

A simple predictive model for the tensile strength of binary tablets

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Abstract

The tensile strength of tablets of single-component powders, such as microcrystalline cellulose (MCC), hydroxypropylmethyl cellulose (HPMC) and starch, and binary mixtures of these powder were measured at various relative densities. It was found that the tensile strength of tablets of powder blends was primarily dependent upon relative density but was independent of the tablet dimensions and compaction kinematics. It was found that the logarithm of tensile strength was proportional to the relative density. A simple model, based upon Ryshkewitch–Duckworth equation that was originally proposed for porous materials, has been developed in order to predict the relationship between the tensile strength and relative density of binary tablets based on the properties of the constituent single-component powders. The validity of the model has been verified with experimental results for various binary mixtures. It has demonstrated that the proposed model can well predict the tensile strength of binary mixtures based upon the properties of single-component powders, such as true density, and the concentrations.

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1. Introduction

Pharmaceutical tablets generally comprise a number of components, which all contribute to the final properties of tablets. It is instructive to predict the properties of the tablets based upon the knowledge of material properties of the constituent substances. However, this is a challenging task due to the complexity and diversity of pharmaceutical blends. An alternative approach would be to identify the dominant substance in terms of the properties of interest, and to predict the tablet properties from the properties of two or more of these dominant constituents. As a starting point, it would be intuitive to concentrate on tablets of binary mixtures, i.e., binary tablets.

Among the tablet properties of interests in pharmaceutical industries, tensile strength is one of the important parameters for characterising the mechanical behaviour of pharmaceutical tablets, as the tablets must possess a minimum mechanical strength to sustain potential loading encountered during processing and handling. Tensile strength of tablets can generally be determined by diametrical compression tests (Fell and Newton, 1970). In the diametrical compression tests, cylindrical tablets are placed between two platens and compressed diametrically until the tablets break/crush. The crushing load is recorded and the tensile strength can be calculated from the crushing load together with the dimensions of the tablets. This procedure can be directly used to measure the tensile strength of tablets made of various components, many studies have hence been performed to explore the correlation of tensile strength with the properties of constituent components, such as tablets porosity, particle shape and size, effective contact

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surface area, etc. (Nikolakakis and Pilpel, 1988; Sebhatu and Alderborn, 1999).

Since thorough understanding of the dependence of the tensile strength of binary tablets is vital to fully understand how the constituent components contribute to the tensile strength of real tablets which are generally of multi-components, there has recently been an increased interest in the study on tensile strength of binary tablets (Chan et al., 1983; Bangudu and Pilpel, 1984; Kuentz and Leuenberger, 2000; Ramírez et al., 2004). Chan et al. (1983) developed a model for tensile strength of binary mixtures by modifying the theory for tensile strength of fine powder developed by Cheng (1968) and introducing the concepts of reference state and a reduced tensile strength. The model took account of the effects of particle size and the composition of binary mixtures. However, it is very difficult to apply the model in practice, as some parameters in the equations are hardly accessible, in particular the parameter describing intrinsic interaction between particles of different materials. Bangudu and Pilpel (1984) measured the tensile strength of tablets of paracetamol and Avicel powders and mixtures of these components and the influence of the concentration of Avicel powder in the binary tablets were explored. Kuentz and Leuenberger (2000) investigated the tensile strength of binary tablets comprising well- and poorly-compactable substances and developed a model using percolation theory. It was assumed that a tablet can only be produced with a relative density higher than a critical relative density (D_c), which is threshold required to build a percolating cluster in the tablets. For tablets with a relative density $D (\geq D_c)$, the tensile strength σ_t is given as

$$\sigma_t = c(D - D_c)^{2.7} \quad (1)$$

where c is a proportional constant. For binary mixtures, the critical relative density D_c was related to the critical relative densities, D_{c1} and D_{c2} , of constituent components as follows,

$$D_c = n_1 D_{c1} + (1 - n_1) D_{c2} \quad (1a)$$

where n_1 is the weight fraction of the well compactable component.

It was shown that this model is primarily applicable if one dominant component in the mixture contributes to the overall strength of the tablets, while the other has nearly zero compactability and negligible contribution. For the cases in which both components can contribute to the tensile strength of binary tablets, a modified model was proposed by Ramírez et al. (2004) who introduced an initial strength parameter σ_0 into Eq. (1), i.e.,

$$\sigma_t = c(D - D_c)^{2.7} + \sigma_0 \quad (2)$$

In the above models, the unknown parameters can be determined by fitting the experimental data for the tensile strength of binary tablets at different relative densities. These models may be used to predict the tensile strength of binary tablets only if the parameters are determined by fitting the experimental data for the same mixtures. However, there is no way

to predict the tensile strength of binary tablets based upon the knowledge of the properties of constituent components. An attempt is hence required to tackle this problem.

