ELSEVIER

International Journal of Pharmaceutics 176 (1998) 99–110

international journal of pharmaceutics

The role of fine particle lactose on the dispersion and deaggregation of salbutamol sulphate in an air stream in vitro

Xian Ming Zeng *, Gary Peter Martin, Seah-Kee Tee, Christopher Marriott

Department of Pharmacy, King's College London, Manresa Road, London SW3 6LX, UK

Received 6 July 1998; received in revised form 2 September 1998; accepted 10 September 1998

Abstract

Sieved (63–90 μm) lactose (L) particles supported on a 63-μm sieve was subjected to a compressed airstream with a flow rate of 160 l/min in order to remove existing fine particles. Fractions of the air-treated L were then blended separately with either 1.5%, w/w micronised L (5.0 μm) or magnesium stearate (7.6 μm, MS) and the blends were further sieved gently using a 45-μm sieve to remove any freely dispersed fine L. Other fractions of the air-treated L were also blended with different quantities of intermediate sized lactose (15.9 μm, IML) to obtain final concentrations of IML between 1.5 and 9% w/w. The various batches of L were then mixed separately with salbutamol sulphate (SS, 5.8 μm) in a ratio of 67.5:1 (w/w). The particle size and shape of L were characterised by laser diffraction, a time-of-flight technique and scanning electron microscopy. The in vitro deposition of SS was measured using a twin impinger after aerosolisation at 60 l/min via a Rotahaler®. Air treatment of the coarse L was found to reduce significantly (ANOVA, $p < 0.01$) the fine particle fraction (FPF) and fine particle dose (FPD) of SS but such an effect was reversible by adding fine L back to the powder formulations. Gentle sieving of coarse-fine L mixtures on a 45-μm sieve removed the majority of freely dispersed fine L thereby reducing significantly ($p < 0.05$) the FPF and FPD of the drug. MS exhibited a similar effect on the dispersion of SS to that of the fine L. The more IML that was added the higher the FPF or FPD of the drug. However, the greatest stepped-increase in the drug FPF occurred when 1.5% w/w of IML was added, which resulted in $> 60\%$ increase in FPF of SS whilst increasing the concentration of the added IML from 1.5 to 9% produced an approximate 50% further increase in the drug FPF.

Keywords: Dry powder inhalers; Lactose; Salbutamol sulphate; Magnesium stearate; Dispersion; Deposition

Abbreviations: A, Hamaker constant; FPD, fine particle dose (also referred to as respirable dose) is the mass of drug particles < 6.4 μm per capsule after tests using a twin impinger; FPF, fine particle fraction (also referred to as respirable fraction) is the % of drug particles < 6.4 μm after tests using a twin impinger; F_{vdw}, van der Waals' forces; GSD, geometric standard deviation; IML, intermediate sized lactose; L, lactose; L_1, untreated lactose; L_2, air-treated lactose; ML, micronised lactose; MS, magnesium stearate; RD, recovered dose is the total mass of drug recovered per capsule after each deposition; SS, salbutamol sulphate; TI, twin stage liquid impinger; TOF, time of flight; VMD, volume median diameter; Z_0, separation distance between two interacting particles.

* Corresponding author. Tel.: +44 171 3334795; fax: +44 171 3515307; e-mail: xianming.zeng@kcl.ac.uk

0378-5173/98/$ - see front matter
PII S0378-5173(98)00300-7

1. Introduction

Drug dispersion and entrainment from dry powder inhalers (DPIs) are usually brought about by the inhalation efforts of the patient. In order for the drug to gain access to the lower airways, it is generally accepted that a prime requirement is that the drug particles have an aerodynamic diameter between 1 and 5 μm (Newman and Clarke, 1983; Gonda, 1990). An important consequence of the requirement of fine particles for inhalation arises from the fact that they generally flow less well than coarser ones. Small particles are also notoriously difficult to disperse (Hickey et al., 1994) due to the highly cohesive nature of fine particles. Two major approaches have been employed to improve the flow and dispersion of drug particles. The first one involves the controlled aggregation of the undiluted drug to form loosely adherent floccules (e.g. Turbohaler®). The alternative approach is to employ a binary ordered mixture comprising fine drug particles blended with coarser carrier particles (e.g. Rotahaler®). α-Lactose monohydrate has been employed most frequently as the carrier and it is usually designed to have a size between 63 and 90 μm for this purpose (Timsina et al., 1994). In most dry powder formulations, drug particles are usually present in low concentrations, with a drug to carrier ratio of 1:67.5 (w/w), being typical (Kassem, 1990). Therefore, the carrier particles are the main component in the formulation and any change in the physico-chemical properties of the carrier particles will result in a change in the delivery of drugs. For example, the respirable fraction (RF) of the salbutamol sulphate was reported to be higher for formulations employing lactose particles with a smoother surface as the carrier than in the case of lactose particles with a rougher surface (Ganderton, 1992). Drug dispersion is also dependent upon the particle size of the carrier particles (French et al., 1996). A reduction in the carrier particle size has been reported to improve the RF of salbutamol sulphate from the Rotahaler® (Ganderton and Kassem, 1992) and budesonide from Spinhaler® (Steckel and Müller, 1997) but reduce the RF of terbutaline sulphate from a Rotahaler® (Byron et al., 1990). The RF of a drug can also be increased by increasing the concentration of the drug particles (Adjei and Gupta, 1997) or addition of ternary components, such as fine particles of magnesium stearate, to the powder formulations (Ganderton and Kassem, 1992). Other ternary materials such as L-leucine have also been employed to improve drug delivery from DPIs (Staniforth, 1996), although the use of a ternary component not previously employed in pulmonary formulations will require toxicological clearance. A more practical strategy to improve the drug delivery efficiency of DPIs may be through the use of a ternary ordered mixture where the third component comprises fine particles of the carrier. We have previously reported that addition of a small amount of fine lactose to the blends of coarse lactose and micronised salbutamol sulphate improved the fine particle fraction (FPF) of salbutamol sulphate (Zeng et al., 1996a,b). Such an effect is further confirmed by a more recent report where fine lactose was found to improve the FPF of spray dried bovine serum albumin (Lucas et al., 1998). In the present study, we have further investigated the role of the presence of fine lactose in drug/carrier blends on the dispersion and deaggregation of salbutamol sulphate, with special attention being paid to the effect of fine lactose concentration. The effect of fine lactose on drug deposition was also compared with that induced by the addition of the fine particles of magnesium stearate.

