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Note

The effect of budesonide particle mass on drug particle detachment from carrier crystals in adhesive mixtures during inhalation

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Abstract

The different fine particle fractions (FPFs) that are obtained, when different dry powder inhalers (DPIs) are used for the same powder formulation at the same flow rate, is the result of different powder de-agglomeration efficiencies for these DPIs. For adhesive mixtures, this is the efficiency with which the kinetic energy of the air flow through the DPI is converted into separation forces that detach drug particles from carrier crystals. We investigated the effect of drug particle diameter (mass) on drug–carrier separation during inhalation with three different inhalers (Sofotec Novolizer, Inhalator Ingelheim and a special test inhaler), at two different flow rates (30 and 60 l/min). Two different size fractions were used as carrier material (45–63 and 100–150 μm). We measured decreasing amounts of residual drug on the carrier crystals after inhalation with increasing drug particle mass for all inhalers at both flow rates. The observed trends were the same for both carrier fractions. The decrease in residual drug on carrier is in agreement with increasing FPFs in an Erweka impactor. However, it has been calculated that the magnitude of the effect decreases with increasing de-agglomeration efficiency.

Keywords: Dry powder inhalation; Adhesive mixtures; Drug particle size; Drug particle detachment; Budesonide; Fine particle fraction

1. Introduction

A standard preparation technique for micronized inhalation drugs is their formulation into so called 'adhesive mixtures'. In these mixtures, typically wedge shaped crystalline alpha lactose monohydrate crystals are frequently used as carrier material. Such carrier crystals have large crystal planes to which fine drug particles are attached by adhesion in a homogeneous distribution during the mixing process. In several papers, the relevance of carrier size distribution and carrier surface properties to the interaction between drug and carrier particles has been discussed [1–3]. Considering the great difference in mean size between the drug and carrier particles in these mixtures and the more or less spherical shape of the micronized drug particles, the type of interparticulate attraction in adhesive mixtures for inhalation is basically that between a sphere and a plane. According to the Van der Waals equation for this type of interaction, the attraction force (F_{vdW}) is proportional to the diameter of the drug particle (D) and inversely proportional to the square of the distance (X) between the particles [4]:

$$F_{vdW} \propto A^*(D/X^2) \quad (1)$$

where A represents the Hamaker constant (for two dissimilar materials).

From Eq. (1), it may be expected that a decrease in drug particle size results in a decreased interaction force. This could raise the expectation that drug particle detachment during inhalation improves with decreasing mean drug particle diameter. However, drug particle detachment does not solely depend on the attraction forces, but on the magnitude of the removal forces during inhalation as well. The balance between these forces determines the fraction of drug discharged as fine particle fraction (FPF) from the inhaler's mouthpiece during inhalation. Different FPFs obtained with different inhalers from the same powder formulation, using the same inspiratory manoeuvre, reflect the differences in de-agglomeration efficiency for these inhalers. For adhesive mixtures, this is the efficiency with which the kinetic energy in the air stream through the dry powder inhaler (DPI) is converted into detachment forces with sufficient strength for the separation of drug and carrier particles.

The type of detachment force, which dominates during

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inhalation depends primarily on the design of the inhaler's powder de-agglomeration principle. Such removal forces may include inertial forces (e.g. during particle collision against inhaler walls), shear forces (from particle friction against inhaler walls) and lift or drag forces (in turbulent air streams). The orders of magnitude of removal forces of different nature may be quite different and depend on the inspiratory flow conditions. Inertial forces on impact ($F_{inertial}$) are proportional to the third power of the particle diameter, whereas drag forces (F_{drag}) relate to the first or second power of the diameter [5]. Air and particle velocities within the DPI increase with increasing inspiratory flow rate, by virtue of which all types of removal forces become more powerful. Certain properties of (components in) the powder formulation may be important too. For example, the efficacy of drag, lift and shear forces decreases with increasing carrier rugosity. Primary drug particles, or even small agglomerates, may find shelter from these forces in carrier discontinuities that are within the micron range, or larger.

