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Research paper

The use of lactose recrystallised from carbopol gels as a carrier for aerosolised salbutamol sulphate

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Abstract

Lactose was crystallised either from Carbopol gel without stirring or from a constantly-stirred aqueous solution, to obtain lactose crystals designated as Carbo and control lactose, respectively. The Carbo lactose was shown to have a more regular shape with smoother surface as compared with the control lactose. These lactoses were fractionated by sieving to produce batches with different sizes before blending separately with salbutamol sulphate (SS, VMD 5.8 μm) in a ratio of 67.5:1 w/w using the same mixing procedure. SS dispersion and deaggregation were investigated using a 4-stage liquid impinger after aerosolisation at 28.3, 60.0 and 96.0 l/min via a Rotahaler. At all flow rates, the Carbo lactose produced significantly higher (ANOVA, $P < 0.01$) emission of SS from the Rotahaler as compared with the control lactose of a similar size. The Carbo lactose also resulted in a significantly ($P < 0.05$) higher fine particle fraction of SS than the control lactose. Moreover, drug emission from formulations containing the Carbo lactose was consistently more reproducible than those of the control lactose blends. In conclusion, the efficiency and reproducibility of drug delivery by dry powder inhalers can be improved using carrier particles of precisely defined morphological features.

Keywords: Lactose; Salbutamol sulphate; Particle engineering; Crystallisation from gels; Dry powder inhaler; Dispersion

1. Introduction

α-Lactose monohydrate has been widely employed as the carrier to overcome the intrinsic cohesiveness of micronised drug particles intended for the aerosolised delivery by dry powder inhalers (DPIs) [1]. The particle size distributions of lactose can vary from 10 to 500 μm, depending on the specific requirement for the characteristics of the final blend such as flowability. Crystallization is routinely conducted to prepare lactose particles and constant stirring is essential for lactose crystallisation from solution so as to avoid caking and the formation of other non-dispersible aggregates. Mechanical stirring is known to induce heterogeneous growth of crystals, resulting in a large variation in the particle size and morphological features of the final products being prepared [2]. It has been reported that drug delivery from DPIs is influenced by the physico-chemical characteristics of lactose particles such as surface texture [3], particle size [4,5] and particle shape [6]. For example, improving the surface smoothness of lactose carrier was shown to increase drug fine particle fraction [3]. Thus, any variation in the physical properties of the carrier might be expected to lead to variability in the resultant fine particle fraction of drug from the DPI formulation which may in turn lead to variability in clinical performances.

We have reported previously that lactose crystals of well-defined shape with smooth surface can be obtained by a novel crystallisation technique from a gel without external disturbance [7]. These crystals were also shown to have a narrower particle size distribution with better flow properties and a higher relative crystallinity than the crystals prepared from solution under constant stirring. Thus, the former may provide an ideal carrier for an efficient and reproducible delivery of drugs to the lower airways. Therefore, it was the aim of the present study to compare the deposition profiles of a model drug, salbutamol sulphate, from formulations containing lactose crystals prepared from a gel and from solution, after aerosolisation at different flow rates from a Rotahaler®.

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2. Experimental

2.1. Materials

Salbutamol sulphate (VMD 5.8 μm of GSD 1.7), Ventolin Rotahaler® and hard gelatin capsules (size 3) were supplied by Glaxo-Wellcome Research and Development Ltd, Ware, UK. α-Lactose monohydrate (Lactochem®) was obtained from Borculo Whey Ltd., Chester, UK. *p*-Hydroxybenzoic acid ethyl ester was purchased from Sigma Chemical Co., Poole, UK, whilst ammonium acetate and methanol of HPLC grade were obtained from BDH Laboratory Supplies, Poole, UK.

2.2. Methods

2.2.1. Preparation of lactose crystals

Lactose was crystallised, using a novel technique, from neutralised Carbopol 934 gels (pH 6–7) using a gel concentration of 0.6% w/v and lactose concentration of 43% w/w, without any external agitation [7].