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, Ware, UK. α-Lactose monohydrate (Lactochem®) was obtained from Borculo Whey, Chester, UK. *p*-hydroxybenzoic acid ethyl ester was purchased from Sigma, Poole, UK. whilst ammonium acetate, magnesium stearate (VMD 7.6 μm of GSD 1.7), methanol of HPLC grade and butan-1-ol of reagent grade were obtained from BDH Laboratory Supplies, Poole, UK.

2.1. Preparation of coarse lactose (63–90 μm)

Lactochem® lactose (100 g) was sieved for 15 min using a sieve shaker (Endecotts, London, UK) through a test sieve with an aperture width of 90 μm (Endecotts, London, UK) which was placed over a test sieve with an aperture width of 63 μm. The particles collected on the 63-μm sieve were divided into two batches. One batch (L_1) was placed in a desiccator over silica gel until further required. Another batch was placed on a 63-μm sieve, and was then blown with an air stream of a flow rate of 160 l/min via a nozzle (I.D. ~1 cm) from a distance of approximately 15 cm above the powder. The compressed air treatment was continued such that the concentration of fine lactose (i.e. particles < 20 μm) reached a constant level, as monitored by laser diffraction. The air-treated (L_2) lactose was then placed in a desiccator over silica gel until further required.

2.2. Preparation of fine lactose

Micronised lactose (ML) was prepared by subjecting coarse lactose to up to nine passes through a jet mill (JM-80, M&M Fryma, Herts, UK) operated at an air pressure of 15 bars whilst the intermediate sized lactose (IML) was obtained using a ball mill (Fritsch Fulverisette, Analysette Laborette, Germany) at an instrument setting level of 8 for 30 min.

2.3. Preparation of powder formulations

All powder mixing was carried out using a Turbula® mixer (Glen Creston, Stanmore, Middlesex, UK) for 30 min.

(a) Salbutamol sulphate was mixed separately with L_1 and L_2 in a ratio of 1:67.5 w/w.

(b) L_2 was blended separately with either micronised lactose or magnesium stearate such that the final concentration of the fine components was 1.5% w/w. A portion of each mixture was placed in a desiccator over silica gel until required. A second portion was placed on a sieve with an aperture width of 45 μm and sieved manually by gentle tapping on the sieve for 30 min with a view to removing loosely bound or free fine particles. Each batch of lactose was finally mixed with salbutamol sulphate in a ratio of 67.5:1 w/w.

(c) L_2 was also blended with IML such that the final concentrations of the IML were 1.5, 3.0, 6.0, 9.0% w/w, respectively. These combinations were then mixed separately with salbutamol sulphate in a ratio of 67.5:1 w/w.

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

2.4. Particle size measurement by laser diffraction

A small amount of lactose powder (about 5 mg) was dispersed in 5 ml butan-1-ol with the aid of sonication (sonic water bath, Model F5100b, Decon Laboratories, Hove, UK) for 1 min. The particle size was measured by laser diffraction (Series 2600c, Malvern Instruments, Malvern, UK) using an independent particle size model and obscuration between 0.16 and 0.18. Each sample was measured at least six times.

2.5. Particle size measurement by time-of-flight technique

An aerosizer with an aero-disperser (API Aerosizer Mach-2, Amberst Process Instruments, MA) was used as supplied. A small amount of powder (about 5 mg) was placed in the sample cup of the aero-disperser. Particle size measurement was then carried out at a medium feed rate, high shear force and a sample run time of 300 s. Time-of-flight (TOF) data were processed with the operating software package vers. 10.09 for API aerosizer Mach-2 and the powder density was taken as that of lactose, 1.52 g/ml. Both number and volume distributions were recorded. Each sample was analysed at least four times.

2.6. Scanning electron microscopy

Double-sided adhesive tape was placed on an aluminium stub and after stripping off the protective covering, 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 up any agglomerates. The particles were then coated with approximately 15–20 nm gold using a sputter coater (Polaron E5100, Polaron Equipment, Watford, UK) with an electrical potential of 2.0 kV and a current of 20 mA. Several photomicrographs were produced by scanning fields, selected randomly, at several magnifications with a Philips SEM501B scanning electron microscope (Einhoven, Holland).

2.7. 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 using UV detection at 276 nm. The HPLC system consisted of a pump (CM 4000 multiple solvent delivery system, LDC Analytical, FL), a multiple wavelength UV detector (SpectroMonitor 3100, LDC Analytical, FL) and a 15 cm $\times$ 4.6 mm I.D. column packed with 5 μm C-18 (Hypersil, Phenomenex, Cheshire, England). The retention times for salbutamol sulphate and the internal standard were 2.71 and 5.49 min, respectively.

2.8. Deposition test of salbutamol sulphate

Deposition was determined using a twin stage liquid impinger (TI, apparatus A, British Pharmacopoeia, 1993) after 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®.

