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General and mechanistic optimal relationships for tensile strength of doubly convex tablets under diametrical compression

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ABSTRACT

We propose a general framework for determining optimal relationships for tensile strength of doubly convex tablets under diametrical compression. This approach is based on the observation that tensile strength is directly proportional to the breaking force and inversely proportional to a non-linear function of geometric parameters and materials properties. This generalization reduces to the analytical expression commonly used for flat faced tablets, i.e., Hertz solution, and to the empirical relationship currently used in the pharmaceutical industry for convex-faced tablets, i.e., Pitt's equation. Under proper parametrization, optimal tensile strength relationship can be determined from experimental results by minimizing a figure of merit of choice. This optimization is performed under the first-order approximation that a flat faced tablet and a doubly curved tablet have the same tensile strength if they have the same relative density and are made of the same powder, under equivalent manufacturing conditions. Furthermore, we provide a set of recommendations and best practices for assessing the performance of optimal tensile strength relationships in general. Based on these guidelines, we identify two new models, namely the *general and mechanistic models*, which are effective and predictive alternatives to the tensile strength relationship currently used in the pharmaceutical industry.

1. Introduction

Pharmaceutical tablets are fabricated by pressing powders into various shapes and geometries. It is important to assure that tablets have sufficient strength to endure post-compaction loading such as coating, packaging, handling and storage. Tablet strength is thus an important quality factor that is tested during tablet production (USP, 2011). There have been many efforts to establish destructive and non-destructive techniques to determine the mechanical strength of compacted powders (see, e.g., (Podczeck, 2012) and references therein). Among these experimental techniques, the diametrical compression test, also referred to as Brazilian test (Carneiro and Barcellos, 1953), is the most conventional method used in the pharmaceutical industry to measure the breaking force of a tablet. The test consists in placing and compressing a tablet along its diameter between two rigid platens. Under the assumption of linear elastic behavior followed by brittle failure (Timoshenko and Goodier, 1970), the breaking force of a cylindrical tablet can be related to its tensile strength by the following expression, known as Hertz solution,

$$\sigma_t = \frac{2F}{\pi D t} \tag{1}$$

where σ_t is the tensile strength, F is the breaking force, D is the diameter of the tablet, and t is its thickness as shown in Fig. 1(a). The above expression is only valid for flat cylindrical tablets that fail in tension across the symmetry plane of the loaded diameter. It bears emphasis that all compacted powders are brittle (Stanley, 2001) and, in sharp contrast to ductile materials, they do not exhibit significant permanent deformations before failure.

Tensile strength and breaking force increase exponentially with increasing relative density for typical pharmaceutical powders, tableting speeds and tablet shapes (see, e.g., Tye et al. (2005), Sinka et al. (2009), Haririan and Newton (1999)). In addition, the breaking force exhibits a strong dependence on the shape of the tablet and only a mild dependence on the diametrical compression speed. Unfortunately, and in sharp contrast to flat faced tablets, there is no closed-form analytical solution that relates tensile strength and breaking force for curved faced tablets (cf. Eq. (1)). In order to amend this situation, Pitt et al. (1989) used a photoelastic method to measure the stress distribution of doubly convex tablets subject to

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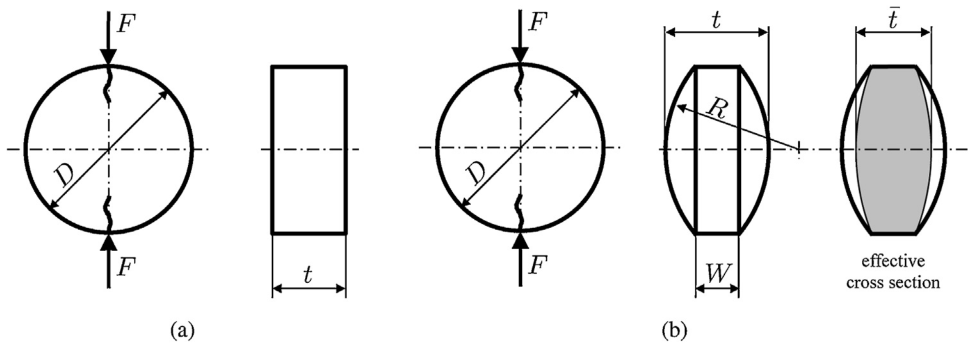

Fig. 1. Geometry and failure behavior (a) in a flat faced cylindrical tablet and (b) in a doubly convex tablet under diametrical compression.

diametrical load. For doubly convex cylindrical gypsum discs, they established the following empirical relationship (Pitt et al., 1988) between geometric parameters, breaking force and tensile strength

$$\sigma_t = \frac{10F}{\pi D^2[2.84(t/D) - 0.126(t/W) + 3.15(W/D) + 0.01]} \quad (2)$$

where W is the length of the cylindrical portion of the tablet (see Fig. 1(b)). This equation is valid for any brittle doubly convex disc with $0.1 \leq W/D \leq 0.3$, and also for discs with $W/D = 0.06$ and $D/R < 1.0$. However, it is worth noting that Pitt's equation (2) does not reduce to the Hertz solution (1) when the geometric parameters correspond to those of a flat faced tablet. Pitt and Heasley (2013) subsequently modified Eqs. (1) and (2) to be applicable for elongated tablets by multiplying both equations by a factor of 2/3—this factor is exact only for the limiting case of large length to width ratios.

Shang et al. (2013a) adopted the form of Pitt's original equation and calibrated its empirical coefficients to an extensive experimental campaign of doubly convex microcrystalline cellulose tablets with various curvatures and of various relative densities. Specifically, they fit experimental measurements to

$$\sigma_t = \frac{F}{\pi D^2[a(t/D) + b(t/W) + c(W/D) + d]} \quad (3)$$

where a, b, c, and d are empirical coefficients (see Table 1 for numerical values). This equation, which from now on is referred to as the *4-parameter model*, has the same application space as Pitt's equation but shows a better fit to experimental data. They also simplified (3) by observing that there are only two independent geometric parameters (e.g., t/D and W/D) and that the correct limiting behavior for flat geometries can be enforced analytically. Thus, they proposed

$$\sigma_t = \frac{F}{\pi D^2[a(t/D) + c(W/D)]} \quad (4)$$

which we refer to as the *1-parameter model*, where $a = 0.14$ and $c = 0.5 - a = 0.36$ are empirical parameters. It is interesting to note that Shang et al. (2013b) reported that the optimal values for a and c do not necessarily sum up to one-half (i.e., they do not enforce the correct limiting behavior in (4)) when calibrated to detailed finite element numerical results (e.g., $a = 0.187$ and $c = 0.284$ are proposed). Furthermore, and in contrast to Shang's results, Podczeck et al. (2013) calibrated finite element simulations to $a = 0$ and $c = 0.5$, for doubly convex geometries with $0.06 \leq W/D \leq 0.5$ and $D/R \leq 1.85$ which fail in accord with Fig. 1(b). These results suggest that the elucidations of optimal tensile strength relationships and optimal procedures to calibrate their parameters are important areas worthy of further research.