Relevant to the inertial removal force during inhalation is not only the particle velocity on impact, but also the mass (m) of the drug particle that is subjected to the deceleration (a) upon carrier particle collision ($F_{inertial} = ma$). Therefore, it seems obvious that the inertial detachment force increases when the drug particle mass increases. This can apply for single particles as well as for small clusters of drug particles with sufficient coherence to be detached as one single entity. Such clusters are the result of incomplete break-up of larger drug agglomerates during the mixing process. Because this break-up may be influenced by the size distribution of primary drug particles too, the net effect of a change in the mean drug particle diameter is rather unpredictable.

The aim of this study was to investigate the effect of the size distribution of budesonide in adhesive mixtures on the fine particle detachment during inhalation. The study was carried out with two different lactose sieve fractions using three different types of inhalers. Conclusions are based on coarse particle fraction and FPFs collected in an Erweka impactor at two different flow rates as well as on residual drug fractions in retained carrier fractions after inhalation, using a special test inhaler [6].

2. Materials and methods

Two different sieve fractions of crystalline alpha lactose monohydrate (45–63 and 100–150 μm) were derived from Pharmatose 200 M (DMV International, Veghel, The Netherlands). Three budesonide samples for inhalation with different size distributions were supplied by Sofotec (Frankfurt, Germany) and Sicor, (Milan, Italy). Two different marketed dry powder inhalers, Novolizer (Sofotec) and Inhalator Ingelheim (Boehringer Ingelheim, Germany), as well as a special test inhaler (University of Groningen) were used. For the test inhaler, pre-weighted doses of 25 mg were inserted manually. The test inhaler has an air classifier for the classification of airborne particles: only small particles in the approximate size range for deposition in the target area are discharged with a cut-off value for lactose of 15 μm at 60 l/min. Larger particles (or unbroken pellets) are retained and stay in circulation as long as there is an air stream through the inhaler. After inhalation, the retained carrier particles are removed from the device and analysed for residual drug.

2.1. Characterisation of the starting materials

Particle size distributions of the starting materials were measured with a Sympatec HELOS compact KA laser diffraction apparatus (Sympatec GmbH, Clausthal-Zellerfeld, Germany), using a RODOS dry powder dispenser (at 3 bar). Lenses of 100 mm (for budesonide samples) and 200 mm (for the lactose fractions) were used and calculations were based on the Fraunhofer theory. All data given are the mean of two measurements.

The masses of the budesonide particles were calculated on the basis of the median particle diameters from laser diffraction analysis, using a true density of 1.24 g/cm^3 (provided by AstraZeneca, Lund, Sweden in personal communication) and assuming that the particles are spherical.

2.2. Mixture preparation and homogeneity testing

Formulations were prepared by mixing 0.4 g budesonide with 25 g lactose in a stainless steel container of 160 cm^3, using a Turbula tumbling mixer type T2C at 90 rpm (W.A. Bachofen, Basel, Switzerland) for 10 min. Homogeneity was determined on 20 samples of 25 ($\pm$1.0) mg per mixture. The samples were dissolved in 20 ml of pure ethanol and the UV absorption measured at 243.7 nm using a Philips PU 8720 UV/VIS scanning spectrophotometer.

2.3. Cascade impactor analyses

The in vitro deposition of the mixtures was tested with a multi-stage liquid impinger of the Astra type (Erweka, Heusenstamm, Germany), using a double tapered metal induction port with a special coupling flange for the inhalers. Each impactor stage was filled with 20 ml of pure ethanol as solvent, except for the final stage, in which a 76 mm dry glass filter (Gelman Sciences, type A/E, Ann Arbor, Michigan, USA) was inserted.

Flow rate through the pre-calibrated inhalers was adjusted to be 30 or 60 l/min on the basis of differential pressure measurement at the position of the coupling flange. For each mixture–inhaler combination, two duplicate measurements of ten inhalations per flow rate were performed.

For the inhalator Ingelheim and test inhaler, 25 mg of mixture was used corresponding to a dose of 400 μg. To determine the dose from the Novolizer, the bulk container filled with 2 g of mixture was weighed before and after the

test. All inhalers were used according to the manufacturers' instructions.

