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International Journal of Pharmaceutics 167 (1998) 13–23

international journal of pharmaceutics

On the relationship between drug and carrier deposition from dry powder inhalers in vitro

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Received 21 October 1997; received in revised form 22 December 1997; accepted 23 December 1997

Abstract

Dry powder inhaler formulations usually contain micronised drug particles and lactose as a carrier. Although the fine particle fraction (FPF) of drug from many different formulations has been reported previously, there have been few studies which have determined the deposition of both drug and carrier. In this study, drug and lactose particle deposition was characterised by means of a twin stage impinger (TSI) and an Andersen cascade impactor (ACI). The flow rate was varied between 28.3–90 l/min. The particle size distribution of the lactose carrier in the formulation highly influenced the drug FPF. The higher the flow rate, the higher the FPF of drug when micronised lactose was employed in the formulation. However, when a larger particle size carrier (Lactochem lactose) was employed in the formulation, the FPF was not changed when the flow rate increased (30–90 l/min). Deposition patterns of fine lactose carrier from each formulation at different air flows were broadly similar to those of the drug. At 28.3 l/min, the drug particles were deaggregated to a median particle size of 4.89 ± 0.11 μm (Lactochem formulation) and 4.07 ± 0.09 μm (micronised lactose formulation). When the flow rate was increased to 60 l/min, the degree of dispersion that resulted led to the deaggregation of the drug to particles with a median size of 2.80 μm in both formulations. The coarser particles of lactose in fractions of carrier containing a wide particle size distribution impacted in the throat and preseparator of the ACI and only particles less than 10 μm entered stage 0 to stage 7. The median size of the lactose obtained in both formulations at a flow rate of 28.3 and 60 l/min varied between 5.67 μm to 4.42 μm and hence the carrier particles did not penetrate to stage 3 in the ACI. These results show that in impactors the deposition pattern of both drug and carrier is highly dependent upon air flow rate and particle size distribution of the carrier used to prepare the formulation.

Keywords: Dry powder inhaler; Salbutamol; Lactose; Mass median aerodynamic diameter

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0378-5173/98/$19.00
PII S0378-5173(98)00037-4

1. Introduction

In most dry powder inhaler (DPI) formulations, micronised drug particles adhere to a carrier surface, included to promote dose uniformity and lactose is widely used as the carrier. After inhalation by the patient, the carrier should deposit in the upper airways and the micronised drug particles should be released into the inspired air with a view to such particles gaining access to the lower airways. Many studies carried out in vitro have determined the deposition of drugs (Vidgren et al., 1988; Zanen et al., 1992; De Boer et al., 1996; French et al., 1996), some employing different flow rates (Newman et al., 1991; Malton et al., 1996; Ross and Schultz, 1996). The choice of suitable test flow conditions was found to be a critical variable determining the emitted dose from dry powder inhalers (Hindle and Byron, 1995). Pitcairn et al. (1994) compared lung deposition of salbutamol inhaled from a dry powder inhaler at two inhalation flow rates (46 and 27.8 l/min). A significantly higher percentage of the dose deposited in the lungs at the faster flow rate ($14.1 \pm 3.2\%$) compared to the slow flow rate ($11.7 \pm 2.3\%$). Newman et al. (1991) examined the effect of inhalation flow rate on drug deposition and efficiency. Their findings indicated that inhalation through a device like the Turbuhaler® should be fast for optimal deposition (> 60 l/min), whereas less deposition in the lungs occurred at a slower flow rate (28 l/min). The degree of pulmonary deposition of inhaled drug is dependent not only upon the inhalation device used but also on drug substance and formulation. There are several studies which have demonstrated the importance of particle size on deposition (Ree et al., 1982; Clay et al., 1990). One reason for including suitably sized carriers with the micronised drug are to make it less cohesive since the final formulation in an aerosol must flow well so that a reproducible dose will be dispensed from the reservoir. Drug particles are detached from the carrier particles if the forces imparted by inhalation exceed the interparticulate forces between drug and carrier particles. Large carrier particles were shown to exert stronger adhesion forces on drug particles than smaller carriers (Staniforth et al., 1982) and the in vitro respirable fractions of salbutamol from smaller lactose particles have been shown to be higher than those from larger lactose particles at flow rates from 60 to 200 l/min (Ganderton and Kassem, 1992). The respirable fraction of the drug depends upon the strength of the interaction between drug and carrier particles and the physical properties of both drug and carrier have been shown to influence these interactions (Hickey et al., 1994). Strong adhesion forces result in lower amounts of drug detaching from carrier particles. Increasing the flow rate of an inhaled air stream was shown to increase the emitted dose from inhalers, which resulted in a higher respirable fraction of drug particles (Hindle et al., 1994). French et al. (1996) pointed out that the active drug in the carrier formulations can enter the oral cavity in a variety of possible states of aggregation which include: (a) individual active drug particles, (b) active–active drug agglomerates, (c) active drug bound to individual carrier particles in mono- or multi-layers, (d) combined active drug and carrier agglomerates. No studies have been carried out which have concomitantly determined the deposition of drug and carrier in impactors when operated at different flow rates.

