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Effect of particle size, air flow and inhaler device on the aerosolisation of disodium cromoglycate powders

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Abstract

Recently, the dispersion of mannitol powders has demonstrated the importance of particle size, air flow and inhaler device (Chew and Chan, 1999). The aim of the present study is to extend our investigation to a different compound, disodium cromoglycate (DSCG) powders. Solid state characteristics of the powders were assessed by particle sizing, scanning electron microscopy, X-ray powder diffraction, moisture content, particle density determination and freeze fracture. The aerosol behaviour of the powders was studied by dispersion using Rotahaler® and Dinkihaler®, connected to a four-stage liquid impinger operating at 30–120 l/min. Three amorphous powders with a mass median diameter (MMD) of 2.3, 3.7, 5.2 μm and a similar polydispersity were prepared. The particles were nearly spherical with a particle density of 1.6 g/cm^3 and moisture content of 6.6 wt.%. Using Rotahaler®, the maximum fine particle fraction (FPF_{max}) for all three powders was only 15 wt.%, attained at the highest flow of 120 l/min. Using Dinkihaler®, the FPF_{max} was two to four times higher, being 36 and 29 wt.% for the 2.3 and 3.7 μm powder, respectively, at 60 l/min; and 18 wt.% for the 5.2 μm powder at 120 l/min. Hence, the study shows that the FPF in the DSCG powder aerosols was determined by the interaction of the particle size, air flow and inhaler design. The attribution of the amorphous nature and the different physico-chemical properties of the powder may explain the incomplete and low dispersibility of DSCG.

Keywords: Amorphous powders; Aerosol inhaler; Particle size; Air flow; Disodium cromoglycate

1. Introduction

In recent years there has been growing interest in dry powder aerosols for the delivery of small molecules and therapeutic proteins (Timsina et al., 1994; Patton et al., 1999). Parameters affecting dry powder aerosol delivery such as humidity (Braun et al., 1996), air flow (de Boer et al., 1996), carrier (French et al., 1996), particle surface characteristics (Fults et al., 1997) and inhaler resistance (Clark and Hollingworth, 1993) have been reported, but they are mainly limited to the existing marketed products. Since the particle size for a given commercial inhalation formulation is fixed

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according to the manufacturing specifications, fundamental studies on the relationship between particle size and powder dispersibility is not feasible. Although it is well known in theory that particle size affects powder cohesion, the experimental data in the literature largely exist for coarse pharmaceutical particles rather than the fine particles (< 10 μm) suitable for inhalation therapy (Staniforth, 1995; Wouters and Geldart, 1996).

Recently, we have begun to study the effect of particle size on the aerosolisation of a powder using different inhalers at various air flows (Chew and Chan, 1999). The powder used in the study was mannitol which is crystalline. In the present article, we have extended our investigation on the effect of particle size, air flow and inhaler device on the aerosolisation of a different compound, disodium cromoglycate (DSCG). Besides being an antiasthmatic agent, DSCG is a widely studied model compound for aerosol delivery. For example, Vidgren et al. have compared the aerosol performance between the micronised (Vidgren et al., 1987) or commercially prepared DSCG powder (Vidgren et al., 1988) with the spray-dried powder. The formulations studied were blended with lactose, which serves as a carrier. In contrast, our present study focuses on the dispersion of pure DSCG, without carrier particles.

2. Materials and methods

2.1. Preparation of DSCG powders

DSCG raw material was a gift from Rhone Poulenc Rorer Australia. Spray-dried DSCG powders of three different particle sizes were obtained using a Büchi 191 Mini Spray Dryer (Flawil, Switzerland). Table 1 provides a summary of the spray-drying conditions. The feed solution contained only DSCG dissolved in deionised water. The different particle sizes were obtained mainly by the adjustment of the liquid feed rate and the compressed air pressure for atomisation. In general, a higher air pressure and a lower liquid feed produce finer droplets and hence smaller particles after drying. The powder production under the specified experimental conditions was found reproducible, with yields of 50–65%. The spray-dried powders after collection were stored over phosphorous pentoxide until use.

