International Journal of Pharmaceutics 662 (2024) 124475

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Empirical Model Variability: Developing a new global optimisation approach to populate compression and compaction mixture rules

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ARTICLE INFO

Keywords:
Empirical Models
Tablet Compression
Tablet Compaction
Mixture Rules
Global Optimisation

ABSTRACT

This study systematically evaluated the predictive accuracy of common empirical models for pharmaceutical powder compaction. A dataset of nine placebo and twelve active pharmaceutical ingredient (API) loaded blend formulations (four APIs at three drug loadings) was fitted to the widely used empirical tablet compression (Gurnham, Heckel, and Kawakita) and compaction (Ryshkewitch-Duckworth and Leuenberger) models. At low API loadings (<20w/w%), all models achieved R^2 above 90 % and RRMSE (relative root mean squared error) below 0.1. However, as API loads increased, overall model performance decreased, notably in the Heckel model. A parameter variability analysis identified multiple parameter pairs achieving acceptable fits. Consequently, a novel global optimization approach was developed populating arithmetic, geometric, and harmonic mixture rules for empirical tuning parameters. This method outperformed the traditional line of best fit approach. A cross validation study revealed that this method is capable of predicting tuning parameters which achieve an acceptable Goodness of Fit for new blends. Finally, with the restriction of maintaining consistent parameters for the placebo blend, the proposed method could substantially reduce the experimental requirements and API consumption for the exploration of new blends.

1. Introduction

Industrialists and researchers have explored computational techniques in the development of new oral solid dosage forms (OSDFs) aiming to minimise resource consumption by predicting quality attributes for new formulations and moving away from the traditional trial-and-error approach. Key attributes of focus in OSDFs development are: tablet porosity, which affects disintegration and dissolution processes, ultimately impacting the drug release profile; and tensile strength, which is critical for ensuring robustness in downstream handling (e.g. coating and packaging), transport and storage (Reynolds et al., 2017; Yu, 2008; Yu et al., 2014).

There has been a large amount of research generated regarding the application of predictive empirical methods to advance the understanding of powder compressibility and compactability. The compressibility of a powder describes the ability of the system to reduce its volume when under pressure, which is typically defined by a reduction in the relative density or void space (i.e. porosity) (Athy, 1930; Cooper & Eaton, 1962; Gurnham & Masson, 1946; Heckel, 1962; Kawakita & Tsutsumi, 1965; Kawakita & Tsutsumi, 1966; Sonnergaard, 2001; Walker, 1923; Zhao et al., 2006). The compactability of a powder describes the ability of the system to be compressed into a reduced volume of specified strength (Duckworth, 1953; Leuenberger, 1982; Leuenberger & Rohera, 1986; Ryshkewitch, 1953; Wu et al., 2005).

Compressibility and compactability models were originally developed and applied to systems which considered a single inorganic or fibrous compound (like ceramics, metals and food stuffs) which behave very differently to – and hence may not be suitable for describing the behaviours of – organic compounds, i.e. most pharmaceutical materials. The performance of compression and compaction models have been discussed for single, binary, or multi-component pharmaceutical powder systems (Kuentz & Leuenberger, 1999; Rue & Rees, 1978; Sonnergaard, 1999; Vreeman & Sun, 2021). However, within these studies there have been inconsistent conclusions regarding: the reliability of the models; the estimations of model tuning parameters; and the interpretation of results to inform or predict behaviours for physically similar tablet formulations. For example, Sonnergaard (1999) highlighted the

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https://doi.org/10.1016/j.ijpharm.2024.124475
Received 11 April 2024; Received in revised form 1 July 2024; Accepted 13 July 2024
Available online 15 July 2024

Nomenclature

Abbreviation

GoF	Goodness of Fit(−)
RoI	Region of Interest(−)
RMSE	Root Mean Squared Error
RRMSE	Relative Root Mean Squared Error(−)

Variable

ε	Tablet porosity(−)
ε_0	Initial tablet porosity(−)
γ	Compression susceptibility(MPa^{-1})
φ	Volume Fraction(−)
σ	Tablet tensile strength(MPa)
σ_0	Tablet tensile strength at zero porosity(MPa)
A_i and B_i	Example tuning parameters(−)
A_{mix} and B_{mix}	Example mixture tuning parameters(−)
b	A tuning parameter which is hypothesized to reflect the resistant and cohesive forces of the particles(MPa^{-1})
B	Grouped tuning parameter(MPa^{-1})
C	A constant(−)
k_b	The bonding capacity(−)
K_G	Compression resistance (Gurnham)(MPa^{-1})
K_H	Compression resistance (Heckel)(MPa^{-1})
K_K	Compression resistance (Kawakita)(MPa^{-1})
P	Compression Pressure(MPa)
P_0	Pressure required to reach a tablet of zero porosity(MPa)
R^2	Coefficient of Determination(−)
V_0	Initial apparent volume of powder bed (m^3)
V_∞	Net volume of powder(m^3)
y_i	Dependent variable(−)
$\widehat{y}_i$	Model prediction of dependent variable(−)
$\bar{y}$	Mean dependent variable(−)

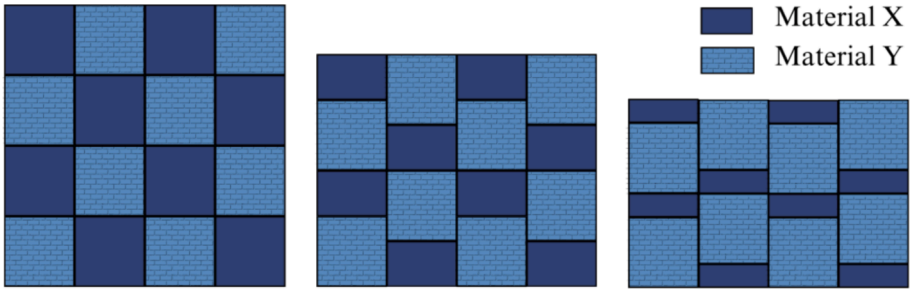

Fig. 1. An illustration showing a binary mixture of compressible (Material X) and incompressible (Material Y) particles at increasing levels of compression (left to right) to demonstrate the idea of component contributions to blend behaviour as a function of volume fraction, φ_i (Reynolds et al., 2017). This is an idealised demonstration where the uniformly distributed particles do not interact with each other and are of the same shape and size.

variety of in-die tuning parameters of the Heckel model for a microcrystalline cellulose (MCC) grade (Avicel® PH-101) and paracetamol. This study reviewed estimates for the apparent yield pressure between authors (calculated from the proportionality constant of Heckel's model) and found ranges for these assumed "material specific" values, which were 48 – 104 MPa and 79 – 124 MPa respectively. They concluded that these ranges exist due to the Heckel model parameters being extremely sensitive to small errors in experimental values and consequently questioned the Heckel model's reproducibility. The sensitivity of Heckel's model was then further investigated by Kuentz and Leuenberger (1999) and they concluded that the limitations of the Heckel model were due to the authors assumption that pressure susceptibility was constant across the pressure range rather than changing with the extent of compression. They also found that Heckel's model was unable to capture the behaviour of out-of-die measurements below the point of mechanical rigidity of the compact and proposed a modified model to address this limitation. A commonly cited inconsistency between these investigations into the Heckel model rests on the methodology being used for in- or out-of-die measurements. The impact that this could have on results was recently evaluated in a study by Vreeman and Sun (2021), where they compared Heckel's in-die and out-of-die parameters to that of previous studies, macro-indentation equivalent values, and the parameters for the model proposed by Kuentz and Leuenberger (1999). Vreeman and Sun (2021) instead concluded that Heckel's in-die parameters were as reliable as their out-of-die counterparts and stated that Heckel's model demonstrated acceptable accuracy within a limited range of process conditions and material properties. Rue and Rees (1978) concluded in their study that – due to the sensitivity of Heckel's model to certain material and process conditions (such as particle size, contact time and die dimensions) – the use of the model to characterise pharmaceutical material behaviours was unreliable; however they state that Heckel's model is an effective method to compare the plastic deformation of different materials. The Heckel model has been subjected to a greater deal of scrutiny in the literature compared to other models (Gurnham, Kawakita, Ryshkewitch-Duckworth, and Leuenberger), yet there is still notable variability in the conclusions drawn regarding the tuning parameters and limitations of these models.

This variability can be attributed to the use of varying model parameter estimation procedures and isolated datasets that consider varying materials and process attributes (Yu et al., 2014). Yet, knowing this, a detailed comparison of compression models based on a singular, large and consistent dataset has not been completed since Kawakita and Tsutsumi (1965). In addition, this comparative study investigated powdered metals, ferrites, and food stuffs and did not consider the Gurnham and Heckel models, which have become popular in pharmaceutical applications. The focus of these studies was to evaluate the Goodness of Fit (GoF) with regards to the model structures and assumptions behind the models. Several studies have investigated the impact of process parameters and material attributes on the GoF, but, due to the blend specificity of these parameters, coupled with the vastness of the design space, it is challenging to wholly investigate the response of these models for every instance of formulation change (Adams & Mckeown, 1996; Frenning et al., 2009; Mazel et al., 2011; Nordström et al., 2008; Sonnergaard, 2001).

A proposed solution to reduce the experimentation required is to estimate the tuning parameters of the individual components that make up the blend. This approach allows the estimation of a material's

Table 1
Formulation information for the API loaded blends. Percentages are given by weight/weight ratios.

Functional Material	Material	Low API (%)	Mid API (%)	High API (%)
API	Ibuprofen 50	5	20	40
	Paracetamol (powdered)	5	10	15
	Paracetamol (granular)	10	20	40
	Mefenamic acid	5	20	35
Filler	Lactose monohydrate	Remainder	Remainder	Remainder
Compression Aid	Microcrystalline cellulose	20	20	20
Disintegrant	Croscarmellose sodium	3.5	3.5	3.5
Lubricant	Magnesium stearate	1	1	1

contribution to the compaction behaviour of a blend by using a weighted average of the materials on a volume fraction basis, φ_i, named 'mixture rules' (Fig. 1) (Jolliffe et al., 2022; Reynolds et al., 2017). A useful mixture rule strikes a balance between the complexity and the cost of computation. The complexity of a model increases with a larger number of parameters, higher order polynomials, or the inclusion of interaction terms in order to capture the non-linearity of a relationship. Simple averaging methods – arithmetic, geometric, or harmonic means – have been studied in the field of pharmaceutical formulation to estimate the mixture rules for tuning parameters while avoiding extensive computational cost. Jolliffe et al. (2022) investigated which combination of arithmetic and geometric means achieved the best GoF. This method proposed extrapolation as a way to estimate pure API parameters for the Gurnham and Ryshkewitch-Duckworth models. It was found that the Gurnham model favoured the arithmetic mean and Ryshkewitch-Duckworth model favoured the geometric mean to estimate mixture parameters. This paper further considers these simple mixture rules, with the addition of the harmonic mean, and assumes no interaction terms are required to reduce computational cost in estimating and evaluating mixture tuning parameters. Eqs. (1)–(3) exemplify the calculation of a mixture's tuning parameter, θ_{mix}, in the context of N materials. Each material, denoted by the tuning parameter θ_i and volume fraction φ_i for material i, contributes to the mixture's tuning parameter that is used in the compression or compaction model for the formulation.

Arithmetic

$$\theta_{\text{mix}} = \sum_{i=1}^{N} \varphi_i \theta_i \tag{1}$$

Geometric

$$\left(\prod_{i=1}^{N} \theta_i^{\varphi_i} \right)^{1/\sum_{i=1}^{N} \varphi_i} \tag{2}$$

Harmonic

$$\frac{\sum_{i=1}^{N} \varphi_i}{\sum_{i=1}^{N} \frac{\varphi_i}{\theta_i}} \tag{3}$$

A majority of studies into these empirical models, particularly those which consider mixture rules, have focussed on excipient (placebo) blends as they behave more ideally than their drug-loaded counterparts (Busignies et al., 2006; Frenning et al., 2009; Mazel et al., 2011; Nordström et al., 2008; Sonnergaard, 2001; Sonnergaard, 2022; Wu et al., 2005, 2006; Zhao et al., 2006). These studies have provided a general understanding of pharmaceutical powder compaction, however, the impact of drug loading has not been as extensively explored (Jolliffe et al., 2022; Jolliffe et al., 2019; Kuentz & Leuenberger, 2000a, 2000b; Wünsch et al., 2019). Active Pharmaceutical Ingredients (APIs) are notoriously non-compactable materials and their presence has been shown to significantly impact the manufacturability of blends and the final quality attributes of products (Wenzel et al., 2017). It is crucial to investigate the impact of drug loading on different aspects of predictive compaction modelling such as the estimation of, and confidence in, model tuning parameters and quality of fit (model accuracy) to ensure industrial relevance of such methods. Although the application of empirical compressibility and compactability mixture rules can significantly reduce experimentation, there are key challenges posed to this theory: 1) limited ability to collect compression data for pure non-compactable materials means that some tuning parameters in this space are unattainable, a crucial barrier for applying this to API loaded blends; and 2) until the reasoning behind the variation in the cited tuning parameters has been defined and addressed for the available models, this method cannot be confidently applied to industry despite the cited successes for applications to placebo blends (Busignies et al., 2006; Frenning et al., 2009; Mazel et al., 2011; Reynolds et al., 2017).