The aim of this study was to investigate the deposition studies of salbutamol and lactose carrier from two formulations in vitro. This was carried out with the view of determining effect of particle size of carrier on drug and carrier deposition at different flow rates. Lactose carriers with different size ranges were prepared and each of these was blended in a ratio of 67.5:1 with salbutamol sulphate.

2. Materials and methods

Micronised salbutamol sulphate was supplied by Glaxo-Wellcome (Ware, UK). Lactochem lactose (medium grade) was obtained from Borculo Whey Ltd. (UK). Micronised lactose was obtained from Meggle (Wasserburg, Germany). The Cyclohaler® device was obtained from Pharbita BV (Nordam, The Netherlands). Capsules (size 3) (Aerocaps) were obtained from Boehringer Ingelheim (Germany).

Table 1
Particle size distribution of salbutamol and lactose determined by laser scattering

Size range (μm)	Percentage by volume		
	Salbutamol sulphate	Micronised lactose	Lactochem lactose
<6.4	91.4	41.0	10.7
6.4–10.0	8.6	27.9	8.6
10.0–20.0	0.0	26.6	32.4
20.0–100.0	0.0	4.5	47.2
Median size (μm)	2.99	8.60	20.10

2.1. Formulation

The formulation was prepared by mixing salbutamol sulphate 0.2 g with lactose 13.5 g in a Turbula® mixer (Basel, Switzerland) for 2 h. Two size ranges of lactose, medium grade Lactochem® (10–50 μm) and micronised lactose (70% < 10 μm), were used as the carrier in the powder blend. Then, 27.4 mg of the blend, equivalent to 400 μg drug, was weighed into each capsule. Uniformity of both blends was 102.2 ± 1.4 and $102.8 \pm 2.4\%$, respectively.

2.2. Particle size measurement

Lactose powder (about 10 mg) was dispersed in 20 ml of chloroform with the aid of water bath sonication for 2 min. Light scattering (Series 2600; Malvern Instruments Ltd, Malvern, UK) was employed to determine the size of lactose and salbutamol sulphate particles (Table 1).

2.3. In vitro deposition studies

2.3.1. Twin stage impinger

The Cyclohaler® device containing one capsule was introduced into the glass throat of the twin stage impinger (TSI, BP1993) which was operated at 30, 60 and 90 l/min. Air was drawn through the device for 20, 10 and 6.7 s, respectively. When operated at these flow rates the effective cut off diameter of the upper stage were found to be 5.5, 6.3 and 7.2 μm, respectively (Srichana et al., 1996). Drug deposition in the lower stage of the TSI was analysed by HPLC using a mobile phase comprising a mixture of acetate buffer pH 4.5 and methanol in a ratio 46:54, a C18 column (Hypersil®, UK) and a UV detector set at a wavelength of 276 nm. The internal standard was ethylparabens (Aldrich, UK). The lower stage deposition was then calculated as a percentage of the nominal dose. Lactose deposition in the lower stage of the TSI was analysed by HPLC using acetonitrile (Rathburn, UK) and water in the ratio 75:25 as a mobile phase, an amino column (Ib-sil®, UK) and a refractive index detector. The internal standard was glucose monohydrate (Fisons, Loughborough, UK). The lower stage deposition was then expressed as the amount in micrograms.

