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The influence of carrier morphology on drug delivery by dry powder inhalers

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Abstract

α-Lactose monohydrate was prepared to have different morphological features but with similar particle size. The crystal shape and surface smoothness of lactose were quantified by a number of shape descriptors and these were supported qualitatively by the visual examination of scanning electron (SE) micrographs of the crystals. All batches of lactose were subjected to a similar history of processing before blending separately with micronised salbutamol sulphate (SS) in a ratio of 67.5:1, w/w, using similar procedures. In vitro deposition of SS from these formulations was investigated after aerosolisation of the formulations at 60 l min^{-1} via the Rotahaler® and the Cyclohaler® into a twin stage liquid impinger. The formulations prepared using the different batches of lactose produced different deposition profiles of SS. The fine particle (< 6.4 μm) fraction (FPF) of aerosolised SS varied from 12.6 ± 2.4 to $25.6 \pm 1.5\%$ after aerosolisation from the Cyclohaler® whilst it changed from 15.0 ± 2.2 to $24.4 \pm 0.8\%$ after aerosolisation from the Rotahaler®. The fine particle dose (FPD) and dispersibility of SS followed a similar trend to the change in the FPF of the drug. No significant difference (ANOVA $P > 0.05$) was observed for the deposition profiles of SS after aerosolisation from the Rotahaler® and the Cyclohaler®. The FPF and dispersibility of SS increased with either the surface smoothness ($P < 0.01$) or elongation ratio ($P < 0.01$) of lactose crystals. The t-ratio values of FPF and dispersibility of SS generated by changes in the surface smoothness were similar to those resulting from changes in elongation ratio. Increasing either the surface smoothness or the elongation ratio of lactose crystals will increase the potentially respirable fraction of SS from dry powder formulations for inhalation.

Keywords: Dry powder inhalers; Lactose; Salbutamol sulphate; Surface smoothness; Crystal habit; Dispersion; Deposition

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1. Introduction

Dry powder formulations for inhalation often consist of micronised drug (1–5 μm) and inert coarse carrier particles (50–200 μm). The carrier particles are used to aid the flow and dispersion of the highly cohesive drug particles. The dispersion and subsequent deposition of drug particles in the respiratory tract from dry powder inhalers (DPIs) are governed by the patients' inhalation flow rate (Hindle et al., 1994), the design of the inhaler device (Dalby et al., 1996) and the physico-chemical properties of both the drug and carrier particles (Timsina et al., 1994). In order to provide the patient with a DPI that can deliver accurately the optimal amount of drug to the targeted sites in the airways, it is crucial that the inhaler device should be carefully constructed in combination with the optimised formulation of the powdered drug.

It is a truism that the factors involved with the formulation of the dry powder are equally, if not more, important than the design of the inhaler device, in the optimisation of drug delivery to the lung. Micronised drug particles are usually present in low concentrations in the powder formulation, with a drug to carrier ratio of 1:67.5 being typical. A large portion of drug particles may therefore be expected to adhere to potential binding sites of the carrier particles or be entrapped in any surface crevices existing on the carrier surfaces. The resultant strong interaction of drug with carrier particles impedes drug detachment from the carrier particles and dispersion in the inhalation airstream and consequently, reduces the overall deposition of drug particles in the respiratory tract. Insufficient detachment of drug from the carrier as a result of strong interparticulate forces may be one of the major causes of low delivery efficiency encountered with most DPIs.

Particle-particle interaction, a surface phenomenon, is mainly dependent upon the physicochemical properties of the interacting particles such as the surface texture (Otsuka et al., 1988), particle size (Zimon, 1982), shape (Mullins et al., 1992), electrostatic properties (Bailey, 1984), hygroscopicity (Karra and Fuerstenau, 1977) and contact area (Zimon, 1982). With respect to drug delivery by DPIs, particulate interactions within the formulation govern both the drug dissociation from carrier particles and the deaggregation of any drug agglomerates into primary particles with the capacity to penetrate deep into the lung. Therefore, any factor that affects drug-carrier interaction will have an impact on the delivery and deposition of the drug. For example, increasing the surface smoothness of lactose carrier particles was shown to improve the potentially respirable fraction of salbutamol sulphate from the Rotahaler® (Ganderton, 1992) and this was attributed to lowered adhesion forces between the drug and carrier particles with a smooth surface. The effect of particle size of the carrier on drug deposition is also well documented (Ganderton and Kassem, 1992; French et al., 1996; Steckel and Müller, 1997). Fine particles of ternary components, such as magnesium stearate and L-leucine, were found to improve drug delivery from DPIs by reducing interparticulate forces between the drug and carrier particles (Staniforth, 1996). More recently, the addition of fine particles of carrier to dry powder formulation was also shown to improve the dispersion and deposition of drug particles by a similar mechanism (Lucas et al., 1998; Zeng et al., 1998). Surface modification of pranlukast hydrate powder with ultrafine hydroxypropylmethylcellulose phthalate nanospheres was reported to reduce the cohesive forces among the drug particles and hence, improve the drug dispersion in an airstream (Kawashima et al., 1998). Although α-lactose monohydate may take a variety of shapes, depending upon crystallisation conditions, no reports have yet dealt with the relationship between drug dispersion and particle shape of the carrier. Therefore, it was the aim of the present study to investigate the effects of carrier morphological features on the dispersion and deaggregation of the drug. Lactose crystals with different shapes but a similar surface-volume mean diameter were blended with a model drug, salbutamol sulphate, under similar mixing conditions. The deposition profiles of the drug from these formulations were studied after aerosolisation via two model inhaler devices, i.e. the Rotahaler® and the Cyclohaler®, and then correlated with a number of shape descriptors of the carrier particles.