Distilled water (400 ml) was agitated at about 500 rev./min with a 4-bladed stirrer (1 × 3 cm) which was situated 2 cm above the bottom of a 500 ml beaker. Carbopol 934 (2.4 g; B.F. Goodrich Chemical Co., Cleveland, Ohio, USA.) with an average molecular weight of approximately 3 000 000, was added into the vortex. When all the Carbopol was dispersed, the liquid was allowed to stand overnight in the dark so as to ensure maximum dissolution of the polymer. Approximately 300 g of lactose (Lactochem®, Borculo Whey Ltd., Chester, UK) was then added to the Carbopol solution, which was then heated up under constant stirring at 500 rev./min until all lactose crystals were dissolved. Sodium hydroxide solution (1 M) was then added dropwise to the solution, whilst stirring at about 800 rev./min until a clear homogeneous gel was produced with a pH of approximately 4.5. At this point, the mixer was often not sufficiently powerful to disperse the gel and hence, the mixing was continued manually with a spatula. Neutralising agent (NaOH) was added to until a pH of 7 was obtained. The gel was then sonicated in a water bath for about 15 min so as to remove any entrapped air bubbles and insoluble particles. The gel was placed in the dark until the majority of the crystals had grown to a size of 63–90 μm, monitored by optical microscopy. Then, the gel was adjusted to pH 3–3.5 with hydrochloric acid (1 M) to obtain a fluid suspension. The crystals were allowed to settle for about 10 min. After decanting the supernatant, the crystals were routinely washed sequentially with 60% ethanol twice and absolute ethanol three times. The crystals (designated Carbo lactose) were finally allowed to dry at room temperature after which, they were poured into a 125 μm test sieve (Endecotts Ltd., London, UK) placed upon a 90 μm test sieve, which in turn had been placed upon a 63 μm sieve. The particles were then sieved manually into four fractions, namely, <63 μm, 63–90 μm, 90–125 μm and >125 μm.

Crystallisation of lactose was also carried out from constantly-stirred aqueous solutions. Lactose solution (50% w/w) was allowed to crystallise under constant stirring at room temperature for 2.5 h. The stirring was carried out with a 4-bladed stirrer (1 × 3 cm) which was situated 2 cm above the bottom of a 500 ml beaker at 500 rev./min The crystals obtained were fractionated by sieving into 63–90 μm and <63 μm size ranges, which were termed, control 1 and control 2, respectively.

All lactose fractions were dried in a vacuum oven at 70 °C for 3 h before transferring to sealed vials and placed in a desiccator over silica gel until required for further investigation.

2.2.2. Characterisation of lactose crystals

The particle size and shape of lactose were measured by optical microscopy and image analysis. A small amount of lactose particles was scattered on a microscope slide using a brush, ensuring that the particles deposited separately. The slide was then mounted on an optical microscope (Labophot-2, Nikon, Japan) and the images of the particles were transferred to an IBM compatible computer through a Nikon camera. Particle images were analysed automatically using analySIS 2.0 (SIS Image Analysis GmbH, Germany). At least three hundred particles were measured for each batch of lactose. The area of the projected image of each particle was recorded and the surface-volume diameter was calculated as the mean diameter of the powder. The particle shape and surface smoothness were quantified by three parameters derived from the length (L), width (W), perimeter (P) and area (A) of the projected images of particles, namely, elongation ratio – $E(L/W)$, shape factor ($4\pi A/P^2$) and surface factor (shape factor $\times (1 + i)^2/\pi E$) [6].

Particle shape and surface textures were also qualitatively compared using scanning electron microscopy (SEM). Double-sided adhesive tape was placed on an aluminium stub and after stripping off the upper side of the adhesive, a small amount of particles was scattered on the stub and dispersed by tapping lightly on the edge of the stub with a spatula to break agglomerates. The particles were then coated with approximately 15–20 nm gold using a sputter coater (Polaron E5100, Polaron Equipment Ltd., Watford, UK) using an electrical potential of 2.0 kV, 20 mA. Several photomicrographs were produced, by scanning fields selected randomly at several magnifications, using a Philips SEM501B scanning electron microscope (Einhoven, Holland).

2.2.3. Blending lactose with salbutamol sulphate

Salbutamol sulphate was mixed separately with different batches of lactose in a ratio of 1:67.5, w/w in accordance with the ratio employed in the commercial 'Ventolin®' formulation. Thus, after drying in a vacuum oven at 40°C for 12 h, salbutamol sulphate was weighed into a 10 ml stoppered sample vial to which had been added one spatula full of lactose crystals. The vial was stoppered and placed on

a Whirlymixer for 5 s. Then, more lactose (similar to the amount of the blend) was added to the vial and the blend was mixed on a Whirlymixer for another 5 s. This process was repeated until all the lactose (1.750 g) had been incorporated into the salbutamol sulphate/lactose blend to obtain a ratio of drug to carrier of 1:67.5, w/w. The stoppered vials were then placed in a Turbula mixer (Glen Creston Ltd., Middlesex, UK) and mixed for 30 min. The samples were then stored in a vacuum desiccator over silica gel until further required.

The content homogeneity of SS in each formulation was examined by analysing the quantity of SS in 33 ± 1 mg of samples from each powder formulation; this weight of sample being equivalent to the filling weight in each capsule. Ten samples were randomly taken from different spots of the blend for measuring SS content. Both % recovery (95 ± 5%) and coefficient of variation (<5%) in SS content were employed to assess content uniformity.