In the TI test, 7 ml of the mobile phase containing 2 μg/ml *p*-hydroxybenzoic acid ethyl ester was introduced in stage 1 and 30 ml of the same solvent in stage 2 of the TI. The capsule to be tested was placed in a Rotahaler®, which had been fitted into a moulded rubber mouthpiece attached to the throat piece of the impinger. Once the assembly had been checked and found to be airtight and vertical, the vacuum pump was switched on. After the pump had run for 5 s, the dose was released. The pump was allowed to run for another 7 s at 60 ± 2 l/min following the release of the dose and it was then switched off. The capsule shells were removed from the inhaler device and the deposition test was repeated until five capsules had been actuated in the same manner. The inhaler body, capsule shells and mouthpiece were washed five times with the mobile phase containing internal standard and the washing solution was made up to 100 ml with the same solvent. The sample thus obtained was used to measure the amount of drug retained in the inhaler device. The same process was carried out for both the upper and the lower stages of the twin-impinger. All the samples obtained were analysed for the concentration of salbutamol sulphate using the HPLC method as described above.

Fine particle dose (FPD), denoted as the quantity (μg) of drug per capsule that deposited in the lower stage of the TI (cut-off diameter < 6.4 μm) after aerosolisation, was determined. Each capsule contained a nominal dose of 480 ± 30 μg salbutamol sulphate. Recovered dose (RD) was taken as the total quantity of drug recovered per capsule after each actuation whilst emitted dose was that emitted from the inhaler device. Percentage emission was calculated as the percentage of emitted dose to total dose. Fine particle fraction (FPF) was the ratio of FPD to RD whilst dispersibility was the percentage of FPD to emitted dose.

3. Results

3.1. Particle size distribution of lactose carrier

The volume median diameter (VMD) as measured by the Malvern was significantly ($p < 0.05$) higher for L_2 in comparison to L_1 whilst there was no significant difference ($p > 0.05$) in the VMD between these lactose samples when measured with the aerosizer (Table 1). Treatment of lactose with compressed air produced a reduction in the fraction of fine lactose particles < 4.8 μm (Table 1) and this effect can also be seen qualitatively from visual examination of SE micrographs of the lactose before (Fig. 1a) and after the treatment (Fig. 1b). L_2 clearly showed fewer fine particles adhering to the larger lactose particles in comparison to L_1, although there was no apparent change