In the present work we propose a general framework for determining optimal relationships for tensile strength of doubly convex tablets under diametrical compression. This approach is based on the observation that tensile strength is directly proportional to the breaking force and inversely proportional to a non-linear function of geometric parameters and materials properties. Under proper parametrization, the tensile strength relationship can be determined from experimental results by solving an optimization problem that minimizes a figure of merit of choice. Based on this general framework, we develop three new optimal tensile strength relationships and three different figures of merit to determine their optimal parameters. We also provide a set of guidelines for assessing the performance of optimal tensile strength relationships, with which we compare the new models with two models previously proposed in the literature (i.e., Eqs. (3) and (4)). This analysis reveals that two of the new models, namely the general and mechanistic models, are effective and predictive alternatives to the tensile strength relationship currently used in the pharmaceutical industry.

2. Materials and methods

In the current study, microcrystalline cellulose MCC (Batch no. 1H59965, Avicel Ph102, FMC biopolymer, Newark, DE) was employed. The true density of the pure MCC was provided by the manufacturer and equal to 1540 kg/m^3 and the original powder has particle sizes between 0.23 μm and 700 μm.

Tablets were manufactured using a 10 mm flat faced B tooling in a linear compaction emulator (Presster, Metropolitan Computing Corp., NJ) to simulate a Fette2080 press. A dwell time of 28.88 ms, corresponding to a production speed of 38,700 tablets per hour, was used. Tablets were stored for two weeks at ambient room temperature and inside a sealed, clear plastic bag prior to the determination of the breaking force. The thickness and diameter of the tablets were carefully measured by a digital caliper (±0.01 mm, Absolute digimatic Caliper), and the weight was recorded by a precision balance (±0.001 g, Adventurer Ohaus). From these measurements, the volume and bulk density of tablets were calculated. The tablets were diametrically compressed using an Instron testing machine at a loading rate of 10 mm/min (see Table A.2 in the appendix for numerical values). All tablets exhibited failure under pure tensile stress with no significant permanent deformations during diametrical loading—verifying the assumption of brittle fracture.

3. Results

3.1. Optimal tensile strength relationships

The tensile strength σ_t is related to the breaking force F under diametrical compression by the following general equation

$$\sigma_t = \frac{F}{\pi D^2 Q} \quad (5)$$

Table 1
A comparison of existing models according to their optimal coefficients, 90% confidence intervals and residual errors obtained from each figure of merit, for all flat and doubly convex tablets. ($\underline{o}$ indicates that o is an assumption.)

Models	a	b	c	d	e	f	g	σ-norm	Q-norm	$Q\sigma$-norm
Pitt's (1988)	0.284	0.0126	0.315	0.001	$\underline{1}$	$\underline{1}$	$\underline{1}$	14.96	0.469	2.26
1-parameter (2013a)	0.14	$\underline{0}$	$\frac{1}{2}-a$	b	$\underline{1}$	–	$\underline{1}$	–	0.260	–
1-parameter	0.1717 ± 4.9 %	$\underline{0}$	$\frac{1}{2}-a$	b	$\underline{1}$	–	$\underline{1}$	–	0.236	–
1-parameter	0.1612 ± 4.2 %	$\underline{0}$	$\frac{1}{2}-a$	b	$\underline{1}$	–	$\underline{1}$	8.11	–	–
1-parameter	0.1530 ± 4.8 %	$\underline{0}$	$\frac{1}{2}-a$	b	$\underline{1}$	–	$\underline{1}$	–	–	1.07
4-parameter (2013a)	0.227	−0.00432	0.117	0.0192	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	0.191	–
4-parameter	0.2256 ± 10 %	−0.0033 ± 60.4 %	0.142 ± 23.7 %	0.0192 ± 36.5 %	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	0.164	–
4-parameter	0.1224 ± 22.9 %	0.0079 ± 46.2 %	0.3267 ± 15.1 %	−0.0055 ± 170.2 %	$\underline{1}$	$\underline{1}$	$\underline{1}$	6.22	–	–
4-parameter	0.1625 ± 14.7 %	0.0027 ± 94.6 %	0.2595 ± 15 %	0.0029 ± 294.2 %	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	–	0.772

where Q is a nonlinear function of geometric parameters and material properties. For example, for flat faced elastic isotropic cylindrical tablets, $Q = t/2D$ when the tablet is under concentrated loads (Timoshenko and Goodier, 1970) and $Q = t/2D[1-(b/D)^2]^{3/2}$ when the tablet is under loads uniformly distributed on a stripe of width b (Tang, 1994). Analytical expressions for Q can also be derived under the assumption of radial pressures acting on the tablet (see, e.g., (Hondros, 1959) for uniform radial pressure and (Kourkoulis et al., 2012) for parabolic radial pressure) and for flattened cylinders subject to uniform diametrical compression (Wang et al., 2004). The function Q may additionally account for the effect of anisotropy (Bagault et al., 2013) and plastic behavior (Procopio et al., 2003), among other material behavior. It may also account for the lack of plane stress conditions, and the size and shape of the tablet, among other geometric characteristics.

For given powder and manufacturing conditions, we firstly presume that the tensile strength σ_t depends on the relative density ρ_R, the size s, and shape S of the tablet,

$$\sigma_t := \sigma_t(\rho_R, s, S) \qquad (6)$$

Basically, there is an inevitable variability in the strength of tablets with same size, shape and relative density distribution. In addition, the relative density distribution depends on the shape of the tablet. These factors will statistically condition the spatial distribution and severity of the microscopic and material defects within the region of the tablet subject to the higher stresses where fracture will initiate and propagate from (Stanley, 2001).