2. Materials and methods

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. The Cyclohaler® was obtained from Pharbita BV, The Netherlands. α-Lactose monohydrate (Lactochem®) was obtained from Borculo Whey Ltd., Chester, UK. p-Hydroxybenzoic acid ethyl ester was purchased from Sigma, Poole, UK, whilst ammonium acetate and methanol of HPLC grade were obtained from BDH Laboratory Supplies, Poole, UK.

2.1. Preparation and characterisation of lactose crystals

A predetermined amount of lactose was dissolved in 100 ml distilled water at approximately 80°C. After filtration through a Whatman filter paper (< 0.45 μm), the solution was transferred to a 150 ml glass beaker which had been placed in either an ice bath (0°C) or a water bath at 40°C. The solution was stirred at 500 rpm (Heidolph Overhead Stirrer, Fisons Laboratory Instruments, UK) with a 4 blade (1×3 cm) stirrer which was situated 2 cm above the bottom of the container. After the crystallization was allowed to continue for a predetermined period of time, the crystals were filtered and washed sequentially with 60% (v/v) and absolute ethanol. The crystals were allowed to dry at room temperature overnight before drying in a vacuum oven at 70°C for 3 h. Then, the lactose crystals were poured into a 90 μm sieve which had been placed upon a 63 μm sieve. The particles were sieved manually for 30 min and the particles retained on the 63 μm sieve, which had a size between 63–90 μm, were transferred separately to sealed vials and placed into a desiccator over silica gel until required for further investigation. Seven batches of lactose were prepared under conditions listed in Table 1. The Lactochem® lactose was also sieved under similar conditions to obtain a size fraction of 63–90 μm.

A number of shape descriptors based on image analysis optical microscopy and surface area measurement were employed to quantify the shape of lactose crystals. In the image analysis, a small amount of lactose particles was scattered on a microscope slide using a small brush ensuring that the particles deposited separately. The slide was then mounted on an optical microscope (Labophot-2, Nikon, Japan) and the images of

Table 1
The crystallization conditions and some shape descriptors of the 63–90 μm lactose particles obtained (mean ± S.D., $n > 150$)

Batch No.	Crystallization			d_{sv} (μm)[a]	Rugosity	Shape factor	Elongation ratio	Surface factor
	C_L[b]	T_C[c]	t_c[d]					
Lact[e]				89	1.89	0.74 ± 0.09	1.68 ± 0.36	1.00 ± 0.12
1	43	40	5	95	2.26	0.69 ± 0.12	1.64 ± 0.33	0.96 ± 0.11
2	33	0	12	94	2.70	0.60 ± 0.14	1.28 ± 0.22	0.77 ± 0.18
3	33	0	24	92	2.58	0.68 ± 0.10	1.29 ± 0.19	0.87 ± 0.13
4	43	0	12	88	2.21	0.72 ± 0.09	1.30 ± 0.23	0.93 ± 0.11
5	50	40	3	97	1.50	0.78 ± 0.06	1.63 ± 0.29	1.05 ± 0.08
6	60	40	0.3	92	2.31	0.68 ± 0.11	2.08 ± 0.61	0.99 ± 0.15
7	60	40	1.5	97	2.54	0.73 ± 0.08	1.71 ± 0.44	1.00 ± 0.11

[a] d_{sv} is the surface-volume mean diameter.
[b] C_L is the concentration of lactose (%w/w).
[c] T_C is the temperature of crystallisation (°C).
[d] t_c is the time of crystallisation (h).
[e] Lact is Lactochem® lactose.

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). The size of each individual particle was calculated as the diameter of a spherical particle that produces a projected image of the same area to the measured particle. At least 300 particles were measured for each batch of lactose and the surface-volume mean diameter (d_{sv}) recorded. The morphology of lactose crystals was quantified by two descriptors, derived from the length (L), width (W), perimeter (P) and area (A) of the projected image of a particle, namely elongation ratio (L/W) and shape factor ($4\pi \times A/P^2$). The shape factor is a two-dimensional shape descriptor used in many image analysis software programs to quantify particle shape (User's Guide to analySIS 2.0, SIS Image Analysis GmbH, Germany). A spherical particle with smooth surface will have a shape factor of 1 whilst non-spherical particles or spherical particles with a rough surface will have a shape factor value between 0 and 1. The more irregular the shape and/or the rougher the surface, the smaller the shape factor.

The specific surface area (SSA) of the powder was measured by air permeation using Fisher subsieve sizing apparatus. This value was expressed as a fraction of the SSA calculated from the mean particle size measured by microscopic method to obtain the rugosity value (Carstensen, 1980).

The particle shape of the various batches of lactose was also characterized 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. Photomicrographs were produced by scanning fields, selected randomly, using a Philips SEM501B scanning electron microscope (Einhoven, Holland).

2.2. 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®' formulations. Thus, 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. More lactose particles (similar to the amount of the blend) were 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. Finally, the samples were stored in a vacuum desiccator over silica gel until required.

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 suphate, which was similar to the unit dose contained in a Ventolin Rotacap®. The filling was performed manually.

2.3. 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^{-1}. p-Hydroxybenzoic acid ethyl ester (2 μg ml^{-1}) as used as an internal standard and the eluant was monitored at a wavelength of 276 nm. The HPLC system consisted of a pump (CM 4000 Multiple Solvent Delivery System, LDC Analytical Inc., FL), a multiple wavelength UV detector (SpectroMonitor 3100, LDC Analytical Inc.) and a 15 cm × 4.6 mm id column packed with 5 μm C-18 (Hypersil, Phenomenex, Cheshire, UK).

2.4. Measurement of the homogeneity of the mixtures

Ten samples were taken randomly from each blend. The sample (approximately 33 mg) was

weighed accurately and the amount of salbutamol sulphate was measured by HPLC. The coefficient of variation in the drug content was employed to assess the homogeneity of the mixtures.

