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Short communication

A modification of the *Pr* value equation for measuring the compactibility of pharmaceutical materials

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ABSTRACT

Various types of lactose were used to study compactibility using *Pr* [11]. The dependence of *Pr* on the compression pressure, used to produce tablets, makes its comparison very difficult and so this phenomenon was studied in detail. It was demonstrated that *Pr* in its original form is the quotient of two linear functions and has a mathematical dependence on compression force. Therefore, a modification of this equation is proposed (termed *Pr'*) that increases its practical usefulness. The equation for pressure-independent *Pr'* allows for comparison of various materials and/or studies in which different compression pressure values are used, even at low pressures where comparison of *Pr* itself is not feasible.

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1. Introduction

Tablets are by far the most frequently used dosage form due to their advantages for both manufacturer and user. Convenience of administration, accurate dosing, and ease of manufacture make tablets a popular and versatile dosage form [1,2].

The compaction properties of pharmaceutical materials are usually separated into two distinct terms for the sake of clarity. These are compressibility (how a powder deforms under pressure) and compactibility (how well the powder can form cohesive, strong compacts) [3]. Compactibility is associated with tablet hardness, which is routinely measured as a quality-control parameter during industrial tablet production. Tablets must have sufficient mechanical strength to resist crumbling or breaking when being handled or processed, especially during packaging. The mechanical strength of a single tablet, or tablet hardness, is determined by the force needed to crush the tablet diametrically (commonly known as the Brazilian test). This procedure is described in the European Pharmacopoeia (Monograph 2.9.8. Resistance to crushing of tablets) [4]. Tablet hardness is therefore important and has practical relevance.

Tablet hardness is dependent upon tablet dimensions at specific compression pressures, so it is normalized to the geometry of the tablet. This is termed tensile strength (σ_x) and can be calculated using Eq. (1), which is valid for flat faced, round tablets [5]:

$$\sigma_x = \frac{2H}{\pi \times d \times h} \quad (1)$$

where H is the tablet hardness, d is the diameter, and h is the height of the tablet.

There are several different ways to quantify compactibility. The simplest is by a one-point estimate; for example, the minimum pressure needed to make a compact of a certain strength [6]. Alternatively, tensile strength can be calculated at a given pressure [7] or porosity [8]. Most commonly, compactibility is expressed graphically in an *XY*-plot as the relationship between tensile strength and compression pressure (compactibility profile). Several examples have shown that compactibility profiles in their full extension have essentially sigmoid shapes [9,10]. However, there is a distinctly linear segment present in a compactibility profile. This linear part is the most relevant and informative because it shows the increase in tablet tensile strength in relation to compression pressure. The compactibility of a particular material is estimated by the slope (*Cp*) of the linear segment in the compactibility profile and therefore the *Cp* values of various materials can be compared.

Another way to quantify compactibility is through *Pr* value, a model [11] in which the tensile strength is normalized with the specific work of tablet compression (W_{spec}; Eq. (2)):

$$Pr = \frac{\sigma_x}{W_{spec}} = \frac{\sigma_x}{E_2/m} \quad (2)$$

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where σ_x is the tensile strength of a tablet and W_{spec} is specific work expressed as the effective work (E_2) invested in the compression of the unit mass of substance (m). E_2 represents the area of hysteresis between the compression and decompression curves in force–displacement measurements during tablet manufacturing. Using Eq. (2), compactibility can be calculated individually for each tablet (hereafter referred to as the measured one-point *Pr*).

Recently this method has received more attention [12–14]. It has been shown that *Pr* is an effective tool for measuring compactibility and has a positive linear relationship with *Cp*. In fact, *Pr* has proven to have superior discriminative ability among similar substances; however, its main drawback is its dependence upon compression pressure [14]. The purpose of this study was to investigate this dependence and to seek modifications to the *Pr* equation that would improve its practical usefulness.

2. Materials and methods

2.1. Materials

Compactibility of lactose Tablettose® 100 (Meggle Pharma, Germany) was studied. Microcrystalline cellulose (Vivapur® 12, JRS Pharma, Germany) was used as a dry binder and magnesium stearate was used as an anti-adhesive agent. All materials were used as purchased.

2.2. Tablet preparation and compactibility

Tablets consisted of 84% w/w lactose, 15% w/w microcrystalline cellulose (MCC) and 1% w/w magnesium stearate. The additions of MCC and lubricant were necessary to eliminate tablet lamination and sticking to the tableting tools. 126 g of lactose and 22.5 g of MCC were mixed for 8 min in a Turbula mixer (WAB, Switzerland) at 50 rpm. Then 1.5 g of magnesium stearate was added and the blend was mixed for 2 more minutes. Tablets were pressed using a single-punch tableting press Korsch EK0 (Germany), which was mounted with strain gauges and a displacement transducer using 10.0 mm flat punches and compression pressures ranging from approximately 60 MPa to 300 MPa at a tableting speed of 36 tablets per minute. Around 20 tablets were made at each compression pressure. Five or six different compression pressures were used for each material. The diameter, thickness, mass, and hardness of tablets were measured 24 h after tableting. Hardness was measured with a Heberlein 2E/205 (Switzerland) apparatus. Compactibility was measured using the *Pr* value (Eq. (2)) and the tensile strength (σ_x) was calculated using Eq. (1).

