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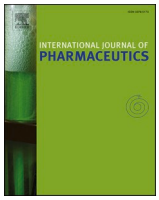

Linked experimental and modelling approaches for tablet property predictions

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ABSTRACT

Recent years have seen the advent of Quality-by-Design (QbD) as a philosophy to ensure the quality, safety, and efficiency of pharmaceutical production. The key pharmaceutical processing methodology of Direct Compression to produce tablets is also the focus of some research. The traditional Design-of-Experiments and purely experimental approach to achieve such quality and process development goals can have significant time and resource requirements. The present work evaluates potential for using combined modelling and experimental approach, which may reduce this burden by predicting the properties of multicomponent tablets from pure component compression and compaction model parameters. Additionally, it evaluates the use of extrapolation from binary tablet data to determine theoretical pure component model parameters for materials that cannot be compacted in the pure form. It was found that extrapolation using binary tablet data – where one known component can be compacted in pure form and the other is a challenging material which cannot be – is possible. Various mixing rules have been evaluated to assess which are suitable for multicomponent tablet property prediction, and in the present work linear averaging using pre-compression volume fractions has been found to be the most suitable for compression model parameters, while for compaction it has been found that averaging using a power law equation form produced the best agreement with experimental data. Different approaches for estimating component volume fractions have also been evaluated, and using estimations based on theoretical relative rates of compression of the pure components has been found to perform slightly better than using constant volume fractions (that assume a fully compressed mixture). The approach presented in this work (extrapolation of, where necessary, binary tablet data combined with mixing rules using volume fractions) provides a framework and path for predictions for multicomponent tablets without the need for any additional fitting based on the multicomponent formulation composition. It allows the knowledge space of the tablet to be rapidly evaluated, and key regions of interest to be identified for follow-up, targeted experiments that that could lead to an establishment of a design and control space and forgo a laborious initial Design-of-Experiments.

1. Introduction

Pharmaceutical production has established processes and unit operations, the vast majority of which are batchwise (Plumb, 2005). Unlike other fields such as oil and gas and petrochemicals where the phenomena are comprehensively understood and which are well described by models (both data-driven and mechanistic), secondary processing of pharmaceuticals often involves the use and handling solid powders in operations that are less well understood, especially when it comes to

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Nomenclature

Symbol	*Definition (units)*
D	Diameter (die) mm
F	Compression force kN
F_b	Breaking force N
h	Height mm
K_G	Gurnham compressibility constant dimensionless
$K_{G,i}$	Gurnham compressibility constant of component I dimensionless
$K_{G,m}$	Gurnham compressibility constant of binary and multicomponent tablets dimensionless
k_b	Bonding capacity dimensionless
$k_{b,i}$	Bonding capacity of component I dimensionless
$k_{b,m}$	Bonding capacity of binary and multicomponent tablets dimensionless
m	Mass g
P	Compression pressure MPa
P_0	Pressure required for zero porosity MPa
$P_{0,i}$	Pressure required for zero porosity of component I MPa
$P_{0,m}$	Pressure required for zero porosity of binary and multicomponent tablets MPa
SF	Solid fraction dimensionless
v	Volume cm^3
x_i	Mass fraction of component I g/g
ε	Porosity dimensionless
ε_i	Estimated porosity of component i if under same compression pressure as the multicomponent tablet dimensionless
ε_m	Porosity of binary and multicomponent tablets dimensionless
$\rho_{bulk,i}$	Bulk density of component I g/cm^3
ρ_{crys}	True density g/cm^3
$\rho_{crys,i}$	True density of component I g/cm^3
σ	Tensile strength Pa or MPa
σ_m	Tensile strength of binary and multicomponent tablets MPa
σ_0	Tensile strength at zero porosity MPa
$\sigma_{0,i}$	Tensile strength at zero porosity of component I MPa
$\sigma_{0,m}$	Tensile strength at zero porosity of binary and multicomponent tablets MPa
φ_i	Pre-compression volume fraction of component I cm^3/cm^3
φ'_i	Post-compression volume fraction of component I cm^3/cm^3

mechanistic models.

In recent years, there has been a drive to enhance the reliability, safety and quality of pharmaceutical production by applying knowledge and techniques that have been developed and used in other industries. The use of process engineering, supported by model-based design and advances in Process Analytical Technology, is an approach encapsulated by the Quality-by-Design philosophy (Armental and Burton, 2015; Lee et al., 2015). Towards this, the modelling of pharmaceutical operations (especially continuous processes) is being actively researched (Troup and Georgakis, 2013), with work ranging from reactions to primary processing, secondary processing, end-to-end whole-flowsheet modelling (Acevedo et al., 2016; Escotet-Espinoza, 2018; Ierapetritou et al., 2016; Schaber et al., 2011; Wang et al., 2017), dry powder feeding (Bascone et al., 2020; Bhalode and Ierapetritou, 2020; Bostijn et al., 2019; Fernandez et al., 2011), dry powder blending (Escotet-Espinoza et al., 2019; Palmer et al., 2020; Toson et al., 2018), and tablet compression and compaction.

The Direct Compaction (DC) of tablets aims to simplify secondary processing and the creation of final dosage forms (Palmer et al., 2020). Essentially, DC is dispensing, blending and subsequent compression and compaction of dry powder mixtures. Regardless of the secondary process stream, the finale dosage form is most likely to be produced via compaction of tablets. For successful compaction there are well established properties such as solid fraction and tensile strength that must be met via formulation, as well as other Critical Quality Attributes such as content uniformity, appearance, disintegration and dissolution.

