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Prediction of mechanical properties of compacted binary mixtures containing high-dose poorly compressible drug

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ABSTRACT

The aim of the study was to develop, compare and validate predictive model for mechanical property of binary systems. The mechanical properties of binary mixtures of ibuprofen (IBN) a poorly compressible high dose drug, were studied in presence of different excipients. The tensile strength of tablets of individual components viz. IBN, microcrystalline cellulose (MCC), and dicalcium phosphate dihydrate (DCP) and binary mixtures of IBN with excipients was measured at various relative densities. Prediction of the mechanical property of binary mixtures, from that of single components, was attempted using Ryshkewitch–Duckworth (R-D) and Percolation theory, by assuming a linear mixing rule or a power law mixing rule. The models were compared, and the best model was proposed based on the distribution of residuals and the Akaike's information criterion. Good predictions were obtained with the power law combined with linear mixing rule, using R-D and Percolation models. The results indicated that the proposed model can well predict the mechanical properties of binary system containing predominantly poorly compressible drug candidate. The predictions of these models and conclusions can be systematically generalized to other pharmaceutical powders.

1. Introduction

Pharmaceutical tablets are the most popular dosage form for drug delivery and account for some 70–80% of all pharmaceutical preparations. Tablets can be made directly from powders, granules, pellets, or film coated multiple units. The prerequisite, however, is that the material must have good mechanical property to form a tablet. The simplest process for tableting is direct compression, in which the drug(s) and excipient(s) are dry mixed and then compacted. Pharmaceutical tablets generally comprise a number of components like diluents, binders, disintegrants, lubricants, and glidants that contribute to the final properties of tablets. The qualitative and quantitative contribution of each component in tablet matrix can also have a bearing on the quality of the final tablet in terms of its mechanical strength. It is desirable to predict the mechanical properties of the tablets based upon the knowledge of properties of individual constituents. Prediction of mechanical properties of pharmaceutically relevant blends are of special interest in case of high-dose poorly compressible drugs that exhibit nonlinear relationship between compression force, solid fraction and tablet tensile strength. However, this is a challenging task due to the diversity and complexity of pharmaceutical blends. An alternative approach could be to identify the dominant substance in terms of the property of interest, and to predict the tablet properties from their individual properties. Tensile strength of tablets is one of the important characteristic of mechanical behavior of pharmaceutical tablets. Tablets must possess a minimum mechanical strength to sustain potential stresses of processing and handling.

Numerous workers have investigated the compaction of binary mixtures (Akande et al., 1998, 1997; Amin and Fell, 2004; Bangudu and Pilpel, 1984; Celik et al., 1996; Kuentz and Leuenberger, 2000; Mattsson and Nystrom, 2001; Schmidt and Leitritz, 1997). In most of the cases, no simple relationship could be derived from the compaction properties of the single materials and their proportions in the mixture, and the results were attributed to the degree and magnitude of bonding between particles of different materials. Few studies proposed a model for mechanical properties of compacted mixtures (Bangudu and Pilpel, 1984; Busignies et al., 2006; Chuan-Yu Wu et al., 2005; Kuentz and Leuenberger, 2000; Leuenberger, 1982, 1999; Veen, 2003; Veen et al., 2004). Some authors tried to develop a model based on the intrinsic interaction between particles of different materials. Therefore, at present a universal model that predicts mechanical properties of binary mixtures does not exist. It is imperative to assess mechanical properties of individual components to understand behaviour of multi-component systems.

The aim of the present work was to predict the mechanical properties of binary mixtures. The mechanical properties of single con-

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stituents were modelled in framework of Ryshkewitch–Duckworth (R-D) and Percolation model. The linear (L) and power law (P) mixing rule were applied to the parameters obtained from these models. The models for prediction of tensile strength of binary mixtures containing high loading of poorly compressible drugs were developed, compared and validated with experimental results. The best model has been proposed based on the distribution of the residuals and Akaike's information criterion (AIC). (Akaike, 1974) Influence of the type of excipient like microcrystalline cellulose (MCC) (plastic material) and dicalcium phosphate dihydrate (DCP) (brittle material), and solid fraction in compact have also been emphasised.

