Linking the structural properties of adhesive mixtures to their observed powder mechanics

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Summary

Mixing larger particles (carriers) with smaller particles (fines) to produce an adhesive, or ordered[1], mixture is a formulation technique used to promote powder flow and reduce the risk of segregation during handling and use. Within the dry powder inhalation (DPI) field, this technique is extensively used as a means of counteracting the cohesive nature of micronized APIs. In order to better understand the interaction between these two dissimilar components the main objective of this study was to investigate the relationship between the content of fine particles and the observed powder mechanics of binary adhesive mixtures and link these observations to a powder structure assessed by imaging techniques.

The mixtures, consisting of lactose, contained one carrier (Lactopress SD) and increasing amounts of fine particles corresponding to different surface coverage ratios (SCR). From the powder mechanics analysis, combined with scanning electron microscopy (SEM), it was found that the fine particles predominantly gather in the cavities of the carrier particles at low SCR (0.25), which effectively increases the carrier particle density and makes the carrier surfaces smoother. This phenomenon was shown to increase the packing density of the mixture and reduce the sensitivity to pressure. Adding more fines beyond a SCR of 0.25 instead leads to a more disordered structure of fine and carrier material, as confirmed by environmental scanning electron microscope images (ESEM). This increasingly disordered structure leads to a gradually reduced packing density and an increased sensitivity to pressure.

Introduction

Adhesive (or ordered) mixture, i.e. a blend of large carrier particles and fine drug particles, is often used in pharmaceutical formulations as a means to promote powder flow and blend uniformity and reduce the risk of segregation during handling and use[1]. This formulation approach has commonly been used for dry powders for inhalation as a means to control the cohesive nature of micronized active pharmaceutical ingredients (APIs).

The term powder mechanics has been used as a collective term for the packing and flow properties of bulk particulate solids[2]. A large number of techniques are available for the study of powder mechanics[3]. Consequently, several reports can be found in the literature with the objective to compare techniques for studying the powder mechanics of different types of particulate solids[4-7]. In the European Pharmacopeia[8], some powder mechanics techniques are suggested that may be used to derive indications of Functionality-related characteristics of powders, i.e. powder properties that may affect the functionality and manufacturability of pharmaceutical formulations.

It is not easy to choose the best methods to study the powder mechanics as many techniques may indicate similar flow properties[3] but different methods may also indicate differences in powder flowability depending on the type of material that is tested, e.g. dependent on particle size, shape and chemical composition. Consequently, it is suggested[5] that the choice of flow characterization technique should be linked to the process application, i.e. for a technique to have predictive capacity should operate under conditions that mimic or reflect the conditions that the powder is exposed to during the intended process. Besides the need to derive powder mechanics information as a means to predict processing properties and subsequently DPI formulation efficiency[9-12], powder mechanics has also the potential to give information about the structural arrangement of the particles in a mixture.

The main objective of this paper was to study the relationship between the content of fine particles and the observed powder mechanics, assessed by different bulk densities exposed to varying levels of compression, of binary adhesive mixtures and link these observations to a powder structure assessed by imaging techniques. Lactose powders were used both as carrier and as fines particles, mimicking an API, and a series of adhesive mixtures with surface coverage ratios (SCR) up to 2.0 was prepared.

Experimental methods

Preparation of adhesive mixtures

The mixtures contained lactose carrier (Lactopress SD, DFE Pharma, Germany) and lactose fines (AstraZeneca AB, Sweden) corresponding to different theoretical Surface Coverage Ratios (SCR). The carrier and fines had a D_{50} particle size of 110 and 2.7 µm, respectively, as determined using Sympatec HELOS laser diffraction equipment (Sympatec GmbH, Clausthal-Zellerfield, Germany). The SCR was calculated according to Eq.1 using the specific surface area (cm^{-1}) of the carrier ($S_{v,c}$) and fines ($S_{V,f}$) acquired through air permeability measurements:

$$\text{SCR} = \frac{\alpha\, m_{\text{f}}\, S_{V,\text{f}}}{m_{\text{c}}\, S_{V,\text{c}}} \quad (1)$$

where m_f and m_c are the masses of fines and carrier particles in the mixture. The packing constant α, equal to 1/π, was used here to assume cubical packing of fines over the carrier surface.

Fine material corresponding to SCRs of 0.25, 0.5, 0.75, 1, 1.5 and 2 was mixed with necessary amount of carrier material in a Turbula T2F Mixer for 1 hr at 46 rpm (1 L vessel at 50 % fill volume). The homogeneity of the blends was determined by studying the fine particle content of 5 samples taken at different positions from each blend. This was done using the Sympatec HELOS laser diffractometer[13].

Assessment of powder mechanics and mixture structure

The powder mechanics of the mixtures were measured using a Freeman FT4 powder rheometer, a Micromeritics GeoPyc (T.A.P. density module) and a PharmaTest PT-TD (bulk- and tap density). In total, the bulk density of the mixtures was determined using three different techniques which involved no force of consolidation other than the force of gravity during testing. These mixtures were then exposed to different levels of consolidation, using the aforementioned techniques, to calculate Hausner ratio in three differentways (HR_{FT4}, HR_{Geo} and HR_{Tap}).

