

Effect of Powder Polydispersity on Aerosol Generation

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Abstract Purpose. We investigated the effect of primary powder polydispersity on the generation of pharmaceutical powder aerosols, using mannitol and bovine serum albumin (BSA) as the model compounds. **Methods.** Primary powders with different polydispersity but comparable physical and mass median aerodynamic diameter (MMAD) were obtained from spray drying. The polydispersity, i.e. the width of the particle size distribution, of the primary powder was measured by the span. $\text{Span} = [\text{particle diameter at 90\% cumulative size}] - [\text{particle diameter at 10\% cumulative size}] / [\text{particle diameter at 50\% cumulative size}]$. A small span indicates a narrow size distribution. Solid state properties and the aerosol behaviour of the powders were determined. **Results.** For both compounds, dispersion of the smaller span powder generated more fine particles below the MMAD of the primary powder, but the increase was less apparent at high air flows or with a high dispersion efficiency inhaler. With the Dinkihaler[®], however, the smaller span powder of BSA, but not of mannitol, was found to experience less impaction loss and capsule and device retention. This could be due to the BSA powder being more cohesive, as it was amorphous and had a higher residual moisture content than that of mannitol. **Conclusions.** The present study has demonstrated that the amount of fines available in the aerosol could be modified by the primary powder polydispersity.

INTRODUCTION

The impelling interest of pharmaceutical dry powder aerosols in recent years is driven by the urge to find a suitable replacement for the CFC-propellant liquid aerosols, as well as the recognition of the lung to deliver drugs systemically (1). Additionally, because of emerging technologies capable of making stable powders of respirable size, as well as devices competent to deliver flexible and accurate dosing, dry powder aerosols are no longer perceived as the “sec-

ond choice” after the propellant driven liquid aerosols for inhaled drugs.

To advance powder aerosol technologies, scientists and manufacturers have recognised the importance of understanding the determinants affecting powder dispersion. The influences of particle surface characteristics (2-4), environmental conditions (5), air flow rate, (6), inhaler resistance (7-8), and excipients (9-10) on aerosol generation are some of the fundamental areas that have been under continuous investigation.

The importance of particle size on aerosol production has recently been demonstrated in our laboratory (11, 16). In those studies, primary powders, i.e., powders obtained from production such as spray drying of the same polydispersity but different particle sizes were prepared and dispersed at various air flows using inhalers of different air resistance. Our results showed that powder aerosol generation is an interplay of particle size, powder properties, air flow and inhaler design.

In contrast, the present study focuses on the effect of primary powders with *different polydispersity* on aerosol generation. Thus far, studies on aerosol polydispersity have been limited to lung deposition by mathematical modelling (12-15). These studies show that aerosols with the same primary particle size but different polydispersity will deposit differently in the lung. However this will only be true if the primary powder can be fully dispersed during aerosol generation.

The aim of the present study is to investigate the effect of powder polydispersity on the aerosol generation in vitro. The model compounds used in this study were mannitol and bovine serum albumin (BSA).

MATERIALS AND METHODS

Powder preparation

Primary powders with a similar mass median diameter (MMD) ($\sim 3 \mu\text{m}$) (see next section for method of determination) but different polydispersity were obtained by spray

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drying (Büchi 191 Mini Spray Dryer, Flawil, Switzerland). The feed solution containing only the compound dissolved in deionised water was spray dried at conditions specified in Table 1. The spray-dried powders after collection were stored over silica gel or phosphorous pentoxide until use.

Table 1: Spray drying conditions for powders. (The aspiration rate was maintained at 57.6 m³/hr except *, which was at 28.8 m³/hr)

Powder	Span	Moisture content (wt. %)	Morphology	Crystallinity	True density (g/mL)	Particle interior structure
Mannitol	1.1	0.2	Spherical	Crystalline	1.5	Non-hollow
	1.7	0.1				
BSA	1.5	6.2	Spherical	Amorphous	1.2	Non-hollow
	1.8	5.7				

Primary particle size distribution and Polydispersity

The particle size distribution of the primary powders was measured in suspensions using a Mastersizer S Laser Diffractometer (Malvern, Worcs, UK) as described previously (11, 16). Chloroform was used as a dispersion medium. The polydispersity of the powder was expressed by the span. $\text{Span} = [D(v,90) - D(v,10)] / D(v,50)$, where $D(v,90)$, $D(v,10)$ and $D(v,50)$ are the equivalent volume diameters at 90, 10 and 50% cumulative volume, respectively. The particle size of the primary powders was described by the volume median diameter (VMD), which is related to the mass median diameter (MMD) by the density of the particles (assuming a size independent density for the particles).

