Article:
Corrigan, J. orcid.org/0000-0002-5238-5577, Li, F., Dawson, N. et al. (4 more authors) (2024) An interaction-based mixing model for predicting porosity and tensile strength of directly compressed ternary blends of pharmaceutical powders. International Journal of Pharmaceutics, 664. 124587. ISSN 0378-5173

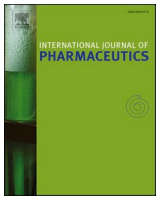
https://doi.org/10.1016/j.ijpharm.2024.124587

International Journal of Pharmaceutics 664 (2024) 124587

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm



An interaction-based mixing model for predicting porosity and tensile strength of directly compressed ternary blends of pharmaceutical powders

Jeremiah Corrigan [a], Feng Li [f], Neil Dawson [b], Gavin Reynolds [c], Stefan Bellinghausen [d], Simeone Zomer [e], James Litster [a,*]

[a] Department of Chemical and Biological Engineering, University of Sheffield, UK
[b] Pfizer Worldwide Research, Development and Medicial, Sandwich, UK
[c] Pharmaceutical Technology and Development, Operations, AstraZeneca, Macclesfield, UK
[d] Siemens GmbH, London, UK
[e] Drug Product Development, Glaxosmithkline R&D, Ware, UK
[f] School of Environmental Science and Engineering, Suzhou University of Science and Technology, Suzhou 215009, PR China

ARTICLE INFO

Keywords:
Compactability
Compressibility
Tensile Strength
Modeling
Direct compression
Formulation design

ABSTRACT

Predicting the mechanical properties of powder mixtures without extensive experimentation is important for model driven design in solid dosage form manufacture. Here, a new binary interaction-based model is proposed for predicting the compressibility and compactability of directly compressed pharmaceutical powder mixtures based on the mixture composition. The model is validated using blends of MCC, lactose and paracetamol or ibuprofen. Both compressibility and compactability profiles are predicted well for a variety of blend compositions of ternary mixtures for the two formulations. The model performs well over a wide range of compositions for both blends and better than either an ideal mixing model or a ternary interaction model. A design of experiments which reduces the amount of API required for fitting the model parameters for a new formulation is proposed to reduce amount of API required. The design requires only three blends containing API. The model gives similar performance to the well-known Reynolds et al. model (2017) when trained using the same data sets. The binary interaction model approach is generalizable to other powder mixture properties. The model presented in this work is limited to curve-fitting of empirical compaction models for mixtures of common pharmaceutical powders and is not intended to provide guidance on the practical operating space (or design space) limits.

1. Introduction

Compaction is used within the pharmaceutical industry to create tablets, which are the most common solid oral dosage forms. Understanding and predicting the compaction behaviour of these powder mixtures is critical to aid in product quality. For example, tablets must be strong enough to retain their form during downstream processing. Direct Compression is a popular continuous manufacturing approach and since the compaction step is one of few critical stages in this process, understanding compaction behaviour of directly compressed powder mixtures is critical. However, predicting this behaviour is difficult to due to diverse blend properties and complex interactions between constituent powders (Busignies et al., 2006).

The compaction behaviour of a powder mixture is typically described by compressibility, compactability and tabletability (Tye et al., 2005). Compressibility refers to how the porosity (or solid fraction) of the powder changes under applied pressure. Compactability is the variation of the tensile strength of the compact for different porosities. The tabletability describes how the tensile strength varies with applied compaction pressure and can be seen as the combination of compressibility and compactability (see Fig. 1). Predicting tabletability of potential formulations can potentially reduce costs associated with extensive experimentation.

Several models have been used previously for predicting compaction behaviour for powder mixtures. However, the biggest challenge is predicting behaviours for mixtures where the formulation properties are not known. Generally, the formulation properties must be measured as an input to some of these models, which requires significant experimentation for process optimisation. Mixture rules can be used to predict compaction behaviour of a mixture based on the formulation properties

* Corresponding author.
E-mail address: James.Litster@sheffield.ac.uk (J. Litster).

https://doi.org/10.1016/j.ijpharm.2024.124587
Received 20 March 2024; Received in revised form 26 July 2024; Accepted 12 August 2024
Available online 13 August 2024

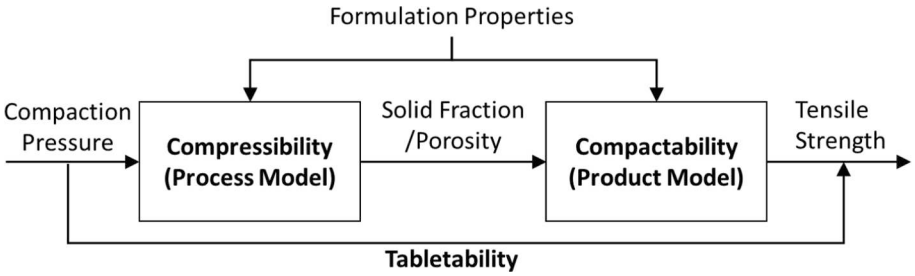


Fig. 1. Overview of the link between compressibility, compactability and tabletability for describing compaction behaviour.

from single component properties, allowing changes in compressibility and compactability to be investigated in silico, thus reducing costs (Reynolds et al., 2017). This is known as Model Driven Design (MDD) and can be used to aid early-stage formulation design for tablets. Without reliable mixture models for compressibility and compaction properties, any model based optimisation of formulation for compaction is impossible. Being able to use model-based approaches has the potential to significantly reduce development time and material used during scale up, as well as reduce the number of failed batches. Mixing rules have also been applied to solid mixtures in other industries. For example, Silva and Miranda (2003) used mixing rules to accurately predict some of the powder mixture properties, such true density and specific surface area, for catalyst applications.

Compressibility models such as the Kawakita (Kawakita and Lüdde, 1971), Heckel (Heckel, 1961) and Gurnham (Zhao et al., 2006) equations can capture the compressibility relationship for a given mixture well. The Kawakita equation is described by the following:

$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a} \tag{1}$$

where P is applied pressure, C is the degree of volume reduction; a and b are fitting parameters. The Kawakita equation is more generally applied to soft powders in vertical vibrating or tapping compaction (Wang et al., 2021). The Heckel equation assumes the compaction is analogous to a first-order reaction and relates the relative density to the applied pressure (Heckel, 1961), as given by:

$$ln\left(\frac{1}{1-\gamma_T}\right) = KP + ln\left(\frac{1}{1-\gamma_I}\right) \tag{2}$$

where γ_T is the relative density of the powder after compaction, γ_I is relative density before compaction and K is a constant that is material-dependent. Denny (2002) presented detailed comparisons between the Kawakita and Heckel models, which concluded that neither model predicts compressibility behaviour well over a wide range of applied pressures and a wide range of materials. Both models are only considered valid for relatively low ranges of applied pressures.

The Gurnham equation (Eq. (3) was proposed by Zhao et al. (2006) as an alternative to the Kawakita and Heckel equations to accurately predict the compressibility of pharmaceutical mixtures. Zhao et al. (2006) proposed and validated using the Gurnham equation, which was well known in chemical engineering but had not been studied for pharmaceutical powder mixtures prior to this work. The results demonstrated predicting compressibility more accurately over wider pressure ranges than the Kawakita or Heckel equations.

The Gurnham equation is given by the following:

$$\varepsilon(P) = -\frac{1}{K} ln\left(\frac{P}{P_0}\right) \tag{3}$$

For modelling compactability, the Ryshkewitch-Duckworth equation (Wu et al., 2005) has been extensively applied due to its simplicity (Etzler et al., 2011, Wang et al., 2021). It is described by the following:

$$\sigma = \sigma_0 e^{-k_b \varepsilon} \tag{4}$$

where σ is the tensile strength of the compacted powder, σ_0 is the tensile strength at zero porosity and k_b is the bonding number. The main alternative to the Ryshkewitch-Duckworth model is the model proposed by Kuentz et al. (1999), which relates tensile strength to the solid fraction before and after compaction, as given by:

$$\sigma = k(\gamma - \gamma_c)^{2.7} \tag{5}$$

where γ and γ_c are the solid fraction before and after compaction respectively, and k is a model parameter. This model was developed based on percolation theory and mainly is applied to powders with relatively low densities. A comparison between Ryshkewitch-Duckworth and Kuentz models by Wang et al. (2021) showed that the Ryshkewitch-Duckworth model produced better tensile strength predictions for ternary mixtures. A more in-depth review of compressibility and compactability models was carried out by Wang et al. (2021).

These compressibility and compactability models are good when the formulation properties are known. However, a change in the formulation, whether a different active pharmaceutical ingredient (API)/excipient is used or the composition of the same ingredients changes, the relationship between porosity and applied pressure is likely to change. This means that the parameters in these models will likely need updating and this will often require further experimentation. Ideally, compaction behaviour of mixtures could be predicted with minimal experimentation based on the properties of the single components of the mixture, i.e., the model can predict compaction properties of a new formulation with the same set of parameters by incorporating mass or volume fractions into the model.

Frenning et al. (2009) proposed a volume-additive model based on the Kawakita equation for predicting compressibility, where the Kawakita parameters of the mixture (effective parameters) are derived from the volumes and parameters of a single component. The authors validated the approach for binary mixtures. Mazel et al. (2011) proposed an improvement to the Frenning model (Frenning et al., 2009) that did not use effective Kawakita parameters. Instead, the authors used the Kawakita parameters of the pure products and applied this to binary mixtures of L-alanine and microcrystalline cellulose (MCC), where good prediction of the compressibility was observed. Busignies et al. (2012) used a very similar approach, however, instead the model was a function of density so that it was more independent of geometry. This approach was also not limited to binary mixtures and was successfully applied to predict the porosity of 4 different mixtures using 4 commonly used pharmaceutical excipients, however, prediction error was significantly higher at lower applied compaction pressures.

Reynolds et al. (2017) took a slightly modified form of the Gurnham equation, as a basis of a method for predicting compressibility of multi-component pharmaceutical powder mixtures and used a volume additive approach to predict the porosity of the mixture based on the Gurnham equation parameters of the single components in the mixture and their volumetric compositions. The main assumption in this model is the "consideration of the volumetric occupancy of each powder under an applied compaction pressure and the respective contribution it then makes to the mixture properties" (Reynolds et al., 2017). As the mixture is compressed there is difference in the relative volumetric proportions

of each constituent. The approach led to accurate predictions of compressibility for binary and ternary mixtures of pharmaceutical excipients.

Wu et al. (2006) proposed a model based on the Ryshkewitch-Duckworth equation to predict the tensile strength of multi-component pharmaceutical mixtures as a function of porosity (compactability). Various mixtures of excipients of up to four components were used to assess the model's performance, which showed good predictions against the experimental data. However, tensile strength was overestimated at a solid fraction of less than 0.55, which has been observed in other work using Ryshkewitch-Duckworth as well. Nevertheless, it was observed that pharmaceutical tablets typically have a solid fraction in the range of 0.7–0.9 where the model predicted well, and so the Ryshkewitch-Duckworth is likely still practically appropriate for compactability modelling for pharmaceutical tabletting. Reynolds et al. (2017) built on this work, and the work by Etzler et al. (2011), by incorporating the volumetric contribution of each component in the mixture, with the tensile strength of the individual components, to predict the tensile strength of the mixture. Binary and ternary mixtures of three commonly used pharmaceutical excipients were characterised and used to validate the model. These results demonstrated the ability to predict the compactability of these mixtures very well, with only the characterisation of the individual excipients necessary to calibrate the model.

Jolliffe et al. (2022) presented an approach involving the extrapolation of binary tablet data for challenging materials where compaction of these pure components is not possible. Then various mixing rules were used for comparison, similar to many of the previously discussed methods, to predict compressibility and compactability of the mixtures. This approach serves as an extension to approaches, such as Reynolds et al. (2017), in circumstances where one of the pure components cannot be compressed. However, the approach has limitations, such as the use of only binary mixtures and that the extrapolation accuracy decreases at high drug loadings and for certain API.

Recently, Aroniada et al. (2023) developed a model based on mixing rules for ternary blends for predicting various flow properties of a mixture based on binary interactions between the components.

Wang et al. (2021) presented a comprehensive assessment of the most popular compressibility models for continuous pharmaceutical tabletting and recommended the Reynolds et al. (2017) model due to its accurate porosity predictions with only 2 parameters.

