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Tensile and shear methods for measuring strength of bilayer tablets

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ABSTRACT

Both shear and tensile measurement methods have been used to quantify interfacial bonding strength of bilayer tablets. The shear method is more convenient to perform, but reproducible strength data requires careful control of the placement of tablet and contact point for shear force application. Moreover, data obtained from the shear method depend on the orientation of the bilayer tablet. Although more time-consuming to perform, the tensile method yields data that are straightforward to interpret. Thus, the tensile method is preferred in fundamental bilayer tableting research to minimize ambiguity in data interpretation. Using both shear and tensile methods, we measured the mechanical strength of bilayer tablets made of several different layer combinations of lactose and microcrystalline cellulose. We observed a good correlation between strength obtained by the tensile method and carefully conducted shear method. This suggests that the shear method may be used for routine quality test of bilayer tablets during manufacturing because of its speed and convenience, provided a protocol for careful control of the placement of the tablet interface, tablet orientation, and blade is implemented.

1. Introduction

The effective treatment of a wide range of diseases frequently requires co-administration of two or more drugs (Ruzicka and Leenen, 2001). In contrast to taking the drugs as separate tablets, a bilayer tablet can simultaneously deliver two (or more for multi-layer tablets) drugs in one tablet. Thus, it is an effective approach for reducing pill burden. Consequently, the bilayer tablets have gained more importance and attracted attention as a dosage form. In bilayer tablets, the physical separation of drugs in different layers reduces the drug-drug contact surface area and thereby minimizes the potential incompatibility among drugs. Through appropriate formulation of each layer, it is also possible to achieve the desired release profiles of each drug in one dosage unit (Abdul and Poddar, 2004; Fassihi and Ritschel, 1993). The pharmaceutical advantages of bilayer tablets also form a basis for new intellectual property opportunities, which are important for life cycle management of drug molecules.

A main challenge in developing bilayer tablet drug products is the weak interfacial bonding strength (IBS) between the two layers, which may lead to visible cracks or even lamination at the interface after ejection or during packaging, shipping and storage. The availability of a standardized method to reliably quantify IBS is critical for investigating the cause of weak IBS. Measuring accurate IBS is the first step for developing a mechanistic understanding of the IBS evolution, which is important for effectively controlling IBS through formulation and process optimization. Accurate measurement of IBS is also required for establishing a minimally acceptable IBS that can be used to guide the formulation development of bilayer tablets, similar to the minimal diametrical tensile strength of 2 MPa proposed for single layer tablets (Sun et al., 2009).

Several methods have been developed to quantify the strength of bilayer tablets, such as tensile test (Akseli et al., 2013; Anuar and Briscoe, 2010; Inman et al., 2007; Kottala et al., 2012a,b), shear test (Klinzing and Zavaliangos, 2013), diametrical compression test (Amin et al., 2012; Niwa et al., 2013; Papós et al., 2015; Wu and Seville, 2009), three point bending test (Busignies et al., 2013; Podczeck, 2011; Podczeck and Al-Muti, 2010; Podczeck et al., 2006), and V-shape punch breaking test (Busignies et al., 2014). Among these, the shear and tensile methods are, by far, the most commonly used for quantifying IBS of bilayer tablets. In the shear method, a shear force parallel to the interface of bilayer tablets is applied, while in the tensile test, a tensile force perpendicular to the interface is applied to the tablet.

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The application of force in the shear method more closely mimics the impacting force experienced by bilayer tablets in real life, where bilayer tablets collide with each other or container wall. Thus, the stresses are more likely to be compressive or shear instead of tensile. Although the shear method is more relevant, it is difficult to explain the IBS obtained by this method due to poorly understood stress distribution at the interface during testing. In addition, the measured shear IBS may also be sensitive to the tablet orientation and placement of the interface relative to the two planes where shear stresses are applied. In contrast, the tensile test yields unambiguous results, because the tensile stress is more uniformly applied in a direction perpendicular to the interface. However, the tensile method is much more time-consuming to perform than the shear method.

The respective advantages and disadvantages in the shear and tensile methods outlined above led to the preference of the former in the industry and the latter in academia research. The main goal of this work was to determine whether IBS values obtained by the shear and tensile methods could be correlated. If a statistically significant and simple relationship is observed, knowledge derived from the research employing the tensile method can be readily adopted to guide the development and characterization of bilayer tablets by shear method.