The objective of this study is to develop a simple predictive model for the tensile strength of binary mixture, which will be based upon the accessible properties of constituent components. Since the majority of pharmaceutical excipients have a certain degree of compactability, we will focus on mixtures of two such components. The tensile strength of tablets of single-components, such as MCC, HPMC and starch, will be measured and interpreted in the context of Ryshkewitch–Duckworth equation, which will also be extended to model the tensile strength of binary mixtures of these powders. The proposed model will be validated with experimental data for various binary mixtures of different concentrations.

2. Materials and methods

2.1. Excipients

The excipients used in this study are microcrystalline cellulose (Avicel PH-102; FMC Corporation, Brussels, Belgium, Lot No. 7201C), HPMC (Methocel K100M; Pfizer Global R&D, Kent, UK, Lot No. 01EXC299) and Starch 1500 (Colorcon Ltd., Kent, UK, Lot No. IN504910), which are widely used in pharmaceutical drug products. Among these, MCC Avicel PH-102 is one of the most used filler-binders in pharmaceutical products, HPMC is a hydrophilic polymer excipient widely used as a diluent, and starch is widely used as a disintegrant, diluent and binder in pharmaceutical products. All the powders were used as received and their mean particle size is in the range of approximately 100 μm .

2.2. Preparation of binary mixtures

Binary mixtures of MCC and HPMC, MCC and starch were produced with different fractions of constituent components. The powders (100 g) were mixed in a Turbula T2F Shaker Mixer (Basel, Switzerland) at 23 rpm for 30 min. The true density of the single-component powders and binary mixtures was measured, using a helium gas displacement pycnometer (Type AccuPyc 1330, Micromeritics®, Bedfordshire, UK). The measured true densities for various powder systems are given in Table 1.

2.3. Tablet preparation

For the tablets of single-component powders (i.e., monolithic tablets of MCC, HPMC and starch), two batches of flat cylindrical tablets were manufactured using different approaches. The first batch was manufactured using a compaction simulator (ESH Testing, Brierley Hill, West Midlands, UK). Samples comprising 200 mg of powder were manually poured into a die of 8 mm in diameter and the

Table 1
Measured true densities for powder systems considered

Notation	Powder	Measured true density (g/cm ³)	Predicted true density (g/cm ³)	R ²
MCC	MCC (Avicel PH-102)	1.5897 ± 0.0028	–	0.9850
HPMC	HPMC	1.3160 ± 0.0003	–	0.9900
Starch	Starch 1500	1.4934 ± 0.0014	–	0.9846
MixA	50% MCC + 50% HPMC (w/w)	1.4420 ± 0.0003	1.4400	0.9963
MixB	10% MCC + 90% HPMC (w/w)	1.3440 ± 0.0008	1.3390	0.9975
MixC	90% MCC + 10% HPMC (w/w)	1.5540 ± 0.0004	1.5573	0.9953
MixAs	50% MCC + 50% starch (w/w)	1.5425 ± 0.0014	1.5400	0.9939
MixBs	20% MCC + 80% starch (w/w)	1.5215 ± 0.0014	1.5117	0.9911
MixCs	80% MCC + 20% starch (w/w)	1.5643 ± 0.0013	1.5695	0.9955

powders were compressed and decompressed at 30 mm/s without holding between the compression and decompression stages, i.e., a V-shaped compaction profile was used. Tablets with different densities were produced by varying the total compaction duration, consequently minimal punch separation and the maximum compression force were also controlled. The second batch was produced using an Instron universal testing machine with a 30 kN load cell (Model 5567, Instron Ltd., Buckinghamshire, UK). Samples comprising 800 mg of powder were filled into a 13 mm evacuable pellet die (Specac Ltd., Kent, UK) and were compressed and decompressed at 0.083 mm/s up to a specified compression force ranging from 3 kN to 18 kN. The latter approach was also employed to produce the binary tablets. No lubricant was used in any of the tablet preparation procedures.