This paper demonstrates a new approach for, and an increased understanding of, populating compressibility and compactability mixture rules of drug-loaded formulations to address the cited inconsistencies in the reliability of common empirical models and the variability of their tuning parameters. This study consists of three main sections: (i) a statistical comparison of the ability for common empirical models – Gurnham, Heckel, and Kawakita models for porosity and Ryshkewitch-Duckworth and Leuenberger for tensile strength – to consistently describe the compaction behaviours of four pharmaceutical powder blends of varying drug loadings; (ii) a parameter variability analysis using placebo data to evaluate how inconsistencies in data collection and parameter estimation can impact the GoF and reproducibility for these models, and (iii) the development of a new, global optimisation approach to populate mixture rules for compression and compaction model tuning parameters for loaded blends.

2. Materials and methods

2.1. Materials

The APIs considered were ibuprofen 50 (BASF, UK), powdered and granular grades of paracetamol (pAPAP and gAPAP, Mallinckrodt, UK), and mefenamic acid (Sigma, UK). The excipients were lactose monohydrate (Fast Flo 316, Kerry, UK), microcrystalline cellulose (Avicel PH-102, DuPont, UK), croscarmellose sodium (Solutab, Roquette, UK) and magnesium stearate (Ligamed MF-2 V, Peter Greven, Netherlands).

2.2. Blending and characterisation of formulations

This study sourced data from Jolliffe et al. (2022). Four APIs were used at three levels of drug loading and in each loaded instance, the ratio of API to filler was varied (Table 1). Note that the inconsistent ranges in API loading was due to flowability causing tablet weight variability. In addition, nine placebo blends were created to explore the trends of tuning parameters with changes to the ratio of filler-to-compression aid (Table 2). The blends were created using a 1 L bin blender (Multiblend MB015, Pharmatech, UK) set at 24 rpm for 20 min before adding the lubricant for a further 3 min at 17 rpm. The true densities of the raw materials were measured using a gas pycnometer (Micro Ultrapyc 1200e, Quantachrome, Austria). The true density of the blends, $\rho_{t,\text{mix}}$, were calculated using the harmonic mean of N raw materials true densities, $\rho_{t,i}$, based on their weight fraction, c_i, Eq. (4):

$$\rho_{t,\text{mix}} = \left(\sum_{i}^{N} \frac{c_i}{\rho_{t,i}} \right)^{-1} \tag{4}$$

Table 2
Formulation information for the placebo blends to be used in the parameter variabilty analysis. Percentages are given by weight/weight ratios.

Material	Mass Percentage (%)								
Lactose monohydrate	95.5	85.5	80.5	75.5	47.75	20.5	15.5	10.5	0
Microcrystalline cellulose	0	10	15	20	47.75	75	80	85	95.5
Croscarmellose sodium	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Magnesium stearate	1	1	1	1	1	1	1	1	1

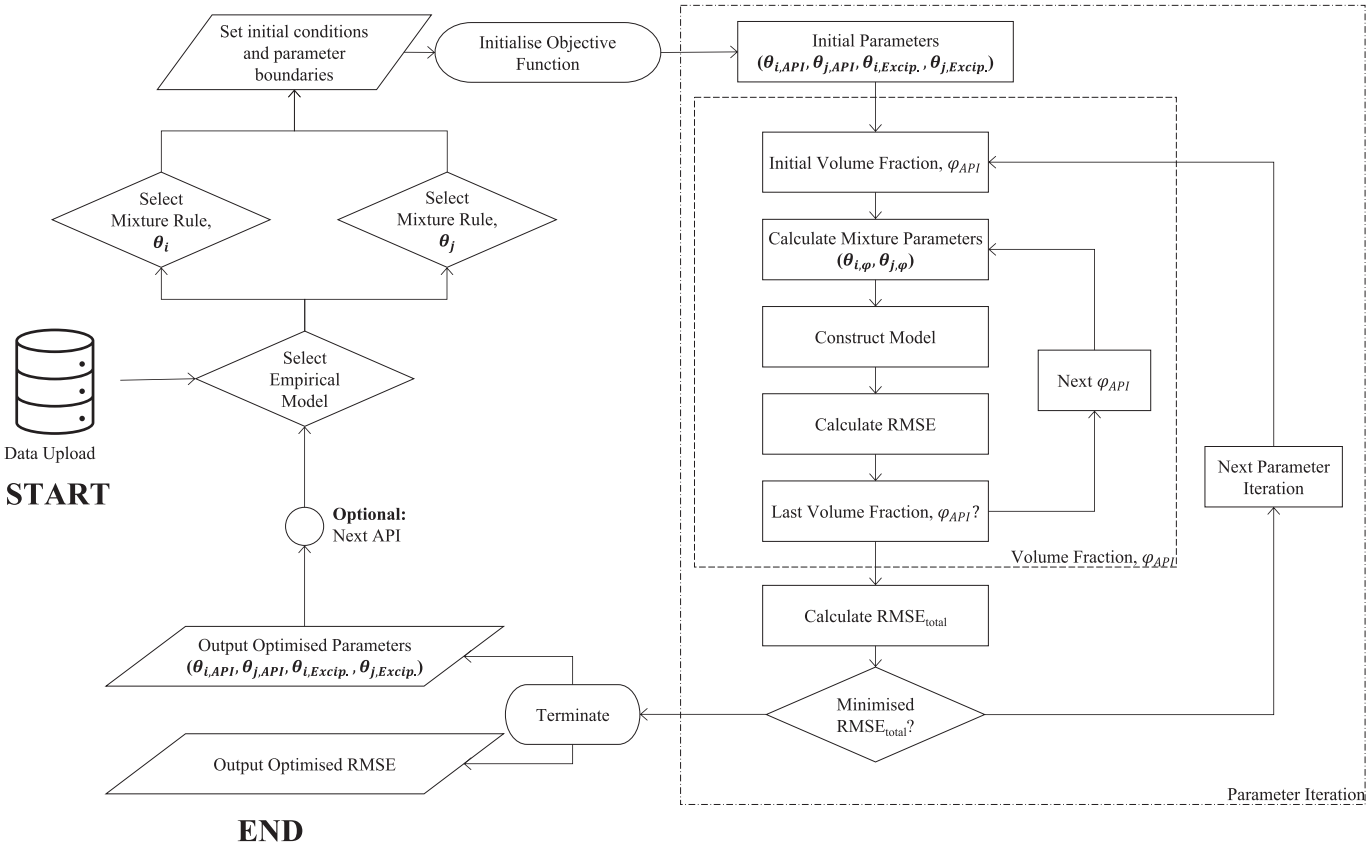

Fig. 2. Workflow showing the structure for the global optimisation of compressibility and compactability mixture models.

Table 3
Parameter pair constraints for the global optimisation of the mixture rules.

Model	Initial Parameters	Parameter Constraints
Gurnham	1	$1 \bullet 10^{-6} \leq \theta \leq 2.5 \bullet 10^{3}$
Heckel	0.25	$1 \bullet 10^{-6} \leq \theta \leq 2$
Kawakita	0.5	$1 \bullet 10^{-6} \leq \theta \leq 2$
	0.5	$-2 \leq \theta \leq 2$
Ryshkewitch-Duckworth	1	$1 \bullet 10^{-6} \leq \theta \leq 1 \bullet 10^{4}$
	1	$-50 \leq \theta \leq 1 \bullet 10^{4}$

2.3. Tablet manufacture

The powders were compacted into 9 mm round flat-faced (B-tooling, i-Holland, UK) tablets of 200 mg by a single punch tablet press (XP 1 Tablet Press, Korsch, Germany). Proprietary software was used to collect data for the compaction profiles (punch force, displacement, and ejection force) for six-to-eight compression pressures, each setting being replicated for ten tablets to achieve a sample average. The number of compression points was selected depending on the ability for the blend to form a compact within the considered pressure range.

2.4. Tablet testing

The placebo tablets created were allowed to rest for an hour before any measurements were taken. A mass balance (Sartorius Quintix 125D-1S, Sartorus, Germany), and manual hardness tester (HC 6.2, Kraemer Electronik GmbH, Darmstadt, Germany, fitted with a Mitutoyo micrometer) were used to measure tablet characteristics such as mass, tablet breaking force and thickness.

2.5. Tablet porosity and tensile strength

The mass, dimensions and breaking force of the tablets were used to estimate the tablet porosity and tensile strength. The compression pressure, P, was estimated from the force of compression, F, which was taken from the tablet press software, and the tablet cross sectional area, Eq. (5). The tablet mass, m_{tablet}, the true density of the blends, ρ_{true}, and the tablet volume, V_{tablet}, was then used to estimate the relative density, ρ_{elative}, and further, the porosity of the tablets, ε, Eq. (6). The offline analytical data for the breaking force, H, thickness, h, and diameter, d, of the produced tablets was then used to calculate the tensile strength, σ, Eq. (7).

$$P = \frac{4F}{\pi d^2} \tag{5}$$

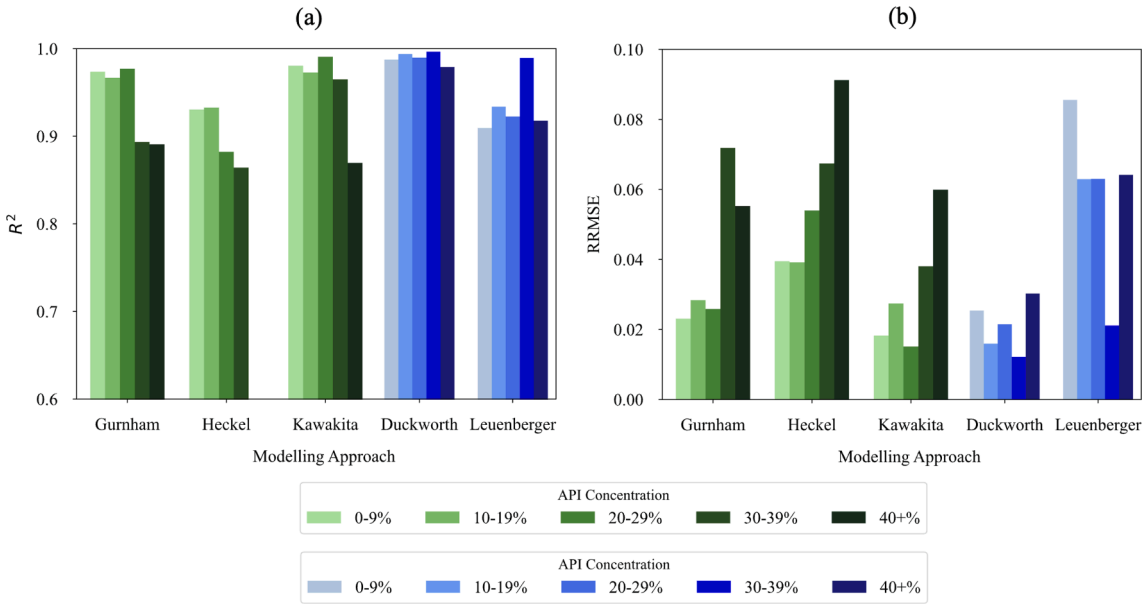

Fig. 3. The averaged Goodness of Fit metrics (a) R^2, and (b) RRMSE for the different modelling approaches as for bins of 10% in blend drug loading.

