

In vitro evaluation of powders for inhalation: the effect of drug concentration on particle detachment

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Summary

Limited information on the effect of the drug concentration on the performance of powders by inhalation is currently published. The aim of this work was to study the influence of drug concentration on the adhesion between drug and carrier and on the drug detachment from the carrier. The study was done with formoterol fumarate blended with lactose Lactohale 200. 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 done in the Twin Stage Impinger. The fine particle fraction increases linearly with the formoterol concentration. Adhesion testing using air-jet sieving assays makes it possible to predict drug separation from the lactose carrier faster and more efficiently than with assays with an impactor.

Introduction

Dry powder formulations for inhalation are often composed of fine drug particles and inert coarse carrier 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. The interactions may also be influenced by the drug concentration. Limited information on the effect of the drug concentration is currently published. Most studies on adhesive mixtures for inhalation focus only on a single drug concentration, for example 1.46% w/w for salbutamol or terbutaline sulphate. However, drugs in very low dose ranges are developed. So it is of interest to consider adhesive mixtures with different drug concentrations and in particular much lower ranges. The aim of this work was to study the influence of the drug concentration on the adhesion between drug and carrier and on the drug detachment from the carrier.

Material and methods

The study was done with formoterol fumarate, a drug used at a low dose, that is to say 6 µg or 12 µg, blended with lactose Lactohale 200 used as the carrier. The Lactohale 200 was mixed with 0.09 %, 0.13 % and 0.17% (w/w) of formoterol fumarate in a batch size of 100 g using a Turbula tumbling mixer at 74 rpm during 60 min. The quality of the blends was examined by analysing the quantity of drug in aliquots (50 mg) of sampled powder which is the amount of powder in each capsule. Fifteen aliquots were taken randomly from each blend and assayed using an UV spectrophotometer with a wavelength of 206 nm. From the results obtained for each sample, the average content for fumarate formoterol was calculated.

To assess the adhesion of respirable-sized drug to carrier particles, a simple method was developed based on aspiration and considering the whole blend as it is used in dry powder inhalers. Adhesion characteristics are evaluated by submitting the mixtures to a sieving action by air depression with the Alpine air-jet sieve. Blends were put on the 32 µm sieve section of the Alpine air-jet apparatus, in a sealed enclosure. Particles are submitted on the one hand to an airflow released by a blow nozzle rotating under the sieve and, on the other hand, to aspiration through the sieve. The drug particles that are detached from the carrier and suspended in air are carried through the sieve thanks to aspiration. Samples were removed from the powder bed after sieving for different lengths of time. For each sample, the percentage of remaining drug was compared to the initial dose which is an indicator of the quantity of drug that adheres to the carrier. Indeed if the drug particles were separated from the carrier, they would be carried away through the sieve by aspiration.

Aerodynamic evaluation of fine particle dose and emitted dose were obtained using a Twin Stage Impinger. Each deposition experiment involved the aerosolization at 60 l/min of ten capsules via the Ingelheim inhalator (Boehringer Ingelheim).

Results and discussion

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

% formoterol fumarate in the blend	0.09 %	0.13 %	0.17 %
Average recovery content (%)	87.57 (+/- 2.92)	94.10 (+/- 8.9)	97.58 (+/- 2.81)

Table 1: Average content in formoterol fumarate for the different blends

When the percentage of formoterol fumarate increases, the drug recovery increases. In fact, a quantity of drug is able to adhere to the container. This quantity is probably the same whatever the formoterol concentration. So, if this quantity is related to the formoterol concentration, the loss will be more important in percentage when the drug concentration is lower.

With regards to the evaluation of adhesion characteristics, the figure 1 presents the percentage of formoterol fumarate remaining fixed on the carrier in relation to time of the Alpine air-jet sieving for the blends containing different percentage of formoterol fumarate. The fomoterol fumarate is rapidly carried away by the airflow. The quantity of drug present after 5 s is an indicator of the quantity of drug that adheres to the carrier. Indeed, as drug particle size is much lower than 32 μm , if the drug particles were separated from in the blend and not adhered on the carrier, they would be carried away through the 32 μm sieve by aspiration. After 5 seconds, about 63%, 53% and 46% of formoterol fumarate remains fixed on Lactohale 200 for the blends containing respectively 0.09%, 0.13% and 0.17% of drug.