2.5. Deposition methods

HPLC mobile phase containing the internal standard (7 ml) was introduced into the upper stage and 30 ml of the same solvent into the lower stage of a twin stage liquid impinger (TSI). The capsule to be tested was placed in a Rotahaler® (GlaxoWellcome, Ware, UK), which had been fitted into a moulded rubber mouthpiece attached to the throat piece of the impinger. The TSI was operated under standard conditions (British Pharmacopoeia Commission, 1999). Each blend was tested at least in triplicate. The same test was also carried out for all blends after aerosolisation from the Cyclohaler® (Pharbita BV, The Netherlands).

A variety of parameters were employed to characterise the deposition profiles of salbutamol sulphate in the TSI. The recovered dose (RD) was the sum of the drug collected in the inhaler device, upper and lower stages of the impinger. The emitted dose (ED) was the amount of drug released from the inhaler device, i.e. the sum of drug collected at upper and lower stages of the impinger. Fine particle dose (FPD) was defined as the amount of drug deposited in the lower stage of the impinger, which had a diameter less than the cut-off diameter of the upper stage of a twin-impinger (6.4 μm at an air flow rate of 60 l min^{-1}). The fine particle fraction (FPF) and dispersibility were calculated as the ratio of FPD to RD and ED, respectively. 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. For example, the theoretical dose of salbutamol sulphate in one capsule was 481 ± 22 μg, which was equivalent to the filling weight (33.0 ± 1.5 mg) of lactose and salbutamol sulphate blends.

3. Results

3.1. Characterization of the morphology of lactose crystals

There were no two equivalent batches of lactose in terms of these shape descriptors (Table 1) and this was supported by the visual comparison of their SE micrographs (Fig. 1), which showed that different batches of lactose had different surface textures and shapes.

Of all three shape descriptors employed, the elongation ratio is the factor solely determined by the macroscopic shape of the particles whilst rugosity and shape factor are the combination of the macroscopic shape and surface textures of the particles. Neither rugosity nor shape factor can distinguish the surface smoothness of two particles if they differ in macroscopic shape substantially. For example, lactose crystals of different values of elongation ratio will have different values of shape factor or rugosity although these particles may have similar surface smoothness. Therefore, in order to compare the surface smoothness of particles having different elongation ratio values more accurately, a new shape descriptor has to be introduced, which takes into consideration both the shape factor and elongation ratio. From visual examination of the SE micrographs (Fig. 1), all the crystals prepared in this study had a shape closer to an elongated cuboid than to a sphere. It would be reasonable to assume that a shape descriptor calculated from the projected image of an elongated cuboid reflects the shape of lactose crystals more closely than the shape factor based upon the projected image of a sphere. The projected images of an elongated cuboid and a sphere are a rectangle and a circle, respectively. By combining the elongation ratio of the rectangle and the shape factor, it is possible to create a new factor that reflects the surface smoothness of the rectangular image of a cuboidal particle only. In order to calculate the new shape factor, the following equations were generated, assuming a rectangular image with length (L) and width (W) that has the same area as that of a circular image with a diameter d.