2.3.2. Andersen cascade impactor

A cascade impactor comprising a preseparator, eight stages and collection plates (Andersen Sampler Inc., Atlanta, USA) was prepared for use. All parts were cleaned and rinsed with deionised water and were then sonicated for 15 min to ensure that there was no clogging of any of the orifices. The stages and plates were dried in a hot air oven before being employed in deposition studies, conducted at 28.3 l/min and 60 l/min for 21 and 10 s, respectively. Two formulations were employed for this study. The first comprised single capsules of salbutamol 400 μg mixed with 27 mg of micronised lactose and the formulation was introduced to the cascade impactor using the Cyclohaler® device. The second formulation was the same with the exception that Lactochem® lactose was employed as carrier. After actuating the dose into the Andersen cascade impactor at 28.3 and 60 l/min,

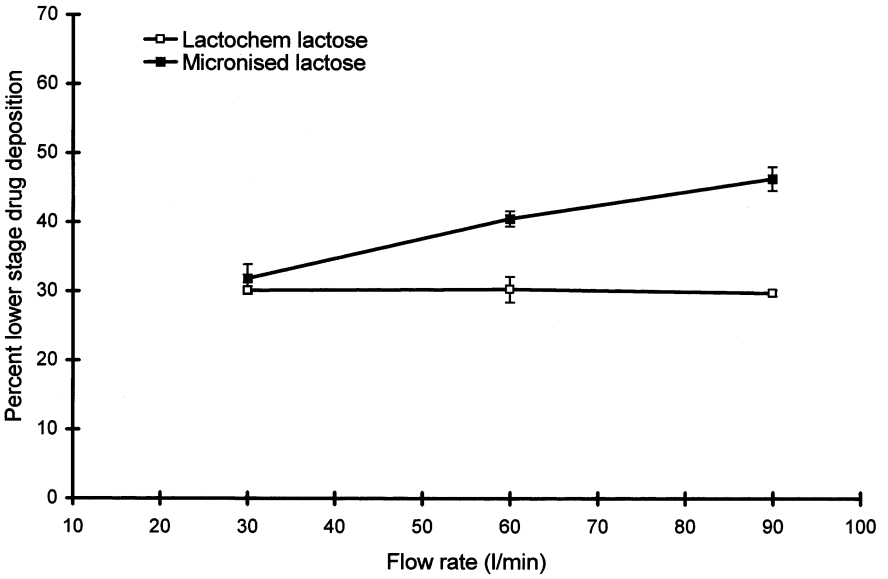

Fig. 1. The effect of flow rate on lower stage drug deposition from two formulations of salbutamol sulphate containing either Lactochem or micronised lactose (mean ± S.D., $n = 6$).

the glass throat, preseparator and each stage were rinsed with 50 ml of mobile phase containing the internal standards before analysing for drug and lactose as described above. The data were analysed for statistical significance using a paired t-test and $p < 0.05$ was considered as significant.

3. Results and discussion

3.1. Particle characterisation

The particle size of the micronised lactose carrier was unimodally distributed and the lactose had a median diameter of 8.6 μm. Lactochem lactose had a multimodal distribution which could be divided into four populations (with median diameters of 4.5, 10, 20 and 45 μm). The particle distributions are summarised in Table 1.

3.2. In vitro deposition studies

3.2.1. Twin stage impinger

When the operated flow rate is increased, the amount of drug depositing in the lower stage might be expected to increase. However, with the formulation which contained Lactochem lactose as a carrier, the amount of drug deposited in the lower stage did not change as the flow rate was increased from 30 to 90 l/min (Fig. 1). Airflow rates of 30 l/min, thus, liberated the respirable drug from the powder formulation as effectively as flow rates of 90 l/min. If the interaction between drug and large sized carrier is large then only a fraction of the drug incorporated in the formulation would expect to be released from the carrier surface. It is apparent that an increase in the rate of air flow within the investigated range did not lead to the detachment of more drug from the surface of the Lactochem carrier particles. However, when micronised lactose was employed, the lower stage deposition increased from 31.85 to 40.49 and 46.26% at flow rates of 30, 60 and 90 l/min, respectively. It has been noted previously that as the fine particle content of the carrier is increased then the fraction of incorporated salbutamol that is potentially respirable increases (Zeng et al., 1996).

With respect to lactose deposition, only about 1 mg of lactose from the Lactochem lactose formulation was found in stage 2 at any flow rate (30, 60 and 90 l/min). Hence an air flow of 30 l/min

