International Journal of Pharmaceutics 472 (2014) 347–355

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Compaction properties of crystalline pharmaceutical ingredients according to the Walker model and nanomechanical attributes

M. Egart [a], I. Ilić [a], B. Janković [a,*], N. Lah [b], S. Srčič [a]

[a] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia
[b] Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 21 April 2014
Received in revised form 24 June 2014
Accepted 25 June 2014
Available online 27 June 2014

Keywords:
Compressibility
Compactibility
Nanoindentation
Walker coefficient
Indentation hardness
Young's modulus

ABSTRACT

This study investigates the extent to which single-crystal mechanical properties of selected active ingredients (famotidine, nifedipine, olanzapine, piroxicam) influence their bulk compressibility and compactibility. Nanomechanical attributes of oriented single crystals were determined with instrumented nanoindentation, and bulk deformational properties were assessed with the Walker and Heckel models as well as the elastic relaxation index. Good correlations were established between bulk and single-crystal plasticity parameters: the Walker coefficient and indentation hardness. The Walker model showed more practical value for evaluating bulk deformational properties of the APIs investigated because their properties differed more distinctly compared to the Heckel model. In addition, it was possible to predict the elastic properties of the materials investigated at the bulk level because a correlation between the elastic relaxation index and compliance was established. The value of using indentation hardness for crystalline APIs was also confirmed because their compactibility at the bulk level was able to be predicted. Mechanically interlocked structures were characteristic of most polymorphic forms investigated, resulting in single crystals having isotropic mechanical properties. It was revealed that in such cases good correlations between single and bulk mechanical properties can be expected. The results imply that innate crystal deformational properties define their compressibility and compactibility properties to a great extent.

1. Introduction

The majority of drug products are solid dosage forms, most of which contain the drug substance in its crystalline state (Katz and Buckner, 2013; Singhal and Curatolo, 2004). Understanding materials' physical, chemical, and mechanical properties is imperative for designing robust solid drug formulations. In all technological processes in which materials are exposed to stress (e.g., milling, roller compaction, and tableting), their mechanical properties are of utmost importance. These properties can be categorized as elastic, plastic, or brittle (Hiestand, 1997; Jain, 1999; Johnson, 1987). Reliable quantification of mechanical properties can be useful for selecting a processing method (i.e., granulation or direct compression) or appropriate excipients in order to improve a blend's poor compressibility, as well as to elucidate defects such as capping or lamination (Amidon et al., 2009; Sun and Grant, 2001) or to avoid unacceptable product damage during the packing procedure and distribution. Compaction properties are mainly governed by compressibility (the ability of the powder to deform under pressure) and compactibility (the ability of the powder to form coherent compacts; Ilić et al., 2013; Khomane et al., 2012; Sonnergaard, 2006). With respect to mechanical properties, a combination of plastic deformation and brittle fracture is desirable and necessary because they are both irreversible and promote tableting (Rasenack and Muller, 2002; Shariare et al., 2012).

Correlations between crystal structure, single-crystal mechanical properties, and powder behavior during processing have mostly been established for milling (Cao et al., 2010; Meier et al., 2009; Perkins et al., 2009; Shariare et al., 2012; Taylor et al., 2004a, 2004b; Zugner et al., 2006). A few attempts have been made to correlate the materials' crystal structure to the tableting performance. Parameters at the crystal level such as slip planes, thermodynamic properties (e.g., heat of fusion), and molecular packaging (e.g., true density) have been correlated with the compressibility and compactibility of pharmaceutical powders (Feng and Grant, 2006; Joiris et al., 1998; Khomane et al., 2012, 2013; Payne et al., 1996; Roberts et al., 1995; Roberts and Rowe, 1996; Sheth and Grant, 2005; Summers et al., 1977; Sun, 2008; Sun and Grant, 2001). The state of the art for predicting a powder's compression properties was set by Roberts and Rowe, who

* Corresponding author. Tel.: +386 1 476 96 17; fax: +386 1 425 80 31.
E-mail address: biljana.jankovic@ffa.uni-lj.si (B. Janković).

http://dx.doi.org/10.1016/j.ijpharm.2014.06.047
0378-5173/

determined deformational properties of pharmaceutical materials according to microindentation hardness, Young's modulus, and yield stress (Roberts and Rowe, 1987). Moreover, pharmaceutical excipients were studied in depth by Govedarica et al. (2012) in a study that predicted bulk plastic and elastic behavior of materials using indentation hardness and Young's modulus.

The objectives of this research study were to estimate and compare the compaction properties of selected APIs (active pharmaceutical ingredients) (famotidine, nifedipine, olanzapine, and piroxicam) at the bulk level by using the Walker and Heckel models. All observations were supported by nanomechanical properties of the single crystals investigated as well as their crystal packaging. Relevant correlations for their compressibility and compactibility were highlighted.

