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2025

Optimisation of Blend Uniformity in a Low Dose Dry Powder Inhaler Formulation: Investigating API and Excipient Interactions and Process Parameters

A dissertation submitted in partial fulfilment of the requirements for the degree of

MSc in Pharmaceutical Business & Technology

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Innopharma Faculty of Pharmaceutical Sciences

Griffith College Dublin

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Supervised by: Catherine McHugh

Declaration

I certify that the dissertation entitled: "Optimisation of Blend Uniformity in a Low Dose Dry Powder Inhaler Formulation: Investigating API and Excipient Interactions and Process Parameters." submitted in partial fulfilment of the MSc in Pharmaceutical Business and Technology, to the department of Pharmaceutical Business and Technology, Griffith College Dublin, is the result of my own work and that where reference is made to the work of others, due acknowledgement is given.

Candidate Signature: Michelle grant

Date: 09 August 2025

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I would like to express my sincere gratitude to all those who have helped and guided me throughout the learning, conducting the research and the completion of this dissertation.

The completion of this dissertation and the entire MSc journey would not have been possible without the unwavering support, belief and encouragement of my very close family and dear friends. Not forgetting the prayers and candles lit by my Granny Betty.

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And of course, Belle, who was always by my side.

Table of Contents

Glossary of Terms

ABS	Acrylonitrile butadiene styrene
API	Active Pharmaceutical Ingredient
BMR	Batch Manufacturing Record
BU	Blend Uniformity
CAB	Cohesive–Adhesive balance
CFC	Chlorofluorocarbons
CMA	Critical Material Attributes
CPP	Critical Process Parameters
COPD	Chronic obstructive pulmonary disease
CQA	Critical Quality Attribute
CV	Coefficient Variable
DoE	Design of Experiments
DPI	Dry Powder Inhaler
D-value	Diameter (Particle size)
EMA	European Medicines Agency
FDA	Food and Drug Administration
Fp	Fluticasone Propionate
GMP	Good Manufacturing Practice
HFA	Hydrofluoroalkane
Kg	Kilogram
LC	Label claim
mg	Milligram
MgSt	Magnesium Stearate
Min	Minute
m/s	Meters per second
NIR	Near-Infrared spectroscopy
NLT	Not less than
NMT	Not more than
OOS	Out of Specification
PAT	Process Analytical Technology
pMDI	Pressurised Metered Dose Inhaler
PPQS	Process Production and Pharmaceutical Quality Systems
RH	Relative humidity

rpm	Rotations per minute
SS	Stainless Steel
SOP	Standard Operating Procedure
SEM	Scanning Electron Microscopy
Sx	Salmeterol
UPLC	Ultra Performance Liquid Chromatography
%RSD	Percentage Relative Standard Deviation
℃	Degrees Celsius
µg	Microgram

Abstract

Optimisation of Blend Uniformity in a Low Dose Dry Powder Inhaler Formulation: Investigating API and Excipient Interactions and Process Parameters

This dissertation investigates the optimisation of blend uniformity in low dose dry powder inhaler (DPI) formulations, focusing on the interplay between active pharmaceutical ingredient (API) and excipient interactions, as well as critical process parameters such as blending time and speed. Through a combination of literature review, experimental analysis, and scale up studies, the research explores how material properties and mechanical energy inputs influence blend performance.

Findings revealed that while process optimisation reduced variability (%RSD) and improved uniformity in several batches, three out of eight failed to meet acceptance criteria, and most exhibited high maximum API content values. Particle size distribution (PSD) and scanning electron microscopy (SEM) analysis confirmed that excipient morphology played a key role in API adhesion and dispersion, with coarse lactose enhancing flow and fine lactose improving binding.

Successful scale up from low shear to high shear blending using matched tip speeds demonstrated reproducibility and robustness, validating the hypothesis that mechanical energy translation supports consistent blend quality. However, limitations such as manual sampling bias, narrow material scope, and lack of real-time analytical tools were acknowledged.

This study contributes a scalable framework for DPI blend optimisation, emphasising the need for integrated formulation and process development. It advocates for a flexible, science-driven approach to manufacturing that enhances product quality and supports commercial feasibility.

Chapter 1 - Introduction

Background

The development of low dose dry powder inhaler formulations presents very unique challenges, with blend uniformity (BU) being one of the most critical factors when ensuring consistent and effective drug delivery to patients suffering with diseases such as chronic obstructive pulmonary disease (COPD) and Asthma.

Blend uniformity of powders refers to the consistent range of distribution of the active pharmaceutical ingredient (API) and excipients throughout the entire final blend. The uniformity of the blend provides a foundation upon which the finished product is built, and, without uniformity, there will be significant knock-on effects on the pharmaceutical performance of the product. Achieving a uniform distribution of the API in the formulation is particularly demanding at low unit doses. Even minor variations in parameters like mixing speed during the manufacturing process or particle interactions between the materials in the formulation can lead to significant fluctuations in delivered dose and ultimately therapeutic effect. The complex relationships and compatibilities between API and excipients must be thoroughly studied to understand their properties and interactions. Properties such as particle size, surface morphology, and other critical material characteristics should be evaluated in both starting materials and final drug product.

The correct materials, together with a suitable manufacturing process using critical parameters like blending time, speed, and environmental conditions, can directly influence the homogeneity of the final blend. In pulmonary drug delivery products, a homogenous blend is critical as it directly impacts dose accuracy, product efficacy and safety, especially for low dose APIs, (e.g., for the purpose of this research, low dose product “Model Inhalation DPI” that delivers just 18 µg of API in a formulation that emits an overall delivered dose of 200µg per actuation).

Reason for study

As a Product Development Scientist working for an inhalations company, I have been leading the development of a dry powder product in early stages of development consisting of a low dose API with over 99% of the formulation consisting of the bulk carrier, “Model Inhalation DPI”.

To ensure blend uniformity, specific regulatory standards and formulation requirements must be satisfied. In order to consistently do so, it is necessary to establish a robust blending process with parameters capable of generating a homogenous final blend. Other considerations such as targeted sample weights, representative sampling locations and sample sizes must be assessed as part of the in-process control during manufacture.

The FDA withdrew its draft guidance document, “Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment,” in August 2013 (Food and Drug Administration, 2003). Despite being a draft, the guidance had been widely adopted across the industry and, in the absence of an alternative, continued to inform practices. Since its withdrawal, manufacturers have been required to justify their methods for assessing blend uniformity. In response, the industry has adopted science and risk based approach, implementing well justified sampling and testing plans to ensure product uniformity and that sample sizes are sufficient to support meaningful statistical evaluation (Naheed Sayeed-Desta *et al.*, 2018)

The current BU sample weight in place for “Model Inhalation DPI” is 35 mg, a target that the formulators have been working to over the last 12 months while this product has been in development, under both formulation and processing assessment. This sample weight is approximately six times the dose weight, which is 5.5 mg per dose, as per the FDA’s withdrawn guidance the sample should be no more than 3 times the weight of an individual dose unless a scientific justification is provided.

The guidance (Code of Federal Regulations, 2008) explains “To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product”.

In a bid to align our sampling process in the early stages of development with previous guidance, a development batch was manufactured (Batch-066), and blend uniformity was assessed., the investigation below was carried out to confirm whether uniformity could be upheld at an approximate dose scale. Table 1 below outlines the BU results for the batch across 2 sets of 10 samples, taken as follows:

- 10 x Sample A - 35 mg per sample
- 10 x Sample B - 7 mg per sample

Table 1: Batch-066 sample weight analysis

Batch	Sample	Weight (mg)	Min	Max	Mean	%RSD	Pass/Fail
Batch-066	A	35	93.5	101.3	98.4	2.6	Pass
Batch-066	B	7	93.3	112.7	103.5	6.4	Fail

The data showed that the uniformity previously achieved at a 35 mg sample weight did not translate to samples at the dose scale of ~5.5 mg (5 mg – 10 mg target) with an out of specification (OOS) result. To further investigate, 3 x 1kg fractions of Batch-066 were taken and added back to the blender one at a time and re-processed as outlined below.

- Batch-066C - Re-blend 1 Kg fraction at higher speed for an additional 6min
- Batch-066D - Re-blend 1 Kg fraction blended for an additional 12min
- Batch-066E - Re-blend 1 Kg fraction slower speed for an additional 6min

1 set of 10 samples were taken from each of the blends, targeting the smaller sample size of 7 mg, with the results shown in Table 2.

Table 2: Reprocessing of Batch-066 across 3 fractions

Batch	Sample	Weight (mg)	Min	Max	Mean	%RSD	Pass/Fail
Batch-066C	C	7	99.2	105.9	103.1	1.9	Pass
Batch-066D	D	7	96.7	112.1	103.5	3.9	Fail
Batch-066E	E	7	95.0	109.2	101.6	4.2	Pass

The results from the uniformity analysis of Batch-066 suggested that the larger samples of 35 mg typically taken for this product may have been diluting or masking inconsistencies in the blend uniformity and inadequacies of the blending process. The further processing of Batch-066, specifically fraction C also suggests that higher blending speed for additional blending time significantly decreased the %RSD.

Literature also tells us that larger sample weights can be more prone to sampling bias, especially with a low dose formulation where the smallest variation can be detrimental, and where factors such as processing parameters have a significant part to play. My secondary research will delve more into this.

Objectives of the primary research

The objective of this research is to understand certain factors that influence Blend Uniformity during the development of a DPI for a low dose formulation. The Model Inhalation DPI is a product with a formulation consisting of two grades of Lactose, which is a combination of a coarse grade (Lactose Y). and a fine grade of lactose (Lactose Z), with the coarse lactose making up the majority of the formulation, both lactose components are combined with a low concentration of API (API X).

Determining the quantities of each grade of lactose is carried out using particle size distribution (PSD) analysis by Sympatec analyser. Lactose fines play a critical role in dry powder formulations, primarily by enhancing the delivery efficiency of the API to the lungs when blended with a coarse lactose carrier. As this product is currently in early development, specifications for specific PSD ranges have not yet been formally established. Currently, the primary focus is on controlling the proportion of particles in the range of %<5 µm, due to the low dose nature of the API. PSD is conducted to quantify the %<5 µm fraction. The remaining portion is made up using a finer grade of lactose to ensure appropriate adhesion and binding.

The main objectives of the research are as follows:

- To identify key factors affecting blend uniformity in low dose API X/lactose blends at a single unit dose of 5.5 mg
- To determine the influence of excipient properties (particle size, surface morphology, flow properties) on the uniformity of a low dose formulation
- To optimise process parameters (blending time, speed) to minimise variability
- To determine whether the process is reproducible if scaled, conduct scale up activity from bench top to pilot scale

The current critical process parameters (CPPs) and operating conditions during the final blending operation for Model Inhalation DPI are as follows:

Blend Speed: 252 rpm (5 m/s)

Blend Time: 12 minutes

Environmental conditions: 20.0 °C ± 5.0 °C and 20% RH ± 5% RH

Significance of the Research

The optimisation of blend uniformity in low dose dry powder inhaler formulations is a critical area of pharmaceutical research, as it directly influences dose consistency, therapeutic efficacy, and patient safety. Low dose formulations, which can be defined as stated in (Mohamed H. Fayed *et al.*, 2020) as formulations "containing less than 2 mg or 2% drug loading (w/w) of active pharmaceutical ingredients", meaning that the APIs are present in microgram quantities and are typically micronised to enhance lung deposition. These micronised particles are inherently cohesive, making them prone to agglomeration and uneven distribution when blended with excipients such as lactose. As a result, achieving blend uniformity is exceptionally challenging.

The significance of this research lies in its focus on understanding and controlling the complex interactions between APIs and excipients, as well as the influence of process parameters on the final blend. Studies have shown that the cohesive/adhesive balance between drug and carrier particles plays a pivotal role in determining whether the API will remain attached to the carrier or detach during inhalation. Optimising this balance requires careful selection of excipients and the many grades available, such as coarse lactose for carrier function and fine lactose to controlled adhesion. Fine lactose particles can occupy high energy binding sites on the carrier surface, reducing excessive drug adhesion and promoting better dispersion. However, their concentration must be precisely controlled, as excessive fines can impair flowability and increase agglomeration risk.

This research also highlights the importance of process parameters such as blending time and speed, which can significantly affect powder movement, segregation, and electrostatic charging. For instance, longer blending times may increase those forces, enhancing drug/carrier adhesion but potentially reducing detachment efficiency. Electrostatic effects, which are often overlooked, can further complicate uniformity by causing charged particles to cluster or adhere to surfaces in the manufacturing equipment chain. Given the nature of the materials utilised in dry powder blends being incredibly dry where charge may not conduct out easily (Lactose generally >5% moisture content and API >1% moisture content) and often very fine with large surface areas for promoting greater charge collection, electrostatics are an ever-present issue.

The experiments conducted as part of this research enables systematic evaluation of these variables, in the hopes of identifying optimal conditions for consistent intermediate blend performance. The literature review piece of this research will look at in-line monitoring techniques, such as near-infrared spectroscopy, offering real-time assessment of blend uniformity as a replacement for manual sampling techniques, now favoured by regulators such as the Food and Drug Administration (FDA).

Ultimately, this research contributes to the advancement of DPI technology by providing a deeper understanding of the physicochemical and mechanical factors that govern powder blending at low doses. It supports the drive to develop a robust and scalable formulation that meet stringent regulatory standards in the hopes of ultimately delivering a reliable, safe and therapeutic product.

Research Hypotheses

This study hypothesises that blend uniformity in a low dose dry powder inhaler formulation can be significantly improved by understanding API/excipient interactions and using that learning to optimise the critical process parameters such as blending time and speed. Specifically, it is expected that excipient properties including particle size, morphology, and surface energy will influence API/lactose adhesion and distribution, thus affecting blend uniformity. The study anticipates that adjusting blending parameters will minimise variability, giving confidence over a consistent and reproducible blend.

Structure of Research

The following describes how the research study is designed and laid out under five main chapter headings and subheadings.

Chapter 1 Introduction

This chapter outlines the background and rationale for carrying out the research, highlighting the challenges associated with achieving blend uniformity in low dose DPI formulations. It explains the reason for the study, presenting the objectives, and sets the context for the investigation into API/excipient interactions and key process parameters that influence blend uniformity.

Chapter 2 Literature Review

This literature review offers a critical examination of current knowledge surrounding low dose DPI formulations, with a focus on raw material interactions and the techniques used to characterise them. It explores how these methods help to explain the physical and chemical behaviours of individual components during blending, while considering the mechanical forces applied throughout processing. The review also highlights how these dynamic interactions influence blend uniformity, which is essential for ensuring dose consistency and product performance. This chapter also looks at relevant studies on cohesive APIs, excipient types and their functionality, electrostatics, and blending mechanisms and equipment. Regulatory guidance around uniformity and technologies used for sampling is included in the research as there are stringent guidelines surrounding this. Identifying gaps in current research and justifying the need for this study.

Chapter 3 Research Methodology

This chapter describes the experimental design, materials selected, and analytical techniques employed to investigate API/excipient interactions and process variables. It details the material characterisation methods (e.g. Particle Size Distribution (PSD), Scanning Electron Microscopy (SEM)). This chapter explains both bench top scale and pilot plant scale manufacture, allowing for a comparative assessment of blending efficiency with a particular focus on blend speed and time, and scalability under controlled conditions.

Chapter 4 Findings and Analysis

The results of the experiments are presented and interpreted, with emphasis on how different material properties and characteristics affect uniformity and the knock on effect this might have on the blending process. Comparative analysis of the blends manufactured at both bench top and at pilot plant scale as parameters are adjusted to reduce the variability, identifying a suitable set of parameters for the product.

Chapter 5 Conclusion and Recommendations

This final chapter summarises the key insights gained from the study, from both primary and secondary research. It offers recommendations for future work, possible formulation and process control optimisations to enhance blend uniformity in low dose dry powder inhalation products.

Module linked to Topic

The module most closely aligned with my research topic is Process Production and Pharmaceutical Quality Systems – (PPQS).

Chapter 2 - Literature Review

Introduction

This chapter provides an extensive review of literature relevant to the optimisation of blend uniformity in low dose DPI formulations. It explores the critical aspects of API and excipient interactions, the influence of material properties, and the impact of various process parameters on blend uniformity. Given the challenges associated with achieving consistent uniformity in low dose DPI products, a thorough understanding of the physicochemical behaviours of formulation components is essential.

The chapter begins with an overview of DPI technologies, focusing on the formulation requirements and the significance of uniformity for therapeutic efficacy and regulatory compliance. This is followed by a discussion around common excipients used in DPI systems, highlighting the key properties that influence their performance during blending. Particular attention is given to the role of carrier particles specifically lactose, and the mechanisms through which they interact with micronised API.

The review delves into blending techniques and processing parameters, such as mixing time, speed and equipment types, examining their effects on homogeneity and the potential for powder segregation. The chapter also considers the latest advances in analytical tools for evaluating blend uniformity, including spectroscopic approaches and their advantages over more traditional and common methods such as manual sampling.

By consolidating current knowledge and identifying key gaps, this review establishes the scientific and practical context for the research presented in subsequent chapters. It lays the groundwork for the experimental studies undertaken into how material attributes and process variables affect blend performance in low dose DPI formulations.

Evolution of Inhalation Products

Inhalation therapy is widely used for treating respiratory conditions such as asthma and chronic obstructive pulmonary disease, and with inhalation therapy dating back over 4000 years, (A. H. de Boer *et al.*, 2016) tells us that the first powder formulation was mixed and inhaled as a bronchodilator, and (Levy *et al.*, 2019) explaining the first use of the word inhaler was used almost 250 years ago, and as such the means and methods of inhalation therapy has evolved throughout the centuries, until the introduction of the pMDI in the 1950s, soon becoming popular due to its compact appearance and low cost. However it soon became apparent that the Chlorofluorocarbons

(CFC) propellants used in the formulation of pMDIs had detrimental effects on the ozone layer, and in the late 1980s the Montreal protocol, which is considered one of the most successful global environmental agreements, set about phasing out the production of CFC formulations (UN Environment Programme, 2020). Figure 1: Inhaler devices including pMDI and DPI Figure 1 shows some of the inhaler types available on the market today, both single dose and multi dose DPI and pMDI.

Figure 1: Inhaler devices including pMDI and DPI

(Justdial, 2025)

Even though pMDI remains the most popular choice, albeit with the use of Hydrofluoroalkane (HFA) propellant in formulations in place of CFC, in recent decades, there has been a focus shift towards the development of DPI as there are many considerable advantages over traditional inhalers. A general comparison is available in Table 3. (Levy *et al.*, 2019) discusses the benefits of DPIs and some of the drawbacks that formulators may face. DPIs are generally easier to use as they are breath actuated, as the medication is released when the patient takes a breath in, there is no need for the coordination required for pMDI dose delivery which makes a DPI much easier to use for elderly patients and children. DPIs are kinder to the environment, (Levy *et al.*, 2019) explains that the carbon footprint of pMDIs has been reported to be over 100-fold greater than that of DPIs which in today's climate a huge positive for DPIs when it comes to inhaler preferences, with such a global focus and a pressure on companies to be environmentally friendly.

Table 3: Comparison between pMDI and DPI

Inhaler	Advantages	Limitations
pMDI (general)	• Portable • Compact • Multi-dose device • Dose delivered and particle size independent of inhalation maneuver • Quick and easy to use • Less expensive than most other inhalers • Suitable for emergencies • Available for most treatments	• Coordination of inspiration and actuation necessary • Not suitable for young children (without use of spacer) • High oropharyngeal deposition of larger particles (without use of spacer) • Dose counter not available in all devices to assess remaining doses • Propellant required • Needs to be shaken well before each inhalation, and primed if not used within a prespecified time period
DPI (general)	• Small and portable • Breath-actuated • Less coordination required • Short treatment time • Available for most treatments	• Moderate to high inspiratory flow required • Not suitable for young children • May not be suitable for emergencies • Partly sensitive to humidity • Need proper dose preparation and loading to achieve optimal available dose for inhalation

(Omar S Usmani, 2019)

With increased patient compliance and use of DPI, the therapeutic effect is thought to be far greater, owing to the deep lung deposition of dry powder products, over propellant driven formulations that may see the API impact in the upper airways or a patient not inhaling the entire emitted dose, due to ill-timed actuation and breath coordination. However, as (Sagar Dhoble *et al.*, 2024) discusses the formulation considerations for optimal lung deposition, formulating and developing a DPI is not as straight forward as their ease of use.

Dry Powder Inhalers

Dry powder inhalers are a popular choice of pulmonary drug delivery system due to their numerous advantages, including enhanced drug stability, ease of use for all patient groups and for their environmental sustainability compared to pMDI. Their formulation and development, however, presents unique challenges that require careful consideration of critical quality attributes (CQA), particularly blend uniformity.

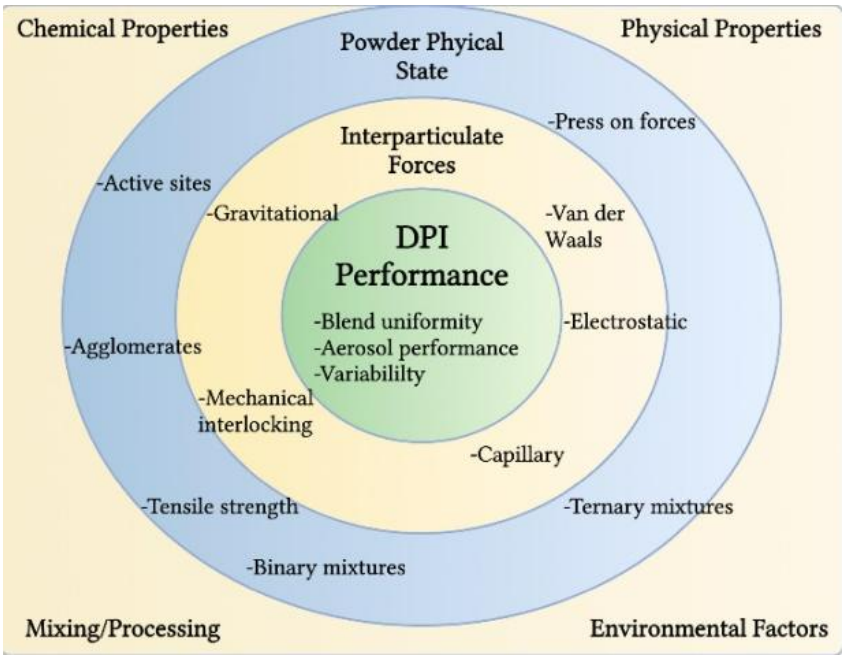
Blend uniformity is essential for ensuring consistent dose delivery, therapeutic efficacy, and patient safety. Achieving homogeneity in DPI formulations involves addressing factors such as particle size and distribution, morphology, surface characteristics, and cohesive-adhesive forces between the API and the carrier.

- Cohesive Forces – API/API interaction
- Adhesive Forces – API/Carrier interaction

Development of DPI products

The development of DPIs is a complex process that requires careful consideration of multiple factors, and achieving consistent drug delivery in the lungs remains a challenge in DPI development. Factors such as the physiochemical properties and characteristics of the powders used in the formulation, specific environmental and manufacturing conditions, device design and packaging to name some of the variables which must be carefully considered, developed and tested throughout early development activities. For the scope of this literature review, the device and engineering design of the device, although critical to achieving product performance is not relevant as blend uniformity is the main focus, as it is an intermediate CQA and must be controlled during the manufacturing process and not the finished product, and so device selection at this point is not important to the study. Figure 2 below provides a visual representation of the chemical and physical properties that affect overall DPI performance.

Figure 2: Chemical and physical properties affecting overall DPI performance

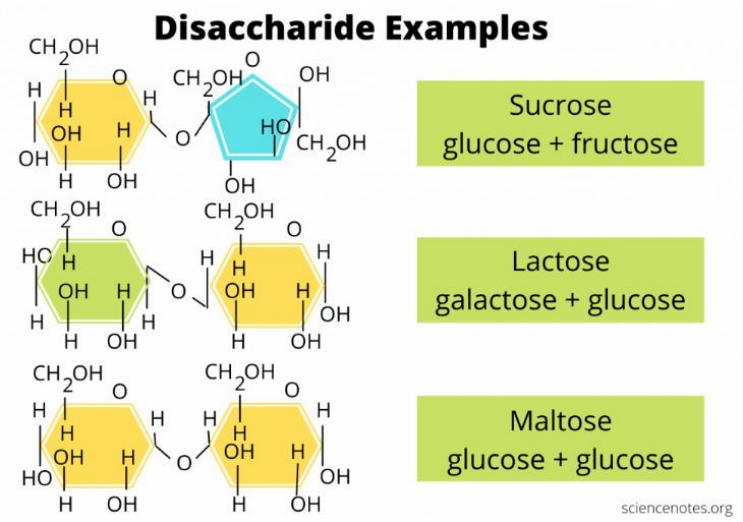


(Jamie E. Spahn *et al.*, 2022)

Formulation considerations

DPIs are carrier-based formulations, also referred to as adhesive mixtures, and are systems specifically designed to accommodate APIs with aerodynamic particle sizes ranging from 1–5 µm, which are optimal for deposition in the lower respiratory tract. The typical formulation for a DPI consists of two principal components: the API and an excipient that functions as a carrier, with the most common being lactose monohydrate, which is a disaccharide carbohydrate, lactose and some examples of these are shown in Figure 3.

Figure 3: Disaccharide Examples



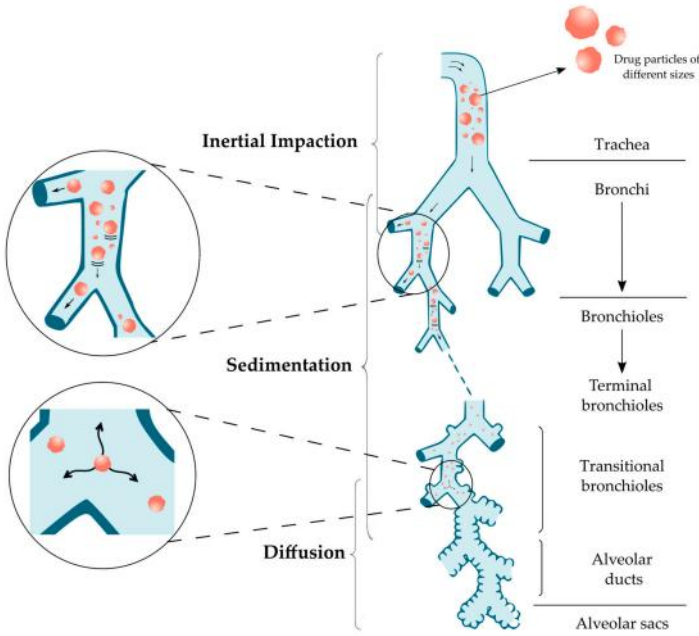
(Riya Mahar *et al.*, 2022)

Lactose contains one molecule of glucose and one molecule of galactose which are linked together by β-1-4 glycoside bonds (Riya Mahar *et al.*, 2022). The lactose is bound to the API during the mixing process, this allows the powder to flow sufficiently though the process, through the device and ultimately into the lungs.