Powder dispersion

The method details have been given elsewhere (11, 16). Briefly, studies were conducted in an airtight perspex glove box temperature and relative humidity controlled at 23 (± 2)°C and 20 (± 5)% respectively. The dispersion behavior (the breaking up of agglomerates to regenerate the primary particles) of the spray dried powders was assessed by the Rotahaler® (Glaxo-SmithKline) and the Dinkihaler® (Aventis) coupled to a 4-stage (plus filter) liquid impinger (Copley, Nottingham, UK) with a glass throat. Capsule filled with 20 mg powders was used. Five capsules containing mannitol powder were dispersed per experiment, whereas four capsules were used for BSA.

Sample Assay

Mannitol was assayed by high performance liquid chromatography (HPLC) using refractive index detection. A 100 μ L aliquot was injected into a Waters (Milford, MA) HPLC

system consisting of a 515 pump, a 410 refractive index detector and a 717 auto-injector. Data analysis was carried out using a Waters Millennium software (version 3.05.01). Mannitol was eluted from a Radial-Pak C18 reverse phase column (8mm id, 5 μ m, Waters, Milford, MA) using a mobile phase containing deionized water only at a flow rate of 1.0 mL/min. The calibration curve of peak area versus mannitol concentration was linear in the concentration range of 0.40 – 2.00 mg/mL ($R^2 = 0.999$, $n = 10$). BSA was assayed by UV spectrophotometry (Model U-2000, Hitachi, Tokyo, Japan) at 750 nm (Bio-Rad DC protein assay kit, Bio-Rad, Hercules, CA). The calibration curve was linear in the concentration range of 0.025 – 0.250 mg/mL ($R^2 = 0.998$; $n = 16$).

Data Analysis

By definition, the primary powder after complete dispersion should have 50 wt.% of the powder with size below or above the mass median aerodynamic diameter (MMAD), which is calculated based on the product of the mass median diameter (MMD) of the primary powder and the square root of the true particle density. Since the two primary powders of each compound in this study have a similar MMD, they should give the same amount of fine particles after dispersion below the MMAD of the primary powder. This, in reality, is generally not true because of the incomplete dispersion of the powder. Here we define the *relative* fine particle fraction (*rFPF*) in the aerosol cloud as the amount of fine particles smaller than or with the same size as the MMAD of the primary powder. This is obtained by interpolation to the cumulative % undersize at the MMAD of each of the primary powder. It is referenced against the recovery (i.e. total dose = emitted dose + device and capsule retention) and is expressed as the means of three experiments.

Impaction loss is the mass fraction of particles collected in the throat and stage 1 of the impinger. Capsule and device retention is the mass fraction of the particles collected at the capsule and device. Both the impaction loss and capsule and device retention were referenced against the recovery.

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 as statistically significant.

Powder characterization

Primary powder morphology - Powder samples were coated with platinum and examined under a Joel JSM 6000F scanning electron microscope (Tokyo, Japan).

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

Moisture content - 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 analyzer (SDT 2960, TA Instruments, DE) controlled by a TA thermal solutions controller 4000. Percent moisture was calculated as the weight loss between room temperature and 130° C (for mannitol) or 200° C (for BSA) where the profiles leveled off.

True particle density - This was determined by a validated buoyancy method (11). Primary 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.

Interior structure of particles - Freeze fracture was carried out for mannitol powders to examine the interior particle structure as described previously (11). The fracture surface was viewed under a transmission electron microscope (Philips 400, Eindhoven, The Netherlands) operating at 100 kV. For BSA, powder samples (approximately 1 - 2 mg) were fixed on a glass slide using glutaraldehyde (0.1 v/v%, Sigma, St. Louis, MO), dried overnight and viewed under a confocal microscope (Biorad Radiance Plus scanning system, Hertfordshire, UK) as described previously (4).

RESULTS AND DISCUSSION

The present study investigated the role of the primary powder polydispersity on the generation of dry powder aerosols, using mannitol and BSA as model compounds. Mannitol and BSA powders were chosen for their different degree of cohesiveness, with BSA being more cohesive than mannitol as shown by their *r*FPF (Fig. 2 – 5).