The modelling of compression and compaction has foundations in work investigating the relative densification and tensile strengths of porous, inorganic materials (Duckworth, 1953; Heckel, 1961; Kawakita and Lüdde, 1971; Ryshkewitch, 1953). More recently, the modelling of organic, pharmaceutically relevant powders has explored and developed alternative equations (Dai et al., 2019; Zhao et al., 2006), and in particular how the equations can be applied to mixtures (Busignies et al., 2012; Gavi and Reynolds, 2014; Michrafy et al., 2007; Reynolds et al., 2017; White et al., 2022).

Typical approaches for modelling compression and compaction of mixtures have been to determine mixture model parameters using pure component parameters using an appropriate weighting method *i.e.* mixing rules; volume fractions are commonly used in these mixing rules (Gavi and Reynolds, 2014; Wu et al., 2005). These volume fractions must be estimated, and more recent work has used the relative compressibilities of the components instead of assuming a fully compressed state (Jolliffe et al., 2019; Reynolds et al., 2017). The method to determine the appropriate mixing rule to use is also a topic of research, with various equation forms used to date, although given the complexity of modelling powder behaviour no systematic way of telling in advance which mixing rule applies has yet been determined (White et al., 2022).

Ideally, these approaches would best suit generation and use of pure component data and pure component parameters, with the application of suitable mixing rules then enabling a model to describe the mixture. However, due to experimental and material property constraints (namely poor flow preventing consistent die filling and materials which are not compactable) it is not always possible to determine pure component properties and hence model parameters; this is often the case with Active Pharmaceutical Ingredients (APIs). The present work attempts to address this.

A typical tablet core formulation comprises API, filler/bulking agent, compression aid, disintegrant and lubricant. There are typical ranges for these components, as well as typical relative ratios. In the present work we have fixed the compression aid, disintegrant and lubricant at typical proportions as one pseudo-component (which is compactable and hence compaction and model parameters are known). The API and filler are treated as two additional components. The model APIs we have selected (ibuprofen, granular paracetamol, powdered paracetamol, mefenamic acid, calcium carbonate) cannot be compacted in the pure form, but combination into a binary mixture with the filler (a lactose blend, of known pure compaction properties) across a range of ratios, allows us to 'back-calculate' the pure component properties and model parameters for the uncompactable API. The model can then be used to predict tablet properties of the entire mixture.

The first aspect of the present work is fitting data of binary tablets of increasing mass loadings of the API to get binary mixture model parameters, and extrapolating/back-fitting to determine model parameter values for a theoretical tablet of pure API. Within the modelling structure, there are a number of options for mixing rules and how they are utilised. Here we evaluate these and the cross-combinations to assess the predictive capability of the model. We also demonstrate the potential of using this combined experimental-model approach for describing viable

multi-component tablet formulations.

2. Materials and methods

2.1. Materials

Five active pharmaceutical ingredients (API) and four commonly used excipients within the pharmaceutical industry have been selected for model calibration and validation. The APIs are ibuprofen 50 (BASF, UK), powdered and granular grades of paracetamol (pAPAP and gAPAP, Mallinckrodt, UK), mefenamic acid (Sigma, UK), calcium carbonate (Merck, UK). The excipients are: microcrystalline cellulose (Avicel PH102, DuPont, UK), lactose monohydrate (Fast Flo 316, Kerry, UK), croscarmellose sodium (Solutab, Roquette, UK) and magnesium stearate (Ligamed MF-2 V, Peter Greven, Netherlands).

2.2. Experimental methods

2.2.1. Densities measurement

The bulk and tapped density measurements have been carried out following the British Pharmacopeia guidelines 2018 (British Pharmacopoeia - Ph. Eur. 10.4 update, 2009). The tapped density has been measured using tapped density analyser (Autotap, Quantachrome, Anton Paar GmbH, Graz, Austria). True density analysis has been measured using a gas Pycnometer (MicroUltrapyc 1200e, Quantachrome, Anton Par GmbH, Graz, Austria) connected to a water bath at 25 °C. The sample weight has been measured using a mass balance (BP211D Analytical model, Sartorious, Surrey, United Kingdom). Measured density data is provided in the supplementary information in Table S1.

2.2.2. Powder formulation and blending

The multicomponent formulations of API and excipients described in section 2.1 have been prepared according to the compositions shown in (Table 1, used for valildation). In addition, binary tablets have been produced (Table 2, used for parameter estimation and curve fitting). A bin-blender (Pharmatech AB-015, Pharmatech, Warwickshire, UK) with a 1 L intermediate bulk container (IBC) has been used to prepare the blends. The blending conditions were 20 min at 24 rpm for the non-lubricated blending step, and 3 min at 17 rpm for lubrication. The mass of the batch sizes were adjusted between 320 g and 420 g of material depending on the bulk density to achieve a 70% fill volume, 30% free headspace as described by methods of Kushner and Moore (2010). The weight has been measured using a balance (BP211D Analytical model, Sartorious, Surrey, United Kingdom).

Table 1
Pseudo-ternary multicomponent tablet formulations (composition given in weight percent).

Functionality	Materials	Low API (%)	Mid API (%)	High API (%)	Blend Composition
Filler (C1)	Lactose monohydrate	70.5	55.5	35.5	Varied
API (C2)	*One of* Ibuprofen Paracetamol (granular) Paracetamol (powder) Mefenamic acid Calcium carbonate	5.0	20.0	40.0	Varied
Pseudo-pure component (C3)		24.5	24.5	24.5	Fixed
Compression aid	Microcrystalline cellulose	20.0	20.0	20.0	Fixed
Disintegrant	Croscarmellose sodium	3.5	3.5	3.5	Fixed
Lubricant	Magnesium stearate	1.0	1.0	1.0	Fixed

Table 2
Binary tablet Fast Flo 316 (C1) and challenging material (C2) weight ratios. These formulations (alongside data for pure Fast Flo 316 tablets) have been used to extrapolate to determine theoretical pure C2 model parameters.

