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Research Article

Validity of a Power Law Approach to Model Tablet Strength as a Function of Compaction Pressure

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Abstract. Designing quality into dosage forms should not be only based on qualitative or purely heuristic relations. A knowledge space must be generated, in which at least some mechanistic understanding is included. This is of particular interest for critical dosage form parameters like the strength of tablets. In line with this consideration, the scope of the work is to explore the validity range of a theoretically derived power law for the tensile strength of tablets. Different grades of microcrystalline cellulose and lactose, as well as mixtures thereof, were used to compress model tablets. The power law was found to hold true in a low pressure range, which agreed with theoretical expectation. This low pressure range depended on the individual material characteristics, but as a rule of thumb, the tablets having a porosity of more than about 30% or being compressed below 100 MPa were generally well explained by the tensile strength relationship. Tablets at higher densities were less adequately described by the theory that is based on large-scale heterogeneity of the relevant contact points in the compact. Tablets close to the unity density therefore require other theoretical approaches. More research is needed to understand tablet strength in a wider range of compaction pressures.

KEY WORDS: compaction; percolation theory; solid dosage form; tensile strength.

INTRODUCTION

The desired state in pharmaceutical research and development is to build quality into products. This approach can, however, not only rely on correlative knowledge and purely heuristic equations, but requires further advancements in the area of mechanistic understanding. Such mechanistic knowledge is currently still limited in many key areas of pharmaceutical technology, as it is for example the case for the relationship of major compaction pressure and tablet strength. Pressure–density relationships are important to find adequate formulations and to define the tableting parameters in a rational way (1). Despite the importance of this functional relationship, its theoretical description is very challenging. The complexity arises from the fact that depending on the material and pressure range used, a specific network of relevant contact points is formed in the tablet. The spatial distribution of these particle contacts as well as their quality mainly define the strength of the evolving tablets (2). Postcompressional changes can add to the complexity (3). Given this inherent complexity of tablet strength, the pioneers Ryshkewitch and Duckworth used a heuristic modeling approach. The compact strength was assumed to decline exponentially with increasing porosity (4,5). An alternative approach used a power law obtained from percolation theory to describe strength as a function of porosity (2). The latter approach has the advantage that a fracture exponent was introduced that could theoretically be explained by means of percolation theory (6). The exponent T_f has a theoretically derived numerical value of 2.7 that is in good agreement with computer simulations (7). Equation 1 displays the proportionality of the tablet's strength σ_T as a function of the relative density ρ, its critical value ρ_c, and the fracture exponent T_f (2):

$$\sigma_T \propto (\rho - \rho_c)^{T_f} \tag{1}$$

The term ρ_c denotes the critical relative density of the tablet, which is needed to exhibit a finite compact strength. This mechanical percolation threshold was further evaluated (8) and the concept was extended to successfully describe the strength of tablets obtained from binary mixtures (9). The study of binary mixtures has been a topic of more recent research and various authors applied different mixing rules (10–14). The reports indicate that in some cases it is possible to predict the tensile strength of multicomponent tablets, whereas it seems far more challenging to find a mathematical relationship applying to all mixtures and pressure ranges.

The present technical note focuses on tablets obtained from low compaction pressures. This low-density range is known to exhibit a high disorder of particle contacts and is

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therefore primarily the range in which the power law of Eq. 1 holds true. In this range, a modified Heckel equation was proposed to describe the relationship of pressure σ_P and relative density including a constant C (15):

$$\sigma_P = \frac{1}{C}\left[\rho_c - \rho - (1-\rho_c)\ln\left(\frac{1-\rho}{1-\rho_c}\right)\right] \quad (2)$$

Equation 2 is the integrated form of a simple differential equation describing the pressure susceptibility of a powder as a critical property (15). Accordingly, this normalized change of porosity with pressure, $-1/\varepsilon(d\varepsilon/d\sigma_P)$ was not considered a constant, as it was previously assumed by the original Heckel model (16). Thus, a better understanding of the compaction process was obtained by this refined model and recently some practical applications were published (17,18).