Despite good predictive capability shown in these previous studies, the Reynolds et al. (2017) model only considers the volumetric contributions of each component in a linear combination. However, Busignies et al. (2006) observed nonlinear interactions when studying multiple binary mixtures of excipients. Therefore, considering nonlinear interactions could lead to a more robust model. Additionally, the Reynolds et al. (2017) model was only validated on a single ternary mixture that only included excipients and so further validation on more ternary mixtures that also include APIs is required.

This study aims to expand on previous studies (Reynolds et al., 2017, Wu et al., 2006) to develop models to predict both the porosity and tensile strength of pharmaceutical mixtures by including higher order interactions in the mixture models as well a comparison with the original Reynolds et al. (2017) model to further validate this model. Additionally, a design of experiments, which reduces the amount of API required for fitting the model parameters for a new formulation, is proposed for model calibration with new formulations. By predicting the compressibility and compactability of the mixtures using minimal experimental data, the tabletability of the formulation can be assessed to aid formulation and process design.

2. Material and methods

2.1. Modelling theory

When considering the compressibility and compactability of directly compressed powder mixtures, mixture rules are typically incorporated into these equations. Reynolds et al. (2017) used a volume additive model which calculated the mixture porosity by considering the volumetric proportions of the porosity of each component within the mixture. The same principal was applied to the tensile strength model.

The Reynolds et al. (2017) compressibility mixture model is given by the following two equations:

$$\varepsilon_{mix}(P) = \sum_i \delta_i \varepsilon_i(P) \tag{6}$$

where ε_{mix} is the porosity of the compacted mixture, $\varepsilon_i(P)$ is the porosity of component i that can be calculated by the Gurnham equation (Equation (3), and δ_i is the variable volumetric composition of component i which can be described as:

$$\delta_i = \frac{x_i/\left((1-\varepsilon_i(P))\rho_{true,i}\right)}{\sum x_i/\left((1-\varepsilon_i(P))\rho_{true,i}\right)} \tag{7}$$

where x_i is the mass fraction of component i in the mixture and $\rho_{true,i}$ is the true density of particles of component i. For this compressibility model, the parameters that require fitting are K and P_0 from Equation (3) for each pure component.

The Reynolds et al. (2017) compactability mixture model is given by the following:

$$\ln(\sigma_{mix}) = \sum_i \delta_i \ln(\sigma_i) \tag{8}$$

where σ_i given by the Ryshkewitch-Duckworth equation (Equation (4). For this compactability model, the parameters that require fitting are σ_0 and k_b from Equation (4) for each pure component.

Wu et al. (2005) proposed a similar mixture model using volumetric proportions for predicting tensile strength with the Ryshkewitch-Duckworth equation. However, instead of an additive model for the porosity of each component (as in (Reynolds et al., 2017)), the mixing rule was for the volumetric contributions of each constant within the model, i.e. the bonding number, k_b, for the mixture was equal to the sum of the bonding numbers of each constituent powder multiplied by the volume fractions of each constituent powder. Further improvements to these mixture models could be made by considering higher order interactions.

Considering a ternary powder mixture; after compaction, the porosity of the mixture can be described by altering Equation (3) to give the following:

$$\varepsilon_{mix}(P) = -\frac{1}{K_{mix}} ln\left(\frac{P}{P_{0,mix}}\right) \tag{9}$$

where ε_{mix} is the porosity of the compacted mixture, K_{mix} is the compressibility constant of the mixture and $P_{0,mix}$ is the pressured needed to produce a compact of zero porosity for the mixture.

We then assume that the two constants in Equation (9) can be described with a binary interaction model of the constants relating to each of the constituent powders, as detailed by the following equations:

$$K_{mix} = K_A y_A + K_B y_B + K_C y_C + K_{AB} y_A y_B + K_{AC} y_A y_C + K_{BC} y_B y_C \tag{10}$$

$$\begin{aligned} \ln(P_{0,mix}) = {} & \ln(P_{0,A}) y_A + \ln(P_{0,B}) y_B + \ln(P_{0,C}) y_C + \ln(P_{0,AB}) y_A y_B \\ & + \ln(P_{0,AC}) y_A y_C + \ln(P_{0,BC}) y_B y_C \end{aligned} \tag{11}$$

where K_i is the compressibility constant for component i, y_i is the volume fraction of component i, K_{ij} is the compressibility constant for a binary mixture of components i and j, $P_{0,i}$ is the P_0 for component i and $P_{0,ij}$ is the P_0 for a binary mixture of components i and j.

The mixture parameters are weighted by volume fractions which are determined from the pure component mass fractions and pure component true densities (Eq. (12).

$$y_i = \frac{\frac{x_i}{\rho_{true,i}}}{\sum_i \frac{x_i}{\rho_{true,i}}} \tag{12}$$

The binary interactions are considered in this proposed model. However, an ideal mixing model (no binary interaction terms) and a ternary interaction mixture model were also tested for comparison. The ideal interaction is given below in Equations (13) and (14), and the ternary interactions in Equations (15) and (16).

$$K_{mix} = K_A y_A + K_B y_B + K_C y_C \tag{13}$$

$$\ln(P_{0,mix}) = \ln(P_{0,A}) y_A + \ln(P_{0,B}) y_B + \ln(P_{0,C}) y_C \tag{14}$$

$$K_{mix} = K_A y_A + K_B y_B + K_C y_C + K_{AB} y_A y_B + K_{AC} y_A y_C + K_{BC} y_B y_C + K_{ABC} y_A y_B y_C \tag{15}$$

$$\begin{aligned} \ln(P_{0,mix}) = {} & \ln(P_{0,A}) y_A + \ln(P_{0,B}) y_B + \ln(P_{0,C}) y_C + \ln(P_{0,AB}) y_A y_B \\ & + \ln(P_{0,AC}) y_A y_C + \ln(P_{0,BC}) y_B y_C + \ln(P_{0,ABC}) y_A y_B y_C \end{aligned} \tag{16}$$

An identical approach can be taken for creating the compactability mixture model, except starting from the Ryshkewitch-Duckworth equation. The tensile strength of a ternary mixture as a function of porosity can be described by the following equation:

$$\sigma_{mix}(\varepsilon) = \sigma_{0,mix} e^{-k_{b,mix}\varepsilon} \tag{17}$$

where σ_{mix} is the tensile strength of the powder mixture, $\sigma_{0,mix}$ is the tensile strength at zero porosity for the mixture and $k_{b,mix}$ is the bonding number of the mixture.

As with the compressibility model, the two constants of the mixture can be described by binary interaction mixture models:

$$\sigma_{0,mix} = \sigma_{0,A} y_A + \sigma_{0,B} y_B + \sigma_{0,C} y_C + \sigma_{0,AB} y_A y_B + \sigma_{0,AC} y_A y_C + \sigma_{0,BC} y_B y_C \tag{18}$$

$$k_{b,mix} = k_{b,A} y_A + k_{b,B} y_B + k_{b,C} y_C + k_{b,AB} y_A y_B + k_{b,AC} y_A y_C + k_{b,BC} y_B y_C \tag{19}$$

where $\sigma_{0,i}$ is the tensile strength at zero porosity for pure component i, $\sigma_{0,ij}$ is the tensile strength at zero porosity for a binary mixture of components i and j, $k_{b,i}$ is the bonding number for pure component i and $k_{b,ij}$ is the bonding number for a binary mixture of components i and j. As with the compressibility model, ideal mixture and ternary interaction mixture models are tested for comparison, as given by the following equations:

$$\sigma_{0,mix} = \sigma_{0,A} y_A + \sigma_{0,B} y_B + \sigma_{0,C} y_C \tag{20}$$

$$k_{b,mix} = k_{b,A} y_A + k_{b,B} y_B + k_{b,C} y_C \tag{21}$$

$$\begin{aligned} \sigma_{0,mix} = {} & \sigma_{0,A} y_A + \sigma_{0,B} y_B + \sigma_{0,C} y_C + \sigma_{0,AB} y_A y_B + \sigma_{0,AC} y_A y_C + \sigma_{0,BC} y_B y_C \\ & + \sigma_{0,ABC} y_A y_B y_C \end{aligned} \tag{22}$$

$$\begin{aligned} k_{b,mix} = {} & k_{b,A} y_A + k_{b,B} y_B + k_{b,C} y_C + k_{b,AB} y_A y_B + k_{b,AC} y_A y_C + k_{b,BC} y_B y_C \\ & + k_{b,ABC} y_A y_B y_C \end{aligned} \tag{23}$$

The fitting of the constants in equations (10) and (11), and (18) and (19), is done using experimental data for various single, binary and ternary mixtures of powders.

2.2. Model evaluation methodology

To evaluate whether the modified Gurnham equation (Equation (3) was able to capture the compressibility relationship well for the experimental data generated in this study, Equation (3) was fitted to each blend, for both formulations. The adjusted R^2 and RMSE were calculated to assess the fit for each blend. Adjusted R^2 is used because it is adjusted for models with different parameters and so allows for comparison between models of different numbers of parameters. Adjusted R^2 is calculated by the following:

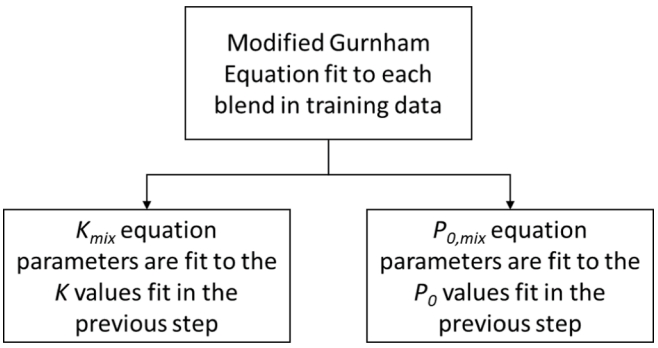


Fig. 2. Overview of the parameter fitting procedure for the compressibility model.

$$R^2_{adj} = 1 - \frac{(1 - R^2)(n - 1)}{n - p - 1} \tag{24}$$

where n is the number of samples and p is the number of features/input variables. The R^2 is given by:

$$R^2 = 1 - \frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{n} (y_i - \bar{y})^2} \tag{25}$$

where y is the actual value of the response, $\hat{y}$ is the predicted response and $\bar{y}$ is the mean of the actual response. The RMSE is calculated as:

$$RMSE = \sqrt{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2} \tag{26}$$

The same process of fitting was repeated with the Ryshkewitch-Duckworth equation (Equation (4) for the compactability profiles. From the fitted compressibility and compactability profiles, the K, P_0, k_b and σ_0 parameters for each blend can be extracted.

To apply the proposed mixing model, first the six parameters in Equation (10) and the six parameters in Equation (11) are fitted to a set of training data. Instead of fitting all 12 parameters on the full porosity data for each blend within the training data set in 1 step, it makes more sense to fit the Equation (10) parameters to the K values for those blends, which are determined by fitting the modified Gurnham equation to those training data blends. Then the same is done for the P_0 and the parameters in equation (11). This essentially leads to a 3-stage fitting procedure, as illustrated in Fig. 2. The parameter estimation was carried out in MATLAB using the *fitlm* function with default conditions.

An identical procedure is applied for the parameter estimation of the proposed compactability model.

Firstly, for initial evaluation of the proposed models, the parameters are estimated using all available blends as the training data. Additionally, to evaluate the use of binary interactions in the mixture models, the parameter fitting procedure was repeated using an ideal mixture model (Eqns. (13), (14), (20) and (21)). The models were then also evaluated with the addition of a ternary interaction term (Eqns. (15), (16), (22) and (23)).

