

INFLUENCE OF FORMULATION VARIABLES AND INHALATION DEVICE ON THE DEPOSITION PROFILES OF CROMOLYN SODIUM DRY POWDER AEROSOLS

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ABSTRACT

Dry powder inhalers (DPIs) have attained considerable attention due to their propellant-free formulations and the patient's inherent coordination with actuation. Generally, DPI formulations consist of a micronized drug alone or mixed with carrier particles. This study was carried out to investigate the effects of carrier particle size and weight fraction on aerosolisation behaviour of cromolyn sodium (CS). Pharmatose® 450M and Pharmatose® 325M, two commercial α -lactose monohydrate with different particle sizes, were blended in two different fractions (30 and 50% w/w) with CS. A low resistance device (Spinhaler®) and a medium resistance device (Cyclohaler®), were used to evaluate the effect of inhaler design on the deposition profiles of CS. The in vitro deposition of the formulations was determined using a twin stage impinger (TSI). Fine particle dose, fine particle fraction and emitted dose of the drug were depended to both formulation and inhalation devices. Fine particle fractions of the drug aerosolised from the formulations ranged from 9.35 up to 36.45%. The highest fine particle fraction was produced by formulation containing 50% Pharmatose® 450M as carrier. Cyclohaler® showed higher efficiency in aerosolisation of CS compared to Spinhaler®.

Keywords: Dry powder inhaler; Cromolyn sodium; Lactose; Particle size; Weight fraction ratio

INTRODUCTION

Drug delivery to the respiratory tract has become an important and effective method for treatment of pulmonary diseases, such as asthma, bronchitis and emphysema (1). Metered dose inhalers (MDIs) are the most commonly used inhalers for pulmonary delivery of pharmaceuticals. The ban on the use of chlorofluorocarbons in MDIs has forced the pharmaceutical industry to introduce dry powder inhalers (DPIs) as an alternative system which utilizes drugs in dry powder form. The poor coordination between inspiration and dose emission, which commonly used to happen by using MDIs, can be avoided by application of DPIs (2). In fact, the inspiratory flow of the patient is the input energy which disperses dry powder formulation.

All DPIs consist of a powder formulation and an inhalation device. The powder formulation is composed of a micronised drug powder, either alone or in combination with carrier particles (3). Since the micronised drug particles are usually highly cohesive, they are usually mixed with coarser carrier particles. This process can also promote dose

uniformity of the formulations (4). During inhalation drug particles must detach from the carrier surface to penetrate into the respiratory airways. The detachment can occur if the forces imparted by inhalation exceed the interparticle forces between drug and carrier particles. Strong adhesion forces result in poor detachment, which in turn, lower respirable fractions of the drug. The adhesion forces depend on physical properties of both drug and carrier particles (5-7). Therefore, the application of particles having suitable physical properties may be considered as one of the most important approaches in design of the formulation of dry powders for inhalation.

Selection of the inhaler device is another important approach in the preparation of an inhalation form of a drug as a DPI (8). The turbulent air stream created in the inhaler during inhalation causes the powder aggregates to break up into primary particles. The efficiency of the turbulence created in the inhaler depends to its internal structure (9-10). Several inhalers are available in the market with different air flow resistance and delivery efficiency (11).

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Cromolyn sodium (CS) is the only drug available in our country in DPI formulation which is used by Spinhaler®. The Spinhaler® is one of the first generation of passive unit dose DPIs (12) which was launched for pulmonary delivery of CS. The effect of various excipients on in vitro deposition of CS aerosolised with Microhaler® has been previously reported (13). The influence of inhaler devices on aerosolisation behavior of pure amorphous CS dry powders spray dried at different conditions has been also investigated (14). No report is available comparing the effects of carrier and device variables on deposition profiles of CS. The aim of this study was to investigate the deposition profiles of aerosolised CS using two inhaler devices with different internal resistance, Spinhaler® and Cyclohaler®. Four formulations of CS and lactose were prepared in order to determine the effects of carrier particle size and weight fraction of carrier on in vitro deposition of the drug. The effects of formulation variables and inhaler devices were compared using an experimental design approach.