2. Materials and methods

Ibuprofen (IBN) (Arbro Pharmaceuticals Ltd., New Delhi, India), microcrystalline cellulose (MCC-low moisture grade) (Avicel® – PH-112, FMC BioPolymer, PA, USA), and dicalcium phosphate dihydrate (DCP) (Emcompress®, JRS Pharma LP, NY, USA) were used.

2.1. Characterization of materials

Median particle size was determined by optical microscopy by measuring diameter along the longest axis for at least 300 particles (DMLP microscope, Leica Microsystems, Wetzlar, Germany). The moisture content of the excipients was determined by Karl Fisher (KF) titration (Metrohm 794 Basic Titrino, Herisau, Switzerland). The instrument was calibrated with disodium tartrate dihydrate for the accuracy of moisture determination. Sample size of 100–120 mg was utilized for the determination of moisture content. Particle density was determined for powder samples in triplicate by helium pycnometry (Pycno 30, Smart Instruments, Mumbai, India) at 25 ± 2 °C temperature and 40 ± 5% relative humidity conditions. The particle density of mixture component (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:

$$\frac{1}{\rho m} = \frac{n_1}{\rho_1} + \frac{n_2}{\rho_2} \quad (1)$$

where, n_1 and n_2 are the weight fractions of the constituent powders, respectively.

2.2. Preparation of the blend

Required amount of drug and excipient were weighed and mixed in double-cone blender (VDM 4SP, Kalweka, Ahmedabad, India) at 20 rpm for 10 min. The following blends were prepared to develop a predictive model for mechanical properties—100% IBN; 100% MCC, 100% DCP; 80% IBN + 20% MCC; and 80% IBN + 20% DCP.

2.3. Tableting and data acquisition

Rotary tablet press (Mini II, Rimek, Ahmedabad, India) was equipped at one of the 8 stations with 8 mm D-tooling with flat punch tip. Feed frame was used for uniform die filling and blind dies were used at all other positions. Precompression rollers were set out of function. Tablets of each material were compressed at constant volume and applied pressure was changed by "pressure-adjustment wheel". Temperature (25 ± 2 °C) and relative humidity (40 ± 5%) conditions were controlled throughout the study.

Data was acquired by Portable Press Analyzer™ (PPA) version 1.2, revision D (Data Acquisition and Analyzing System, PuuMan Oy, Kuopio, Finland), through an infrared (IR) telemetric device with 16-bit analog-to-digital converter (6 kHZ). Force was measured by strain gauges at upper and lower punches (350 Ω, full Wheatstone bridge; I. Holland Tableting Science, Nottingham, UK), which were coupled with displacement transducers (linear potentiometer, 1000 Ω). Upper and lower punch data were recorded and transmitted on separate channels by individual amplifiers ("Boomerangs"). The amplifiers truncated the raw data from 16 bit to 12 bit after measuring to check IR transmission (data transmission rate-50 kbaud; Internal data buffer–1024 measurement points). Analysis of compaction data was carried out by PPA Analyze software (version 1.2, revision D). Accuracy of force and displacement transducers was 1% and 0.02%, respectively. The suitability of the data acquisition system has previously been reported (Matz et al., 1999). The tableting speed was kept constant at 13.8 RPM.

2.4. Characterization of compacts

Porosity (ε) was calculated based on the apparent density and the true density of the compacted powders.

$$\varepsilon = 1 - \frac{\text{Apparent density}}{\text{True density}} \quad (2)$$

Breaking force of the tablets was measured using a tablet hardness tester (Tablet hardness tester, Erweka, USA). Tablet dimensions were measured with a digital caliper (Digimatic Mitutoyo Corporation, Japan). Tensile strength was calculated using the equation, to eliminate the undesirable effect of variable tablet thickness on measured breaking force (Fell and Newton, 1971)

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

where, σ_t is the tensile strength (MPa), F is the observed breaking force (N), d is the diameter (mm), and t is the thickness of the compact (mm).