Secondly, a design of experiments was proposed to recommend a reduced set of blends as the training data for model calibration for future formulations. This experimental design tested different sets of blends as training data and evaluated the resulting average RMSE. The different sets of training data were developed to minimise API usage and use as many of the binary excipient-excipient blends as possible. If simply the API is swapped in the formulation, then only experiments using the ternary blends would need to be performed because the binary excipient

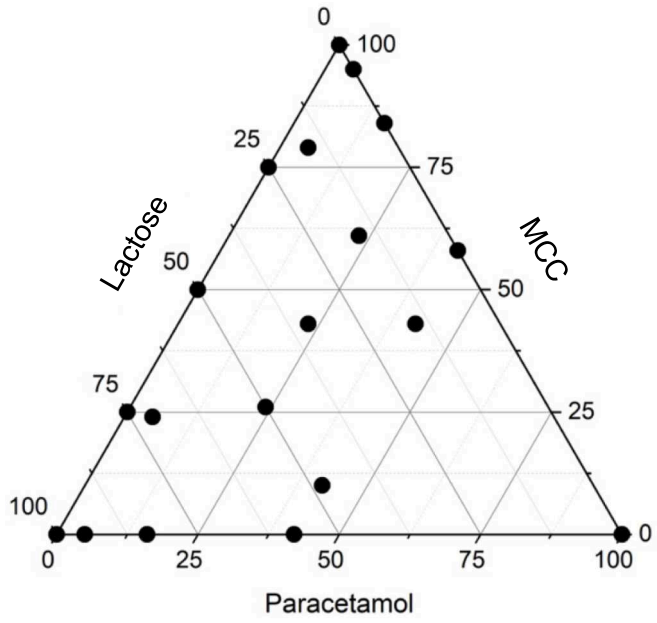


Fig. 3. Mass percentages of the paracetamol, MCC and lactose that were varied to create 19 blends for formulation 1 (Table 1).

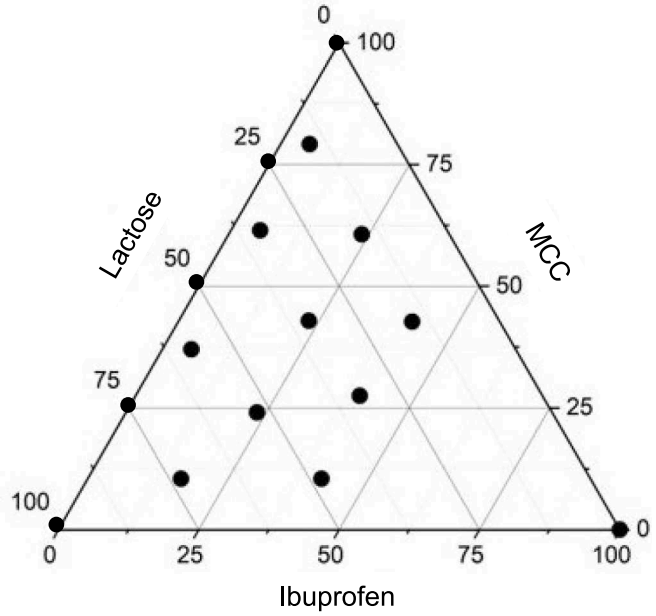


Fig. 4. Mass percentages of the ibuprofen, MCC and lactose that were varied to create 11 blends for formulation 2 (Table 2).

Table 1
Mass percentages of the mixtures for formulation 1 (paracetamol).

Blend	Paracetamol (%)	MCC (%)	Lactose (%)	Ac-di-sol (%)	Magnesium Stearate (%)
1	96	0	0	3	1
2	40	56	0	3	1
3	40	0	56	3	1
4	40	41	15	3	1
8	5	91	0	3	1
9	15	81	0	3	1
10	5	0	91	3	1
11	15	0	81	3	1
12	22	41	33	3	1
13	5	23	68	3	1
14	23	25	48	3	1
15	5	76	15	3	1
16	40	10	46	3	1
17	22	59	15	3	1

Table 2
Mass percentages of the mixtures for formulation 2 (ibuprofen).

Blend	Ibuprofen (%)	MCC (%)	Lactose (%)	Ac-di-sol (%)	Magnesium Stearate (%)
1	96	0	0	3	1
2	22.78	58.22	15.00	3	1
3	22.23	41.18	32.59	3	1
4	5.00	76.00	15.00	3	1
5	40.00	41.00	15.00	3	1
6	5.00	59.03	31.97	3	1
7	16.00	10.00	70.00	3	1
8	40.00	10.00	46.00	3	1
9	22.45	23.09	50.46	3	1
10	38.37	26.39	31.24	3	1
11	5.00	35.52	55.48	3	1

Table 3
Mass percentages of excipient blends.

Blend	API (%)	MCC (%)	Lactose (%)	Ac-di-sol (%)	Magnesium Stearate (%)
12	0	96	0	3	1
13	0	0	96	3	1
14	0	48	48	3	1
18	0	24	72	3	1
19	0	72	24	3	1

blends had been performed previously and the data could be stored for future use for model calibration.

After the training data set to reduce API usage was selected, the remaining blends were used for model validation. This proposed experimental design was developed on the paracetamol formulation and validated on the ibuprofen formulation.

2.3. Experimental methods

Two formulations were used in this study for model calibration and validation, both incorporating four commonly used excipients within the pharmaceutical industry: lactose monohydrate (Lactose SuperTab 21AN), microcrystalline cellulose (MCC) (Avicel PH102), Ac-Di-Sol (disintegrant) and magnesium stearate (lubricant). The first formulation, denoted as formulation 1, had the addition of Micronized Paracetamol (Mallinckrodt Pharmaceuticals, USA) as the active pharmaceutical ingredient (API); the second formulation, denoted as formulation 2, added Ibuprofen 50 (BASF, USA) as the API.

To understand the effect of different compositions on compaction, the mass fraction of API, lactose and MCC was varied within a ternary phase diagram to create different blends, with Ac-Di-Sol and magnesium stearate kept at a constant amount, of 3 % and 1 % w/w respectively, throughout. For formulation 1; 7 ternary blends; 6 binary blends including paracetamol, 1 single paracetamol blend, and 5 binary blends of lactose and MCC are used. These 19 blends are illustrated on a ternary phase diagram in Fig. 3, calculated on an Ac-Di-Sol/Magnesium Stearate free basis, and described in Table 1 for exact mass fractions. For formulation 2; 10 ternary blends were created, with a single ibuprofen blend. In addition, the binary lactose/MCC blends from formulation 1 were used in model development for formulation 2. More ternary blends were used in formulation 2 to provide additional data for validation of the modelling approach, as typically ternary blends with API are of interest. Fig. 4 illustrates these ibuprofen blends on a ternary phase diagram, including exact mass fractions in Table 2. The mass fractions for

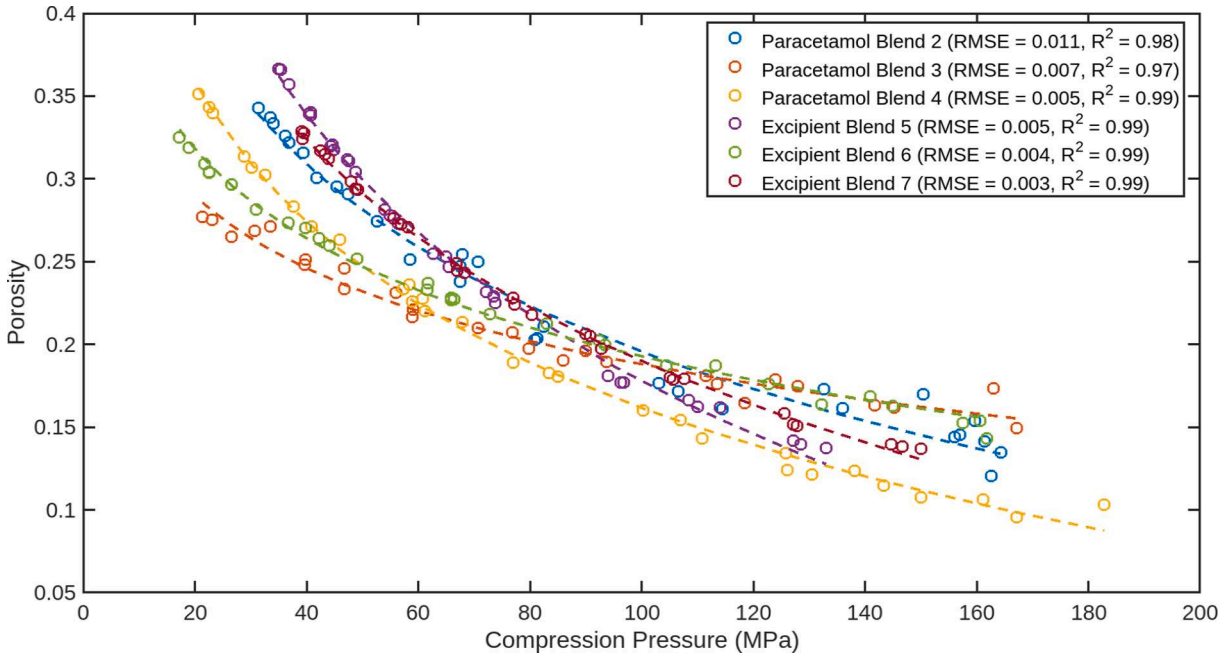


Fig. 5. Experimental compressibility curves with fits from the modified Gurnham equation for paracetamol formulations blends 2 to 4, and excipient blends 5 to 7.

the excipient only blends are displayed in Table 3.

A 3 L bin mixer (Sinoped, China) was used to prepare the different mixtures for both formulations. For each mixture, the API (paracetamol/ibuprofen), lactose, MCC and Ac-Di-Sol were pre-mixed in the bin mixer with 65 % filling ratio and 20 rpm rotational speed for 20 min. The required amount of magnesium stearate is then added to the bin mixer and the mixture is lubricated with a 40 % headspace, at 20 rpm, for 8 min and 40 s.

For each blend, tablets were manufactured via direct compression using a Phoenix Compaction Simulator (Phoenix, Rubery Owen, Telford, England). The compaction simulator was fitted with 10 mm flat faced punch and die. Punch surface and die were lubricated using magnesium stearate (Mallinckrodt Pharmaceuticals, USA) suspended in methanol. The methanol was allowed to evaporate before use. 300 mg fill weight was used for all materials, using manual filling. The powder was compressed to 10 different compression heights, using a single ended V shape profile with a punch speed of 30 mm/s. For each tablet compact successful ejected, digital callipers (CD-6″C Digital Calliper, Mitutoyo, UK) were used to measure height and diameter, followed by measuring a diametrical breaking force, using a Hollands C50 tablet hardness tester (Hollands C50, Engineering Solutions, Nottingham, UK).

The compaction pressure was calculated from the average of the upper and lower compression forces, divided by the punch tip cross-sectional area. The porosity of the tablet was calculated from the following:

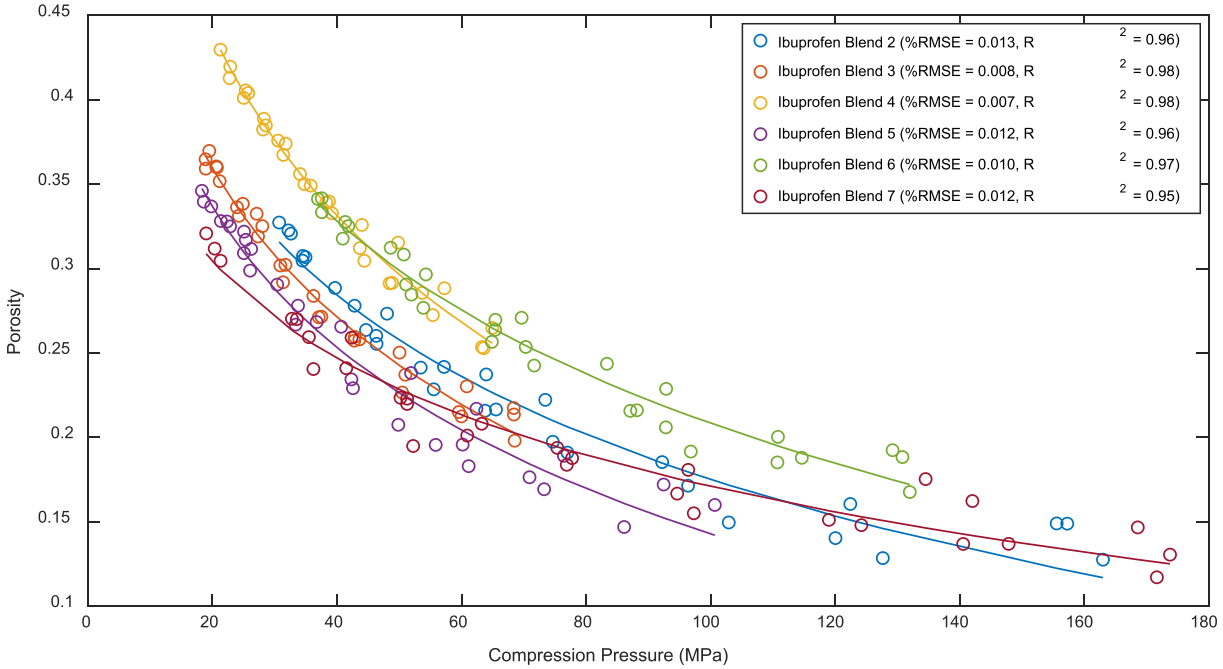


Fig. 6. Experimental compressibility curves with fits from the modified Gurnham equation for ibuprofen formulations blends 2 to 7.

