INFLUENCE OF POWDER MIXING PROCESS ON AGGLOMERATE BEHAVIOUR OF FLUTICASONE PROPIONATE WITHIN DRY POWDER INHALERS FORMULATIONS

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INTRODUCTION

Dry Powder Inhalers (DPI) formulations are often composed of fine drug particles and inert coarse carrier particles, typically α-monohydrate lactose. DPI formulation and production require an adequate optimization in order to deagglomerate the very cohesive drug particles and to produce a uniform mixture with the coarser carrier[1]. Powder mixing is therefore a critical operation. Powder mixing in DPI manufacturing is generally performed using high shear mixing principle, or low-shear tumble blending with or without mixing aids[2]. The influence of powder blending operation on DPI formulation performance is widely studied but its influence on drug agglomeration behaviour in mixture is not clearly understood. The aim of this work was to study the influence of the blending process using low shear tumble mixing with and without mixing aids on the drug and carrier characteristics within DPI mixtures.

EXPERIMENTAL METHODS

Fluticasone Propionate (FP), at a concentration of 2.5% w/w was mixed with Lactohale LH200 (Friesland Foods Domo) in a Turbula mixer for 2 hours at 90 rpm under controlled relative humidity and temperature. Each blend was prepared in 5 grams quantity. Silicagel beads (diameter approx. 3-5 mm, 25 beads for 1 gram readily equilibrated with ambiance) were used as mixing aids based on ball-milling effect for deagglomerating drug particles. Five blends were prepared with 0%, 10%, 20%, 30% and 40% of these beads. The quality of the blends was expressed by the uniformity of drug content (n=20). Quantitative analysis was carried out by validated HPLC method.

Methods

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

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

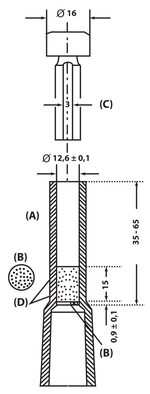

Figure 1. Blaine's Apparatus - Powder Cell

The particle size of Fluticasone propionate was determined with a laser size analyser Mastersizer S by the wet way on liquid dispersions in ethanol/water (10:90 %v/v) containing 0.1%v/v Polysorbate 80. Sonication for 6 min is needed to sufficiently deagglomerate very cohesive FP particles into primary particles.

The particle size of fluticasone propionate in mixture was assessed by laser size analyser. Sample 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 three determinations. For quantifying the deagglomeration efficiency of mixing process, dispersion indices (DI) are proposed as following equation:

$$DI = \frac{V^{mixture}_{<5.69\mu m}}{V^{Drug}_{<5.69\mu m}}$$

$V^{mixture}_{<5.69\mu m}$: cumulative percent volume <5.69µm of FP particles in mixture

$V^{drug}_{<5.69\mu m}$: cumulative percent volume <5.69µm of FP particles – raw material.

The particle size of lactose in mixture was also measured with a laser size analyser. About 20 mg of mixture was suspended in absolute ethanol. The suspension was sonicated using an ultrasonic water bath for one minute. The Fluticasone propionate particles dissolved while the lactose particles remained in the solution. The results are the mean of three determinations.

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

The recovered drug content of all mixtures is close to the theoretical values (Table 1). FP content uniformity is lower than 5% that indicates a good homogeneity of all blends. 0% Silicagel mixture has a lower homogeneity than other mixtures ($p < 0.001$).

Mixtures	Content	RSD
0% Silicagel Mixture	2.44%	4.96%(*)
10% Silicagel Mixture	2.42%	1.45%
20% Silicagel Mixture	2.46%	1.73%
30% Silicagel Mixture	2.45%	1.22%
40% Silicagel Mixture	2.40%	0.77%(*)

Table 1. characteristics of the lactose fractions
(*) statistically different (Fischer test, α =0.05)

Using silicagel beads as mixing aid improves the homogeneity of FP mixture. At 40% silicagel, the mixture shows the best uniformity.

In terms of aerodynamic performance of powder mixture, the fine particle fraction (FPF) of mixtures with mixing aids is significantly greater than simple Turbula-processed mixture (e.g. 7.29%) as it can be seen in Figure 2. FPF improvement depends on the amount of added silicagel beads. FPF reaches a peak when 30% of silicagel beads was added and shows no significant improvement with increasing the amount of mixing aid.