The “span” measures the width of the particle size distribution as described in the British Standards (17). Hence, a small span value indicates a narrow particle size distribution. For each compound, we have prepared two primary powders of comparable MMD (thus MMAD since both powders have the same true particle density) and particle morphology, but different spans. It has been demonstrated previously that the particle morphology is dependent on the nature of the compound, the spray drying process and the formulation variables (18, 19). In keeping the same particle morphology for the same compound, the two spans achieved were 1.5 and 1.8 for BSA, and 1.1 and 1.7 for mannitol (Fig. 1).

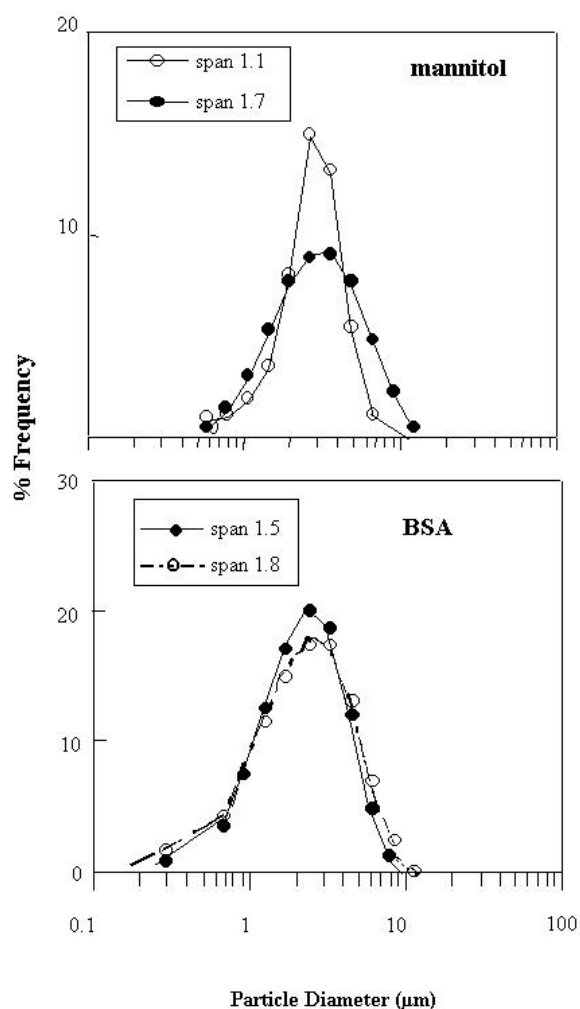


Figure 1: Primary Particle size distributions of mannitol and BSA powders.

Table 2 summarizes the solid-state characteristics of these spray-dried powders. While both compounds yielded

spherical non-hollow particles, BSA particles were amorphous with a higher residual moisture content, which presumably contributes to the cohesive nature of the powder.

Table 2: Spray-dried powders characteristics.

Powder	Feed concentration (mg/mL)	Inlet Temperature (°C)	Outlet Temperature (°C)	Feed rate (mL/min)	Atomising air pressure (kPa)	Particle size (MMD) (sd)	Span (sd)
Mannitol	100	130	88	1.4	750 - 800	3.0 (0.1)*	1.1 (0.0)
	37.5	130	90	1.4	750 - 800	3.1 (0.1)	1.7 (0.0)
BSA	100	45	36	1.4	600	2.8 (0.0)	1.5 (0.0)
	300	45	36	1.4	750-800	3.1 (0.1)	1.8 (0.0)

Since the two powders of each compound have a similar MMD, they should give the same η FPF after complete dispersion below the MMAD of the primary powder. In reality, the powders will not necessarily be fully dispersed due to the cohesiveness as commonly found for dry powder inhaler systems (20). This is indeed the case for BSA and a disparity was seen (discussed below). In contrast, mannitol being less cohesive (Fig. 2 & 3, comparing with Fig. 4 & 5 for BSA) is easier to disperse by the Dinkihaler® (11) and the two different span powders of mannitol did show a comparable η FPF when dispersed by the Dinkihaler®. At 30 L/min when the flow was not sufficient for powder deagglomeration, a difference in the η FPF began to show up, with the larger span powder generating less fine particles in the aerosol. The same applied to the Rotahaler® which has a lower dispersion efficiency than the Dinkihaler®: a lower η FPF of mannitol was produced by the larger span powder (the opposite occurs at 120 L/min but the difference is not statistically significant with $p = 0.07$). For BSA, the difference in the η FPF between the two different span powders became even more obvious (Fig. 4 & 5). This is in concordance with the increased cohesiveness of the powders. As shown in Fig. 4, the span 1.8 powder has significantly lower η FPFs than the span 1.5 powder ($p < 0.05$, except at 120 L/min with the Rotahaler®) when dispersed at the same air flow.