2. Materials and methods

2.1. Materials

Famotidine, nifedipine, olanzapine, and piroxicam were obtained from local suppliers. For bulk studies, commercially available thermodynamically stable forms were used as received. In the case of famotidine, in which the kinetically favored form B is used in drug production, recrystallization was necessary to obtain the thermodynamically stable form A. The solvents (acetonitrile, methanol, benzyl alcohol, ethyl acetate, and acetone) used for recrystallization steps were supplied by Merck (Darmstadt, Germany). Single crystals of specific polymorphic form were prepared according to literature data with certain modifications (Caira et al., 2003; Hassan et al., 1997; Hegedus, 2001; Lu et al., 2007; Overgaard and Hibbs, 2004; Reutzel-Edens et al., 2003; Vrečer et al., 2003). For single-crystal characterization and identification, single-crystal X-ray diffractometry was used. Crystalline powders used for tableting were examined by DSC (differential scanning calorimetry) and FTIR (Fourier transform infrared spectroscopy) in order to confirm the presence of specific polymorphic forms.

2.2. Methods

2.2.1. Assessment of the bulk mechanical properties

To eliminate the influence of particle size on bulk mechanical properties, the materials studied were first ground to approximately comparable sizes. This was confirmed with laser diffractometry (Mastersizer S, Malvern Instruments, Malvern, UK). Water dispersions of powders were prepared and particle size was measured using a small volume dispersion unit. For nifedipine, olanzapine, and piroxicam, a few drops of 1% SDS solution was added to improve powder wettability. In the case of famotidine, whose water solubility is better, acetonitrile (solubility in acetonitrile 0.344 mg/ml) was used as a dispersion medium. All measurements were performed in triplicate.

Bulk mechanical properties were determined by compressing the APIs with a fully instrumented single-punch tableting press (SP300, Kilian, IMA, Cologne, Germany) using round flat-faced punches (d = 12 mm) without a beveled edge. The compression force was measured by full Wheatstone bridge strain gauges at the lower and upper punches, coupled with a linear displacement transducer mounted at the upper punch. Tablets of each sample investigated were compressed at pressures ranging from 30 to 200 MPa at a tableting rate of 25 tbl/min. Raw data were recorded with 20-bit precision at a sampling frequency of 2400 Hz using MS2000 software (Kilian, IMA, Cologne, Germany). Prior to the compression, the punches were lubricated with a 1% w/w suspension of Mg stearate in isopropanol. Tablet mass was determined using a precise analytical balance (Sartorius 1773, Gottingen, Germany). The true density of API powders was measured in triplicate with a helium pycnometer at room temperature (AccuPyc 1330, Micromeritics, Norcross, GA, USA).

2.2.1.1. Compressibility. Compressibility of the polymorphic forms investigated was determined using the Heckel and Walker models. Prior to measurements, the instrumented single-punch tableting press was calibrated as an important step for obtaining reliable force-displacement profiles (Ilkka and Paronen, 1993). Heckel and Walker are empirically based models and differ in the parameter by which they describe compressibility (Rasenack and Muller, 2002). The Walker model (Walker, 1923) relies on change in the tablet's relative volume with respect to compression pressure. The model has been modified by Sonnergaard (1999) such that relative volume has been replaced by specific volume, omitting the unnecessary normalization with true density. The modified Walker–Sonnergaard model is represented by the following equation (Eq. (1)):

$$V' = -w' \times \log P + V'_{sp} \quad (1)$$

in which V' is the specific volume of the tablet, w' (slope) is the Walker coefficient expressing the volume reduction corresponding to one decade change in pressure P, and V'_{sp} is the specific volume at 1 MPa of pressure. Absolute value multiplied by 100 was used as a measure of compressibility because w' is a negative coefficient.

The most frequently applied method in pharmaceutical technology for evaluating compressibility is the Heckel model (Heckel, 1961). In spite of its frequent application, it has received some criticism regarding its accuracy and robustness (Ilić et al., 2013; Sonnergaard, 1999). Heckel developed his model by assuming that powder pore-volume reduction during compression follows a first-order process represented by the following equation (Eq. (2)):

$$\ln\varepsilon = \ln\left(\frac{1}{1-D}\right) = P \times K + A \quad (2)$$

in which D is the relative density of the compact at pressure P, and K and A are constants obtained when plotting $\ln(1/(1-D))$ against applied pressure P. The slope of the linear regression line of the Heckel profile represents the Heckel coefficient (K) by which compressibility or plasticity of powder is assessed, A is associated with the particle rearrangement before deformation, and ε is porosity. The reverse value of the Heckel coefficient is yield pressure (P_y) and is a compression parameter. A high Heckel coefficient indicates a material's propensity towards fragmentation, whereas a low value means that the material is plastically deformable (Nordstrom et al., 2012; Robert and Rowe, 1987).

An in-die or out-die approach can be used for both models. Using the in-die approach, the upper punch displacement, lower punch position, and force of the upper and lower punch are used to calculate tablet dimensions. The machine and punch deformation was experimentally determined to be 10.26 μm/1 kN altogether (Ilić et al., 2011), which was taken into consideration for accurate measurement of both punch positions during loading. The in-die compressibility profile can be determined by compressing only one tablet. These data are obtained under load during compression, when the tablet has not returned the elastic energy stored within. Therefore, the in-die parameter includes the plasticity as well as the elasticity of the material. In-die Heckel coefficients were determined as slopes using linear regression in a range from 20 to 90 MPa, and Walker coefficients at log P between 1.50 and 1.93, corresponding to 32 and 85 MPa, respectively. This range was chosen in order to maintain a high degree of linearity ($R^2 > 0.99$). The in-die Walker and Heckel coefficients were calculated as an average value of three coefficients determined in this range using