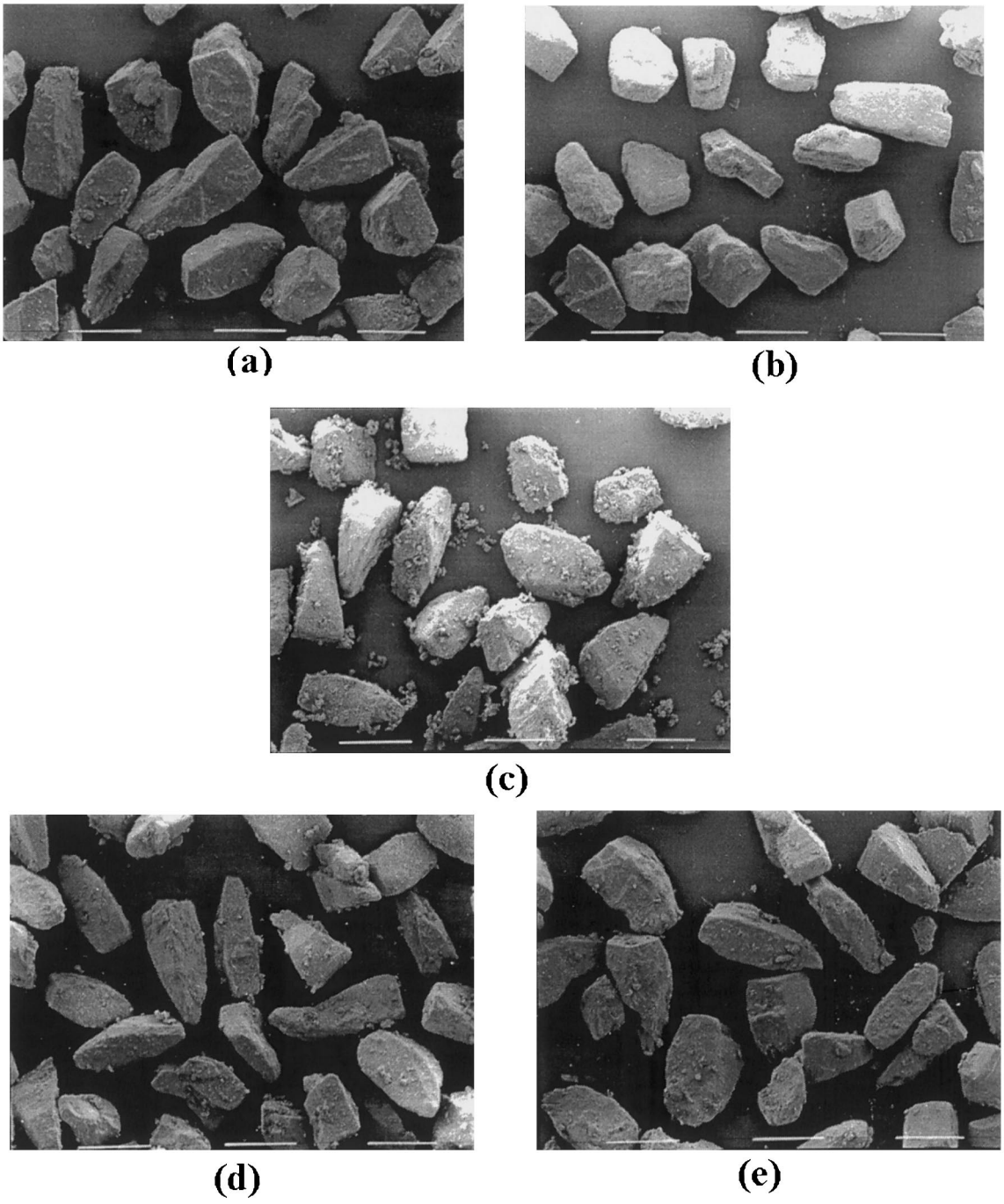

Fig. 1. Scanning electron micrographs of untreated lactose (a), air-treated lactose (b), air-treated lactose with 6% fine lactose (c), air-treated lactose with 6% fine lactose post-sieving (d), and air-treated lactose with 6% magnesium stearate post-sieving (e). Scale bars denote 100 μm.

Table 1
Particle size distribution of different lactose particles measured by Malvern and Aerosizer (mean ± S.D., $n = 4$–6)

Formulations	VMD (μm)		% Particles (<4.8 μm)	
	Malvern	Aerosizer	Malvern	Aerosizer
L_1	74.2 ± 7.8	65.2 ± 2.5	12.8 ± 2.9	0.03 ± 0.02
L_2	90.8 ± 5.0	67.7 ± 2.2	7.1 ± 1.5	0.00
L_2 + ML[a]	72.2 ± 6.8	63.2 ± 1.3	14.1 ± 4.6	0.12 ± 0.04
L_2 + ML sieving[b]	79.8 ± 1.2	66.5 ± 1.2	8.9 ± 1.5	0.04 ± 0.03
L_2 + MS sieving[c]	80.3 ± 1.5	65.5 ± 1.5	9.3 ± 2.1	0.08 ± 0.02

L_1, untreated lactose; L_2, air-treated lactose; ML, micronised lactose; MS, magnesium stearate.
[a] Blend of L_2 and ML.
[b] Blend of L_2 and ML after tap-sieving.
[c] Blend of L_2 and MS after tap-sieving.

in the morphology of lactose particles in response to the treatment with compressed air. Addition of 1.5% micronised lactose to L_2 was shown to reduce significantly ($p < 0.05$) VMD of lactose but increase the concentration of fine lactose < 4.8 μm (Table 1). Some of the added fine lactose particles were shown to adhere to the coarse lactose whilst others were freely dispersed in the powder (Fig. 1c). Sieving the blend of coarse-fine lactose resulted in a slight but insignificant ($p > 0.05$) increase in VMD of lactose although the concentration of fine lactose was significantly ($p < 0.05$) reduced by sieving the coarse-fine mixtures. The majority of the free fine particles were removed by sieving, but this process was clearly unable to dislodge the adhered fine lactose from the coarse particles (Fig. 1d). There was no significant difference ($p > 0.05$) in the VMD and fractions of fine particles between the sieved samples containing micronised lactose and magnesium stearate (Fig. 1e) and this can also seen qualitatively from the SE micrographs of the two samples. The VMD measured by laser diffraction was significantly higher ($p < 0.05$) than the VMD of the corresponding lactose determined by TOF and the corresponding percentages of fine lactose in each blend were always higher when measured by laser diffraction than when measured by TOF (Table 1). Although the various batches of lactose exhibited a similar particle size distribution in volume when measured by TOF (Fig. 2a), these particles showed different particle size distributions in number (Fig. 2b). All batches of lactose exhibited two peaks in size distribution, i.e. one between 0.5 and 10 μm and another between 30 and 100 μm (Fig. 2b). Batch L_1 clearly showed a large portion of particles less than 10 μm whilst after treatment with compressed air, the majority of the smaller particles had been removed. Addition of micronised lactose to the coarse lactose was shown to increase the concentration of particles < 10 μm whilst gentle tap-sieving of the coarse-fine mixtures reduced the content of fine lactose and this can be qualitatively seen from the increased area of the peak corresponding to the larger particle size.

3.2. Effects of existing fine lactose on the deposition of salbutamol sulphate

Compressed air treatment of the carrier particles was shown to reduce significantly ($p < 0.01$) the delivery efficiency of salbutamol sulphate (Table 2). Formulations composed of L_1 as the carrier produced a drug FPF of 11.8 ± 0.7%, which was nearly twice the FPF (6.7 ± 0.6%) of the formulations employing L_2. Accordingly, the average FPD was reduced from 41.4 μg for the formulations containing L_1 to 28.9 μg for formulations containing L_2. However, there was no significant difference ($p > 0.05$) between the two formulations in terms of drug emission, approximately 70–80% RD being emitted from the inhaler device.