2.2. Solid state characterisation

2.2.1. Particle sizing of spray-dried powders

Particle size distribution of the powders was measured in suspensions using a Mastersizer S Laser Diffractometer (Malvern, Worcs, UK) as described previously (Chan et al., 1997; Chew and Chan, 1999). Chloroform was used as a dispersion medium. Particle size analysis was based on the refractive index (RI) of DSCG (1.680), $RI_{imaginary}$ of DSCG (0.100) and RI of chloroform (1.444). The size distribution was expressed by the volume median diameter (VMD) and span. VMD is related to the mass median diameter (MMD) by the density of the particles (assuming a size-independent density for the particles). Span is a measure of the width of the size distribution. Span $= [D(v, 90) - D(v, 10)]/D(v, 50)$, where $D(v, 90)$, $D(v, 10)$ and $D(v, 50)$ are the equivalent volume diameters at 90, 10 and 50% cumulative volume, respectively.

2.2.2. Scanning electron microscopy (SEM)

Powder samples were mounted onto metal sample plates and coated with platinum. The samples were then examined under a Jeol JSM 6000F scanning electron microscope (Tokyo, Japan) operating at 3 kV.

2.2.3. X-ray powder diffraction (XRD)

Powder crystallinity was assessed by XRD. Samples were packed on a glass sample plate under the storage humidity and analysed on a Siemens D5000 X-ray powder diffractometer (Hamburg, Germany) using CuKα radiation generated at 40 kV and 30 mA, with an angular increment of 0.05°/s.

2.2.4. Moisture content determination

Samples (~ 10 mg) were placed in platinum pans and heated at a rate of 5°/min under a nitrogen purge (~ 30 ml/min) in a thermogravimetric analyser (SDT 2960, TA Instruments, DE)

Table 1
Spraying conditions for DSCG powders

Feed concentration (mg/ml)	Inlet temperature (°C)	Outlet temperature (°C)	Feed rate (ml/min)	Aspiration (m^3/h)	Compressed air pressure (kPa)	Particle size (MMD)
80	135	89	2.8	57.6	550–575	2.3
100	100	64	1.4	57.6	400–500	3.7
100	100	58	4.0	57.6	350–400	5.2

controlled by a TA thermal solutions controller 4000. Percent moisture was calculated as the weight loss between room temperature and 200°C where the profiles levelled off.

2.2.5. Density determination

The particle density of the spray-dried powders was determined by a validated buoyancy method (Chew and Chan, 1999). Powder samples (1–2 mg) were placed in a density gradient liquid (comprising bromoform and 1-hexanol) and centrifuged (Jouan CT422, Saint Herblain Cedex, France) at 3500 rpm and 5°C for 30 min. The particle density was equal to the density of the liquid where the particles remained suspended after centrifugation.

2.2.6. Freeze fracture of spray-dried powders

To examine the interior of the individual particles, freeze fracture was carried out and a replica of the fracture surface was made as described previously (Chew and Chan, 1999). The fracture surface was viewed under a transmission electron microscope (Philips 400, Eindhoven, The Netherlands) operating at 100 kV.

2.3. Aerosol characterisation — effect of flow and particle size

The method details have been given elsewhere (Chew and Chan, 1999). Briefly, studies were conducted in an airtight perspex glove box ($45 \times 75 \times 80$ cm) at known temperature (23 ± 2°C) and relative humidity (15 ± 5%). The dispersion behaviour (the breaking up of agglomerates to regenerate the primary particles) of the spray-dried powders was assessed by Rotahaler® (Allen & Hanburys) and Dinkihaler® (Aventis) coupled to a four-stage (plus filter) liquid impinger (Copley, Nottingham, UK) with a glass throat. Details of the dispersion mechanism of Dinkihaler® has been described previously (Chew and Chan, 1999). Powder (20 mg) was filled into the capsule (which was pre-equilibrated over saturated potassium carbonate solution at 44% RH) just prior to the experiment, and was then dispersed immediately. A single capsule was dispersed per experiment. DSCG was assayed by UV spectrophotometry (Model U-2000, Hitachi, Tokyo, Japan) at 326.5 nm. A calibration curve was constructed using standard solutions of DSCG at 0.005–0.050 mg/ml [Absorbance = 15.8 concentration (mg/ml), $n = 10$, $R^2 = 0.999$.]

Fine particle fraction (FPF) is defined as the mass fraction of particles ≤ 5 μm. FPF is obtained by interpolation to the cumulative % undersize at 5 μm. FPF is referenced against the recovery (i.e. total dose = emitted dose + device and capsule retention), and is expressed as the means of triplicate runs ($n = 3$). Data were subjected to analysis of variance (ANOVA) and Student's t-test (Microsoft Excel version 4.0), with probability values of less than 0.05 considered to be statistically significant.