Here, as a first order approximation, we assume that σ_t is a material property that solely depends on ρ_R of the tablet, for given powder and manufacturing conditions, as also shown in Tye et al. (2005) and Iyer et al. (2013). To this end, several assumptions are taken into consideration. First, the spatial distribution of density is assumed to have a second order effect. Second, the size-dependency of tablet strength is not taken into account for flat and doubly convex tablets with very similar diameters. This simplification is based on the observation that the region of the tablet subject to the higher stresses under diametrical compression is centered in the cross section. Third, the variability of tablet strength is assumed negligible, that is the Weibull modulus m of the material (i.e., a reciprocal measure of the strength variability of the brittle material) is assumed to have a very large value and thus the distribution of measured strength to be very narrow.

The function $\sigma_t(\rho_R)$ can then be readily obtained from an experimental campaign of flat faced cylindrical tablets. We also assume that Q is strictly a geometric function, for given powder properties or manufacturing variables. Based on such assumptions, the function Q can be determined from experimental results by solving the following optimization problem

$$\min_{Q:\mathcal{S}\to\mathbb{R}} \left[\sum_{\{S_i,\rho_i\}\in\mathcal{S}\times\mathcal{D}} \left(\sigma_t(\rho_i) - \frac{F_i}{\pi D_i^2 Q(S_i)} \right)^2 \right]^{1/2} =: \min_{Q:\mathcal{S}\to\mathbb{R}} \sigma - \text{norm}$$

where $\mathcal{S}$ is the space of all possible tablet shapes that fail in tension under diametrical compression, $\mathcal{D}$ is an interval of tablet relative densities (e.g., from the smallest density at which a solid tablet free of macroscopic defects is formed, to full compaction or relative density of 1.00), and D_i is the diameter of shape S_i along which the breaking force F_i is applied. In the above expression, $\sigma_t(\rho_i)$ obtained from a flat faced cylindrical tablet made with the same powder and under the same manufacturing conditions is employed for making the tablet with shape S_i and relative density ρ_i. Alternatively, the function Q can be determined by solving any of the following equivalent problems

$$\min_{Q:\mathcal{S}\to\mathbb{R}} \left[\sum_{\{S_i,\rho_i\}\in\mathcal{S}\times\mathcal{D}} \left(Q(S_i) - \frac{F_i}{\pi D_i^2 \sigma_t(\rho_i)} \right)^2 \right]^{1/2} =: \min_{Q:\mathcal{S}\to\mathbb{R}} Q - \text{norm}$$

$$\min_{Q:\mathcal{S}\to\mathbb{R}} \left[\sum_{\{S_i,\rho_i\}\in\mathcal{S}\times\mathcal{D}} \left(Q(S_i)\sigma_t(\rho_i) - \frac{F_i}{\pi D_i^2} \right)^2 \right]^{1/2} =: \min_{Q:\mathcal{S}\to\mathbb{R}} Q\sigma - \text{norm}$$

It bears emphasis that these equivalent optimization problems determine Q by enforcing Eq. (5), that is they determine an optimal tensile strength relationship. If there were no experimental uncertainty and the second order effects mentioned above were negligible, these three optimization problems behaved similarly and had the same solution. However, in reality, experimental uncertainty is unavoidable and the form of Q has to be approximated and parametrized. Thus, our goal is to find the optimal form for Q and the most stable optimization problem to determine its fitting parameters (i.e., for example, the minimization of the Q-norm, the σ-norm or the $Q\sigma$-norm).

In the interest of applicability, we restrict attention to doubly convex tablets whose shapes can be parametrized by t/D, t/W, and W/D as depicted in Fig. 1(b). Specifically, we consider MCC tablets for which Shang et al. (2013a) have obtained the relationship between tensile strength and relative density using flat faced tablets (see Fig. 2 and Table A.1 in the Appendix for the numerical values extracted from (Shang et al., 2013a)). The experimental data is best fit to an exponential function, that is

$$\sigma_t = A e^{B\rho_R} \qquad (7)$$

where $A = 24.68$ kPa and $B = 6.516$. Shang and co-workers have additionally reported results for an extensive experimental campaign

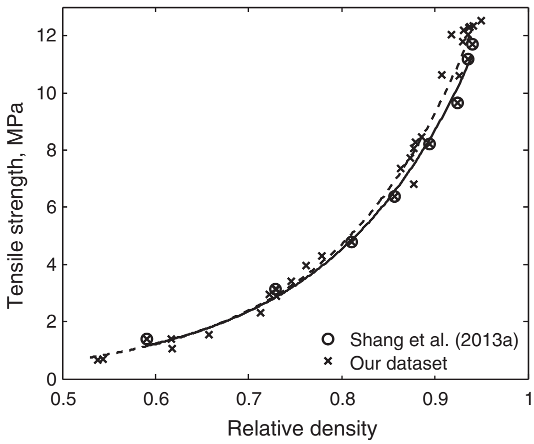

Fig. 2. Relationship between tensile strength and relative density of flat faced tablets. According to Eq. (7), A and B are 24.68 kPa and 6.516 for the full curve and 20.65 kPa and 6.787 for the dashed curve, respectively.

of doubly convex tablets with various curvatures and of various relative densities. The relative density of each tablet is computed by dividing the tablet density over the material true density, i.e., 1590 kg/m^3 for microcrystalline cellulose (Shang et al., 2013b).

For the sake of simplicity, we assume a form for Q that only captures the leading order term of each geometric parameter, that is

$$Q = a\left(\frac{t}{D}\right)^e + b\left(\frac{t}{W}\right)^f + c\left(\frac{W}{D}\right)^g + d$$

with the constraint that $Q \to t/2D$ as $W \to t$, in order to enforce the correct limit for flat tablets. Thus, the relationship between tensile strength, breaking force and geometric parameters, i.e., Eq. (5), simplifies to