3. Results and discussions

3.1. Characterization of materials

Particle size, moisture content, and particle density determined for each material is reported in Table 1. Free moisture content of all the materials was below 2% (w/w) and is expected not to affect compaction properties.

3.2. Prediction of mechanical properties

The predictions of the mechanical properties of binary mixtures from the characteristics of the individual components were attempted using R-D model (Duckworth, 1953) and Percolation theory (Leuenberger, 1999). L and P mixing rules were applied for the determination of the parameters obtained from R-D and Percolation models. The volume fraction of the materials was taken as multiplications and power relation with the parameters obtained from R-D and Percolation models. As a consequence, eight models were analyzed, validated and compared with experimental measurements using criteria based on the standard deviation from the mean values.

3.2.1. Ryshkewitch–Duckworth model

R-D model was first applied to the tensile strength of porous sintered alumina and zirconia (Duckworth, 1953). The model transforms the logarithmic relationship between tensile strength, σ_t and porosity of the compact:

$$\sigma_t = \sigma_{0r} e^{-k\varepsilon} \quad (4)$$

where ε is the porosity of the compacts, σ_{0r} is the tensile strength at zero porosity, and k is a constant representing the bonding capacity (Wu et al., 2005; Duckworth, 1953).

Table 1
Particle size, moisture content and particle density for each material.

Material	Particle size (μm)	Moisture content (%, w/w, $n = 3$)	Particle density (g/cm^3)
IBN	210–540; $d_{50} = 250$	0.11 ± 0.032	1.117
MCC	160–380; $d_{50} = 210$	1.34 ± 0.198	1.570
DCP	220–480; $d_{50} = 280$	0.26 ± 0.075	2.389

The R-D parameters were derived for all the materials. The experimental results showed good correlation between the tensile strength and porosity (Table 2). The higher correlation coefficient between tensile strength and porosity indicated a first-order change in tensile strength, upon reduction in porosity. The values of σ_{0r} were found to be 1.35, 22.66 and 21.39 for IBN, DCP, and MCC, respectively. The relationship between the tensile strength and porosity is presented in Fig. 1 for all the materials, which further indicated the suitability of R-D model to describe the relationship between tensile strength and porosity.

The results of σ_{0r} indicated that IBN has very poor inherent bonding propensity as a result of elastic deformation and porosity expansion. The values of σ_{0r} for MCC and DCP indicated that both materials have stronger bonding propensity. The overall results of single component systems indicted the dependence of tensile strength on quantitative solid–solid interaction.

3.2.2. Percolation model

Percolation theory transforms the exponential relationship between tensile strength and the relative density (Kuentz and Leuenberger, 2000; Leuenberger, 1999). It defines critical tablet densities (ρ_c) as the value after which the mechanical properties start to change. Tablets with a relative density $\rho_r > \rho_c$ (critical relative density that is the minimum density required for forming a coherent compact), the tensile strength σ_t is given as:

$$\sigma_t = \sigma_{0p}(\rho_r)^{T_f} \quad (5)$$

σ_{0p} and T_f are the tensile strength at zero porosity and the fracture exponent, respectively.

The Percolation parameters were derived for all the materials. The experimental results showed good exponential correlation between the tensile strength and relative density (Table 2). The relationship between the tensile strength and relative density, for all materials is presented in Fig. 2.

The values of σ_{0p} were found to be 1.29, 15.29 and 14.84 for IBN, DCP, and MCC, respectively. The results further indicated the suitability of Percolation model to describe the relationship between tensile strength and relative density on exponential scale. The lower values of σ_{0p} for IBN confirmed the findings of R-D model, wherein IBN had exhibited very poor inherent bonding propensity.

3.2.3. Application of L and P mixing rule to R-D and Percolation models

This section discusses the predictive model for multi-component systems in which the volume fractions of the materials are related linearly and powerly to the parameters of R-D and Percolation models. The various combinations of L and P mixing rule were applied to the parameters of R-D and Percolation models.