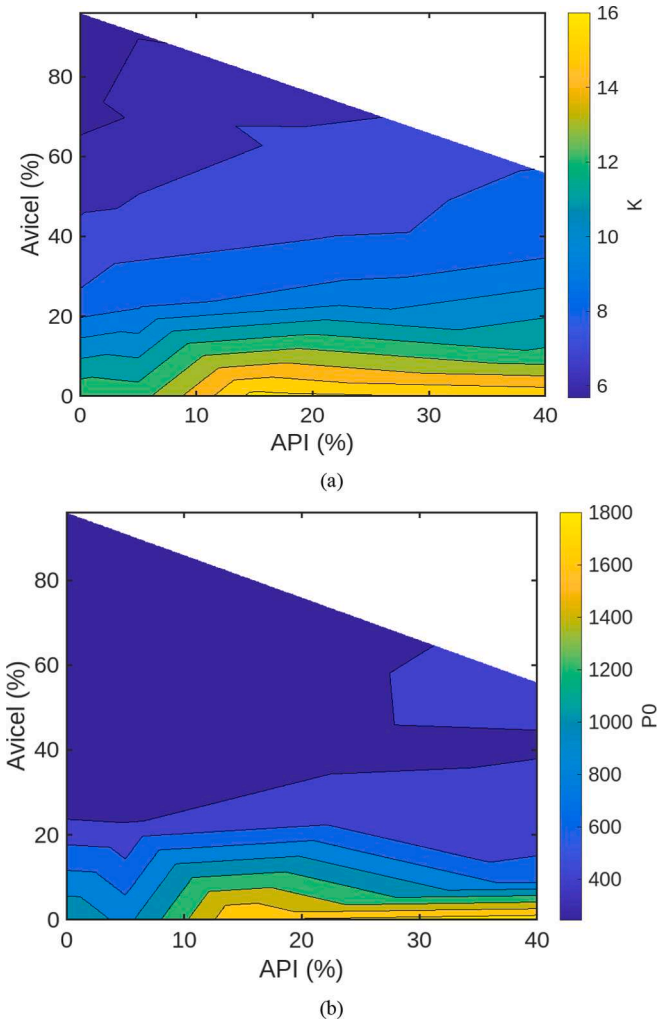


Fig. 7. Variation of modified Gurnham equation parameters with blend composition for the paracetamol formulation: (a) K, (b) P0.

$$\varepsilon = 1 - \frac{m}{\rho \frac{\pi D^2}{4} t} \tag{27}$$

where m is the weight of the tablet, ρ is the true density of the powder mixture, D is the major diameter of the tablet, and t is the tablet thickness. The true density of the powders was measured using a helium gas displacement pycnometer (AccuPyc II 1340, Micromeritics) with a 1 cm^3 cup.

The tensile strength of the compact, σ, is calculated from the tablet geometry and diametrical breaking force through the following equation:

$$\sigma = \frac{2F}{\pi D t} \tag{28}$$

where F is the breaking force (i.e., the hardness).

Blend 1 had issues compacting well due to lamination, for both formulations, and so this blend was not used for the modelling.

3. Results and discussion

3.1. Compressibility model evaluation

For the paracetamol and ibuprofen formulations, the experimental data and the fit with the Gurnham equation, for the first 6 blends, along with the R^2_{adj} and %RMSE (root mean squared error) values, are shown in Figs. 5 and 6 respectively. Details of the formulations in the blends labelled in these figures are shown in Tables 1 and 2. Only blends 2–7 are displayed in these figures, with the remaining blends are omitted to prevent cluttered figures. However, the remaining blends produced very similar fits.

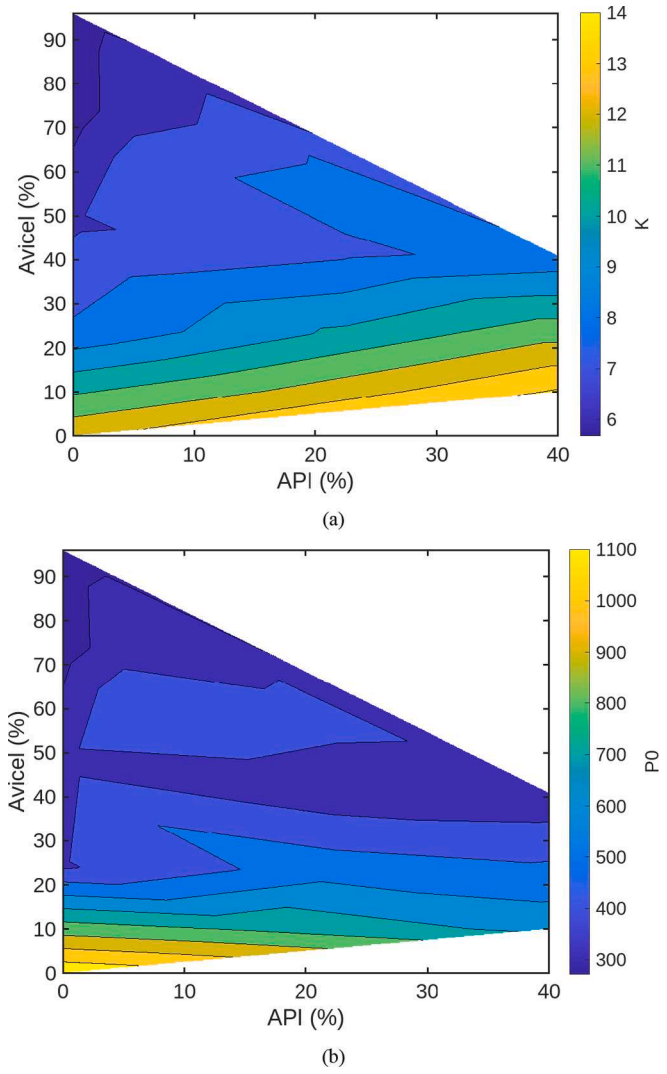


Fig. 8. Variation of modified Gurnham equation parameters with blend composition for the ibuprofen formulation: (a) K, (b) P0.

From these compressibility fits and the associated metrics (above 0.95 R^2 and below 0.013 RMSE, approximately), for both formulations, the modified Gurnham equation captures the relationship between porosity and applied pressure very well for each blend. This validates the selection of this model form on which to base the interaction-based mixture model.

To initially assess whether the proposed interaction mixture model for the parameters within the Gurnham equation is acceptable, the fitted parameters, K and P_0, for each blend are plotted with respect to the mass fraction of the 3 main constituent powders in the mixtures, as illustrated in Figs. 7 and 8. These plots suggest trends in the K and P_0 values associated with the composition of the blend. The relationship is nonlinear indicating including the binary interactions in the mixture model is likely necessary to be able to predict the Gurnham parameters as a function of the ternary blend composition.

Table 4
Compressibility model performance (average RMSE and R^2_{adj} across all blends) against mixing rule for the parameters for both paracetamol and ibuprofen formulations (For concision, X indicates any one of the parameters that incorporates a mixture model).

Mixing Rule		Paracetamol RMSE/R^2_{adj}	Ibuprofen RMSE/ R^2_{adj}
Ideal	$X_{mix} = \sum_i y_i X_i$	0.018/0.89	0.020/ 0.86
Binary	$X_{mix} = \sum_i y_i X_i + \sum_{ij} y_i y_j X_{ij}$	0.012/0.95	0.012/ 0.94
Ternary	$X_{mix} = \sum_i y_i X_i + \sum_{ij} y_i y_j X_{ij} + y_i y_j y_k X_{ijk}$	0.011/0.96	0.011/ 0.95

3.1.1. Parameter estimation using all data

To assess the performance of the proposed model form, all the available blends were used for training data to estimate the model parameters. All 3 mixture rules were assessed and the average RMSE across all blends for each of these mixture rules is displayed in Table 4 for both the paracetamol and ibuprofen formulations.

For the paracetamol formulation, the average RMSE across the training data was 0.012 and the average R^2_{adj} was 0.95 for the proposed binary interaction mixture model. As indicated in the previous section, RMSE<0.013 indicates a very good fit and therefore this indicates acceptable performance for the binary model on average. Comparing the different mixing rules, there is a 33 % improvement in average RMSE going from ideal to binary mixture rules. Since the model complexity is changing from the increase in parameters, it is important to also observe the change in average R^2_{adj}, which account for changes in the number of parameters as discussed previously. Going from ideal to binary rules, the average R^2_{adj} improves from 0.89 to 0.95, which is still a significant improvement. However, only an 8 % improvement in average RMSE comes from the addition of the ternary interaction term, with a negligible 0.4 % change in average R^2_{adj} (0.953 to 0.957). For the ibuprofen formulation, the differences in average RMSE are almost identical, with an even greater improvement from ideal to binary mixture rules, and so the same conclusions can be made. Based on these results, the binary interaction rules were chosen within the model because it provided significant improvements over the ideal mixture rule, but the ternary interaction rule gave negligible improvements when adjusting for the additional model complexity (R^2_{adj}).

Figs. 9 and 10 show examples of these predictions for the paracetamol and ibuprofen blends respectively. The blends in these plots are selected to demonstrate the range of compressibility as well as the extremes in accuracy. Table 5 shows the fitted parameters and the associated 95 % confidence intervals for both formulations. The confidence intervals are reasonable and do not contain zero, further demonstrating that the binary interaction parameters are significant.

3.1.2. Experimental design to reduce API usage for model development

To determine the experiments for model training with reduced API usage, different sets of training data were evaluated and the one which minimised the trade-off between number of experiments using API and model performance was selected as the design of experiments. All five excipient binary blends were used, noting that these data can be collected once and then used for any API formulation. Training sets using additional 2 to 6 ternary blends containing API were then tested (see Table 6). Table 5 shows the average RMSE for all training data sets. There is a significant decrease in RMSE occurs moving from 2 to 3 API blends in training data. This is expected because 3 blends with API should be required as minimum to properly fit the 3 parameters K_A, K_{AB}, K_{AC} (or P_{0A}, P_{0AB}, P_{0AC} from the other model). However, there is no substantial decrease in average RMSE with increasing from 3 to 6 API blends. Therefore, the proposed experimental design to reduce API usage is to perform only 3 experiments using blends at 25 % and 40 % API, plus the 5 available excipient-excipient blends, to give the most robust, minimum experimental design for model calibration. Note that doing experiments with pure API is not recommended, as the pure API may not effectively compress. The current design with three formulations uses only 1.25 times more API than a single 100 % API experiment. Similar results were seen for the ibuprofen formulation. Given this recommendation, a minimum amount of material can be used in the characterisation process to allow for the formulation and process decisions to be made at a very early stage of development.

