

Building a resource-sparing direct compression
formulation optimiser to accelerate medicine development.

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Abstract

The development of directly compressed oral solid dose (OSD) tablets traditionally relies on resource-intensive, trial-and-error approaches, which are costly, wasteful, and hinder the potential to formulate rarer, more expensive, medications. A major challenge lies in systematically understanding the complex interactions between material properties, process parameters, and critical quality attributes - namely porosity and tensile strength. This thesis introduces a digital approach designed to predict how material contributions affect these quality attributes and support formulation scientists in navigating formulation development through data-informed experimental strategies.

The research begins by evaluating common empirical models for compressibility and compactability to determine their ability to predict drug-loaded formulation behaviour. A literature review revealed significant variability in reported fitting parameters for these models, into which further investigation revealed that the existence of multiple parameters was not a detriment to model performance but instead indicated the models' inherent flexibility. Building on this, previous work on mixture rules for predicting material contributions to blend behaviour was advanced. A newly developed algorithm leverages this flexibility through a global optimization approach, identifying optimal component parameters that, when applied via mixture rules, can accurately predict compression and compaction behaviours based on a blends composition. Finally, a Model-Based Design of Experiments (MBDoE) is proposed to guide experimental campaigns, reducing reliance on trial-and-error methods.

Results demonstrate that integrating MBDoE with optimised mixture rules can reduce active pharmaceutical ingredient (API) consumption by over 30% across all formulations studied, with median savings consistently exceeding 75–95% under the Accept-

able and Good performance thresholds, as determined through performance threshold crossing analysis of both the Kawakita and Ryshkewitch–Duckworth compaction models. Savings were found to decrease with increasing threshold stringency, with the widest variability observed in the ibuprofen formulations under the Excellent performance criterion. The Kawakita model consistently supported API reductions across all threshold levels, whilst the Ryshkewitch–Duckworth model was more limited in its capacity to achieve crossings beyond the Acceptable threshold for several formulations. These reductions were achieved without compromising tablet quality, although the MB-DoE approach did not consistently outperform random selection across all formulation spaces, suggesting that the threshold-based optimisation framework itself is the primary driver of API reduction rather than the experimental design strategy employed.

Overall, this work establishes a systematic methodology for tablet formulation development by combining predictive modelling with structured experimental design. By bridging material science and computational optimisation, the proposed framework contributes toward more sustainable and efficient pharmaceutical development.

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List of Abbreviations

Abbreviation	Definition
ABPI	Association of the British Pharmaceutical Industry
AI	Artificial Intelligence
API	Active Pharmaceutical Ingredient
BCS	Biopharmaceutics Classification System
CADD	Computer-Aided Drug Discovery
CERSI	Centres of Excellence for Regulatory Science and Innovation
CFD	Computational Fluid Dynamics
CMA	Critical Material Attribute
CQA	Critical Quality Attribute
CPP	Critical Process Parameter
DEM	Discrete Element Method
DoE	Design of Experiments
EMT	Effective Medium Theory
FDA	Food and Drug Administration
FEM	Finite Element Method
FIM	Fisher Information Matrix
GoF	Goodness of Fit

Abbreviation	Definition
ICH	International Council for Harmonisation
MBDoE	Model-Based Design of Experiments
MCC	Microcrystalline Cellulose
MCS	Manufacturing Classification System
MHRA	Medicines and Healthcare products Regulatory Agency
OSD	Oral Solid Dosage
PBM	Population Balance Model
PBPK	Physiologically Based Pharmacokinetic
QbD	Quality by Design
QbDD	Quality by Digital Design
QTPP	Quality Target Product Profile
RMSEP	Root Mean Squared Error of Prediction
RoI	Region of Interest
rpm	Rotations per Minute
TCS	Tabletting Classification System
UK	United Kingdom

Nomenclature

Table 2: Latin symbols and their definitions.

Parameter	Definition
A_K	Kawakita Parameter A
A_{RD}	Ryshkewitch-Duckworth Parameter A
a	Maximum achievable volume reduction (Kawakita)
a_i	Fraction of compression behavior (Cooper-Eaton)
B	Kawakita combined fitting parameter
B_K	Kawakita Parameter B
B_{RD}	Ryshkewitch-Duckworth Parameter B
b	Constant (Kawakita, Athy)
C	Constant (Heckel, Walker)
C_K	Fractional volume reduction
d	Tablet diameter
F_h	Free head space in blender
f	Transformation function
H	Breaking force
h	Tablet thickness
k	Proportionality constant

Parameter	Definition
K_G	Compressibility resistance (Gurnham)
K_H	Mean/Apparent yield pressure (out-of-/in-die, Heckel)
k_b	Bonding capacity (Ryshkewitch)
K_{ij}	Van der Waals interaction parameter
k_i	Pressure magnitude at maximum of PDF (Cooper-Eaton)
MAE	Mean Absolute Error
m_{tablet}	Tablet mass
n	Number
N	Total number
N_i	Number of holes
$N_{i,\infty}$	Total number of available holes
P	Compression pressure
P_0	Pressure required to achieve zero porosity (Gurnham)
PD	Probability density
P_m	Mean pressure value (Sonnergaard)
P_y	Apparent yield pressure
R^2	Squared correlation coefficient
$(R)RMSE$	(Relative) Root Mean Squared Error
S	Sensitivity matrix
t	Blending time
V	Volume (subscript 0 denotes the initial value, ∞ denotes infinite pressure)
V_e	Volume at zero pressure (Sonnergaard)

Parameter	Definition
V_1	Volume at 1 MPa (Sonnergaard)
W	Change in volume with $\log(P)$ (Walker)
w	Change in volume with $\log(P)$ (Sonnergaard)
w_i	Weighting factors (such as volume fraction)
x_i	Constituent properties in mixture rules
$\hat{y}_i$	Predicted values
y_i	Measured variables
$\bar{y}$	Mean of the measured values

Table 3: Greek symbols and their definitions.

Parameter	Definition
Φ	Design variables in MBDoE
ϕ_i	Volume fraction
ρ	Density
ρ_c	Critical relative density threshold
ρ_t	True density (subscript i for individual component, <i>mix</i> for mixture)
σ	Tensile strength
σ_0	Tensile strength at zero porosity (Ryshkewitch) Nominal yield strength of material (Heckel)
$\sigma_{\max}$	Maximum deformation hardness at zero porosity (Leuenberger)
σ_θ	Standard deviation in error propagation

Nomenclature

Parameter	Definition
θ	Parameter in a mixture rule (subscript i denotes the material parameter, mix denotes the mixture parameter)
θ_{ij}	Binary interaction parameter
α	Characteristic length constant
χ_P	Pressure susceptibility
δ	Perturbation
ε	Porosity
ε_0	Initial porosity
ε_c	Critical porosity
ε_s	Average porosity of surface clays (Athy)
γ	Compressibility resistance (Leuenberger)
ω	Blender rotational speed

Acknowledgements

How do we know what we want to be when we grow up? I have never known how to answer that question. From a young age, everyone else around me seemed to find it so easy to know what they wanted to do, and who they wanted to be. There were the classics of cowboy, astronaut and superhero; each slightly more unattainable than the last, as if this was an early promise to our peers of what we were capable of and how it was greater than their previous exclamation. As we got older, the jobs started to become more grounded, which required us as teenagers to start making what we were told were the right choices in life to apply for roles like teachers, doctors, and in one case an oddly specific ophthalmologist. Yet, after years of education and extracurricular activities, when we progressed through university there was a cleaving of mindsets, with teachers travelling the world to work as baristas, doctors becoming high-flying data scientists, and the ophthalmologist becoming a jacked crossfit influencer. So I guess there is no real way, especially in this time, to know where we will be in ten years. We started by being inspired to become that which is exciting to our younger selves, which is then tailored by becoming what is achievable — maybe inspired by those people in our lives — and then, to those of us who are extremely brave and fortunate, coming full circle to do what makes us happy.

I was very fortunate to be raised by parents who supported me to do what made me happy, whilst pushing me to do that which others might say is a pipedream. With a motorcyclist father who apprenticed as an engineer before working his way up the ranks in Oil and Gas, and an artistic mother who followed her passions at every step, alongside making me and my brothers' lives full of fun and whimsy — my brothers, who provided no shortage of healthy competition and support — I have never been lacking in

inspiration. At 5, I wanted to be a wizard, creating magnificent spells that would make life more wondrous. By 12, I wanted to travel the world as an orchestral violinist, living it large and captivating audiences with our performances. By 16, I shifted to wanting to help other kids become more confident in themselves through musical education. Then at 18 — after a brief period of wanting to own and run a McDonald’s franchise — I realised that future me would probably benefit from becoming something other than my current fixation. Note that this was a realisation that came to me with great help from my grandmother, the most level-headed, hard-working, generous woman I have ever met. Granny, through our long chats over copious amounts of coffee, cocktails and curry, you are a ray of sunshine in my life, which has always inspired me to challenge myself and push boundaries with a smile on my face. And with this, I pivoted and decided to pursue Chemical Engineering, which I guess was the best decision of my life.

Now, as my PhD is coming to a close, it seems that I have exceeded all expectations that my past self put in place. My life has been full of pivots, and each one a serendipitous opportunity and a leap of faith to whatever could be rather than what should be. This plunge into pharmaceutical manufacturing research has felt different; there has been a sense of grounding and purpose that I have not felt in any of my other vocations, and this is what I expect could only mean that I have finally, and somewhat blindly, come to find that I enjoy what I do.

This PhD has been a whirlwind of scary things which have whisked me to incredible places, with passionate and intelligent people, allowing me to contribute to something so much larger than any one person. All of this made possible by working with a team of hardworking and ambitious industry partners — Richard, Magdalini, and Andrew — who have tethered me with a purpose and exposed that the research need not stay research and can be applied in their day-to-day, giving this project more than just a sense of personal accomplishment, but something which is providing quantifiable progression of one of the largest industries in the world. Amongst the chaos, I have had the absolute pleasure of being guided by what can only be described as the most dynamic duo that this field could have presented me with. Daniel and John, you have provided me with a level of care and compassion that has driven me to achieve above and beyond what

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Attending university and leaving my small hometown, I have been able to surround myself with people who did not only want to achieve things that sounded good on paper or in the media that they consumed, but those who were striving to discover and become the best versions of themselves in everything that they did. With that, I would like to acknowledge my friends (a.k.a. the Rothienormal People) for being the highest-achieving, bubbliest bunch of creative miscreants who make everywhere we go feel like home. Especially Ben and Leah (the B. and L. to my T.): there are a million things I could write here, but I guess I would like to acknowledge you guys most for simply acknowledging me. Of everyone that I have met in my life, you two have been the ones who have helped shape me the most, and I would not have chased down half of my accomplishments or grown the way I have if it was not for you two cheering me on (and telling me off) along the way.

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Finally, I would like to unashamedly acknowledge myself. You may not have become a wizard, but you are doing pretty wondrous things.

For all the inquisitive kids who incessantly ask why and can never sit at peace until they have all the information. Comparison is the thief of joy, so don't let perfect be the enemy of good.

Research Outputs

Peer Reviewed Publications

Tait, T., M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson and D. Markl (2024). Empirical Model Variability: Developing a new global optimisation approach to populate compression and compaction mixture rules, Elsevier B.V. 662.

Conference Contributions

1. **T. Tait**, M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson, D. Markl.
A Systematic, Model-based Decision-Making Framework for Compression and Compaction of Directly Compressed Tablets.
Pharmaceutical Solid State Research Cluster (PSSRC), Cambridge, UK, 2023.
Oral Presentation
2. **T. Tait**, M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson, D. Markl.
Advanced Formulation Mixture Rule Optimisation for Enhancing Predictability of Tablet Compressibility and Compactability.
Pan-European Process Analytical Technology Science Conference (EuPAT). Glasgow, UK. 2023. **Poster Presentation**
3. **T. Tait**, M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson, D. Markl.
Advanced Formulation Mixture Rule Optimisation for Enhancing Predictability of Tablet Compressibility and Compactability
CMAC Open Days. Glasgow, UK. 2023. **Flash Presentation, Poster Presentation**

4. **T. Tait**, M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson, D. Markl. Advanced Formulation Mixture Rule Optimisation for Enhancing Predictability of Tablet Compressibility and Compactability. Compaction Simulation Forum. Dublin, Ireland. 2024. **Poster Presentation**.
5. **T. Tait**, M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson, D. Markl. Advanced Formulation Mixture Rule Optimisation for Enhancing Predictability of Tablet Compressibility and Compactability. PSSRC. Dortmund, Germany. 2024. **Oral Presentation**
6. **T. Tait**, M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson, D. Markl. Advanced Formulation Mixture Rule Optimisation for Enhancing Predictability of Tablet Compressibility and Compactability. CMAC Open Days 2025. Glasgow, UK. 2025. **Flash Presentation, Poster Presentation**
7. **T. Tait**, M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson, D. Markl. Resource-sparing direct compression formulation optimizer to accelerate medicine development. EuPAT. Kuopio, Finland. 2025. **Oral Presentation**
8. **T. Tait**, M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson, D. Markl. Advanced Formulation Mixture Rule Optimisation for Enhancing Predictability of Tablet Compressibility and Compactability. Accelerate Conference. Toronto, Canada. 2025. **Poster Presentation**
9. **T. Tait**, M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson, D. Markl. Resource-sparing direct compression formulation optimizer to accelerate medicine development. The 8th International Symposium on Solid Oral Dosage Forms. Mölndal, Sweden. 2025. **Poster Presentation**
10. **T. Tait**, M. Salehian, M. Aroniada, A. P. Shier, R. Elkes, J. Robertson, D. Markl. Model-Based Design of Experiments to accelerate the formulation of directly-

compressed oral solid dosages.

PSSRC. Graz, Austria. 2025. **Oral Presentation**

Supervisory Roles

Co-supervised with Natalie Maclean. MSc thesis “Impact of Elastic Recovery on the Properties of Directly Compressed Tablets” by Nitesh Govind Shirode (University of Strathclyde, 2023), supervised by Prof. Daniel Markl.

Outreach Projects

These were four week projects run with the Chemical and Process Engineering Department at Strathclyde alongside Dr Sylvia Battock and Dr Mark Haw.

Young Chemical Ambassadors: Formulation, Optimisation, and Manufacturing of... Bath Bombs. 2022.

Students were set out to test a selection of commercially available, food-safe powdered ingredients to design a marketable bath bomb. Optimisation came with financial cost which they had to balance with performance (size and fizz) and visual (colour and smell) attributes. The motivation for this process was for students to first come up with a design of experiments to test what formulations would make a usable bath bomb, before considering the market (their classmates) and what would make a sustainable and desirable product. Final results were collated and demonstration presented to panel of judges and competitor schools, awarded second place.

Are We Really Ethical Engineers: AI in Medicine. 2023.

Students were prompted to consider a problem that they see in the world, and to come up with some fantastical solution (unbound by any constraints). Their task was to consider the ethical considerations that their solution might pose, and pitch their arguments to a panel of judges and competitor schools. The motivation was for the students to think outside the curriculum and understand that solutions are not always

for everybody, or can provide solutions that may be less than obvious. Awarded first place.

Chapter 1

Introduction

Chapter Summary

This chapter outlines the transition from traditional Quality by Testing approaches toward Quality by Digital Design and discusses the key components required to support this shift across pharmaceutical development. It explores the broader advantages of digital transformation within the drug discovery and development pipeline, with particular focus on its potential to improve efficiency, strengthen decision-making, and support more sustainable innovation. The chapter further considers the industrial, regulatory, and governmental requirements necessary to enable adoption, emphasizing their importance in supporting the UK's global competitiveness and contributing to a more sustainable future for public health. In this context, the chapter establishes the relevance of this project in supporting the application of predictive modelling approaches within pharmaceutical development.

1.1 Designing Quality into Pharmaceutical Products

The pharmaceutical industry operates under rigorous regulatory standards. Due to the direct impact on public health and well-being, it is imperative that the products delivered are high in quality and meet strict standards with regards to their efficacy, consistency, and safety. However, the attainments of these standards have remained focussed at individual product levels rather than developing a holistic understanding of how changes to certain process parameters can impact the products quality (Duarte et al., 2025). Prior to the turn of the millennium, the quality of drug products was governed by raw material and end-product testing. As a result, in the case that the regulations and standards were not met, production would be stopped and the product discarded, usually without fully understanding the root cause (Yu, 2008).

This reactive approach also limited manufacturers' ability to optimise or adapt processes efficiently, as any post-approval changes required extensive regulatory submissions and review (FDA, 2025). As highlighted by the United States Food and Drug Administration (FDA), this framework contributed to persistent quality challenges across the industry, including high rates of product recalls linked to inherent process and design flaws, difficulties in manufacturing scale-up, and recurring production disruptions arising from outdated equipment and insufficient quality management systems. Furthermore, regulatory oversight relied heavily on periodic inspections and pre-commercialisation data, offering limited insight into actual manufacturing performance and failing to reliably predict quality risks. Collectively, these shortcomings defined the need for more systematic, knowledge-driven approaches capable of linking process understanding directly to product quality.

In 2008, there was a developmental shift from testing for quality to designing it into new products driven by the formalisation of QbD principles by the International Conference on Harmonisation (ICH) regulatory framework (Yu, 2008). This proactive approach to product quality was proposed as an alternative, not just to meet product quality specifications but to increase production capabilities by developing a better understanding of how variations in the materials and manufacturing process variables

impacts a products quality, as outlined in the ICH's Quality Guidelines, Q8-Q11 (ICH, 2009, 2023, 2008, 2012). These guidelines have supported the implementation of systematic, science-based, risk-managed approaches to the development of pharmaceuticals and drug substances. The 8th Quality Guideline, Q8, defines the central principles of QbD in pharmaceutical development, and states that the process should consist of the following elements, Figure 1.1:

- the setting of goals for quality, safety and efficacy termed a Quality Target Product Profile (QTPP)
- the identification of the critical quality attributes (CQAs) for the drug product
- the determination of the critical material attributes (CMAs) of the components and estimating their quantities in a formulation to deliver the QTPP
- selecting the appropriate manufacturing route and identifying the critical process parameters (CPPs),
- a systematic evaluation and understanding of both the formulation and manufacturing process, with a focus on identifying any functional relationships which may exist between the material attributes and process parameters
- a defined control strategy to track performance and quality which could support the continuous improvement throughout the product lifecycle.

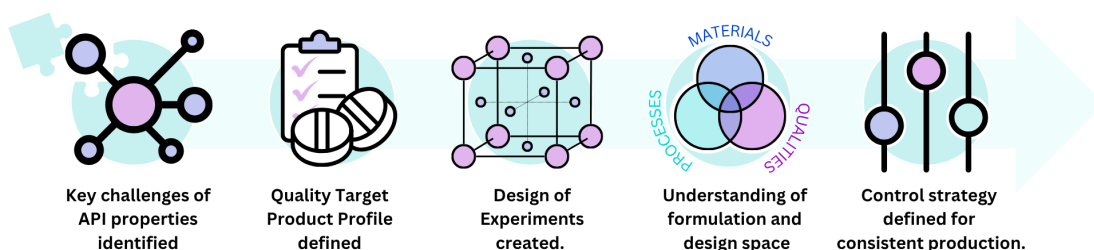


Figure 1.1: A simplified summary of objectives for pharmaceutical formulation development.

The QTPP acts as the basis for drug product development. This outlines the intended use of the product, such as the dosage and delivery form, with performance requirements such as stability and drug release. To achieve the QTPP, an understanding of the CMAs of the materials (the physical, chemical, and biological characteristics) and the CPPs (the key manufacturing process variables), in the context of the desired dosage form is required (Yu et al., 2014) (This is summarised further in Section 2.2).

Applying the QbD approach helps to map out and understand what changes can be made to a formulation or manufacturing process to maintain – or provide quantified evidence for deviations – in a products quality. By holistically implementing this approach of establishing relationships between the CMAs and CPPs to the CQAs, the pharmaceutical industry are able to build their knowledge throughout the lifecycle of a drug product to create new, sustainable approaches without compromising on product quality; this is currently cited to have optimised development times by 40% by optimising formulation parameters prior to mass manufacturing which can reduce the amount of materials wasted by up to 50% through having a defined design space allowing for more control and less batch failures (Duarte et al., 2025).

1.2 Quality by Digital Design

Whilst QbD has increased the efficiency of product development, the quantity of exploratory experimentation required to get to a well-defined understanding of a design space is still resource-intensive. Now, with the growing digital advancements from the most recent Industrial Revolutions, there is the possibility to further refine the pharmaceutical development process. By embedding this approach with predictive modelling and emerging digital technologies, the industry can upgrade to a Quality by Digital Design (QbDD) approach to support and expedite development procedures (Mustoe et al., 2025).

Embracing QbDD has the potential to permanently transform the drug development pipeline scientifically, technologically, and organisationally, Figure 1.2 (Huanbutta et al., 2024). So far, there have been significant studies into employing Computer-Aided Drug Discovery (CADD), which has generated a bounty of innovations through applied

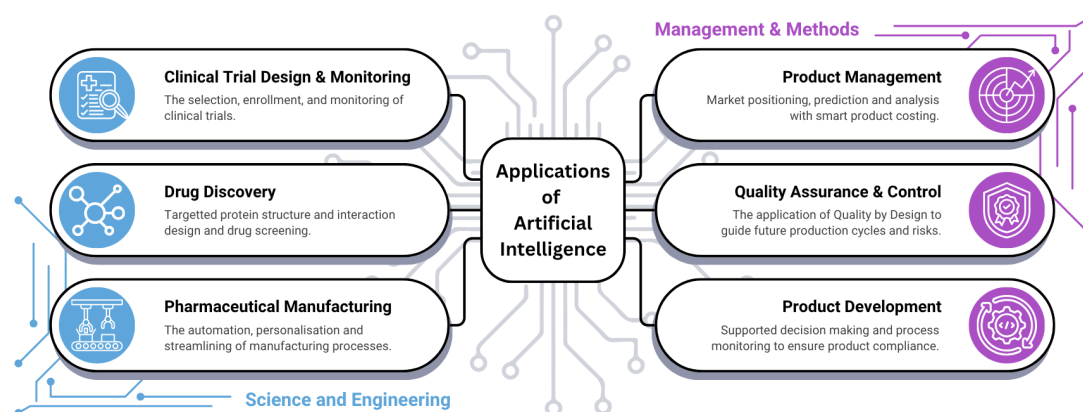


Figure 1.2: Examples of how Artificial Intelligence can be applied in different fields of the pharmaceutical industry, inspired by Paul et al. (2021).

molecular modelling and virtual screening to aid in the prediction and understanding of the biological activities for compounds old and new. Applications range from developing protein language models and deep-learning networks to categorize and evaluate drug effectiveness and also potential harmful reactions for anti-cancer treatments, to widening the accessibility of the drug discovery process through the creation of platforms for generating molecules designed for specific application scenarios (Zhang et al., 2025). Through these integrations, there has been a noted reduction in time, resource consumption, and cost for discovery. With the traditional methods, the development and approval of a new drug product can take up to 15 years and over \$1 billion to deliver with a high rate of attrition¹, Figure 1.3 (Mak and Pichika, 2019; Rehman et al., 2025; Deloitte, 2025) but the applications to drug discovery is proof of how Artificial Intelligence (AI) can help to reduce attrition rates through a Right First Time approach (Mak and Pichika, 2019; Paul et al., 2021; Mendhi et al., 2025).

The adoption of digital methods in the formulation and manufacturing stages, however, has not been as productive in comparison (Zühlke, 2025). If these stages are not at pace with the discovery of new drug substances, this will act as a bottleneck for innovative development and ultimately patients access to new products. Conventional methods for formulating drug products which are suitable for manufacturing relies on repetitive trial-and-error experimentation, which excessively consumes resources, labour, and fi-

¹Drug candidates which are unsuccessful in development and do not make it market.

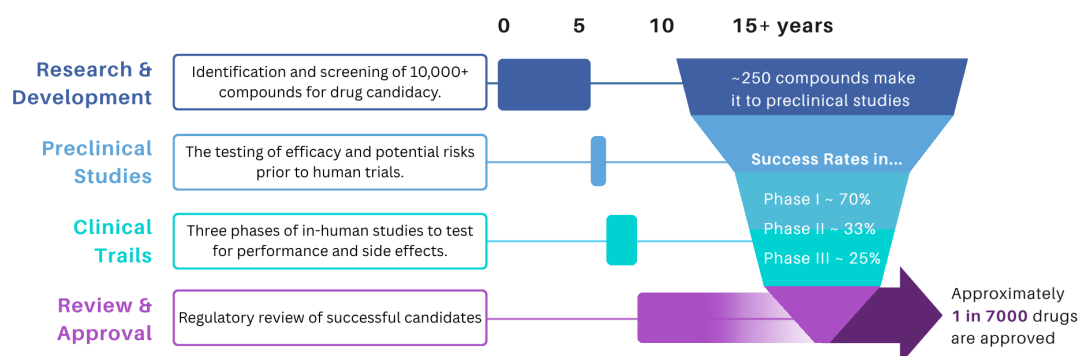


Figure 1.3: A summary of traditional pharmaceutical development stages highlighting the timelines and approximated attrition rates (Brunning, 2020).

nances. QbDD can equip researchers and manufacturers with new ways of working which can assist in overcoming barriers which previously were too complex to tackle let alone overcome, further increasing process development efficiency. Zühlke (2025) provides guidance for what must change in current manufacturing methods to open this bottleneck; in terms of this project, the key focus relates to utilising AI to identify correlations among drug formulations, operating parameters, and quality attributes of products and the proactive use of real-time data to optimise working methods and outcomes (Huanbutta et al., 2024).

To fully embrace QbDD, investment into the development of new technologies and the data infrastructure is needed for acquiring, curating, storing, and analysing data generated. Recently, there have been significant investments and initiatives that have emerged involving the United Kingdom (UK) which aim to support this. As of October 2025, the UK's Medicines and Healthcare products Regulator Agency (MHRA) and the United States' FDA announced a strengthened partnership to foster a globally harmonised regulatory environment to accelerate patients access to the latest medical innovations powered by AI (MHRA, 2025b). Prior to this, the MHRA launched the National Commission into the Regulation of AI in Healthcare to connect clinical experts to those in AI and regulation to advise on the formation of new regulatory frameworks (Pinching, 2025; MHRA, 2025a). Complimenting this Commission, the Association of the British Pharmaceutical Industry's (APBI) Pharmaceutical Industry Investment and

Competitiveness Framework 2025 (ABPI, 2025a) outlines the need and requirements for supportive policies to maintain the UK’s global positioning for innovation. The UK Government have reinforced this through providing financial support of £6.2 million across seven Centres of Excellence for Regulatory Science and Innovation (CERSIs) to help drive research in this topic; one of these being the Digital Transformation of Medicines Development and Manufacturing at the University of Strathclyde (UK Research and Innovation, 2025).

With this being said, the APBI framework also highlights the importance of external collaboration and the relationship between field experts and government. They provide a critique of how the current version of the UK’s Voluntary Scheme for Branded Medicines has created clawback rates² high enough to deter companies from investing in the UK (ABPI, 2025b). Not only has policy deterred investment, since its implementation in 2022, almost £2 billion of funding has been pulled from the UK by key companies such as AstraZeneca, Pfizer, Merck and Eli Lilly and Company (Kollewe, 2025).

For the successful implementation of these tools into the industry, a coordinated global commitment regarding the safe, effective and transparent application of AI is essential. With this, fostering international partnerships between academia, industry and government will be crucial to nurture a sustainable future for public health.

1.3 Project Relevance

This thesis seeks to contribute to the knowledge and computational tools that support the application of predictive modelling in pharmaceutical formulation development. In particular, it aims to accelerate the development of directly-compressed tablet formulations by providing a structured, model-driven method to support informed decision-making during early stage formulation development reducing the experimental effort and material resources required to reach a successful OSD product.

²the proportion of money that companies must refund into the National Health Service (NHS) when spending exceeds a set spending cap

Chapter 2

Literature Review

Chapter Summary

This chapter reviews the foundational literature relevant to the development of predictive modelling approaches for direct compression pharmaceutical formulations. It begins by introducing OSD formulation and the classification systems used to understand material behaviour, before outlining the key design considerations for tableting processes, including quality attributes, material selection, blending, environmental influences, and processing equipment. The chapter then examines the mechanisms governing direct compression and introduces the mathematical modelling approaches used to describe powder compression and compaction behaviour, with particular focus on empirical models and their application to pharmaceutical powders. This is followed by a discussion of mixture models and experimental design strategies as essential tools for understanding formulation behaviour and enabling efficient model development. Collectively, the literature presented in this chapter establishes the scientific and methodological context for this project, identifies the current limitations in existing approaches, and highlights the key knowledge gaps that motivate the application and advancement of predictive modelling within pharmaceutical development.

2.1 Oral Solid Dosage Formulation

OSDs remain the most widely developed and prescribed dosage form, reflected by the dominance of tablets within global medicine portfolios (Grand View Research, Inc., 2025). This dominance arises not only from their convenience and acceptability to patients, but also from the manufacturing scalability, cost-effectiveness, and process flexibility (Bittorf et al., 2010). Despite their widespread use, the development of robust tablet formulations and the selection of appropriate processing routes remain highly non-trivial (Sohail Arshad et al., 2021), motivating continued research into their design and manufacture.

A successful OSD form will consistently and safely deliver the desired therapeutic response of the drug. This requires the formulation to be manufacturable on a large scale with reproducible product quality which maintains its mechanical integrity, and its chemical and physical stability from production to the end of shelf life (Aulton, 2017). To achieve these goals, there must be careful consideration given to: (i) the biopharmaceutical attributes, which govern the absorption of drug, (ii) the physical and chemical properties of the drug substance, which can impact the drug delivery as well as manufacturability, and (iii) the therapeutic effects of the formulation, which covers the factors which may negatively impact the stability or side-effects of the product (Aulton, 2017).

The biopharmaceutical attributes of drug formulation covers the physical, chemical and biological qualities of the drug that dictate the absorption, distribution, metabolism in, and excretion from, the patients body. Drug substances used in OSDs, traditionally, are absorbed via passive diffusion driven by concentration gradients (high to low) across absorbing membranes in the gastrointestinal tract. The rate of this absorption defines the extent of delivery for a drug and is a function of its solubility and permeability. These attributes are crucial qualities which define the further scientific and engineering processes required during the formulation development stages to tailor the desired drug delivery mechanisms. Yet, this is no easy feat as they can be sensitive to certain conditions – particularly when exposed to heat, moisture, shear stress, or through

interactions with other additives (Aulton, 2017; Dahan and Miller, 2012).

Dosage forms are designed with a target time-to-action for the therapeutic effect, ranging from seconds (achieved by intravenous administration) to weeks (achieved with implantable systems) (Aulton, 2017). For OSDs the typical delivery rests between minutes to hours, due to the time taken to reach the gastrointestinal tract and the dissolution mechanisms of the drug product. A further formulation challenge is presented here as the drug substance must traverse the adverse conditions of the digestive system whilst remaining intact so that it can be broken down, solubilised and absorbed in the gastrointestinal tract. Due to their inability to form mechanically-sound compacts to achieve this, as well as the low mass related to common doses, drug substances are rarely administered as pure chemical substances and rely on the addition of additives (excipients) to address their undesirable attributes. Thus the absorption rate and manufacturability must be tailored to meet the formulation objectives through considering the physicochemical properties of the drug substance to inform the appropriate selection of excipients and processing route (Aulton, 2017; Bittorf et al., 2010).

2.1.1 Classification Systems in OSD Formulation

To rationalise the complexity of the biopharmaceutical and manufacturing considerations, and to provide a common understanding of associated risks, classification frameworks such as the Biopharmaceutics Classification System (BCS) (ICH, 2019) and the Manufacturing Classification System (MCS) (Leane et al., 2015) have been developed to relate the properties of the drug to anticipated processing and formulation challenges. These systems were created as extensive collaborations between industry and academia, aiming to provide evidence-supported systematic boundaries based on shared knowledge and expertise to guide the consistent development of high-quality OSD products.

The Biopharmaceutical Classification System

To identify biopharmaceutical challenges associated with drug performance, the BCS classifies drug substances according to their solubility and permeability. The solubility of a substance refers to its ability to dissolve in a specific solvent, to form a dispersed

solution at a specified temperature and pH. The permeability is the ability for the drug substance to diffuse across a membrane, enabling absorption (Aulton, 2017). Ideally, a drug would be developed with high solubility and high permeability, however the presence of drugs with low solubility is common in the current portfolios (Dahan and Miller, 2012; Karagianni et al., 2018). The solubility of a material can be increased through adjusting the temperature and pH of the container system, however these are not controllable variables within the patient. There are alternative methods which alter the chemical qualities of the substance, such as altering the molecular structure of the solute (e.g. the introduction of hydrophilic hydroxyl groups), or the crystal characteristics (e.g. altering the crystallisation parameters to produce polymorphs) can be controlled by crystallisation scientists; however, these methods can impact the stability of the substance to be processed which is undesirable. A common method which is used to increase the solubility and dissolution rate relies on the reduction of particle size and the alteration of particle morphology to increase the surface area exposed to the solvent. This change to the solid-states physical characteristics increases the dissolution and absorption rate, but also poses a risk to the manufacturability of the powders (e.g. flowability and segregation) due to irregular shapes or changes to cohesive/adhesive properties and large differences in density between components (Chendo et al., 2023).

The Manufacturing Classification System

Whilst the BCS is capable of grouping drugs by their biopharmaceutical characteristics, it offers no insight into their processing challenges. Thus, the MCS was inspired by this classification system to support the decisions for manufacturing process selection.

The powders used in pharmaceutical OSD formulation development must meet certain requirements for successful processing. They must:

- flow well without adhering to surfaces
- mix well to form blends of uniform content, and
- be compactable into tablets of sufficient strength (or consistently fill capsule shells, which relates back to powder flowability).

Failure to meet these, necessitates additional processing steps or the addition of excipients to counter the poor processing qualities of the drug properties (excipients and their functional properties are discussed in greater depth in Section 2.2.2).

The MCS acts to formalise how processing decisions are made by classifying drug substances according to their particle properties and dose, then relates these attributes to the feasibility of different tableting technologies. This system categorises tableting technologies according to their ability to accommodate increasingly challenging material properties, with higher classes associated with greater processing complexity, cost, and exposure to external stresses.

The central objective of the MCS is to rationally guide formulators toward the simplest processing technology capable of delivering a product of consistent quality with minimal risk. The Classes are outlined as follows:

- **Class I: Direct Compression**

Direct compression involves blending the active pharmaceutical ingredient (API) with excipients followed by immediate compaction into tablets. This route requires powders with adequate flowability, blend uniformity, and compactability, as no intermediate processing steps are used to modify particle properties. As a result, direct compression subjects materials to minimal mechanical and environmental stress and is associated with high process efficiency, scalability, and low manufacturing cost. However, its applicability is limited to formulations with favourable material properties and appropriate dose levels.

- **Class II: Dry Granulation**

Dry granulation is employed when powder flowability or content uniformity is insufficient for direct compression. The process involves densification of the powder blend through roller compaction or slugging, followed by milling and recompression. While dry granulation improves flow and reduces segregation risk, it introduces additional shear and compaction stresses, which may adversely affect particle integrity and compressibility. Nevertheless, the absence of liquid exposure makes this route suitable for moisture-sensitive APIs.

- **Class III: Wet Granulation**

Wet granulation is used to address more severe deficiencies in powder properties by forming granules through the addition of a liquid binder, followed by drying and finally compression. This approach provides increased control over flow, content uniformity, and compressibility but subjects materials to elevated shear, moisture, and thermal stress during granulation and drying. These conditions can induce polymorphic transformation, degradation, or changes in compaction behaviour, increasing development risk and process complexity.

- **Class IV: Other Technologies**

Class IV encompasses alternative or enabling manufacturing approaches employed when conventional tableting routes are inadequate to meet product requirements. These may include specialised granulation techniques, hot-melt extrusion, or other advanced processing routes. Such technologies offer greater flexibility in handling challenging APIs but are associated with the highest levels of complexity, cost, and risk, and are typically considered only when simpler MCS routes are not viable.

The MCS acts as a systematic, universal method to increase knowledge and understanding of the links between materials properties and ease of manufacturing to streamline the development for OSDs. It also acts as a way to communicate process decisions to non-formulators through the creation and visualisation of evidence-based, peer-reviewed operation spaces for the technologies.

The first iterations of the MCS were primarily focused on the more traditional approach of batch manufacturing, while the longer-term goal of progressing towards continuous manufacturing was only gradually introduced (Leane et al., 2024). This is particularly important because continuous manufacturing relies on steady-state operation, making the relationship between material properties and process performance more apparent, particularly through their influence on powder flow and feeding behaviour. It has been shown that increasing API concentration can introduce further complexity through its effect on powder handling and downstream process performance, which

causes the transition through higher manufacturing classes. However, Leane et al. (2024) summarised that continuous direct compression can, in some cases, be more tolerant to variation in API properties than would be expected from the original batch-focused MCS perspective, particularly where segregation and poor blend flow would otherwise limit batch direct compression performance. As a result, the design space for direct compression may be broader in continuous systems, especially at lower drug loadings where continuous feeding and blending can reduce some of the segregation risks typically associated with batch processing. This does not remove manufacturability risk, but instead shifts it, with the key challenge often lying less in the downstream compaction step itself and more in the ability to accurately and consistently handle and feed the raw materials into the process, particularly at low dose levels. As such, the move towards continuous manufacturing increases the need for predictive, mechanistic, and data-rich classification frameworks, as formulation properties may have a more direct influence on both manufacturability risk and final product quality than in conventional batch-based systems.

Even with these classification systems, the problem-solving involved in developing a successful formulation still relies – albeit less – on prior expertise and experimentation to characterise the required developability properties (e.g. properties which define the dissolution, flowability, uniformity, and manufacturability) (Leane et al., 2015, 2024).

To reduce this experimental burden, predictive modelling toolboxes have been developed which utilise these classification systems within a system of predictive models to facilitate the shift towards QbDD (White et al., 2022; Moreno-Benito et al., 2022; Mustoe et al., 2025). These toolboxes enable the relationships between material properties, process parameters and product attributes to be mapped out using digital methods to define control limits prior to physical development. However, these approaches predominantly operate at the level of process selection and there has been less attention given to how changes in the formulation composition (such as variations in API loading or excipient ratio) influences process performance and product attributes.

While these classification systems provide valuable insights into the drug substance

and particle attributes, they do not account for the influence of formulation composition or component fractions within a blend. Consequently, there is currently no systematic framework that links formulation design and mechanical attributes to CQAs in tablets.

2.2 Design Considerations for a Tableting Process

Building on the prior definition, a successful tablet product must have the physical strength to withstand downstream processing and logistics, whilst remaining stable over its shelf-life to consistently, and safely, deliver the desired drug delivery profile (Bittorf et al., 2010). To achieve this, there are key design decisions for the formulation material attributes, mechanical set-up and processing parameters that must be carefully evaluated, these are summarized in Figure 2.1.

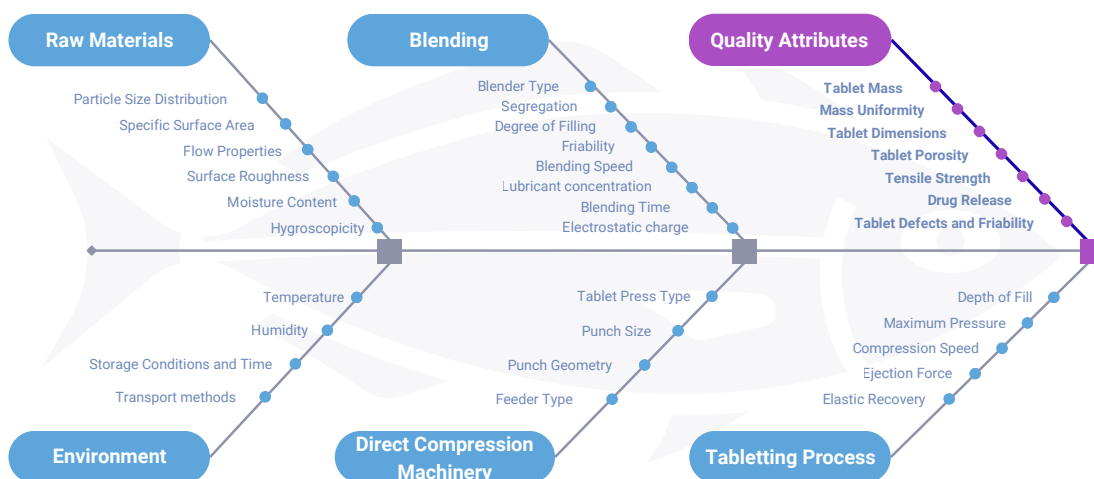


Figure 2.1: Fishbone diagram highlighting some examples of contributing material attributes and process parameters to a tablets list of quality attributes inspired by Tho and Bauer-Brandl (2011).

2.2.1 Quality Attributes

Quality attributes are properties or characteristics which should be within set limits, ranges or distributions to achieve the desired product quality. These can be physical, chemical, or (micro)biological and for directly compressed OSDs, they typically address the purity and strength of the product as well as the drug release and stability. Quality

attributes that are deemed critical are those which, when existing outside of the specified bounds, may pose a degree of severity to the patient; thus, they are used as a reference point for the establishment of boundaries across design decisions (ICH, 2009; Yu et al., 2014). A product’s quality is shaped by development decisions, and a QbD approach seeks to quantify and control how these decisions affect the final product, ensuring outcomes remain within the boundaries defined by the CQAs. For example, changes to the pre-processing conditions of a material may alter the particle size of the drug substance, which in turn can affect drug release. Depending on whether the particle size is increased or reduced, the formulation may result in an unintended rapid release leading to dose dumping, or insufficient drug release that fails to achieve the desired therapeutic effect due to solubility limitations (Kaur et al., 2018).

2.2.2 Materials

The manufacturing of tablets involves repeated powder handling steps, including transfer, blending, and compression. As such, the physical properties of the constituent powders – such as particle size and shape distribution – must be carefully considered when developing a formulation.

The selected API for a drug product will have specific physical, chemical and biological properties. These properties directly influence powder flow, segregation tendency, compressibility, and sensitivity to processing conditions, and therefore play a central role in achieving consistent manufacturability and final tablet quality (Yu et al., 2014; Aulton, 2017). APIs are classically crystalline in form and hence are not typically able to form compacts on their own. To counter the non-desirable attributes, excipients are required to aid in the processing of APIs through enhancing the stability, manufacturability (i.e. flowability and uniformity), tablet properties (i.e. tablet porosity and tensile strength) and delivery (i.e. disintegration and solubility) of the drug (Yu et al., 2014).

Excipients can be categorised by their functional properties that they may provide to a formulation (Table 2.1), with the most commonly used in tablets being: fillers and binders, disintegrants, and lubricants (Aulton, 2017; Bittorf et al., 2010).

Fillers are incorporated to increase the bulk volume of the formulation to create a

tablet of a practical size for handling. This is critical for formulations of lower dose as a lower limit of powder mass is required (cited to be at least 50 mg per tablet) to achieve adequate die filling, mass uniformity, and mechanical integrity (Aulton, 2017; British Pharmacopoeia Commission, 2022). An ideal filler must meet a series of requirements relating to compatability, biopharmaceutical and mechanical properties, taste and cost. This is not usually achieved by a single component, meaning a combination of fillers (traditionally carbohydrates or inorganic salts) are used to be appropriate (Aulton, 2017; Polak et al., 2023; Jadav et al., 2022). The most common fillers used due to their fulfillment of the mentioned criteria are lactose and cellulose. Lactose is a cheap option to increase the flowability and fragmentation to provide favourable dissolution characteristics, but this brittle characteristic can limit the tensile strength of the end product. In contrast, cellulose provides a more plastic deformation which can increase the tensile strength but may limit the flowability of the blend. It is common for these components to be used in unison to find a balance which maximises their desirable properties.

Disintegrants ensure that when the tablet comes in contact with a liquid, it can break up into smaller fragments to increase the surface area and promote dissolution. This is commonly achieved by swelling mechanisms such as via mechanisms such as swelling, capillary action, and interruption of particle-particle bonds that ruptures the tablets structural integrity. Common examples of disintegrants are native starches, particularly potato, maize and corn starches due to their cost and their safety for consumption (Aulton, 2017; Polak et al., 2023; Jadav et al., 2022); however genetic, physical and chemical modifications are used to alter their structure to produce disintegrants with better pharmaceutical functionality, particularly relating to their compressibility (?).

Lubricants reduce the friction between solids and exposed metal surfaces which is helpful in reducing the chances of tablet defects during the ejection from the die (see Section 2.2.5). Stearate salts are the most common lubricants used in

OSDs due to their fine particle size and low resistance to shearing allowing for effective boundary lubrication (i.e when a thin layer of lubricant coats the solid components allowing them to slide with reduced friction). Lubricants may also hinder the desirable properties of the tablet when the concentration is too high, or via excessive blending, this is discussed further in Section 2.2.3 (Aulton, 2017; Kushner and Moore, 2010).

Table 2.1 illustrates the wide range of functionalities that excipients can contribute to a formulation. Some excipients may complement each other, others may counteract one another, and in certain cases, they may even be chemically incompatible. Navigating the large number of variables and managing the resulting complex datasets to identify the optimal balance of these contributions remains a challenge (Yu et al., 2014; White et al., 2022; Bittorf et al., 2010).

Table 2.1: Functional categories of pharmaceutical excipients grouped by primary formulation purpose (Rowe et al., 2012; Pharma Excipients, 2013).

Function Group	Functional Category	Description of Function
Bulking & Binding	Diluent (Filler)	Material added to increase bulk and improve handling of formulations containing low drug load, aiding uniformity and compressibility.
	Binder	Promotes particle adhesion to form granules or cohesive tablets with sufficient mechanical strength.
	Disintegrant	Facilitates tablet breakup upon contact with fluids to promote rapid drug release and dissolution.
	Dissolution Enhancer	Improves drug wettability, solubility, or surface area exposure to increase dissolution rate.
Disintegration & Dissolution	Solubilizing Agent	Increases apparent solubility of poorly soluble drugs via complexation or micellar mechanisms.
	Complexing Agent	Forms non-covalent complexes with drug molecules to enhance solubility, stability, or bioavailability.
	Granulation Aid	Enhances wetting, aggregation, or flow during granule formation in wet or dry granulation processes.
Processing Aids	Lubricant	Reduces friction between tablet and die wall during compression and ejection, preventing sticking and wear.
	Glidant	Improves powder flow properties by reducing interparticle friction and cohesion.
	Antiadherent	Prevents material from sticking to punches, dies, and processing equipment during compression.
	Adsorbent	Absorbs liquids or oils onto solid surfaces to improve powder handling and stability.

Function Group	Functional Category	Description of Function
Coating & Controlled Release	Coating Agent	Forms protective or functional layers on tablets or pellets to modify release, mask taste, or improve stability.
	Film Former	Produces continuous polymeric films used in tablet coatings or controlled-release systems.
	Controlled-Release Matrix Former	Creates a solid matrix that governs drug diffusion or erosion to achieve prolonged release profiles.
	Plasticizer	Increases flexibility and reduces brittleness of polymer films used in coatings or matrices.
	Thickening Agent	Increases viscosity or structural consistency in dispersions or coating formulations.
Stabilization & Preservation	Stabilizing Agent	Protects drug substances from physical or chemical degradation during processing and storage.
	Antioxidant	Prevents oxidative degradation of drugs and excipients sensitive to oxygen or free radicals.
	Buffering Agent	Maintains formulation pH within a desired range to ensure stability and consistent drug performance.
	Acidulant	Adjusts acidity for pH control, stability enhancement, or sensory properties.
	Water-Activity Reducing Agent	Lowers available moisture to improve chemical and microbiological stability.
Palatability & Texture	Humectant	Retains moisture within formulations to prevent drying and improve texture or stability.
	Sweetening Agent	Enhances palatability of oral dosage forms, particularly chewable or dispersible tablets.
	Confectionery Base	Provides bulk, sweetness, and mouthfeel in chewable or lozenge-type solid dosage forms.

2.2.3 Blending

Content uniformity of a blend aids in the consistency of product quality both in terms of drug dosage per tablet, as well as helping to minimise weight variation which may arise due to segregation of powders (ICH, 2011). For batch-scale direct-compression formulations, the blending unit operation is conventionally carried out in rotating vessels which tumble the API with the selected excipients until a blend of uniform content is achieved (Mendez et al., 2010; Bautista et al., 2025). In these systems, physical powder properties (density, shape, size, and surface ad/cohesion) as well as blender design and operation (degree of filling, rotational speed and mixing time) must be considered to ensure the suitable mixing of the powders is achieved (Mendez et al., 2010).

The suitability of a blending process is not limited to the content uniformity of the blend, but is also relevant to achieve the defined product profile of the final product; most particularly for the addition of lubricants (Jolliffe et al., 2024). It was cited that lubricants, such as the popular magnesium stearate, have the capability to coat the individual component particles during the blending process. It is due to the hydrophobic nature and poor bonding properties of magnesium stearate that can then reduce the surface wettability and tensile strength of the final drug product (Kushner and Moore, 2010). It is therefore important to consider the incorporation of lubricants in a formulation with care to ensure that the blend receives the appropriate amount of aid whilst

not being detrimental to the quality attributes. This has been studied further, particularly for the scale-up of processes, and development of continuous direct compression lines to evaluate how blending parameters can be controlled to ensure consistent quality of blends (Kushner and Moore, 2010; Kushner IV, 2012; Kushner and Schlack, 2014; Jolliffe et al., 2024).

2.2.4 Environmental Considerations

Pharmaceutical stability refers to the ability of a drug substance and its finished dosage form to maintain quality, safety, and efficacy when exposed to environmental conditions encountered during manufacture, storage, and use. Key factors include temperature, humidity, light, and microbiological exposure, which can induce physical, chemical, or microbiological changes in the API, excipients, and dosage form (United States Pharmacopeial Convention, 2006).

For solid oral dosage forms, environmental factors such as moisture and temperature fluctuations can significantly alter powder and tablet properties, including crystallinity, hygroscopicity, interparticle bonding, mechanical strength, and dissolution behaviour. These changes can affect not only chemical stability but also manufacturability and in-use performance (Aulton, 2017). A challenge in formulation development is ensuring that a tablet maintains its quality and performance across a range of environmental conditions. A formulation optimized for one climate may not be suitable in another, highlighting the need for flexible strategies that can accommodate variability in both storage and use conditions (Risha et al., 2003).

2.2.5 Direct Compression Machinery

Powder compression and compaction machinery applies external loads to increase the density of particulate systems into closely packed structures capable of supporting applied stresses (Leuenberger, 1982; Aulton, 2017). In tablet manufacturing, the choice of press type, either single-punch eccentric presses (Figure 2.2) or rotary presses (Figure 2.3), is largely dictated by the required production rate and scale of operation.

Eccentric presses consist of a single die with one upper and one lower punch, where

compaction is achieved through the downward motion of the upper punch driven by an eccentric shaft, resulting in single-sided compression with minimal dwell time at peak pressure (Çelik, 2011). Rotary presses, by contrast, employ a rotating turret containing multiple dies and corresponding punch pairs, with both punches guided by cam tracks and pressure rollers to produce double-sided compression. The inclusion of punch flats introduces a short dwell time at maximum pressure, which can influence powder densification behaviour (Natoli et al., 2017). While eccentric presses are mechanically simpler and well suited to laboratory-scale formulation development due to their ease of control and maintenance, rotary presses enable high-throughput continuous manufacturing and integration with automated feeding, monitoring, and ejection systems (Palmieri et al., 2005). These mechanical differences influence not only production capacity but can also the compaction dynamics and final tablet quality.

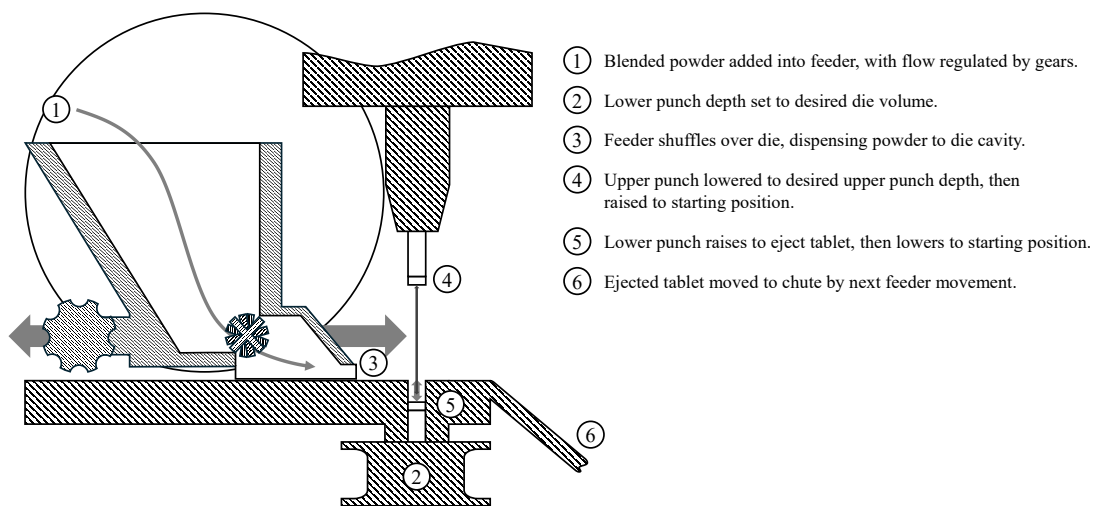


Figure 2.2: A simplified illustration of a single punch eccentric tablet press for manufacturing directly compressed tablets. (Figure created by author).

The eccentric press represents the simplest mechanical configuration, comprising a feeder, die cavity, and upper and lower punches (Figure 2.2). During operation, the blended formulation is delivered to the feeder and used to fill the die cavity, with the lower punch position controlling the volume of powder and thus the tablet mass. Consistent die filling is critical to ensuring uniform tablet weight, with excess material removed through metering mechanisms where necessary. Compaction is initiated by

lowering the upper punch into the die cavity, compressing the powder bed between the punches to a specified force or punch depth. Following compression, the upper punch retracts and the lower punch rises to eject the formed tablet (Gerhardt, 2010; Natoli et al., 2017).

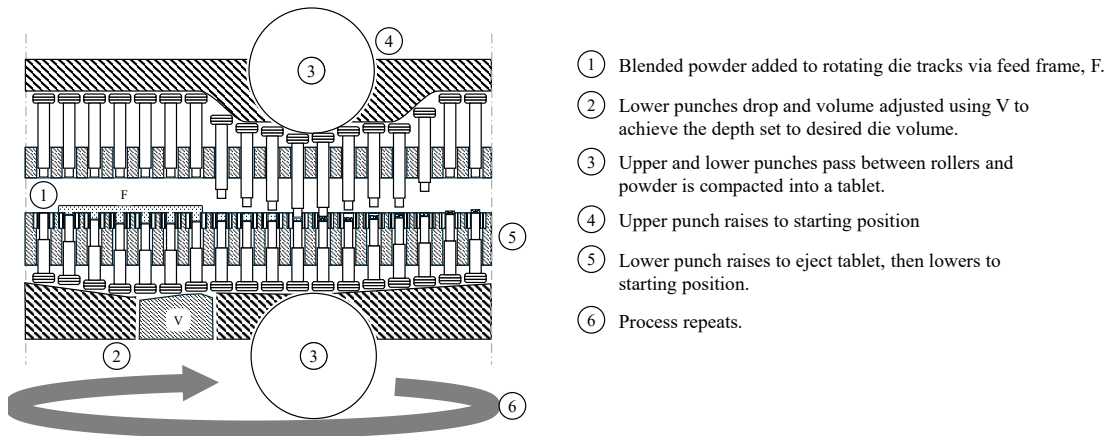


Figure 2.3: A simplified illustration of a rotary tablet press for manufacturing directly compressed tablets, referenced from (Aulton, 2017). Figure created by author)

Although eccentric presses are predominantly used in laboratory-scale studies (Bittorf et al., 2010), notable mechanical differences exist between eccentric and rotary presses, particularly in punch displacement profiles and dwell time. The increased dwell time characteristic of rotary presses has been shown to affect tablet properties and contribute to inconsistencies when scaling from pilot to manufacturing operations (Wünsch et al., 2020). Given the time-dependent viscoelastic behaviour governing some of the compaction mechanisms (Section 2.3), variations in displacement profiles can alter the compactability of ductile materials and increase the likelihood of defects such as lamination and capping during scale-up (Wünsch et al., 2020; Palmieri et al., 2005). To address these challenges, compaction simulators were developed to enable computer-controlled punch motion capable of replicating industrial press profiles within a single-station system (Aulton, 2017; Wünsch et al., 2020).

The tablet press configuration introduces several CPPs relevant to direct compression. Tooling design governs tablet diameter and geometry – including flat-faced, con-

vex, and complex shapes – which directly influences the stress distribution within the compact and susceptibility to mechanical defects (Natoli et al., 2017). Additional CPPs arise from punch positioning and compression profiles, providing control over tablet mass, porosity, and tensile strength through regulation of powder fill volume, applied force, and loading rate (Yu et al., 2014).

2.3 Mechanisms of Direct Compression

The consolidation of a loose powder into a tablet involves a number of mechanisms which are driven by the application of a compaction force to the powder within a confined volume (Buckton, 2016). These mechanisms (depicted in Figure 2.4) can be separated into those which define the compression and compaction behaviours.

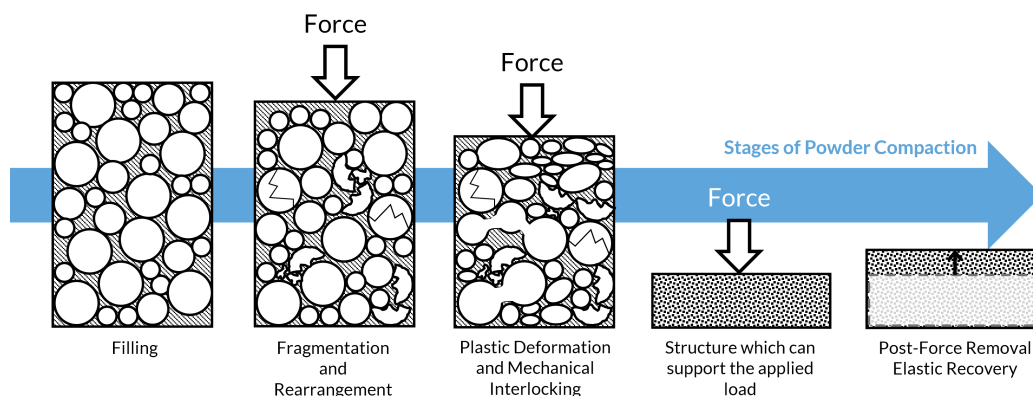


Figure 2.4: A schematic showing the compression behaviours as separate stages throughout the process. The elastic recovery is constrained to one direction in two-dimensional space where realistically it will relax in three-dimensions, both upon punch removal (immediate recovery) and after ejection (extended recovery).

Prior to compression, as the powder is added into the die, the particles will fill the volume gravimetrically (i.e. acting purely under the force of gravity) with the smaller particles percolating through those which are larger where they can, rearranging themselves into a settled state.

The compression process is then initiated with the application of a compaction force from the upper punch into the filled die. As pressure is introduced to the system,

the particles will undergo interparticular slippage which would allow the particles to achieve a closer packing. As the pressure increases, the particles may achieve a closer-packing through changes in either their shape via elastic or plastic deformation or their size via fragmentation into smaller discrete particles (Russell et al., 2022; Aulton, 2017). These mechanisms depend on the mechanical and structural properties of the materials (such as the particle size and shape, and the yield stress) as well as the processing parameter of the compression force.

Elastic deformation – which is dominant at lower compression forces and in materials with high elastic moduli – is reversible and occurs when the stored mechanical energy is released upon the removal of the external force, allowing the particle to recover, or partially recover, to its original shape. If this form of deformation is excessively present in a tablet, then the elastic recovery may overcome the particle-particle bonds resulting in defects. In contrast, plastic deformation involves the irreversible change in shape once the applied stress exceeds the materials yield stress. This form increases the interparticle contact area and promotes particle-particle bonding to increase the tensile strength. Fragmentation – which is dominant in brittle materials – occurs when the compression force exceeds the materials fracture strength. This process increases the number of smaller particles and fresh surfaces available for bonding to increase tensile strength.

Compression will continue until a point where a structure is developed which can support the applied load, and no further volume reduction is experienced (Aulton, 2017; Wünsch et al., 2021; Cooper and Eaton, 1962; Leuenberger and Rohera, 1986).