In one very informative article (Sagar Dhoble *et al.*, 2024) explains about the importance and impact of particle size, and how the difference in particle sizes allow for lung deposition via three main mechanisms, outlined below:

- **Diffusion** - this allows smaller particles the greater residence time in the respiratory tract and promotes deep deposition.
- **Sedimentation** – which, as a result of gravity, sees the particles typically in the 1–5 µm range deposited in the walls of airways.
- **Impaction** - sees the largest carrier particles impact in the upper airways and throat. The image in Figure 4 gives a good visual of these mechanisms and the deposition in the lung.

Figure 4: Lung deposition mechanisms as a result of particle size control



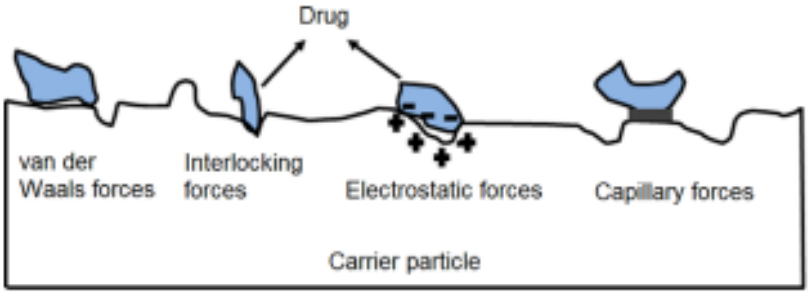
(Sabrina Magramane *et al.*, 2023)

The image gives an idea of the importance of a number of factors working together to ensure that the dose is delivered to the intended site, which are particle size, and the cohesive and adhesive forces present. These forces must be strong enough to ensure that the blend is uniform up to the point of actuating and yet weak enough to allow the API to detach so that it can travel in the airways and into the deep lung.

The blending process is integral to ensuring that the required forces are generated, it is during this process, and with the mixing energy over time that the smaller API particles adhere to the surface of larger carrier particles through these interparticulate forces, allowing the formation of a stable adhesive mixture. The forces involved in this adhesion include van der Waals forces, electrostatic interactions, capillary forces, and mechanical interlocking forces. See Figure 5 which shows how each of these forces interact differently and how the material adheres to the larger particle. (Tingting Peng *et al.*, 2016).

A thorough understanding of interparticle forces is essential for the development of dry powder formulations with improved blend uniformity. Optimising both formulation design and manufacturing parameters is critical in controlling these forces to minimise agglomeration. Typically, van der Waals attractions, capillary interactions, and electrostatic charges contribute to particle agglomeration during blending and handling. Furthermore, particles with high sphericity and smooth surface morphology tend to exhibit stronger van der Waals interactions, which may enhance cohesion and compromise dispersion within the blend, this is why characterisation of material is important.

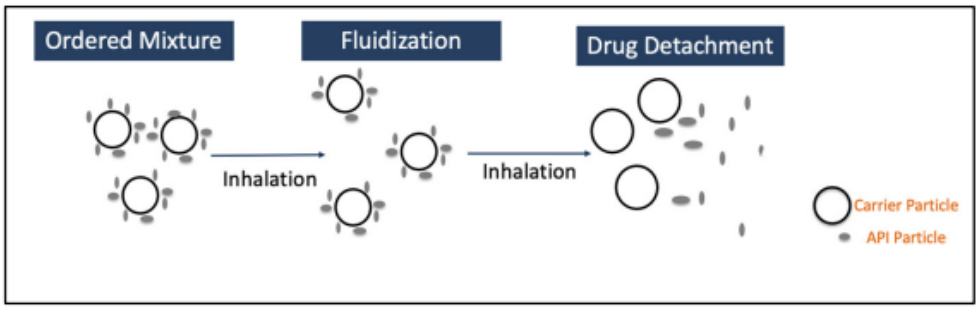
Figure 5: Interactive Forces



(Tingting Peng *et al.*, 2016)

Achieving optimal API/carrier adhesion is essential; the binding forces must be strong enough to maintain a homogenous and stable blend during manufacturing and storage but weak enough to allow detachment of drug particles from the carrier upon actuation and inhalation. This balance is critical because it ensures consistent dose delivery while enabling effective aerosolisation of the API during patient use, the image presented in Figure 6 below shows the principle of a DPI and how on inhalation the API should be freed with ease from the carrier to effectively make its way to the site of action

Figure 6: Principle of a DPI



(Tanu Mehta *et al.*, 2025)

Typically, coarse carrier particles, such as lactose, are incorporated into the mixture to enhance powder flowability and ensure dose reproducibility. Coarse carriers generally have particle sizes around 50-100 µm, with the smaller particles ranging from 1-5 µm, this will be modified though depending on the formulation requirements (Gerald A. Hebbink *et al.*, 2022). The use of a finer lactose may also be added to aid the delivery process and provides a fine particle fraction, which allows for the API to penetrate deeper into the lung for a more targeted therapeutic effect. The majority of the literature that I have reviewed such as (Alyami *et al.*, 2017) who explains that blend homogeneity largely relies on particle size and distribution to ensure an even spreading of the API and carrier in the final blend. (Waseem Kaialy, 2016) includes in their review on the topic of DPI formulation that the most commercially available DPIs on the market do contain a mix of a wide range of particles, aiding powder flow and deposition via the mechanisms discussed earlier. So, using a combination of lactose grades in a formulation appears to be common amongst marketed inhalation products.

The carriers serve multiple critical roles, including providing bulk to the formulation, especially in low dose formulations, improving flow properties, reducing particle agglomeration, facilitating powder handling by increasing formulation volume, and aiding in the dispersion of micronised and low dose drugs during inhalation. The performance of the carrier plays pivotal role not only in helping the API reach the lungs, but in achieving a uniform blend, as well as the blending operation itself. Figure 7 gives an overview of the differences in particle size and shape that different excipient materials exhibit under a microscope, (a) starch, (b) pregelatinised starch, (c) MCC and (d) ergocalciferol.

Figure 7: Examples of differences in particle size and shape

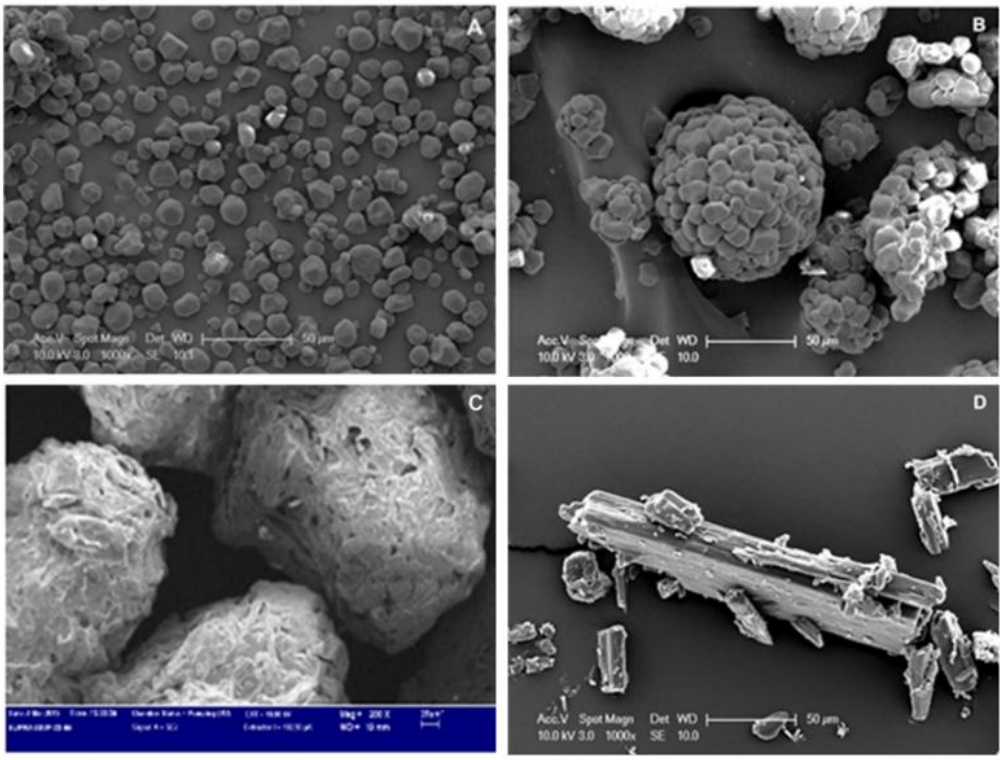


Fig 3. Scanning electron microscopy micrographs at 1000 times magnification of (a) starch (b) pregelatinised starch (c) MCC and (d) ergocalciferol.

Material characterisation

Material characterisation is an essential part of any developmental study, its main function is to understand the behaviour of the formulation, analysing the stand-alone constituents as well as the final bulk blend as (Tong Deng *et al.*, 2021) explains, in the pharmaceutical industry, uniformity of final blend mixtures is key in manufacturing, which requires particle adhesion and flow properties at the same time. To gain insightful information on these attributes, particle adhesion must be measured along with known powder physical properties such as particle size distributions, non-uniformed particle shapes and true solid density. As well as knowing how materials interact with it other, for compatibility reasons, it will aid in determining whether the manufacturing process and the chosen processing parameters is likely to be successful in generating a uniform blend, giving confidence for on target product performance of the final product in finished product testing.

Characterisation Techniques

Accurate material characterisation is fundamental to understanding dynamics of dry powders and their role and influence on DPI formulations. Variations in particle size, morphology, and flow properties can significantly influence API dispersion, adhesion to carrier particles, and overall blend uniformity. Below are just some of the techniques employed to characterise key excipients and APIs. These include laser diffraction for PSD, SEM for surface morphology, and flowability assessment methods to evaluate powder handling performance.

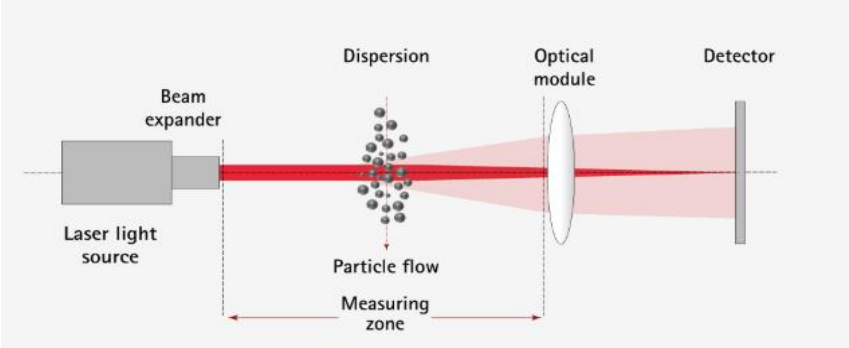
PSD

Particle size distribution measures the range and proportion of particle sizes in a known sample. It is a critical quality attribute in pharmaceuticals, PSD testing is not only used for DPIs but can be applied as an analytical tool for various dosage forms such as tablets and pMDIs, as particle size affects many CQA's such as uniformity and dissolution and can also influence processing capabilities. In particular, particle size is crucial for DPIs as it directly impacts lung deposition as well as uniformity.

(Rajia Sultana Nijhu *et al.*, 2024) provides an excellent review of the many technologies for determining PSD, such as sieving, rotary riffling, Stream Scanning and Field Scanning, also suggesting that PSD analysis by laser diffraction as leading method for PSD analysis across industries, which is confirmed by the many literature sources available on the topic of PSD applications.

The below imagine in Figure 8 sourced from (Sympatec GmbH, 2025) gives a visual of sample analysis by laser diffraction, where a small quantity of powder is loaded into a disperser and subjected to either airflow or liquid flow. As the powder particles travel through the laser path, a diffraction pattern is captured by detectors and processed, using a software the results are presented a volume-based distribution curve, from which values such as D10, D50, and D90 are extracted.

Figure 8: PSD analysis by Laser Diffraction



(Sympatec GmbH, 2025)

An explanation into why these values is important is detailed below:

- **D10 (10%) -** reflects the fine particle fraction and is particularly important for applications such as DPIs, where particles smaller than 5 µm are required for lung deposition. A higher proportion of fines may enhance aerosolisation but also increase the risk of agglomeration and reduce powder flowability.
- **D50 (50%)** - or the median particle size, is a central measure used to benchmark material consistency. It divides the sample equally by volume, allowing for comparisons between batches and formulations. The D50 value is closely linked to powder blending characteristics, having a consistent D50 supports predictable particle interaction and controlled dispersion.
- **D90 (90%) -** indicates the threshold below which the majority of the sample exists. It helps identify the presence of oversized particles that may impair flow, cause segregation during blending. The D90 value is also indicative of the powder's bulk behaviour.

Surface morphology, energy and adhesion

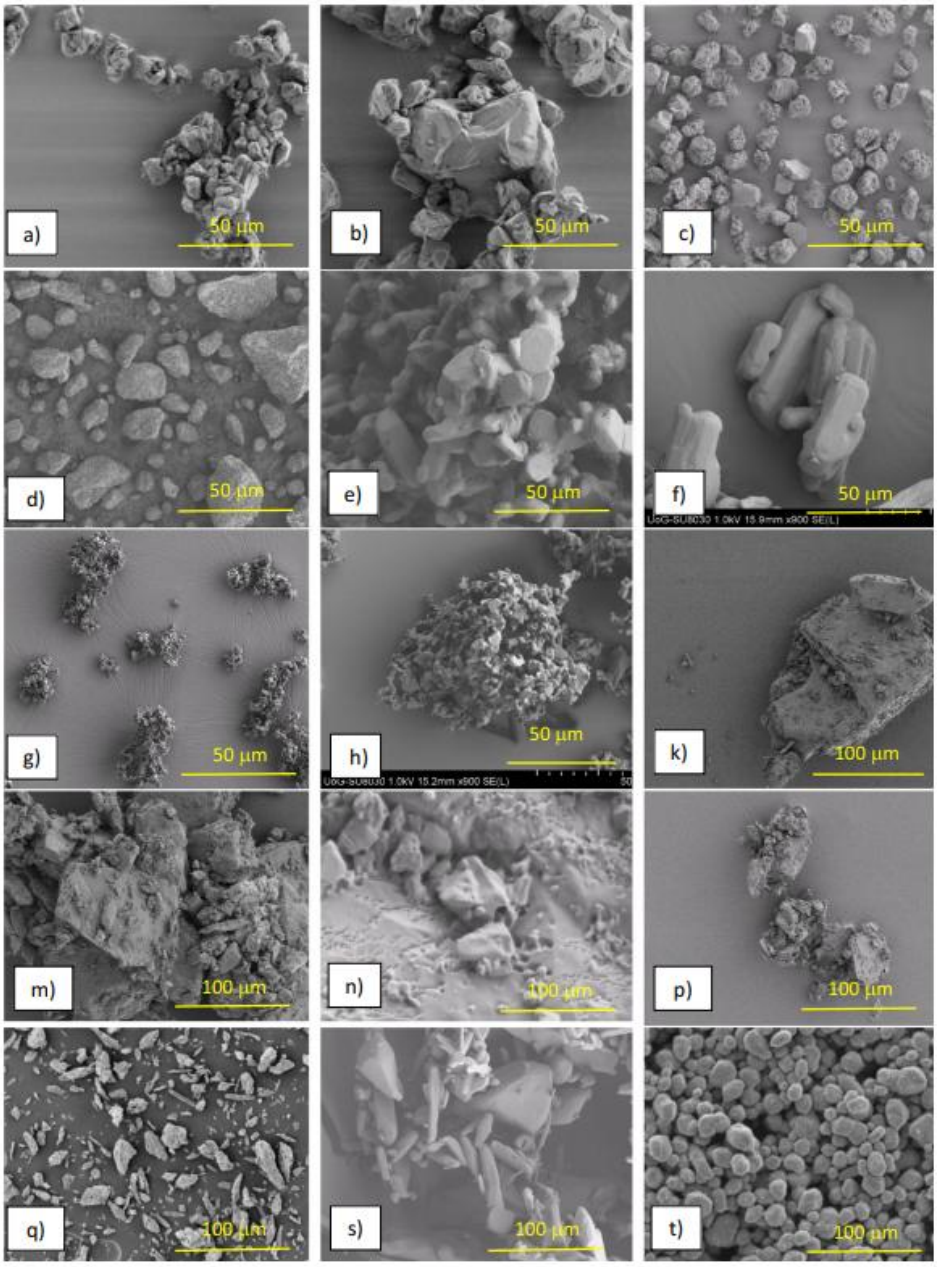
Particle morphology, surface energy, and particulate adhesion all contribute to powder behaviour and ultimately, good uniformity. Material particles that are irregular in shape and texture affect how those particles interact during blending, while surface energy determines the strength of van der Waals forces between the API and carrier particles. High surface roughness can enhance adhesion sites, but may also lead to agglomeration or electrostatic buildup, which can hind achieving uniformity. These attributes can be examined by using SEM

SEM is an imaging technique used to scan the surface of a material. The technique is widely used for material surface analysis, where samples are typically sputter coated with metals like gold to achieve optimum imaging. It is a technology regularly discussed in publications and journals such as (Yanet Rodrı´guez Herrero *et al.*, 2023) explaining that its highly versatile tool for the structural characterization of materials, the study looked at scanning and imaging of biobased products.

Another study carried out by (Tong Deng *et al.*, 2021) using this technology gives examples of the many materials, well known and mostly widely used in the chemical processing side of the pharmaceutical spectra, see Figure 9 for an example of different types of exhibiting a range of material properties such as particle size and density. The SEM image includes, a) Eskal 2, b) Eskal 4, c) Eskal 10, d) Eskal 15, e) Ibuprofen, f) Ibuprofen 25, g) Ibuprofen 50, h) Ibuprofen 50_Jet milled, k), Lactose 140, m) Lactose 200, n) Lactose 230, p) Lactose 70, q) Microcrystalline Cellulose, s) Paracetamol, t) Titanium dioxide. This shows the importance of understanding materials, being able to identify the material attributes and how they influence compatibility, powder flowability, size and shape. These images may suggest that a material needs further

processing such as milling, or micritisation, allowing for careful consideration and selection for a formulation.

Figure 9: SEM images - Range of particle size



(Tong Deng *et al.*, 2021)

Electrostatics

Although extensive research has been conducted on aerosol characteristics of DPIs such as particle size analysis and flow properties, (Martin W. Jetzer and Bradley D. Morrical, 2019) reported a notable gap in the literature regarding electrostatic properties and its ability to introduce variability into the uniformity of a blend, particularly in low dose API blends. Their investigation focused on the role of electrostatic charge accumulation in promoting agglomeration and adhesion of drug powders, specifically during the production, filling, and transport operations and under different processing conditions. Using Fluticasone Propionate (FP) and Salmeterol (SX) as model API's, the study showed significant variability in electrostatic charging across different formulations and device materials.

Also assessing the influence of device composition, the authors compared a standard capsule based inhaler made of acrylonitrile butadiene styrene (ABS) plastic with a custom designed titanium device of identical dimensions, with the results confirming that FP particles acquired substantially higher electrostatic charges than SX or excipients, except for the magnesium stearate (MgSt) which typically acts as a particle surface coating technology, reducing the cohesion and adhesion between particles (Mingpu Yuan *et al.*, 2025). The behaviour observed for FP was attributed in part to the chemical structure, which includes halogen containing functional groups that may enhance its electrical resistivity and charge retention. Strongly suggesting that electrostatic interactions contribute to particle agglomeration and adhesion within powder blends, thus introducing variability.

Lactose fines

The incorporation of lactose fines can play a critical role in controlling the adhesive interactions between the API and the coarser carrier lactose. During blending, the API particles are compressed against the surface of the coarse lactose due to mechanical mixing forces. As mixing energy increases, so does the magnitude of these forces, enhancing the contact area and thereby strengthening the adhesive interaction.

This increased adhesion can potentially reduce drug detachment upon inhalation, impairing optimum lung deposition. Supported by the "active site" theory, (Gerald A. Hebbink *et al.*, 2022) explains that active sites are generally spots of irregularity on a lactose particle, such as peaks and troughs, and by adding lactose fines, this can mitigate this effect by occupying high energy binding sites on the carrier surface, thereby moderating adhesion strength and enhancing drug dispersion during the patient's inhalation.

Just to note, however, by adding a finer lactose to the formulation, it can give positive and desirable results in finished product performance of a DPI but is not necessarily going to guarantee

a uniform blend, the concentration of lactose fines in a blend must be carefully researched, considering the formulation, and further optimised in a design of experiment type of approach, where key variables such as fine/coarse lactose ratio, blending parameters, and API characteristics are systematically evaluated.

Material selection

Lactose monohydrate is the most widely used excipient in DPIs due to its inertness, favourable flow properties, biocompatible and wide regulatory acceptance by FDA and European Medicines Agency (EMA). However, its surface properties such as roughness and particle size distribution significantly influence API/carrier adhesion and detachment. Choosing the correct lactose grade is essential to balance powder flow, to ensure blend uniformity, and aerosol performance in DPIs. (Gerald A. Hebbink *et al.*, 2022) provides insight into the use and role of lactose monohydrate in DPI formulation, the article also provides a list of products launched over the last decade, each of them including lactose monohydrate as the excipient of choice, however also expressing that not all formulations are the same, so carefully selecting excipients is critical. Figure 10 gives an overview of just some the number of marketed products that include lactose monohydrate as its main bulk carrier.

Figure 10: Marketed products using lactose as main carrier

Drug product	Drug	Carrier	Indications	Manufacturer
ProAir Respiclick	Albuterol sulfate	Lactose monohydrate	Asthma and COPD	Teva
Pulvinal Salbutamol	Salbutamol sulfate	Lactose monohydrate	Asthma and COPD	Chiesi
Easyhaler Salbutamol Sulfate	Salbutamol sulfate	Lactose monohydrate	Asthma and COPD	Orion
Serevent Diskus	Salmeterol xinafoate	Lactose monohydrate	Asthma and COPD	GlaxoSmithKline
Foradil Aerolizer	Formoterol fumarate	Lactose monohydrate	Asthma and COPD	Novartis
Foradil Certihaler	Formoterol fumarate	Lactose monohydrate, Magnesium stearate	Asthma and COPD	Novartis
Oxis Turbohaler	Formoterol fumarate	Lactose monohydrate	Asthma and COPD	AstraZeneca
Easyhaler Formoterol	Formoterol fumarate	Lactose monohydrate	Asthma and COPD	Orion
Arcapta Neohaler	Indacaterol maleate	Lactose monohydrate	Asthma and COPD	Novartis
Spiriva Handihaler	Tritropium bromide	Lactose monohydrate	Asthma and COPD	Boehringer Ingelheim
Tudorza Pressair	Aclidinium bromide	Lactose monohydrate	Asthma and COPD	Forest
SeebriBreezhaler	lycopyrronium bromide	Lactose monohydrate, Magnesium stearate	Asthma and COPD	Novartis

(Riya Mahar *et al.*, 2022)

Aside from Lactose monohydrate, and to give an idea of how many different types of lactose are out there for excipient selection for DPIs, DFE Pharma are one of the leading suppliers of lactose to the industry, with over 70 types of lactose available (DFE, 2025), each with their own properties and characteristics, which are obtained by different engineering techniques such as spray drying or milling, all of which will contribute in different ways to achieving blend uniformity and

optimum product performance of the DPI. An example of some of the other lactose grades apart from lactose monohydrate and their unique characteristics is outlined in Table 4.

Table 4: Lactose Types and associated properties

Lactose	Function	Description	Particle shape & Flow
Respitose® SV003	Carrier	Sieved inhalation lactose is a crystalline lactose with tomahawk-shaped	Narrow shape, smooth surface. Good flow
Pharmatose® 200	Carrier	Pure white and highly crystalline, milled monohydrate grade	Varying degrees of particles sizes. Does not tend to flow well
Lactochem®	Carrier	Sieved to produce relatively narrow size distributions	Varying degrees of particle sizes. Contributing to formulations where flow is of key importance
BioHale® Sucrose	Stabiliser/ Carrier	Non-reducing crystalline disaccharide made up of one glucose and one fructose molecule joined via a glycosidic linkage	Crystalline, smooth surface, good flow

Material Properties

(Alyami *et al.*, 2017) explains that when blending powders, two distinct classes of material properties must be carefully evaluated, Cohesive and Non-Cohesive properties. Cohesive powders exhibit strong interparticle forces, leading to aggregation and poor flowability such as micronised API, and such behaviour can result in uneven mixing, caking of the blend which can affect uniformity, while non cohesive powders demonstrate excellent flowability, but they are prone to segregation due to particle size or density differences, which can compromise blend uniformity also.

The interaction of the input materials together with the time and speed at which the powder is mixed all contribute to the final blend being homogenous. During the blending process the API and lactose carriers become an adhesive mixture, binding to each other through physical interactions such as Van der Waal forces and electrostatic energy. An adhesive mixture promotes blend uniformity with a reduced risk that particles will segregate.

(David H. Wagner *et al.*, 2009) talks about the impact of the blending process on these forces that are necessary for agglomeration and deagglomeration. And so, there must be a balance when considering the blending operation and its parameters, the energy that will breakdown those forces, and allows the drug to break from the larger carrier particles, and with the assistance of the finer carrier particles, the API is carried deep inside the lung. There must be a balance of interactions, and input energy is crucial.

During the review of article (Alyami *et al.*, 2017) the theory that many factors such as materials, processing parameters, equipment all contribute toward a uniform blend is achieved, translates not only when lactose monohydrate is used as the carrier in the formulation but for other excipients like microcrystalline cellulose and starch. This paper talks about ordered mixing of the materials as a processing method used to promote uniformity, it was an interesting read as this will form part of an experiment that will be conducted during my primary research to assess whether variation in blend uniformity results reduces. Showing that powders used in a DPI formulation regardless of their use must be characterised to understand their properties and how they will affect overall performance.

Manufacturing process development

The manufacturing process development of DPIs, particularly low dose formulations, requires a deep understanding of powder blending science to ensure consistent dose delivery. The key objectives in process development include identifying critical material attributes (CMAs) and critical process parameters (CPPs), ensuring they are understood and controlled to minimise variability. Techniques such as Design of Experiments (DoE) are integrated to optimise such areas as blending efficiency and equipment selection. The transition from bench top experiments to pilot plant manufacturing provides essential insights into mixing dynamics, possible segregation risks, and electrostatic effects under processing and environmental conditions. Emphasis is placed on producing a capable, robust and reproduceable process, while ensuring compliance with regulatory expectations and standards.

Mixing mechanisms

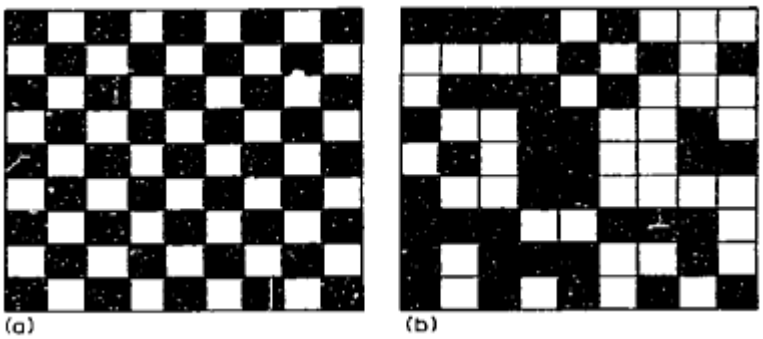
A review by (Jamie E. Spahn *et al.*, 2022) suggested that, despite the critical nature of the mixing process in DPI systems, recent literature lacks comprehensive analysis or understanding of the current state of knowledge. However, this claim appears debatable given the substantial body of recent research available on the topic. The journal delves into the thought process behind developing mixing parameters using a randomised approach which could be statistically quantified, but this technique didn't really consider material science and the forces at play within the blends, (Jamie E. Spahn *et al.*, 2022), the author went on to explain that the blending of dry powders can be broadly categorised into two mechanisms: random mixing and ordered mixing.

