

INFLUENCE OF LACTOSE PARTICLE SIZE ON FLUTICASONE PROPIONATE AGGLOMERATE SIZE WITHIN INTERACTIVE MIXTURES FOR DRY POWDER INHALERS

V.N.P. Le^{1,2}, E. Robins³, M.P. Flament^{1,2}

¹Université Lille Nord de France, College of Pharmacy, Lille, France

²INSERM U1008, Controlled Drug Delivery Systems and Biomaterials, Lille, France

E-mail: marie-pierre.flament@univ-lille2.fr

³Aptar Pharma., route des Falaises, BP 37, 27100 Le Vaudreuil, France

INTRODUCTION

In inhalation therapy, the typical size of respirable particles is generally less than 5 micrometers. Due to their small size, drug particles are very cohesive and naturally form agglomerates that could prevent good aerosolisation¹. Thus, formulations with fine drug particles and coarse carrier particles, usually α -lactose monohydrate have been commonly used to facilitate aerodynamic dispersion and flow. Interactions between particles are mainly dependent on the physicochemical characteristics of the interacting particles that will influence the drug/carrier blend process and also drug delivery from the carrier and its dispersion. Among these properties, the influence of the carrier particle size on aerodynamic performance of DPI formulations was extensively performed². However, its influence on agglomeration behaviour of drug particles was not investigated further.

The aim of this work was to assess the influence of carrier size on the drug particle characteristics in DPI interactive mixture and on its aerodynamic performance.

EXPERIMENTAL METHODS

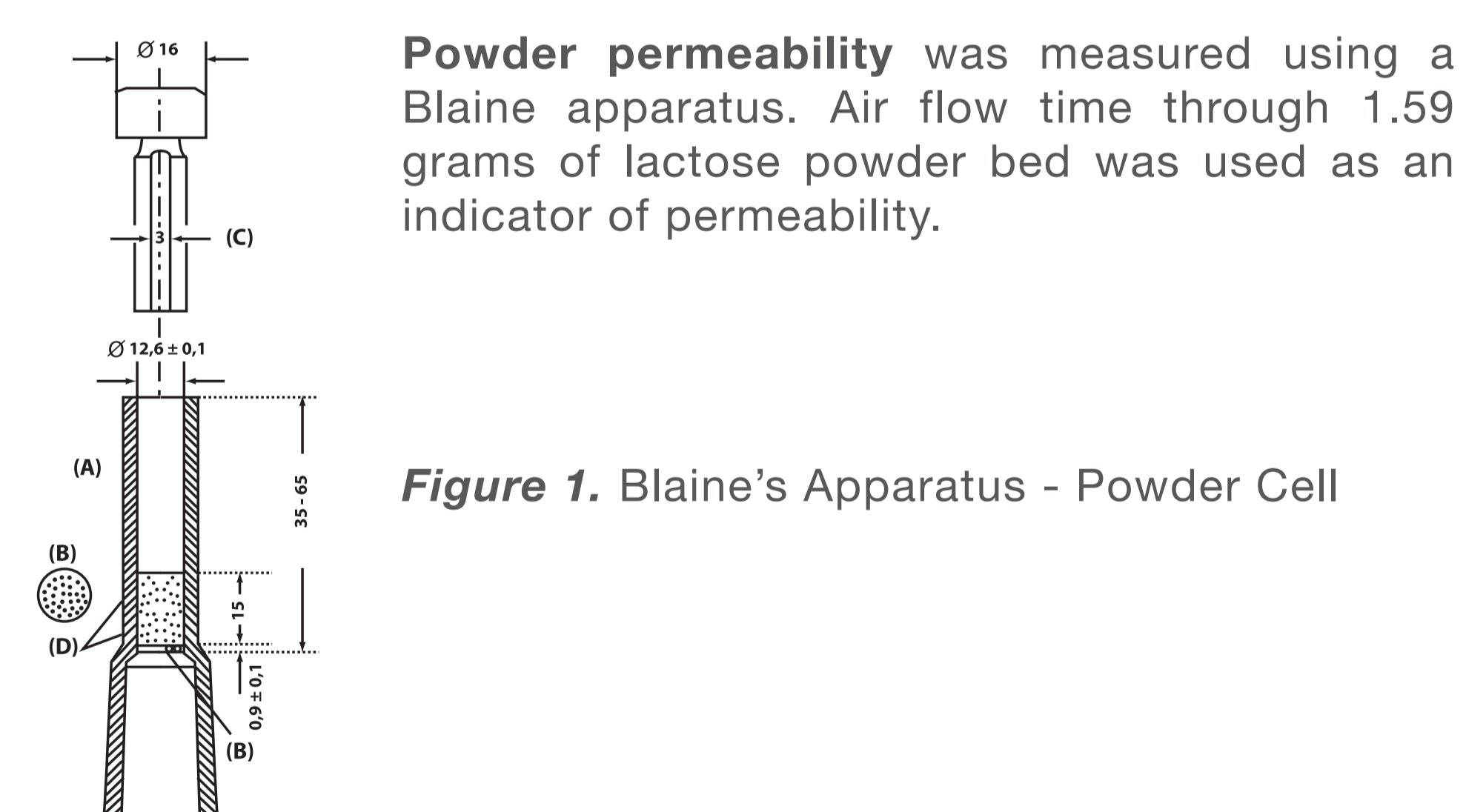
Materials: Intrinsic fine particles of lactose were removed from Lactohale LH200 (Friesland Foods Domo, The Netherlands) by air-jet sieving through a 32 μ m sieve for 30 minutes with an airflow that produces a pressure drop of 4 kPa. This lactose without small particles was further sieved through 40, 63, 90, and 125 μ m sieves to obtain 3 fractions: 40-63 μ m; 63-90 μ m and 90-125 μ m. Fluticasone Propionate (FP) (Volume Mean Diameter (VMD) of 2.65 μ m) at a concentration of 2.5% w/w was mixed with each lactose fraction in a low shear blending (Turbula) for 2 hours at 90 rpm under controlled relative humidity. Each blend was prepared in 50 g quantity. The quality of the blends was expressed by the uniformity of drug content (n=15). Quantitative analysis was carried out by validated HPLC method.