Challenging material C2	Low C2 loading (g:g)		Medium C2 loading (g:g)		High C2 loading (g:g)	
	C2	C1	C2	C1	C2	C1
Ibuprofen	5.0	70.5	20.0	55.5	40.0	35.5
gAPAP	10.0	65.5	20.0	55.5	40.0	35.5
pAPAP	5.0	70.5	10.0	65.5	15.0	60.5
Mefenamic acid	5.0	70.5	20.0	55.5	35.0	40.5
Calcium carbonate	5.0	70.5	20.0	55.5	40.0	35.5

2.2.3. Tabletting

Tablets have been manufactured using a single punch tablet press (XP1, KORSCH AG, Berlin, Germany) with tooling comprising of 9 mm diameter flat-faced punch and die (B-Tooling, i-Holland, UK). Punch force, displacement, and ejection force have been recorded using proprietary KORSCH software. The maximum upper punch compression force has been used for establishing the compaction pressure used in the modelling. The tablets have been made at rate of 20 tablets per minute. The punch separation has been varied to produce tablets at a range of solid fractions/hardness/thickness/compaction force at a target weight of 200 mg. For each punch gap separation, 10 tablets were produced for analytical offline measurements. The tablet hardness and thickness have been measured using a manual tablet hardness tester (HC 6.2, Kraemer Elektronik Gmbh, Darmstadt, Germany, fitted with a Mitutoyo micrometer) and the diameter has been taken as the die diameter. The tablet weight has been measured with a balance (Sartorius Quintix 125D-1S, Sartorius, Gottingen, Germany).

Experimental values for the tablet tensile strength are calculated as follows:

$$\sigma = \frac{2F_b}{\pi D h} \tag{1}$$

where F_b is the tablet breaking force in Newtons (referred to as hardness), h is tablet thickness in mm, and D is die diameter in mm (Fell and Newton, 1970). Eq. (1) is applicable for round flat-faced tablet and considered when the tablet breaks under radial compression.

Experimental values for the tablet solid fraction (SF, also known as relative density) and porosity (ε) are calculated as follows:

$$SF = \frac{m}{\rho_{crys} v} \tag{2}$$

$$\varepsilon = 1 - SF \tag{3}$$

where ρ_{crys} is the true density, m is tablet weight, and v is tablet volume post-compression.

The compaction pressure P is computed from the force of compression and tablet die cross-sectional area:

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

The SF is referred to as the tablet's relative density, and Eq. (3) show the relationship between the two. The compaction pressure (P) is derived from the applied force and the punch's cross-sectional area.

External lubrication (die wall) is used for pure Fast Flo 316, and for the binary tablets. External lubrication is also required to prevent sticking and capping in high drug loading cases observed with mefenamic acid in pseudo-ternary tablets.

3. Tablet compaction modelling

The present work explores various model structures for compression and compaction via combinations of various mixing rules to predict multicomponent tablet properties. The model equations for compression and compaction, the mixing rules used alongside them for extrapolation and for forward-predicting multicomponent tablet properties, are described in this section.

3.1. Compression, compaction, and mixing rules

The Gurnham compression model is used for relating porosity to pressure; it was developed to address some of the limitations of the prior approaches (Reynolds et al., 2017):

$$\varepsilon = -\frac{1}{K_G}\ln\frac{P}{P_0} \tag{5}$$

Here P is compression pressure, P_0 is the pressure required to reach zero porosity and K_G is a constant (the latter two are fitting parameters).

For compaction, the Ryshkewitch-Duckworth model (Duckworth, 1953; Ryshkewitch, 1953) is used; it describes the change in tensile strength of the powder σ due to the change in porosity ε:

$$\sigma = \sigma_0 e^{-k_b \varepsilon} \tag{6}$$

where σ_0 is the tensile strength at zero porosity, and k_b is bonding capacity; both are fitted parameters. Equation (6) applies for a specific formulation used in the fitting of the parameters; transferability is limited.

For multicomponent tablets, the same equations are used:

$$\varepsilon_m = -\frac{1}{K_{G,m}}\ln\frac{P}{P_{0,m}} \tag{7}$$

$$\sigma_m = \sigma_{0,m} e^{-k_{b,m}\varepsilon_m} \tag{8}$$

Where the variables and parameters now have the subscript m, indicating multicomponent tablets. To get model parameters for the multicomponent mixture, there are two approaches: direct fitting to multicomponent tablet compaction data, or prediction from pure component parameters. This work evaluates routes to the latter.

In the literature, various mixing rules are used to estimate the fitting parameters in Eqs. (7) and (8). Mixture parameters are often estimated by use of arithmetic summation or geometric combination of the pure components, referred to as 'linear' and 'power' mixing rules in this work (Michrafy et al., 2007; Wu et al., 2005); weighting is often done by a volume fractions that are estimated in some manner (White et al., 2022).

In some approaches, mixture compaction parameters are determined from volume fractions in turn determined from pure component mass fractions and pure component true densities (Eq. 18), while other approaches attempt to estimate the volume fractions at a given pressure based on the varying compressibilities of the pure components (Eq. 19) (Reynolds et al., 2017; Jolliffe et al., 2019). In the case of the latter, the compressibility equation (Eq. (5)) is used for each pure component to calculate relative rates of densification.

In this work, a linear mixing rule based on pre-compression volume fractions is used for compression model parameters, and combinations of power and linear mixing rules are evaluated for compaction (as suggested by Michrafy and co-workers, 2007), which are outlined in Table 3.