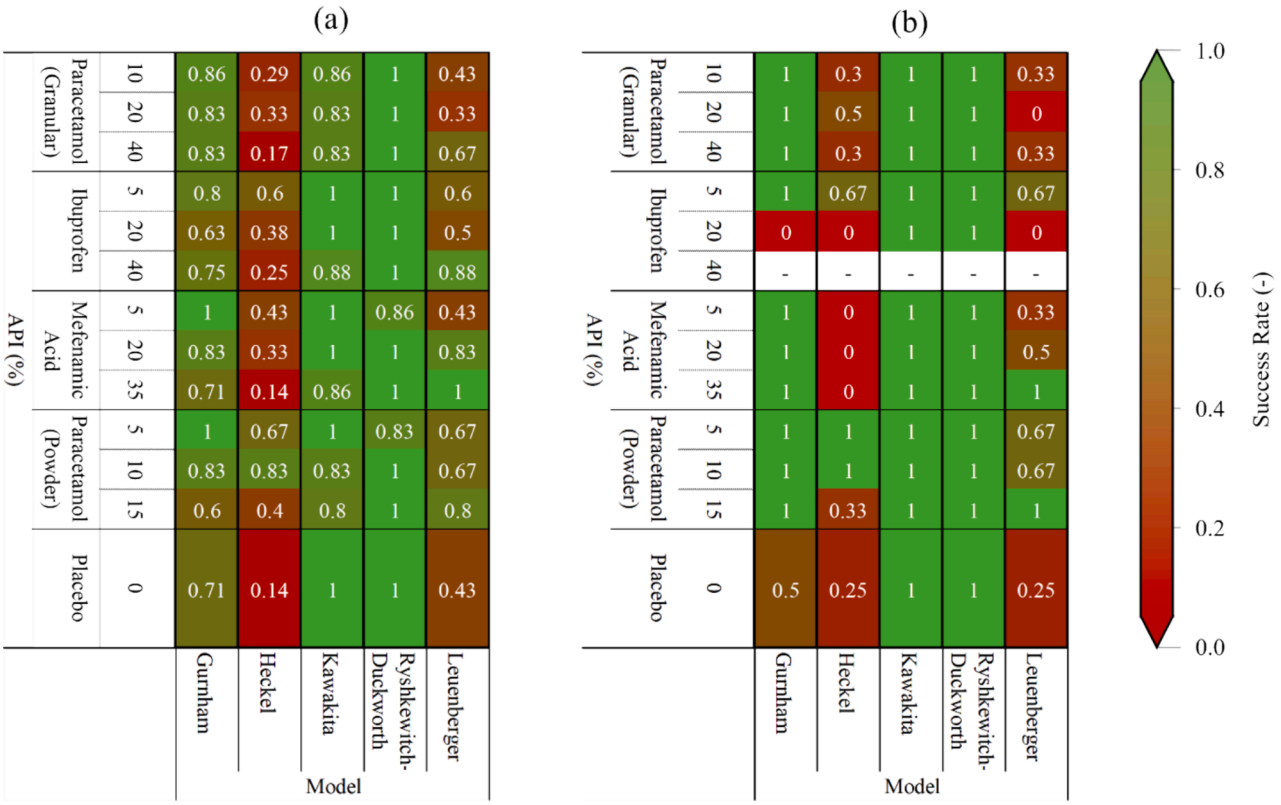

Fig. 4. Success rates showing the fraction of blend data which meets the acceptance criteria ($\varepsilon\pm$ 0.02, and $\sigma\pm$ 0.25 MPa) for (a) the entire compression pressure range and (b) the RoI.

$$\varepsilon = 1 - \rho_{\text{relative}} = 1 - \frac{m_{\text{tablet}}}{\rho_{\text{true}} V_{\text{tablet}}} \quad (6)$$

$$\sigma = \frac{2H}{\pi d h} \quad (7)$$

2.6. Statistical analysis methods

The data points for each individual blend were fitted to the models, and their respective tuning parameters were optimised using weighted regression methods. The weights were defined by the standard deviation of the dependent variable across the ten tablet samples. The GoF was defined by the squared-correlation coefficient, R^2, and the relative root-mean squared error, RRMSE, to assess the prediction performance of the

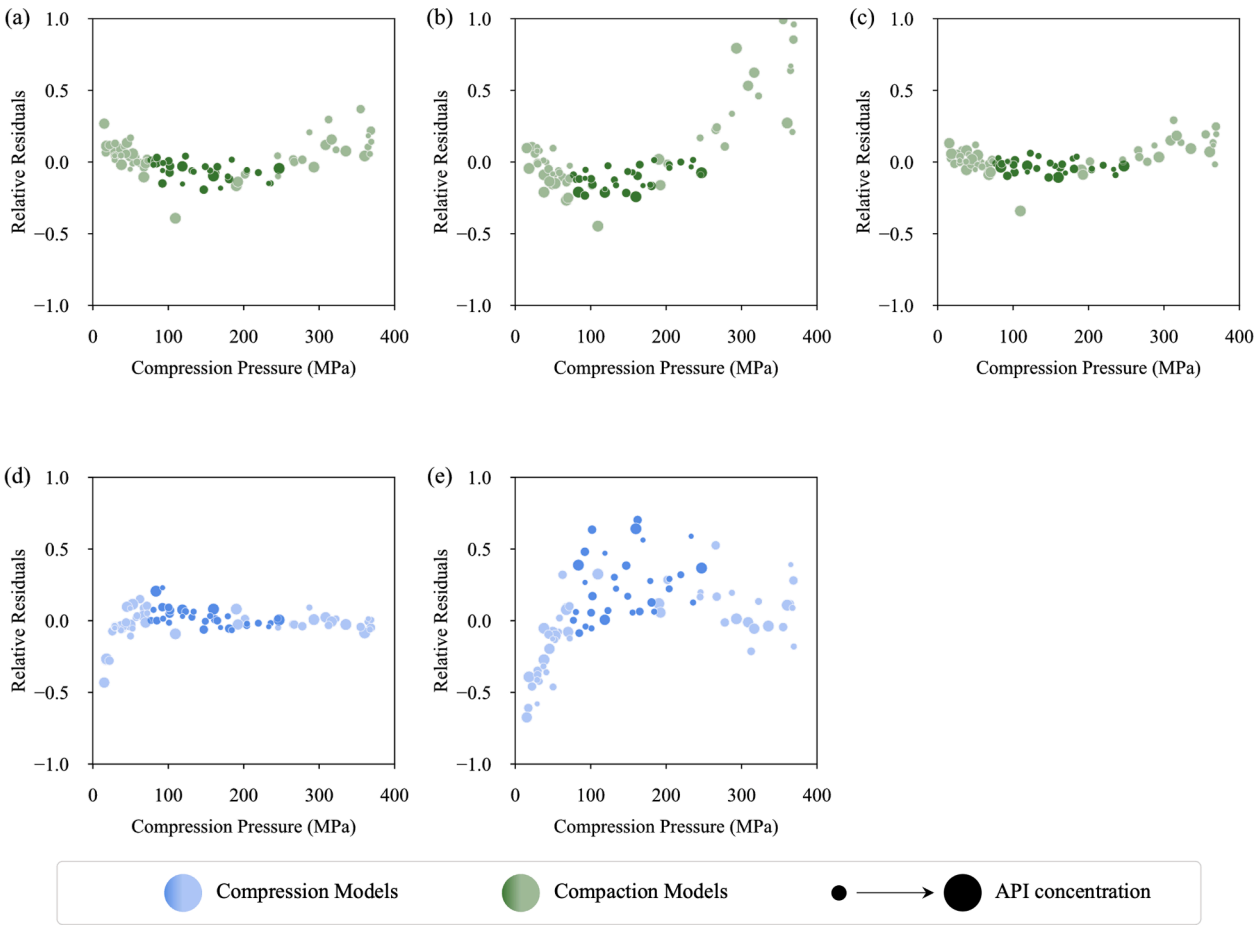

Fig. 5. The relative residual errors for the modelling approaches (a) Gurnham, (b) Heckel, (c) Kawakita, (d) Ryshkewitch-Duckworth, and (e) Leuenberger as a function of compression pressure and API concentration. The highlighted data points show points that fall within the RoI. The size of the data points correspond to the drug loading of the blends.

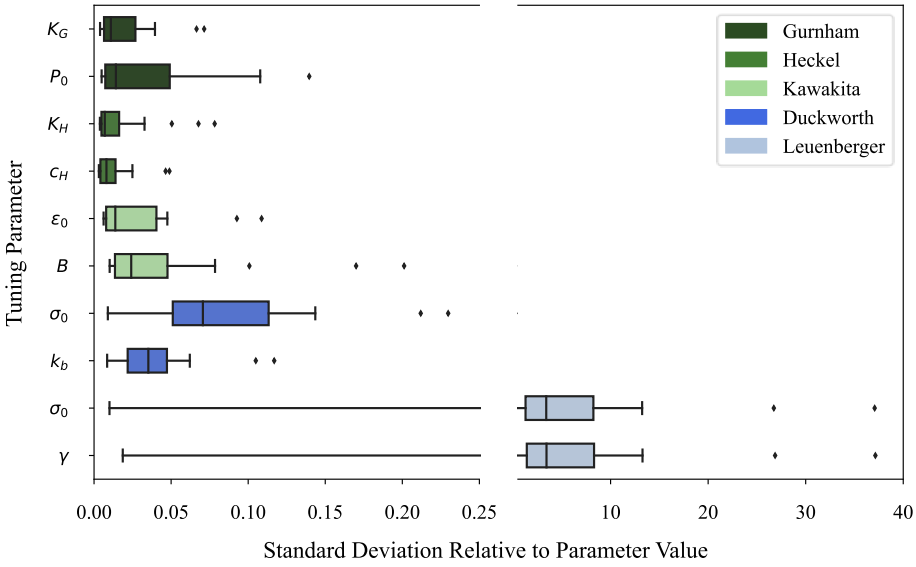

Fig. 6. A box plot (whisker scale = 1.5 IQR) showing the standard deviations of the tuning parameters relative to their predicted values of the fitting of loaded datasets (Table 1) for the common empirical models.

models. The coefficient of determination, R^2, describes how well a model fits a dataset by evaluating the proportion of variance in the predicted, $\hat{y}_i$, and observed, y_i, dependent variable, Eq. (8). This metric can have a value between 0 and 1, with the latter reflecting a model whose predictions match the data exactly. The Relative Root Mean Squared Error (RRMSE) was used to normalise the metric by scaling the

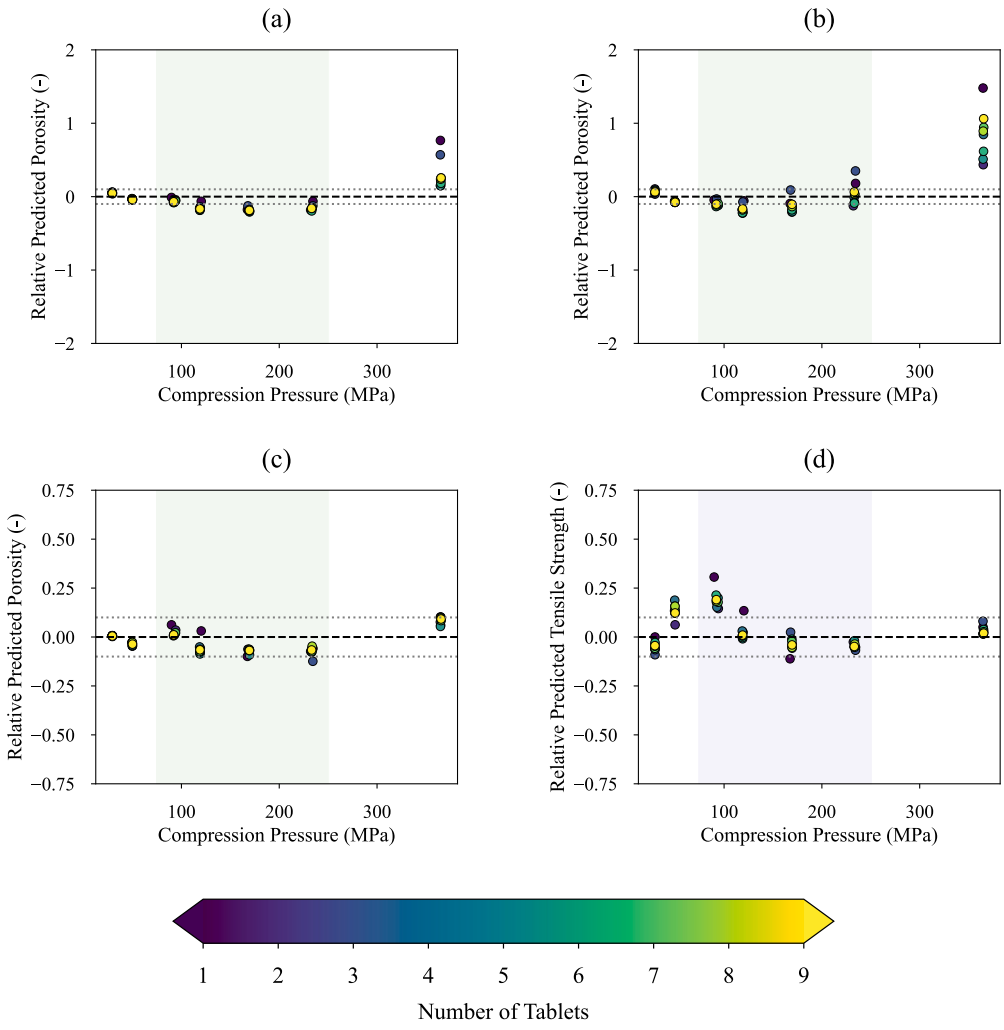

Fig. 7. The relative residuals for quality attribute predictions for the placebo (20% MCC) using (a) Gurnham, (b) Heckel, (c) Kawakita, and (d) Ryshkewitch-Duckworth. The colour of the data point represents the number of tablets used for the sampling. The shaded area in each plot represents the Region of Interest, which are the data points which are of relevance for industrial application. Due to the different magnitudes of accuracy between (a) and (b), and (c) and (d) the y-axes are of different ranges to better display the data for each individual model.