Characterisation of the lactoses

Particle size was determined by dispersion in ethanol with a laser size analyser Mastersizer S (Malvern) and the small sample dispersion unit.

The true density of powder was measured by helium pycnometer (AccuPyc 1330, Micromeritics, USA) using a 3 cm³ sample cell.

Apparent bulk volume (V₀) and volumes after 10 taps (V₁₀) and 500 taps (V₅₀₀) for 50 g powder were determined using the method described in the European Pharmacopoeia. The **packing ability** V₁₀ - V₅₀₀ was also calculated.



Powder permeability was measured using a Blaine apparatus. Air flow time through 1.59 grams of lactose powder bed was used as an indicator of permeability.

Figure 1. Blaine's Apparatus - Powder Cell

Pore distribution of lactose fractions was assessed by mercury intrusion porosimetry (Micromeritics® Autopore IV 9500). Mercury pressure working range was from 0.0034 MPa to 15 MPa in order to avoid particle compression or collapse due to high pressure. The interparticular pore size was calculated based on pressure at which the percolation begins.

The particle size of fluticasone propionate in mixture was assessed by laser size analyser. About 30 mg of mixture was suspended in ethanol/water (10:90; v/v). The lactose particles dissolved while the fluticasone propionate particles were suspended in the solution. The particle size distributions of suspensions were measured. The results are the mean of six determinations.

Evaluation of adhesion

Adhesion characteristics were evaluated by submitting the blend to a sieving action by air depression with the Alpine air-jet sieve. 30 g of blend was placed on the 32 μ m sieve section of the Alpine air-jet apparatus, in a sealed enclosure. Three samples of 20 mg were removed from the powder bed after sieving for different lengths of time: 5, 30, 60, 150 and 300 seconds.