- **Random mixing** involves the stochastic distribution of particles, where uniformity is achieved through repeated movement and redistribution. However, this approach is often insufficient for low dose DPI products due to the high risk of segregation and poor content uniformity, as there is no guarantee that the blend will be uniform once the blending process has finished.
- **Ordered mixing** in contrast, relies on the adhesion of fine API particles and lactose fines onto the surface of larger carrier particles, forming stable adhesive units. This structured arrangement minimises the randomness seen in stochastic mixing and helps ensure that each unit dose contains a consistent amount of API, which is of utmost important when the API is present in microgram quantities, as it promotes blend uniformity and facilitates drug detachment during inhalation.

(J.A. HERSEY, 1975) was the first to introduce ordered mixing, which he considered at the time to be quite different from random mixing since it does not require equally sized or weighted particles, "it requires particle interaction, i.e. adsorption, chemisorption, surface tension,

frictional, electrostatic or any other form of adhesion". It resulted in an ordered arrangement of the particles, in his paper he best describes it with an image of the same amount of black and white particles inside a cube, (a) an ordered mix and (b) a random mix. See Figure 11, with ordered mixing showing a uniform spread of the particles.

Figure 11: Ordered versus Random Mixing



The success of either mixing strategy also depends heavily on several critical process parameters, including blending time, mixing speed and order of addition. For instance, even with ordered mixing applied, prolonged blending may lead to deagglomeration of API particles and improved distribution, but excessive mixing can also cause over coating or detachment of API from the carrier, reducing aerosol performance. Similarly, the sequence in which lactose fines, API, and carrier are introduced can influence the formation of stable adhesive mixtures.

Mixing Equipment and Techniques

The choice of types of powder mixing used to produce ordered mixes is plentiful, with the most popular standing the test of time, in a journal published almost two decades ago (Vikas Anand Saharan *et al.*, 2008) describes the many variations of mixing available such as adhesion, fluidisation and blending, all effective in their own right, dependant of course on the intended formulation, materials and their properties. For the purpose of the study, the type of mixing that I researched further into, and the mixing type that I employed during my primary research was blending, and the various techniques that go with it.

Like any of the mixing options out there, within blending, there are different techniques to choose from, (Alyami *et al.*, 2017) describes the three main mechanisms of blending and their suitability for certain powder blends: convection, diffusion, and shear.

Convective blending encompasses gross movement of particles within the blend, usually by paddles or blades, whereas diffusion is a slower blending process where the powder is gently agitated. Lastly, the shear mechanism of blending comprises of blending material while passing along forced slip planes which aid in breaking agglomerates and enable blending.

Shear mixing, being the most relevant to this research study, refers to the distribution of particles along a plane, high and low shear equipment further explained below:

- **Low shear mixers**, such as the Turbula® or V-blenders, image provided in Figure 12, facilitate a gentle tumbling action suitable for preserving particle integrity and minimising the risk of segregation, making them ideal for ordered mixing. These are often used in early stages of development, for instance, at bench top scale, when making pre-blends or when handling electrostatically sensitive powders.

Figure 12: Low Shear Tumble Blender

(WAB-GROUP, 2025)

- **High shear mixers**, like the Diosna® or PMA Bottom-drive High Shear blender, image shown in Figure 13, apply intense mechanical energy to break agglomerates and promote uniform dispersion of the API, which can be beneficial for cohesive APIs but may risk damaging fragile particles or altering surface properties.

Figure 13: PMA High Shear Blender

(GEA Group Aktiengesellschaft 2025, 2025)

The selection between high and low shear blending depends on the formulation's sensitivity and desired homogeneity. Ultimately, the development of a robust DPI manufacturing process demands a balance between equipment capability, the properties of the material, and process control. A comparison of both techniques is shown with some examples in Figure 14 which gives an idea of the outcomes using both low and high shear with various formulation compositions, to further support the extensive consideration that must be given to the selection of equipment for a blending process ensuring the final blend is uniform.

Figure 14: High Shear and Low Shear mixing

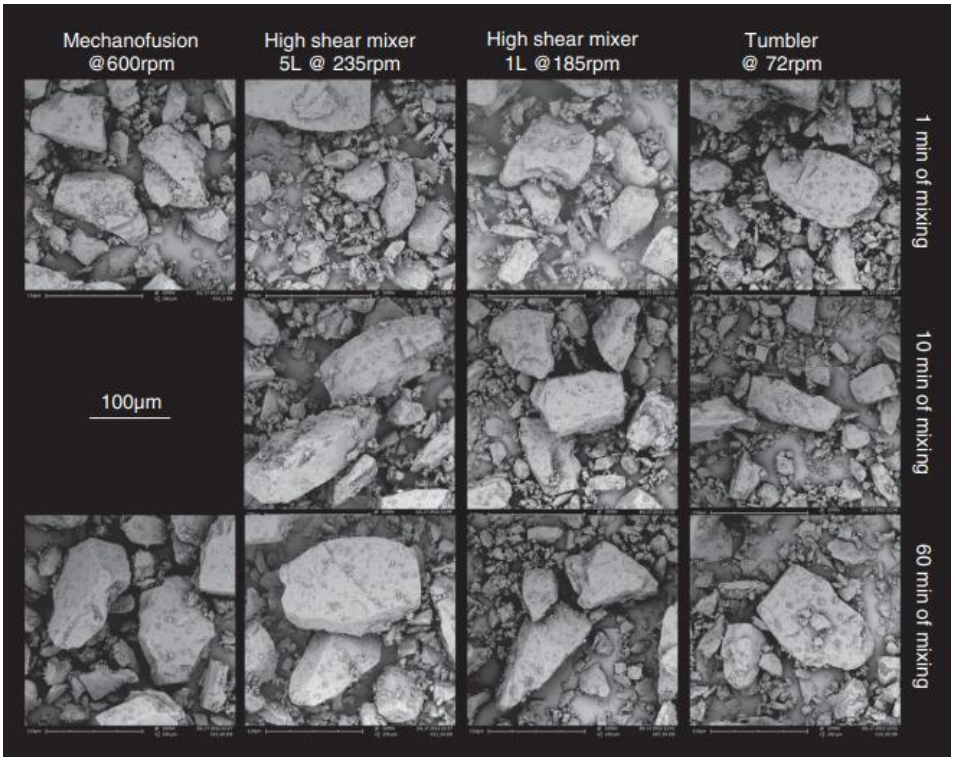
High shear and low shear mixing comparison studies for dry powder mixtures for inhalation.

Author	Mixer style A	Mixer type A	Mixer style B	Mixer type B	Drug	Carrier	Ternary agents	Study comparison	Key conclusions
Sarkar et al. (2017)	High shear	HSM (KG5 Model; Key International, Inc., Cranbury, NJ)	Low shear	DCM blender	None, used fine lactose	Lactose LH100	None	Comparison of high shear and low shear blending of fine lactose and carrier lactose	High shear blending produced homogenous blends faster than low shear blending. Loss of fine material was observed to be higher in high shear blending. Press on forces were comparable.
Shur et al. (2008)	High shear	High shear mixer (Braun KSM2, Kronberg, Germany)	Low shear	Turbula T2F (Willy A Bachofen AG, Basel, Switzerland)	Budesonide	Lactose	None	Comparison of high shear and low shear blending of budesonide and carrier lactose	High shear blending of lactose generated in situ fines which resulted in an increase in FPF.
Jetzer et al. (2018)	High shear	Collette MicroGral 2 L (GEA Pharma Systems, Bubendorf, Switzerland)	Low shear	Turbula T2F mixer 2 L (Willy A. Bachofen AG, Basel, Switzerland)	Fluticasone propionate and salmeterol xinafoate	Lactose	Magnesium stearate	Comparison of high shear and low shear blending of fluticasone propionate with magnesium stearate	Magnesium stearate distribution on the carrier differed between blending methods and impacted aerosol performance. Low shear blending with magnesium stearate increased the FPF of salmeterol xinafoate while high shear blending with magnesium stearate increased FPF for both salmeterol xinafoate and fluticasone propionate as compared to no magnesium stearate.

(Jamie E. Spahn *et al.*, 2022)

The impact of blending equipment and techniques on materials and intermediate products is widely studied, owing to it being one of the most critical operations in the process. If your blend has not been mixed sufficiently, none of the subsequent unit operations in the manufacturing chain matter as your product performance is already failing. (David Barling *et al.*, 2014) as part of a study, conducted an experiment where a series of lactose powders (white) with 1 wt.% sub-micronised iron oxide tracer (dark red) by weight were blended with three different mixing technologies such as mechanofusion and shear under a range of processing conditions and times, scanning electron microscopic (SEM) images for several blends were recorded to see if the effects of mixing time and technology on particle interactions and behaviours could be observed, results are shown in Figure 15. Although the author explains that the results may be attributed to image resolution, it suggests that no real change in particle interaction has occurred as a result.

Figure 15: SEM images of particle behaviour post mixing



(David Barling *et al.*, 2014)

(Jamie E. Spahn *et al.*, 2022) gives a comprehensive overview of types of mixers for blending, and details comparison studies that have been conducted, using high and low shear type blenders, in one of the studies it was found that high shear mixing was more efficient than low shear mixing although no differences in blend uniformity were detected. Also noting in the review that the relationship between mixer type, key parameters, and blend performance has much room to be investigated.

Critical Processing Parameters

Defining the optimum parameters for a mixing process are critical to the success of the blending operation, this is typically done through a series of studies called design of experiments. One study conducted by (V. N. P. Le *et al.*, 2012) looked at the influence of parameters such as speed and time on BU, the API used in the study was Fluticasone Propionate, a cohesive API, widely used in inhalation therapy, mixed with a lactose carrier where 10 blends were manufactured using a low shear process, see Figure 16 for a breakdown of the batches, and the experimental design.

Figure 16: Experimental Design

Blend	Carrier	Mixing speed (rpm)	Mixing time (min)
1	Lactohale 200	54	60
2	Lactohale 200	74	60
3	Lactohale 200	90	60
4	Lactohale 200	100	60
5	Lactohale 200	90	180
6	Lactohale 200	90	120
7	Lactohale 200	90	120+30+30
8	Lactohale 200	90	60+30
9	Lactohale 200	90	90+30
10	Lactohale 200	90	120+30

(V. N. P. Le *et al.*, 2012)

Each blend was mixed for a predefined time and speed. The study concluded that the longer the blending time the better dispersion of the API, a liner relationship was evident through batches 1 – 4, but suggested that the achievement of a homogeneous mixture from a formulation containing a low dose, cohesive API and coarse excipients required the use of "powerful" shear mixers to break down the aggregates so that the adhesive forces (API/carrier interaction) exceeded the cohesive forces (API/API interaction) between the fine particles. The study suggested that a hold time during blending yielded more favourable results in terms of uniformity, likely due to static dissipation or a relaxing of cohesive forces in the blend.

For comparison, a similar study was conducted by (Maarten Jaspers *et al.*, 2024) using different input materials to make two blends, a low dose and a medium dose formulation, both assessing speed and time and the impact it had on uniformity, expressed as percentage relative standard deviation (%RSD) of API concentration and then compared to each other. Figure 17 shows the breakdown of the batches, and the experimental design.

Figure 17: Experimental Design

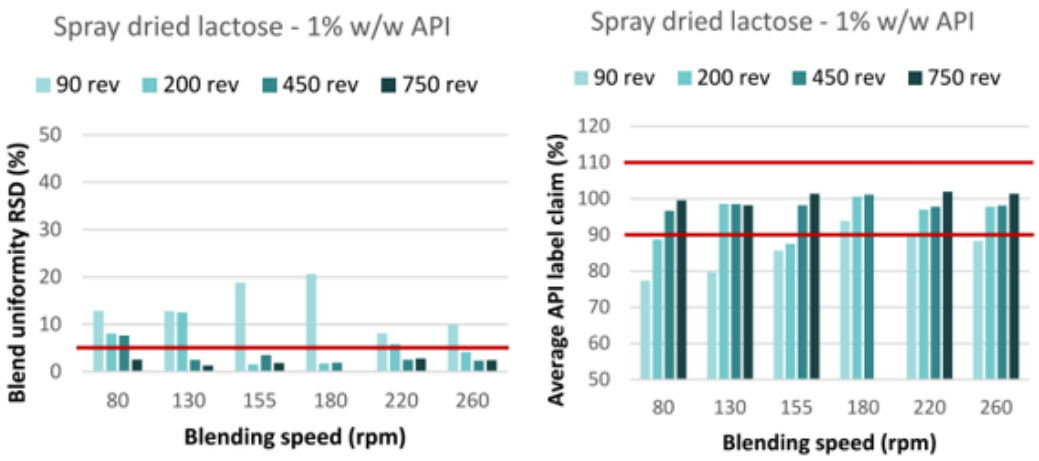
No. of revolutions	80 rpm	130 rpm	155 rpm	180 rpm	220 rpm	260 rpm
90	68 s	42 s	35 s	30 s	25 s	21 s
200	150 s	92 s	77 s	67 s	55 s	46 s
450	338 s	208 s	174 s	150 s	123 s	104 s
750	563 s	346 s	290 s	250 s	205 s	173 s

Remaining within the scope of the research, and to allow for a more direct comparison with the experiments carried out as part of the primary research, the following focusses only on the low dose batch manufactured as part of the study conducted by (Maarten Jaspers *et al.*, 2024) using the lactose excipient, graphed results are shown in Figure 18.

At low blending speeds, the results show (a) more pronounced decrease in %RSD values upon increasing the number of blender revolutions (b) results generally show that the average API label

claim is well below 100% after 90 blender revolutions. This indicates incomplete mixing, in line with the high %RSD values obtained after 90 revolutions (c) at increased blender speeds of 155 rpm and higher, the blends generally reach an average API label claim close to 100% within 450 blender revolutions.

Figure 18: Blending speed impact on BU %RSD and API content %LC



(Maarten Jaspers *et al.*, 2024)

This study concluded that mixing efficiency is relatively independent of API concentration, when higher blending speeds are used, and in conclusion that blending efficiency of the process shows a clear dependency on the blending speed.

Experiments such as these are essential for learnings when determining the optimum speed and time for achieving uniformity. Both studies showed that lower shear processing takes significantly more time to achieve a uniform blend, whereas with high shear, speed was the deciding factor, reducing the time it takes to come to the blending endpoint for uniformity. Carrying out the type of experiments such as (Maarten Jaspers *et al.*, 2024) allows different blending techniques to be assessed, as one of the authors discovered that low shear was not the best fit for this formulation due to the material characteristics of the powders in the formulation, showing how critical experiments such as these are to the development of the process.

Environmental Conditions

High relative humidity plays a major role in DPI performance since the adsorption of water on the surface of a powder has a significant impact on the capillary forces, solid bridge formation and electrostatic forces. High relative humidity may increase interparticulate forces due to increased capillary interactions resulting in the formation of larger agglomerates that are less breakable (V. N. P. Le et al., 2012), also lactose monohydrate may dissolve and then recrystallize resulting in solid bridges producing stronger agglomerates that do not disperse, this will have a

detrimental effect on a dry powder blend. To determine whether a product requires stringent controlled environmental conditions such as low humidity, a design of experimental type of study should be performed to assess product performance under various conditions to find the most suitable.

Current techniques for analysing dry powder blends

Dry powder blend analysis has evolved significantly with the integration of advanced techniques that enhance process understanding and control. Real-time analytical technologies, used in many applications such chemical manufacturing and biopharmaceutical production (Gabriella Gerzon *et al.*, 2021) are increasingly being adopted in dry powder formulation, offering timely insights into blend uniformity, with the end goal of controlling quality at all stages of product manufacturing.

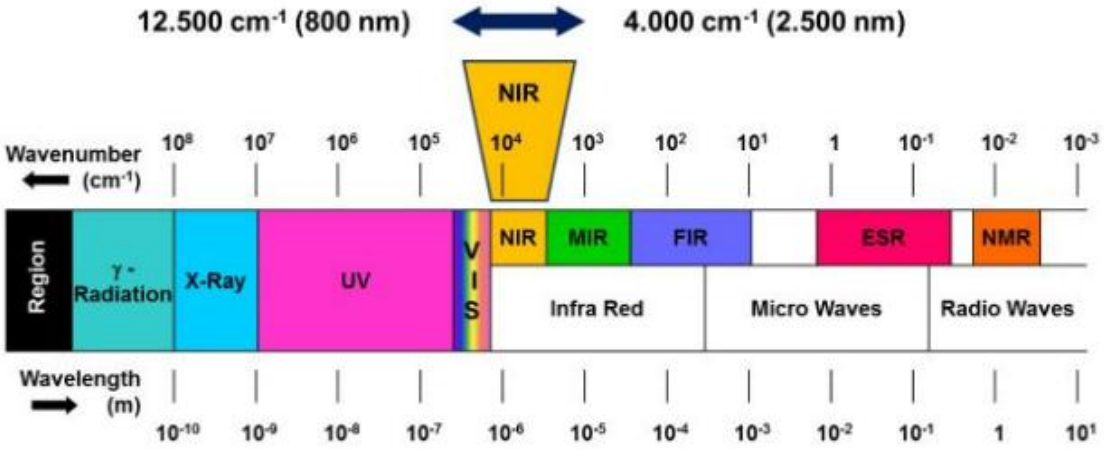
(Asachi *et al.*, 2018) paper is particularly helpful in that the authors have researched a lot of the technologies and techniques currently available for the in line and on line testing of powder blends. The article talks to the various methods for powder blending, giving a description of the two main pieces of equipment used, giving insight into some of sampling methods employed, explaining how ensuring that the samples that are taken must be representative of the bulk blend, which is crucial, and so the technologies must be sophisticated enough to replicate this at each sampling point during the blending process.

Reliance on such intrusive methods is increasingly discouraged in process development. (Asachi *et al.*, 2018) article tells us “In recent decades, non-invasive analytical technologies have been developed such as Near-Infrared spectroscopy (NIR), Raman spectroscopy and Electrical Capacitance Tomography with no interference with the blending process”. By using technologies such as NIR, testing can be completed in real time by using on line and in line sampling, the blending process can continue uninterrupted.

- **Traditional sampling method** such as the use of sampling thieves are among the most applied techniques in powder blend analysis. However, these approaches are highly invasive and can disrupt the integrity of the blend by introducing physical disturbances. This is particularly problematic for cohesive and electrostatically active blends, where even minor interference can lead to segregation or sampling bias.
- **Near-Infrared spectroscopy** is an analysis method, using the NIR region of the electromagnetic spectrum (800 - 2,500 nm) see image of the spectrum in Figure 19 as presented by (Bruker, 2025). It measures the absorption of light from the sample in the NIR region at different wavelengths. The recorded NIR spectrum consists of overtones

and combination vibrations of molecules that contain CH, NH or OH groups (hydrogen atom bonded to carbon, nitrogen, or oxygen).

Figure 19: Electromagnetic Spectrum highlighting NIR



(Bruker, 2025)

The differences between in line and on line sampling is explained, as (Maryam Asachi *et al.*, 2018) gives a better understanding of the process and also an idea of the advantages and disadvantages for each type of technology which is useful information to have at the outset from a research perspective, as this can help with selecting a model or technology for potential use during proof of concept trials as part of primary research to be carried out. Both types of analysers offer advantages for process monitoring and control, depending on the specific requirements of the process and product.

- In line sampling – In line analysers are directly integrated into the process, this technology will provide real-time measurements without interrupting the blending process
- On line sampling – On line analysers collect samples from the process for analysis in the laboratory, which is a much simpler set up and a good starting point with a view to progressing the automaton of the operation and the level of sophisticated technology as part of scale up activities as the project progresses.

Having a robust process can absorb routine variation without compromising product quality, while reproducibility guarantees the same high quality outcome across batches and scales. Combined with real-time analysis, such as near-infrared spectroscopy or PAT tools, manufacturers gain actionable insight during processing, enabling immediate adjustments, preventing possible OOS in real time and enhancing confidence in batch quality. It supports “right first time” manufacturing by reducing the risk of rework or batch failures, reducing waste in terms of materials, energy, and time. (Rajagopal Ramachandran, 2017) tells us that, Process Analytical

Technology (PAT), was designed in alignment with "Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, a Risk Based Approach, which not only promotes sustainable resource use, but also streamlines development and commercial scalability.

Regulatory expectations for ensuring blend homogeneity

Regulatory agencies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) have strict guidelines in place and quality standards that must be met during the development of pharmaceutical products and in achieving a homogenous blend, as previously stated, BU being one of the critical quality attributes (CQA) for a DPI. Research into optimising blending parameters, excipient properties, and processing conditions supports the development of robust formulations and products that consistently meet predefined specifications. As regulatory scrutiny of products in development intensifies, having scientifically justified blending methods and analytical test methods is vital for successful approval of the product and its pathway throughout the development stages, through the rigorous clinical trial and ultimately for market entry.

The FDA withdrew their guidance on sampling for blend uniformity in 2013 (Food and Drug Administration, 2003) as it no longer represented the FDA's current thinking, the FDA also expressed that the traditional sample retrieval methods of using a manual sampling thief had its drawbacks and limitations, such as causing disturbance to the powder bed, powder segregation, or other sampling errors, all which can lead to variability in uniformity of the blend. However, sampling thief retrieval remains widely used and provides reliable results in many cases. The FDA do encourage pharmaceutical companies to adopt more innovative approaches to ensuring adequacy of mixing, such as Process Analytical Technology (PAT) (Food and Drug Administration, 2024) which is a sign of the changing times for pharmaceutical companies, incorporating automated technology has many benefits such as reduced processing times, and streamlining benefits such as less waste and resources. Ideally this is where a process needs to be in terms of having control over the blending operation, but realistically at early development stages, such sophisticated technology is not an option in terms of investment unless the equipment is at hand to test its integration into the process.

Noted gaps in the literature

The reviewed literature demonstrated a vast body of work focused on DPI formulation, blending strategies, and excipient performance. Foundational studies, such as those by (A. H. de Boer *et al.*, 2016) and (Waseem Kaialy, 2016) offer comprehensive insights into carrier-based DPI systems and the physicochemical interactions that influence drug delivery. However, despite advancements, the existing literature lacks guidance on the practical integration of material characterisation data into manufacturing decision making, particularly for low dose products where variability tolerance is minimal.

While many studies such as (e.g. (Alyami *et al.*, 2017) and (Gerald A. Hebbink *et al.*, 2022)) investigate the role of materials, particle size, morphology, and blending trials assessing optimum parameters, they typically operate within laboratories or smaller development manufacturing spaces, and not on a scaled up commercially ready production line under GMP control. If the output of the trial at bench top is successful, that doesn't guarantee that results will translate at scale.

Similarly, publications such as (Jamie E. Spahn *et al.*, 2022) and (Maryam Asachi *et al.*, 2018) describe powder mixing principles and evaluation techniques but give no suggestions of an integrated approach that connects these findings to actionable strategies for optimisation manufacturing processes. Studies are used to compare techniques such as low and high shear blending, but not in a direct comparison, such as input materials and directly translated parameters using both methods.

The literature presented limited discussion on the role of electrostatic effects, container handling, and sampling position, all of which were found to impact low dose uniformity. Blend sampling and sample sets and sizes etc, it is quite subjective, as there is no set guidance at this stage of development, it is a lot of trial and error, without defined batch sizes, or equipment types and vessel volume changes from batch to batch, it is hard to know if issues seen with blend uniformity are truly happening in the blender or in the formulation and not as a result of sampling bias. To be further explored.

Summary

This chapter has examined the key themes related to blend uniformity, including critical process parameters, raw material characteristics, regulatory frameworks and emerging technologies. Also highlighting some existing gaps in the literature, signalling the need for empirical, primary research exploring how the material attributes (e.g. particle size distribution, surface morphology) and mechanical blending parameters contribute to blend uniformity. The current study addresses this by integrating material characterisation techniques with both development and pilot scale

manufacturing trials to quantify and compare blend uniformity outcomes across various processing conditions as well as showing scalability as part one study.

The manufacturing experiments carried out as part of this study aligns with the work of (Maarten Jaspers *et al.*, 2024) particularly in its evaluation of the effect of blending speed and number of revolutions (time) on the uniformity of low dose blends. Similar to (V. N. P. Le *et al.*, 2012) using energy to hypothesize an improvement in uniformity.

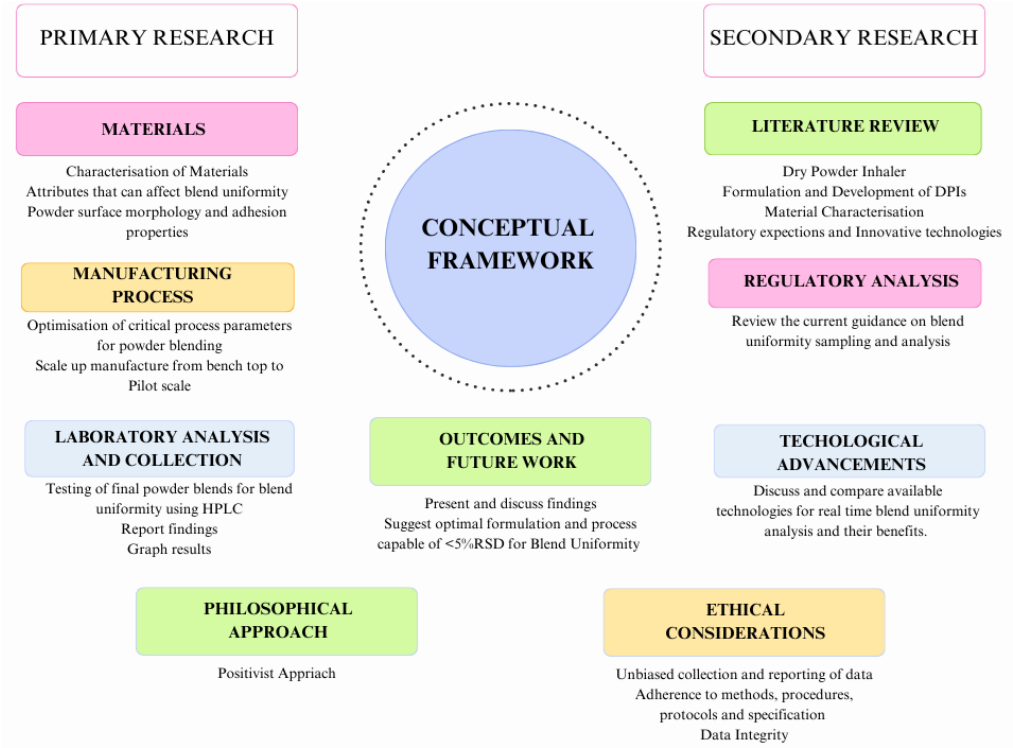
However, the findings from (V. N. P. Le *et al.*, 2012) stress the importance of particle interactions in formulations containing cohesive APIs. Although the paper did not address the impact of lactose fines on adhesion properties and particle binding within the blend, due to a lack of theoretical focus or supporting data on the subject, the author discussed implications and the absence of fine particles of lactose influencing the flowability, evident in his characterisation study.