3.2. Routes to pure component model parameter estimation for uncompactable materials

Many previous materials available to the authors of the current work can be successfully compacted and the compaction data used to establish the parameters in equations such as Eqs. (5) and (6). However, some materials are uncompactable when pure. This presents a challenge in using the modelling approaches outlined above, as they rely on data fitting of pure component tablets to get parameters for use in mixing rules. If a material cannot be compacted pure, then the parameters for these materials cannot be directly arrived at via measurement and fitting of data of the said pure component. This is true of many APIs encountered in industry, as well as the APIs used in the present work, and requires an alternative approach.

Table 3
Summary of mixing rules. Subscript m indicates mixture, and subscript i indicates pure components.

Compressibility				
Linear mixing rule	$P_{0,m} = \sum_i \varphi_i P_{0,i}$	$K_{G,m} = \sum_i \varphi_i K_{G,i}$	(9)	(10)
Pre-compression volume fraction	$\varphi_i = \frac{\frac{x_i}{\rho_{bulk,i}}}{\sum_i \frac{x_i}{\rho_{bulk,i}}}$			(11)
Compactability				
Linear $\sigma_{0,m}$ – Linear $k_{b,m}$ mixing rule (LL)	$\sigma_{0,m} = \sum_i \varphi'_i \sigma_{0,i}$	$k_{b,m} = \sum_i \varphi'_i k_{b,i}$	(12)	(13)
Power $\sigma_{0,m}$ – Power $k_{b,m}$ mixing rule (PP)	$\sigma_{0,m} = \prod_i (\sigma_{0,i})^{\varphi'_i}$	$k_{b,m} = \prod_i (k_{b,i})^{\varphi'_i}$	(14)	(15)
Power $\sigma_{0,m}$ – Linear $k_{b,m}$ mixing rule (PL)	$\sigma_{0,m} = \prod_i (\sigma_{0,i})^{\varphi'_i}$	$k_{b,m} = \sum_i \varphi'_i k_{b,i}$	(14)	(16)
Linear $\sigma_{0,m}$ – Power $k_{b,m}$ mixing rule (LP)	$\sigma_{0,m} = \sum_i \varphi'_i \sigma_{0,i}$	$k_{b,m} = \prod_i (k_{b,i})^{\varphi'_i}$	(12)	(17)
Constant post-compression volume fraction	$\varphi'_i = \frac{\frac{x_i}{\rho_{crys,i}}}{\sum_i \frac{x_i}{\rho_{crys,i}}}$			(18)
Variable post-compression volume fraction	$\varphi'_i = \frac{\frac{x_i}{(1-\varepsilon_i)\rho_{crys,i}}}{\sum_i \frac{x_i}{(1-\varepsilon_i)\rho_{crys,i}}}$			(19)

Including uncompactable-when-pure material C2 (*i.e.* an API) in a binary tablet with a compactable material C1 across a sufficient range of compositions to obtain binary tablet properties (porosity, tensile strength) and fitting this data to Eqs. (7) and (8) provides the mixture parameters as a function of composition (Fig. 1). By extrapolation and back-fitting using a mixing rule (Eqs. 9, 10, 12–15, depending on the property in question), pure component parameters for C2 can be determined. The extrapolation can be performed by optimising for the theoretical value of the model parameter for pure challenging material that produces the best fit to the data. The equation form used for extrapolation is either linear or power averaging using volume fraction weighting, as outlined in Table 3. The extrapolated C2 pure component parameters can then be used alongside other pure component parameters in mixing rules to predict multicomponent tablet properties.

4. Results and discussion

4.1. Pure component parameters: Direct fitting and extrapolation

Pure-component tablets have been produced for both component C1 (Fast Flo 316) and pseudo-component C3 (blend of compaction aid, disintegrant and lubricant in fixed ratios). The data has been used to determine compressibility and compactability model parameters via direct fitting; results are presented in Table 4.

In the case of the challenging materials (C2 components), direct fitting is not possible as these materials cannot be compacted in the pure component form; extrapolations from binary C1–C2 tablet data (Table 2) have been performed.

In the literature, a wide range of property responses to tablet composition have been reported, including extremely non-ideal cases (Sun, 2016). With the many possible contributing factors to how

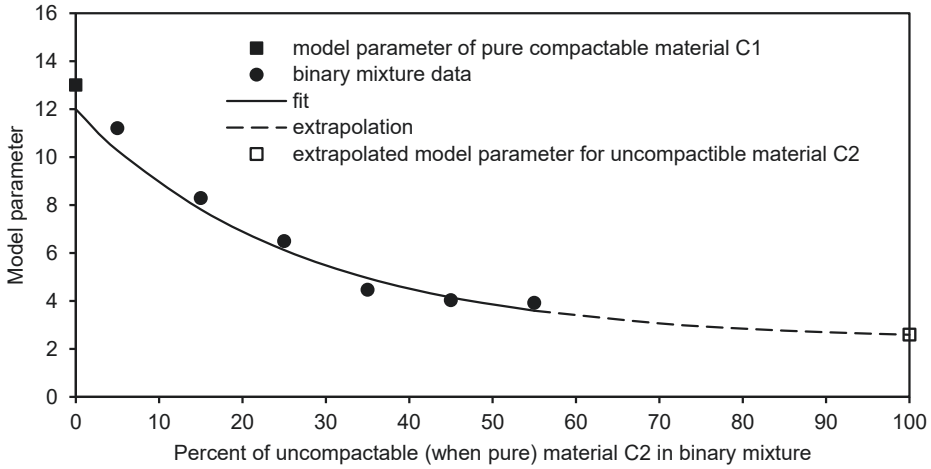

Fig. 1. Extrapolation of binary mixture model parameters to determine otherwise inaccessible pure component model parameters for materials that cannot be compacted when pure.

Table 4
Pure component compression and compaction model parameters (determined either by direct fitting or by extrapolation from C1-C2 binary tablets).

