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Gaining insight into tablet capping tendency from compaction simulation

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ABSTRACT

Capping or lamination is an unsolved common problem in tablet manufacturing. Knowledge gaps remain despite an enormous amount of effort made in the past to better understand the tablet capping/lamination phenomenon. Using acetaminophen – containing formulations, we examined the potential use of a compaction simulator as a material-sparing tool to predict capping occurrence under commercial tableting conditions. Systematical analyses of the in-die compaction data led to insight on the potential mechanism of tablet capping/lamination. In general, capping strongly correlates with high in-die elastic recovery, high Poisson's ratio, low tensile strength, and radial die-wall pressure. Such insight can be used to guide the formulation design of high quality tablet products that are free from capping problems for challenging active pharmaceutical ingredients.

1. Introduction

Over 70% of the marketed drugs have been formulated as tablets as it is a simple and cost effective solid dosage form (Gupta et al., 2009). Although the process of tablet die compression is straightforward, successful manufacturing of intact tablets with sufficient mechanical strength is not always possible. Mechanical strength of a tablet depends on the interplay between bonding area and bonding strength among particles (Osei-Yeboah et al., 2016). The development of inter-particulate bonding area is, in turn, influenced by compaction pressure, tableting speed, and the mechanical properties of constituent particles (Bag et al., 2012; Hiestand, 1997; Krishna et al., 2015; Tye et al., 2005). In the process of tablet compression, the tablet is compressed by the upper and lower punches in the vertical (axial) direction but radially confined by a rigid die wall. Factors that can influence the mechanical properties of finished tablets include mechanical properties of the particles, (e.g., plasticity, elasticity, and brittleness) (Sun, 2009), environmental factors, e.g., temperature and humidity (Osei-Yeboah et al., 2016; Sun, 2008), and process conditions, e.g., compression speed, pressure, and tooling design (Elowe et al., 1954; Tye et al., 2005). In general, the irreversible plastic deformation and brittle fragmentation favor tablet formation but the reversible elastic deformation does not. The stored elastic energy during the compression phase is recovered axially during decompression and radially when tablet exits the die during ejection. Due to anisotropic properties of most pharmaceutical crystals and the non-uniform stress distribution in the powder bed during compression, tablet structure is usually anisotropic (Sun, 2017). If not properly treated, such structure anisotropy may lead to undesired consequence in tablet integrity and performance.

Common problems in tablet manufacturing include insufficient mechanical strength (Hiestand, 1997), sticking to punches (Booth and Newton, 1987), uncontrolled dissolution (Basalious et al., 2011), and capping or lamination (Fassihi and Parker, 1986). The typical symptom of capping is the complete removal of top part of the tablet upon ejection or in subsequent handling and physical testing (Garr and Rubinstein, 1991). A closely related tablet manufacturing problem is lamination, ranging from a presence of micro cracks visible on the side of a tablet to multiple separated layers. With the current emphasis on quality by design of pharmaceutical products (Yu et al., 2014), the need for mechanistic understanding of tablet capping is now more urgent. The problem of capping or lamination has been recognized since the birth of powder tableting technology. Various factors have been suggested

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to play a role in tablet capping, including tableting speed (Ruegger and Celik, 2000), tooling design (Sugimori and Kawashima, 1997; Sugimori et al., 1989), air entrapment (Mazel et al., 2015), uneven stress distribution within tablet (Wu et al., 2008), and deformation characteristics of the powder (Akseli et al., 2013, 2014; Shotton and Ganderton, 1961). Computational modeling of powder compaction has also been employed to elucidate capping mechanisms based on the changes in tablet microstructure and stress distribution (Sinka et al., 2004; Wu et al., 2008). Despite the extensive research efforts, gaps in our understanding of this phenomenon still exist. There remains a strong need of a reliable, material-sparing, and easy-to-perform method, which can be used to gain more insight into the phenomenon of tablet capping at an early stage of tablet product development.

One technique that likely meets that need is compaction simulation, which can be used to study powder compaction behavior on different tablet presses and using different compression parameters while using only a small amount of powder (Michaut et al., 2010). Using an instrumented die, useful information from in-die data could be obtained to characterize a number of elastic properties of powders (LaMarche et al., 2014; Mazel et al., 2012; Wu et al., 2008, 2005), which are expected to be relevant to study capping propensity of tablets. This study is aimed at evaluating the suitability of compaction simulation for predicting tablet capping propensity under realistic compaction conditions and identifying its possible correlation with in-die parameters obtained from compaction simulation. Such knowledge can be used to guide formulation optimization to eliminate the tablet capping problem.