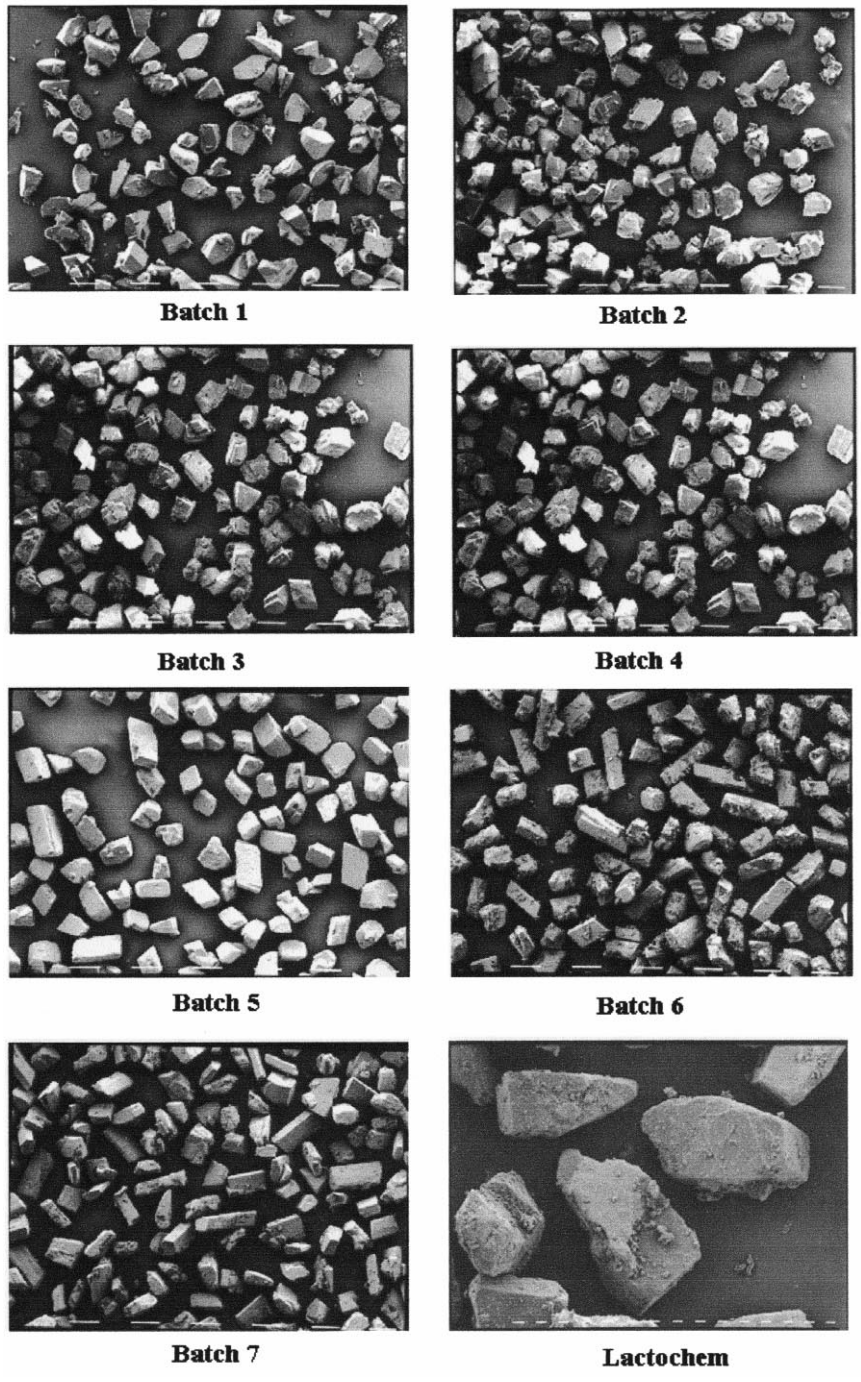

Fig. 1. Scanning electron micrographs of different batches of lactose (scale represents 100 μm).

Since the area of a rectangle $(A_{rec}) = W \times L$
If Elongation ratio $(E) = L/W$, then

$$A_{rec} = L^2/E;$$

Perimeter of the rectangle (P_{rec})

$$\begin{aligned} &= 2(W + L) \\ &= 2(L + L/E) \\ &= 2L(1 + E)/E \end{aligned} \quad (1)$$

Since the area of a circle $(A_{cir}) = \pi(d/2)^2$
if $A_{cir} = A_{rec}$, then

$$L^2/E = \pi \times (d/2)^2 \quad \text{or} \quad d = \frac{2L}{\sqrt{\pi E}}$$

Perimeter of a circle (P_{cir})

$$P_{cir} = \pi d = 2L\sqrt{\frac{\pi}{E}} \quad (2)$$

By dividing Eq. (2) by Eq. (1), the following equation is obtained:

$$P_{cir} = \frac{\sqrt{\pi E}}{1 + E} P_{rec} \quad (3)$$

Therefore, the shape factor of a rectangle (S_{rec}) can be calculated as:

$$\begin{aligned} S_{rec} &= \frac{4\pi \ \text{area}}{P_{rec}^2} = \frac{4\pi \ \text{area}}{P_{cir}^2} \times \frac{(1 + E)^2}{\pi E} \\ &= S_{cir} \times \frac{(1 + E)^2}{\pi E} \end{aligned} \quad (4)$$

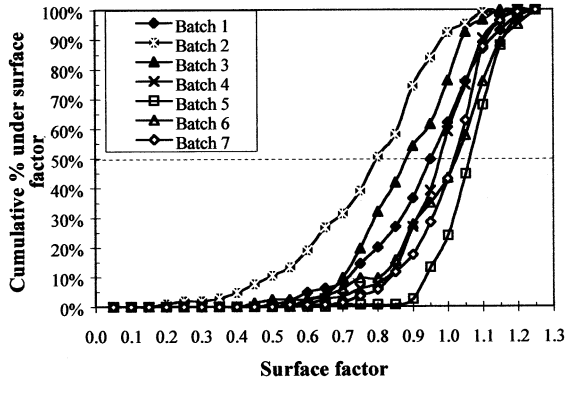

Fig. 2. The distribution of 'surface factor' values of different batches of lactose.

where S_{cir} is the shape factor calculated according to a circle and this has been the shape factor derived from the image analysis. S_{rec}, as defined above, is a factor assuming a shape of rectangle with a known elongation ratio. It should theoretically reflect the surface smoothness of cuboidal particles and therefore, it is termed 'surface factor'. If the shape factor (S_{cir}) and elongation ratio (E) of a cuboidal particle is known, then the 'surface factor' of that particle can be calculated according to Eq. (4). The value of the 'surface factor' should theoretically be between 0 and 1 because in Eq. (4), the numerator (4π area) will never exceed the denominator (P_{rec}^2). A cuboidal particle with perfectly smooth surface should have a value for the 'surface factor' of 1. The rougher the surface, the smaller the 'surface factor' will be.

The calculated values of the 'surface factor' of all batches of lactose crystals are shown in Table 1 and Fig. 2. Different batches of lactose produced significantly (ANOVA $P < 0.001$) different values of the 'surface factor' although each batch of lactose had a range of the 'surface factor' values. Batch 5 lactose showed the highest value of 'surface factor' whilst batch 2 had the lowest value of the factor (Fig. 2). The 'surface factor' values would appear qualitatively to provide a better factor to characterise the surface smoothness of lactose crystals in place of either the shape factor or rugosity. For example, low values of the shape factor (e.g. a value of 0.68 for batch 6) were indicative of either an elongated shape or rough surface or the combination of the two. According to the SE micrograph (Fig. 1), most of the crystals of this batch of lactose were elongated with a smooth surface. Such an observation was in agreement with a mean value of 'surface factor' of 0.99. Furthermore, batches 2 and 3 had the lowest values of 'surface factor' (0.77 ± 0.18 and 0.87 ± 0.13, respectively) of all the batches of lactose crystals, indicating both batches of lactose had the roughest surface. This was confirmed by the SE micrographs obtained (Fig. 1). However, it has to be acknowledged that the use of a single factor, derived from a two-dimensional measurement, to reflect a complex three-dimensional property, is a simplistic approach. Like other shape descriptors such as the elongation ratio, the surface factor value of an individual particle is a