2. Materials and methods

2.1. Materials

Lactose monohydrate (SuperTab 11SD and 30GR), lactose anhydrate (24AN) and microcrystalline cellulose (MCC, Pharmacel PH102) were gifts from DFE Pharm (Goch, Germany). Lactose is hard and brittle, while MCC is soft and ductile (Duberg and Nyström, 1981; Gong and Sun, 2015; Osei-Yeboah and Sun, 2015; Patel and Sun, 2016; Rees and Rue, 1978). Binary mixtures exhibit a wide range of material properties, ranging between those of the two pure materials. These commonly used excipients were selected in this work for their relevance to bilayer tablet formulation and manufacturing in the pharmaceutical industry.

A portion of each powder was used to make colored tracer particles by spraying a 1% (w/w) methanol solution of a food dye. To ensure uniformity, a small amount of the solution was sprayed onto the raw powder using a spray bottle, followed by gentile mixing with a spatula and air drying. This process was repeated until the powder showed the desired color intensity. Such colored powders had similar particles size and shape to the untreated powders. A small amount of the colored tracer powder (1%, w/w) was mixed with untreated powder. When making a bilayer tablet, one layer used an as-received material while the other layer used a powder containing colored tracer particles to aid the identification of the interface. Prior to compression, all powders were lubricated with 0.5% (w/w) of magnesium stearate (Mallinckrodt Pharmaceuticals, St. Louis, MO) and equilibrated in a 32% relative humidity (RH) chamber (over a saturated $MgCl_2$ solution) for at least three days before bilayer tablet compaction.

2.2. Methods

2.2.1. Powder blend preparation

Powder mixing was carried out in a V-shaped blender (Blendmaster, Patterson Kelley, East Stroudsburg, PA) at 25 rpm for 10 min. A typical batch size was 100 g, and the volume of the blender was 1 quart.

2.2.2. Bilayer tablet compaction

Cylindrical bilayer tablets were compressed on a Materials Testing Instrument (Zwick- Roell 1485, Ulm, Germany) using 8 mm flat round tooling. An illustration of the bilayer tableting process is shown in Fig. 1. Approximately 150 mg of powder was manually loaded into the die and compressed at a pressure, P1, of 20 MPa to make the first tablet layer (Fig. 1a). Without ejecting the first layer, 150 mg of a second powder was again manually added to the die and the second (final) compression was carried out at P2, which was 200 MPa (Fig. 1b). All second layers were colored, while the first layer was not. All tablets were ejected from the die by pushing the second layer downward with the punch (Fig. 1c). Bilayer tablets were stored at 32% RH overnight, before they were tested for IBS. Environmental RH was ~50% during compaction and IBS determination. To minimize the impact of RH variation on compaction behavior, care was taken to minimize exposure of the powder to the environment by carrying out the compression immediately after powder was added to the die.

2.2.3. Force application

In both shear and tensile methods, as illustrated in Fig. 2, force was applied using a texture analyzer (TA-XT2i, Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK).

2.2.4. Shear method

For each group of six bilayer tablets prepared under identical compaction conditions, three tablets were inserted into the holder cavity (round, 8.02 mm diameter) with the first layer inside and the

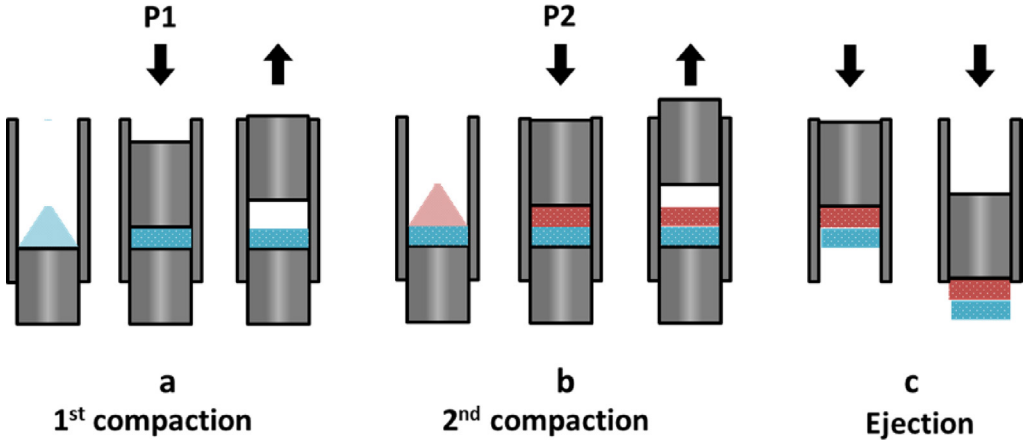

Fig. 1. Illustration of the process for making bilayer tablets. (a) The first layer was formed by compressing a powder at P1; (b) Without ejecting the first layer, a second powder was added and compressed at P2 to form a bilayer tablet; (c) The bilayer tablet was ejected downward out of the die.