3. Results and discussion

In our previous study [14], we observed that the measured one-point *Pr* is dependent upon the maximum compression pressure used to produce the tablet. One-point *Pr* increases with increased compression pressure, and at certain pressures (e.g., around 120 MPa for Tablettose 100) the beginning of a plateau is evident where *Pr* value begins to level off (Fig. 1). This means that when comparing results among various studies, the one-point *Pr* should be reported at its plateau level. This is undesirable from a practical point of view.

Mathematically, one-point *Pr* is calculated as the quotient of tensile strength and specific work. If the tensile strength is measured in its linear segment, then the reason for a non-linear change in *Pr* may originate from the non-linear relationship between specific work and compression pressure. Specific work values may also change depending on tablet mass probably due to different levels of energy dissipation, however, in our experiments,

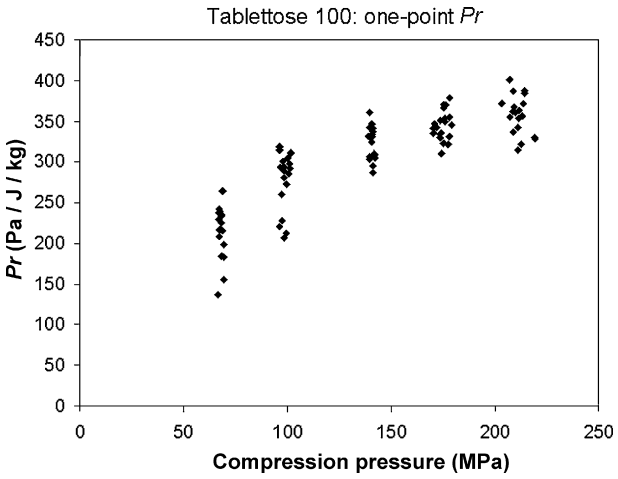

Fig. 1. The compression pressure dependence of one-point *Pr* for Tablettose 100 (each ♦ represents an individual tablet).

tablet mass was kept constant (e.g., 349.0 ± 2.6 mg for Tablettose 100).

Fig. 2 shows how tensile strength and specific work change depending on compression pressure in the case of Tablettose 100. Fig. 2 shows that tensile strength has a linear relationship (R^2 = 0.987) with compression pressure. This was an expected result because earlier research reported that lactose has a wide linear range [15]. However, specific work also yielded a linear relationship (R^2 = 0.986). This means that *Pr* can be expressed as the quotient of two linear functions and should remain independent of compression pressure. Provided, that the two linear functions pass through the origin of the coordinate system, which is not the case here due to the sigmoid nature of tensile strength. Both tensile strength and specific work have a negative apparent *y*-intercept and positive apparent *x*-intercept (shown in Fig. 2 as point ***A*** and ***B***). As compression pressure increases, tensile strength and specific work are less influenced by the apparent negative *y*-intercept and a more realistic and comparable *Pr* can be measured. Fig. 3 represents the plot of calculated *Pr* values (referred to as Pr_{calc}), based on the linear functions of tensile strength and specific work, versus compression pressure. Point ***A*** gives the smallest compression pressure that produced a coherent compact. Points on the graph between ***A*** and ***B*** represent the average one-point *Pr* (n = 19–20) at five different compression pressures. A very good fit between the measured one-point *Pr* and

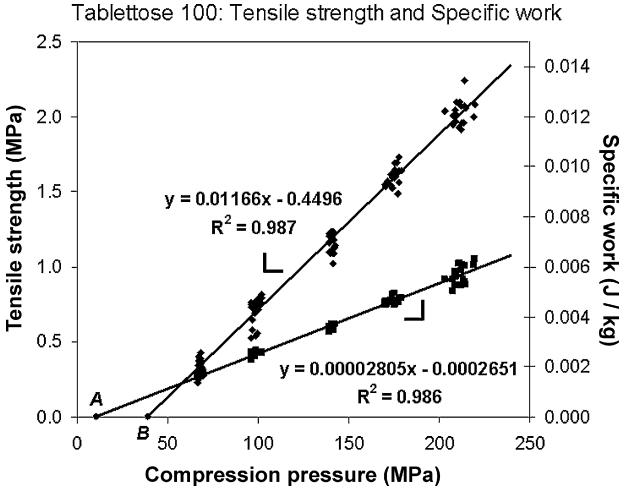

Fig. 2. Tensile strength (♦) and specific work (■) versus compression pressure for Tablettose 100.

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