3. Results

3.1. Solid state characterisation

The spray-drying conditions employed in this study produced powders with unimodal particle size distributions. The three DSCG powders had mass median diameters (MMD) of 2.3, 3.7 and 5.2 μm with spans of 2.1, 2.0 and 2.0, respectively. SEM showed that the particles were nearly spherical (Fig. 1a). All three powders were amorphous (Fig. 2), had a consistent water content of 6.6 wt.% and a density range 1.55–1.57 g/cm^3, which agrees closely with the literature values for DSCG (Cox et al., 1971). The density values indicated that the particles were solid. Voids were not found in freeze fracture images of different sizes of the particles (Fig. 1b), confirming that the particles were not hollow. Hence, the mass median aerodynamic diameters (MMAD) of the DSCG powders could be calculated from the product of MMD (obtained from the laser diffraction) and the square root of the particle density (Gonda, 1992).

3.2. Aerosol characterisation

3.2.1. Rotahaler®

Dispersion using Rotahaler® was rather poor with a maximum fine particle fraction (FPF_{max}) of only 15 wt.% for all three powders (Fig. 3a).

When the 2.3 μm powder was dispersed, increasing the flow (30–120 l/min) increased the fine particle fraction (FPF) proportionately, with the FPF_{max} attained at 120 l/min. A similar effect was also observed for the 3.7 and 5.2 μm powders, where the FPF_{max} also occurred at 120 l/min.

Fig. 4 compares the particle size distribution curves of the original powders (determined by laser diffraction) to that of the aerosols generated by Rotahaler® (determined by the multiple stage liquid impinger). The aerosol curves are situated above the original powder curve, indicating that the powders were not sufficiently dispersed by the inhaler to recover the primary particle size distribution. Consistent with the FPF results, the aerosol curve for the 2.3 μm powder was shifted toward the original powder curve as the air flow was increased (Fig. 4a). However, even at the highest flow of 120 l/min, the primary particle size distribution was not recovered. Similar observations were found for the dispersion of the 3.7 and 5.2 μm powders (Fig. 4b and c).

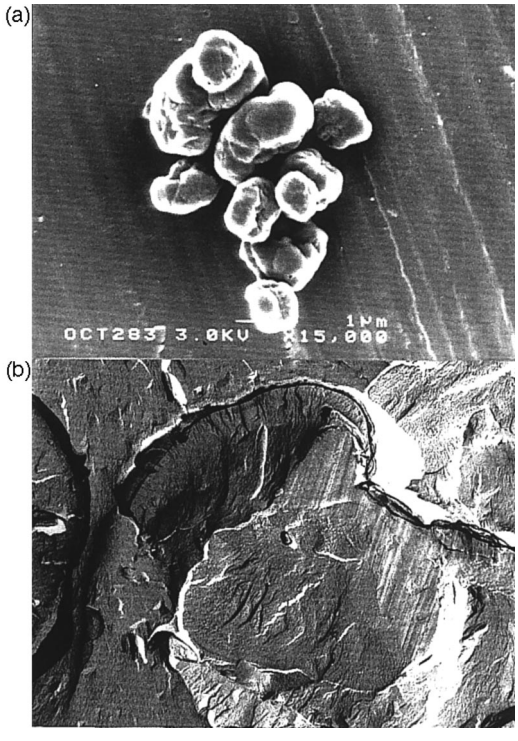

Fig. 1. (a) Scanning electron micrograph of spray-dried DSCG powder, MMD 2.3 μm; scale bar 1 μm (similar particle morphology was observed for the 3.7 and 5.2 μm powders). (b) Transmission electron micrograph of a freeze-fractured DSCG particle (magnification 12 500 ×). Similar freeze fracture images were found for the different sizes of the particles.

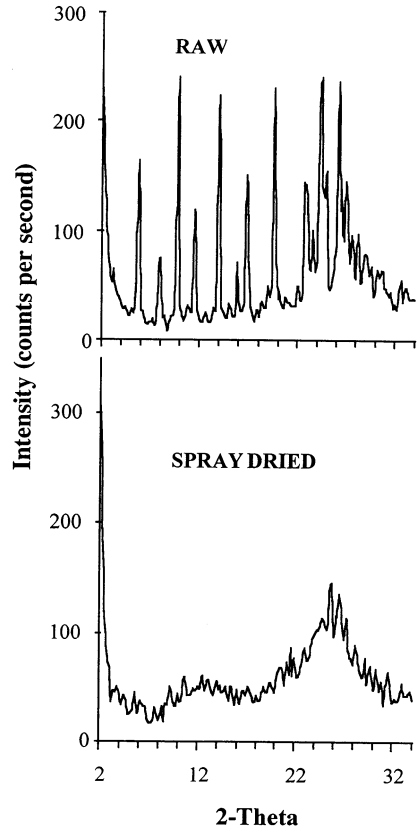

Fig. 2. X-ray diffraction patterns of raw material and spray-dried DSCG powders, MMD 2.3 μm (similar pattern observed for the 3.7 and 5.2 μm powders).