Component	i	Compression parameters (Eq. (5))		Compaction parameters (Eq. (6))		Method
		$K_{G,i}$ (–)	$P_{0,i}$ (MPa)	$\sigma_{0,i}$ (MPa)	$k_{b,i}$ (–)	
Fast Flo 316	C1	8.44	665.4	16.08	14.16	Fitted
Ibuprofen 50	C2	20.17	487.6	1.11	8.25	Extrapolated
gAPAP	C2	6.68	2238.8	2.30	29.29	Extrapolated
pAPAP	C2	14.73	198.3	0.06	8.55	Extrapolated
Mefenamic acid	C2	19.95	903.2	0.36	15.30	Extrapolated
Calcium carbonate	C2	11.82	1864.0	153.58	16.28	Extrapolated
Blend (Avicel PH-102 + Solutab + Ligamed MF-2 V)	C3	7.62	519.0	10.45	7.35	Fitted

compression and compaction vary with tablet composition, there is no clear case for the selection of either a linear or a power mixing rule (whether for predicting multicomponent tablet properties or for extrapolating binary tablet data); there is often not an obvious reason a certain mixture system will behave in a certain way. Given this context, a pragmatic approach has been taken where combinations of linear and power mixing rules (for various model parameters) have been evaluated to compare outcomes (agreement between predictions and measured data for multicomponent tablet properties).

Evaluating the available data for binary tablets (compositions of which are outlined in Table 2), it has been observed that for compression model parameters (Eq. (7)) the linear mixing rule (Eqs. 9 and 10) performed better in extrapolation *i.e.* a better fit could be achieved with the data. Conversely, for the compaction model (Eq. (8)) the power mixing rule (Eqs. 14 and 15) performed better. In the remainder of the discussion and values presented hereafter, compression model parameters have been extrapolated using the linear mixing rule and compaction model parameters have been extrapolated using the power mixing rule (Table 4).

In the extrapolations for the binary C1-C2 systems described above, the pure component C1 (Fast Flo 316) model parameter values have been allowed to be adjustable *i.e.* have been optimised best fit alongside the extrapolated parameter for pure component C2; the data for pure C1 has been included in the fitting dataset alongside the data for the binary tablets. Parameter extrapolation for gAPAP is presented in Fig. 2 for illustrative purposes, and the results for other C2 materials are given in Table 4.

Whilst it is possible to extrapolate to get pure parameters for C2 materials (using linear mixing for compression parameters and power mixing for compaction parameters), many of the C1-C2 binary systems hint at deviations from ideal mixing (example for gAPAP given in Fig. 2); this was often more pronounced for compaction parameters, perhaps unsurprising given powder mixing behaviour reported in the literature (Sun, 2016). Of note are the wide range of parameter values between the materials considered in this work, with materials such as pAPAP and mefenamic acid having predicted tensile strengths at zero porosity well below one MPa, whilst calcium carbonate has a predicted value above 150 MPa (Table 4).

4.2. Multicomponent tablet property prediction and validation

The set of material parameters in Table 4 can be used to predict the properties (compression and compaction) of multicomponent tablets, and these predictions can be compared against experimental values for the multicomponent formulations. Three levels of mass loading (5%, 20%, and 40%) have been evaluated per challenging component C2, as shown in Tables 1 and 2.

In the analysis, various options have been considered for the predictions. The mixing rules for compaction parameters have been either linear–linear (for tensile strength at zero porosity $\sigma_{0,m}$ and bonding capacity k_b, respectively), linear-power, power-linear, or power-power (Table 3, Eqs. 12–17). For compression parameters, linear mixing was used (Table 3, Eqs. 9 and 10). The four options for mixing rules have been applied for three prediction scenarios:

1. Using constant post-compression volume fractions (Eq. 18) in the mixing rules and using measured porosity to predict tensile strength (Eq. (8)).
2. Using constant post-compression volume fractions (Eq. 18) in the mixing rules and using predicted porosity (Eq. (5)) to predict tensile strength (Eq. (8)).
3. Using variable post-compression volume fractions (Eq. 19) in the mixing rules and using predicted porosity (Eq. (5)) to predict tensile strength (Eq. (8)).

The first approach theoretically should be most accurate, as there is no need to predict porosity (which could introduce inaccuracy). The latter two approaches have more potential usefulness as they suggest the pressure required with a tablet press to achieve the porosities in question (also, use of variable post-compression volume fractions requires