The compaction process comprises of two key mechanisms which increase the mechanical strength of the formed compact: attractions between solid particles and the formation of solid bridges (Leuenberger and Rohera, 1986; Wu et al., 2006; Buckton, 2016; Adolfsson et al., 1997; Fischmeiseter, 1982; Russell et al., 2022). Attractive interfacial forces contribute to a tablets tensile strength through the process of adsorption. As the compression process evolves, the particles undergo

an increasing degree of deformation and fragmentations to create a greater contact area between particles. Across this contact area, intermolecular forces like hydrogen bonding and Van der Waals arise forming multiple particle-particle bonds. A solid bridge occurs when two solids form a continuous phase due to the high stresses at localised contact points. These regions of extreme pressure, combined with the heat due to friction, is sufficient to cause the melting to occur. Once the pressure is removed, these surfaces return to their crystalline state. This process will occur throughout the reduced volume, forming a structured network which gives the tablet its strength (Buckton, 2016; Aulton, 2017).

Upon removal of the compression force, if the stored elastic energy is sufficient to overcome the energy of adhesion between the particles at the contact interfaces, an increase in volume will be observed, termed ‘elastic recovery’. The extent and rate at which this is present is dependent on the material properties of the formulation as well as the conditions at which the tablets are stored at (Picker, 2001).

These mechanisms are highly dependent on the CMAs, and unlike the CPPs these attributes that are not constant but exist as distributions (particle size and shape) or are defined at the microscale (cohesive and adhesive properties, electrostatic properties, plasticity, elasticity, brittleness). This is further complicated as tablet formulations consist of multiple components which provide their own unique distribution of properties. This presents an important challenge of determining, and modelling how these mechanisms are influenced when processing multiple, distinct components.

2.4 Mathematical Modelling Approaches

Mathematical models are used to create representations of systems to understand, analyse and predict its behaviours. Generally, the creation of a model requires the observation of the behaviours to identify the key variables which control them. These variables are then used to construct equations or relationships which can then be tested and validated using relevant data (Yang, 2017; Pekker-Friedman, 2025). Once established, these models can be used to help decision-making, develop and explore scientific principles,

communicate knowledge and make predictions of a physical system. In a manufacturing capacity, these models have been used to support planning and design, to optimise processes and to establish monitoring and control to mitigate risks (Fisher et al., 2020). Depending on the level of prior knowledge about said system, such as the underlying physics, these models can be subdivided into three different categories: knowledge-driven, data-driven, hybrid (which is a balanced combination of the prior) or empirical (Destro and Barolo, 2022).

Knowledge-driven models seek to use the underlying mechanistic understanding of a system to create a mathematical understanding of said systems behaviours. These models often rely on first-principle understandings of the conservation of mass, energy and force to translate into mathematical equations with parameters of physical definitions which take variables as inputs and outputs (Djuris, 2024). Some classic examples of this category include Navier-Stokes equations which govern fluid motion, and the heat equation which describes the heat transfer through the conservation of energy (Bird et al., 2002). Although these models provide descriptions of physical systems, solutions can be difficult to obtain for real systems. Real systems typically give rise to nonlinear differential equations in both spatial and temporal dimensions and are subject to complex initial and boundary conditions. This mathematical complexity can be addressed through the use of numerical techniques to break down the system in order to obtain approximate solutions, which forms the basis of computational modelling approaches such as:

- Discrete-Element Method (DEM),
- Finite Element Method (FEM) ,
- Population Balance Models (PBM), and
- Computational Fluid Dynamics (CFD)

Depending on the complexity of the system to be modelled, deriving the corresponding equations can be challenging, particularly when the underlying physics is not fully understood. Once developed, these models can often be used reliably to extrapolate results *in-silico*, without requiring extensive experimental data.

However, some models can also be computationally demanding to run at relevant length- and time-scales, which may limit their practical applicability. Additionally, if the physics is incompletely captured, predictions may still be unreliable or unrealistic.

Data-driven models seek to represent system behaviour directly from available data, without relying explicitly on underlying physical mechanisms. These models establish mathematical relationships between input and output variables, where parameters typically do not have direct physical meaning, although interpretability may be possible for simpler systems (Djuris, 2024; Tsialiamanis, 2022). Data-driven models are particularly useful when the governing physics is poorly understood, highly nonlinear, or too complex to model mechanistically. They are often faster to develop than knowledge-driven models and can capture subtle patterns and correlations in high-dimensional data. However, they generally require larger volumes of high-quality data to train effectively and may perform poorly when extrapolating beyond the range of observed conditions (Destro and Barolo, 2022; Djuris, 2024): Examples of data-driven modelling approaches include:

- Regression models,
- Multivariate models,
- Neural Networks, and
- Probability based models (Djuris, 2024; Destro and Barolo, 2022).

The application of these models has increased in manufacturing through the rise in cyber-physical systems and smart factories which can expedite the consistent collection of high-quality, structured datasets (Fisher et al., 2020). A key challenge with this category rests with the adequate training of the models to ensure that the model is generalised and has not been overfitted. The generalisation of the model defines the capability of a data-driven model to fit and make predictions using data which was not used to train the model. Overfitting occurs when a model learns not only the underlying patterns of the data but also from the errors in the training dataset, causing it to perform well for the training but not for

new data (Fisher et al., 2020; Montesinos-López et al., 2022). This is common when datasets are small, but can be addressed by increasing the sample size or by running cross-validation (Montesinos-López et al., 2022).

Hybrid models combine knowledge-driven and data-driven approaches within a single framework. A prominent example in pharmaceutical sciences is physiologically-based pharmacokinetic (PBPK) modeling, where mechanistic representations of absorption, distribution, metabolism, and excretion are integrated with data-driven adjustments from experimental or clinical datasets. This hybrid approach improves predictive performance across populations, supports dose selection, and aids the translation of preclinical findings to clinical scenarios (Habiballah and Reisfeld, 2023; Sayama et al., 2013).

Empirical models are based on fitting experimental observations to functional forms, such as linear, polynomial, or logarithmic equations. Unlike knowledge-driven models, empirical models do not require a mechanistic understanding of the system, but their pre-defined functional form can limit adaptability compared to flexible data-driven models. Their parameters are typically determined by regression or curve-fitting techniques and generally do not have direct physical meaning. Empirical models are often simpler to develop and require fewer data points than complex data-driven models, but they may perform poorly when extrapolating beyond the experimental range or when system behaviour changes under new conditions (Spanos, 1999). This approach assumes that the available data are of sufficient quantity and quality to define the system, and it has been widely applied in process manufacturing. Its popularity continues to grow due to the increased capabilities offered by modern computational methods (Fisher et al., 2020).

The selection of an appropriate modelling approach will depend on a case-by-case basis, governed by: the aim of the model, the level of understanding of the system of interest, as well as the availability of resources, high-quality data and the capabilities with regards to modelling expertise (Djuris, 2024; Destro and Barolo, 2022; Fisher et al., 2020). A survey from Destro and Barolo (2022) reported that statistical and data-driven

models were more readily applied to pharmaceutical industry operations compared to knowledge-driven due to their relative simplicity of development. Despite this, the knowledge-driven models were recognised by participants for their superiority in process understanding and extrapolation capabilities. The article also highlighted the growing interest for knowledge-driven and hybrid models within the QbD frameworks. Among pharmaceutical unit operations, powder compression presents unique modelling challenges arising from complex particulate behaviour and formulation-dependent responses. Consequently, the highly nonlinear and multiscale nature of particulate compaction complicates the development of fully mechanistic knowledge-driven models, while the large number of interacting formulation and process variables can limit the feasibility of purely data-driven approaches due to the extensive experimentation required to adequately characterise the design space. As a result, empirical modelling strategies have gained popularity as a pragmatic balance between physical insight, data requirements, and predictive capability.

2.5 Modelling Compression and Compaction

Before delving into the intricacies of modelling compression and compaction, it is important to first differentiate between the processes of compression and compaction and understand how they cooperate in the direct compression of powders. The compressibility of a powder describes the ability of the system to reduce its volume when under pressure, this is typically defined by a reduction in the relative density or porosity; where porosity is a measure of void space, and is estimated as the ratio of the volume of pore space to the whole volume of a mass. The compactability of a powder describes the ability of a system to be compressed into a reduced volume of specified mechanical strength, which is commonly quantified using the radial tensile strength of the resulting tablet (Reynolds et al., 2017). In practice, tensile strength is calculated from the tablet crushing force (often referred to as tablet hardness) measured during diametral compression testing. Tensile strength represents the maximum tensile stress that a compact can withstand before fracture and is therefore a more appropriate, geometry-independent descriptor of compactability (Leuenberger, 1982). It should be noted that this definition

of tablet hardness differs from indentation hardness, which characterises local resistance to plastic deformation and is typically used to infer intrinsic material properties. These mechanisms, though defined separately are not so easily separated physically. They occur simultaneously and are influenced by a complex web that connects them to material attributes, compression equipment specifications and process conditions making them challenging to model.

Commonly, previous modelling approaches for powder compression and compaction have focussed on describing the microscale behaviours mechanisms using macroscale approaches. Capitalising on the computational advancements in numerical simulation, there is the opportunity to integrate microscopic information of particle-particle interactions to explore the microstructural changes during compaction using DEM and FEM (Russell et al., 2022; Li et al., 2025). DEM considers the motion and interactions of individual particles through the application of Newton’s Second Law of Motion which relates the acceleration of an object to the force acting upon it. Depending on the assumptions applied to the model, the particles can be treated as discrete hard or elastic objects to simulate the microscopic behaviours of particles. This method, however, requires the reduction of the numbers of particles in a system, as well as the application of very general assumptions with regards to particle geometries and the symmetry of particle interactions to reduce the computational power and time required for simulations (Zunker et al., 2025). FEM can help to reduce this complexity through breaking the studied domain into finite elements. This approach seeks to solve partial derivative equations which describes some characteristic behaviour for each element, and assembles them to better understand how they vary over the entire domain (Russell et al., 2022). Most commonly, this method is used for simulating the macroscale compaction process through solving stress-strain patterns in powder mechanics which has proven to be useful in understanding tablet failure mechanisms and the effects of punch geometries on tensile strength (Li et al., 2025). Whilst there have been significant developments in the use of FEM models in the design of the tableting process, the quantity of experimental data required to parameterize them is significant. A recent study by van der Haven et al. (2022) sought to combine FEM modelling approaches with the underlying physics

to reduce this data dependency. This work was inspired by that of Queiroz et al. (2019), Wu et al. (2005, 2006), and Reynolds et al. (2017) who applied percolation theory and volumetric mixing rules to estimate pure component contributions to a blends compression and compaction behaviours. van der Haven’s work aimed to tailor these methods by considering the stress distributions within the tablet rather than considering only the bulk deformations as dictated by the macroscale empirical models.

The methods described could play a pivotal role in developing predictive methodologies for understanding powder compression and compaction, particularly in the detection of defects; however, due to their computational complexity, and the generalisation of their assumptions, DEM and FEM are not currently suitable to provide adequate real-time support for decision making in formulation science of component systems of more than two components.

2.5.1 Empirical Modelling Overview

A review from Sonnergaard (2001) highlighted that previous attempts to model the compression and compaction of powders has followed two contrasting routes: empirical and theoretical. The empirical expressions, being derived purely from the fitting of data to a curve, provide what they deemed an oversimplification of the complex mechanisms which frequently resulted in questioned interpretations of the fitting parameters. On the other hand, the theoretical investigations created complicated mathematical expressions where the parameters have limited practical relevance to the formulation of pharmaceuticals and quality control. Based on the multivariate nature of powder compaction, it would not be reasonable to use the traditional QbD approach to explore the high-dimensionality of direct-compression formulation spaces. Further, Sonnergaard (2001) emphasised that the traditional empirical expressions faced limitations in their creation which, with the available computing power at present, should no longer be a factor in the development and analysis of models. A successful model should be built with parameters of physical relevance to the powder properties which are sensitive to changes in formulation and process variables.

The particle behaviour and interactions during the compression and compaction

process is a well-disputed topic in this field of research, with an extensive number of empirical and mathematical modelling approaches being considered by researchers from a collection of disciplines (Athy, 1930; Cooper and Eaton, 1962; Gurnham and Masson, 1946; Heckel, 1962; Kawakita and Tsutsumi, 1966; Leuenberger and Rohera, 1986; Ryshkewitch, 1953; Sonnergaard, 2001; Walker, 1923; Zhao et al., 2006). Despite this, there has been no firm conclusion for which a model can accurately capture these processes in their entirety. Instead – at least within the scope of the investigations covered by this project – researchers have attempted to break down the compression and compaction processes for single, binary or multi-component systems by interpreting what they postulate to be a model which provides an adequate balance between goodness of fit (GoF) and simplicity. However, upon this simplification, there exists cited variations regarding the reliability of fit, the definitions of fitting parameters, and the interpretation of results. The reasoning behind these inconsistencies has not been confidently defined or proven quantitatively in the literature considered. Therefore, no certain decision could be made based on literature for selecting a model to apply when predicting the behaviours of the powders to be compacted by studies prior to this project.

A substantial quantity of models exist, this review will focus on the models which have been more popular in the field under the assumption that this correlates to their improved predictability for these phenomena compared to the less established models. The review will follow a structure which will first introduce the models and how they were founded and then aims to discuss their predictability of the mechanisms which they describe.

The models considered in this review, summarised in Table 2.2, describe the compression or compaction process by using empirical models to fit porosity (or volume reduction) and compression pressure or tensile strength and porosity data respectively; with the exception of a probability-based mathematical model which is briefly mentioned for an additional perspective. The fitting equations tend to offer two fitting parameters in which the authors have attempted to relate to some description of the powders physical attributes or behaviours during compression.

These models date back to the 1930s and have been scrutinised by generations of aca-

demics and researchers (Athy, 1930; Cooper and Eaton, 1962; Gurnham and Masson, 1946; Heckel, 1961; Kawakita and Tsutsumi, 1966; Nordström et al., 2008a; Sonnergaard, 1999; Uniyal et al., 2020; Vreeman and Sun, 2021), with the main controversies surrounding these models being:

- the physical definitions of the fitting parameters;
- the ability for a simple expression being able to capture the entirety of the processes complexity;
- the ranges of applicability with respect to the independent variables;
- whether the information offered has any practical relevance to the formulation of pharmaceutical products.

Further, these models were initially developed on non-pharmaceutical materials such as metals, ceramics and even fibrous organic material. When these were then applied to formulation development, there has not been any notable adaptation found which accounts for the differences in material properties or processing parameters. This becomes particularly relevant when considering the previous comment regarding the compactability as a function of the material surface interactions. This is emphasised by some of the models not having the capability to differentiate between materials of different physical or mechanical properties.

By grouping the materials rather than identifying them based on their individual qualities, such as particle size, there is scope for potentially erroneous generalisations of results. An evaluation of whether the fitting results change with different grades of a material and whether this is correlated to specific material attributes is of import, however no literature was found supporting this statement.

Table 2.2: A summary of the compression and compaction models considered.

Model	Year	Equation	Parameter Definitions
Heckel	1961	$\varepsilon(P) = e^{-(K_H P + C)}$	K_H : Mean/Apparent Yield Pressure (out-of-/in-die) C : Constant
Kawakita	1965	$C(P) = \frac{V_0 - V}{V_0} \approx \frac{abP}{1 + bP}$	a : Maximum achievable volume reduction b : Constant
Cooper-Eaton	1962	$\dot{V}(P) = a_1 e^{-k_1/P} + a_2 e^{-k_2/P}$	k_i : Pressure magnitude at max. of PDF a_i : Fraction of compression behavior
Walker	1923	$V = C - W \log(P)$	C : Constant W : Change in volume with $\log(P)$
Sonnergaard	2001	$V(P) = (V_1 - w \log P) + V_e e^{-P/P_m}$	V_1 : Volume at 1 MPa w : Change in volume with $\log(P)$ V_e : Volume at zero pressure P_m : Mean pressure value
Athy	1930	$\varepsilon = \varepsilon_s e^{-bz}$	ε_s : Average porosity of surface clays b : Constant
Gurnham	1946	$\varepsilon(P) = -\frac{1}{K_G} \ln\left(\frac{P}{P_0}\right)$	K_G : Compressibility resistance P_0 : Pressure required to achieve zero porosity
Ryshkewitch	1953	$\sigma(\varepsilon) = \sigma_0 e^{-k_b \varepsilon}$	σ_0 : Tensile strength at zero porosity k_b : Bonding capacity
Leuenberger	2000	$\sigma(P, \varepsilon) = \sigma_{\max}(1 - e^{-\gamma P(1-\varepsilon)})$	$\sigma_{\max}$: Max deformation hardness at zero porosity γ : Compressibility resistance

2.5.2 Compression Models

Heckel

As the most used model in the considered literature, Heckel considered the concept of compressibility and highlighted that a predictive solution was required to tackle the extensive time and material requirements to complete this type of investigation. Heckel sought out to understand the relationship between compression pressure and powder density through the single punch compression of metal powders using a Baldwin tension-test machine (Heckel, 1961). By using the punch dimensions and movements to measure the reduction in volume of a known mass of powder as a function of pressure (10,000 – 120,000 psi), Heckel could calculate the in- and out-of-die density -pressure relationship. From their analysis, they considered the compression of powders to be comparable to a first-order chemical reaction, where the porosity and densification replaced the reactant concentration and kinetics respectively, Equation 2.1. This was then reduced mathematically to present an expression which could be plotted and used for predicting the porosity of a compact as a function of the compression pressure, Equation 4.11, which is the linearised form that has been commonly used.

$$\frac{d\varepsilon}{dP} = K_H \varepsilon \quad (2.1)$$

$$\varepsilon(P) = \exp(-(K_H P + C)) \quad (2.2)$$

Where ε is the porosity of the compact, K_H is the proportionality constant, P is the compression pressure, and C is a constant to be estimated from the fitting of data. Heckel found this equation to provide good predictability over medium to high pressure ranges (25,000 – 120,000 psi), but found qualitatively that the curve present in the lower pressure range limited overall predictive accuracy for this model.

Both the plots of porosity as a function of compression pressure obtained and the definitions of K_H and C from Heckel's analysis have been inspected in the literature. With the plots, discussion has been centred around what the observed change in K_H , the curve in the lower pressure region, represents and its impact on prediction accuracy. By carrying out this investigation, Heckel found that materials which were brittle and densified mainly by crushing were less likely to have linear regions within the porosity versus compression pressure plots and offered mainly a curved relationship over the considered pressure range. From this, the authors concluded that the curves at lower pressure regions may represent the extent of particle rearrangement observed. This has been supported by Klevan et al. (2009) where they considered the qualitative extension of the Heckel plots by Shapiro (1994) which splits the plots into three regions, representing rearrangement and/or fragmentation, deformation, and elastic recovery. However, the discussion of increasing the practical relevance rests with the definitions of the fitting parameters and their ability to quantitatively capture information about the compression process.

Heckel originally defined C as a representation of the degree of packing achieved by rearrangement at low pressures, which is a function of the materials shape and size; this definition has been widely accepted within the literature. As for the proportionality constant, K_H , this was defined as a measure of the materials ability to undergo plastic deformation. An extended analysis of metal powder compression resulted in a later publication by Heckel (1962) where they redefined K_H as being related to the nominal yield strength of the material, σ_0 , Equation 2.3. For in-die analysis, this was deemed equivalent to the apparent yield pressure, P_y , and then mean yield pressure for out-of-die

analysis.

$$K \approx \frac{1}{3\sigma_0} \quad (2.3)$$

This opens an interesting – and new at the time – conversation whereby the fitting parameters of these models may provide quantitative understanding of the compression and compaction process. In saying this, the definitions were not universally accepted (Kuentz and Leuenberger, 1999; Sonnergaard, 1999; Vreeman and Sun, 2021; Zhang et al., 2017).

Kawakita

The work of Kawakita is prominent in the field of compression, not just for their model, but also their comparative evaluation of the different compression models available in the 1960s; although, this comparison did not include the Heckel or Gurnham model. Kawakita et al. (1965) found that when compressing spherical glass particles over a pressure range, the relationship between porosity and pressure was generally represented by Equation 2.4.

$$-\frac{d\varepsilon}{dP} = k\varepsilon^2 \quad (2.4)$$

Where k is a proportionality constant. This investigation – similar to the extension of Heckel by Shapiro and Konopicky – also provided evidence of dominating, distinct behavioural stages in the compression process at different pressure ranges. Additionally, the authors suggested that particles of varying size would demonstrate these behaviours at different pressure ranges, with the breakage of smaller particles occurring at higher pressure as the observed general relationship followed: the larger the particle the larger the degree of rapid volume reduction at lower pressures. Further, when compressing a mixture of small and large particles, they could identify a limit with regards to the ratio of these particles and the identified dominating compression behaviour. This introduces the notion that these models, when applied to materials of different size, shape and material characteristics, may produce different results; also when considering

mixtures, there may be a way of quantitatively identifying limits for incompressible materials within a compressible mixture.

A later paper by Kawakita and Tsutsumi (1966) expanded their previously proposed relationship to create an empirical relationship for volume reduction which became popular in literature, Equation (5) (linearised in Equation (6)).

$$C = \frac{V_0 - V}{V_0} \approx \frac{abP}{1 + bP} \quad (2.5)$$

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \quad (2.6)$$

Where C is the fractional volume reduction (V defining the volume and the subscript 0 denoting the initial value), and a and b are fitting parameters.

Cooper & Eaton

It is accepted that the compression process consists of several distinct stages and therefore a simple expression may struggle to capture the mechanisms as a whole. Holman (1991) and Shapiro (1994) attempted to write expressions for the separate stages but with the knowledge that these are occurring simultaneously presented issues in the separation of said stages. The only model commonly cited in the literature that was capable of simultaneously capturing the compression mechanisms and presenting them as distinct stages, was that proposed by Cooper and Eaton (1962). Cooper and Eaton investigated the compression of four ceramic powders of varied hardness. They mathematically analysed the compression process of their system as the “filling of pores”, which are either smaller or of the same size as the particle. They deemed that compression would happen either by the rearrangement of particles (filling the larger holes) or by the fracturing of particles to fill the smaller holes. Due to the disordered nature of powders and ‘holes’, a distribution of pressures would be required to fill these; for this, Cooper and Eaton applied a probabilistic approach. They related the ratio of change in the fraction of filled holes and the incremental increase in pressure required for this change to the probability density of hole filling. It was deemed unrealistic to build a

detailed understanding of these factors, so they applied a simple function of pressure for the probability density, PD , which was easy to integrate, Equation 2.7.

$$PD \equiv \frac{1}{N_{i,\infty}} \frac{dN_i}{dP} = \frac{k_i}{P^2} \exp\left(-\frac{k_i}{P}\right) \quad (2.7)$$

Where N_i is the number of large or small holes which have been filled, $N_{i,\infty}$ is the total available number of large or small holes filled at infinite pressure, and k_i is a constant with dimensions of pressure.

By representing the filling of large and small holes, the authors reached their expression for fractional volume reduction, $\dot{V}$ as a function of pressure, Equation 2.8.

$$\dot{V} = a_1 \exp\left(-\frac{k_1}{P}\right) + a_2 \exp\left(-\frac{k_2}{P}\right) \quad (2.8)$$

Where k_i indicates the magnitude of pressure where the process' probability density function is at its maximum, and the dimensionless coefficients, a_i , represent the fraction of theoretical compression that would be achieved at infinite pressure; for the sum of a_i to be unity, the expression is fully defined by these individual processes. Their generalisation does not account for, but also does not explicitly neglect, the deformation behaviours as this could be represented by an additional expression. This model still stands as found by Uniyal et al. (2020), yet this model yields no quantitative information relevant for pharmaceutical applications and was suggested for qualitative use only to better understand the contribution of different compression mechanisms.

Walker

Walker studied the bulk density, compressibility and flowability of powders due to growing interest in the use of machine packing in the chemical industry in the early 1900s. Part of this investigation focussed on two methods of determining the compression resistance of powders by, first, applying a static load, and then, by impact (Walker, 1923). For each case, a measured mass of powdered metals or salts were placed in a steel cylinder and a compression force of increasing magnitude was applied to these powders either using a hand operated plunger (static) or by dropping weights of increas-

ing mass at a fixed height (impact). The volume of powder after each application of compression pressure was measured. The plotted results for fraction volume reduction, V , and compression pressure, P , offers a straight line for a majority of the data, with asymptotic relationships at the initial and final pressure conditions; this was true for both investigations. Although not explicitly stated by Walker to be an equation for the prediction of powder behaviour, Equation 2.9, has been cited as Walker's model of powder compression by several found sources (Balshin, 1938; Kawakita and Tsutsumi, 1966; Sonnergaard, 1999).

$$V = C - W \log(P) \quad (2.9)$$

Where W is the change in volume when the pressure is changed by a factor of 10, and C is a constant to be estimated from the data.

Sonnergaard

There was doubt concerning whether such a simple expression as Heckel's would be sufficient, and Sonnergaard (1999) provided a critical evaluation of the Heckel equation by summarising the differences in published parameters between authors and from their own investigation which used an in-die method. Through this they questioned the concept of the yield pressures obtained from Heckel slopes and compared the applicability of Heckel's equation to the less cited, Walker equation. It was this, along with Cooper and Eaton's approach of splitting the expression by the processes to investigate them simultaneously, that Sonnergaard proposed using non-linear regression techniques to form their expression for powder compression. Equation 2.10.

$$V = (V_1 - w \log(P)) + V_e \exp\left(-\frac{P}{P_m}\right) \quad (2.10)$$

Where V is the relative volume, w is a fitting parameter which represents the fractional logarithmic change in volume, P is the compression pressure (MPa), V_1 is the volume at 1 MPa, V_e is the volume at zero pressure, and P_m is the mean value of pressure. The motivation for this model was to provide a quantitative definition of a

materials brittle or plastic nature. The bracketed term represents a modified version of Walkers' investigation for the volume reduction. This expression displays the reduction by fragmentation as an empirical logarithmic decay. The second term is the density distribution of the statistical exponential distribution similar to the expression observed in Cooper and Eaton's model to provide a – though confessed to be over-simplified – consideration to the apparent plastic deformation through the exponential decay.

Athy

Athy provided a laboratory method to determine the bulk density and porosity of sedimentary rocks to quantitatively address their importance in the development of structure in geology. This was the earliest instance found in which the prediction of compressibility was investigated. By studying the density of materials found at different levels of burial in the Earth, the porosity could be calculated and plotted as a function of burial depth, Equation 2.11, (Athy, 1930)

$$\varepsilon = \varepsilon_s \exp(-bz) \quad (2.11)$$

Where ε is the average porosity of surface clays, z is the burial depth, and b is a constant. This was later considered for powder compression by Kawakita and Tsutsumi (1966) where they replaced z , for the compression pressure, P , and compared this expression to other's available at the time.

Gurnham

Gurnham and Masson (1946) considered the pressing of liquids from fibrous synthetic material. Despite several industries using compression in their manufacturing, the authors noticed that there was a lack of work in this field and they set out with the aim to form a general expression using data from different industries which could be applied to all materials. They mentioned that their choice to study the compression of fibrous materials was due to early attempts which considered granular solids offered “unsatisfactory” results with regards to control and reproducibility. So, the difficulties with

understanding the compression behaviour of powders dated back to some of the earliest research available.

Materials were pressed with a manual, gauge-driven laboratory press and the volume of material to be compressed was measured as the volume of the test cylinder at the height of mass in question. Pressure was applied to the materials (paper pulp, sawdust, woollen yarn, cotton, woollen felt, and asbestos fibre) until a constant volume was achieved, and then until maximum available pressure was achieved. By relating the reduction of volume to the compression pressure, the authors found that Equation 2.12 was followed.

$$\log(P) = a + \frac{b}{V} \quad (2.12)$$

They found this expression to give a close fit for most materials, however for the lower and higher end of the pressure range there was notable deviation which they respectively attributed to compression behaviours occurring simultaneously and also to solid deformation. There was no effort made to assign physical definitions to the fitting parameters until Zhao et al. (2006) revisited the Gurnham equation. They based their work on the research conducted by Sonnergaard (2001) which found that the alternative compression models provided consistent limitations when estimating the compressibility and predicting the compression behaviour of pharmaceutical powders. By revisiting Gurnham's equation, slight adaptations were made to introduce a new parameter which proposed the slope of the line to represent the materials compressibility. A further amendment was found to be made by Reynolds et al. (2017), where they defined one of the parameters to represent the pressure required to produce a tablet with zero porosity to reduce the impact of the inaccuracy of the lower porosities. The amended Gurnham equation which is now used widely in the field of predicting compression of pharmaceuticals is shown in Equation 4.10.

$$\varepsilon(P) = -\frac{1}{K_G} \ln\left(\frac{P}{P_0}\right) \quad (2.13)$$

Where, ε , is the porosity of the compact, P is the compression pressure, K_G is related

to the resistance to compression, P_0 is the pressure required to reach zero porosity. This expression has been shown to offer a good representation for the compression of a wide range of pharmaceutical powders, particularly in pressure ranges relevant to tableting. The most beneficial argument for the use of Gurnham's equation is that it has been able to capture the behaviours of granulations and multicomponent mixtures (Reynolds et al., 2017; Jolliffe et al., 2022; Corrigan et al., 2024).

2.5.3 Compaction Models

Ryshkewitch-Duckworth

The developed understanding of compaction was less controversial than that of compression. The first instance of compaction prediction found was carried out on porous sintered ceramics by Ryshkewitch (1953) which was soon to be commented on and modified that same year by Duckworth (1953). The Ryshkewitch-Duckworth model was developed to consider the balance between a construction materials weight and strength through an investigation of the influence of controlled porosity. It was found that low porosity samples would show negligible physical change during compression and would then reach a point in which the sample 'explosively' disintegrated. When the porosity of samples was increased and plotted against the compression strength of the samples, a gradual compaction profile could be observed. Duckworth then progressed this investigation by affirming the methods and results by comparing their work to Battelle who utilised a different compression test method for a similar study. They then went on to conclude that from both investigations, that the relation between tensile strength and porosity could be predicted using an exponential model, Equation 2.14.

$$\sigma = \sigma_0 \exp(-B\varepsilon) \quad (2.14)$$

Where σ represents the strength of the porosity compact and the subscript 0 is the strength of the same material at zero porosity. B was defined to represent the curve of the plotted data. The fitting parameters were later better defined by Wu et al. (2005) who applied the model to pharmaceutical mixtures, to give the model which is used to

date, Equation 2.15.

$$\sigma = \sigma_0 \exp(-k_b \varepsilon) \quad (2.15)$$

Where the definition of σ and σ_0 was agreed upon and they introduced a definition for the gradient of the curve to be k_b which was deemed to represent the materials bonding capacity. This model is still widely accepted today due to its ability to describe the change in tensile strength with porosity for a number of materials.

Leuenberger

Leuenberger (1982) identified that the aims of the models which were applied to pharmaceuticals were to define the compressibility of the materials, yet few went as far as to consider predicting the industrially relevant characteristic of compactability. Leuenberger published a theoretical approach, similar to that previously completed by Cooper & Eaton and Sonnergaard, to simultaneously quantify the compressibility and compactability of a powder system. Their model, Equation 2.16, assumed that the cross-sectional area of a compact is made up of bonding and non-bonding sites, with a compacts deformation hardness, σ , being proportional, γ , to the number of bonding sites, which changes with an externally applied compression force, P , and relative density, $(1-\varepsilon)$.

$$\sigma = \sigma_{max}(1 - \exp(-\gamma P(1 - \varepsilon))) \quad (2.16)$$

Where the fitting parameter, σ_{max} , the maximum deformation hardness of the compact at zero porosity, is achieved when applying boundary conditions of maximum deformation, and can be used to quantify compactability. The proportionality factor, γ , was termed the compression susceptibility as it indirectly described the volume reduction. Leuenberger and Rohera (1986) tested their formed expression – for which they found good predictability – against single and binary mixtures of common pharmaceutically-relevant materials, such as: aspirin, ibuprofen, and lactose.

It can be seen that Equation 2.16 of a similar form to Ryshkewitch-Duckworth,

Equation 2.15, with the difference that this model not only considers how the tensile strength changes with the porosity but also the compression pressure.

2.5.4 Discussion of Modelling Approaches

Heckel

Throughout the years, there has been doubt concerning whether such a simple expression would be sufficient in defining the complexity of powder compression. Sonnergaard (1999) provided a critical evaluation of the Heckel equation by summarising the differences between published Heckel parameters from their in-die method and other authors. Through this they questioned the concept of the yield pressures obtained from Heckel slopes and compared the applicability of Heckel's equation to the less established, Walker equation. One of the main arguments in this paper is that due to the mathematical transformations to achieve the Heckel equation, predictions are more sensitive to erroneous measurements than Walker's model. This may be the reason why Walker is able to offer better predictions in the lower pressure region; although, it should be noted that Heckel provides a better prediction in higher-pressure regions. A second argument is that Walkers' parameter, W , which defines the irreversible compressibility of the compact, may be of more reliability and relevance than Heckel's proposal of yield stress, K_H . This second argument becomes particularly prominent when the author compared the published parameters from both equations. Firstly, K_H provided similar values for different grades of microcrystalline cellulose (MCC) between authors; conversely, Walker's W was able to differentiate between the three unique forms.

Despite Sonnergaard showing that the Walker model could discriminate between materials and had higher reproducibility than the Heckel model, the Heckel model still dominated the literature comparatively. These drawbacks of the Heckel model were identified before Sonnergaard's investigation by Rue and Rees (1978); but in this case, the conclusion was that despite the apparent drawbacks, Heckel still offered some level of predictability. Rue and Rees stated that Heckel must be used with caution due to the impact that various independent variables may have on the results.

Yet, even with this evidence, Sonnergaard's findings were recently challenged by

Vreeman and Sun (2021) when they compared the in-die P_y with three established out-of-die plasticity parameters as defined by Heckel, Kuentz and Leuenberger (1999), and from results macro-indentation analysis conducted by the authors. Vreeman and Sun found strong correlations between the compared parameters and the powders plasticity and deemed Heckel analysis as an “excellent” method for not just prediction but also for evaluating the effects of compression speed, lubrication sensitivity, pressure, and tooling on the materials plasticity.

Kawakita

This was one of many models which had been created to describe the reduction in volume due to applied pressure, and each had their own fitting parameters, definitions and applied assumptions. Kawakita highlighted that these models had a similar but slightly different form and were applied to describe the behaviour of different materials, such as: ceramics, fibrous organic material, metals, and salts. Kawakita and Tsutsumi (1966) qualitatively evaluated each of these models, including their own, and their ability to predict the compression behaviours for metal, ceramic, and organic powders. They summarised that each of the models offered near consistent predictions across the materials but the Kawakita and Athy models were the only models which could be applied over all pressure ranges with Kawakita obtaining a better description in the lower pressure region. An argument of bias could be made for this investigation being carried out by Kawakita themselves; however, the authors did point out that the results from their model may be impacted considerably if erroneous initial volume measurements are used. This investigation supported the notion that these different models can all capture, to an extent, the compression behaviour of various materials; but difference in results was likely due to the models simplifying alternative aspects of compression which then captures different areas and magnitudes of complexity.

Despite this success for Kawakita’s model, there is one clear gap with this model compared to the others: the definitions of the fitting parameters a and b . Kawakita defined a as representing the limit of volume reduction at infinite compression, as their relation tends to a as pressure approaches infinity. Their definition of b is less clear.

Their initial evaluation supposed b to represent the resistant and cohesive forces of the particles which has not been readily accepted.

Adams and Mckeown (1996) conducted a micromechanical analysis which estimated Kawakita's b to represent the strength of a single agglomerate, after subjecting the expression to frictional constraints and extrapolations. Due to the depth considered in this investigation, the theory has not been considered any further for this review.

More generally, Nordström et al. (2008a) investigated four materials of differing mechanical strength and found that a indeed offered an acceptable approximation of the total degree of compression. This was then compared to the Young's modulus which resulted in a near linear relationship further agreeing with their hypothesis that this parameter can describe the materials plasticity; although it should be noted that this conclusion was based on four data points. Nordström's study agreed both with Kawakita's definition of a and Adams' analysis of Kawakita's model, but summarised that there was still no confidence in their definition of fitting parameter, b ; although, they speculated that this does seem to capture some meaning. Potentially, b offers a reflection of a materials fracturing failure, as it differs from material to material, and somewhat describes the magnitude of pressure's effect on volume compression.

Sonnergaard

Sonnergaard (2001) compared their model to the Cooper and Eaton and the Kawakita models for 48 components. Through analysing the squared correlation coefficients and the standard deviations, they found that all the models could fit the data well with the Kawakita offering a slightly more limited range of applicability. There was a brief mention of the residuals being "random[ly] distributed", however based on their cited figure this conclusion was questioned as there appears to be random distribution around a trend of errors. Although, Sonnergaard's was the only investigation which included a statistical analysis of the proposed model.

The parameters from Sonnergaard's model provided more information about dominating compression mechanisms than the compared models and when considering different qualities of microcrystalline cellulose their model was able to provide unique results

between different grades of microcrystalline cellulose.

Ryshkewitch-Duckworth

The only discussion point which was questioned by the considered literature was that made by Pazesh et al. (2019) with regards to the ability for the Ryshkewitch-Duckworth model to predict the behaviours of disordered powders. Pazesh et al. applied this model to a series of powders with different degrees of disorder. They found that the powders with the highest degree of disorder displayed behaviours which deviated markedly to that of crystalline powders, which was the basis for the widely accepted definition of the bonding capacity, k_b (Steendam and Lerk, 1998; Wu et al., 2005, 2006).

When applying the model to their results, the crystalline powders offered linearity in agreement to literature but the disordered powders offered a plateau over a range of porosities. Pazesh et al. attributed this to the increased plasticity and fracture behaviour which they expected was to be observed in the disordered particles. This brings another aspect of inconsistency to these models universal applicability surrounding the material's form, which is of particular relevance to pharmaceuticals.

Leuenberger

Further investigations into Leuenberger's definition of compression susceptibility within their tablet hardness models was conducted by Kuentz and Leuenberger (1999). This linked back to the previous discussions in which a critical point in compression pressure, porosity, or material ratios exists which determines dominating behaviours in the compression process. Heckel defined a pressure where rearrangement would be dominated by deformation; Kawakita defined a ratio of small and large glass particles which would control the compression behaviours; and Ryshkewitch-Duckworth noted a limit for porosity in which the compression would be negligible until a compact would disintegrate rapidly and aggressively.

Kuentz and Leuenberger highlighted that the most-cited compression models make an approximation of uniformly shrinking pores throughout the compression of a powder (Cooper and Eaton, 1962; Heckel, 1961; Leuenberger, 1982). However, with the under-

standing that the initial stages of compression is dominated by particle rearrangement, it would be expected that a small increase in the compression pressure would result in larger reductions in porosity compared to the final stages of compression. Due to this concept, specifically Leuenberger's compression susceptibility, γ , and Heckel's proportionality constant, K_H , should not be a constant over the entirety of compression, and should instead be represented as a differential function of the compact porosity, Equation 2.17.

$$\frac{d\rho}{dP} = \chi_P(1 - \rho) \quad (2.17)$$

The relation to Heckel's K_H can be observed when the system reaches steady state, where this becomes equal to χ_P , the pressure susceptibility. Implementing Equation 2.17, it is expected that χ_P would take high values for rearrangement dominated behaviour, and once a structure of rigidity is formed within the compact – at a threshold relative density or porosity – this parameter would gain relevance. This concept was then applied to modify Heckel's relation, Equation 2.1, and produced a new model which highlighted the critical relative density threshold, ρ_c , Equation 2.18.

$$P = \frac{1}{C}[\rho_c - \rho - (1 - \rho_c) \ln(\frac{1 - \rho}{1 - \rho_c})] \quad (2.18)$$

Where C is a constant to be defined from the data, said to be proportional to the degree of particle packing. Upon validating this equation by studying the compression of polymers, it was found that applying Equation 2.18 resulted in “superior” results compared to assuming constant pressure susceptibility based on a comparison of achieved squared-correlation coefficients.

By working through Leuenberger's original theoretical approach but instead substituting in Heckel's equation – in differential form – to define the change in relative density with pressure, Kuentz and Leuenberger (2000a) defined a new model for tablet hardness, Equation 2.19.

$$\sigma = \sigma_{max}[\varepsilon - \varepsilon_c - \ln(\frac{\varepsilon}{\varepsilon_c})] \quad (2.19)$$

The introduction of this new parameter for critical porosity, ε_c , is of particular industrial relevance. The critical porosity has been defined as the largest porosity that can initiate the strengthening process of tablets. Knowing this value could act as a reference point for formulation scientists as the minimum requirement to form a structurally-sound tablet. This was not the first instance where some critical value for a variable was mentioned in the literature.

2.6 Mixture Models

Empirical modelling has been shown to effectively describe the compression and compaction behaviour of drug-loaded blends; however, its predictive capability is largely confined to the range of experimental conditions used to construct the model. Despite the commonality of this approach, the prediction of the behaviours for new mixtures of materials remains challenging without a clear understanding of the underlying physical phenomena or significant quantities of data. Whilst there may be the opportunity of machine learning models to traverse these large databases, in the instance where material consumption is a limiting factor, this is not a viable option. Therefore, simpler methods of compaction behaviour estimation and prediction is needed.

A proposed approach to reduce the experimental effort required to understand or predict the behaviour of new mixed systems is to estimate the contributions of individual components to the overall blend response. Basic averaging rules, such as the arithmetic, geometric, and harmonic means, are commonly used to describe heterogeneous systems. These averaging forms differ in their underlying assumptions regarding how constituent properties combine, namely whether contributions are additive (arithmetic), multiplicative (geometric), or governed by limiting behaviour (harmonic). These means can be expressed within a general framework of the form in Equation 2.20,

$$\bar{x} = f^{-1} \left(\sum_{i=1}^n w_i f(x_i) \right), \quad (2.20)$$

where x_i are the constituent properties, w_i are weighting factors (such as volume or mass fractions), and $\sum_{i=1}^n w_i = 1$. Different choices of the transformation function $f(\cdot)$

give rise to commonly used averaging operators and reflect different assumptions about how constituent properties combine to produce the overall system response (Nielsen, 2025).

When $f(x) = x$, the arithmetic mean is obtained,

$$\bar{x} = \sum_{i=1}^n w_i x_i, \quad (2.21)$$

which assumes that contributions from each constituent combine additively and independently.

Choosing $f(x) = \ln x$ leads to the geometric mean,

$$\bar{x} = \exp\left(\sum_{i=1}^n w_i \ln x_i\right) = \prod_{i=1}^n x_i^{w_i}, \quad (2.22)$$

which captures multiplicative interactions between constituents and is invariant under changes in scale. This averaging rule is often used for properties that span several orders of magnitude or for systems in which relative differences between constituents are more important than absolute values.

Alternatively, selecting $f(x) = 1/x$ yields the harmonic mean,

$$\bar{x} = \left(\sum_{i=1}^n \frac{w_i}{x_i}\right)^{-1}, \quad (2.23)$$

which emphasises the influence of smaller constituent values and reflects systems governed by limiting behaviour. In such cases, the overall response is constrained by the weakest or least effective component.

These laws go beyond describing a central value and instead reflect assumptions about how the components influence the overall behaviour by adjusting the choice of averaging operator and weighting scheme (Nielsen, 2025).

From the literature, mathematical averages (or mixture rules) have been applied in a range of disciplines to predict the properties of multiple component systems based on the known behaviour of their individual contributions. This provides a method of estimating how changes in a composition will influence overall performance without the

need for extensive experimental testing, making mixture rules a key tool for formulation or material design. Some examples of this include: estimating the heat capacity, density or viscosity of liquid mixtures in process design (Southard and Rowley, 2018); predicting the strength and conductivity (both thermal and electrical) in polymer and composite design (Progelhof et al., 2004; Clingerman et al., 2001); and also the prediction of density and flow behaviours (Salehian et al., 2024; Aroniada et al., 2023). Most of these examples rely on simple averaging methods under the assumption that behaviours are additive (i.e. the weighting of a contribution is simply defined by the ratio or volumetric contribution of the component). However, in some instances the contributions of the materials are non-linear or non-additive and demonstrate interactions which simple mixture rules cannot predict and more powerful, modern data-driven modelling techniques may be better applied (at the cost of a larger quantity of data). This assumption of additivity, though not always valid, can provide a reasonable first approximation which balances simplicity and understanding, which has proven to be the case with predicting tensile strength in tablet formulation design (Valekar and Buckner, 2025).

For the instance of the empirical modelling of direct compression: this approach would aim to estimate a material’s contribution to the behaviour of a blend by using a weighted average of the materials behaviours – as defined by the empirical model tuning parameters – on a volume fraction basis, ϕ_i (Figure 2.5) (Jolliffe et al., 2022; Reynolds et al., 2017). A majority of studies into the application of mixture models for pharmaceutical compression and compaction 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., 2008b; Sonnergaard, 2001, 2022; Wu et al., 2005, 2006; Zhao et al., 2006). These studies have provided a general understanding of pharmaceutical powder mixture compaction, however, the impact of drug loading has not been as extensively explored (Jolliffe et al., 2022; Kuentz and Leuenberger, 2000b,c; Wünsch et al., 2019). 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 (Wünsch et al., 2019). Therefore,

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.

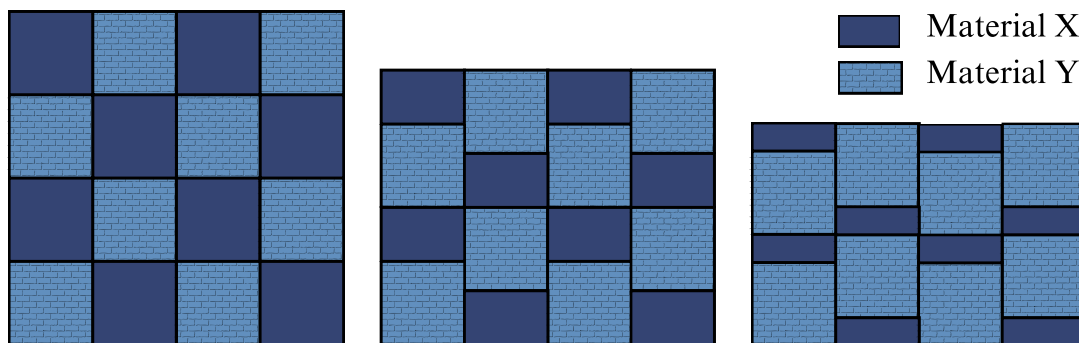


Figure 2.5: An illustration showing a binary mixture of compressible (Material X) and incompressible (Material Y) particles at increasing levels of compression (left to right) to demonstrate the idea of component contributions to blend behaviour as a function of volume fraction, ϕ_i (Reynolds et al., 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.

Despite these advances, relatively few studies have investigated mixture rules for predicting tensile strength in drug-loaded blends of three or more components (Valekar and Buckner, 2025). Of the 15 studies identified in Valekar and Buckner (2025) review of the literature, only 6 considered drug-loaded systems, 5 investigated ternary placebo blends, and only 2 examined drug-loaded ternary systems. Among these two studies, Jolliffe et al. (2022) explored parameter estimation within drug-loaded three component blends and attempted back-extrapolation to infer pure-component parameters for the non-compactable APIs; however, the ternary component (in this case, microcrystalline cellulose) fraction was held constant, effectively restricting the analysis to a two-dimensional compositional space. The second study was conducted by Corrigan et al. (2024) which investigated systems employing binary and ternary interaction mod-

els rather than classical mixture rules. Their study utilised a binary-interaction model to predict component parameters across formulation spaces and employed a brute-force cross-validation across a fixed Design of Experiments (DoE). Through this approach, training datasets of active formulations were selected to balance the experimental burden and predictive power, applied to micronized paracetamol (Mallinckrodt Pharmaceuticals, USA) and ibuprofen 50 (BASF, USA) ternary spaces. Although it was noted that lubrication conditions were fixed across all formulations, which, according to Kushner and Moore (2010) impacts the consistency of blend preparation through an inconsistent impact on the tensile strength via lubrication. While this method describes a standard protocol to reduce the experimental requirements for calibrating compression and compaction models across pharmaceutical formulations, powder mixtures do not always behave consistently; some materials can dominate compaction behaviours in a formulation space (Kuentz and Leuenberger, 2000a; Sun, 2016). As a result, generalised approaches may be insufficient to capture unique formulation requirements.

2.7 Experimental Design

Experimental design is the systematic process of planning, conducting, and analysing investigations to examine causal relationships between independent variables (factors) and dependent variables (responses), with the aim of maximising information gained while minimising experimental effort (Bos, 2010; Steeno, 2010). A structured experimental design methodology typically involves the following steps (Beg, 2021):

1. **Definition of objectives**

This establishes the purpose of the experimental campaign by identifying specific questions to be answered, hypotheses to be tested, and key responses of interest.

2. **Mapping of cause-and-effect relationships**

This captures prior knowledge of how input variables may influence system responses. These relationships are often visualised using tools such as fishbone diagrams, as shown in Figure 2.1, to support structured thinking about potential sources of variability.

3. Identification of critical variables and responses

This focuses the experimental effort on the most influential factors. In pharmaceutical development, where many variables may affect a given response, screening designs (e.g. fractional factorial or Plackett-Burman designs) are commonly used to identify the factors that have the greatest impact on the response(s) of interest.

4. Design and optimisation of factor settings

This involves fitting mathematical or statistical models to experimental data in order to describe the relationship between factors and responses. Once these relationships are established, experimental designs such as full factorial, mixture, or optimal designs can be used to efficiently explore the response surface and identify factor settings that achieve desired performance targets.

Commonly within a QbD framework, systematic factorial DoEs are used to define a grid of experimental conditions within a targeted subspace prior to running experiments. When combined with response surface methodology, the relationships between experimental conditions and response variables are identified through regression analysis. While this approach provides a simple and consistent methodology, it also presents several notable drawbacks. First, the predefined grid does not incorporate results from previously collected experimental data, nor does it account for any prior knowledge of the system when proposing new experimental points. Second, the experimental points may be highly correlated, limiting the amount of information gained from each experiment. Third, the initial sampling of the design space may fail to target important features of the response surface (Yu, 2008; Yu et al., 2014).

In response to these limitations, iterative and adaptive decision-making strategies have gained increasing attention in recent years. Prominent examples include Bayesian optimisation, evolutionary strategies, particle swarm optimisation, and simulated annealing (Bos, 2010). These modelling-based approaches aim to explore the design space intelligently, either to locate optimal operating conditions or to enhance model parameterisation. While they differ in how they balance exploration and exploitation, they share a common limitation in that they do not explicitly incorporate mechanistic un-

derstanding of the system being optimised.

Given that empirical models already exist which can effectively describe powder compaction behaviour, there is strong motivation to adopt MBDoE approaches that integrate such models into experimental optimisation. By weighting candidate experiments according to their predicted contribution to model parameterisation, MBDoE has demonstrated success in complex dynamic chemical and biological systems involving multiple variables, decisions, and uncertain parameters (Geremia et al., 2026). More recently, this methodology has gained traction within pharmaceutical manufacturing, where it has been shown to reduce experimental effort and material consumption when parameterising models for processes such as lubrication rate effects on tablet strength (Bouchkira and Benyahia, 2024; Cenci et al., 2022), continuous wet granulation and drying (Matsunami et al., 2023), and freeze-drying operations (De-Luca et al., 2020). MBDoE frameworks leverage current model predictions alongside associated uncertainties to sequentially select experiments that maximise expected information gain, thereby enhancing both parameter estimation efficiency and process understanding.

The most notable work addressing the experimental burden of direct-compression formulation remains that of Corrigan et al. (2024), discussed above. Beyond demonstrating that binary-interaction models could predict component parameters across formulation spaces, this study offered the first evidence-based guidance on minimising and standardising the experimental effort required to calibrate compression and compaction models, and reported the approach to be generalisable to other powder mixtures. This generalisability claim, however, sits uneasily alongside the recognition that powder mixtures do not always behave consistently across formulation design spaces, with certain materials exerting a more dominant influence on compaction behaviour than others (Kuentz and Leuenberger, 2000a; Sun, 2016). A single, generalised protocol may therefore struggle to capture formulation-specific behaviour, motivating the need for smarter, data-driven methodologies capable of adapting accordingly.

2.8 Summary of the Literature

Formulation development and design for directly-compressed OSD tablets is a bottleneck in the drug product pipeline which need not exist with the available digital technologies. Coupling experimental design with predictive modelling and optimisation can provide an innovative solution to increase the capabilities and throughput of formulation development negating the reliance on prior knowledge and resource-intensive trial-and-error approaches. In order to make this shift towards digital design, a reliable and robust model which captures the compression and compaction behaviours of multi-component systems at varying processing conditions must be established.

The selection of appropriate modelling strategies is highly context dependent, governed by modelling objectives, system understanding, and available resources. While data-driven models are increasingly adopted due to their relative ease of implementation, knowledge-driven mechanistic models are recognised for interpretability and extrapolation potential. However, powder compression presents unique challenges arising from nonlinear behaviours and formulation-dependent responses. These complexities limit the feasibility of fully mechanistic modelling while simultaneously increasing the experimental burden required for purely data-driven approaches.

Within this landscape, empirical compression models have emerged as a pragmatic compromise between physical insight, data requirements, and predictive performance. However, the simplicity of the empirical models used to predict compression and compaction behaviours has been questioned, particularly as these models were developed on alternative materials. Yet, the simplification of this complex problem appeared to provide acceptable predictions across multiple investigation. Zhao's interpretation of Gurnham's model and also through Kawakita's comparison of the compression models available to them demonstrated that the empirical models all managed to adequately predict the behaviours for a range of materials which included pharmaceuticals. However, if a quantitative estimate of the compression and compaction stages is required, or an evaluation of the defect potential for a tablet, then the mathematical interpretations of the microscale mechanisms may be of more relevance.

In saying this, and despite the quantity of literature available, there was no confident consensus regarding how the performance of these empirical models and why results between materials and authors have been inconsistent. The literature highlighted the ‘issues’ with Heckel’s model yet provided no insight into why the found deviations between investigations may have occurred. Similarly, with the Kawakita model and its parameters, the models’ ability to predict volume reduction has been accepted even if the ‘how’ and ‘why’ was not. This has proven to be a common theme with compression models and a substantial knowledge gap in each case.

For the models considered there was a general comment made on their accuracy at different ranges of the pressure or porosity scales. Most commonly, as evident in the Gurnham and Heckel models discussion, these deviations appeared at the lower and/or upper end of the independent variable scales. Whether the ranges mentioned are within the relevant design space for the direct compression of pharmaceuticals – the ‘Region of Interest’ (RoI) as it were – is yet to be determined. If not, then this drawback for the models would be irrelevant when practically applied; however, when conducting the fitting procedure, care must be taken to ensure data points outside of this range are not affecting overall fit.

A majority of the models considered had fitting parameters whose physical definitions either have little practical relevance or no firm physical definition or estimation reached. The lack of physical relevance of these parameters was deemed inconsequential as it is the ability for the models to fit the data to a curve with good reproducibility which is of import for predicting mixture behaviours. The variability of the parameters however made for a more intriguing challenge to address. If these parameters define the compression and compaction behaviours of materials, it is counter intuitive that they would change between authors. Finding confident estimations in these parameters for raw materials, or determining the reason for their variability, will either develop the understanding of powder compression or provide a more stable base to build upon for predicting the behaviours of mixtures in which the component powders demonstrate different levels of compressibility and compactability.

As an additional comment, the proposed model by Kuentz and Leuenberger in-

troduced the interesting concept of a critical porosity, ε_c , at which a compact can be formed; the application of which could be essential in narrowing the operation space for formulation scientists yet not the formulation space. This was not the only comment made on some critical point in either compression force or material ratios which impacted the compressibility or integrity of the compact. API's are notoriously non-compactable which is why excipients are used to provide attractive physical attributes to a blend. There may be a concentration for components for which their presence in blend becomes dominating, impacting the trends in behaviours across different component ratios; this may make predictions with respect to the formulation composition more complicated.

It is evident that, at least at a basic level, these models can adequately predict the behaviours observed by pharmaceutical powders. However, it appeared that some models were more relevant in different scenarios, particularly with regards to: compression pressure ranges; porosity ranges; material forms; whether the investigations are consider in- or out-of-die results; and whether the investigations consider single components or mixtures. It is of interest to investigate quantitatively these conclusions from literature to identify whether areas of applicability do in fact exist for these models to aid in the decision of which model is appropriate for use.

Developing models capable of predicting tablet compressibility and compactability from individual component contributions represents only part of the broader challenge in formulation development, as formulation scientists must also navigate complex interdependencies between CMAs, CPPs, and CQAs. The interaction between formulation composition, press mechanics, tooling design, and processing conditions creates a highly multidimensional experimental space that is poorly suited to conventional trial-and-error experimentation, which is often resource intensive and generates large datasets which can be difficult to interpret. Alleviating the formulation development bottleneck therefore requires not only improved predictive models, but also smarter experimental strategies that enable effective use of historical and newly generated data to inform formulation and manufacturing decisions.

Implementing QbD in OSD formulation therefore demands experimental strategies

capable of navigating highly nonlinear and interdependent formulation–process spaces while remaining resource efficient. Conventional factorial DoE relies on static experimental grids that neither exploit accumulating data nor prioritise the most informative regions of the design space, frequently leading to redundant or suboptimal experimentation. Although adaptive optimisation techniques offer improved exploration efficiency, they typically operate as black-box approaches that lack mechanistic interpretability. In contrast, MBDoE integrates predictive models directly into experimental planning, enabling sequential, information-driven selection of experiments that systematically improve model reliability while minimising experimental burden. As such, MBDoE provides a natural framework that can couple empirical compression models with smart experimental planning to address both predictive accuracy and formulation development efficiency.

2.9 Highlighted Knowledge Gaps

I. Empirical model performance has not been systematically evaluated across multiple APIs and formulation compositions.

While empirical models – such as Gurnham, Kawakita, Heckel, Ryshkewitch-Duckworth and Leuenberger – are widely used to describe powder compression and compaction behaviour, there is limited consensus on how well these models perform in pharmaceutical formulations and whether the presence or concentration of API affects predictive accuracy. A systematic evaluation across multiple APIs and increasing drug loads would provide a consistent dataset to quantitatively compare model performance and inform the selection of models for future studies.

II. Estimated empirical model parameters are often inconsistent, creating an unstable foundation for applying mixture rules to predict blend behaviour from individual component contributions.

Empirical models have proven to be effective at describing the compression or compaction behaviour of individual formulations, but their extension to multi-component, drug-loaded blends remains challenging. Predicting how each compo-

nent contributes to overall blend behaviour requires additional data collection and often relies on the extrapolation of line-of-best fit approaches to mixture models introducing unnecessary margins for error. While mixture models have shown promise, particularly in formulations dominated by excipients or placebo systems, variability in model parameters and sensitivity to component ratios reduce confidence in their reliability. Investigating the causes of parameter variability and developing a standardised approach to estimate blend behaviour from individual components would improve formulation design, reduce unnecessary experiments, and provide a more reliable framework for model-driven decision making.

III. Experimental strategies for formulation development remain inefficient and resource-intensive.

Exploring the multidimensional interactions between material properties and processing conditions through conventional trial-and-error experimentation is resource-intensive, consuming excessive quantities of API and time, while generating complex datasets that are difficult to interpret. Few studies leverage historical data or mechanistic understanding to guide the selection of subsequent experiments, resulting in redundant or suboptimal testing. There is a clear need for iterative, model-driven experimental strategies that can efficiently explore formulation space, minimise resource use, and improve the predictive accuracy of compaction and compressibility behaviour. Incorporating empirical or hybrid models into such frameworks would allow more strategic experiment prioritisation and accelerate the development of robust, manufacturable formulations.

Chapter 3

Aims and Objectives

This project proposes to develop a resource-sparing formulation optimisation approach for directly-compressed tablets by considering three main objectives:

- I. **Use statistical analyses to identify empirical models which consistently describe the compression and compaction behaviours for various APIs in blends with different drug loadings.** A dataset comprising nine placebo formulations and twelve API-loaded blends, representing four APIs at three drug loadings, was fitted to widely used empirical compression models (Gurnham, Heckel, and Kawakita) and compaction models (Ryshkewitch-Duckworth and Leuenberger). This study systematically evaluated the predictive performance of these common empirical models for pharmaceutical powder compaction by examining statistical fit metrics, residual error behaviour, and sensitivity to methodological choices, including sample size, weighted regression biasing, and the propagation of experimental error on parameter estimate variability.
- II. **Develop and validate an approach for optimising the selection and parametersiation of compression and compaction mixture models for loaded blends.** Using the dataset from Objective I, a sensitivity analysis was conducted to identify multiple parameter pairs capable of achieving acceptable fits. Based on this, a novel global optimisation approach was developed to populate arithmetic, geometric, and harmonic mixture rules for empirical tuning param-

eters. The method included systematic evaluation of parameter variability, the application of constraints to maintain consistency for placebo formulations, and comparison against traditional approaches, providing a framework for efficiently exploring formulation design spaces.