Table 2
R-D and percolation parameters for single component system. The values in parenthesis indicate the minimum experimental points taken for regression analyses.

Material	R-D Model			Percolation model		
	σ_{0r}	κ	R^2	σ_{0p}	T_f	R^2
IBN ($n > 150$)	1.35	9.94	0.9290	1.29	8.92	0.9243
DCP ($n > 110$)	22.66	12.66	0.9672	15.29	9.46	0.9678
MCC ($n > 150$)	21.39	7.38	0.9918	14.84	4.83	0.9915

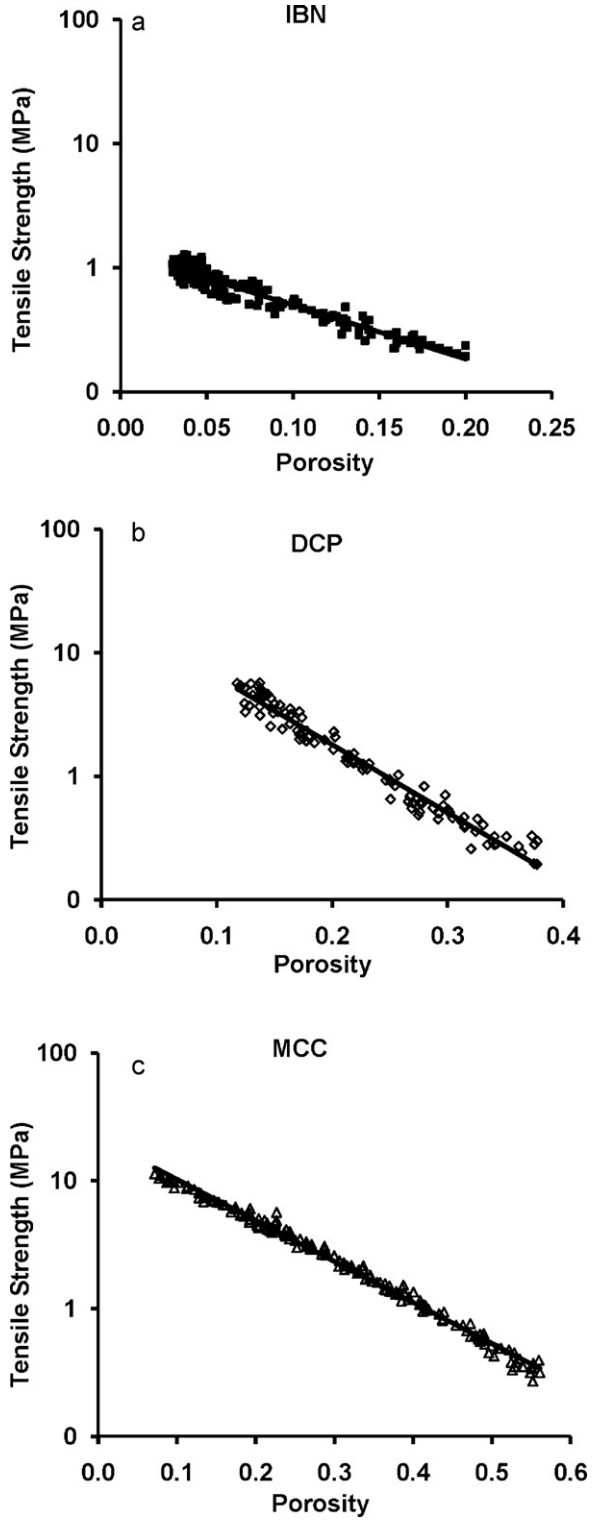

Fig. 1. The relationship between the tensile strength and porosity for (a) IBN, (b) DCP, and (c) MCC.