The polydispersity of the primary powder affected the impaction loss. There was a greater proportion of larger particles present in the larger span powder, and these particles would have the potential to impact at the throat. Larger particles could also act as carriers with 'binding sites' onto which the smaller particles adhere (20, 21), forming agglomerates for impaction. In comparison with the smaller span powder, the impaction loss for larger span powders was much higher and was flow-dependent, as

impaction loss is proportional to the air flow and square of particle or agglomerate size (22).

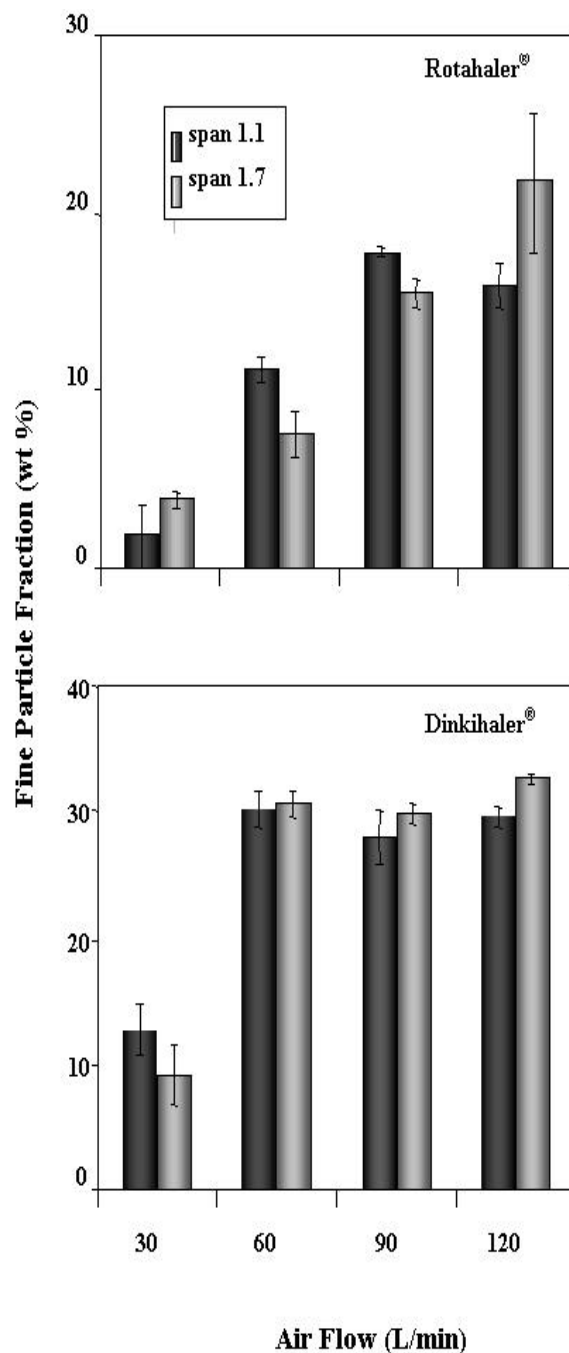


Figure 2: Fine particle fraction of the mannitol powders dispersed by the Rotahaler® and the Dinkihaler®.