$$\sigma_t = \frac{F}{\pi D^2[a(t/D)^e + b(t/W)^f + c(W/D)^g + d]} \tag{8}$$

where the parameters $\{a, b, c, d, e, f, g\}$ are either assumed known or optimally estimated from a set of experimental observations (e.g., Shang's dataset (Shang et al., 2013a)) using different figures of merit (e.g., σ-norm, Q-norm, and $Q\sigma$-norm). If $e = f = g = 1$, the 4-parameter model is recovered, i.e., Eq. (3). However, if Pitt's coefficients are used in the 4-parameter model then the correct limit for flat tablets is not attained, indicating that there is a different set of coefficients that further minimizes the problem presented above. Similarly, if $b = 0$, $c = 1/2 - a$ and $e = g = 1$, the 1-parameter model is recovered, i.e., Eq. (4). Table 1 summarizes the optimal values for the parameters of these two particular forms of Q when determined from the dataset reported in Shang et al. (2013a) using MATLAB multistart algorithm (MATLAB, 2012) and each of the three figures of merit. In addition, the 90% confidence bound of each optimal parameter and the residual error obtained from each optimization are reported in the table. It bears emphasis that the optimization is performed under the assumption that a flat faced tablet and doubly curved tablet have the same tensile strength if they have the same relative density. The minimization of the Q-norm has been used by previous authors and therefore the corresponding fitted parameters are close to those reported in Shang et al. (2013a). It is interesting to note that our optimal values for the parameters result in a smaller residual error than that obtained with previously reported values. This may be attributed to the good performance of the multistart algorithm employed or to rounding errors in the values of $\sigma_t(\rho_R)$ retrieved from Shang et al. (2013a). In the case of the 4-parameter model, the improvement over Pitt's equation is evident. These results also reveal that the 1-parameter model leads to a well-defined stable optimization problem (i.e., error bounds are small and solutions are less sensitive to the figure of merit) and that the 4-parameter model leads to a better physical description of the tensile strength (i.e., the residual errors are systematically smaller than those obtained with the 1-parameter model).

It is important to note that the fidelity and robustness of these optimal tensile strength relationships can be further improved by: (i) considering a more general, mechanistically informed expression for Q, (ii) extending the size and variety of the experimental dataset, (iii) restricting attention to those tablets which failed under pure tensile stress (see, e.g., (Shang et al., 2013a,b; Podczeck et al., 2013) for other failure mechanisms). These three aspects are examined next in turn.

3.1.1. General model

The correct limit of Q for flat tablets, i.e., $Q \to t/2D$ as $W \to t$, can be imposed analytically by writing Eq. (8) as follows

$$\sigma_t = \frac{F}{\pi D^2[a(W/D)^e + b(t/W)^f + 1/2(t/D) - a(t/D)^e - b]} \tag{9}$$

where $\{a, b, e, f\}$ are the fitting parameters. We note that (9), referred to as the *general model*, not only exhibits the correct limit for flat geometries and captures the leading order behavior of Q but it also reduces the dimension of the search space from 7 to 4. Coincidentally, the general model and the 4-parameter model (i.e., any re-calibration of Pitt's equation) have a search space of dimension 4. Therefore, the general model requires a computation effort for the optimization of its parameters similar to that of previous models but it allows for a better physical description of the tensile strength. Moreover, by imposing $e = f = 1$ on (9)—or the correct limit on (3)—a new *2-parameter model* is recovered

$$\sigma_t = \frac{F}{\pi D^2[a(t/D) + b(t/W) + (1/2 - a)W/D - b]} \tag{10}$$

where $\{a, b\}$ are the fitting parameters.

In order to assess the behavior of the proposed models, we restrict attention to those tablets with diameter $D = 10.318$ mm reported in (Shang et al., 2013a) which exhibited crack formation and propagation under pure tensile stress. Specifically, we excluded ball ($D/R = 1.842$), extra deep ($D/R = 1.374$) and some deep tablets ($D/R = 0.988$) having $W/D \approx 0.2$ and $t/D \approx 0.45$. The optimal values for the parameters of the 1-parameter (4), 2-parameter (10), 4-parameter (3) and general (9) models are reported in Table 2. Confidence bounds and residual errors are also reported in the table.

The residual errors for 1-parameter and 4-parameter models are noticeably reduced in comparison to Table 1, confirming that those tablets that did not fail under tensile stress should not be included and treated as the rest of the tablets. Furthermore, it is evident from the table that the 2-parameter outperforms the 1-parameter model, suggesting that t/W is required in the expression for Q—though perhaps to a power f different from 1. Finally, the 4-parameter and the general models have very similar residual errors for all three figures of merit and, in particular, the 4-parameter model exhibits a better performance for the Q-norm.

This last observation provides additional insight into the role of flat faced tablets in the optimization process. The 4-parameter model does not have the correct limiting behavior for flat faced tablets. However, only 5.7% are flat faced tablets in the dataset and thus their contribution to the overall residual error is negligible. In other words, the optimization process reduces the error for doubly convex tablets in detriment to the predictability of the model for shallow/flat tablets. Specifically, the 4-parameter model exhibits, in average, a 65% larger error for flat faced tablets and a 5% smaller error for curved tablets than the general model. The inclusion of