The training data set for this experimental design is shown

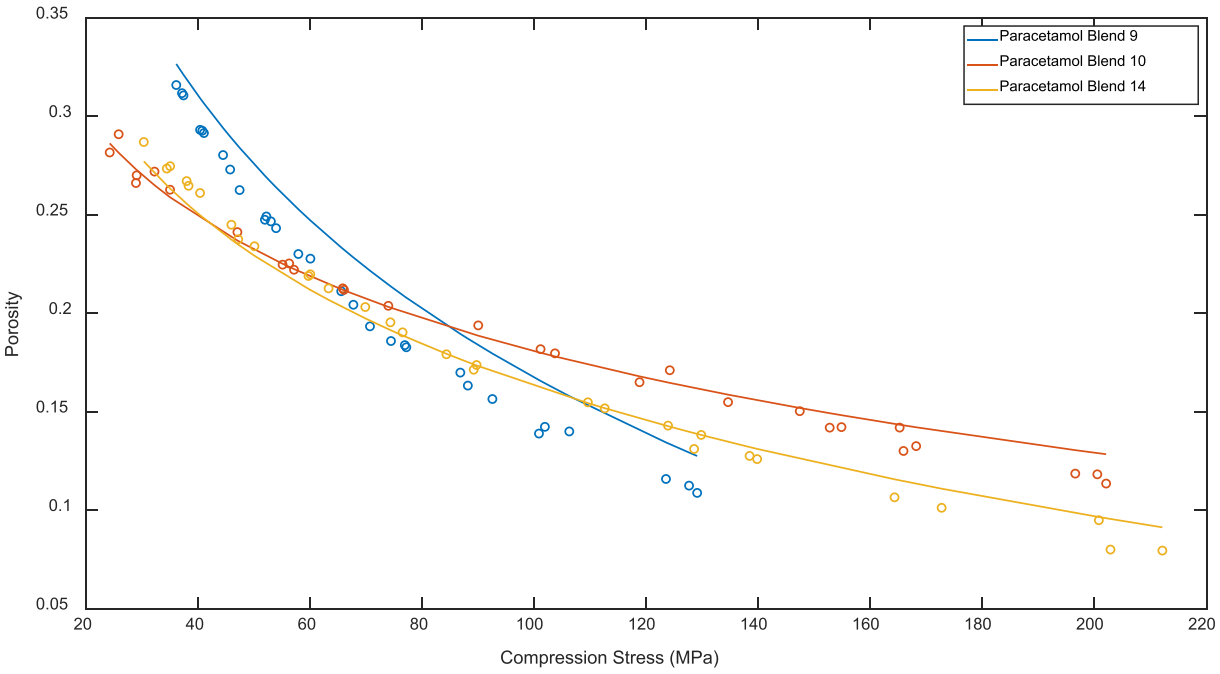


Fig. 9. Measured and predicted compressibility for blends 9, 10 and 14 using the proposed binary mixture model for the paracetamol formulation (model trained using all data).

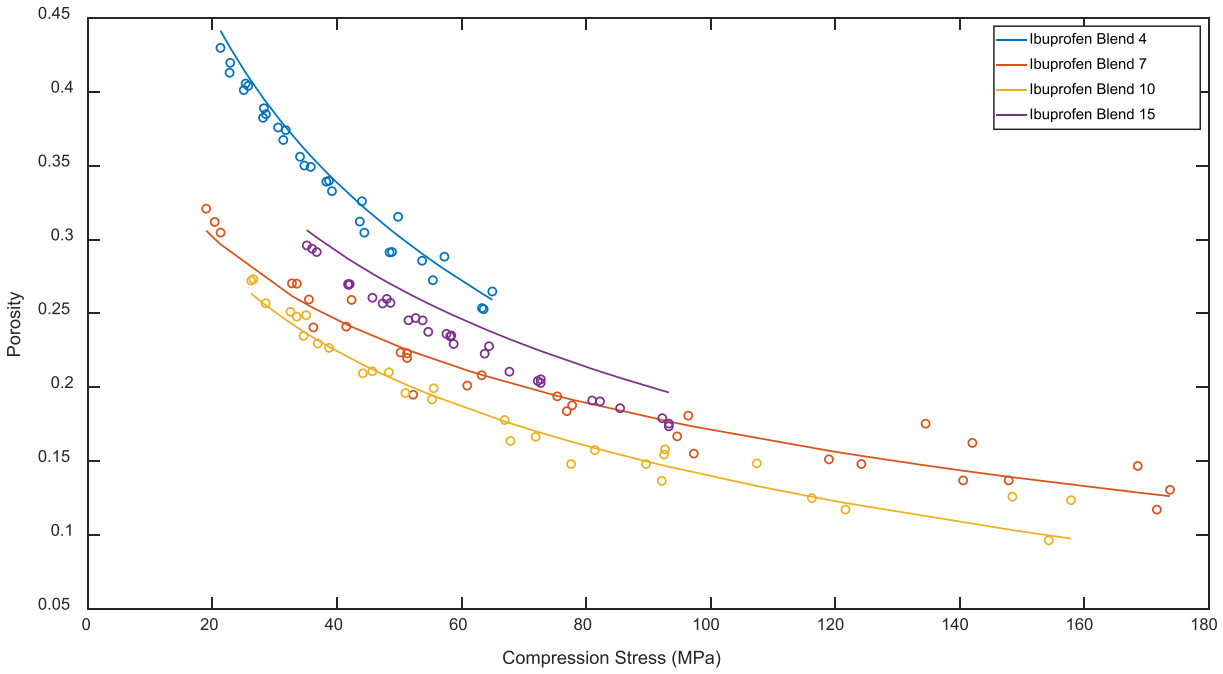


Fig. 10. Measured and predicted compressibility for blends 9, 10 and 14 using the proposed binary mixture model for the ibuprofen formulation (model trained using all data).

Table 5
Fitted parameters for Eq. (10) and Eq. (11) and their 95% confidence intervals for both formulations for the compressibility model.

Formulation	K_A (−)	K_B (−)	K_C (−)	K_{AB} (−)	K_{AC} (−)	K_{BC} (−)
Paracetamol	10.7 ± 3.5	6.3 ± 1.5	12.8 ± 1.4	−4.6 ± 4.3	13.1 ± 10.5	−14.3 ± 6.1
Ibuprofen	13.0 ± 4.5	6.3 ± 1.4	12.8 ± 1.4	−6.1 ± 3.1	11.4 ± 3.4	−14.3 ± 6.1
	$P_{0,A}$ (MPa)	$P_{0,B}$ (MPa)	$P_{0,C}$ (MPa)	$P_{0,AB}$ (MPa)	$P_{0,AC}$ (MPa)	$P_{0,BC}$ (MPa)
Paracetamol	1801 ± 851	321.1 ± 115	1098 ± 693	0.1 ± 0.2	1.0 ± 1.3	0.2 ± 0.2
Ibuprofen	52.6 ± 121	321.1 ± 115	1098 ± 693	23.3 ± 19.3	56.4 ± 34.1	0.2 ± 0.1

Table 6
Average RMSE across training blends for number of additional experiments using API (in addition to 5 excipient-excipient binary blends).

Number of blends in training data using API	API blends used (from Table 1)	Average RMSE training
2	4, 12	0.0086
3	4, 12, 16	0.0069
4	4, 12, 15, 16	0.0065
5	4, 12, 15, 16, 17	0.0067
6	4, 12, 13, 15, 16, 17,	0.0064

graphically in Fig. 11. Given this training data set, the region of feasibility is limited to the edges of formulation spaced illustrated in Fig. 11. Due to the empirical nature of the model, it should not be extrapolated to formulations outside of this space (above 40 % API for example).

The model parameters with 95 % confidence intervals fitted using the reduced training set are shown in Table 7 and can be compared to the parameters where the full data set is used for fitting (Table 5). The confidence intervals for K_A and $P_{0,A}$ would be lower if the single API blends compaction experiments were successful. This would also likely

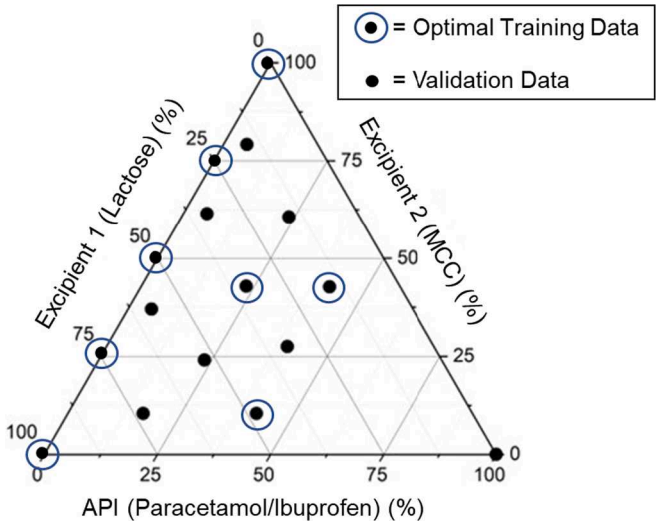


Fig. 11. Ternary phase diagram illustrating the blends for model training for the reduced experimental design.

lead to improved performance of the model. All the binary interaction parameters have confidence intervals that do not contain zero, which indicates that these interaction predictor variables have an effect on the porosity.

Figs. 12 and 13 show parity plots for training and validation data sets for K_{mix} and $P_{0,mix}$ for paracetamol and ibuprofen formulations respectively. Broadly speaking, the reduced training set model predicts similar mixture model parameters to those using the full data set for training. Experimental values of K_{mix} and $P_{0,mix}$ are predicted well except for the two binary paracetamol/lactose blends showing the highest values of K_{mix} and $P_{0,mix}$.

3.2. Compactability model evaluation

An assessment of the fit of Equation (4) to the experimental data was

Table 7
Fitted parameters for Eq. (10) and Eq. (11) and their 95% confidence intervals for both formulations for the compressibility model using reduced training data set.

Formulation	$K_A(-)$	$K_B(-)$	$K_C(-)$	$K_{AB}(-)$	$K_{AC}(-)$	$K_{BC}(-)$
Paracetamol	12.4 ± 13.6	5.9 ± 2.4	12.6 ± 2.4	−6.7 ± 2.2	6.6 ± 1.9	−10.9 ± 8.9
Ibuprofen	20.2 ± 19.2	5.9 ± 2.4	12.6 ± 2.4	−22.7 ± 6.2	3.1 ± 1.2	−10.9 ± 8.9
	$P_{0,A}$(MPa)	$P_{0,B}$(MPa)	$P_{0,C}$(MPa)	$P_{0,AB}$(MPa)	$P_{0,AC}$ (MPa)	$P_{0,BC}$(MPa)
Paracetamol	672 ± 508	289 ± 26.1	1070 ± 89.9	0.5 ± 0.2	9.6 ± 3.7	0.11 ± 0.1
Ibuprofen	771 ± 625	289 ± 26.1	1070 ± 89.9	0.2 ± 0.1	1.2 ± 0.7	0.11 ± 0.1

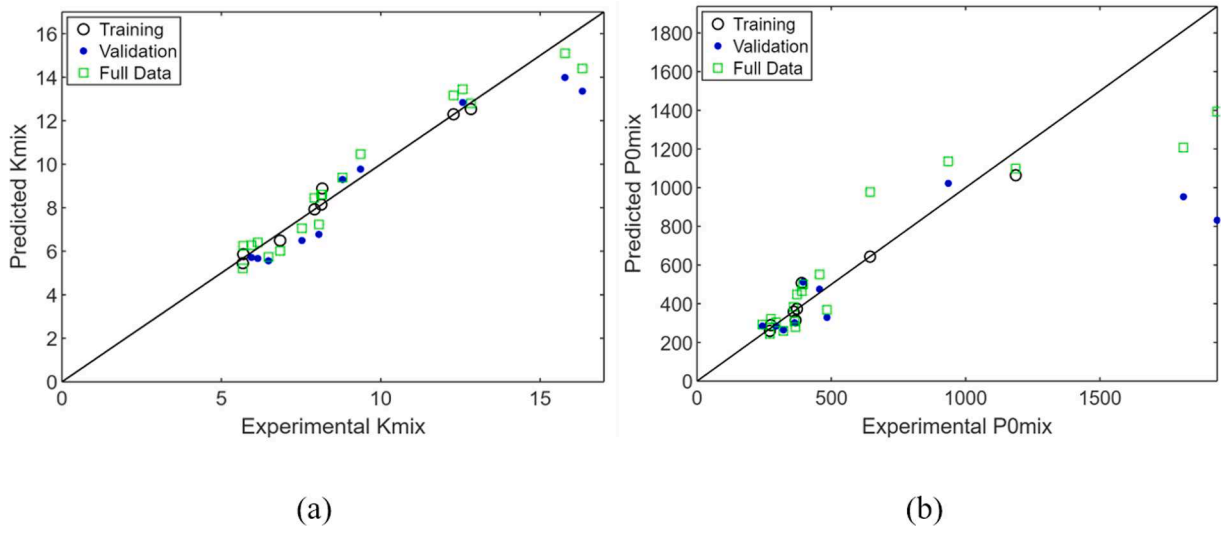


Fig. 12. Parity plot of model predictions from the reduced training set with those fitted from the full data set for the paracetamol formulation (a) Kmix; (b) P0,mix.

