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Comparison of breaking tests for the characterization of the interfacial strength of bilayer tablets

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ABSTRACT

The bilayer tableting technology is gaining more acceptance in the drug industry, due to its ability to improve the drug delivery strategies. It is currently assessed by the European Pharmacopoeia, that the mechanical strength of tablets can be evaluated using a diametral breaking tester. This device applies a force diametrically, and records the tablet breaking point. This approach has been used to measure the structural integrity of single layer tablets as well as bilayer (and multi-layer) tablets. The latter ones, however, have a much complex structure. Therefore, testing a bilayer tablet with the currently used breaking test methodology might not be appropriate.

The aim of this work was to compare results from several tests that have been proposed to quantify the interfacial strength of bilayer tablets. The obtained results would provide an indication on which tests are appropriate to evaluate the robustness of a bilayer tablet.

Bilayer tablets were fabricated using a model formulation: Microcrystalline Cellulose (MCC) for the first layer, and spray dried lactose (SDLac) as second layer.

Each set of tablets were tested using the following tests: Diametral Test, Shear Test and Indentation Test.

The tablets were examined before and after the breaking test using Scanning Electron Microscopy (SEM). When a bilayer tablet was subjected to shearing or indentation, it showed signs of clear delamination. Differently, using the diametral test system, the tablets showed no clear difference, before and after the testing. However, when examining each layer via SEM, it was clear that a fracture occurred in the layer made of SDLac. Thus, the diametral test is a measure of the strength of one of the two layers and therefore it is not suited to test the mechanical strength of bilayer tablets.

1. Introduction

The compressed tablet is one of the most popular dosage form in use today. Moreover, the association of drugs in a single tablet is a therapeutic strategy that is gaining more acceptance. Therefore, bilayer (or multilayer) tablets are gaining popularity due to a confluence of factors. It can reduce the burden for patients by administering two or more active pharmaceutical ingredients (APIs) in a single dosage form. The bilayer tablets can be designed to overcome chemical incompatibility between two active components. Lastly, those tablets are also developed to control the delivery rate of one or more APIs, by interposing layers with different releasing properties (Abebe et al., 2014; Kottala et al., 2014).

The manufacture of a bilayer tablet is a delicate procedure: it needs to ensure both the physical and chemical endurance (the Critical Quality Attributes) of the tablet itself during the industrial processing procedures (manufacturing, handling, packaging and shipping) and to enable the activity of the drugs after the tablet administration, to reach the Target Product Profile (Kottala et al., 2014). The construction of such complex oral dosage forms requires on one hand the complete control of any aspects of its formulation and compression processes, i.e. the Critical Material Attributes and the Critical Process Parameters, and on the other hand the control of the release of each active substance with an individual and controlled manner.

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Although the manufacture of bilayer tablets has been successful for over 50 years, there is still a need for improvement, in order to ensure that the manufacturing process will make possible to satisfy both technological and therapeutic specifications as well as regulatory requirements (Abdul and Poddar, 2004).

In fact, the main problem that occurs during the manufacturing of bilayer is delamination (Podczeck, 2011; Vaithiyalingam and Sayeed, 2010). It corresponds to the splitting of the tablet at the interface between the layers. This separation between the layers may take place just after compaction or later during the storage (Kottala et al., 2012b). Some explanation of the delamination phenomenon can be found in the literature, and it is related to different parameters such as the elastic recovery of the two layers (Anuar and Briscoe, 2010; Busignies et al., 2013; Podczeck and Al-Muti, 2010; Podczeck et al., 2006) or the roughness of the interface (Kottala et al., 2012a). It was also shown that the process parameters can influence the interfacial strength. For example to ensure a good cohesion, the pressure applied on the first layer should be kept to a minimum, and the pressure applied on the second layer should be high enough (Dietrich et al., 2000; Inman et al., 2007, 2009; Vaithiyalingam and Sayeed, 2010).

Due to the importance of the adhesion at the interface between layers, it is critical to have a relevant and robust method to quantify its strength. This is a matter that is becoming more interesting with the development of Quality by Design (QbD) for the manufacturing of a bilayer tablet. Product and processing understanding is a key element to QbD (Yu, 2008). As such, it is clear that the control of each single step and the quantification of each single parameter should be as accurate as possible.

When applying the QbD methodology to the design of a bilayer tablet, the accurate quantification of the mechanical resistance of interface between the two layers is necessary to correctly assess the quality attributes of the final product.