MATERIALS AND METHODS

Micronised CS was supplied by Profarmaco, Italy. Two commercial grades of lactose, Pharmatose® 450M (P450) and Pharmatose® 325M (P325), were obtained as α -Lactose monohydrate from DMV, The Netherlands. The devices including Spinhaler® (Fisons, UK) and Cyclohaler® (ISF, The Netherlands) were available commercially. Capsules (sizes 2 and 3) were obtained from Cipla, India.

Particle size measurement

A small amount (about 5 mg) of CS and lactose powders were dispersed separately in 5 mL of n-butanol with the aid of water bath sonication (Starsonic 60, Liarre, Italy) for 3 min. The powders were not soluble in n-butanol and were easily suspended upon addition to the vehicle. The particle sizes of the powders were measured by laser diffraction (Mastersizer X, Malvern Instruments, Malvern, UK) at obscuration between 0.18 and 0.20. Each sample was measured in triplicate. The size distribution was expressed by equivalent volume diameters at 10 ($d_{10\%}$), 50 ($d_{50\%}$) and 90% ($d_{90\%}$) cumulative volume and the mode(s).

Surface area analysis

The surface area of lactose powders was measured in triplicate with a Quantachrome surface area analyzer (NOVA 2000 e, Quantachrome, USA), applying the BET equation. Nitrogen gas was used as the adsorbate.

X-ray diffraction (XRD)

Crystalline properties of the lactose samples were examined using a X-ray diffractometer (D5000, Siemens, Germany). Samples were placed in a quartz holder and measured using Cu K α radiation with angular increments of $2\theta = 0.030^\circ$ in the range of $5-35^\circ$.

Experimental design

A 2^3 factorial design was carried out using Statgraphics software (Statgraphics Plus 2.1, Statistical Graphics Corp., USA) to investigate the influence of inhalation device and formulation parameters on aerosolisation behavior of micronized CS. Different experiments were run by changes in three factors, the particle size of carrier, the weight fraction of carrier and the type of inhalation device (Table 1). Each factor had two levels and thus a total of 8 combinations were possible (Table 2). These factors are the most important parameters influencing the efficiency of drug delivery from DPIs.

Preparation of dry powder formulations

The formulations were prepared by mixing CS with lactose in a turbula mixer (Dorsa Novin Afzar, Tehran, Iran) for 60 min. Homogeneity of the mixtures was evaluated by removal of ten randomly selected samples from different parts of the vessel, each weighing 40 ± 0.5 mg, for assay of CS content. The degree of homogeneity was expressed in terms of coefficient of variation (CV) in CS content. All formulations were filled in hard gelatin capsules (size 2 for Spinhaler® and size 3 for Cyclohaler®) manually in a way that each capsule contained 20 ± 0.5 mg of the drug.

Assay of the drug

Aqueous solutions of CS were assayed by UV spectrophotometry (V 530, Jasco, Japan) at a wavelength of 326.5 nm (14). Linearity was achieved using standard aqueous solutions of CS between 5 and 50 $\mu\text{g/ml}$ ($R^2 = 0.999$).

In vitro deposition test

Deposition of CS from each formulation was determined using a twin-stage impinger (TSI; Apparatus A, European Pharmacopoeia, 2000, Copley, Nottingham, UK) after aerosolisation at 60 ± 5 L/min with 7 and 30 ml of purified water placed into stages 1 and 2 of the impinger, respectively (15). The device to be tested was placed into a rubber mouthpiece attached to the throat of the TSI and the pump was switched on. The pump was operated for 5 second so that the flow rate of 60 ± 5

Table 1. Variables in the factorial design

Variables	Levels	
	Low (-1)	High (+1)
Particle size of carrier	Pharmatose® 450M (fine carrier)	Pharmatose® 325M (coarse carrier)
Weight fraction of carrier	30% (w/w)	50% (w/w)
The type of device	Spinhaler® (low resistance)	Cyclohaler® (medium resistance)

L/min was established. At this time the pierced capsule was released and the pump was allowed to run for another 5 second which allowed the aspiration of 5 L of air in the apparatus, as recommended by the European Pharmacopoeia (2000). Each section (inhaler, capsule shell, stages 1 and 2) was rinsed with purified water. The rinsing liquid was collected and diluted to an appropriate volume. The CS content was determined by the above described UV spectrophotometry method.