Table 2
Deposition of salbutamol sulphate from different batches of lactose in a twin-impinger after aerosolisation at 60 l min^{-1} via a Cyclohaler® (mean (S.D.), $n = 4$)

Batch No.	RD (μg)[a]	ED (μg)[b]	FPD (μg)[c]	FPF (%)[d]	Dispersibility	Recovery (%)	Emission (%)
Lact[e]	460 (20)	320 (37)	101 (12)	21.8 (1.7)	31.6 (3.5)	95.7 (4.2)	69.3 (6.0)
1	398 (28)	257 (34)	69 (18)	17.2 (3.3)	26.6 (3.6)	82.7 (5.9)	64.6 (4.0)
2	432 (18)	276 (15)	54 (10)	12.6 (2.4)	19.8 (3.9)	89.7 (3.8)	63.8 (0.9)
3	425 (24)	294 (10)	64 (2)	15.1 (0.8)	21.8 (0.7)	88.3 (5.0)	69.1 (1.7
4	454 (20)	319 (14)	91 (8)	20.0 (1.9)	28.5 (1.9)	94.4 (4.1)	70.2 (1.9)
5	391 (48)	217 (29)	101 (18)	25.6 (1.5)	46.2 (3.8)	81.2 (10.0)	55.6 (2.5)
6	508 (13)	359 (5)	113 (5)	22.3 (1.6)	31.5 (1.9)	105.5 (2.7)	70.8 (0.8)
7	450 (35)	344 (40)	108 (7)	21.8 (2.5)	31.9 (5.4)	103.9 (7.3)	68.7 (3.7)

[a] RD is the recovered dose of drug.
[b] ED is the emitted dose of drug.
[c] FPD is the fine particle dose of drug.
[d] FPF is the fine particle fraction of drug.
[e] Lact is Lactochem® lactose.

function of the orientation of the particle. Although such an effect of particle orientation on the mean value might be averaged out if a large number of the particles are measured, some individual results may be either over-estimated or under-estimated, depending on the orientation of the particles. This may account for the observation that some particles showed a surface factor value of > 1. Further, the projected images of some particles take a shape between a rectangle and a triangle and hence, the value of surface factor, derived from a rectangular shape, of these particles would be slightly over 1 if they have perfectly smooth surface.

3.2. Uniformity of salbutamol sulphate content in the formulations

All mixtures were found to be homogenous with a coefficient of variation in salbutamol sulphate content of $< 2.2\%$ ($n = 10$).

3.3. Deposition from the Cyclohaler®

The deposition data in Table 2 were calculated according to the content of one capsule. The recovered dose (RD) of salbutamol sulphate varied from 391 μg for the blend containing batch 5 lactose to 508 μg for the blend composed of batch 6 lactose, corresponding to a % recovery of between 81.2–105.5% with an average drug recovery being 94.1%. The average drug emission from all eight formulations was 66.5%, indicating that a significant portion (33.5%) of the drug was retained in the inhaler device.

The blends containing batch 5, 6, 7 and Lactochem® lactose produced a similar fine particle dose (FPD) of salbutamol sulphate, which was significantly higher ($P < 0.01$) than that obtained from the blends which were composed of batch 2, 3 or 4 lactose. The blends containing batch 5 lactose produced the highest FPF (25.6%) and dispersibility (46.2%), which were more than twice those of the formulations containing batch 2 lactose, the FPF and dispersibility of the latter being 12.6 and 19.8%, respectively. These batches of lactose particles were sieved under the same conditions and were measured to have a similar mean diameter (Table 1, Fig. 1). Since all the powders are composed of the same batch of salbutamol sulphate, the differences in the deposition profiles of the drug may largely be as a result of the differences in particle shape and surface texture of lactose carrier particles.

The effect of the surface smoothness and particle shape of lactose on the deposition of salbutamol sulphate is seen by plotting the surface factor (Fig. 3) and elongation ratio (Fig. 4) of the carrier particles against the FPF and dispersibility of the drug. It can be seen that increasing the surface smoothness of lactose carrier particles, as expressed

by the 'surface factor', generally resulted in an increase in the FPF and dispersibility of salbutamol sulphate after aerosolisation at 60 l min^{-1} via a Cyclohaler. Interestingly, increasing the elongation ratio of the lactose carrier particles also appeared to result in an increase in the FPF of salbutamol sulphate (Fig. 4). These results suggest that apart from surface smoothness, the elongation of carrier particles may also play an important role in determining the FPF of the drug.

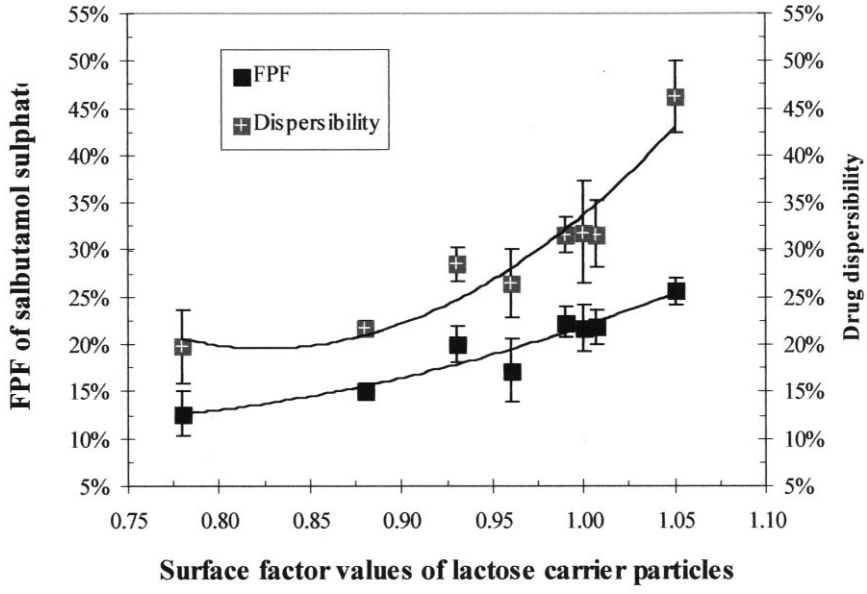

Fig. 3. The relationship between mean 'surface factor' of lactose particles and the FPF of salbutamol sulphate aerosolised at 60 l min^{-1} via a Cyclohaler® (error bars denote S.D., $n = 4$).

