Journal of Pharmaceutical Sciences 106 (2017) 1331-1338

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Effect of the Curvature of the Punches on the Shape of the Interface and the Delamination Tendency of Bilayer Tablets

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ARTICLE INFO

Article history:
Received 21 October 2016
Revised 12 January 2017
Accepted 18 January 2017
Available online 28 January 2017

Keywords:
bilayer
tablet
tableting
mechanical properties
compaction

ABSTRACT

Bilayer tablets are of special interest in the pharmaceutical industry. The main problem during their manufacturing is the occurrence of delamination during or after the ejection from the die. This work studies the influence of using punches with a curvature on the interfacial strength and thus on the delamination tendency of bilayer tablets. Bilayer tablets were produced with a compaction simulator using different flat and concave punches with different radii of curvature. The main compaction pressure was kept constant but the tamping force was varied. Two bilayer model systems were studied. The interfacial strength was determined using a previously described indentation test. The factors studied were analyzed for statistical significance with respect to the responses. The curvature of the interface was found to be higher when the curvature of the punch and the tamping force increased. Breaking tests then demonstrated that, for bilayer tablets obtained using the same compression parameters, the interfacial strength was lower when the curvature of the interface increased. As a consequence, when producing bilayer tablets with concave punches, it is important to choose properly the tableting parameters in order to have an interface between the layers as flat as possible to avoid delamination issues.

Introduction

Oral drug combination in a single dosage form is a well-known therapeutic system in the pharmaceutical industry, and it is gaining interest and popularity in the medical field, due to its advantages. The administration of multiple drugs in a single dosage form can promote their synergy, thus reducing the dosage of each single drug. Finally, this may result in a reduction of adverse effects, improving the patient compliance. The simplest way to formulate these dosage forms is to disperse the drugs in a homogenous system. This is effective only when it is possible to assess with certainty that no physical or chemical incompatibilities exist between the mixed powders, otherwise the physical integrity and, clearly, the drug administration of the form are severely compromised.[1]

An alternative solution is to organize the drugs in layers, preparing a multilayer tablet. This dosage form reduces the problem of incompatibilities. It also makes it possible to decrease the "pill burden" on the patient leading to better patient compliance and patent/exclusivity extensions. Considerations about the advantages of such a form can be found in the literature.[2-4]

However, the development of such layered tablets is a complex procedure, which starts with the formulation of each single layer (that has to respect the desired drug amount and release profiles) and end with the combination of the previously formulated layers in a single tablet. This final product must be prepared taking into account its physical and chemical stability, thus modifying certain procedure parameters that will exert a relevant effect on the multilayer tablets' critical mechanical properties. In fact, the currently used procedure to prepare multilayer tablets is to subject the powder of the lower layer to a precompression (tamping) pressure and then, once the powder of the second layer is distributed above the precompressed first layer, to apply a main compression pressure.[2] The precompression step is critical: a high precompression force not only reduces the possibilities of cross-contamination between the layers (which prevents chemical instabilities due to possible incompatibilities between the different powders) but also decreases the roughness of the interfacial surface, diminishing the contact surface between the layers, thus enhancing the probability of a delamination.[5] It is also critical to consider the difference in mechanical properties under compression between the different powders. Not only plasticity and brittleness but also size and shape of the particles can interfere with the interfacial adhesion. These parameters are all studied extensively in the current pharmaceutical literature.[6]

However, the study of the compaction of pharmaceutical powders in multilayer tablets is often performed on flat-faced tablets due to the difficulty in precisely measuring the compression

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http://dx.doi.org/10.1016/j.xphs.2017.01.020
0022-3549/

parameters (stresses applied and punch displacement) when using complex-shaped punches. Unfortunately, the results obtained using flat punches cannot always be generalized to the cases of more complex punch shapes.[7] This is in contrast to the industrial tendency to use convex-shaped punches when preparing both single layer and multilayer tablets. This is not only because a convex shape is more commercially appealing, but also because of technical reasons. For example, convex tablets tend to be less friable and powdery and it is easier to perform a coating on convex tablets, because this shape prevents the adhesion between tablets during the coating procedure.[8] Additional advantages of using shaped tablets include swallowability by patients, tablet flow during downstream coating and packaging operations, and an increase in the surface area available to water during release.

Previous experimental and numerical studies performed on tablets with convex shape showed that the density and stress distributions are different from the ones obtained on flat-faced tablets.[7] A recent publication[9] underlined that, in the case of convex tablets, the density distribution is also influenced by the thickness of the compact. Then, even if they are produced under the same compression load, tablets obtained using different punch curvatures are difficult to compare and may have different mechanical properties.