3.2.2. Dinkihaler®

The DSCG powders were more effectively dispersed with Dinkihaler®, with the FPF_{max} being two to four times higher than those using Rotahaler® at the same air flows (Fig. 3b). Furthermore, the size distribution curves of the aerosols were closer to the primary particle size distribution (Fig. 5). Dispersion of the 2.3 μm powder exhibited a flow dependence, but the FPFs were higher than with Rotahaler®. Significant increase in FPF ($P < 0.05$, ANOVA) was found when flow was increased from 30 to 90 l/min. However, even

at the highest flow of 120 l/min, the powders were still not completely dispersed to regenerate the primary particle size distribution. In fact, none of the DSCG powders was completely dispersed at any air flow by either of the inhalers. Consequently, the aerosol curves were situated above the powder curve at all flows (Fig. 5). For the 3.7 μm powder, the FPF increased significantly ($P < 0.05$) only from 30 to 60 l/min.

3.2.3. Impaction loss of powders

Increasing amounts of 3.7 and 5.2 μm powders were found in the throat and stage 1 of the liquid impinger with increasing air flow. At 30, 60, 90 and 120 l/min, using Dinkihaler®, the amount collected was 9, 21, 26, 38 wt.%, respectively, for the 3.7 μm powder and 17, 36, 44 and 49 wt.%, respectively, for the 5.2 μm powder. When using Rotahaler® at the same air flows, it was 18, 30, 29 and 40 wt.%, respectively, for the 3.7 μm powder and 26, 23, 39 and 48 wt.%, respectively, for the 5.2 μm powder. Impact of the 2.3 μm powder was much less than that of the 3.7 and 5.2 μm powders, (Rotahaler®; 38, 26, 26 and 22 wt.%; Dinkihaler®; 3, 14, 22 and 32 wt.% for 30, 60, 90 and 120 l/min, respectively).

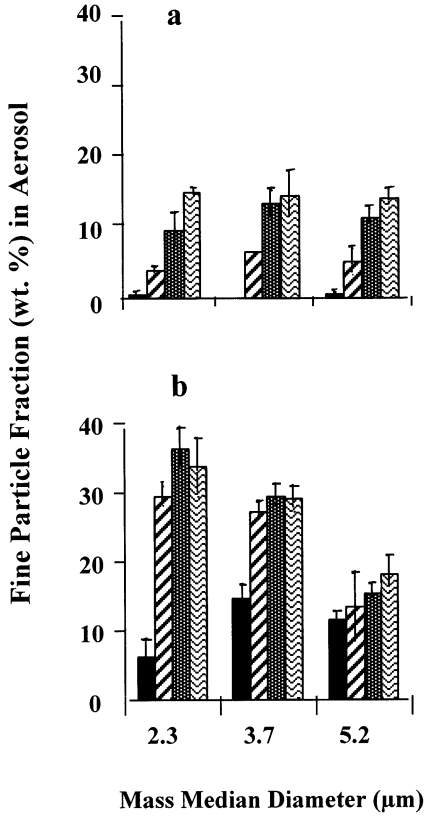

Fig. 3. (a) Effect of particle size and air flow (30 l/min ■, 60 l/min ▨, 90 l/min ▩, 120 l/min ▩) on the dispersion of spray-dried DSCG powders using Rotahaler®. The inset shows the interpolated FPF based on particles ≤ 5 μm (see text). (b) Effect of particle size and air flow (30 l/min ■, 60 l/min ▨, 90 l/min ▩, 120 l/min ▩) on the dispersion of spray-dried DSCG powders using Dinkihaler®. The inset shows the interpolated FPF based on particles ≤ 5 μm (see text).

