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Effects of the granule composition on the compaction behavior of deformable dry granules

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ABSTRACT

Calibration of the Drucker Prager Cap (DPC) model parameters provides a means for a deeper understanding of the impact of granule composition on the compaction properties of dry granules independent of their solid fraction. In this study, monodisperse granules of mixtures of microcrystalline cellulose and mannitol (0%, 25%, 50%, 75% and 100% mannitol) prepared as small cylindrical compacts with well-defined size, shape and solid fraction (0.58) were used as model dry granules. DPC parameters–namely, cohesion, internal friction angle, cap eccentricity, and hydrostatic yield strength of materials–were determined from the diametrical and uniaxial compression, and in-die compaction tests. Elastic properties such as Young's modulus and Poisson's ratio were also determined from the in-die compaction test. Higher level of mannitol in granules required a lower compression pressure to obtain a low solid fraction tablet but higher compression pressure to obtain a high solid fraction tablets. Properties such as cohesion and diametrical tensile strength go through a maximum as the mannitol level increases in the binary granules, and clearly do not follow a simple linear mixing rule. At an industrially-relevant tablet solid fraction of 0.88, granules with 75% mannitol exhibited the highest cohesion, and produced the strongest tablet. Other properties either approximately follow the linear mixing rule (e.g., hydrostatic yield strength, Young's modulus and Poisson's ratio) where limited interactions between the constituents are present, or not sensitive to the composition (e.g., internal angle of friction). In general, the compaction behavior of granules of a multi-component system may not be precisely estimated from the properties of individual components, simply by using the linear mixing rule.

1. Introduction

Most pharmaceutical tablets are manufactured from a homogeneous blend of powders of varying physical, mechanical, and functional properties. The mechanical properties of a formulation are typically balanced by using a combination of plastically deformable excipients such as microcrystalline cellulose (MCC), pregelatinized starch, cellulose, polyethylene glycol (PEG) and brittle excipients such as dicalcium phosphate, lactose, and mannitol (MNT). In general, a granulation step is involved, where larger multi-particulate entities of drug and excipient mix are produced [1]. Granulation locks the powder blend homogeneity, ensures robust downstream processing of the formulation to produce tablets with desired physico-mechanical properties (e.g., solid fraction, tensile strength, friability) and critical quality attributes (content uniformity and dissolution). Granules that are composed of appropriate ingredients, at an appropriate ratio, with appropriate properties, are important for robust production of quality tablets.

In our previous study, we have demonstrated that solid fraction (SF) of dry granules of a single component MCC significantly impacts the tablet fracture and tensile strength (TS) [2,3]. By calibrating the Drucker Prager Cap (DPC) model parameters we have also showed that MCC granule SF does not affect the plastic strain driven densification in a confined compression process but increases the propensity to fail [4]. In a multicomponent system, the compaction behavior of one component is expected to interact with that of the other

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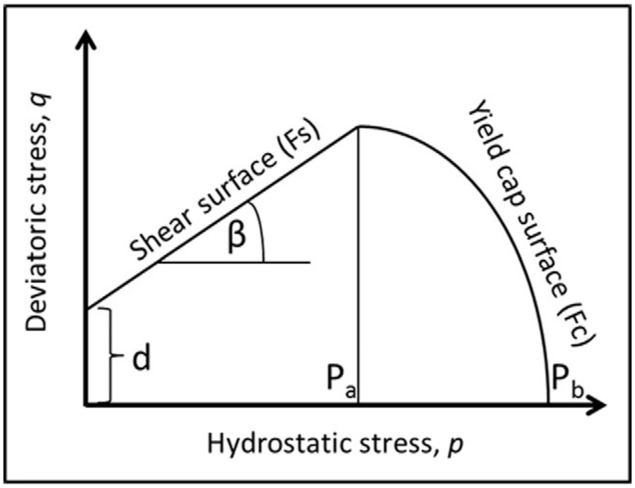

Fig. 1. 2D yield surface of the Drucker Prager Cap model [4].