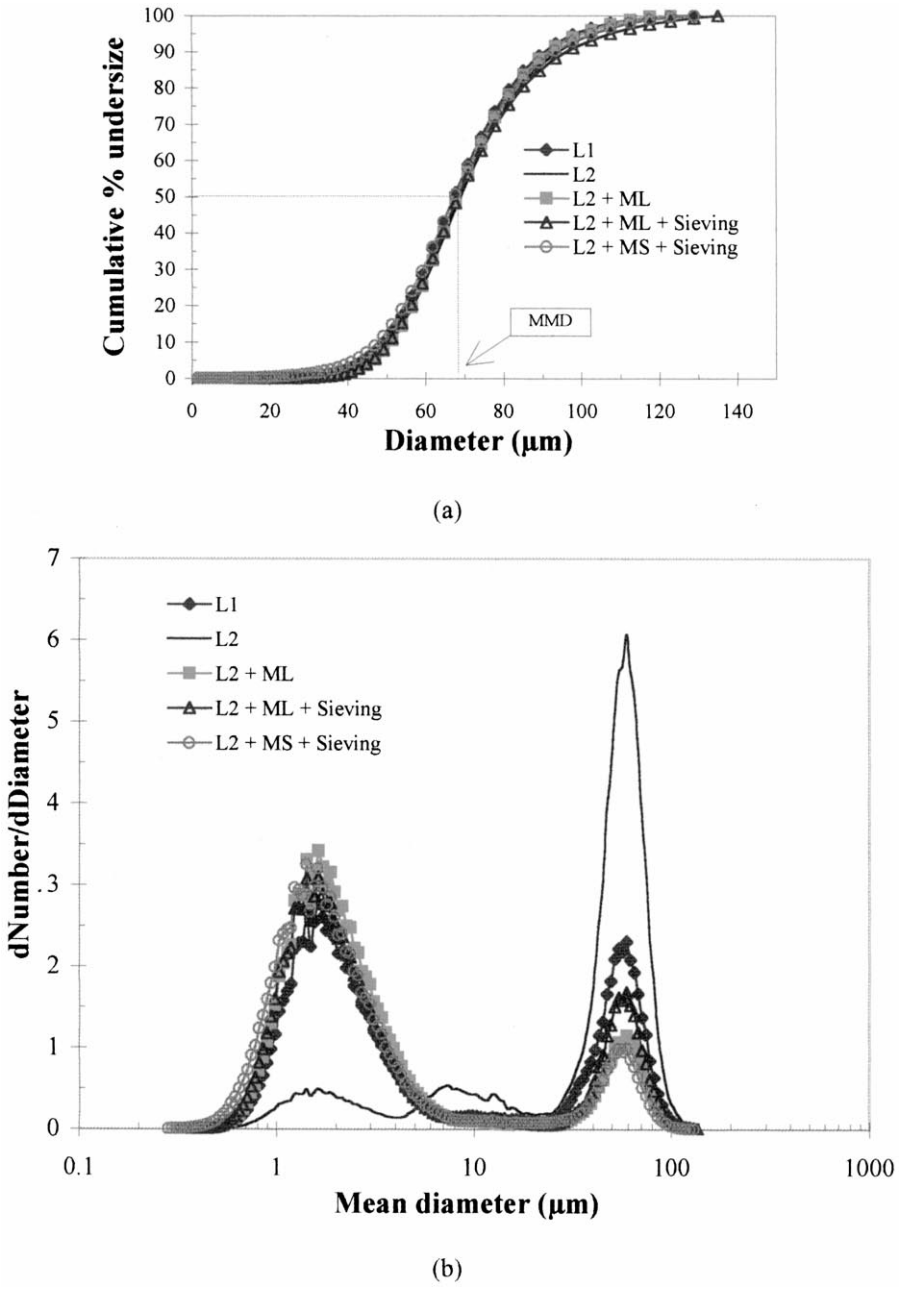

Fig. 2. Particle size distribution of various batches of lactose as measured by TOF in volume (a) and number (b).

Addition of 1.5% ML to L_2 was shown to increase markedly both FPD and FPD of salbutamol sulphate (Table 2). Although there was a slight decrease in the % emission of salbutamol sulphate from formulations containing ML, the latter still produced an average FPD of salbutamol sulphate (61.0 μg), which was over twice as high as the drug FPD (28.9 μg), of the formulation without added fine lactose. Furthermore, the ternary mixture containing the ML also produced

Table 2
Deposition of salbutamol sulphate in a TI after aersolisation from a Rotahaler® at 60 l/min (mean ± S.D., $n = 3$–6)

Formulations	FPD (μg)	FPF (%)	Dispersibility (%)	Emission (%)
L_1 + SS	41.4 ± 3.9	11.8 ± 0.7	16.4 ± 1.6	72.0 ± 5.6
L_2 + SS	28.9 ± 2.6	6.7 ± 0.6	8.6 ± 1.3	79.7 ± 2.5
L_2 + ML + SS[a]	61.0 ± 4.6	14.7 ± 1.1	19.8 ± 1.2	74.4 ± 0.8
L_2 + ML sieving + SS[b]	45.1 ± 4.4	11.3 ± 1.1	14.5 ± 1.6	77.9 ± 2.3
L_2 + MS sieving + SS[c]	39.5 ± 1.6	9.8 ± 0.4	13.1 ± 2.3	74.9 ± 2.1

L_1, untreated lactose; SS, salbutamol sulphate; L_2, air-treated lactose; ML, micronised lactose; MS, magnesium stearate.
[a] Formulation prepared by first blending L_2 with ML before mixing with SS.
[b] Formulation prepared by first blending L_2 with ML followed by tap-sieving before mixing with SS.
[c] Formulation prepared by first blending L_2 with MS followed by tap-sieving before mixing with SS.

significantly higher ($p < 0.05$) dispersibility and FPF of salbutamol sulphate than the binary mixture containing the untreated lactose.

The formulation, prepared by first blending L_2 with 1.5% ML followed by passage through a 45-μm sieve, produced values for the average FPD (45.1 μg) and FPF (11.3%) of salbutamol sulphate, which were significantly lower ($p < 0.05$) than those of the unsieved mixture but significantly higher ($p < 0.05$) than the corresponding values obtained for L_2 (Table 2).