III. Design and implement an iterative smart experimental planning framework which utilises the optimised mixture models to maximise the predictability of the model while minimising the consumption of API materials. Datasets comprising three grades of paracetamol and ibuprofen, each formulated with a consistent placebo base, were used to evaluate the proposed optimisation approach. Placebo data were collected once, with selected blends duplicated to assess consistency. the disintegrant and lubricant concentrations were kept constant with API loadings systematically varied from 0 w/w% to 40 w/w% with excipient ratios adjusted accordingly. This study extends the work presented in Chapter 6 to evaluate how global optimisation can reduce experimental requirements and reliance on prior formulation knowledge in the development of directly compressed OSD products. The investigation is conducted in two parts: (i) the development and validation of a global optimisation method to populate mixture rules for ternary formulations of paracetamol and ibuprofen with varying particle size distributions, and (ii) the application of MBDoE to guide experiment selection, comparing D-, A-, and E-optimality criteria against random selection to provide a systematic, resource-efficient framework for improving model accuracy.

Chapter 4

Materials and Methods

Chapter Summary

This chapter outlines the materials and methods employed throughout the subsequent investigation chapters. It describes the general methodological framework used across the project, including formulation design and blending considerations, tablet manufacturing and characterisation methods, statistical analysis metrics, and the empirical and mixture modelling approaches applied. It also details the coded methodologies developed for global optimisation and MBDoE. Where appropriate, additional chapter-specific methods are described within the relevant individual chapters.

4.1 Formulations

4.1.1 Historical Data

The statistical study completed in Chapter 5 utilised historical data which was sourced from Jolliffe et al. (2022). This data considered four APIs which were blended with two fillers and a disintegrant before their lubrication. Each API was used to create blends at three levels of drug loading, where the ratio of API to brittle filler were varied leaving the elastic filler, disintegrant, and lubricant concentrations constant, Table 4.1. The APIs considered were ibuprofen 50 (BASF, UK), powdered (pAPAP) and granular grades (gAPAP) of paracetamol (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-2V, Peter Greven, Netherlands).

Table 4.1: Formulation information for the API loaded blends. Percentages are given by weight/weight ratios.

Material	Low (%)	Mid (%)	High (%)
Ibuprofen 50	5	20	40
Paracetamol (powdered)	5	10	15
Paracetamol (granular)	10	20	40
Mefenamic acid	5	20	35
Placebo	0	-	-
Lactose monohydrate	Remainder		
Microcrystalline cellulose	20	20	20
Croscarmellose sodium	3.5	3.5	3.5
Magnesium stearate	1	1	1

Note that the inconsistent ranges in API loading was due to flowability causing tablet weight variability.

In addition to the data sourced from Jolliffe et al. (2022), nine placebo blends were created using the same excipient base to explore the trends of tuning parameters with changes to the ratio of brittle-to-elastic filler ratio for a placebo formulation space for

Chapter 6, as detailed in Table 4.2.

Table 4.2: Excipient composition for Study One blends. Percentages are given by weight/weight ratios.

Blend	Lactose monohydrate (%)	Microcrystalline cellulose (%)	Croscarmellose sodium (%)	Magnesium stearate (%)
A	95.5	0	3.5	1
B	85.5	10	3.5	1
C	80.5	15	3.5	1
D	47.75	47.75	3.5	1
E	20.5	75	3.5	1
F	15.5	80	3.5	1
G	10.5	85	3.5	1
H	0	95.5	3.5	1

4.1.2 New Experimental Work

For the ongoing work completed for this project, the materials and blend compositions were provided by the funding partners at GSK as they were of industrial relevance. The motive was to select APIs which were known to be compactable, but test different particle size distributions to determine whether this had an impact in the predictive models and optimisation. In this case, to provide a distribution of data points across the ternary formulation space while maintaining the concentration of disintegrant (3.5 w/w%) and lubricant (1 w/w%), the API concentration was varied along with both the plastic and elastic filler within the bounds outlined below, again set by the funding partners, visualised with Figure 4.1.

These datasets consist of four placebo blends and nine loaded blends for each API with the exception of micronized paracetamol which was unsuccessful in tableting for formulations of > 22 w/w% API (Table 4.3). A random selection of blends were duplicated to assess experimental variability and are indicated in Figure 4.1 with red crosses and Table 4.3 with asterisks.

$$0 \leq x_{\text{API}} \leq 40 \text{ w/w}\%,$$

$$10 \leq x_{\text{elastic}} \leq 90 \text{ w/w}\%,$$

$$x_{\text{API}} + x_{\text{elastic}} + x_{\text{plastic}} = 100 - x_{\text{disintegrant}} - x_{\text{lubricant}} \text{ w/w}\%.$$

Table 4.3: Blend information for the collected paracetamol and ibuprofen datasets. Placebo data was collected once, with the exception of the duplicated blends highlighted by an asterisk. All blends include 3.5 w/w% Croscarmellose sodium and 1 w/w% Magnesium stearate.

Blend Number	API (w/w%)	Microcrystalline cellulose (w/w%)	Anhydrous lactose (w/w%)
*1	0.0	14.3	81.2
2	0.0	52.5	43.0
3	0.0	33.4	62.1
*4	0.0	69.2	26.3
5	5.5	86.0	4.1
6	11.0	14.3	70.2
7	14.3	64.0	17.2
8	19.1	47.8	28.7
*9	22.0	14.3	59.2
10	26.7	28.7	40.1
11	31.5	64.0	0.0
*12	31.5	47.8	16.2
13	38.2	28.7	28.7

The APIs considered were dense, powdered and micronized grades of acetaminophen USP / paracetamol (Mallinckrodt™, United States), as well as ibuprofen 50, ibuprofen 38, and ibuprofen 25 (BASF, UK). The excipients were anhydrous lactose (SuperTab® 21AN, DFE Pharma, Germany), microcrystalline cellulose (Avicel PH-102, DuPont, UK), croscarmellose sodium (Ac-Di-Sol® SD-711, DuPont, Ireland) and magnesium stearate (Ligamed MF-2V, Peter Greven, Netherlands). Note that the change from lactose monohydrate to anhydrous was informed by the industries preference.

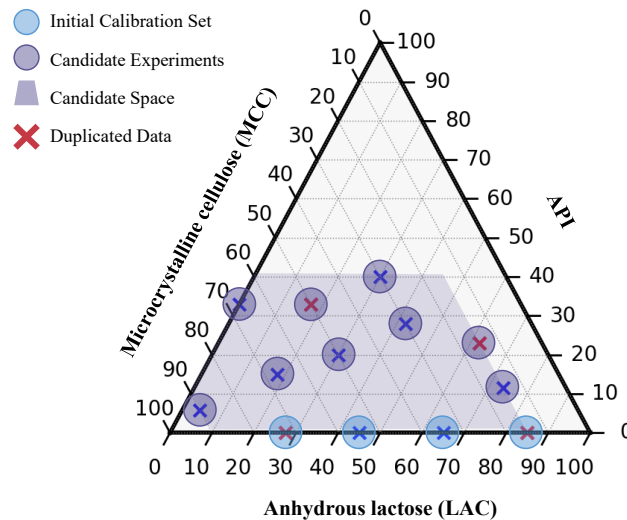


Figure 4.1: Ternary mixture design with four placebo mixtures and nine drug loaded mixtures for model development. Red crosses show datasets for which collection was duplicated. Circled blends show the initial calibration (blue) and candidate (purple) data splits for use in the MBDoE. Ternary space does not account for the disintegrant and lubrication fractions as they were kept constant.

4.2 Raw Material Characterisation

The true densities of the raw materials were measured using a gas pycnometer (Micro Ultrapyc 1200e, Quantachrome, Austria). The true density of the blends, $\rho_{t,mix}$, were calculated using the harmonic mean of N raw materials true densities, $\rho_{t,i}$, based on their weight fraction, x_i , Equation 4.1:

$$\rho_{t,mix} = \left(\sum_{i=1}^N \frac{x_i}{\rho_{t,i}^{-1}} \right) \quad (4.1)$$

4.3 Blending

4.3.1 Historical Data

The blends were created using a 1 L bin blender (Multiblend MB015, Pharmatech, UK) set at 24 rpm for 20 minutes before adding the lubricant for a further 3 minutes at 17 rpm.

4.3.2 New Experimental Work

The approach for blending was adjusted from that of Jolliffe et al. (2022) as it was found that although the concentration of the lubricant was consistent, the *extent* of lubrication was not, which can have a direct impact on the tensile strength of the tablets manufactured (Kushner and Moore, 2010). Therefore, the blends were created using a 1 L polyethylene mixing container (Turbula 2GE, WAB, Switzerland) set at 23 rpm for ten minutes before adding the lubricant. The blending time, t , for the lubrication step was calculated for each blend to maintain a consistent extent of lubrication, K , of 100 dm as estimated by the Kushner-Moore equation, Equation (4.2) (Kushner IV, 2012). The reasoning of this value for K is presenting in Appendix A.1.

$$K = \alpha V^{\frac{1}{3}} F_h \omega t \quad (4.2)$$

where α is a characteristic length constant, set to 1.5 for the Turbula 2GE (Kushner IV, 2012); V is the container volume in litres; F_h is the fraction of free space in the container (which must lie between 30% and 70%); and ω is the rotation speed in rpm.

4.4 Tablet Manufacture

A single punch tablet press (XP 1 Tablet Press, Korsch, Germany) was used to manufacture the powders into 9 mm round flat-faced tablets of 200 mg. The punch force, displacement, and ejection force was collected using proprietary software for ten tablets at eight compression forces (5, 7.5, 10, 12.5, 15, 20, 25 and 30 kN). The raw data was then used to achieve a sample average of the ten tablets at each of the compression points.

At higher drug loadings for powdered (Blends 11-13) and micronized (Blend 9) paracetamol, and ibuprofen 25 (Blends 10-13), the flowability did not allow for consistent die filling using the Korsch XP 1. Tablets in these blends were thus collected using a compaction simulator (HB50, Huxley Bertram Engineering Limited, UK) with a setting of three shuffles on the feeder to achieve consistent die filling.

4.5 Tablet Testing

The tablets were allowed to rest for an hour post-compaction to allow for immediate elastic recovery before any dimension measurements were taken. The tablet characteristics of mass, breaking force, diameter and thickness were measured using a mass balance (Sartorius Quintix 125D-1S, Sartorius, Germany), and a manual hardness tester (HC 6.2, Kraemer Elektronik GmbH, Darmstadt, Germany) fitted with a Mitutoyo micrometer respectively.

4.6 Tablet Porosity and Tensile Strength

The compression pressure, P , was estimated using the compression force, F , which was extracted from the tablet press software, and the cross-sectional area of the tablet (Equation 4.3). Offline measurements of tablet mass, m_{tablet} , diameter, d , thickness, h , and breaking force, H , were used to calculate the tablet porosity (Equation 4.4) and tensile strength (Equation 4.5).

$$P = \frac{4F}{\pi d^2} \quad (4.3)$$

$$\varepsilon = 1 - \rho_{\text{relative}} = 1 - \frac{m_{\text{tablet}}}{\rho_{\text{true}} V_{\text{tablet}}} \quad (4.4)$$

$$\sigma = \frac{2H}{\pi dh} \quad (4.5)$$

In the new experimental work, there were signs of over-compaction (a reduction in tensile strength with lower porosity) in the ibuprofen datasets, most notable at compression pressures above 350 MPa for formulations that had higher concentrations of the smaller sizes of API. To negate the impact that these outliers may have on the fitting process, they have been removed from the dataset (Appendix D.1).

4.7 Statistical Analysis

4.7.1 Goodness of Fit Metrics

Throughout this work, the data points for each individual blend were fitted to the model 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 performance of the regression was evaluated using the squared-correlation coefficient (R^2) (Equation (4.6)) and the root-mean-squared error (RMSE) (Equation (4.7)).

The R^2 provides information on the proportion of variation in the dependent variable, usually within the range of 0 (poor prediction) to 1 (perfect prediction). It is possible for this metric to return negative values, as is the case with some results shown in this study. This occurs when the prediction is poorer than if the model proposed fitting the data to the mean of dependent observations, making the residual sum of squares larger than the total sum of squares. The Root Mean Squared Error (RMSE) was used to quantify the average magnitude of the residuals between predicted and measured values, Equation 4.7. As RMSE retains the original units of the measured quantity, it is not directly comparable across different measurement types; the Relative Root Mean Squared Error (RRMSE) was therefore also used to normalise the metric by scaling individual residuals against their data value, allowing comparison across compression and compaction measurements, Equation 4.8.

$$R^2 = 1 - \frac{\sum_i (y_i - \hat{y}_i)^2}{\sum_i (y_i - \bar{y})^2} \quad (4.6)$$

$$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{n}} \quad (4.7)$$

$$\text{RRMSE} = \sqrt{\frac{\frac{1}{n} \sum_{i=1}^n (y_i - \hat{y}_i)^2}{\frac{1}{n} \sum_{i=1}^n y_i^2}} \quad (4.8)$$

where y_i are the measured values, $\hat{y}_i$ are the predicted values, $\bar{y}$ is the mean of the

measured values, and n is the number of observations.

For the analysis of the MBDoE, the mean absolute error (MAE) was estimated to account for the reducing size of the candidate set upon increasing the number of iterations (Equation (4.9)):

$$\text{MAE} = \frac{\sum_{i=1}^n |y_i - \hat{y}_i|}{n} \quad (4.9)$$

4.7.2 Region of Interest

A RoI was defined to assess model performance at industrially relevant conditions: compression pressures of 75 to 250 MPa and tablet porosities of 10 to 35 % (which was later changed to 5 % - 35 % in Chapter 7 to better describe the collected data).

4.7.3 Acceptance Criteria

Acceptance criteria were defined to assess whether a model can be deemed acceptable for use in industry (Chapters 5 and 6) by estimating if the results errors were within appropriate limits for the quality attribute: $\varepsilon \pm 0.02$ and $\sigma \pm 0.25$ MPa (Nassar et al., 2021).

4.8 Empirical Models and Mixture Rules

4.8.1 Empirical Models

The five models used in this thesis have been categorised into two groups: compressibility models and compactability 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 Equations 4.10 - 4.12 respectively.

$$\varepsilon(P) = -\frac{1}{K_G} \ln \frac{P}{P_0} \quad (4.10)$$

$$\varepsilon(P) = \exp(-(K_H P + C)) \quad (4.11)$$

$$\varepsilon(P) = \frac{\varepsilon_0}{\left(1 + \frac{V_\infty}{V_0} b P\right)} = \frac{\varepsilon_0}{1 + B P} \quad (4.12)$$

Here 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 and Mckeown, 1996). To reduce the number of parameters in Kawakita model and simplify the fitting process, the ratio of volumes V_∞/V_0 and the constant b were grouped into the single tuning parameter B .

The selected compactability models were those created by Ryshkewitch (1953) and Leuenberger and Rohrer (1986), following Equations 4.13 and 4.14 respectively.

$$\sigma(P) = \sigma_0 \exp(-k_b \varepsilon) \quad (4.13)$$

$$\sigma(P, \varepsilon) = \sigma_0 (1 - \exp(\gamma P(1 - \varepsilon))) \quad (4.14)$$

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. The initial observations showed that the tuning parameters do not directly account for physical properties of tablets or process conditions as these parameters aggregate multiple physical attributes into one single parameter.

4.8.2 Mixture Rules

The mixture rules considered in this study follow from previous work (Jolliffe et al., 2022; Polak et al., 2023; Reynolds et al., 2017), namely the arithmetic, geometric, and harmonic means (Equations (4.15)–(4.17)):

$$\theta_{\text{mix},A} = \sum_{i=1}^N \phi_i \theta_i \quad (4.15)$$

$$\theta_{\text{mix},G} = \left(\prod_{i=1}^N \theta_i^{\phi_i} \right)^{\frac{1}{\sum_{i=1}^N \phi_i}} \quad (4.16)$$

$$\theta_{\text{mix},H} = \frac{\sum_{i=1}^N \phi_i}{\sum_{i=1}^N \frac{\phi_i}{\theta_i}} \quad (4.17)$$

These averaging laws estimate how an individual component's (i of N) parameter, θ_i , contributes to the overall parameter of a mixture, θ_{mix} , as a function of its volumetric contribution, ϕ_i . For the purposes of this study, particles are assumed to be of constant size and shape. Estimating how individual components deform within a blend over the compaction process is challenging; therefore, post-compression volume fractions were used. This was calculated using the true density and mass fractions of the pure materials to estimate their volumetric contribution to the blend at zero porosity. This contribution then determines the weighting of the individual component parameters for estimating the mixture parameters A and B using one of the defined mixture rules (Equations (4.15)–(4.17)). These equations are applied to each of the individual parameters A and B for an empirical model, and thus each combination of these rules (Rule A for parameter A and Rule B for parameter B for model parameters has also been investigated.

4.8.3 Optimisation

An optimisation process, Figure 4.2, was created with the core objective function to minimize the global RMSE across all datapoints in the compression or compaction dataset, k to K , for all unique mixtures in an API's formulation space, j to J , for a

total of N datapoints:

$$\mathbf{f}(\boldsymbol{\theta}) = \sqrt{\frac{1}{K} \sum_{j=1}^J \sum_{k=1}^K (y_{k,j} - \hat{y}_{k,j})^2} \quad (4.18)$$

$$\min_{\boldsymbol{\theta}} \mathbf{f}(\boldsymbol{\theta}) \quad (4.19)$$

with $\boldsymbol{\theta}$ being the excipients and pure API estimates for the parameter pairs (Gurnham: $\boldsymbol{\theta}_G = \{K_G, P_0\}$; Heckel: $\boldsymbol{\theta}_H = \{K_H, c_H\}$; Kawakita: $\boldsymbol{\theta}_K = \{\varepsilon_0, B\}$; Ryshkewitch-Duckworth: $\boldsymbol{\theta}_{RD} = \{\sigma_0, k_b\}$). This algorithm estimates one unique pair of tuning parameters $\boldsymbol{\theta}$ Equation 4.18 and 4.19 shows the objective function for this.

The porosity or tensile strength data is represented by $y_{k,j}$ and $\hat{y}_{k,j}$ (with the value denoted with k , in blend j) as the measured and predicted data, respectively. $\hat{y}_{k,j}$ is predicted by the empirical model using the estimated mixture parameter pair θ_{mix} . θ_{mix} is calculated using one of the three mixture rules together with the list of volume fractions of the materials in the formulation ($\boldsymbol{\Phi} = \phi_{API}, \phi_{brittle}, \phi_{elastic}$). The disintegrant and lubricants were assumed negligible due to their low contribution, consistency across the space, and constant lubrication extent as estimated using Kushner–Moore (Equation 4.2).

Initial values for all parameters were set to 1 and constraints for the optimisation were set for the parameters based on the results from the model comparison analysis (Kawakita: $1 \times 10^{-7} \leq \theta \leq 10$, Ryshkewitch–Duckworth: $1 \times 10^{-7} \leq \theta \leq 1000$). The minima for RMSE was found to cover a significant area in the parameter space, thus the tolerance for termination of the optimisation (`scipy.optimize.minimize` using the Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm with Python 3.10.11) should be set appropriately to provide stricter success constraints for this procedure; for this investigation, the tolerance was set to 10^{-10} . The optimisation method was conducted for different combinations of mixture rules.

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

Table 4.4: Model Initial Parameters and Parameter Constraints.

Model	Initial Parameters	Parameter Constraints
Gurnham	1	$0.000001 \leq \theta \leq 2500$
Heckel	0.25	$0.000001 \leq \theta \leq 2$
Kawakita	0.5	$0.000001 \leq \theta \leq 2$
	0.5	$-2 \leq \theta \leq 2$
Ryshkewitch-Duckworth	1	$0.000001 \leq \theta \leq 10000$
	1	$-50 \leq \theta \leq 10000$

curve fitting, and also the traditional method of mixture rule population. The latter was evaluated 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 mixture rules to estimate the unique blends compressibility and compactability profiles.

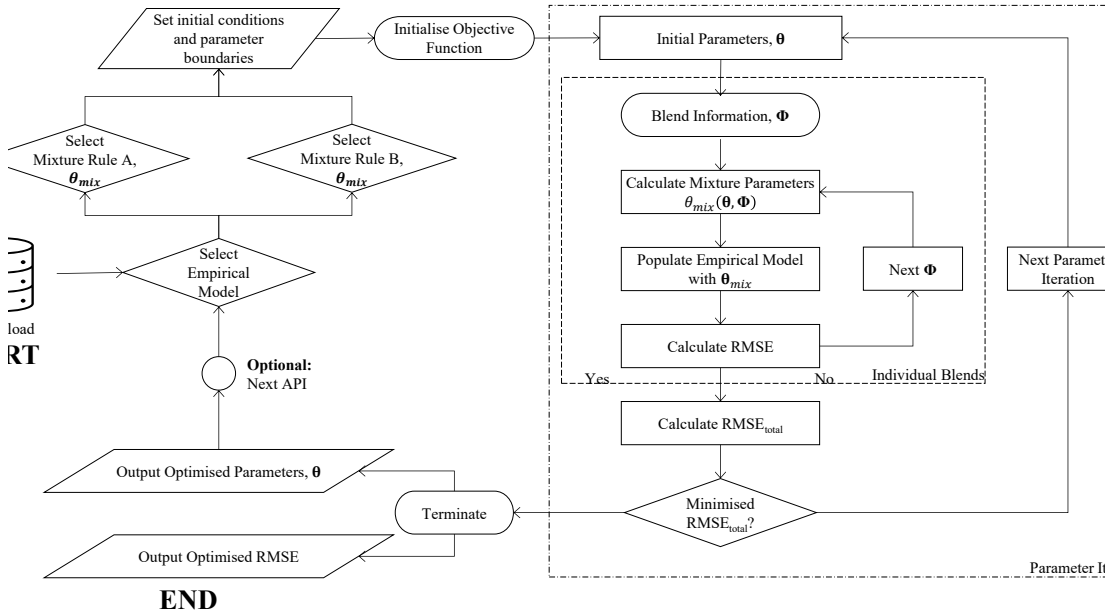


Figure 4.2: Workflow illustrating the global optimisation framework for compressibility and compactability mixture models.

4.8.4 Evaluation of Experimental Efficiency Using MBDoE and Random Selection

MBDoE

A MBDoE aims to maximise the information obtained from a set of experiments by sequentially informing mathematical- or science-based models with the newly collected data. This can be completed to discriminate between available models, or as in this case, to improve the precision of parameter estimates. The goal of this MBDoE (Figure 4.3) was to optimise the selection of experiment design variables, $\phi = (\phi_{API}, \phi_{Filler1}, \phi_{Filler2})$ (the volume fractions of API, anhydrous lactose and microcrystalline cellulose) such that the precision of their pure material parameters, $\theta = (A_{API}, B_{API}, A_{Filler1}, B_{Filler1}, A_{Filler2}, B_{Filler2})$, and the prediction precision of tablet attributes (tablet porosity and tensile strength) across the formulation space are maximised with minimal experimentation (Galvanin, 2010; Wang and Dowling, 2022).

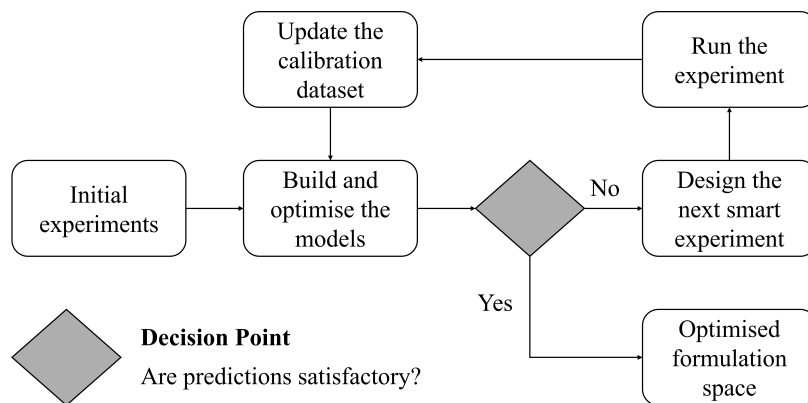


Figure 4.3: Workflow showing the Model-Based Design of Experiments approach to mixture rule optimisation for compressibility and compactability models using a pre-defined formulation dataset.

The Fisher information matrix (FIM) provides the information content of candidate experiments by estimating the sensitivity of the model response with respect to each of the estimated parameters. This sensitivity was estimated using finite difference approximation which assesses how small changes ($\delta = 10^{-8}$) to each parameter affected

the models output (Equation 4.20).

$$\frac{\partial y}{\partial \theta_i} \approx \frac{y(\theta_i + \delta) - y(\theta_i - \delta)}{2\delta}. \quad (4.20)$$

This analysis was performed across all parameters, θ , for each of the experimental points, Φ , resulting in a matrix of partial derivatives for each experiment, S (Equation 4.21). These sensitivity matrices were used to calculate the FIM for the experiments (Equation 4.22).

$$S = \begin{bmatrix} \frac{\partial y_1}{\partial \theta_1} & \cdots & \frac{\partial y_1}{\partial \theta_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial y_n}{\partial \theta_1} & \cdots & \frac{\partial y_n}{\partial \theta_n} \end{bmatrix} \quad (4.21)$$

$$\text{FIM} = \frac{1}{\epsilon^2} S^T S \quad (4.22)$$

The prediction variance was found to be approximately constant across the range of compression pressures, the noise, ϵ , used in the estimation of the FIM was assumed to be constant. A fixed value of 0.03 (-) and 0.1 (MPa) was selected for compressibility and compactability noise. These were estimated as the mean value of standard deviation across the whole dataset, rather than estimating ϵ individually for each experimental condition, in order to reduce computational cost while maintaining sufficient accuracy for design comparison (Franceschini and Macchietto, 2008). Future models may account for the local sensitivity by accounting for the individual variances to emphasise the data points that are more accurate.

The DoE selects the design variables, Φ , in such a way to optimise the information content of the experiments by maximising the scalar metrics of the FIM, ψ : D-optimality, A-optimality, or E-optimality. These metrics use different approaches to increase the confidence in estimated model parameters. D-optimality, which is estimated as the determinant of the FIM, seeks to minimise the overall variance across all parameters. A-optimality, represents the trace of the FIM and minimizes the average variance of the parameter estimates. Finally, E-optimality maximises the minimum eigenvalue

of the FIM which corresponds to minimising the maximum variance of parameter estimates. In short, D-optimality focusses on overall parameter precision, A-optimality on the average precision per parameter, and E-optimality on the worst-defined parameter.

The objective function of the MBDoE for a system bounded by upper and lower formulation bounds, ϕ_l and ϕ_u , is reflected in Equation 4.23.

$$\max_{\phi_l \leq \phi \leq \phi_u} \psi(FIM(\theta, \phi)) \quad (4.23)$$

The MBDoE was developed to sequentially select predefined formulation experimental conditions (API, filler 1 and filler 2 concentrations (Table 4.3)) which maximised the precision of unknown model parameters to reduce the MAE of predictions for new blends (Figure 4.3).

To achieve this, the datasets were split into calibration and candidate datasets; for initialisation, the placebo data was used for the initial calibration as this was consistent across the API formulation spaces and there were six datasets to parameterise the six parameters. The initial calibration was used to return the parameters from the optimisation of the mixture rules (Section 4.8.3). The remaining datasets were used first to validate the model through the estimation of the MAE using the current estimation of the optimisation parameters, and then to be treated as candidate experiments for the MBDoE to evaluate their sensitivity and information content. The candidate which achieved the objective function for the MBDoE (Equation 4.23) was then removed from the candidate set and placed in the calibration set to repeat the optimisation. This loop was repeated until all candidate experiments were selected. The definition of a successful endpoint for the MBDoE is discussed further in Section 4.9.

Random Selection of Experiments

Three iterations of randomly selected experiments were performed. The procedure followed the same framework as the MBDoE approach, with the exception that experiments were chosen randomly from the pool of candidate formulations rather than being guided by an optimality criterion. This allowed for a comparison between strategically guided experiment selection and purely random sampling in terms of model calibration

and parameter estimation.

4.9 MBDoE Performance Estimation

Model performance was evaluated using the MAE. Performance thresholds for Acceptable, Good, and Excellent regimes were defined in collaboration with industry partners for the Kawakita and Ryshkewitch-Duckworth model (Table 4.5).

Table 4.5: Model-specific performance thresholds used for MAE-based convergence analysis.

Model	Acceptable	Good	Excellent
Kawakita	± 0.03	± 0.02	± 0.01
Ryshkewitch–Duckworth	± 0.5	± 0.25	± 0.1

To determine when the models achieved the defined performance thresholds, direct visual identification was not reliable due to variability in MAE across the MBDoE iterations. Therefore, a performance criterion was introduced to identify the first iteration at which a model consistently satisfies a given performance threshold (Equation 4.24).

For a sequence of MAE values $\{\text{MAE}_i\}$, the iteration i^* is defined as:

$$i^* = \min \{i \mid \forall j \in \{i, i+1, \dots, i+k-1\}, \text{MAE}_j \leq \tau\} \quad (4.24)$$

where τ denotes the performance threshold (Table 4.5) and $k = 3$ defines the minimum number of consecutive iterations required to confirm sustained attainment of the threshold. The value $k = 3$ was selected as it provided a balance to address the fluctuations between iterations while remaining appropriate relative to the total number of optimisation iterations.

The corresponding performance level is reported as MAE_{i^*} , representing the first sustained attainment of the specified performance regime. This performance criterion ensures that threshold attainment reflects stable predictive performance rather than isolated improvements caused by variation in the optimisation process.

The analysis was repeated for each optimality criterion and random selection. The related API consumption for the unique formulation spaces were quantified as the cu-

mulative mass of API used up to iteration i^* , and reported as a percentage relative to the total API required to populate the full formulation space.

Chapter 5

Comparative Evaluation of Empirical Models for Tablet Compression and Compaction Prediction

Chapter Summary

This chapter presents an investigation into the common empirical models used to predict pharmaceutical powder compressibility and compactibility. These models are compared using statistical metrics to provide a systematic and quantitative method to compare how their GoF was impacted by different APIs and their drug loading. Further, a sensitivity analysis was conducted to consider how sample size and erroneous measurement may impact the quality of attribute predictions.

Declaration

The contents of this chapter have been published in the International Journal of Pharmaceutics (see page xlv)

5.1 Introduction

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. Yet, there is still notable variability in the conclusions drawn regarding the limitations and viable applications of these models.

A major challenge in this area is that variability in reported model behaviour and parameter estimation may arise not only from the assumptions embedded within the model structures, but also from differences in estimation procedures, experimental methodology, material attributes, and process conditions (Yu et al., 2014). As a result, it is difficult to distinguish whether observed differences in model performance reflect genuine material behaviour or methodological inconsistency. Although a number of studies have explored the influence of formulation and process variables on model fitting, these investigations are often based on isolated datasets or narrow formulation spaces, limiting broader comparison across empirical models and pharmaceutical blend types (Adams and Mckeown, 1996; Frenning et al., 2009; Mazel et al., 2011; Nordström et al., 2008b; Sonnergaard, 2001).

Consequently, there is a need for a consistent, systematic, and qualitative method to compare and determine the most appropriate empirical model for a given application. This chapter aims to address this through two studies: (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, and (ii) a sensitivity analysis to demonstrate how sample size and the errors from data sampling, curve fitting, and model structure can impact predictions of tablet compaction properties.

5.2 Materials and Methods

The following information can be found in Chapter 4:

- Materials (Section 4.1.1)

- Characterisation of Materials (Section 4.2)
- Blending of Formulations (Section 4.3.1)
- Tablet Manufacture (Section 4.4)
- Tablet Testing (Section 4.5), and,
- Tablet Porosity and Tensile Strength (Section 4.6)

5.2.1 Compressibility and Compactability Models

The empirical models used in this Chapter can be found in Chapter 4 under Section 4.8.1.

5.2.2 Statistical Analysis Methods

A summary of the fitting procedure as well as the definitions for the GoF metrics can be found in Section 4.7.1. The definitions of the RoI and the acceptance criteria can be found in Sections 4.7.2 and 4.7.3 respectively.

The residuals for the loaded dataset (Table 4.1) 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 for the data within the RoI as defined above, to consider how this acceptance criteria may change when at the expected operation conditions.

A box plot, with whisker scaling equivalent to 1.5 times the interquartile range 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.

5.2.3 Sensitivity Analysis Methods

The quality of predictions may be impacted through the data collection methods (i.e. experimental error), the model structure (i.e. limitation of the model parameters in

capturing the system behaviours) or the fitting procedure (i.e. the optimisation to minimise the error between the model prediction and the experimental data). Based on this, the sensitivity analysis was split into three parts: (i) an investigation into the appropriateness of sample size using Monte Carlo methods; (ii) a study of weighted linear regression methods to determine the impact of inconsistent accuracy on in data collection on reproducibility of tuning parameters; and (iii) an investigation into how errors in the tuning parameters may impact quality attribute prediction across the compaction profiles.

(i) Monte Carlo Sampling To investigate the sampling methods, the sample size (i.e. the number of tablets included in each averaged data point) and the averaging method of the individual data points was analyzed using Monte Carlo sampling (Shapiro, 2003). For each sample size (one to nine tablets), this method randomly selected and averaged tablet results, then repeated the process five times. This number of iterations was selected 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 rather than the expected ten due to not all points in the placebo dataset having ten tablets worth of data due to human error. The outputs of the Monte Carlo sampling were then fitted to the models and the GoF metrics and tuning parameters were analyzed as a function of the sample size to determine whether current methods of data collection are sufficient to obtain consistent, high-quality results which reflect the system.

(ii) Weighted Regression 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.

(iii) Error Propagation Finally, error propagation was used to address how arbitrary errors in the tuning parameters affect the prediction accuracy for the quality attributes. This analysis was completed at four levels of compression pressure (or porosity for the compaction model) to understand whether the sensitivity of these parameters is consistent across the compression profile and which of the parameters has the most impact on prediction accuracy. An outline of the calculations can be found in Appendix B.1

Given the large number of blends involved and the specific nature of the results pertaining to each blend formulation, the sensitivity analyses were performed using the data from the placebo blend. This was selected to negate the potential impact of having non-compactable APIs present in the blend.

Reducing the quantity of API used during development is a key objective for implementing predictive modelling in pharmaceutical manufacturing. An ideal solution would be to use the placebo data to predict the quality attributes of loaded blends. To test this theory, the estimated tuning parameters for the placebo blend was used to fit the data of the loaded blends and their relative residual errors plotted. To simplify the results for this, only data points blend closest to 15% porosity for each blend were considered.

5.3 Results

5.3.1 Goodness of Fit

For the fitting of loaded datasets (Table 4.1), each model achieved an R^2 of above 0.90 and an RRMSE of close to zero in the instances of low drug loading (Figure 5.1). 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.

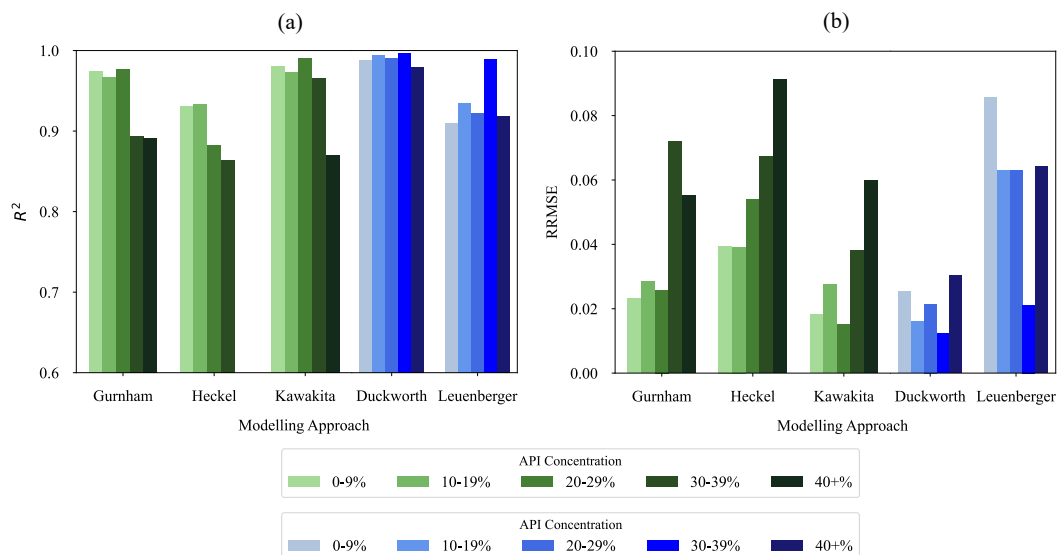


Figure 5.1: The averaged Goodness of Fit metrics (a) R^2 and (b) RRMSE for the different modelling approaches as for bins of 10% in blend drug loading.

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 (Figure 5.2(a)) and the RoI (Figure 5.2(b)).

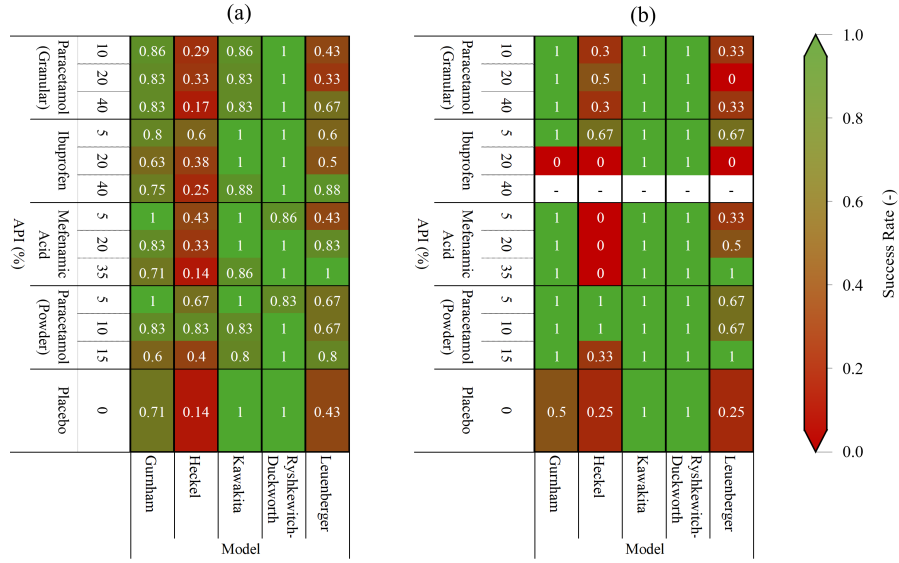


Figure 5.2: Success rates showing the fraction of blend data which meets the acceptance criteria ($\varepsilon \pm 0.02$, and $\sigma \pm 0.25$ MPa) for (a) the entire compression pressure range and (b) the RoI.

Figure 5.2 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 blend 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 (Figure 5.3). 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 Appendix B.2 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 were located outside of the RoI, represented by the lightened points. This supports both the conclusions from Kuentz and Leuenberger (1999) regarding Heckel’s limitations and Vreeman 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 deviation of the tuning parameters relative to themselves (Figure 5.4), 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 (Appendix B.3). This was expected due to this plot reflecting a dataset of different materials and blends, for which the drug loading has already 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 (Equation 4.14). Due to the magnitude of this variation, Leuenberger has not been considered further in this work.

5.3.2 Sensitivity Analysis

Monte Carlo sampling methods were used to estimate whether the sample size of ten tablets is adequate for achieving consistent results (Figure 5.5).

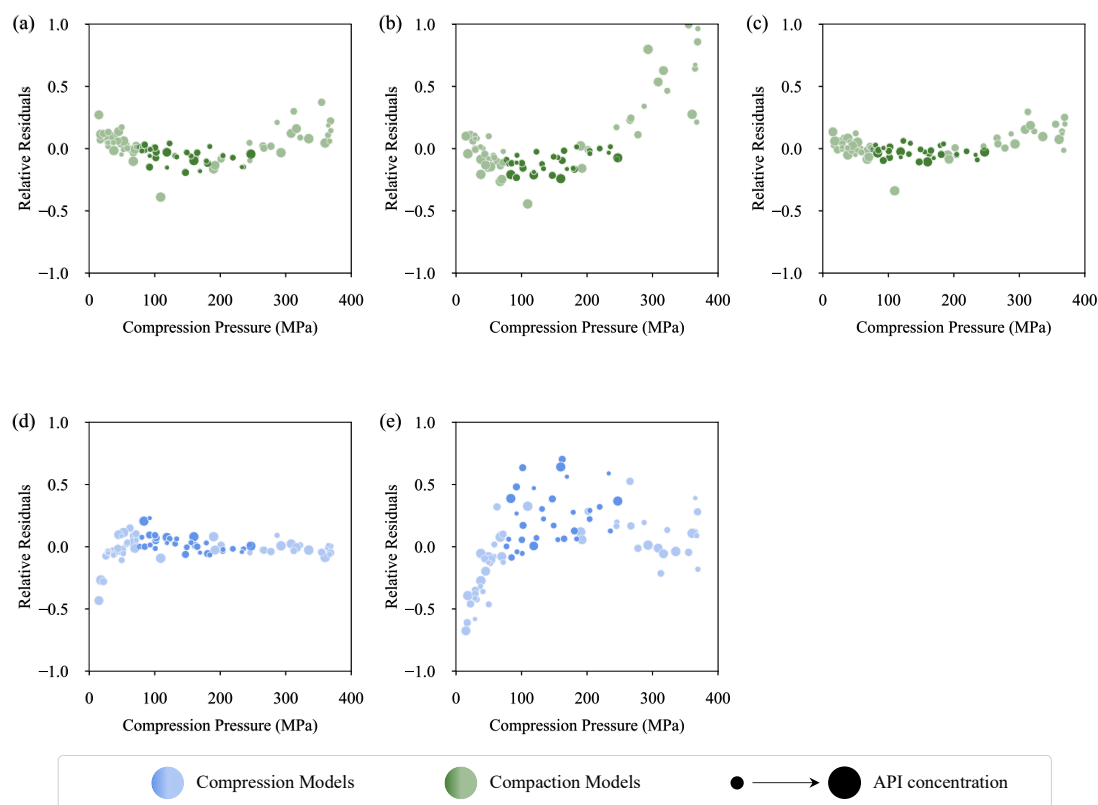


Figure 5.3: The relative residual errors for the modelling approaches (a) Gurnham, (b) Heckel, (c) Kawakita, (d) Ryshkewitch-Duckworth, and (e) Leuenberger as a function of compression pressure and API concentration. The highlighted data points show points that fall within the RoI. The size of the data points corresponds to the drug loading of the blends.

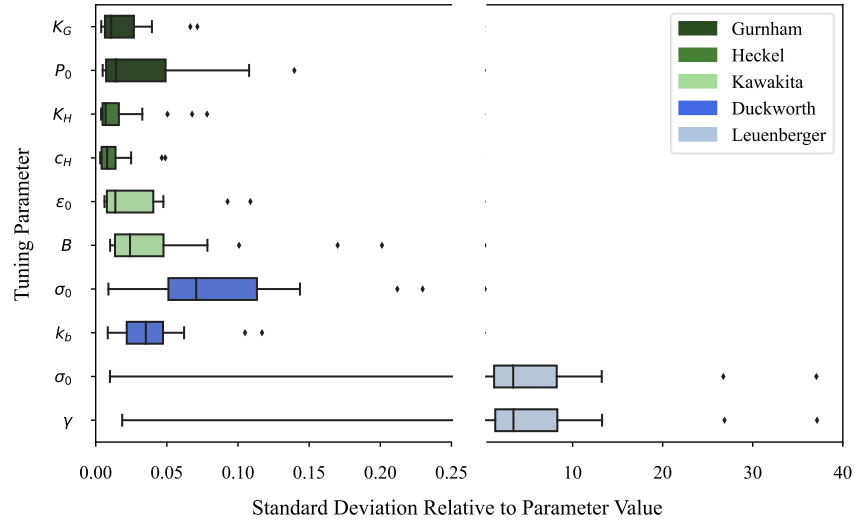


Figure 5.4: A box plot showing the standard deviations of the tuning parameters relative to their predicted values of the entire dataset for the common empirical models.

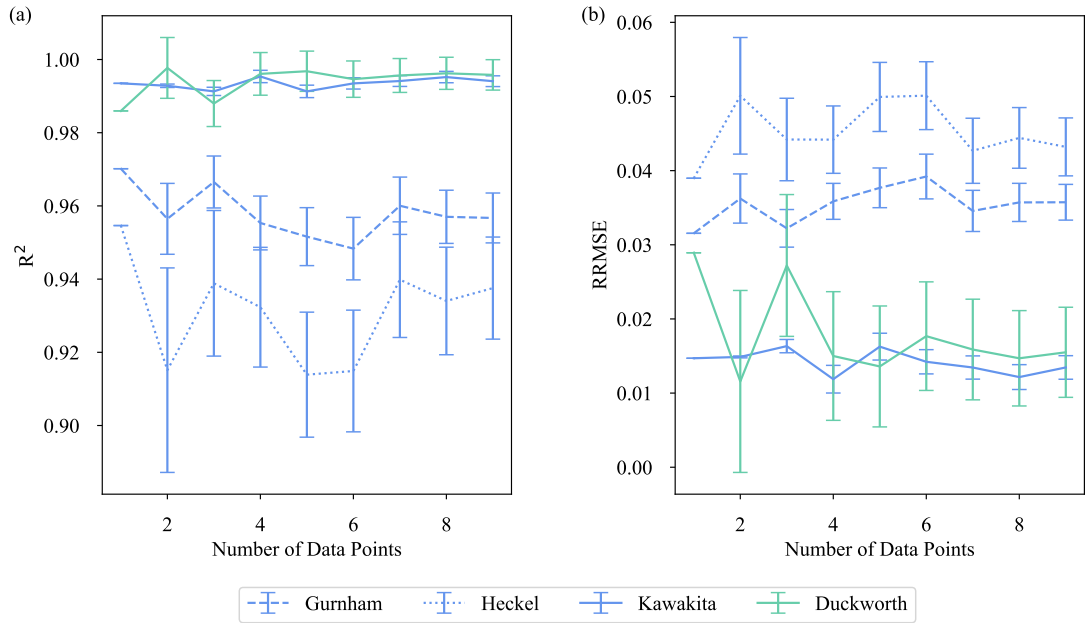


Figure 5.5: Results from the Monte Carlo sampling showing the (a) The squared-correlation coefficient, R^2 , and (b) relative root mean squared error, RRMSE, for different models with respect to sample size.

From the plateau observed in these metrics around 6 – 8 tablets, it was determined that the current approach of sampling ten tablets was sufficient to achieve consistent results in the GoF metrics for each of the models. It can be seen here that Kawakita outperforms the other compression models from observing not only the higher R^2 and lower RRMSE values but also in the consistency of results and the magnitude of associated error. The Ryshkewitch-Duckworth model also offered consistent results although the errors are significantly greater than those of Kawakita. No clear reduction in the error bars of the GoF metrics and fitting parameters with different sample sizes was observed due to the small size of datasets.

The tuning parameters of these models are assumed to be material- or blend-specific but there are inconsistencies in the cited parameters from the literature. An investigation into the fitting procedure was conducted to consider: first, how varying the experimental error impacted the GoF (Figure 5.6); and then, how erroneous estimations of tuning parameters may impact the confidence in attribute prediction (Figure 5.7).

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 (Figure 5.6) and the estimated ranges of tuning parameters (Table 5.1). The general trends in relative residuals observed in Figure 5.6 resemble those displayed previously in Figure 5.3, 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 dis-

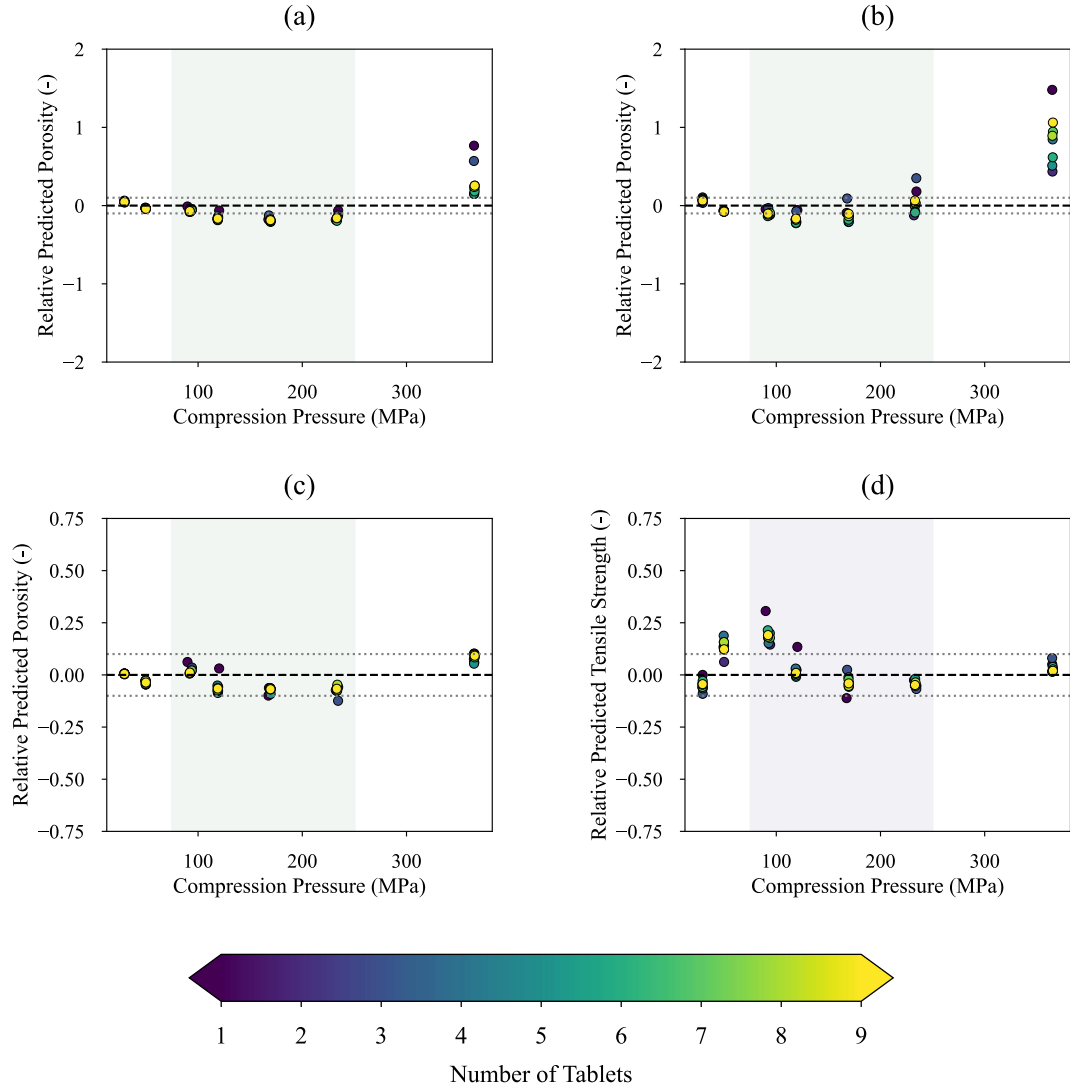


Figure 5.6: The relative residuals for quality attribute predictions for the placebo (20% MCC) using (a) Gurnham, (b) Heckel, (c) Kawakita, and (d) RyshkewitchDuckworth. The colour of the data point represents the number of tablets used for the sampling. The shaded area in each plot represents the Region 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.

played 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 5.1, the parameter estimates also showed variation across the samples, with this being most evident with Gurnham's P_0 and Ryshkewitch–Duckworth's 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, the extent of this is challenging to quantify.

Table 5.1: Model Tuning Parameters and their Ranges.

Model	Tuning Parameter	Min.	Max.
Gurnham	K_{Gurnham}	7.61	14.5
	P_0	430	1080
Heckel	K_{Heckel}	0.00547	0.00895
	c_{Heckel}	0.787	1.000
Kawakita	ε_0	0.445	0.709
	B	0.0143	0.0273
Ryshkewitch-Duckworth	σ_0	10.5	15.3
	k_b	7.61	15.8

Analysing the impact of relative error of tuning parameters on model prediction (Figure 5.7 showed the high sensitivity of tensile strength to the error associated with Ryshkewitch-Duckworth model parameters. Additionally, the trend in the contour plots for each model shows that the sensitivity of predictions to these parameters is not consistent across their respective independent variables. The gradient controlling parameters appeared to have the greatest influence for all models bar Gurnham which showed that the parameter which controlled the x-intercept, P_0 , had greater influence.

From Figure 5.8, it was evident that this solution is not currently viable for any of the models. There appears to be a trend in the materials with increased drug load, a further investigation into tuning parameters with formulation changes is required to address this. Note that these results appear similar between the compression models. This is due to Figure 5.8 reflecting points that fall within the RoI, at which the models were all shown to achieve an acceptable and similar quality of prediction as found in

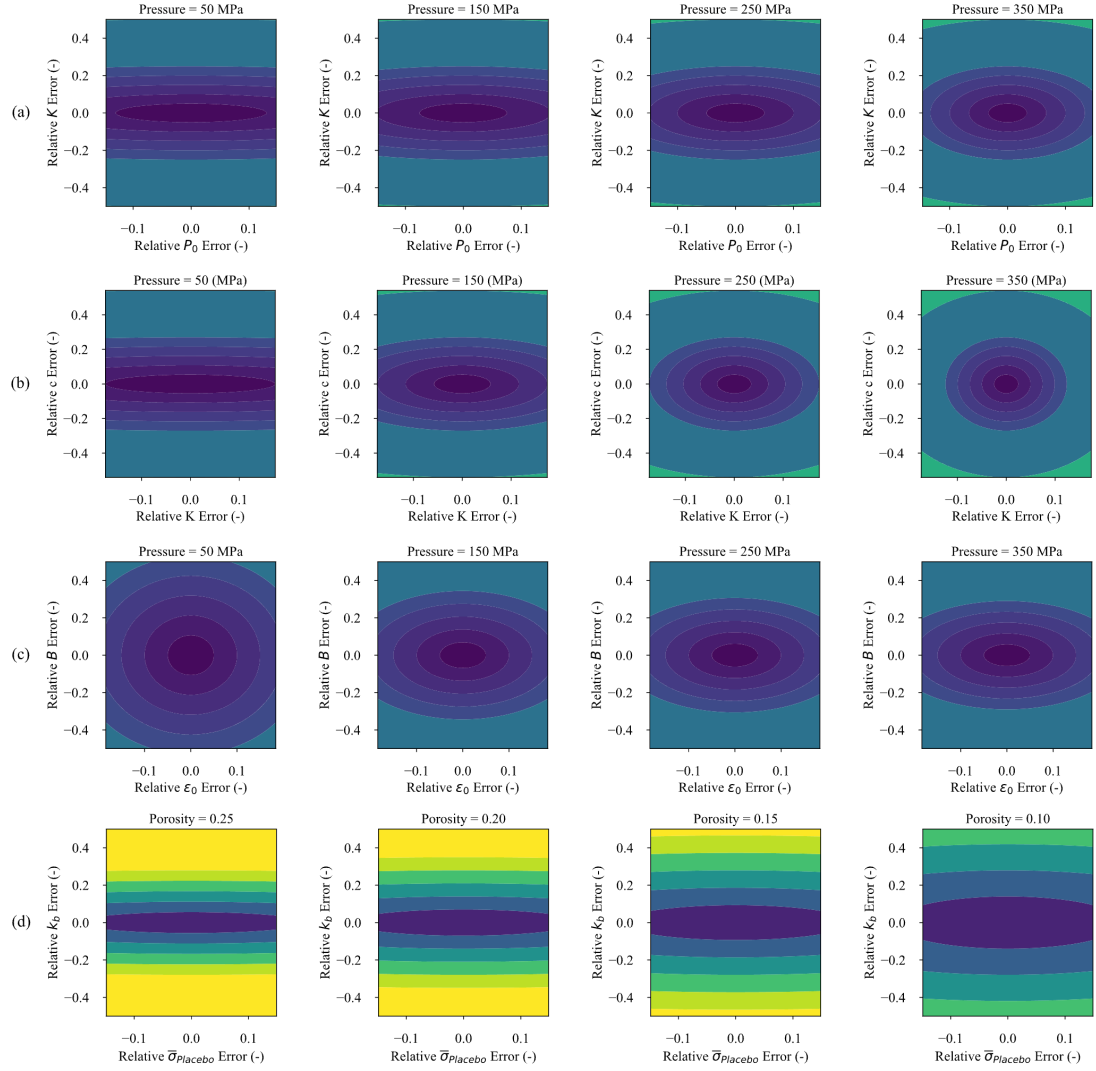


Figure 5.7: A visualization of how erroneous estimations in the fitting parameters for the (a) Gurnham, (b) Heckel, (c) Kawakita, and (d) Ryshkewitch-Duckworth models impacts their respective dependent variable relative to different levels of independent variable. These results are relevant for the placebo blend.

Figure 5.5.

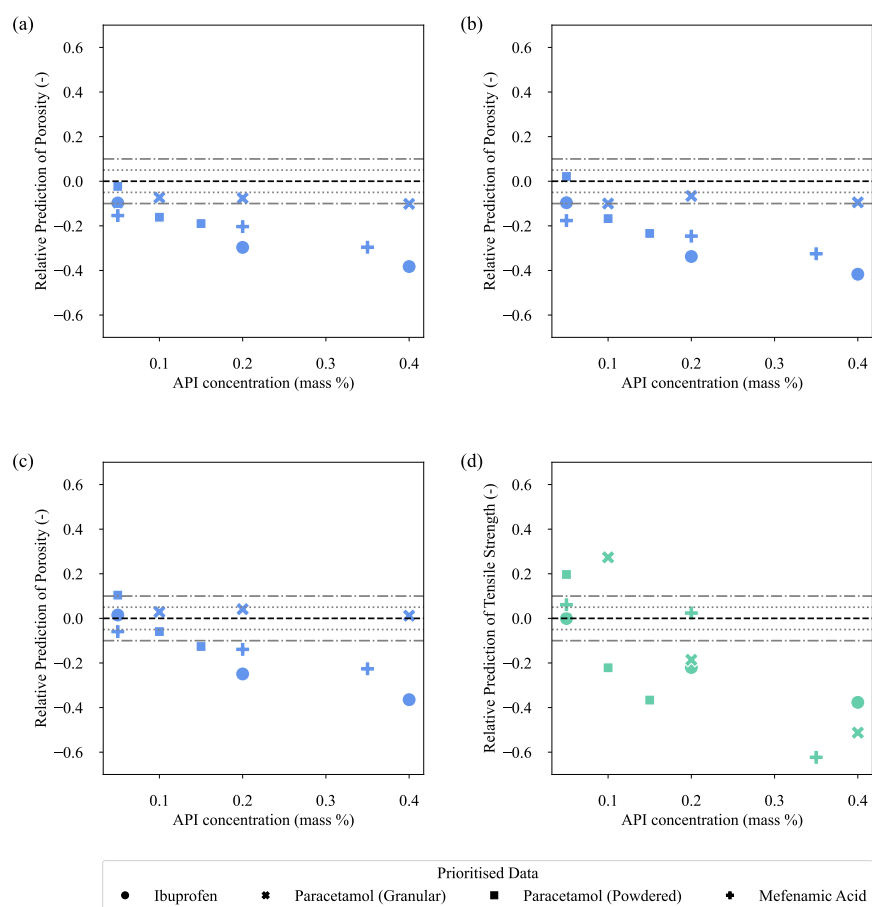


Figure 5.8: The relative deviation of the empirical data from the placebo prediction line for (a) Gurnham, (b) Heckel, (c) Kawakita, and (d) Ryshkewitch-Duckworth. This was a function of drug loading and compression pressure for the data points which were closest to a 15% porosity, highlighting the 5% and 10% deviation limits.

5.4 Discussion

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-Duckowrth models adequately captured the compression or compaction profiles across 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, 2001).