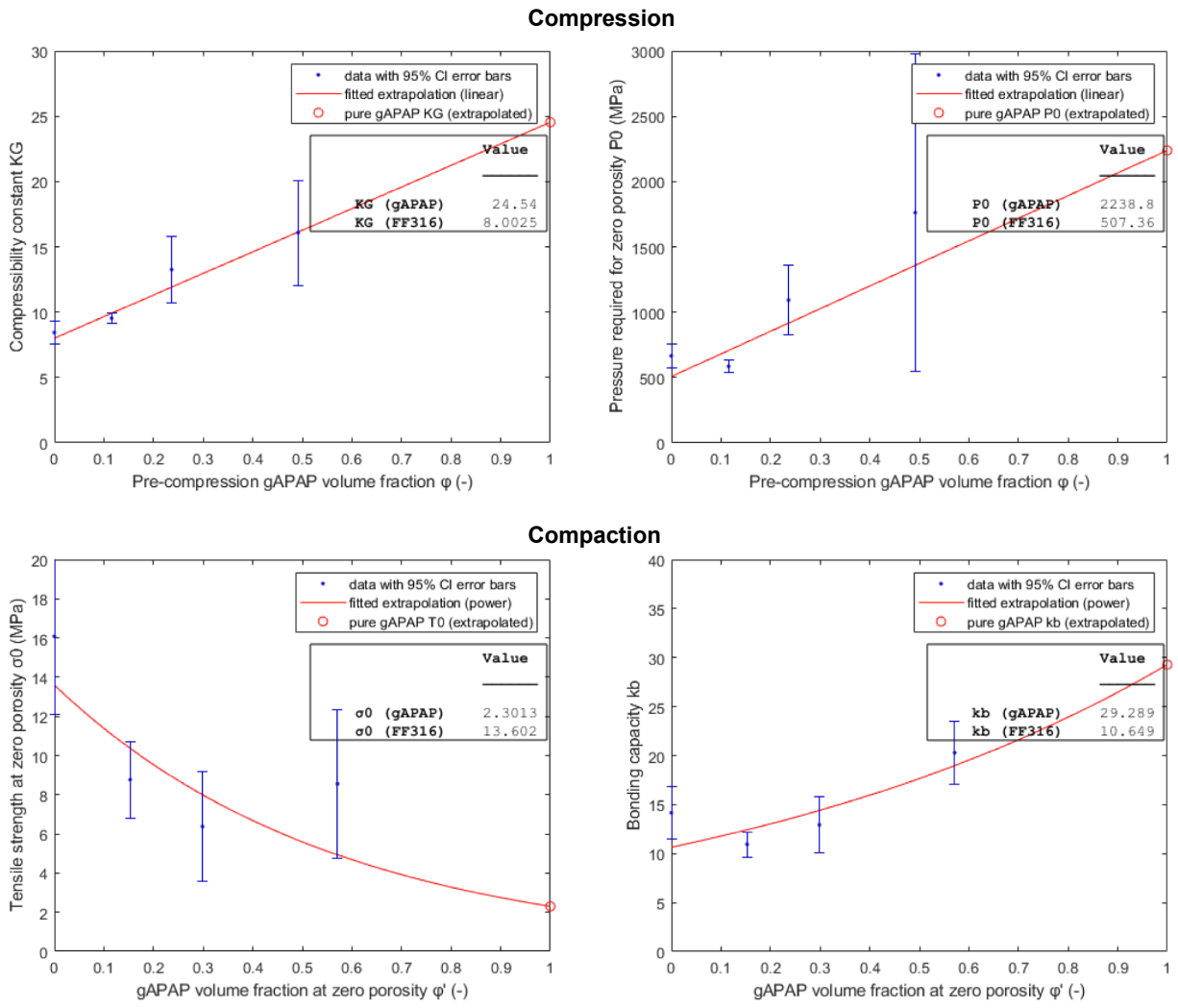

Fig. 2. Extrapolation to get gAPAP (component C2) compression model parameters K_G (-) and P_0 (MPa) (Eqs. 9 and 10) and compaction model parameters σ_0 (MPa) and k_b (-) (Eqs. 14 and 17). Fitting was done on data of pure Fast Flo 316 (component C1) and three binary compositions. Inverse of standard deviation was used to weight data for fitting.

porosity predictions).

The results of analysing these approaches with the various mixing rule options (Table 3), and using the pure component parameters (Table 4), for the all the multicomponent tablets (five different C2 options, each with three C2 mass loadings; Table 1), are presented in Table 5.

In general, the use of power mixing rules for both tensile strength at zero porosity and bonding capacity (PP) is more likely to result in better agreement between predictions and observations of multicomponent tablet properties. The only case where it is not is the use of measured porosity data, where there is no clear optimal choice. When predicted porosity values are being used – which would be the case when performing calculations purely in-silico – power mixing rules are most likely to agree with experimental data (high R^2, low RMSE). Deeper evaluations that take into account close margins and thresholds for prediction performance (*e.g.* values of $R^2 \geq 0.8$ in Table 6) reach the same conclusion *i.e.* power mixing rules more frequently result in higher R^2 values and lower RMSE values. This outcome also holds for higher R^2 thresholds. A full breakdown of the various mixing rule accuracies are provided in supplementary information Tables S2 and S3.

In industrial practice, a tablet produced via DC which has a tensile strength of 1.7 MPa at a porosity of 0.15 will be sufficiently robust to withstand subsequent downstream processing and handling, including by the final end user (the patient) (Leane et al., 2015). Interpolating the experimental data for the multicomponent tablets we can compare values at 0.15 porosity with predictions (Table 5). Using variable volume fractions results in smaller residuals than using constant volume fractions in all but three cases (the three cases being calcium carbonate at 5% mass loading, mefenamic acid at 20% mass loading, and gAPAP at 40% mass loading). In the literature, the use of variable volume fractions has been shown to offer advantages (when the pure component parameters can be accurately determined via direct fitting without the need for extrapolation as in the present work) (Reynolds et al., 2017).

4.3. *Approach transferability, advantages and limitations*

The approach presented in this work uses direct fitting to get pure component parameters when the material is compactable, extrapolation to get pure component parameters when material is not compactable, and averages these based on volume fractions of a multicomponent tablet to predict properties (porosity, tensile strength) of said multicomponent tablets using mixing rules. One of the chief advantages of this approach is that it uses no additional fitting parameters or scaling factors for the multicomponent tablets. This allows rapid evaluation of the probable design space. Within the scope of the current work, we caution and highlight that the following conditions may be the constraints to the presented approach:

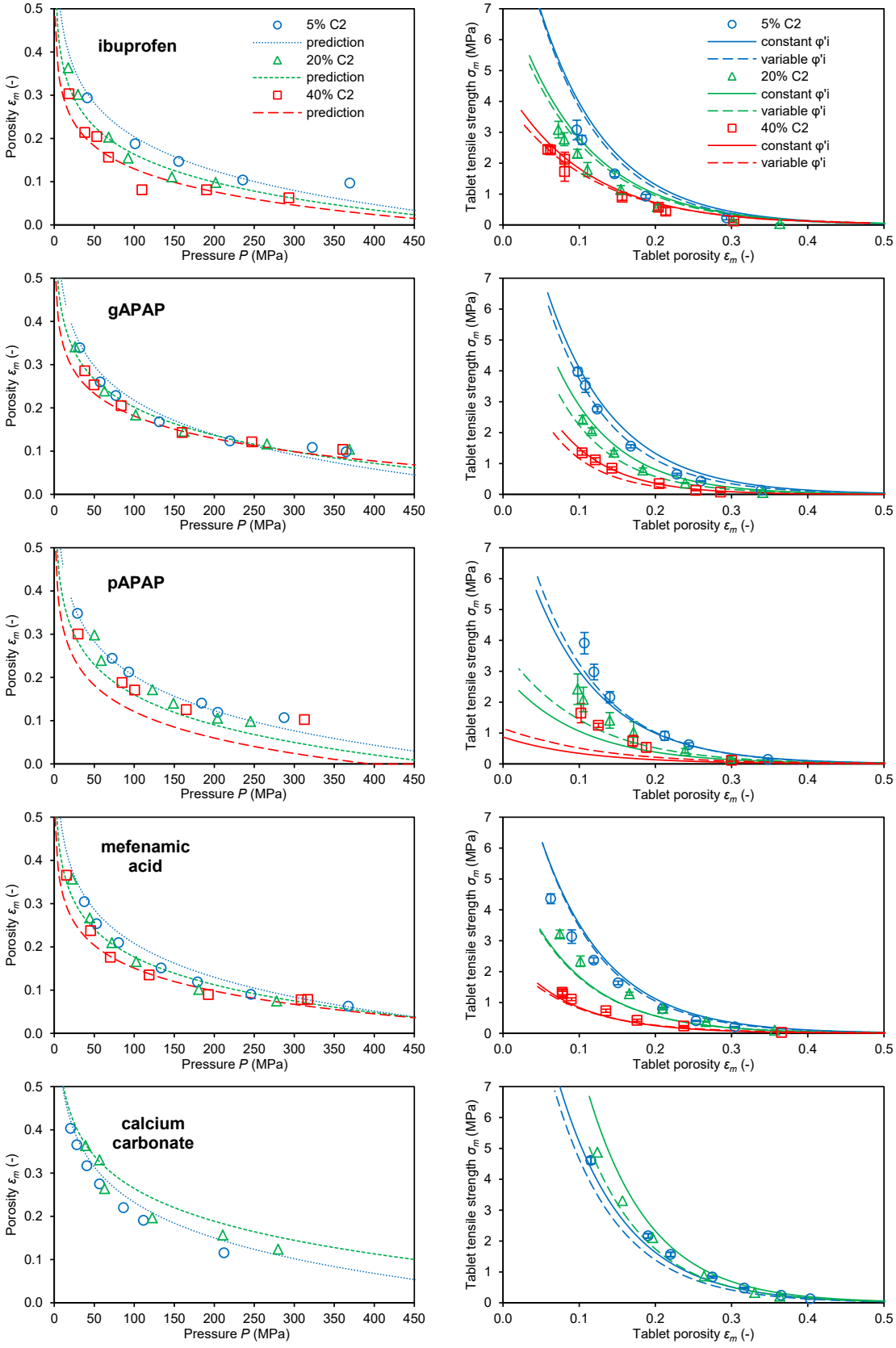

Fig. 3. Predicted and measured multicomponent C1-C2-C3 tablet properties. Linear mixing rules used for porosity, power mixing rules used for tensile strength (Table 3).

Table 5
Tensile strength predictions using power mixing rules for multicomponent C1-C2-C3 tablets at 0.15 porosity. For full profiles see Fig. 3.

Component C2 and % mass loading	Tensile strength at 0.15 porosity $\tau_{\varepsilon=0.15}$ (MPa)		
	Experimental data (interpolated)	Predicted (Eq. 18, constant φ'_i)	Predicted (Eq. 19, variable φ'_i)
Ibuprofen			
5	1.594	2.274	2.133
20	1.218	1.682	1.584
40	0.963	1.149	1.090
gAPAP			
5	2.042	2.333	2.049
20	1.295	1.525	1.131
40	0.791	0.732	0.537
pAPAP			
5	1.992	1.730	1.825
20	1.287	0.638	0.864
40	0.973	0.216	0.334
Mefenamic acid			
5	1.661	1.991	1.900
20	1.542	1.022	1.012
40	0.620	0.458	0.459
Calcium carbonate			
5	3.486	2.917	2.540
20	3.629	4.273	3.213

Table 6
Mixing rule performance across all multicomponent tablet datasets (all five C2 materials and all three respective C2 mass loadings). Tensile strength predictions use either measured or predicted (from measured compaction pressure) porosity values as inputs. Pure component model parameters are combined using either linear–linear mixing rules (LL, for tensile strength at zero porosity and bonding capacity, respectively), linear-power (LP), power-linear (PL) or power-power (PP) (see Table 3 for equations).

