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Role of the elasticity of pharmaceutical materials on the interfacial mechanical strength of bilayer tablets

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ABSTRACT

The effect of the elasticity of various pharmaceutical materials on the interfacial adhesion in bilayer tablets was investigated. The elastic properties of five pharmaceutical products were characterized by their total elastic recovery. To test the interfacial strength of the bilayer tablets a new flexural test was proposed. Thanks to the test configuration, the experimental breaking force is directly correlated with the interfacial layer strength. Depending on the materials, the fracture occurred over the interface or in one of the two layers. In most cases, the highest breaking forces were obtained when the materials had close elastic recovery. On the contrary, for materials with different elastic recovery, the breaking forces were reduced. The observed changes in the interfacial mechanical strength were statistically analyzed. Such an approach has an importance in the growing interest in the Quality by Design (QbD) concept in pharmaceutical industry.

1. Introduction

Bilayer tablets are characterized by several advantages which are listed for example in the mini review of Vaithiyalingam and Sayeed (2010). Nevertheless, these bilayer tablets are not always easy to design and to manufacture. The main manufacturing challenge is to obtain tablets that do not fracture at the interface because of insufficient adhesion (Akseli et al., 2013; Kottala et al., 2013). The delamination can be observed during manufacturing, packaging or storage (Klinzing and Zavaliangos, 2013; Kottala et al., 2012a–c). Lots of methods for testing the adhesion at the interface were proposed (Akseli et al., 2013; Niwa et al., 2013; Podczeck, 2011; Podczeck et al., 2006). These methods are sometimes not easy to perform and currently, no method is preferably recommended.

Several reasons for delamination at the bilayer interface have been proposed. The difference of mechanical properties of the layers such as Young's modulus is always suggested as a cause for the delamination of bilayer tablets. Some previous works tried to link measurement of the strength of bilayer tablets with Young's modulus (Anuar and Briscoe, 2010; Podczeck and Al-Muti, 2010; Podczeck, 2011; Podczeck et al., 2006). However, the elastic properties of the used materials were, in most cases, not determined for the studied materials but taken from previous published works. The use of these values could be problematic. In fact, these values are often Young's moduli at zero porosity which are not always obtained by applying a same mathematical model. Moreover, Young's modulus at zero porosity is often not representative of the elastic behavior of materials in the conditions of manufacturing of the bilayer tablets since the porosity of tablets are mostly different from a zero porosity. It was also pointed out that the Young's modulus was insufficient to characterize the elastic behavior of pharmaceutical products due to the variations of Poisson's ratio. To analyze the influence of the elastic properties on the delamination of bilayer tablets, the elastic characterization of the materials should be revised. It was shown that the bulk modulus of pharmaceutical materials which associate the Young's modulus and the Poisson's ratio is well correlated with the elastic recovery (Mazel et al., 2013). This last parameter could be easily determined by tablet measurements performed under pressure and out of die.

Nowadays, a great interest for the Quality by Design (QbD) concept is observed in the pharmaceutical industry. This concept emphasized the importance of understanding the influence of materials properties and process parameters on product quality. For bilayer tablets, understanding about critical parameters that influenced the layer adhesion is requested.

The aim of this work is to investigate the effect of the elasticity of various pharmaceutical materials on the interfacial adhesion in bilayer tablets. Then, five pharmaceutical products commonly used in compaction were chosen to compose one of the two layers of the tablets. The elasticity of these products was characterized by the measurement of their total elastic recovery. The mechanical strength of all the bilayer tablets were assessed with a new flexural

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test adapted to the bilayer tablets. We presented the experimental results obtained when the composition of the two layers was changed. Finally, the influence of the elasticity of the layer materials on the strength of the bilayer tablets was statistically analyzed. This approach is one stage in the application of the QbD concept for the formulation of bilayer tablets.

2. Materials and methods

2.1. Pharmaceutical materials

Five commercial pharmaceutical materials used in tableting were studied in this work: calcium phosphate, CP (Emcompress Premium®, JRS Pharma, Germany); hydroxyl propyl methyl cellulose, HPMC (Metolose 90SH-4000SR, ShinEtsu, Japan); lactose, Lac (Fast Flo®, Foremost, US); pregelatinized starch, PS (Lycatab C®, Roquette Pharma, France); microcrystalline cellulose, MCC (Vivapur 12®, JRS Pharma, Germany). These five powders were lubricated with 1% (w/w) of magnesium stearate (Magnesium Stearate MF3V, Peter Greven, Bad Munstereifel, Germany) in a Turbula mixer (Type T2C, Willy A Bachofen, Muttenz, Switzerland) at 50 rpm during 5 min. Before use, all the lubricated materials were stored for at least three days and at room temperature (around 20 °C) in a close chamber with a saturated $NaHSO_4$, H_2O solution corresponding to a relative humidity of 48 ± 6%.