Hard gelatin capsules (Size 3) were filled with 33.0 ± 1.5 mg of the powder mixture so that each capsule contained 481 ± 22 μg salbutamol sulphate, which was the unit dose contained in a Ventolin Rotacap®. The filling was performed manually.

2.2.4. HPLC analysis of salbutamol sulphate

Salbutamol sulphate was analysed by HPLC employing a mixture of methanol and 0.1% w/w aqueous ammonium acetate (45:55, pH 4.5) as a mobile phase running at a flow rate of 0.8 ml/min, *p*-hydroxybenzoic acid ethyl ester (2 μg/ml) as an internal standard and UV detection at 276 nm. The HPLC system consisted of a pump (CM 4000 Multiple Solvent Delivery System, LDC Analytical Inc., Florida, USA), a multiple wavelength UV detector (Spectro-Monitor 3100, LDC Analytical Inc., Florida, USA) and a 15 cm × 4.6 mm id column packed with 5 μm C-18 (Hypersil, Phenomenex, Cheshire, England).

2.2.5. Deposition test

Twenty millilitres of the HPLC mobile phase with internal standard was introduced to each of the upper stages of a 4-stage liquid impinger. A Whatman filter paper (<0.45 μm) was placed in stage 4 of the impinger. The throat was connected to the neck of the upper stage and wrapped with sealing film to ensure the connection was airtight. A Rotahaler (GlaxoWellcome Group Ltd, Ware, UK) was then fitted into the moulded rubber mouthpiece attached to the throat of the impinger. Finally, a capsule was mounted in the inhaler device. Once the assembly had been checked and found to be airtight and the inhaler device aligned with the horizontal axis of the throat of the impinger, the vacuum pump was switched on. The pump was operated for 5 s so that the flow rate of the air stream was established, and the dose was released. The pump was allowed to run at 60 ± 1 l/min until 4 l of air was drawn following the release of the dose and was then switched off. The capsule shells were then removed from the inhaler device and the deposition test was repeated, until four more capsules were actuated in the same manner. Each stage of the impinger was then washed separately and thoroughly using the mobile phase before the concentration of salbutamol sulphate in each of the samples was analysed, using the HPLC method as outlined above.

Similar deposition tests were carried out at flow rates of 28.3 and 96 l/min following the same operational and washing procedures. Each experiment was carried out four times. The low flow rate was chosen since it is utilised for testing aerosol using Andersen cascade impactor and it is close to 30 l/min, widely used to represent the inspiratory flow rate achievable by severe asthmatic and paediatric patients. The United States Pharmacopoeia requires dry powder inhalers to be tested at 100 ± 5 l/min, should they generate a flow rate more than 100 l/min at a pressure drop of 4 kPa across the devices [8]. Thus, a flow rate of 96 l/min was chosen to reflect a typical flow rate that can be achieved from this device by patients.

2.2.6. Data analysis

A variety of parameters was employed to characterise the deposition profiles of salbutamol sulphate in the impinger. The recovered dose (RD) was the sum of the drug collected in the inhaler device, throat piece and four stages of the impinger, whilst the emitted dose (ED) was the amount of drug released from the inhaler device. The effective cut-off diameter of the impinger changes with aerosolization flow

Table 1
The particle size and shape of different lactose batches[a]

Lactose	Diameter (μm) $n > 300$	Shape factor $n > 300$	Elongation ratio $n > 300$	Surface factors $n > 300$
Carbo <63 μm	65.6 ± 17.9	0.62 ± 0.15	1.52 ± 0.28	0.82 ± 0.16
Carbo 63–90 μm	104.1 ± 19.1	0.76 ± 0.07	1.58 ± 0.33	1.02 ± 0.08
Carbo 90–125 μm	174.6 ± 19.6	0.71 ± 0.07	2.02 ± 0.37	1.02 ± 0.09
Carbo >125 μm	211.8 ± 26.9	0.66 ± 0.06	1.83 ± 0.21	0.92 ± 0.08
Control 1 (63–90 μm)	104.7 ± 15.8	0.65 ± 0.08	1.79 ± 0.31	0.90 ± 0.09
Control 2 (<63 μm)	68.6 ± 15.8	0.65 ± 0.10	1.55 ± 0.30	0.87 ± 0.11

[a] Mean ± SD.

rate [9]. The fine particle dose (FPD) was taken as the amount of drug collected in stage 4 for aerosolization at 28.3 l/min (<4.5 μm) but the sum of stages 3 & 4 for aerosolisation at either 60 (<6.8 μm) or 96 l/min (<5.4 μm). The fine particle fraction (FPF) was calculated as the ratio of FPD to RD whilst the dispersibility is the FPD as a function of ED. The total recovery (% recovery) of the drug was assessed by the ratio of the RD to the theoretical dose, the latter being the dose of salbutamol sulphate in the capsules. Analysis of variance (ANOVA) was used for all statistical analyses.