Occurrences of a mixing rule having the best fit (highest R^2 and smallest RMSE)

Tensile strength prediction approach	**Mixing rules**			
(Porosity, volume fraction)	**LL**	**LP**	**PL**	**PP**
Measured porosity, constant φ'_i	4	1	5	4
Predicted porosity, constant φ'_i	3	0	2	9
Predicted porosity, variable φ'_i	2	0	1	11

Occurrences of a mixing rule having an R^2 value above 0.8

Tensile strength prediction approach	**Mixing rules**			
(Porosity, volume fraction)	**LL**	**LP**	**PL**	**PP**
Measured porosity, constant φ'_i	5	4	8	10
Predicted porosity, constant φ'_i	4	3	7	7
Predicted porosity, variable φ'_i	5	2	6	9

1. Only one component in the multicomponent pseudo-ternary tablet was uncompactable-when-pure (the challenging material C2). Having more than one component require extrapolation could introduce increasing levels of prediction uncertainty and error.
2. Binary tablets of the challenging component another major component (*e.g.* filler) should be compactable up to a reasonable mass fraction of the challenging component; this minimises errors from extrapolation.
3. The relative quantities of any remaining components in the multicomponent tablet (*e.g.* compaction aid, disintegrant, lubricant) should fixed, and treated as a single pseudo-component.

The first condition is due to the potential uncertainty that is introduced by performing the extrapolations to get theoretical pure component parameters for the challenging material. The difficulty of accurately predicting multicomponent tablet properties rapidly increases once more than one component requires extrapolation.

The second condition also follows from the extrapolation. The smaller the degree of extrapolation required the better. Some materials such as pAPAP are such that binary tablet feasibility does not stretch far enough to allow accurate extrapolation, especially for high API mass loadings. For this and similar materials, multicomponent prediction should not be attempted for mass loadings higher than that which could be achieved in tablets used for extrapolation (although multicomponent tablets of such high mass loadings may not be possible in practice in any case).

The third condition is a limitation keeping in mind the analysis done in the current work. Here, the other components (Avicel PH-102 for compaction aid, Solutab for disintegrant, and Ligamed MF-2V for lubricant) have been pre-blended and treated as a single pseudo-component (C3). One reason this has been done is to simplify the prediction from that of a five-component tablet to that of a three-component one. Whilst it is of course mathematically possible to do predictions (use the mixing rules and compression and compaction equations) for any number of components assuming the pure component parameters are available, the present work simplifies the problem and only considers three, and results about prediction accuracy cannot easily be extended to formulations with more components. Furthermore, some materials such as the lubricants have such a large impact on tablet properties relative to their balance in the formulation that attempting to treat them as a pure component is likely to be extremely difficult; the present work has used sensible ranges for these materials (*e.g.* disintegrant and lubricant) that reflect commercial formulations.

In summary, the approach presented in this work allows the user to determine with some utility means for exploring what formulations will result in given tensile strengths at given porosities. Whilst any predictions are likely to have a degree of error, especially at higher mass loadings of API, they allow a more targeted experimental design space to be identified that potentially minimises the material and time requirements.

There are ways the current approach could be extended to improve the reliability of the extrapolation, but these all require additional experimental capacity. One way is to simply have more data points used in the extrapolation *i.e.* use more than three binary tablet mass loadings. This approach however has an upper limit as above a certain mass loading the binary tablets are no longer compactable. Another way might be to perform the extrapolation with multiple formulations *i.e.* binary tablets of challenging component C2 being repeated for multiple C1 components (in the present work, only Fast Flo 316 was used for C1). Of course, the experimental work required proportionally increases. As formulation development progresses in conjunction with increasing quantity and quality of data, alongside the emergence of clear preferred components (such as from stability studies) additional experimental and modelling work could target specific formulations (*e.g.* where C1 and C3 components are known and finalised after a prior selection/evaluation process) and compression/compaction conditions in depth to enhance the model within a clear, localised design space.

5. Conclusions

Given the resource and time demand of extensive Design-of-Experiments for multicomponent tablet direct compaction, the present work has evaluated the potential for using various mixing rules to predict the properties of multicomponent tablets from pure component compression and compaction model parameters. Additionally, it provides a method and evaluates the use of extrapolation with binary tablet data to determine theoretical pure component model parameters for materials that cannot be compacted in the pure form.

Extrapolation using binary tablet data – where one component can

be compacted pure and the other challenging material cannot – is possible, although if a material is extremely challenging a suitable range of binary tablets may be difficult to achieve, impacting the accuracy of the extrapolations. Within the present work, *i.e.* the evaluation of the mixing rules, linear averaging (using pre-compression volume fractions) has been found to be the most suitable for compression modelling. For compaction, it has been found that averaging using a power law equation form produced the best agreement with experimental data most often, although depending on the formulation in question an alternative may produce better predictions; a power law based averaging approach is recommended as a first option. Different assumptions regarding the post-compression volume fractions used in the averaging have also been evaluated, and using estimations based on theoretical relative rates of compression of the pure components has been found to perform slightly better than using constant volume fractions (that assume a fully compressed mixture).

The approach presented in this work (extrapolation of, where necessary, binary tablet data combined with mixing rules using volume fractions) provides a framework and path for predictions for multi-component tablets without the need for any additional fitting based on the multicomponent formulation composition. It allows the knowledge space of the tablet to be rapidly evaluated, and key regions of interest to be identified for follow-up, targeted experiments that that could lead to an establishment of a design and control space and forgo a laborious initial Design-of-Experiments.

CRediT authorship contribution statement

Hikaru G. Jolliffe: Methodology, Software, Validation, Formal analysis, Data curation, Writing – review & editing, Visualization. **Ebenezer Ojo:** Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft. **Carlota Mendez:** Methodology, Software, Validation, Formal analysis, Investigation. **Ian Houson:** Project administration, Funding acquisition. **Richard Elkes:** Supervision, Methodology. **Gavin Reynolds:** Supervision, Methodology. **Angela Kong:** Supervision, Methodology. **Elizabeth Meehan:** Supervision, Methodology. **Felipe Amado Becker:** Supervision. **Patrick M. Piccione:** Supervision. **Sudhir Verma:** Supervision. **Aditya Singaraju:** Supervision. **Gavin Halbert:** Supervision. **John Robertson:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2022.122116.

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