The amount of CS that deposited in stage 2 of the TSI (effective cut-off diameter < 6.4 μm) was considered as the fine particle dose (FPD). The recovered dose (RD) was defined as the total amount of CS recovered from inhaler, capsule shell, stages 1 and 2 after each actuation. The emitted dose (ED) considered being the amount that emitted from the inhalation device and capsule into the TSI. Fine particle fraction (FPF) was the ratio of FPD to RD, expressed as percentage, while dispersibility was expressed as the percentage of FPD to ED (16).

RESULTS AND DISCUSSION

Physical properties of the materials

The presence of α -lactose and β -lactose in a lactose sample can be detected by XRD analysis (17). The sharp diffraction peaks in XRD patterns of commercial lactose samples were shown crystalline nature for both materials (fig. 1). The presence of α -lactose monohydrate in P450 and P325 was supported by a peak at diffraction angle of 12.6°. No peak at diffraction angle of 10.6° was observed for β -lactose form at XRD profiles of L450 and L325. α -Lactose monohydrate is a non-hygroscopic material which is typically used as a carrier in the preparation of DPI formulation.

Table 3 shows the particle size distribution data of the materials employed in this study. The CS powder had a $d_{50\%}$ of 1.52 μm and a mode at 2.1 μm . The commercial CS sample with a particle size predominantly smaller than 3.03 μm exhibited a suitable particle size range for DPI formulation. P450 had a $d_{50\%}$ of 12.3 μm with two modes at 2.8 and 18.7 μm . The size distribution pattern of P325

exhibited a $d_{50\%}$ of 53.5 μm with a bimodal pattern at 3.3 and 54.0 μm . Therefore, P450 having particles predominantly between 2.5-26.4 μm was considered as a fine carrier and P325 which contained particles with sizes mainly ranged from 6.6 μm up to 74.1 μm was considered as a coarse carrier. These differences in particle sizes of the lactose samples were verified qualitatively by their SEM pictures (fig. 2). The surface area exhibited by P450 was about two times higher than P325 (table 3). Therefore, P450 and P325 were considered as completely crystalline samples of α -lactose monohydrate which exhibited different particle size and surface area.

Table 2. Factorial design matrix^a

Run	Particle size of carrier	Weight fraction of carrier	The type of device
1	+1	+1	-1
2	+1	+1	+1
3	-1	+1	+1
4	-1	-1	+1
5	-1	-1	-1
6	-1	+1	-1
7	+1	-1	-1
8	+1	-1	+1

^a The levels (-1 and +1) of each variable are described in table 1.

Content uniformity

Table 4 shows the recovery and coefficient of variation in CS content obtained with all formulations. The lowest recovery was found for formulation containing coarse carrier (P325) in lower weight fraction. All formulations presented a CV less than 3%, therefore, mixing of samples seems to be quite satisfactory.

In vitro deposition data

Table 5 shows the results of all experiments of the factorial design. The RD measured for different experiments was ranged from 18.95 \pm 0.85 mg to 19.16 \pm 1.07 mg. The data suggested that the independent variables had no significant effect ($p > 0.05$) on RD which was calculated for all experiments.