The carrier and mixture structure was visualized using a combination of Environmental Scanning Electron Microscope (ESEM) and high-vacuum SEM. The SEM samples were sputter coated with gold/platinum and exposed to pressurized air to remove any loose material. For the ESEM, the samples were gently sprinkled over the carbon films and examined without further treatment. High-vacuum SEM can provide images with higher resolution but compromises the mixture structure through rougher sample preparation (i.e. pressurized air).

Results

Mixture structure

The carrier particles had a nearly spherical or slightly elongated shape (Fig. 1). However, the surface structure was markedly irregular due to cavities of varying size and shape. It was found that when adding the fine particles, they predominantly reside in the cavities of the carrier particles at low SCR (see 'A'). This was also confirmed from ESEM imaging. When adding fines beyond a certain point the fines would start to gather on the outside of the carrier particles forming a complex network of carrier and fine particles (see 'B'). The ESEM image for SCR 2 indicates that the fines gathered on the outer carrier surfaces are quite loosely attached, as these are completely gone in the SEM image (see 'C'). However, the fines residing in the cavities are still present in this image.

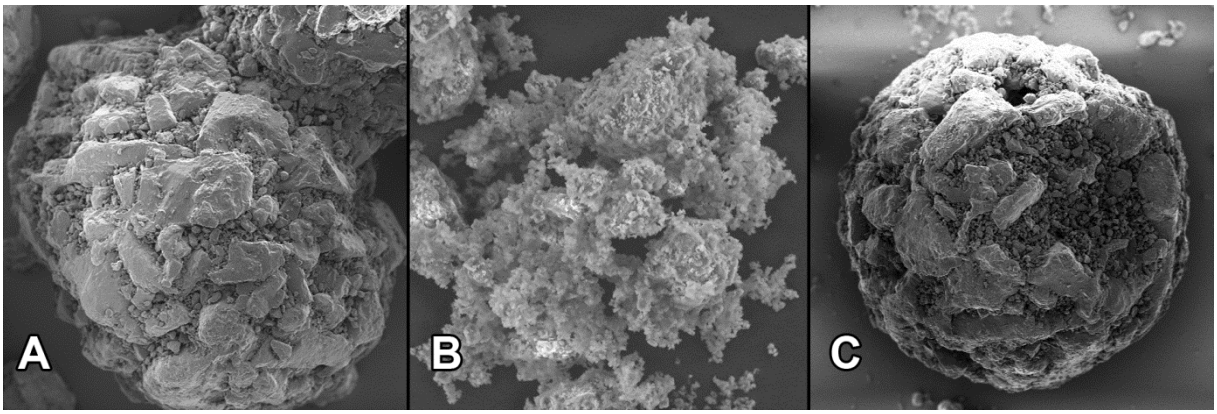

Figure 1 – Electron microscope images over A) SCR 0.25 (2000x, SEM); B) SCR 2 (500x, ESEM); C) SCR 2 (2000x, SEM)

Powder mechanics

The structural change in the mixture, when adding fines, have implications on the powder mechanics as shown in Fig 2. Fig. 2a illustrates the mixtures sensitivity to increasing pressure. The uncompressed bulk density has its highest value for SCR 0.25. A marked initial increase in bulk density is seen at 1 kPa for all mixtures. However, the order remains the same compared to the unconsolidated samples. After this point, the pure carrier and the SCR 0.25 are less compressible than the other mixtures. At pressures above 4kPa, the mixtures with higher SCR attain higher densities than the pure carrier and the SCR 0.25 blend. Applying more pressure and they are eventually surpassed in density (see 30 kPa). The corresponding Hausner ratios (see Fig. 2b) indicate that SCR 0.25 has the best flow, while the mixtures beyond SCR 0.25 are more compressible. The three different methods used give different values for the Hausner ratio, but are in agreement as regards the ranking of the mixtures.