Table 4
Estimated tuning parameter ranges for the sample weighted regression analysis of the placebo blend (20% MCC). Values rounded to three significant figures.

Model	Tuning Parameter	Minimum Value	Maximum Value
Gurnham	$K_{Gurnham}$	8.38	9.11
	P_0	503	638
Heckel	K_{Heckel}	0.00563	0.00829
	c_{Heckel}	0.806	0.958
Kawakita	ε_0	0.570	0.617
	B	0.0203	0.0247
Ryshkewitch-Duckworth	σ_0	10.6	11.8
	k_b	8.38	14.0

individual residuals against its data value, allowing the comparison of different measurements: compression and compaction. This metric represents the error of a model by its average magnitude with regards to the measured data, Eq. (9), where n is the number of data points.

$$R^2 = 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - \bar{y})^2} \tag{8}$$

$$RRMSE = \sqrt{\frac{\frac{1}{n}\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{n} (\hat{y}_i)^2}} \tag{9}$$

The validity of the models was analysed using the relative residual errors to eliminate the problem of different magnitudes of data and model parameters when comparing models. The general impact of API concentration on models' prediction performance was investigated by splitting the results into bins of 10 % intervals of drug loading across all APIs and averaging the GoF metrics within these.

To evaluate the practical accuracy of these models in pharmaceutical applications, a Region of Interest (RoI) was defined to highlight the graphed data points and ranges which have industrial relevance: compression pressures between 75 and 250 MPa; and tablet porosities of 10 to 35 %.

Acceptance criteria were then defined to assess whether a model can be deemed acceptable for use in industry by estimating if the residual errors were within appropriate limits for the quality attribute: $\varepsilon \pm 0.02$, and $\sigma \pm 0.25$ MPa (Nassar et al., 2021). The residuals for the loaded dataset (Table 1) were evaluated for this acceptance criteria and their success rate was estimated for each blend. The success rate was defined as the fraction of data points in each dataset which met the acceptance criteria and visualised as a heat map. This was repeated to consider the

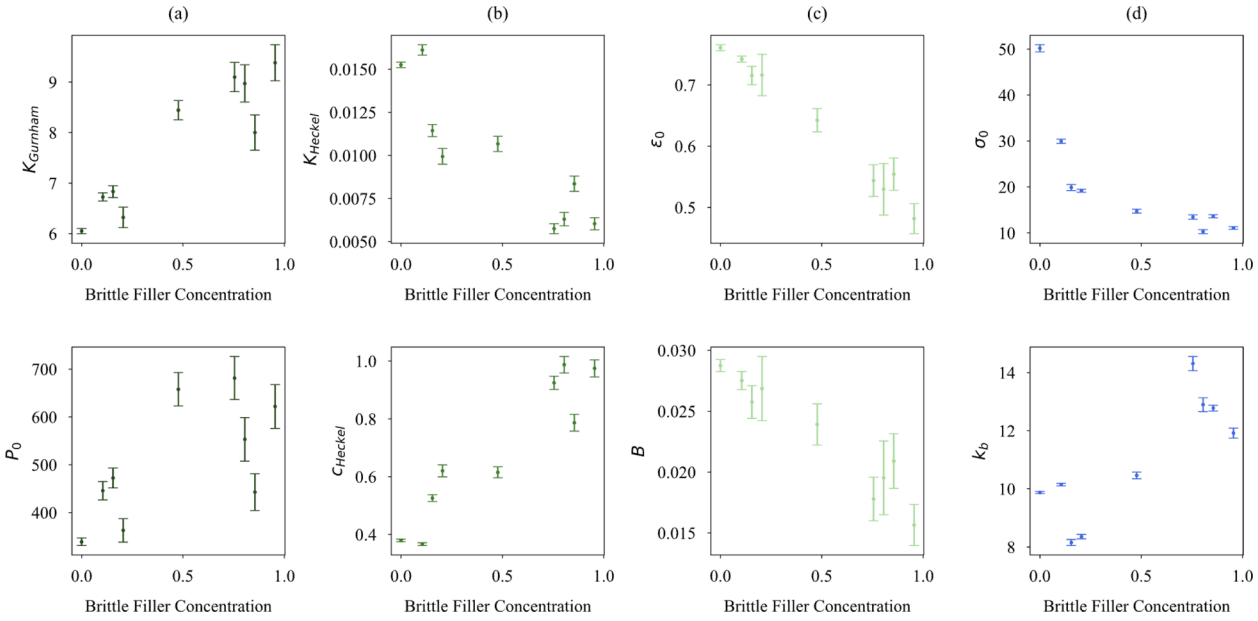

Fig. 8. Estimated tuning parameters and their standard errors for the placebo blends with respect to the brittle filler (lactose monoydrate) concentration for (a) Gurnham, (b) Heckel, (c) Kawakita, and (d) Ryshkewitch-Duckworth.

data within the RoI as defined above, to consider how this acceptance criteria may change when at expected operation conditions.

A box plot, with whisker scaling equivalent to 1.5 times the inter-quartile range (IQR), was used to show the distribution of tuning parameter standard deviations relative to the estimated parameter values. This method was used to investigate the confidence achieved in parameter estimations for the initial model fitting.

2.7. Parameter variability analysis

To consider the impact of variable tuning parameter estimations in literature, an analyses into the fitting method and tuning parameters were conducted. This was divided into two parts: (i) an investigation of weighted linear regression methods to determine the impact of inconsistent accuracy in data collection on reproducibility of tuning parameters; (ii) an investigation into the impact of the variability of tuning parameters on GoF. These analyses were performed using the data from the placebo blend which best matched the loaded data, 20 % MCC in Table 2.

(i) Weighted Regression Analysis: In weighted linear regression, the standard deviations of the dependent variables define the weighting allocation used in the fitting procedure, i.e. a smaller standard deviation results in a larger weight for the data point. Through randomly sampling the placebo dataset, the measured averaged values and their standard deviations (or weights) used in the weighted regression can be varied around the value used in the initial fitting and their impact on GoF and estimated parameters compared.

For each sample size (one to nine tablets), a sample dataset was randomly generated. Tablet measurements were averaged, and standard deviations estimated. This sampling process was repeated five times to reduce the impact of randomness on the averaging, whilst avoiding the evaluation of every potential scenario which would have produced a constant result for each case. Note that only nine tablets were used as the maximum of this study rather than the expected ten due to not all compression points in the placebo dataset having ten tablets worth of data due to human error. The outputs of the sampling were then fitted to the models and the GoF metrics and tuning parameters were analysed to understand whether the cited variations in model tuning parameters between authors could be attributed to data consistency.

(ii) Tuning Parameter Variation Evaluation: To assess how tuning parameter variations may impact the GoF for a particular blend, and iterative trial of tuning parameters was conducted. The performance of different parameter combinations for the 20 % MCC placebo blend were evaluated. For this, new parameters were generated within a ± 75 % range with 1.5 % step size in relation to the initial curve fitting estimates to explore the parameter space. The RRMSE was evaluated for each parameter pair, displayed using contour plots to provide a gradient of prediction accuracy across the parameter space. The RRMSE was selected with a upper limit of 0.25 for the colour axes as this offered a clearer demonstration for the conclusions reached compared to the alternatives (Figs. S1–S4).

2.8. Global optimisation of mixture rules

An optimisation process (Fig. 2) was developed with the aim to estimate placebo and pure API parameters for the empirical compression and compaction mixture models which minimised the total RMSE between the model predictions and observed data for the unique API datasets, i.e. all data, including the placebo data, for each loading of said API was considered. This algorithm estimates one unique pair of tuning parameters θ, Eq. (10) shows the objective function for this.

$$f(\theta,\Phi)=\sum_{j}^{J}\sum_{k=1}^{K}\sqrt{\frac{1}{K}\left(y_{kj}-\widehat{y}_{kj}(f_{\mathrm{mix}}(\theta,\phi)\right)^2} \tag{10}$$

$$\min_{\theta} f(\theta,\Phi) \tag{11}$$

with θ being the placebo and pure API estimates for the parameter pairs (Gurnham: $\theta_G = \{K_G, P_0\}$; Heckel: $\theta_H = \{K_H, c_H\}$; Kawakita: $\theta_K = \{\varepsilon_0, B\}$; Ryshkewitch-Duckworth: $\theta_{RD} = \{\sigma_0, k_b\}$). For all j to J represents the number of unique APIs. For all k to K represents the number of unique data points in the compression or compaction datasets. The porosity or tensile strength data is represented by y_{kj} with $\widehat{y}_{kj}$ representing the value as estimated by the mixture model fitting. The mixture parameter pair θ_{mix} is calculated using one of the three mixture rules, denoted in a general form as $f_{\mathrm{mix}}(\theta,\phi)$, where ϕ contains the list of volume fractions of the N materials in the formulation.

Initial values and constraints were set for the parameters based on the results from the model comparison analysis, Table 3. The optimisation for the Kawakita and Ryshkewitch-Duckworth models were

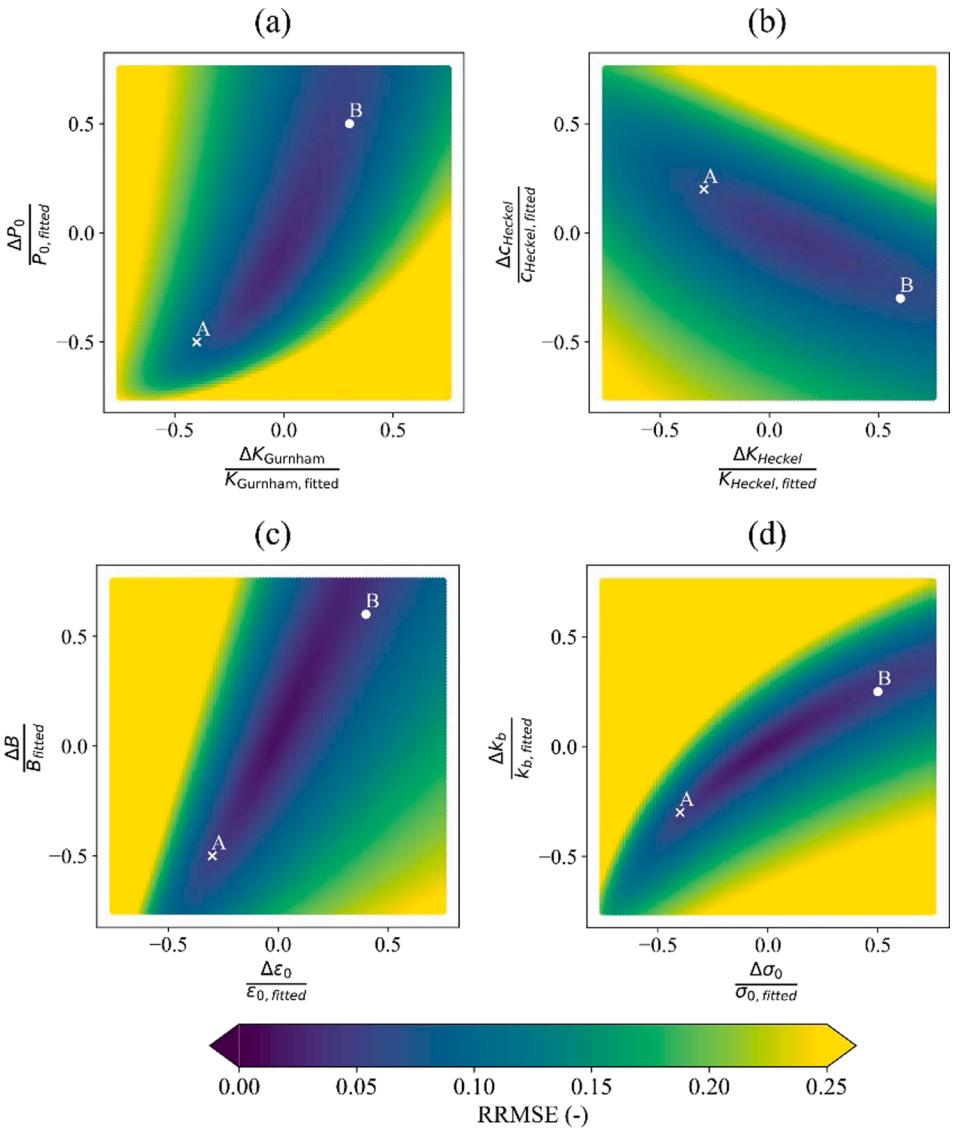

Fig. 9. Contour plots showing how variations of tuning parameters (relative to those estimated by the curve fitting) for the (a) Gurnham, (b) Heckel, (c) Kawakita and (d) Ryshkewitch-Duckworth models impacts the Relative Root Mean Square Error of quality attribute predictions for the placebo (20% MCC) blend. Highlighted on each of these plots are points A and B, which are the tuning parameter pairs used to construct Fig. 10.

constrained by the lower bounds which required these to be expanded into the negative, which was deemed reasonable as these parameters were no longer assumed to reflect physical attributes of a material; however, the geometric mean can only handle positive data. The minima for RMSE was found to cover a significant area in the parameter space. The tolerance for termination of the optimisation (scipy.optimise_minimise using the Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm with Python 3.10.11.) should be set appropriately to provide a stricter success constraint for this procedure; for this investigation, the tolerance of termination was set to 10^{-10}. The optimisation method was conducted for different combinations of mixture rules, $f_{mix}(\theta, \phi)$ of weighted arithmetic, geometric, and harmonic means.