The formulation which comprised a sieved blend of coarse and micronised lactose prior to the addition of the drug produced a slightly but insignificantly ($p > 0.05$) greater dispersibility, FPF and FPD of salbutamol sulphate than the sieved mixture of MS (VMD 7.9 μm with GSD 1.8) blended with L_2 (Table 2). Both formulations produced a similar emission of salbutamol sulphate from the inhaler device (Table 2), suggesting that the incorporation of MS was not superior to ML in terms of increasing the potentially respirable fraction of salbutamol sulphate aerosolised from Rotahaler® at 60 l/min.

3.3. Effect of IML concentrations on the delivery of salbutamol sulphate

Increasing the concentration of added IML was shown to increase drug dispersibility, FPF and FPD (Table 3 and Fig. 3). For example, FPD was increased from 29.7 ± 7.5 μg, for formulations containing L_2 without any added IML, through 48.0 ± 1.5, to 73.7 ± 9.3 μg for those containing 1.5 and 9.0% w/w, added IML, respectively. The more IML that was added, the higher the FPF of salbutamol sulphate (Table 3). All the formulations composed of the added IML produced a similar % emission of approximately 68%, which was significantly lower ($p < 0.05$) than that of the formulation without added IML (Table 3). This was due to more drug being retained in the inhaler device and gelatin capsules after aerosolization of the formulations containing added IML. However, the lower % emission of drug from formulations with added IML was more than compensated by the higher dispersibility of the drug from such formulations in comparison to those without added IML and, consequently, significantly higher ($p < 0.01$) FPD and FPF of salbutamol sulphate was achieved from the former than the latter.

4. Discussion

The increase in the VMD of lactose after treatment with compressed air is likely to be due to removal of a portion of the fine lactose from the bulk powder. However, complete removal of fine particles was not achieved by this treatment, indicating that the energy input was not sufficient to remove the more strongly adhered fine particles. These strongly adhered fine particles were not separated from the coarse lactose during measurement using TOF, leading to a negligible level of fine particles < 4.8 μm from the air-treated lactose samples when measured by Aerosizer. In

Table 3
Dose distribution of salbutamol sulphate from powder formulations with different contents of added IML after aerosolisation at 60 l/min via a Rotahaler® into a TI (nominal dose 480 μg, mean $\pm$ S.D., $n = 3$–6)

Contents of IML (% w/w)	Emitted dose (μg)	Drug emission (%)	FPD (μg)
0.0	343.9 $\pm$ 59.4	79.6 $\pm$ 2.5	29.7 $\pm$ 7.5
1.5	300.5 $\pm$ 21.0	68.8 $\pm$ 4.7	48.0 $\pm$ 1.5
3.0	298.0 $\pm$ 42.1	67.5 $\pm$ 0.9	52.1 $\pm$ 6.6
6.0	298.3 $\pm$ 16.6	69.0 $\pm$ 0.5	57.4 $\pm$ 8.4
9.0	298.9 $\pm$ 26.4	68.5 $\pm$ 2.2	73.7 $\pm$ 9.3

comparison to the results obtained with an aerosizer, the concentration of fine lactose < 4.8 μm was consistently higher after measurement using laser diffraction and this can be explained by the fact that for the latter analysis, the sample was suspended in butan-1-ol, which is likely to disperse particle aggregates more completely than the air stream generated by the Aerosizer.

All formulations contained coarse lactose particles originally from the same sieved fraction with a view to minimising the potential influence of other factors such as particle shape and surface smoothness of the carrier particles on the deposition of drug. Therefore, different deposition profiles of salbutamol sulphate from these formulations are likely to be largely attributable to the difference in concentration of fine lactose particles of the blends. Thus, removal of fine lactose from the coarse lactose carrier reduces the dispersibility of salbutamol sulphate, although such an effect was shown to be reversible by adding fine lactose back to the coarse carrier particles.

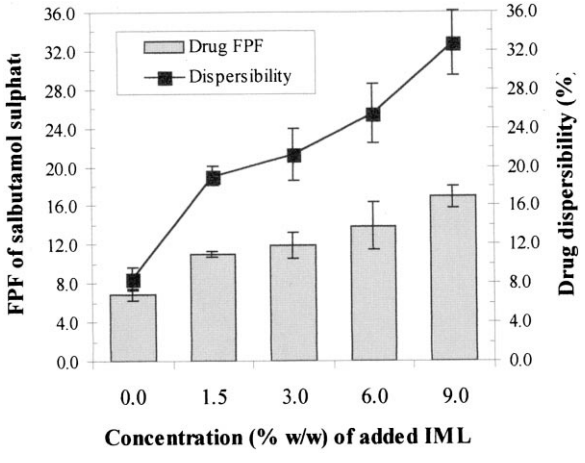

Fig. 3. A relationship between the concentrations of added IML and the FPF and dispersibility of salbutamol sulphate, as measured by a TI after aerosolisation at 60 l/min. Error bars denote standard deviation, $n = 3$–6.

The fine L and MS resulted in a similar deposition profile of SS. Given the unknown toxicological implications of the chronic pulmonary delivery of magnesium stearate, it is thus reasonable to assume that the use of micronised lactose is preferential to the use of magnesium stearate. According to Staniforth (1996), lactose developed an electronegative charge; salbutamol sulphate developed an electropositive charge, whilst magnesium stearate developed an electropositive charge. Therefore, pre-blending magnesium stearate with lactose would render the carrier surface an electropositive charge and this would reduce the attraction between salbutamol sulphate and the coarse carrier, thereby improving the FPF of the drug. However, such a mechanism is unable to account for a similar effect on FPF of salbutamol sulphate observed for fine lactose and magnesium stearate since these two materials would be expected to differ in their electrostatic properties. Addition of fine lactose to the powder formulations may result in the formation of mono- or multi-layers of the fine lactose adhered to the coarse lactose, filling of surface crevices and saturation of the strong binding sites on the coarse lactose. Therefore, fine particles of lactose would be expected to reduce the interparticulate forces between the drug and the coarse lactose and consequently, enhance the detachment of the drug from the carrier thereby improving FPF of the drug.

