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Identification of inter-particular forces by atomic force microscopy and how they relate to powder rheological properties measured in shearing tests

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ABSTRACT

In this study, we used atomic force microscopy (AFM) to measure and identify the nature of the forces acting between single pharmaceutical powder particles, namely a crystalline and a semi-crystalline form of lactose. The experiments done at different moisture level, namely from 20% to 60% of relative humidity, identified capillarity as the main source of adhesion between single particles. A strong correlation was observed between the AFM adhesion results and cohesion measurements taken with a FT4 torsional type powder shear tester. This correlation between adhesion and cohesion allows the identification of capillary forces as the main source of the cohesion measured in shearing experiments in ambient moisture conditions. In the case of the semi-crystalline lactose powder, a sharp decrease in both the adhesion and cohesion at 50% RH was linked to absorption of water accumulated at the particle surfaces to fuel a phase transition of the non-crystalline domains to crystalline lactose, hence limiting the capillary action between particles at this specific moisture condition.

1. Introduction

One of the main challenges in the manufacturing of pharmaceutical solid dosage forms is to avoid segregation in particulate (powders and granules) mixtures as well as inhomogeneity in the final formulations. This challenge is bound to become even more crucial, as low dosage formulations become more common [1].

In the past years, the use of shearing tests as a means to macroscopically measure the bulk cohesion and the friction properties of powders has contributed considerably in quantifying the rheological behaviour of granular media. This knowledge has been used for equipment design, quality control and for the assessment of average powder flow properties [2,3]. Generally, the data obtained with shearing testers are analysed with the Mohr–Coulomb failure criterion [4].

$$\tau = \sigma \tan\theta + C \qquad (1)$$

where τ is shear stress, σ, normal stress, θ, the angle of internal friction, and C, the cohesion parameter. This equation describes also the friction interaction between two single particles, to which a cohesion (or adhesion) term is added (see Fig. 1). In this simpler case, the shear stress corresponds to a friction force parallel to the particle contact surface and the normal stress corresponds to the normal force between the two particles. In the terminology traditionally used in contact mechanics, the cohesion is referred to as an adhesion force, and we will thus use the term adhesion when referring to single particle attractive forces.

The physical nature of the cohesion term in the Mohr–Coulomb failure criterion is difficult to determine and often the subject of speculations. For instance, the addition of magnesium stearate in pharmaceutical formulations is known to decrease the cohesion measurements of the mixture to which it is added, thus producing a lubrication effect. This lubrication effect has been simultaneously explained by a limitation of the capillarity forces [5], a modification in the van der Waals interaction between particles [6], and a reduction of friction by filling the asperities in the excipient particle surfaces [7]. Indirect evidence also suggests that cohesion mainly originates from the creation of capillary liquid bridges between particles [8,9].

We present results showing that the cohesion term in the Mohr–Coulomb equation derives from an adhesion force which can be directly measured between two particles, by recording force–distance curve obtained with an atomic force microscope (AFM). This type of measurement allows measuring the interaction between two particles as they approach each other, deform and ultimately detach and retract from each other. The information provided by the force–distance curve, that is the amplitude of the force and the range of interaction, allows for the identification and quantification of the forces involved in the particles' interaction [10].

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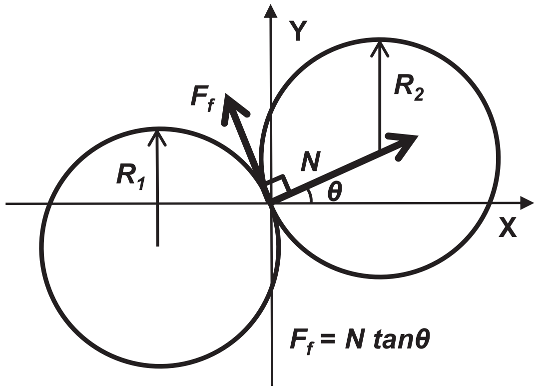

Fig 1. Schematic of two spherical particles interacting through frictional, normal and adhesion forces.

In order to study the contribution of capillary forces on the strength of the adhesion and the cohesion, we vary the relative humidity level in both AFM measurement and shearing tests. We used crystalline and semi-crystalline lactose particles to show the correlation between average adhesion values and cohesion. Even though the chemical composition of these particles is the same, they show radically different flow properties which are in part due to their different morphology, and also to the difference in crystal arrangement. The presence of an amorphous phase in semi-crystalline particles makes them particularly interesting as we show that the water absorption depends strongly on relative humidity levels due to a water-driven phase transition, thus having unexpected impacts on the adhesion and the rheological properties of semi-crystalline lactose powder as ambient humidity levels are varied.

