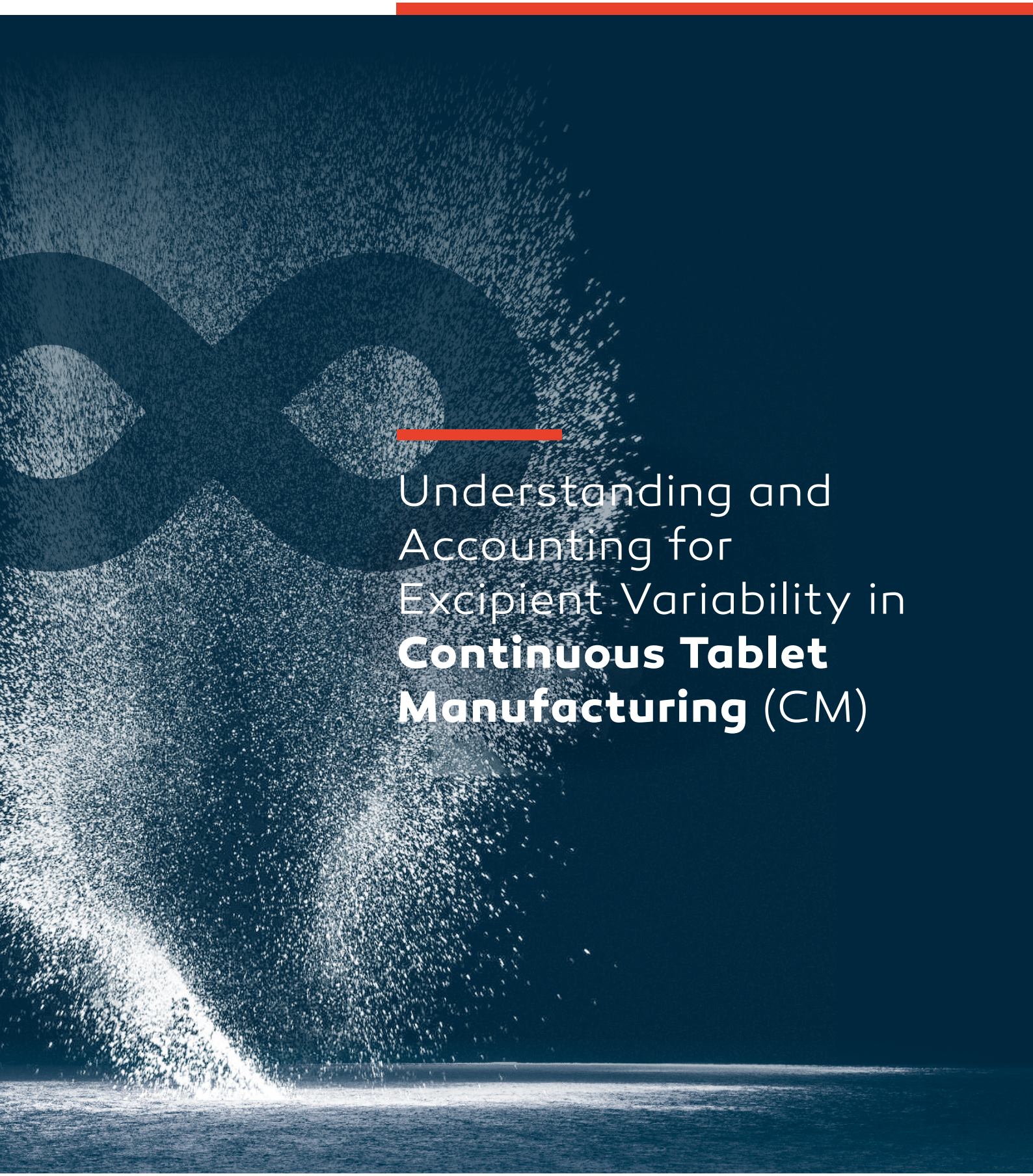
DFE pharma



Understanding and Accounting for Excipient Variability in **Continuous Tablet Manufacturing** (CM)

Content Overview

Introduction

As pharmaceutical production moves from batch-wise to continuous manufacturing, individual processing steps, such as blending of the active pharmaceutical ingredient (API) with excipients, have to be re-designed to continuous operations.

Whilst the cost and quality benefits of CM are well documented, successful implementation relies on an in-depth understanding of how raw materials and their mixtures – including excipients – behave in continuous processes.

This whitepaper will outline some of the key learnings from DFE Pharma's excipients in CM processes variability experiments, before setting out DFE Pharma's Stretch Batch Approach and how it can work in practice. Ultimately, it will demonstrate why DFE Pharma is fast becoming the pharma industry's preferred global partner in the robust development of continuous tablet manufacturing processes.