2.4. Tablet characterisation

The tablet weight was measured using an electronic balance (Type AG204, Mettler-Toledo Inc., Leicester, UK) and the diameter and the thickness were measured with digital callipers (Brown & Sharpe Ltd., Wiltshire, UK). From these measurements, the volume and density of the tablets were determined. The relative density (D) was calculated by dividing the tablet density by the true density of the powders used.

The tensile strength of the tablet was determined from diametrical compression tests, which were performed using an Instron universal testing machine with a 1 kN load cell in order to accurately measure the maximal diametrical crushing force (F). Together with the measured diameter and thickness of the tablets, the tensile strength (σ_t) is then calculated as follows (Fell and Newton, 1970)

$$\sigma_t = \frac{2F}{\pi dt} \quad (3)$$

where d and t are the diameter and thickness of the tablet, respectively.

2.5. Tensile strength of binary mixtures

Ryshkewitch (1953) investigated the tensile strength of porous sintered alumina and zirconia and showed that the tensile strength is related to the porosity. It was found that the logarithm of the tensile strength is inversely proportional to the

porosity. A discussion of Ryshkewitch's paper by Duckworth (1953) leads to the following equation for the correlation of tensile strength with the porosity:

$$\ln \left(\frac{\sigma_t}{\bar{\sigma}} \right) = -k\varepsilon \quad (4)$$

where ε is the porosity of the compacts and $\varepsilon = 1 - D$, $\bar{\sigma}$ is the tensile strength of the same materials at zero porous (i.e., $\varepsilon = 0$ and $D = 1$), and k is a constant representing the bonding capacity. A higher value of k corresponds to stronger bonding of primary particles (Steendam and Lerk, 1998). It has been demonstrated that the Ryshkewitch–Duckworth equation (Eq. (4)) can well represent the variation of tensile strength with the porosity for a wide range of porous materials (Steendam and Lerk, 1998; Barralet et al., 2002; Gbureck et al., 2003; Shin et al., 2003).

For binary mixtures, assuming that the volumes of constituent powders do not change during the tableting process, the tensile strength at zero porosity can be approximated using a mixing rule, i.e.,

$$\bar{\sigma}_m = \bar{\sigma}_1 \delta_1 + \bar{\sigma}_2 \delta_2 \quad (5)$$

Similarly, it is assumed that the mixing rule can be used to approximate the bonding capacity of binary mixture. Hence, we have

$$k_m = k_1 \delta_1 + k_2 \delta_2 \quad (6)$$

In Eqs. (5) and (6), $\bar{\sigma}_m$ and k_m are the tensile strength at zero porosity and the bonding capacity of binary mixture. $\bar{\sigma}_1$ and $\bar{\sigma}_2$ are the tensile strengths at zero porosity, and k_1 and k_2 are the bonding capacity of the constituent powders of single component, respectively. $\bar{\sigma}_1$, $\bar{\sigma}_2$, k_1 and k_2 can be determined by fitting the experimental data for the single-component powders with Eq. (4). In Eqs. (5) and (6), δ_1 and δ_2 are the volume fractions of the constituent powders, which can also be expressed in terms of weight fractions as

$$\delta_1 = \frac{V_1}{V_m} = \frac{n_1 G_m / \rho_1}{G_m / \rho_m} = \frac{n_1 \rho_m}{\rho_1} \quad (7)$$

$$\delta_2 = \frac{V_2}{V_m} = \frac{n_2 G_m / \rho_2}{G_m / \rho_m} = \frac{n_2 \rho_m}{\rho_2} = \frac{(1 - n_1) \rho_m}{\rho_2} \quad (8)$$

where V_1 , V_2 and V_m are the volume of single-component powders (1 and 2) and their mixtures, respectively. ρ_1 , ρ_2

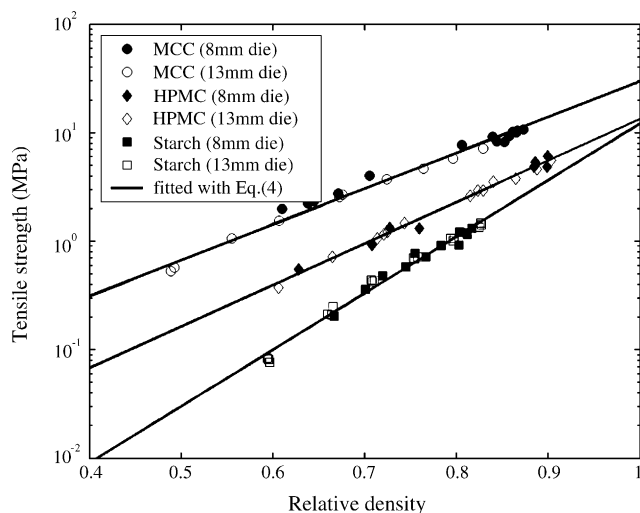


Fig. 1. The variation of tensile strength with relative density for single-component powders.