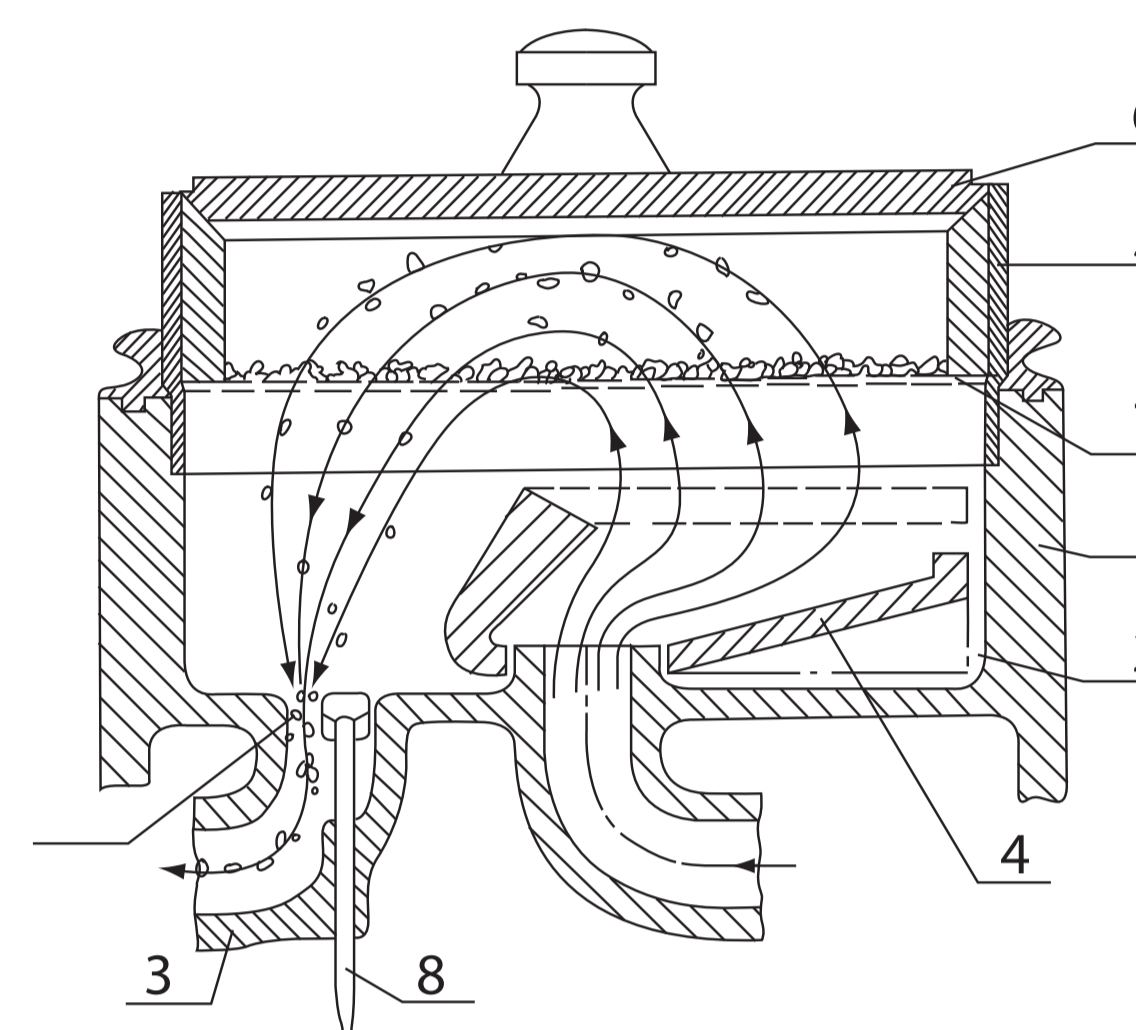


Figure 2. Alpine Air-Jet Siever for Adhesion Evaluation

Aerodynamic evaluation of fine particle fraction (FPF) and emitted dose

This is determined by using a Twin-Stage Impinger (TSI). Each deposition experiment involved the aerosolisation at 60 l/min via an Inhalator Ingelheim of five capsules (n=3). All experiments were performed under controlled temperature and relative humidity (20°C and 40-45%).

RESULTS AND DISCUSSION

In this study, small particles of lactose (lower than 32 μ m) were removed from the initial carrier. Measurements by optical microscopy demonstrated effective removal. Therefore, the influence of fine particles of lactose, < 32 μ m, on the DPI formulation performance could be excluded.