This optimisation approach was compared to the results for the alternative methods. Results for the total RMSE of the optimisation which returned the lowest total RMSE were compared to the total RMSE of individually estimating parameter pairs using curve fitting, and also the traditional method of mixture rule. The traditional method (that which was not optimised) was determined by estimating the line of best fit for the tuning parameters of the individual formulations. The placebo and pure API parameters were extrapolated and used as the parameters in the objective function. In contrast to the new optimisation approach, there was not a unique (across all formulations) placebo tuning parameter pair identified using the traditional mixture rule approach.

2.9. Cross validation

To test the optimisation's ability to predict tuning parameters across new blends, a cross-validation was conducted. Each dataset consisted of four distinct groups: placebo, low drug load, mid drug load, and high drug load. To calibrate the optimisation model, the datasets were split to include only the placebo group and one of the API-loaded blends (either low, mid or high). Following the calibration, the models performance was evaluated using the remaining two API-loaded blends as validation datasets. The RMSE of Prediction (RMSEP) was used to quantify the performance of the model for each case. This provided a measure of the predictive accuracy of the models for the validation datasets by describing the deviation of predicted quality attribute values from their observed values. This 'fit-for-purpose' method was applied, primarily due to the small size of the dataset (four tuning parameter points, one for each distinct group in the model) but also to investigate the significance of drug loading on the calibration of the model.

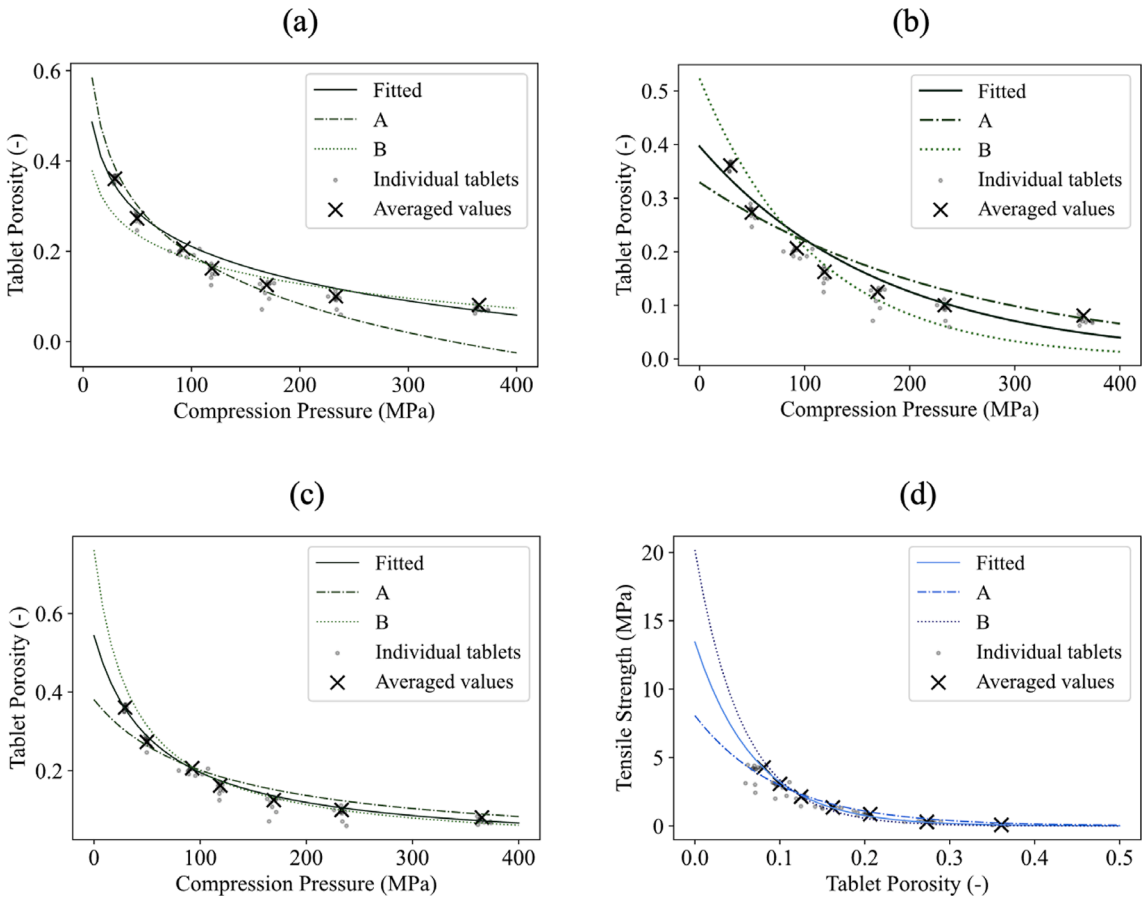

Fig. 10. Compression and compaction curves showing highlighted tuning parameter combinations, A and B from Fig. 9 compared to that of the fitted data (corresponds to (0,0) in Fig. 9) for (a) Gurnham, (b) Heckel, (c) Kawakita, and (d) Ryshkewitch-Duckworth models. These lines were fitted to averaged tablet data, however the individual tablet data has also been included to better visualise underlying variability of the data.

2.10. Compressibility and compactability models

The five models used in this paper have been categorised into two groups: compressibility models (results identified throughout paper with a green colouration) and compactability (results identifiable throughout paper with a blue colouration) models. The models considered were those most commonly cited in the literature. The selected compressibility models were established by Gurnham and Masson (1946), Heckel (1962) and Kawakita et al. (1965) as described in Eqs. (12)–(14), respectively.

$$\varepsilon(P) = -\frac{1}{K_G}\ln\left(\frac{P}{P_0}\right) \tag{12}$$

$$\varepsilon(P) = e^{-(K_H P + C)} \tag{13}$$

$$\varepsilon(P) = \frac{\varepsilon_0}{1 + \left(\frac{V_\infty}{V_0}\right)bP} = \frac{\varepsilon_0}{1 + BP} \tag{14}$$

where ε is the porosity of the compact and P is the compression pressure. Denoting the model tuning parameters, for Gurnham model, K_G explains the resistance to compression and P_0 is the pressure required to reach zero porosity; for Heckel, K_H is the proportionality constant, and C is a constant; for Kawakita, ε_0 is the initial powder bed porosity, V_∞ is the net volume of powder, V_0 is the initial apparent volume of powder, and b is a tuning parameter which is hypothesised to reflect the resistant and cohesive forces of the particles (Adams & Mckeown, 1996). To reduce the number of parameters in Kawakita model and simplify the fitting process, the ratio of volumes $\frac{V_\infty}{V_0}$ and the constant b were grouped into the single tuning parameter.

The selected compactability models were those created by Ryshkewitch (1953) and Leuenberger and Rohera (1986), following Eqs. (15) and (16) respectively.

$$\sigma(P) = \sigma_0 e^{-k_b \varepsilon} \tag{15}$$

$$\sigma(P, \varepsilon) = \sigma_0\left(1 - e^{-\gamma P(1-\varepsilon)}\right) \tag{16}$$

where σ represents the strength of the tablet and σ_0 is the strength at zero porosity, k_b represents the material's bonding capacity, and for Leuenberger model, γ denotes the compression susceptibility as it indirectly described by the volume reduction.

3. Results

3.1. Individual datasets

3.1.1. Goodness of fit

For the fitting of loaded datasets (Table 1), each model achieved an R^2 of above 0.90 and an RRMSE of close to zero in the instances of low drug loading (Fig. 3). This confirms that the models can offer acceptable accuracy in predicting the compression and compaction profiles, although it is observed that an increase in drug loading resulted in a reduction in the GoF metrics for each model. Kawakita and Ryshkewitch-Duckworth perform consistently well below 40 % API concentration, at which a significant reduction in GoF is observed. The Gurnham and Heckel models present a stronger reduction in GoF metrics with higher drug loadings in this instance.

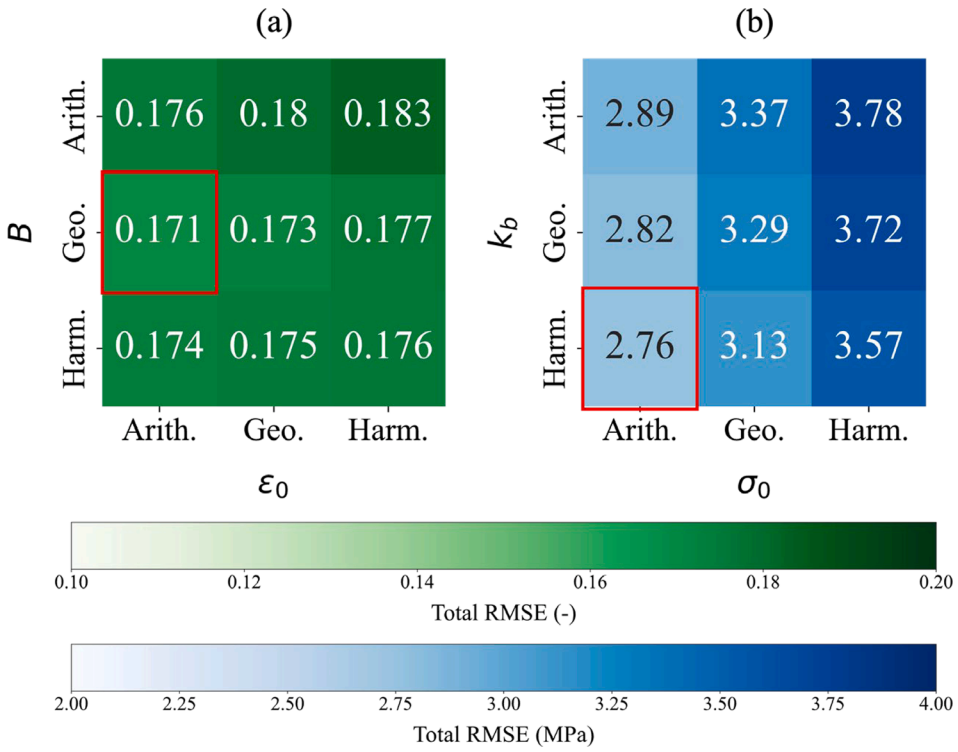

Fig. 11. Total RMSE estimations for the different combinations of arithmetic (Arith.), geometric (Geo.), and harmonic (Harm.) mixture rules for the optimisation of parameter pairs of the (a) Kawakita, and (b) Ryshkewitch-Duckworth models. The lowest estimation of total RMSE is outlined in red.