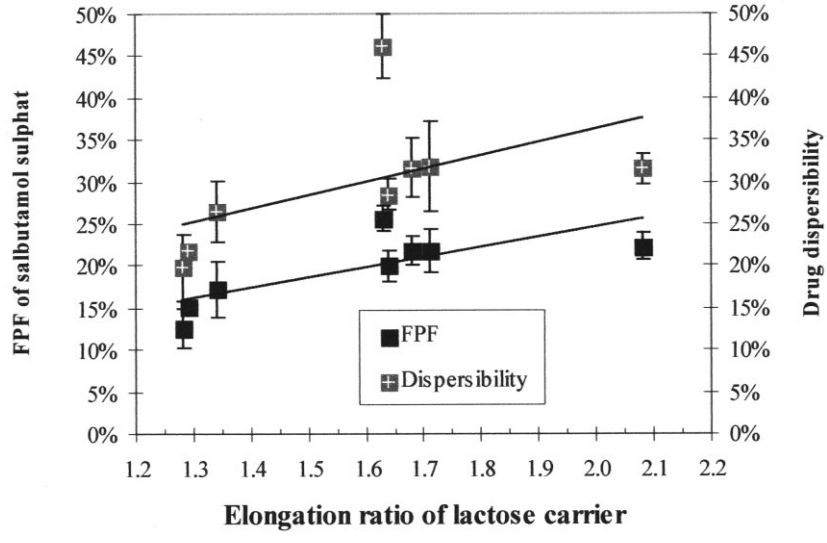

Fig. 4. The relationship between elongation ratio of lactose particles and the FPF of salbutamol sulphate aerosolised at 60 l min^{-1} via a Cyclohaler® (error bars denote S.D., $n = 4$).

Table 3
Deposition of salbutamol sulphate from different batches of lactose in a twin-impinger after aerosolisation at 60 l min^{-1} via a Rotahaler® (mean (S.D.), $n>3$)

Batch No.	RD (μg)[a]	ED (μg)[b]	FPD (μg)[c]	FPF (%)[d]	Dispersibility	Recovery (%)	Emission (%)
Lact[e]	565 (13)	339 (7)	97 (7)	20.8 (1.0)	28.5 (1.7)	96.6 (2.6)	72.9 (2.5)
1	436 (21)	328 (17)	84 (3)	19.3 (0.3)	25.6 (0.9)	90.5 (4.3)	75.4 (1.7)
2	482 (12)	367 (15)	75 (2)	15.6 (0.4)	20.6 (1.1)	100.0 (2.5)	76.2 (2.9)
3	430 (4)	333 (4)	64 (9)	15.0 (2.2)	19.4 (3.0)	89.3 (0.9)	77.4 (0.4)
4	475 (13)	335 (20)	99 (6)	20.8 (0.8)	29.5 (0.8)	98.5 (2.7)	70.6 (2.3)
5	457 (25)	336 (12)	102 (5)	22.4 (0.9)	30.5 (1.1)	95.0 (5.1)	73.5 (2.2)
6	419 (10)	275 (20)	102 (2)	24.4 (0.8)	34.1 (2.5)	86.9 (2.2)	65.6 (3.3)
7	462 (13)	344 (17)	108 (6)	23.4 (1.5)	31.5 (2.3)	95.9 (2.8)	74.4 (2.4)

[a] RD is the recovered dose of drug.
[b] ED is the emitted dose of drug.
[c] FPD is the fine particle dose of drug.
[d] FPF is the fine particle fraction of drug.
[e] Lact is Lactochem® lactose.

3.4. Deposition from a Rotahaler®

The % recovery varied from 86.9% for the formulation containing batch 6 lactose to 100% for the powder containing batch 2 lactose after aerosolisation at 60 l min^{-1} via a Rotahaler® (Table 3). The average recovery of salbutamol sulphate from all the blends investigated was 94.1%, which was similar to that after actuation via a Cyclohaler®, suggesting that the overall deposition, washing and analytical procedures were reliable and reproducible.

Different FPD/FPF of salbutamol sulphate were determined from these formulations. The blends containing batch 2 or 3 lactose produced the lowest FPD, FPF and dispersibility whilst the blends composed of batch 5, 6 or 7 lactose produced the highest FPD, FPF and dispersibility of the drug. The formulations containing batches 1, 4 and Lactochem® lactose produced an intermediate drug dispersion. As mentioned above, the difference in the FPF and dispersibility of the drug may be as a result of the difference in morphological properties of lactose carrier particles. Thus, values of either 'surface factor' or elongation ratio of each batch of lactose were plotted against the FPF of salbutamol sulphate from the corresponding formulations (Figs. 5 and 6). Similar to the results obtained from the Cyclohaler®, the FPF and dispersibility of salbutamol sulphate from the Rotahaler® were also dependent upon either the surface smoothness or the elongation of lactose particles. Increasing the surface smoothness and/or elongation ratio of lactose carrier particles, was shown to increase the FPF and dispersibility of salbutamol sulphate.