1 CM as The Future Of Manufacturing

"Whilst excipients are a small element of the overall drug development process, they are crucial. Having studied how the natural parameters of excipient variation impact continuous processes, DFE Pharma is emerging as the global pharmaceutical excipient expert contributing to robust drug development. Robust drug development and successful CM starts with, and is dependent on dialogue and collaboration between the pioneers and experts in their respective fields"

Mara van Haandel
Innovation Manager,
DFE Pharma

Continuous processing or manufacturing is at the forefront of advance for the pharmaceutical market. Unlike the stop and start mode of batch manufacturing, in CM, materials are continuously fed into a closed system within which all process steps take place.

The benefits to pharma include:

- Manufacturing lead times are significantly reduced
- Plant footprint is reduced
- Processing times are decreased
- Unnecessary steps are eliminated
- Contamination risks are minimised
- Reduces the likelihood of human error
- Allows for real-time monitoring
- Requires less physical space
- Reduces scale-up times
- Reduces amount of API usage
- Crucially, CM could be 40 to 50% less expensive to run than batch processing.

Since 2015, the FDA has approved seven drug products manufactured by CM, and at least 20 more are in the pipeline.

With FDA support for companies transitioning to CM, and the significant benefits of this streamlined approach resulting in high-quality drug products through plant-wide Quality-by-Design approach, CM is very much the future for our industry.

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Understanding Excipient Variation Within the CM Process

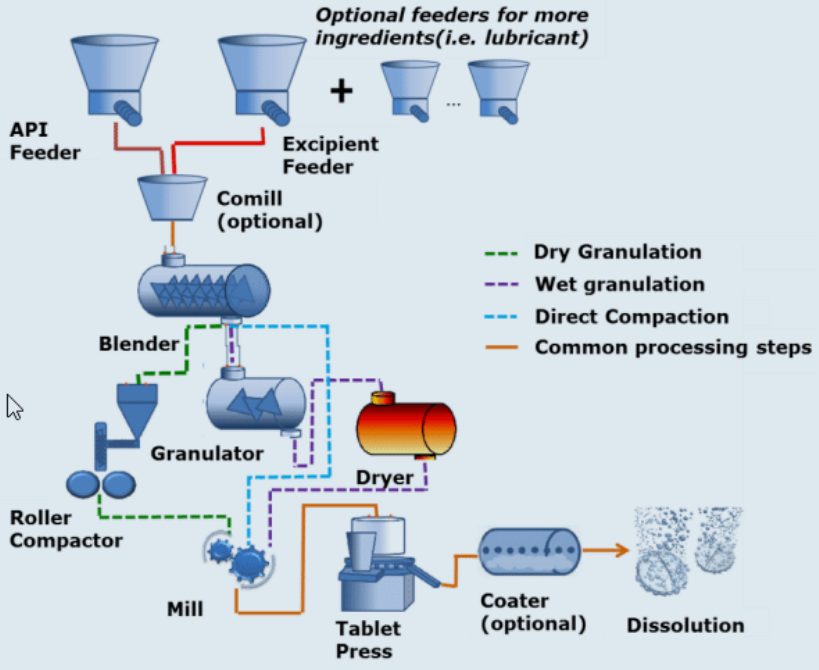
(The Science Behind the Understanding)

Any variation in how individual products flows into the manufacturing line will affect the final product, yet variability in excipients is inevitable. They can vary by type, or grade, from vendor to vendor, and even from batch to batch, with each one of these variables able to impact processability and functionality.

When building CM processes that result in consistent end-products, regardless of variability, we need fundamental knowledge of how excipients behave at each stage.

Mechanistically understanding the behaviour of powders in the feeders/hoppers is a crucial first step, based on the properties of APIs, excipients, and the total formulation. Yet there is little scientific evidence on the interplay between equipment performance and input materials.

Electrostatic powder charging, for example, is an important consideration for the quality of the end-product. Different excipients will have higher or lower charging potentials, and the higher the value, the higher the likelihood of a non-constant flow. Obviously, this could have implications for the safety and efficacy of the resulting tablets.



A schematic illustration of continuous tablet manufacturing using direct compression, wet granulation, and roller compaction.