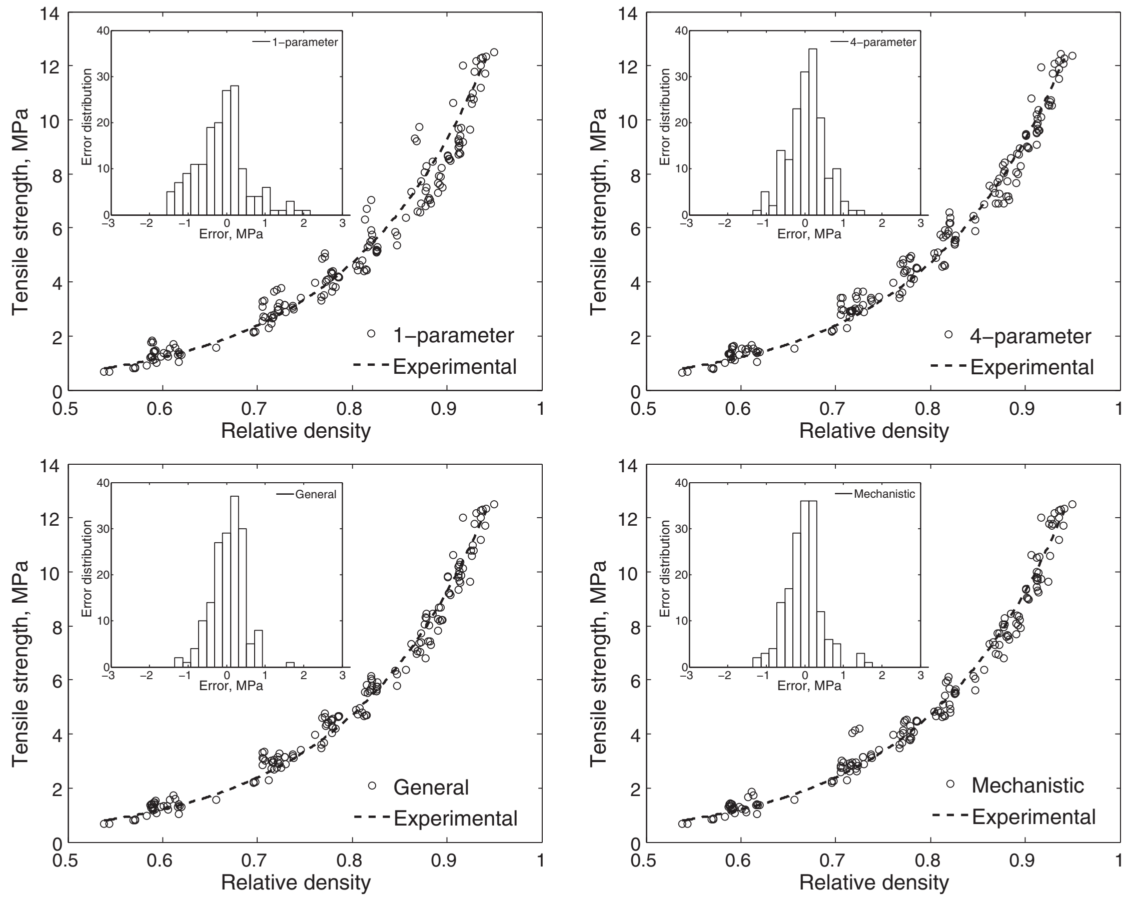

Fig. 3. The relationship between tensile strength and relative density of the experimental data using σ – norm along with their corresponding error distribution.

more flat tablets in the dataset may, however, have the opposite effect. We further study this issue in the next subsection.

3.1.2. *Role of flat faced tablets in the optimization process*

We extended the experimental dataset in Shang et al. (2013a) with a new series of tests on flat faced tablets. Specifically, 28 flat tablets of pure MCC were manufactured according to the description explained in Section 2. The new fitting parameters to the exponential function (7) are A = 20.65 kPa and B = 6.787, as depicted in Fig. 2. We specifically tested few tablets with relatively low and high relative densities to capture a wider range. Even though, the manufacturing conditions were different, the two fitting exponential curves are very close to each other. Thus, combining the data points is acceptable for the purpose of this study.

Table 3 shows the optimal values for the parameters of the 1-parameter (4), 2-parameter (10), 4-parameter (3) and general (9) models when calibrated with the extended experimental campaign. Flat faced tablets now represent 21.3% of the total number of tablets (cf. 5.7% in the previous section). In contrast to results in Table 2, the general model exhibits smaller residual errors than those of the 4-parameter model for all the figures of merit. This result confirms that, by including more flat faced tablets in the dataset, the limiting behavior of the 4-parameter model is improved only in detriment of its overall behavior. Specifically, the 4-parameter model now exhibits, in average, a 1% smaller error for flat faced tablets and a 17% larger error for curved tablets than the general model. The general model, however, automatically exhibits the correct limit, rendering the unnecessary need of a large number of experiments for flat geometries. The cost- and time-effectiveness of using the general model is evident.

It bears emphasis that experimental errors and uncertainty in the functionality of the geometric function Q render the problem ill-posed (i.e., the solution is not unique, sensitive to errors, and dependent on the norm which is minimized). Experimental errors cannot be eliminated but one can minimize the figure of merit that provides more stability to the optimization process. According to our case study, this is the case of the σ – norm and thus the optimization problem reduces to

$$\min_{a,b,e,f}\left[\sum_{i\in\mathcal{P}}\left(\sigma_t(\rho_i)-\frac{F_i}{\pi D_i^2\left[a\left(\frac{W_i}{D_i}\right)^e+b\left(\frac{t_i/D_i}{W_i/D_i}\right)^f+\frac{1}{2}\left(\frac{t_i}{D_i}\right)-a\left(\frac{t_i}{D_i}\right)^e-b\right]}\right)^2\right]^{1/2}$$

where $\mathcal{P}$ is a set of experimental points and $\sigma_t(\rho_i)$ is obtained from a small number of flat faced tablets.

3.1.3. *Mechanistic interpretation*

A major source of uncertainty is the fact that the functionality of Q is unknown in general. However, further insight can be gained by recasting the problem in terms of an effective cross-sectional surface area, $\bar{A}$, associated with strength, that is

$$\sigma_t = \frac{2F}{\pi\bar{A}} \qquad (11)$$

where $\bar{A} = tD$ for flat-faced tablets (cf. Eq. (1)). For doubly convex tablets, we parametrize $\bar{A}$ by an effective thickness $\bar{t}$ (see Fig. 1(b))

Table 2
A comparison between all models according to their optimal coefficients, 90% confidence intervals and residual errors obtained from each figure of merit, for only those flat and doubly convex tablets that failed under pure tensile stress. ($\underline{\circ}$ indicates that $\circ$ is an assumption.)

Models	a	b	c	d	e	f	g	σ-norm	Q-norm	$Q\sigma$-norm
Pitt's (1988)	0.284	0.0126	0.315	0.001	$\underline{1}$	$\underline{1}$	$\underline{1}$	13.3	0.43	2.13
1-parameter	0.1316± 10.1 %	$\underline{0}$	$\frac{1}{2}-a$	b	$\underline{1}$	–	$\underline{1}$	–	0.196	–
1-parameter	0.1236± 7.5 %	$\underline{0}$	$\frac{1}{2}-a$	b	$\underline{1}$	–	$\underline{1}$	6.43	–	–
1-parameter	0.1016± 9.5 %	$\underline{0}$	$\frac{1}{2}-a$	b	$\underline{1}$	–	$\underline{1}$	–	–	0.739
2-parameter	−0.0202± 164.7 %	0.0285± 20.7 %	$\frac{1}{2}-a$	$-b$	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	0.16	–
2-parameter	−0.0538± 51.3 %	0.0278± 16 %	$\frac{1}{2}-a$	$-b$	$\underline{1}$	$\underline{1}$	$\underline{1}$	4.71	–	–
2-parameter	−0.0550± 50.1 %	0.0278± 16.9 %	$\frac{1}{2}-a$	$-b$	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	–	0.568
4-parameter	0.1406± 35 %	0.0077± 107.7 %	0.2626± 28.8 %	−0.0037± 430.5 %	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	0.139	–
4-parameter	−0.0382± 114.8 %	0.0296± 24.9 %	0.5615± 13.3 %	−0.0390± 37.2 %	$\underline{1}$	$\underline{1}$	$\underline{1}$	4.5	–	–
4-parameter	−0.0132± 328.5 %	0.0262± 29.5 %	0.5193± 14 %	−0.0332± 46.5 %	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	–	0.539
General	0.3231± 10.9 %	0.0240± 36 %	a	$\frac{1}{2}\frac{t}{D}-b$	1.6963± 12 %	−263.5± ∞ %	e	–	0.146	–
General	0.0484± 267.6 %	0.8688± 83 %	a	$\frac{1}{2}\frac{t}{D}-b$	−0.8553± 82.7 %	−0.3147± 43.4 %	e	3.85	–	–
General	0.7289± 689.1 %	2.3185± 409 %	a	$\frac{1}{2}\frac{t}{D}-b$	−0.3151± 283.8 %	−0.2156± 209.9 %	e	–	–	0.463