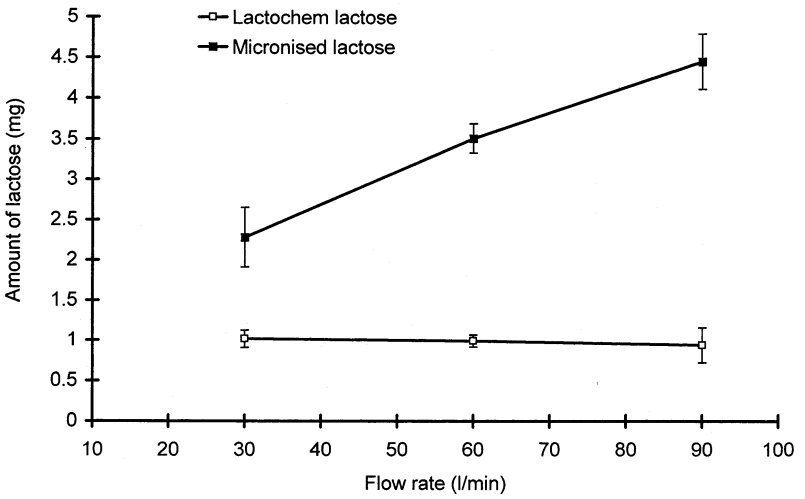

Fig. 2. The effect of flow rate on lower stage deposition of lactose from two formulations of salbutamol sulphate containing either Lactochem or micronised lactose (mean ± S.D., $n = 6$).

was sufficient to release all the fine particles of lactose present in the Lactochem formulation. However, when micronised carrier was employed in the formulation, the fine particle fraction in the lower stage increased dramatically from 30 to 90 l/min (Fig. 2). These results show that the deposition pattern of salbutamol sulphate and fine lactose carrier were similar. One possible explanation for these findings is that the drug and carrier particles released from the surface of larger lactose particles travelled either independently or as small aggregates of lactose and drug into the impactor after aerosolisation. As the amount of lactose in the lower stage increased, the FPF of drug also increased. The drug to carrier ratio as FPF did not change with the Lactochem® formulation, however, in the formulation containing micronised lactose, the ratio increased significantly as a function of air flow rate (Table 2). To understand further the mechanism of drug and lactose delivery in the powder mix, an Andersen cascade impactor (ACI) was employed.

Table 2
Drug to carrier ratio of material deposited in the lower stage of a twin stage impinger[a]

Flow rate (l/min)	Lactochem lactose formulation	Micronised lactose formulation
30	1:8.45	1:17.89
60	1:8.20	1:21.63
90	1:7.91	1:24.02

[a] The drug:lactose composition in the original formulation was 1:67.5.

3.2.2. Andersen cascade impactor

The size distribution of the fine lactose and drug delivered from the two formulations at 28.3 and 60 l/min are presented in Figs. 3–6. The amount of drug delivered as FPF was formulation and air flow rate dependent. Drug particles penetrated to stage 5 (Fig. 3) of the ACI when the Lactochem lactose formulation was aerosolised at 28.3 l/min but with the same formulation when the flow rate was increased to 60 l/min, some drug travelled through the impactor, as far as stage 6 (Fig. 4). Some lactose could be detected as depositing on stage 4 (Fig. 3) of the ACI at a flow rate of 28.3 l/min whereas at a higher flow rate carrier particles could only be determined as reaching stage 3 (Fig. 4). Drug particles were detached from the carrier in higher quantities at the higher flow rate but it would appear that there were differences in the aerodynamic properties of carrier and drug particles at the different flow rates. Figs. 3 and 4 clearly indicate that the FPF of drug particles can penetrate deeper than fine

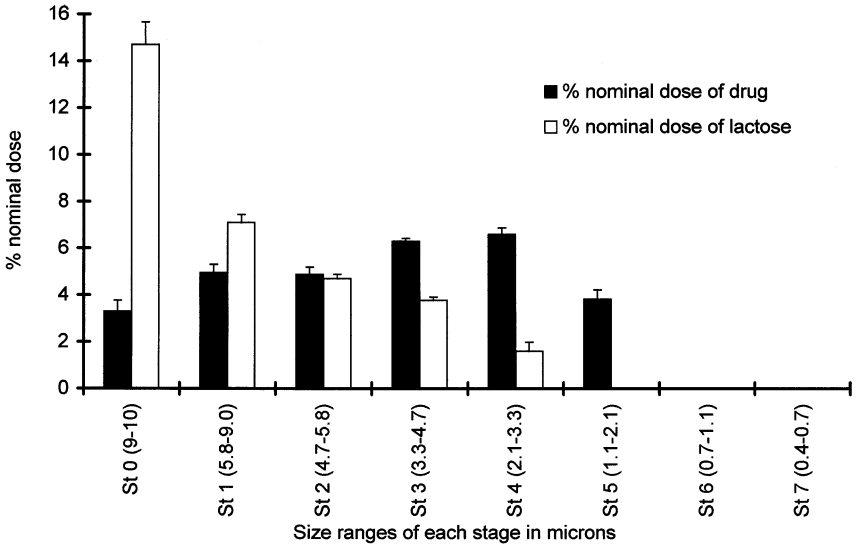

Fig. 3. The size distribution of drug and lactose from the formulation of salbutamol sulphate containing Lactochem lactose using an ACI at 28.3 l/min (mean ± S.D., $n = 5$).

lactose particles contained within the formulation but when the flow rate was increased, despite more drug penetrating deeper into the impactor, the amount lactose depositing on the lower plates was less.