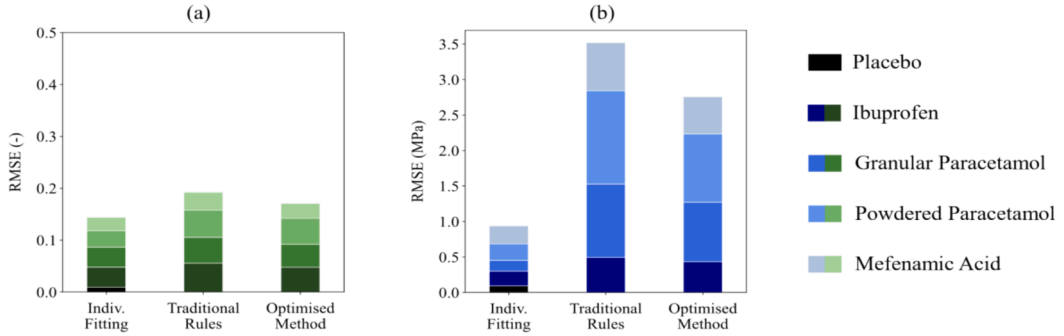

Fig. 12. Stacked bar plots showing the contributions for the loaded blends and 20% MCC placebo to the total RMSE for (a) Kawakita, and (b) Ryshkewitch-Duckworth models. Three methods of tuning parameter estimation were compared: individually fitting the datasets; calculating a line of best fit for the estimated tuning parameters and interpolating the results; and the proposed global optimisation method. The contributions were separated by colour to show the individual contributions of each API, with this including three blends worth of compression or compaction data.

To verify whether the models were acceptable, the success rate for the model predictions that met the defined acceptance criteria ($\varepsilon\pm$ 0.02, and $\sigma\pm$ 0.25 MPa) was estimated for each of the individual blends. This was completed for the whole compression pressure range (Fig. 4 (a)) and the RoI (Fig. 4 (b)).

Fig. 4 shows that the Kawakita and Ryshkewitch-Duckworth models had the highest success rate for each API, with Gurnham performing well but less consistently so. Heckel and Leuenberger had the lowest success rates and also the largest range in results. When considering only the data within the RoI, it was found that the success rates mostly increased with the Gurnham, Kawakita and Ryshkewitch-Duckworth models performing at 100 % acceptability except in the instance where Gurnham was unable to capture any acceptable predictions for the 20 % ibuprofen blend. Note that the 40 % ibuprofen data contained no points which rested within the RoI. The RoI success rates for the Heckel and Leuenberger models showed inconsistent improvements, and conversely some datasets showing 0 % success rates, verifying that these models are not appropriate for modelling these datasets. Note, that the success rate only defines whether the results are within certain expected bounds and does not capture the magnitude of the residuals. The causes of the differences in the RRMSE and success rates were better demonstrated by analysing the relative residual errors for each model (Fig. 5). A well-fitted model would show a scattering of data points around zero across the pressure range. Any trends in the data would imply that the model does not fully capture the information within the data. A visualisation for the extreme cases of GoF for the Heckel model can be found in Fig. S5 in the Supporting Information for clarity on residual errors in relation to the compression curve. It was found that each model offers a trend in the relative residual errors, localised to the lower- and upper-most limits of the pressure; this is most prominent for the Heckel and Leuenberger models. It was observed that the most prominent deviations are located outside of the RoI, represented by the lightened plot points. This supports both the conclusions from Kuentz and Leuenberger (1999) regarding Heckel's limitations, and Vreeman

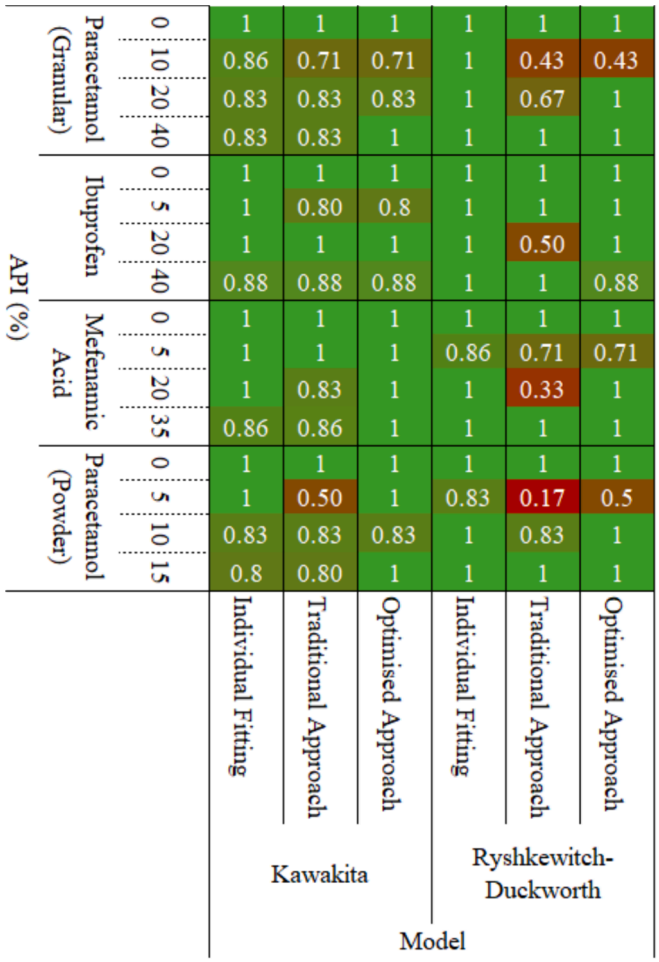

Fig. 13. Success rates for the individual fitting, and the traditional and optimised approaches to mixture rule population for the Kawakita and Ryshkewitch-Duckworth models showing the fractions of data which meets the acceptance criteria across the whole range of compression data for the loaded dataset, Table 1.

and Sun (2021) who discussed Heckel's reliability under certain process conditions. The convergence of data points in the RoI provides visual evidence supporting the increased success rates discussed.

When considering whether these models could be used to achieve reproducible results for industrial application, the predictability should be considered along with the confidence and consistency in the estimated tuning parameters. By considering the standard deviations of tuning parameters relative to themselves (Fig. 6), it can be seen that Leuenberger's tuning parameters demonstrated the most variability and offered standard deviations in its parameters which were a magnitude of ten greater than themselves. The remaining models also demonstrate a skewed median, inconsistent whisker lengths and extreme values which are characteristic of an asymmetric or skewed distribution of parameters (Fig. S6 in the Supporting Information). This was expected due to this plot reflecting a dataset of different materials and blends, for which the drug loading has already been shown to impact predictability; however, these errors are more acceptable as they remain within a satisfactory 20 % error margin. The variability of Leuenberger's tuning parameters may be due to overfitting with the inclusion of two independent variables, pressure and porosity (Eq. (16)). Due to the magnitude of this variation, Leuenberger has not been considered further in this work.

3.1.2. Parameter variability analysis on fitting procedure

The quality of predictions can be impacted through the data collection methods (i.e. the experimental error), the model structure (i.e model limitation to accurately predict the response parameter), and the fitting procedure (i.e. optimisation procedure to minimise the error between model prediction and experimental data). With the inconsistency of tuning parameters in the literature, and with the use of weighted linear regression to process data, the response of these models to variations in experimental errors (or weighting factors) was prioritised. This investigation considered the impact experimental error variability had on the quality of fit (Fig. 7) and the estimated ranges of tuning parameters (Table 4).

The general trends in relative residuals observed in Fig. 7 resemble those displayed previously in Fig. 5, with Gurnham and Heckel showing residuals greater than those achieved by Kawakita for compression prediction. The residuals of different sample sizes did result in variations in each case. These variations were more prominent in the upper half of the compression axis for Gurnham and Heckel. The Kawakita and Ryshkewitch-Duckworth models showed less variation and a better quality of fit in comparison. Ryshkewitch-Duckworth displayed a consistent amount of, and trend in, scattering across the compression pressure axis; Kawakita performed well with little variation between samples. Considering the estimated parameter ranges shown in Table 4, the parameter estimates also showed variation across the samples, with this being most evident with Gurnham's P_0 and Ryskewitch-Duckworths k_b. These results reveal that a lack of consistency in the data collection can have (and may have had in the literature) an impact on the estimation of parameters, although the extent of this is challenging to quantify.

3.1.3. Parameter variability analysis on Goodness of fit

The tuning parameters for the Gurnham, Heckel, Kawakita and Ryshkewitch-Duckworth models were evaluated across the placebo space, Table 2 (Fig. 8). From the literature, it was expected that the compression and compaction parameters would follow a linear and non-linear trend, respectively (Jolliffe et al., 2022). This can be best observed in the Kawakita and Ryshkewitch-Duckworth parameters, although both show a degree of scattering around this trend and Ryshkewitch-Duckworth's k_b seems to represent a sinusoidal relationship rather than the expected logarithmic trend. For Gurnham and Heckel, there is a larger degree of scattering which would not be adequately captured by either a linear or non-linear correlation. This scattering was expected for Heckel based on the discussion of parameter variability by Sonnergaard (1999), however there was no evidence found to support the scattering of Gurnham's parameters. It was of interest to determine how deviations from the fitted tuning parameters may impact the GoF before continuing to develop a mixture model methodology.

The contours of RRMSE for different parameter iterations (for the 20% MCC placebo blend) demonstrate that there is, in fact, a large region of acceptable GoF, highlighted by the darker blue-purple areas (Fig. 9). Due to this valley-like space around the minima, there are numerous parameter pairs which can acceptably capture the compressibility and compactability profiles. This contrasts the prior belief that there are only singular (material specific) parameters of best fit, and provides reasoning behind the inconsistent estimates for yield pressure using Heckel's proportionality constant (Sonnergaard, 2022). The sensitivity of the parameters can also be observed here, with small changes to Ryshkewitch-Duckworths k_b having a greater impact on the RRMSE compared to σ_0. The influence this has was better demonstrated in Fig. 10, where the highlighted parameter pairs A and B (selected for their low RRMSE and large deviation from the fitted tuning parameters at (0,0) to capture the flexibility of these models) for each model have been compared to the compression or compaction curves as estimated by the original curve fitting. For the Kawakita and Ryshkewitch-Duckworth models, it was shown that a change in parameters can still adequately predict the data, with the deviations localised to the lower range of the independent variable. The Gurnham and Heckel models show less consistency in the apparent deviations, as the models seem inadequate at capturing the required rate of change of the dataset, with the deviations

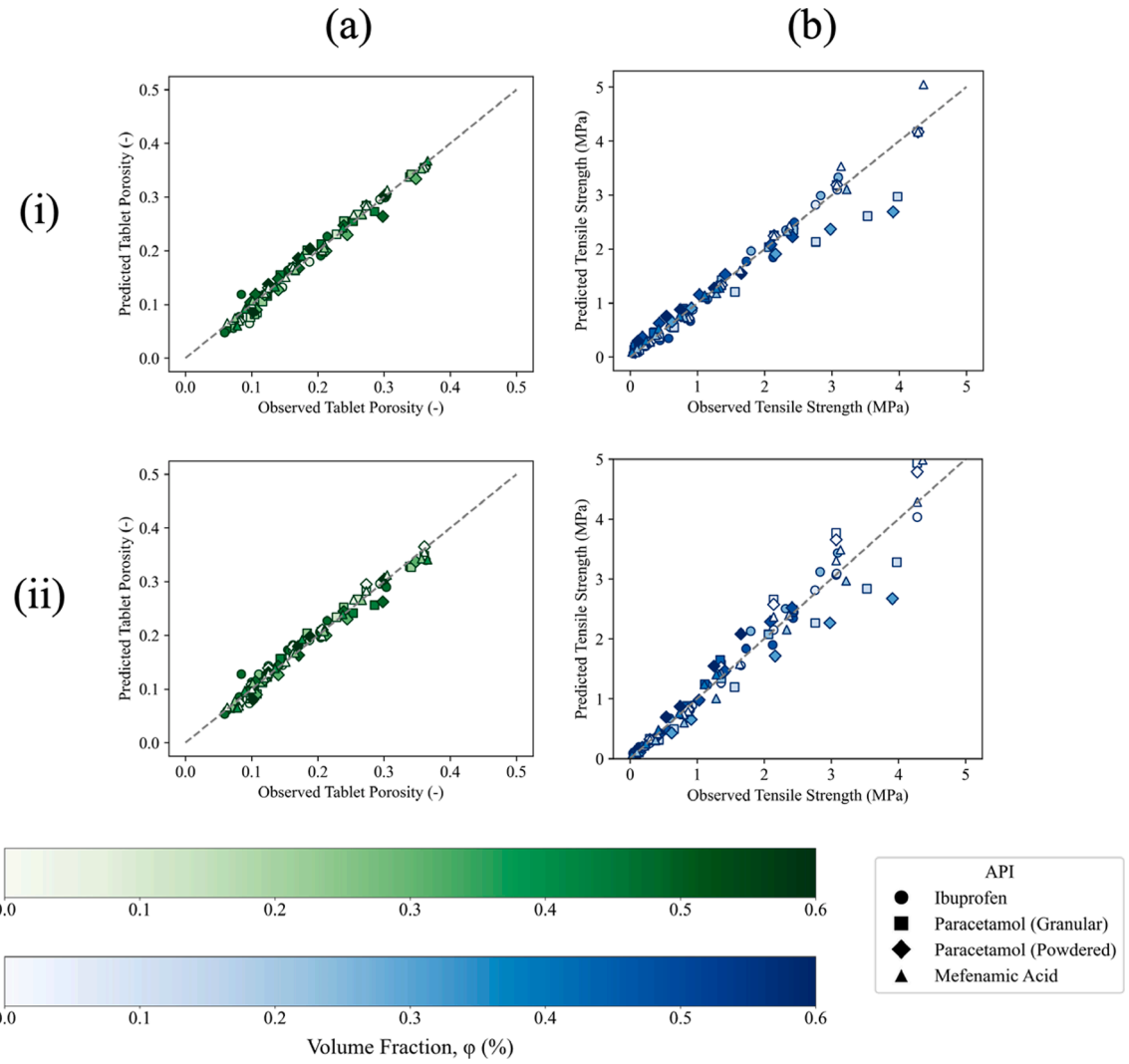

Fig. 14. Parity plots comparing the observed versus predicted critical quality attributes for (a) Kawakita, and (b) Ryshkewitch-Duckworth models using (i) the new optimised approach and (ii) the traditional approach to mixture rule population.

reflecting the residual errors demonstrated in Fig. 5.