4. Discussion

No significant difference ($P>0.6$) was observed in the FPF and dispersibility of salbutamol sulphate after delivery from either a Cyclohaler® or a Rotahaler®. Therefore, drug deposition data from each batch of lactose measured by the two inhaler devices were combined, and analysed by a 'stepwise forward algorithm' in multiple regression using a Minitab® for Windows (Version 10.2) to generate the following equations:

$$\mathrm{FPF} = 6.56E + 24.5S_{\mathrm{rec}} - 13.9 \quad r^2 = 0.901 \qquad (5)$$

$$\mathrm{Dispersibility} = 8.81E + 34.6S_{\mathrm{rec}} - 19.0 \quad r^2 = 0.895 \qquad (6)$$

where E and S_{rec} were the elongation ratio and 'surface factor', respectively.

The FPF and dispersibility of salbutamol sulphate increases almost linearly with the values of either the elongation ratio or the 'surface factor', with a linear coefficient, r^2 of approximately 0.90.

The coefficients for the 'surface factor' (24.5 and 34.6 for FPF and dispersibility, respectively) were larger than those of the elongation ratio (6.56 and 8.81 for FPF and dispersibility, respectively) and thus, drug FPF would appear to increase faster with 'surface factor' than with the elongation ratio. However, the relative significance of the two parameters is difficult to judge from these coeffi-

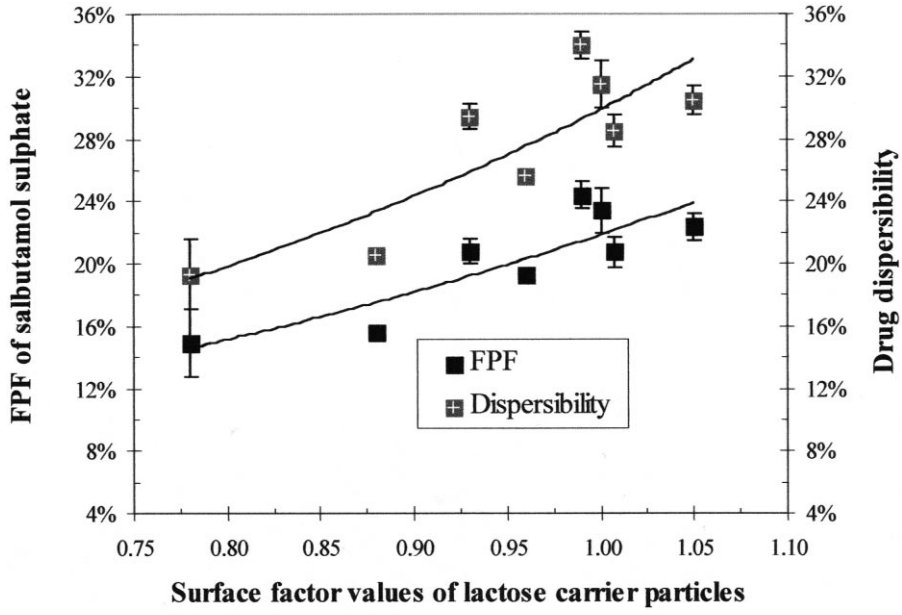

Fig. 5. The relationship between the 'surface factor' of lactose and the FPF of salbutamol sulphate after aerosolisation at 60 l min^{-1} via a Rotahaler® (error bars denote S.D., $n = 4$).

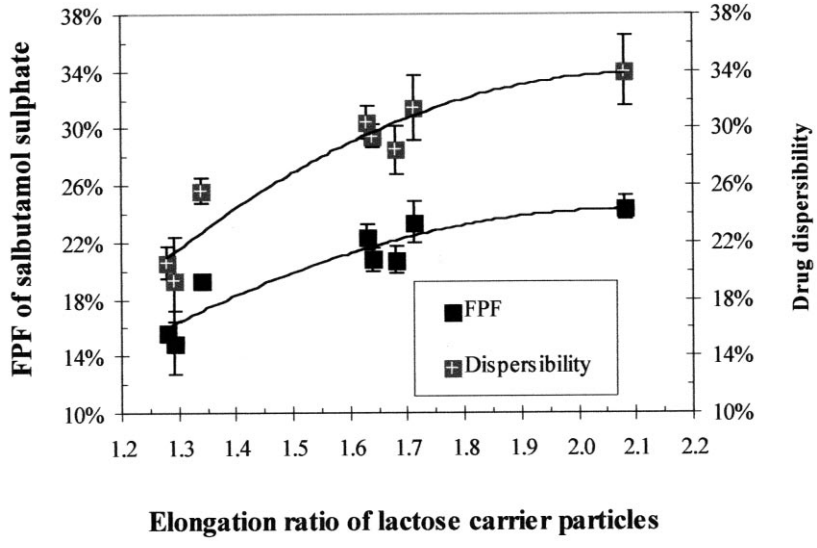

Fig. 6. The relationship between the elongation ratio of lactose and the FPF of salbutamol sulphate after aerosolisation at 60 l min^{-1} via a Rotahaler® (error bars denote S.D., $n = 4$).

Table 4
Regression analysis and ANOVA of the deposition data obtained with a twin-impinger

Predicator	FPF			Dispersibility		
	SEQ SS	*t*-ratio	*P*	SEQ SS	*t*-ratio	*P*
Elongation ratio	137.7	4.19	0.001	259.9	3.96	0.002
'Surface factor'	36.6	4.99	0.000	73.1	4.94	0.000

cients because the values of 'surface factor' (≤ 1) were less than the values of elongation ratio (≥ 1). The statistical details of the regression analysis are listed in Table 4, confirming that both drug FPF and dispersibility increased as the values of either elongation ratio ($P < 0.01$) or 'surface factor' ($P < 0.01$) were increased. The *t*-ratio values of the FPF generated by changes in the 'surface factor' were similar to those resulting from changes in elongation ratio. These results suggest that the elongation ratio is equally important as the surface factor in determining the dispersion and deaggregation of salbutamol sulphate.