Under normal experimental conditions, adhesion forces are dominated by London–van der Waals' forces, which can be calculated using following equation (Rumpf, 1977; Zimon, 1982) assuming sphericity of particle shape with each particle having a smooth surface:

$$F_{vdw} = \frac{A}{12Z_0^2}\left(\frac{d_1 d_2}{d_1 + d_2}\right) \quad (1)$$

where A is the Hamaker constant, Z_0 the separation distance and d_1, d_2 are the diameters of interacting particles.

Thus, salbutamol sulphate particles with a diameter of 5.8 μm would have an average theoretical F_{vdw} of $5 \times 10^{-7} A/Z_0^2$ N, when they are adhered directly to the coarse carrier particles. However, if the drug particles are adhered first to fine lactose particles, then the overall F_{vdw} acting on the drug particle will be primarily due to the force from the fine lactose. The separation distance between the coarse lactose and drug particle increases drastically from the 0.1–1 nm for normal interacting particles (Krupp, 1967; Visser, 1989), to a value which corresponds to the diameter of the fine lactose (e.g. 5 μm) adhering to the coarse lactose particles. Therefore, the F_{vdw} acting on the drug particle from the coarse lactose becomes negligible in comparison to that from the fine lactose (approximately $2 \times 10^{-7} A/Z_0^2$ N). Thus, the average adhesion force of the drug to the carrier particles due to van der Waals' force, is more than halved if a mono-layer of the fine lactose is formed on the coarse lactose. Furthermore, it has been reported that some areas of the carrier surfaces have stronger binding sites than others (Hersey, 1975). These strong binding sites may include surface cavities, amorphous regions or regions of high surface energy on the carrier surface, as well as the regions on which electrostatic charge, if any, is concentrated. Occupation of these sites on the coarse lactose by fine lactose leads to more drug particles being adhered to relatively weak binding sites and thereby reducing the overall adhesion force between the drug and carrier. Such a reduction in the adhesion force may be one of the main reasons for the observed increased dispersibility of the drug particles with the formulation containing the fine lactose.

Normal tap-sieving can be expected to be less effective in separating fine lactose from the coarse lactose particles as compared with the conditions employed during compressed air treatment. After sieving, some of the free and loosely bound fine lactose is likely to have been removed but a portion of the particles that were more strongly adhered to the coarse particles are likely to be retained in the mixture. Thus, the concentration of fine lactose in the sieved coarse-fine lactose mixture was higher than that of the air-treated lactose but lower than the same mixture before sieving. The sieved mixture of coarse and fine lactose produced a higher FPF, FPD and dispersibility of salbutamol sulphate than the air-treated lactose but the resultant FPF and dispersibility of salbutamol sulphate was nevertheless lower than the corresponding values obtained for the original mixture of coarse and fine lactose. The mixture of coarse and fine lactose contained both bound and free fine lactose whilst the sieved mixture of coarse and fine lactose only retained the fine lactose that was bound to the coarse lactose with the majority of free lactose being removed from the powder by normal tap-sieving. Therefore, the higher drug FPF and dispersibility observed for the former as compared with those of the latter suggested that the presence of free fine lactose in the blend may also increase FPF or FPD of the drug. These freely dispersed fine lactose particles may have an effect similar to that of a lubricant and by reducing the friction between the larger carrier particles, the fine lactose is likely to reduce any electrostatic charge generated on the surface of the larger particles. Further, it has been shown that some drug particles may adhere to the fine carrier to form drug-fine lactose multiplets (Lucas et al., 1998) and these drug particles can be expected to be more readily dispersed than those attached to coarser carrier particles due to a smaller interparticulate forces between smaller particles (Lam and Newton, 1992). Some multiplets with particle size < 6.4 μm may have reached the lower stage of the twin impinger as an intact particle, thereby increasing the potentially respirable fraction of the drug.

Since adhesion occurs for particles having a diameter less than 10 μm (Visser, 1995), a majority of the particles of intermediate sized lactose are too large to adhere to the coarse carrier particles. Only approximately 35% (w/w) of intermediate sized lactose that were less than 10 μm may be adhered to the coarse lactose. The concentration of fine lactose that could theoretically form a close-packed monolayer on the coarse particle can be calculated using the following equation (Jones and Pilpel, 1965):

$$C_{\min} = 2\pi d \frac{(D+d)^2}{\sqrt{3}\, D^3} \quad (2)$$

where D and d are the diameters of the coarse and fine lactose, respectively.

A concentration of approximately 0.49% w/w of fine lactose with a VMD of 10 μm, corresponding to 1.4% w/w of the intermediate sized lactose, would be required to form a complete monolayer coating on the coarse lactose particles with a VMD of 90.8 μm. Thus, in the formulation containing 1.5% added intermediate sized lactose, this would theoretically form a complete mono-layer on the coarse lactose. Further increase in the concentration of intermediate lactose would increase the portion of free fine lactose dispersed in the mixtures. After blending salbutamol sulphate with these mixtures, some of the fine particles may act as a carrier for the drug. Therefore, increasing the concentration of the freely dispersed fine lactose particles would be expected to improve the dispersibility and FPF of salbutamol sulphate. However, the greatest increase in the drug FPF occurred when 1.5% w/w of intermediate lactose was added, which resulted in $>60\%$ increase in FPF of salbutamol sulphate whilst increasing the concentration of the added intermediate lactose from 1.5 to 9% produced an approximate 50% further increase in the drug FPF. Thus, fine lactose that is bound to coarse lactose may contribute to the improved dispersibility of salbutamol sulphate to a greater extent than the free fine lactose present in the mixture. Therefore, saturation of the binding sites on the coarse carrier particles may be a more dominant mechanism than the formation of multiplets of drug and fine carrier in increasing the FPF of salbutamol sulphate. Increasing the concentration of fine lactose in order to increase the FPF of the drug still further may not be practical since this may result in poorer flow properties of the powder formulation, which is one of the primary reasons for incorporating coarse carrier particles within the formulation.