2. Materials and methods

The materials studied are monohydrate crystalline lactose (Foremost 310) and a spray-dried mixture of crystalline and amorphous lactose monohydrate (Foremost Fast Flo 316), both with particle diameter ranging between 45–75 μm. The size of the particles was controlled by mechanical screening via the use of a vibrating sieve (Gilson Sieve Shaker, SS-8R). These materials are both used as excipient in the pharmaceutical industry, but have fundamentally different rheological properties, which are explained in part by the grain morphology (see Fig. 2). The crystalline form of lactose is obtained by heating an aqueous solution of lactose below 93.5 °C. The formed crystals are then milled to obtain a powder of particles with significantly irregular shapes. On the other hand, spray-dried lactose is produced by spray drying a suspension of fine lactose crystals in a concentrated lactose solution. The so-obtained lactose particles have a rounded shape, which is at the origin of their "fast flow" properties by decreasing the cohesion and the friction between particles [11,12].

In order to study the influence of the relative ambient humidity on the shearing properties, the powder samples were exposed for at least 24 h prior to experiment to a fixed controlled humidity ranging between 20 and 60%. The humidity level was controlled by an automatic control system and maintained within a range of ± 1.5%. In order to ensure a uniform exposition, power samples were spread into a millimetre thin bed and thoroughly mixed at least twice during the 24 h exposition. For the single particle interaction experiments, the controlled humidity pre-exposition was limited to 1 h prior to experiment, as the volume of materials did not justify a longer pre-exposition.

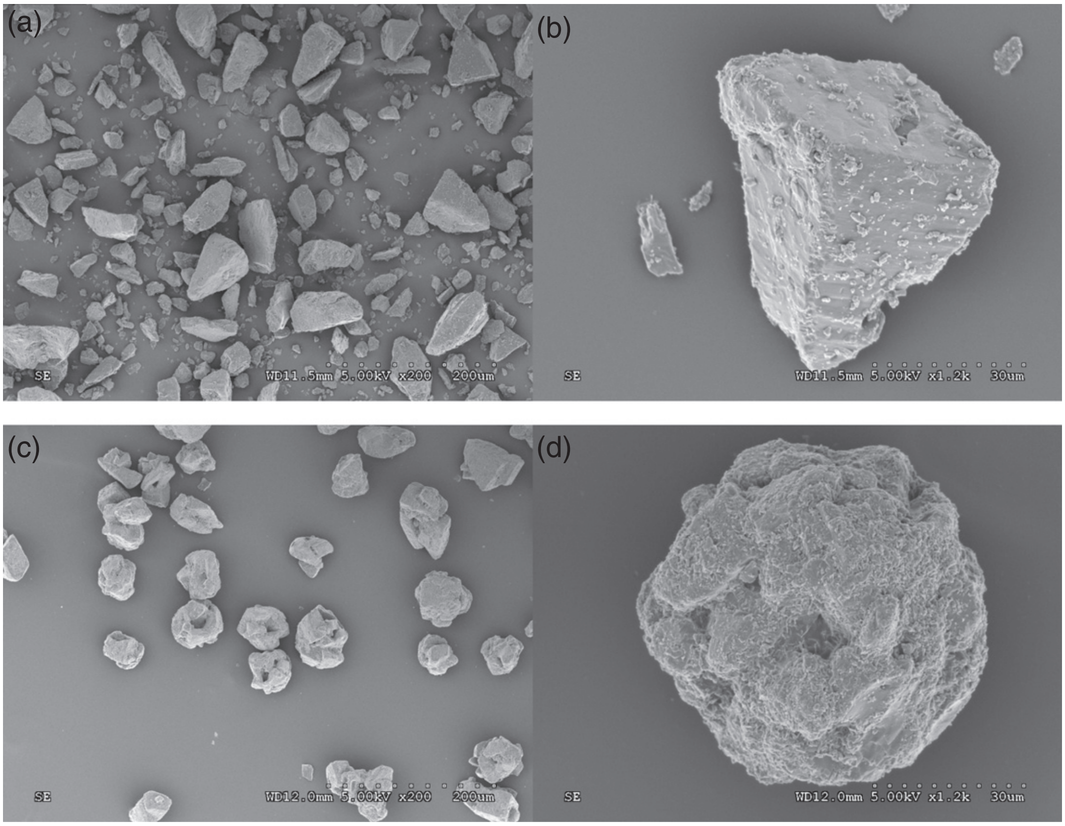

Fig 2. (a) SEM micrograph of crystalline lactose magnified 200×. (b) SEM micrograph of crystalline lactose magnified 1200×. (c) SEM micrograph of semi-crystalline (spray dried) lactose magnified 200×. (d) SEM micrograph of semi-crystalline (spray dried) lactose magnified 1200×.