3. Results and discussion

3.1. The morphological features of different batches of lactose

The various fractions of Carbo lactose were shown to have different values of elongation ratio, shape factor and 'surface factor' (Table 1), suggesting that they have different shape and/or surface smoothness. These differences in the morphological features of these fractions, which had

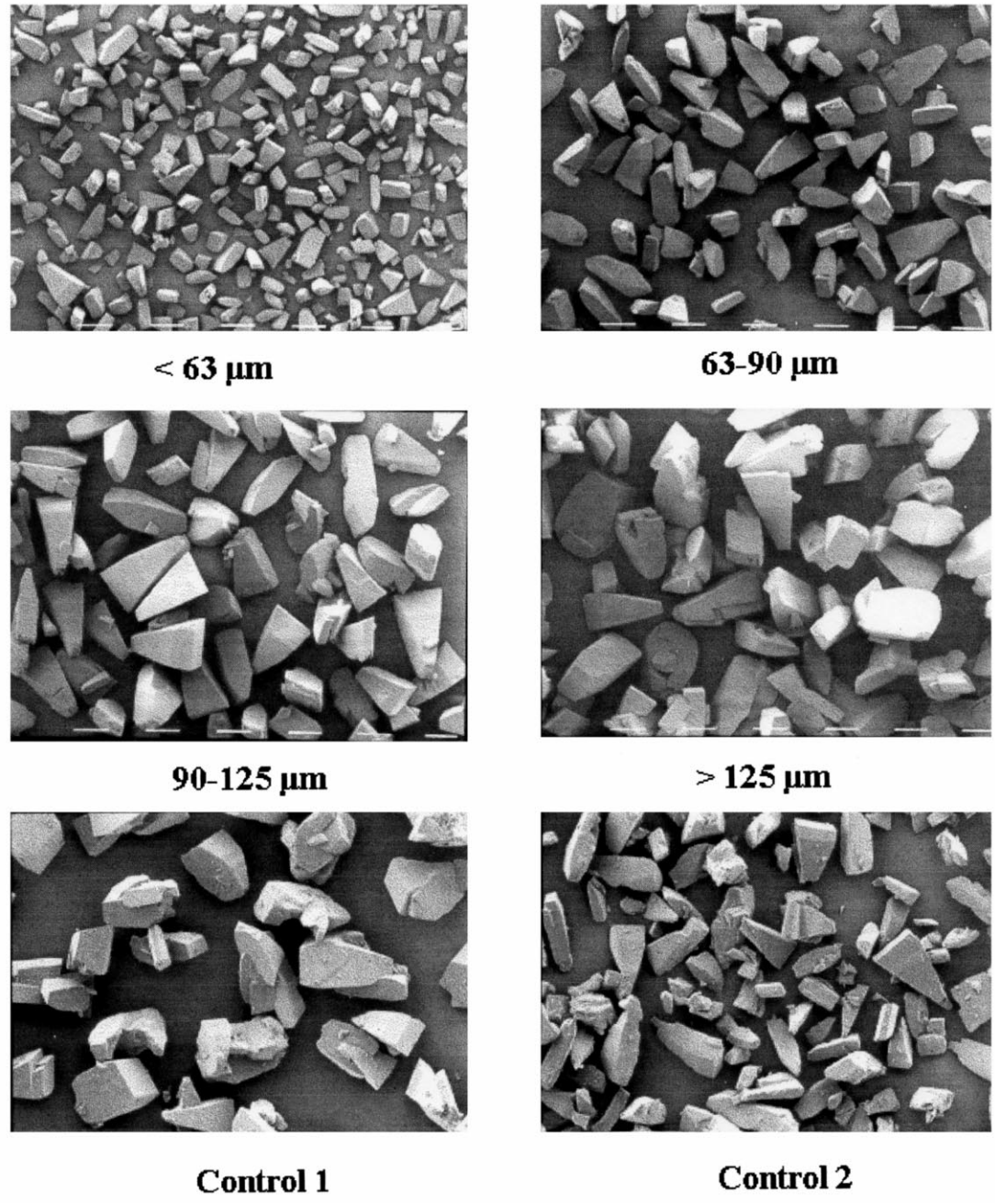

Fig. 1. SE micrographs of the different size fractions of Carbo lactose and control lactose (Scale bars denote 100 μm).