2. Materials and methods

2.1. Materials

Acetaminophen (ACM, Form I) (Sigma Aldrich, St Louis, MO), a well-known poorly compressible drug, was used as a model drug to study the capping phenomenon. Microcrystalline cellulose (MCC, Avicel PH102; FMC Biopolymer, Philadelphia, PA) and magnesium stearate (Mallinckrodt, St Louis, MO) were used as tablet excipients.

2.2. Methods

2.2.1. Preparation of direct compression formulation

Binary mixtures of ACM and MCC were prepared with 25% increments in ACM loading. All powders were lubricated with a fixed concentration of magnesium stearate (0.5%, w/w). All ingredients were passed through a #30 mesh sieve and blended in a mixer (Turbula, Glen Mills Inc., Cliffton, NJ) for 2 min at 100 rpm.

2.2.2. Determination of bulk and tapped density

Each powder blend (~10 g) was poured in a graduated glass cylinder and its volume was recorded. The cylinder was dropped on to a padded bench top from a height of approximately 2 cm. Powder volume was determined after 50 taps. The process was repeated until the difference in tapped volume was <2.0% between two consecutive volume readings. Bulk and tapped density were calculated based on the untapped and tapped volumes, respectively. All measurements were triplicated. The ambient relative humidity ranged 32–35% throughout this study.

2.2.3. Tableting parameters

The influence of both ACM loading and tableting speed, measured by dwell time, on capping tendency was studied using a fully instrumented compaction simulator, equipped with an instrumented die (Presster, Metropolitan Computing Corporation, NJ) simulating a Korsch XL 400 press (29 stations) using 9.5 mm round flat-faced punches. For each batch, 10–12 tablets were obtained over a pressure range of 25–300 MPa. Maximum die-wall pressure (MDP), residual die-wall pressure (RDP), and ejection force (EF) for each tablet were recorded. Initially, formulations containing ACM in 25% increments were studied at 10 ms dwell time (103,000 tablets/h), using pure MCC as a control. Subsequently, the 75% ACM loaded formulation was further studied at three additional tableting speeds, i.e., dwell times of 15 ms, 25 ms, and 100 ms.

2.2.4. Determination of friction coefficient

The interaction between tablet and die-wall during ejection was quantified in term of friction coefficient (μ) according to Eq. (1) (Sun, 2015):

$$\mu = \frac{EF}{\pi \cdot RDP \cdot D \cdot h'} \tag{1}$$

where D and h' are the tooling diameter and in-die tablet thickness at the end of decompression phase, respectively. It is possible that tablet can still slightly expand axially after the decompression phase. If this happens, the actual μ would be lower than that calculated using Eq. (1). However, this effect is expected to be small.

2.2.5. Determination of radial tensile strength

Tablets obtained after compaction were immediately subjected to diametrical breaking test using a texture analyzer (Texture Technologies Corp., Surrey, UK). The radial tablet tensile strength (TS) was calculated according to Eq. (2) (Fell and Newton, 1970).

$$TS = \frac{2F}{\pi \cdot d \cdot H} \tag{2}$$

where F, d, and H are the breaking force, tablet diameter, and thickness, respectively. The TS of capped tablets were also determined by gently rubbing the intact portion of the tablets on a fine sand paper (superfine grade – P400, 3M Inc., Saint Paul, MN) to obtain approximately cylindrical tablets. Intact tablets were also polished by the sand paper to remove possible flashing for accurate thickness determination. The sand paper treatment is critical for calculating accurate tablet porosity, especially for plastic materials compressed at a high pressure (Paul et al., 2017).

2.2.6. Determination of true density of pure components and mixtures

The true density of ACM (1.294 g/mL) was calculated from its room temperature single crystal structure (Haisa et al., 1976). The true density of MCC equilibrated at 30% RH (1.467 g/mL) was obtained from the literature (Sun, 2008). The true density of mixtures (ρ_n) was obtained according to Eq. (3) (Sun, 2004):

$$\frac{1}{\rho_n} = \sum_{i=1}^{n} \frac{x_i}{\rho_i} \tag{3}$$

where x and n refer to the weight fraction and number of constituents in the mixture, respectively.

2.2.7. In-die Heckel analysis

Heckel analysis was performed using the in-die data since out-of-die data could not be obtained for capped tablets. The Heckel equation (Eq. (4)) describes the change of compact porosity (ε) with compaction pressure (P) (Heckel, 1961b):

$$-ln\varepsilon = k \cdot P + A \tag{4}$$

where the reciprocal of the slope, 1/k, known as mean yield pressure (P_y), has been used to assess plasticity of a material