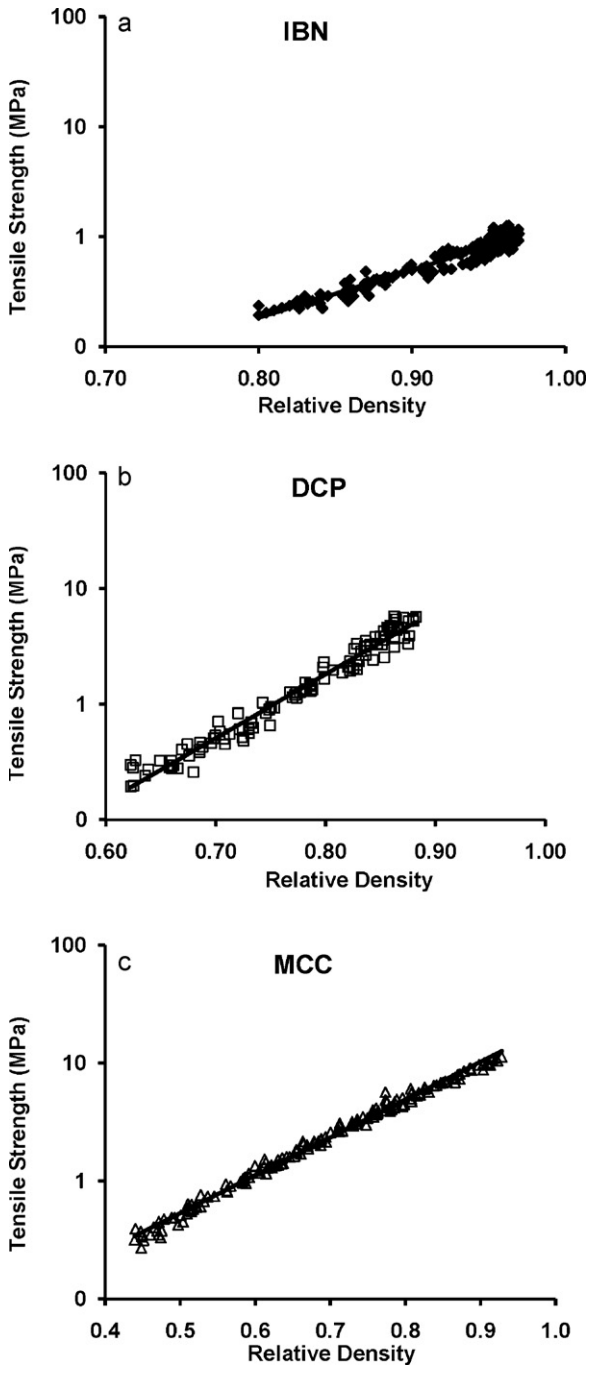

Fig. 2. The relationship between the tensile strength and relative density for (a) IBN, (b) DCP, and (c) MCC.

For mixtures, assuming that the volumes of constituent powders do not change during the tableting process, the tensile strength at zero porosity (σ_{0rm}) and bonding capacity (k_m) of mixture can be approximated using a L mixing rule using following equations (Eqs. (6) and (7)) (Kuentz and Leuenberger, 2000; Leuenberger, 1985)

$$\sigma_{0rm} = \sum_{i=1}^{n} \sigma_{0ri}\delta_i \tag{6}$$

$$k_m = \sum_{i=1}^{n} k_i\delta_i \tag{7}$$

where, $i = 1,2,3\ldots$ which indicates the number of components in blend. δ_i is the volume fractions of the constituent powders, which can also be measured using particle density and weight fractions of constituent powders. Similarly, the tensile strength at zero porosity (σ_{0rm}) and bonding capacity (k_m) of mixture can be approximated using P rule with the help of following equations (Eqs. (8) and (9)) (Kuentz and Leuenberger, 2000; Leuenberger, 1985):

$$\sigma_{0rm} = \sum_{i=1}^{n} (\sigma_{0ri})\delta_i \tag{8}$$

$$k_m = \sum_{i=1}^{n} (k_i)\delta_i \tag{9}$$

The tensile strength (σ_{tm}) of the mixture can hence be obtained using modified R-D equation for a given porosity.

$$\sigma_{tm} = \sigma_{0rm} e^{-k_m(s)} \tag{10}$$

As a consequence four different models were derived and analyzed. The parameters obtained after modeling were compared with experimental results.