Table 2
The deposition profiles of salbutamol sulphate in a 4-stage liquid impinger after aerosolisation at 28.3 l/min via a Rotahaler®[a]

Batch no.	RD (μg)	ED (μg)	FPD (μg)	FPF (%)	Dispersibility (%)	Recovery %	Emission %
Carbo 63–90 μm	508 (6)	398 (4)	27 (1)	5.3 (0.2)	6.8 (0.3)	103.1 (1.2)	78.3 (0.3)
Control 1	414 (2)	169 (24)	11 (3)	2.6 (0.8)	6.5 (2.4)	86.1 (1.7)	40.8 (2.8)
Control 2	439 (20)	130 (22)	25 (2)	5.7 (0.8)	19.3 (4.7)	91.3 (2.1)	29.6 (5.9)

[a] Mean (SD), $n = 4$.

been prepared from the same solution, can be verified qualitatively by the visual examination of their SE micrographs (Fig. 1). Although these crystals generally had a tomahawk shape, there was a slight difference in terms of the shape and surface texture. For example, the fraction <63 μm contained a combination of prismatic, pyramidal and tomahawk shaped particles. Smaller particles tended to be prismatic, larger particles appeared to be pyramidal whilst the majority of the largest particles were tomahawk-shaped. However, the majority of the 63–90 and 90–125 μm fractions were tomahawk-shaped with similar surface textures. The fraction >125 μm were also tomahawk-shaped but some aggregates were observed in this size fraction.

The lactose controls (<63 and 63–90 μm) possessed values of the shape factor and surface factor, which were generally lower than the Carbo lactose, suggesting that the control lactose had less regular shape with more surface asperities than the Carbo lactose. This was supported by the SE micrographs of these batches of lactose (Fig. 1), which showed that the Carbo lactose was more uniformly shaped with smoother surface in comparison to the controls.

3.2. Deposition at 28.3 l/min

After actuation at 28.3 l/min via a Rotahaler (Table 2), a large portion of drug particles were not emitted from the inhaler for the control formulations, indicating that a flow rate of 28.3 l/min was not able to deliver efficiently the drug-lactose blends from the inhaler. Drug emission was shown to increase with the size of lactose particles since control 1 lactose had a higher mean diameter (104.7 μm) than control 2 lactose (68.6 μm) (Table 1). More powders were found to adhere to the inner walls of the inhaler device after actuating the blends composed of finer lactose than those containing coarser lactose, leading to a smaller amount of drug released from the inhaler. In contrast, the blends containing Carbo 63–90 μm lactose produced drug emission of 78.3% total dose, which was significantly higher ($P < 0.01$) than those of either control. Such a high drug emission from formulations containing Carbo 63–90 μm lactose at a flow rate as low as 28.3 l/min may have been largely due to the better flow properties of this lactose, as a result of the uniform shape with smooth surface [7].

The blends containing Carbo 63–90 μm lactose and control 2 lactose produce similar FPF and FPD, which were more than twice the respective values of the blends containing control 1 lactose. Control 2 lactose was the finer fraction (<63 μm) of the same batch of lactose from which the control 1 (63–90 μm) was also fractionated. The higher FPF and FPD, despite a lower drug emission, for formulations containing the former lactose fraction, was indicative of a more efficient dispersion and deaggregation of the drug from control 2 as compared with control 1. Thus, the blends containing control 2 lactose exhibited a drug dispersibility, which was over 3-fold higher than from blends containing control 1 lactose. Carbo 63–90 μm lactose produced a FPF and FPD of salbutamol sulphate, which was similar to the blends containing control 2 lactose but much higher than the blends containing control 1 lactose. The relatively efficient delivery of salbutamol sulphate from blends containing the Carbo 63–90 μm lactose may be largely attributable to a high drug emission from this blend since it produced a similar drug dispersibility to the blend containing control 1 lactose (Table 2). The blends containing Carbo 63–90 μm and control 2 lactose resulted in a higher fraction of salbutamol sulphate being aerosolised having an aerodynamic diameter (d_a) of 4.5–18.9 μm than blends containing Control 1 lactose (Fig. 2). The use of Carbo 63–90 μm lactose appeared to produce more reproducible % emission of salbutamol sulphate than either of the control lactoses (Table 2).

3.3. Deposition at 60.0 l/min

As shown in Table 3, all the blends had a similar drug emission from the inhaler with an average of 78.9%, indi-

Table 3
The deposition profiles of salbutamol sulphate in a 4-stage liquid impinger after aerosolisation at 60.0 l/min via a Rotahaler®[a]

Batch no.	RD (μg)	ED (μg)	FPD (μg)	FPF (%)	Dispersibility (%)	Recovery %	Emission %
Carbo 63–90 μm	514 (22)	405 (21)	111 (11)	21.5 (1.2)	27.3 (1.4)	104.3 (4.4)	78.7 (0.8)
Control 1	442 (18)	362 (10)	76 (6)	14.7 (1.3)	18.1 (2.6)	94.5 (2.9)	81.2 (3.9)
Control 2	448 (24)	348 (20)	90 (3)	17.5 (1.3)	23.3 (1.2)	94.0 (2.9)	74.9 (3.5)

[a] Mean (SD), $n = 4$.