Together, studies such as these reinforce the principle that optimal blending conditions must be explored across a series of parameters, the selected should be formulation specific, considering not only time and speed and blender size, but also API characteristics and its behaviour, excipient properties and how all of the input materials interact. This supports the experimental design of the primary research outlined in the next chapter.

Conceptual framework for conducting primary and secondary research

Building on the findings from the literature review, the conceptual framework presented in Figure 20 integrates key theoretical insights with primary experimental data to form a comprehensive approach to understanding the independent variables influencing blend uniformity. By combining empirical evidence with technological advancements, the study aimed to optimise the formulation and development processes while ensuring regulatory compliance and therapeutic efficacy of the product.

Figure 20: Conceptual Framework

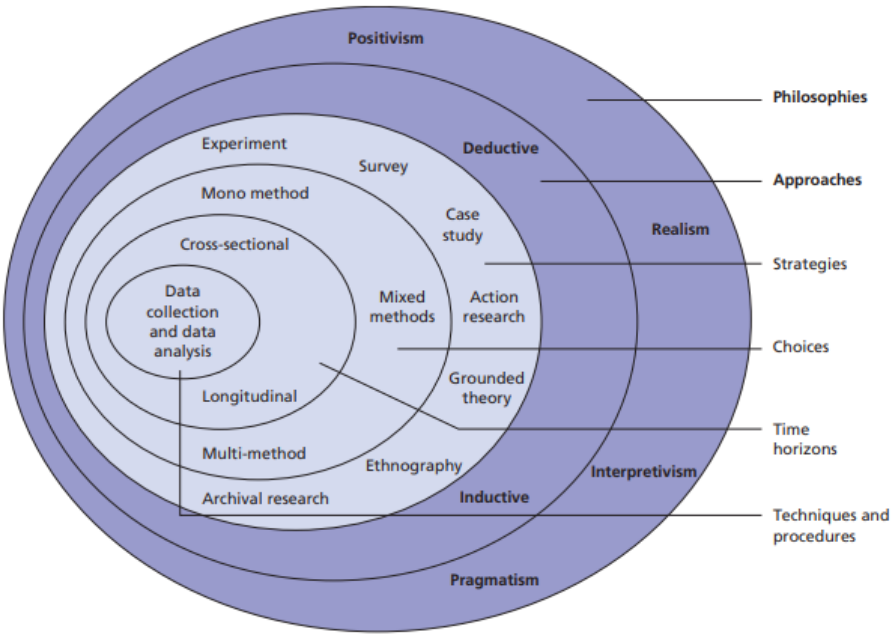


Chapter 3 – Research Methodology

Introduction

This chapter outlines the research methodology undertaken for the study, detailing the philosophical stance, research design, and methodological choices. The approach was structured using Saunders' Research Onion shown in Figure 21 (Mark Saunders *et al.*, 2009), which provided a systematic framework for methodological decisions, ensuring coherence between philosophical assumptions, data collection techniques, and analysis.

Figure 21: Saunders Research Onion



(Mark Saunders *et al.*, 2009)

Research Design

Research Philosophy and approach

The primary research adopted a positivist view, with a set of defined objectives and a stringent timeline for completion. There was a systematic approach to carrying out the research using practical investigations, experiments and testing, objective material characterisation and analysis, and quantitative methodologies.

Positivism, as a philosophical approach and deductive research is aligned with the focus of conducting controlled experiments, free from bias, and subjective interpretation to generate data, linking it back to the research question and original hypothesis.

Research Strategy

A quantitative research strategy was appropriate because it aligns with a positivist philosophy. It was designed to address the outlined objectives of investigating blend uniformity, and the key factors and parameter that influence it and introduce variability. It focused on collecting quantitative data related to raw materials, process parameters and blend homogeneity analysis. Results were obtained and will be presented as a combination of tabulated and graphed data for review and critique.

Choice

The research used a multi-method approach, which involved using multiple research techniques and tools such as characterisation and analysis, and manufacturing all within the same overarching research paradigm. Unlike mixed-method designs, which integrate both qualitative and quantitative approaches, multi-method designs maintain consistency by staying entirely within either the qualitative or the quantitative domain.

Time Horizon

For this study, a cross-sectional research design was adopted. All data was collected at different timepoints during the manufacturing process, such as immediately sampling batch 1 and proceeding the next batch and so on until batch 6 was blended and sampled over the duration of the campaign. The sampling of the batches was not longitudinal in nature, as it did not involve repeated observation of the same batch over an extended period. The focus was on comparing fixed process conditions rather than tracking time based changes, thereby aligning the study with cross-sectional methodology principles.

Methodology

The primary research into evaluating the factors that influence variability in blend uniformity was conducted using an experimental methodology. A method chosen to directly investigate the formulation and manufacturing dynamics of a dry powder blend.

A series of pre-defined experiments were carried out. Input materials (formulation) were characterised and the output of these experiments informed choice of material. This was followed by a manufacturing study which evaluated the impact of blending time and speed. Manufacturing was carried out at bench scale (1 kg batch) and Pilot Scale (6.6 kg batch) Resulting blends were sampled, and the blend uniformity was measured by determination of API content using Ultra Performance Liquid Chromatography (UPLC).

Material Characterisation

The API and both grades of lactose were procured from the respective vendors with an agreed targeted PSD range, a range known to be suitable for this product from previous development work undertaken. The following characterisation techniques are essential to confirm that the PSD values are within the specified range, and SEM imagery supports that the properties exhibited are aligned with the characteristics of that specific material, (e.g. flow, binding, agglomerates etc.)

Particle Size Distribution

This study was conducted in a materials laboratory, in accordance with company test methods and protocols, to determine the PSD of the batch of coarse lactose (Lactose Y) used in the formulation for the manufacturing part of the study.

Materials

- **Test Sample**: Lactose Y, Batch 123456

Equipment

- **Material dispensing**: 50g of Lactose Y was dispensed into a stainless steel (SS) container using a SS scoop, the lactose was sieved through a 500 µm mesh sieve to eliminate any agglomerates.

Instrumentation

- **Analyzer**: Sympatec HELOS laser diffraction system, reference Figure 22 and Figure 23
- **Dispersion Module**: RODOS/M
- **Accessory**: Vibri (vibrating chute for powder feeding)

- **Optical Setup**: Lens configuration R5 (Measurement range: ~0.5 µm to ~875 µm)
- **Software**: PAQXOS software for data capture and analysis

Measurement Procedure

- **Sample Dispersion**: A 5 g portion of lactose was loaded into the RODOS unit and dispersed using compressed air at 1.5 bar. This setting was selected to simulate typical dry powder handling conditions without inducing particle attrition.
- **Replicate Testing**: The lactose sample was analysed in triplicate to ensure reproducibility. Background measurements were recorded prior to each run to eliminate signal interference.
- **Data Capture**: Particle size distribution was reported on a volume basis. The following key parameters were extracted:
    - **D10, D50, D90, %<5**: Representing the particle diameters below which 10%, 50%, and 90% of the sample. Reporting %<5 mcm for lactose pre-blend.

Data Analysis

The resulting PSD values were expressed as mean, standard deviation and %RSD across three replicate samples. Descriptive statistics were used to evaluate the degree of polydispersity for comparison and suitability against DPI formulation benchmarks.

Figure 22: Sympatec PSD analyser

Figure 23: Sympatec Vibri accessory

Surface morphology

Morphology testing was carried out in a materials laboratory, in accordance with company test methods and protocols to determine the surface morphology of the API and both grades of lactose used in the formulation for the manufacturing part of the study.

Materials

- **API-X**: Micronised API
- **Coarse Lactose**: Lactose Y
- **Fine Lactose**: Lactose Z

Equipment

- **Material dispensing**: 50g of Lactose Y, 50g of Lactose Z and 5g of API X was dispensed into separate SS containers using a SS scoop, each of the materials were sieved through a 500 µm mesh sieve to eliminate any agglomerates.

Instrumentation

- **Microscope**: Scanning Electron Microscope (SEM) – Phenom P-series
- **Magnifications Used**: 500x – 7500x
- **Sample Preparation Tools**:
    - Carbon adhesive
    - Aluminium pin stub

- Tweezers and sample holder

Sample Preparation

Each powder sample was gently transferred onto carbon-coated pin stubs and fixed to minimize particle drift. Samples were coated with a thin layer of gold using a sputter coater as seen in Figure 24 and Figure 25 to improve surface conductivity. Using a sample holder the tin stub was inserted for analysis as can be seen in Figure 26.

Imaging Procedure

- SEM imaging was performed under Argon vacuum.
- For each material, images were captured at various magnifications to document particle shape, edge sharpness, surface roughness, and agglomeration tendency.

Data Analysis

Representative images were captured for each material. Qualitative observations were recorded, including:

- Particle morphology (e.g. spherical, plate-like, rod-like)
- Surface texture (smooth, porous, roughness)
- Presence of agglomerates

Descriptive comparisons were used to conclude potential blending and dispersion behaviour in DPI formulations.

Figure 24: Sputter coater

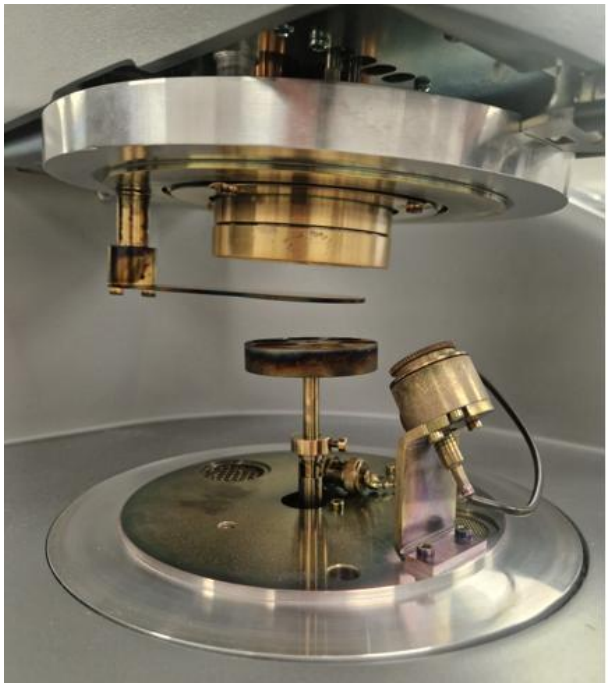
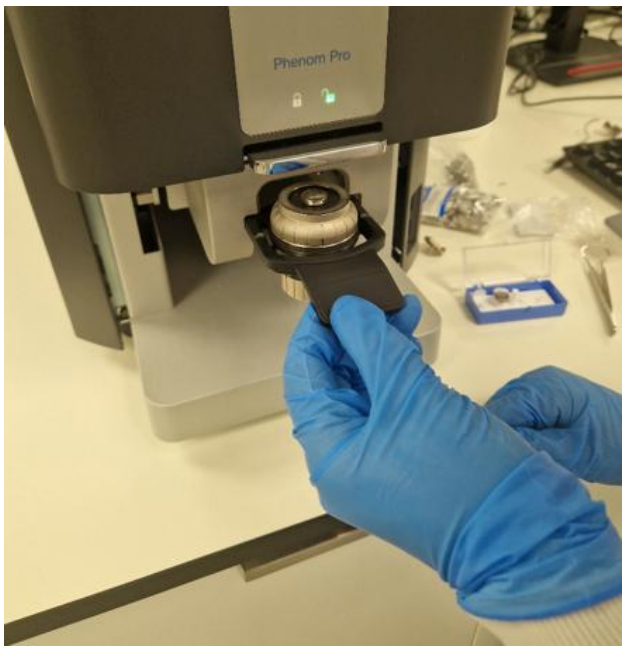


Figure 25: Sputter coater complete set up

Figure 26: SEM and sample holder ready for analysis



Manufacturing Campaigns

A series of manufacturing trials were conducted at bench top scale in a development laboratory and at pilot scale in a GMP manufacturing suite and documented using batch manufacturing records (BMR). The aim was to explore cause-and-effect relationships between processing parameters (e.g. blending time and speed) and blend uniformity, only possible through experimental trials.

Materials

Micronised API X, Coarse Lactose Y, Fine Lactose Z

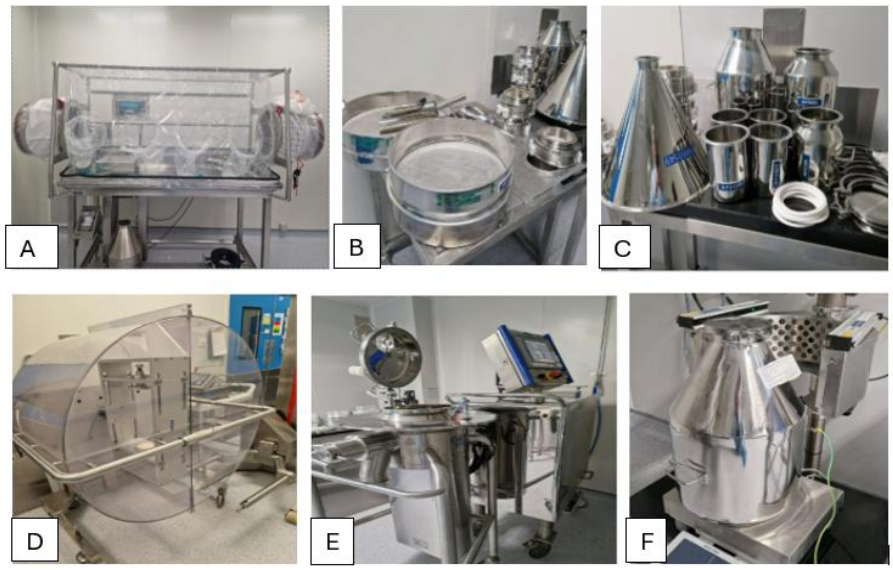
Methods

Equipment

Low shear Turbula blender/unit, 3L PMA blend bowl, 20L PMA high shear blender, SS containers for holding dispensed quantities of materials and final blends, passive vales for addition of material to the blender, horseshoe extraction unit, isolator, antistatic bars, stainless steel scoops for dispensing of materials, sampling thief for retrieval of powder samples for uniformity analysis, scintillation vials and lids for sample collection, tabletop calibrated analytical balance for material dispensing and sample weighing, environmental monitoring system for RH and temperature control (RH 20% ± 5%, Temp 15.0 – 25.0ºC) throughout the manufacturing process.

A visual of some of the equipment listed here is shown below in Figure 27: (a) Isolator, (b) sieve, (c) SS containers, (d) low shear tumbling unit, (e) 20L PMA high shear blender, (f) 20L container, horseshow extraction

Figure 27: Manufacturing Equipment



Experimental design – Small scale manufacturing

Six batches at 1kg scale per batch were manufactured in a development laboratory. Each of the batches consisted of a lactose pre-blend with a corresponding batch number which was combined with API before the final blending step. The formulation composition for each of the batches and the lactose pre blend is shown n Table 5.

Table 5: Formulation Composition

Batch	Blend	Material	Quantity per Blend (g)	Concentration in Blend (% w/w)
Batch-072	Lactose Pre-blends	Lactose Z	55.6	5.056
Batch-073				
Batch-076		Lactose Y	1044.4	94.944
Batch-077				
Batch-078				
Batch-079				
			1100.0	
Batch-072	Active Blends	Lactose Pre-blend	995.91	99.591
Batch-073				
Batch-076				
Batch-077				
Batch-078		API X	4.09	0.409
Batch-079				
			1000.0	**100.000**

Lactose pre-blending was carried out in a low shear Turbula blender, then combined with API using a 3L PMA blender. The lactose pre-blend is a method already in use for the manufacture of this product, its blend speed and time is already defined and so a parameter assessment for this step is not in scope of the experiment. A breakdown of the speed and time per batch for the lactose pre-blend is outlined in Table 6 and for the active blend in Table 7.

Table 6: Lactose Pre Blend Parameters

Batch No	Lactose Pre-Blend Speed (rpm)	Lactose Pre-Blend Time (min)
Batch-072	15	10
Batch-073		
Batch-076		
Batch-077		
Batch-078		
Batch-079		

Table 7: Active Blend Parameters

Batch No	Active Blending Speed (m/s)	Active Blending Speed (rpm)	Total Active Blending Time (min)
Batch-072	6	567	18
Batch-073	4	378	45
Batch-076	3	284	18
Batch-077	4	378	18
Batch-078	5	473	18
Batch-079	6	567	21

Meters per second (m/s) represents the linear tip speed of the mixing blade or impeller in a blender, it's a measure of how fast the edge of the blade moves through space (the vessel/blend bowl), not just how many times it rotates per minute. Observing different rpm over various speeds gives an indication of the energy needed from the blending process to obtain uniformity without the risk of over mixing the blend. API dispersion depends on mechanical energy, especially in low dose formulations.

Process steps – Small scale

Each of the six batches were prepared using the same method as follows:

1.1 kg Lactose Pre-Blends

Lactose pre-blends were prepared at a scale of 1.1kg. As per dispensing quantities outlined in the respective BMR, both grades of lactose were sieved and dispensed into 6 SS containers under a horseshoe extraction system. The 6 SS containers comprised of 5 x Lactose Y and 1 x Lactose Z. Contents of each SS container was added to the 3L blend bowl using a layering technique, first lot of Lactose Y, followed by Lactose Z and then the remaining 4 lots of Lactose Y with 3 of these lots used to rinse the Lactose Z container ensuing that all material was transferred to the 3L bowl. The Turbula blender was set with the speed and time values outlined in Table 6, parameters were confirmed, and the blending operation commenced.

1 kg Active Blends

The active blends were prepared at a scale of 1kg. As per BMR, the corresponding lactose pre-blend was dispensed into 5 SS containers under a horseshoe extraction system; the API was dispensed inside an isolator into 1 SS container. The lactose pre-blend and API were loaded into 3L PMA blending bowl using the layering technique. Lot 1 of lactose pre blend, followed by the API and then the remaining 4 lots of Lactose pre blend with 3 of these lots used to rinse the API container ensuing that all material was transferred to the 3L container. The PMA blender was set with the speed and time values outlined in Table 7 pertaining to each specific batch, parameters were confirmed, and the blending operation commenced.

Blend Sampling

Once blending was finished, the 3L blend container was connected to an earthing point for not less than (NLT) 12 hours to allow for any static build up to dissipate before sampling. As per site sampling procedure, 10 samples were taken for blend uniformity analysis using a manual sampling thief, image of thief shown in Figure 28, and placed into individual glass vials. Blend uniformity samples were taken from predefined locations within the blend to ensure that they were representative, they were taken samples 1-3 from top, 4-7 from middle and 8-10 from bottom as shown in Figure 29.

Figure 28: Sampling Thief for manual powder retrieval

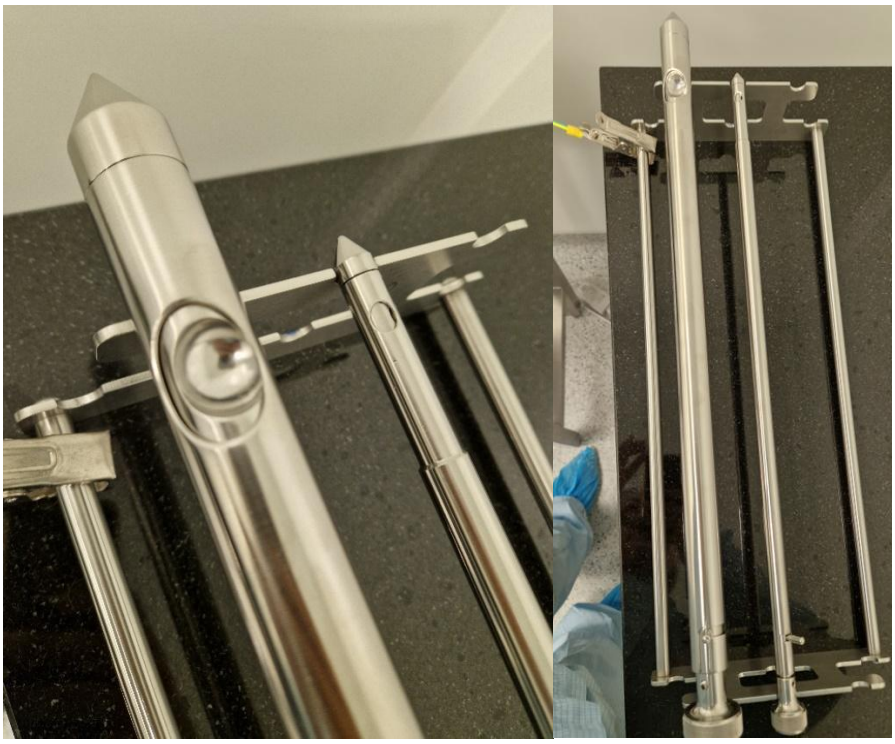
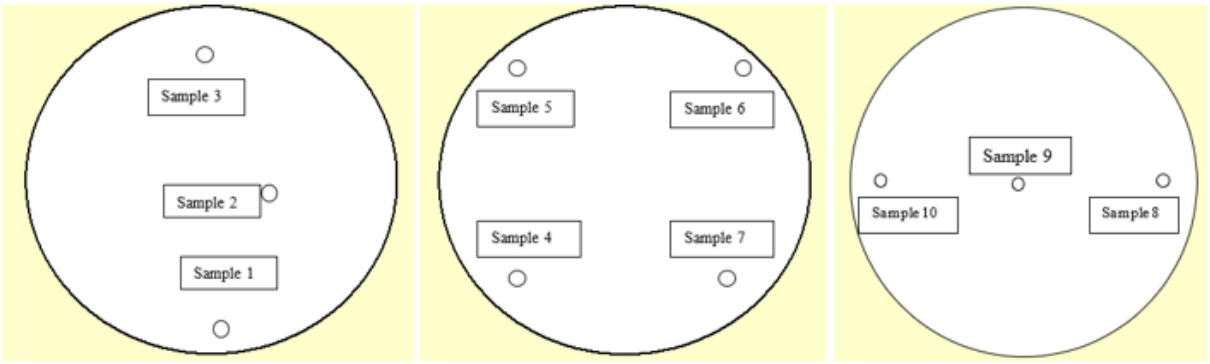


Figure 29: Sampling Locations within the container



Each sample once retrieved from the blend bowl was placed into a tared vial, weighed, and weight recorded. The vials were then sent to the laboratory for UPLC analysis.

Sample Preparation and Analysis

Following a site analytical method for this product, in an analytical laboratory, samples were prepared by adding 15 mL of diluent down the side of each vial and vortex for 20 seconds. The contents of each vial were transferred to an individual 100 mL amber volumetric flask using a funnel, each vial and cap was rinsed with the diluent and the rinsings transferred into the corresponding volumetric flask. This step was repeated until all samples were transferred into the volumetric flasks. The volumetric flasks were filled to 75 mL with diluent and samples were sonicated for 10 minutes. Once a check of the solution to confirm that it is clear, the samples were

allowed to cool to room temperature. The samples were diluted to volume with diluent and mixed thoroughly before vialing. The samples were analysed using UPLC.

Blend Uniformity Results

As per internal specification referenced Appendix 2, the acceptance criteria for Blend Uniformity - 10 blend samples should be within 90.0-110.0% of the target label claim. The %RSD of the 10 samples is equal or not more than (NMT) 5.0%. All individual results are within +/- 10.0% of the mean of the result. The results of the six batches is discussed further on in Chapter 4. Based on the blend uniformity performance across the initial six batches, Batch-079 was selected as the optimal candidate for the pilot scale batches.

Experimental design – Pilot scale manufacturing

Building on the selection of Batch-079 as the optimal candidate for scaling up, two identical batches were subsequently manufactured under the same blending parameters (6 m/s) 302 rpm for 21 minutes to evaluate the viability and reproducibility of the process at pilot scale. These batches were intended to confirm that the blending conditions established during laboratory development would consistently achieve acceptable uniformity at scale. To note, as previously explained, (m/s) represents the linear tip speed of the mixing blade in a blender, it's a measure of how fast the edge of the blade moves through the blend bowl, and so with a scale up the blender size is increased, in this case from a 3L to a 20L vessel, and so the rpm has increased for the pilot scale batches.

Lactose pre-blending at a scale of 7kg was carried out in a low shear Turbula blender, then combined with API using a 20L High shear PMA blender to give a final blend batch at a 6.6kg scale. An overview of the speed and time per batch for the scaled lactose pre-blend is outlined in Table 8 and for the scaled active blend in Table 9.

Table 8: Lactose Pre Blend Parameters

Batch No	Lactose Pre-Blend Speed (rpm)	Lactose Pre-Blend Time (min)
Batch-082	15	10
Batch-083		

Table 9: Active Blending Parameters

Batch No	Active Blending Speed (m/s)	Active Blending Speed (rpm)	Total Active Blending Time (min)
Batch-082	6	302	21
Batch-083	6	302	21

Process steps – Pilot scale

Each of the 2 batches were manufactured using the same method as follows:

Lactose Pre-Blends

Lactose pre-blends were produced at a scale of 7 kg. Both grades of lactose were sieved and dispensed into 6 SS containers under a horseshoe extraction system, 5 lots of Lactose Y and 1 lot of Lactose Z. The lactose was added to a 20L container using a layering technique, first lot of Lactose Y, followed by Lactose Z and then the remaining 4 lots of Lactose Y with 3 of these lots used to rinse the Lactose Z container ensuring that all material was transferred to the 20L container. The Turbula blender was set with the speed and time values outlined in Table 5, parameters were confirmed, and the blending operation commenced.

Active Blends

The active blend was produced at a scale of 6.6 kg. Lactose pre-blend was dispensed into 5 SS containers under a horseshoe extraction system; the API was dispensed inside an isolator into 1 SS container. The lactose pre-blend and API were loaded into 20L PMA blending bowl, which is contained system, passive valves are used to add each of the lots to the blend bowl. Using the layering technique, loading of first lot of lactose pre blend, followed by the API and then the remaining 4 lots of lactose pre blend with 3 of these lots used to rinse the API container ensuring that all material was transferred to the blending bowl. The PMA high shear blender was set with the speed and time values outlined in Table 9, parameters were confirmed, and the blending operation commenced. Once the blending operation finished, the blend was discharged into a 20L SS container and earthed for NLT 12hrs before sampling.

Blend Sampling

Blend sampling of the scaled up batch was carried out with adherence to the same steps as the small scale blend, with the same sampling locations to ensure representative samples, according to BMR and standard operating procedures (SOP).

Sample Preparation and Analysis

Sample preparation and analysis was carried out with adherence to the same analytical method that was followed for the small scale blend according to site procedures.

Data Analysis

PSD output for Lactose Y (D10, D50, D90, %<5 µm) from triplicate sample sets were summarised using descriptive statistical analysis. SEM images for all three materials used in the study were reviewed qualitatively to categorise particle shape, surface roughness, and agglomeration tendencies and their impact on performance.