and ρ_m are the corresponding true densities. n_1 and n_2 are the weight fractions of the constituent powders, respectively. G_m is the weight of the binary mixture. Using the mixing rule, the true density of binary mixtures ρ_m can be expressed as a function of the true densities of the constituent single-component powders, ρ_1 and ρ_2 , as follows:

$$\frac{1}{\rho_m} = \frac{n_1}{\rho_1} + \frac{n_2}{\rho_2} \quad (9)$$

The measured true density (using pycnometer) and predicted true density for the binary mixtures considered in this study are given in Table 1. It is clear that the measured and predicted true densities are very close, which indicates that Eq. (9) can well predict the true density of binary mixtures. Therefore, all the calculations hereafter are based upon the predicted true densities using Eq. (9).

Substituting Eqs. (7) and (8) into (5) and (6), we can obtain $\bar{\sigma}_m$ and k_m for the binary mixture based upon the corresponding values of n , $\bar{\sigma}$ and k of the constituent powders and the true densities. Once $\bar{\sigma}_m$ and k_m are known, the tensile strength of binary tablets (σ_{tm}) can hence be obtained using Eq. (4) for a given relative density (D_m), i.e.,

$$\ln\left(\frac{\sigma_{tm}}{\bar{\sigma}_m}\right) = -k_m(1 - D_m) \quad (10)$$

or

$$\sigma_{tm} = \bar{\sigma}_m e^{-k_m(1-D_m)} \quad (11)$$

3. Results and discussion

3.1. Tensile strength for single-component powders

Fig. 1 shows the variation in tensile strength with relative density for the tablets of single-component powders. In this figure, the data obtained with an 8 mm diameter die are shown

Table 2

Tensile strength at zero density $\bar{\sigma}$ and bonding capacity k for the single-component powders considered

Powder	$\bar{\sigma}$ (N/m ²)	k
MCC	29.964	7.6
HPMC	13.464	8.8
Starch	12.183	12.0

in solid symbols, while the open symbols show the results with a 13 mm diameter die. It is interesting to note that the data obtained from two different approaches coalesce into three master curves for different powders. This indicates that the tensile strength of tablets is independent of their dimension, but primarily depends upon the relative density or porosity. In addition, for a given relative density, MCC tablets had the highest tensile strength, and starch tablets had lowest, with the HPMC tablets in between. For all three single-component powders considered, the relationships between the logarithm of the tensile strength and the relative density is nearly linear, and correlation coefficients R^2 (by linear regression) are all higher than 0.98, as shown in Table 1. This is consistent with the analysis of other researchers (Ryshkewitch, 1953; Duckworth, 1953; Steendam and Lerk, 1998; Barralet et al., 2002; Gbureck et al., 2003; Shin et al., 2003). The experimental data can be well fitted by Ryshkewitch–Duckworth equation (i.e., Eq. (4)) according to the principle of least squares, as shown in Fig. 1 in solid lines. The fitting gives the tensile strength at zero porosity $\bar{\sigma}$ and bonding capacity k for the single-component powders considered. The corresponding values are presented in Table 2. It is clear that MCC had the highest tensile strength at zero porosity, while starch had the lowest. However, starch had the highest bonding capacity while the bonding capacities for MCC and HPMC were similar.

3.2. Tensile strength for binary mixture

The variation of tensile strength with the relative density for binary mixtures is given in Fig. 2, in which the binary mixtures of MCC and HPMC are shown in Fig. 2a and those of MCC and starch in Fig. 2b. In this figure, the fitted lines for single-component powders shown in Fig. 1 are also superimposed as shown in dashed lines. It appears that the logarithm of the tensile strength is almost proportional to the relative density. This can be confirmed by linear regression, from which correlation coefficients R^2 are determined and given in Table 1. It is shown that the correlation coefficients, which measure the strength of the linear relation between two variables, are essentially close to unity. This indicates that the data points can be well represented by straight lines. The solid lines in Fig. 2 show the predictions using Eqs. (5)–(11) together with the values given in Table 2. It is clear that experimental data almost lie on the lines given by Eqs. (5)–(11), which implies that Eqs. (5)–(11) can well predict the variation of tensile strength with the relative density for the binary mixtures of various fractions. It