The tensile strength at zero porosity (σ_{0pm}) and fracture exponent (T_{fm}) derived from Percolation model for the mixture can be approximated using a L mixing (Eqs. (11) and (12)) and P mixing rule (Eqs. (13) and (14)):

$$\sigma_{0pm} = \sum_{i=1}^{n} \sigma_{0pi}\delta_i \tag{11}$$

$$T_{fm} = \sum_{i=1}^{n} T_{fi}\delta_i \tag{12}$$

$$\sigma_{0pm} = \sum_{i=1}^{n} (\sigma_{0pi})\delta_i \tag{13}$$

$$T_{fm} = \sum\nolimits_{i=1}^{n} (T_{fi})\delta_i \tag{14}$$

$$\sigma_{tm} = \sigma_{0pm}(\rho_{rm})^{T_{fm}} \tag{15}$$

σ_{0pm} and T_{fm} are the tensile strength at zero porosity and the fracture exponent for mixture.

The prediction of tensile strength was performed according to L + L, P + P, L + P, and P + L for R-D and Percolation models. The predicted parameters using all combination of L mixing rule and P relation for R-D and Percolation models are summarized in Table 3. The application of L mixing rule to the parameters of R-D and Percolation models showed the greater deviation from predicted and experimental results. Using L mixing rule, the inherent bonding propensity was predicted to be 4.57 for R-D and 3.47 for Percolation models, which is more than actual experimental results of 2.04 for R-D and 1.98 for Percolation models. Good prediction was apparent as the minimum deviation between predicted trend line and experimental trend line was observed for 80% IBN + 20% MCC (Figs. 3a and 4a) and 80% IBN + 20% DCP (Figs. 3b and 4b) using R-D (Fig. 3) and Percolation models (Fig. 4) treated with P and L mixing rule. All models were statistically analyzed to compare and model selection criterion was applied.

3.2.4. Model selection criterion

3.2.4.1. Residual Sum of Squares (RSSQ). It is a measure of the closeness between the experimental and predicted data. A near to zero RSS indicates a tight fit of the model to the data. It is obtained using

Table 3
The predicted parameters using linear mixing (L) and power law relation (P) for R-D model.

Blend	Model	R-D Model				Percolation model			
		Predicted		Experimental		Predicted		Experimental	
		σ_{tm}	κ_m	σ_{tm}	κ_m	σ_{tm}	T_{fm}	σ_{tm}	T_{fm}
80% IBN + 20% MCC	L + L	4.57	9.53	2.04	9.05	3.47	8.26	1.98	8.04
	P + P	2.92	8.25			2.78	7.56		
	L + P	4.57	8.25			3.47	7.56		
	P + L	2.92	9.53			2.78	8.26		
80% IBN + 20% DCP	L + L	3.58	10.23	2.22	10.68	2.76	8.97	2.12	9.56
	P + P	2.69	9.12			2.59	8.36		
	L + P	3.58	9.12			2.76	8.36		
	P + L	2.69	10.23			2.59	8.97		

following expression.

$$\mathrm{RSSQ} = \sum_{i=1}^{n} [Y_{i\,\mathrm{Expermental}} - Y_{i\,\mathrm{predicted}}]^2 \quad (16)$$

where, n is the number of experimental points.

3.2.4.2. Akaike's information criterion (AIC). AIC is used next to the correlation coefficient and the analysis of the residuals to choose the best model to fit the obtained data (Akaike, 1974). The AIC was calculated from the following equation:

$$\mathrm{AIC} = n \ln \mathrm{SSQ} + 2p \quad (17)$$

where, AIC is the Akaike's information criterion, n is the number of experimental points, SSQ is the sum of the squares of the residuals, and p is number of parameters of the adjusting function.