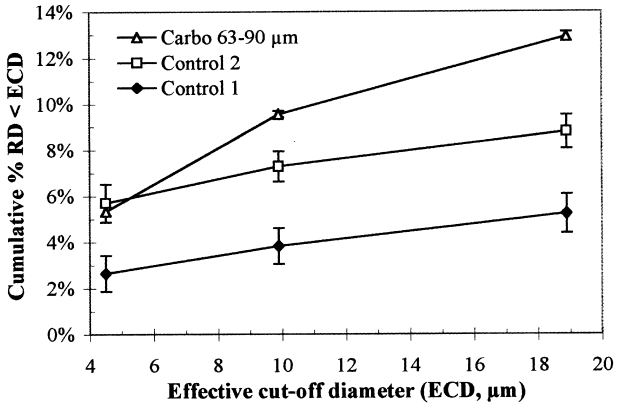

Fig. 2. The particle size distribution of salbutamol sulphate after aerosolisation from different batches of lactose at 28.3 l/min via a Rotahaler Rotahaler® (Error bars denote standard deviation, $n = 4$).

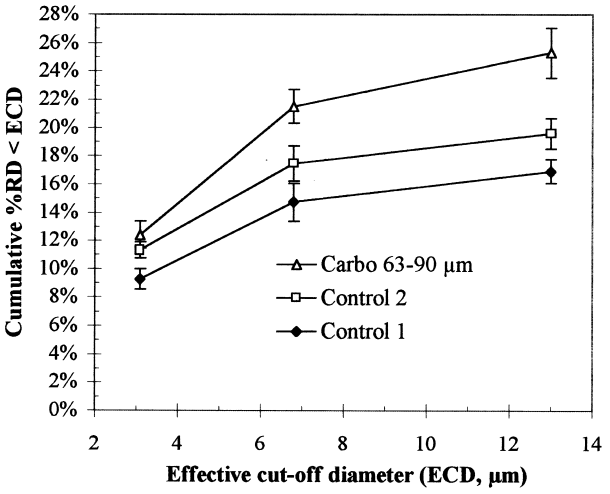

Fig. 3. The particle size distribution of salbutamol sulphate after aerosolisation using different batches of lactose at 60 l/min via a Rotahaler Rotahaler® (Error bars denote standard deviation, $n = 4$).

cating that a flow rate of 60 l/min was able to dislodge the aerosol blends from the inhaler devices. Increasing the flow rate of an inhaled air stream has been reported previously to increase the emission of drug from DPIs [10]. The blends containing the smaller lactose particles (control 2), as when aerosolised at 28.3 l/min, produced a slightly lower drug emission than those containing the corresponding larger lactose particles (control 1). However, unlike aerosolisation at 28.3 l/min, the dependence of drug emission on carrier particle size became statistically insignificant ($P > 0.05$) at an aerosolisation flow rate of 60 l/min.

Similar to the deposition at 28.3 l/min, lactose crystals of smaller size fraction produced a higher FPD or FPF of salbutamol sulphate with the fractions of fine drug from control 2 lactose being significantly higher ($P < 0.05$) than that of drug from control 1 lactose. However, formulations containing Carbo 63–90 μm lactose produced FPD, FPF and dispersibility of salbutamol sulphate, which were significantly ($P < 0.05$) higher than those of the formulations containing control 2 lactose although the former had larger particle size than the latter. The potentially more respirable particles of the drug from formulations containing Carbo 63–90 μm lactose in comparison to the controls may have largely been due to the smoother surface of this batch of lactose. This can be further seen by comparing the particle size distribution of aerosolised salbutamol sulphate from formulations containing the three batches of lactose as carrier (Fig. 3). Formulations containing Carbo 63–90 μm lactose consistently led to more drug particles being aerosolised, with the fractions of salbutamol sulphate with d_a between 3.2 and 6.8 μm being higher than those containing either of the control lactose fractions.

