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Research paper

# Adhesion forces in interactive mixtures for dry powder inhalers – Evaluation of a new measuring method

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**Abstract**

Dry powder inhalers mostly contain carrier based formulations where micronized drug particles are adhered to coarse carrier particles. The performance of the dry powder inhaler depends on the inhaler device, the inhalation manoeuvre and the formulation. The most important factor influencing the behaviour of the formulation is the adhesion force acting between the active ingredient and the carrier particles, which can be measured using different methods, for example the centrifuge technique or atomic force microscopy. In this study the tensile strength method, usually applied to determine cohesion forces between powder particles of one material, is optimized for adhesion force measurements between powder particles of unlike materials. Adhesion force measurements between the carrier materials lactose or mannitol and the drug substance salbutamol sulphate using the tensile strength method and the atomic force microscopy show higher values with increasing relative humidity. Consequently, the fine particle fraction determined using the Next Generation Impactor decreases with increasing relative humidity as a result of the enhanced interparticle interactions.


*Keywords:* Adhesion forces; Atomic force microscopy; Dry powder inhalers; Interparticle interactions; Tensile strength measurements

## 1. Introduction

Application of active ingredients to the deeper part of the lungs requires particle sizes between 1 and 5 μm. Therefore a micronization of the active ingredient is needed. The micronization causes particles of high surface area, which can form a cohesive system where the particles adhere to each other. The flowability and dispersion properties of these systems are poor, causing problems during dosage form manufacturing and application. Because of these problems dry powder inhalers very often contain interactive mixtures consisting of a coarse carrier material and the micronized active ingredient. The most common carrier material is α-lactose-monohydrate. Alternative materials like mannitol and trehalose are also under investigation [1].

During the mixing process formation of the interactive mixture depends on two forces: The above mentioned cohesion forces between the drug particles and the adhesion forces of the active ingredient to the carrier particles. Only if the adhesion force between the two substances is high enough the mixing process will be complete and no agglomerates of the active will be left. On the other hand the redispersion of the drug affecting the performance of a dry powder inhaler is influenced by three factors: The inhaler device, the inhalation manoeuvre of the patient and the formulation. These factors determine the fine particle fraction which is that part of the active supposed to

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reach the deeper part of the lungs. The fine particle fraction can be determined by one of the impactors described in the European Pharmacopoeia [2], for example the Next Generation Impactor (NGI).

With respect to the formulation several parameters are discussed that are relevant for the performance of a dry powder inhalate, like carrier rugosity and active carrier sites. Those can be manipulated for example by adding fines of the carrier material or other materials [3,4]. Manipulations of the carrier material cause changes of the adhesion force between carrier and active ingredient. The adhesion forces should not be too high so that the detachment of the drug particles during inhalation is possible and impaction of the active together with the carrier in the upper airways is avoided. Therefore the adhesion force is a key parameter for the behaviour of the interactive mixture.

Different methods are described for the measurement of interparticle interactions e.g. the centrifuge technique where particles of an interactive mixture are adhered to a disc in a special device rotating in a centrifuge. The amount of detached particles depending on the centrifugation speed is determined [5]. The adhesion force is calculated from the centrifugation speed. Another method which is used in this study is the atomic force microscopy (AFM). This method, which was first used as an excellent tool for high resolution imaging of surface topography, became important for sensitive adhesion force measurements. The method enables the user to measure the adhesion force of a single particle on a given substrate. This is also called colloid probe technique and is used to understand surface forces in different areas of interest [6]. For both methods the correlation between the adhesion force obtained and the fine particle fraction of the respective interactive mixtures was investigated and the usefulness of the methods to support the development process of dry powder inhalers was evaluated [7–9].

Another method to determine interparticle forces is the tensile strength method where the forces acting between two powder layers are measured. The method is mostly used for the determination of cohesion forces between like materials for example to evaluate the influence of porosity of powder bed [10], relative humidity [11] or flow conditioners [12] and rarely used for the determination of forces between unlike materials [13]. For the cohesion force measurements the powder layers are formed during the measurement by dipping the measuring device covered with a sticky agent in a loose powder bed. After a determined contact time it is removed and the force acting between the two powder layers, the one sticking to the measuring device and the one left behind in the powder bed, is measured. For the adhesion force measurements the two powder layers are prepared prior to the measurement by fixing one of them on the measuring device, the other one on a second disc which is in parallel to the measuring device. The powder layers are brought into contact and separated again after a given contact time.

The aim of the first part of this study is to further adapt the tensile strength method to determine adhesion forces between unlike materials. Therefore an optimization of the experimental setup and especially the measuring device was necessary. In the second part the ability of the method to determine different adhesion forces was investigated and the results obtained are compared to the results of the measurements obtained using the atomic force microscope. Furthermore, these results are discussed with respect to the fine particle fraction determined using the next generation impactor. As model drug substance the $\beta_2$-sympathomimeticum salbutamol sulphate was used in combination with the common carrier material $\alpha$-lactose monohydrate and the alternative carrier material mannitol. Measurements were carried out at different relative humidities.

## 2. Materials and methods

### 2.1. Materials

$\alpha$-Lactose-monohydrate (InhaLac®70) ($x_{10} = 92.25$ µm, $x_{50} = 189.76$ µm, $x_{90} = 310.25$ µm) was given by Meggle AG, D-Wasserburg, Mannitol (Pearlitol SD 200) ($x_{10} = 16.49$ µm, $x_{50} = 141.57$ µm, $x_{90} = 264.34$ µm) by Roquette, F-Lestrem. Salbutamol sulphate was received from Stada, D-Bad Vilbel. It is micronized using an Air Jet Mill 50 AS (Hosokawa Alpine, D-Augsburg). The obtained powder exhibits a particle size distribution of $x_{10} = 0.67$ µm, $x_{50} = 2.05$ µm and $x_{90} = 5.68$ µm. Particle size distributions are determined using laser diffraction (see Section 2.2.5).

### 2.2. Methods

#### 2.2.1. Determination of tensile strength

The powder layer on the upper disc is prepared by placing a double-sided tape (Plano GmbH, D-Wetzlar) onto the surface of the measuring device and dipping it into a powder bed. Loose particles are removed with a brush. This is repeated several times. Finally the surface is cleared from loosely adhered particles using compressed air at a pressure of 5 bar.

The powder layer on the lower disc is prepared by placing a double sided tape onto a metal disc, pouring a powder layer of 0.3 mm height on it and loading this with a 500 g weight for about 30 s. Loose powder is removed and the load is applied again. Unfixed powder particles are removed using compressed air at a pressure of 5 bar before performing the measurement.

The measuring device consists of aluminum. The diameter of the disc is 40 mm. It hangs on a sphere of steel with a diameter of 10 mm which is connected to the balance by a rod.

The measurements are performed using a tensiometer K100 (Kruess GmbH, D-Hamburg) with two fixed powder layers, one on the measuring device and one on the disc located on the table of the tensiometer (Fig. 1). The load