Generally, the GoF results between the compression models were less consistent than that of the compaction models, with drug loading having a larger influence for Gurnham and Heckel. 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. These deviations support the claims of the literature which highlighted that models may be less accurate at certain operating conditions. From the error propagation analysis this was visualised with all models showing a trend of accuracy across the independent variable axes, with the gradient parameter proving to be the most sensitive.

Considering this further for the compression models, they 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 Equations 5.1, 5.2, 5.3 respectively.

$$\frac{d\varepsilon}{dP} = \frac{-1}{K_G P} \quad (5.1)$$

$$\frac{d\varepsilon}{dP} = K_H \varepsilon \quad (5.2)$$

$$\frac{d\varepsilon}{dP} = -K_K \varepsilon^2 \quad (5.3)$$

Gurnham's definition of compression rate does not account for the correlation be-

tween the extent of compression and the powders compressibility (i.e. porosity is not considered). Conversely, Heckel and Kawakita’s perspectives acknowledge that the extent of compression of a powder will contribute to a powder’s 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), and will cross the x-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 unexpected as Heckel (1961) stated that their expression was valid between compression pressures of 35 – 170 MPa depending on the powder being investigated.

The investigation into the weighted regression (Figure 5.6) 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.

It was clear that drug loading negatively impacted 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 rate of change in porosity with compression pressure was more than what the Heckel model was capable of capturing. 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. From Figure 5.8, the impact of drug loading was found to be dependent on the API used, with mefenamic acid only showing a decrease in tensile strength prediction at it's highest drug loading, compared to powdered paracetamol which was consistently outside of the 10% relative error margins. This phenomena has already been studied by Kuentz and Leuenberger (2000c) 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 and Leuenberger, 2000c; Queiroz et al., 2019). Whilst using placebo data to predict loaded blends may not be a possibility, understanding whether there is a limit, and if so what, at which the non-compactability of a material becomes a dominating behaviour for a blend is important to develop an accurate model which will be universally applicable.

5.5 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 sensitivity 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.

The tuning parameter variability may be partially addressed by the inconsistencies in data collection accuracy and applied methods between authors, particularly with respect to the pressure and porosity ranges investigated. However, the extent to which this contributes to the variability of parameters was difficult to quantify. Until this is reviewed more rigorously, the stability of the hypothesis for finding ‘true parameters’ for materials to populate mixture rules for blend behaviours prediction remains uncertain.

Chapter 6

Development and Evaluation of a New Method for Populating Mixture Rules

Chapter Summary

This chapter evaluates a new method for populating mixture rules to improve the predictive application of empirical compressibility and compactability models for pharmaceutical powder systems. The study investigates the validity of candidate mixture rules through statistical analysis, parameter variability assessment, and cross-validation, alongside the use of global optimisation to identify the most suitable mixture rule structures for describing formulation behaviour. By systematically testing and comparing these approaches, the chapter assesses their ability to capture the influence of formulation composition on model parameters and predictive performance. In doing so, it establishes the extent to which optimised mixture rule population can strengthen formulation modelling and support more reliable predictive tools for direct compression development.

Declaration

The contents of this chapter have been published in the International Journal of Pharmaceutics (see page xlv)

6.1 Introduction

Although empirical compressibility and compactability mixture rules offer a promising route to reducing experimental burden, several fundamental challenges currently limit their practical application. First, the inability to generate compression data for pure non-compactable materials restricts access to regions of the parameter space, rendering certain model tuning parameters inaccessible. This presents a major obstacle to extending these approaches to API-loaded formulations. Second, despite reported success in placebo systems (Busignies et al., 2006; Frenning et al., 2009; Mazel et al., 2011; Reynolds et al., 2017), the mechanistic basis for variation in the reported tuning parameters remains poorly understood across the available empirical models. Until these sources of variability are clearly identified and addressed, the reliable application of this methodology in industrial formulation development remains uncertain.

To investigate these challenges, a sensitivity analysis was conducted to examine the identifiability of the empirical tuning parameters and the extent to which multiple parameter combinations could produce similarly acceptable fits. On this basis, a novel global optimization framework was developed to populate arithmetic, geometric, and harmonic mixture rules for the empirical tuning parameters, while constraining the placebo blend parameters to remain consistent.

6.2 Materials and Methods

The following information can be found in Chapter 4:

- Materials (Section 4.1.2)
- Characterisation of Materials (Section 4.2)
- Blending of Formulations (Section 4.3.2)
- Tablet Manufacture (Section 4.4)
- Tablet Testing (Section 4.5), and,
- Tablet Porosity and Tensile Strength (Section 4.6)

6.2.1 Statistical Analysis Methods

A summary of the fitting procedure as well as the definitions for the GoF metrics can be found in Section 4.7.1. The definitions of the RoI and the acceptance criteria can be found in Sections 4.7.2 and 4.7.3 respectively.

The residuals for the loaded dataset (Table 4.1) 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 for the data within the RoI as defined above, to consider how this acceptance criteria may change when at the expected operation conditions.

6.2.2 Compressibility and Compactability Models

The empirical models used in this Chapter can be found in Chapter 4 under Section 4.8.1, with the exception of the Leuenberger model (Equation 4.14) which was neglected in Chapter 5.

6.2.3 Parameter Variability Analysis

It was found in Chapter 5 that the tuning parameter variability could be attributed to the consistency of data collection between authors, yet this did not provide any information as to how the different parameters could offer acceptable GoF.

To assess how parameter variations may impact the GoF for a particular blend, an 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 with a $\pm 75\%$ range with 1.5 % step size in relation to the initial curve fitting estimated 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 an upper limit of 0.25 for the colour axes as this offered a clearer demonstration for the conclusions reached compared to the alternatives (Appendix C.1).

6.2.4 Global Optimisation of Mixture Rules

The global optimisation procedure is outlined in Chapter 4 under Section 4.8.3.

6.2.5 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 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 parameters points, one for each distinct group in the model) but also to investigate the significance of drug loading on the calibration of the model.

6.3 Results

6.3.1 Testing Mixture Rule Validity

The tuning parameters for the Gurnham, Heckel, Kawakita and Ryshkewitch-Duckworth models were evaluated across the placebo space (Figure 6.1). 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.

The contours of RRMSE for different parameter iterations (for the 20% MCC

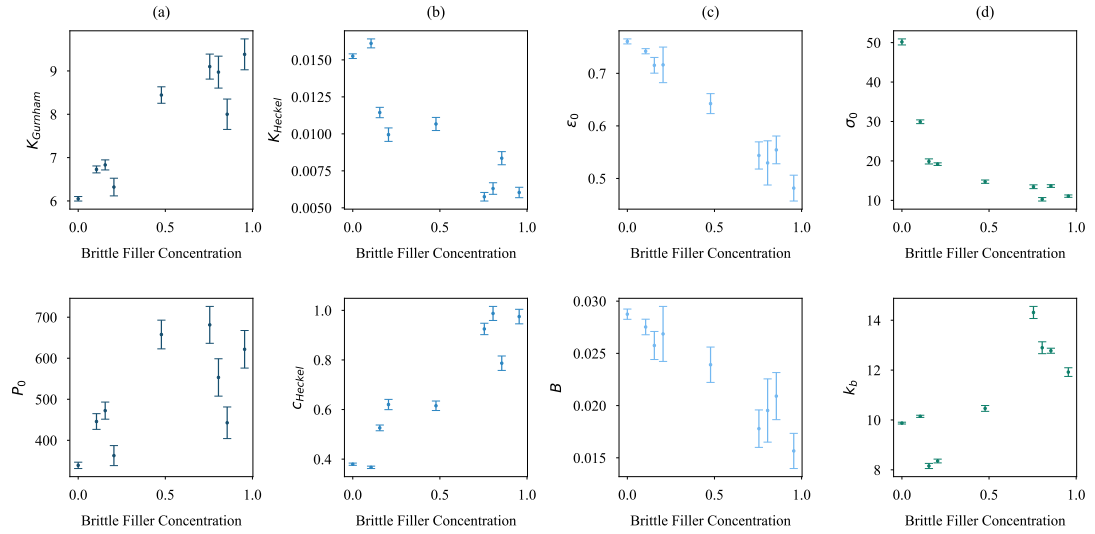


Figure 6.1: Estimated tuning parameters and their standard errors for the placebo blends with respect to the brittle filler (lactose monohydrate) concentration for (a) Gurnham, (b) Heckel, (c) Kawakita, and (d) Ryshkewitch-Duckworth.

placebo blends) demonstrate that there is, in fact, a large region of acceptable GoF, highlighted by the darker blue-purple areas (Figure 6.2). 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-Duckworth’s k_b having a greater impact on the RRMSE compared to σ_0 . This influence that this has was better demonstrated in Figure 6.3, 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 model seem inadequate at capturing the required rate of change of the dataset, with the deviations reflecting the residuals demonstrated in Figure 5.3 in Chapter 5.

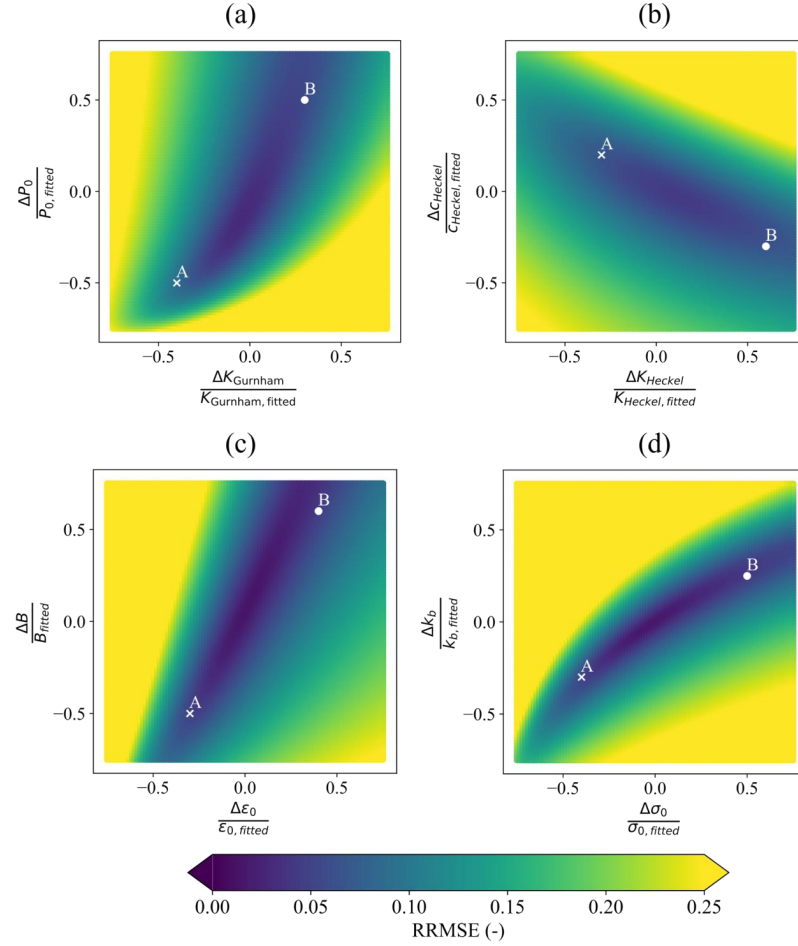


Figure 6.2: Contour plots showing how variations of tuning parameters (relative to those estimated by the curve fitting) for the (a) Gurnham, (b) Heckel, (c) Kawakita and (d) Ryshkewitch-Duckworth models impacts the Relative Root Mean Square Error of quality attribute predictions for the placebo (20% MCC) blend.

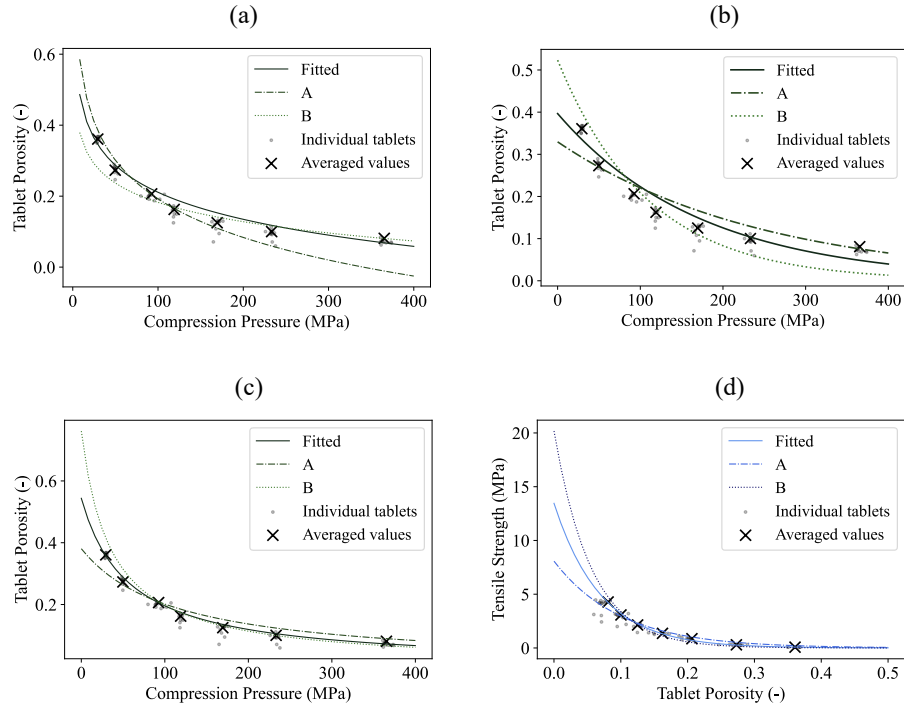


Figure 6.3: Compression and compaction curves showing highlighted tuning parameter combinations, A and B from Figure 6.2 compared to that of the fitted data (corresponds to (0,0) in Figure 6.2) for (a) Gurnham, (b) Heckel, (c) Kawakita, and (d) Ryshkewitch-Duckworth models. These lines were fitted to averaged tablet data, however the individual tablet data has also been included to better visualise underlying variability of the data.

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 capitalised on the flexibility of the parameter space. Results for the mixture model evaluation for these models however can be found in Figures C.5 to C.8.

6.3.2 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 (Figure 6.4). It was observed that changing the mixture rule for both parameters did not have a substantial impact on the total RMSE estimation for the compression models. The axes for the compression models were kept consistent as an additional method for model comparison which showed Kawakita to be the most capable at capturing the compressibility of the powder blends when using the arithmetic mixture rule. The Ryshkewitch-Duckworth model was more sensitive to the changes in applied mixture model, with σ_0 having the most influence on the GoF.

The optimised method was compared to the traditional method for populating mixture models (Figure 6.5). 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 Figure 6.4): arithmetic-geometric for Kawakita; and arithmetic-harmonic for Ryshkewitch-Duckworth. Both methods of mixture model population performed well for predicting compressibility, and slightly less so for the compatibility with the paracetamol blends contributing significantly to the total RMSE (Figure 6.5). The individual contributions of the API to the total RMSE can be interpreted more practically when we compare the success rates of the individually fitting datasets and the optimised mixture model (Figure 6.6) and the predicted values against the observed data (Figure 6.7).

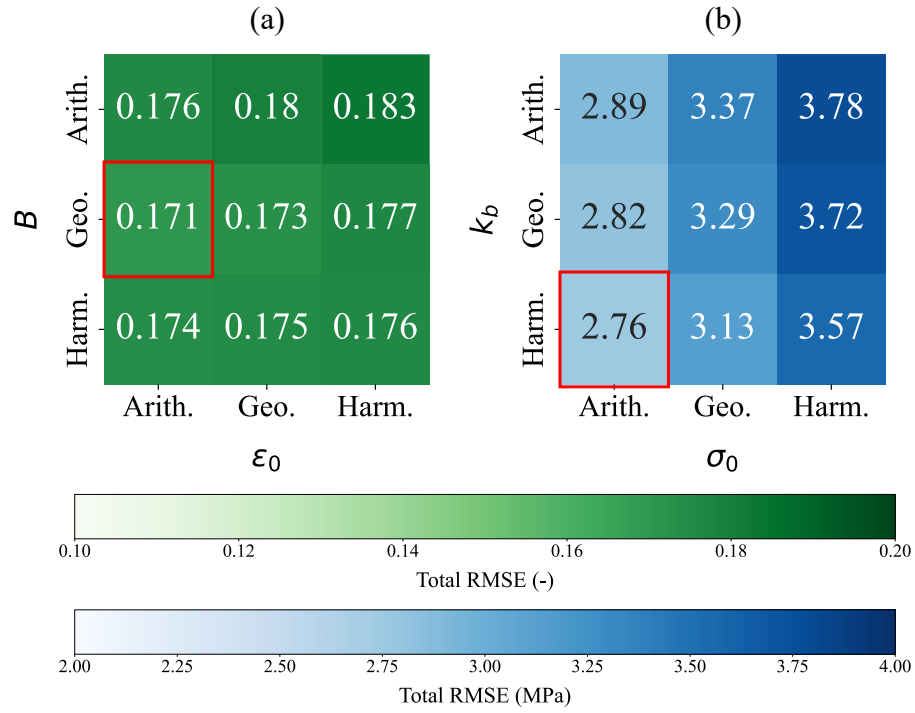


Figure 6.4: Total RMSE estimations for the different combinations of arithmetic (Arith.), geometric (Geo.), and harmonic (Harm.) mixture rules for the optimisation of parameter pairs of the (a) Kawakita and (b) Ryshkewitch-Duckworth models. The lowest estimation of total RMSE is outlined in red.

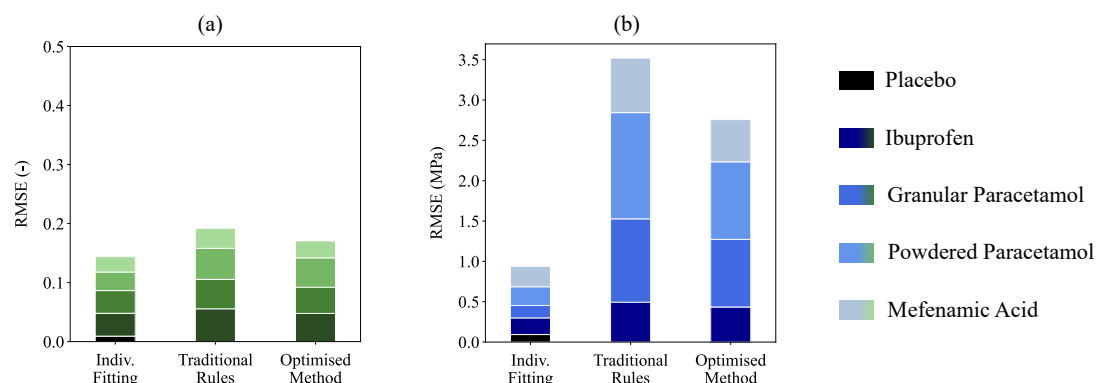


Figure 6.5: Stacked bar plots showing the contributions for the loaded blends and blend D to the total RMSE for (a) Kawakita and (b) Ryshkewitch-Duckworth models. Three methods of tuning parameter estimation were compared: individually fitting the datasets; calculating a line of best fit for the estimated 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.

These results demonstrate the excellent performance of the Kawakita and Ryshkewitch-Duckworth models, with only a decrease in success rates observed in the lowest loading for Ryshkewitch-Duckworth. The deviations observed in the compactability parity plot increase with the 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 these deviations was found by considering the relative residual errors for these models and comparing these to the relative residuals achieved when individually fitting the datasets (Figure 6.8).

Here, it was observed that the relative 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 a large contribution to the RMSE shown in Figure 6.5. The optimised mixture rule

API (%)		Model					
		Kawakita			Ryshkewitch-Duckworth		
		Individual Fitting	Traditional Approach	Optimised Approach	Individual Fitting	Traditional Approach	Optimised Approach
API (%)	Paracetamol (Granular)	0	1	1	1	1	1
		10	0.86	0.71	0.71	0.43	0.43
		20	0.83	0.83	0.83	0.67	1
		40	0.83	0.83	1	1	1
	Ibuprofen	0	1	1	1	1	1
		5	1	0.80	0.8	1	1
		20	1	1	1	0.50	1
		40	0.88	0.88	0.88	1	0.88
	Mefenamic Acid	0	1	1	1	1	1
		5	1	1	0.86	0.71	0.71
		20	1	0.83	1	0.33	1
		35	0.86	0.86	1	1	1
	Paracetamol (Powder)	0	1	1	1	1	1
		5	1	0.50	1	0.17	0.5
		10	0.83	0.83	0.83	0.83	1
		15	0.8	0.80	1	1	1

Figure 6.6: 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 4.1.

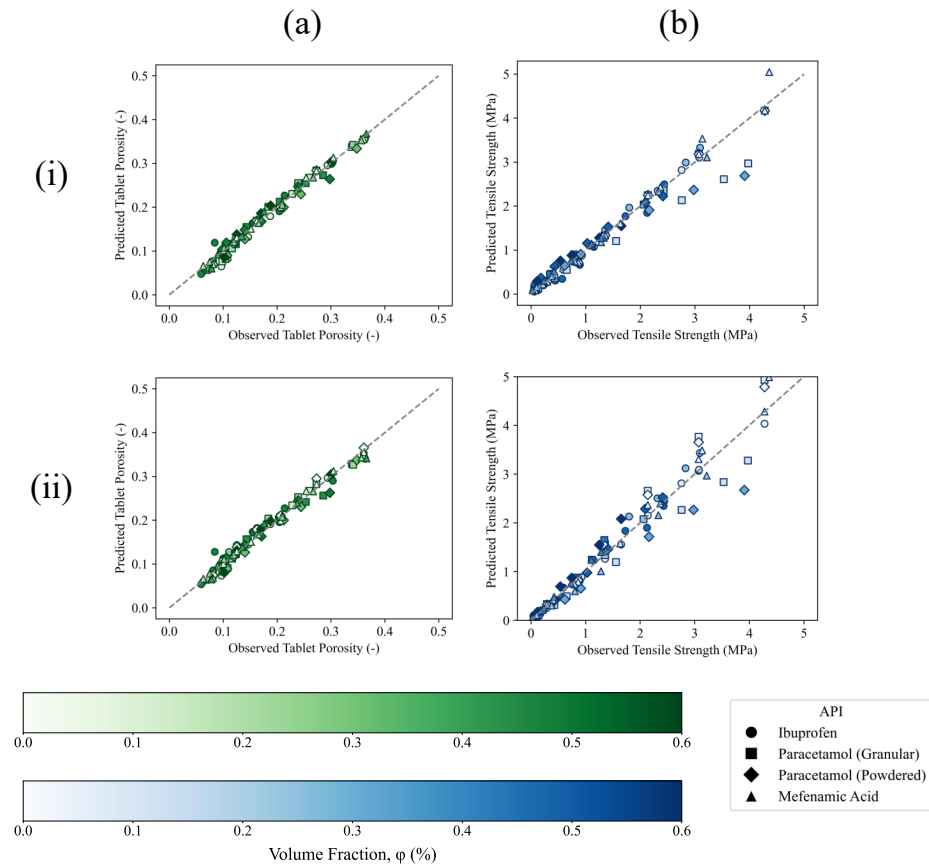


Figure 6.7: Parity plots comparing the observed versus predicted critical quality attributes for the (a) Kawakita and (b) Ryshkewitch-Duckworth models using (i) the new optimised approach and (ii) the traditional approach to mixture rule population.

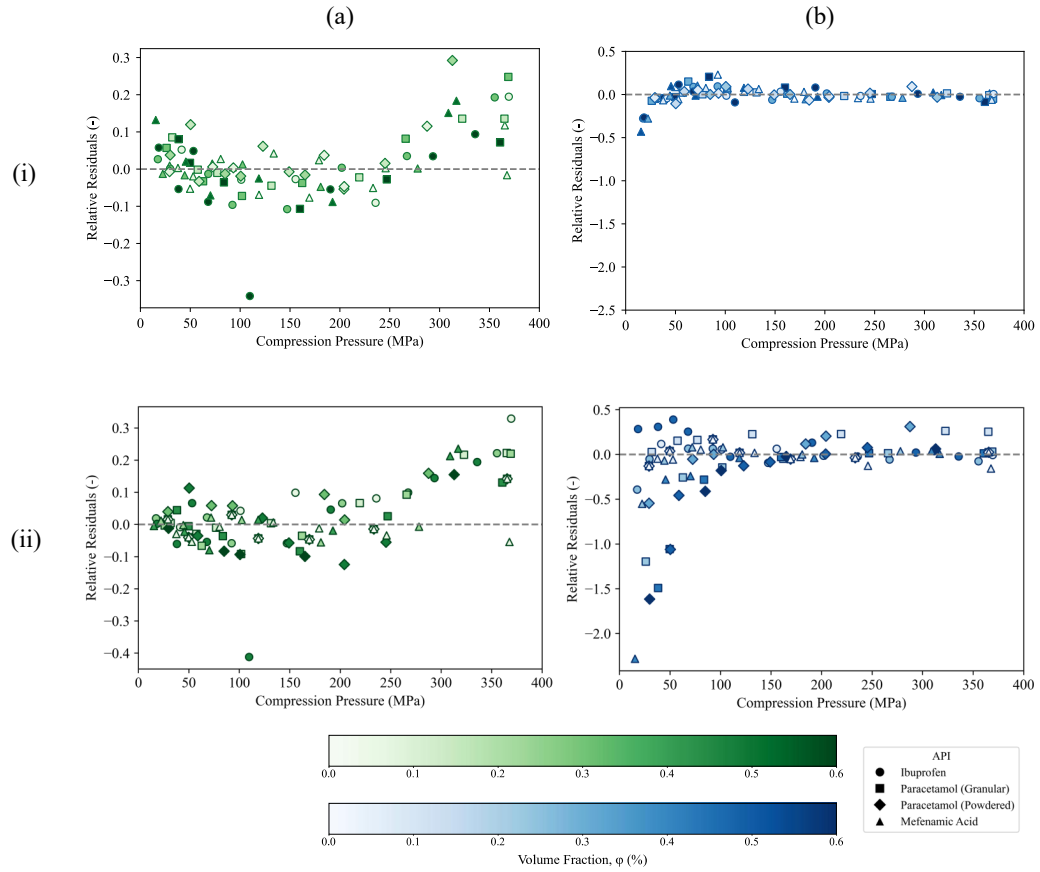


Figure 6.8: Relative residual errors for the (a) Kawakita and (b) Ryshkewitch-Duckworth models as estimated by the (i) individual fitting of datasets and (ii) the optimised approach to mixture modelling for the loaded dataset.

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 the industry specifications of a tensile strength greater than 2 MPa (Polak et al., 2023). Further, these large deviations below and around the lower boundary of the RoI, which shows that these models are accurate for the intended purposes of tablet manufacturing but may require models of increased complexity to further improve upon predictability.

6.3.3 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 (Figure 6.9). The use of the lower API concentration with the placebo blend in the calibration resulted in a large RMSEP for the remaining validation sets (mid and high drug loading). When replaced with a higher drug loading, 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.

6.4 Discussion

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 fitting 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 (Figure

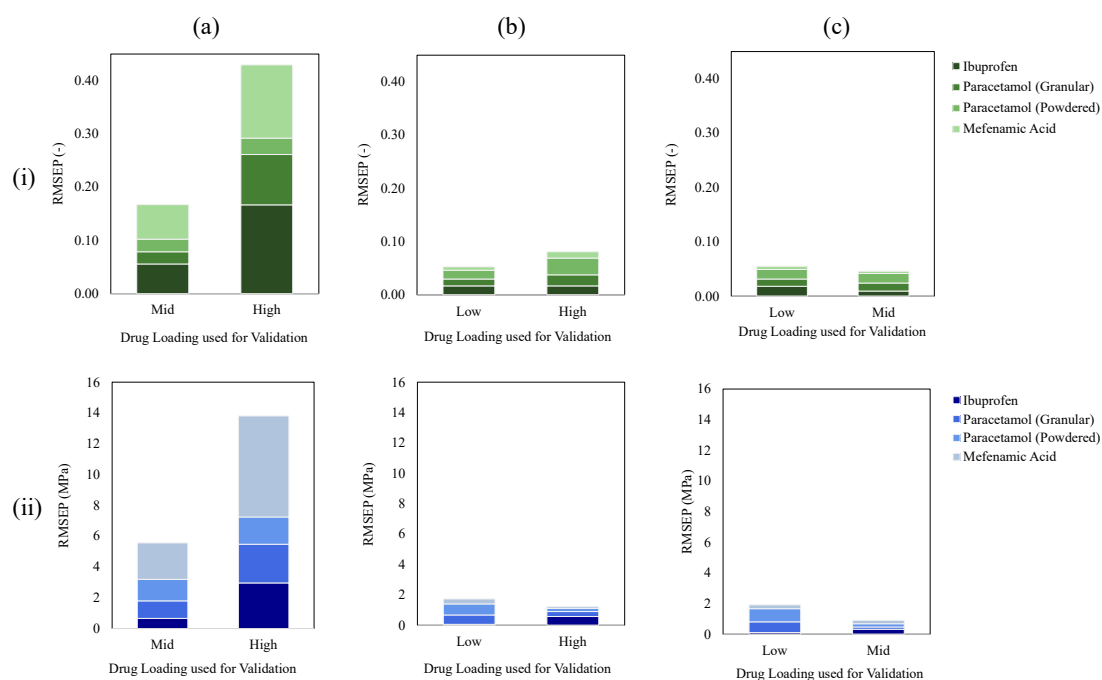


Figure 6.9: The Root-Mean-Squared Error of Prediction (RMSEP) of validation datasets from the cross validation analysis which used the placebo and (a) low loading, (b) mid loading, and (c) high loading datasets for calibration. Results shown reflect the (i) Kawakita and (ii) Ryshkewitch-Duckworth models with the colours showing the contributions of the different API datasets.

C.9). Knowing that a large degree of scattering could be observed in the estimated tuning parameters (Figure 6.1) and that there may be alternative tuning parameters which better fit the linear correlation to this as based on the contour plots (Figure 6.2), an alternative method can be developed to capitalise on the new-found flexibility of these parameters. By designating arbitrary values for the ‘pure’ material parameters – for now, in a binary space – 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 (Figure C.10 in Appendix C.5). 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. 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 blends to construct a mixture rule, reducing API usage by up to 50%. The total error for this new method is lower than that of the traditional method and provides an acceptable GoF, but for the compactability model this is still greater than individually estimating the fitting parameters for each formulation. Efforts to minimise the error of the global optimisation should consider expanding this method beyond the binary API-placebo space to better capture the contribution of the individual components.

6.5 Conclusions

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. 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 by 50% as only one formulation may be required.

Chapter 7

Assessing Material-Sparing Parameterisation Approaches for Ternary Mixtures

Chapter Summary

This chapter investigates the optimisation of mixture rules and empirical model parameters for ternary direct compression formulations, with a particular focus on predictive performance through reducing the required experimental effort. The chapter starts with a comparison traditional approaches to the expanded global optimisation, then assesses the influence of placebo inclusion on the performance of the optimisation. It also discusses the use of MBDoE relative to random experiment selection, providing a framework for resource-efficient formulation development and empirical model parameterisation.

7.1 Introduction

There has been a marked increase in the number of digital tools being developed that are reshaping the possibilities of pharmaceutical manufacturing, broadening the opportunities to accelerate the development of new medicines (Mustoe et al., 2025). QbD principles have helped to lay the foundations of embedding quality and minimizing risk in the development of these; however, the implementation of this for an OSD involves a rigorous, science-driven evaluation of how a system’s material attributes and process parameters may impact product quality attributes (Yu, 2008; Yu et al., 2014). This evaluation is often dominated by prior knowledge and trial-and-error methods requiring a substantial amount of material and labour, only to gain information that is highly specific to a definite design space.

Effectively implementing QbD in OSD formulations requires careful consideration of numerous material and process variables, many of which are interdependent or exhibit nonlinear behaviours across a formulation space. This complexity often makes traditional DoE approaches convoluted or impractical to execute comprehensively. Advances in mixture and empirical models now provide an opportunity to replace traditional, experience-driven experimentation with data-driven strategies that reduce the number of required experiments while maintaining predictive reliability. One promising approach is MBDoE, which guides experimentation by mathematically evaluating the information content of potential experiments and their impact on model calibration and parameter estimation (Cenci et al., 2023; Franceschini and Macchietto, 2008; Wang and Dowling, 2022).

This chapter extends the work presented in Chapter 6 to explore how the global optimisation approach can be used in a ternary system to reduce experimental requirements and dependence on prior formulation knowledge during the development of directly compressed OSD products. The study is presented in two parts: (i) the development and validation of a global optimisation method to populate mixture rules for ternary formulations of different particle size distributions of paracetamol and ibuprofen; and (ii) the application of a MBDoE to guide the selection of experiments, comparing different opti-

quality criteria (D-, A-, and E-optimality) against random experiment selection to assess their effectiveness in improving model accuracy while minimising API consumption.

7.2 Materials and Methods

The dataset considered in this chapter considers six different formulation spaces of paracetamol and ibuprofen of different particle size distributions. The formulation spaces are made up of four placebo blends and nine API-loaded blends, in which the concentrations of the API and two fillers were varied for each compound. An exception is observed for micronized paracetamol, where tableting was unsuccessful at API loadings exceeding 22 w/w%, limiting the accessible formulation space (Table 4.3). To assess experimental variability, a subset of blends was randomly duplicated; these replicates are indicated by red crosses in Figure 4.1 and marked with asterisks in Table 4.3.

The APIs considered were dense, powdered and micronized grades of acetaminophen USP / paracetamol (MallinckrodtTM, United States), as well as ibuprofen 50, ibuprofen 38, and ibuprofen 25 (BASF, UK). The excipients were anhydrous lactose (SuperTab® 21AN, DFE Pharma, Germany), microcrystalline cellulose (Avicel PH-102, DuPont, UK), croscarmellose sodium (Ac-Di-Sol® SD-711, DuPont, Ireland) and magnesium stearate (Ligamed MF-2V, Peter Greven, Netherlands).

A full summary of information can be found in Chapter 4 concerning:

- Materials (Section 4.1.2)
- Characterisation of Materials (Section 4.2)
- Blending of Formulations (Section 4.3.2)
- Tablet Manufacture (Section 4.4)
- Tablet Testing (Section 4.5), and,
- Tablet Porosity and Tensile Strength (Section 4.6)

7.2.1 Compressibility and Compactability Models

The models considered were those found to be most consistently capable of predicting the compressibility (Kawakita (Equation 7.1)) and compactability (Ryshkewitch-Duckworth (Equation 7.2)) behaviours of pharmaceutical formulations from Chapter 5.

$$\varepsilon(P) = \frac{A_K}{1 + B_K P} \quad (7.1)$$

$$\sigma(\varepsilon) = A_{RD} e^{-B_{RD} \varepsilon} \quad (7.2)$$

where ε is the porosity of the compact, and σ represents the strength of the tablet. Chapter 6 identified that there was a large range of model parameter values that can be applied to predict the compressibility and compactability behaviours of a blend. Thus, the model parameters have been denoted as A and B as this study does not consider the physical definitions of the parameters themselves.

7.2.2 Mixture Rules and their Population

The mixture rules considered in this chapter are outlined in Chapter 4 under Section 4.8.2.

7.2.3 Traditional Approach for Model Parameter Estimation

Prior to the development of the global optimisation approach, mixture rule parameters were determined by fitting lines of best fit to parameter estimates obtained from datasets spanning a range of API volume fractions (Busignies et al., 2012; Frenning et al., 2009; Jolliffe et al., 2022; Mazel et al., 2011). In this study, the parameters of the individual blends were first estimated using the Kawakita (Equation 4.12) and Ryshkewitch–Duckworth (Equation 2.14) models. The three mixture rules considered (Equations 4.15–4.17) were then fitted to these parameter estimates as a function of composition.

The resulting fits were used to infer the parameters associated with the individual components, as defined by each mixture rule. The GoF of these models was evaluated and compared across the different mixture rule formulations (Appendix D.2).

7.2.4 Extension of Optimisation to Ternary Formulation Space

The optimisation framework described in Section 4.8.3 was extended from binary (API–excipient) systems to ternary formulations comprising an API and two excipients (Filler 1 and Filler 2) where the disintegrant and lubricants were assumed negligible due to their low contribution, consistency across the space, and constant lubrication extent as estimated using Kushner-Moore (Equation 4.2). The underlying objective function and optimisation strategy remain unchanged, with the total RMSE minimised across all formulations for a given API. However, the parameter vector $\boldsymbol{\theta}$ is expanded to include individual parameter pairs for each component in the formulation, rather than grouping excipients into a single contribution.

Accordingly, the mixture parameter estimation, previously defined for binary systems, is generalised to account for $N = 3$ components through the mixture rule $\mathbf{f}_{mix}(\boldsymbol{\theta}, \boldsymbol{\phi})$, where $\boldsymbol{\phi}$ represents the vector of volume fractions for the API and both excipients. This enables component-specific contributions to compressibility and compactability behaviour to be resolved within the optimisation.

The same set of mixture rules (arithmetic, geometric, and harmonic) and optimisation procedure (BFGS minimisation of total RMSE) are retained. This extension therefore preserves the original modelling framework while increasing the resolution of parameter estimation, allowing the influence of individual formulation components to be explicitly captured across the ternary design space.

7.2.5 Statistical Analysis

A summary of the fitting procedure as well as the definitions for GoF metrics can be found in Section 4.7.1.

7.2.6 Evaluation of Experimental Efficiency Using MBDoE and Random Selection

With the observed non-identifiability in the model parameters, the justification for using MBDoE as a tool for parameter estimation is reduced. To assess this further, and to determine whether the optimisation still offers predictive benefit, the MBDoE approach was tested against randomly selected experiments. This allows evaluation of whether a structured experimental design framework is necessary, or whether similar performance can be achieved through non-informed sampling.

The methodology used to construct the MBDoE, alongside the comparative framework employing randomly selected experiments for global optimisation, is detailed in Chapter 4 (Section 4.8.4). This section focuses on quantifying the resulting reduction in experimental burden and evaluating the efficiency gains achieved through the MBDoE strategy relative to non-informed sampling approaches.

7.3 Results

7.3.1 Comparing Traditional Approaches to Optimisation of Mixture Rules

The optimisation framework was applied to the experimentally collected datasets spanning the ternary formulation space and compared against the traditional line-of-best-fit approach used to parameterise the compressibility and compactability mixture rules. For each considered combination of mixture rules used to populate parameter A and B , the total RMSE was estimated for each approach (Figure 7.1).

Across all rule combinations, the optimisation-based approach produced lower total RMSE values than the traditional approach. This trend was observed for both the Kawakita and Ryshkewitch-Duckworth models. However, the Ryshkewitch-Duckworth model showed greater variation in RMSE across the tested rule combinations, particularly with changes in the rule used to estimate A_{RD} .

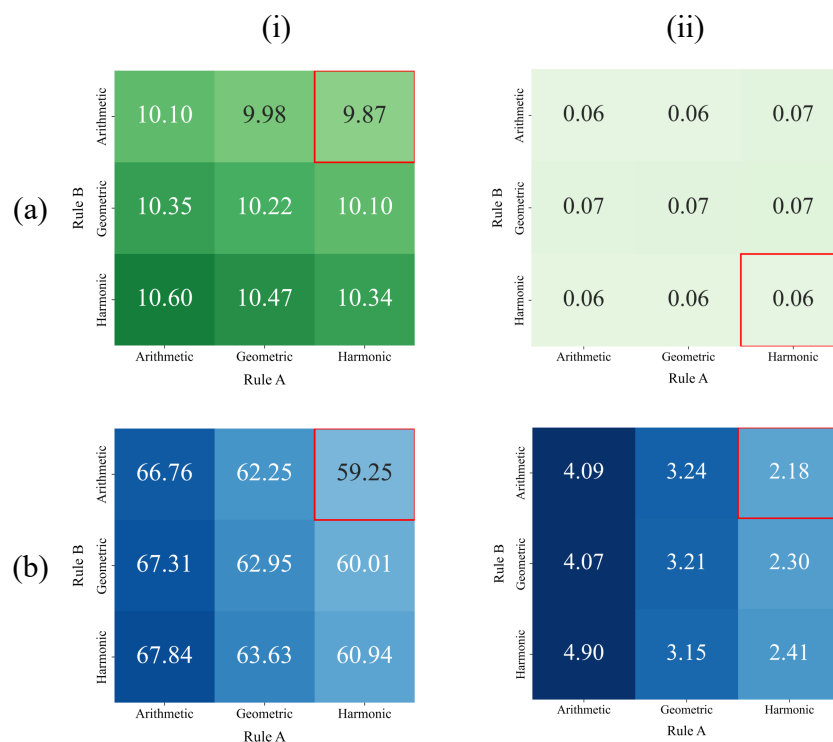


Figure 7.1: Matrices showing the RMSE for different mixture rule combinations for optimisation of the (a) Kawakita and (b) Ryshkewitch-Duckworth models using the (i) Traditional and (ii) Optimised Approach. These results show the total across all API formulation spaces. The combination with the lowest RMSE is outlined in red. These plots include all of the paracetamol and ibuprofen datasets to provide a comparison of overall performance.

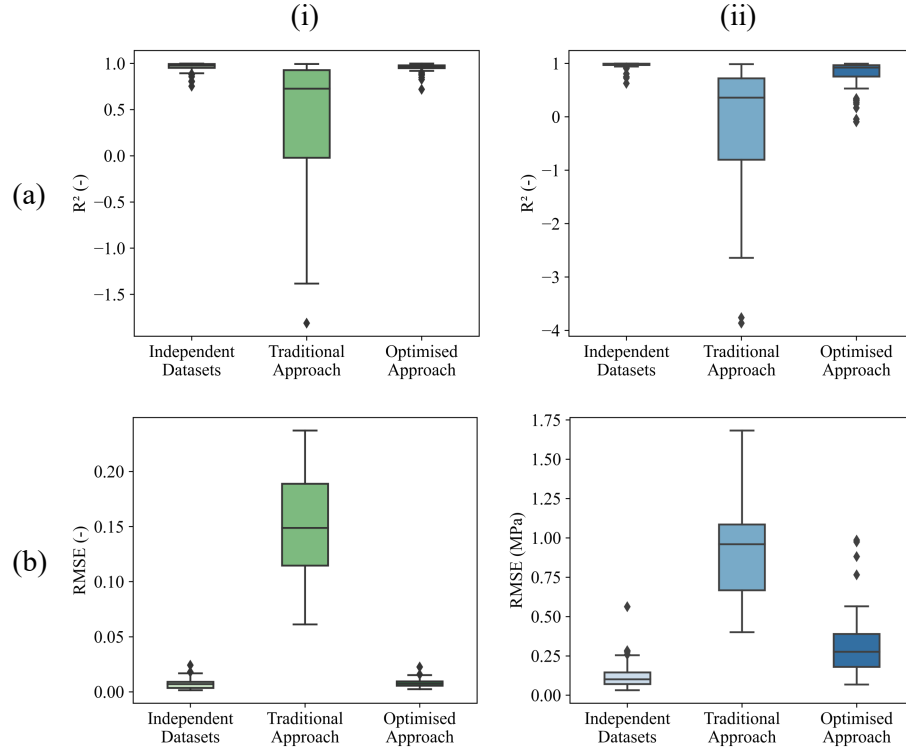


Figure 7.2: Box plots showing the distribution of (a) R^2 and (b) $RMSE$ for the (i) Kawakita and (ii) Ryshkewitch-Duckworth models. Each plot compares the different use cases: the blend-by-blend fitting of the independent datasets (treating each individual blend as a unique dataset to parameterise single compression or compaction curves), the traditional approach to parameterise mixture rules and the global optimisation of the model mixture rules.

The combination of mixture rules which returned the lowest *RMSE* for each model (outlined in red) were selected to show an overall comparison of performance (Figure 7.2). This box-plot shows the R^2 and *RMSE* for the different methods of using the modelling approaches for the Kawakita and Ryshkewitch-Duckworth. As expected, treating the blends independently (i.e. parameterising every individual blend rather than developing a predictive model) provided the best quality of fit for each empirical model; however, this approach does not provide a solution to predict compressibility or compactability of a new blend in the ternary space. As with the selection of mixture rules for parameters *A* and *B*, the optimized approach provided a competitive advantage to the alternative traditional method as it was capable of achieving a tighter spread of GoF metrics closer to their target values.

7.3.2 Optimisation Performance

Although a single combination of mixture rules appeared to perform best when evaluated across the full dataset (highlighted in red in Figure 7.1), this pooled analysis does not account for formulation-specific behaviour. Examination of the individual formulation DoEs revealed that the optimal mixture rule combination differed between design spaces (Kawakita in Table 7.1, Ryshkewitch–Duckworth in Table 7.2), indicating that mixture rule selection is likely formulation-dependent rather than dictated by a single universally optimal model.

Table 7.1: Optimum rule selections to optimise the parameterisation of the Kawakita model using mixture rules, with averaged Goodness of Fit metrics and standard deviations estimated from the API datasets across the formulation space.

API	Rule A	Rule B	R^2	RMSE (-)
Dense Paracetamol	Harmonic	Arithmetic	0.968 ± 0.020	0.008 ± 0.003
Powdered Paracetamol	Arithmetic	Harmonic	0.945 ± 0.045	0.010 ± 0.004
Micronized Paracetamol	Arithmetic	Geometric	0.970 ± 0.020	0.009 ± 0.003
Ibuprofen 50	Harmonic	Geometric	0.947 ± 0.038	0.009 ± 0.003
Ibuprofen 38	Arithmetic	Geometric	0.969 ± 0.025	0.007 ± 0.003
Ibuprofen 25	Geometric	Arithmetic	0.943 ± 0.076	0.009 ± 0.005

Table 7.2: Optimum rule selections to optimise the parameterisation of the Ryshkewitch-Duckworth model using mixture rules, with averaged Goodness of Fit metrics and standard deviations estimated from the API datasets across the formulation space.

API	Rule A	Rule B	R^2	RMSE (MPa)
Dense Paracetamol	Geometric	Arithmetic	0.952 ± 0.072	0.225 ± 0.110
Powdered Paracetamol	Harmonic	Geometric	0.944 ± 0.054	0.251 ± 0.121
Micronized Paracetamol	Harmonic	Arithmetic	0.928 ± 0.095	0.386 ± 0.215
Ibuprofen 50	Harmonic	Geometric	0.700 ± 0.365	0.367 ± 0.192
Ibuprofen 38	Harmonic	Geometric	0.829 ± 0.261	0.310 ± 0.192
Ibuprofen 25	Harmonic	Geometric	0.757 ± 0.312	0.334 ± 0.161

The optimisation of Kawakita performed consistently well across all six API grades (Figure 7.3). However, Ryshkewitch-Duckworth’s optimisation whilst consistent across particle sizes showed a difference in performance across APIs as the paracetamol blends were observed to have performed better than the ibuprofen blends (Figure 7.4).

Residual error distributions were analysed within the industrially relevant RoI to assess model performance under expected operating conditions (Figure 7.5), with summary descriptors reported in Table 7.3 and Table 7.4 (full dataset results are provided in Appendices D.3 and D.4). Approximately 60% of the collected experimental data for each API fell within the RoI, indicating comparable data coverage across the datasets. Within this practically relevant space, the Kawakita model showed residuals that remained tightly clustered around zero for all APIs, with slightly negative mean values indicating a small systematic underprediction of tablet porosity and relatively low variability. In contrast, the Ryshkewitch–Duckworth model exhibited greater variation in both residual mean and spread across the paracetamol blends, alongside a tendency to overpredict tensile strength for the ibuprofen blends. These findings indicate that, even when analysis is restricted to the most industrially relevant portion of the design space, deviations from expected model performance remain formulation-dependent. It should be noted that the larger absolute residual values observed for the Ryshkewitch–Duckworth model reflect the larger numerical scale of tensile strength measurements relative to porosity, rather than inherently greater model uncertainty.

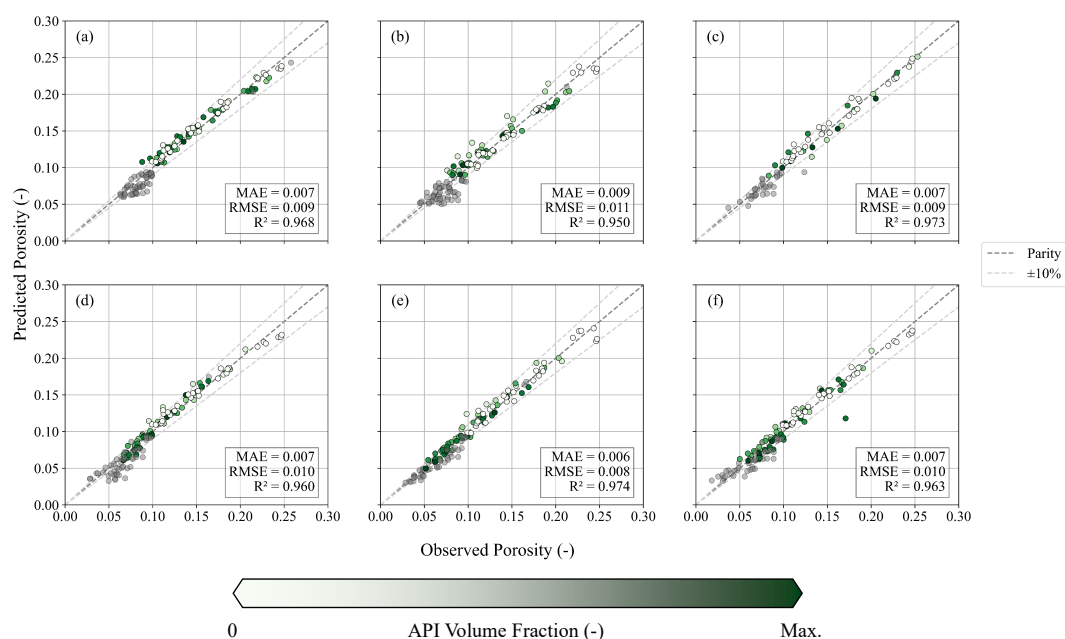


Figure 7.3: Parity plots for the predicted and true porosity using the optimised mixture rule approach for the Kawakita model for (a) Dense, (b) Powdered, and (c) Micronized Paracetamol, and Ibuprofen (d) 50, (e) 38, and (f) 25. Data points which lie within the defined RoI are highlighted in colour which reflects their API mass fraction. The $\pm 10\%$ limits are represented with the dashed grey lines. Data points which exist within the defined Region of Interest being highlighted in colour which reflects their API volume fraction.

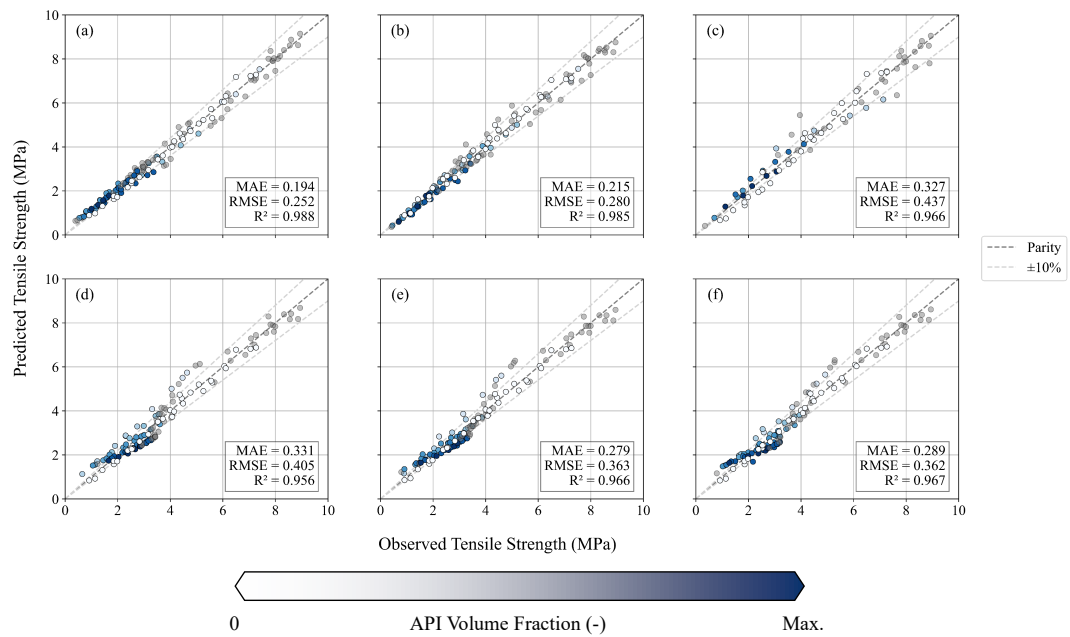


Figure 7.4: Parity plots for the predicted and true tensile strength using the optimised mixture rule approach for the Ryshkewitch-Duckworth model for (a) Dense, (b) Powdered, and (c) Micronized Paracetamol, and Ibuprofen (d) 50, (e) 38, and (f) 25. Data points which lie within the defined RoI are highlighted in colour which reflects their API mass fraction. The $\pm 10\%$ limits are represented with the dashed grey lines. Data points which exist within the defined Region of Interest being highlighted in colour which reflects their API volume fraction.

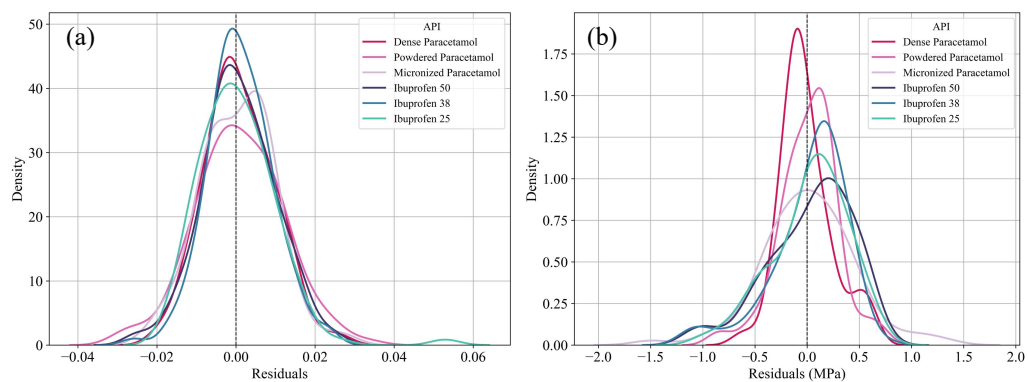


Figure 7.5: Probability density plots of the residual errors that lie within the RoI for the (a) Kawakita and (b) Ryshkewitch-Duckworth models.

The overall residual distribution shapes were broadly consistent across APIs for the Kawakita model. In contrast, the greater variability observed in the Ryshkevitch–Duckworth residual distributions suggests a stronger dependence of model behaviour within the RoI on material-specific characteristics, such as particle properties and particle size distribution. The presence of bimodality suggests that some formulation-dependent behaviour was not fully captured by the current model and optimisation framework. A supplementary evaluation of interaction-based model extensions (Appendix D.5) indicated that, although additional parameters and model complexity could improve representation in some cases, the performance gains were limited relative to the increase in model complexity.

Table 7.3: Descriptors for the probability density functions of the Kawakita residuals for the independent API datasets within the RoI.

API	Number of Datapoints	Mean	Variance $\times 10^{-5}$	Modality
Dense Paracetamol	81	-0.003	5.4	2
Powdered Paracetamol	80	-0.002	5.7	2
Micronized Paracetamol	48	-0.002	6.3	2
Ibuprofen 50	83	-0.002	4.2	2
Ibuprofen 38	82	-0.002	5.4	2
Ibuprofen 25	83	-0.001	8.1	2

Table 7.4: Descriptors for the probability density functions of the Ryshkevitch–Duckworth residuals for the independent API datasets within the RoI.

API	Number of Datapoints	Mean (MPa)	Variance (MPa)	Modality
Dense Paracetamol	81	-0.014	0.044	2
Powdered Paracetamol	80	0.023	0.030	2
Micronized Paracetamol	48	0.020	0.138	2
Ibuprofen 50	83	0.010	0.136	2
Ibuprofen 38	82	0.023	0.099	2
Ibuprofen 25	83	0.029	0.099	2

7.3.3 Evaluation of Optimisation Performance Discrepancy

To examine the discrepancy in the performance of the optimisation between paracetamol and ibuprofen further, the relationship between tensile strength and API volume fraction was considered (Figure 7.6). Paracetamol formulations exhibited a more consistent decrease in tensile strength with increasing API concentration across all particle sizes. In contrast, ibuprofen formulations show a pronounced drop in tensile strength upon initial API addition, followed by a more gradual decrease with increasing API volume fraction.

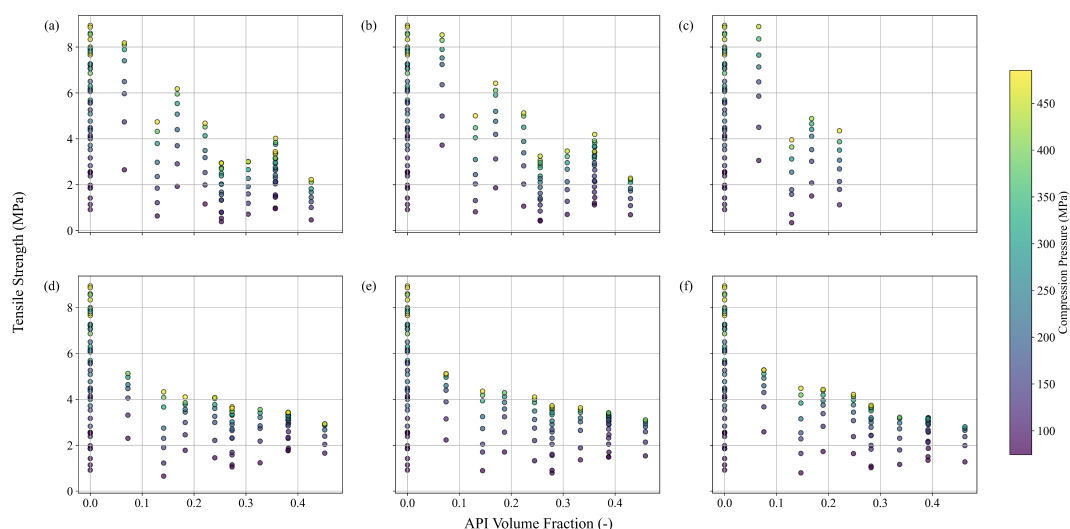


Figure 7.6: Tensile strength data with respect to API volume fraction for (a) Dense Paracetamol, (b) Powdered Paracetamol, (c) Micronized Paracetamol, (d) Ibuprofen 50, (e) Ibuprofen 38, and (f) Ibuprofen 25. The colour represents the compression pressure use to manufacture the tablets.

To test whether the observed change in ibuprofen behaviour at low API load was contributing disproportionately to model error, the optimisation was repeated with placebo data excluded; for consistency, this sensitivity analysis was applied to both models and all APIs. Excluding placebo data improved performance for both the Kawakita (Figure 7.7) and Ryshkewitch–Duckworth (Figure 7.8) models, with the greatest improvement observed for the ibuprofen formulations.

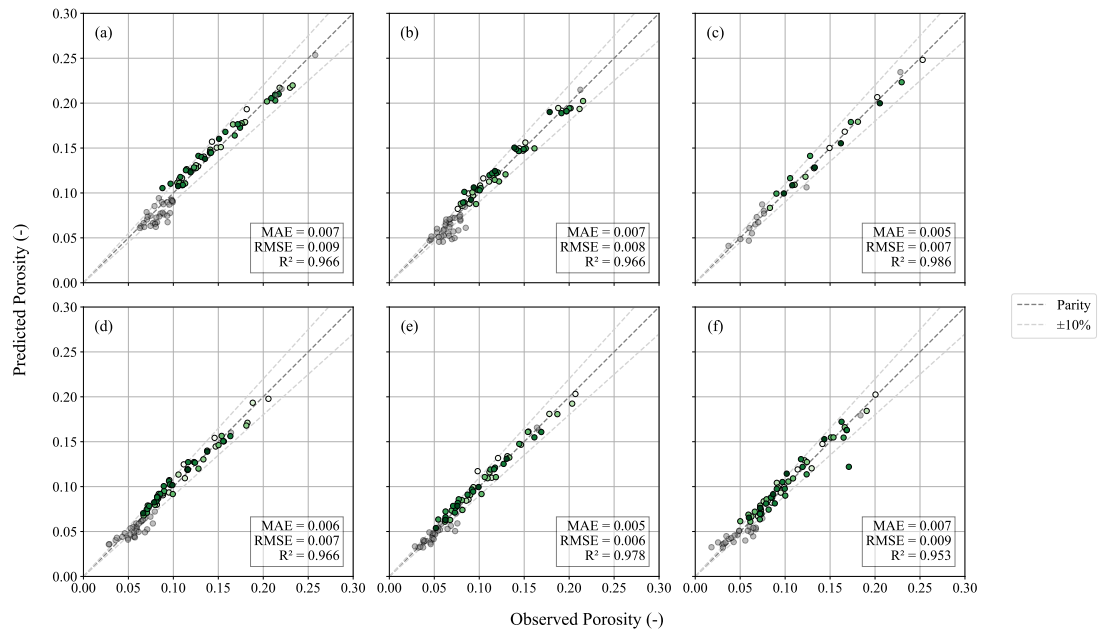


Figure 7.7: Parity plots for the predicted and true tensile strength using the optimised mixture rule approach for the Kawakita model with the placebo data excluded from the calibration. Data points which lie within the defined RoI are highlighted in colour which reflects their API mass fraction. The $\pm 10\%$ limits are represented with the dashed grey lines. Data points which exist within the defined Region of Interest (defined in Section 4.7.2) being highlighted in colour which reflects their API volume fraction.

