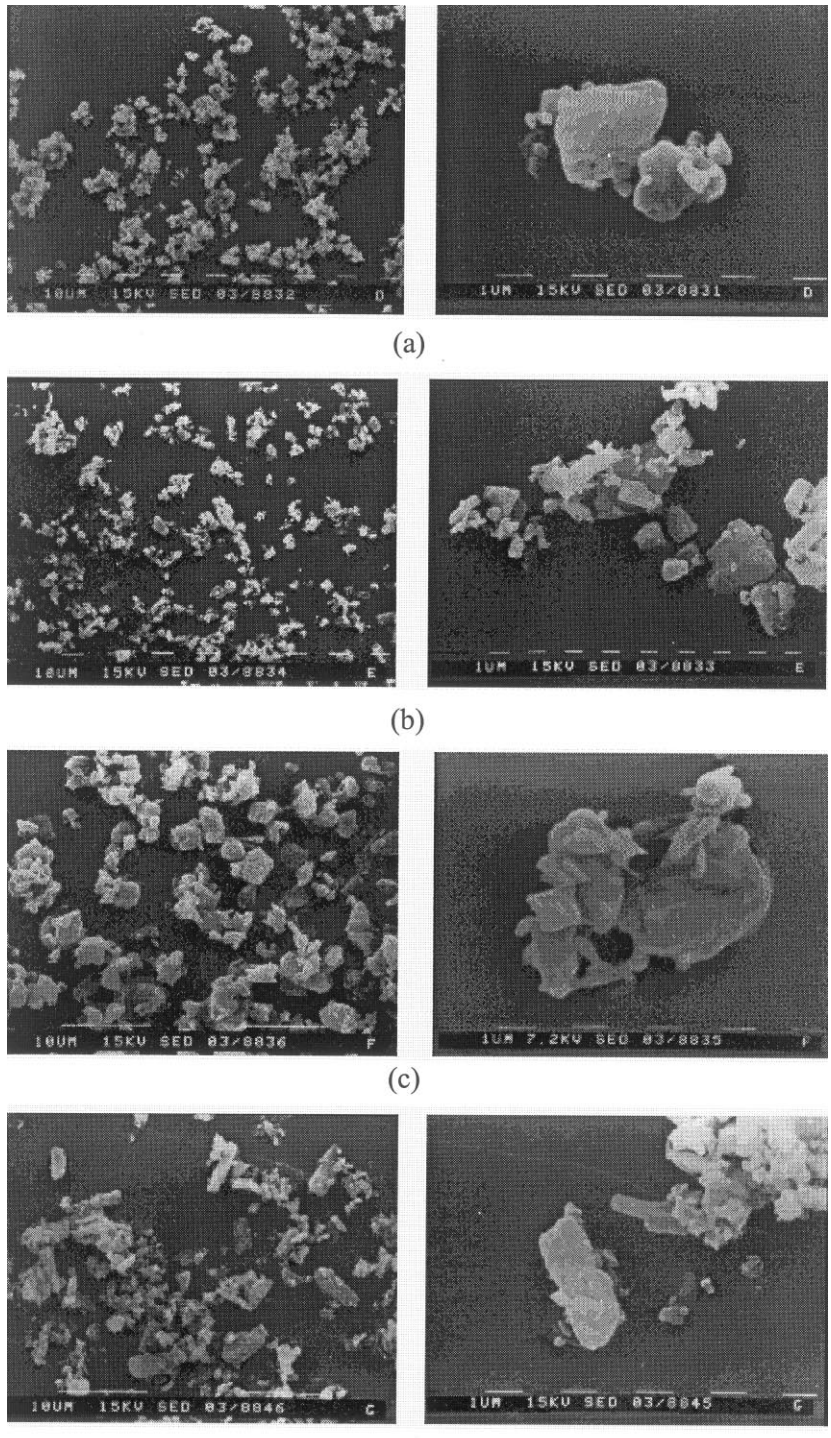

Fig. 2. Scanning electron micrographs showing agglomerates of (a) fine lactose, (b) fine mannitol, (c) fine sorbitol and (d) micronised salbutamol sulphate.

Table 2
Shape factors (mean value ± S.D.) of different batches of coarse sugar carriers ($n = 500$ particles)

Shape factor	Coarse carrier		
	Lactose (CL)	Mannitol (CM)	Sorbitol (CS)
Roundness	1.41 (1.32)	1.69 (0.87)	1.27 (0.15)
Elongation	1.64 (0.12)	1.96 (0.14)	1.39 (0.11)

ferences in the morphological features of the different coarse carriers is confirmed qualitatively by the SE micrographs (Fig. 1).

