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Discrete particle modeling and micromechanical characterization of bilayer tablet compaction

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ABSTRACT

A mechanistic particle scale model is proposed for bilayer tablet compaction. Making bilayer tablets involves the application of first layer compaction pressure on the first layer powder and a second layer compaction pressure on entire powder bed. The bonding formed between the first layer and the second layer particles is crucial for the mechanical strength of the bilayer tablet. The bonding and the contact forces between particles of the first layer and second layer are affected by the deformation and rearrangement of particles due to the compaction pressures. Our model takes into consideration the elastic and plastic deformations of the first layer particles due to the first layer compaction pressure, in addition to the mechanical and physical properties of the particles. Using this model, bilayer tablets with layers of the same material and different materials, which are commonly used pharmaceutical powders, are tested. The simulations show that the strength of the layer interface becomes weaker than the strength of the two layers as the first layer compaction pressure is increased. The reduction of strength at the layer interface is related to reduction of the first layer surface roughness. The reduced roughness decreases the available bonding area and hence reduces the mechanical strength at the interface. In addition, the simulations show that at higher first layer compaction pressure the bonding area is significantly less than the total contact area at the layer interface. At the interface itself, there is a non-monotonic relationship between the bonding area and first layer force. The bonding area at the interface first increases and then decreases as the first layer pressure is increased. These results are in agreement with findings of previous experimental studies.

1. Introduction

Bilayer tablets or multi-layer tablets are highly suitable for drug delivery of many therapeutic areas (Abebe et al., 2014), for controlled drug delivery of two different active ingredients (Abebe et al., 2014; Abdul and Poddar, 2004), and separation of chemically incompatible drugs (Divya et al., 2011). The production of such tablets has proved design and manufacturing challenges as the layered tablets are prone to fracture by delamination, usually along the interfaces between two layers, because of their inherent insufficient strength (Akseli et al., 2013; Kottala et al., 2012). The residual stress distribution in bilayer tablets is one of the major sources of inhomogeneity of the micromechanical properties causing the tablets to fracture and split apart (Inman et al., 2007). Thus, one of the main manufacturing challenges is to obtain tablets that do not fracture at the interface because of insufficient mechanical strength. Understanding and predicting the mechanical strength of these bilayer tablets is of commercial significance because tablet failures due to weak mechanical strength can lead to economic losses.

The mechanical strength of bilayer tablets depends on many factors. Using axial tensile strength tester, Akseli et al. (2013) experimentally studied the strength of bilayer tablets made up of microcrystalline cellulose (MCC) and starch powders. It was found that the tensile strength of the bilayer tablets increases as the second layer compaction force is increased. However, the tensile

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strength of the bilayer tablets does not have a monotonic relationship with the first layer compaction force. The tensile strength initially increases with the first layer compaction force and then decreases as the first layer force is increased further. It was also noted that the bilayer tablets break at the interface at large first layer compaction force (Kottala et al., 2012; Inman et al., 2009). At higher compaction force, the particles deform permanently reducing the particle asperities and irregularities. The permanent deformation, along with the rearrangement of the particles, reduces the surface roughness of the first layer. Smoother surfaces reduce the possibility of a better contact between the layers, and hence result in weaker tablets.

In addition to the applied forces, the physical and mechanical properties of the layer materials also play a critical role in the tensile strength of the tablet (Podczeck and Al-Muti, 2010; Podczeck et al., 2006; Inman et al., 2007; Busignies et al., 2013). Using a three-point bending experiment, Podczeck and Al-Muti (2010) showed that both particle size and modulus of elasticity influenced the overall strength of layered tablets/beams. They found that if the material forming the lower layer was more elastic, then the beam strength was reduced due to tension introduced into the system, acting especially at the layer interface and potentially causing partial or complete delamination. Larger differences in the particle size of the materials forming the tablet layers also resulted in an overall reduced tensile strength. In another flexure test experiment, Busignies et al. (2013) showed that the fracture occurred at the interface or in one of the two layers depending on the materials properties. In most cases, the highest tensile strength was obtained when the materials had similar elastic recovery. On the contrary, for materials with different elastic recovery, the tensile strengths were reduced.

