Powder Technology 291 (2016) 328–336

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Compaction mechanics of plastically deformable dry granules

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ARTICLE INFO

Article history:
Received 10 October 2015
Received in revised form 10 December 2015
Accepted 19 December 2015
Available online 22 December 2015

Keywords:
Deformable dry granules
Tablet
Solid fraction
Tensile strength
Drucker Prager Cap (DPC) model

ABSTRACT

To improve the understanding of how dry granulation and in particular, granule solid fraction (SF) impact the compaction behavior of plastically deformable microcrystalline cellulose (MCC), in this study, the Drucker Prager Cap (DPC) model parameters were calibrated using monodisperse MCC dry granules as model granules. Dry granules were produced as directly compressed small cylindrical compacts of MCC with SF in the range of 0.40 to 0.70 which were monodisperse in both size and SF. Virgin MCC powder and granules were compressed into tablets with SF in the range of 0.70 to 0.90. The DPC parameters (cohesion, internal friction angle, cap eccentricity, and hydrostatic yield stress), Young's modulus and Poisson's ratio were experimentally determined from diametrical and uniaxial compression, and in-die compaction tests. Results showed that calibration of the shear failure surface only may be adequate for MCC granules when the DPC model is completely calibrated for virgin MCC. Increasing granule SF significantly decreased the cohesion only. All other parameters were impacted by the tablet SF only. In the 2D yield surface, only the shear failure surface expanded as the granule SF increased. MCC of any granulation status requires the same in-die compaction stress state for densification to a given tablet solid fraction.

1. Introduction

Granulation and tableting are common processing steps in the pharmaceutical industry. Powders are converted into granules via various granulation techniques and then forward processed into tablets of desired quality attributes such as tensile strength (TS), content uniformity, and dissolution. Despite the much-advanced understanding of the compaction processes and the availability of state-of-the-art compaction equipment, robust production of quality tablets still remains a significant challenge. Problems such as low TS, chipping, lamination, or capping of tablets can occur upon scale-up [1,2]. Identifying these issues early in development will allow necessary adjustments to the composition, processes, or even to equipment and tooling to avoid or at least minimize process and product upsets at large scale.

In the literature, MCC has been frequently used as a model compound to study the effects of dry granulation on TS of tablets of plastically deformable formulations. Dry granules of MCC require a higher compression pressure or tablet SF to achieve the same tablet TS as the virgin MCC. Different mechanisms that have been proposed for this are strain hardening [3,4,5], granule size enlargement [6], and over-lubrication of granules during milling [4]. Sun et al. [6] proposed that higher roller compaction force increased MCC granule size and thus decreased the binding area during tablet preparation and produced weaker tablets. Later, Herting et al. [3] and Patel et al. [5] demonstrated that both the higher granule SF and larger granule size of MCC decreased tablet TS. This is possibly due to the influence of granule solid fraction or strength to the microstructure of tablets [7,8,9]. Akseli et al. [10] also demonstrated that the mechanical strength of MCC tablets were decreased due to applied lubrication and increased ribbon solid fraction. However, He et al. [4] demonstrated that internal lubrication of MCC and over lubrication during ribbon milling process overshadowed the ribbon SF effect.

Studying the impact of dry granulation to tablet TS has been expanded to other excipients as well. It has been reported that granulated grades of mannitol and dry granulated spray dried mannitol produced weaker tablets than the virgin spray dried mannitol [11]. The authors proposed strain hardening and/or decreased surface area as the potential contributing factors. Freitag et al. [12] have evaluated different types of magnesium carbonate and showed that ribbons with higher micro-hardness produced tablets with lower tensile strength. However, in contrast, Wu et al. [13] and Souihi et al. [14] studied similar impacts using mannitol, lactose and dicalcium phosphate and proposed that dry granulation does not impact TS of tablets of brittle excipients. Interestingly, there are studies in the literature although limited in number that showed increased tablet TS after roller compaction of virgin powder. Kuntz et al. [15] showed that roller compaction increased the surface area of acetames and produced stronger tablets.

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http://dx.doi.org/10.1016/j.powtec.2015.12.022
0032-5910/

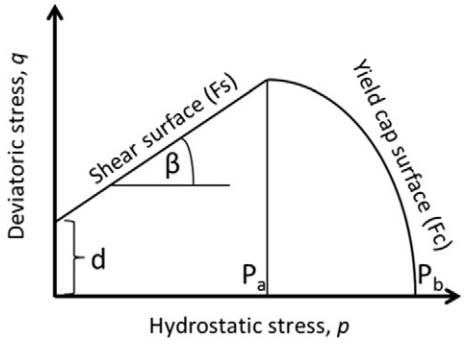

Fig. 1. 2D yield surface for the Modified Drucker Prager Cap (DPC) model.