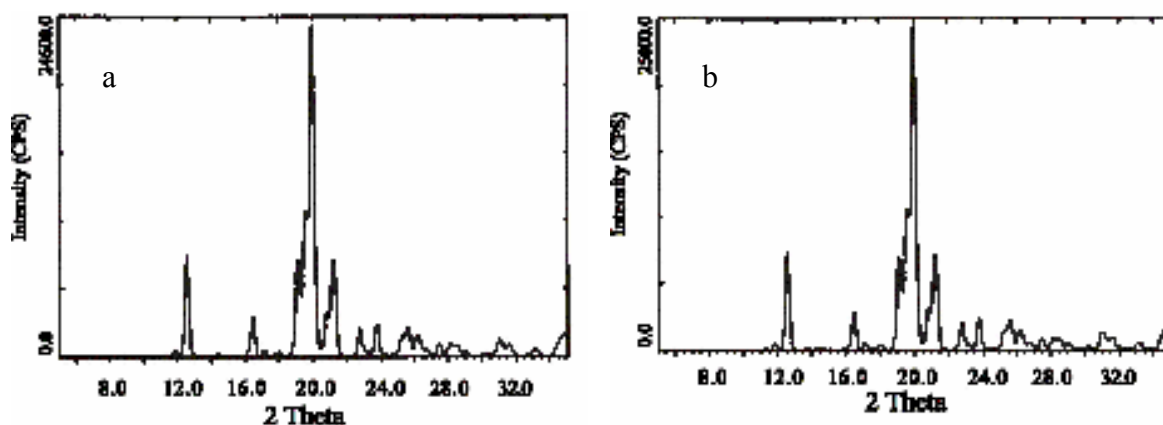


Fig. 1. X-ray diffraction patterns of lactose samples: (a) Pharmatose® 450M and (b) Pharmatose® 325M.

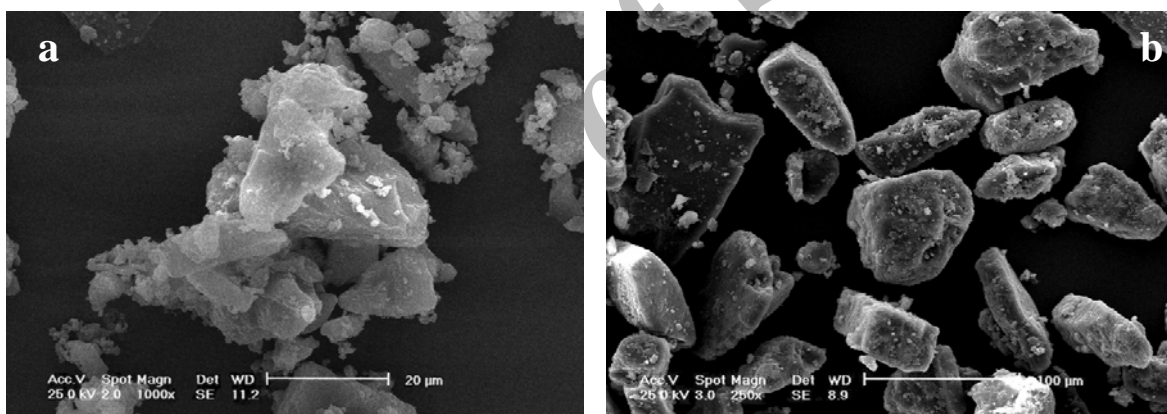


Fig. 2. Scanning electron micrographs of (a) Pharmatose® 450M and (b) Pharmatose® 325M.

Table 3. Particle size distributions and surface areas of the materials (mean ± SD, n = 3)

Material	Cumulative percent (undersize) ^a			Mode (s) (µm)	< 5 µm (%)	Surface area (m ² /g)
	d _{10%} (µm)	d _{50%} (µm)	d _{90%} (µm)			
Cromolyn sodium	0.7 ± 0.1	1.52 ± 0.2	3.03 ± 0.02	2.1 ± 0.1	100 ± 0	ND ^b
Pharmatose® 450M	2.5 ± 0.3	12.3 ± 0.8	26.4 ± 0.7	18.7 ± 1.5 2.8 ± 0.3	25.5 ± 1.3	0.712 ± 0.03
Pharmatose® 325M	6.6 ± 0.8	53.5 ± 4.3	74.1 ± 3.8	54.0 ± 2.1 3.3 ± 0.2	8.5 ± 2.1	0.371 ± 0.01

^a Equivalent volume diameters at 10 (d_{10%}), 50 (d_{50%}) and 90% (d_{90%}) cumulative volume.