Drug particles aerosolised at 28.3 l/min were found to deposit as far as stage 6 when micronised lactose was employed as an excipient in the formulation and at this stage drug particles were apparently separated from carrier particles (Fig. 5). When flow rates were increased to 60 l/min drug particles from the micronised lactose containing formulation penetrated to stage 7 whereas carrier particles reached only stage 4 (Fig. 6).

The two flow rates gave a clear indication that the interactions which existed between the particles of lactose and drug were different in the two formulations. At higher flow rates more drug particles were separated from the lactose carrier irrespective of the formulation. However, a flow rate of 60 l/min gave higher entrainment of potentially respirable drug from large carrier particles (Lactochem lactose) than small carrier particles (micronised lactose). The increased respirable fraction may not be an indication of an improved detachment of drug particles from carrier because both small sized carrier particles and drug may travel together to a particular stage depending upon their inertial impaction and momentum.

Drug and lactose deposition in the throat part and preseparator of the ACI is shown in Table 3. The amount of drug depositing in the throat was greatest when the Lactochem formulation was aerosolised at 28.3 l/min. However, the percentage nominal dose of drug depositing in the preseparator from this formulation was markedly less than occurred after aerosolisation at 60 l/min, despite less drug depositing in the throat at the higher flow rate. When the micronised formulation was aerosolised there was no change in the percentage drug depositing in the throat as a function of air flow, but an increase in drug depositing in the preseparator again occurred at the higher flow rate. In most cases there was good agreement between the data derived from the TSI and the ACI. However there were some apparent discrepancies. For example, when the TSI was employed no change in the FPF of drug was detected as the flow rate was increased from 30 to 90 l/min, the value remaining at approximately 30% nominal dose (Fig. 1). In contrast the data derived from the ACI indicated that the %FPF of drug increased from 21.56 to 29.76% as the flow rate increased from 28.3 to 60 l/min. It should be

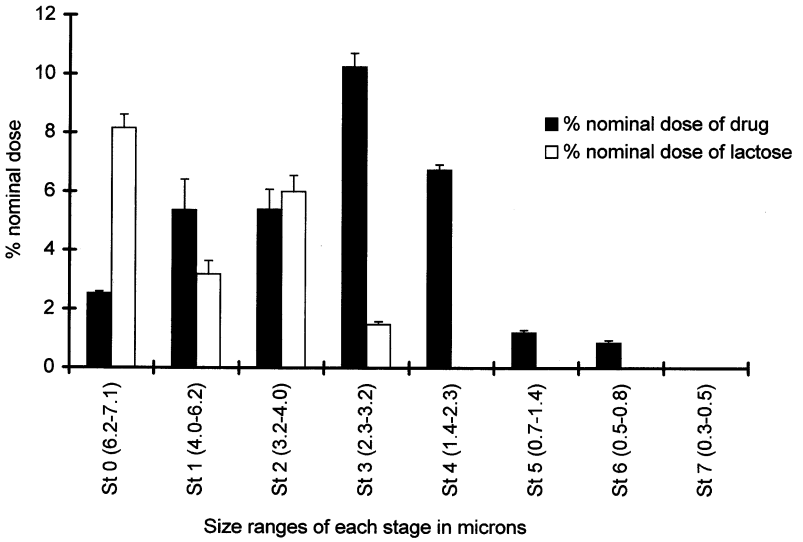

Fig. 4. The size distribution of drug and lactose from the formulation of salbutamol sulphate containing Lactochem lactose using an ACI at 60 l/min (mean ± S.D., $n = 5$).

appreciated that comparisons between these two methods can only be made with a degree of caution, since the effective cut off diameter of the stages in the two impactors vary and also alter as a function of air flow rate. Nevertheless both the TSI and ACI results show an increase in FPF of both drug and lactose from the formulation containing micronised lactose. As the flow rate was increased drug appeared to be detached less efficiently from the carrier lactose, since the FPF of lactose increased more than the FPF of drug (Tables 2 and 3).