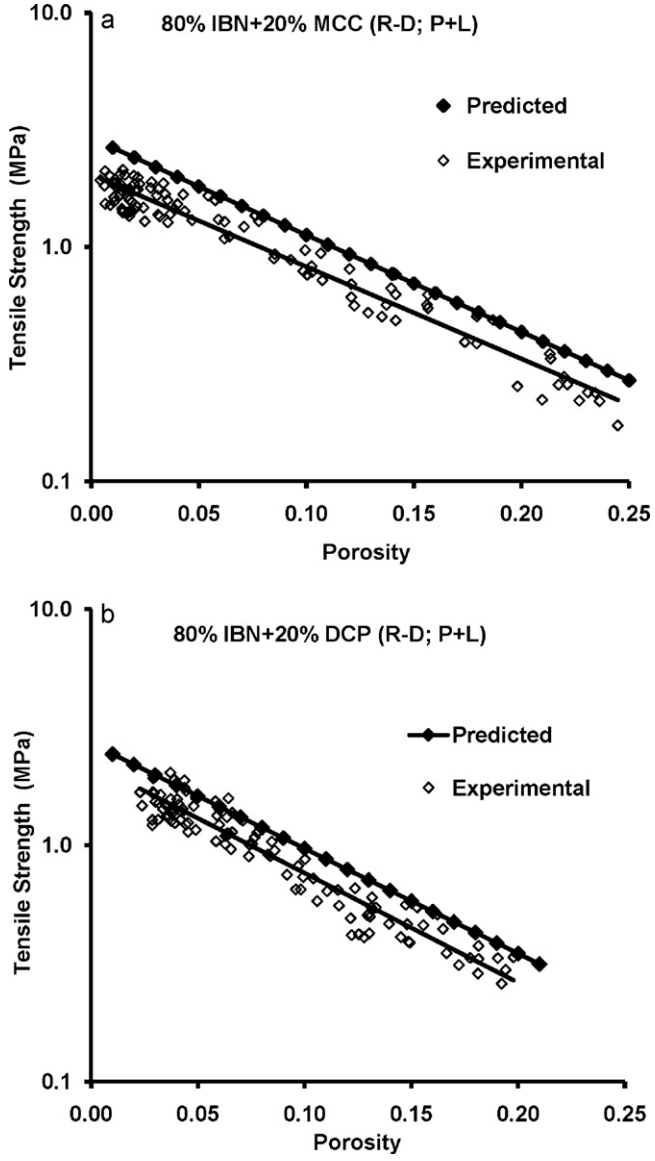

Fig. 3. Predicted and experimental trend line for (a) 80% IBN + 20% MCC and (b) 80% IBN + 20% DCP using R-D model treated with power law mixing and linear mixing rule..