^b Not determined

P450 produced significantly ($p < 0.05$) higher FPD of the drug in comparison to P325, employed at the same weight fraction. This result was unexpected because increase in free surface, and hence free surface energy, due to the decrease in carrier particle size (Table 3) should result in higher adhesive forces between drug and carrier particles. However, when design of the inhalers is considered, the differences observed in FPD of the formulations will be more defined. In both inhalers used in this study, the capsules were pierced at the start of the experiments using the metal needles of the inhalers. When the air flow was drawn through the inhalers, the capsules started to rotate and the drug/carrier particles dispersed out of the rotating capsules under the inertia force. Therefore, powders containing carrier with larger particle size and higher mass deposited on the inhaler wall due to their higher inertia. The differences between the amounts of CS emitted from the devices after aerosolisation of the formulations containing P450 or P325 were not significant ($p > 0.05$) (Table 5). A reduction in carrier particle size was also shown to improve the aerosolisation of budesonide from Spinhaler® (18) and salbutamol sulphate from Rotahaler® (19). Increasing the amount of P450 in the mixture led to an increase in the FPD. The presence of P450 in 50% ratio resulted in breakage of more agglomerates of the drug microparticles. Therefore, single CS particles ($d_{90\%} < 5.4 \mu\text{m}$) had a markedly higher probability to reach to the lung. The same trend was observed for binary mixtures of CS with P325. These results were in agreement with a report for binary mixtures of CS with excipients which were aerosolised from Microhaler® (13).

Table 4. Percent recovery and coefficient of variation (CV) in cromolyn sodium content obtained from different formulations (n = 10)

Formulation ^a	% recovery \pm SD	%CV
CS – P450 (70:30)	98.60 \pm 1.96	2.14
CS – P450 (50:50)	97.74 \pm 2.15	2.35
CS – P325 (70:30)	97.35 \pm 2.13	2.29
CS – P325 (50:50)	98.49 \pm 1.57	1.72

^a CS: cromolyn sodium; P450: Pharmatose® 450M; P325: Pharmatose® 325M

The factorial design revealed that the type of inhalation device, the particle size of carrier and the weight fraction of carrier have significant influences

on the FPF of the drug ($p < 0.01$, Fig. 3a). The highest FPF was obtained for formulations containing 50% P450 (Fig. 4). The FPF of the drug aerosolised from this formulation using Spinhaler® and Cyclohaler® were found to be about 19.35% and 36.45%, respectively. Compared to Spinhaler®, all formulations which were aerosolised by the use of Cyclohaler® yielded significantly higher FPF ($p < 0.01$). At the same flow rate, a higher linear velocity will be expected to generate in Cyclohaler® which exhibits higher air resistance than Spinhaler® (20). The drag force and turbulence of the air stream, which influences on the deaggregation and detachment of drug particles from the surface of carrier, are governed by the linear velocity. Therefore, it is expected to obtain higher FPF and dispersibility of fine CS particles from formulations which were aerosolised using Cyclohaler®, compared to Spinhaler®. Different FPF was observed for amorphous spray dried CS aerosolised from Dinkihaler® and Rotahaler® (14). The dependence of FPF of salbutamol sulphate on the design of inhalation devices has also been reported in the literature (11). The factorial design showed that the type of inhalation device and the weight fraction of carrier have a strong influence of on dispersibility of aerosolised CS ($p < 0.05$, Fig. 3b). Increasing the weight fraction of carrier resulted in interaction of more carrier particles with the drug particles during mixing process. This in turn improved the deagglomeration of micronized CS particles and probably caused the attachment of more single CS particles to the surface of carrier. The energy required for detachment of micronized particles from the surface of carrier was lower than required energy for disruption of aggregates of micronized particles. The lower effect of particle size of carrier in comparison to the other factors may be related to the presence of higher proportion of particles $< 5 \mu\text{m}$ in P450. This fraction of carriers can make some agglomerates with drug particles so strongly that may not deagglomerated by Spinhaler®, of the low resistant device, at 60 l/min. It has been shown that the presence of carrier particles $< 5 \mu\text{m}$ in a proportion higher than 10% resulted in a decrease in FPF of aerosolised salbutamol sulphate (21).