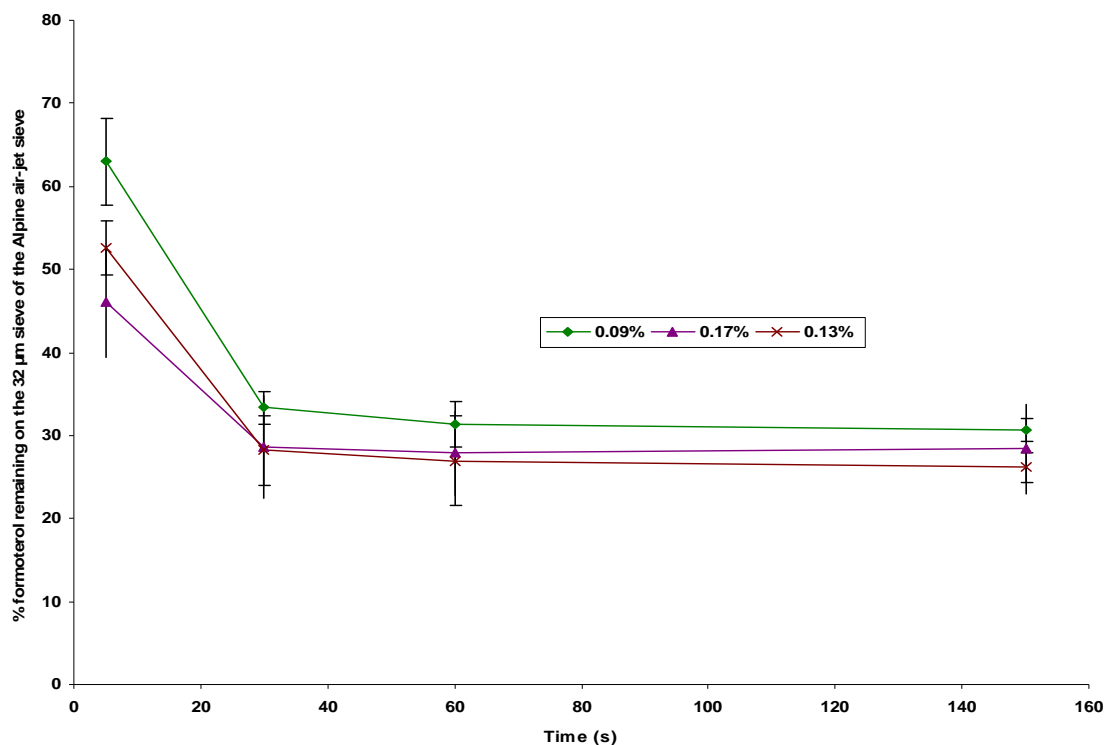


Figure 1 : Percentage of formoterol fumarate remaining fixed to the carrier in relation to the functioning time of the air-jet sieve

When the concentration in formoterol increases, a linear decrease ($R_2= 0.983$) of the quantity of drug remaining on the sieve after 5 seconds was observed. The behaviour of the lactose-drug blend during the assay can give an estimation of the drug capacity to separate from the carrier during inhalation from a Dry Powder Inhaler. Strong adhesion of the micronised drug during the assay pre-supposes difficult separation of the drug after patient inhalation or the need for greater inhalation airflow. 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 Twin Stage Impinger (Table 2). Indeed, the fine particle fraction increases with formoterol concentration.

% formoterol fumarate in the blend	0.09 %	0.13 %	0.17 %
Emitted dose (%)	72.90 (+/- 4.81)	81.58 (+/- 10.79)	80.67 (+/- 3.73)
Fine particle fraction (%)	14.99 (+/- 0.59)	19.41 (+/- 0.36)	26.20 (+/- 3.77)

Table 2: Formoterol fumarate deposition in the Twin Stage Impinger

A linear relationship ($R_2 = 0.985$) between the fine particle fraction and the formoterol fumarate concentration was observed (figure 2). It may be related to the fact that the detachment of formoterol fumarate from the Lactohale 200 is lower when the concentration is low in the mixture since 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 carriers.