With the ambiguity of the parameters from these results, interpreting physical meaning to the tuning parameters of these models – for example, defining a blends apparent yield pressure via Heckel's proportionality constant – is difficult and unnecessary. Kawakita and Ryshkewitch-Duckworth have proven to be the models which predict the datasets most consistently with the least sensitivity. Due to this Gurnham and Heckel have not been considered for the next section which develops an optimised approach for populating mixture rules that capitalises on the flexibility of the parameter space. Results for the mixture model evaluation for these models however can be found in the supplementary document in Figs. S7–S10.

3.2. *Mixture Rule Implementation: Global optimisation and identification of optimal mixture rule*

The combinations of arithmetic, geometric and harmonic mixtures for optimising the model parameter pairs were tested on the loaded dataset (Fig. 11). It was observed that changing the mixture rule for both parameters did not have a substantial impact on the total RMSE estimation for the Kawakita model. The Ryshkewitch-Duckworth model was more sensitive to the changes in applied mixture model, with the estimation method of k_b having the most influence on the GoF matching the observations in Fig. 8.

The optimised method was compared to the traditional method for populating the mixture models. The rules selected to estimate the parameters in this comparison were those which achieved the lowest RMSE from the rule comparison study (as highlighted in Fig. 11): arithmetic–geometric for Kawakita: $\theta_K = \{\varepsilon_0, B\}$; and arithmetic-harmonic for Ryshkewitch-Duckworth: $\theta_{RD} = \{\sigma_0, k_b\}$. Both methods of mixture model population performed well for predicting compressibility, and slightly less so for the compactability with the paracetamol blends contributing significantly to the total RMSE (Fig. 12). The individual contributions of the API to the total RMSE can be interpreted more practically when we compare the success rates of the individually fitted datasets and the optimised mixture model (Fig. 13) and the predicted values against the observed data (Fig. 14). These results demonstrate the excellent performance of the Kawakita and Ryshkewitch-Duckworth models, with only a decrease in success rates observed in the lowest loadings for the Ryshkewitch-Duckworth model. The deviations observed in the compactability parity plot increase with increasing tensile strength. The greatest deviations occur above a tensile strength of 2 MPa which is commonly used as the minimum target value in industry to avoid damage to tablets during further processing and handling (Polak et al., 2023). Further analysis into the origin of the deviations was found by considering the relative residual errors for these models (Fig. 15), and comparing these to the relative residuals achieved when individually fitting the datasets. Here, it was observed that the relative

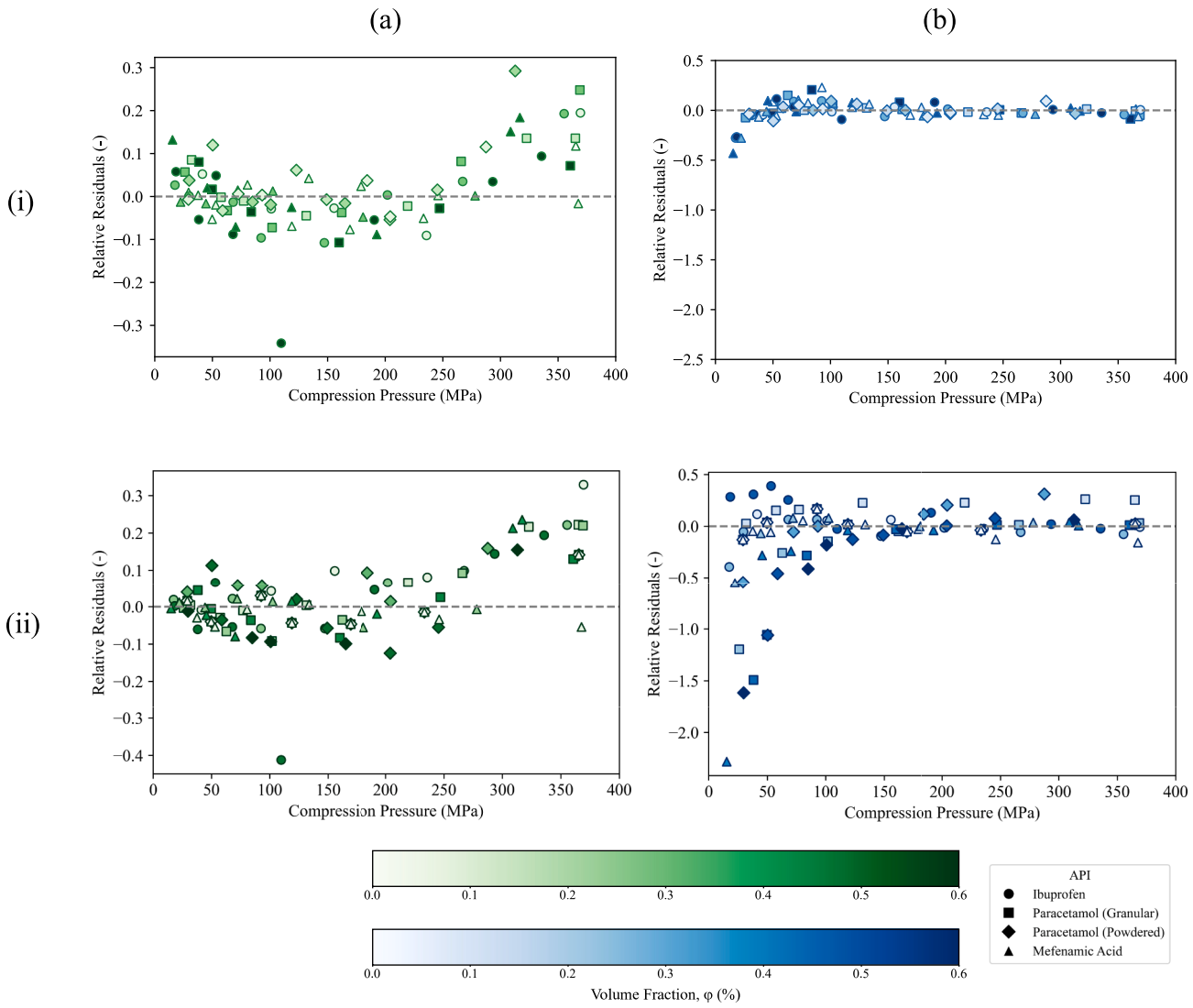

Fig. 15. Relative residual errors for the (a) Kawakita and (b) Ryshkewitch-Duckworth models as estimated by the (i) individual fitting of datasets and (ii) the optimised approach to mixture modelling for the loaded dataset.

residuals from the optimisation approach demonstrated a similar trend to that of the individual fits for both models. Kawakita showed a greater degree of scattering within a similar magnitude of deviations for the optimised approach. Ryshkewitch-Duckworth also showed a similar trend in the relative residuals but for the optimised approach the underpredictions at the lower pressure range (0–100 MPa) was considerably greater than the individual fitting approach having considerable contribution to the RMSE as shown in Fig. 12. The optimised mixture rule underpredicts the strength unlike the traditional method which is showing a scattering of both under- and over-prediction in the parity plot. The underprediction of tensile strength is of less significance as tablets still meet industry specifications of a tensile strength of > 2 MPa (Polak et al., 2023). Further, these large deviations below and around the lower boundary of the RoI (Compression Pressure = 75 – 250 MPa) which shows that these models and accurate for the intended purposes of tablet manufacturing but may require models of increased complexity to further improve upon predictability.

3.3. Cross validation

The datasets were split into calibration and validation sets based on their drug load. This provided an investigation which considered the ability for this optimisation method to predict tuning parameters for new blends, whilst determining the significance of drug loading on reducing the RMSEP (Fig. 16). The use of the lower API concentration with the placebo blend in the calibration (Fig. 16 (a)) resulted in a large RMSEP for the remaining validation sets (mid and high drug loading). When replaced with a higher drug loading (Fig. 16 (b) and (c)), the RMSEP is reduced, yielding an acceptable fit for each validation set. This demonstrates that applying this method to a new system, a small amount of data can still achieve a good estimation of tuning parameters which would achieve an acceptable GoF, particularly when said data covers the placebo and high loaded blends.

4. Discussion

4.1. Model comparison

From the initial comparison of the GoF and the evaluation of the success rates of these models to meet the defined acceptance criteria, it was evident that the Gurnham, Kawakita and Ryshkewitch-Duckworth models adequately captured the compression or compaction profiles across the different drug loadings. This evidence is contrasted against previous studies which questioned the oversimplification of empirical models in predicting tablet porosity and tensile strength (Sonnergaard, 1999; Sonnergaard, 2001).

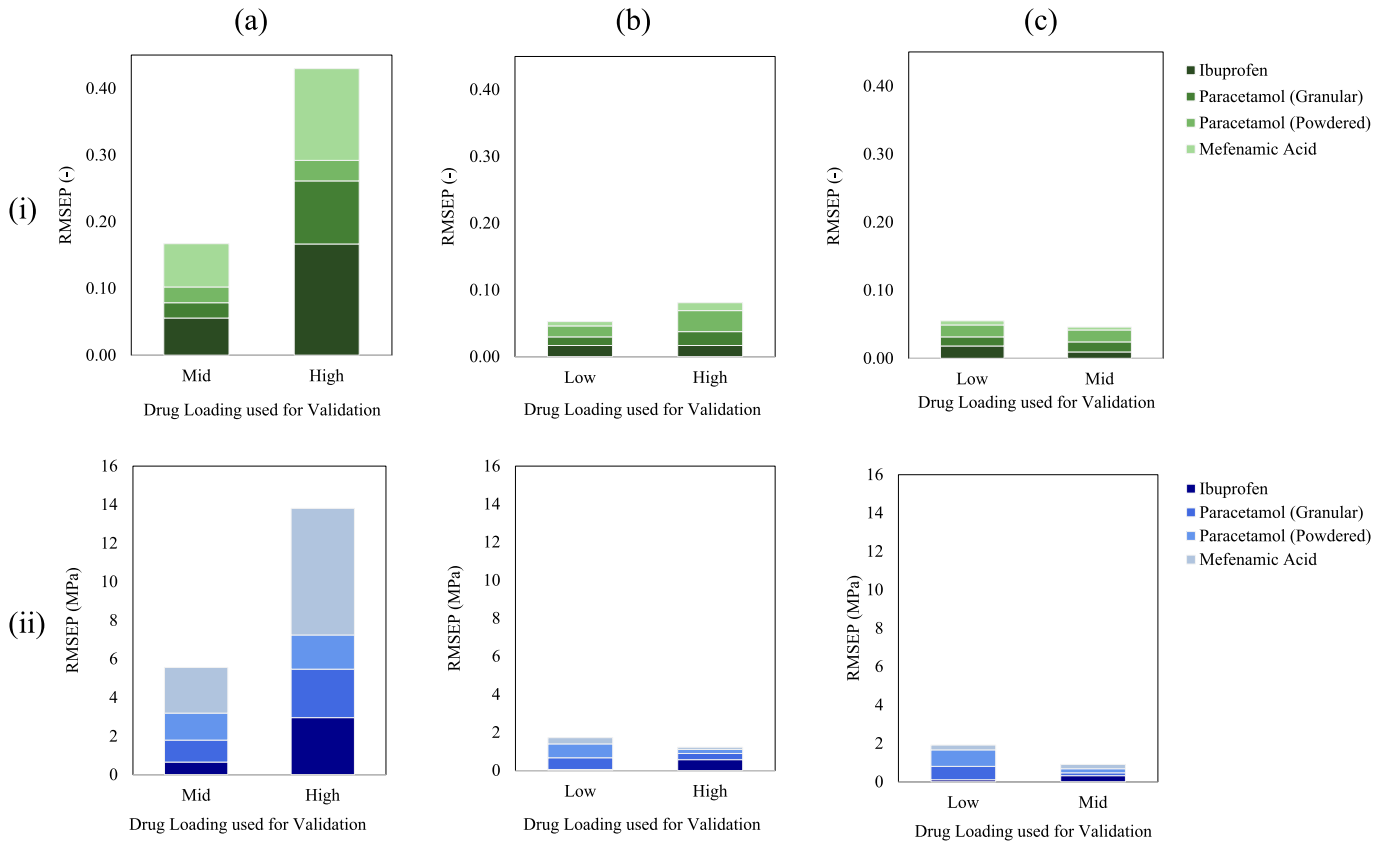

Fig. 16. The Root-Mean-Squared Error of Prediction (RMSEP) of validation datasets from the cross validation analysis which used the placebo and (a) low loading, (b) mid loading, and (c) high loading datasets for calibration. Results shown reflect the (i) Kawakita and (ii) Ryshkewitch-Duckworth models with the colours showing the contributions of the different API datasets.