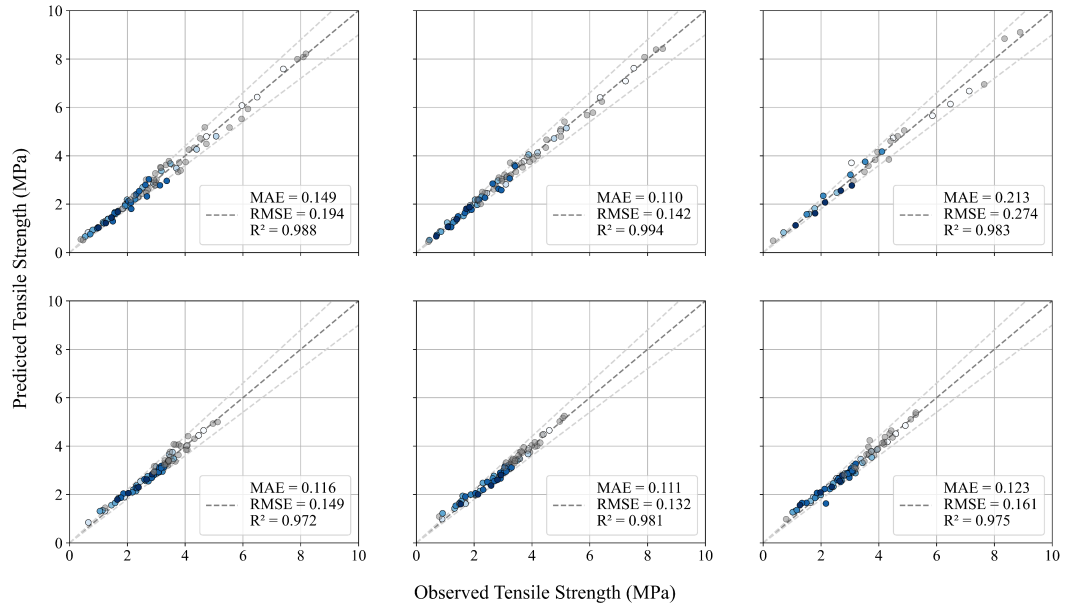


Figure 7.8: Parity plots for the predicted and true tensile strength using the optimised mixture rule approach for the Ryshkewitch-Duckworth model with the placebo data excluded from the calibration. Data points which lie within the defined RoI are highlighted in colour which reflects their API mass fraction. The $\pm 10\%$ limits are represented with the dashed grey lines. Data points which exist within the defined Region of Interest (defined in Section 4.7.2) being highlighted in colour which reflects their API volume fraction.

Despite the improved performance observed when placebo data were excluded, the full dataset was retained for the subsequent experimental reduction analysis. This decision was due to the number of placebo formulations matching the number of unknowns to parameterise the ternary mixture model. Further as the placebos are consistent across the formulation spaces, this established a baseline from which the effect of adding API-containing experiments can be assessed. Retaining this baseline allows subsequent API-loaded formulations to be evaluated in terms of their contribution to improving predictive performance, rather than simply fulfilling the model’s parameter requirements.

7.3.4 Evaluation of Experimental Reduction

To evaluate the potential to reduce the experimental workload, optimisation performance was assessed as a function of the number of API-loaded blends added to the baseline calibration (placebo only) dataset. These experiments were selected either using a MBDoE strategy or through random selection, allowing the efficiency of model-guided experiment prioritisation to be assessed. This comparison was used to determine whether MBDoE could provide a reliable route to improving model performance while minimising additional experimental burden.

For each calibration iteration, the MAE was calculated using the candidate dataset (i.e. the data which has not yet been used to parameterise the model) for the Kawakita (Figure 7.9) and Ryshkewitch–Duckworth (Figure 7.10) models. In most cases, the introduction of API-loaded blends improved predictive performance relative to placebo-only calibration (iteration 0), but this reduction in MAE was not consistent to the expectations of a MBDoE. Additional experiments did not always lead to further improvement, and in some cases temporary increases in MAE were observed. The Kawakita model generally approached benchmark performance more rapidly and with greater consistency than Ryshkewitch–Duckworth.

The influence of different MBDoE optimality metrics (D-, A-, and E-optimality) was assessed to determine whether any one metric consistently outperformed the others. These metrics generated distinct experimental routes (example shown in Figure 7.11;

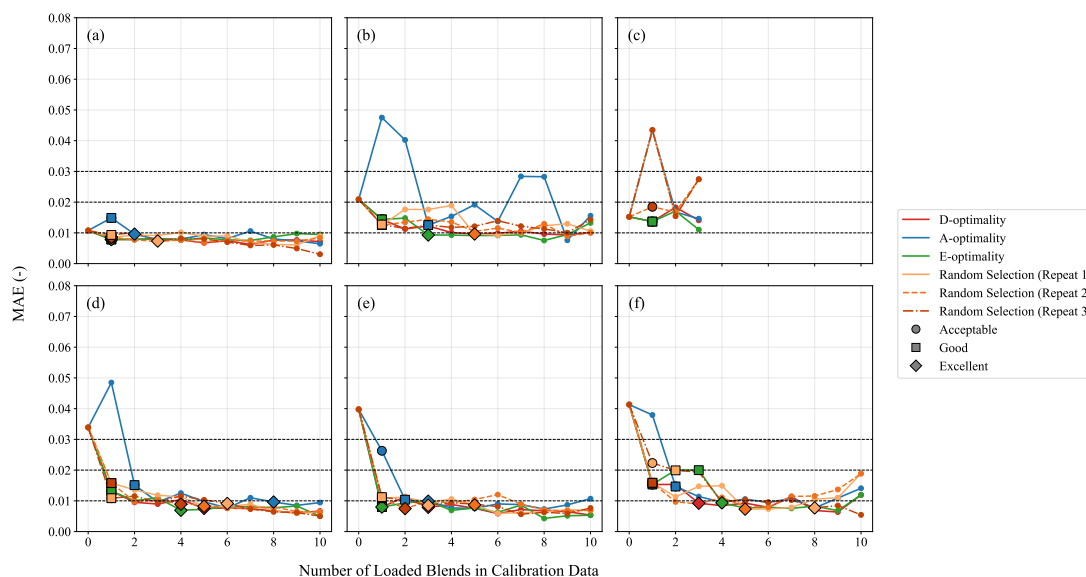


Figure 7.9: Mean absolute error (MAE) as a function of the number of drug-loaded blends included in the optimisation of the Kawakita model for (a) dense, (b) powdered, and (c) micronized paracetamol, and (d) ibuprofen 50, (e) ibuprofen 38, and (f) ibuprofen 25. Colours distinguish optimality-based sampling strategies from random selection, with individual random repeats further differentiated by line style. Horizontal dashed lines indicate user-defined prediction quality thresholds: Acceptable (0.03), Good (0.02), and Excellent (0.01). Markers denote the minimum number of blends required to achieve predictions at or below a given threshold for three consecutive experiments: circles (Acceptable), squares (Good), and diamonds (Excellent), coloured according to the corresponding strategy.

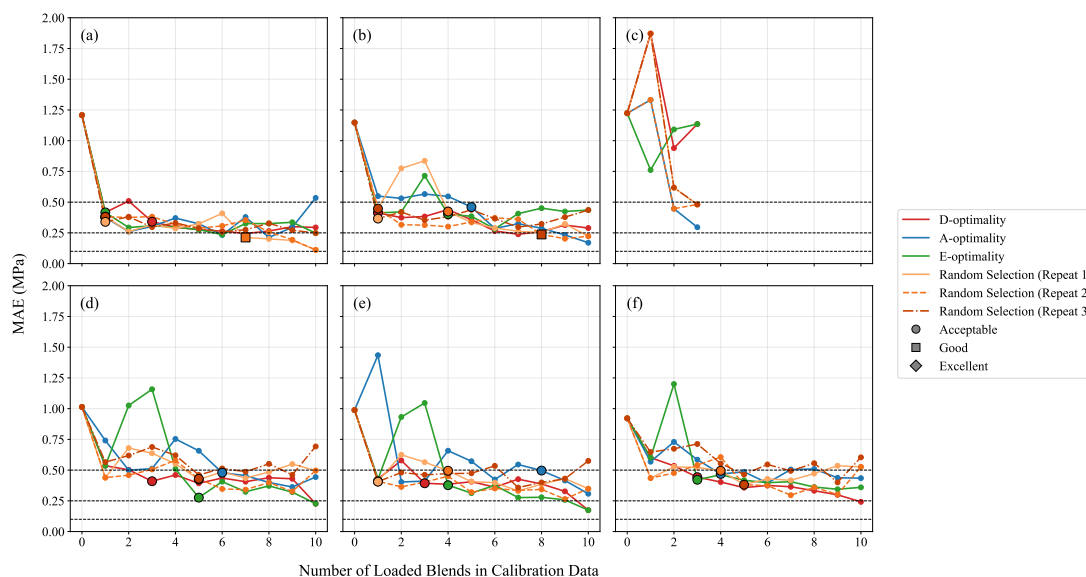


Figure 7.10: Mean absolute error (MAE) as a function of the number of drug-loaded blends included in the optimisation of the Ryshkewitch-Duckworth model for (a) dense, (b) powdered, and (c) micronized paracetamol, and (d) ibuprofen 50, (e) ibuprofen 38, and (f) ibuprofen 25. Colours distinguish optimality-based sampling strategies from random selection, with individual random repeats further differentiated by line style. Horizontal dashed lines indicate user-defined prediction quality thresholds: Acceptable (0.50 MPa), Good (0.25 MPa), and Excellent (0.10 MPa). Markers denote the minimum number of blends required to achieve predictions at or below a given threshold for three consecutive experiments: circles (Acceptable), squares (Good), and diamonds (Excellent), coloured according to the corresponding strategy.

remaining routes in Appendix D.6), but no single metric consistently outperformed the others. Likewise, MBDoE did not universally outperform random selection: while model-guided routes sometimes reached lower MAE more efficiently, random selection performed similarly or occasionally better in other cases.

A key observation across the estimated optimality metrics (Appendix D.7) is the rapid convergence with increasing numbers of loaded blends in the calibration data. In the majority of formulations, stabilisation was achieved by approximately 4–5 blends, with only minor fluctuations observed thereafter. This indicates that the model-based design of experiments framework identifies near-optimal experimental designs with relatively few calibration experiments, which is a central objective of the proposed approach. The consistency of this convergence behaviour across all six formulation spaces — spanning both paracetamol and ibuprofen APIs — demonstrates the generalisability of the framework across chemically distinct systems.

It was expected that parameter estimates and selected mixture rules would converge as the calibration dataset increased. Figures 7.12 and 7.13 show the parameter trends for the Ibuprofen 50 formulation, which exhibited some of the greatest variability across the datasets. Parameter trends for the remaining formulations are provided in Appendix D.8. For the API-specific parameters, partial convergence was observed in the Ryshkewitch–Duckworth model (Figure 7.13), whereas the Kawakita model showed greater variation, with confidence intervals remaining substantial throughout the iterations (Figure 7.12). This higher variability in the Kawakita parameters is further reflected in the inconsistent selection of mixture rules during MBDoE (Figure 7.14); plots for the remaining formulation spaces are provided in Appendix D.9.

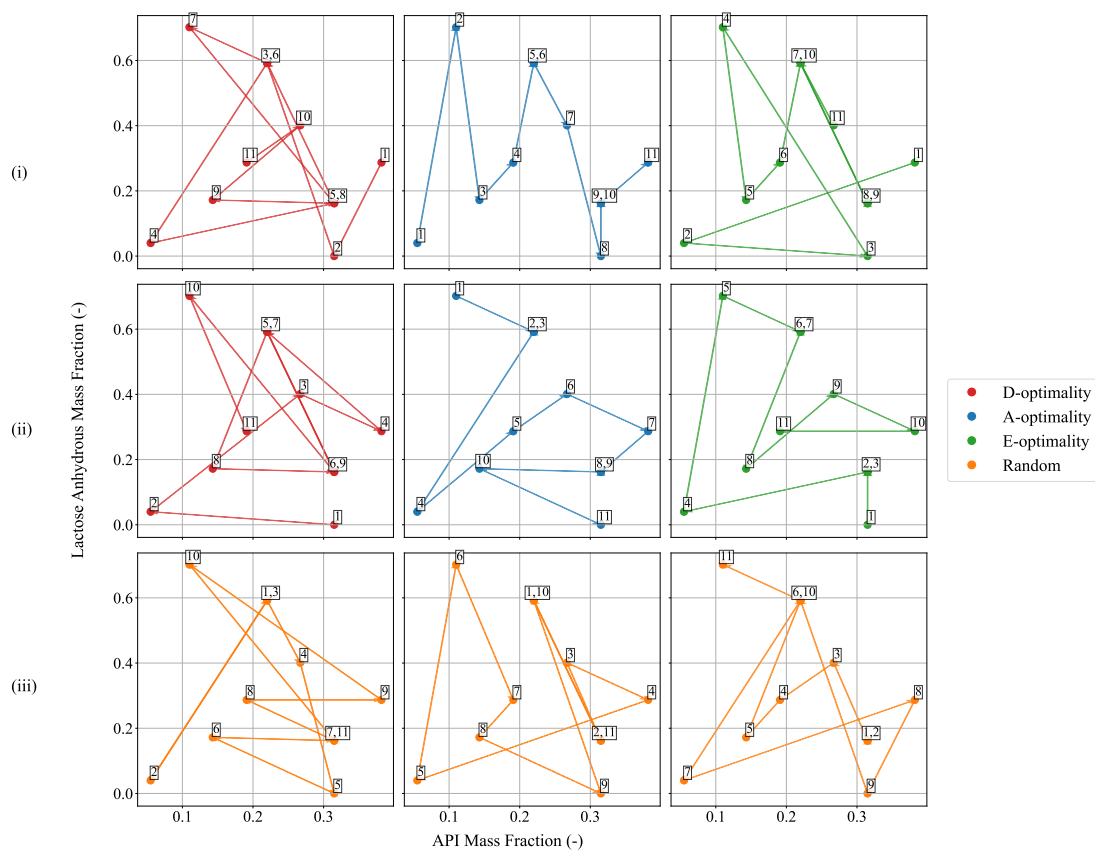


Figure 7.11: An example showing the experimental routes taken by the Model Based Design of Experiments for (i) Kawakita and (ii) Ryshkewitch-Duckworth models and the routes taken by the three iterations of (iii) Random Selection to predict behaviours for ibuprofen 50.

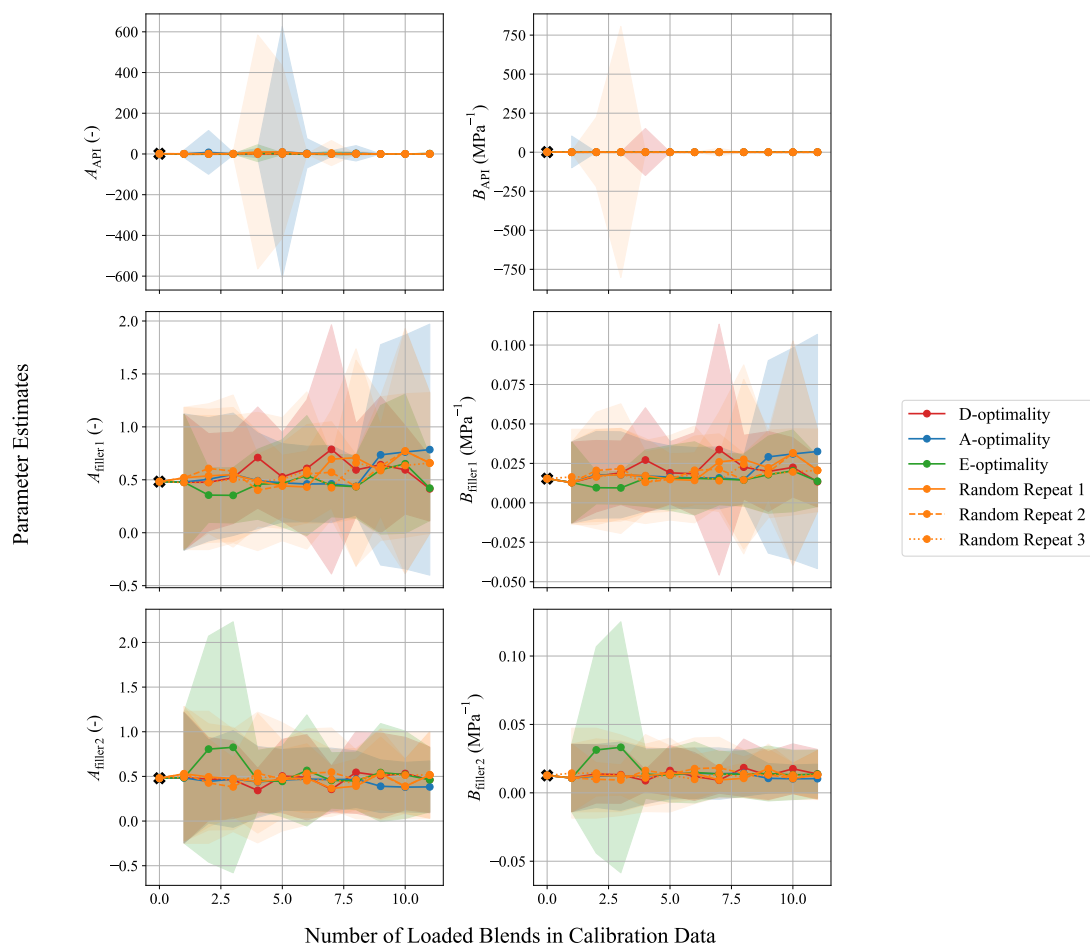


Figure 7.12: An example plot showing component parameter estimations with increasing blends added to the MBD_{oE} or random selection for the Kawakita model for ibuprofen 50. Coloured shaded areas represent the 95% confidence intervals estimated from the covariance matrix.

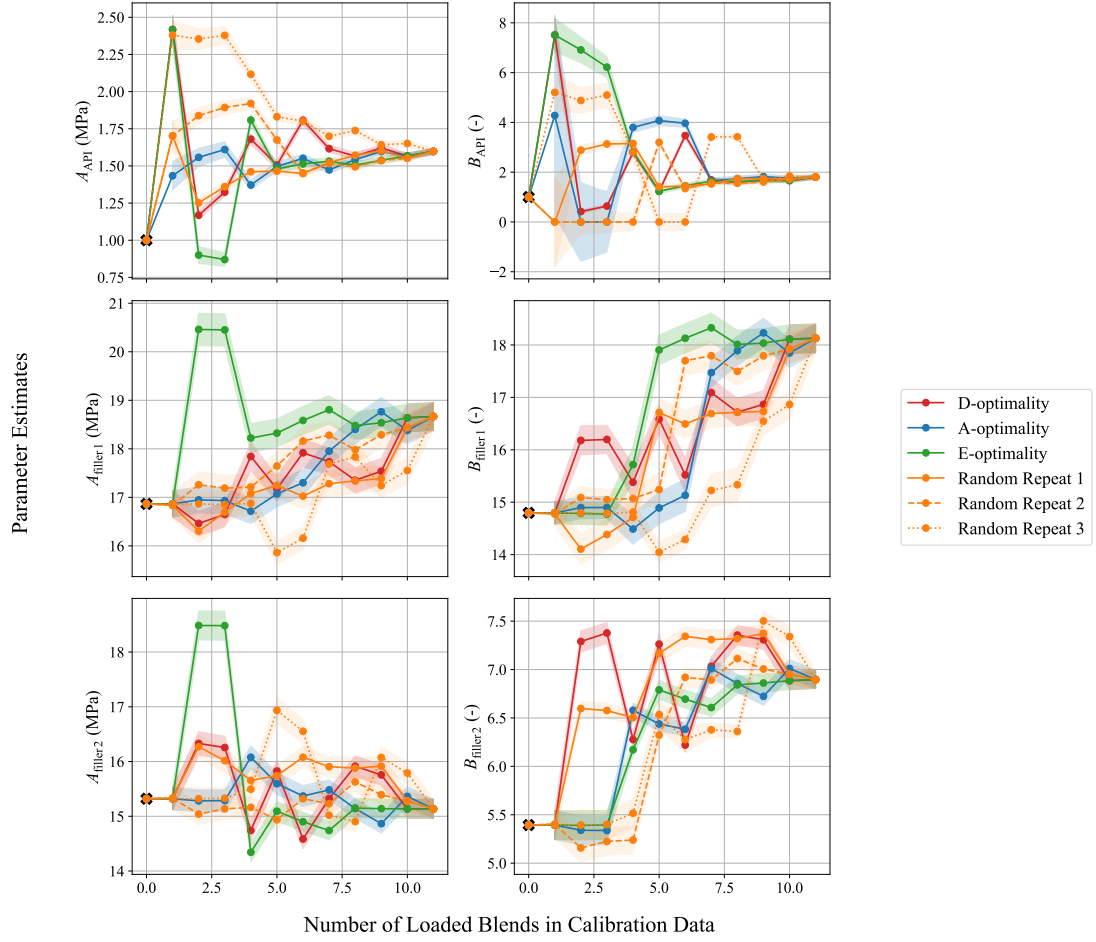


Figure 7.13: An example plot showing component parameter estimations with increasing blends added to the MBDoE or random selection for the Ryshkewitch-duckworth model for ibuprofen 50. Coloured shaded areas represent the 95% confidence intervals estimated from the covariance matrix.

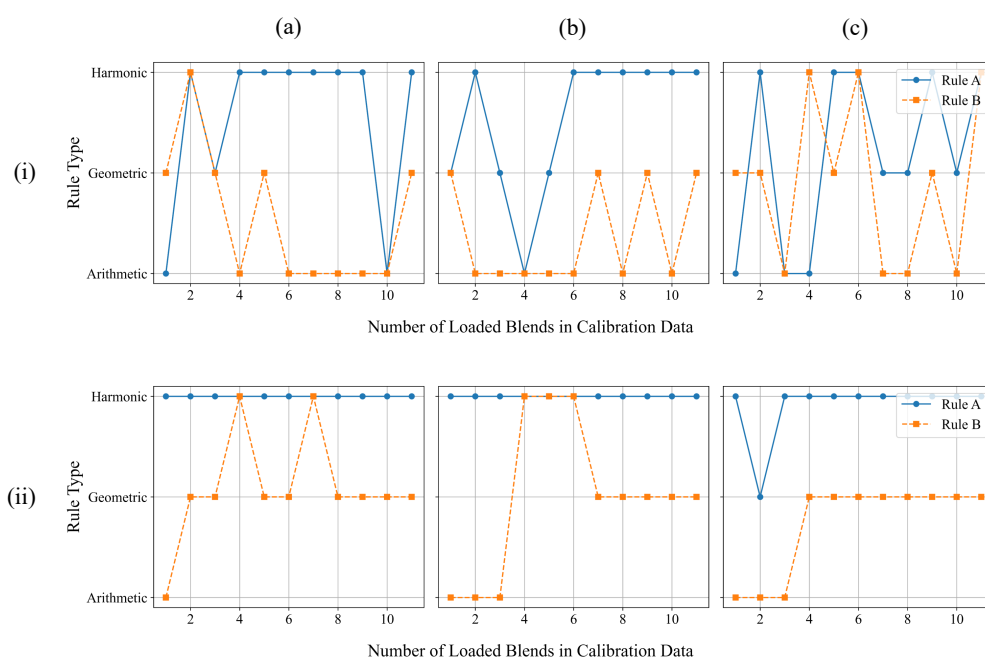


Figure 7.14: Returned mixture rules used to estimate the mixture parameters for A and B using (i) Kawakita and (ii) Ryshkewitch-Duckworth for Ibuprofen 50 based on (a) D-, (b) A-, and (c) E-Optimality.

Overall, parameter values did not converge consistently, particularly for the Kawakita parameters. Despite this, model predictions remained reasonably accurate, indicating that the parameters are non-identifiable within the current model structure and experimental dataset. In other words, multiple parameter combinations can produce similarly accurate predictions, highlighting that high predictive performance does not necessarily imply reliable parameter estimation (consistent with results from Chapter 6, Figure 6.2). These observations suggest that, while MBDoE may still provide systematic advantages for exploring the formulation space and reducing reliance on prior knowledge, its utility for improving parameter convergence alone is limited in this case.

The MBDoE framework was developed to reduce the mass of API required to characterise formulation design spaces in terms of compressibility and compactability, offering a more resource-efficient alternative to traditional, prior-knowledge-driven trial-and-error experimentation. To assess potential reductions in API usage, cumulative material consumption was tracked along the suggested experimental routes for the Kawakita (Figure 7.15) and Ryshkewitch–Duckworth (Figure 7.16) models. These results are shown for the Ibuprofen 50 formulation, with consumption across the remaining formulation spaces provided in Appendix D.10.

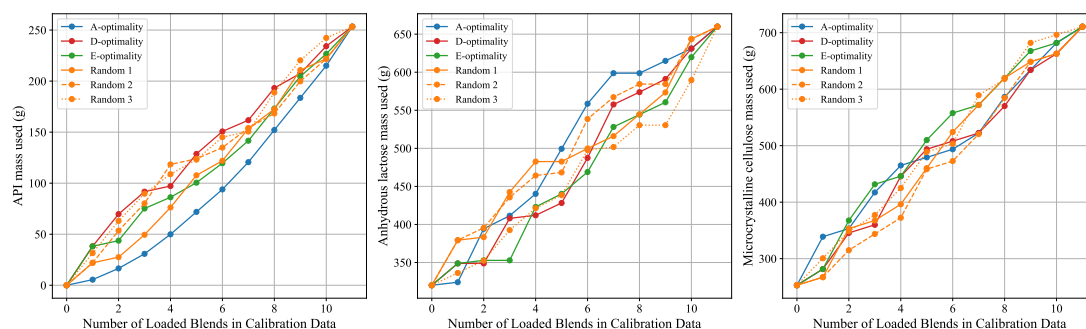


Figure 7.15: Comparison of MBDoE optimality metrics (D-, A-, and E-optimality) with random experiment repeats, showing the cumulative usage of API and excipients in the calibration experiments. Data are based on the Kawakita model and illustrate how experimental selection impacts material consumption during formulation development.

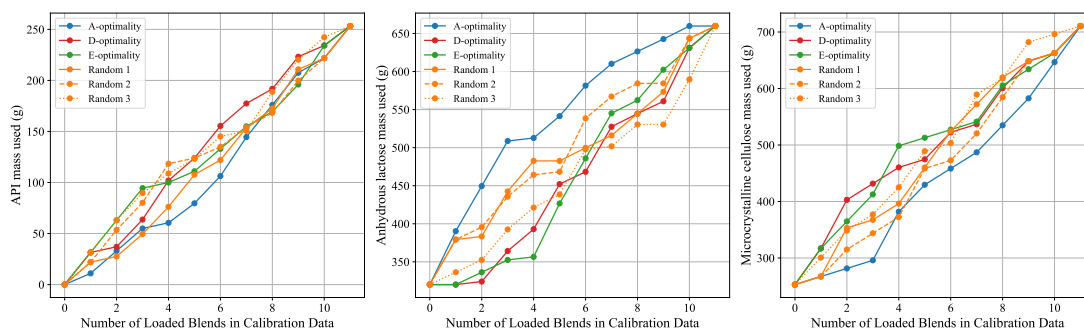


Figure 7.16: Comparison of MBDoe optimality metrics (D-, A-, and E-optimality) with random experiment repeats, showing the cumulative usage of API and excipients in the calibration experiments. Data are based on the Ryshkewitch–Duckworth model and illustrate how experimental selection impacts material consumption during formulation development.

Using the performance criterion defined in Section 4.9, the iteration at which additional experiments produced minimal improvement in MAE was identified as i^* (Section 4.8.4). This point represents the first iteration at which the MAE remained below the defined performance threshold for $k = 3$ consecutive iterations, indicating stabilised model performance. The reduction in API consumption was then estimated by evaluating cumulative material usage up to iteration i^* , and comparing this against the total API required to characterise the full formulation space (253.3 g total API used across 17 blends (each normalised to 100 g per blend (Table 4.3)) (Figures 7.17 and 7.18 with full results presented in Tables in Appendix D.11). These results are summarised through the presentation of the distributions of API savings across the different formulation spaces (Figure 7.19).

The Kawakita model consistently demonstrated substantial reductions in the API required to parameterise the model across all three performance threshold levels. For the paracetamol formulations, savings under the Acceptable and Good thresholds were tightly distributed in the 85–95% range, indicating that near-complete API conservation is robustly achievable for these APIs under less stringent criteria. Under the Excellent threshold, savings remained high for the paracetamol formulations, though with increased variability, while the ibuprofen formulations exhibited considerably wider distributions, with Ibuprofen 50 and Ibuprofen 25 spanning approximately 40–95% un-

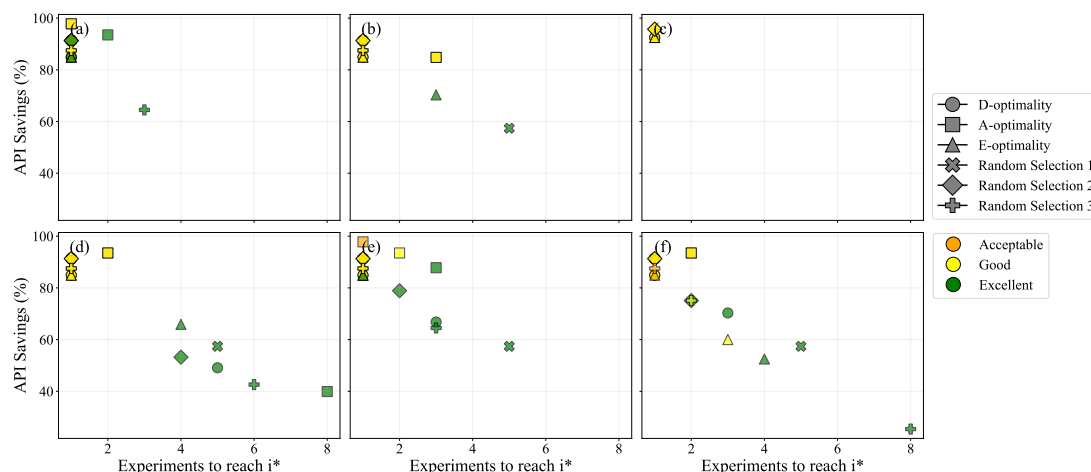


Figure 7.17: Performance of experimental design strategies for the Kawakita model for (a) dense, (b) powdered, and (c) micronized paracetamol, and (d) ibuprofen 50, (e) ibuprofen 38, and (f) ibuprofen 25. Results are shown as the number of experiments required to reach predefined MAE thresholds and the corresponding API savings at that point. Model-based design of experiments (MBDoE) strategies (D-, A-, and E-optimality) are compared against repeated random selection runs. Marker shape denotes the strategy (circles: D-optimality; squares: A-optimality; triangles: E-optimality; X: Random Selection 1; diamonds: Random Selection 2; +: Random Selection 3), while marker colour indicates the threshold level (orange: Acceptable; yellow: Good; green: Excellent). Each point represents the iteration at which a given threshold is first achieved, with associated API savings at that stage. Variability in random selection is illustrated through independent repeats. Absence of points indicates that the threshold was not reached within the available experiments.

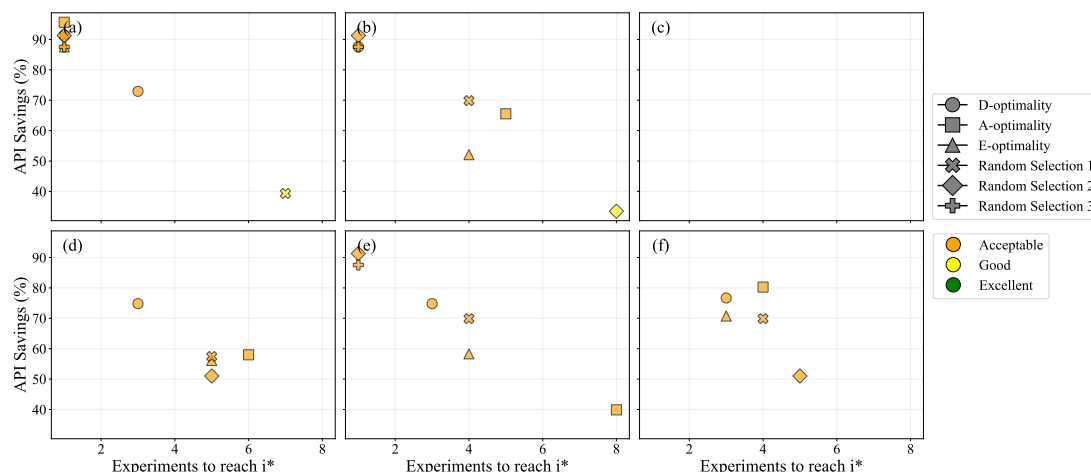


Figure 7.18: Performance of experimental design strategies for the Ryshkewitch–Duckworth model for (a) dense, (b) powdered, and (c) micronized paracetamol, and (d) ibuprofen 50, (e) ibuprofen 38, and (f) ibuprofen 25. Results are shown as the number of experiments required to reach predefined MAE thresholds and the corresponding API savings at that point. Model-based design of experiments (MBDoE) strategies (D-, A-, and E-optimality) are compared against repeated random selection runs. Marker shape denotes the strategy (circles: D-optimality; squares: A-optimality; triangles: E-optimality; X: Random Selection 1; diamonds: Random Selection 2; +: Random Selection 3), while marker colour indicates the threshold level (orange: Acceptable; yellow: Good; green: Excellent). Each point represents the iteration at which a given threshold is first achieved, with associated API savings at that stage. Variability in random selection is illustrated through independent repeats. Absence of points indicates that the threshold was not reached within the available experiments.

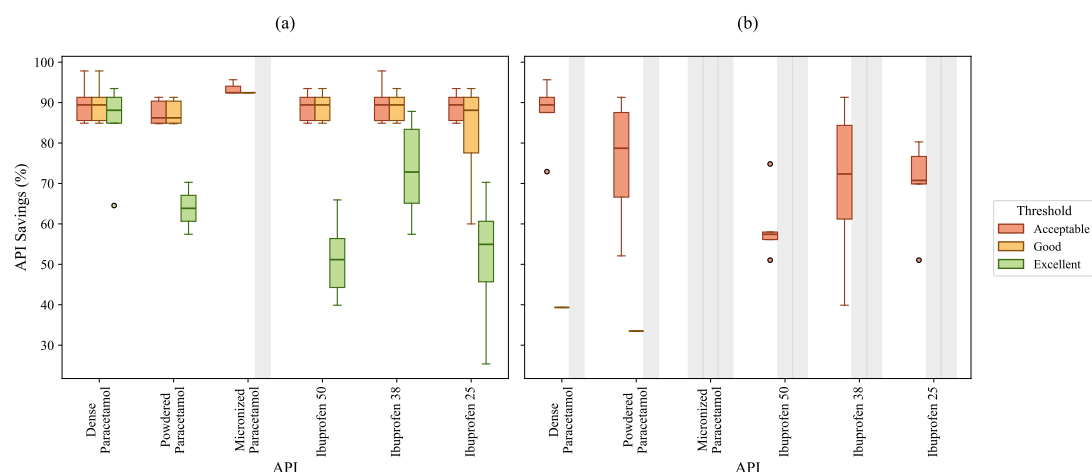


Figure 7.19: Distribution of API savings (%) across six formulations resulting from the model-based design of experiments and random selection approach to parameterising the Kawakita and Ryshkewitch–Duckworth compaction models via the novel global optimisation framework. API savings represent the percentage of active pharmaceutical ingredient not required relative to a conventional design, as determined through performance threshold crossing analysis of the (a) Kawakita and (b) Ryshkewitch–Duckworth models. These distributions represent the data reported in the tables found in Appendix D.11. Boxes span the interquartile range with the median indicated by the horizontal line; whiskers extend to $1.5\times$ the interquartile range. Boxes are coloured by performance threshold level: Acceptable (orange), Good (yellow), and Excellent (green). Grey shaded regions indicate formulations for which no threshold crossing was detected within the experimental compaction space.

der the Excellent criterion. This suggests that whilst the Kawakita model supports large API reductions across all formulations, the achievability of the most stringent threshold is more sensitive to formulation-specific compaction behaviour, particularly for ibuprofen-based systems.

The Ryshkewitch–Duckworth model also yielded meaningful API savings; however, the breadth of achievable threshold levels was more limited. For several formulations, threshold crossings were only consistently detected at the Acceptable level, with Good and Excellent threshold crossings either absent or associated with considerably reduced and more variable savings. Micronized Paracetamol produced no detectable threshold crossing under any level in the Ryshkewitch–Duckworth model, in contrast to its performance under the Kawakita model, this can be attributed to the reduced data available as this formulation was not appropriate for direct-compression.

Despite differences in experiment selection behaviour between the two constitutive models, both were able to capture the dominant trends in compressibility and compactability. This indicates that, even in the presence of non-unique parameter identifiability, the optimisation of the mixture rules to parameterise these empirical models retain sufficient flexibility to represent the observed formulation behaviour.

7.4 Discussion

7.4.1 Mixture Model Optimisation

It was found that the global optimisation of the mixture rule parameters provided a competitive advantage to the traditional line-of-best-fit approach, performing close to that of independently fitting the datasets for both Kawakita and Ryshkewitch–Duckworth. Upon closer inspection into the individual formulation design spaces, the performance of the optimisation was found to be inconsistent between paracetamol and ibuprofen, with the latter showing clear trends in the residual errors with API volume fraction (Appendix D.3).

There has been extensive discussions in the literature regarding the relative dominance of component behaviours within powder blends. Response surfaces of tablet

tensile strength (at 15% porosity) across the formulation space (Figure D.12) were created to better visualise the impact of the different components on the tensile strength at matching porosities. A description of how these surfaces were created are outlined in Appendix D.12.

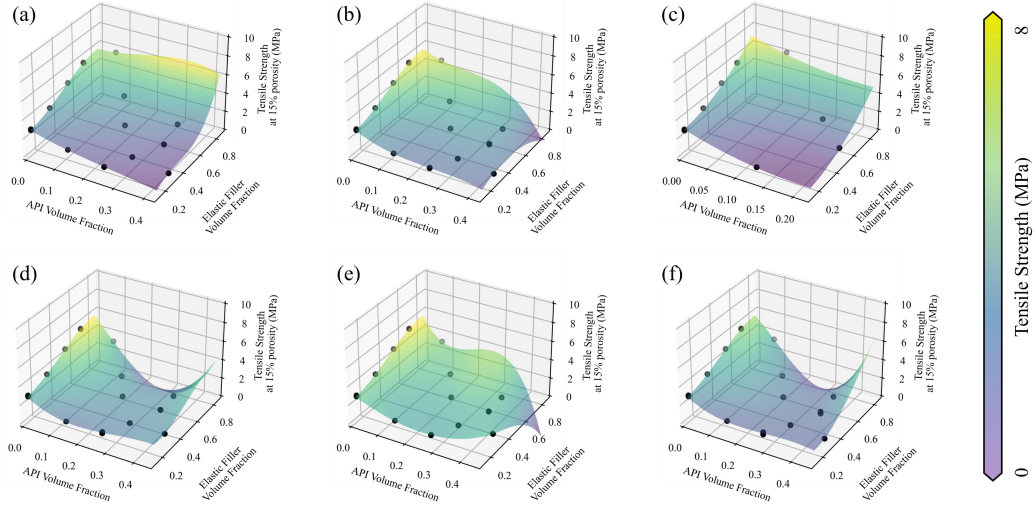


Figure 7.20: Response surfaces with respect to the concentration of API and elastic filler in the formulation showing the tensile strength of tablets at approximately 15% porosity for (a) Dense Paracetamol, (b) Powdered Paracetamol, (c) Micronized Paracetamol, (d) Ibuprofen 50, (e) Ibuprofen 38, and (f) Ibuprofen 25.

Paracetamol formulations exhibited relatively planar surfaces, whereas ibuprofen formulations showed pronounced inflections with respect to API volume fraction (Note, that these inflections may not fully represent reality as there are regions where no data was present to inform the surface creation; this is merely a representation of the differences between the formulation spaces). Profiles extracted at varying filler ratios (Figure 7.21) confirmed that, while the filler composition influenced absolute tensile strength (with larger fractions of brittle lactose (Filler 1) decreasing the tensile strength of the formulation (Shi et al., 2023)), the overall trends remained governed by API concentration. In particular, ibuprofen formulations displayed a sharper initial decrease in ten-

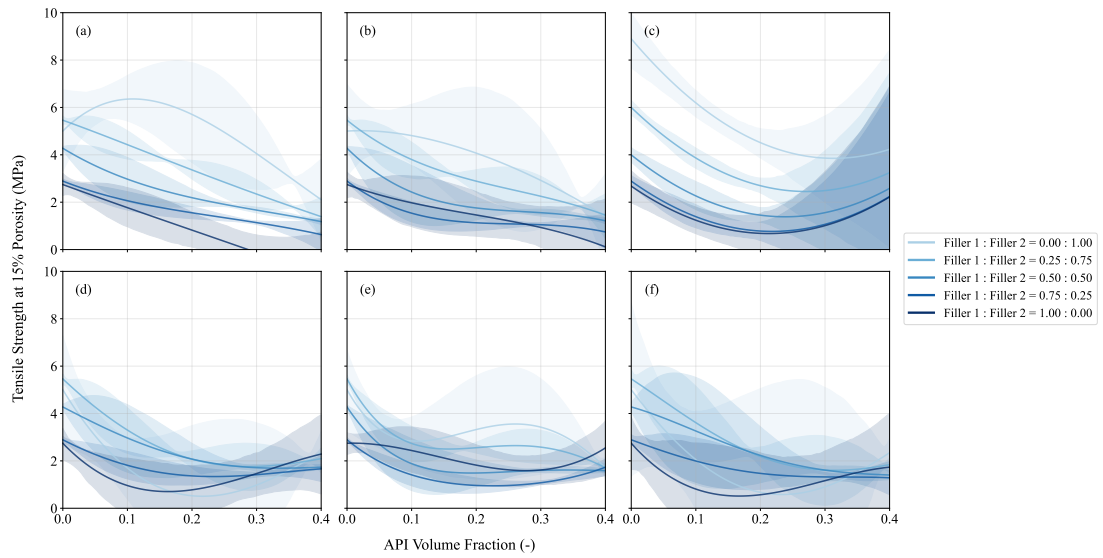


Figure 7.21: Trend lines show the profiles of the response surfaces in Figure 7.20 at different ratios of elastic and brittle fillers. These trends are plotted against API concentration for (a) Dense Paracetamol, (b) Powdered Paracetamol, (c) Micronized Paracetamol, (d) Ibuprofen 50, (e) Ibuprofen 38, and (f) Ibuprofen 25 to demonstrate the impact of API concentration on tensile strength of tablets at approximately 15% porosity. Shaded areas show the 95% confidence interval for each profile, which are considerably large in the regions where no data was present to inform the surface creation, (e.g. Subplot (c) above 20 % v/v for micronized paracetamol).

sile strength upon API addition, followed by stabilisation across the remaining design space. In contrast, paracetamol formulations – especially the dense grade – demonstrated more gradual, near-linear behaviour across all filler ratios. When interpreted within the Tableting Classification System (TCS) framework (Sun, 2016), both APIs fall under Type III systems, where the API exhibits negligible bonding propensity. However, paracetamol more closely aligns with ideal Type III(a) behaviour due to its near-linear response, whereas ibuprofen exhibits greater non-linearity, indicating more complex blend behaviours.

Without further characterisation of the materials and investigation of deformation mechanisms across the compression pressure axis, it is difficult to elucidate the exact reasons underlying these differences. However, in the case of comparing paracetamol and ibuprofen, it is hypothesised that particle morphology could be a key contributor. The differing tensile strength-composition relationships observed for the two powders suggest that the introduction of a needle-shaped particle population of ibuprofen (Cano et al., 2001) alters the underlying mechanism by which tablet structure develops during compression.

The tensile strength of a tablet depends on both the bonding strength (controlled by the intermolecular interactions) and the bonding area (controlled by the morphology which varies with compression pressure) amongst the particles in the tablet (Paul et al., 2020; Wang et al., 2024).

For the powder composed of particles with broadly similar morphologies, as expected for the paracetamol formulations, the gradual decline in tensile strength with increasing volume fraction is consistent with a progressive reduction in compactability, whereby each incremental increase in paracetamol concentration continuously weakens the strength-bearing contact network within the compact. This behaviour is in line with the well-documented compression response of paracetamol, which is generally characterised by dominant fragmentation behaviour combined with a relatively high propensity for elastic recovery, particularly for the monoclinic form I used in this study, which lacks well-developed slip planes to facilitate extensive plastic deformation (Beyer et al., 2001; Gharaibeh and Al-Ard, 2011; Joiris et al., 1998). As the paracetamol

fraction increased, the ability of the powder bed to form and retain sufficiently strong interparticulate bonds during compression was therefore progressively reduced, resulting in weaker compacts. At high concentrations of powdered and micronised paracetamol, this balance became sufficiently unfavourable that tablets with adequate mechanical integrity could not be produced for testing.

In contrast, the powder containing a dispersed population of needle-shaped particles (the ibuprofen formulation space) exhibits a sharp initial decrease in tensile strength followed by a plateau-like response, indicating that relatively small additions of the acicular material could be sufficient to disrupt the packing and contact architecture of the powder bed early in the composition range. This suggests that there may be a morphology-driven threshold effect, in which the needle-shaped particles act disproportionately as structural disruptors by reducing packing efficiency, and introducing anisotropy into the developing compact microstructure. This theory is supported as the further increases in the needle-shaped fraction appear to have a lessened effect on tensile strength than the paracetamol blends, with less variation in the tensile strength between formulations which vary the brittle and elastic filler fractions.

Collectively, these results imply that particle morphology heterogeneity can change the driving effect of strength loss from a continuous composition-driven deterioration (namely due to bonding propensity and surfaces energy) to an early structural transition, highlighting that tensile strength in such systems is likely governed not only by composition, but also by the extent to which particle shape modifies densification behaviour, bond formation, and the efficiency of the resulting contact network.

7.4.2 Impact of Placebo Inclusion on Optimisation Outcomes

The variable performance between paracetamol and ibuprofen formulations introduced a potential limitation in the optimisation as the inclusion of placebo data reduced the ability to capture the behaviours of the low-loaded ibuprofen systems. Removing the placebo data improved the predictive accuracy for the loaded blends; however, this would increase the number of API-loaded blends required to initially populate the model, which counters the goal of developing a smarter experimental method which minimises

API usage. This creates a trade-off for the intended application of the optimisation as an experimental framework. Including placebo data may reduce predictive accuracy across the formulation space but provides valuable insight into the system and the contributions of the API to blend behaviours. Conversely, removing placebo data improves predictive capability for loaded blends at the cost of additional API usage. To address this, the workflow in Figure 7.22 defines a systematic approach in which placebo data are initially incorporated to compensate for insufficient loaded-blend data. As more loaded-blend experiments are performed, the number of independent observations becomes sufficient relative to the number of unknown parameters. Once this condition is met, the placebo data are excluded from model training. This approach represents a step towards a more informed and structured framework for experimental design.

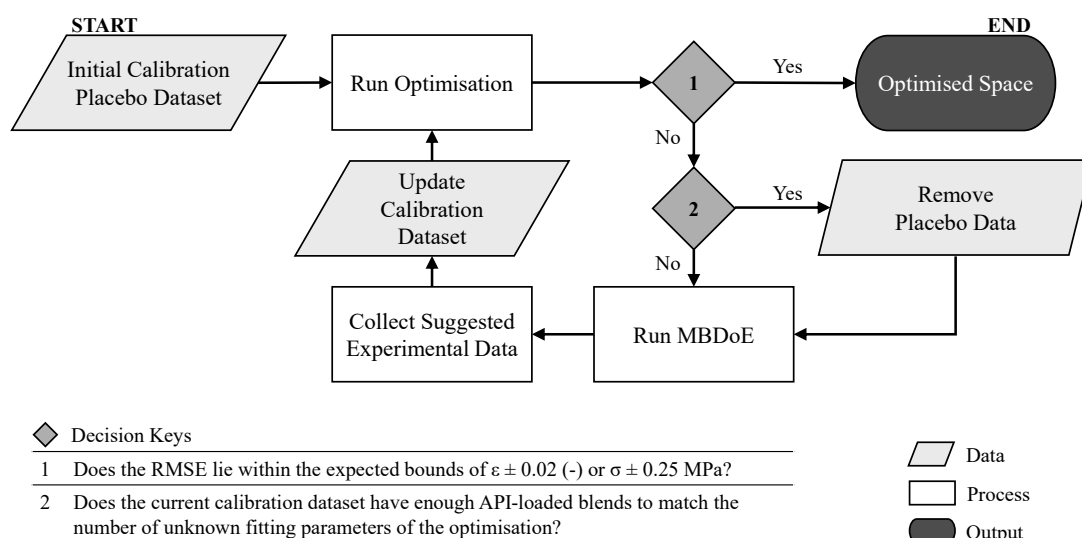


Figure 7.22: A workflow showing the process of applying the proposed MBDoe to guide formulation development with emphasis on understanding whether to include placebo data in the calibration data in the instance that there may be an irregular jump in data as was with the ibuprofen datasets.

Even with the observed differences in performance for the materials studied, the optimisation and MBDoe methodologies remain broadly applicable across particle size and shape distributions. Although, extrapolation to systems with substantially different morphology or mechanical properties should be approached with caution.

7.4.3 A Consideration of Optimisation Oversimplification

In cases where non-linear behaviour is observed in compression or compaction, the current modelling framework may be insufficient to capture these effects. The applied mixture rules assume a smooth variation of model parameters across the formulation space, governed by the optimised pure component parameters. Parameter values for intermediate formulations are obtained through composition-based interpolation alone. This neglects the possibility of non-linear interactions or dominance effects, whereby the influence of a given material on the overall behaviour may be disproportionate relative to its volume fraction. Yet, the previously discussed morphological considerations are a feature not explicitly captured by the model. As a result, the current optimisation framework is unable to account for abrupt changes in tableting behaviours.

Consequently, the trends observed in the residuals arise as the optimisation balances predictions between the placebo and drug-loaded data to minimise the overall RMSE, rather than fully capturing the true underlying behaviour of the system. This can be visualised through a comparison of the surface plots of the tensile strength at 15 % porosity as estimated by the optimisation when considering the dataset with and without placebo (Figures 7.23 and 7.24). Methodology for how these plots were created can be found in Appendix D.12.1.

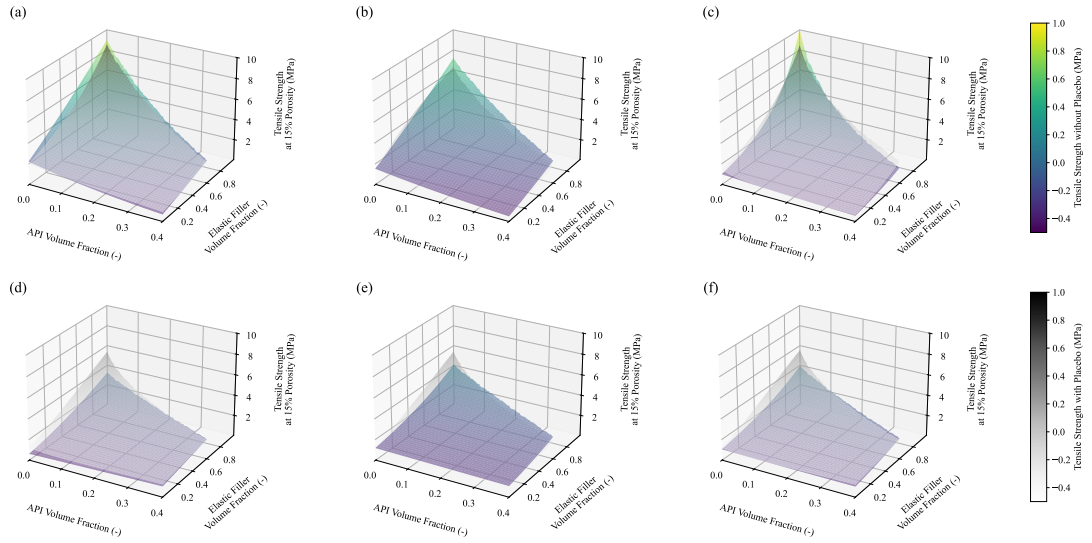


Figure 7.23: Comparison of predicted tensile strength surfaces at 15% porosity for formulations optimised with and without placebo inclusion for (a) dense, (b) powdered, (c) micronized paracetamol and (d) ibuprofen 50, (e) ibuprofen 38, (f) ibuprofen 25. Surfaces are shown as a function of API and elastic filler volume fractions, with the remaining fraction assigned to the second filler. The viridis surfaces represent models optimised without placebo data, while the greyscale surfaces correspond to models including placebo data. A fixed colour scale (0–10 MPa) is applied across all subplots to enable direct comparison.

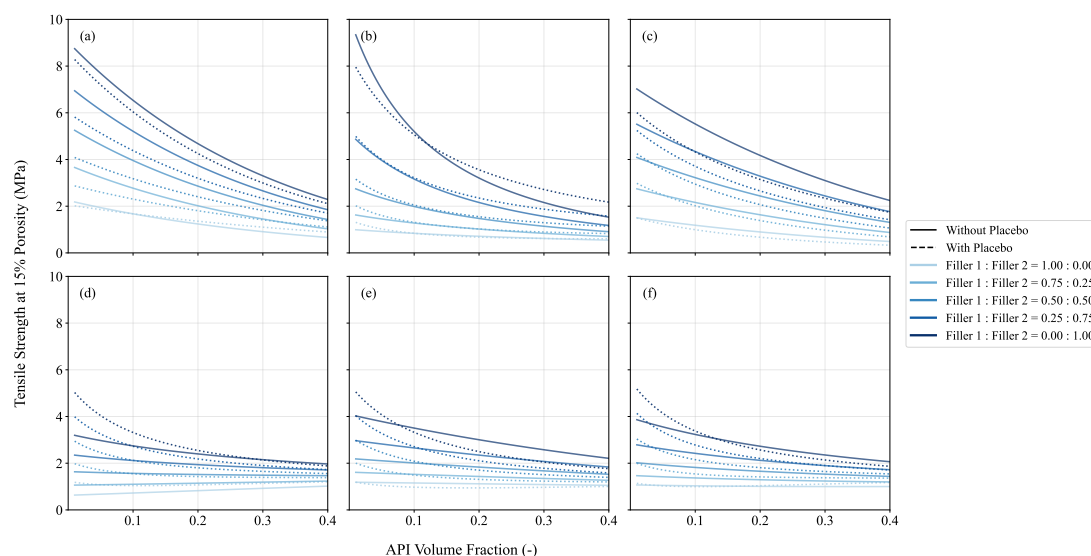


Figure 7.24: Predicted tensile strength at 15% porosity as a function of API volume fraction for (a) dense, (b) powdered, (c) micronized paracetamol and (d) ibuprofen 50, (e) ibuprofen 38, (f) ibuprofen 25. Comparing models trained with and without placebo inclusion. Each subplot shows composition trajectories across varying filler 1 : filler 2 ratios. Solid lines correspond to models excluding placebo data, while dotted lines represent models including placebo constraints. Line colour indicates the filler composition ratio.

The response surfaces for the paracetamol formulation space showed minimal change upon removal of the placebo data during optimisation. In contrast, the ibuprofen surfaces exhibited a more planar profile when the placebo was excluded, with a reduction in tensile strength in the low API region. This adjustment improved alignment with the experimental ibuprofen data, as reflected in the parity plots (Figure 7.8), which demonstrate enhanced prediction of drug-loaded blend compactability in the absence of placebo data.

In future, to address this, rather than relying on the removal of placebo data, it may be beneficial to incorporate parameters capable of identifying dominant material behaviours or detecting transition points, such as percolation thresholds. However, while the addition of such parameters may improve model flexibility and generalisability, this must be weighed against the associated increase in experimental and computational burden. A short exploratory evaluation of interaction parameters (Appendix D.5) showed that the added degrees of freedom of the considered models did not provide sufficient

benefit to justify their inclusion within the present framework, particularly when simpler adjustments, such as excluding placebo data points, were able to improve predictive performance.

To further improve model performance and understand the factors that contribute to these irregular behaviours, future work should extend the framework to a broader range of APIs with differing mechanical and morphological properties, alongside collecting complementary data on particle morphology and surface characteristics. Systematic investigations of how these properties influence optimisation performance would also help clarify the mechanistic drivers of model behaviour, while allowing the optimisation framework itself to be used to localise and prioritise subsequent studies that distinguish poorly and well-performing formulations. Also, perhaps the consideration of a piecewise regression (Krausbauer et al., 2008) or Effective Medium Theory (Choy, 2015) may be able to accommodate the abrupt changes in behaviours, however the application of such methods goes beyond the scope of this study.

7.4.4 MBDoE Compared to Random Selection

It was found that the MBDoE did not outperform the random selection iterations for informing the experiments to be prioritised in the model calibration with increasing calibration dataset size.

Within the MBDoE, the optimality metrics ranked the candidates based on the information that they could provide to the population of the empirical models via the FIM; if the models themselves have inherent errors or the parameters are non-identifiable (i.e. different combination of parameters lead to similar solutions of fit (Simpson, 2025)) then this information may be different to that which was estimated, perhaps impeding the MBDoE performance.

It was expected that the estimated model parameters would converge as the MBDoE introduced more experiments to the calibration of the optimisation, resulting in a reduction of MAE that plateaus. Whilst the MAE was reduced for both empirical models, there were few examples of parameter convergence, and thus performance did not match the expectations. Despite this, the reduction of MAE was near instant-

neous for most selection methods. Kawakita’s parameters have been found to show a high degree of correlation, and hence low identifiability (see Figure 6.2 in Chapter 6; meaning, as long as the ratio of the parameters A and B is constant, within the range of our data the observed trendlines will converge. This correlation (also termed "structural non-identifiability") results in there being a large minima for the optimisation to navigate, each with a very similar performance (Grabowski et al., 2023). Due to this, the optimisation may return a number of “optimum” mixture rules and parameter estimates whilst maintaining predictive accuracy depending on the optimisation tolerance and perturbation used for the sensitivity matrix. This provides some insight into the sharp decrease in MAE with only one additional experiment. If it is truly the ratio of A and B which is of import rather than the true values, then perhaps only one experiment is required to inform this unknown, at least for the materials considered in this study. This ratio was observed in Chapter 6 where the ranges of parameters on the GoF were tested. In this study, the Kawakita model was found to consistently capture the compressibility behaviours for different formulations compared to it’s more commonly cited counterpart, the Gurnham model, which makes the false assumption that porosity may extend beyond the known limits of 0 and 1. Gurnham’s structure (Equation 7.3) is more sensitive to changes in parameters, which can affect the slope, curvature, and asymptotic behaviour rather than simply the scale as is the case with Kawakita.

$$\varepsilon(P) = -\frac{1}{A} \ln \left(\frac{P}{B} \right) \quad (7.3)$$

The Kawakita was found to outperform the Gurnham on the materials considered thus far, but the base placebo blend has been consistent. There is the potential that if the blend demonstrates a different dominating compression mechanism (rearrangement, brittle fracture, elastic and/or plastic deformation), Gurnham may be better suited to model this. Further, if the motivation is to use this MBDoE to identify material parameters which can inform future predictions without the need for further experimentation, the use of Gurnham may offer more consistency in parameter estimates though perhaps at the cost of predictive accuracy. Despite this discussion, the MBDoE framework developed demonstrated clear advancements in systematically reducing the experimental

burden of formulation development by guiding users to make smarter decisions, particularly for the modelling of powder compaction.