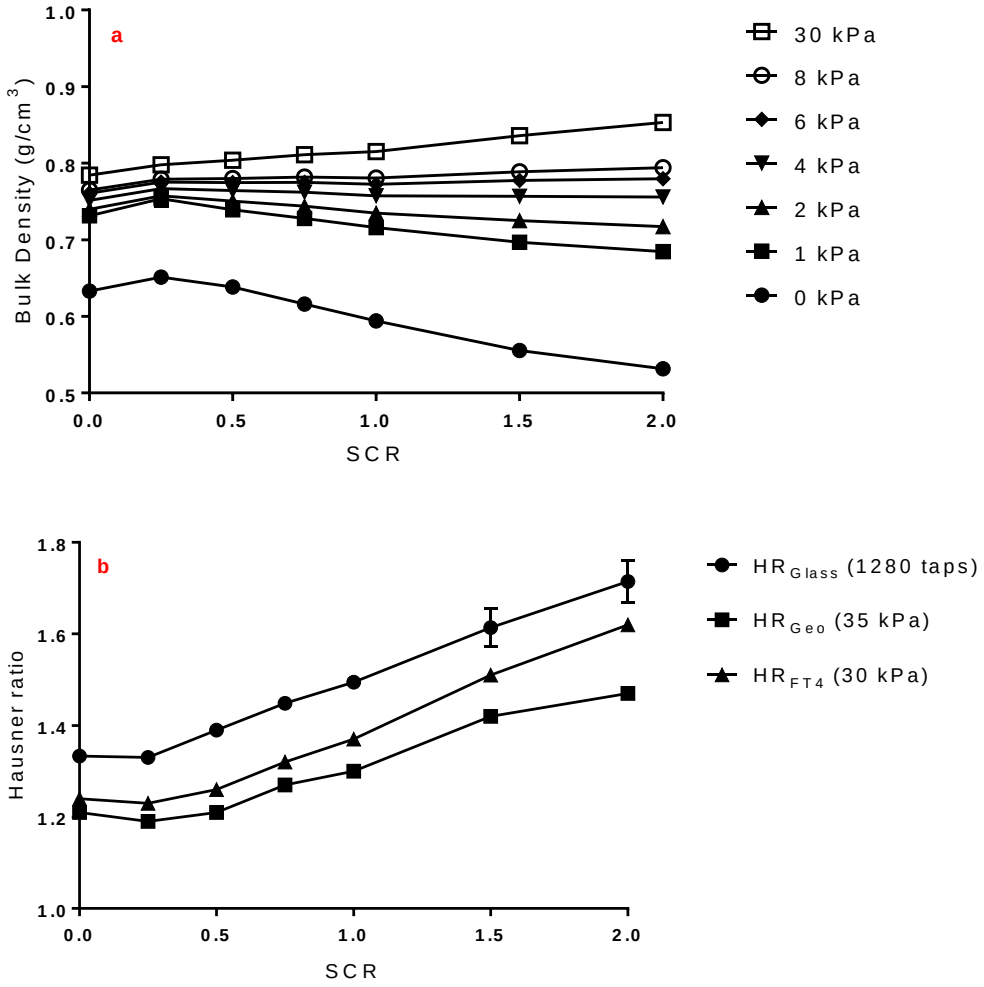

Figure 2 – a) Mixtures exposed to different levels of compression (using FT4 Powder rheometer) and - b) Hausner ratios (obtained from three different tests), plotted versus Surface coverage ratio (SCR). Average values (n=3) with standard deviation, some too low to be visible.

Discussion

It is apparent that the fine particles gather in the cavities of the LactoPress carrier particles at SCR 0.25, and that these fines are resistant to relocation and thus compression, as confirmed by the SEM imaging. The initial increase in the bulk density over the pure carrier and the lower Hausner ratio could be attributed to the fact that filling the cavities of the carrier particles effectively increases the carrier particle density and/or makes the carrier surfaces smoother. This effect may be similar to the way glidants work[14] (e.g. small silica particles). When the fines start to add to the outer layer of the carrier particles (above SCR 0.25) the fines are more susceptible to compression and restructuring, leading to higher Hausner ratios. For the bulk density to increase, the excessive fines at higher SCR must have been forced in between the carrier particles thus filling the void spaces leading to higher packing densities. This structural arrangement of carrier and fines is illustrated schematically in Fig 3. The *black line* shows the unconsolidated bulk density while the *grey line* shows the bulk density when compressed with a pressure of 30 kPa.

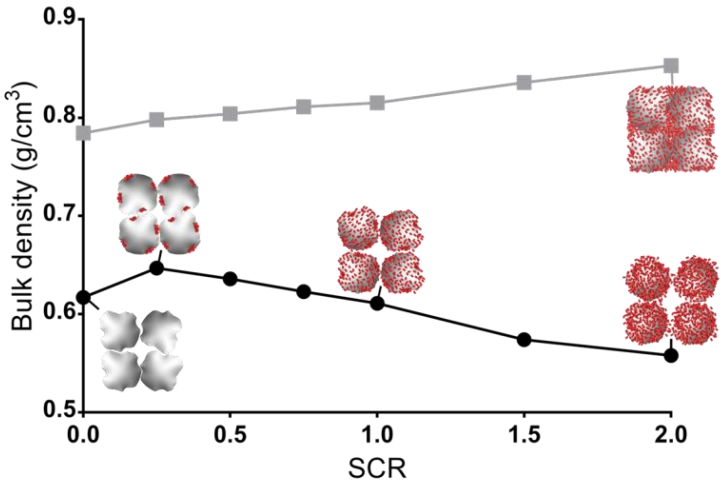

Figure 3 – Bulk density used as a parameter to explain the mixture structure for un-consolidated mixtures *(black line)* and after consolidation *(30 kPa, greyed line)*

Conclusions

Through the combination of powder mechanics and visual imaging techniques it was possible to explain the structural arrangement of adhesive mixtures for inhalation as a function of the surface coverage ratio (SCR). For the studied carrier, Lactopress SD, a lower compressibility was initially observed at SCR 0.25. After this there was a transition towards a more irregular, intricate, structure of fines and carrier particles that leads to an increased sensitivity to pressure and thus higher Hausner ratios was observed.

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