For all lactose fractions, the water content is about 5% which is in agreement with the lactose alpha-monohydrate specifications of the European Pharmacopoeia. True density determined by helium pycnometer is from 1.541 to 1.549 g/cm³, comparable with other published values.

	Fraction 125-90 μ m	Fraction 90-63 μ m	Fraction 63-40 μ m
V ₁₀ (mL)	65.67	64.67	70.67
V ₅₀₀ (mL)	61.33	59.33	63.33
V ₁₀ -V ₅₀₀ (mL)	4.33	5.33	7.33

Table 1. characteristics of the lactose fractions

All lactose fractions have a good flowability. Bulk volumes, volumes after 10 taps and packing ability are comparable for the two fractions 125-90 μ m and 90-63 μ m, but are higher for the 63-40 μ m fraction (Table 1). The arrangement between particles for small size powders is more difficult than bigger sized powders.

The drug average contents are all included in an interval of $\pm 5\%$ around the nominal dose. The coefficients of variation are lower than 5% for all blends.

When blends are submitted to the Alpine air-jet sieve, drug is rapidly carried away by the airflow.

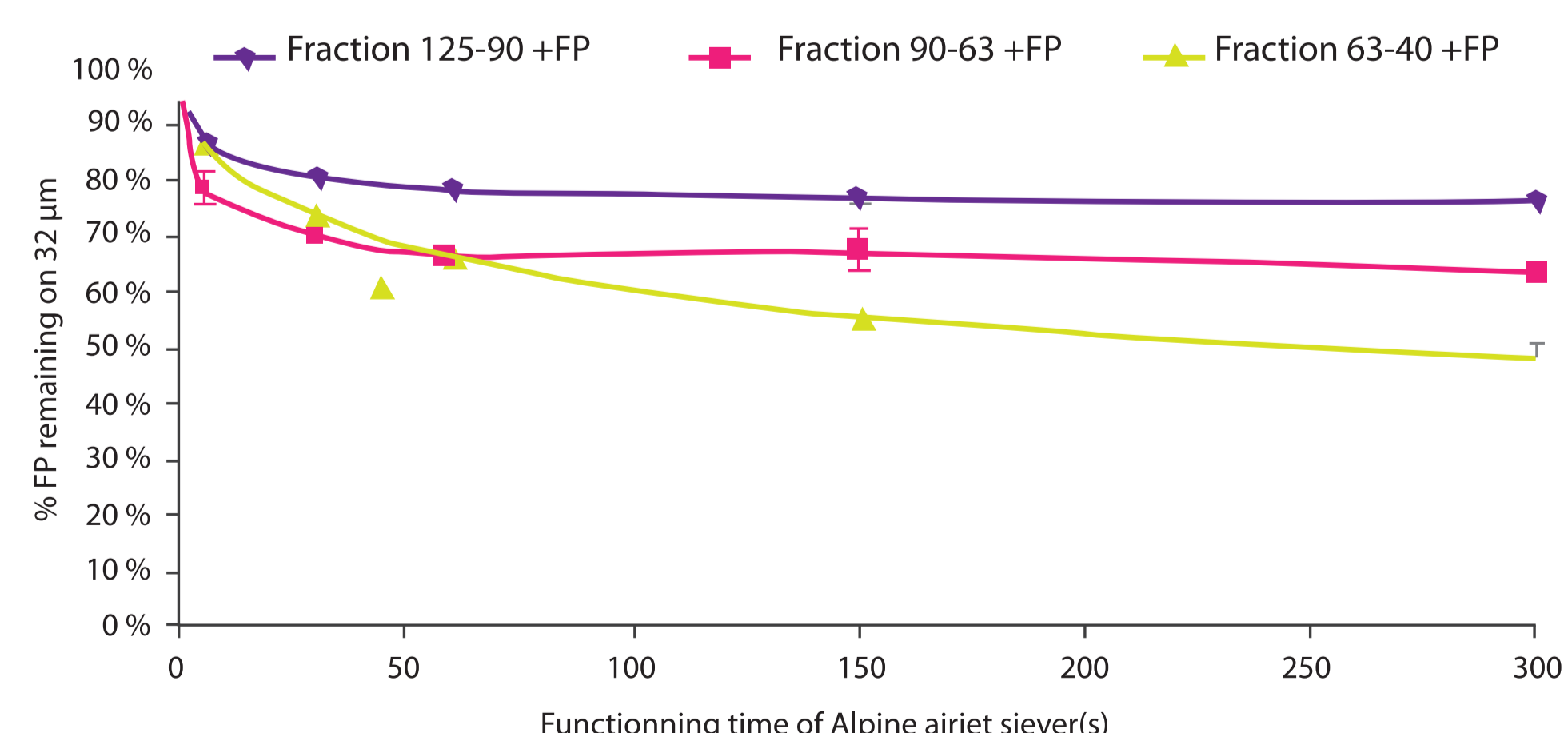


Figure 3. Percentage of FP remaining in the blend in relation to the functioning time of the air-jet sieve

The quantity of drug remaining after 30 seconds is an indicator of the quantity that adheres to the carrier. It was observed that the bigger the carrier particle size is, the greater is the fraction of drug that remains attached to the carrier. This is confirmed by the assays carried out using the TSI (Table 3).

	Air flow time (s)	
	Lactose	Lactose/FP Mixtures
Fraction 125-90 μ m	1.25	1.99
Fraction 90-63 μ m	1.74	2.67
Fraction 63-40 μ m	2.23	3.56

Table 2. Air permeability of lactose fraction and its mixtures with Fluticasone

After mixing the lactose with the drug, a reduction in air permeability of each mixture was observed (Table 2). It can be explained that beside the adhesion on carrier particles, drug particles could distribute in the interstitial space between carrier particles and therefore it is more difficult for the air to move through the powder bed.

	Fraction 125-90 μ m	Fraction 90-63 μ m	Fraction 63-40 μ m	Lactohale LH200
Interparticular pore size (μ m) of lactose	33.62	26.07	21.36	17.6