After completion of a series of ten inhalations, the drug fractions on the impactor stages were allowed to dissolve for at least 1 h, before they were removed for further processing. Prior to UV-measurement (at 243.7 nm in a Philips PU 8720 UV/VIS), the solutions were clarified by removing non-dissolved particles in a centrifuge (Hettich Rotana, Tuttlingen, Germany) during 5 min rotation at 3000 rpm. Carrier fractions that were retained by the special test inhaler after inhalation were treated similarly. Residual drug in these carrier fractions was extrapolated to 100% retainment and presented as carrier residue (%CR).

3. Results and discussion

The volume median diameters (VMDs) of the budesonide samples from laser diffraction analysis are 1.08 (0.37–2.40), 1.32 (0.64–2.70) and 1.56 (0.68–3.43) μm; the values between the brackets represent the X_{10} and X_{90}-values. Corresponding calculated mean particle masses are 0.818, 1.493 and 2.465×10^{-12} g. The relatively high lower sieve diameters of 45 and 100 μm for the carrier fraction compared to the cut-off diameters of the first impactor stage for lactose at 30 and 60 l/min (23.8 and 16.9 μm, respectively) guarantee that practically all carrier crystals are deposited on this first stage, and so is the drug fraction that has not been detached from the carrier crystals during inhalation (residual drug fraction). Fig. 1 shows the residual drug fractions on carrier fraction 100–150 μm, as a function of the particle mass, for the Inhalator Ingelheim and Sofotec Novolizer. The residual drug fraction from inhalation with the test inhaler is obtained from analysis of the retained carrier particles. Residual and detached drug fractions are complementary to 100%. The carrier residues from the test inhaler at 60 l/min are not shown: the line would interfere with those for the FPFs. The de-agglomeration efficiency of the test inhaler at this flow rate is so high that the carrier residue values are around 10% for all drug fractions (no significant difference between these fractions).

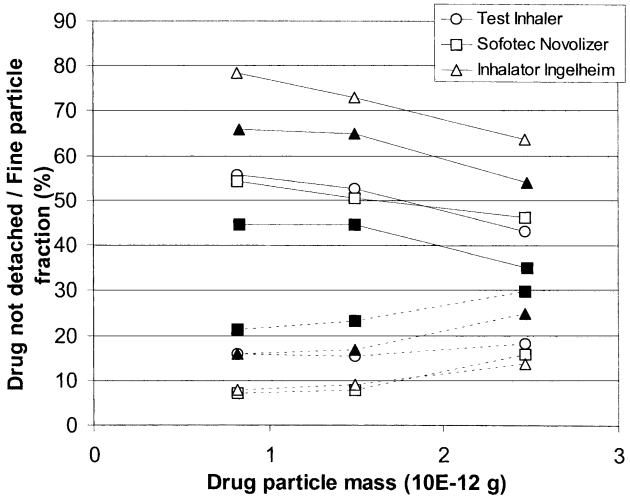

Fig. 1. Drug fractions not detached (symbols with solid lines) from lactose carrier crystals (fraction 100–150 μm) during inhalation, represented by first stage depositions for Inhalator Ingelheim, Sofotec Novolizer and carrier residue for the special test inhaler (see text). Also the FPFs (symbols with dotted lines) from the Erweka impactor (stages 3, 4 and filter) are given. Open symbols refer to 30 l/min; closed symbols to 60 l/min. Both the drug fractions not detached and the FPFs are noted as function of the drug particle mass.