The Andersen cascade impactor permits direct determination of the drug and carrier mass distribution of different aerodynamic size intervals. The percentage particle size distribution of both drug and lactose depositing on various stages were transformed to a Z-score to obtain the normal distribution (Figs. 7 and 8). The MMAD corresponds to a Z-score of 0 and the geometric standard deviation (G.S.D.) was obtained using the size at Z-score = 1 divided by the size obtained at Z-score = 0 (Carstensen, 1977). If the particle size exhibited a Gaussian distribution such plots would be straight lines. However, the drug and lactose carrier was bimodally and multimodally distributed respectively. Since the data could not be completely fitted to a straight line, the best fit around a Z-score of 0.8 to −0.8 was used to fit the line. Fig. 7 shows that salbutamol sulphate in the Lactochem lactose formulation gave an MMAD of 4.89 ± 0.11 μm at a flow rate of 28.3 l/min (Table 4). When the flow rate was increased, the drug was dispersed more effectively and an MMAD of 2.81 ± 0.04 μm was obtained from the ACI data which was very close to the original size of the drug determined by laser light diffraction (2.99 μm). These two techniques have been shown to generate comparable data (Clark, 1995). The lactose carrier in Lactochem® formulation was deaggregated further as air flow was increased with an MMAD of 5.67 ± 0.05 μm at 28.3 l/min, being reduced to 4.48 ± 0.11 μm at 60 l/min (Table 4). A fraction of the Lactochem lactose even at an air flow rate of 28.3 l/min is clearly potentially respirable. However, salbutamol would appear to have a greater chance of reaching the more peripheral lung regions at higher flow rates because it was dispersed more efficiently into particles with a much smaller size distribution. In the case of the micronised lactose formulation, the drug was deaggregated to give an MMAD of 4.07 ± 0.09 μm at 28.3 l/min which was smaller than with the Lactochem formulation

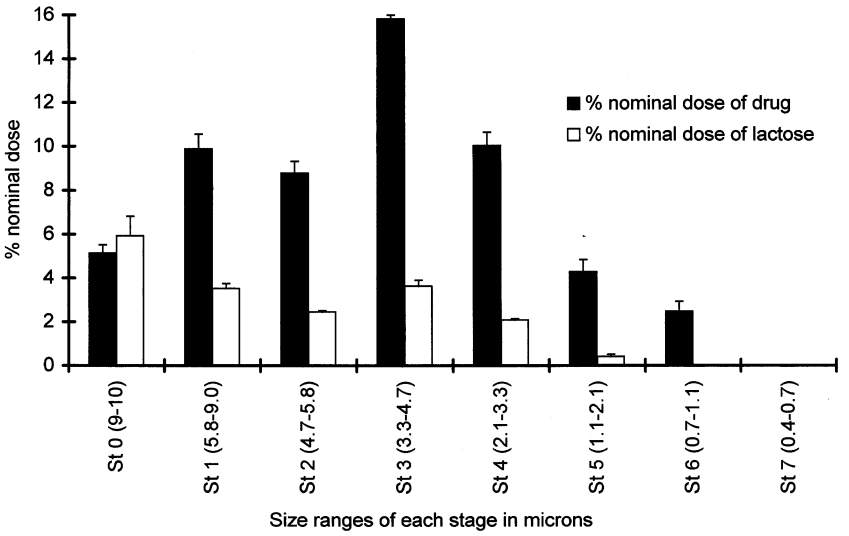

Fig. 5. The size distribution of drug and lactose from the formulation of salbutamol sulphate containing micronised lactose using an ACI at 28.3 l/min (mean ± S.D., $n = 5$).

at the same flow rate. The adhesion forces acting between drug and different sized carriers were presumably different since the drug appeared to interact less with the micronised lactose carrier than with Lactochem lactose. However, when the flow rate was increased to 60 l/min, the size of the drug released from these two formulations was not significantly different (2.81 and 2.80 μm). Hence, this flow rate had overcome the adhesion forces acting between drug and carrier particles and the release of adhered drug appears to have been maximised. The MMAD of micronised lactose at 28.3 l/min was 5.10 ± 0.11, being smaller than for Lactochem lactose at the same flow rate. Such particles from this formulation would be expected to penetrate deeper into the airways than