3.4. Deposition at 96.0 l/min

Over 77% drug was found to be emitted from the inhaler device after aerosolisation at 96.0 l/min (Table 4). No significant ($P > 0.05$) difference was observed in drug emission from the three formulations, nor was there any difference between the emission of drug when the device was operated at either 60 or 96 l/min. Again, the smaller sized, control 2 lactose produced FPF and dispersibility of salbutamol sulphate, which were significantly higher ($P < 0.05$) than the corresponding values which resulted from the use of the larger-sized, control 1 lactose. In contrast to the lower flow rates, no significant difference was observed in the deposition profiles of salbutamol sulphate after aerosolisation at 96 l/min from formulations containing Carbo 63–90 μm lactose and control 2 lactose. However, use of the Carbo 63–90 μm lactose in the formulation produced a slightly higher percentage of aerosolised salbutamol sulphate than the control 2 lactose, which in turn resulted in a higher fraction of the aerosolised drug (Fig. 4). A flow rate of 96 l/min was shown to produce reproducible

Table 4
The deposition profiles of salbutamol sulphate in a 4-stage liquid impinger after aerosolisation at 96.0 l/min via a Rotahaler[a]

Batch no.	RD (μg)	ED (μg)	FPD (μg)	FPF (%)	Dispersibility (%)	Recovery %	Emission %
Carbo 63–90 μm	496 (8)	399 (4)	129 (1)	26.1 (0.2)	32.4 (0.0)	100.6 (1.7)	80.5 (0.5)
Control 1	444 (5)	337 (9)	104 (9)	19.2 (0.6)	24.6 (1.8)	95.7 (0.6)	78.3 (3.3)
Control 2	455 (17)	353 (14)	118 (9)	24.3 (0.9)	31.5 (1.1)	98.6 (0.4)	77.1 (0.6)

[a] Mean (SD), $n = 4$.

Table 5
Deposition of salbutamol sulphate from different size fractions of Carbo lactose in a 4-stage liquid impinger after aerosolisation at 60 l/min[a]

Size fraction	RD μg	ED μg	FPD μg	FPF %	Dispersibility %	Emission %
< 63 μm	515 (8)	371 (39)	149 (14)	28.9 (2.5)	40.2 (2.9)	72.0 (1.8)
63–90 μm	514 (22)	405 (21)	111 (11)	21.5 (1.2)	27.3 (1.4)	78.7 (0.8)
90–125 μm	440 (2)	382 (4)	51 (5)	11.5 (1.1)	13.3 (1.1)	86.8 (1.3)
> 125 μm	470 (12)	430 (11)	38 (5)	8.0 (1.2)	8.9 (1.2)	91.4 (0.3)

[a] Mean (SD), $n = 4$

deposition profiles of salbutamol sulphate from all formulations, since. The CV in FPF and dispersibility from the three formulations was less than 5%, although the formulation containing Carbo 63–90 μm still exhibited the smallest variation in the drug deposition.

3.5. Drug deposition from different size fractions of Carbo lactose

The deposition profiles of salbutamol sulphate from Carbo lactose of different size fractions after aerosolisation at a flow rate of 60 l/min are shown in Table 5. The % emission of the drug increased from 72.0% for formulations containing <63 μm lactose to 91.4% for those using >125 μm lactose as the carrier. Thus, increasing the particle size of lactose particles recrystallised from Carbopol gels increased the entrainment of the particles into the air stream and this was in agreement with some previous reports using lactose particles crystallised under constant stirring [11,12].

Similar to the previous results, both the FPD and FPF of salbutamol sulphate decreased with increasing particle size of lactose. A more pronounced decrease was observed for the dispersibility with an increase in the particle size of the carrier. For example, drug dispersibility was found to decrease from 40.2% for the <63 μm lactose to 8.9% for the >125 μm lactose. All these results show that increasing the particle size of the carrier increased the emission of drug from the inhaler devices. However increasing the carrier particle size decreased drug detachment from the carrier particles so greatly that the overall drug FPD or FPF was reduced as the particle size of the carrier increased.

The fraction of aerosolised salbutamol sulphate with d_a of 3.1–13 μm was shown to increase consistently with a reduction in the particle size of lactose (Fig. 5). Thus, similar to the carrier obtained under constant stirring conditions, the smaller sized fractions of lactose crystallised from Carbopol gels, when incorporated within powder formulations, resulted in more salbutamol sulphate being aerosolised, and producing a highly potentially respirable fraction of the drug. However, the FPF and FPD obtained from the current study were relative low, due to Rotahaler® being an inefficient device, which has been shown to deliver less than 10% total drug to the lower airways [13].