This MBDoE was conducted on a pre-existing dataset to demonstrate the capability of the proposed methodology within a formulation development context. API consumption reductions were defined as the point at which the model consistently attained a MAE within a specified performance threshold for a defined number of consecutive experiments. Performance thresholds were set in accordance with commonly adopted industry standards, providing a practically relevant benchmark against which the framework could be evaluated. While the magnitude of API savings is inherently dependent on the stringency of the threshold applied, the results demonstrate that savings exceeded 30% across all formulations studied even under the most stringent Excellent performance criterion, highlighting the robustness of the approach across a range of quality requirements.

In practice, the successful completion of a MBDoE should be defined by a model which can reliably predict these behaviours for new formulations within limits of material consumption and experimental effort. For the application to a new system, the definition of the completion point and the calibration experiments required would need to be adapted based on system- or user-specific criteria.

7.5 Conclusion

This study demonstrates the use of combining the global optimisation of mixture rules for parameterising empirical compressibility and compactability models with MBDoE to accelerate formulation development while reducing reliance on resource-intensive experimental campaigns. Although the empirical models are structurally simple and their accuracy is constrained by their underlying assumptions, they nevertheless provide a useful foundation for shifting formulation development from a trial-and-error exercise towards a more systematic process. In this context, the optimisation framework is valuable not only for improving predictive performance, but also for identifying systems and formulation spaces that exhibit distinct or poorly captured behaviours, thereby highlighting areas that require further mechanistic investigation.

The investigations considered datasets for three grades each of paracetamol and ibuprofen with a consistent placebo base. The global optimisation approach outperformed the traditional line-of-best-fit method for mixture rule parameterisation, with particle size showing little influence on performance. In the ibuprofen datasets, a clear shift in compaction behaviour with increasing API concentration led to skewed residuals, typically resulting in overprediction at low API concentrations ($< 15\%$ v/v). Excluding the placebo data improved the accuracy of the optimisation, suggesting that future applications should reconsider the definition of the initial six calibration experiments in the MBDoE framework depending on the desired application.

For all cases, the MBDoE was shown to reduce API consumption while maintaining predictive capability, although no single optimality metric consistently outperformed the others. Furthermore, the MBDoE did not consistently outperform random selection in prioritising experiments for model calibration as the calibration dataset increased in size. This may reflect the structural non-identifiability of the model parameters, whereby multiple parameter combinations can produce similarly acceptable fits, meaning that the information content estimated by the MBDoE framework may not accurately represent the true experimental value of candidate formulations. As a result, the effectiveness of the MBDoE in guiding experiment selection may be reduced. Nevertheless, the approach still provides a systematic alternative to prior knowledge-driven experimentation and demonstrates the broader value of optimisation-based strategies for improving the efficiency and objectivity of formulation development.

While the optimisation and MBDoE framework developed in this work demonstrated success in predicting tablet porosity and tensile strength, its validation was necessarily limited to a reduced formulation and processing space. Only a small subset of APIs, fillers, and particle size fractions were investigated, and several material and processing variables — including placebo choice, disintegrant concentration, lubrication extent, and mechanical setup (die geometry, compression speed, and dwell time) — were held fixed throughout the study. As such, the generalisability of the optimisation to formulations and materials outside this tested space cannot yet be confirmed. In particular, new APIs and excipients may exhibit compaction behaviours, particle interactions, or failure

mechanisms (such as overcompaction) that differ from those captured in the current datasets, meaning further validation on a wider range of materials is required before the approach can be considered broadly applicable across formulation space.

Overall, this work demonstrates a systematic and resource-efficient approach that can be applied to the development of directly compressed formulations. Future studies may consider the identification and description of discontinuities in compaction behaviours (i.e. percolation thresholds), or the use of alternative compression models, to support further advancement of mixture rules and improve the consistency with which material contributions are represented.

Chapter 8

General Conclusions and Future Work

8.1 General Conclusions

The motivation for this project was to embrace the growing digital capabilities to move OSD development away from the traditional trial-and-error methods which have been driven by prior knowledge; ultimately, to create a rapid, responsive, green approach to formulation and production development for future medicines. This work has focussed on building upon the empirical modelling methods for predicting the porosity and tensile strength of directly-compressed tablets; specifically by investigating how individual components in a formulation contribute to the compressibility and compactability behaviours of a blend.

From a systematic statistical review of models commonly cited in the literature, it was found that Kawakita and Ryshkewitch-Duckworth were the most consistent in their respective predictions of compressibility and compactability for a historic database of API loaded blends. The other compression models (Gurnham and Heckel), showed stronger trends in their residual errors for porosity prediction, yet they were found to still be capable of making adequate predictions in the defined RoI for tablet manufacturing.

The analysis of parameter variability found that there were in fact multiple parameter pairs which were capable of achieving similar GoF for the explored formulations.

This countered the prior belief that there are only singular (material specific) parameters which can describe – and hold some physical meaning for – a materials compression or compaction; which was the limiting factor for the reliable application of mixture rules to predict pharmaceutical blend behaviours.

Capitalising on this new found flexibility in the model parameters, a new global optimisation approach to the selection and population of arithmetic, geometric and harmonic mixture rules for model fitting parameters of blends was developed. The objective of this function is to return raw material fitting parameters for the API, brittle-, and elastic fillers which, when used in a mixture rule weighted by said materials volume fractions, populates the empirical models in such a way to minimise the RMSE for the collected data in a formulation space. This work was conducted on formulation spaces designed by the industrial partner, GSK, for three different grades of paracetamol and ibuprofen – chosen for their relevance and different particle size distributions. This method was primarily applied to the Kawakita and Ryshkewitch-Duckworth models, and was found to not only outperform the traditional approach to mixture rule population, but also provide a method to reduce the experimental load.

A key finding of this work was that the optimized mixture rule framework reduced the number of API-loaded experiments required to populate the empirical models. Based on the structure of the empirical models, each containing two unknown parameters, and the corresponding mixture rule optimization framework, in which each model parameter is represented by three unknown raw material parameters, a minimum of six experiments would be required to populate the equation system. However, when placebo data were already available, only two additional API-loaded experiments were needed to adequately define the models. Although MBDoE was implemented to guide experiment selection during formulation development, it performed similarly to random selection. This is attributed to the structural non-identifiability of the model parameters, which reduces the distinction in information content between candidate experiments and therefore limits the usual advantage of MBDoE.

A key limitation across this thesis is that the optimisation and MBDoE framework was validated only across a reduced formulation and processing space, with a limited set

of APIs, fillers, and particle size fractions studied under fixed material and processing conditions. Consequently, further validation across a broader range of materials and processing conditions is needed to establish the generalisability of the approach beyond the systems tested here.

Despite this, the framework still provides a systematic method for selecting experiments, reducing reliance on intuition or prior formulation knowledge. Further work is required for systems exhibiting non-linear responses across the formulation space, particularly for tensile strength, where dominant material effects above threshold concentrations may not be fully captured by the current optimization approach. Nevertheless, for the systems investigated here, excluding placebo data from the calibration set appeared sufficient to account for this behaviour without materially reducing predictive accuracy.

8.2 Future Work

Formulating an OSD tablet requires numerous decisions, as both material attributes and processing parameters ultimately influence product quality. The optimisation and MBDoE developed in this project was designed to support decision-making by reducing the experimental resources required to explore formulation space, specifically for predicting tablet porosity and tensile strength. However, this work was conducted under controlled constraints, including fixed placebo choice, disintegrant concentration, lubrication extent, and mechanical setup (die geometry, compression speed, and dwell time). To assess the broader applicability of the approach, future work should validate the optimisation across expanded formulation and processing dimensions. Such an extension would require substantial data generation; therefore, integration with an autonomous manufacturing platform – such as the Tableting Data Factory at CMAC, University of Strathclyde – would enable accelerated data acquisition and systematic exploration of formulation space beyond manual experimental workflows.

Results presented in Chapter 7 revealed an unexpected behaviour in the influence of API concentration on mixture tensile strength. Ibuprofen formulations exhibited a more drastically negative contribution to tensile strength at low doses compared to the paracetamol datasets. Although removal of placebo data mitigated this effect within the scope of this study, the reasons underlying this apparent ‘percolation’ of component behaviour warrant further investigation.

It is necessary to determine both where this abrupt change in behaviour occurs and why it arises. Identifying the location of such transitions within formulation space is valuable in itself, as it allows regime boundaries to be mapped and experimentally avoided or targeted. Predicting this on the other hand will require mechanistic understanding. Therefore, it is of equal importance to investigate which material properties may be driving this change in behaviour and whether quantifiable relationships exist between physical properties and morphology, component volume fractions within the blend, and the resulting mechanical performance.

As a reference, the regression models applied in this work assume smooth and continuous relationships, to identify potential discontinuities in tensile strength as a function of formulation composition, the following modelling approaches may be considered:

Piecewise regression. Piecewise regression fits separate functions to different regions of the input space, with breakpoints estimated directly from the data. This enables the detection of abrupt shifts in behaviour that cannot be captured by a single continuous function (Muggeo, 2003). The approach has been successfully applied to identify structural “breakpoints” and model multiple regressions within a single dataset in ecological systems (Toms and Lesperance, 2003). In the pharmaceutical context, Krausbauer et al. (2008) applied a piecewise model to determine the minimal disintegrant volumetric ratio in binary drug–disintegrant mixtures, demonstrating that disintegration behaviour changes abruptly at a critical percolation threshold. Their model accurately predicted the optimal ratio for spherical particle compacts, showing strong agreement between estimated and experimental values.

Within the scope of this research, piecewise regression would be valuable for identifying threshold regions in formulation space where sufficient data are available. However, while effective for detecting regime shifts, the method alone does not provide a mechanistic basis for predicting such transitions in previously unobserved systems.

An alternative application may lie in incorporating overcompaction behaviour into the compaction datasets rather than just considering how the tensile strength with formulation changes. Rather than excluding overcompaction data from curve fitting, breakpoint detection could be used to define failure regions, thereby informing predictive models of formulation limits instead of removing these data during preprocessing.

Effective Medium Theory (EMT). EMT provides a framework for estimating the overall properties of a mixture based on the known properties and proportions of its individual components. By treating the mixture as a single ‘effective’ material,

EMT can predict how bulk properties such as tensile strength evolve with composition. Within this framework, it is possible to identify critical compositions where behaviour changes rapidly, offering a method for locating thresholds in a formulation space (Choy, 2015; Snarskii et al., 2020).

A deeper investigation of these discontinuities may enable links to be established between observed regime shifts and underlying material properties, thereby strengthening both understanding of powder compression and the predictive modelling framework developed in this thesis.

A successful formulation must not only produce a structurally sound tablet, but also meet key drug delivery performance criteria, including content uniformity, disintegration, and dissolution. It would therefore be of considerable interest to extend the mixture modelling framework developed in this work to predict a broader range of formulation properties from individual component concentrations. Such an expansion would allow formulation design and optimisation to move beyond tablet porosity and tensile strength, encompassing the full spectrum of critical quality attributes required for a viable pharmaceutical product.

8.3 Closing Remarks: Bringing Digital into Pharmaceutical Drug Product Development

Despite the efficiencies introduced by QbD, there remains significant scope for improvement in pharmaceutical drug product development. The latest industrial revolutions have demonstrated the transformative power of data and information technologies, with the Information Technology sector consistently outperforming other industries over the past decade (Hunzinger et al., 2025; Kalaria et al., 2020), Figure 8.1. In contrast, the pharmaceutical sector, while profitable, has shown comparatively slower growth, highlighting an opportunity for strategic digital adoption.

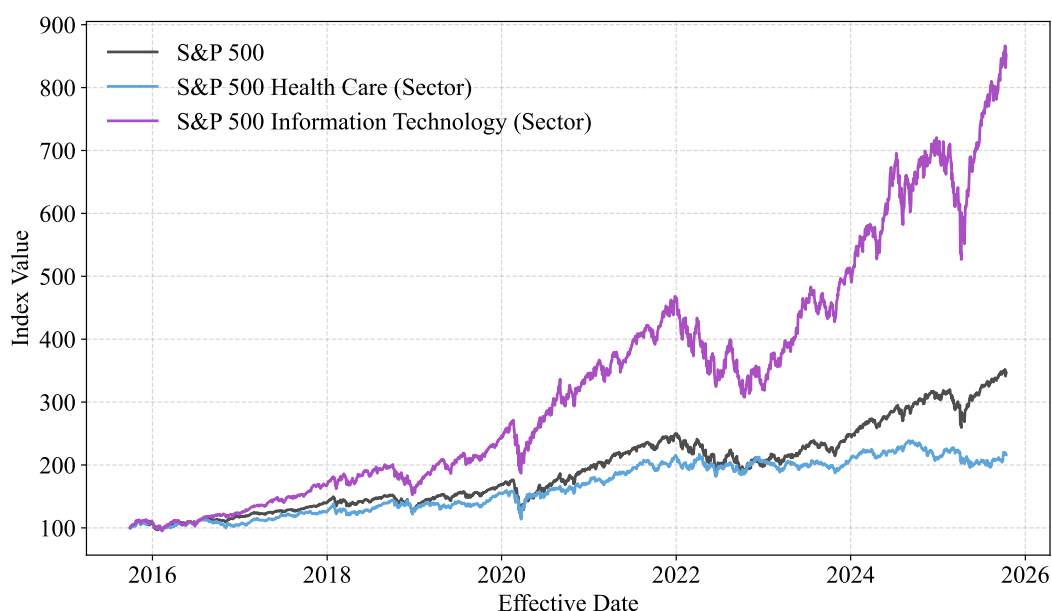


Figure 8.1: S&P 500 and sector performance over time with data based at 100. Source: S&P Dow Jones Indices LLC (S&P Dow Jones Indices, 2025).

The ongoing digital transformation of pharmaceutical development provides a potential route to address this gap. By leveraging predictive modelling, knowledge infrastructures, and digital twins, the industry can move towards more sustainable, agile, and resilient manufacturing environments (Mustoe et al., 2025). These tools offer value not only in automating repetitive tasks, but also in enabling complex analyses and

decision-making processes that would otherwise require substantial time and resource investment (Sarker, 2022; Huanbutta et al., 2024; Paul et al., 2021).

In parallel, the emergence of Model Context Protocols (Maclean et al., 2026) offers a further opportunity to reduce barriers to the practical use of advanced computational methods. By allowing researchers to integrate custom coded capabilities into existing large language models, these systems may enable users to interact with an expanding repertoire of modelling techniques through natural language. In principle, this could support tasks such as data auditing, rapid value checking, troubleshooting, and exploratory model-based analysis through agentic AI systems (Hou et al., 2026). Within drug development, such capabilities could help shift formulation design from a largely reactive process towards a more proactive and informed mode of exploration, with the potential to accelerate optimisation, improve product quality, and reduce resource consumption. However, the adoption of such approaches must be accompanied by a clear understanding of the underlying logic, assumptions, and scientific basis of the methods used, to ensure that these tools support critical decision-making rather than encourage uncritical reliance.

This thesis contributes directly to this vision. By integrating predictive empirical modelling, mixture rule optimisation, and MBDoE, it demonstrates a practical approach for intelligent, data-driven formulation development. The frameworks developed here provide a foundation for linking material properties and processing parameters to tablet performance, identifying critical regions of behaviour, and ultimately supporting more informed and efficient decision-making.

As the pharmaceutical industry faces increasing regulatory pressure, rising sustainability expectations, and ongoing supply chain vulnerabilities, embracing digital and predictive tools is no longer optional – it is essential. The work presented in this thesis offers a stepping stone toward a future where data-driven approaches enable smarter, faster, and more sustainable development of OSD forms, bridging the gap between experimental capability and industrial need.

Appendix A

Methods

A.1 Estimation of Lubrication Extent, K .

The constant, K , which is used to describe to explain the “lubrication extent” within the Kushner-Moore model was selected to be 100 dm as desired by industrial partners. The lubrication process – both in the quantity of lubricant added to a formulation and parameters (free headspace, blending speed and time) – has been shown to have a direct impact on a tablets tensile strength (Kushner and Moore, 2010).

To ensure that the selected value for K was appropriate (i.e. any incremental changes to aforementioned lubrication factors would not significantly impact the tablets tensile strength and thus the consistency of collected data), the compaction profiles for two different K values were evaluated. To achieve this the blending time was adjusted to achieve $K = 100$ dm and $K = 110$ dm (Figure A.1) as calculated by Equation 4.2. The findings show a slight reduction in the compaction profile for the blend with a greater lubrication extent. Whilst the significance of this was not explicitly evaluated statistically, the variation was deemed reasonably negligible for the purposes of this study. Note that for a more scientifically rigorous approach, the lubrication extent could be evaluated across all formulations to ensure that the extent selected is appropriate for all formulations, however due to the industrial relevance of this selection, and also the similarity of the formulation design spaces, this was deemed unnecessarily excessive but is noted as a potential for further validation.

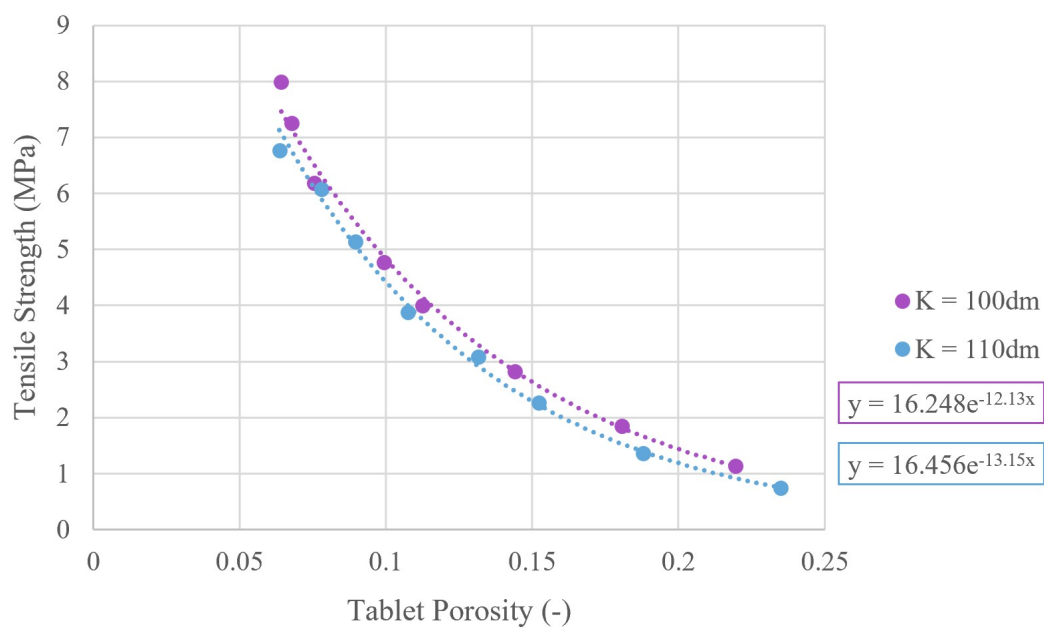


Figure A.1: Compaction profiles comparing how a change in lubrication extent, $K = 100\text{ dm}$ versus $K = 110\text{ dm}$, impacts the tensile strength of placebo tablets (Sample taken from Blend 1 in Table 4.3).

Appendix B

A Comparative Study of Empirical Models

B.1 Error propagation

Uncertainties in model predictions arising from parameter estimation are quantified here using first-order linear error propagation. For a scalar function ($y = f(\boldsymbol{\theta}, x)$) with parameter vector ($\boldsymbol{\theta} = (\theta_1, \dots, \theta_n)$) and measured input x - assuming the contributions are independent and x is certain for simplicity - the variance of y can be approximated by Equation B.1

$$(\sigma_y)^2 \approx \sum_i \left(\frac{\partial f}{\partial \theta_i} \right)^2 (\sigma_{\theta_i})^2 \quad (\text{B.1})$$

Where the standard error (uncertainty) of y is σ . Below are the partial derivatives and the resulting propagation formulae for each empirical models considered in the text.

B.1.1 Gurnham

Equation 4.10:

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

Treating K_G and P_0 as uncertain, the partial derivatives are:

$$\frac{\partial \varepsilon}{\partial K_G} = \frac{1}{K_G^2} \ln\left(\frac{P}{P_0}\right), \quad \frac{\partial \varepsilon}{\partial P_0} = -\frac{1}{K_G} \frac{1}{P_0}.$$

Hence, using (B.1):

$$(\sigma_\varepsilon)^2 \approx \left(\frac{\ln(P/P_0)}{K_G^2}\right)^2 (\sigma_{K_G})^2 + \left(\frac{1}{K_G P_0}\right)^2 (\sigma_{P_0})^2. \quad (\text{B.2})$$

B.1.2 Heckel

Equation 4.11:

$$\varepsilon(P) = \exp(-(K_H P + C))$$

Treating K_H and C as uncertain, the partial derivatives are:

$$\frac{\partial \varepsilon}{\partial K_H} = -P \exp(-(K_H P + C)), \quad \frac{\partial \varepsilon}{\partial C} = -\exp(-(K_H P + C)).$$

Hence, using (B.1):

$$(\sigma_\varepsilon)^2 \approx \left(P e^{-(K_H P + C)}\right)^2 (\sigma_{K_H})^2 + \left(e^{-(K_H P + C)}\right)^2 (\sigma_C)^2. \quad (\text{B.3})$$

B.1.3 Kawakita

Equation 4.12:

$$\varepsilon(P) = \frac{\varepsilon_0}{1 + BP}$$

Letting ε_0 and B be uncertain, the partial derivatives are:

$$\frac{\partial \varepsilon}{\partial \varepsilon_0} = \frac{1}{1 + BP}, \quad \frac{\partial \varepsilon}{\partial B} = -\frac{\varepsilon_0 P}{(1 + BP)^2}.$$

Hence, using (B.1):

$$(\sigma_\varepsilon)^2 \approx \left(\frac{1}{1 + BP}\right)^2 (\sigma_{\varepsilon_0})^2 + \left(\frac{\varepsilon_0 P}{(1 + BP)^2}\right)^2 (\sigma_B)^2. \quad (\text{B.4})$$

B.1.4 Ryshkewitch–Duckworth

Equation 4.13:

$$\sigma(P) = \sigma_0 \exp(-k_b \varepsilon)$$

Treating σ_0 and k_b as uncertain, the partial derivatives are:

$$\frac{\partial \sigma}{\partial \sigma_0} = \exp(-k_b \varepsilon), \quad \frac{\partial \sigma}{\partial k_b} = -\sigma_0 \varepsilon \exp(-k_b \varepsilon).$$

Hence, using (B.1):

$$(\sigma_\sigma)^2 \approx \left(e^{-k_b \varepsilon}\right)^2 (\sigma_{\sigma_0})^2 + \left(\sigma_0 \varepsilon e^{-k_b \varepsilon}\right)^2 (\sigma_{k_b})^2. \quad (\text{B.5})$$

However, in the instance where the empirical models are used in series to predict the porosity and then the tensile strength, the variability of the porosity predictions will propagate and care must be taken. This simple evaluation was completed to consider the variability of the model parameters and the accuracy of models at different operating conditions.

B.2 Best and Worst Case Fit Comparisons

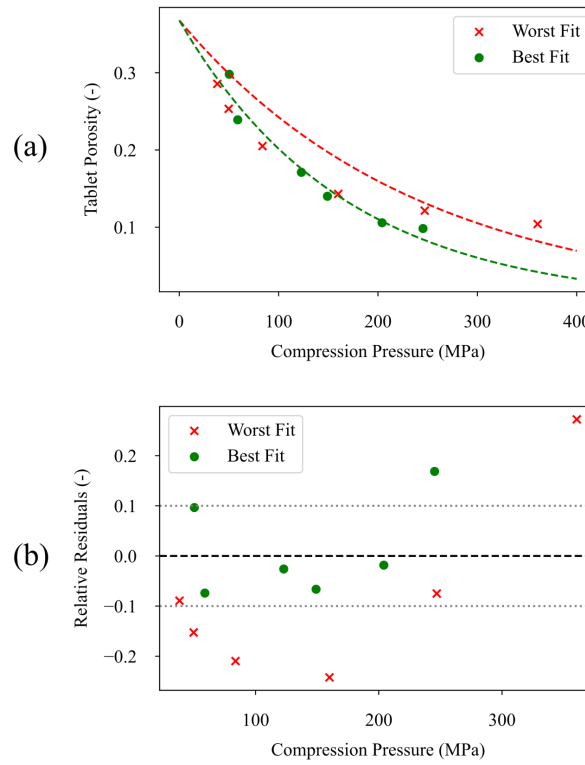


Figure B.1: An illustration of Heckel compression curves and matching relative residuals for the best and worst fits as defined by their correlation coefficient (R^2).

B.3 Tuning Parameter Histograms

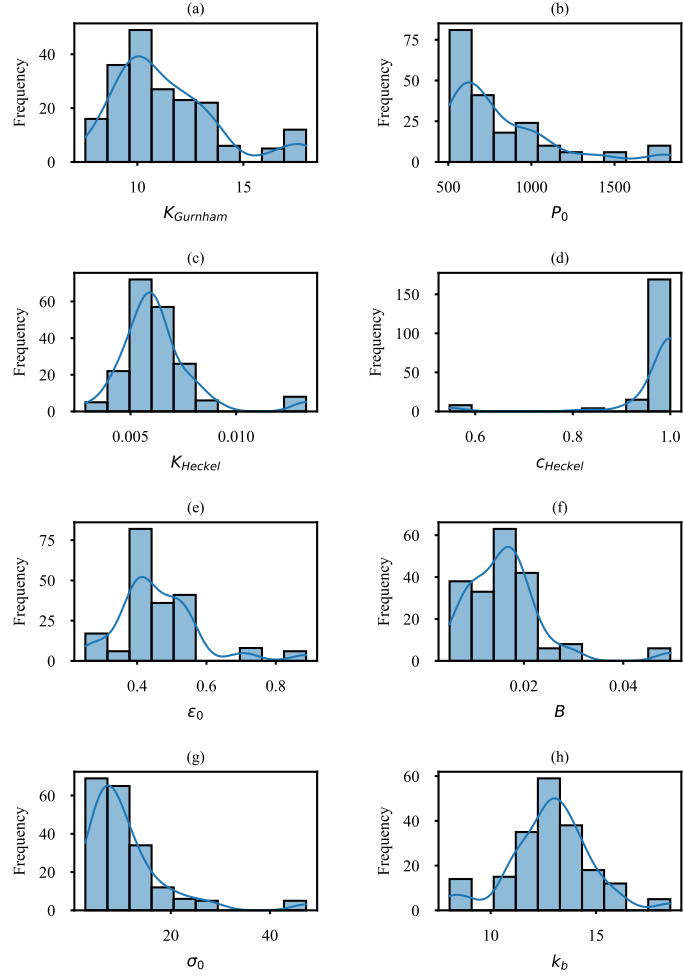


Figure B.2: Tuning parameter histograms from the initial data fitting for (a) (b) Gurnham, (c)(d) Heckel, (e)(f) Kawakita, and (g)(h) Ryshkewitch-Duckworth.

Appendix C

Testing a New Method for Populating Mixture Rules

C.1 Parameter Variability Contour Plots

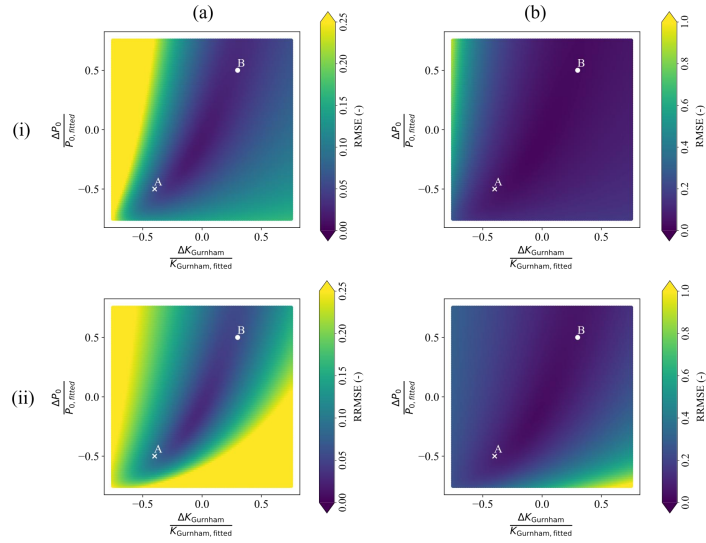


Figure C.1: Contour plots showing how variations of tuning parameters (relative to those estimated by the curve fitting) for the Gurnham model impacts the (i) Root Mean Square Error and (ii) Relative Root Mean Square Error of quality attribute predictions for the placebo (20% MCC) blend. The colour bars have been capped at (a) 0.25 and (b) 1 to compare which conditions best demonstrate the size and shape of the contour minima. Highlighted on each of these plots are points A and B, which are the tuning parameter pairs used to construct Figure 6.3 in the main manuscript.

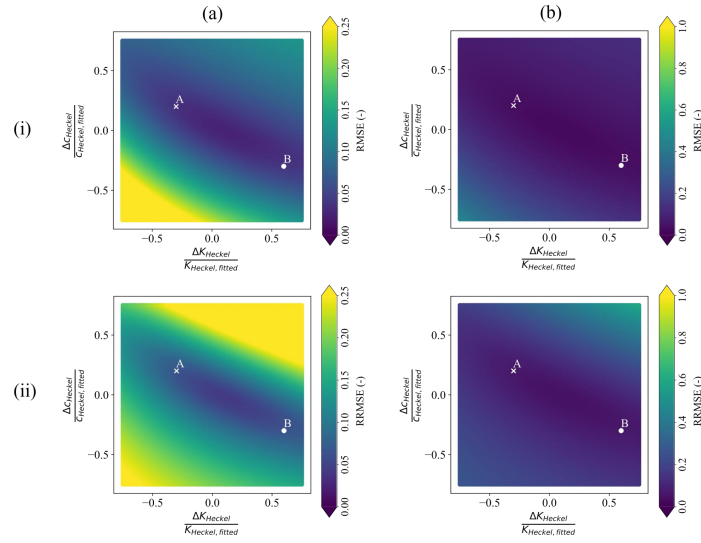


Figure C.2: Contour plots showing how variations of tuning parameters (relative to those estimated by the curve fitting) for the Heckel model impacts the (i) Root Mean Square Error and (ii) Relative Root Mean Square Error of quality attribute predictions for the placebo (20% MCC) blend. The colour bars have been capped at (a) 0.25 and (b) 1 to compare which conditions best demonstrate the size and shape of the contour minima. Highlighted on each of these plots are points A and B, which are the tuning parameter pairs used to construct Figure 6.3 in the main manuscript.

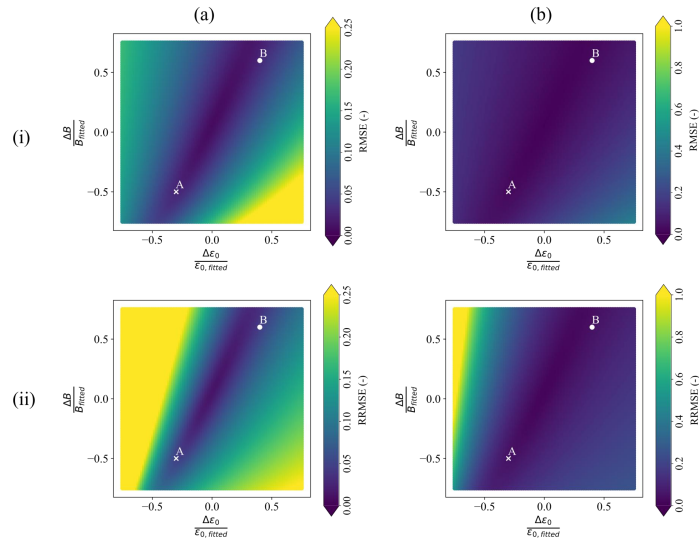


Figure C.3: Contour plots showing how variations of tuning parameters (relative to those estimated by the curve fitting) for the Kawakita model impacts the (i) Root Mean Square Error and (ii) Relative Root Mean Square Error of quality attribute predictions for the placebo (20% MCC) blend. The colour bars have been capped at (a) 0.25 and (b) 1 to compare which conditions best demonstrate the size and shape of the contour minima. Highlighted on each of these plots are points A and B, which are the tuning parameter pairs used to construct Figure 6.3 in the main manuscript.

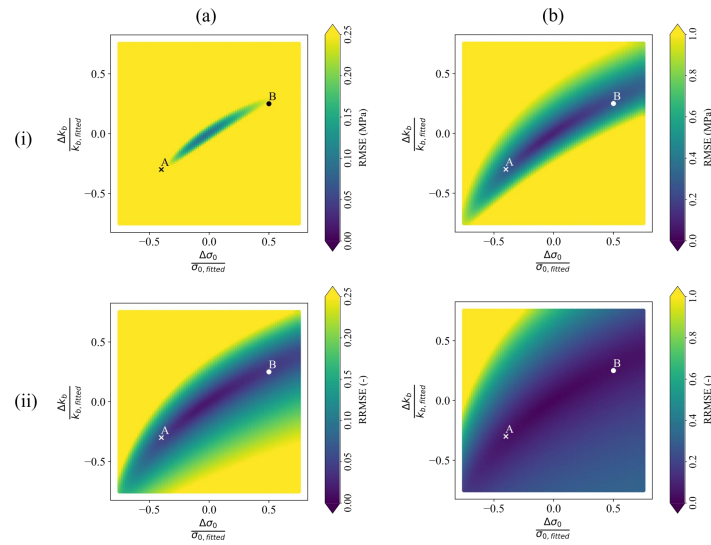


Figure C.4: Contour plots showing how variations of tuning parameters (relative to those estimated by the curve fitting) for the Ryshkewitch-Duckworth model impacts the (i) Root Mean Square Error and (ii) Relative Root Mean Square Error of quality attribute predictions for the placebo (20% MCC) blend. The colour bars have been capped at (a) 0.25 and (b) 1 to compare which conditions best demonstrate the size and shape of the contour minima. Highlighted on each of these plots are points A and B, which are the tuning parameter pairs used to construct Figure 6.3 in the main manuscript.

C.2 Goodness of Fit for Mixture Rule Combinations

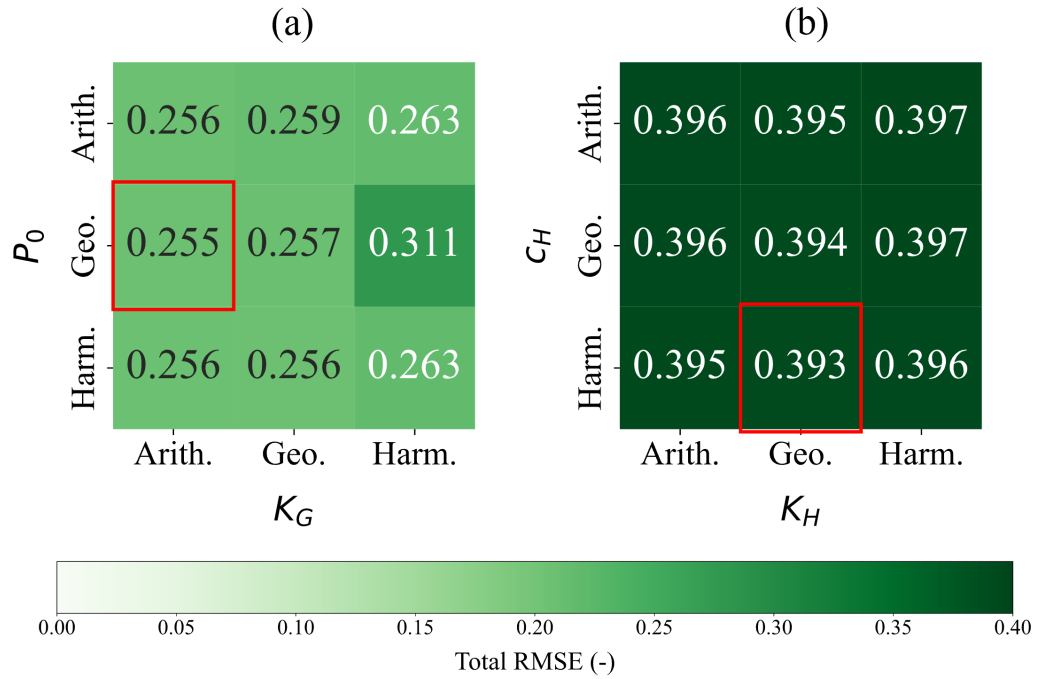


Figure C.5: Total RMSE estimations for the different combinations of arithmetic (Arith.), geometric (Geo.), and harmonic (Harm.) mixture rules for the optimisation of parameter pairs of the (a) Gurnham, and (b) Heckel models. The lowest estimation of total RMSE is outlined in red.

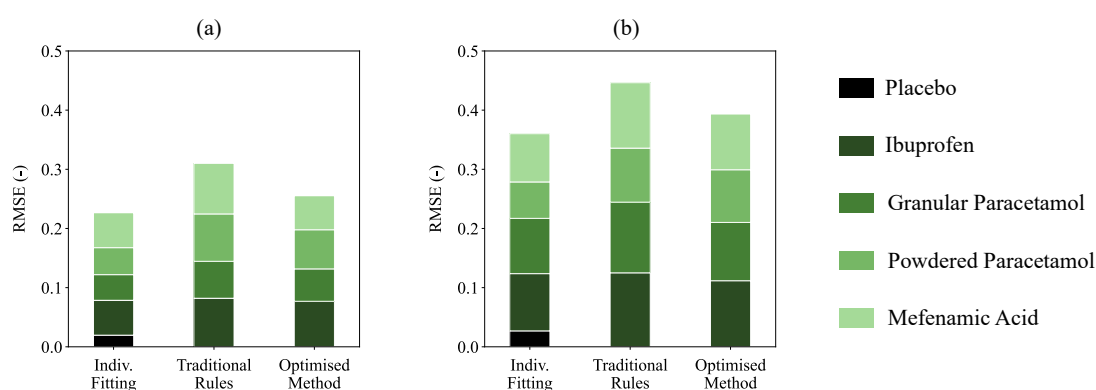


Figure C.6: Stacked bar plots showing the contributions for the loaded blends and 20% MCC placebo to the total RMSE for (a) Gurnham, and (b) Heckel models. Three methods of tuning parameter estimation were compared: individually fitting the datasets; calculating a line of best fit for the estimated tuning 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 data.

C.3 Parity Plots

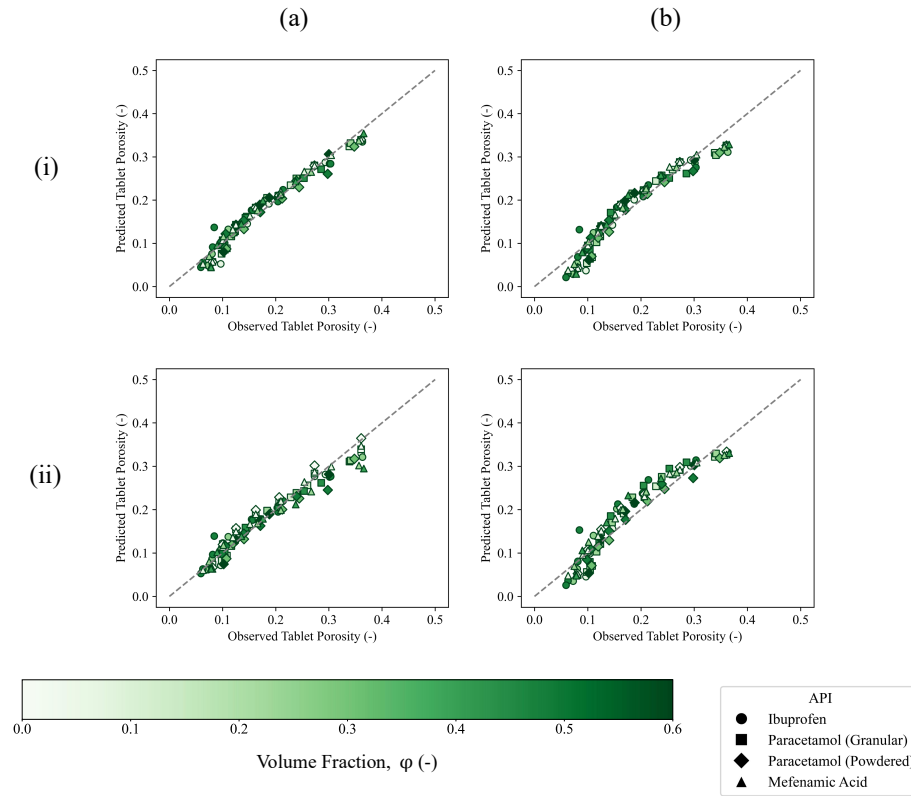


Figure C.7: Parity plots comparing the observed versus predicted critical quality attributes for (a) Gurnham, and (b) Heckel models using (i) the new optimised approach and (ii) the traditional approach to mixture rule population.

C.4 Residual Errors

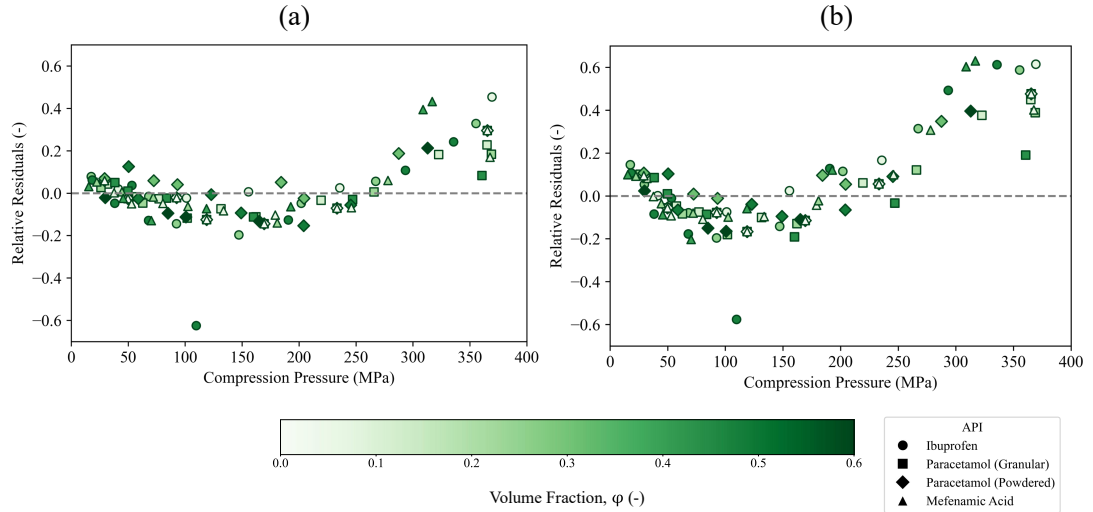


Figure C.8: Relative residual errors for the (a) Gurnham and (b) Heckel models as estimated by the (i) individual fitting of datasets and (ii) the optimised approach to mixture modelling for the loaded dataset.

C.5 Mixture Rule Parameter Estimates

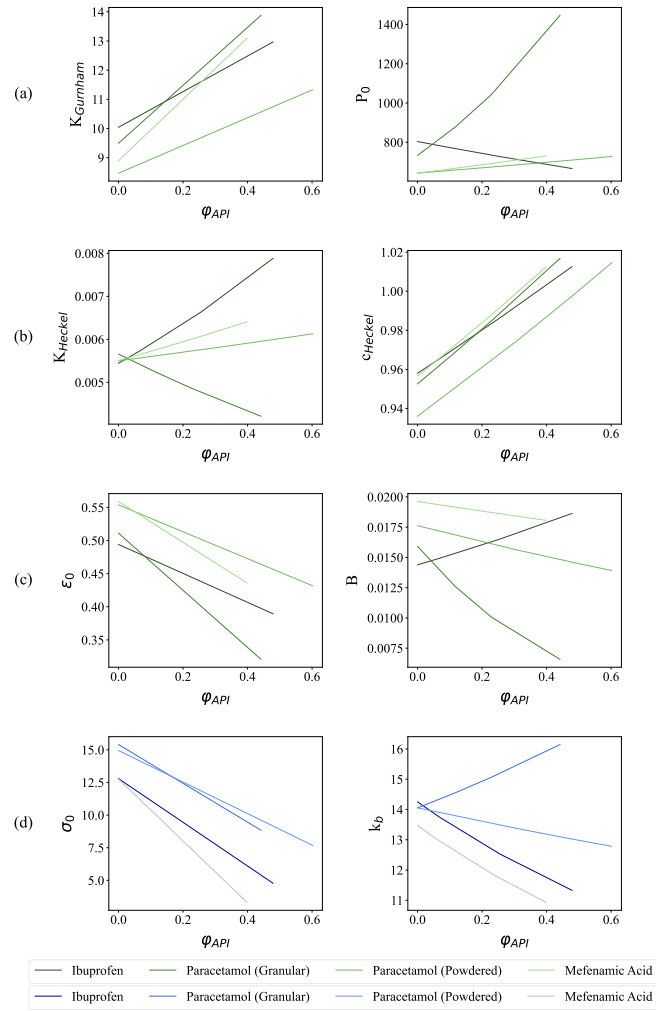


Figure C.9: Tuning parameters as estimated by the traditional mixture rule approach for the (a) Gurnham, (b) Heckel, (c) Kawakita and (d) Ryshkewitch-Duckworth models. Trends follow those highlighted as the most optimum from the comparison of arithmetic, geometric and harmonic mixture rules. Note that the placebo parameters are different in each instance.

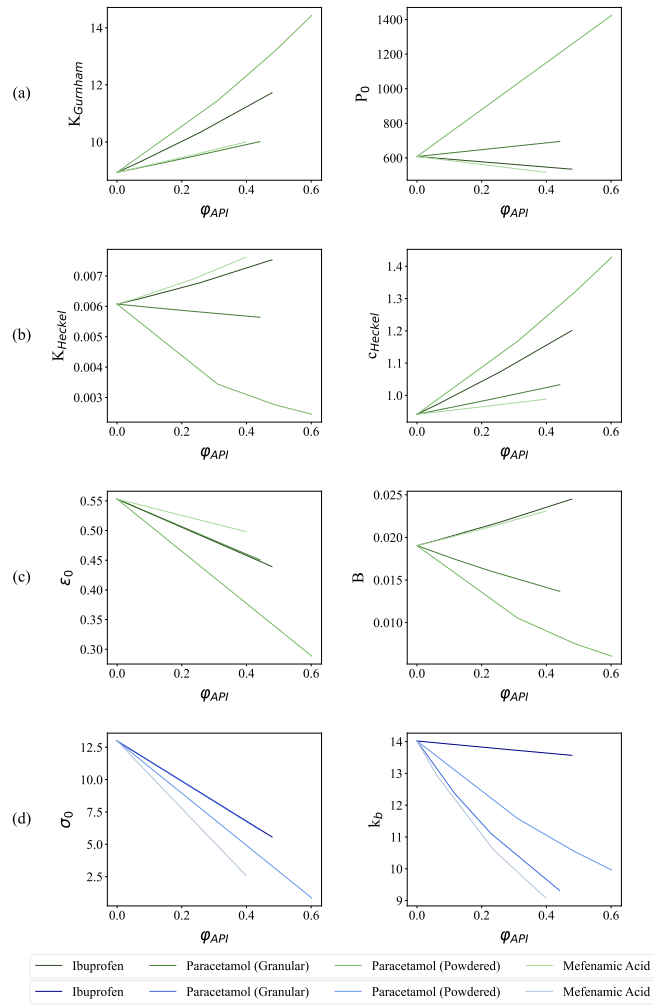


Figure C.10: Tuning parameters as estimated by the optimised mixture rule population for the (a) Gurnham, (b) Heckel, (c) Kawakita and (d) Ryshkewitch-Duckworth models. Trends follow those highlighted as the most optimum from the comparison of arithmetic, geometric and harmonic mixture rules.

Appendix D

Optimising Experimental Design for Direct Compression Formulations

D.1 Data cleaning for over-compaction removal

There were signs of over-compaction (a reduction in tensile strength with lower porosity) in the ibuprofen datasets, most notable in the higher concentrations of the smaller sizes of API, Figure D.1. This occurs due to inadequate formulation design and excessive compression pressure, which may cause defects that ultimately impact tablet tensile strength measurements.

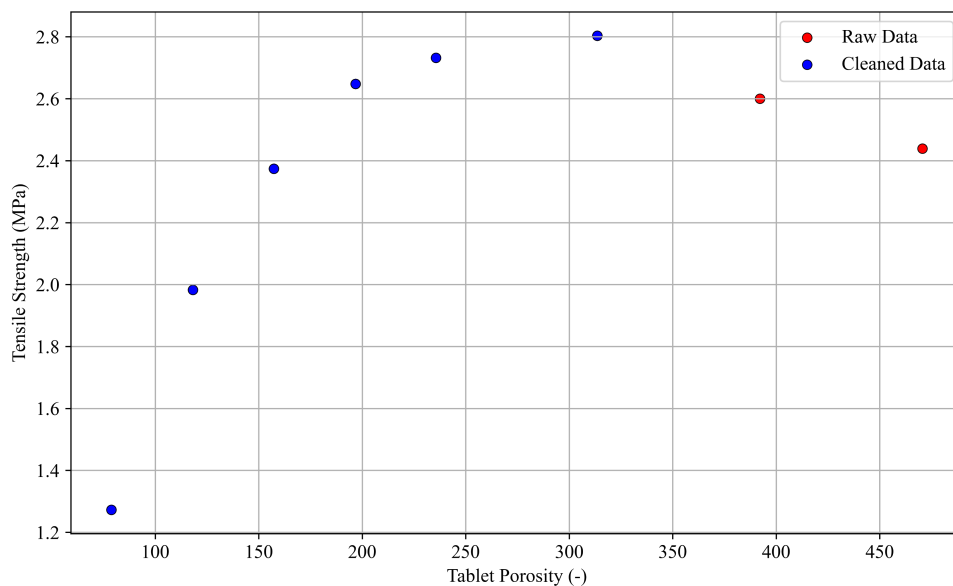


Figure D.1: Example of over compaction in Ibuprofen 25 dataset for tablets of 31.5% mass. Red data represented the over compacted data which was removed from the dataset for cleaning.

To address this, an automated procedure was used to identify and remove over-compacted points prior to model fitting. Within each dataset, data points were sorted in ascending order of compression pressure to ensure a physically consistent progression. Overcompaction was then identified on a point-by-point basis: tensile strength was expected to increase or remain constant as compression pressure increased; any data point where tensile strength decreased relative to the preceding point was flagged as evidence of overcompaction, a phenomenon in which excessive compression pressure induces structural damage (e.g., cracking or delamination) that reduces tablet strength rather than increasing it, as shown in Figure D.1. Flagged points were removed from the dataset, and the corresponding blend composition (API and filler volume fractions) and number of excluded points were recorded for review whenever overcompaction was detected.

In practice, the number of points flagged as overcompacted was small, rarely exceeding a single point per compaction dataset. The most affected cases were the smallest particle size fractions of ibuprofen, where up to three of eight data points were excluded;

however, these points fell outside the RoI for industrial manufacturing, meaning their removal is unlikely to compromise the practical relevance or reliability of the resulting fits. Removing these points was to improve the stability and interpretability of curve fits (e.g., Ryshkewitch–Duckworth) by preventing the model from being pulled toward non-physical, artefactual behaviour at high pressures. Given the low frequency of exclusions and their concentration outside the pressure range of practical interest, the impact on sample size and fit reliability within the RoI is expected to be minimal. Some caution is still warranted at the extremes of the pressure range or for the finest particle size fractions, where a higher proportion of points were excluded and fits should be interpreted with awareness that any real overcompaction effects at higher pressures have been deliberately excluded rather than modelled.

These points were removed from the datasets and the optimisation was repeated with the 'cleaned' dataset, which slightly increased the performance of instances where the Arithmetic rule was applied. This was not enough, however, to solve the trends in the residual errors.

D.2 Traditional Mixture Rules

To evaluate the traditional approach to populating mixture rules for modelling compressibility and compactability tuning parameters, the parameters were estimated from the application of Kawakita (A_K and B_K) and Ryshkewitch-Duckworth (A_{RD} and B_{RD}) models on the individual datasets. These parameters, y , were then plotted as a scatter with respect to API concentration, x , and used to fit the three relevant mixture rules: arithmetic (Equation D.1), geometric (Equation D.2) and harmonic means (Equation D.3).

$$y = a * x + b \tag{D.1}$$

$$y = a * x^b \tag{D.2}$$

$$y = \left(\frac{x}{a} + \frac{1-x}{b} \right)^{-1} \tag{D.3}$$

The mixture parameters were then estimated from the fitted line equations at the corresponding API concentrations. These parameters were used in the empirical models to re-estimate the GoF using the different combinations of mixtures for parameters A and B .

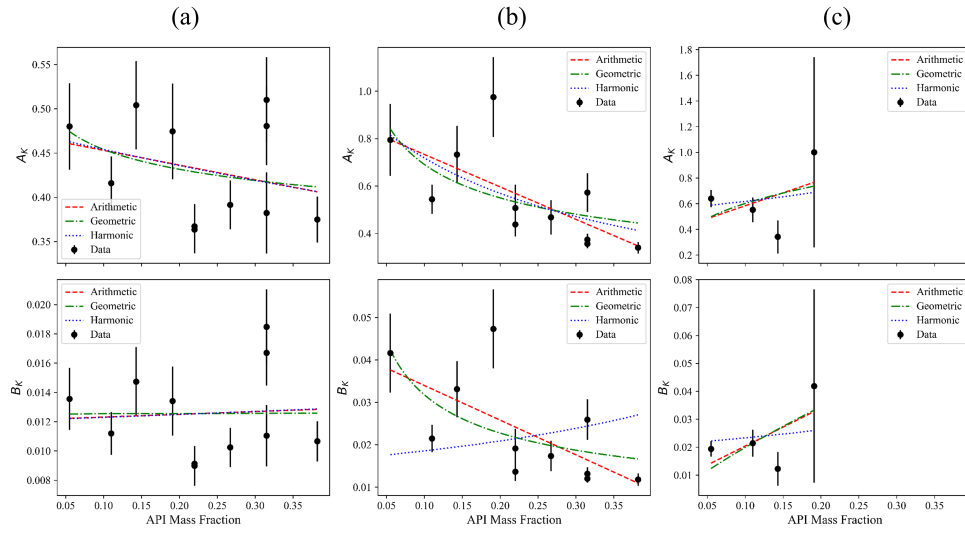


Figure D.2: Traditional approach to populating mixture rules for Kawakita for (a) dense, (b) powdered, and (c) micronized paracetamol.

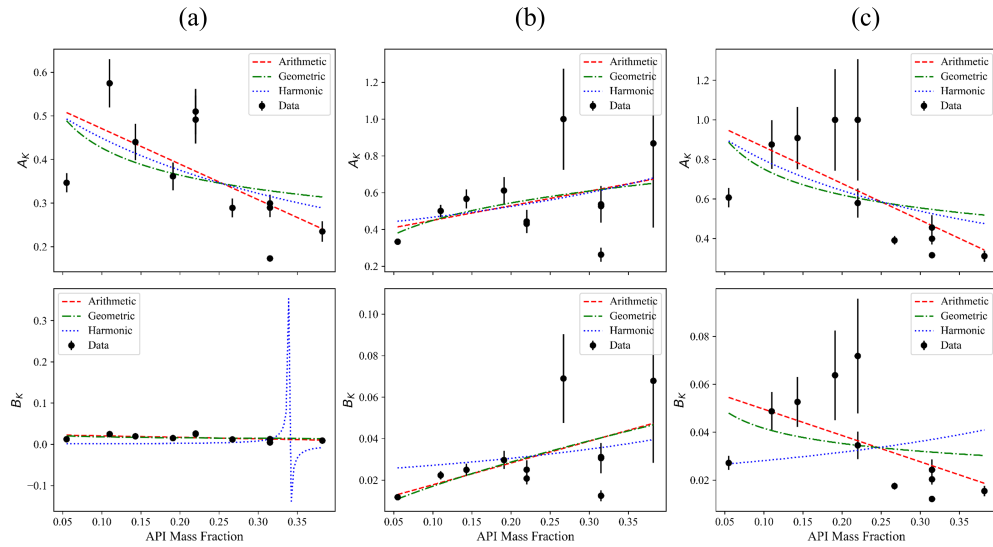


Figure D.3: Traditional approach to populating mixture rules for Kawakita for Ibuprofen (a) 50, (b) 38, and (c) 25.

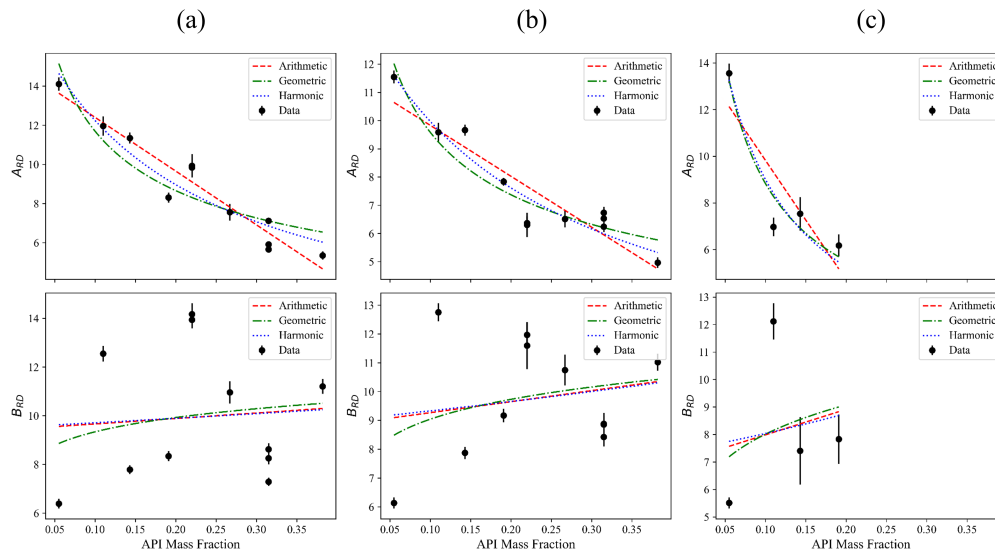


Figure D.4: Traditional approach to populating mixture rules for Ryshkewitch-Duckworth for (a) dense, (b) powdered, and (c) micronized paracetamol.

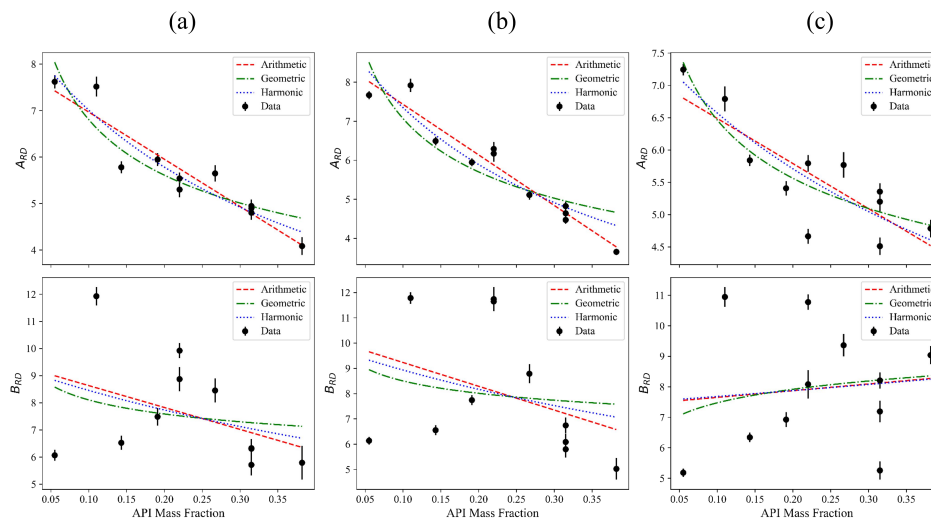


Figure D.5: Traditional approach to populating mixture rules for Ryshkewitch-Duckworth for Ibuprofen (a) 50, (b) 38, and (c) 25.