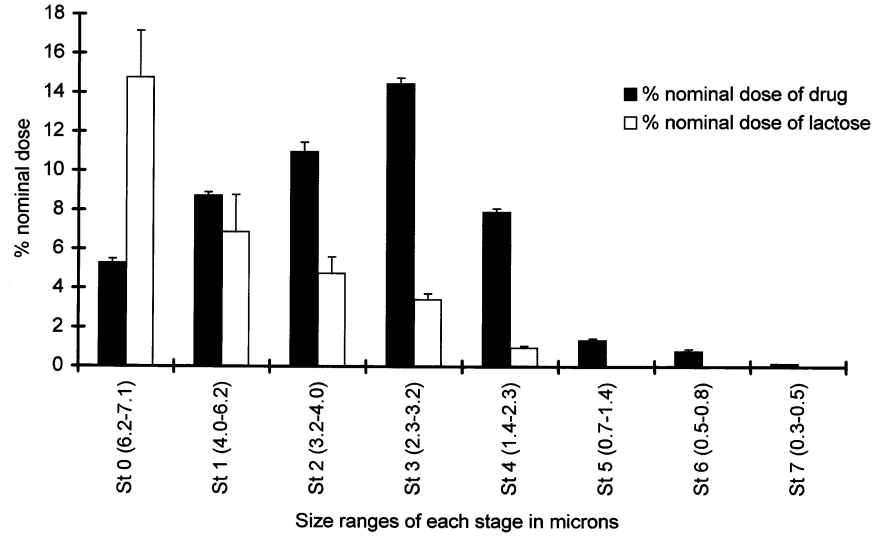

Fig. 6. The size distribution of drug and lactose from the formulation of salbutamol sulphate containing micronised lactose using an ACI at 60 l/min (mean ± S.D., $n = 5$).

Table 3
Percent nominal dose of salbutamol and lactose deposition on each stage of the Andersen cascade impactor (Mean ± S.D., $n = 5$)

Part	Lactochem lactose formulation				Micronised lactose formulation			
	Drug Deposition (l/min)		Lactose deposition (l/min)		Drug deposition (l/min)		Lactose deposition (l/min)	
	28.3	60	28.3	60	28.3	60	28.3	60
Throat	31.50 ± 1.82	22.93 ± 1.45	35.96 ± 3.55	35.55 ± 0.59	20.71 ± 1.18	19.78 ± 1.22	34.29 ± 0.67	40.56 ± 0.55
Preseparator	14.24 ± 0.18	21.74 ± 0.95	12.40 ± 0.74	18.78 ± 0.89	8.63 ± 1.28	9.07 ± 0.67	19.10 ± 0.13	19.06 ± 0.63
Stages 0–7	30.42 ± 1.10	32.29 ± 1.20	31.85 ± 0.96	18.81 ± 0.88	56.39 ± 2.10	49.56 ± 1.10	17.96 ± 0.89	30.74 ± 1.18
Dose emitted	84.85 ± 1.82	85.92 ± 1.62	85.29 ± 0.93	82.10 ± 0.48	85.50 ± 1.10	88.20 ± 1.60	86.76 ± 0.70	96.77 ± 0.77
%fine particle fraction[a]	21.56 ± 0.47	29.76 ± 0.69	10.03 ± 0.96	10.55 ± 0.56	41.35 ± 0.86	44.29 ± 1.30	8.55 ± 0.27	16.00 ± 0.93

[a] Particle size less than 5.8 μm and 6.2 μm at 28.3 l/min and 60 l/min, respectively.

lactose from the Lactochem formulation. However, at a flow rate of 60 l/min there proved to be no difference in the MMAD of the lactose deposited on the plates of the ACI from the Lactochem and micronised lactose containing formulation. The G.S.D. of drug and carrier were around 2 which indicated that the particles were widely distributed in size (Table 4).

4. Conclusions

When a larger amount of carrier fine particles were included in dry powder inhaler formulations, a higher amount of drug penetrated to the lower stage of the TSI. The interaction of the drug with the smaller and/or larger size of the carrier must therefore change as the carrier fine particle con-