The same FPF was observed for formulations containing 30% P450 or 50% P325. Since the presence of fine carrier may exhibit more difficulty in powder handling during filling process, the strategy of using coarse carrier in an optimum weight fraction can be beneficial to improve both powder flow and fluidization properties.

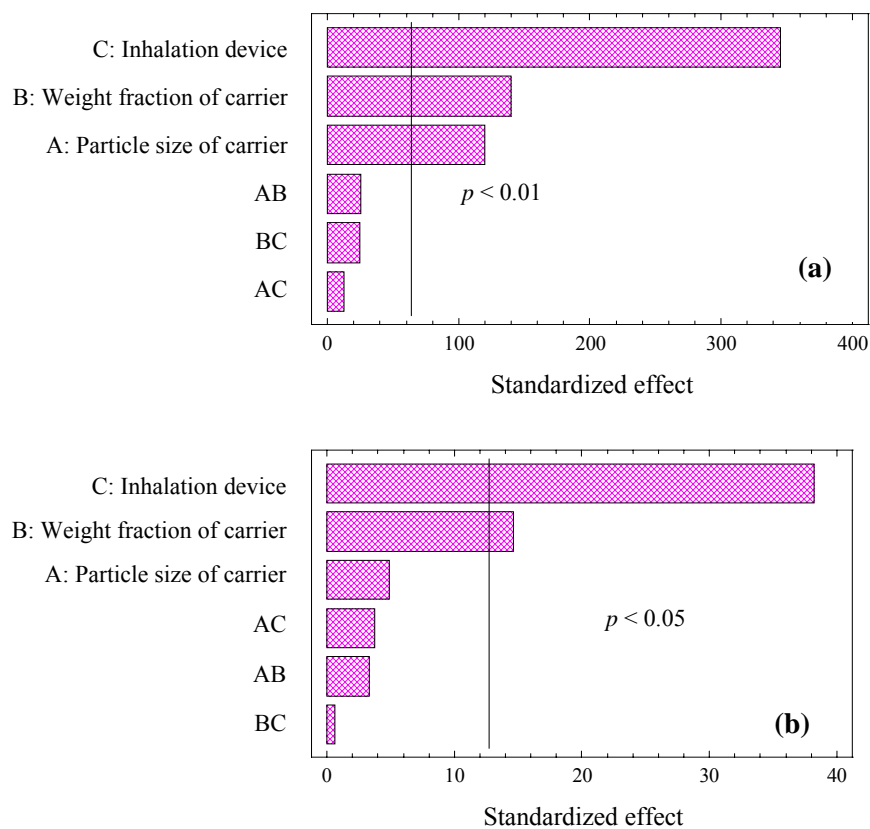


Fig. 3. Pareto charts for (a) fine particle fraction (FPF) and (b) dispersibility of the drug aerosolised from different formulations using Spinhaler® or Cyclohaler®.