Blend uniformity results for all eight batches (n=10 sampling locations per batch) were analysed for minimum, maximum, mean content, and %RSD relative to the 100 % label claim using a multi statistical approach. The results generated from testing was imported into JMP® software for statistical processing.

The following chapter presents the results derived from the material characterisation and manufacturing experiments. This includes a comprehensive analysis of the data obtained, with a focus on interpreting trends, evaluating outcomes, and assessing the implications in relation to blend uniformity.

Ethical considerations

Ethical considerations in research involving experiments and quantitative data analysis of intermediate and finished products emphasize objectivity, reproducibility, and transparency. As positivism is grounded in empirical evidence and measurable data, there is an ethical obligation to ensure that raw data and collection methods are systematic, unbiased, and replicable.

In this study, the integrity of the data was maintained by strictly adhering to site standardised testing methods, protocols, and procedures, thereby minimising any potential for subjective interpretation. Ethical practice also requires the accurate reporting of all findings, including results that may contradict hypotheses or indicate failure. To uphold validity, the reporting of data must avoid manipulation or selective presentation.

Additionally, data confidentiality and proper attribution of sources were upheld, particularly given the proprietary nature of the information related to the intermediate and finished products under development. Signed ethics form can be found in Appendix 1.

Chapter 4 - Findings and Analysis

Introduction

This chapter presents the findings of material characterisation and manufacturing campaigns obtained through the primary experimental investigation into blend uniformity variability, targeting the unit dose weight for a low dose DPI. Adopting a positivist research philosophy, supported by a well structured quantitative strategy, the study aimed to evaluate how specific material characteristics and manufacturing process parameters influence the consistency and homogeneity of powder blends.

To establish a robust framework for this analysis, the findings laid out in this section integrates data from two complementary research streams. First, secondary research findings were explored through a critical literature review of academic, investigative and regulatory sources. Such studies by (Alyami *et al.*, 2017), (Jamie E. Spahn *et al.*, 2022) and (Vikas Anand Saharan *et al.*, 2008) laid the theoretical groundwork, highlighting the significance of particle size distribution, surface morphology, and blending dynamics to be considered in achieving uniformity. These insights aligned with the design of the experimental methodology and guided the interpretation of primary results outlined in this chapter.

The primary research was conducted through systematic experimental trials comprising two stages: material characterisation and a manufacturing campaign, which included the execution of small scale and pilot scale manufacture of eight blends in total. Characterisation focused on particle size distribution (PSD), surface morphology, and flowability of excipients and API, while the manufacturing stage involved the production of powder blends in two different controlled blending environments assessing various processing parameters at small and pilot scale.

By aligning empirical findings with theoretical insights, this chapter aims to discuss cause-and-effect relationships, identify sources of variability, and interpret the findings. The analysis not only addresses the original research questions but also expands upon gaps identified in the literature reviewed and makes suggestions for future studies to expand and include other variables that can also influence blend uniformity.

Material Characterisation

Particle Size Distribution – Findings

The aim was to characterise Lactose Y which is a coarse bulk excipient, equating to over 95% of the formulation. By obtaining the D10, D50, and D90 values, this helps determine the proportion of fines, the median particle size, and the presence of coarse particles, respectively, as these parameters directly impact adhesion dynamics, surface area exposure, powder flowability, and the energy needed for deagglomeration during blending operations.

As per (European Pharmacopoeia, 2016), PSD was evaluated via laser diffraction using a Sympatec HELOS system. Descriptive statistics were used to evaluate the degree of polydispersity for comparison and suitability against DPI formulation benchmarks and expressed as mean, standard deviation and %RSD across three replicate samples.

Although formal PSD specifications for this product have not yet been established due to the early stage of development, the testing was conducted to assess the bulk lactose characteristics as stated above, with one key value of particular interest, the %<5 µm which directly impacts formulation performance given the low dose API. Based on the PSD results achieved for lactose Y outlined in Table 10, the finer grade lactose Z is supplemented into the formulation for manufacturing in order to achieve a total fines content of 12.5% within the blend, which was identified as the optimal level of fines for the formulation based on prior development studies.

With a known %<5 µm value for Lactose Y, the calculation used to determine the quantity of Lactose Z for the formulation is shown below:

Lactose-Z (w/w%) = (Target Lactose pre blend fines - %<5 µm in Lactose-Y) / (100 - %<5 µm in Lactose-Y)

The PSD results for the three samples from Batch 12345 of Lactose Y analysed are shown in Table 10 below. The graphs showing the curved distribution for the three batches of Lactose Y analysed can be found in Appendix 3

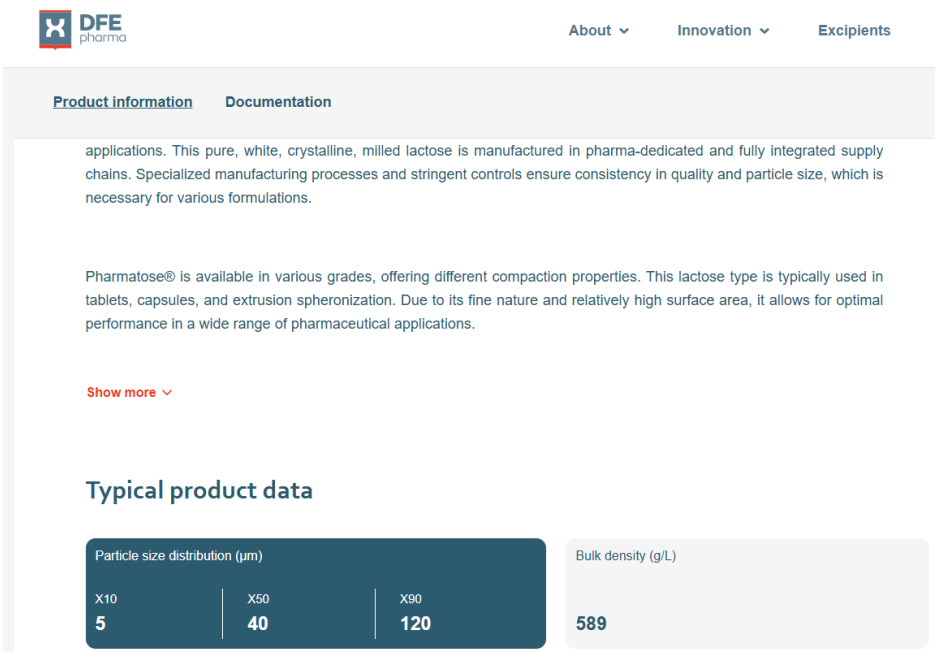
Table 10: PSD results for Lactose Y, Batch 12345

Lactose Y, Batch 12345 – Bulk excipient PSD results						
Sample	D10	D50	D90	%<5	%<10	%<30
1	4.79	37.61	111.2	10.41	18.83	42.65
2	4.8	37.62	111.43	10.38	18.82	42.65
3	4.78	37.57	110.7	10.41	18.82	42.67
Average	4.79	37.60	111.11	10.40	18.82	42.66
Standard deviation	0.01	0.03	0.37	0.02	0.01	0.01
%RSD	0.21	0.07	0.34	0.17	0.03	0.03

Analysis of PSD results

The PSD results show low variability across the three samples with %RSD. The median particle size (D50) of 37.60 µm, paired with a controlled coarse fraction (D90 = 111.11 µm), indicates an ideal profile for bulk carrier performance in DPI blending, with the values approximately aligned with those provided by the supplier for this specific lactose grade, see Figure 30: Product information for PSD values from DFE Pharma Figure 30 for vendors product information (DFE, 2025).

Figure 30: Product information for PSD values from DFE Pharma



(DFE, 2025)

The measured fine particle content %<5µm was approximately 10.40%. This level provides an adequate surface area to facilitate effective API adhesion. By supplementing with lactose Z to increase the total fines content to 12.5%, it will allow the formulation to maintain balance between excessive cohesion or electrostatic interactions, leading to improved uniformity.

As noted above, given the absence of a defined PSD specification for Lactose Y for this product, comparative data from two previously characterized batches used in other manufacturing campaigns not related to this study have been provided in Table 11: Example 1 - PSD results (Previously characterised batch of Lactose Y)Table 11 and Table 12 below to show batch to batch consistency, giving confidence in the reliability of the material.

Table 11: Example 1 - PSD results (Previously characterised batch of Lactose Y)

Sample	D10	D50	D90	%<5	%<10	%<30
1	4.7	39.28	114.06	10.56	18.75	41.42
2	4.72	39.47	114.78	10.52	18.62	41.23
3	4.66	38.92	113.05	10.65	18.89	41.7
Average	4.69	39.22	113.96	10.58	18.75	41.45
Standard deviation	0.03	0.28	0.87	0.07	0.14	0.24
%RSD	0.65	0.71	0.76	0.63	0.72	0.57

Table 12: Example 2 - PSD results (Previously characterised batch of Lactose Y)

Sample	D10	D50	D90	%<5	%<10	%<30
1	4.87	40.43	113.64	10.23	18.02	40.26
2	4.88	40.55	115.49	10.21	17.99	40.19
3	4.94	41.06	116.65	10.11	17.8	39.81
Average	4.90	40.68	115.26	10.18	17.94	40.09
Standard deviation	0.04	0.33	1.52	0.06	0.12	0.24
%RSD	0.77	0.82	1.32	0.63	0.67	0.60

PSD plays a pivotal role in blend reproducibility, particularly in such a low dose product where the quantity of API is extremely small (<0.5% w/w). The tight distribution of Lactose Y gives

confidence over precise dispersion, predictable sampling behaviour, and robust process scalability.

In short, there is no universal acceptance criteria for PSD analysis across all pharmaceutical excipients. Instead, PSD specifications are guided by the manufacturer's product documentation and technical datasheets such as those provided by (DFE, 2025) which outline typical D-values and expected performance profiles for grades like Lactose Y. These specifications are reviewed and considered during material selection to ensure compatibility with the intended dosage form and processing requirements.

From a regulatory perspective, agencies such as the EMA (European Medicines Agency, 2024) emphasize that PSD control should be driven by the CQAs of the drug product. According to (Nashwa El-Gendy *et al.*, 2022), Lactose PSD acceptance criteria should be established based on actual PSD data generated from several micronised lactose lots, including lots used in manufacturing. PSD acceptance criteria must be validated within the context of the formulation, supported by performance based data such as blend uniformity. Values such as D10, D50, and D90 should not only fall within manufacturing tolerance but also demonstrate consistent contribution to reproducibility and scalability across batches.

Therefore, while no generic threshold exists, PSD acceptance criteria as outlined in guidance is product specific and functionally justified, linking material characterisation directly to the successful performance of the product in development.

Surface Morphology – Findings

As per regulatory guidance such as (Food and Drug Administration, 2018) there is no mandate for surface morphology testing outright on materials but it does emphasize the importance of physicochemical properties including particle shape and surface texture when they influence performance, especially flowability, adhesion and API/excipient interactions. For this reason, surface morphology testing is essential for the development of inhalation products to provide critical information on the materials used in the formulation.

The aim of the characterisation work was to further understand and evaluate surface properties, particle size and shape and adhesion potential of the API and lactose materials to determine their impact on uniformity.

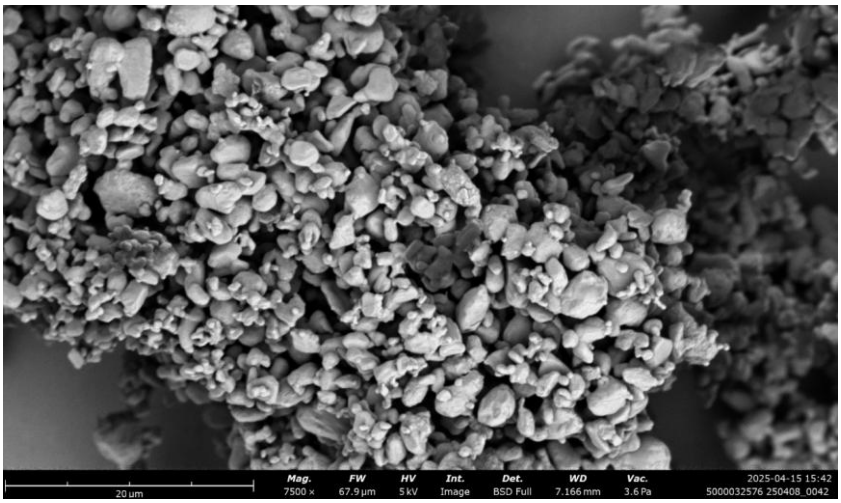
Analysis was conducted by SEM, an imaging technology that allows a microscopic view of the materials, this section presents the images taken of API X, Lactose Y and Lactose Z and also images taken of one of the final blends manufactured as part of the campaign (Batch-082) to give a visual insight into the binding of the API and finer lactose particles to the bulk lactose.

Morphology results

API-X

The SEM images revealed plate-like particles with high surface area and irregular morphology, typical of this micronised API. These structural traits promote adhesive interactions with carrier particles but also increase the tendency for agglomeration and electrostatic charge build-up within the powder, which may prove tricky in the low humidity environment where the blending is processed. This could compromise flowability and dispersion if not adequately controlled by antistatic measures. SEM images for of the API lot used in the manufacturing campaign is shown in Figure 31 at x7500 magnification. Additional SEM mages for API X can be found in Appendix 4 – Material Characterisation Images.

Figure 31: API X at x7500 magnification

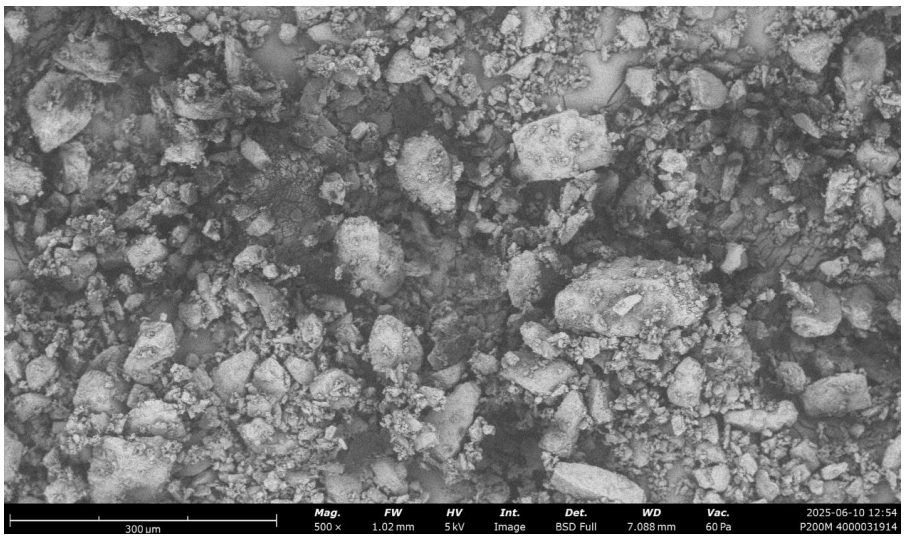


This API undergoes a micronisation process, an engineering technique that reduces the size of the particles, you can see that there are oddly shaped particles with textured surfaces, with some smooth and others indented. Anything atypical that might show in an SEM image that can affect binding to lactose carrier can be investigated before the material is used which is why morphology even though it is not compulsory, it is very necessary.

Lactose Y

Lactose Y showed rounded, smoother particles with minimal irregularity, these are traits associated with improved powder flow and bulk handling. The flowability of lactose Y supports uniform distribution of the active across the blend. Its coarse structure of this bulk material provides a stable platform for fine API during blending and sampling. SEM images of Lactose Y used in the manufacturing campaign is shown in Figure 32at x5000 magnification. Additional images and magnifications can be found in Appendix 4 – Material Characterisation Images

Figure 32: Lactose Y at x500 magnification



Lactose Z

Conversely, you can see a distinctly different shape to lactose Y. The images taken for lactose Z exhibited fragmented, angular particles with high surface roughness. This creates increased contact points for API adhesion which supports good binding and efficiency in this carrier based formulation with such low dose loading. However, the irregular structure and much finer particle size reduce flowability due to surface energy allowing for greater cohesive forces. As a result, Lactose Z could reduce overall powder flow, but prevention is achievable by controlling the % fines target in the formulation, which is controlled by PSD analysis of the bulk lactose as previously discussed, giving the ability to control any negative impact to blend uniformity, albeit taking a lot of development work to get to an optimum formulation.

Lactose Z is shown in Figure 33 at x3000 magnification and Figure 34 at x7500 magnification. The two images give a visual of how different this lactose grade is to lactose Y, it is evident that it is much finer, with many microscopic particles. These particles promote excellent adhesion of the API to the bulk lactose, allowing for good uniformity in the blend.

Figure 33: Lactose Z at x3000 magnification

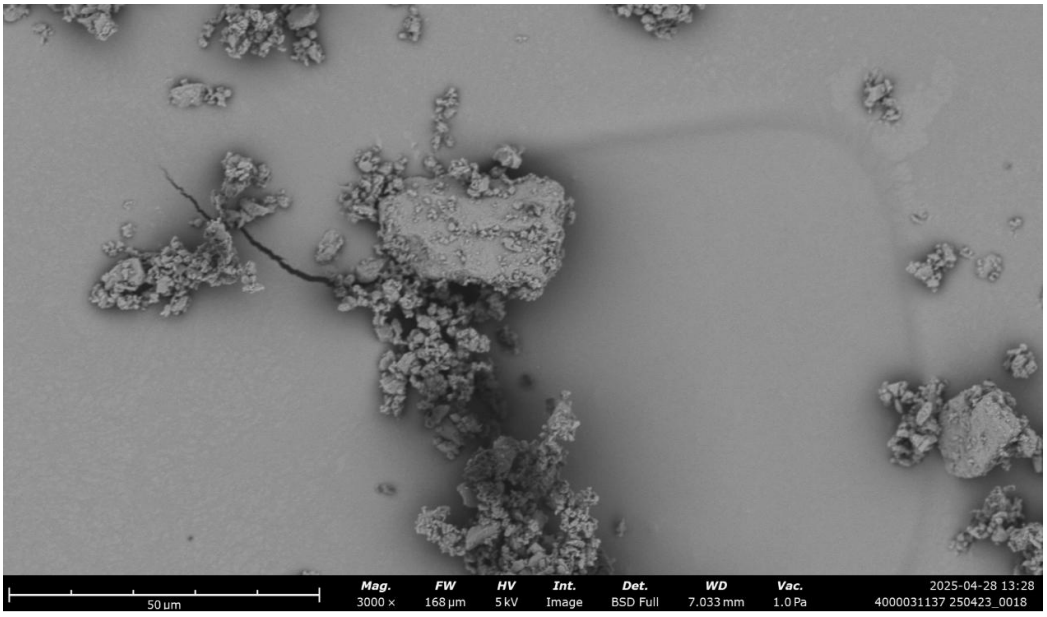
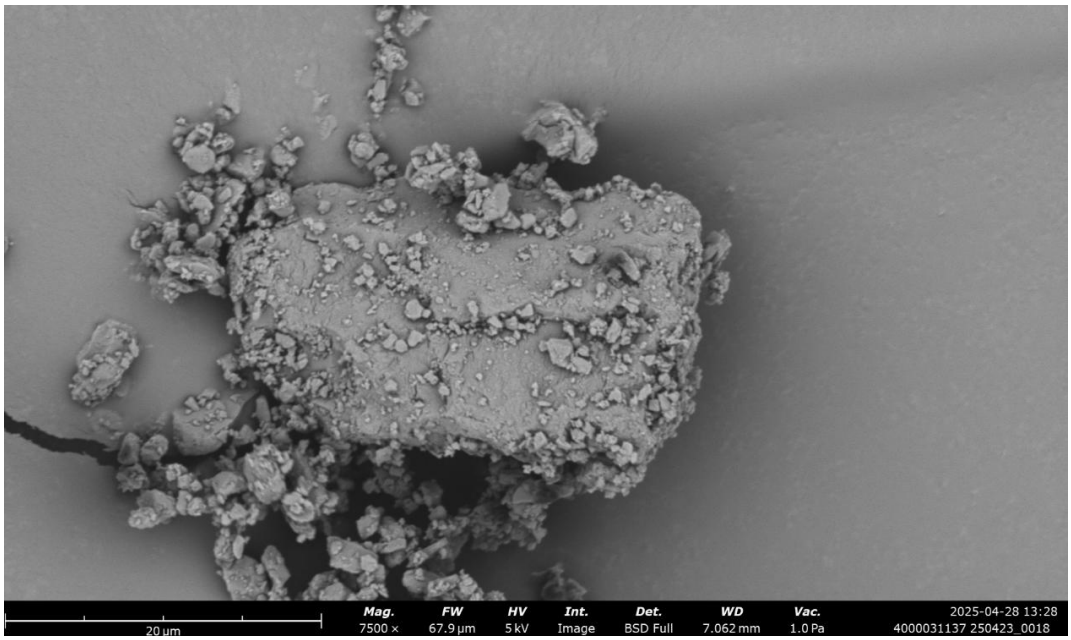


Figure 34: Lactose Z at x7500 magnification



Analysis of SEM results

The flow properties and morphological features observed in the SEM images produced for each material play complementary roles in ensuring uniformity, such as:

- **API X** showing its typical structure, being highly cohesive with poor flowability, relies on coordinated ordered mixing and a bulk carrier with a controlled fines lactose quantity for good binding support, coupled with a robust blending process for reproducible and even dispersion.
- **Lactose Y** stabilises the blend through its flow properties and supports blend uniformity, dosing and sampling. Notable from the images presented, this bulk material should provide a stable platform for fine lactose and micronised API attachment.
- **Lactose Z** exhibits much finer particles compared its counterpart lactose used in the formulation. While this will enhance adhesion, the quantities must be balanced carefully to avoid blend segregation or clumping, achievable by controlling the fines % in the blend.

In summary and with the aid of the final SEM images for this part of the study, when the materials were combined, their coordinated and controlled functionality was reflected in the positive blend uniformity outcomes observed in the manufacturing campaign, further supporting the data and the literature that sufficient mechanical energy is needed for optimum particle adhesion. To visualise what that looks like, SEM images were analysed for the final blend using Batch-082 as an example is shown in Figure 35 at x1000 magnification and Figure 36 at x2000 magnification. These images show particle adherence, without agglomeration or clustering, which suggests an even dispersion of particles.

Figure 35: Batch-082 x1000 magnification

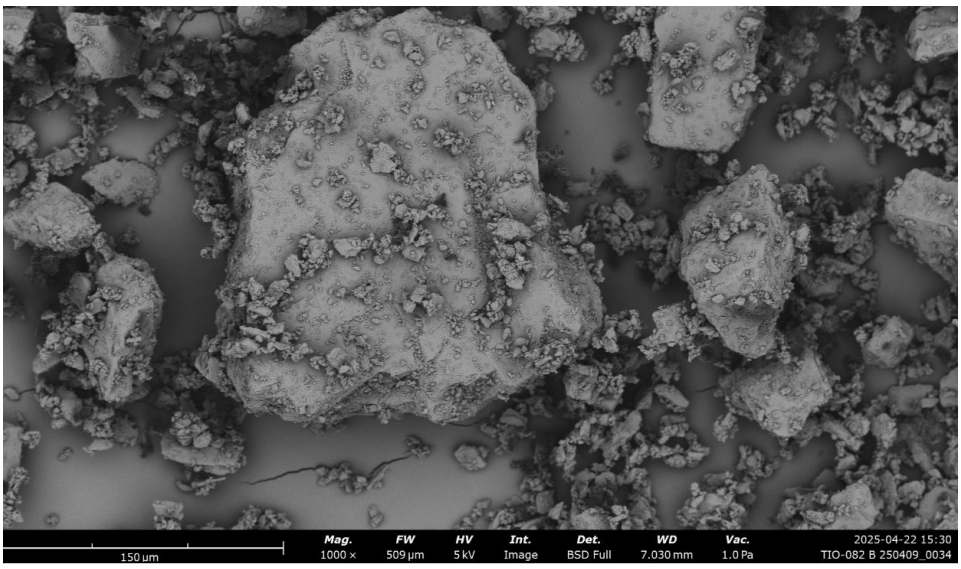
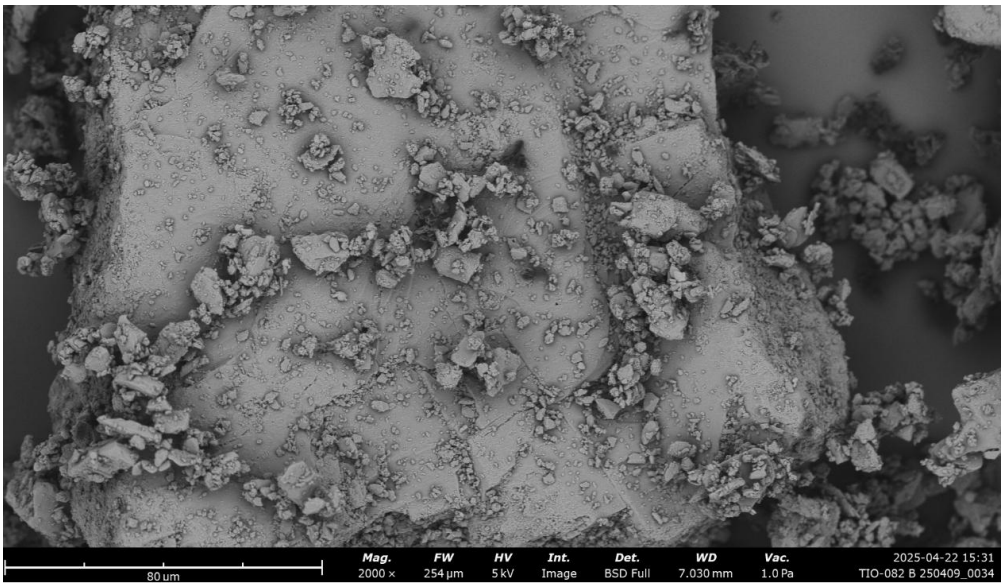


Figure 36: Batch-082 x2000 magnification



Manufacturing

Blend uniformity results - Small Scale Manufacture

The objective of this study was to minimise variability in the final blend samples through process optimisation. This was done by manufacturing a series of batches which included six small scale batches, each manufactured at a 1 kg scale using a Turbula low shear blending process. The study varied active blend parameters, specifically rotational speed and blending duration to assess their influence on uniformity and variability in the blend.

Each batch was sampled and tested according to site analytical procedures, with blend uniformity measured across ten samples taken from representative locations in each blend container, an approximate weight between 5 mg – 10 mg was targeted (5.5 mg being the unit dose for the product) using a SS thief.

Results are reported in terms of minimum and maximum API content, mean %BU label claim, and relative standard deviation (%RSD). Acceptance criteria required all individual samples to fall within 90.0–110.0% of target, with an RSD ≤ 5.0%. Results for each of the batches are listed below in Table 13.