5. Conclusions

Adding lactose fine particles to the dry powder aerosol formulation appears to reduce the drug-carrier interaction by occupying possible drug binding sites on the larger lactose particles. The formation of multiplets between fine lactose and drug may also occur in the presence of excess fine particles, thereby hindering direct contact between the drug and the coarse carrier thus promoting drug particle detachment from the carrier surface during aerosolisation. However, the occupation of binding sites on the surface of the coarser carrier particles by the fine lactose may be predominant over other mechanisms. The concentration of added fine lactose has to be carefully controlled such that a desired dispersibility of the drug can be achieved without substantially affecting powder flow properties. However, the role of fine particles of carrier on drug delivery from other inhalation devices or other powder formulations is a subject of further investigation.

Acknowledgements

XMZ would like to acknowledge financial support in the form of a Maplethorpe Trust Fellowship.

References

Adjei, A.L., Gupta, P.K., 1997. Dry powder inhalation aerosols. In: Adjei, A.L., Gupta P.K. (Eds.), Inhalation Delivery of Therapeutic Peptides and Proteins. Marcel Dekker, New York, pp. 625–665.

British Pharmacopoeia Commission, 1993. Pressurised inhalations: deposition of the emmited dose. British Pharmacopoeia, vol. II. HMSO, London, A194–196.

Byron, P., Jashnani, R., Germain, S., 1990. Efficiency of aerosolization from dry powder blends of terbutaline sulfate and lactose NF with different particle size distribution. Pharm. Res. 7, S81.

French, D.L., Edwards, D.A., Niven, R.W., 1996. The influence of formulation on emission, deaggregation and deposition of dry powders for inhalation. J. Aerosol Sci. 27, 769–783.

Ganderton, D., 1992. The generation of respirable cloud from coarse powder aggregates. J. Biopharm. Sci. 3, 101–105.

Ganderton, D., Kassem, N.M., 1992. Dry powder inhalers. In: Ganderton, D., Jones, T. (Eds.), Advances in Pharamaceutical Sciences, vol. 6. Academic Press, London, pp. 165–191.

Gonda, I., 1990. Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract. CRC Rev. Ther. Drug Carrier Syst. 6, 273.

Hersey, J.A., 1975. Ordered mixing: a new concept in powder mixing practice. Powder Technol. 11, 41–44.

Hickey, A.J., Concessio, N.M., Van, M.M., Platz, A.M., 1994. Factors influencing the dispersion of dry powders as aerosols. Pharm. Technol. 18, 58–82.

Jones, T.M., Pilpel, N., 1965. Some physical properties of lactose and magnesia. J. Pharm. Pharmacol. 17, 440–448.

Kassem, N.M., 1990. Generation of deeply inspirable dry powders, PhD thesis, University of London.

Krupp, K., 1967. Particle adhesion theory and experiment. Adv. Colloid Interface Sci. 2, 111–239.

Lam, K.K., Newton, J.M., 1992. Influence of particle size on the adhesion behaviour of powders, after application of an initial press-on forces. Powder Technol. 73, 117–125.

Lucas, P., Anderson, K., Staniforth, J.N., 1998. Protein deposition from dry powder inhalers: fine particle multiplets as performance modifiers. Pharm. Res. 15, 562–569.

Newman, S.P., Clarke, S.W., 1983. Therapeutic aerosols. I. Physical and practical considerations. Thorax 38, 881–886.

Rumpf, H., 1977. Particle adhesion, In: Sastra, K.V.S. (Ed.), Agglomeration 77, American Institute of Mining, Metallurgical and Petroleum Engineers, New York, pp. 97–129.

Staniforth, J.N., 1996. Improvement in dry powder inhaler performance: surface passivation effects. Proc. Drug Delivery to the Lungs VII (London), pp. 86–89.

Steckel, H., Müller, B.W., 1997. In vitro evaluation of dry powder inhalers. II. Influence of carrier particle size and concentration on in vitro deposition. Int. J. Pharm. 154, 31–37.

Timsina, M.P., Martin, G.P., Marriott, C., Ganderton, D., Yianneskis, M., 1994. Drug delivery to the respiratory tract using dry powder inhalers. Int. J. Pharm. 101, 1–13.

Visser, J., 1989. An invited review: Van der Waals' and other cohesive forces affecting powder fluidization. Powder Technol. 58, 1–10.

Visser, J., 1995. Particle adhesion and removal: a review. Part. Sci. Technol. 13, 169–196.

Zeng, X.M., Tee, S.K., Martin, G.P., Marriott, C., 1996a. Effects of mixing procedure and particle size distribution of carrier particles on the deposition of salbutamol sulphate from dry powder inhaler formulations. Proc. Drug Delivery to the Lung VII (London), pp. 40–43.

Zeng, X.M., Tee, S.K., Martin, G.P., Marriott, C., 1996b. Improving the delivery efficiency of dry powder inhaler (DPIs) by adding fine carrier particles to powder formulations. Thorax 51 (3), P195.

Zimon, A.D., 1982. Adhesion of Dust and Powder, 2nd ed. Consultant Bureau, London.