International Journal of Pharmaceutics 490 (2015) 438–445

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

# Predictive model for tensile strength of pharmaceutical tablets based on local hardness measurements

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ARTICLE INFO

*Article history:*
Received 16 March 2015
Received in revised form 27 May 2015
Accepted 30 May 2015
Available online 1 June 2015

*Keywords:*
Caffeine (PubChem CID: 2519)
Microcrystalline cellulose (PubChem CID: 14055602)

*Keywords:*
Tablet tensile strength
Powder mixture
Predictive model
Direct compression
Nanoindentation
Diametral compression test

ABSTRACT

In the pharmaceutical field, tablets are the most common dosage forms for oral administration. During the manufacture of tablets, measures are taken to assure that they possess a suitable mechanical strength to avoid crumbling or breaking when handling while ensuring disintegration after administration. Accordingly, the tensile strength is an essential parameter to consider. In the present study, microscopic hardness and macroscopic tensile strength of binary tablets made from microcrystalline cellulose and caffeine in various proportions were measured. A relationship between these two mechanical properties was found for binary mixture. The proposed model was based on two physical measurements easily reachable: hardness and tablet density. Constants were determined from the two extreme compositions of this given system. This model was validated with experimental results, and a comparison was made with the one developed by Wu et al. (2005). Both models are relevant for this studied system. Nonetheless, with this model, the tablet tensile strength can be connected with a tablet characteristic at microscopic scale in which porosity is not needed.



## 1. Introduction

In the pharmaceutical field, tablets are the most common dosage form for oral administration and these forms occupy two thirds of the global drug market (Wu and Seville, 2009). Tablets are composed of numerous particulate materials that are bound together under pressure in order to be delivered as a unit. The nature of these compounds (physical and chemical) as well as the processing conditions are crucial for the properties of the blend and, consequently, the tablet ones (Tejedor et al., 2015). For example, it is well known that the macroscopic dissolution of tablets depends on the physicochemical properties of the micrometric powders such as contact angle, surface area and particle size (Tran et al., 2015; Leonardi and Salomon, 2013). In the same way, recent studies have been conducted on mechanical properties (Tejedor et al., 2015; Al-Khattawi et al., 2014; Sun, 2011; Narayan and Hancock, 2003). However, the relationship between mechanical properties at different scale is not yet fully understood. Concerning the processing conditions for the tablets manufacturing, the use of direct compression has rapidly increased in the past few years due to its economic interest and its process which avoids the steps of the wet granulation and drying processes.

During tablet manufacturing, measures are taken to ensure that tablets possess a suitable mechanical strength to avoid crumbling or breaking when handling. According to the European Pharmacopoeia (2014) two mandatory tests are proposed to determine mechanical strength of tablets: friability of uncoated tablets and resistance to crushing of tablets based on diametral compression test (Sections 2.9.7 and 2.9.8, respectively). The latter one, using a tablet tester, determines the force, usually expressed in Newton (N), needed to disrupt tablets by crushing. The literature has

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http://dx.doi.org/10.1016/j.ijpharm.2015.05.078
0378-5173/

suggested other tests for the practical determination of the mechanical strength of tablets like the three-point bending test, biaxial compression test, etc. (see Podczeck (2012) for a complete review). Nevertheless, the diametral compression test is the easiest to implement.

A more thorough study of tablets requires the knowledge of other characteristics. Density and porosity, were generally used to study the compression behaviour of the powder mixture corresponding to powder compactability and powder compressibility (ability to reduce their volume under pressure). In the literature, several studies dealt with the understanding of the compressibility according to the properties of the pure components. These studies were based on global models commonly used in the pharmaceutical field such as Heckel model (Heckel, 1961; Ilkka and Paronen, 1993; Van Veen et al., 2000) or Kawakita model (Kawakita and Lüdde, 1970; Frenning et al., 2009; Mazel et al., 2011; Busignies et al., 2012). However, Denny (2002) made a comparison between these two equations and finally concluded that Kawakita equation is a specific case of the modified Heckel equation. In addition, there is no proven relationship between the powder compressibility and the physical and mechanical properties of tablets.

Many authors have been interested in the study of tablet tensile strength of binary mixtures, using the relative proportion of the two pure components (Chan et al., 1983; Kuentz and Leuenberger, 2000; Ramirez et al., 2004; Michrafy et al., 2007). In all these studies, several unknown parameters were needed. These parameters are not easily accessible such as characteristic parameters describing intrinsic interaction between particles (Chan et al., 1983) or critical relative density for models using percolation theory (Kuentz and Leuenberger, 2000; Ramirez et al., 2004; Michrafy et al., 2007).