The results between the compression models were less consistent than that of the compaction models, with drug loading having a larger influence on Gurnham and Heckel's GoF (Fig. 3). Further, the trends and magnitude of deviations observed from the residual error analysis were most prominent in these models too; in the case where Leuenberger is neglected due to the magnitude of errors in the estimated tuning parameters, possibly due to the overfitting of this model as it relates tensile strength to both compression pressure and tablet porosity (Eq. (16)).

The compression models differ in their assumptions of the relationship that tablet porosity has with increasing compression pressure; hence the variation in their model structures. Gurnham, Heckel and Kawakita describe the rate of compression in three different ways, as are outlined by Eqs. (17)–(19) respectively.

$$\frac{d\varepsilon}{dP} = -\frac{1}{K_G P} \tag{17}$$

$$\frac{d\varepsilon}{dP} = -K_H \varepsilon \tag{18}$$

$$\frac{d\varepsilon}{dP} = -K_K \varepsilon^2 \tag{19}$$

Gurnham's definition of compression rate does not account for the correlation between the extent of compression (i.e. porosity is not considered) and the powders compressibility. Conversely, Heckel and Kawakita's perspectives acknowledge that the extent of compression of a powder will contribute to a powders ability to undergo further compression, which would be expected in a system which has undergone plastic deformation. It was also noted that Gurnham's model assumes that the initial porosity of the powder bed would be infinite (as the gradient will increase exponentially towards the porosity axis), which contradicts the definition of porosity as this cannot be less than zero or greater than one. Although, with the magnitude of the considered pressure range in direct compression, this is inconsequential. Despite Heckel accounting for the extent of compression, this model did not perform as well as Gurnham. Heckel's model was found to consistently underpredict at low compression pressures compared to Kawakita and Gurnham which were able to capture the initial compression results with higher accuracy. These observed deviations were expected as Heckel (1961) stated that their expression was valid between compression pressures of 35 – 170 MPa depending on the powder being investigated. It was unexpected, however, that the largest deviations from Heckel's model were observed at the upper limit of the pressure range studied as a majority of previous discussions have focussed on investigating the presence of particle rearrangement and fracturing to explain the different gradients of their plots.

It was clear that drug loading negatively impacts the GoF for each of the models, more prominent for Heckel, which showed a large drop in R^2 at loadings of 40 % and above. The residual error trends show that, in each of the models, the points converge at the RoI pressure range with the largest deviations observed being an under prediction of the blends with high drug loading. This suggests that as the loading was increased, the models' definition for the rate of change in porosity with compression pressure became increasingly inadequate at capturing the curvature of the compression data, this idea was visualised in Fig. 10 (b). The varying influence that drug loading had on the predictability of the models may be attributed to the assumption of compressibility, which might not be applicable to non-compactable APIs compared to the materials on which the models were developed, such as soaked fibrous materials, metals, and ceramics. This has already been studied by Kuentz and Leuenberger (2000b) and Queiroz et al. (2019) who showed that a threshold of non-compactable material exists, at which the blend will

likely fail as a compact. This threshold has been cited as a percolation threshold or dilution capacity (Kuentz & Leuenberger, 2000b; Queiroz et al., 2019). It is crucial to determine whether there is a limit, potentially dependent on the material, at which non-compactability becomes a dominating behaviour for a blend.

4.2. Parameter variability analyses

There has been a concerted effort to identify the tuning parameters which best represent the compressibility and compactability of individual materials to be used in mixture rules (Busignies et al., 2006; Frenning et al., 2009; Jolliffe et al., 2022; Kloefer et al., 2010; Kuentz & Leuenberger, 2000b; Mazel et al., 2011; Michrafy et al., 2007; Reynolds et al., 2017; Wu et al., 2006). Before this, the discussions in the literature centred around the physical meaning of these parameters, or questioned the simplicity of the model structures, to address the variability of the reported values between studies. It was expected from the iterative study of the tuning parameters that the contour plots would show a minimum RRMSE at the fitted ('best-fit') parameters, which would then increase as the parameters strayed from this centre point. Instead, the contour plots in Fig. 9 show the first qualitative proof that there are, in fact, multiple parameter pairs which exist across a large space that achieve acceptable predictability for compression and compaction behaviour as demonstrated in Fig. 10. The correlations observed between the parameters and their RRMSE (linear for Heckel and Kawakita, and non-linear for Gurnham and Ryshkewitch-Duckworth) confirms that there are behaviours which are not being captured by the tuning parameters, as expected from the trends observed in the residual plots (Fig. 5). The investigation into the weighted regression (Fig. 7) showed that inconsistencies in data collection may influence GoF and also the tuning parameter estimations. Therefore, the variability in accuracy of the collected data may have contributed somewhat to the variations observed in reported tuning parameters in the literature, particularly with the evidence that a significant deviation in the tuning parameters could only have minimal impact to the GoF.

Overall, it was found that Kawakita and Ryshkewitch-Duckworth were the superior models in their respective applications based on the consistent, high quality of their metrics and success rates over the whole compression range and the RoI. The success of Kawakita was unexpected based on the frequency of Gurnham's use – and Kawakita's absence – in recent years. For this reason, Kawakita and Ryshkewitch-Duckworth were the focus of the mixture model work, however results for Gurnham and Heckel can be found in the Supporting Information in Figs. S7–S10 in Supporting Information. Whether these models can be further manipulated, be that in their structure or parameters, to include these unidentified behaviours to create a model which would generate the contour plots as expected has not been addressed. This finding, however, demonstrates that although these models are simple, and their parameters variable, they are not as fragile as previously suggested. Focus now should move away from perfecting the estimations of these tuning parameters based on physical attributes, and instead capitalise on this flexibility to work towards understanding how these models can be used with mixture rules to predict compressibility and compactability of new formulations, e.g. varying API, drugs loadings, particle size distributions, and physical attributes.

4.3. Discussion of multiple parameter pairs and mixture model optimisation

Without consistent estimations for material specific parameters across industry and academia, it has been challenging to develop a foundation for the application of mixture rules. Traditionally, a line of best fit was used to estimate the mixture rule for a models tuning parameters with respect to a components contribution (mass or volume fraction, for example) to the blend. This required the collection and analysis of compaction data for numerous individual blends, with an increased number of blends maximising information for the line fitting, and would result in a placebo blends parameters to vary between APIs even though the blend itself remains the same (Fig. S11 in Supporting Information). Knowing that a large degree of scattering could be observed in the estimated tuning parameters (Fig. 8) and that there are alternative tuning parameters which can also adequately fit the linear correlation to this as based on the contour plots (Fig. 9), the inconsistency in parameter estimations from literature has been addressed. With this, an alternative method to populating mixture models has been developed to capitalise on the new-found flexibility of these tuning parameters. By designating arbitrary values for the 'pure' material parameters – for now, in a binary space of API and brittle filler – and varying them between expected bounds, a global optimisation procedure was developed. The benefit of applying global optimisation for the estimation of the tuning parameters circumvents the challenge of not being able to collect data for pure, non-compactable APIs. A restriction was set for the optimisation that the tuning parameters for the placebo blend were to remain constant between blends as the formulation of this was not changing (Fig. S12 in Supporting Information). This made it possible to conduct this analysis for the entire dataset simultaneously, providing maximum information to estimate placebo parameters which were more universally applicable.

A cross validation (Fig. 16) showed that this optimisation method is capable of predicting tuning parameters which can achieve an acceptable GoF for new blends, particularly when calibrated using placebo and blends of high drug loading. This provides a theory that once the estimation of the placebo tuning parameters are confident (i.e. tested against multiple loaded blends of differing physical properties), then the introduction of a new API with no prior knowledge could require only one loaded blend to construct a mixture rule, reducing API usage considerably.

The total error for this new method was lower than that of the traditional method of populating mixture rules, and comparable to the accuracy of individually fitting the datasets as observed by the GoF (Fig. 12) and success rates for the acceptance criteria (Fig. 13). This method performs particularly well when applied to industrially relevant conditions, however further testing of the mixture rules (particularly for Ryshkewitch-Duckworth) is required to better capture compaction data at compression pressure of less than 100 MPa (Fig. 15). This may involve: alternative weighting factors, as the increase in tensile strength is due to surface interactions which may be incorrectly weighted when considering the volume fraction rather than the surface area fraction; adding in interaction terms to the mixture model, to better capture the behaviours through a response surface rather than a linear relationship; or by considering the percolation threshold, to evaluate how a change in the materials which dominate the compression or compaction behaviour may influence how the behaviours are captured by the implemented mixture rule.

5. Conclusions

A systematic statistical analysis of common compression and compaction models was completed. This work used a large and consistent dataset which made it possible to draw comparative conclusions between models and unique formulations. These formulations considered four APIs which were blended at different concentrations with a common excipient blend to address the impact that drug loading may have on the prediction of tablet porosity and tensile strength. By delving deeper into the comparison of these models, this work was able to provide evidence for the reported discrepancies between previous investigations. The Kawakita and Ryshkewitch-Duckworth models were found to be those (of their respective applications) which performed the most consistently well across formulations in both GoF metrics and their parameter variability analyses. This is not to say that the alternative models performed poorly, particularly when considering the application to the RoI for the pharmaceutical industry – bar that of Leuenberger

which was inadequately fitted for the materials used in this investigation. It was found that drug loading did negatively impact the predictability of these models; however, the extent of this for the Kawakita and Ryshkewitch-Duckworth models was not significant.

A parameter variability analysis was conducted to address the reported variations in model tuning parameters across the literature. This considered how the accuracy of data collection can impact the weighted linear regression when fitting these models, and also investigated the existence of multiple parameter pairs. It was discovered that there are a large number of parameter combinations which can achieve acceptable GoF for each of the considered models. This knowledge provided the basis for the development of a new global optimisation approach to the population of arithmetic, geometric, and harmonic mixture rules which performed better than the traditional line of best fit approach and more comparably with the individual fitting of datasets when operating and industrially relevant conditions. The optimisation's predictability performance for new blends was validated using a cross validation study. It was found that the mixture rule applied did not impact the compressibility models but care should be taken when selecting a model for Ryshkewitch-Duckworth's k_b. With the found flexibility of the tuning parameters, the barrier of finding consistent pure-material parameters to populate mixture rules can be ignored. The greatest benefit of this new approach is that the placebo parameters can be maintained constant for each considered API. This may minimise the experimental requirements for the population of mixture models of new APIs considerably as only one formulation may be required.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Chat Generative Pre-Trained Transformer (Chat GPT) by Open AI in order to improve language, grammar and punctuation within the Introduction and Discussion sections. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

CRediT authorship contribution statement

Theo Tait: Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mohammad Salehian:** Writing – review & editing, Supervision, Conceptualization. **Magdalini Aroniada:** Writing – review & editing, Supervision, Conceptualization. **Andrew P. Shier:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Richard Elkes:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **John Robertson:** Writing – review & editing, Supervision, Conceptualization. **Daniel Markl:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Daniel Markl reports financial support was provided by GlaxoSmithKline Research & Development Limited. Daniel Markl reports financial support was provided by Scottish Funding Council. If there are other authors, they 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

Data will be made available on request.

Acknowledgements

This work was funded and supported by GSK and the DataLab. The authors would like to acknowledge that this work was carried out in the CMAC National Facility supported by UKRPIF (UK Research Partnership Fund) award from the Higher Education Funding Council for England (HEFCE) (Grant Ref HH13054).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2024.124475.

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