2.2. Bilayer tablets preparation

The bilayer tablets tested in this work were parallelepipedical and were obtained by uni-axial compaction using a hydraulic press (Perrier Labotest, France). The tablet size (especially the height) was adapted to the mechanical test presented in the following part. The punch dimension was $40 \times 5\ mm^2$. The mass of powder for each layer was adjusted to have a total height of about 14 mm after compaction at the chosen maximal pressure (i.e. about 7 mm for each layer). The corresponding weighting mass were 1.4 g for CP, 0.9 g for HPMC and PS, 1.0 g for Lac and MCC. The two powders which composed the two layers were sequentially and manually introduced in the die and sequentially compacted to form the bilayer tablets (Fig. 1). Lots of previous studies have shown the impact of the compaction pressure on the first layer (Akseli et al., 2013; Dietrich et al., 2000; Inman et al., 2007, 2009; Kottala et al., 2012b, 2013; Vaithiyalingam and Sayeed, 2010). The first compaction pressure affects the surface roughness of the bottom layer and then, the adhesion between the two layers. That is why, it is generally recommended to reduce the first compaction pressure. In this work, a same low compaction pressure of 20 MPa was applied on each first layer. Then, layer 1 and layer 2 were compacted at 200 MPa. Then, as it is generally the case when using a pre-compression to produce pharmaceutical tablets, the value of the first pressure represents 10% of the pressure applied for the main compaction. As shown in Fig. 1, the die was completely dismantled after compaction to avoid the delamination of the bilayer tablets during the ejection. The first and the second layer were composed of one of the five lubricated materials (25 bilayer tablet compositions, $n = 3$ for each composition). To appreciate the variation in results, 9 repeated experiments were also performed with bilayer tablets composed of MCC in the two layers.

Moreover, tablets composed of one layer of each material were obtained. A mass corresponding of those used for the bilayer tablets composed of the same material in the two layers was introduced in the die and compacted under a pressure of 200 MPa.

2.3. Measurement of the interfacial mechanical strength

Immediately after compaction, the bilayer tablets were tested using a flexural test that was adapted to the bilayer tablet size. As a consequence, the effect of the environmental conditions on the tablets and its mechanical strength was reduced (Klinzing and Zavaliangos, 2013; Kottala et al., 2012a–c). The bilayer tablets were put on two cylindrical supports (distance between the two supports of 10 mm) like in a three point flexural test (Fig. 2). The support for loading was set up at the interface and the bilayer tablet was stressed at a constant velocity of $0.050\ mm\ min^{-1}$ until breakage. The breaking force (F_r in N) was recorded. Due to the test configuration, the maximal tensile stress is located on the lower side of the compact, at the interface between the two products. Then, the breaking force is directly correlated with the interfacial layer strength. Moreover, for all the tablets, the surface of the interface was almost the same since it was defined by the die dimensions. Then, it was possible to compare the recorded breaking forces.

The same test was also performed on tablets composed of one layer of each material to compare the strength of the materials compacted alone.

2.4. Measurement of the elasticity of pharmaceutical materials

The hydraulic press was not equipped with displacement transducers. Then, it was not possible to determine the elasticity of the five materials using this press. Therefore, the five lubricated materials were compacted using a StylOne Evolution tableting machine (Medelpharm, France) that made possible to monitor the punch displacements during compaction. The pressure on the two punches and the punch displacements were measured during the compaction cycle. For the measurement of the punch displacements, the deformation of the punches and of the machine was considered. Standard Euro B round flat-faces punches (diameter of 11.28 mm) were used. The die height was kept constant at a value of 10 mm. Tablets were obtained by applying a compaction pressure (mean of the pressure applied by the upper and the lower punches) of 200 MPa.

A recent work showed the relationship between elastic recovery immediately after compaction and elastic moduli, Poisson's ratio and bulk modulus (Mazel et al., 2013). Experimentally, the determination of the elastic recovery is easy contrary to those of the elastic moduli. That is why this approach was chosen in this work with the calculation of the total elastic recovery (*ERt*) from the following equation (Armstrong and Haines-Nutt, 1974; Picker, 2001):

$$ERt = \frac{V_f - V_{min}}{V_{min}} \times 100 \quad (1)$$

In this equation, V_f is the final volume of the tablet. It was obtained by the measurement of its diameter and height immediately after ejection using a micrometer (Mitutoyo, Japan). V_{min} is the minimal volume under compaction. It was determined from the minimal distance between the punches recorded during compaction and the die diameter.

As suggested in some previous works (Anuar and Briscoe, 2010; Podczeck and Al-Muti, 2010; Podczeck, 2011; Podczeck et al., 2006), an elastic material mismatch between material layers can induce delamination. To evaluate the elastic mismatch between two materials, the difference of total elastic recovery (*DERt*) between the materials which composed the two layers of a bilayer tablets was evaluated using:

$$DERt = |ERt_1 - ERt_2| \quad (2)$$