FP size in mixture	VMD (μ m) 19.58 (± 0.50)	11.3 (± 0.28)	5.43 (± 0.36)	5.59 (± 0.3)
Aerodynamic Performance	Emitted dose (%) 79.17 (± 1.61)	72.17 (± 1.34)	75.54 (± 1.93)	70 (± 6.6)
	FPF (%) 4.29 (± 0.28)	7.67 (± 0.70)	9.46 (± 1.07)	25.2 (± 3.7)

Table 3. Emitted dose and FPF, fluticasone particle size in mixture and interparticular pore size of lactose fractions obtained by mercury porosimetry.

The FPF of fluticasone increased when the particle size of the different sieved fractions of lactose decreases. This observation can be explained by particle-particle interaction force proposed by Hamaker¹. A further decrease of the lactose fraction (32-40 μ m) improves the FPF but it remains much lower than the one obtained with the Lactohale LH200 used as received. By dissolving lactose in the measurement liquid, the size of agglomerates of fluticasone can be assessed by laser size analyser. It can be noted that even after mixing with lactose for 120 minutes, drug particles still remain in agglomerate form. Agglomerate sizes were found in good correlation with the pore size between carrier particles ($R^2=0.9431$). It can be speculated that during mixture, the natural agglomerates of drug should be dispersed and divided to small agglomerates according to the interstitial space size between the bigger particles of carrier.

CONCLUSION

Carrier particle size plays an important role on the inhalation performance of interactive powder mixtures. Decreasing carrier particle size leads to a decrease of particulate interaction between drug-carrier. The reduced adhesion between drug and carrier particles increased drug detachment. In this study, drug agglomeration in mixture was investigated. Beside adhesion on the carrier particles, drug particles could distribute in the interstitial space between carrier particles in agglomerate form. The agglomerate size is a function of pore size formed between the carrier particles.

REFERENCES

- [1] J. Zhu, Fluidization of Fine Powders, in: Granular Materials, Fundamentals and Applications, The Royal Society of Chemistry, 2004: p. 270-295.
- [2] P. Stewart et al., Effect of carrier size on the dispersion of salmeterol xinafoate from interactive mixtures, J. Pharm. Sci. 93 (2004) 1030-1038.