The results of the present study indicate that an increase in surface smoothness of lactose carrier generally resulted in an increase in the FPF of salbutamol sulphate. Although this was in agreement with the results obtained previously (Kassem, 1990), the effects of the carrier surface smoothness on drug deposition were found to be less pronounced than might have been expected from this previous report. The FPF of salbutamol sulphate from recrystallised lactose was reported to be almost 6 times as high as that from the Lactochem® lactose as a result of a very low drug FPF (4%) observed when the latter carrier was employed (Kassem, 1990). However, the direct comparison of drug deposition from a formulation containing Lactochem® lactose with that from formulations employing recrystallised lactose might not reveal the true effect of carrier surface smoothness on the deposition of the drug. This is likely to be a result of the commercial Lactochem® lactose having been subjected to different processing history from that of the recrystallised lactose. For example, Lactochem® lactose, as supplied, had previously undergone a milling process whilst the recrystallised lactose did not undergo any such treatment and such a difference in the processing is likely to have induced a change in the surface energy and amorphous content on the particle surface. Furthermore, as is shown in the present study, the recrystallised lactose and the commercial lactose had different particle shapes. However, none of these factors were taken into account in these earlier studies and the data were not subjected to sound statistical analysis (Kassem, 1990; Ganderton, 1992).

In order to investigate the effects of a specific morphological characteristic of the carrier on drug deposition, the possible effects of all the other properties of the carrier have to be minimised ideally, or kept at a similar level. This was achieved in the present study by comparing drug deposition from different batches of lactose particles that had undergone similar preparative procedures (Zeng et al., 1998). The formulations containing Lactochem® lactose produced a higher FPF and dispersibility of salbutamol sulphate than most of those containing recrystallised lactose and this may have largely been as a result of the higher concentration of residual fine lactose present in the former lactose. For example, the sieved fraction of Lactochem® lactose was shown to contain approximately 12% residual fine particles < 5.0 μm, measured by laser diffraction after dispersion in butan-1-ol, in contrast to approximately 5% fine lactose < 5.0 μm in all the re-crystallised lactose (data not shown). The higher concentration of fine lactose in the commercial lactose may have contributed to the relatively high FPF and dispersibility of salbutamol sulphate in the blend containing this lactose as carrier (Zeng et al., 1998). All recrystallised lactose had a similar mean diameter, contained a similar concentration of fine lactose and had been sub-

jected to similar processing conditions. Any differences observed for the deposition profiles of salbutamol sulphate from formulations containing these batches of lactose may largely be due therefore to different morphological features of the carrier particles.

The elongation ratio of lactose particles was shown to have a similar effect on the FPF of salbutamol sulphate to that of the surface smoothness. Increasing the elongation ratio of lactose particles increased FPF of the salbutamol sulphate. In aerosol science, the use of elongated particles has attracted much interest. Long objects, such as fibres and needle-like crystals, have aerodynamic diameters almost independent of their length and the diameter is approximately equal to the short dimension of the particle in question (Hinds, 1982). Thus, elongated particles may exhibit a much smaller aerodynamic diameter than spherical particles of similar mass or volume. For example, Hickey et al. (1992) obtained elongated disodium cromoglycate particles after the treatment of the aerosol with a hydrophobic molecule, lauric acid. The equivalent diameters of the particles (i.e. the diameters of spherical particles that have the same volume as the elongated particles) deposited on each stage of an inertial impactor were found to be markedly higher than the nominal cut-off diameters of the stages. As the cut-off diameters were calibrated using spherical particles, the results of these workers suggested that elongated particles with larger volume or mass can deposit at the same stage as spherical particles having a smaller volume or mass. The same hypothesis may also be invoked to account for the fact that more drug particles were dispersed when more elongated carrier particles were used. More elongated lactose particles may be expected to travel a longer distance before impaction occurs in comparison to less elongated carrier particles of a similar mass, as a result of the lower relative aerodynamic diameters of the former. Therefore, drug particles adhered to more elongated carrier particles may be subjected to the drag forces of the air stream for a longer period of time. This would result in more drug particles being detached from the carrier particles, leading to a higher FPF of the drug. Plate-like elongated crystals of lactose (Fig. 1, batches 5, 6 and 7) would be expected to have smaller surface crevices than the less elongated tomahawk-shaped crystals (Fig. 1, batches 1, 2 and 3). Consequently, drug adhesion to plate-like lactose crystals as a consequence of mechanical interlocking of particles is less likely to occur than when tomahawk-shaped carrier particles are employed in the formulation. This would reduce the overall adhesion forces between the drug and the carrier particles and hence, increase the portion of drug particles that are dissociated from the carrier after suspension in the airstream.

5. Conclusion

Increasing either the surface smoothness or elongation of lactose increases the fine particle fraction and dispersibility of salbutamol sulphate after aerosolisation of the formulations via either the Rotahaler® or the Cyclohaler®. The particle shape of the carrier particles appears to be equally important to the carrier surface smoothness in determining the dispersion and deaggreagation of salbutamol sulphate. The findings of the present study are important in at least two respects. First, there have been no strict criteria to control the morphological features of the carrier particles employed as the carrier for inhalation aerosols and variation in such factors may be one of the main causes of the batch-to-batch variation in drug delivery encountered for most dry powder aerosol formulations. Second, the engineering of carrier particles to produce precisely designed shape may provide an important strategy to improve the delivery efficiency of drug delivery to the lower airways by dry powder inhalers.

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