An older application of this pressure–density relationship was its use in modeling mechanical tablet strength (9). The initial terms of a Taylor series (Eq. 3) were considered around the critical density ρ_c:

$$\sigma_p(\rho) \cong \sum_{n=0}^{2} \frac{\sigma_p^{(n)}(\rho_c)}{n!}(\rho - \rho_c)^n \quad (3)$$

This Taylor expansion of Eq. 2 was combined with the Eq. 1 to result in a simple relationship for the tensile strength of compacts close to the critical relative density (9):

$$\sigma_T \propto \sigma_p^{T_f/2} \quad (4)$$

The above relationship indicates that the compact strength increases at low relative densities with a power of $T_f/2 \cong 1.35$ in accordance with experimental data (9). However, it should be kept in mind that the range of validity is *a priori* limited. We can only expect with porous tablets that a disorder of particle contact points dominates, which is the basis for Eqs. 1, 2, 3, and 4. Such a more than linear increase of strength with compaction pressure is unlikely to occur in a high-pressure range, in which a tablet could rather be viewed as a porous body than a particle packing having voids (19). The high-pressure range also involves further physical aspects like the increased radial stress relief of the ejected tablets that can lead to lamination and capping of more brittle materials. The tablet strength is therefore well known to increase in a less-than-linear way at higher compression forces. Such effects are highly dependent on the nature of the compressed material, as it can be inferred from the data of Davies *et al.* for example (20).

From a practical viewpoint, the use of Eq. 4 requires a better knowledge of its validity range with respect to the compaction pressure. The present article aims to study this range of validity for two types of microcrystalline cellulose and qualities of lactose, as well as mixtures thereof. Finally, a "rule of thumb" should be proposed, indicating up to which pressure or corresponding density the power law applies.

MATERIALS AND METHODS

Materials

The chosen model excipients are widely used in the pharmaceutical industry. The commercial grades Vivapur® 102 and Vivapur® 302 were selected as examples of microcrystalline cellulose. Both excipients were produced by JRS Pharma and obtained from Albert Isliker and Co. Inc. (Zurich, Switzerland). The mean particle size of the two types of microcrystalline cellulose was approximately 100 μm, but their apparent and true densities were different as can be inferred from Table I.

Apart from the microcrystalline cellulose, two agglomerated lactose qualities with different mean particle sizes were used. Tablettose® 70 (mean particle size of about 212 μm) and Tablettose® 80 (mean particle size of approximately 180 μm) were purchased from Meggle Ltd. (Wasserburg, Germany). This company was also the supplier of the commercial blend Cellactose® 80 (mean particle size of roughly 180 μm), which consisted of 75% (*w*/*w*) alpha lactose monohydrate and 25% (*w*/*w*) cellulose powder. All powders were used as received.

Table I shows measured physical characteristics of the excipients and the blends used. The true density of the individual components and of the binary mixtures was determined, using a helium gas pycnometer of the type Multi-Pycnometer® (Quantachrome Ltd. Odelzhausen, Germany). The bulk and tapped densities were analyzed in a graduated cylinder using a type SVM 102 bulk density instrument (Erweka Ltd. Heusenstamm, Germany) and was operated according to USP Method II. Finally, a moisture balance type HB43 (Mettler-Toledo Greifensee, Switzerland) provided the loss of drying (LOD) results of the different materials (Table I).

Tablet Manufacture and Testing

Materials were weighed and added into 500 mL amber plastic bottles and blended for 15 min in a TURBULA T2A shaker-mixer (Willy A. Bachofen AG, Muttenz, Switzerland). The subsequent tableting step was conducted on an instrumented excenter press CPR-6 (Dott. Bonapace, Milano, Italy). The machine had a fixed speed of 2,400 tablets per hour. Materials were filled into the 8 mm die, slightly biconcave punches were used and the maximal load of the force–displacement curve was recorded. To determine the apparent density the diameter and thickness of each tablet was measured. The solid fraction or relative density ρ was subsequently obtained by dividing the tablet's apparent density by its true density.

Compact strength was measured five times for each compaction pressure using a diametric compression tester TBH 220 T of Erweka (Heusenstamm, Germany). According to Fell and Newton the tensile strength of the tablets σ_T was calculated using the following equation (21):

$$\sigma_T = \frac{2F}{\pi dt} \quad (5)$$

where F is the maximum diametric crushing force, d the tablet diameter, and t its thickness.

RESULTS AND DISCUSSION

Tablets with a low relative density cannot be manufactured from all pharmaceutical materials. To obtain highly porous compacts, excipients must show excellent compact-

Table I. Physical Characteristics of the Excipients and the Blends Used

	Bulk density (g/mL)	Tapped density (g/mL)	True density (g/mL)	LOD (%)
Vivapur® 102	0.346±0.006	0.500±0.017	1.533±0.003	4.943±0.035
Vivapur® 302	0.388±0.003	0.552±0.015	1.530±0.000	4.890±0.010
Tablettose® 70	0.533±0.005	0.629±0.008	1.542±0.012	0.047±0.021
Tablettose® 80	0.563±0.006	0.692±0.009	1.539±0.000	0.050±0.017
Cellactose® 80	0.422±0.012	0.520±0.010	1.534±0.003	1.133±0.055
Tablettose® 80: Vivapur® 302 (50:50% *w/w*)	0.468±0.006	0.619±0.000	1.534±0.001	2.467±0.023
Tablettose® 80: Vivapur® 302 (25:75% *w/w*)	0.431±0.004	0.592±0.007	1.535±0.003	3.773±0.035

ability, which was the case for the chosen grades of microcrystalline cellulose in the present study. Another advantage of MCC is its general abundance in tablet formulations; which also applies to lactose. For this reason two agglomerated lactose grades were chosen as additional model excipients.