As with micronised materials, the particles tended to be cohesive and form agglomerates as is apparent from the SE micrographs (Fig. 2). There was no readily distinguishable difference in the morphology of these fine particles except that fine mannitol appeared to be more angular than fine sorbitol and salbutamol sulphate.

3.2. Particle size distribution of coarse sugar carriers, fine sugar particles and micronised salbutamol sulphate

The jet milling process produced micronised salbutamol sulphate and fine sugar particles with a volume mean diameter (VMD) ranging between 3.19 and 7.10 μm (Table 3). The salbutamol sulphate exhibited a VMD of 3.19 with over 99% of particles less than 10 μm, suggesting that this material was suitable for use as inhalation aerosol. The FL and FS were slightly larger than the FM and salbutamol sulphate. Only 5% of the mannitol particles present had a VMD > 10 μm, whereas over 25% of the lactose present in the FL was sized > 10 μm (Table 3). Such a difference in the particle size is interesting since all the samples were micronised using similar conditions. The VMD of coarse sugar carriers were shown to be in the decreasing order of sorbitol > lactose > mannitol. Such a difference in VMD may be attributed in part to the differences in the particle shape of these coarse sugar particles. As shown above, mannitol is the most elongated, followed by lactose with sorbitol the roundest. Elongated particles such as mannitol can present either in their longest or shortest diameters to the sieve during sieving process. More elongated particles would have passed through the 63-μm sieve if the condition was in favour of the latter and elongated particles with their shortest diameter larger than the sieve size would be retained on the sieve. Therefore, the VMD of the sieved particles retained on a 63-μm sieve will be smaller for powder composed of more elongated particles.

3.3. In vitro deposition profiles of salbutamol sulphate

3.3.1. Formulations containing coarse lactose as the carrier

Coarse lactose (CL) produced a low delivery efficiency of salbutamol sulphate (SS) from the Rotahaler®. Only 30 μg of SS out of a nominal dose of 480 μg drug had an aerodynamic diameter of < 6.4 μm (Table 4). Such a relatively low FPD is comparable to those produced by other formulations aerosolised from a Rotahaler® (Srichana et al., 1998b; Vidgren et al., 1988). The FPD, FPF and dispersibility were increased when fine parti-

Table 3
Particle size distribution of salbutamol sulphate, the coarse and fine carrier particles

Drug/excipients	Volume mean diameter ± GSD (μm)	% <10 μm (mean ± GSD)	% <5 μm (mean ± GSD)
Salbutamol sulphate	3.19 ± 1.37	99.8 ± 0.2	84.2 ± 8.3
Fine lactose	7.10 ± 2.12	72.3 ± 15.7	31.1 ± 9.3
Fine mannitol	4.31 ± 1.58	95.3 ± 5.1	60.6 ± 9.7
Fine sorbitol	6.17 ± 1.78	79.6 ± 8.7	31.9 ± 7.7
Coarse lactose	92.73 ± 1.50	2.0 ± 0.2	1.0 ± 0.6
Coarse mannitol	80.73 ± 1.95	5.0 ± 3.1	2.8 ± 1.5
Coarse sorbitol	114.22 ± 1.48	1.4 ± 0.2	1.1 ± 0.1

Table 4
Deposition of salbutamol sulphate in a TSI after aerosolisation from dry powder formulations containing coarse lactose as carriers via a Rotahaler® at 60 l/min (mean ± S.D., $n = 6$–8)

Formulations	FPD (μg)	ED (μg)	RD (μg)	Emission (%)	FPF (%)	Dispersibility (%)
L0	29.7 ± 4.3	346.9 ± 23.9	463.8 ± 16.0	75.4 ± 5.2	6.4 ± 1.0	8.6 ± 1.3
Ll1	33.7 ± 6.9	331.1 ± 21.6	463.5 ± 4.5	71.3 ± 4.7	7.3 ± 1.5	10.2 ± 2.0
Ll2	58.6 ± 16.5	302.4 ± 25.0	470.1 ± 50.9	66.0 ± 5.4	12.3 ± 2.2	19.3 ± 4.1
Lm1	51.3 ± 6.3	337.1 ± 22.3	459.1 ± 9.3	74.3 ± 4.9	11.2 ± 1.4	15.2 ± 1.6
Lm2	63.0 ± 4.2	325.3 ± 31.1	466.6 ± 34.4	68.3 ± 6.5	13.5 ± 0.9	19.4 ± 1.4
Ls1	49.6 ± 3.7	353.1 ± 3.7	449.4 ± 10.2	81.3 ± 0.9	11.0 ± 0.9	14.1 ± 1.1
Ls2	63.6 ± 4.1	375.9 ± 18.4	476.7 ± 19.1	79.9 ± 3.9	13.3 ± 0.7	16.9 ± 0.9