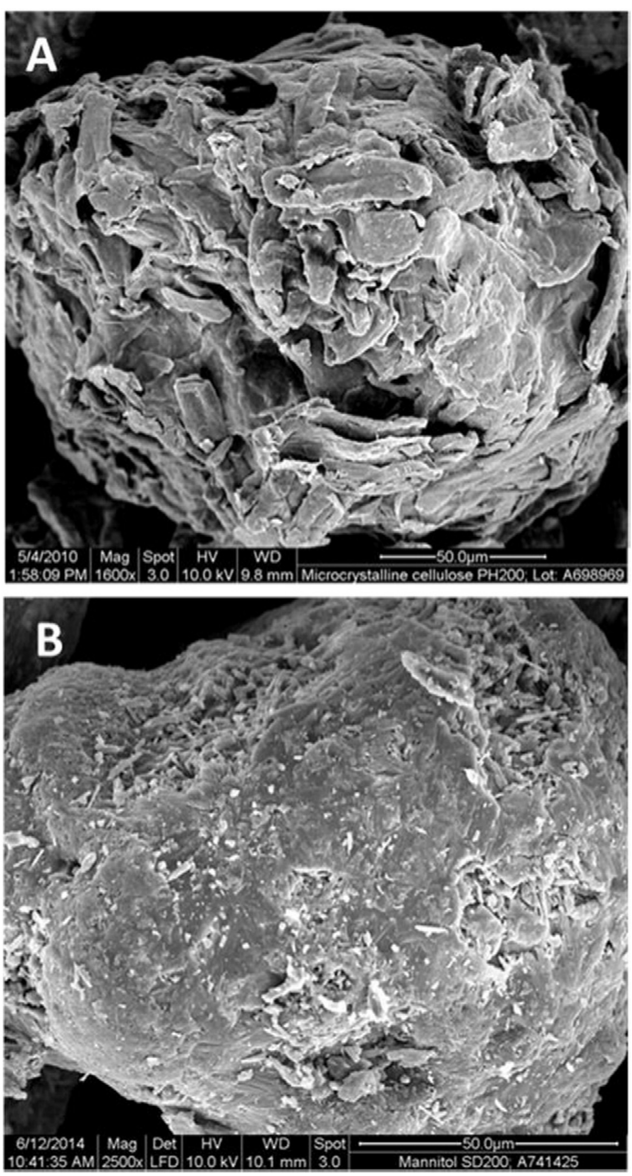

Fig. 2. SEM images of (A) MCC particle, and (B) MNT particle.

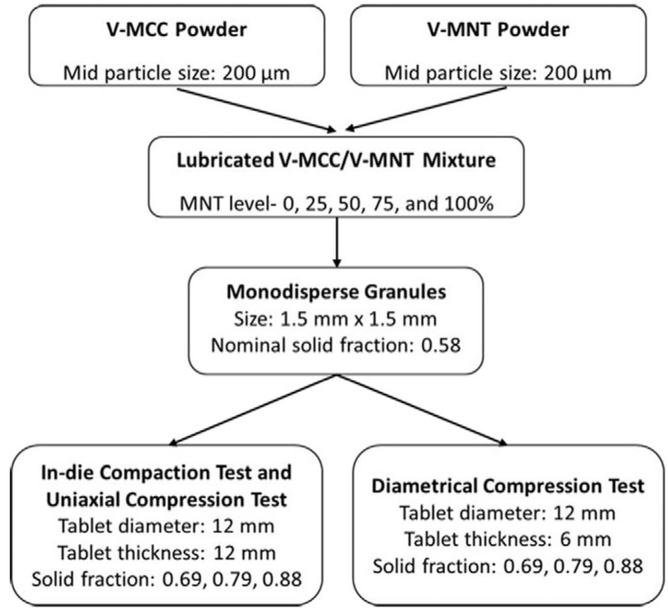

Fig. 3. Schematic diagram of the study design.

components, and alter the granule and tablet properties. In the literature [5–10] the effects of an individual component on the compaction behavior of other components in the granule have not been studied with adequate separation from the effect of granule physical and mechanical properties. To mechanistically understand this, granule composition and granule properties need to be precisely controlled and independently varied. This study presents calibration of the DPC parameters using simple systems that allow analysis of effects of the levels of MNT on the compaction behavior of MCC/MNT binary granules without any interference from the granule SF. In addition, elastic properties such as Poisson's ratio and Young's modulus of compacts made from the granules are presented.

2. DPC model

The DPC model illustrates the strength of powder compacts as a function of SF in the hydrostatic stress-effective stress (p-q) plane. p causes volumetric changes and q causes shear-based distortion without volume change. A given yield envelope, such as that shown in Fig. 1, pertains to a powder compact of a given SF. Application of stress states within the envelope produce only elastic distortions. Stress states exceeding the yield envelop produce permanent deformation. The deformation involves fracture if the linear portion of the envelope is exceeded, but involves further densification of the powder compact if the elliptical cap portion is exceeded. During densification, the yield envelope expands to the extent that the applied stress state remains on the (growing) cap surface. This gives rise to a series of yield surfaces as a function of SF which describe the complete behavior of a material. Four independent yield surface parameters are required at each SF for complete calibration of the model. These include the cohesion (d), internal angle of friction (β), cap eccentricity parameter (R) and hydrostatic yield stress (p_b). A detailed description of the model is available in the literature [11].