Table 3
Recalibration of optimal coefficients, 90% confidence interval and residual errors for flat and doubly convex tablets that failed under pure tensile stress, using a larger group of flat faced tablets in the optimization process. ($\underline{\circ}$ indicates that $\circ$ is an assumption.)

Models	a	b	c	d	e	f	g	σ-norm	Q-norm	$Q\sigma$-norm
1-parameter	0.1145± 12.4 %	$\underline{0}$	$\frac{1}{2}-a$	b	$\underline{1}$	–	$\underline{1}$	–	0.229	–
1-parameter	0.0949± 11 %	$\underline{0}$	$\frac{1}{2}-a$	b	$\underline{1}$	–	$\underline{1}$	8.95	–	
1-parameter	0.0654± 17.7 %	$\underline{0}$	$\frac{1}{2}-a$	b	$\underline{1}$	–	$\underline{1}$	–	–	1.025
2-parameter	−0.0380± 99 %	0.0287± 23.3 %	$\frac{1}{2}-a$	$-b$	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	0.200	–
2-parameter	−0.1117± 29.4 %	0.0321± 16.6 %	$\frac{1}{2}-a$	$-b$	$\underline{1}$	$\underline{1}$	$\underline{1}$	6.90	–	–
2-parameter	−0.1205± 29.1 %	0.0330± 18.2 %	$\frac{1}{2}-a$	$-b$	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	–	0.838
4-parameter	0.0442± 109 %	0.0198± 46.6 %	0.4183± 18.1 %	−0.0185± 99.5 %	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	0.187	–
4-parameter	−0.1187± 31.2 %	0.0415± 15.7 %	0.6975± 7.9 %	−0.0655± 18.8 %	$\underline{1}$	$\underline{1}$	$\underline{1}$	6.26	–	–
4-parameter	−0.1316± 29.2 %	0.0444± 16.6 %	0.7211± 8 %	−0.0720± 20.8 %	$\underline{1}$	$\underline{1}$	$\underline{1}$	–	–	0.776
General	3.0992± 1313 %	3.9923± 972.5 %	a	$\frac{1}{2}\frac{t}{D}-b$	−0.1640± 593.1 %	−0.2006 ± 508.3	e	–	0.178	–
General	0.0342± 278.9 %	0.6553± 76.4 %	a	$\frac{1}{2}\frac{t}{D}-b$	−0.9648± 82 %	−0.436 ± 41.1	e	5.54	–	–
General	0.1344± 517.8 %	0.8150± 199.8 %	a	$\frac{1}{2}\frac{t}{D}-b$	−0.6065± 182.4 %	−0.4411 ± 186.3	e	–	–	0.687

Table 4
Mechanistic model optimal coefficients, 90% confidence bound and residual errors from each figure of merit, for those tablets in extended dataset that failed under pure tensile stress.

Model	α	β	σ-norm	Q-norm	$Q\sigma$-norm
Mechanistic	0.5817 ± 8.6%	3.9736 ± 25.5%	–	0.172	–
Mechanistic	0.5562 ± 9.4%	3.9877 ± 15.4%	5.97	–	–
Mechanistic	0.5377 ± 9.4%	5.0030 ± 18.3%	–	–	0.699

Table 5
A systematic comparison of the proposed and existing models based on four different performance criteria.

Model	Equation	Number of parameters	Limiting behavior	Stability (1:best–5:worst)	Predictability (1:best–5:worst)
1-parameter	(4)	1	√	1(σ-norm)	5
2-parameter	(10)	2	√	3 (σ, Qσ-norm)	4
4-parameter	(3)	4	×	4 (σ, Qσ-norm)	3
General	(9)	4	√	5 (σ-norm)	1
Mechanistic	(13)	2	√	2 (σ-norm)	2

as follows

$$\bar{A} = D^2 \left[2\left(\frac{\bar{t}}{D} - \frac{W}{D}\right) \left[\frac{1}{3} + \frac{1}{15}\left(\frac{\bar{t}}{D} - \frac{W}{D}\right)^2\right] + \frac{W}{D} \right] + \mathcal{O}\left(\frac{(\bar{t}-W)^5}{D^3}\right) \quad (12)$$

This parametrization is made only in the interest of simplicity. However, a geometric interpretation of the above equation suggests that $\bar{t}/D$ may be a function of D/R, which we postulate to be

$$\frac{\bar{t}}{D} = \frac{W}{D} + \alpha\left(\frac{D}{R}\right)^{\beta}\left(\frac{t}{D} - \frac{W}{D}\right)$$

where $\alpha > 0$ and $\beta \geq 0$ are fitting parameters. As a result, a new relationship between geometric parameters, breaking force and tensile strength is obtained, i.e.,

$$\sigma_t = \frac{2F}{\pi D^2 \left[2\alpha\left(\frac{D}{R}\right)^{\beta}\left(\frac{t}{D} - \frac{W}{D}\right)\left[\frac{1}{3} + \frac{\alpha^2}{15}\left(\frac{D}{R}\right)^{2\beta}\left(\frac{t}{D} - \frac{W}{D}\right)^2\right] + \frac{W}{D} \right]} \quad (13)$$

which is referred to as the *mechanistic model*. It is interesting to note that the mechanistic model has a substantially different functionality compared to the one of the general model (9).In the case of $\bar{t} = (t + W)/2$, however, the 1-parameter model is approximately recovered with $a = 1/6$, which is very close to the optimal value obtained in our case study (see Table 1). Thus, a more clear connection between the mechanistic model and the general model is desirable, if beyond the scope of this work.