D.3 Residual Errors

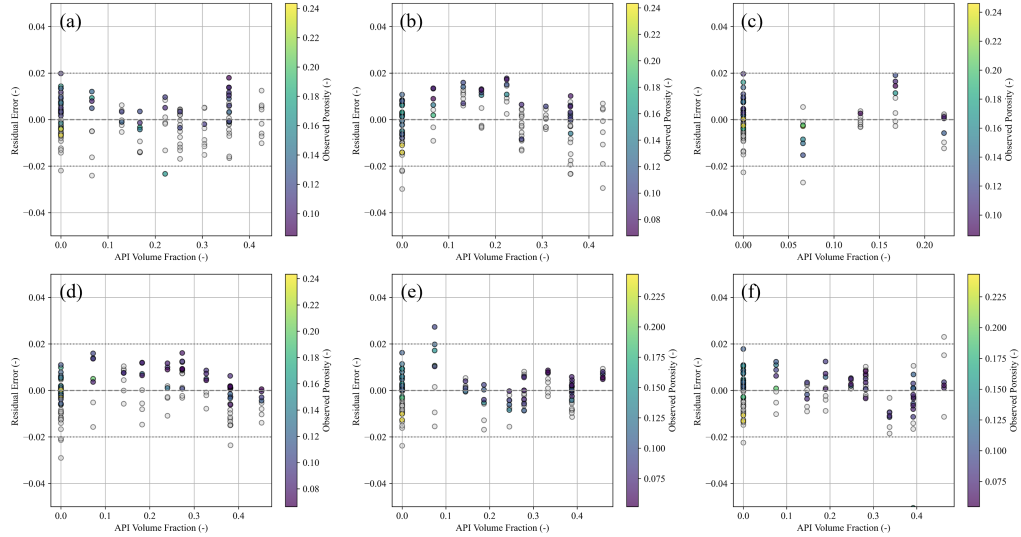


Figure D.6: Residual errors with respect to the API volume fraction from the Kawakita estimation of tablet porosity for (a) dense, (b) powdered, and (c) micronized paracetamol, and ibuprofen (d) 50, (e) 38, and (f) 25. The colour bar represents the observed porosity with the highlighted points showing those which lie within the defined Region of Interest. Error limits of ± 0.02 are shown to demonstrate acceptable error region.

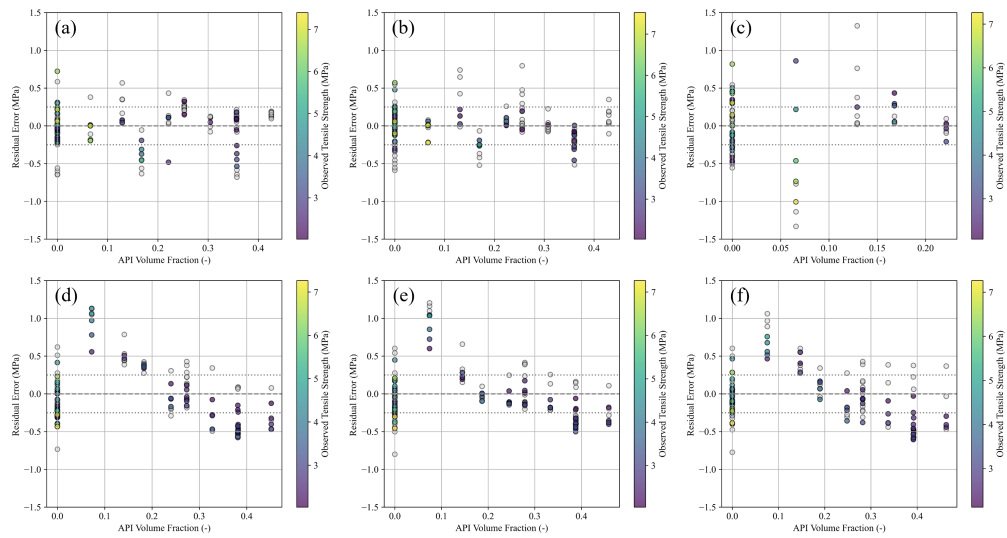


Figure D.7: Residual errors with respect to the API volume fraction from the Ryshkewitch-Duckworth estimation of tablet tensile strength for (a) dense, (b) powdered, and (c) micronized paracetamol, and ibuprofen (d) 50, (e) 38, and (25). The colour bar represents the observed porosity with the highlighted points showing those which lie within the defined Region of Interest. Error limits of ± 0.25 MPa are shown to demonstrate acceptable error region.

D.4 Probability Distribution of Residual Errors for the Whole Dataset

The probability distributions of the residual errors across the whole datasets are shown in Figure D.8 with numerical descriptors outlined in Table D.1 and Table D.2 for the Kawakita and Ryshkewitch-Duckworth model respectively.

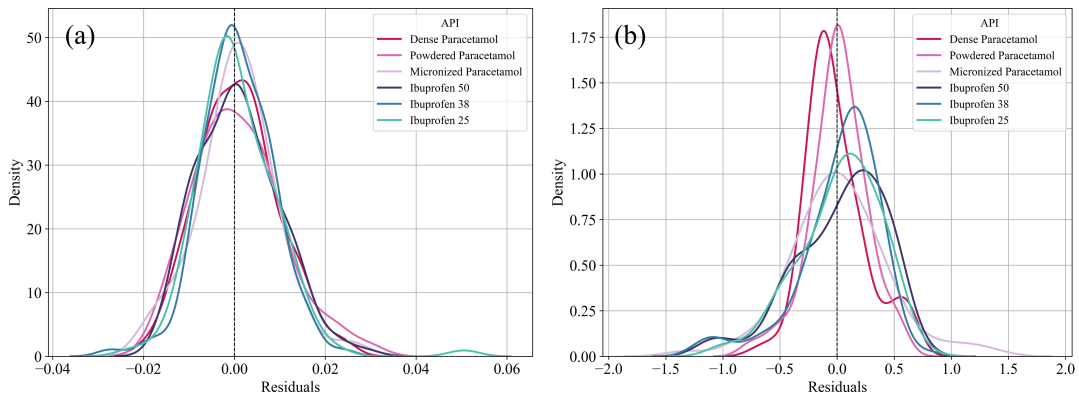


Figure D.8: Probability Density plots of the residual errors across the entire datasets for the (a) Kawakita and (b) Ryshkewitch-Duckworth models.

Table D.1: Descriptors for the probability density functions of the Kawakita residuals for the independent API datasets across the whole dataset. Full number of datapoints includes the placebo data.

API	Number of Datapoints	Mean ($\times 10^{-4}$)	Variance ($\times 10^{-5}$)	Modality
Dense Paracetamol	135	7.85	7.40	2
Powdered Paracetamol	132	8.92	9.50	2
Micronized Paracetamol	78	5.27	7.40	2
Ibuprofen 50	132	8.55	7.90	2
Ibuprofen 38	130	6.34	6.00	2
Ibuprofen 25	125	7.26	8.10	2

Table D.2: Descriptors for the probability density functions of the Ryshkewitch–Duckworth residuals for the independent API datasets across the whole dataset. Full number of datapoints includes the placebo data.

API	Number of Datapoints	Mean	Variance	Modality
Dense Paracetamol	135	-0.01	0.07	2
Powdered Paracetamol	132	0.01	0.06	2
Micronized Paracetamol	78	0.01	0.18	2
Ibuprofen 50	132	0.03	0.16	2
Ibuprofen 38	130	0.02	0.13	2
Ibuprofen 25	125	0.03	0.13	2

D.5 Interaction Rule Evaluation

Non-linear relationships were observed in the compactability behaviours across a mixtures composition (Figure 7.6). For compaction, it has been hypothesized that this may be due to the dominance of the non-compactable components or an interaction between the components themselves. The current code utilizes linear mixture rules which assumes that the materials contributions are independent to each other and also contribute equally depending on their volume fraction (i.e. there is no additional weighting factor which may account for “dominance”). By introducing interaction terms either via a linear mixture rules with interaction terms or by considering the Van der Waals equation of state (comparing the flowability of powders to that of liquids) it may be possible to better capture the non-linear behaviours observed in the prediction of new pharmaceutical blends compactability.

A linear rule with pairwise interaction terms was tested by Corrigan et al. (2024) (Equation D.4), along with linear terms without interaction, and with ternary interaction terms. Particularly for the purposes of reducing experimentation, the introduction of additional degrees of freedom will have a direct impact on the number of experiments required to inform them, for which the binary interaction terms were found to be a sufficient balance in this regard.

$$\theta_{\text{mix}} = \sum_{i=1}^N \phi_i \theta_i + \sum_{i<j}^N \phi_i \phi_j \theta_{ij} \quad (\text{D.4})$$

Where θ_{mix} is a mixtures parameter, estimated based on the volumetric contribution, ϕ_i , of a components parameter, θ_i , accounting for the interaction parameter of material pairs, θ_{ij} .

Aroniada et al. (2023) formulated a Van der Waals mixing rule to estimate mixture parameter, θ_{mix} , used to predict the flowability of new powder mixtures. This assumes that the powders used in OSD formulation uses fine, dry and uncharged powders which are dominated by interparticle cohesive forces (Van der Waals) described by the interaction term. The linear term gives a representation of the volume taken up by the particles of component i .

$$\theta_{mix} = \sum_{i=1}^N \phi_i \theta_i + \sum_i^N \sum_j^N \phi_i \phi_j \sqrt{\theta_i \theta_j} (1 - K_{ij}) \quad (D.5)$$

Where θ_{mix} is a mixtures parameter, estimated based on the volumetric contribution, ϕ_i , of a components parameter, θ_i , accounting for the Van der Waals interaction parameter of material pairs, K_{ij} . The difference here is that the interaction matrix is consistent across parameters A and B in the empirical models, reducing the number of variables compared to the Linear Rule with pairwise interaction terms.

D.5.1 Coding Methodology for Interaction Rules

A gradient-based global optimisation was conducted to populate the interaction models such that the Root-Mean Squared Error was minimised across the design spaces for dense, powered, and micronized paracetamol, and ibuprofen 50, 38, and 25. The model predictions require estimations for A_{mix} and B_{mix} for use in the Ryshkewitch-Duckworth (Equation 2.14) equations of powder compactability (i.e. the increase of tablet tensile strength, σ , with decreasing tablet porosity, ε).

For each API system, the parameter vector, θ , includes six pure component parameters, $[A_{API}, B_{API}, A_{LAC}, B_{LAC}, A_{MCC}, B_{MCC}]$ and the set of interaction parameters, θ_{ij} or K_{ij} (Equation D.6).

$$\theta_{ij} \mid K_{ij} = \begin{bmatrix} 0 & \theta_{\text{API,LAC}} & \theta_{\text{API,MCC}} \\ \theta_{\text{API,LAC}} & 0 & \theta_{\text{LAC,MCC}} \\ \theta_{\text{API,MCC}} & \theta_{\text{MCC,LAC}} & 0 \end{bmatrix}, \quad \begin{cases} \theta_{ij} \in \{A, B\} \\ K_{ij}^{(A)} = K_{ij}^{(B)} = K_{ij} \end{cases} \quad (\text{D.6})$$

The optimisation employs the package `scipy.optimize.minimize` using the Broyden–Fletcher–Goldfarb (BFGS) algorithm with Python 3.10.11., the bounds are outlined in Table D.3. The initial estimates were randomly selected within the bounds and replicated five times to ensure appropriate exploration of the parameter spaces avoiding trapping at local minima. The iteration which minimised the objective function was used for further investigation.

Table D.3: Set parameter boundaries for the optimisation of interaction mixture rules.

Parameter Type	Parameter Bounds
θ	$[10^{-6}, 250]$
θ_{ij}, K_{ij}	$[-500, 500]$

D.5.2 Results and Discussion

Parity plots and residual errors were used to investigate the GoF for the studied interaction models (Figure S44 - Figure S47). There was little change between the performance of the two interaction models, with only the low loading of ibuprofen 50 showing any notable deviations between the two methods. Considering the residuals for the interaction models prediction of ibuprofens behaviour, it can be seen that the model performs differently for the lower and higher loaded blends, as observed in the sinusoidal relationship in the residuals – the relationship predicts well at the placebo space, then shifts from overpredicting to underpredicting as the API concentration increases (Figure D.9 and Figure D.12). This is evidence that the models performance is dependent on the structural behaviours of the formulation. This may be due to the inherent error in the Ryshkewitch-Duckworth model itself, or that the compaction behaviours are non-linear with the change in API concentration, with low loadings showing insufficient percolation

of API and high fractions dominating the mechanical deformations.

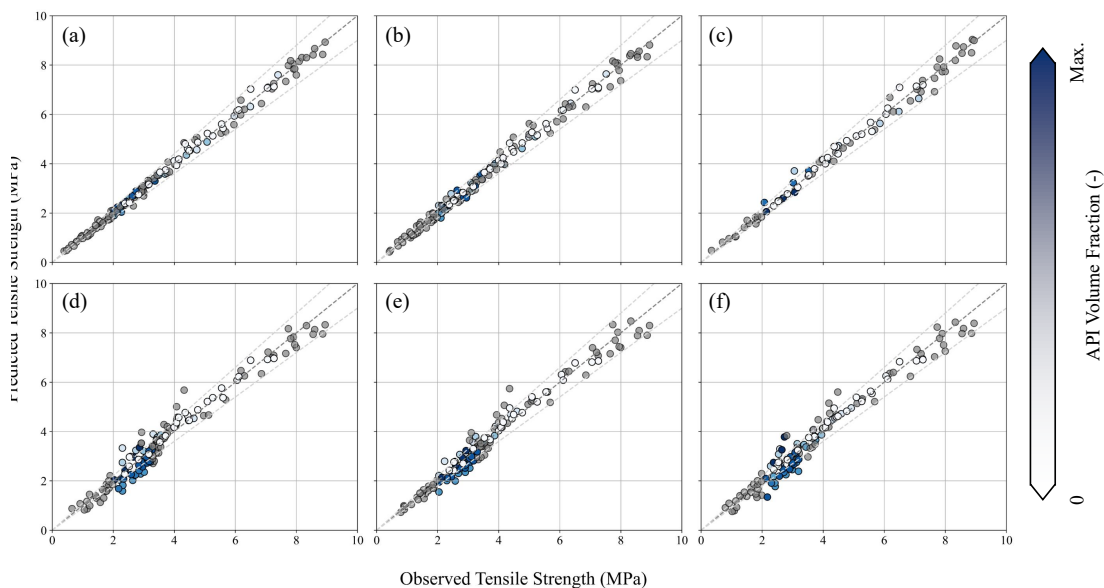


Figure D.9: Parity plots for the predicted and true tensile strength using the Van der Waals interaction mixture rule approach for the Ryshkewitch-Duckworth model model for (a) Dense, (b) Powdered, and (c) Micronized Paracetamol, and Ibuprofen (d) 50, (e) 38, and (f) 25. Data points which lie within the defined Region of Interest are highlighted in colour which reflects their API volume fraction.

D.5.3 Conclusions

The implementation of additional parameters (i.e. interaction parameters or parameters to help indicate the point of behavioural change) in the mixture rules can aid in the understanding and diagnosing of formulation (mis)behaviours. Yet, as the ambition is to reduce the experimentation to develop a manufacturable formulation, the basic combination of mixture rules to populate the empirical models along with the MBDoE methodology should suffice in narrowing the field of vision.

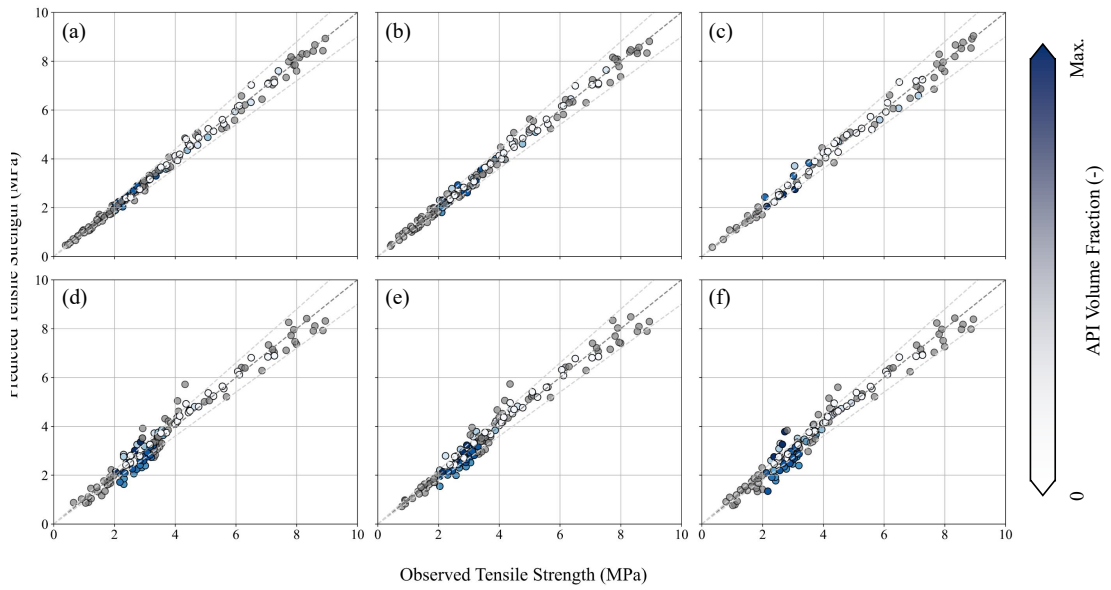


Figure D.10: Parity plots for the predicted and true tensile strength using the Binary interaction mixture rule approach for the Ryshkewitch-Duckworth model model for (a) Dense, (b) Powdered, and (c) Micronized Paracetamol, and Ibuprofen (d) 50, (e) 38, and (f) 25. Data points which lie within the defined Region of Interest are highlighted in colour which reflects their API volume fraction.

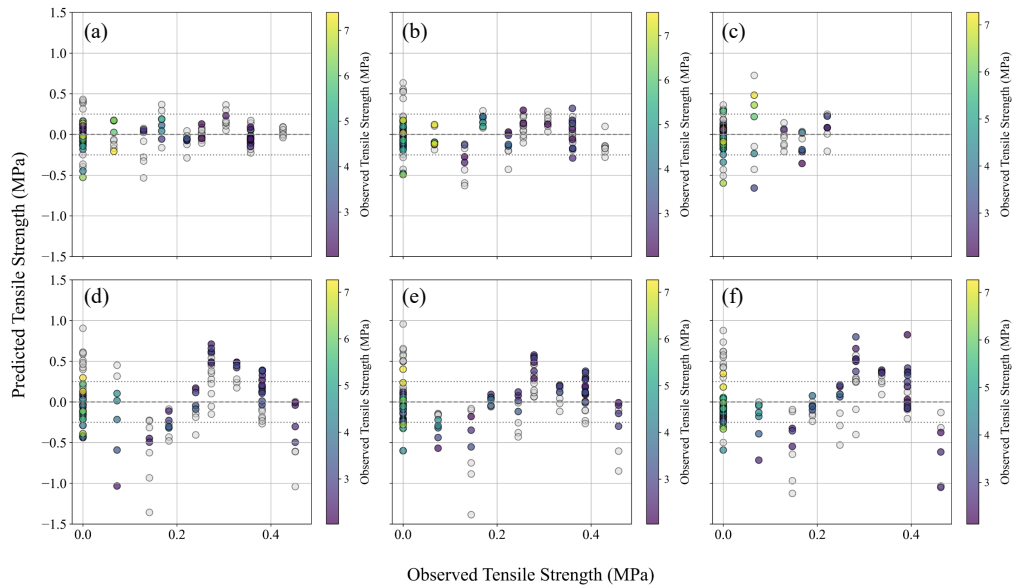


Figure D.11: Residual errors for the predictions of tensile strength using the Van der Waals interaction model to populate the Ryshkewitch-Duckworth model for (a) Dense, (b) Powdered, and (c) Micronized Paracetamol, and Ibuprofen (d) 50, (e) 38, and (f) 25.

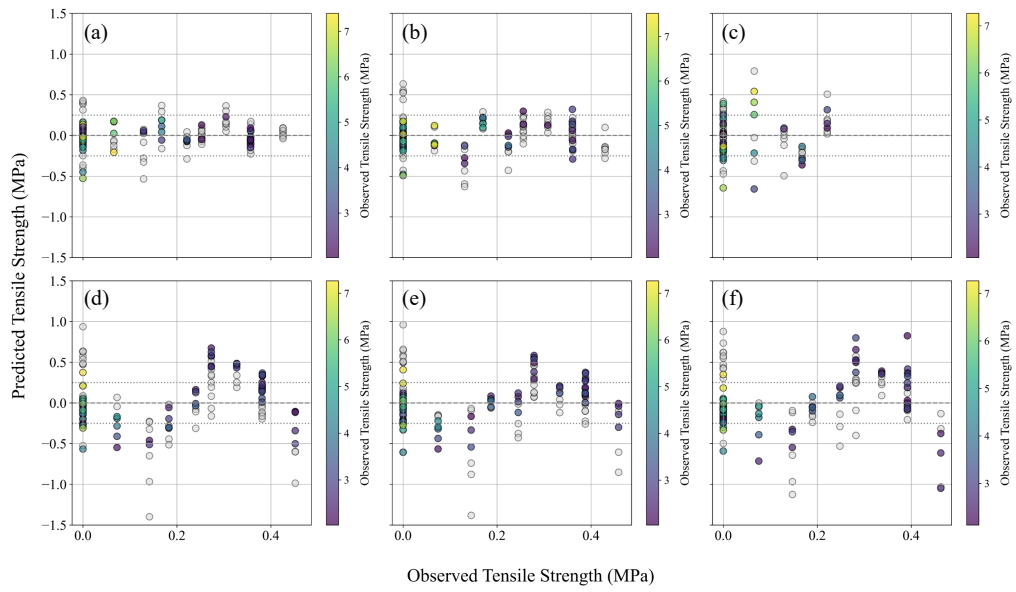


Figure D.12: Residual errors for the predictions of tensile strength using the Binary interaction model to populate the Ryshkewitch-Duckworth model for (a) Dense, (b) Powdered, and (c) Micronized Paracetamol, and Ibuprofen (d) 50, (e) 38, and (f) 25.

D.6 Optimality Routes

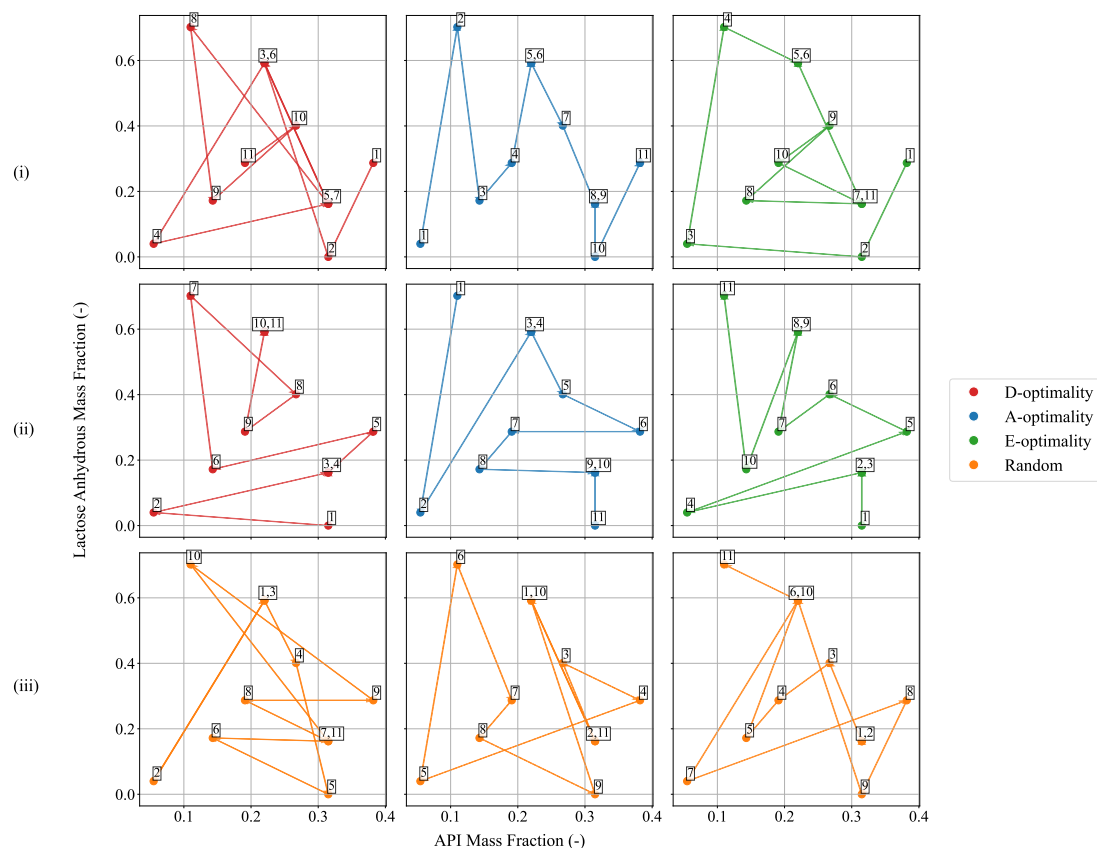


Figure D.13: An example showing the experimental routes taken by the Model Based Design of Experiments for (i) Kawakita and (ii) Ryshkewitch-Duckworth models and the routes taken by the three iterations of (iii) Random Selection to predict behaviours for dense paracetamol.

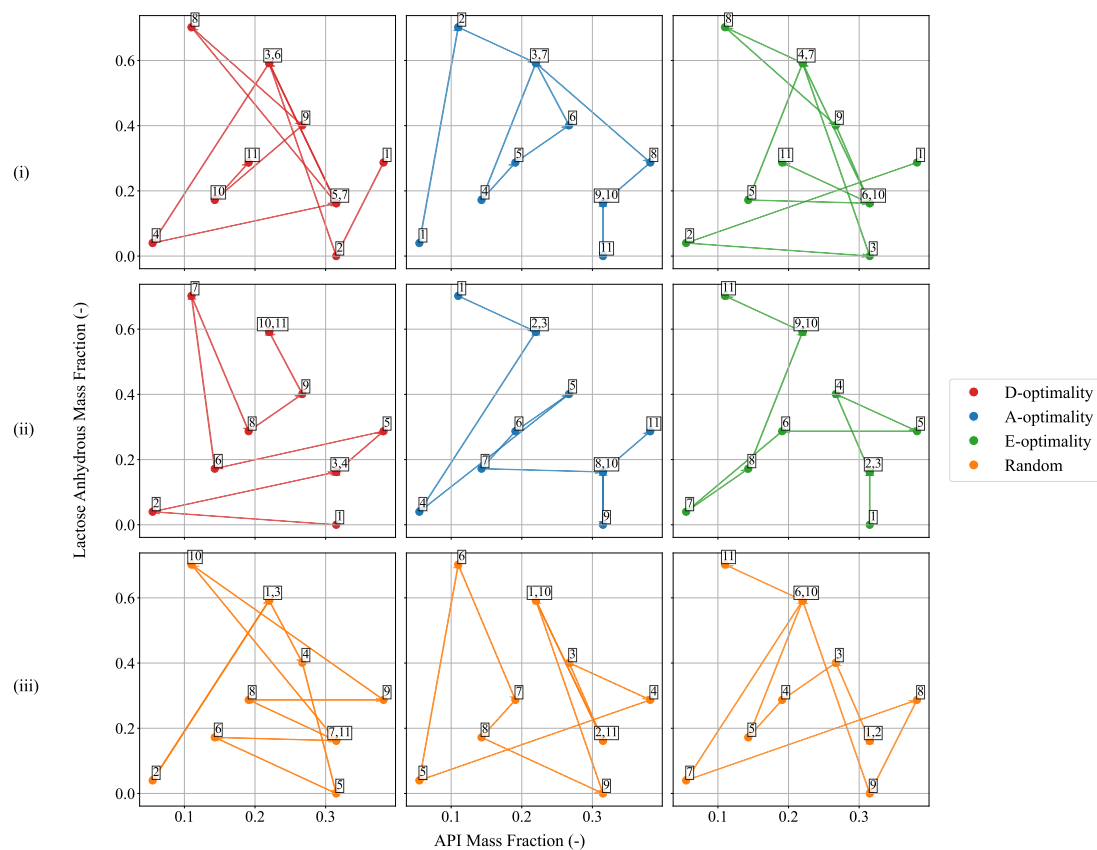


Figure D.14: An example showing the experimental routes taken by the Model Based Design of Experiments for (i) Kawakita and (ii) Ryshkewitch-Duckworth models and the routes taken by the three iterations of (iii) Random Selection to predict behaviours for powdered paracetamol

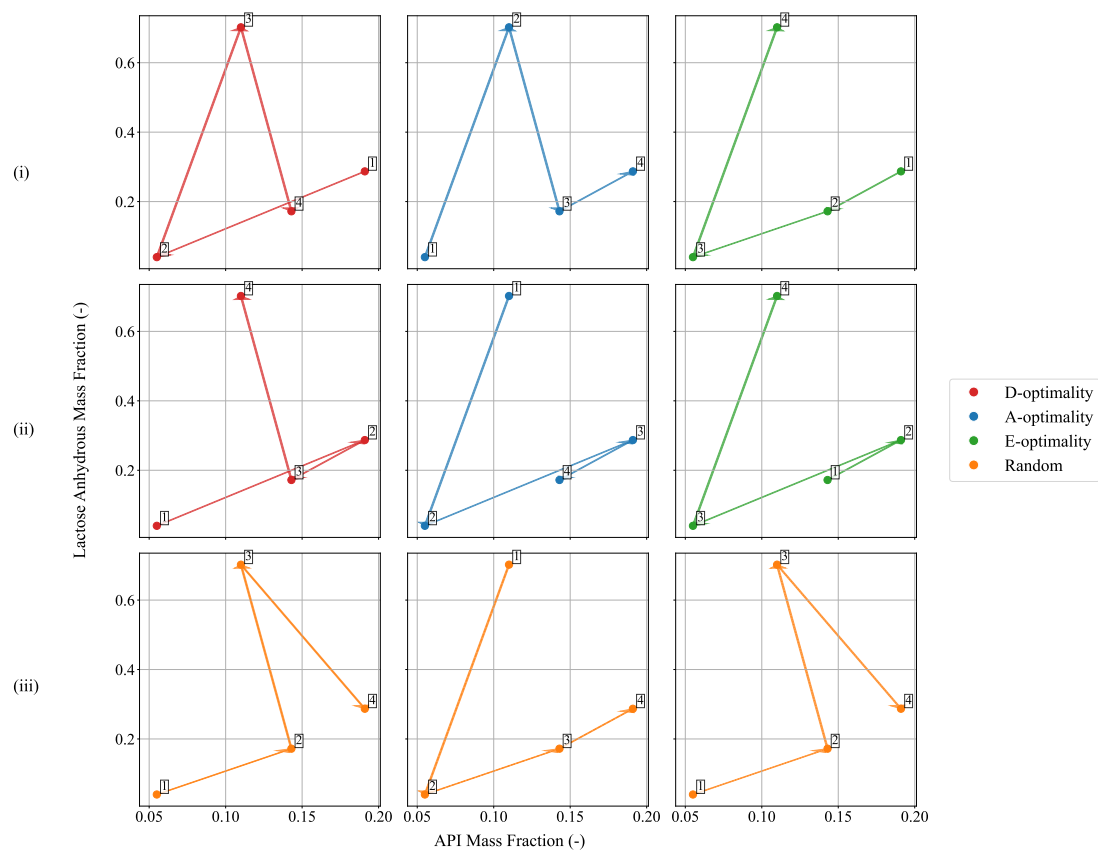


Figure D.15: An example showing the experimental routes taken by the Model Based Design of Experiments for (i) Kawakita and (ii) Ryshkewitch-Duckworth models and the routes taken by the three iterations of (iii) Random Selection to predict behaviours for micronized paracetamol.

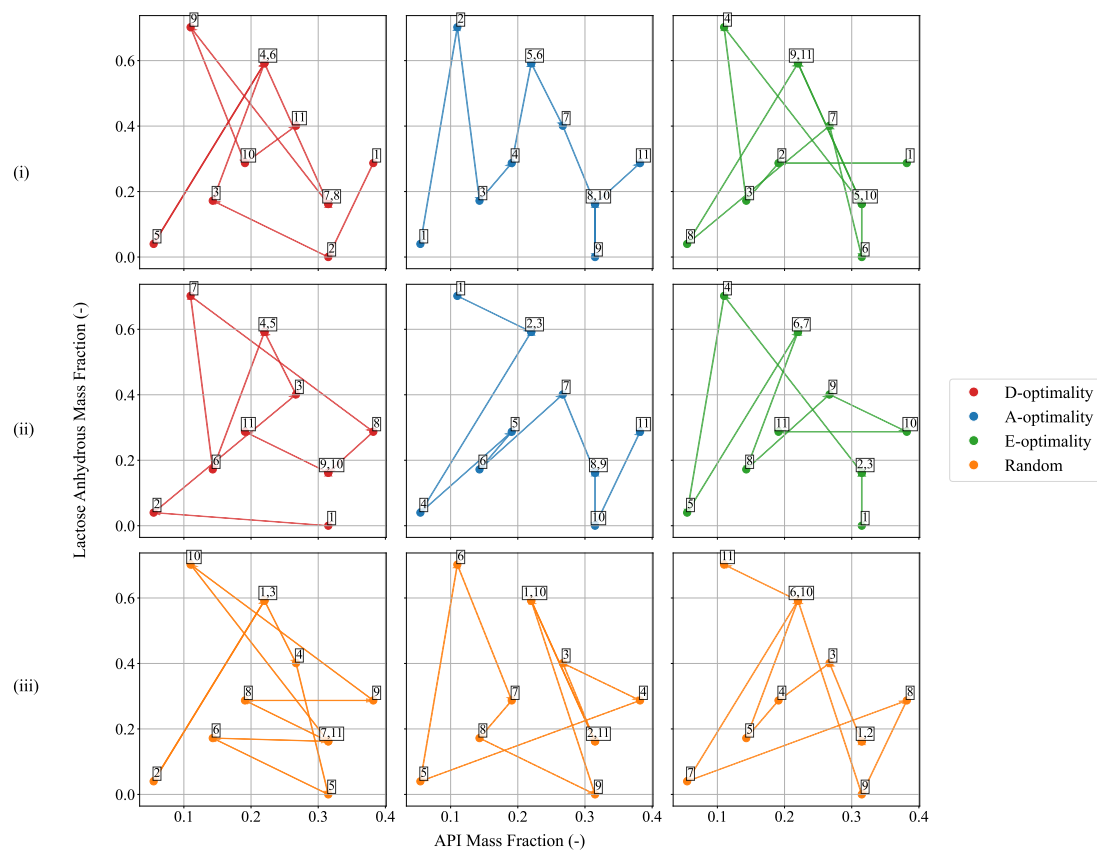


Figure D.16: An example showing the experimental routes taken by the Model Based Design of Experiments for (i) Kawakita and (ii) Ryshkewitch-Duckworth models and the routes taken by the three iterations of (iii) Random Selection to predict behaviours for ibuprofen 38.

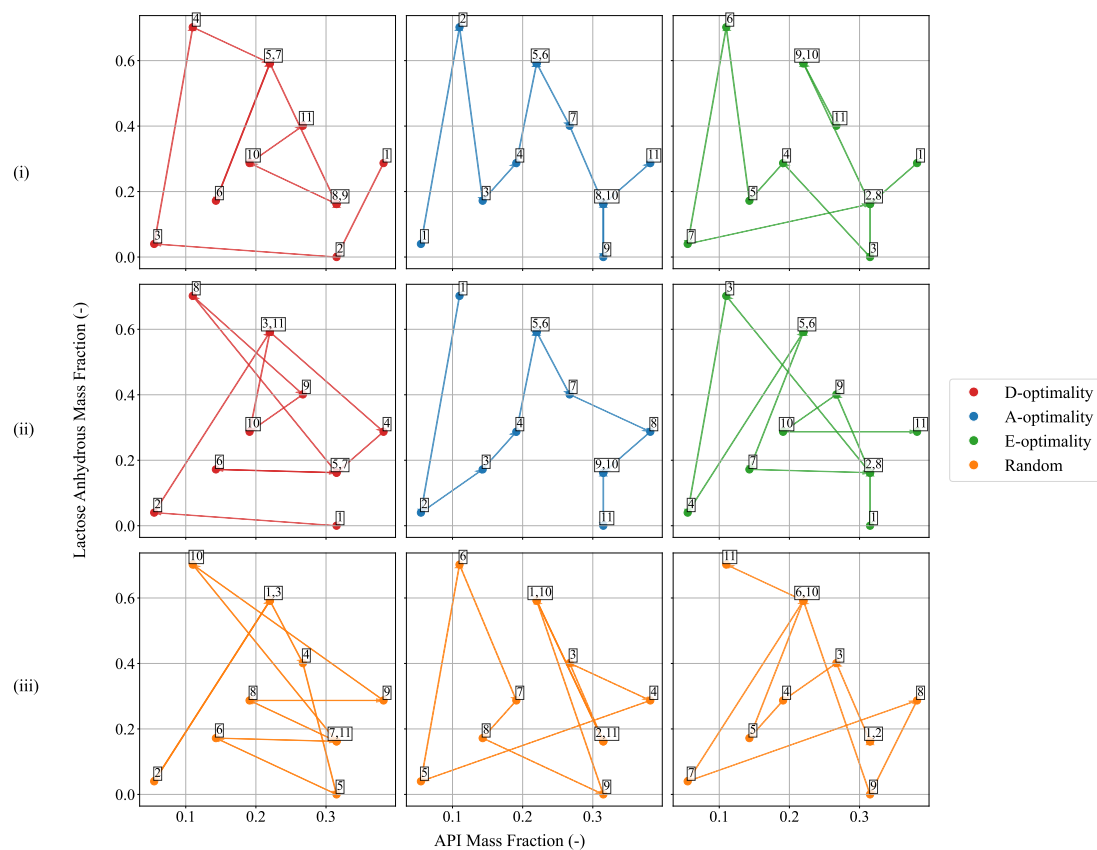


Figure D.17: An example showing the experimental routes taken by the Model Based Design of Experiments for (i) Kawakita and (ii) Ryshkewitch-Duckworth models and the routes taken by the three iterations of (iii) Random Selection to predict behaviours for ibuprofen 25.

D.7 Optimality Metrics with Increasing Calibration Set Size

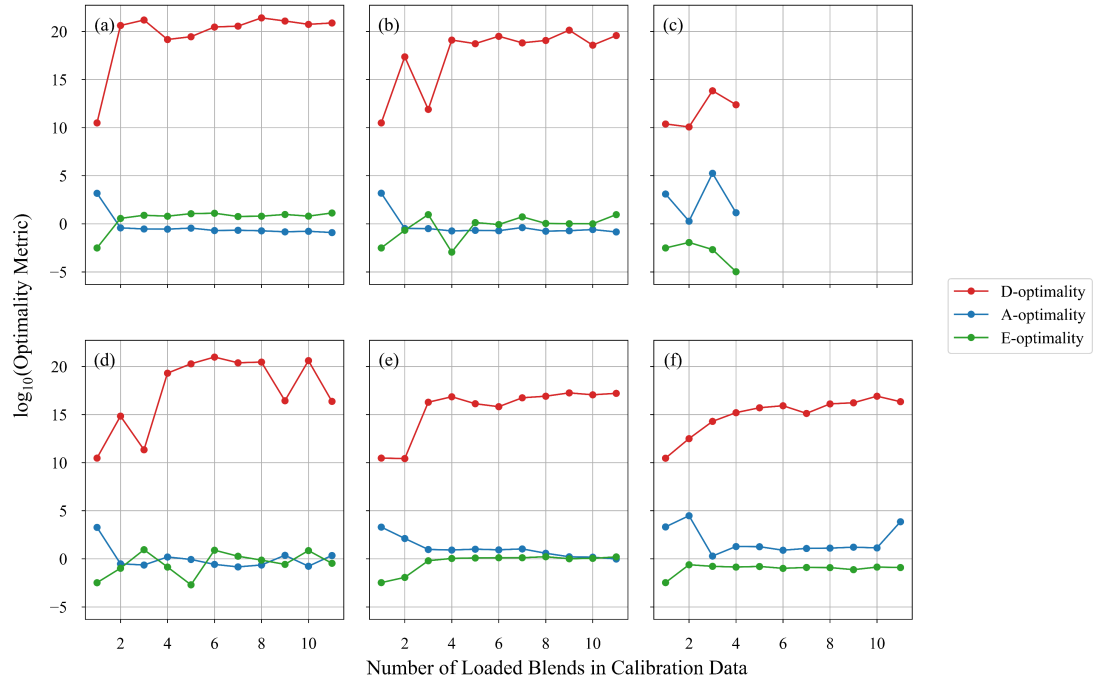


Figure D.18: Information content for the different optimality metrics (D-, A- and E-) for parameterising the Kawakita model for (a) Dense Paracetamol, (b) Powdered Paracetamol, (c) Micronized Paracetamol, (d) Ibuprofen 50, (e) Ibuprofen 38, and (f) Ibuprofen 25.

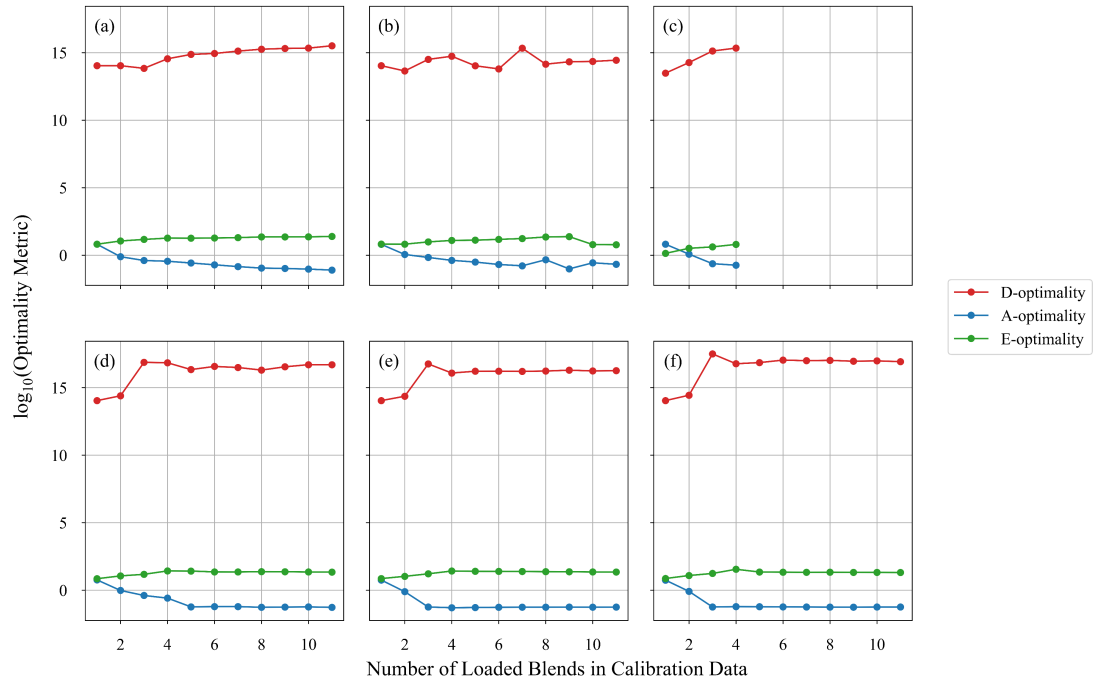


Figure D.19: Information content for the different optimality metrics (D-, A- and E-) for parameterising the Kawakita model for (a) Dense Paracetamol, (b) Powdered Paracetamol, (c) Micronized Paracetamol, (d) Ibuprofen 50, (e) Ibuprofen 38, and (f) Ibuprofen 25.

D.8 Model-Based Design of Experiment Parameter Estimations

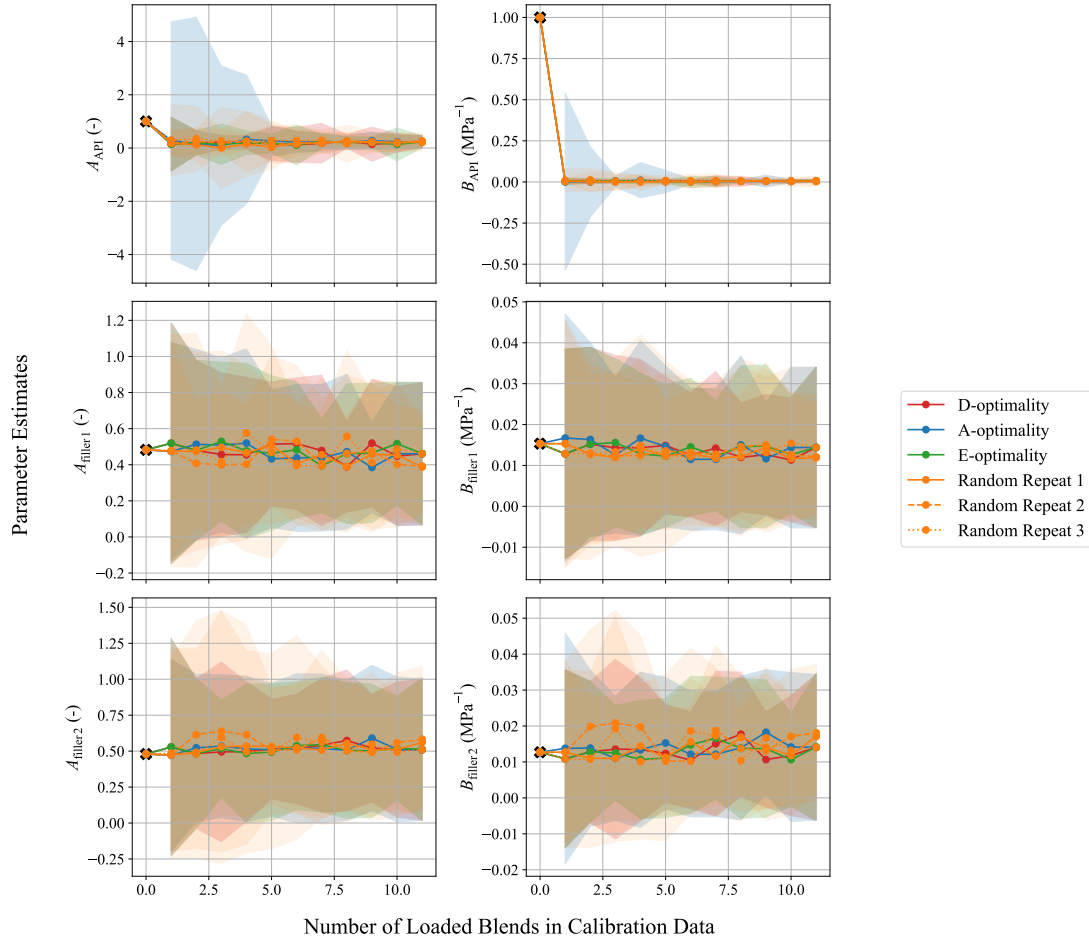


Figure D.20: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Kawakita model of dense paracetamol. Colours indicate the MBDoE optimality criterion, while line type distinguishes the different random selection iterations.

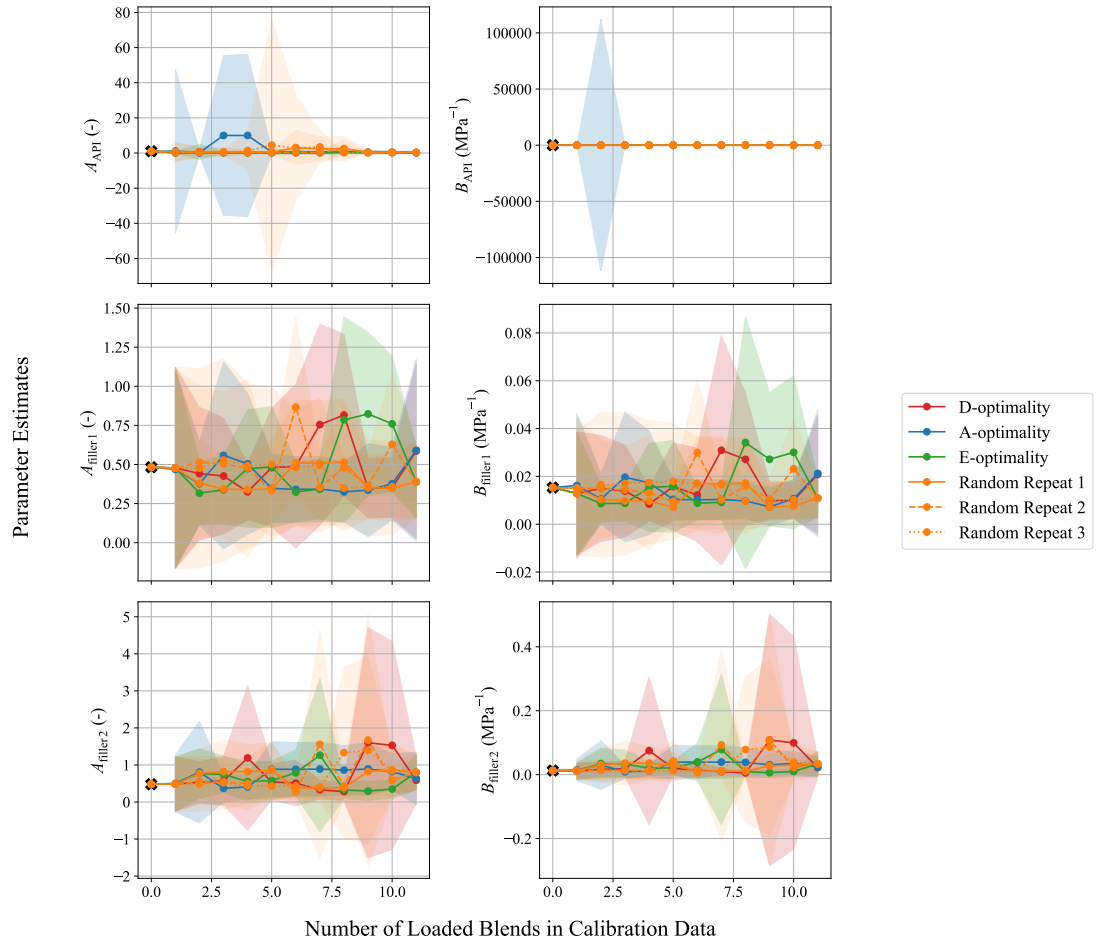


Figure D.21: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Kawakita model of powdered paracetamol. Colours indicate the MBDoE optimality criterion, while line type distinguishes the different random selection iterations.

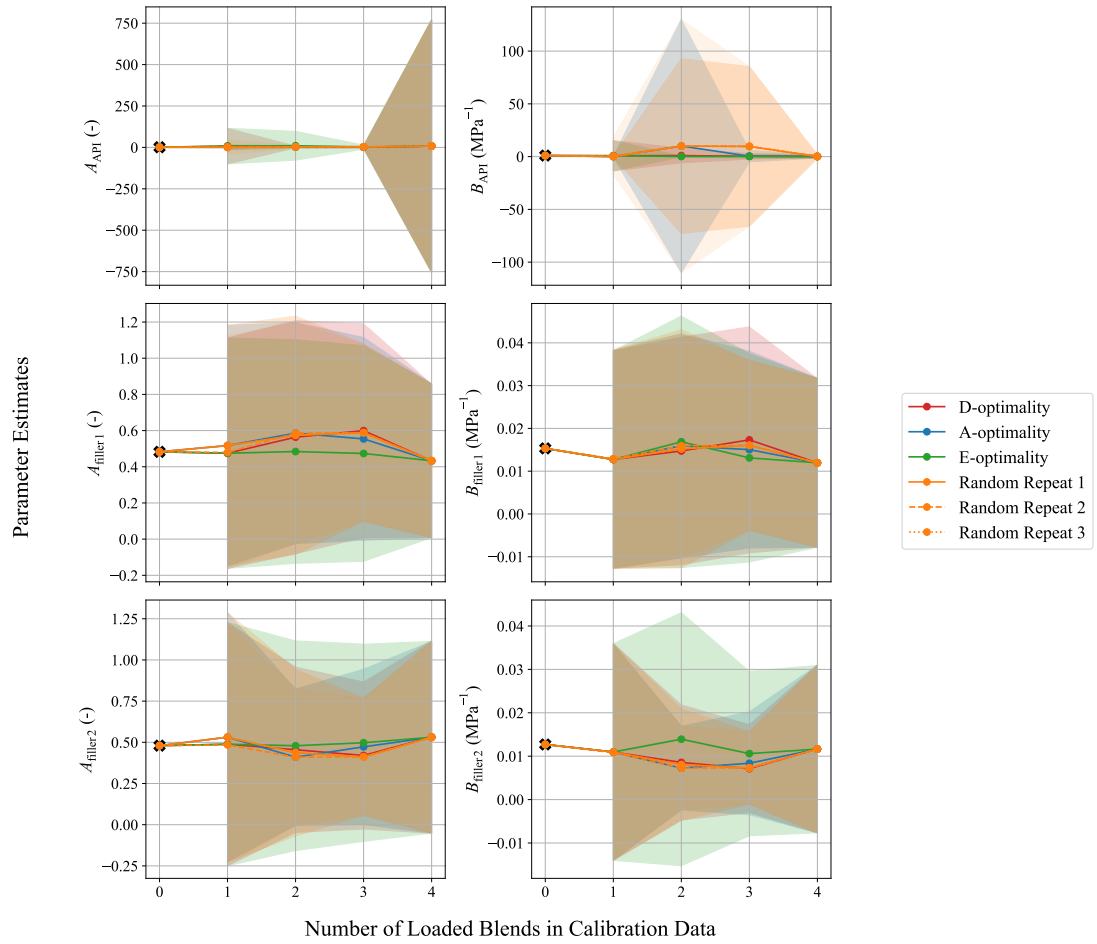


Figure D.22: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Kawakita model of micronized paracetamol. Colours indicate the MBDoE optimality criterion, while line type distinguishes the different random selection iterations.

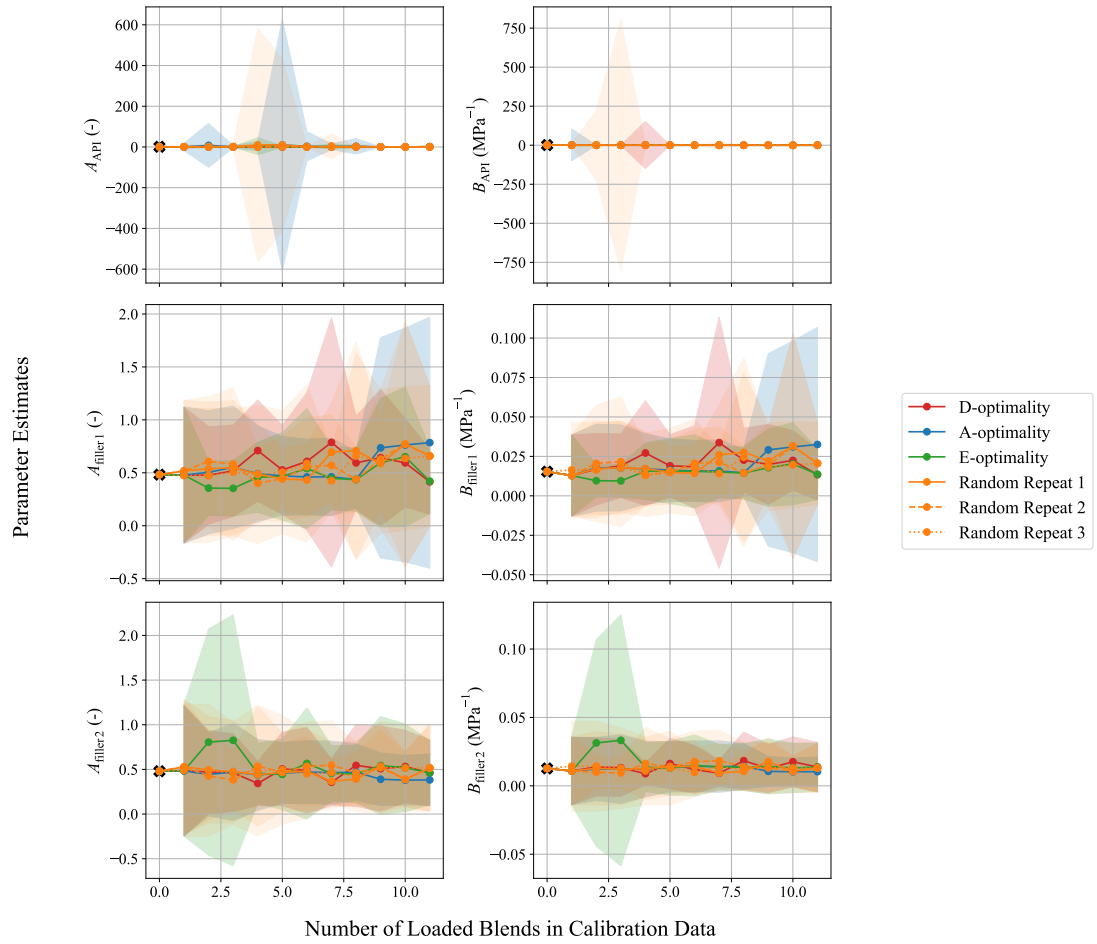


Figure D.23: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Kawakita model of ibuprofen 50. Colours indicate the MBDoE optimality criterion, while line type distinguishes the different random selection iterations.

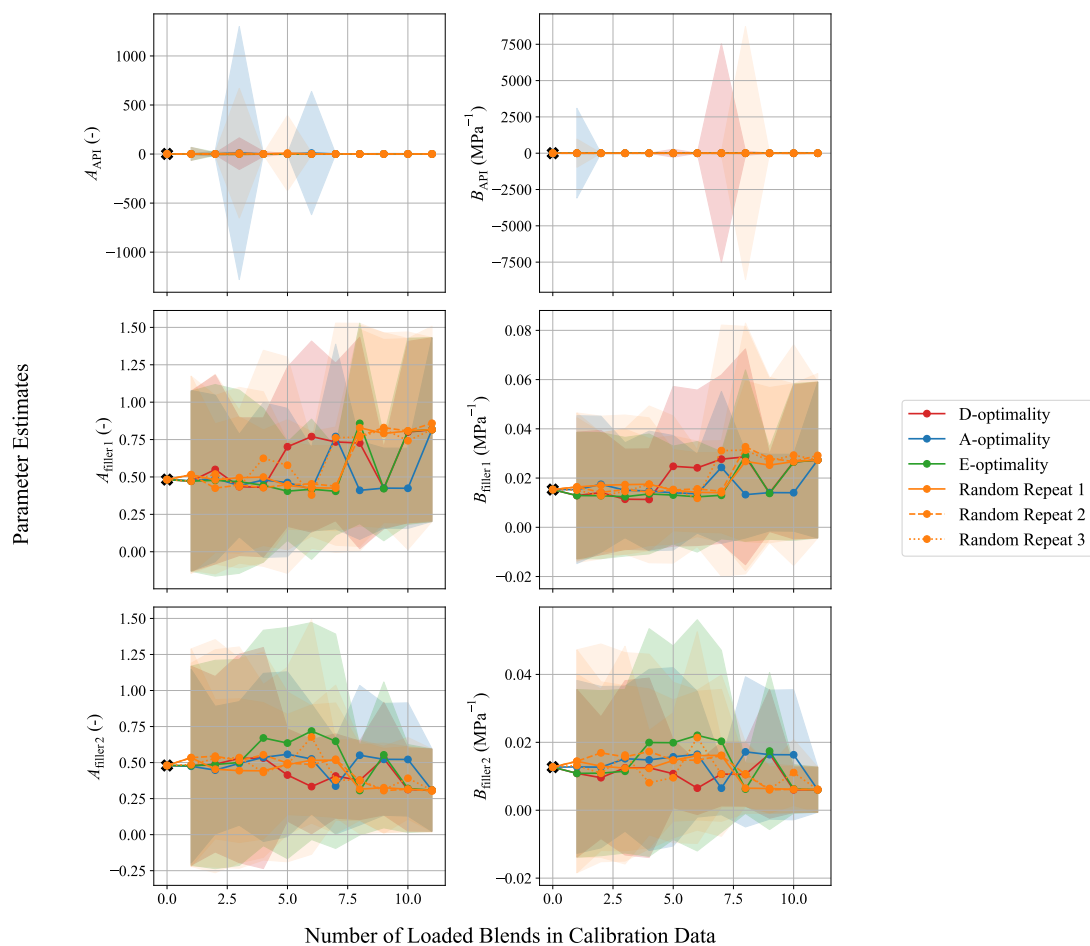


Figure D.24: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Kawakita model of ibuprofen 38. Colours indicate the MBDoE optimality criterion, while line type distinguishes the different random selection iterations.