cles of the same and different sugar were added to the formulation, and the increase was related to the amount of fine particles included within the formulation. The addition of lower amounts of fine particles of different sugar was shown generally to be more effective in enhancing the FPD, FPF and dispersibility than the addition of a lower amount of fine particles of the same sugar as the coarse particles. However, no significant difference was observed between the deposition profiles of salbutamol sulphate from formulations containing higher concentrations of fine particles of different sugars (Table 4).

3.3.2. Formulations containing coarse mannitol as the carrier

For formulations containing coarse mannitol as the carrier, the FPF/FPD of SS was found to increase significantly ($P < 0.01$) with the concentration of added fine lactose whilst little change was observed when fine mannitol or sorbitol was added to the formulations (Table 5). For example, the mean FPD of SS was found to increase from 40.9 μg for the formulation containing coarse mannitol only as the carrier to 73.1 μg for the formulation using the mixture of coarse mannitol with fine lactose (64.5:3, w/w) as the carrier. The formulations containing mixtures of coarse-fine mannitol in ratios of 66.5:1 and 64.5:3 w/w, produced mean SS FPD of 45.8 and 36.1 μg, respectively, which are not statistically different from the mean SS FPD (40.9 μg) for the formulation without added fine carrier particles. There was a slight but statistically significant ($P < 0.05$) reduction in the FPD of SS by increasing the amount of fine mannitol in coarse-fine mannitol mixtures from coarse mannitol/fine mannitol ratio of 66.5:1 to 64.5:3 w/w. A statistically significant increase in FPF/FPD of SS was observed when fine sorbitol was introduced to give a ratio of coarse mannitol/fine sorbitol of 64.5:3 as compared to the FPF/FPD of SS from the binary mixture.

3.3.3. Formulations containing coarse sorbitol as the carrier

Addition of fine sugar particles to the formulations containing coarse sorbitol as the carrier resulted in a significant increase in the FPD/FPF of SS regardless of the chemical entities of the fine sugars (Table 6). Increasing the amount of fine lactose in coarse sorbitol-fine lactose mixtures from coarse sorbitol/fine lactose ratio of 66.5:1 to 64.5:3 resulted in a corresponding increase in the FPF/FPD of SS. However, no further increase in the drug FPF/FPD was achieved by increasing the concentration of fine mannitol from coarse sorbitol/fine mannitol ratio of 66.5:1 to 64.5:3. Considering all the formulations then it was found generally that those containing the highest amount of fine lactose generated FPF/FPD of SS which were significantly higher than those from the formulations containing the fine sorbitol or mannitol.

4. Discussion

It is apparent from the current study that chemical entity of the sugar plays a more important role in determining drug dispersion and deaggre-

gation when it is used as the coarse carrier than when it is used as the fine carrier. In the binary mixtures, i.e. those without added fine sugars, formulations containing mannitol as the carrier produced FPD, FPF and dispersibility of SS which were significantly ($P < 0.05$) higher than those from formulations containing either lactose or sorbitol. All binary mixtures failed to produce efficient drug delivery with FPF less than 10% under the test conditions. Such a low FPF can be attributed to the combined effect of the device, the inhalation flow rate and the formulation (Timsina et al., 1994). The Rotahaler® is a relatively inefficient device, which has been shown to deliver less than 10% total drug to the lower airways (Vidgren et al., 1988). In the current study, the in vitro deposition test was conducted at a flow rate of 60 l/min, which is recommended for use of TSI. 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 (Snell and Ganderton, 1999; United States Pharmacopoeia, 1999). The Rotahaler® is a low air-resistance device, with a specific resistance, R_D, of 0.040 (cm $H_2O)^{1/2}$ l/min (Clark and Hollingworth, 1993). It is possible to calculate the flow rate, Q, that will be achieved across the Rotahaler® at a pressure drop, ΔP, of 4 kPa (40.8 cm H_2O) using the following equation:

$$\Delta P^{1/2} = R_D Q \quad (3)$$

Therefore, a flow rate of 160 l/min can be achieved across the Rotahaler® at a pressure drop of 4 kPa, which is much higher than the flow rate (60 l/min) employed for the in vitro test. Thus, the current testing conditions might be expected to under-estimate significantly the real performance of the device. In addition, the low FPF/FPD of SS is also partly attributable to the sub-optimal formulations since these binary mixtures consisted of micronised 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/FPD of SS from formulations containing coarse mannitol as compared with those containing coarse lactose and sorbitol may have been partly due to a higher concentration of finer particles (i.e. < 10 μm) existing in the former carrier (Table 3). The more elongated shape of coarse mannitol may also have partly contributed to the higher FPF of SS since the incorporation of such carrier particles in a formulation has been reported to promote a higher FPF/FPD of salbutamol sulphate (Zeng, 1997).

Active binding sites have been proposed to exist, distributed unevenly on the surface of carrier particles (Hersey, 1975). The addition of fine lactose is likely to affect drug dispersion by interacting with some of the active sites which would otherwise adhere to drug strongly. This displaces drug from such sites on the coarse lactose and hence more of the drug is located at sites where

Table 5
Deposition of salbutamol sulphate in a TSI after aerosolisation from dry powder formulations containing coarse mannitol as the carrier via a Rotahaler® at 60 l/min (mean ± S.D., $n = 6$–8)

Formulations	FPD (μg)	ED (μg)	RD (μg)	Emission (%)	FPF (%)	Dispersibility (%)
M0	40.9 ± 4.4	364.0 ± 26.4	455.6 ± 15.6	78.3 ± 5.7	9.0 ± 0.9	11.2 ± 1.2
Ml1	57.7 ± 4.6	364.0 ± 12.6	468.2 ± 8.3	78.8 ± 2.7	12.3 ± 1.0	15.9 ± 1.0
Ml2	73.1 ± 9.1	334.4 ± 15.9	462.0 ± 22.3	71.9 ± 3.4	15.8 ± 1.8	21.9 ± 2.7
Mm1	45.8 ± 5.9	332.9 ± 13.1	449.2 ± 4.2	73.2 ± 2.9	10.2 ± 1.3	13.8 ± 1.7
Mm2	36.1 ± 8.1	324.6 ± 12.7	454.1 ± 13.6	71.7 ± 2.8	8.0 ± 1.9	11.1 ± 2.1
Ms1	50.0 ± 6.3	361.3 ± 12.2	462.3 ± 10.3	78.8 ± 2.7	10.8 ± 1.5	13.9 ± 1.9
Ms2	61.0 ± 4.8	367.5 ± 4.8	474.2 ± 14.9	80.7 ± 3.4	12.9 ± 1.0	16.6 ± 1.3

Table 6
Deposition of salbutamol sulphate in a TSI after aerosolisation from dry powder formulations containing coarse sorbitol as the carrier via a Rotahaler® at 60 l/min (mean ± S.D., $n = 6–8$)

Formulations	FPD (μg)	ED (μg)	RD (μg)	Emission (%)	FPF (%)	Dispersibility (%)
S0	30.5 ± 3.0	371.8 ± 8.1	470.9 ± 12.2	78.5 ± 1.7	6.5 ± 0.6	8.2 ± 0.7
Sl1	53.8 ± 5.9	356.8 ± 21.7	452.7 ± 20.7	77.4 ± 4.7	11.9 ± 1.4	15.1 ± 1.8
Sl2	76.3 ± 9.3	358.0 ± 30.6	478.7 ± 31.6	77.3 ± 6.6	15.9 ± 0.9	21.3 ± 1.0
Sm1	43.8 ± 1.5	350.0 ± 16.9	464.8 ± 10.4	73.2 ± 3.5	9.4 ± 0.4	12.6 ± 0.9
Sm2	43.4 ± 2.6	353.5 ± 12.5	471.9 ± 31.4	76.7 ± 2.7	9.3 ± 1.1	12.3 ± 1.0
Ss1	45.1 ± 3.7	358.8 ± 12.7	456.1 ± 2.7	77.1 ± 2.7	9.9 ± 0.8	12.6 ± 1.4
Ss2	50.0 ± 3.2	368.5 ± 11.7	466.3 ± 7.4	82.8 ± 2.6	10.7 ± 0.5	13.6 ± 0.7

the binding interaction might be weaker (Staniforth, 1995; Zeng et al., 1998). Consequently, the more weakly adhered drug particles are dislodged and detached more readily from the surface of carrier particles, and dispersed in the airstream prior to inhalation. More recently, the addition of fine lactose to the formulations containing coarse lactose as the carrier was shown to reduce the magnitude of electrostatic charge (Bennett et al., 1999). Therefore, the more fine lactose that was added, the higher the FPF/FPD of the drug. The current findings for the lactose-based formulations were in agreement with those reported previously (Zeng et al., 1998). Interestingly, the fine sorbitol and mannitol exhibited an effect on drug dispersion which was similar to that of fine lactose, suggesting that the effect of the fine carrier at higher concentration is independent of the chemical structure of the fine materials when coarse lactose is used as the coarse carrier.