The optimal values for α and β, determined from the extended dataset with four different shapes of tablets (Section 3.1.2) using each of the three figures of merit, are presented in Table 4. The residual errors are comparable to those of the general model and the stability is remarkable, as shown by the tight confidence bounds. The optimal values are clearly insensitive to the figure of merit. In addition, the search space of the mechanistic model is of dimension 2 whereas the one of the general model is of dimension 4. Fig. 3 shows that the mechanistic model has the largest number of small errors compared to the other models. Thus, the mechanistic model is preferable both in terms of efficacy and efficiency.

4. Summary and discussion

We have proposed a general framework for determining optimal relationships for tensile strength of doubly convex tablets under diametrical compression. The approach is based on the observation that tensile strength is directly proportional to the breaking force and inversely proportional to Q, a nonlinear function of geometric parameters and materials properties. This generalization reduces to the analytical expression commonly used for flat faced tablets, i.e., Hertz solution, for $Q = t/2D$. Here, we have assumed that Q is solely a function of geometric parameters that, for doubly convex tablets, reduce to t/D and W/D, and a combination thereof. Based on such assumptions, the function Q can be determined from experimental results by solving an optimization problem that minimizes a figure of merit of choice. We have postulated that this figure of merit has to be based on the assumption that a flat faced tablet and doubly curved tablet have the same tensile strength if they have the same relative density and are made of the same powder, under equivalent manufacturing conditions.

We have specifically investigated three different figures of merit, which we referred to as σ-norm, Q-norm and $Q\sigma$-norm, and we have proposed three new optimal tensile strength relationships, which we referred to as *general model*, *2-parameter model* and *mechanistic model*. The general model captures the leading order behavior of Q on the geometric parameters, it has the exact limiting behavior for flat faced tablets, and it has four optimal parameters to be determined. The 2-parameter model simplifies the general model by assuming that Q is linear on the geometric parameters, and thus the number of parameters is reduced to two while the correct limiting behavior is retained. The mechanistic model is based on an effective cross-sectional surface area associated with strength (i.e., in contrast to previous models, it has a well-defined mechanistic interpretation), it exhibits the exact limiting behavior for flat geometries, and it only has two optimal parameters.

Here, we present guidelines for assessing the performance of optimal tensile strength relationships. Under this framework, other expressions for the nonlinear function Q can be explored and the assumption that Q only depends on geometric parameters can even be relaxed. Similarly, figures of merit other than those studied here (i.e., σ-norm, Q-norm and $Q\sigma$-norm) can be examined. It bears emphasis that, regardless of the choice of Q and the optimization procedure, the performance of a new model can be assessed following the same procedure presented here. A desirable model needs to have a small number of optimal parameters to make it less computationally expensive. It has to have the correct analytical limiting behavior for flat tablets (i.e., Hertz solution), so that the tensile strength can be obtained from a small number of flat faced tablets. It has to be predictive, i.e., the optimization has to result in a narrow and symmetric distribution of errors around zero, for a given figure of merit. This figure of merit in turn has to render the optimization problem stable, i.e., it has to provide optimal parameters with tight confidence bounds.

We have assessed the performance of the proposed new models together with two models previously proposed in the literature, i.e., Shang's model (a 1-parameter model introduced in Shang et al.

(2013a)) and a 4-parameter model (based on the model introduced by Pitt et al. (1989) which is widely used in the pharmaceutical industry (USP, 2011)), as shown in Table 5. It shows that the general and mechanistic models are more predictive than previously proposed tensile strength relationships. Both models automatically exhibit the correct limit for flat geometries, thus only a small number of flat faced tablets has to be tested in order to accurately capture the strength-relative density relationship. Our analysis also indicates that the mechanistic model is the most stable among the predictive models. This is in sharp contrast to the 4-parameter model, i.e., a re-calibration of Pitt's equation, that leads to an unstable optimization problem which, in addition, requires a large number of flat faced tablets in order to remain predictive in the limit of shallow/flat tablets. It is interesting to note that although stability and predictability are generally inversely correlated, with a Spearman's rank correlation coefficient of −0.7 for the five models studied in this work, the mechanistic model exhibits the opposite behavior, i.e., it is highly stable and predictive. The predictability of the mechanistic model is a consequence of a simple mechanical concept that turns out to be mathematically more complex than other models (cf. (13) and (4)). Its stability is due to the small number of fitting parameters in this model.

It bears emphasis that experimental errors and uncertainty in the functionality of the geometric function Q may render the problem ill-posed. Therefore, these guidelines have to be followed with caution to resolve ambiguities in the results.

These observations suggest that both general and mechanistic models are cost- and time-effective, predictive alternatives to the tensile strength relationship currently used in the pharmaceutical industry. Furthermore, our analysis showcases the benefits of adopting a general framework for developing and evaluating the performance of optimal relationships for tensile strength of doubly convex tablets under diametrical compression.

We close by pointing out some limitations of our analysis and possible avenues for extensions of the general framework.

First, it is clear that the proposed parametric approximations for Q are not the only nonlinear functions of geometric parameters that exhibit the correct limit for flat faced tablets. In addition, tensile strength of flat faced tablets may not be optimally described by an exponential function of the relative density. It is also possible that the function Q has to depend on powder properties or manufacturing variables in some cases of industrial relevance. The systematic investigation of functions Q of the type proposed here, the elucidation of their properties and the determination of the best optimal relationships in each area of application, are worthwhile directions of future research.

Second, our general framework relies in the assumption that, for given powder and manufacturing conditions, a flat faced tablet and doubly curved tablet have the same tensile strength if they have the same relative density. This is indeed a good first order approximation for the case study presented here (i.e., pure microcrystalline cellulose pressed at low compaction speeds). There are experimental techniques that can assess the density distribution of a tablet such as gamma-ray attenuation or solid state-NMR. However, there is a lack of experimental technique that can test directly the point-to-point strength of the material, (i.e., most techniques perform indirect measurements of effective properties, with the exception of a beam-bending test that suffers from the difficulty of requiring ad-hoc geometries for the specimen. Thus, particle mechanics simulations capable of describing strength formation and evolution during the compaction process are desirable (Gonzalez and Cuitiño, 2012, 2015a,b), if beyond the scope of this paper.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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Appendix A.

Table A.1
Tensile strength and relative density of flat faced tablets extracted from Shang et al. (2013a).

Relative density	Tensile strength (MPa)
0.5910	1.39
0.7290	3.14
0.8103	4.79
0.8568	6.38
0.8942	8.22
0.9239	9.63
0.9355	11.19
0.9406	11.70

Table A.2
Characteristics of flat faced tablets and their calculated tensile strength values. Tensile strength values were calculated using Hertz solution Eq. (1).