Table 13: Blend Uniformity results - Small scale blends

Batch	Parameters	Min	Max	Mean %BU LC	%RSD	Pass/Fail
Batch-072	567 rpm/18 min	97.9	108.5	103.1	3.1	Pass
Batch-073	378 rpm/45 min	104.3	110.0	107.5	1.6	Pass
Batch-076	284 rpm/18 min	92.1	116.7	105.5	7.5	Fail
Batch-077	378 rpm/18 min	96.4	111.8	101.4	4.9	Fail
Batch-078	473 rpm/18 min	99.9	110.3	103.3	3.2	Fail
Batch-079	567 rpm/21 min	99.9	104.2	102.2	1.5	Pass

Blend uniformity results - Pilot Scale Manufacture

Following the successful outcome of at least one small scale batch, a second objective was to assess the reproducibility of the optimised process when scaled up, thereby determining its robustness under pilot scale manufacturing conditions.

Batch-079 which was processed at 567 rpm (6 m/s) for 21 minutes was selected as the optimal candidate for the scale up batch. Batch-079 demonstrated the lowest RSD of 1.5%, indicating low variation in the blend, with a tightly controlled range (99.9–104.2%) and a mean content of 102.2%, which gives confidence and comfortably falls within regulatory acceptance limits.

There were two identical blends manufactured at a scale of 6.6kg under the same controlled conditions with the same material lots, with the exception of the blending technique, the two scale up batches were blended using a high shear blending process. Maintaining the same tip speed across scales ensures similar mechanical energy input, so to directly compare processes the same energy was used, 6 m/s which translates from 567rpm in a 3L blender to 302rpm in a 20L blender, adjusting for vessel size.

The results are reported in Table 14 below applying the same acceptance criteria, across the same parameter values allowing for direct comparison, in terms of minimum and maximum API content (% label claim), mean percentage, and %RSD.

Table 14: Blend Uniformity results - Pilot scale blends

Batch	Parameters	Min	Max	Mean	%RSD	Pass/Fail
Batch-082	302 rpm/21 min	99.4	110.0	103.0	3.0	Pass
Batch-083	302 rpm/21 min	98.8	108.0	103.2	2.8	Pass

Findings from Manufacturing Campaigns

Small scale batches

A summary of these initial findings and an interpretation of the results for each of the batches is provided in Table 15.

Table 15: Interpretation of findings from small scale manufacture

Batch	Parameters	%RSD	Interpretation of results	Result
Batch-072	567 rpm / 18 min	3.1	Highest speed over the shortest time variable, achieved acceptable uniformity; all values within 90–110% but trending on the high side for max value. %RSD is below 5%.	Pass
Batch-073	378 rpm / 45 min	1.6	Longest blend time at moderate speed resulted in exceptional uniformity in terms of %RSD showing low variability and all samples met criteria. Although is on the upper level of the specification for max % LC	Pass
Batch-076	284 rpm / 18 min	7.5	Lowest speed and shortest duration, suggesting poor dispersion, the %RSD is far above acceptance limit at 7.5% and sample range exceeded 90–110%, showing the most variable of all batches	Fail
Batch-077	378 rpm / 18 min	4.9	Although %RSD was just within the acceptable limit this result would be unsatisfactory, max value exceeded 110.0%, failing this batch. The blending time in this instance was most likely insufficient as the same rpm was used for Batch-073 for a longer time which yielded in spec results, clearly demonstrating the impact of time here	Fail
Batch-078	473 rpm / 18 min	3.2	Moderate speed combined with a short blend time gave an acceptable %RSD, but batch failed on the max value exceeding 110.0%, indicating uneven blending as per the acceptance criteria despite adequate variability.	Fail
Batch-079	567 rpm / 21 min	1.5	Results show an optimal combination of high speed and a slightly extended time from the other batched, led to excellent blend uniformity and full compliance with acceptance criteria. This batch yields the best results of all six batches	Pass

Pilot scale batches

The findings for the two batches manufactured at scale using the same material inputs and processing parameters as Batch-079 are presented below. Variability, expressed as %RSD, was evaluated in response to speed and time as part of the scale-up study. An interpretation of the results from the pilot scale batches is outlined in Table 16.

Table 16: Interpretation of findings from Pilot scale manufacture

Batch	Parameters	%RSD	Interpretation of results	Result
Batch-082	302 rpm / 21 min	3.0	Considering that the rpm was calculated based on the increase in size of the vessel from 3L to 20L the same mechanical energy was employed for this batch. The max is on the upper acceptance limit and just within specification, with a tight %RSD giving in acceptable results	Pass
Batch-083	302 rpm / 21 min	2.8	This batch was made as an exact replica of Batch-082. Also trending on the high end for max value but a touch lower, variability is also slightly better at 2.8 %RSD, batch is also within the acceptance criteria	Pass

Discussion

Insufficient mechanical energy input, as seen in Batch-076 (284 rpm for 18 minutes), led to unacceptable variability (%RSD = 7.5%), highlighting the importance of both blending speed and time in achieving uniform API dispersion. By contrast, extended blending time at a moderate speed used for Batch-073 (45 min at 378 rpm) compensated effectively, also achieving a low %RSD (1.6%).

Evidently the impact of blend time on %RSD is the comparison of Batch-073 and Batch-077 where it was shown that blended for an additional 27 mins at the same rpm gave a significant reduction of 3.3% in variability, bringing an almost out of specification batch well under the acceptable limits. Although Batch-073 resulted in an excellent %RSD, all the results trended high, with the maximum on the upper limit.

Batch-079 was selected for scale up due to the shorter blend time taken to achieve the lowest %RSD, though there was additional energy expended, the shorter blending time would be more favourable from a business point of view, inevitably contributing to a more efficient streamlined manufacturing process in terms of lead times and ultimately, a reduction in cost.

The results for all six batches trended on the high side, with three batches falling out of specification and a fourth at the upper limit. Notably, the two batches with the highest rpm had the lowest maximum values, indicating that increased energy input corresponded with lower %RSD values.

Possible reasons for high trending results could be due to the following:

- Manual sampling of the blend, can disturb the powder bed and lead to sampling variability
- Loss of lactose due to manufacturing process losses, this will give higher concentrations of API in the blend
- Segregation during transfer, where finer or denser API particles may concentrate unevenly in the blend

Even though the results are trending on the upper end of the specification, these initial results reinforce that mechanical energy, expressed as tip speed (rpm) and blending time (min), are critical process parameters for driving down variability in the blend.

While the results for both scaled up batches remained within specification, an increase in variability was observed at scale. The %RSD values rose from 1.5% in Batch-079 to approximately 3% in the scaled up batches. Notably, Batch-082 recorded a maximum value of 110.0%, which is at the upper end of the specification but still within the acceptable limits.

This trend may indicate changes introduced by scaling factors, potentially affecting powder flow and mass movement efficiency. Contributing factors could include:

- Increased powder bed depth, which may lead to uneven settling, increased blend compaction, or electrostatic effects.
- Variations in blender geometry, despite adjustments made to account for volume and rpm during scale up.
- Presence of dead zones within the larger vessel, potentially reducing blending efficiency
- Differences in fill level-to-blender volume ratio, which may impact mixing dynamics
- Changes in material handling and transfer methods, possibly introducing segregation or loss of finer excipients with the use of valves to transfer materials to the blender

Statistical Analysis of results

The objective of this statistical analysis is to evaluate the impact of speed and mixing time both independently and in combination on % BU label claim and associated %RSD values. This analysis was conducted to better understand how these critical process parameters influence uniformity and variability, particularly in the context of scale up manufacture and process optimisation.

Box-and-whisker plots were used to visually compare the performance of the six small scale blends, as shown in Figure 37. A side-by-side comparison of the optimal small scale blend (Batch-079) with the two scaled up high shear blends (Batch-082 and Batch-083) is also presented in Figure 38. Additional visual data representations are available in Appendix 6 – Additional Graphs.

In the plots below, the Y-axis represents the % Label Claim for BU results, while the X-axis lists the individual batch numbers. The mean and CV (coefficient variable) which represents %RSD for each batch is annotated at the top of the graphs, allowing a direct visual assessment of central tendency and variability for each of the batches.

Figure 37: Box and whisker plot - Comparison of small-scale batches

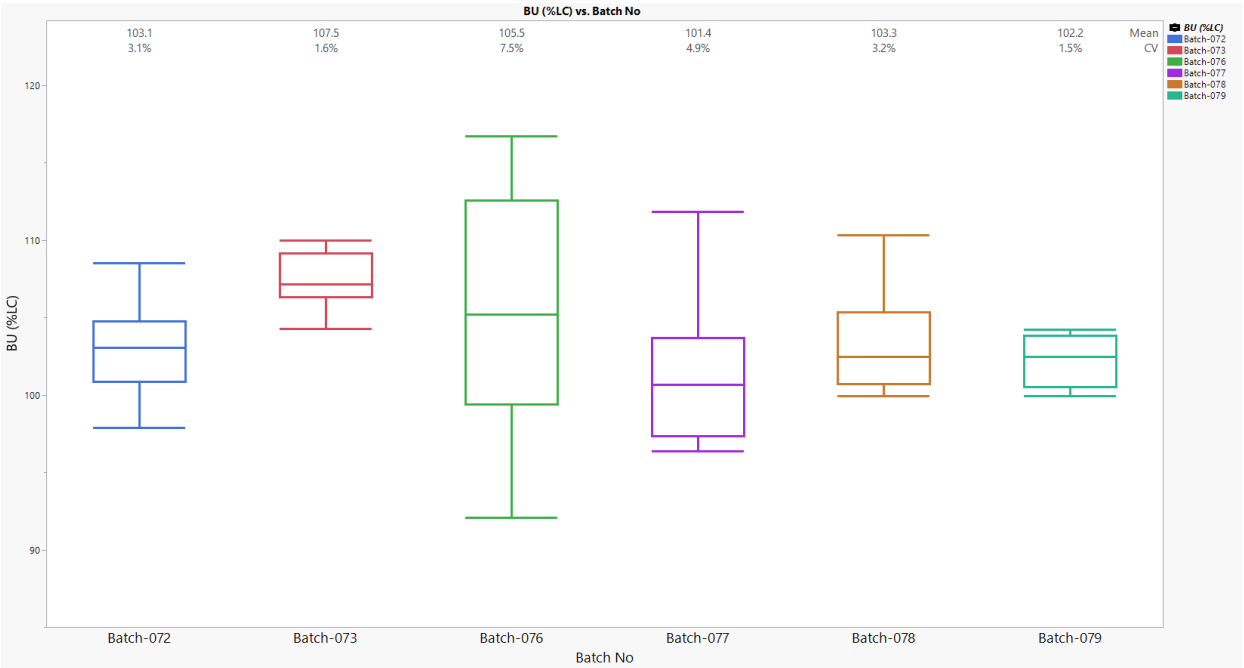
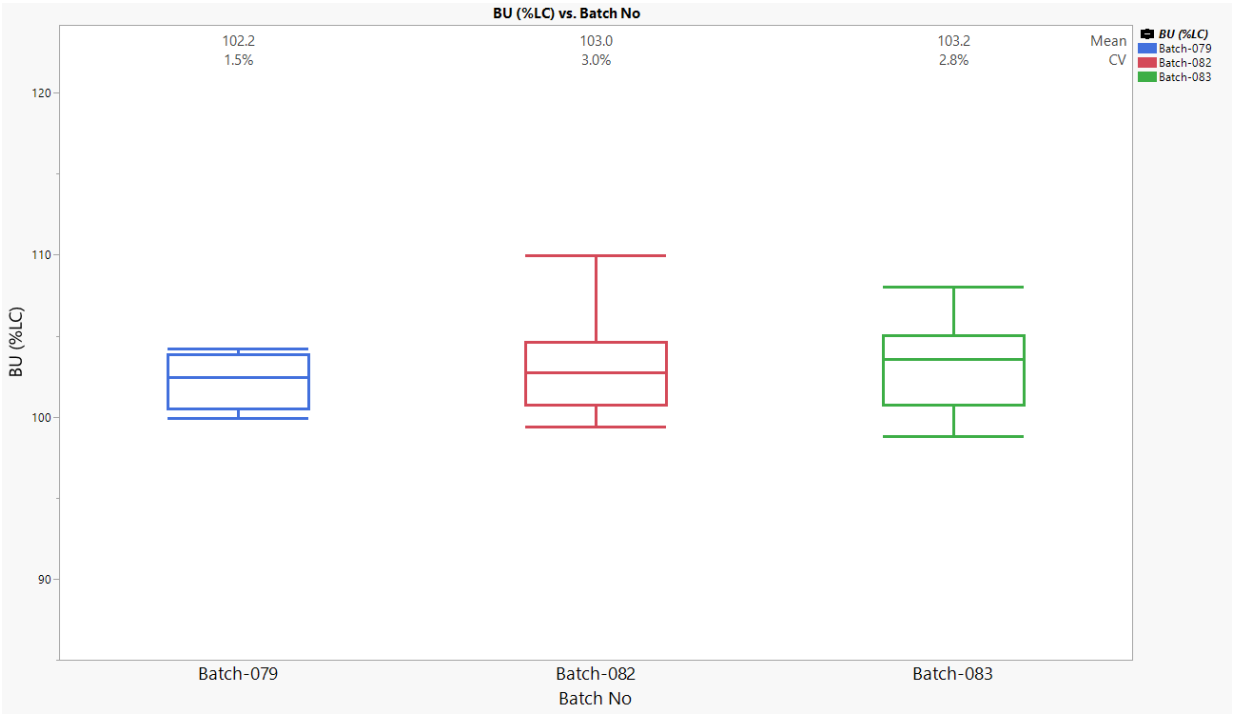


Figure 38: Box and whisker plot - Comparison of Batch-079 to Batch-082 and Batch-083



Significance of results from the manufacturing study

Impact of blend speed and time on BU results (%LC)

To assess the influence of blend speed (rpm), blend time (min) on % LC BU, A two-way ANOVA was performed using a factorial design in JMP® statistical software. The analysis was aimed at determining whether these variables have a statistically significant impact on the outcome.

Figure 39 presents leverage plots used to visualize the effects. These plots display a fitted regression line and confidence intervals shown in blue and red, respectively. The shaded areas represent 95% confidence bands around the fit.

The plots indicate minimal slope and wide confidence intervals, especially for blend time and the interaction term, suggesting weak or no correlation. This visual trend is consistent with the associated p-values as outlined in Table 17, which are well above the 0.05 threshold, confirming that none of the factors had a statistically significant effect on %LC BU.

These results support the conclusion that blend speed, time, and their interaction do not meaningfully influence blend uniformity within the operating range explored in this study.

Figure 39: Leverage plots - Effect of blend speed, time, and interactions on BU (%LC)

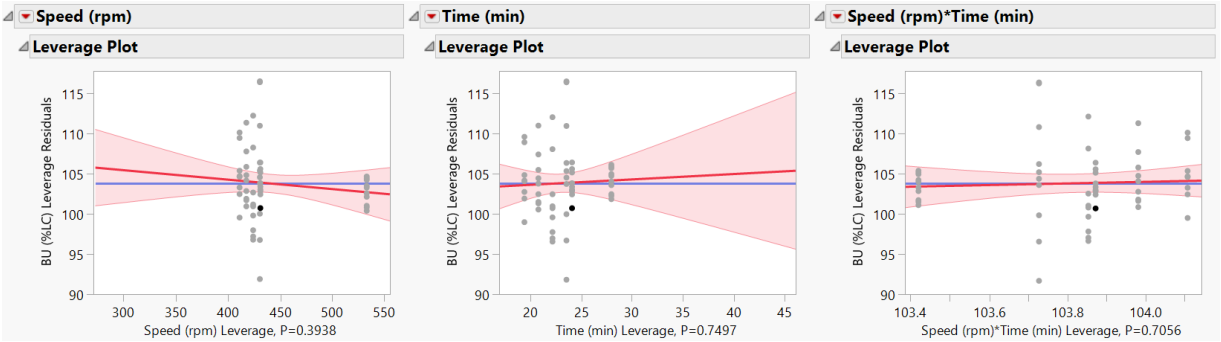


Table 17: Statistical Analysis of the effects of blend speed, time, and their interaction on Blend Uniformity (%LC)

Factor	Response	p-Value	Interpretation
Blend Speed (rpm)	BU %LC	0.3938	Not statistically significant
Blend Time (min)	BU %LC	0.7497	Not statistically significant
Speed × Time Interaction	BU %LC	0.7056	Not statistically significant

Summary

In statistical hypothesis testing, a p-value (probability value) helps determine whether an observed effect or difference is likely due to random chance or reflects a real underlying effect, a p-value less than 0.05 typically indicates a statistically significant effect on the response variable, in this case %LC BU. Since all three p-values are above 0.05, it can be concluded that:

- Neither blend speed nor blend time individually affects %LC BU in a statistically meaningful way.
- There is no significant interaction, meaning the combination of the two variables does not produce a joint effect either. The variation in the results is likely not driven by blend speed or time.
- Other factors might be influencing the variability such as material properties, order of material addition to the blend bowl or the sampling method.
- It could also suggest that the process is already optimised, and possibly not centered within the target range but is instead skewed towards the higher end, evident in the results from the blend analysis.

Impact of Blend speed and time on %RSD

Following the evaluation of blend speed and time on % LC BU, a second statistical analysis using the same factorial design was conducted to investigate their effect on %RSD. While %LC BU provides insight into the average potency of the blend, %RSD is a critical indicator of variability and consistency across the individual samples.

This analysis aimed to determine whether variations in blending speed, blending time, or their interaction contribute significantly to the observed %RSD values, and whether these parameters influence the reproducibility of blend performance. The results of this analysis, including p-values and interpretation, are presented in Figure 40and Table 18below.

Figure 40: Leverage plots - Effect of blend speed, time, and their interaction on %RSD

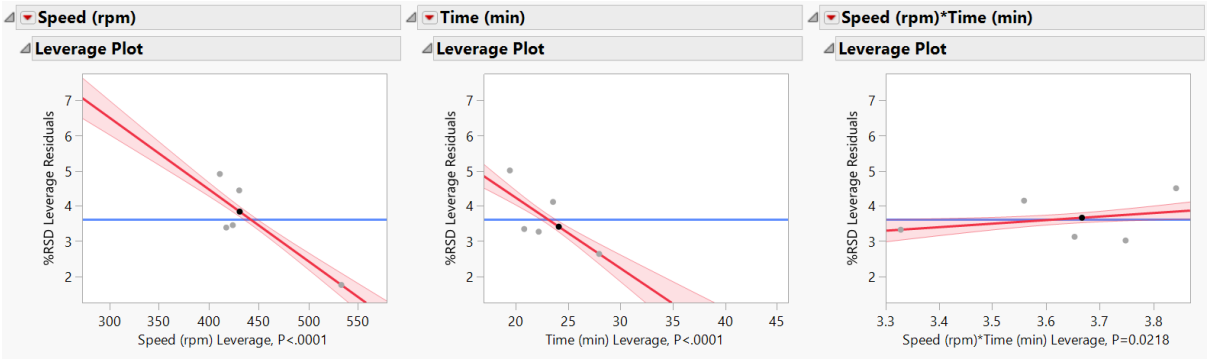


Table 18: Statistical Analysis of the effects of blend speed, time, interaction on %RSD

Factor	Response	p-Value	Interpretation
Blend Speed (rpm)	%RSD	< 0.0001	Highly statistically significant
Blend Time (min)	%RSD	< 0.0001	Highly statistically significant
Speed × Time Interaction	%RSD	0.0218	Statistically significant

Summary

In contrast to the findings for %LC BU, where blend speed and time showed no statistically significant impact, the analysis of %RSD reveals a different outcome. All three p-values obtained from the leverage plots in Figure 39 are below 0.05, indicating that blend speed, blend time, and their interaction have a statistically significant effect on blend variability. This suggests that, unlike the average label claim, blend uniformity, %RSD is highly sensitive to these process parameters.

Since all three p-values for leverage plots are below 0.05, it can be concluded that:

- Both blend speed and blend time have a strong influence on %RSD
- The interaction effect is also significant, indicating that the impact of one factor depends on the level of the other.
- Speed and time aren't just influencing %RSD independently, they're synergistic.
- The optimisation of the blending process in terms of adjusting speed and time isn't straightforward, further studies will be necessary to achieve right combination of speed and time, rather than tweaking one in isolation.

Summary of Material Properties and Manufacturing Outcomes

This study provided a comprehensive evaluation of the impact of both material characteristics and process parameters on blend uniformity for a low dose DPI formulation. The analysis combined results from detailed material characterisations, including PSD analysis and surface morphology with a robust manufacturing campaign and statistical evaluation of the key process variables.

The PSD analysis confirmed that Lactose Y, the bulk excipient, exhibited a controlled particle distribution with minimal batch to batch variability, supported by additional data provided to allow for comparison of performance across different batches. The fine particle content (%<5 µm) of 10.4% was consistent across samples and aligned with supplier data, providing a stable foundation for controlled API adhesion when supplemented with Lactose Z, the finer grade lactose, to target a specific % of fines in the blend, critical for enhancing adhesion in such a low dose formulation.

SEM analysis supported these findings by visually confirming the distinct morphological features of each component. The micronised API displayed typical plate shaped, cohesive particles prone to agglomeration, while Lactose Y offered smooth, rounded structures for stable blending. Lactose Z presented rougher, angular particles, ideal for adhesion albeit controlled, so that flowability of the blend was not negatively impacted. SEM images of the final blend (Batch-082) showed effective particle adhesion without agglomeration, indicating successful integration of materials and process.

From a manufacturing perspective, mechanical energy input defined by blend speed and time was found to be a critical determinant of %RSD, with statistical analysis (two-way ANOVA) confirming significant effects for both speed and time and their interaction. In contrast, these parameters did not significantly influence %LC BU within the experimental range, with uniformity results consistently trended towards the upper specification limit.

These findings suggest that while the process is likely optimised in terms of uniformity, it is not fully centered within the target specification, posing a potential risk of future drift. Additionally, the scale up study demonstrated acceptable performance but a moderate increase in variability, warranting further optimisation work.

Suggestions for future work

Building upon the findings, some suggestions in the following areas are proposed for future investigational work.

Process centering & control study – The reduced %RSD in process appears well optimised for variability, even results that trended at the upper end of the acceptance range for %LC. Future work should include process centering studies to shift the average label claim closer to target the midpoint of the specification (~100%), thereby increasing margin for any variability and reducing the risk of out of specification results.

Material & Process interaction assessment- Results from manufacturing campaigns can identify material related challenges, Expand the current factorial design to incorporate material variables (% fines targets, morphology) alongside process parameters to better understand their combined effect on blend performance. Conduct material assessment studies, considering factors such as material age or alternative PSD ranges and their impact on uniformity.

Additional variables - Given the high trending %LC results, further investigation into non process parameters is warranted. This includes:

- Order and method of material addition
- Powder flow properties (e.g., particle size, cohesion, density)
- Environmental conditions (e.g., humidity, electrostatics)
- Current sampling method and location consistency

Refinement of sampling technique - Evaluate alternative sampling methods to the manual retrieval using a SS thief to minimise variability introduced during manual blend sampling, particularly given the cohesive nature of the formulation and the static nature of the blend. If alternative methods are not available, tweaking the current method to reduce variability in how samples are taken and analysed could yield benefits.

Scale Up verification - While scaled up batches met acceptance criteria, the %RSD for the batches doubled. Additional work should evaluate:

- The effect of powder bed depth, blender fill ratio, and blender geometry on mixing dynamics, equipment changes from low to high shear process and its impact on the blend, considering material/surface interactions.

By aligning future work with the core findings of this study, the manufacturing process for low dose DPI formulations can be further optimised, scaled with confidence, and made robust against sources of variability, ultimately ensuring consistent uniformity across batches.

Chapter 5 - Conclusions and Recommendations

Introduction

This dissertation has explored “Optimisation of Blend Uniformity in a Low Dose Dry Powder Inhaler Formulation: Investigating API and Excipient Interactions and Process Parameters”, presenting a comprehensive review of the literature sourced, analysis of experimental findings, methodologies, and theoretical implications. In this final chapter, the key outcomes of the study are summarised, the research question is revisited in light of the results generated, and the significance of the work is discussed. Additionally, the limitations of the study are acknowledged, and all recommendations for future were proposed in Chapter 4.

Conclusions

The hypothesis that blend uniformity in a low dose dry powder inhaler formulation could be significantly improved by evaluating API/excipient interactions and optimising critical process parameters such as blending time and speed was only partially validated. While the study demonstrated that process variables influenced blend performance resulting in a reduction in %RSD within the blends, the results revealed that three out of the eight batches failed to meet uniformity acceptance criteria, and all but one exhibited a high maximum API content value.

The observed variability could point to underlying complexities in API/excipient interactions such as segregation tendencies, electrostatic effects, or inadequate dispersion that require further investigation, with results also suggesting that the process is likely optimised in terms of uniformity, but not fully centered within the target specification.

PSD and SEM analysis of API X and lactose excipients Y and Z revealed morphology and size compatibility that promote effective adhesion of API and lactose. Coarse lactose (Y) provided good flow and stability within the blend, while fine lactose (Z) improved API dispersion and binding, both contributing positively to uniformity, which can be visualised in the SEM images for Batch-082, confirmed by the passing uniformity results with acceptable variation, even if the results trended high.

The manufacturing process was successfully scaled up. Blends made at a 1 kg using a low shear process scaled to a 6.6 kg using a high shear technique for blending at a matched tip speed of 6 m/s (from 567 rpm in 3L blend bowl to 302 rpm in a 20L vessel) demonstrated that energy translation across both scales supported a reproducible and in specification performance, with both pilot scale batches passing blend uniformity criteria and within acceptable variation (%RSD < 3.0%), confirming the original hypotheses producing successful scaled blend post optimisation of the process.

While low shear and high shear methods differ in terms of mechanisms, equipment and energies, applying matched energy levels during scale up and with consistent material controls, led to reliable uniformity across processes. The study outcome not only confirms the effectiveness of the optimised mechanical energy but also highlights the adaptability of blending strategies when guided by known material properties such as particle size and surface morphology. The ability to switch between blending techniques without negatively impacting product quality reinforces the robustness of the formulation and supports scalable, cost effective manufacturing and flexibility, giving confidence to commercial scale feasibility without compromising product quality.

Limitations and Contributions of the study and literature

This research advanced understanding of blend uniformity in low dose dry powder inhaler formulations by highlighting the impact of specific API/excipient interactions coupled with varied blending parameters and its response on blend variability. The study showed that optimising blending time and speed can improve uniformity, even though results trended high, the optimisations yielded some favourable results, offering practical guidance for process development.

However, limitations emerged, where three of eight batches failed to meet specification, and a consistent high trend in maximum values suggested challenges with dispersion and possibly sampling reliability. The narrow scope of materials used, with two grades of lactose and one API used in the study, findings may not directly apply to other excipient systems or drug substances.

Manual sampling methods can introduce bias and being a manual operation, inherent variability operator to operator can be an issue. Advanced techniques like NIR or PAT tools could not be incorporated for the study, which would have provided real time blend uniformity analysis without the need for sampling.

Results are based on Turbula low shear blending and PMA high shear blending processes, outcomes may differ with other blending technologies. Nonetheless, the work provides a valuable framework for future studies and reinforces the need for an integrated and holistic approach, by combining material science, process and formulation control, and a reliable sampling technique to achieve consistent and scalable blend performance.