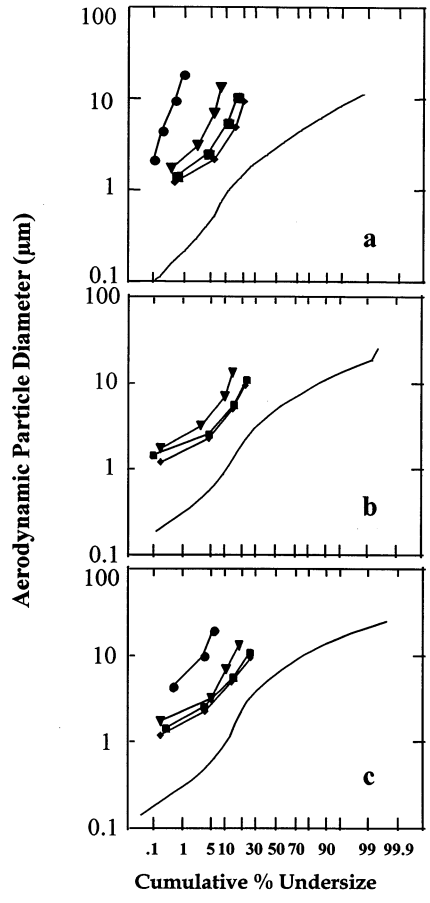

Fig. 4. Comparison of the particle size distribution of spray-dried DSCG powders (a, 2.3 μm; b, 3.7 μm; c, 5.2 μm) before (solid line) and after dispersion using Rotahaler® at different air flow (30 l/min -●-, 60 l/min -▼-, 90 l/min -■-, 120 l/min -◆-).

3.2.4. Powder emptying from inhalers

Similar amounts (81 ± 5 wt.%) of the 3.7 and 5.2 μm powders were emptied from Dinkihaler® at flows ≥ 60 l/min, but for the 2.3 μm powder, the amount of powder emptied was dependent on the air flow (78, 75 and 60 wt.% at 120, 90 and 60 l/min, respectively). At the low flow of 30 l/min, 45 and 64 wt.% was emptied for the 3.7 and 5.2 μm powders, respectively, as compared with 18 wt.% only for the 2.3 μm powder. For Rotahaler®, the amount of powder emptied was independent of the air flow for the 2.3 μm powder (39 ± 4 wt.%). Conversely, the emptying was increased proportionately with the air flow for the 3.7 and 5.2 μm powders (at 30, 60, 90 and 120 l/min, the amount emptied was 18, 45, 53 and 63 wt.%, respectively, for the 3.7 μm powder and 31, 38, 65 and 75 wt.%, respectively, for the 5.2 μm powder), indicating insufficient powder emptying from the inhaler at low air flows.

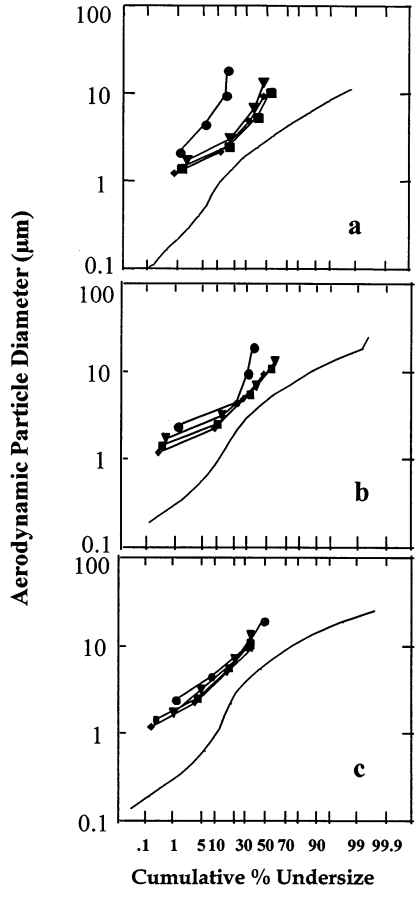

Fig. 5. Comparison of particle size distribution of spray-dried DSCG powder (a, 2.3 μm; b, 3.7 μm; c, 5.2 μm) before (solid line) and after dispersion using Dinkihaler® at different air flows (30 l/min -●-, 60 l/min -▼-, 90 l/min -■-, 120 l/min -◆-).

4. Discussion

This study showed that, like crystalline mannitol, aerosolisation of the amorphous DSCG powders depends on an interplay between the particle size, air flow and inhaler efficiency (Chew and Chan, 1999). However, despite being of similar morphology and sizes to those of mannitol, the DSCG powders were physico-chemically different and much more difficult to be dispersed.