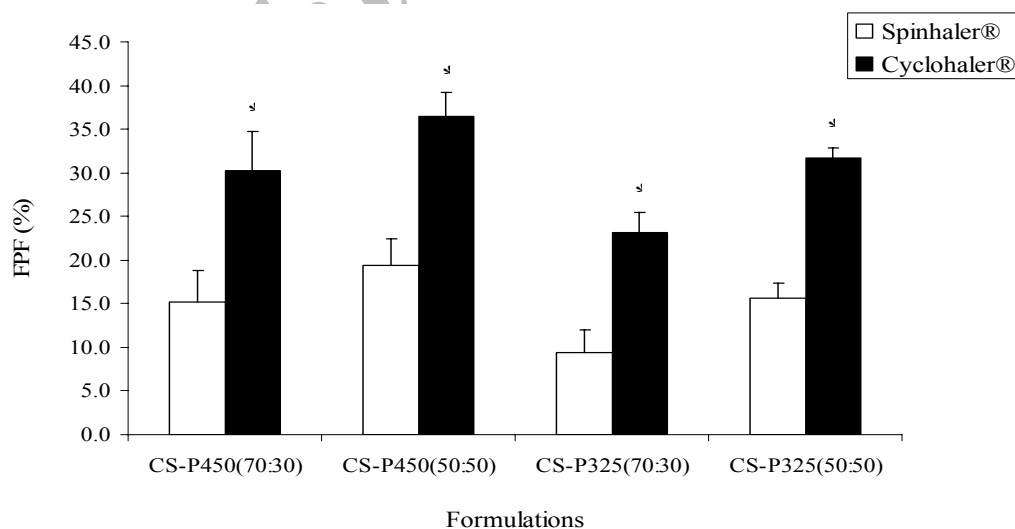


Fig. 4. Fine particle fraction (FPF) of cromolyn sodium (CS) from different formulations containing either Pharmatose® 450M (P450) or Pharmatose® 325M (P325) aerosolised by Spinhaler® or Cyclohaler®.

* Represent a significant difference at $p < 0.01$ compared with the similar formulation aerosolised with Spinhaler®.

Table 5. Recovered dose (RD), fine particle dose (FPD) and emitted dose (ED) of cromolyn sodium aerosolised from different formulations (mean \pm SD, n = 3)

Device/Formulation ^a	RD (mg)	FPD (mg)	ED (mg)
Spinhaler®			
CS-P450 (70:30)	18.95 \pm 0.85	2.87 \pm 0.57	13.74 \pm 0.52
CS-P450 (50:50)	19.02 \pm 0.51	3.71 \pm 0.57	14.19 \pm 1.10
CS-P325 (70:30)	18.98 \pm 0.63	1.76 \pm 0.46	12.57 \pm 0.60
CS-P325 (50:50)	19.12 \pm 0.56	3.05 \pm 0.43	12.80 \pm 0.81
Cyclohaler®			
CS-P450 (70:30)	19.16 \pm 1.17	5.92 \pm 0.58	15.34 \pm 1.59
CS-P450 (50:50)	19.15 \pm 0.27	7.12 \pm 0.55	15.64 \pm 0.45
CS-P325 (70:30)	18.96 \pm 0.67	4.40 \pm 0.41	11.97 \pm 0.73
CS-P325 (50:50)	19.09 \pm 1.03	6.05 \pm 0.45	13.12 \pm 0.66

^a CS: cromolyn sodium; P450: Pharnatose® 450M; P325: Pharnatose® 325M

CONCLUSION

FPD, FPF and dispersibility of the drug were depended on both particle size and weigh fraction of the carriers used in the formulation as well as the type of inhalation device. Overall, coarse lactose (P325) produced lower delivery efficiency of CS than fine lactose (P450), when were compared at the same weight fraction. Increasing the amount of carrier in the formulation improved the resultant drug deposition in vitro. Different inhaler design

was shown to have different efficiency in the breaking up of the agglomerates into finer particles. The maximum FPD, FPF and dispersibility were obtained with formulation containing P450 in 50% weight fraction using Cyclohaler® as the inhalation device. The results of this study reveal that varying the dry powder formulation and the inhaler efficiency can change the in vitro deposition profiles of CS considerably.