In the same way, a simple model predicting the tensile strength of binary mixtures was developed by Wu et al. (2005). These authors have adapted the Ryshkewitch–Duckworth equation (Duckworth, 1953) in which tensile strength of tablets made from a single compound depended on their porosity, irrespective of the tablet dimensions. Using this approach two mixtures were studied: microcrystalline cellulose (MCC)/hydroxypropylmethyl cellulose (HPMC) and MCC/Starch, each for three compositions (90, 50 and 10 wt% of MCC and 80, 50 and 20 wt% of MCC, respectively). Tablets were produced using an Instron universal testing machine and 800 mg powder samples were compressed into a 13 mm die to a specified compression force ranging from 3 kN to 18 kN (corresponding to a compression load ranging from 22 MPa to 135 MPa). A good estimation of the tablet tensile strength was obtained for the two studied systems with an overestimation of the tensile strength for high relative densities ($\geq$0.85).

The purpose of the present study was to develop a simplified model in order to predict the tensile strength of binary tablets from a local mechanical measurement performed at the surface of the tablet (i.e. hardness) and the tablet density. The performance of the present model was compared to the one developed by Wu et al. (2005). The binary mixture contained anhydrous caffeine as the active pharmaceutical ingredient (API) and microcrystalline cellulose (Avicel® PH-102, FMC Biopolymer) as diluent. This model will be applied to predict the tablet tensile strength of a given system, for all compositions and within a wide range of compression loads.

## 2. Materials and methods

### 2.1. Materials

Two anhydrous caffeine crystalline forms exhibiting an enantiotropic relationship are known and called Form I, stable from about 145 °C to its melting point 236 °C (Pinto and Diogo, 2006) and Form II, stable from room temperature to 145 °C. The material used in this study was caffeine Form I (CFI). It was obtained using the same method than Hubert et al. (2011) (based on the one suggested by Derollez et al. (2005) and Griesser et al. (1999)) as follows. Commercial anhydrous caffeine Form II (purchased from Cooper) was heated to 170 °C in an oven for 24 hours in order to anneal the Form II. Freshly Form I was quickly cooled in liquid nitrogen until room temperature. On each batch a differential scanning calorimetry (DSC) analysis was performed at a heating rate of 10 °C/min from 20 °C to 270 °C and no trace of the transition II → I was found. Microcrystalline cellulose (MCC), Avicel® PH-102, was obtained from FMC Biopolymer. For each pure component the true particle density ($\rho$) was determined using a helium pycnometer (Hubert, 2012).

The particle size distribution for these two materials was measured with AeroS dry dispersion unit (Malvern Instruments, U. K.). Three measurements of the particle size distribution were performed on each powder. The resulting volume density distribution was averaged. Their minimum, mean and maximum diameters (respectively $d_{10}$,$d_{50}$, $d_{90}$) were calculated. Their values with their standard deviations are listed in Table 1.

### 2.2. Tablet preparation

Cylindrical tablets were prepared with a binary mixture of anhydrous caffeine Form I (one day after its manufacture) and MCC as a diluent. These two materials were mixed in various proportions with caffeine content of 0, 10, 20, 30, 40, 50, 60, 78, 90 and 100 wt%. The blending was performed with a tridimensional mixer (Turbula® T2F) at a rotational rate of 49 rpm for 10 min. The homogeneity of the blend was assessed by measuring the caffeine content after mixing by DSC. The measurements were realized in triplicate for each composition (three sampling performed in three positions in the mixing vial). The relative difference between the measure and the theoretical caffeine content was less than 5%. All tablets were made at constant mass (about 300 mg) by using a compaction simulator Styl'One Classic (Medelpharm, Beynost, France) and its data acquisition software (Analis, 2.03 versions, Medelpharm). This tableting press was a single station press where compression was made by the lower punch. The compression forces were measured with an accuracy of 0.5% of full scale, and the displacements of the punches were monitored using Linear Variable Differential Transformers (LVDTs) with an accuracy of 50 μm for the lower punch. Standard Euro D tools with flat-faces and 11.28 mm of diameter were fitted on the simulator. The device deformation (including punch deformation) was taken into consideration and measured before each experiment to correct the values of the displacement. In the present study, tablets were produced with one main compression under three different compression forces (5 kN, 10 kN, 20 kN) corresponding to a pressure of 50 MPa, 100 MPa and 200 MPa, respectively. In the following of this study, these three pressures will be called compression loads.

**Table 1**
Particle size distribution parameters of CFI and MCC ($n$ = 3).

| Powders | $d_{10}$[a] (μm) | $d_{50}$[a] (μm) | $d_{90}$[a] (μm) |
|---|---|---|---|
| CFI | 19.7 ± 0.7 | 67.8 ± 2.1 | 160.5 ± 3.5 |
| MCC | 28.3 ± 0.1 | 119.0 ± 0.0 | 268.7 ± 1.2 |

[a] Average calculated from 3 measurements.