It was possible to obtain porous tablets with the used excipients and therefore a broad pressure range was covered in this study. The very porous tablets were rather particle aggregates than dense compacts. It can be assumed that in this range the tablets were mainly held together by contact points that could exhibit different qualities depending on the local pressure and geometry. Local deformation was expected to lead to new adjacent surface areas. Such generation of surface area can result in microscopic strength, caused by Van der Waals forces or hydrogen bonding. The macroscopic tensile strength on the other hand was a property that strongly depended on the geometric distribution of the relevant contact points in the tablet. For Eq. 4 to be applicable to the tensile strength of tablets, such a network of relevant contact points must be disordered (2).

To check the validity of the power law (Eq. 4), the strength data were transformed to obtain a theoretical linearity as a function of compaction pressure. Figures 1, 2, 3, and 4 show the data for which an inverse power of the tensile strength exponent (i.e. $2/T_f$) was applied for a theoretical linearization with pressure. The validity range was then inferred from the initial linear range. Microcrystalline cellulose 102 (Fig. 1a) obeyed the power law very well up to about 90 MPa with a very high regression coefficient (R^2= 0.997). For higher values a clear deviation was observed. This upper range displayed an increase of tensile strength that was lower than predicted by the power law. Such a deviation can to a certain extent be explained by a decrease of contact point disorder that was, however, not the only reason for the limitation of the validity range.

Interestingly, the power law of Eq. 1 was earlier found to have a quite broad validity range in terms of the density (2). A reason for the more confined range in the present study lies in the derivation of Eq. 4. Thus, a pressure–density relationship was introduced and instead of the complex Eq. 2, only a Taylor approximation was calculated. Therefore, this density relationship is also only accurate at low relative densities and further limits the range of the strength power law (Eq. 4).

The microcrystalline cellulose grade Vivapur® 302 also showed two distinct ranges (Fig. 1b). Optimal linear regressions were observed up to nearly 100 MPa corresponding to about 27% porosity. The excellent regression (R^2=0.996) agreed well with the theoretical concept of the low-density tensile strength. Adding more data to the regression line produced lower R^2 values and also the residuals indicated an increasing deviation from the theoretical model.

The lactose tablets generally provided a slightly lower fitting adequacy compared to microcrystalline cellulose tablets. However, the transformed data of Tablettose® 70 still displayed linearity up to about 140 MPa (≅25% porosity; Fig. 2a). Interestingly, a positive intercept was obtained for both types of agglomerated lactose. This observation was in line with a previous report, in which an initial cohesion σ_0 was added to the power law of Eq. 1 (8). Certainly the network of relevant contact points is mainly formed during the compression process, however, extrapolation to zero pressure may still result in notable initial bulk cohesion, as it was shown in case of the lactose grades.

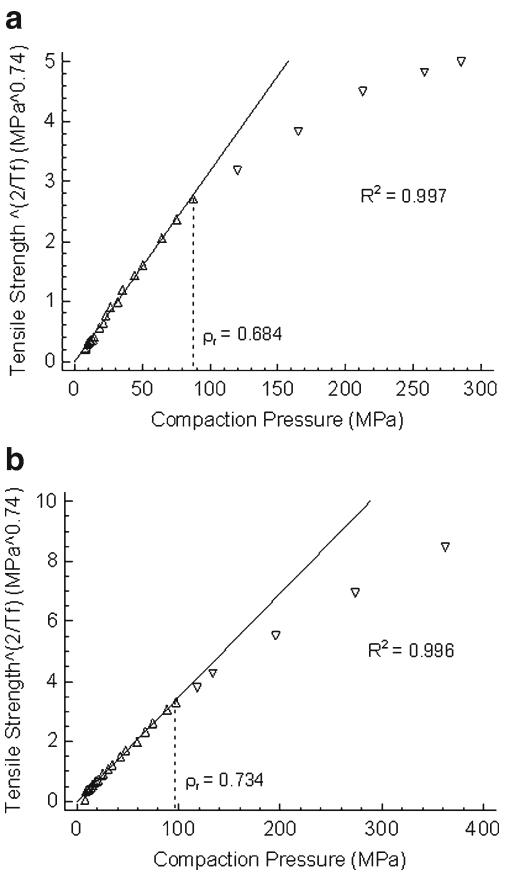

Fig. 1. Linearization of the tensile strength data according to Eq. 4: **a** Vivapur® 102 and **b** Vivapur® 302