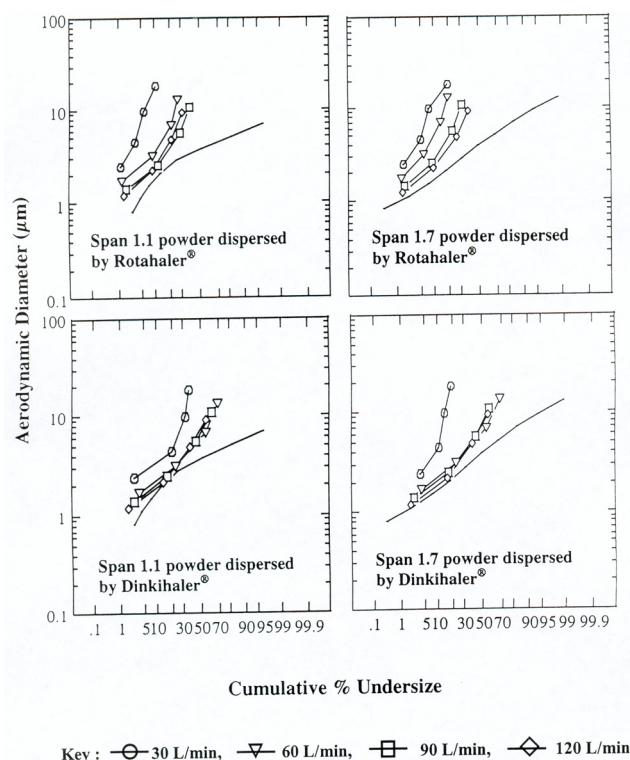


Figure 3: Particle size distribution of the spray-dried mannitol powders before (without symbol) and after dispersion using the Rotahaler® and Dinkihaler® at different air flows.

Significantly higher ($p < 0.05$) impaction loss with the larger span powder was evidenced especially at high air flows (Table 3) for both mannitol and BSA. The polydispersity of the primary powder also affected capsule and device retention (Table 3). The effect tends to be more prominent at low air flows when there was not sufficient energy for powder emptying, as illustrated with the span 1.7 mannitol powder dispersed at 30 L/min using the Dinkihaler® (Table 3a), and with the span 1.8 BSA powder dispersed at 30 and 60 L/min (Table 3b).

Table 3: Capsule and device retention, and impaction loss from the dispersion of (a) mannitol, (b) BSA powders.

(a)									
Air flow (L/min)	Rotahaler®				Dinkihaler®				Impact loss (wt. %) (sd)
	Capsule and device retention (wt. %) (sd)		Impact loss (wt. %) (sd)		Capsule and device retention (wt. %) (sd)		Impact loss (wt. %) (sd)		
	Span 1.1	Span 1.7	Span 1.1	Span 1.7	Span 1.1	Span 1.7	Span 1.1	Span 1.7	
30	76.4 (11.0)	67.7 (1.9)	12.8 (3.7)	13.1 (0.8)	56.0 (3.5)	60.4 (7.8)	8.1 (0.1)	21.6 (4.5) *	
60	44.7 (1.3)	49.8 (4.1)	28.4 (3.1)	30.7 (1.5)	20.3 (1.7)	21.1 (1.1)	11.1 (0.9)	10.8 (0.8)	
90	35.7 (4.2)	33.6 (0.7)	26.0 (2.8)	35.2 (1.8) *	18.0 (1.6)	18.7 (0.3)	20.0 (1.5)	24.6 (7.3)	
120	35.2 (1.1)	32.3 (2.1)	26.9 (5.3)	37.0 (2.1) *	18.2 (1.9)	18.0 (1.4)	26.5 (2.9)	26.7 (2.0)	

(b)									
Air flow (L/min)	Rotahaler®				Dinkihaler®				Impact loss (wt. %) (sd)
	Capsule and device retention (wt. %) (sd)		Impact loss (wt. %) (sd)		Capsule and device retention (wt. %) (sd)		Impact loss (wt. %) (sd)		
	Span 1.5	Span 1.8	Span 1.5	Span 1.8	Span 1.5	Span 1.8	Span 1.5	Span 1.8	
30	59.7 (7.4)	63.2 (7.4)	32.6 (5.5)	36.7 (7.2)	42.5 (0.5)	69.4 (1.6) *	9.9 (3.3)	10.0 (0.4)	
60	47.5 (3.5)	52.5 (0.9)	27.0 (3.7)	39.5 (0.7) *	23.2 (3.8)	42.8 (1.9) *	13.1 (4.8)	14.4 (1.3)	
90	34.8 (4.5)	41.6 (5.7)	25.3 (3.9)	39.6 (5.1) *	23.7 (5.1)	23.6 (4.3)	28.8 (3.7)	34.6 (0.7)	
120	34.2 (4.2)	37.9 (2.9)	27.5 (2.8)	34.5 (5.6)	18.4 (2.4)	17.9 (0.5)	30.2 (3.0)	41.3 (5.9) *	