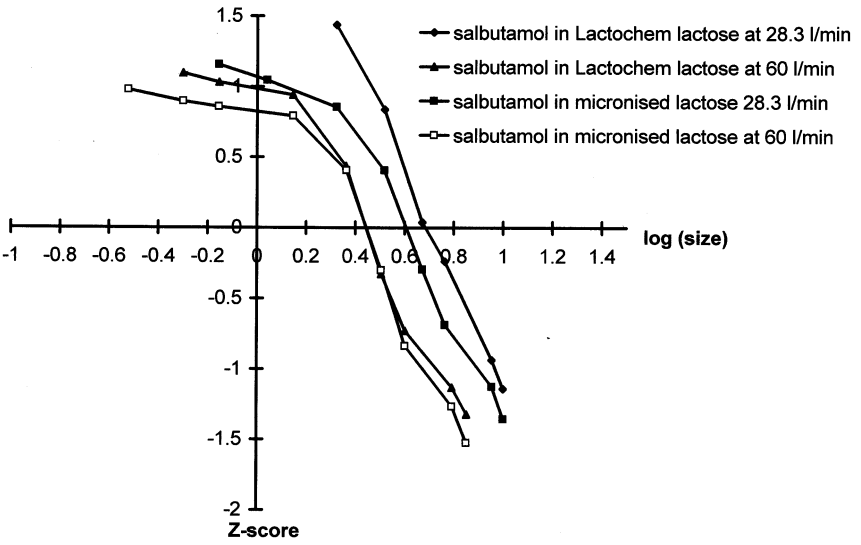

Fig. 7. The particle size distribution of salbutamol sulphate in two formulations of salbutamol sulphate containing either Lactochem or micronised lactose as diluent after aerosolised at either 28.3 or 60 l/min.

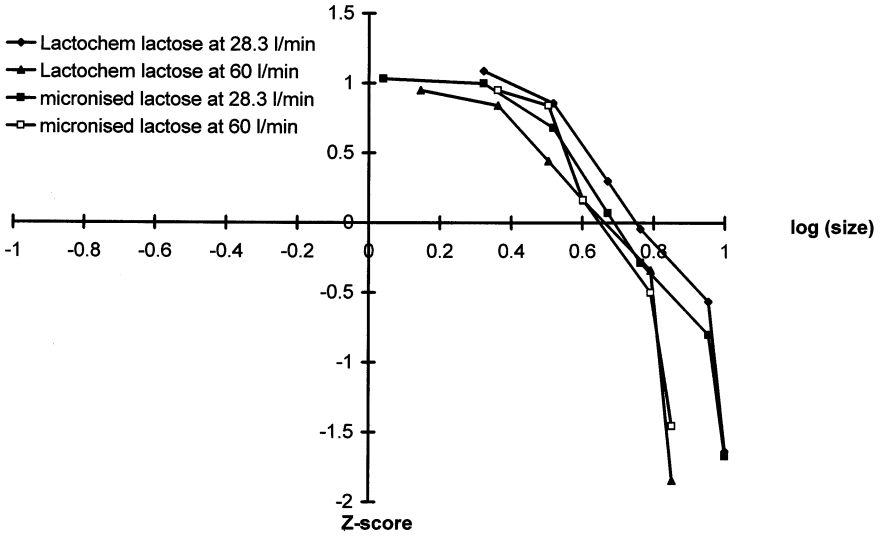

Fig. 8. The particle size distribution of lactose in two formulations of salbutamol sulphate containing either Lactochem or micronised lactose as diluent after aerosolised at either 28.3 or 60 l/min.

tent increases. The smaller sized carrier might be expected to occupy sites on the larger sized carrier which would otherwise have been occupied by drug particles. Therefore, when more fine lactose carrier particles were added to the formulation, the adhesive force between the drug and carrier could be reduced. It is possible for the drug to be detached from the carrier surface if the interaction with the carrier is sufficiently low. The interaction between drug and carrier are essential in determining drug availability from dry powder inhalers, which is a major application of developing the in vitro deposition of drug and carrier concomitantly. The drug requires aerosolisation as fine particles into the inspired air in order to reach the peripheral airways. A flow rate about 60 l/min was sufficient to disperse drug particles into respirable fine particles (2.8 μm) at least from the formulations used in this work and the Cyclohaler device under the prevalent experimental conditions. Some of the drug and carrier particles appear to travel together to the lower airways although drug particles alone were shown to have the capacity to reach lower regions of the lung. The amount of lactose that is potentially respirable is not surprisingly dependent upon the particle size of the lactose employed to prepare the formulation.

Table 4
MMAD of salbutamol sulphate and lactose carrier obtained from Andersen cascade impactor data (Mean ± S.D., $n = 5$)

Formulation	Flow rate (l/min)	MMAD (μm) of drug	G.S.D. (μm) of drug	MMAD (μm) of lactose	G.S.D. (μm) of lactose
Lactochem lactose	28.3	4.89 ± 0.11	1.74 ± 0.03	5.67 ± 0.05	1.95 ± 0.01
	60	2.81 ± 0.04	2.00 ± 0.02	4.48 ± 0.11	1.65 ± 0.10
Micronised lactose	28.3	4.07 ± 0.09	2.01 ± 0.10	5.10 ± 0.11	2.02 ± 0.03
	60	2.80 ± 0.02	1.86 ± 0.04	4.42 ± 0.22	2.30 ± 0.04

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