	Actual weight (g)	Thickness (mm)	Actual diameter (mm)	Break force (N)	Tensile strength (MPa)
1	0.2969	2.79	10.04	339.4	7.71
2	0.272	2.55	10.03	323.1	8.04
3	0.2718	2.58	10.05	299.1	7.34
4	0.2706	2.84	10.06	193.1	4.30
5	0.268	3	10.06	136.7	2.88
6	0.2687	3.03	10.08	141.4	2.95
7	0.267	3.42	10.08	84.2	1.55
8	0.2428	3.66	10.1	38.7	0.67
9	0.2416	3.61	10.09	39.3	0.69
10	0.2828	3.03	10.07	189.6	3.96
11	0.2696	3.02	10.06	150.2	3.15
12	0.2701	2.96	10.06	159.6	3.41
13	0.3022	2.8	10.04	372.7	8.44
14	0.2995	2.8	10.04	299.9	6.79
15	0.2999	2.8	10.04	365.6	8.28
16	0.3105	2.82	10.02	472.0	10.63
17	0.3261	2.9	10.02	483.1	10.58
18	0.3249	2.86	10.01	553.4	12.30
19	0.3584	3.17	10.03	588.5	11.78
20	0.357	3.2	10.03	606.2	12.02
21	0.3592	3.15	10.01	610.3	12.32
22	0.3626	3.19	10.02	616.1	12.27
23	0.3661	3.24	10.02	621.0	12.18
24	0.3775	3.28	10.01	645.4	12.51
25	0.3726	3.28	10.02	620.5	12.02
26	0.2716	3.58	10.08	59.2	1.04
27	0.2693	3.56	10.07	78.8	1.40
28	0.2659	3.05	10.06	110.6	2.29

References

Bagault, C., Nelias, D., Baietto, M., Ovaert, T.C., 2013. Contact analyses for anisotropic half-space coated with an anisotropic layer: effect of the anisotropy on the pressure distribution and contact area. Int. J. Solids Struct. 50, 743–754.

Carneiro, F., Barcellos, A., 1953. Tensile strength of concrete. Rilem Bull. 13, 97–123.

Gonzalez, M., Cuitiño, A.M., 2012. A nonlocal contact formulation for confined granular systems. J. Mech. Phys. Solids 60, 333–350.

Gonzalez, M., Cuitiño, A.M., 2015a. Generalized Loading–Unloading Contact Laws for Elastic-Plastic Spheres with Bonding Strength (in preparation).

Gonzalez, M., Cuitiño, A.M., 2015b. Microstructure Evolution of Compressible Granular Systems under Large Deformations (Submitted for publication).

Haririan, I., Newton, M., 1999. Tensile strength of circular flat and convex-faced avicel ph102 tablets. DARU J. Pharm. Sci. 7, 36–40.

Hondros, G., 1959. The evaluation of Poisson's ratio and the modulus of materials of a low tensile resistance by the Brazilian (indirect tensile) test with particular reference to concrete. Aust. J. Appl. Sci. 10, 243–268.

Iyer, R., Hegde, S., Zhang, Y.-E., Dinunzio, J., Singhal, D., Malick, A., Amidon, G., 2013. The impact of hot melt extrusion and spray drying on mechanical properties and tableting indices of materials used in pharmaceutical development. J. Pharm. Sci. 102, 3604–3613.

Kourkoulis, S.K., Markides, C.F., Chatzistergos, P.E., 2012. The Brazilian disc under parabolically varying load: theoretical and experimental study of the displacement field. Int. J. Solids Struct. 49, 959–972.

MATLAB, 2012. Release 2012. The MathWorks Inc., Natick, MA.

Pitt, K.G., Heasley, M.G., 2013. Determination of the tensile strength of elongated tablets. Powder Technol. 238, 169–175.

Pitt, K.G., Newton, J.M., Stanley, P., 1988. Tensile fracture of doubly-convex cylindrical discs under diametral loading. J. Mater. Sci. 23, 2723–2728.

Pitt, K.G., Newton, J.M., Stanley, P., 1989. Stress distributions in doubly convex cylindrical discs under diametral loading. J. Phys. D: Appl. Phys. 22, 1114.

Podczeck, F., 2012. Methods for the practical determination of the mechanical strength of tablets from empiricism to science. Int. J. Pharm. 436, 214–232.

Podczeck, F., Drake, K.R., Newton, J.M., 2013. Investigations into the tensile failure of doubly-convex cylindrical tablets under diametral loading using finite element methodology. Int. J. Pharm. 454, 412–424.

Procopio, A.T., Zavaliangos, A., Cunningham, J.C., 2003. Analysis of the diametrical compression test and the applicability to plastically deforming materials. J. Mater. Sci. 38, 3629–3639.

Shang, C., Sinka, I.C., Jayaraman, B., Pan, J., 2013a. Break force and tensile strength relationships for curved faced tablets subject to diametrical compression. Int. J. Pharm. 442, 57–64.

Shang, C., Sinka, I.C., Pan, J., 2013b. Modelling of the break force of tablets under diametrical compression. Int. J. Pharm. 445, 99–107.

Sinka, I.C., Motazedian, F., Cocks, A.C.F., Pitt, K.G., 2009. The effect of processing parameters on pharmaceutical tablet properties. Powder Technol. 189, 276–284.

Stanley, P., 2001. Mechanical strength testing of compacted powders. Int. J. Pharm. 227, 27–38.

Tang, T., 1994. Effects of load-distributed width on split tension on unnotched and notched cylindrical specimens. J. Test. Eval. 22, 401–409.

Timoshenko, S.P., Goodier, J.N., 1970. Theory of Elasticity. Mcgraw-hill, New York.

Tye, C.K., Sun, C.C., Amidon, G.E., 2005. Evaluation of the effects of tableting speed on the relationships between compaction pressure, tablet tensile strength, and tablet solid fraction. J. Pharm. Sci. 94, 465–472.

USP, 2011. The United States Pharmacopeia, 34th ed. US Pharmacopeial Convention, Rockville, MD.

Wang, Q.Z., Jia, X.M., Kou, S.Q., Zhang, Z.X., Lindqvist, P.A., 2004. The flattened Brazilian disc specimen used for testing elastic modulus, tensile strength and fracture toughness of brittle rocks: analytical and numerical results. Int. J. Rock Mech. Min. Sci. 41, 245–253.