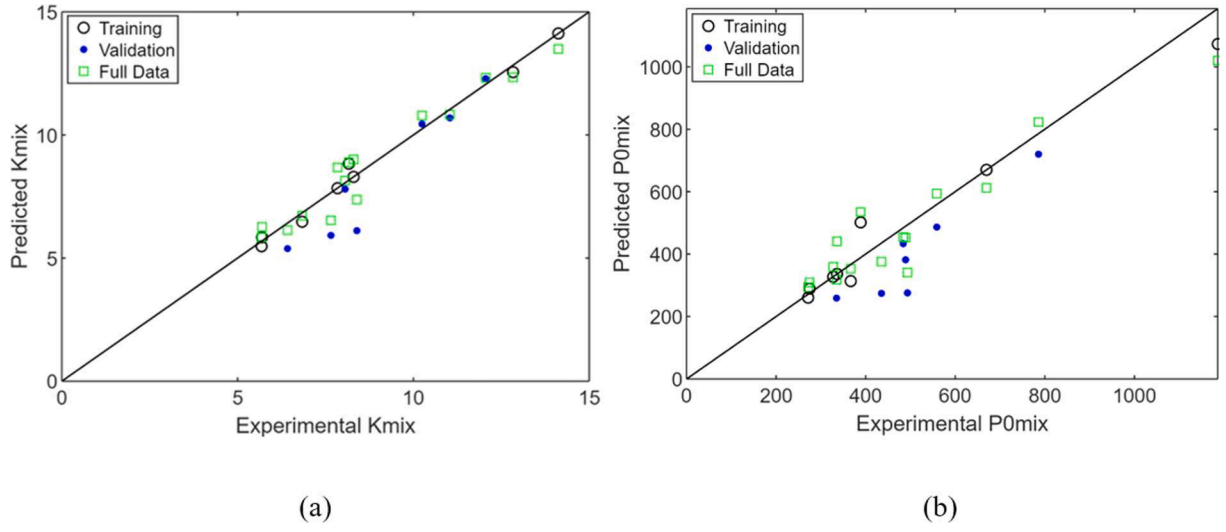


Fig. 13. Parity plot of model predictions from the reduced training set with those fitted from the full data set for the ibuprofen formulation (a) Kmix; (b) P0,mix.

carried out in the same way as the fitting of Equation (3) for the compressibility data. Fig. 14 and Fig. 15 show the experimental compactability curves for the paracetamol formulation and ibuprofen formulation respectively, with fits from the Ryshkewitch-Duckworth equation (Equation (4), including R^2_{adj} and RMSE values for each blend. As with the compressibility model structure evaluation, only blends 2–7 are displayed, with the remaining blends are omitted to prevent cluttered figures. However, the remaining blends produced similar fits. These performance metrics (very high R^2_{adj} (above 0.95 and low RMSE (below 0.15)) and visual inspection of the fits indicate that the form of Ryshkewitch-Duckworth equation is, as expected, a very good fit for the experimental data and so is a good basis for the proposed interaction-based model for predicting tensile strength based on the blend composition as well as porosity.

3.2.1. *Parameter estimation using all data*

As with the compressibility model, initially all the data was used for training to fully assess the capability of the proposed model. All 3 mixture rules were assessed and the average RMSE across all blends for each of these mixture rules is displayed in Table 8 for both the paracetamol and ibuprofen formulations. Similar conclusions can be drawn to those for the compressibility model. There is notable improved performance when going from the ideal to binary interaction model but negligible improvement by including a ternary interaction term.

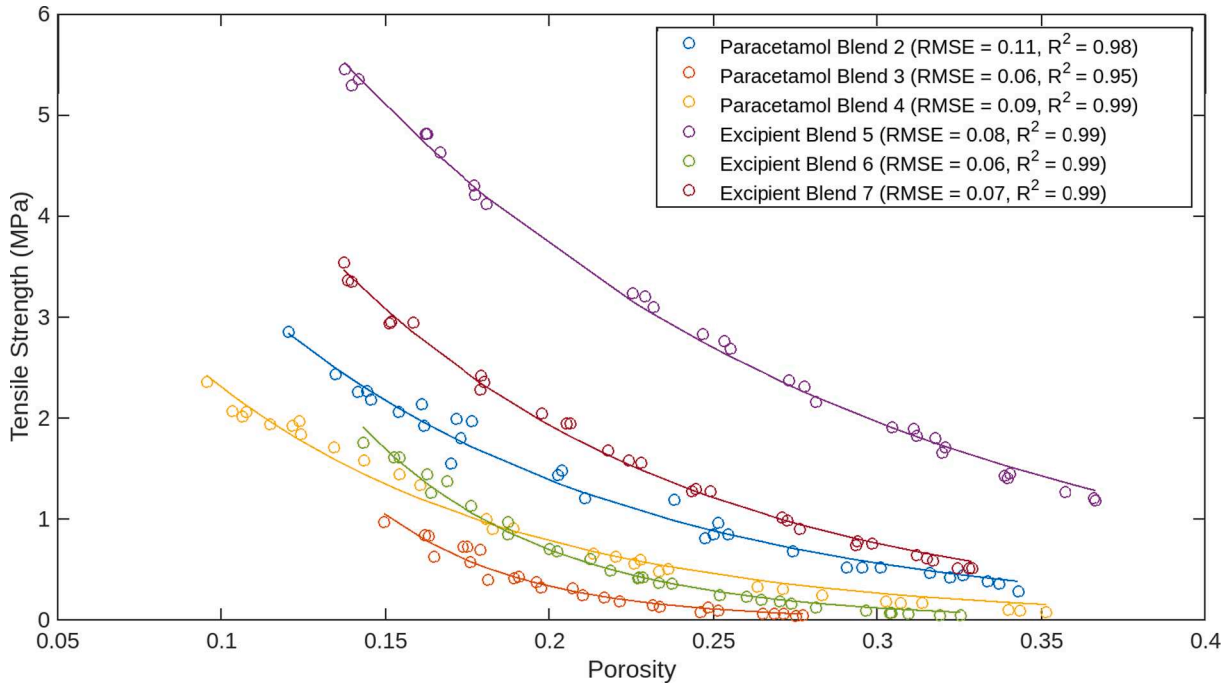


Fig. 14. Experimental compactability curves with fits from the Ryshkewitch-Duckworth equation (Eq. (4) for paracetamol formulation blends 2 to 4, and excipient blends 5 to 7.

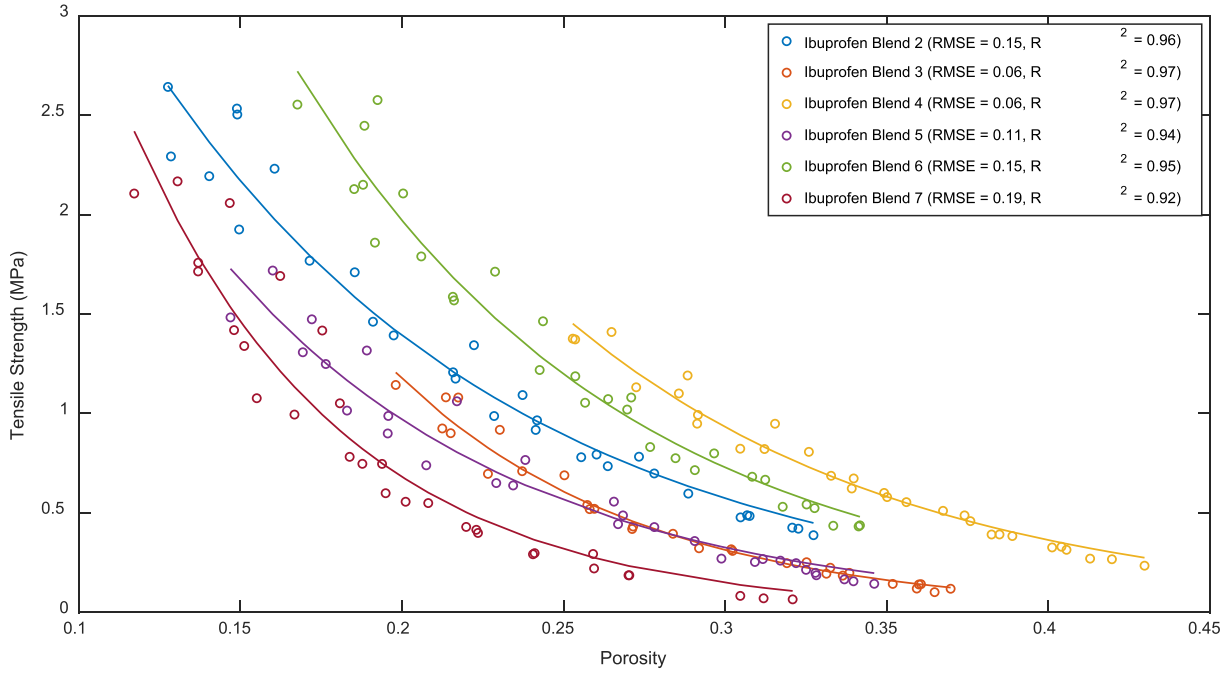


Fig. 15. Experimental compactability curves with fits from the Ryshkewitch-Duckworth equation (Eq. (4) for ibuprofen formulation blends 2 to 7.

Therefore, the binary interaction model is chosen for further study. Figs. 16 and 17 show examples of these predictions using the binary interaction model for the paracetamol and ibuprofen respectively. The blends in these plots were selected to demonstrate the range of compressibility as well as the extremes in accuracy. These two plots demonstrate some measure of the confidence in the model when it is trained on the full data set. Table 9 shows the fitted parameters and the associated 95 % confidence intervals for both formulations. The confidence intervals are reasonable and do not contain zero, further demonstrating that the binary interaction parameters are significant.

3.2.2. *Experimental design to reduce API usage for model development*

The procedure for training the compactability model was identical to the compressibility model in the previous section, with the exception that the parameters in Equations (18) and (19) are being fit instead. The parameters were fitted on the same training data and the model validated on the same validation data as the compressibility model (Fig. 11).

Table 10 shows the model performance metrics on the validation data for the paracetamol formulation. As with the compressibility model, most of the validation blends have very good fits, with R^2 above 0.93–0.95 and %RMSE below 5 %, however, 3 of the blends have much

Table 8
Compactability model performance (average RMSE and R^2_{adj} across all blends) against mixing rule for the parameters for the paracetamol and ibuprofen formulations (For concision, X indicates any one of the parameters that incorporates a mixture model).

Mixing Rule		Paracetamol Average RMSE/ R^2_{adj}	Ibuprofen Average RMSE/ R^2_{adj}
Ideal	$X_{mix} = \sum_i y_i X_i$	0.282/0.84	0.198/0.86
Binary	$X_{mix} = \sum_i y_i X_i + \sum_{ij} y_i y_j X_{ij}$	0.229/0.87	0.159/0.90
Ternary	$X_{mix} = \sum_i y_i X_i + \sum_{ij} y_i y_j X_{ij} + y_i y_j y_k X_{ijk}$	0.220/0.88	0.162/0.90

poorer predictions (blends 3, 9,13). For example, paracetamol blend 9 (15 % API, 81 % MCC) does exhibit relatively poor validation performance and so could indicate it is a formulation outside of the feasible region. However, in this case, paracetamol blend 8 has very good validation performance and is very similar in formulation to blend 9. Therefore, this indicates that the poor validation performance of blend 9 relates to experimental error or poorly fitted model parameters.

For the ibuprofen formulation (Table 11), the model performance is slightly better than the same formulation for the compressibility model and for the paracetamol formulation for this compactability model, with the majority of R^2 above 0.94 and %RMSE below 5 %. The model does not predict as well on blend 2. However, for the remaining blends the fit is very good. The prediction plots for all the blends for both formulations are in the supporting information.

