

INFLUENCE OF DRUG CONCENTRATION ON THE PERFORMANCE OF DRY POWDER INHALERS



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INTRODUCTION

Dry powder formulations for inhalation are often composed of fine drug particles and inert coarse particles, typically alpha monohydrate lactose. The fine drug particles are expected to adhere to the carrier surface to form adhesive mixtures. Interactions between particles are mainly dependent on the physicochemical characteristics of the interacting particles [1,2]. The interactions may also be influenced by the drug concentration[3] Limited information on the effect of the drug concentration is currently published.

OBJECTIVES

The aim of this work was to study the influence of drug concentration on the adhesion between drug and carrier, dose uniformity and aerodynamic properties of the drug.

EXPERIMENTAL

Materials :

The Lactohale 200, used as the carrier, was mixed with 0.09%, 0.13%, 0.17% (w/w) of formoterol fumarate, and with 1.5%, 2.5%, 3.5% of fluticasone propionate in a batch size of 100 g using a Turbula tumbling mixer. The quality of the blends was examined by analysing the quantity of drug in aliquots of sampled powder which is the amount of powder in each capsule (50 mg for formoterol blends, 20 mg for fluticasone blends). Fifteen aliquots were taken randomly from each blend and assayed using a UV spectrophotometer with a wavelength of 206 nm for the formoterol fumarate and using HPLC for the fluticasone propionate.

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 µm sieve section of the Alpine air-jet apparatus, in a sealed enclosure. Three samples of 20 mg or 50 mg were removed from the powder bed after sieving for different lengths of time: 5, 30, 60 and 150 seconds. For each sample, we compared the percentage of drug remaining to the initial dose. These assays enabled us to assess the ease with which the drug can be separated from the carrier.

Aerodynamic evaluation of fine particle dose and emitted dose :

Determined using a Twin-Stage Impinger (TSI). Each deposition experiment involved the aerosolisation at 60 l/min via an Inhalator Ingelheim of ten capsules. (n=3).

RESULTS

Table 1 presents the percentage of recovery of drug in the different samples compared to the nominal dose for the different blends

% drug in the blend	Average recovery content (%)
Formoterol fumarate	
0.09 %	87.57 (cv: 2.92 %)
0.13 %	94.10 (cv: 8.9 %)
0.17 %	97.58 (cv: 2.81 %)
Fluticasone propionate	
1.5 %	94.14 (cv: 7.33 %)
2.5 %	96.97 (cv: 5.62 %)
3.5 %	103.35 (cv: 11.34 %)

Table 1 : Average content in drug (w/w) for the different blends

When the percentage of drug increases, the drug recovery increases. In fact, a quantity of drug is able to adhere to the container. This quantity is probably the same for a given drug whatever the drug concentration. So, if this quantity is related to the drug concentration, the loss will be more important in percentage when the drug concentration is lower. The blend with 3.5% fluticasone propionate presents greater variations. There is probably an excess of drug that can not be fixed on the Lactohale 200.

When blends are submitted to the Alpine air-jet sieve, drug is rapidly carried away by the airflow. Figure 1 shows an example representative for the blends tested.

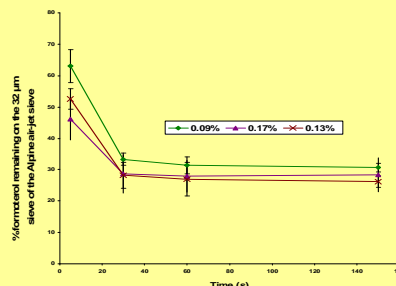


Figure 1: Percentage of formoterol fumarate fixed to the carrier in relation to the functioning time of the air-jet sieve

The quantity of drug present after 5 s is an indicator of the quantity that adheres to the carrier. For the higher concentration of formoterol, it seems that a lower quantity of drug adheres to the lactose and/or the adhesion force is lower. This is confirmed by the aerosolization assays realised in the TSI (table 2).

% drug in the blend	Fine Particle Fraction (%)
Formoterol fumarate	
0.09 %	14.99 (cv: 0.59 %)
0.13 %	19.41 (cv: 0.36 %)
0.17 %	26.20 (cv: 3.77 %)
Fluticasone propionate	
1.5 %	33.79 (cv: 2.75 %)
2.5 %	40.28 (cv: 0.47 %)
3.5 %	36.02 (cv: 2.69 %)

Table 2 : Fine particle fractions obtained from the different blends

In the case of formoterol, the fine particle fraction increases with the drug concentration. A linear relationship between the formoterol fumarate concentration and the fine particle fraction was observed (fig.2)

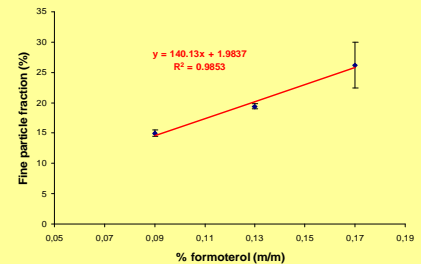


Figure 2: Fine Particle Fraction in relation to the concentration of formoterol fumarate

The drug particles initially adhere to the high energy adhesion sites on the carrier. An increase in the drug concentration leads to the saturation of the carrier sites with the strongest binding forces. At higher drug concentrations, more drug particles may be adhering to sites with less strong binding affinities on the surface of carrier.

A correlation is observed between adhesion characteristics and inertial impaction (fig.3).

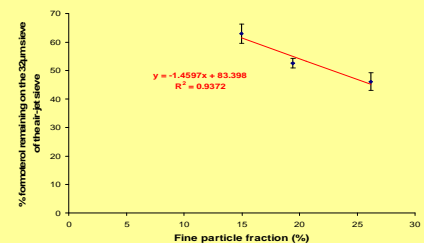


Figure 3 : Relation between Fine Particle Fraction and percentage of formoterol remaining on the air-jet sieve after 5 s.

In the case of fluticasone, the influence of the concentration is different. First, the fine particle fraction increases with the concentration and then decreases with a further increase of the fluticasone concentration. This could be explained either by the lack of homogeneity when the fluticasone concentration is high, either by the chemical characteristics of this drug.

CONCLUSION

Drug concentration in dry powder inhalers influences adhesion, content uniformity and in vitro deposition of the drug. It is difficult to extend the influence of drug concentration. It would be interesting to test other drugs to study thoroughly this influence.

REFERENCES

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