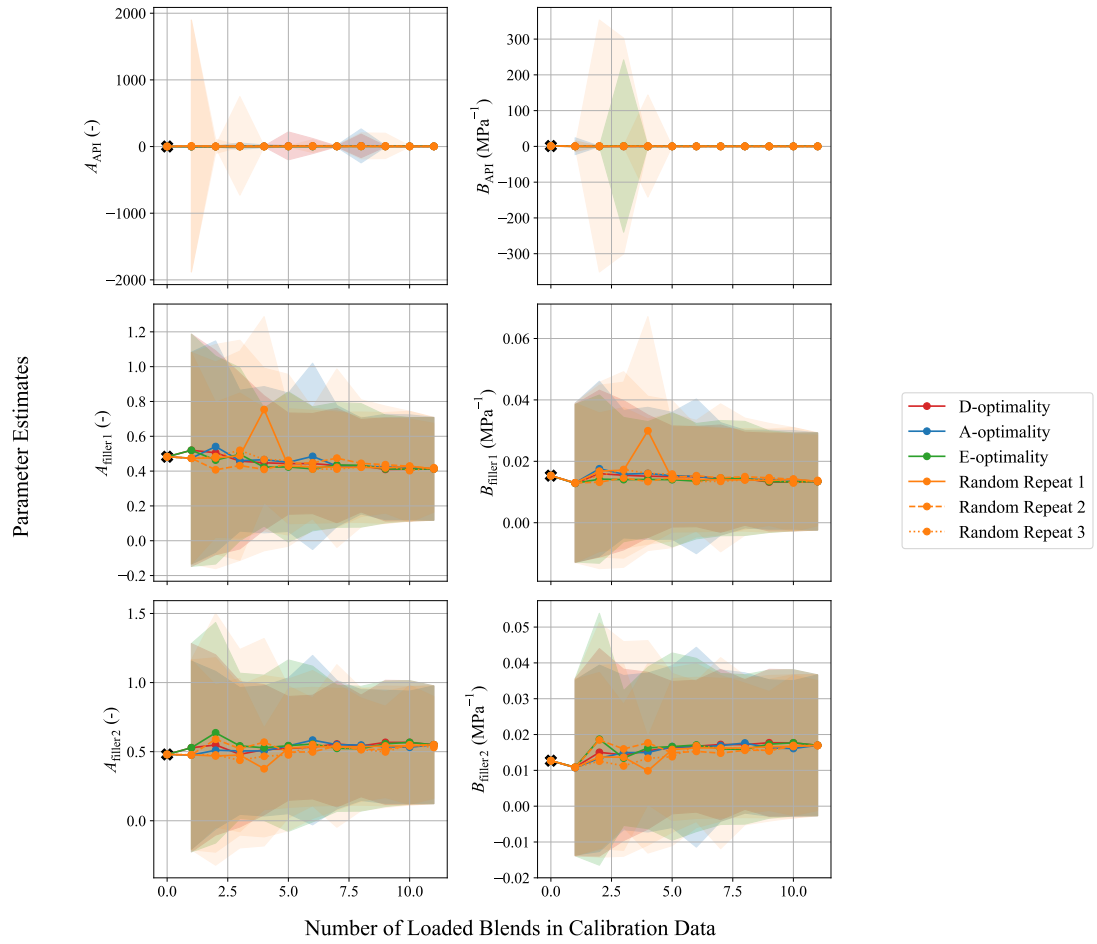


Figure D.25: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Kawakita model of ibuprofen 25. Colours indicate the MBDoE optimality criterion, while line type distinguishes the different random selection iterations.

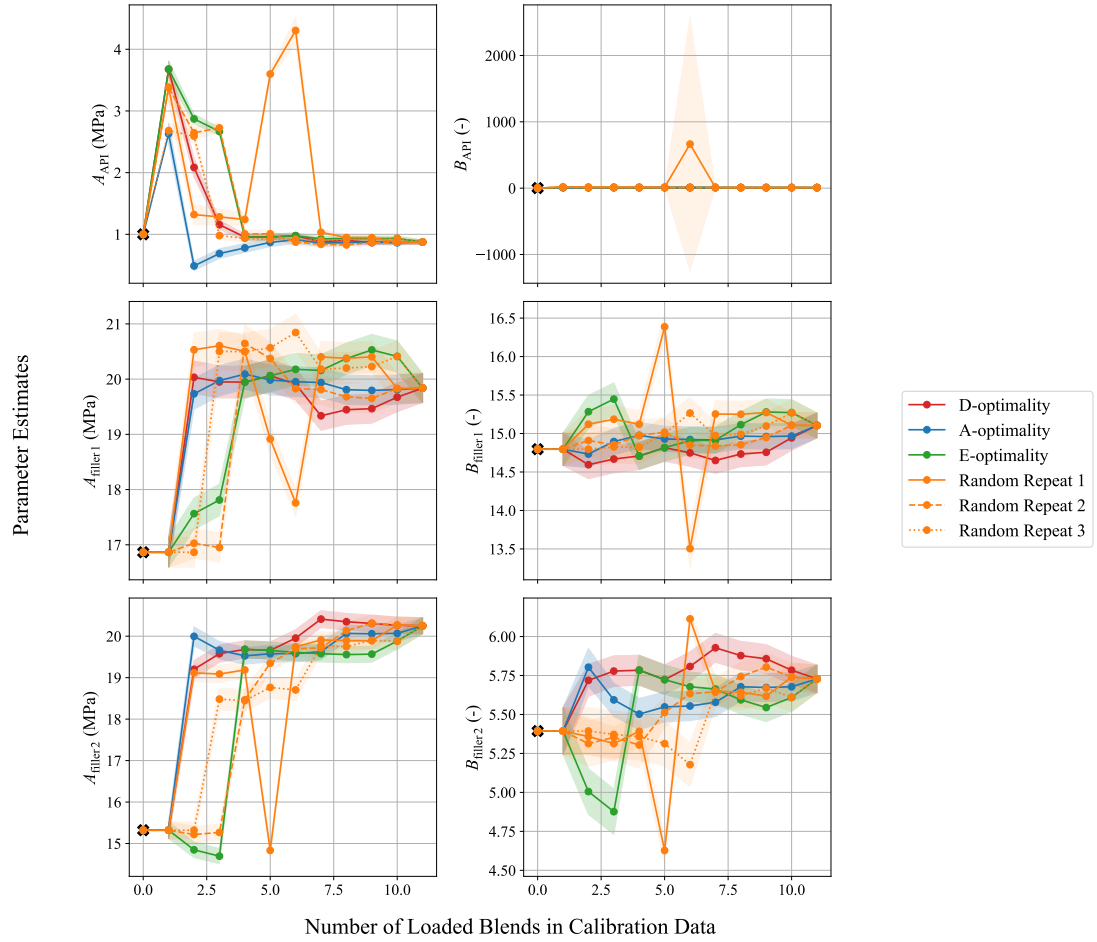


Figure D.26: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Ryshkewitch-Duckworth model of dense paracetamol. Colours indicate the MBDoE optimality criterion, while line type distinguishes the different random selection iterations.

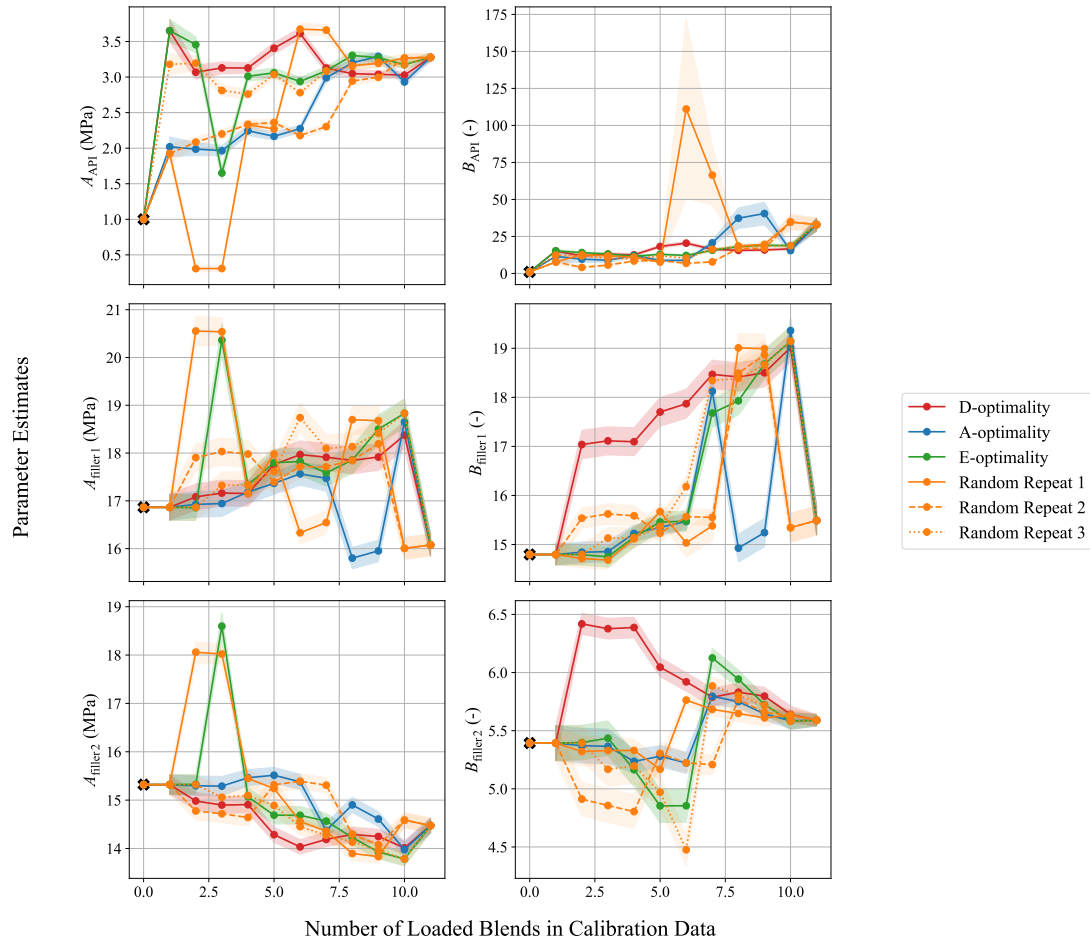


Figure D.27: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Ryshkewitch-Duckworth model of powdered paracetamol. Colours indicate the MBDoe optimality criterion, while line type distinguishes the different random selection iterations.

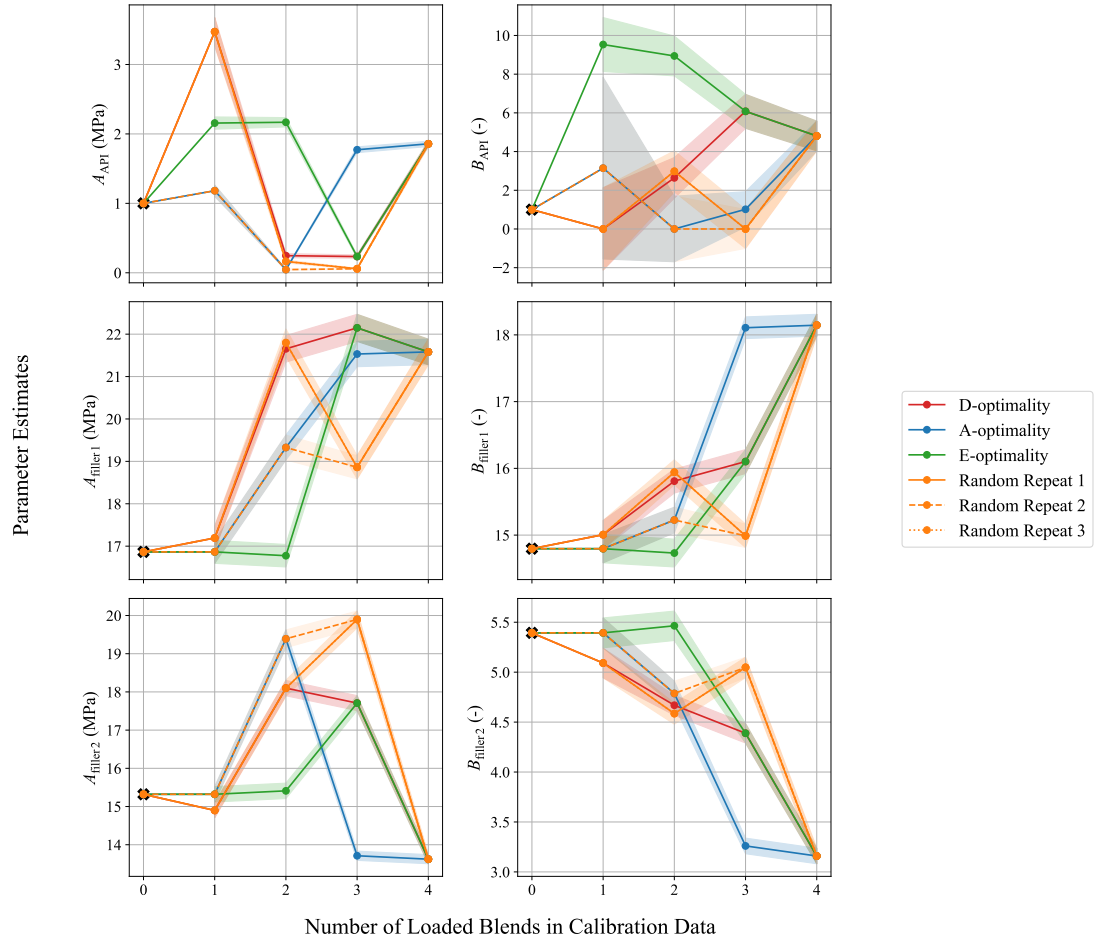


Figure D.28: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Ryshkewitch-Duckworth model of micronized paracetamol. Colours indicate the MBD_{oE} optimality criterion, while line type distinguishes the different random selection iterations.

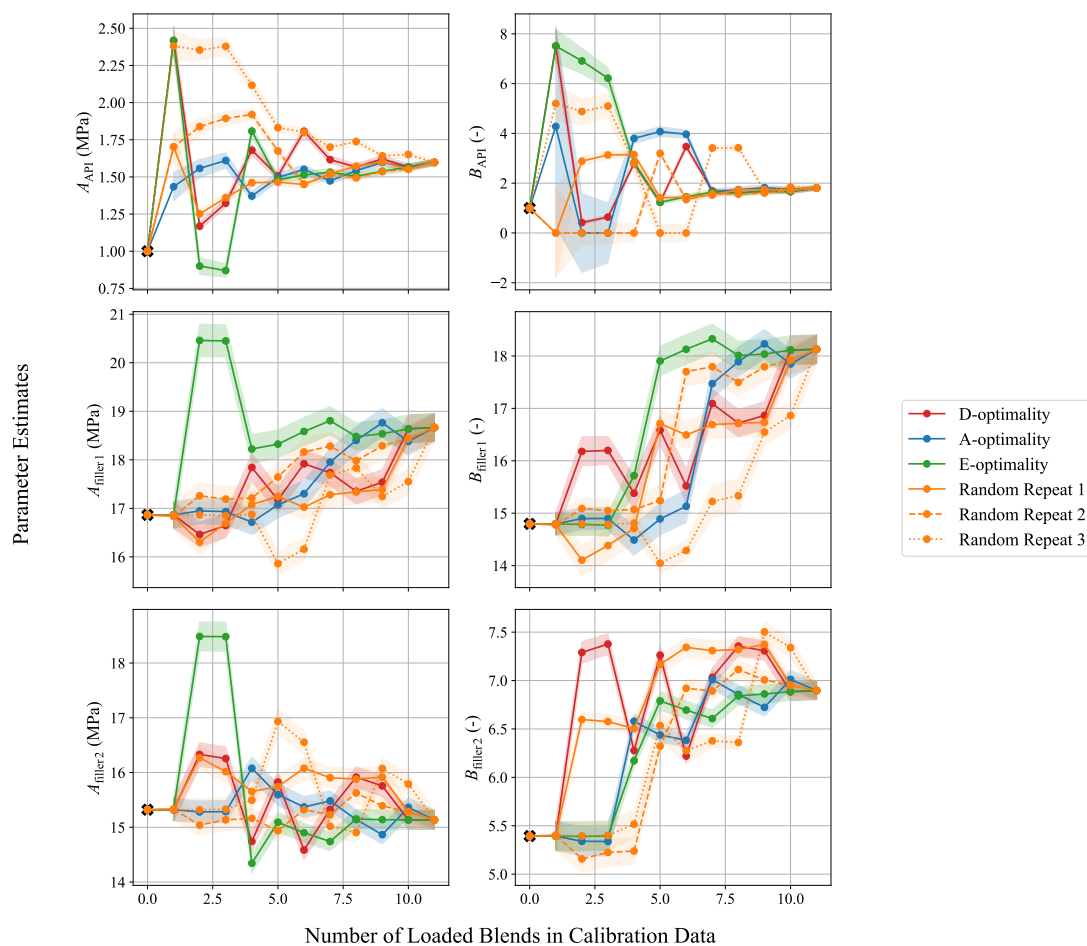


Figure D.29: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Ryshkewitch-Duckworth model of ibuprofen 50. Colours indicate the MBDoE optimality criterion, while line type distinguishes the different random selection iterations.

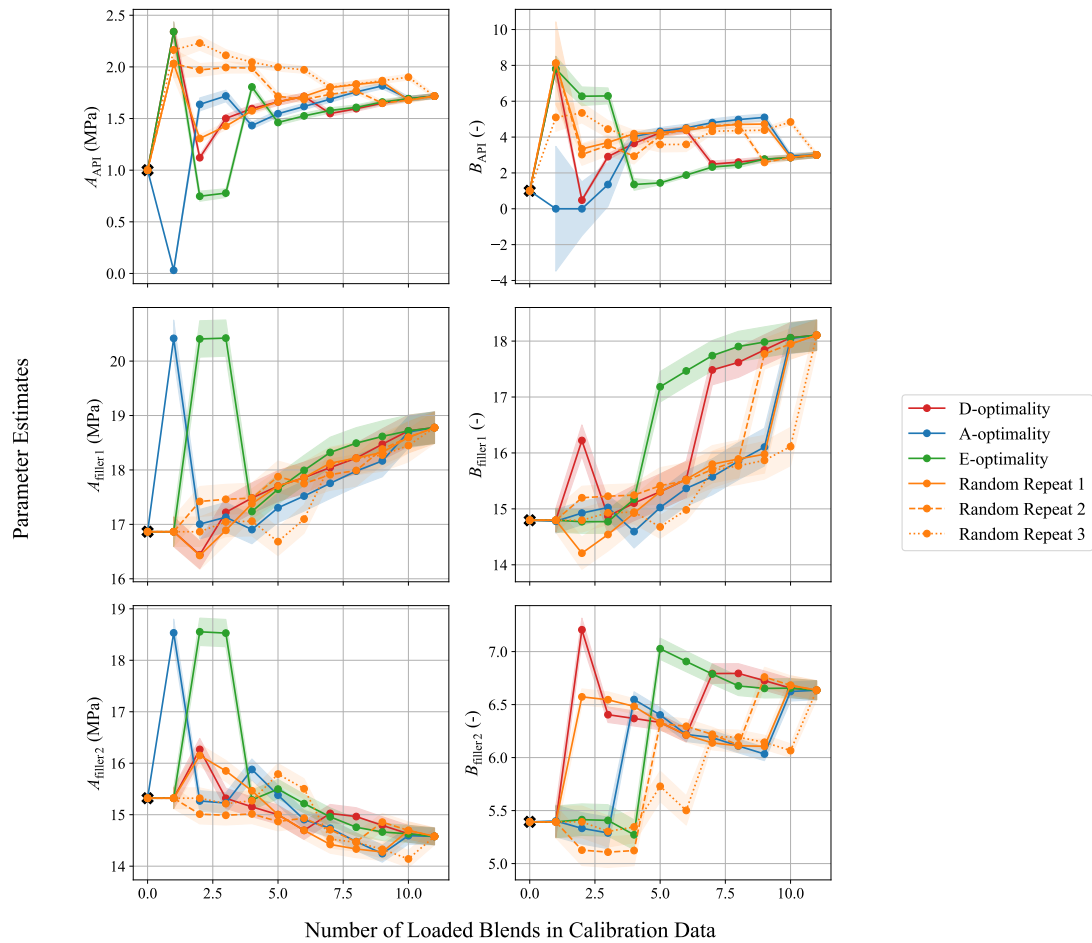


Figure D.30: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Ryshkewitch-Duckworth model of ibuprofen 38. Colours indicate the MBDoE optimality criterion, while line type distinguishes the different random selection iterations.

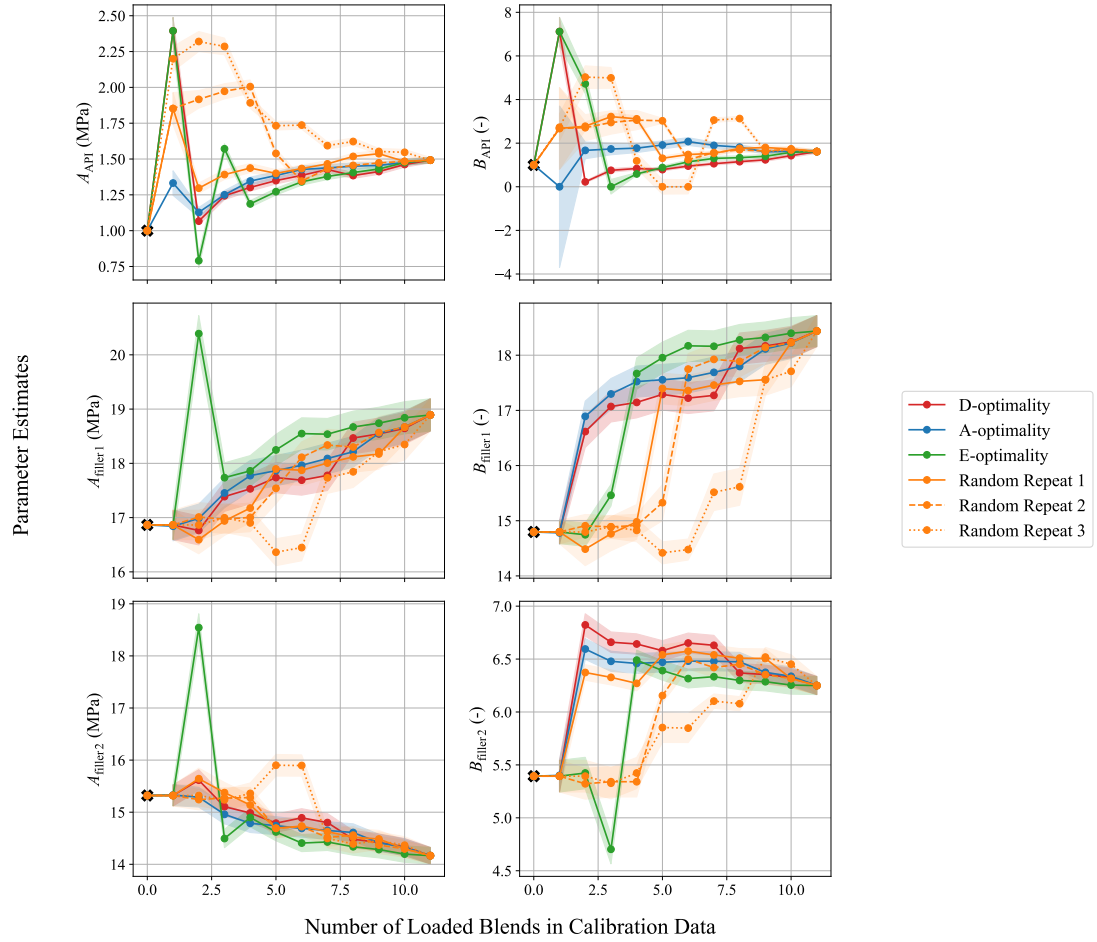


Figure D.31: Component parameter estimates as increasing numbers of blends were added to the calibration dataset for the Ryshkewitch-Duckworth model of ibuprofen 25. Colours indicate the MBDoe optimality criterion, while line type distinguishes the different random selection iterations.

D.9 Mixture Rule Selections across the iterations of the MBD_oE

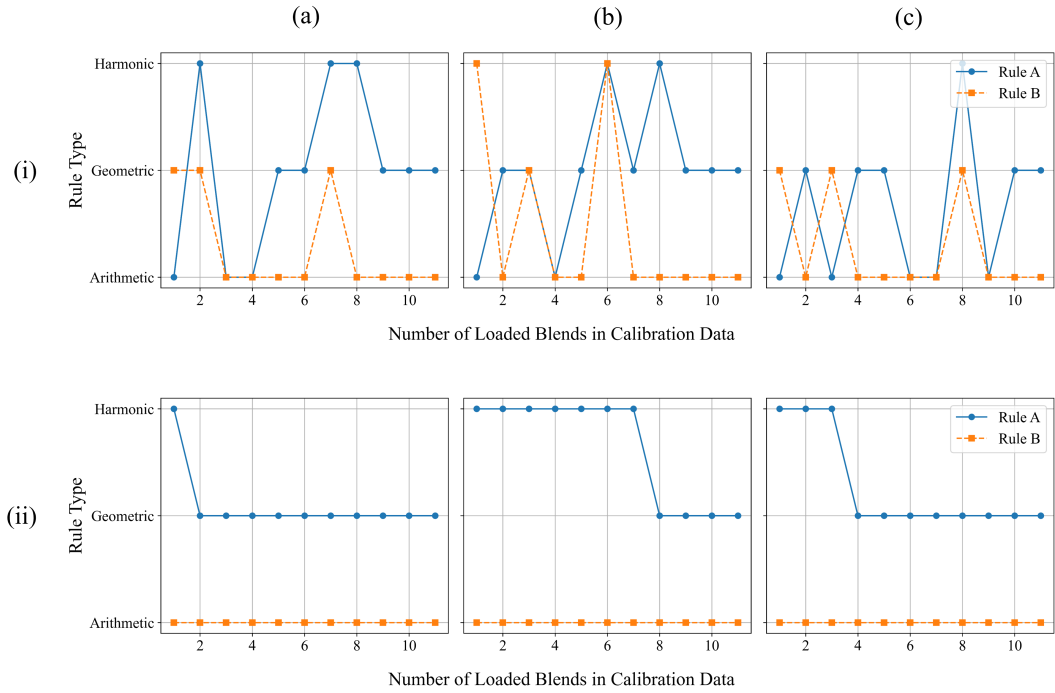


Figure D.32: Returned mixture rules used to estimate the mixture parameters for A and B using (i) Kawakita and (ii) Ryshkewitch-Duckworth for dense paracetamol based on (a) D-, (b) A-, and (c) E-Optimality.

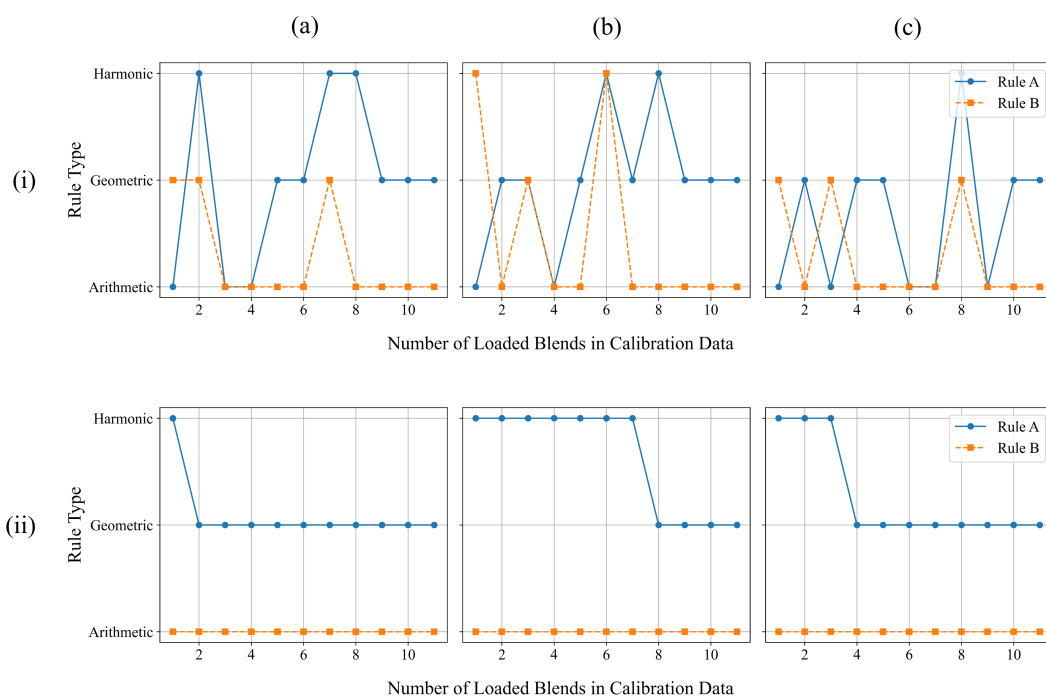


Figure D.33: Returned mixture rules used to estimate the mixture parameters for A and B using (i) Kawakita and (ii) Ryshkewitch-Duckworth for powdered paracetamol based on (a) D-, (b) A-, and (c) E-Optimality.

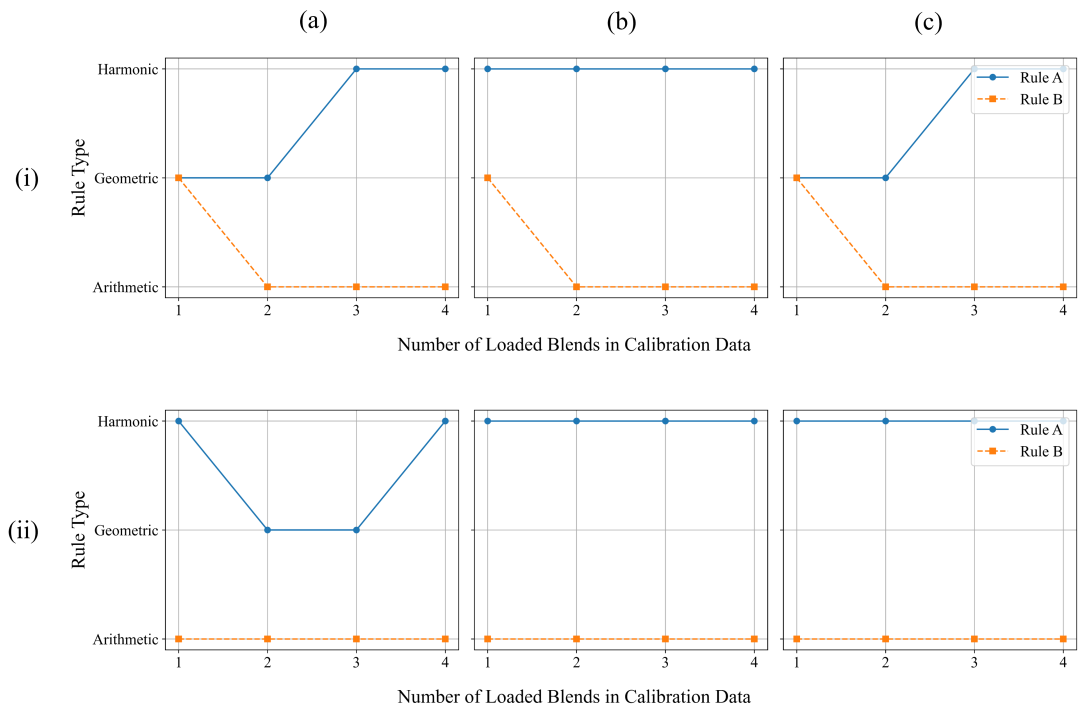


Figure D.34: Returned mixture rules used to estimate the mixture parameters for A and B using (i) Kawakita and (ii) Ryshkewitch-Duckworth for micronized paracetamol based on (a) D-, (b) A-, and (c) E-Optimality.

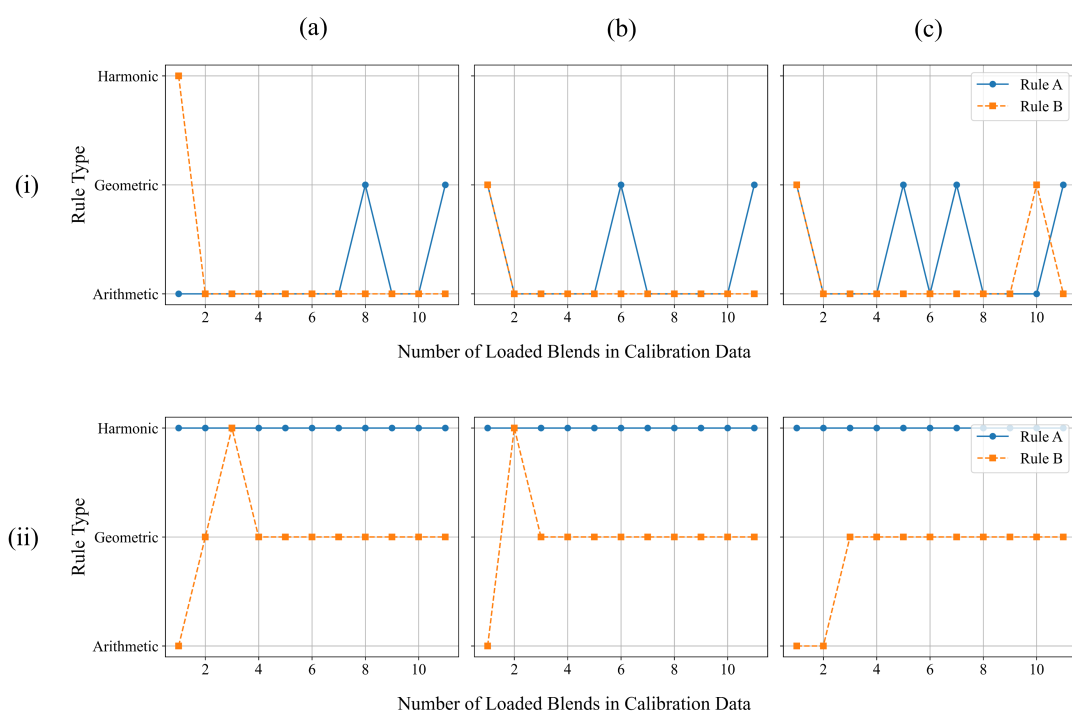


Figure D.35: Returned mixture rules used to estimate the mixture parameters for A and B using (i) Kawakita and (ii) Ryshkewitch-Duckworth for ibuprofen 38 based on (a) D-, (b) A-, and (c) E-Optimality.

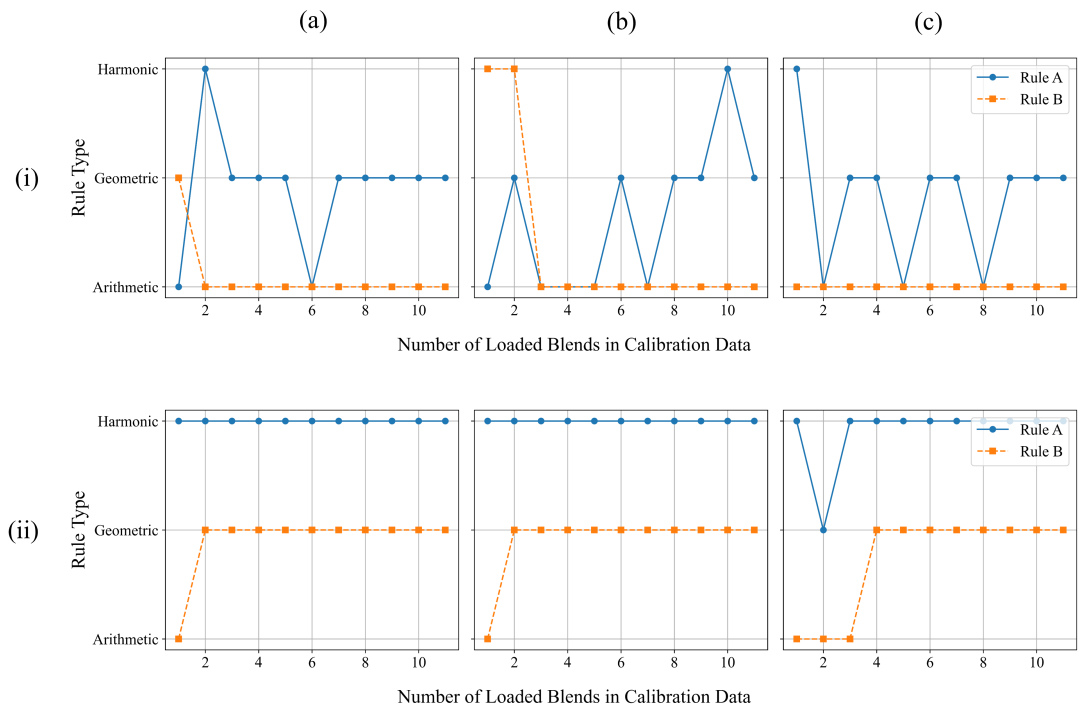


Figure D.36: Returned mixture rules used to estimate the mixture parameters for A and B using (i) Kawakita and (ii) Ryshkewitch-Duckworth for ibuprofen 25 based on (a) D-, (b) A-, and (c) E-Optimality.

D.10 Material Consumptions for Model-Based Design of Experiments

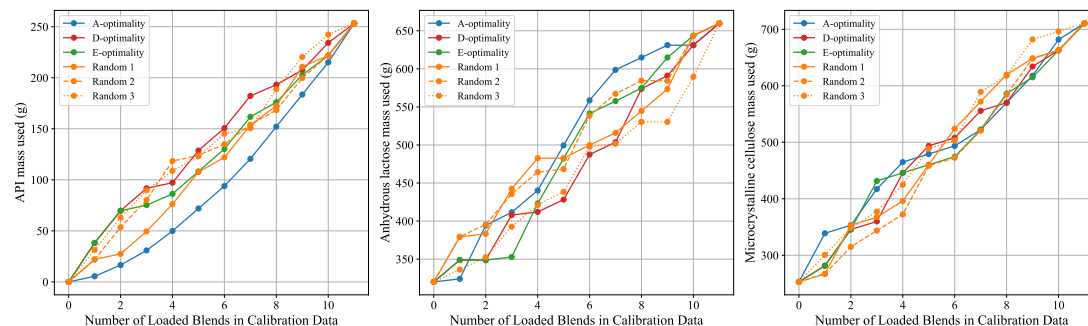


Figure D.37: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBDoE or randomly selected datasets to populate the Kawakita model for dense paracetamol.

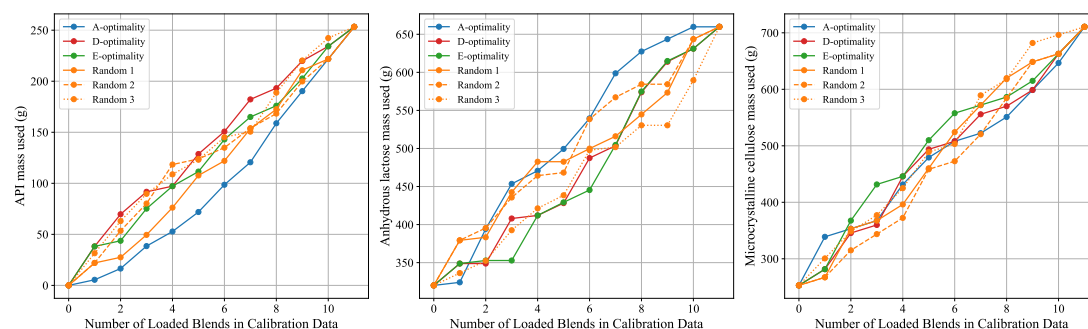


Figure D.38: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBDoE or randomly selected datasets to populate the Kawakita model for powdered paracetamol.

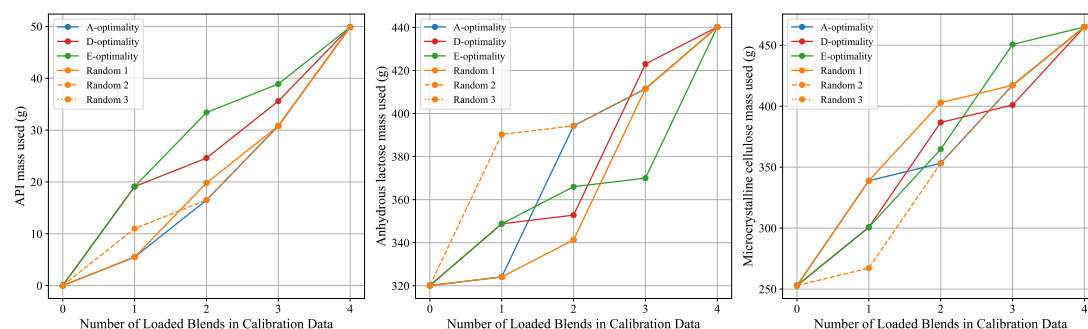


Figure D.39: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBDoE or randomly selected datasets to populate the Kawakita model for micronized paracetamol.

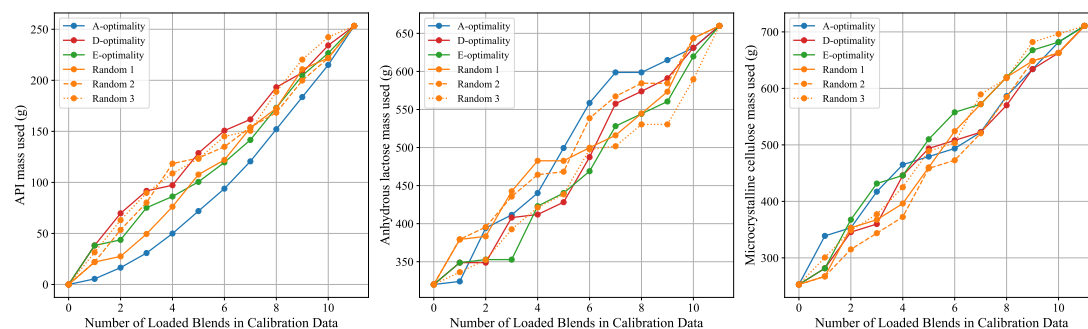


Figure D.40: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBDoE or randomly selected datasets to populate the Kawakita model for ibuprofen 50.

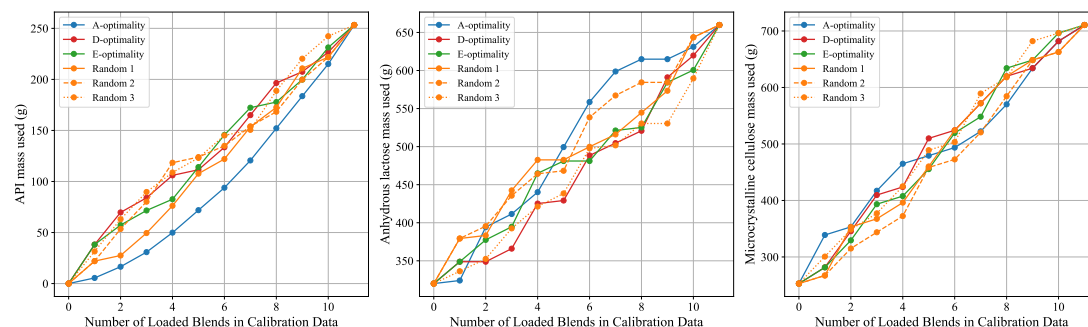


Figure D.41: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBDoE or randomly selected datasets to populate the Kawakita model for ibuprofen 38.

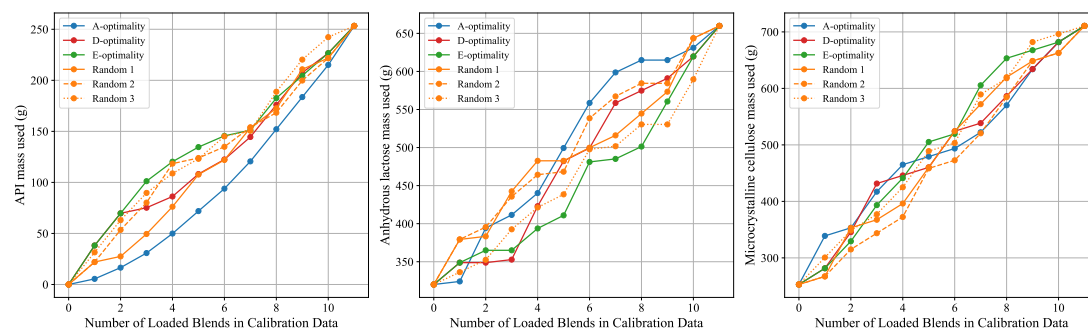


Figure D.42: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBDoE or randomly selected datasets to populate the Kawakita model for ibuprofen 25.

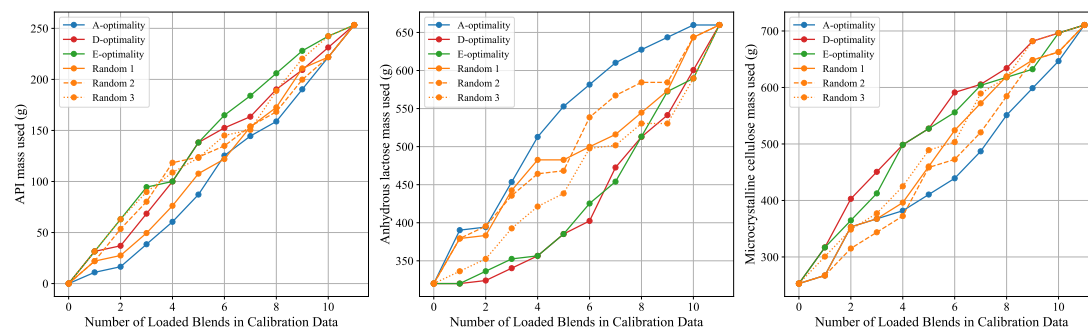


Figure D.43: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBD_{oE} or randomly selected datasets to populate the Ryshkewitch-Duckworth model for dense paracetamol.

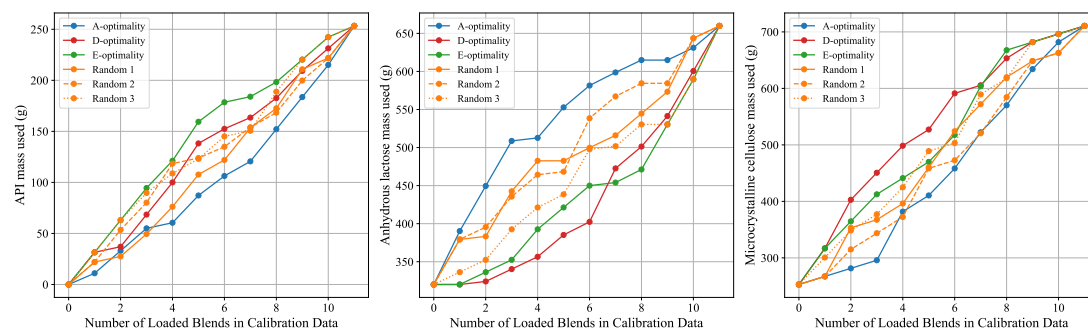


Figure D.44: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBD_{oE} or randomly selected datasets to populate the Ryshkewitch-Duckworth model for powdered paracetamol.

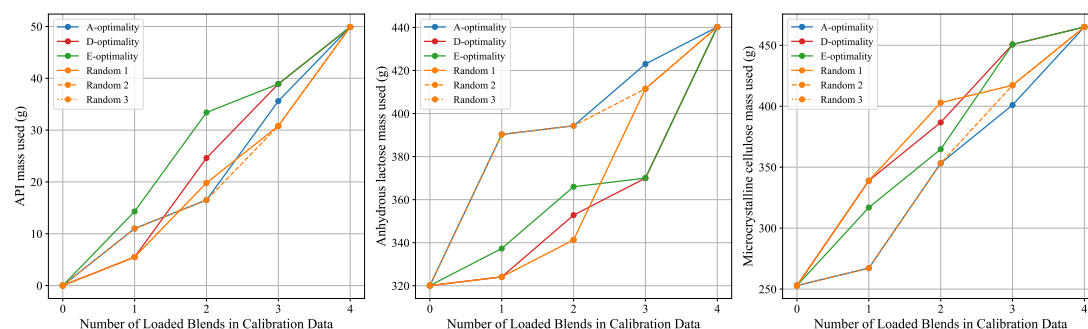


Figure D.45: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBDoe or randomly selected datasets to populate the Ryshkewitch-Duckworth model for micronized paracetamol.

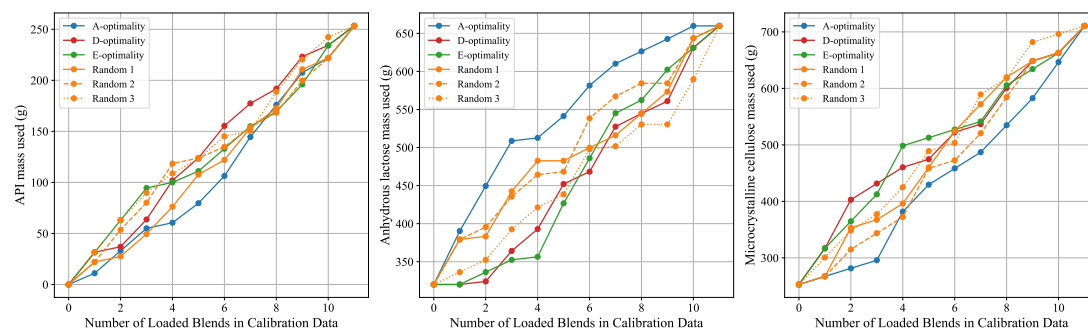


Figure D.46: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBDoe or randomly selected datasets to populate the Ryshkewitch-Duckworth model for ibuprofen 50.

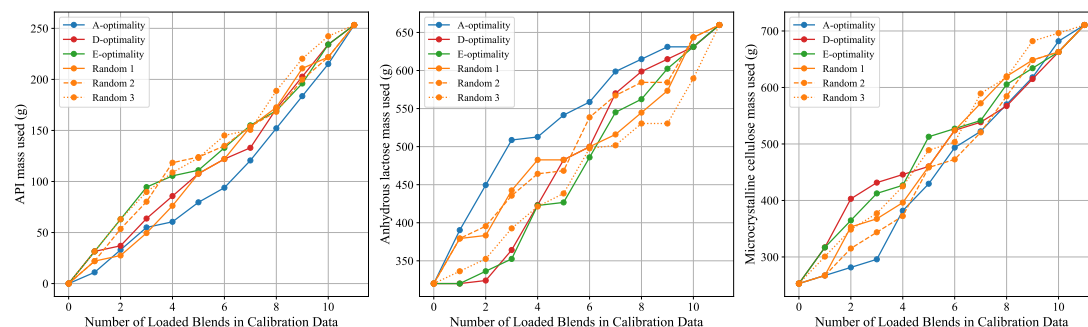


Figure D.47: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBD_{oE} or randomly selected datasets to populate the Ryshkewitch-Duckworth model for ibuprofen 38.

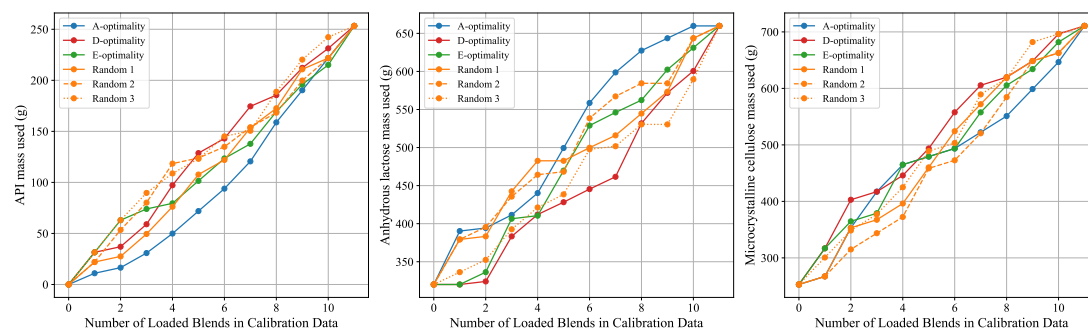


Figure D.48: Material consumption in grams of API, anhydrous lactose, and microcrystalline cellulose with respect to the number of drug loaded formulation datasets added to calibration sets. The colours represent the results achieved using the different approaches to the MBD_{oE} or randomly selected datasets to populate the Ryshkewitch-Duckworth model for ibuprofen 25.

D.11 Performance Thresholds and API Consumption

D.11.1 Kawakita MBDoE Performance

Table D.4: Number of experiments to reach MAE thresholds (i^*) for Dense Paracetamol using the Kawakita model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	1	1	1	84.9	84.9	84.9
A-optimality	1	1	2	97.8	97.8	93.5
E-optimality	1	1	1	84.9	84.9	84.9
Random Selection 1	1	1	1	91.3	91.3	91.3
Random Selection 2	1	1	1	91.3	91.3	91.3
Random Selection 3	1	1	3	87.5	87.5	64.5

Table D.5: Number of experiments to reach MAE thresholds (i^*) for Powdered Paracetamol using the Kawakita model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	1	1	-	84.9	84.9	-
A-optimality	3	3	-	84.8	84.8	-
E-optimality	1	1	3	84.9	84.9	70.3
Random Selection 1	1	1	5	91.3	91.3	57.4
Random Selection 2	1	1	-	91.3	91.3	-
Random Selection 3	1	1	-	87.5	87.5	-

D.11.2 Duckworth MBDoE Performance

Table D.6: Number of experiments to reach MAE thresholds (i^*) for Micronized Paracetamol using the Kawakita model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	1	1	-	92.5	92.5	-
A-optimality	-	-	-	-	-	-
E-optimality	1	1	-	92.5	92.5	-
Random Selection 1	-	-	-	-	-	-
Random Selection 2	1	1	-	95.7	95.7	-
Random Selection 3	-	-	-	-	-	-

Table D.7: Number of experiments to reach MAE thresholds (i^*) for Ibuprofen 50 using the Kawakita model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	1	1	5	84.9	84.9	49.1
A-optimality	2	2	8	93.5	93.5	39.9
E-optimality	1	1	4	84.9	84.9	65.9
Random Selection 1	1	1	5	91.3	91.3	57.4
Random Selection 2	1	1	4	91.3	91.3	53.2
Random Selection 3	1	1	6	87.5	87.5	42.6

Table D.8: Number of experiments to reach MAE thresholds (i^*) for Ibuprofen 38 using the Kawakita model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	1	1	3	84.9	84.9	66.8
A-optimality	1	2	3	97.8	93.5	87.8
E-optimality	1	1	1	84.9	84.9	84.9
Random Selection 1	1	1	5	91.3	91.3	57.4
Random Selection 2	1	1	2	91.3	91.3	78.9
Random Selection 3	1	1	3	87.5	87.5	64.5

Table D.9: Number of experiments to reach MAE thresholds (i^*) for Ibuprofen 25 using the Kawakita model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	1	1	3	84.9	84.9	70.3
A-optimality	2	2	-	93.5	93.5	-
E-optimality	1	3	4	84.9	60.0	52.5
Random Selection 1	1	1	5	91.3	91.3	57.4
Random Selection 2	1	1	2	91.3	91.3	75.1
Random Selection 3	1	2	8	87.5	75.1	25.4

Table D.10: Number of experiments to reach MAE thresholds (i^*) for Dense Paracetamol using the Ryshkewitch-Duckworth model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	3	-	-	72.9	-	-
A-optimality	1	-	-	95.7	-	-
E-optimality	1	-	-	87.5	-	-
Random Selection 1	1	-	-	91.3	-	-
Random Selection 2	1	7	-	91.3	39.3	-
Random Selection 3	1	-	-	87.5	-	-

Table D.11: Number of experiments to reach MAE thresholds (i^*) for Powdered Paracetamol using the Ryshkewitch-Duckworth model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	1	-	-	87.5	-	-
A-optimality	5	-	-	65.5	-	-
E-optimality	4	-	-	52.1	-	-
Random Selection 1	4	-	-	69.9	-	-
Random Selection 2	1	8	8	91.3	33.5	33.5
Random Selection 3	1	-	-	87.5	-	-

Table D.12: Number of experiments to reach MAE thresholds (i^*) for Micronized Paracetamol using the Ryshkewitch-Duckworth model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	-	-	-	-	-	-
A-optimality	-	-	-	-	-	-
E-optimality	-	-	-	-	-	-
Random Selection 1	-	-	-	-	-	-
Random Selection 2	-	-	-	-	-	33.5
Random Selection 3	-	-	-	-	-	-

Table D.13: Number of experiments to reach MAE thresholds (i^*) for Ibuprofen 50 using the Ryshkewitch-Duckworth model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	3	-	-	74.8	-	-
A-optimality	6	-	-	58.0	-	-
E-optimality	5	-	-	56.1	-	-
Random Selection 1	5	-	-	57.4	-	-
Random Selection 2	5	-	-	51.0	-	-
Random Selection 3	-	-	-	-	-	-

Table D.14: Number of experiments to reach MAE thresholds (i^*) for Ibuprofen 38 using the Ryshkewitch-Duckworth model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	3	-	-	74.8	-	-
A-optimality	8	-	-	39.9	-	-
E-optimality	4	-	-	58.3	-	-
Random Selection 1	4	-	-	69.9	-	-
Random Selection 2	1	-	-	91.3	-	-
Random Selection 3	1	-	-	87.5	-	-

Table D.15: Number of experiments to reach MAE thresholds (i^*) for Ibuprofen 25 using the Ryshkewitch-Duckworth model and corresponding API savings for each strategy. Random selection is reported across independent repeats.

Strategy	A	G	E	A (%)	G (%)	E (%)
D-optimality	3	-	-	76.7	-	-
A-optimality	4	-	-	80.3	-	-
E-optimality	3	-	-	70.8	-	-
Random Selection 1	4	-	-	69.9	-	-
Random Selection 2	5	-	-	51.0	-	-
Random Selection 3	-	-	-	-	-	-

D.12 Surface Construction and Analysis

The surfaces of tensile strength at 15% porosity, z , across the API, x , and microcrystalline cellulose, y , volume fractions were constructed using a 3rd order polynomial surface (Figure 7.20) with interaction terms up to the fourth order (Equation D.7).

$$z = a + bx + cy + dx^2 + ey^2 + fx^3 + gy^3 + hxy + ix^2y + jxy^2 + kx^3y + lxy^3 + mx^2y^2 \quad (\text{D.7})$$

This form was selected to match the number of variables to the number of datapoints to ensure the complexities of the surface were adequately captured. For the construction of the micronized paracetamol surface where less datapoints were captured, this equation was reduced (Equation D.8).

$$z = a + bx + cy + dx^2 + ey^2 \quad (\text{D.8})$$

Cross sections from these surfaces at a range of anhydrous lactose and microcrystalline cellulose ratios, were created to observe the behaviour of the surfaces with respect to API concentration across the surfaces (Figure 7.21). The confidence intervals were estimated using Monte Carlo sampling of 1000 sets based on the uncertainty in the fitted parameters from Equations D.7 and D.8 calculated from the covariance matrix estimated using the scipy optimize "curve fit" package on Python.

Note that there are large confidence intervals presented in the plots, most evident at the extremes of filler ratio of 0 (lightest blue) and 1 (darkest blue), due to there being less data present across these profiles. Further, due to the smaller dataset available, the surface and profiles for the micronized paracetamol space were limited to a lower order polynomial to balance the unknown parameters and available data. In addition, the micronized paracetamol dataset only achieved data at loadings of less than 22%, thus producing large confidence intervals for volume fractions greater than 0.2.

D.12.1 Optimisation Comparison of Placebo Inclusion

Parameter optimisation was performed independently using datasets with and without inclusion of placebo formulations, resulting in two distinct sets of fitted model parameters for each API system. These parameter sets were subsequently implemented within the selected mixture-rule framework to generate composition-dependent model coefficients for each formulation component. Response surfaces were then constructed by evaluating the resulting model over a defined region of formulation space as 15% porosity to estimate the tensile strength, parameterised by API and filler volume fractions and constrained by a mass balance requirement such that all component fractions summed to unity.

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