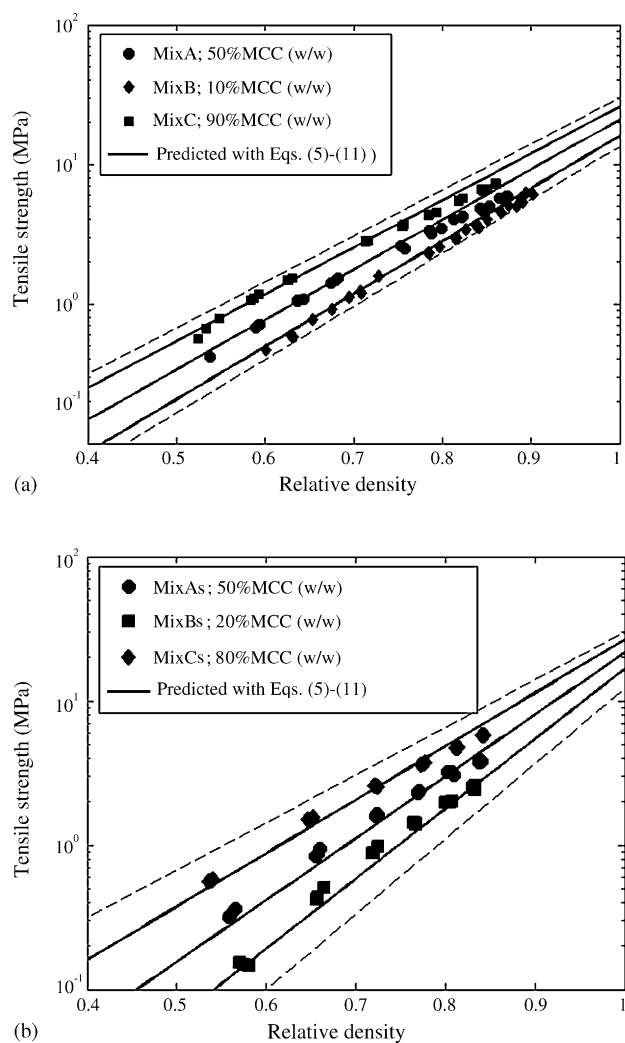


Fig. 2. The variation of tensile strength with relative density for binary mixtures. (a) Binary mixtures of MCC and HPMC. (b) Binary mixtures of MCC and starch.

is also clear from Fig. 2 that the lines for all mixtures lie between those of the single-component powders, and shift towards that of single-component powder with higher concentration in the mixture. It appears that the proposed model tends to overestimate the tensile strength at high relative densities (say ≥ 0.85 , see Fig. 2a). This is attributed to the fact that the powder bed has to experience high compression pressure in making tablets of such high relative density. At such high compression pressures, significant deformation of primary particles in the powder bed can be produced. Therefore, if the deformation of the particles is predominantly plastic (e.g., for MCC powder), significant plastic deformation will be induced to make the tablets of high relative density. Since plastic deformation of a material is non-recoverable, this results in the reduction in the volumes of powder particles. Consequently, the assumption that during the tableting process the volume of the constituent single-component powders are not altered is questionable. That is why the proposed model might overestimate the tensile strength of the high-

density tablet. However, since most pharmaceutical tablets have relative densities of 0.7–0.9 (Hancock et al., 2003), the present model can generally give very good estimation of the tensile strength of binary mixture in this realistic density range. Most significantly, the proposed model can predict the tensile strength of binary tablets merely from the readily accessible properties of the constituent single-component powders.

4. Conclusions

The tensile strengths of tablets made of single component MCC, HPMC and starch and of their binary mixtures of various concentrations were determined. It has been shown that the tensile strength of tablets of a particulate powder is primarily a function of its porosity or relative density, irrespective of the dimensions of the tablets. The logarithm of tensile strength is proportional to relative density. Based upon the Ryshkewitch–Duckworth equation, a simple predictive model has been developed. The validity of this model has been demonstrated with experimental data for various binary mixtures. It has been illustrated that it is possible to satisfactorily predict the tensile strength of binary mixture from the readily accessible properties of the constituent single-component powders with the proposed model, which is of practical value in pharmaceutical formulation engineering.

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