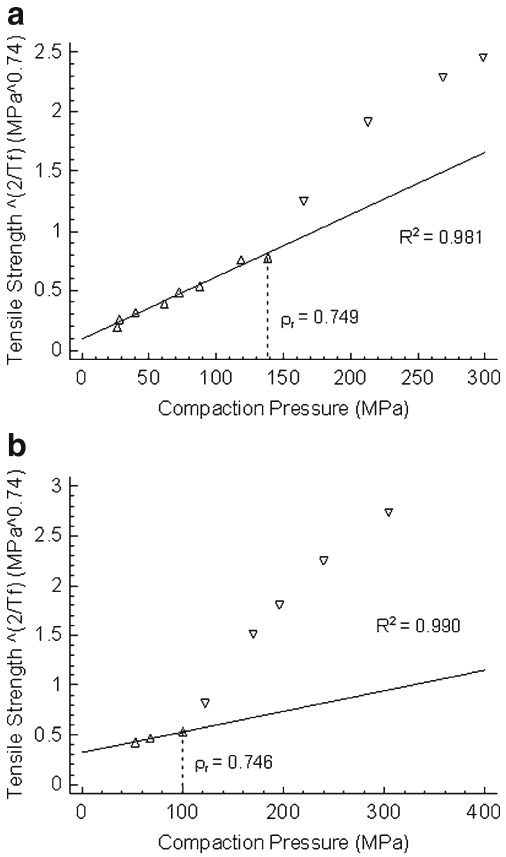

Fig. 2. Linearization of the tensile strength data according to Eq. 4: **a** Tablettose® 70 and **b** Tablettose® 80

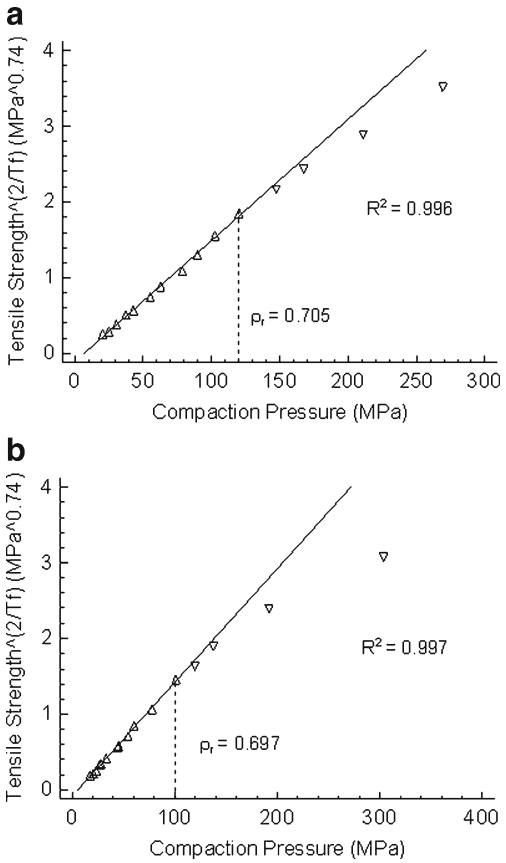

Fig. 3. Linearization of the tensile strength data according to Eq. 4: **a** Cellactose® 80 and **b** Tablettose® 80: Vivapur® 302 (50:50% *w*/*w*)

It was also remarkable that the higher compaction range exhibited a model deviation towards higher tensile strengths (Fig. 2), which was not observed with microcrystalline cellulose. The untransformed tensile strength data even showed two different ranges of the compaction pressure.

We know that in general lactose and microcrystalline cellulose show different compaction mechanisms. Lactose particles tend towards fragmentation; whereas cellulose shows predominantly plastic deformation characteristics (22,23).

The excipient Tablettose® mainly consists of aggregated α-lactose monohydrate crystals (22), exhibiting a comparatively high bulk volume (Table I), which in itself limited the range of tablets that can be obtained at low densities. Yet the abrupt end of the low-density range was most likely because of a change in the compaction mechanism, due to fragmentation of the α-lactose agglomerates. It can be well imagined that the generated smaller particles also suddenly increased the surface bonding area, thus strongly promoting an increase in tablet strength at higher pressures, marking the end of a low-density range.