Computational simulations can also be used to investigate detailed micromechanical properties to assess the mechanical strength of tablets. Several computational methods have been developed to model compaction of monolayer tablets, but there is no computational framework for modeling bilayer tablets. However, the methods that are used to model monolayer tablets can be modified to model bilayer or multi-layer tablets. Some of these methods are based on Finite Element Method (FEM) (Klinzing et al., 2010), Discrete Element Method (DEM) (Sheng et al., 2004; Martin and Bouvard, 2004; Skrinjar and Larsson, 2004; Olsson and Larsson, 2013; Cundall and Strack, 1979), or combined Discrete-Finite Element Method (DFEM) (Zheng and Cuitiño, 2002; Zavaliangos, 2002; Zhang, 2009; Zhang and Zavaliangos, 2011; Koynov et al., 2011). In FEM, usually, only the global values of the physical properties are assumed, while in DEM the interaction between individual particles are accounted for, which enables modeling the heterogeneity of powders at the microscopic/particle scale. Hence, DEM gives more accurate particle scale details than continuum methods that consider global physical properties of the material. DEM was originally developed for application pertaining to very small elastic deformations (Cundall and Strack, 1979). In recent years, DEM has been used to model plastic deformation (Sheng et al., 2004; Martin and Bouvard, 2004; Olsson and Larsson, 2013) and bonding between particles (Potyondy and Cundall, 2004).

Since the main difference between monolayer and bilayer tablets is the presence of a layer interface in the latter case, the computational methods developed for monolayer tablets can be used to model bilayer tablets by taking into consideration the particles at the layer interface. In this paper, we propose a contact model for particle–particle interactions at the layer interface to computationally model a bilayer tablet compaction. The model is built upon a previous model that has been shown to work for monolayer tablets (Yohannes et al., 2016). Yohannes et al. (2016) used the model to calibrate the material properties and predict the tensile strength of tablets made from MCC and lactose powders. Although, the shape of the tablet is known to influence the tensile strength of the tablet (Franck et al., 2015), this article focuses only on cylindrical flat tablets. First, the contact model for the layer interface is presented followed by comparisons of the simulation results with experimental results for bilayer tablets. Then, factors affecting the mechanical strength of the tablets are discussed based on the simulation results. Finally, challenges and possible extension of the model are presented.

2. Numerical simulation

The procedure of making a bilayer tablet computationally is similar to the procedure of making a tablet experimentally. It involves the following steps:

1. Depositing the first layer particles
2. Compacting the first layer particles (application of the first layer compaction force)
3. Removing the first layer compaction force
4. Depositing the second layer particles
5. Compacting the bilayer tablet (application of the second layer compaction force)
6. Removing the second layer compaction force, and
7. Ejecting the tablet

The steps for making monolayer and bilayer tablets are similar except for the deposition of the second layer, and application and removing of the second layer force for the bilayer tablet.

Both the first and the second layer particles were deposited using ballistic gravitational deposition method (Jullient et al., 1992; Koynov et al., 2011; Bratberg et al., 2002; Mueller, 1997; Bagi, 2005; Yohannes et al., 2016). The first layer particles were deposited on a flat surface in a cylindrical die, whereas the second layer particles were deposited on top of the first layer after the application of the first layer compaction force.

The first layer and second layer compaction forces are applied through upper and lower punches. The compaction simulation was a strain controlled simulation, where a small displacement is applied to the two punches. The pressure on the punches is computed based on the contact forces from the particles. During the compaction, unloading, and ejection simulations, the contact forces between the particles are computed based on the deformation and mechanical properties of the particles. During loading mode, the particles are restricted to follow a power-law plasticity model (Storåkers et al., 1997; Storåkers et al., 1999; Mesarovic and Johnson, 2000; Martin and Bouvard, 2004; Yohannes et al., 2016),

$$\sigma = k\varepsilon^{1/m}, \tag{1}$$

where ε and σ are strain and stress in the particles, respectively. k is the material strength parameter and m is the strain-hardening exponent. During the loading phase the contact force (F) between two particles, particle 1 and particle 2, is always compressive (compressive force is assumed positive) and is computed as

$$F = k_p a^{2+1/m}, \tag{2}$$

where k_p is a constant that is a function of of the material properties (Yohannes et al., 2016). a is the radius of the circular contact area between the pair of contacting particles. a is computed using the overlap (γ) between a pair of particles, such that

$$\gamma = (R_1 + R_2) - (\mathbf{X_1} - \mathbf{X_2})\cdot\mathbf{n_{12}}, \tag{3}$$