In the case of bilayer tablets, the shape of the punches could thus play an important role in the adhesion between the layers. Nevertheless there is, to our knowledge, only 1 study about the effect of the punch curvature on the interfacial strength of bilayer tablets.[10] In this study, the comparison was performed between bilayer tablets manufactured with 2 different sets of tooling: 12.77-mm-diameter round flat-faced B-type tooling, and 20.47 mm × 10.90 mm capsule-shaped D-type tooling. The authors compared the interfacial strength of bilayer tablets obtained with these 2 sets under the same compression force. Unfortunately, these 2 punch sets have a very different projected surface area. The tablets obtained can thus be hardly compared and the results showed in this article should be taken with caution.

Considering the existing literature on convex tablets, 2 main differences are expected between bilayer tablets made with flat or concave punches. The first one is the possibility of having a curved interface, depending on the respective values of the precompression and main compression pressure. The second one is the fact that the concave punches give a different stress distribution in the tablet compared to flat punches, as already demonstrated on monolayer tablets.[7,9] This difference in stress distribution is thus also expected to happen at the interface. These 2 aspects could have an influence on the interfacial strength of the tablet, and this is the focus of the present study.

This work aims at comparing the interfacial strength of convex and flat-faced bilayer tablets. For this purpose, several batches of tablets were produced (flat-faced, biconvex) but also tablets obtained with 1 flat punch and 1 concave punch. The nonsymmetric configuration was used to try to separate the effects due to the curvature of the interface and those due to the stress distribution. The interfacial strength was tested using a previously optimized indentation test.[11] The factors studied were analyzed for statistical significance with respect to the responses, and these results are presented.

Materials and Methods

Tablet Production

Three classical excipients were used: microcrystalline cellulose (MCC; Vivapur 12, JRS Pharma, JRS PHARMA GmbH & Co, Rosemberg, Germany), calcium phosphate dihydrate (DCP; Emcompress premium, JRS Pharma, JRS PHARMA GmbH & Co, Rosemberg, Germany) and spray-dried lactose (Lac; Flowlac® 90, Meggle, Wasserburg, Germany). Each powder was lubricated adding 1% (w/w) of magnesium stearate (Cooper, Melun, France).[12] The blending was performed at 50 rpm for 5 min using a turbula mixer (type T2C, Willy A Bachofen, Muttenz, Switzerland). MCC was always the first layer as it was the more compressible product. Two different bilayer systems were produced: MCC/DCP (MCC first layer, DCP second layer) and MCC/Lac (MCC first layer and Lac second layer). In all the studies, the filling height was kept constant at 6 mm for the layer MCC and at 5 mm for layers of Lac and DCP which corresponded to layers with a mass around 150 mg.

Table 1
Punch configurations Used for Both MCC/DCP and MCC/Lac Bilayer Tablets

Configuration	Radius of Curvature (mm)	
	Upper Punch	Lower Punch
UF/BF	Flat	Flat
UC/BF	11	Flat
	8	Flat
	6	Flat
UF/BC	Flat	11
	Flat	8
	Flat	6
UC/BC	11	11
	8	8
	6	6

All the punches were round Euro B with a diameter of 8 mm. In order to produce tablets with different interfacial shapes, 4 different punches were used: flat-faced and concave-faced with 3 radii of curvature (6, 8, and 11 mm). Four different punch configurations were used: upper flat/bottom flat (UF/BF), upper flat/bottom curved (UF/BC), upper curved/bottom flat (UC/BF), and upper curved/bottom curved (UC/BC). For each configuration with curved punches, the 3 radii of curvature were used. For the UC/BC configuration, both punches had the same curvature. Table 1 summarizes the different punch configurations used.

For each configuration, tablets were produced varying the tamping force as follows: 0.5 kN, 1.5 kN, 3.5 kN, and 5 kN. These forces correspond to applied pressure of 10 MPa, 30 MPa, 70 MPa, and 100 MPa, respectively. The main tableting force was set to 10kN (i.e., a compacting pressure of 200 MPa). This makes it possible on the one hand to produce tablets with different interfacial strength and on the other hand to vary the shape of the interface as it will be explained below. The force values were chosen based on our experience on the studied products.[13]

The compaction experiments were performed using a Styl'One Evolution compaction simulator (Medelpharm, Lyon, France). This device is a single-punch tableting press, monitored by Analis software. The displacements of the upper and lower punches are electronically controlled, and the pressures applied are measured with strain gauges. During the compression, both punches are moving and the pressure is applied symmetrically.

Tablet Testing

Indentation Test

The test used was already described in detail elsewhere.[11] The bilayer tablets were put on a V-support with an opening angle of 90° and a depth of 6 mm. The samples were then stressed with a punch designed for the experiment. The punch tip was a half-cylinder shape with a diameter of 2.80 mm and a width of 6 mm. The system was designed to apply a stress, through the tip of the punch, exactly at the interface between the layers (Fig. 1). The