Unfortunately, as currently stated by the European Pharmacopoeia (ver. 8), there is no standard methodology to measure the interfacial strength of bilayer tablet. The only methodology that is described in the European Pharmacopoeia to test the strength of tablet is the diametral compression test but in the corresponding monograph, there is no reference of its use in the case of bilayer tablets. Nevertheless, several articles in the literature can be found that perform the diametral compression test to characterize the interfacial strength of a bilayer tablet (and therefore the final robustness of the tablet itself) (Wu and Seville, 2009; Papós et al., 2015).

On the other hand, other testing methodology are acknowledged, such as the relatively new indentation test (Busignies et al., 2014). This test proved, with a pharmaceutical Quality by Design approach, to be suitable for the measurement of the interfacial adhesion of bilayer tablets. Another test that is currently under investigation is the shear test (Dietrich et al., 2000; Klinzing and Zavaliangos, 2013). This device is described carefully in the materials and methods part of this publication. Lastly, it is possible to measure the interfacial strength via traction testing (Akseli et al., 2013). This testing is operatively complicated to execute, because the examined bilayer tablets must be individually glued to two tablet holders using a cyanoacrylate-based fast-acting glue and left for an hour to ensure a good adhesion. It must be also ensured that no glue migrates through the pores up to the interface of the examined bilayer tablets.

To try to clarify the testing conditions, we chose in this work to use three different tests to study the interfacial strength of a model formulation: diametral compression test, shear test and indentation test. These three tests were chosen because they are easy to perform, applicable to various compacts shape and they do not necessitate specific sample preparation. As such, they could be chosen as a standard test at an industrial level. The aim was to study if these three tests were indeed able to discriminate tablets with different interfacial strength or if they should be avoided for the characterisation of the interfacial strength of bilayer tablets.

2. Materials and methods

2.1. Manufacturing of tablets

As studied in previous works, and as explain above, the main process parameters that have an influence on the strength of bilayer tablets are the applied pressure on the first layer and the main compaction pressure. Then, in order to compare the ability of each test to discriminate the robustness of a bilayer tablet, tablets with different mechanical strength at the interface were produced by varying these two process parameters.

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 the Analis software. The displacement of the upper and lower punches is controlled electronically.

The pressure applied by the punches to the powder bed is measured with strain gauges. The machine can be also controlled to reach a given pressure. For all the experiments, the tablets were produced using standard Euro D round and flat punches with a diameter of 11.28 mm.

Bilayer tablets were manufactured using a model formulation: Microcrystalline cellulose, MCC (Vivapur 12, JRS PHARMA GmbH & Co, Rosemberg, Germany) for the first layer, and spray-dried lactose, SDLac (Flowlac 90, Meggle, Wasserburg, Germany) as second layer, adding 1% of Magnesium Stearate to both powders as a lubricant (Wang et al., 2010). The filling height for the layers was adjusted to obtain a total height of about 10 mm before compaction

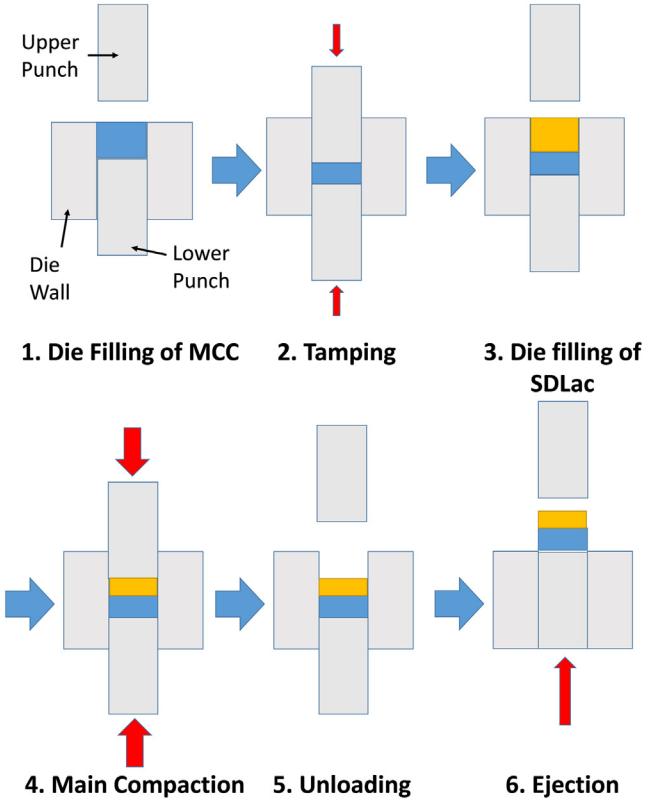

Fig. 1. Bilayer compression cycle used in this work.