Although the addition of fine materials to formulations containing coarse mannitol or sorbitol generally increased the FPF/FPD of SS, the relationship between drug FPF/FPD and concentrations of fine materials was found to be slightly different to that of formulations containing coarse lactose as the carrier. The FPF/FPD of SS increased as the concentration of added fine lactose was increased. However, no additional increase in FPF/FPD was seen when the concentration of fine sorbitol or mannitol was increased from the lower to higher levels. At the higher ratio of fine to coarse carrier (3:64.5), fine lactose consistently produced higher FPD, FPF and dispersibility of SS than equivalent amounts of fine sorbitol or mannitol.

Sorbitol and mannitol are stereo-isomers with different physical properties, although sorbitol is more hygroscopic than mannitol. Nevertheless, when used as either coarse or fine carriers in the dry powder formulations, the two sugars produced more or less similar in vitro deposition profiles of SS. These results suggest that either the difference in physical properties between sorbitol and mannitol is not sufficient to produce any significant difference in the drug deposition or the current testing conditions are not sufficiently sensitive to differentiate between these two carriers.

Apart from the effects upon FPF and FPD, fine carrier particles were also shown to affect the emission of salbutamol sulphate from the Rotahaler®. Adding fine lactose to the formulations generally reduced drug emission from the device. For example, the emission of SS from formulations containing coarse lactose as the carrier was found to decrease from 75.4% for formulation without added fine particles to 66.0% for formulation containing the higher ratio of (3:64.5 w/w) fine lactose. Drug emission from the Rotahaler® is a function of powder flow properties: the better the powder flows the higher the drug emission will be in binary interactive mixtures (Concessio et al., 1999). Adding fine lactose to a blend is likely to decrease the powder flowability and consequently reduce the emission of SS from the inhaler device. However, such an explanation is not always true since adding fine sorbitol to the powder formulation tended to increase drug emission slightly. For example, the emission of SS from the lactose-formulation was shown to increase from 75.4 to 81.3% if the smaller ratio (1:66.5, w/w) of sorbitol

was added to the formulation. Interestingly, the formulations containing coarse sorbitol as the carrier produced the most consistent drug emission, which was the least affected by the fine carrier particles. As described earlier, the sorbitol particles were closer to sphericity in shape than either lactose or mannitol and, therefore, the sorbitol particles would be expected to have a better flowability than lactose or mannitol. This would be expected to improve the drug emission from the inhaler device.

Increasing the fine particle size of the fraction would appear to promote the FPF or FPD of SS, irrespective of the nature of the sugar employed. If lactose was employed as the coarse carrier, then the incorporation of further amounts of fine particles of lactose would appear to provide the best strategy of improving the FPF or FPD of drug. This may not be true for all drugs, in which case it may be feasible on the basis of the results from this study to attempt to promote FPF by incorporating a tertiary component comprising a second sugar of reduced particle size into a binary mixture of coarse carrier and drug.

5. Conclusions

The effects of fine lactose in promoting drug delivery from formulations containing coarse lactose as the carrier reported previously (Zeng et al., 1999) would appear to be similar when included as a component in formulations which contain other sugars as the coarse carrier. The chemical nature of the fine carrier appeared to play a less important role in determining delivery of the drug in comparison to the concentration of the fine carrier particles. Under the conditions employed in the current study, the use of different coarse carriers resulted in similar deposition profiles of drug although subtle differences in the drug emissions were observed. It could be concluded that mannitol or sorbitol as well as could be employed in place of lactose as possible coarse carriers for inhaled drugs. Increasing the concentration of fine carrier particles, as well as their chemical nature, can influence the resultant drug deposition in vitro.

Acknowledgements

S.K. Tee would like to acknowledge the financial support from the Royal Pharmaceutical Society of Great Britain and the provision of an Overseas Research Studentship by the Committee of Vice Chancellors and Principals, UK.

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