The solid state of the material also influences the ribbon and granule properties. Inghelhem et al. [16] demonstrated that disrupted crystalline order in anhydrous lactose and amorphous content (15%–20%) in spray-dried lactose facilitated better bonding and consolidation. Thus, in the literature, there are a number of alternative explanations on the mechanism for the impacts of dry granulation of various excipients on mechanical strength of their tablets; however, a clear mechanistic understanding is still lacking.

It is difficult to develop a holistic understanding of the evolution of tablet structure as well as tableting problems using the typical empirical methods such as Heckel analysis, Kawakita equation, and Hiestand indices [17]. To accomplish this, the Drucker Prager Cap (DPC) model, a phenomenological model originally developed for soil mechanics, has recently been adopted in the pharmaceutical industry [18,19]. In this model, the powder aggregates are regarded as continuum medium and powder compaction is regarded as a forming event as the properties of the material evolve [19]. Commonly used material parameters such as cohesion, angle of internal friction, and yield stress, and their dependence on tablet solid fraction (SF), are used to calibrate the model. DPC parameters are used as input in the Finite Element Model (FEM) to predict local mechanical properties evolved during the consolidation of powder in a tableting or roll compaction operation [18,19,20,21,22].

To date, DPC model parameters have been mostly reported for virgin powders, and to a limited extent, for their mixtures. Calibration of the DPC model parameters for various systems of microcrystalline cellulose (MCC) powder, such as MCC PH101 [18,23], MCC PH102 [19,23], MCC PH 200 [23], lubricated MCC PH101 [21], MCC PH102 with unlubricated die [20], a binary mixture of 90% MCC PH102 and 10% acetaminophen [23] were reported in the literature. Diarra et al. [24] reported DPC parameters of a cosmetic powder composed of talc and 5% fatty substance. In a more recent work, LaMarche et al. [25] determined DPC parameters of MCC PH102, pregelatinized starch, lactose monohydrate, lactose anhydrate, and dicalcium phosphate and evaluated tableting risk associated with each material. They also determined DPC parameters of various high shear wet granulated and roll-compacted formulations, and searched for correlation among the material properties and tableting issues (e.g., crack, sticking, capping, chipping, and low strength). However, granule properties were not completely controlled in this study, making understanding of their impact on the DPC parameters difficult.

Dry granules are particle agglomerates produced under pressure. The physical changes that occur to granules during a confined compression process are important in the evolution of the tablet microstructure. Granule size, shape, and density, as well as granule-granule friction and granule-tooling surface friction could also affect the consolidation process. In our previous study, we have demonstrated that TS of tablets decreased approximately linearly as the dry granule SF increased [7]. Monodisperse granules of MCC (as model dry granules) produced by directly compressing virgin MCC powder and typical milled granules were used in this study. While the model monodisperse granules have precisely controlled size, shape and solid fraction, these properties are covaried in typical milled granules produced by roller compaction or slugging followed by milling. The use of the model monodisperse granules enabled studying the effects of granule SF on the compaction of dry granules without interferences from granule size, shape, etc.

Recently we also have demonstrated that (i) tablets formed from deformable dry granules fracture both intra-granularly and extra-granularly, (ii) the proportion of each type is dependent on the deformation potential (defined as tablet SF − initial SF of the packed granule bed), (iii) the tablet TS is correlated to the deformation potential, and (iv) a coherent compact cannot be achieved until deformation of the granule bed exceeds the critical deformation potential [26]. In the current study, DPC parameters of monodisperse MCC granules of varying SF were determined to improve the mechanistic understanding of the effect of dry granule SF on the compaction behavior of MCC, as well as guide the development of FEM models for compaction of granules.

2. DPC model

A detailed description of the DPC model is available in the literature [19]. The model describes yielding of materials as a function of hydrostatic stress (p), deviatoric stress (q) and SF of the tablet. The material is considered to be isotropic. p causes densification, whereas q causes material distortion. Material distortion could be associated with volume change for not fully densed granular materials ($SF < 1$) or without volume change for fully densed material ($SF = 1$) and for linear elastic materials [19,27]. During consolidation, the yield loci expand as the compact SF increase, which signifies a greater resistance to further plastic deformation. Fig. 1 shows the 2D yield surface of the material as a limiting curve $F(q, p, SF) = 0$.

The model consists of two curves in the p–q plane as shown in Fig. 1.

1. A shear failure (F_s) showing increasing q value with increasing p value. The shear line characterizes the shear stress in a powder necessary to cause fracture. F_s in the p–q plane is defined as:

$$F_s(q,p) = q - d - p\tan\beta = 0 \quad (1)$$

where q is the deviatoric stress, p is the hydrostatic stress, d is the material cohesion, and β is the internal angle of friction. The intersection

Table 1
Monodisperse granules and tablets prepared there from.

V-MCC Particle Size (μm)	Monodisperse granules			Tablet		
	Diameter (mm)	Nominal thickness (mm)	Nominal solid fraction	Nominal solid fraction	Nominal thickness (mm)	Nominal weight (mg)
200	1.5	1.5	0.42 0.54 0.60 0.69	0.69 0.79 0.89	6	745 850 955
					12	1485 1705 1905