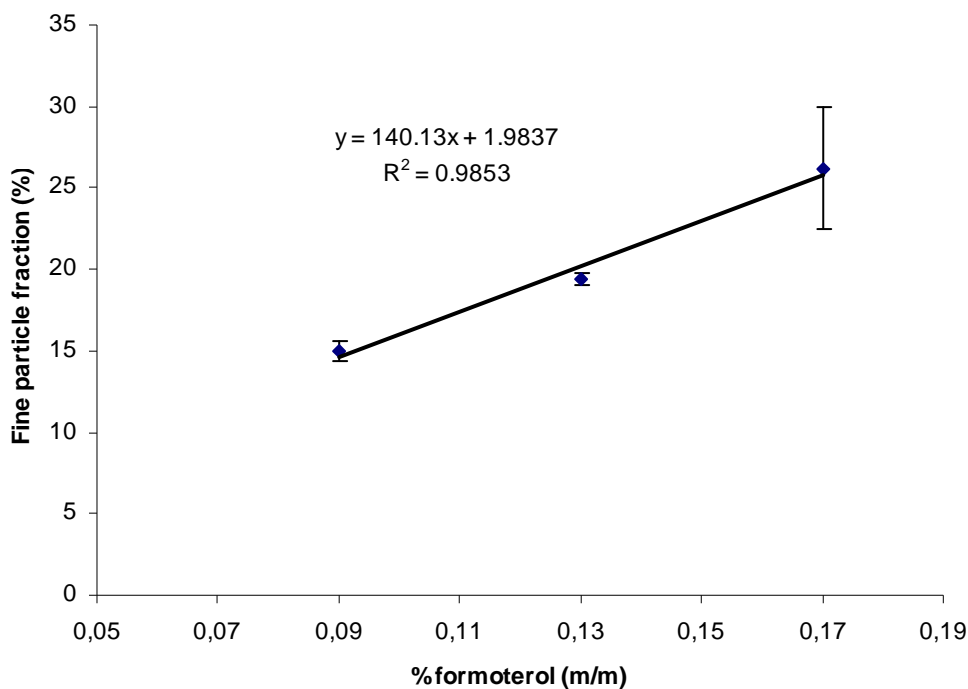


Figure 2 : Fine particle fraction in relation to the concentration of formoterol fumarate

The results of drug separation from the carrier by sieving with the Alpine air-jet sieve were compared with those obtained from in vitro deposition studies with the Twin Stage Impinger. Figure 3 represents the relationship between fine particle fraction and the percentage of formoterol fumarate remaining on the 32 μm sieve of the air-jet sieve after 5 seconds. A linear relationship was noted between them with a coefficient R^2 of 0.937 which indicates a good correlation between these two parameters. These results relate to the first 5 seconds of aspiration which could be compared to the inhalation time of a patient when using a dry powder inhaler.

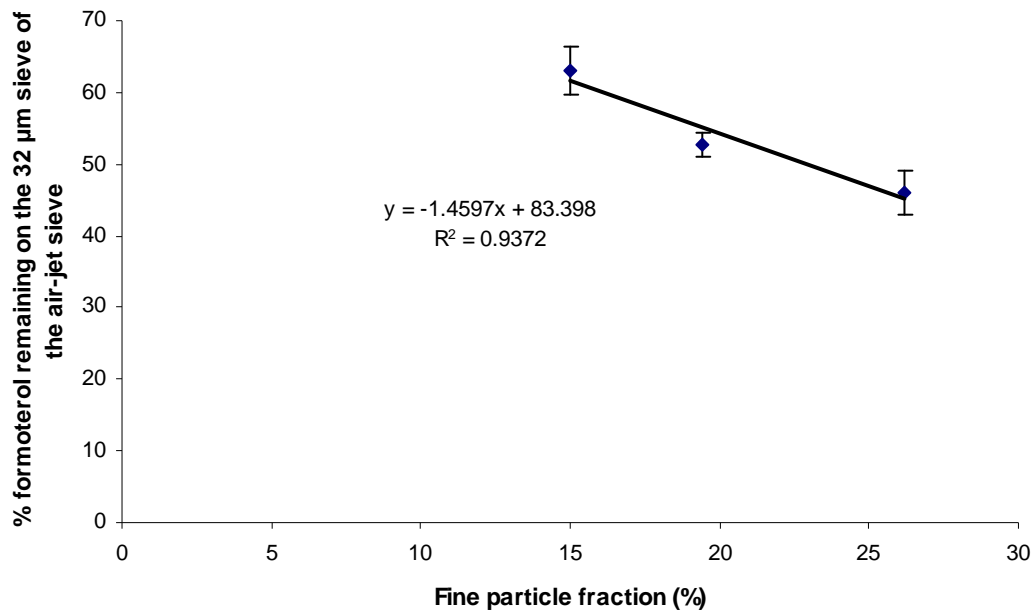


Figure 3 : Relation between fine particle fraction and percentage of formoterol fumarate remaining on the 32 μm sieve of the air-jet sieve after 5 seconds

Conclusion

The formoterol fumarate concentration in adhesive mixtures influences its adhesion with Lactohale 200 and its detachment from this carrier. For the higher concentration of formoterol fumarate, a lower quantity of drug adheres to the lactose and/or the adhesion force is lower. The fine particle fraction increases with the formoterol fumarate concentration. There is a linear relationship between the formoterol fumarate concentration and the fine particle fraction. Adhesion testing using air-jet sieving assays makes it possible to predict drug separation from the lactose carrier faster and more efficiently than from assays with an impactor.