The spray-dried DSCG powders consisted of solid, non-porous particles with a consistent particle density. Since the powders also had unimodal particle size distributions with a similar polydispersity, it was rational to use the median particle size for comparing the dispersion behaviour.

Since DSCG is hygroscopic, moisture transfer from capsule to powder may occur (Bell et al., 1973). In this experiment, the powder was stored and dispersed at low relative humidity to minimise effects such as moisture-induce agglomeration/recrystallisation. The powder was dispersed immediately after it was transferred to the capsule (pre-equilibrated at 44% RH). To reduce moisture transfer further, the contact time between the powder (stored at 15% RH) and the capsule was kept within a minute. Using dynamic water vapour sorption (DVS-1, Surface Measurement Systems Ltd., London, UK), we found that at 44% RH, the powder showed a weight increase of less than 1%/min in the first 5 min, thus confirming the minimal water uptake by the powder inside the capsule).

Since dispersion was carried out at a low RH, electrostatic charge interaction is likely to contribute to the adhesion of particles in a dry environment. The electrostatic contribution which was not determined in this study is rather complex and is dependent on many factors (Kulvanich and

Stewart, 1987; Ranade, 1987; Staniforth, 1994; Corn, 1996; Xie, 1997) such as the nature of the contact surface material (which would be constant for a given inhaler), the nature and the intensity of agitation of the powder bed (which would change with air flow), and the time lapse between the agitation and the measurement (which has been kept constant in this study).

Smaller particles are expected to be more difficult to disperse into aerosols due to cohesion. The cohesion between particles by contact surfaces is proportional to the specific surface area, hence the particle size. Also, the cohesion by the universal van der Waals force per unit mass is inversely proportional to the square of the particle size (Zimon, 1969). Furthermore, in turbulent flows the critical shear velocity of air required to detach the particles is proportional to (particle diameter)$^{-n}$, where n depends on the theoretical model employed (Soltani and Ahmadi, 1994). In the present study the flows were turbulent as the Reynolds number by calculation (Hinds, 1999) at the mouth piece of the inhalers ranged from approximately 4000 at 30 l/min to 15 000 at 120 l/min. As predicted, the 2.3 μm powder generated lower FPF in the aerosols than the other powders (using Rotahaler® at 30–90 l/min and Dinkihaler® at 30 l/min). This was also evidenced by the poor emptying of the powder from the inhalers. On the contrary, large particles are easier to disperse (lower specific surface area, lower cohesion, stronger and lower shear velocity requirement), and consequently, the dependence of dispersion on air flow and inhaler would also be weaker, as observed in the 3.7 and 5.2 μm powders. These powders also showed better capsule and device emptying as the air flow was increased.

Increasing the air flow would increase the energy input for powder dispersion and enhance particle detachment (i.e. more fine particles in the aerosol cloud), as observed in the 2.3 μm powder. However, increasing the flow velocity would also increase the impaction loss of particles at the throat of the impinger (Brain and Blanchard, 1993; Chew and Chan, 1999). Since impaction is proportional to the air flow and the square of particle size, it becomes more important for larger particles. This accounts for the slight decrease of FPF at higher air flows for the 3.7 and 5.2 μm powders using Dinkihaler®. This was confirmed by the increasing amount of the 3.7 and 5.2 μm powder collected at the throat and stage 1 of the impinger with increasing air flow.

Increasing the inhaler dispersion efficiency is expected to enhance the breaking up of the agglomerates into finer particles. The maximum FPF was obtained with the 2.3 and 3.7 μm powders using Dinkihaler® at 90 l/min and with the same powders using Rotahaler® at 120 l/min (Fig. 3a and b). Both inhalers have similarly low resistance (0.03–0.04 $cmH_2O^{1/2}$/l per min). Due to the higher dispersion efficiency of Dinkihaler® (Chew and Chan, 1999), the FPF was much higher with Dinkihaler® than with Rotahaler®. Furthermore, for the 3.7 μm powder using Rotahaler®, an increase in the air flow from 90 to 120 l/min does not further change the FPF. The same applies to the 2.3 μm powder using Dinkihaler® when the flow increases from 90 to 120 l/min. This indicates that the impaction loss at the higher air flows is balanced by the availability of more fine particles. The low flow (30 l/min) is insufficient to disperse the powder by both inhalers, as shown in all three powders. The present study thus demonstrated that the maximum FPF is the result of a balance of the particle cohesion and inhaler efficiency against the fine particles available at a specific air flow. This has also been observed in an earlier study using mannitol powders (Chew and Chan, 1999).

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