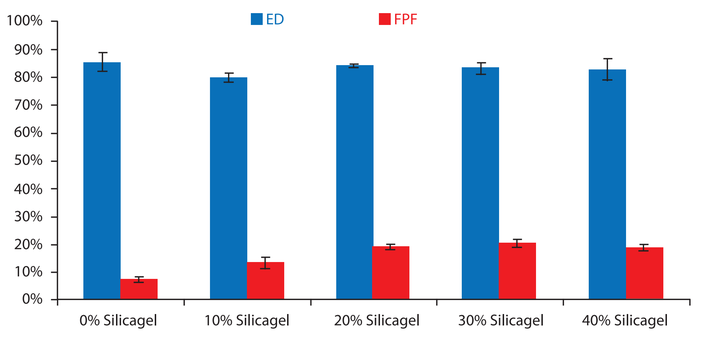

Figure 2. Aerodynamic Performance of FP Mixtures

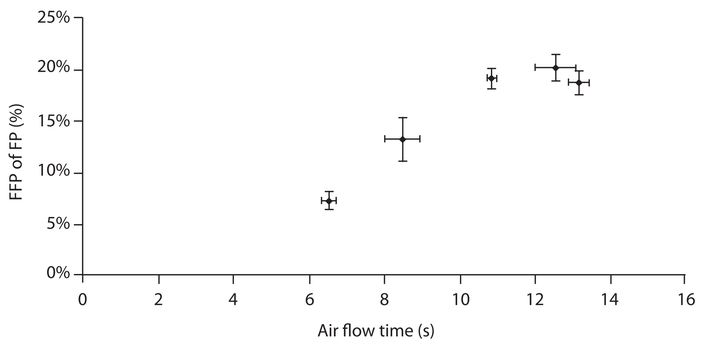

Figure 3. Relationship between air permeability of powder and fine particle fraction

Figure 4. Lactose size in mixture

The effect of amount of silicagel beads on the size of lactose and drug particles was investigated and is presented in Figures 4 and 5. There is a milling effect of the lactose when using silicagel beads. Practically unchanged when 10% of Silicagel beads are added, the lactose particle size decreases gradually to a minimum when 30% of mixing aids are added (Figure 4).

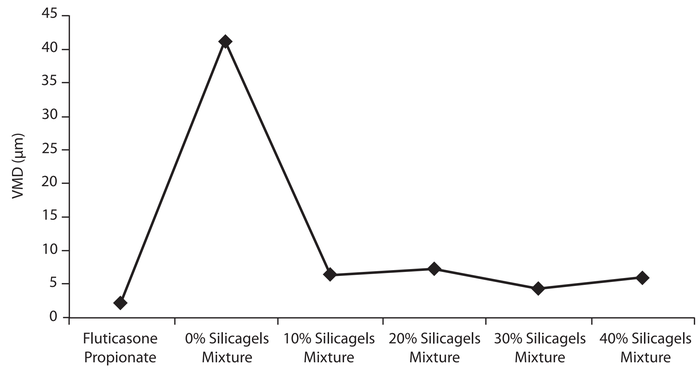

Figure 5. Fluticasone Propionate size in mixture

Without mixing aids, drug is not sufficiently dispersed. FP agglomerates are found in the mixture. Adding silicagel beads improves the dispersion indices. With 30% silicagel beads, DI reaches its highest value (0.83) that corresponds to the best FPF (e.g. 20.26%). On the other hand, decreasing fluticasone propionate agglomerate size improves the uniformity of drug in mixture.

Apparently, the improvement in the aerodynamic performance of FP formulations is caused by both reduction of FP agglomerates and lactose particle size in the mixture. This is confirmed by air permeability of powder.

CONCLUSION

Mixing process is a critical operation in the manufacturing of DPI formulations. Whereas simple low-shear tumbling mixer (Turbula) allows to achieve an acceptable homogeneity, agglomerates of very cohesive drug, such as Fluticasone propionate, remain in the final mixture. Mixing aid using ball-milling effect improves the mixture homogeneity and the aerodynamic performance thanks to its de-agglomeration efficiency. Furthermore, the quantity of fine lactose particles is also increased due to the milling effect. However there is a threshold where an optimal amount of mixing aids should be used. Not only the drug des-aggregation reaches its peak but the increase in drug-carrier adhesion due to high energy input should balance the de-agglomeration capacity of mixing process. This approach provides a potential alternative in DPI formulation processing.

REFERENCES

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