* Significant difference (p < 0.05) from the value of the smaller span powder

* Significantly different ($p < 0.05$) from that of the smaller span powder

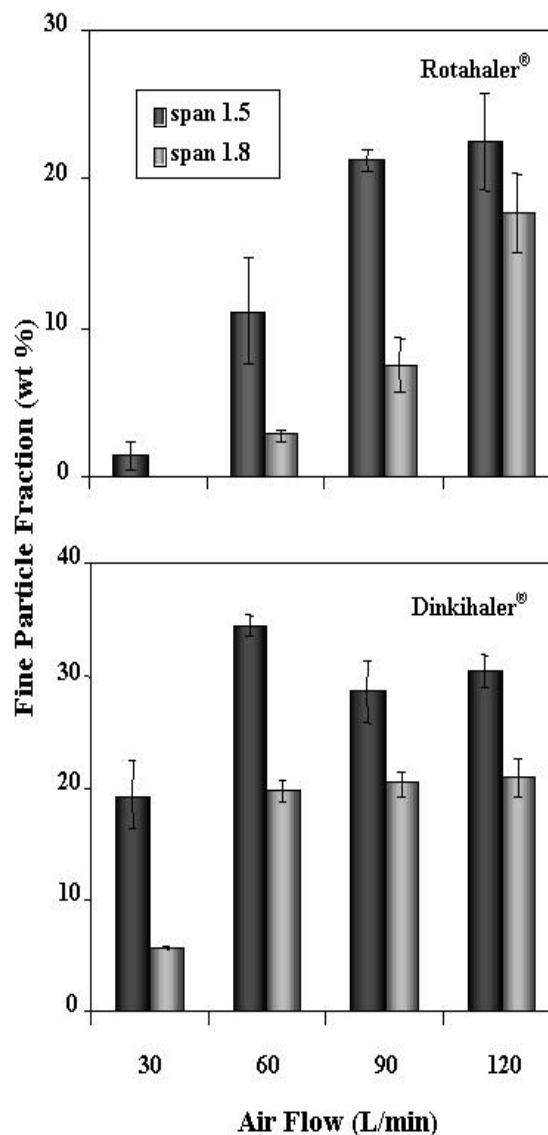


Figure 4: Fine particle fraction of the BSA powders dispersed by the Rotahaler® and the Dinkihaler®

In conclusion, this study has shown that the primary powder polydispersity would affect the amount of fine particles (FPF) generated in the aerosol clouds. Powders with a higher polydispersity have produced lower FPF, higher impaction loss and higher capsule and device retention. Thus, for a given powder, a lower polydispersity could be chosen to optimize its aerosol performance. The effect is particularly significant when the powder is cohesive, or when a relatively low amount of energy (due to air flow or with a low dispersion efficiency inhaler) is available for powder dispersion.

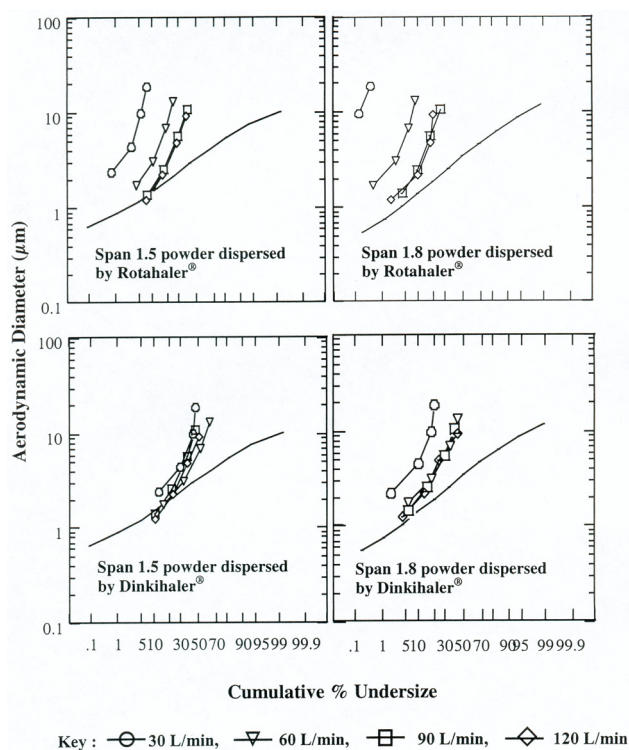


Figure 5: Particle size distribution of the spray-dried BSA powders before (without symbol) and after dispersion using the Rotahaler® and Dinkihaler® at different air flows

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