Figs. 18 and 19 show parity plots for training, validation, and combined data sets for $k_{b,mix}$ and $\sigma_{0,mix}$ for paracetamol and ibuprofen formulations respectively. Generally, as with the compressibility model, the reduced training set model predicts similar mixture model parameters to those using the full data set for training. Again, as with the compressibility model, experimental values of $k_{b,mix}$ and $\sigma_{0,mix}$ are predicted well except for the two binary paracetamol/lactose blends showing the highest values of $k_{b,mix}$ and $\sigma_{0,mix}$.

The fitted parameters and the 95 % confidence intervals for the compactability model is detailed in Table 12. Several of the parameters have large confidence intervals, however, they could be improved if the pure API blend (component A) compacted successfully. Issues with compacting single component APIs are common, so perhaps attempting a high, but not 100 % mass fraction, which would give successful compaction data, would be better ensuring better parameter fitting. Some of these confidence intervals include 0 and so indicate that those components/interactions of components do not influence the output response greatly. However, this can be due to a lack of data points with high mass fraction of component A, which will affect the component A parameters and the interaction parameters including component A. The confidence in the B and C parameters and BC interaction parameters are better and indicate there is interaction between these components that affect the tensile strength.

3.3. Comparison with Reynolds et al. (2017) model

The proposed interaction-based mixture models are compared with the compressibility and compactability models proposed by Reynolds et al. (2017) so that the significance of this model can be evaluated. The Reynolds models have been shown to be some of the best available in the literature through an assessment of the most popular models by Wang et al. (2021).

The Reynolds model parameters are fitted on the same training optimum data (Table 6) as the interaction-based model in the previous sections and validated on the same validation data set. The predictions for every blend for both formulation comparing the interaction-based model with the Reynolds model are displayed in the supporting information. For the paracetamol formulation, the compressibility models give largely similar results. The average validation RMSE for the interaction-based compressibility model on the paracetamol formulation is 0.0176, which is 9.7 % better than the Reynolds model (0.0193). For the ibuprofen formulation, the average validation RMSE for interaction-based compressibility model is 0.0216, which is 27.8 % worse than the Reynolds model (0.0156).

A paired t-test was carried out with a hypothesis that the mean validation RMSE between the two models is different, and a null hypothesis that the mean of the difference between the validation RMSE

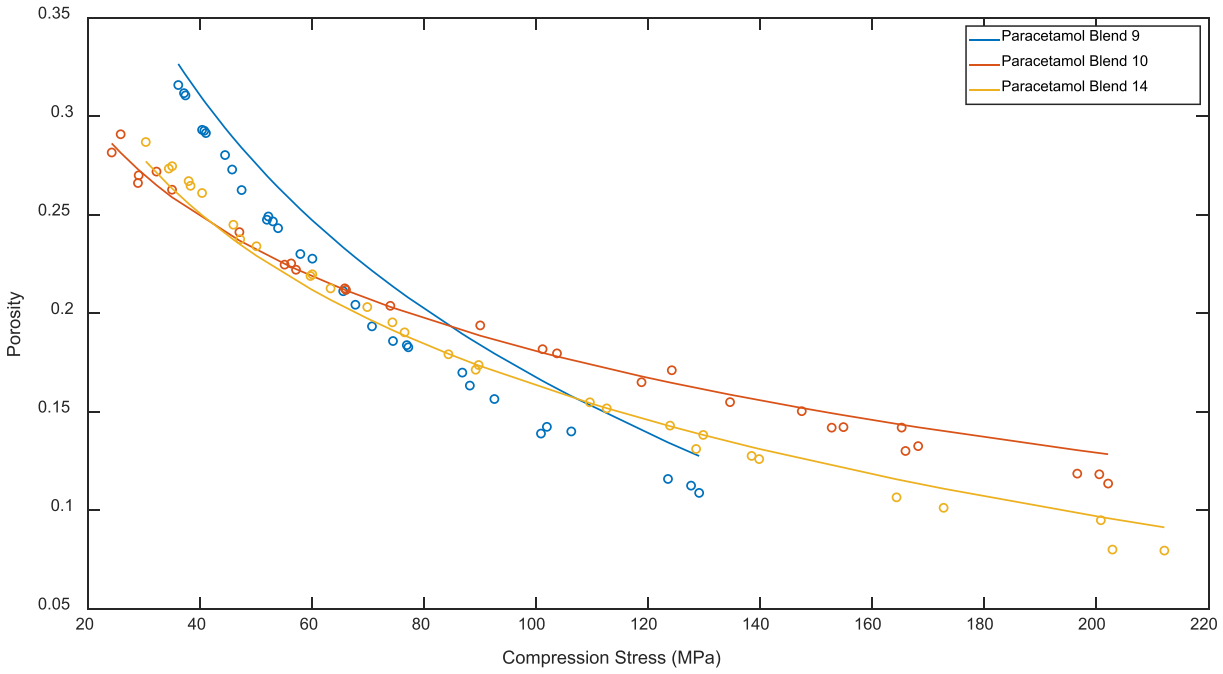


Fig. 16. Measured and predicted compressibility for blends 9, 10 and 14 using the proposed binary mixture model for the paracetamol formulation (model trained using all data).

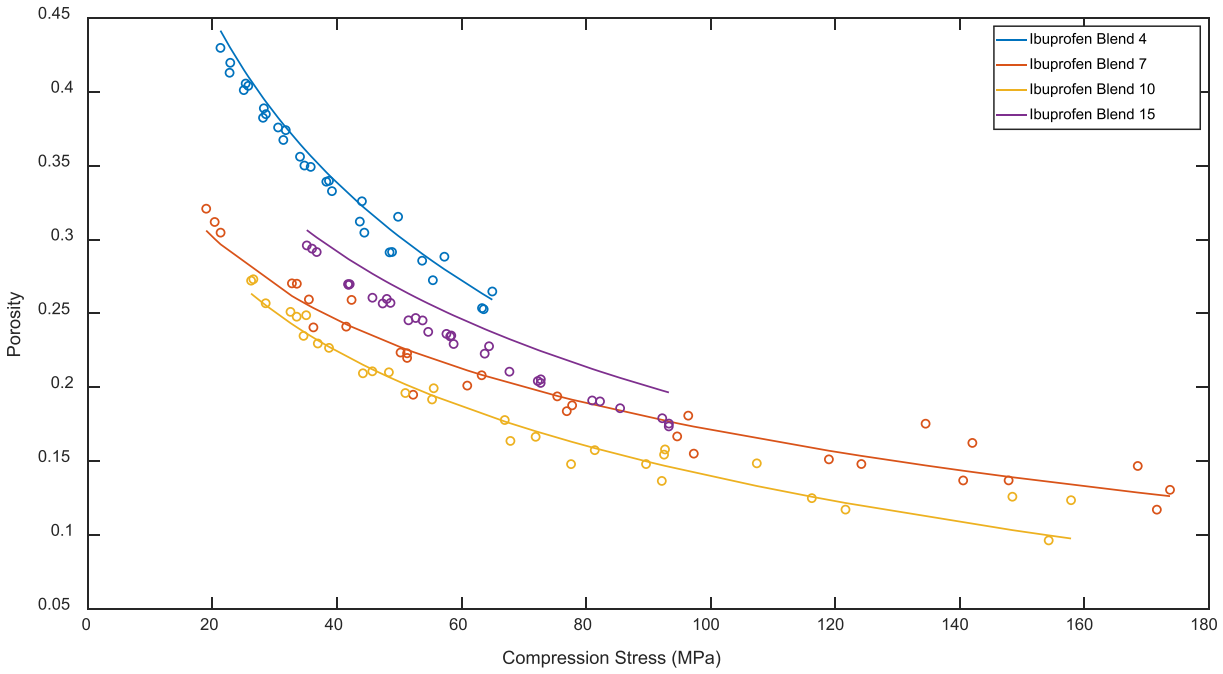


Fig. 17. Measured and predicted compressibility for blends 9, 10 and 14 using the proposed binary mixture model for the ibuprofen formulation (model trained using all data).

Table 9
Fitted parameters for Eq. (10) and Eq. (11) and their 95% confidence intervals for both formulations for the compactability model.

Formulation	$\sigma_{0,A}$ (MPa)	$\sigma_{0,B}$ (MPa)	$\sigma_{0,C}$ (MPa)	$\sigma_{0,AB}$ (MPa)	$\sigma_{0,AC}$ (MPa)	$\sigma_{0,BC}$ (MPa)
Paracetamol	3.8 ± 2.5	4.7 ± 0.9	5.0 ± 0.8	−8.4 ± 5.5	−1.2 ± 0.5	−7.4 ± 6.2
Ibuprofen	−1.0 ± -0.8	2.6 ± 0.4	3.1 ± 0.4	4.4 ± 3.5	3.3 ± 2.8	−1.3 ± 0.7
	$k_{b,A}$	$k_{b,B}$	$k_{b,C}$	$k_{b,AB}$	$k_{b,AC}$	$k_{b,BC}$
Paracetamol	22.3 ± 15.2	11.7 ± 4.3	29.0 ± 3.4	−24.8 ± -13.5	29.2 ± 16.1	−38.2 ± -20.5
Ibuprofen	−1.1 ± 0.9	6.5 ± 2.1	17.8 ± 2.2	27.9 ± 21.0	18.8 ± 12.5	−8.2 ± 6.3

Table 10
R^2_{adj}, RMSE and %RMSE performance metrics on unseen validation blends for the compactability model, for the paracetamol formulation.

Blend	Validation R^2_{adj}	Validation RMSE	Validation %RMSE
2	0.95	0.17	3.31
3	0.35	0.23	4.63
8	0.99	0.14	2.74
9	0.64	0.61	12.01
10	0.96	0.13	2.68
11	0.93	0.11	2.27
13	0.53	0.56	10.97
14	0.96	0.16	3.10
15	0.96	0.24	4.81
17	0.99	0.10	2.16

values for both models is equal to zero. The p-values, and whether the null hypothesis was rejected or not, for these t-tests are described in Table 13. Although the null hypothesis was rejected for the ibuprofen formulation, for the paracetamol formulation and both formulations combined, the null hypothesis was not rejected. Therefore, overall, it cannot be said that there is a statistically significant difference between the generalisation performance of the two compressibility models.

Table 11
R^2_{adj}, RMSE and %RMSE performance metrics on unseen validation blends for the compactability model, for the ibuprofen formulation.

Blend	Validation R^2_{adj}	Validation RMSE	Validation %RMSE
2	0.57	0.47	12.77
4	0.79	0.16	4.49
6	0.96	0.15	3.93
7	0.88	0.23	6.25
9	0.94	0.18	4.84
10	0.94	0.16	4.24
11	0.94	0.15	4.12

For the compactability models, the same analysis was carried out. For the paracetamol formulation, the average validation RMSE of the interaction-based compactability model was 0.246 MPa, which is 19.2 % higher than the Reynolds model (0.203 MPa). For the ibuprofen formulation, the average validation RMSE of the interaction-based model was 0.213 MPa, which is 46.5 % lower than the Reynolds model (0.312 MPa). The associated paired t-tests results are shown in Table 14. None of the null hypothesis are rejected and so the difference between the interaction-based and Reynolds compactability models is not statistically significant with a 5 % significance level.

On the basis of these data, both the binary interaction model and the Reynolds model are suitable as mixing models to predict parameters for compressibility and compaction models for processing formulations. The Reynolds model has less parameters and so is simpler. The binary interaction model is more general in approach, analogous to thermodynamic mixing models and can be used for other bulk powder properties, such as flow properties (Aroniada et al., 2023). Furthermore, both models should be assessed further with a wider range of formulations of varied materials.