REFERENCES

1. Suarez S, Hickey AJ. Drug properties affecting aerosol behavior. *Respiratory Care* 2000; 45: 652-666.
2. Prime D, Atkins PJ, Slater A, Sumbly B. Review of dry powder inhalers. *Adv Drug Deliv Rev* 1997; 26: 51-58.
3. Ganderton D. The generation of respirable clouds from coarse powder aggregates. *J Biopharm Sci* 1992; 3: 101-105.
4. Zeng, XM, Martin GP, Marriott C. Particulate Interactions in Dry Powder Formulations for Inhalation, Taylor & Francis, London; 2001. p. 74-80.
5. Dickhoff BHJ, de Boer AH, Lambregts D, Frijlink HW. The effect of carrier surface and bulk properties on drug particle detachment from crystalline lactose carrier particles during inhalation, as function of carrier payload and mixing time. *Eur J Pharm Biopharm* 2003; 56: 291-302.
6. Lahrib H, Martin GP, Marriott C, Prime D. The influence of carrier and drug morphology on drug delivery from dry powder formulations. *Int J Pharm* 2003; 257: 283-296.
7. Harjunen P, Lankinen T, Salonen H, Lehto VP, Jarvinen K. Effects of carriers and storage of formulation on the lung deposition of a hydrophobic and hydrophilic drug from a DPI. *Int J Pharm* 2003; 263: 151-163.
8. Vidgren M, Karkkainen A, Karjalainen P, Paronen P, Nuntinen J. Effect of powder inhaler design on drug deposition in the respiratory tract. *Int J Pharm* 1988; 42: 211-216.
9. Timsina MP, Martin GP, Marriott C, Ganderton D, Yianneskis M. Drug delivery to the respiratory tract using dry powder inhalers. *Int J Pharm* 1994; 101: 1-13.
10. Berner B, Fymys B, de Boer A, Gottenauer W, Wolf-Heuss E. Acta Medica multiple dose dry powder inhaler. In: Dalby, R.N., Byron, P.R., Farr, S.J, ed. *Respiratory Drug Delivery VI*, Interpharm Press, Buffalo Grove; 1998. p: 475-477.

11. Srichana T, Martin GP, Marriott C. Dry powder inhalers: the influence of device resistance and powder formulation on drug and lactose deposition in vitro. *Eur J Pharm Sci* 1998; 7: 73-80.
12. Bell JH, Hartley PS, Cox JSG. Dry powder aerosols I: a new powder inhalation device. *J Pharm Sci* 1971; 60: 1559-1564.
13. Braun MA, Oschmann R, Schmidt PC. Influence of excipients and storage humidity on the deposition of disodium cromoglycate (DSCG) in the Twin Impinger. *Int J Pharm* 1996; 135: 53-62.
14. Chew NYK, Bagster DF, Chan HK. Effect of particle size, air flow and inhaler device on the aerosolisation of disodium cromoglycate powders. *Int J Pharm* 2000; 206: 75-83.
15. European Pharmacopoeia (Supplement 2000) Preparations for inhalation: Aerodynamic assessment of fine particles-Fine particle dose and particle size distribution. Council of Europe. Strasbourg, p. 89-90.
16. Zeng XM, Martin GP, Marriott C, Pritchard J. The influence of carrier morphology on drug delivery by powder inhalers. *Int J pharm* 2000; 200: 93-106.
17. Chidavaenzi OC, Buckton G, Koosha F. The effect of co-spray drying with polyethylene glycol 4000 on the crystallinity and physical form of lactose. *Int J Pharm* 2001; 216: 43-49.
18. Steckel H, Muller BW. In vitro evaluation of dry powder inhalers II: influence of carrier particle size and concentration on in vitro deposition. *Int J Pharm* 1997; 154: 31-37.
19. Ganderton D, Kassem NM. Dry powder inhalers. In: Ganderton, D. Jones, T, ed. *Advances in pharmaceutical sciences*, Vol. 6, Academic Press, London. 1992. p: 165-191.
20. Zeng XM, Martin GP, Tee SK, Ghoush AA, Marriott C. Effects of particle size and adding sequence of fine lactose on the deposition of salbutamol sulphate from a dry powder formulation. *Int J Pharm* 1999; 182: 133-144.
21. Louey MD, Razia S, Stewart PJ. Influence of physico-chemical carrier properties on the in vitro aerosol deposition from interactive mixtures. *Int J Pharm* 2003; 252: 87-98.

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