A notable example is the study by (David Barling *et al.*, 2014) which investigated the optimisation of blending conditions using five different DPI formulations across seven mixer types and various fill volumes. While this work provides valuable insights into process flexibility and equipment selection, its extensiveness also highlights a challenge found in many such studies namely, the difficulty in isolating and comparing individual variables when so many are concurrently

adjusted. In such cases, determining what constitutes an ‘optimal’ process becomes less clear, as direct comparisons between sub-studies are limited due to the changing parameters and materials.

The study assessing speed and tine carried out by (V. N. P. Le *et al.*, 2012), was again an informative study, but the entire experiment took place in the same blender, assessing the parameters but not the impact of taking the formulation from an actual low shear technological process to a geometrically different high shear process and evaluating how it translates.

There is a lack of simplified, scalable methodologies. Few studies demonstrate a stepwise approach where a formulation is first manufactured at a small scale, confirmed to meet blend uniformity specifications, and then scaled up using matched mechanical energy inputs and identical material properties. Such a framework would allow for better reproducibility and comparison across scales, while also offering more practical relevance to industry.

From the literature reviewed, there is a recognition that the complex nature of DPIs, and the many formulations that exist across a range of applications, makes it very difficult for a one fits all process. This complexity presents a major challenge to standardising a universal manufacturing process or fitting a process to a known formulation. Instead, both formulation and process development must be approached in an integrated manner, with each informing and guiding the other.

To summarise, addressing blend uniformity challenges within DPI development demands a flexible, scientifically justified, and collaborative approach between formulation and processing teams. This integrated methodology can improve overall product quality, shorten development timelines, and enable consistent delivery of safe and effective inhalation products.

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Appendix 1 – Ethics Form

Innopharma education

GRIFFITH COLLEGE

Ethics Application & Declaration Form

DISSERTATION TITLE: "Optimisation of Blend Uniformity in a Low-Dose Dry Powder Inhaler Formulation: Investigating API and Excipient Interactions and Process Parameters"

RESEARCHER'S NAME: Michelle Grant

PROGRAMME OF STUDY: MSc in Pharmaceutical Business and Technology

SUPERVISOR'S NAME: Catherine Mchugh

DECLARATION:
The information in this application form is accurate to the best of my knowledge. I undertake to abide by the principles outlined by Innopharma/Griffith College ethics policy in my research dissertation. I confirm that I have completed a full ethics assessment for my research dissertation as per the college guidelines. I will not begin my primary research until such approval from my supervisor and/or ethics Committee has been obtained.
I pledge to carry out my research according to the Innopharma/Griffith College academic integrity standards. Any results presented in my dissertation will be from my own, original research, I will reference and/or acknowledge any material or sources used in its preparation and I will not plagiarise the work of anyone else.

For Student:
STUDENT SIGNATURE: Michelle Grant
DATE: 28/05/2025

The research contained within this research dissertation proposal has been approved.

For Supervisor:
Ethics Committee Approval Required: Yes ☐ No ☒NO
SUPERVISOR SIGNATURE: CMcHugh
DATE: 10th June 2025

For Ethics Committee (if required):
Ethics Committee Approval Given: Yes ☐ No ☐
ETHICS COMMITTEE MEMBER SIGNATURE:
DATE:

NOTE: Supervisors are responsible for ensuring their students fill in this form correctly and that all ethical areas have been considered.

SECTION 1: DESCRIPTION OF RESEARCH STUDY

1.1 Purpose and objectives of research:

The purpose of the research is to understand the factors that influence blend uniformity during the development of a low dose formulation for a capsule Dry Powder inhaler product. The key objectives are as follows:

- To identify key factors that can affect blend uniformity in low-dose API-X/lactose blends at a single unit dose
- To determine the influence of excipient properties (particle size, morphology, surface energy) on the uniformity of a low dose formulation
- To optimise process parameters (blending time, speed) to minimise variability
- To determine whether the process is reproducible if scaled, conduct scale up activity from bench top to pilot scale and assess using BU analysis

1.2 Research methodology:

The primary research will be carried out using practical investigations, experiments and testing, objective material characterisation and analysis and quantitative methodologies. It is designed to address the outlines objectives of investigating blend uniformity, and the key factors that influence it and introduce variability into the homogeneity of the final powder blend. It focuses on collecting quantitative data related to raw materials, process parameters and blend homogeneity analysis, results will be obtained and presented as graphed data for review and critique. The secondary research will involve a review of existing literature on dry powder inhalers as a treatment for respiratory conditions, with a particular focus on low-dose formulations.

SECTION 2: POSSIBLE ETHICAL ISSUES

Answer 'yes' or 'no' to the following questions.

SUBJECT MATTER

Does the research proposal involve:

Research into specific company activities that would be deemed sensitive or confidential	Yes No
Research into politically and/or racially/ethnically and/or commercially sensitive areas	Yes No
Sensitive, personal, professional or corporate issues	Yes No

RESEARCH PROCEDURES

Does the research proposal involve:

Research that might damage the reputation of companies or participants	Yes No
Research that may negatively affect the reputation of Griffith College/Innopharma	Yes No
Use of personal records without consent	Yes No
Use of company data without consent	Yes No
The offer of any inducements to participate	Yes No
Audio or visual recording without consent	Yes No
Using a language other than English	Yes No

PARTICIPANTS

Does the research proposal involve:

People who are not competent and/or fluent in English	Yes No
Does your research group include any of the following vulnerable groups	Yes No

(Adults with psychological impairments; Adults with learning difficulties; Adults under the protection/control influence of others (e.g. in care/prison); Relatives of ill people (e.g. parents of sick children); Hospital or GP participants recruited in a medical facility; persons under the age of 18)

If you have answered NO to ALL questions, please go straight to Section 4.

If you have answered YES to ANY question in SECTION 2, you must fill in SECTION 3.

SECTION 3: STEPS TAKEN TO AVOID ETHICAL ISSUES

[Only fill in this section if you answered YES to ANY of the questions in Section 3. For example, if you answered yes to including participants who are not fluent in English, you might put forward a plan that offers your survey in two languages to take this into account. Another example could be a study where the researcher wants to include information about the care received by children with a long-term condition but it would not be ethical to approach the children directly but it might be acceptable to instead ask parents questions about their child's care. If these plans are acceptable to your supervisor, you may not need to apply for ethical approval from the Ethics Committee].

3.1 If your ethics relates to ***Subject Matter***, outline your action plan to work around any sensitive issues.
3.2 If your ethics relates to ***Research Procedures***, outline your action plan to deal with possible ethical issues in your research procedures.
3.3 If your ethics relates to ***Participants***, outline how you will protect vulnerable persons or those that do not have English as their first language.

SECTION 4: ABOUT YOUR PARTICIPANTS

4.1 Outline your participant profile and why you have chosen them for this study *[Do not provide names except where it is deemed impossible to conceal identity].*
There are no study participants

4.2 How do you plan to gain access to/contact/approach your participant(s).
There are no study participants

SECTION 5: INFORMATION, CONSENT AND CONFIDENTIALITY

5.1 **Participant Information Letter (PIL) for participants**
There are no participants, not applicable

[You must submit an information letter for participants with this application, as part of your appendices document. For online surveys, it is sufficient to include a paragraph summarising and explaining the purpose of the research at the beginning of the survey. In all other research e.g. interviews, phonecalls, a PIL should be provided to each participant before they are asked for their consent to take part. A template PIL is available in Moodle].

Please confirm below that your information letter covers:

Description of the research topic and method	Yes No
Details of what participation will involve	Yes No
Rights to anonymity	Yes No
Confidentiality	Yes No
Rights to withdraw from the research	Yes No
The contact details of the researcher and supervisor (if necessary)	Yes No

5.2 **Informed Consent Form (ICF) for participants**
There are no participants, not applicable

[Informed consent is required for most research. For online surveys, it is sufficient to get the participant to tick two boxes at the beginning of the survey – one to state they understand the research and one to give consent. In all other research e.g. interviews, phonecalls, a signed consent form is required. If the data is gathered online e.g. zoom, a signed consent form can be scanned and sent to the researcher. A template ICF is available in Moodle. The signed

ICFs, along with the surveys, audio files or interview notes etc. must be stored in the primary data folder on moodle and can be accessed by Innopharma staff for the purposes of verifying the authenticity of the research carried out and the data collected].

Please indicate below if your research requires a signed consent form by selecting the relevant option only:
There are no participants, not applicable

Yes: my research requires signed consent and I have attached an ICF in the appendices of my application.
No: my research study involves an online survey only and/or does not require signed consent

SECTION 6: STORAGE OF DATA

[Please ensure that you are abiding by GDPR and the national Data protection laws https://www.hrb.ie/funding/gdpr-guidance-for-researchers/gdpr-and-health-research/).

The student is responsible for storage of data and this will be handed over to the college in an electronic format as part of the thesis submission i.e. primary data and completed ICFs where applicable will be added to the primary data folder on moodle. The rationale is to keep data ***as long as it is still useful*** *and there is an intention to use it further* ***for research*** *so if this is not the case then this can be stipulated here and a shorter retention period given.]*

6.1. How will you store the research data and for how long? How will you manage data protection issues?

The data collected as part of this study will be laboratory based and will be stored on internal systems and databases in my workplace, in accordance with internal policies and procedures. All data will be uploaded as part of my final dissertation.

SECTION 7: NON-DISCLOSURE AGREEMENT & STUDENT CONSENT

7.1 **Non-Disclosure Agreement (NDA)**
Will the final dissertation contain any information pertaining to any source what would warrant the use of a Non-Disclosure Agreement (NDA) e.g. industry-based research?

Yes No

7.2 **Student consent**
If a Non-Disclosure Agreement (NDA) is not required, does the Student consent to allow their completed dissertation to be held/published by Innopharma/Griffith College?

Yes No

SECTION 8: RECORDING AND RETENTION OF DISSERTATION VIVA

8.1 **Viva Recording**
The Dissertation viva will be recorded. This recording may be used to facilitate assessment by Innopharma staff, a third reader if necessary and/or if requested by the external examiner for the Programme. The recording will be held in line with current GDPR guidelines and will not be made publicly available.

SECTION 9: DOCUMENT CHECKLIST

NOTE: Applicants must attach the following documents in electronic format to the appendix.

Which documents are added to the appendix? Please tick N/A if not applicable:

9.1 Participant Information Letter (PIL) for participant	Yes N/A
9.2 Informed Consent Form (ICF) for participant	Yes N/A
9.3 Questions/survey for interviewees/focus groups etc *(can be in draft form)*	Yes N/A
9.4 Any other documents e.g. Non-Disclosure Agreement	Yes N/A

I confirm that this application is complete and all required documents are included in the appendix.

For Student:

STUDENT SIGNATURE: Michelle Grant

DATE: 28/05/2025

SECTION 10: APPENDIX

Appendix 2 – Blend Uniformity Specification

Internal specification and acceptance criteria for blend uniformity.

Specification Type:	Blend Uniformity Specification
Product Name:	[redacted] Capsule Dry Powder Inhaler [redacted] cDPI)
Product Code:	IB0140, 32104256

BLEND UNIFORMITY SPECIFICATION FOR [redacted] CDPI

Table 1: In-process Control Acceptance Criteria

Test	Test Method number	Specification source	Acceptance Criteria
Blend Uniformity N=10	QDP[redacted]	In-House	Determine the mean blend content and %RSD of the 10 blend uniformity samples from set A. The mean blend content of the 10 blend uniformity samples should be within 90.0–110.0% of target. The %RSD of the 10 samples is ≤ 5.0%. All individual results are within ±10.0% of the mean result
Blend Assay N=3	QDP[redacted]	In-House	Determine the mean blend content and %RSD of the 3 blend assay samples from set A. The mean blend content of the 3 blend assay samples should be within 90.0–110.0% of target. The %RSD of the 3 samples is ≤ 5.0%. All individual results are within ±10.0% of the mean result

Appendix 3 – PSD analysis

These PSD graphs provide an overview of how particle sizes are distributed within a sample. Showing the range of particle sizes and how frequently different sizes occur, helping to understand whether the sample is made up mostly of fine, coarse, or mixed size particles.

Figure 41: PSD analysis – Distribution Curve – Sample 1 of Batch 12345

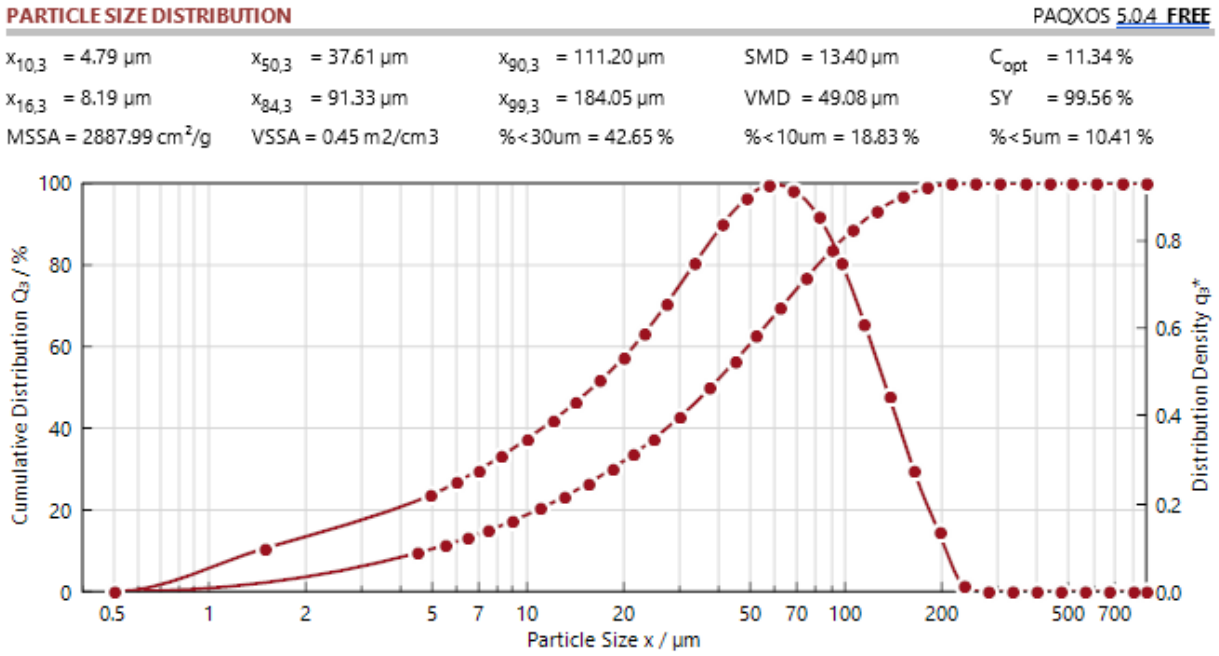


Figure 42: PSD analysis – Distribution Curve – Sample 2 of Batch 12345

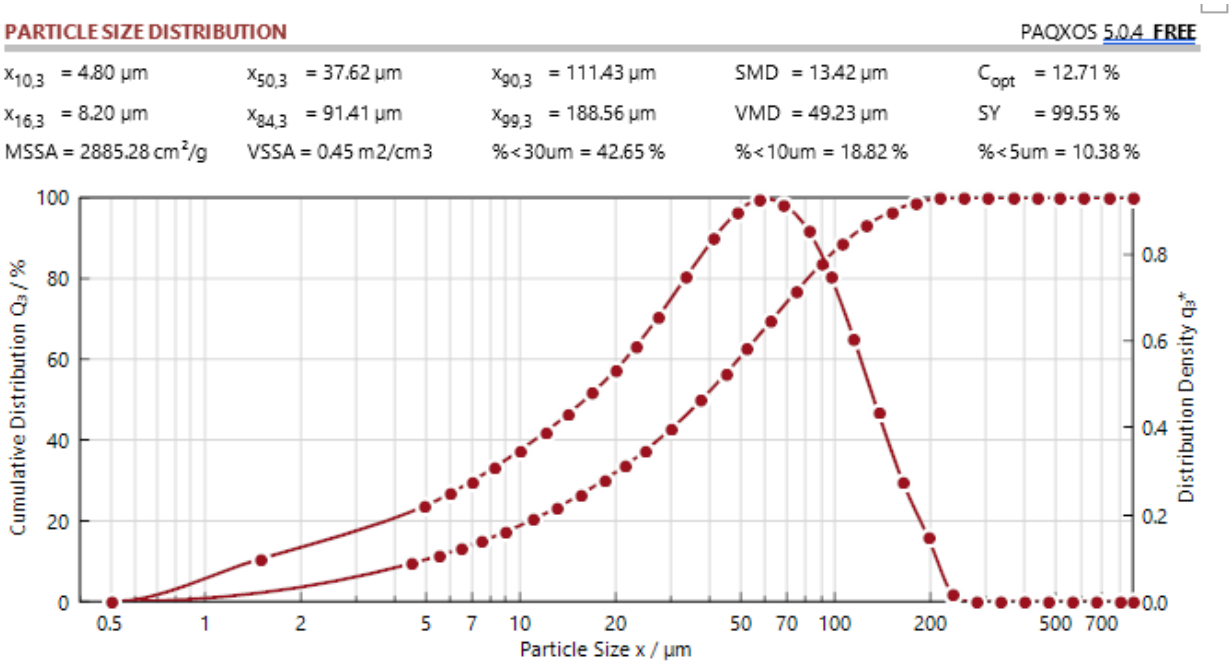
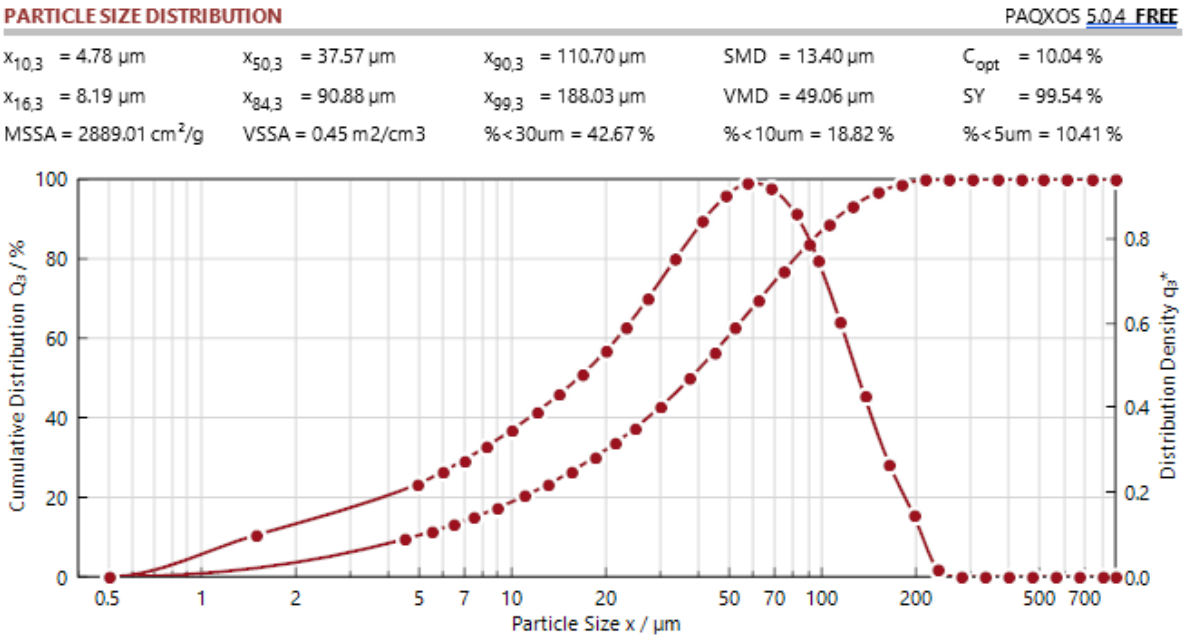


Figure 43: PSD analysis – Distribution Curve – Sample 3 of Batch 12345



Appendix 4 – Material Characterisation Images

Additional SEM images of input materials used in the formulation for the study and the final blend Batch-082.