4. Conclusions

A new binary interaction mixture model is used to predict the compressibility, via the modified Gurnham equation, and compactability, via the Ryshkewitch-Duckworth equation, of pharmaceutical

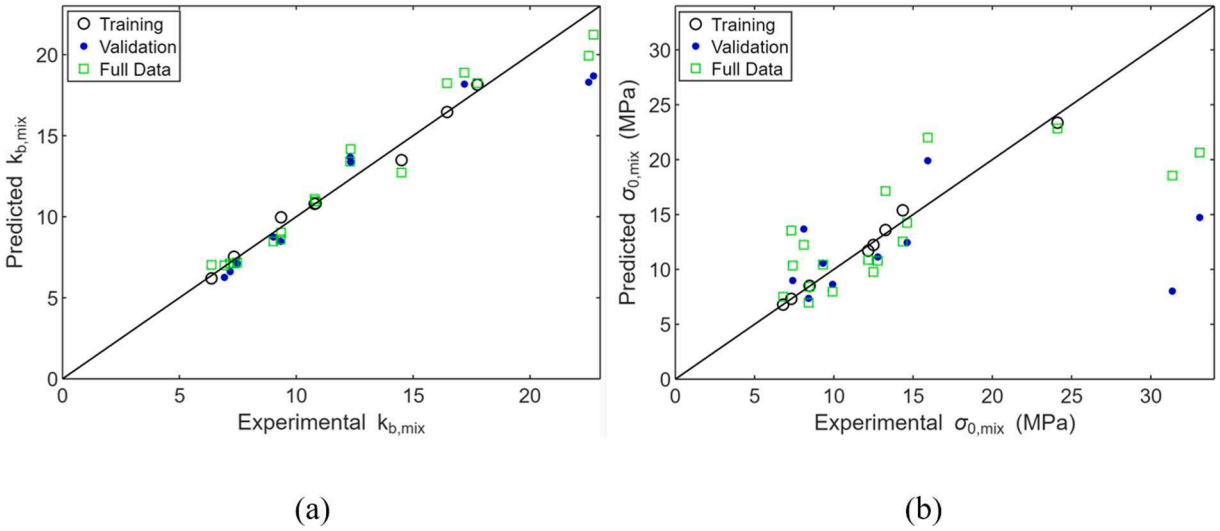


Fig. 18. Parity plot of model predictions from the reduced training set with those fitted from the full data set for the paracetamol formulation (a) kb,mix; (b) σ0,mix.

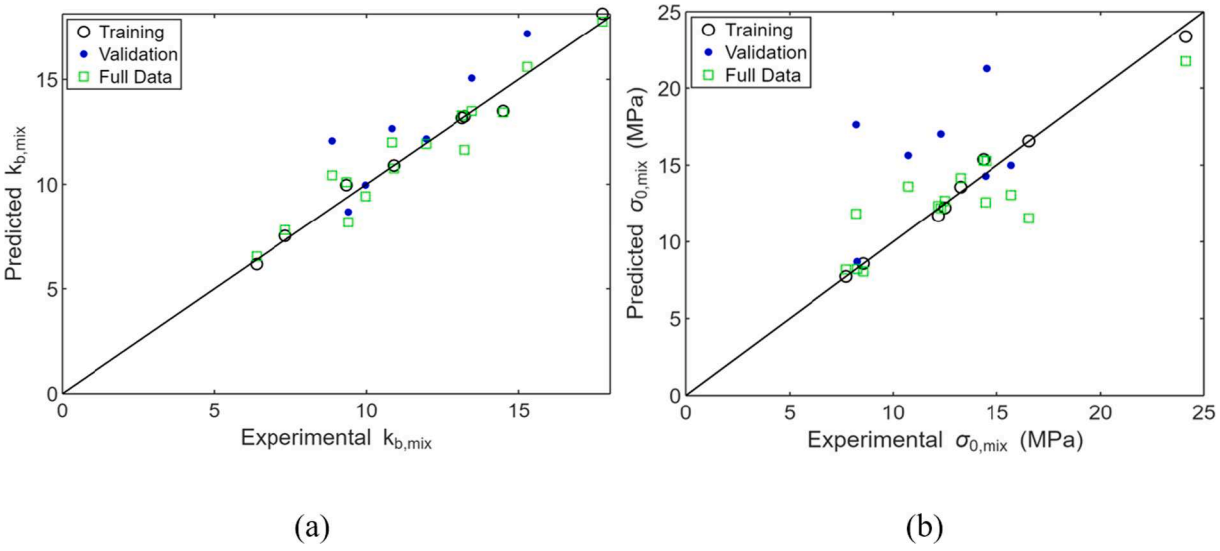


Fig. 19. Parity plot of model predictions from the reduced training set with those fitted from the full data set for the ibuprofen formulation (a) kb,mix; (b) σ0,mix.

Table 12
Fitted parameters for Eq. (18) and Eq. (19). and their 95% confidence intervals for both formulations for the compactability model fitted on the optimised training data set.

Formulation	$\sigma_{0,A}$ (MPa)	$\sigma_{0,B}$ (MPa)	$\sigma_{0,C}$ (MPa)	$\sigma_{0,AB}$ (MPa)	$\sigma_{0,AC}$ (MPa)	$\sigma_{0,BC}$ (MPa)
Paracetamol	1.9 ± 1.5	4.3 ± 0.4	5.0 ± 0.5	−1.2 ± 0.9	−3.1 ± 2.5	−4.0 ± 3.2
Ibuprofen	−6.0 ± 4.5	2.6 ± 0.2	3.2 ± 0.3	13.5 ± 7.2	11.2 ± 7.7	−1.5 ± 1.2
	$k_{b,A}$	$k_{b,B}$	$k_{b,C}$	$k_{b,AB}$	$k_{b,AC}$	$k_{b,BC}$
Paracetamol	26.2 ± 20.5	10.3 ± 6.0	28.8 ± 5.7	−28.9 ± 19.4	−2.6 ± 1.8	−23.2 ± 8.9
Ibuprofen	−23.1 ± 18.2	6.2 ± 3.6	18.1 ± 15.1	67.9 ± 25.1	54.9 ± 31.0	−8.8 ± 7.9

Table 13
Paired *t*-test results to compare whether the difference between validation RMSE values for the interaction-based and Reynolds compressibility models are statistically significant.

Formulation	Binary Interaction Av. RMSE (range)	Reynolds Av. RMSE (range)	p-value	Reject Null Hypothesis at 95 %
Paracetamol	0.0176 (0.006–0.047)	0.0193 (0.006–0.037)	0.148	No
Ibuprofen	0.0216 (0.010–0.029)	0.0156 (0.008–0.028)	0.013	Yes
Combined	0.0193 (0.006–0.047)	0.0170 (0.006–0.037)	0.909	No

powder mixtures. Two different ternary formulations of commonly used pharmaceutical powders were compacted to generate experimental data to train and validate the model. Both the Gurnham equation for compressibility and the Ryshkewitch-Duckworth equation for compactability capture the compressibility and compactability relationships well for all data sets and so are a good basis for the proposed interaction-based mixture model. The binary interaction mixing model performed well when trained with the full data set and was better than either the ideal mixing model, or a model including ternary interactions.

A robust, minimal design of experiments has been recommended to

Table 14
Paired *t*-test results to compare whether the difference between validation RMSE values for the interaction-based and Reynolds compactability models are statistically significant.

Formulation	Binary Interaction Av. RMSE (range)	Reynolds Av. RMSE (range)	p-value	Reject Null Hypothesis at 95 %
Paracetamol	0.246 (0.105–0.612)	0.203 (0.092–0.305)	0.537	No
Ibuprofen	0.213 (0.145–0.470)	0.312 (0.108–0.586)	0.100	No
Combined	0.233 (0.105–0.612)	0.249 (0.092–0.586)	0.477	No

reduce API usage to calibrate the proposed mixture model for a new formulation, using only 3 experiments containing API, at 25 % and 40 % API. To enable effective model-based optimisation for formulation decisions to be made at a very early stage of development, using the minimum amount of material for characterisation to calibrate the model for a new formulation is critical. There are no existing guidelines for choosing the minimum number of experiments to develop the mixing rules nor any validation. Therefore, the results and recommendations of this paper are significant.

The model demonstrated a strong capability of predicting the compressibility and compactability of a wide range of ternary mixture compositions, for two different formulations. This model gave similar performance to the Reynolds et al. (2017) model for both compressibility and compactability when trained using the same data sets. The binary interaction model is general in approach and should be suitable for predicting model parameters for other important powder mixture properties.

Considering the application of both approaches in potential workflows; the Reynolds model could be used early on in formulation design as fewer experiments are required and the model is simpler, but as the formulation is narrowed, the proposed interaction model can be used to refine the prediction of the formulation space using more experiments for fitting, when the API availability is likely higher at a later stage in development.

CRediT authorship contribution statement

Jeremiah Corrigan: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Feng Li:** Writing – review & editing, Formal analysis, Conceptualization. **Neil Dawson:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Gavin Reynolds:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Stefan Bellinghausen:** Writing – review & editing, Supervision, Software, Conceptualization. **Simeone Zomer:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **James Litster:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Acknowledgments

Funding for this work was provided by Innovate UK Project No: 41299 *Digital Design Accelerator Platform to Connect Active Material Design to Product Performance.* The Material Assessment Laboratory team at Pfizer, Sandwich is acknowledged for their work in performing the compaction simulator experiments to generate the key data for this work. GSK are thanked for providing all of the materials used to generate the blends.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2024.124587.

References

Aroniada, M., Bano, G., Vueva, Y., Christodoulou, C., Li, F., Litster, J.D., 2023. A novel mixing rule model to predict the flowability of directly compressed pharmaceutical blends. International Journal of Pharmaceutics 647, 123475.
Busignies, V., Leclerc, B., Porion, P., Evesque, P., Couarraze, G., Tchoreloff, P., 2006. Investigation and modelling approach of the mechanical properties of compacts made with binary mixtures of pharmaceutical excipients. European Journal of Pharmaceutics and Biopharmaceutics 64, 51–65.
Busignies, V., Mazel, V., Diarra, H., Tchoreloff, P., 2012. Prediction of the compressibility of complex mixtures of pharmaceutical powders. International Journal of Pharmaceutics 436, 862–868.
Denny, P.J., 2002. Compaction equations: a comparison of the Heckel and Kawakita equations. Powder Technology 127, 162–172.
Etzler, F.M., Bramante, T., Deanne, R., Sienkiewicz, S., Chen, F.J., 2011. Tablet Tensile Strength: An Adhesion Science Perspective. Journal of Adhesion Science and Technology 25, 501–519.
Frenning, G., Nordström, J., Alderborn, G., 2009. Effective Kawakita parameters for binary mixtures. Powder Technology 189, 270–275.
Heckel, R.W., 1961. Density-pressure relationship in powder compaction. Transaction of the Metallurgical Society of AIME 221, 671–675.
Jolliffe, H.G., 2022. Linked experimental and modelling approaches for tablet property predictions. International Journal of Pharmaceutics 626, 122116.
Kawakita, K., Lüdde, K.-H., 1971. Some considerations on powder compression equations. Powder Technology 4, 61–68.
Kuentz, M., Leuenberger, H., Kolb, M., 1999. Fracture in disordered media and tensile strength of microcrystalline cellulose tablets at low relative densities. International Journal of Pharmaceutics 182, 243–255.
Mazel, V., Busignies, V., Duca, S., Leclerc, B., Tchoreloff, P., 2011. Original predictive approach to the compressibility of pharmaceutical powder mixtures based on the Kawakita equation. International Journal of Pharmaceutics 410, 92–98.
Reynolds, G.K., Campbell, J.I., Roberts, R.J., 2017. A compressibility based model for predicting the tensile strength of directly compressed pharmaceutical powder mixtures. International Journal of Pharmaceutics 531, 215–224.
Silva, M.A., Miranda, M.N.N., 2003. Estimation of properties of ternary mixtures of solids using the mixing rule. Powder Technology, pp. 16–23.
Tye, C.K., Sun, 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. Journal of Pharmaceutical Sciences 94, 465–472.
Wang, L.G., Omar, C., Litster, J.D., Li, J., Mitchell, N., Bellinghausen, S., Barrasso, D., Salman, A., Slade, D., 2021. Tableting model assessment of porosity and tensile strength using a continuous wet granulation route. International Journal of Pharmaceutics 607, 120934.
Wu, C.-Y., Best, S.M., Bentham, A.C., Hancock, B.C., Bonfield, W., 2005. A simple predictive model for the tensile strength of binary tablets. European Journal of Pharmaceutical Sciences 25, 331–336.
Wu, C.-Y., Best, S.M., Bentham, A.C., Hancock, B.C., Bonfield, W., 2006. Predicting the Tensile Strength of Compacted Multi-Component Mixtures of Pharmaceutical Powders. Pharmaceutical Research 23, 1898–1905.
Zhao, J., Burt, H.M., Miller, R.A., 2006. The Gurnham equation in characterizing the compressibility of pharmaceutical materials. International Journal of Pharmaceutics 317, 109–113.