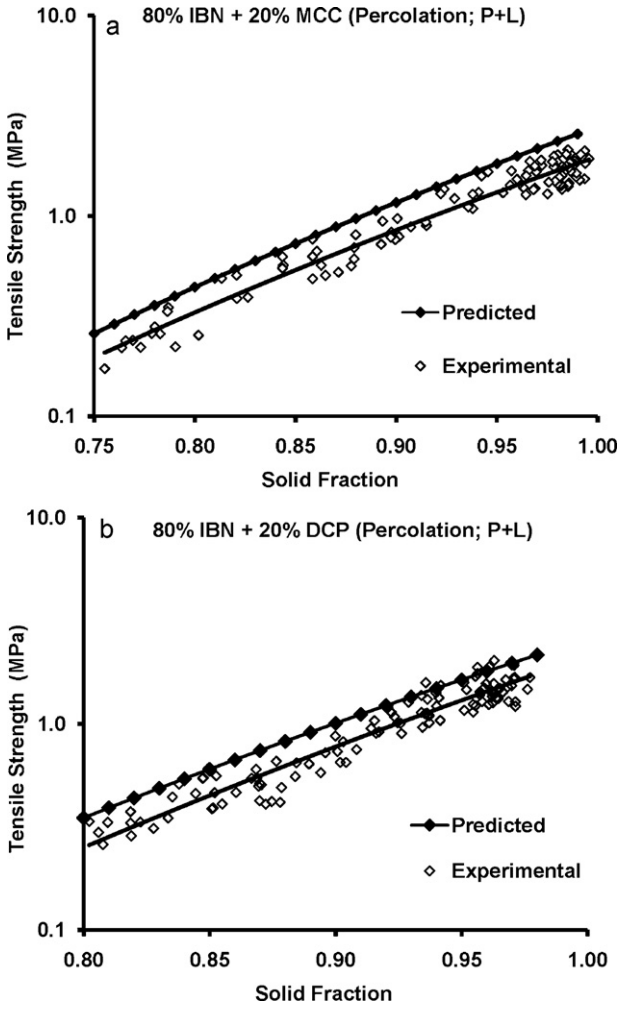

Fig. 4. Predicted and experimental trend line for (a) 80% IBN + 20% MCC and (b) 80% IBN + 20% DCP using Percolation model treated with power law mixing and linear mixing rule.

Table 4
Statistical analysis and model selection criterion RSSQ and AIC.

Blend	Model	RSSQ				AIC			
		L	P	L+P	P+L	L	P	L+P	P+L
80% IBN + 20% MCC	R-D	29.10	5.39	38.35	3.26	107.1	56.52	115.4	41.48
	Percolation	11.14	4.26	13.70	3.14	78.31	49.50	84.52	40.30
80% IBN + 20% DCP	R-D	8.80	2.30	12.06	1.23	71.24	30.94	80.69	12.20
	Percolation	2.41	2.02	3.24	1.40	32.44	27.12	41.31	16.13

3.2.4.3. R-D model. As per the results, the R-D models using L + L, P + P, and L + P showed RSSQ values of 29.10, 5.39, and 38.35, respectively for 80% IBN and 20% MCC blend. The R-D models using L + L, P + P, and L + P showed RSSQ values of 8.80, 2.30, and 12.06, respectively for 80% IBN and 20% DCP blend. R-D model with P + L showed minimum value of RSSQ (3.26 for 80% IBN + 20% MCC blend and 1.23 for 80% IBN + 20% DCP blend) and AIC (41.48 for 80% IBN + 20% MCC blend and 12.20 for 80% IBN + 20% DCP blend) which indicated closeness between experimental and predicted results (Tables 3 and 4).

3.2.4.4. Percolation model. The percolation models using L + L, P + P, and L + P showed RSSQ values of 11.14, 4.26, and 13.70, respectively for 80% IBN and 20% MCC blend. The Percolation model using L + L, P + P, and L + P showed RSSQ values of 2.41, 2.02, and 3.24, respectively for 80% IBN and 20% DCP blend. Percolation model with P + L showed minimum value of RSSQ (3.14 for 80% IBN + 20% MCC blend and1.40 for 80% IBN + 20% DCP blend) and AIC (40.30 for 80% IBN + 20% MCC blend and 16.13 for 80% IBN + 20% DCP blend) which indicated the good agreements with experimental results (Tables 3 and 4).

4. Conclusion

The results indicated that the R-D and Percolation models based on combinations of P + L can well predict the mechanical properties of binary system containing predominantly poorly compressible drug candidate. The R-D and Percolation models for multi-component systems can be systematically generalized to other powders. Formulation development of high-dose poorly compressible drugs is challenging, as limited quantity of excipients can be incorporated in the unit formula. The present study can help in designing of compacted solid dosage forms, using the data base generated for individual excipients like diluents. An understanding of compaction behavior of powder mixtures shall enable defining of the design space, during formulation development. The proposed model uses relationship between porosity/density and tensile strength, without need for sophisticated instrumentation. The compaction profiling of commonly used excipients and drugs in terms of their bonding strength would facilitate qualitative and quantitative selection of excipients during formulation development.

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