In conclusion, the use of lactose crystals that have well-defined shape with smooth surface was shown to improve the dispersion and deaggregation of salbutamol sulphate after aerosolisation at various flow rates. Lactose crystals from Carbopol gels generally resulted in a more reproducible delivery of salbutamol sulphate as compared with control lactose. Similar to the crystals prepared under constant stirring, reducing the size of lactose crystals from Carbopol gels increased the fine particle dose and fine particle fraction of salbutamol sulphate. Therefore, engineered

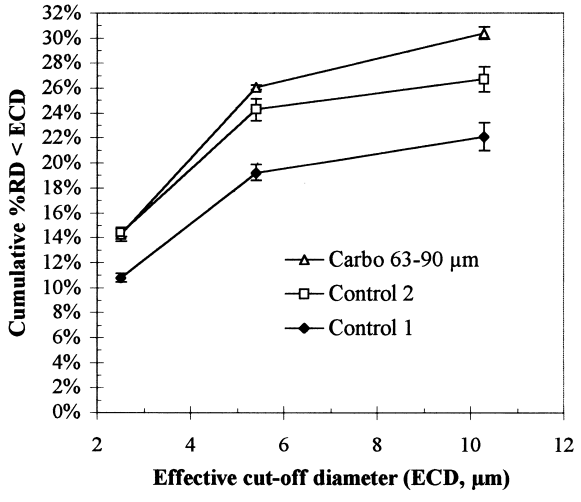

Fig. 4. The particle size distribution of salbutamol sulphate after aerosolisation using different batches of lactose at 96 l/min via a Rotahaler® (Error bars denote standard deviation, $n = 4$).

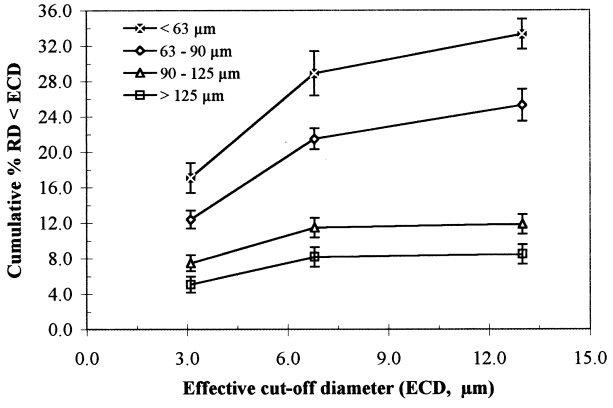

Fig. 5. The particle size distribution of aerosolised salbutamol sulphate from fractionated Carbo lactose after aerosolisation at 60 l/min (Error bars denote standard deviation, $n = 4$).

crystal growth under controlled conditions can improve the potential respirable fraction of drug from dry powder inhalers. Such crystals may prove to be particularly beneficial for reservoir-type inhalers, which usually require a good flow property of the powder to ensure a uniformity delivery of the drug.

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References

[1] M.P. Timsina, G.P. Martin, C. Marriott, D. Ganderton, M. Yianneskis, Drug delivery to the respiratory tract using dry powder inhalers, Int. J. Pharm. 101 (1994) 1–13.
[2] H.K. Henisch, Crystals in Gels and Liesegang Rings, Cambridge University Press, Cambridge, 1988.
[3] D. Ganderton, The generation of respirable cloud from course powder aggregates, J. Biopharm Sci. 3 (1992) 101–105.
[4] D.L. French, D.A. Edwards, R.W. Niven, The influence of formulation on emission, deaggregation and deposition of dry powders for inhalation, J. Aerosol Sci. 27 (1996) 769–783.
[5] H. Steckel, B.W. Müller, In vitro evaluation of dry powder inhalers II. Influence of carrier particle size and concentration on in vitro deposition, Int. J. Pharm. 154 (1997) 31–37.
[6] X.M. Zeng, G.P. Martin, C. Marriott, J. Pritchard, The influence of carrier morphology on drug delivery by dry powder inhalers, Int. J. Pharm. 200 (2000) 93–106.
[7] X.M. Zeng, G.P. Martin, C. Marriott, J. Pritchard, Crystallisation of lactose from Carbopol gels, Pharm. Res. 17 (2000) 879–886.
[8] The United States Pharmacopoeial Convention Inc., United State Pharmacopoeia, Rockville, 601 (1999),pp. 4933-4949.
[9] S. Hugosson, J. Lindberg, T. Loof, B. Olsson, Proposals for standardised testing of powder preparations for inhalation, Pharm. Forum. 19 (1993) 5458–5466.
[10] H. Hindle, R.N. Jashnani, P.R. Byron, Dose emissions from marketed inhalers: influence of flow, volume and environment, Respir. Drug Deliv. IV (1994) 137–142.
[11] J.H. Bell, P.S. Hartley, J.S.G. Cox, A new powder inhalation device, J. Pharm. Sci. 60 (1971) 1559–1564.
[12] J.N. Staniforth, Improvement in dry powder inhaler performance: surface passivation effects, Aerosol Sci. Technol. 22 (1995) 346–353.
[13] M. Vidgren, A. Karkkainen, P. Karjalainen, P. Paronen, J. Nuutinen, Effect of powder inhaler design on drug deposition in the respiratory tract, Int. J. Pharm. 42 (1988) 211–216.