The results show for all three inhalers at both the flow rates, that an increase in mean drug particle mass, gives an increased amount of drug being detached during inhalation. The increases in FPFs (from the cascade impactor) are in agreement with this observation (Fig. 1), although there is a discrepancy between released drug fractions and the measured FPFs, due to fine particle losses in the inhaler's mouthpiece, the induction port to the impactor and the connecting tubes between the impactor stages. Therefore, residual drug fractions and measured FPFs are not complementary to 100%. The adhesive mixtures with carrier fractions 45–63 μm yielded comparable results. For the clarity of Fig. 1, they are not shown. The relatively high residual drug fractions indicate that the removal forces generated by the inhalers in the study at 30 and 60 l/min are unable to overcome all interaction forces between the drug and carrier particles in the adhesive mixtures. Only between 20 and 65% of the drug is released (except for the test inhaler at 60 l/min), showing that detachment efficiency is only poor to moderate. There not only exists a great difference in detachment efficacy between the inhaler devices at the same flow rate but Fig. 1 shows that there is also a considerable effect of flow rate on the performance of all three DPIs. The net effect from increasing the drug particle mass is in disagreement with what one would expect on the basis of the Van der Waals equation for adhesion (Eq. (1)). This suggests that detachment is predominated by inertial forces, which is not unreasonable to assume, considering the types of inhalers used for the study.

The order of magnitude, for the effect of drug particle mass on the efficiency of drug–carrier separation is different for all three inhalers used in the study. This may not be clear from Fig. 1, showing the absolute decrease in residual drug fraction for all inhalers. However, when the ratios of 'fraction detached for the coarsest drug sample' to 'fraction detached for the finest drug sample' are calculated (for experiments with the same inhaler, same carrier fraction and the same flow rate), a strong indication is obtained that the effect of drug mass on the detached drug fraction increases with decreasing detachment efficiency. This ratio is presented in Fig. 2 as function of the fraction detached for the finest drug sample. As this detached fraction for the finest drug sample is the worst case situation in our study, the calculated ratios may be considered as the relative improvement obtained from increasing the drug particle mass. The greatest relative improvement (by a factor of 1.68) has been found for the Inhalator Ingelheim (for the

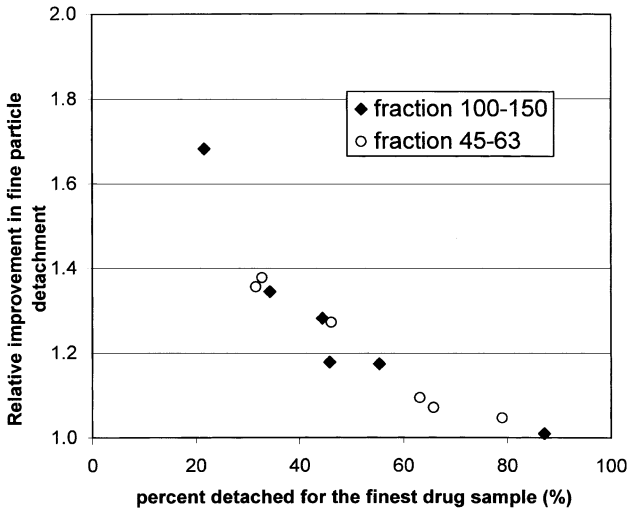

Fig. 2. Relative improvement in fine particle detachment expressed as ratio of detachment for the coarsest drug fraction to detachment for the finest drug fraction (see text).

carrier fraction 100–150 μm), which exhibited lowest detachment efficacy for the finest drug sample at 30 l/min. The smallest relative improvement (by a factor of 1.01) is for the test inhaler (also for carrier fraction 100–150 μm) with highest detachment efficacy for the finest drug sample at 60 l/min. So, the relative improvement increases with decreasing detachment efficiency. Fig. 2 includes all data for all three inhalers in the study at both flow rates as well as for both carrier fractions, showing that the relationship is rather unique.

There is no evidence for differences in fine particle break-up during mixing, neither from mixture homogeneities (r.s.d. being within the range from 0.8 to 1.2% for all mixtures) nor from the graphs in Figs. 1 and 2.

4. Conclusions

By increasing the mean budesonide particle diameter (1.08–1.56 μm) in adhesive mixtures, the drug released from the carrier crystals during inhalation is increased. For the inhalers used in this study, the influence of budesonide particle size decreases with an increase in de-agglomeration (detachment) efficiency. It can therefore, be concluded that the greater the de-agglomeration efficiency of an inhaler, the lower the variation in the fine particle fraction caused by batch to batch variation in budesonide particle size.

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