The existence of two distinct ranges was particularly well observed using Tabletose 80, which had the slightly higher bulk density compared to Tablettose® 70 (Table I). Compaction pressures above 100 MPa were already beyond the validity range of the power law (Eq. 4). The limiting porosity was very similar to Tablettose® 70 showing analogous densification processes. However, subtle differences in the particle packing of the various grades (Table I) resulted in altered compaction ranges since the pressure is a response to the individual packing characteristics.

It was also interesting to study mixtures of lactose and microcrystalline cellulose. A commercially available blend is Cellactose® 80 and the compact strength is shown by Fig. 3a. Even though this blend contains 75% (*w*/*w*) α-lactose monohydrate, the presence of 25% (*w*/*w*) cellulose powder must be responsible for the altered compaction mechanism. Qualitatively, the strength increased in a similar way as observed for the pure microcrystalline cellulose. The power law described again very well the strength data, with a limiting pressure around 120 MPa (≅30% porosity).

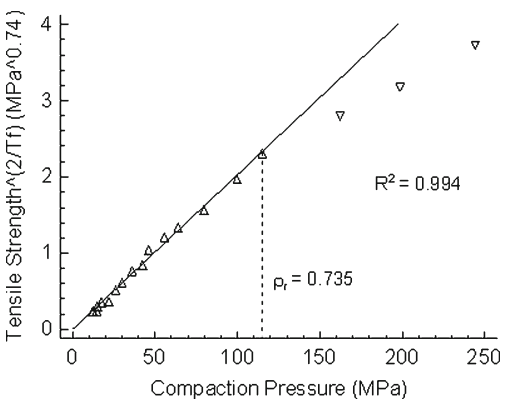

Fig. 4. Linearization of the tensile strength data according to Eq. 4: Tablettose® 80: Vivapur® 302 (25:75% *w*/*w*)

The observation of prevailing cellulose effects in Cellactose® 80 was also observed in a 50% (*w*/*w*) blend of lactose (Tablettose® 80) and microcrystalline cellulose 50% (*w*/*w*). The pressure–strength curve is depicted in Fig. 3b. A power law according to Eq. 4 excellently described the data up to a porosity of ≅30%, which corresponded to a pressure of about 100 MPa. Finally, tablets with a lactose mixture containing 75% (*w*/*w*) microcrystalline cellulose were also studied. Figure 4 shows that the power law was again found to adequately describe the strength data at low densities. For tablets with a porosity of higher than ≅27%, an R^2 value of 0.994 was calculated. At higher pressures, a deviation from the theoretical model was again recorded.

Summarizing the obtained results, it was difficult to propose a general rule for the range of power law validity (Eq. 4). This range was highly dependent on the individual excipient or blend characteristics. However, as a rule of thumb the power law behavior was able to adequately describe the strength of tablets up to about 30% porosity. In our examples the tablets below a pressure of roughly 100 MPa generally obeyed the theoretical power law. In case of the lactose grades an initial cohesion σ_0 was significant, which agreed with a previous report (8). Most remarkable was the fitting adequacy in all cases keeping in mind that the fracture exponent is a theoretical prediction (2). The power law therefore provides a semi- heuristic equation, because the proportionality constant in Eq. 4 was not theoretically predicted, but must be experimentally adjusted.

CONCLUSIONS

The present article studied the validity range of a tensile strength power law as a function of the compaction pressure. The theoretical power law described accurately the evolving compact strength for tablets of different types of microcrystalline cellulose, agglomerated lactose, and blend thereof. The validity range was not universal for the different materials, but as a rule of thumb, tablets with higher than 30% porosity or tablets being compressed below 100 MPa were well explained by the power law. Some tablets obtained at higher pressures may also be acceptably described by the power law, but in all cases a deviation from the theoretical model was observed, once the tablets were considerably more compacted. This was theoretically expected since tablets show less heterogeneity at higher densities and therefore a theoretical percolation approach is in this range less appropriate. However, other theoretical concepts may explain the tablet behavior in the high-pressure range. Close to the unity density, opportunities arise to describe the tablet as a rather homogenous body and theoretical concepts may start from the mechanical properties of the single crystals. In the future, this may be one approach to have theories at hand that are able to explain the tensile strength of tablets in different pressure ranges. More research is therefore needed to improve the mechanistical understanding of the strength formation in tablets. It may not be enough to rely entirely on heuristic equations aiming at predicting the tablet strength for given systems. Purely heuristic equations are entitled to their own right in the control space and design space of a quality by design concept. However, the embedding knowledge space should be based on at least some mechanistic knowledge. The more we understand the compact strength and other tablet properties, the better it is possible to built quality into this important dosage form.

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