Figure 44: API X below at x500 magnification

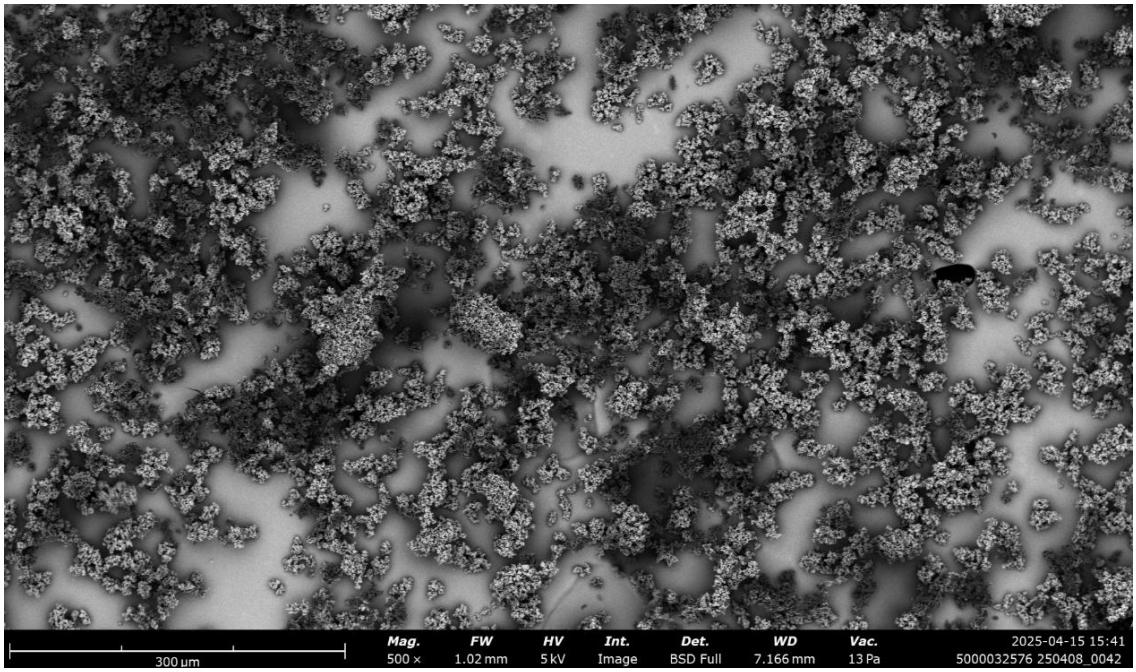


Figure 45: Lactose Y below at x1000 magnification

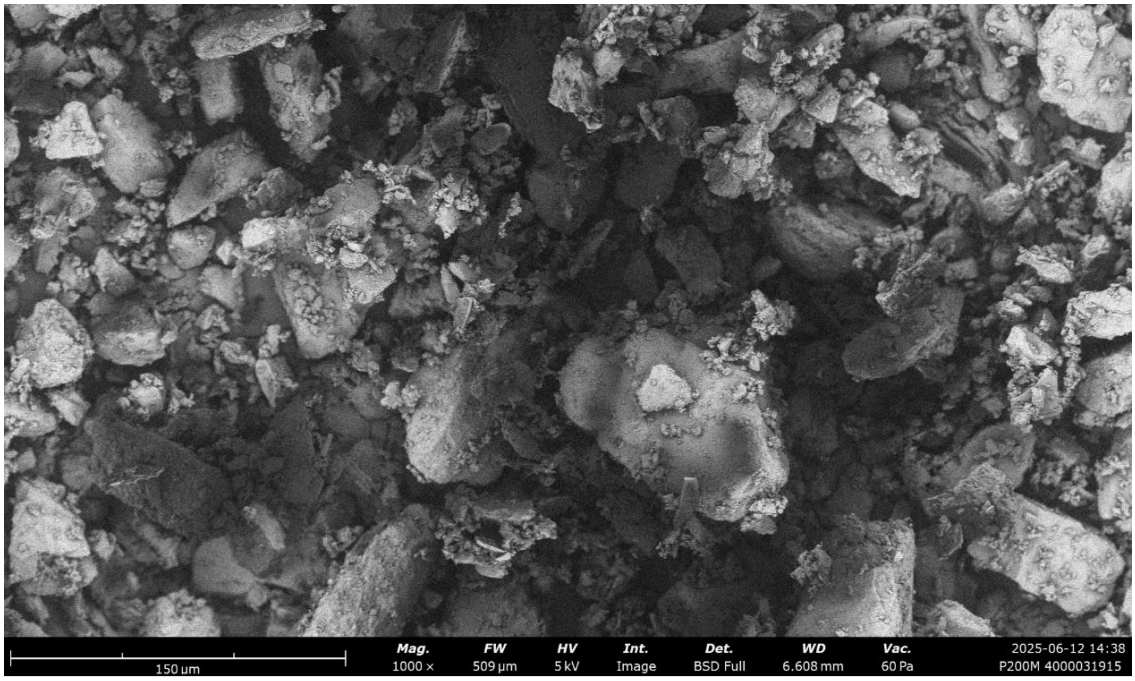


Figure 46: Lactose Y below at x5000 magnification

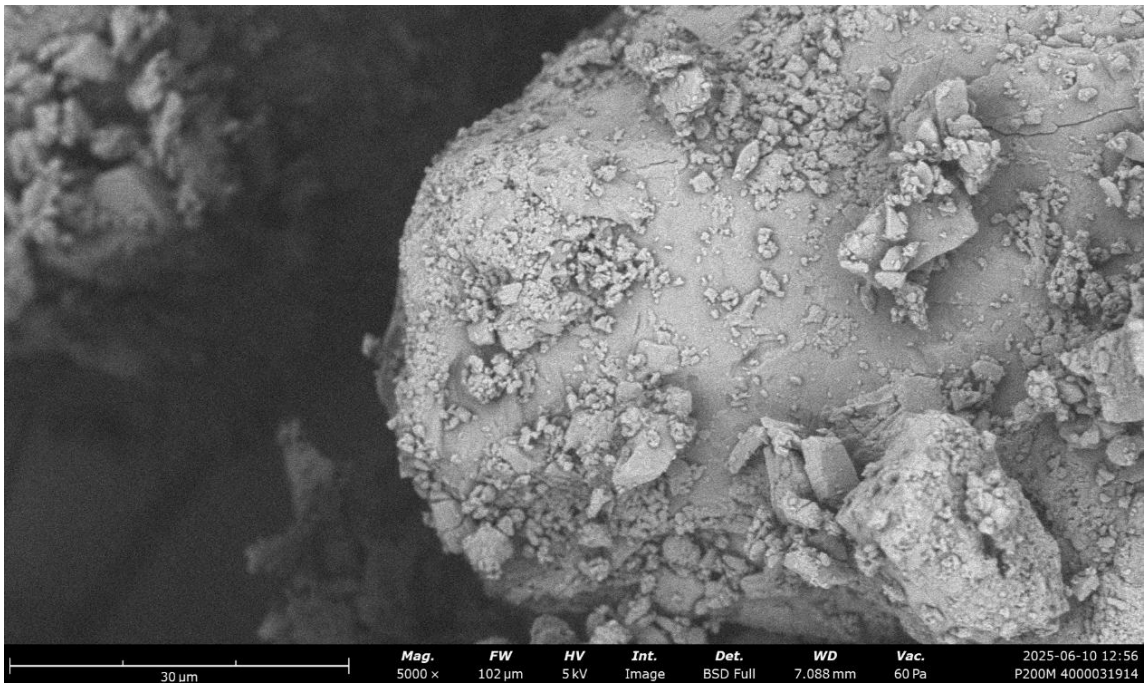


Figure 47: Batch-082 x500 magnification

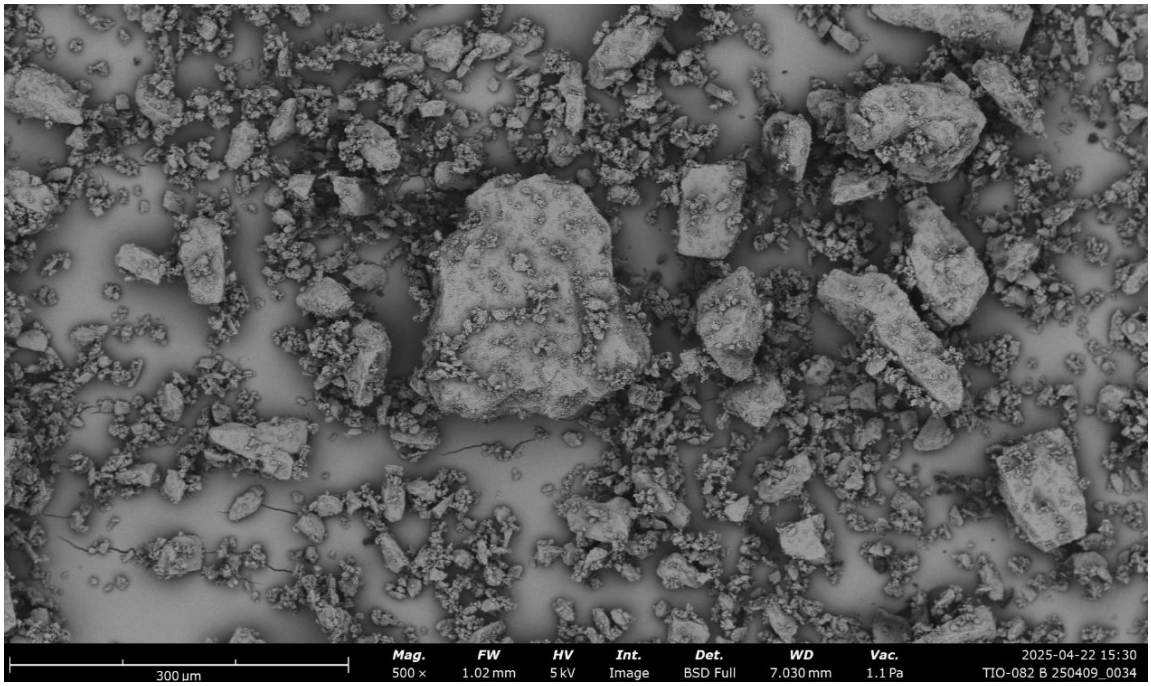


Figure 48: Batch-082 x2000 magnification

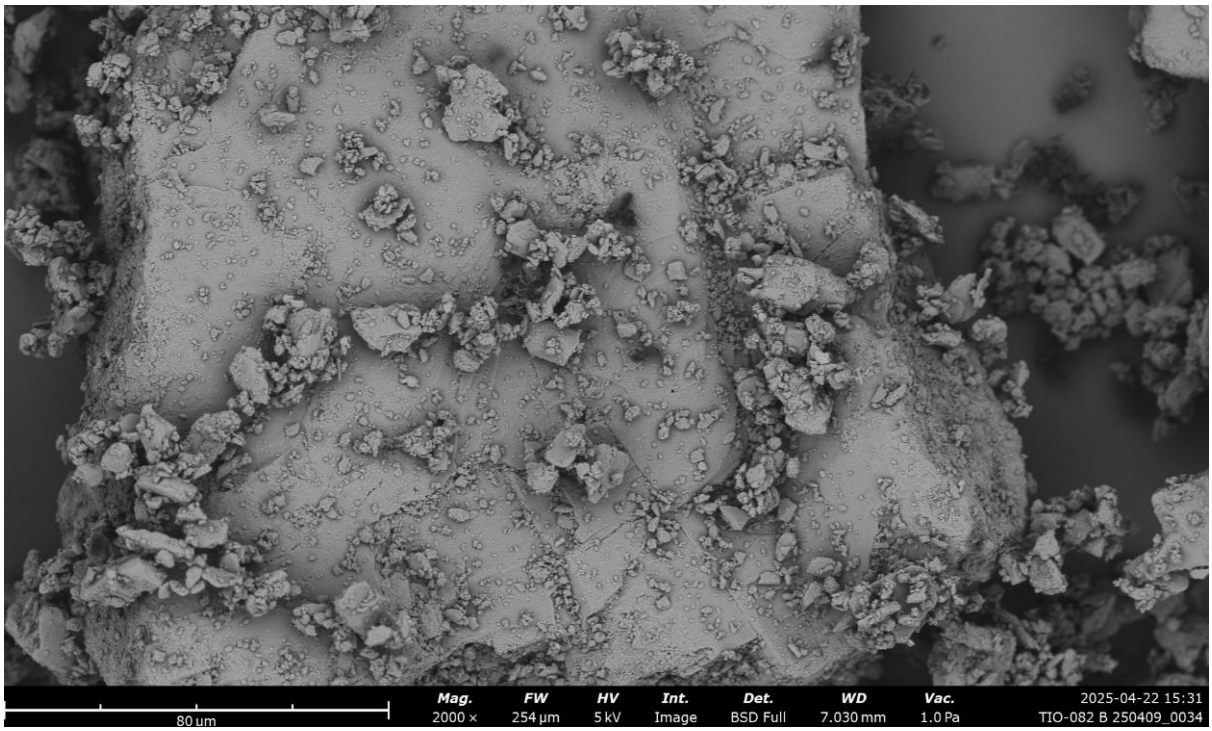
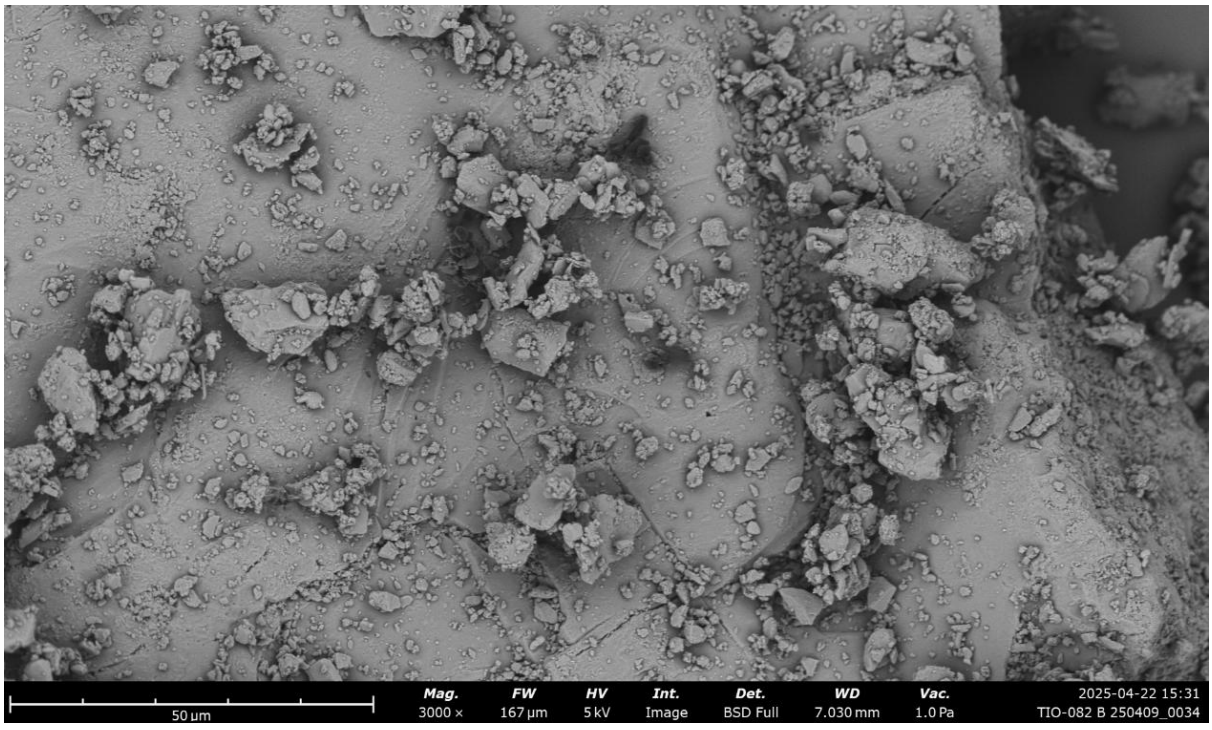


Figure 49: Batch-082 x3000 magnification



Appendix 5 – Batch Manufacturing Record

Below is an example of a batch manufacturing record that was executed for one of the small scale batches – Batch-072, to give an overview of the process and what is captured within the batch documentation, covering equipment, process, parameters and sampling.

BATCH-072

Batch-072 Small Scale Blend

Stage:	Batch-072 Proposal:
1.	Manufacture 1.1Kg lactose pre blend at target 12.5% fines using the Turbula tumble blender for 10 minutes @ 15rpm
2.	Manufacture a 1Kg active blend consisting of 0.0041Kg of API (0.409%) to 0.9959Kg lactose premix (99.591%) for 18 minutes 567rpm (6m/s).
3.	Blend BU sampling is to be completed as follows: • Once the blend procedure is complete, empty the blender as per the instructions outlined in this BMR • Earth the blend and let rest for NLT 12 • BU sampling to be performed with the de-ionising bars switched on

DAILY CALIBRATION OF BALANCE

BU Sampling Precision Balance Daily Calibration Checks: Calibrate with a 1Kg (1.0000K g) weight (weight tolerances ± 0.0005Kg) Attach Balance printouts to space provided.				
Daily Calibration Check (**Circle as appropriate)			Repeat Daily Calibration Check (N/A if not required)	
1.0000Kg wgt Balance value (x):				
	Yes	No	Yes	No
Daily Calibration Performed by/Date:				
Checked by/Date:				

LACTOSE DISPENSING

Lactose as part of the lactose pre-mixing step **is to be sieved** and is to be dispensed into stainless steel containers. Quantities shall be entered as per below. Container numbers 1 and 5 will contain bulk amounts of lactose Y to be entered below as per results. Lactose is transferred to the pre-tared container. All Lactose containers are to be sealed with lid.

Lactose to be dispensed into the correct containers as follows:

- Zero the balance, press print, place the container, seal, clamp and lid on the balance, press print, re-tare and press print
- Weigh the correct quantity of sieved lactose as per the container numbers below
- Press print and attach the printout in the space provided

Lactose Y Dispensing

	Container No/Lot:	Container	Qty to be Dispensed	Actual Dispensed Qty	Use of Lactose
1	1	2L Stainless steel container	0.4444Kg	Kg	First Bulk Lactose Y
	2	1L Stainless steel container	0.1000Kg	Kg	First Rinse Lactose Y
	3	1L Stainless steel container	0.1000Kg	Kg	Second Rinse Lactose Y
	4	1L Stainless steel container	0.1000Kg	Kg	Third Rinse Lactose Y
	5	2L Stainless steel container	0.3000Kg	Kg	Second Bulk Lactose Y
Total amount of Lactose Y dispensed:			1.0444Kg	Kg	
Lactose Z Dispensing					
2	6	1L Stainless steel container	0.0556Kg	Kg	Small and only Lactose Z portion

RECORD REQUIRED EQUIPMENT FOR TRIAL

All the following trials to be carried out in the R&D Dry Powder Development lab			
Record all equipment required for trials			
Equipment Description	Ref ID No.	Performed by/Date	Checked by/Date
Low shear Turbula blender/unit			
3L PMA blend bowl			
2LSS Container for blend storage			
2LSS Container for blend storage			
2LSS Container for blend storage			
2LSS Container for blend storage			
2LSS Container for blend storage			
2LSS Container for blend storage			
1L SS Container for blend storage			
1L SS Container for blend storage			
1L SS Container for blend storage			
1L SS Container for blend storage			
1L SS Container for blend storage			
1L SS Container for blend storage			
SS Scoop			
Isolator			
Extraction horseshoe unit			
Precision balance			
Sampling thief Die Size: mm			
Antistatic Bars			
Ensure sample containers, labels and glass vials and lids for sampling blend are present in room.			

LACTOSE MIXING/BLENDING OPERATION

1	Place a container onto the balance and zero to achieve the tare weight of the container. Empty Lot 1 into container on the balance	
2	Transfer Lot 6 (Lactose Z) into the lot 2 container	
3	Transfer lot 2 into the empty Lactose Z container and rinse by hand.	
4	Repeat step 3 for Lot 3 containing the 2nd Lactose Y rinse	
5	Repeat step 3 for Lot 4 containing the Lactose Y rinse	
6	Add Lot 5 of Lactose Y to the container	
7	Record the final weight of the combined Lactose pre blend and attach printout below:	**Kg**
8	Close the container with the lid.	
9	Attach a printout of the Lactose pre blend final quantity below.	

LACTOSE TUMBLING/COMBINING OPERATION

1	Confirm that the Turbula blender is assembled with the bands to ensure the container is secured within the cage.			
2	Prior to operating the Turbula, remove the side panel and confirm the drive belt is in the correct position for required rpm. Once rpm is confirmed, replace the panel. Press start on the Turbula and using a stopwatch ensure that the pre blend is tumbled as per proposal capturing values below.			
	Tumbling Speed:	rpm	Elapsed Time:	min
			Performed by/Date:	
			Checked by/Date:	

LACTOSE PRE BLEND DISPENSING

Lactose pre blend is to be dispensed into a total of 5 stainless steel containers of the sizes and quantities as follows:

- Zero the balance, place the container on the balance, re-tare and ensure readout is at zero
- Transfer required quantity of lactose pre blend into the container. Press print and record net quantity in the BMR
- Attach all printouts to the BMR ensuring balance ID and batch number is listed on each printout
- Seal each container with either a lid and clamp or MC100 valve

			Target Blend Quantity:	**1.0000Kg**
	Lot #	**Container**	**Amount of Lactose**	**Use of Lactose**
	Lot 1	2L SS container	0.4238Kg	First lactose pre blend bulk - to be transferred to the blending bowl to coat the bowl.
	Lot 2	1 L SS container	0.0954Kg	For adding to the API container
	Lot 3	1 L SS container	0.0954Kg	For rinsing the API container
	Lot 4	1 L SS container	0.0954Kg	For rinsing the API container
	Lot 5	2 L SS container	0.2861Kg	2nd lactose pre blend bulk – to be added to the bowl after all other components added.
			Total required for blend manufacture:	**0.9959Kg**
			Performed by/Date:	
			Checked by/Date:	

API DISPENSING

API (Lot 6) Dispensing – (Qty 0.0041Kg)			Performed by/Date	Checked by/Date
Prior to commencing record the identification number of the container to be used for dispensing.				
Lot 6 API Dispensing Container:	**AP:**			
Tare the balance. Place the API container on the balance and press print. Re-tare the balance with the container assembly in place and ensure the read out is at zero and press print.				
Using a scoop dispense the required quantity of API directly into the sieve and transfer sieved material into the SS container. Press print and record the net quantity of API dispensed.				
Net quantity of sieved API dispensed:	**Kg**			

BATCH-072 BLEND OPERATION

1. **Load the 3L PMA the blending bowl as follows:** • Load bulk into the bowl, set the timer to 3 sec and impeller speed to 100rpm. • Press start and record the actual impeller speed and the elapsed process time			
Actual Impeller speed:	**rpm**	Actual time elapsed:	**sec**
• Load the first rinse into the API container and mix prior to adding to the PMA 3 blending bowl. • Load the second rinse into the API container and rinse the container with the lactose ensuring all powder is released from the container. • Repeat above step with the final rinse. • Set the timer to 3 sec and impeller speed to 100rpm. Press start and record the actual impeller speed and the elapsed process time			
Actual Impeller speed:	**rpm**	Actual time elapsed:	**sec**

2. Blending operation

Set the Pharmaconnect process timer and Impeller rpm values listed below.

Ensure that the process time end point is active. Press the reset button and ensure the timer is at zero.

Mixing Process Time:	**18min**	**00sec**
Impeller set point as per BOM:	**567rpm**	**6m/sec**

Press the start button to start the impeller. Confirm that the actual impeller speed is within ±5 rpm of the above required speed. Record actual rpm value below.

Actual Impeller speed:	**rpm**	**Chopper:**	**N/A rpm**

Monitor the blending and make sure the blending stops when the timer reaches the required set point. Record the elapsed mixing process time on the completion of blending.

Elapsed process mixing time:	**min**	sec

3. Blend Discharge

Place the 3L container with lid on the balance and tare. Press enter to obtain the weight of blend produced printout. Record values and attach printout in space provided.

4. Press enter to obtain the weight of blend produced printout. Record values and attach printout in space provided.

IBC Tare Weight:	Kg	(A)
IBC Gross Weight with Bulk Blend:	Kg	(B)
**Actual Yield of Blend Produced:	Kg	(C)

**Actual Yield of Blend: (B) – (A) = (C)

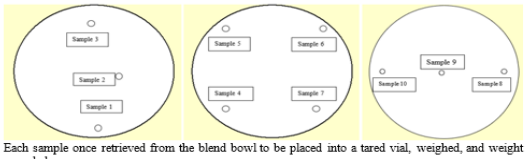
5. On completion of blend, ensure the container is attached to an earthing cable, and perform a minor clean on the blending bowl in preparation for the next batch.

Steps performed by/date:		Checked by/date:	

SAMPLING

As per site sampling procedure, 10 samples to be taken for blend uniformity analysis using a manual sampling thief and placed into individual glass vials. Blend uniformity samples are to be taken from predefined locations within the blend to ensure that they are representative. Samples must be taken 1-3 from top, 4-7 from middle and 8-10 from bottom as shown below.

Sampling Locations within the container



Each sample once retrieved from the blend bowl to be placed into a tared vial, weighed, and weight recorded.

1. Record the start time of the sampling operation (ensure this time is NLT the rest time specified in the BOM).	
2. Prior to sampling obtain a suitable container for the reject blend samples. Obtain a tare weight printout and record here.	g

Sample	D	E	F
1.	g	g	g
2.	g	g	g
3.	g	g	g
4.	g	g	g
5.	g	g	g
6.	g	g	g
7.	g	g	g
8.	g	g	g
9.	g	g	g
10.	g	g	g
additional sample (if applicable):	g		

Performed by/Date:	
Checked by/Date:	

Appendix 6 – Additional Graphs

Additional graphs for comparison of small scale batches, Batch-079 compared to both pilot scale batches, and a final graph representing BU results for all eight batches, graphs show individual results for each batch, for a visual representation of the spread of data.

Figure 50: Small scale batches - BU %LC

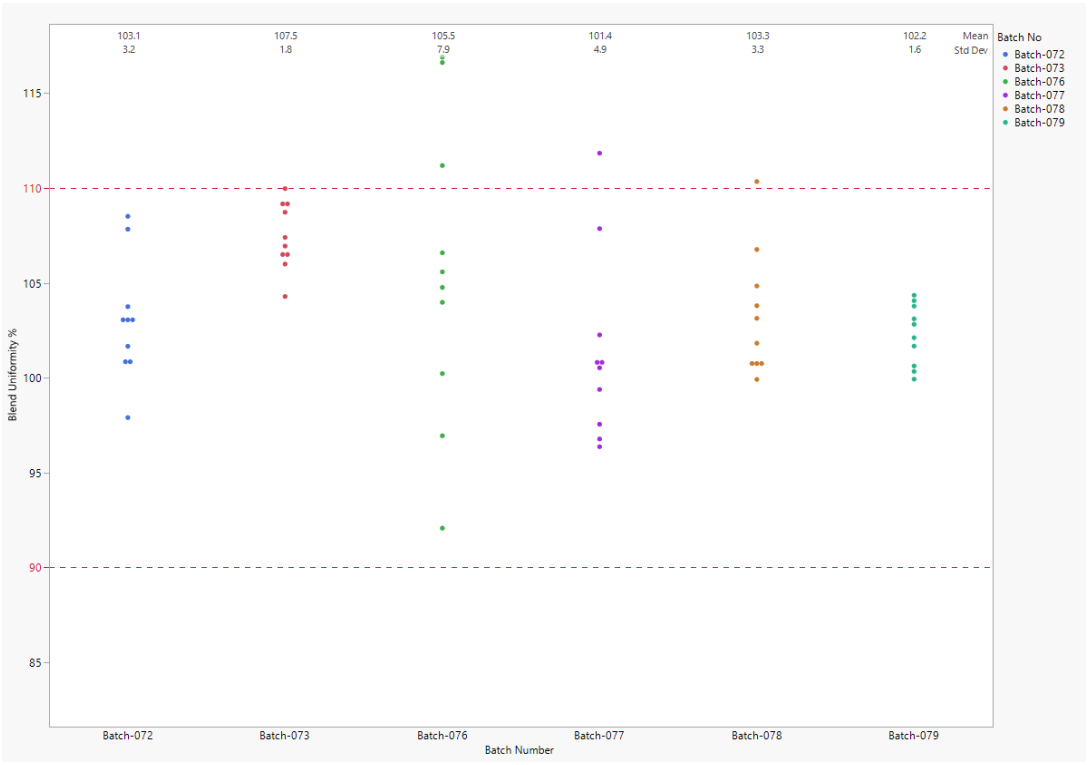


Figure 51: Pilot scale batches - BU %LC

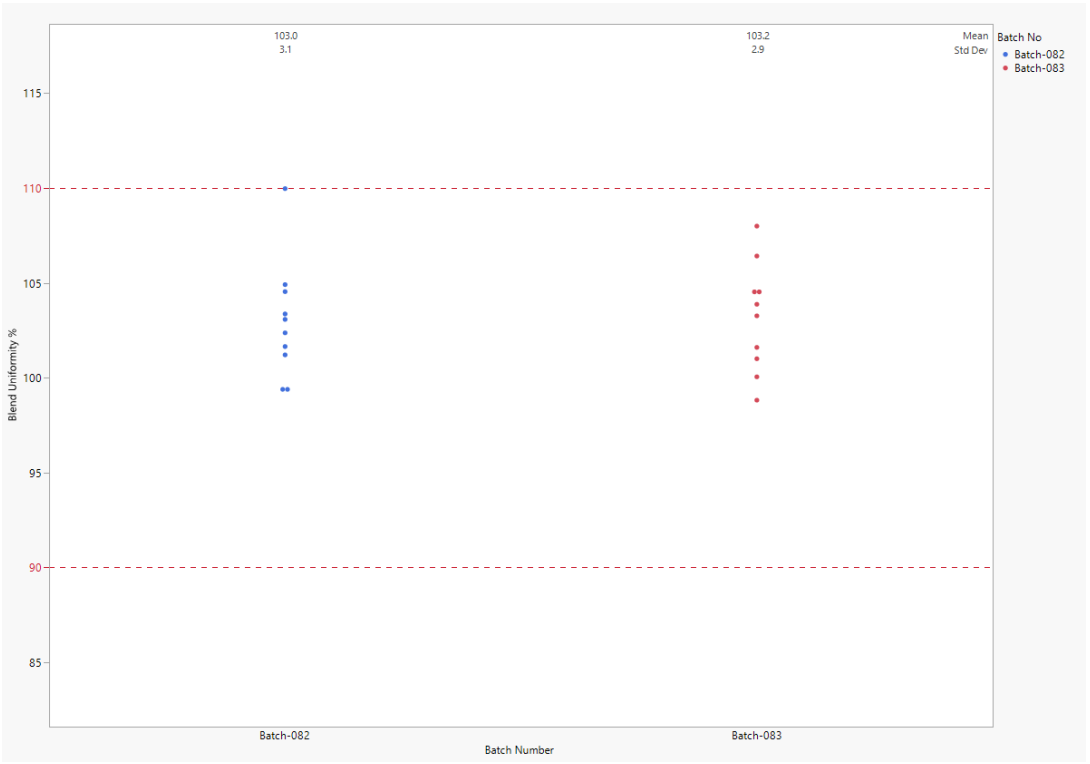


Figure 52: Comparison of Batch-079 and two Pilot scale batches - BU %LC

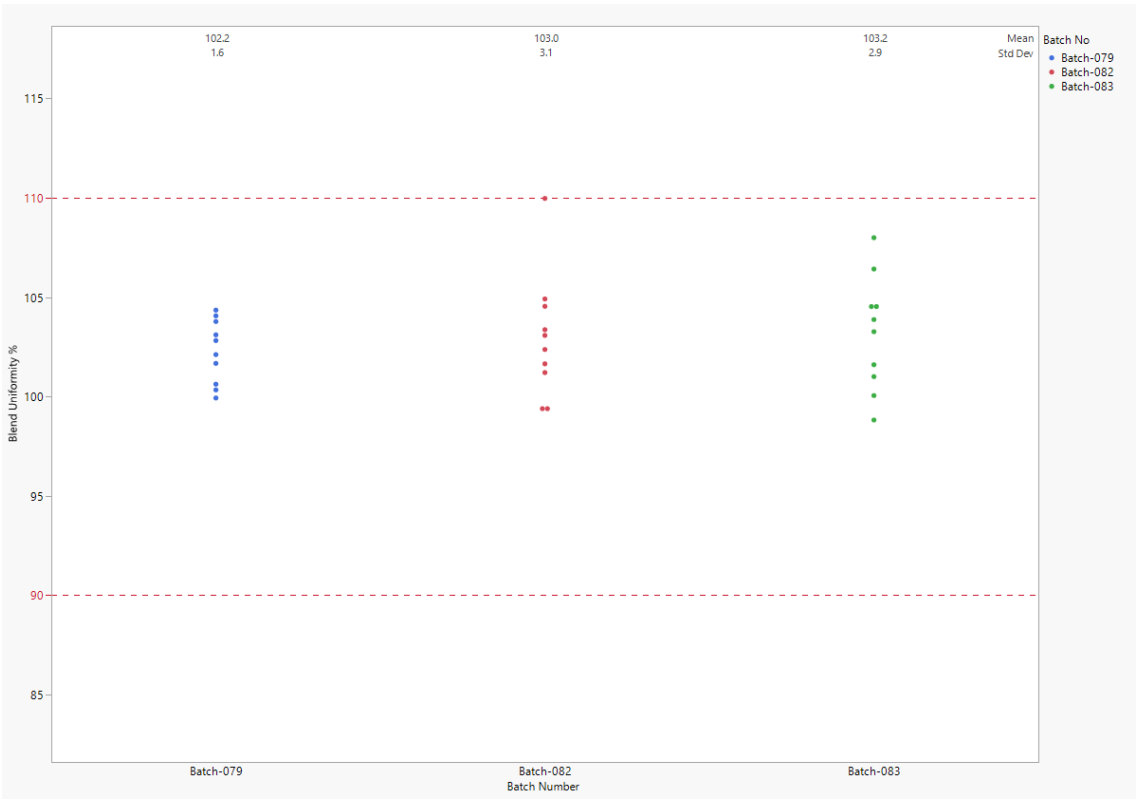


Figure 53: Comparison of small scale and pilot scale batches expressed as BU% LC mean and %RSD