Source: Sebastian Escotet, Fernando Muzzio

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The Experiments

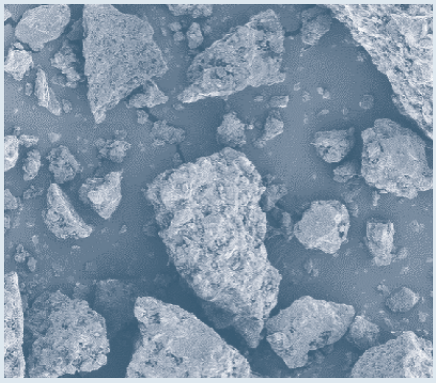
Understanding excipient variability is integral to the CM process but it is extremely complex. The parameters that dictate control vary from product to product, and even from grade to grade. For example, while particle size distribution (PSD) may be crucial for one product, for another it may be beta content or surface area.

As experts in this field, DFE Pharma evaluated the behaviour of differing grades of our own brands of lactose, microcrystalline cellulose and superdisintegrants when applied to CM processes. We confirmed that the varying intrinsic properties of the different grades of the well-established, regulatory-approved excipients, had differing effects on equipment performance.

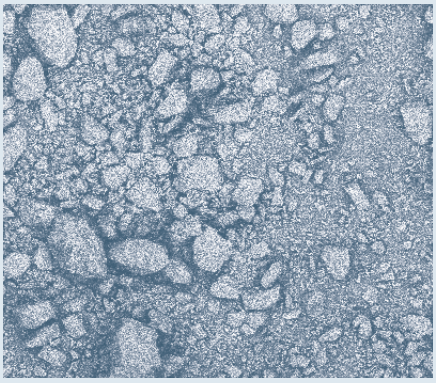
Using a stainless-steel hopper, we were able to show, for example, that differing particle shapes impacted on the performance of the hopper when varying hopper fill.

Despite being free-flowing, SuperTab 21AN, an anhydrous lactose with a shard shape, resulted in more flow around the outside of the equipment than the inside, as the hopper was being filled. The average trend showed the mass increasing as the hopper emptied.

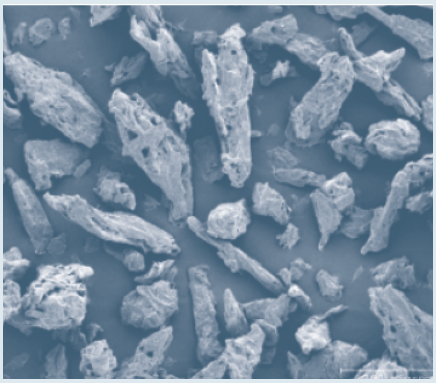
Pharmatose 200M, a monohydrate lactose with a tomahawk particle shape, was found to be a flowing excipient with a medium density and constant mass flow. This was also the case for Pharmacel 101, a fibrous microcrystalline cellulose (MCC).



SuperTab® 21AN



Pharmatose® 200M



Pharmacel® 101

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When the hopper was filled constantly, with material being continuously added to the product, SuperTab 21AN, in contrast to the varying fill scenario, showed a constant mass flow (see figures on the next page).

This was also seen with Pharmatose 200M and Pharmacel 101, but changes were observed as powder was added. We found that systems needed a five- to 20-second window for stabilisation when using these products. Such insights are invaluable in the design of CM processes.

Gericke Loss-in-weight feeders

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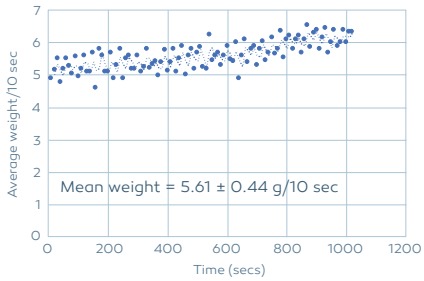
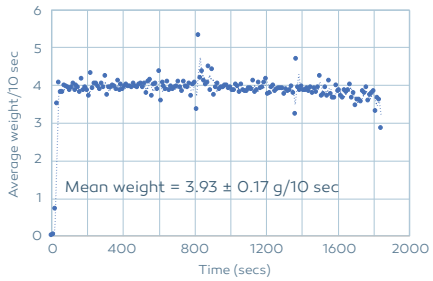
Result of feeder excipient behaviour – Varying hopper fill

SuperTab® 21AN



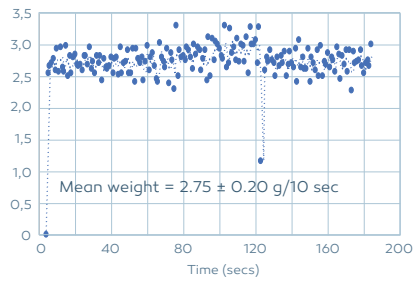
- Free flowing excipient
- Highest density
- Core flow observed
- Powder mass increasing with emptying of hopper

Pharmatose® 200M



- Flowing excipient
- Medium density
- Constant mass flow

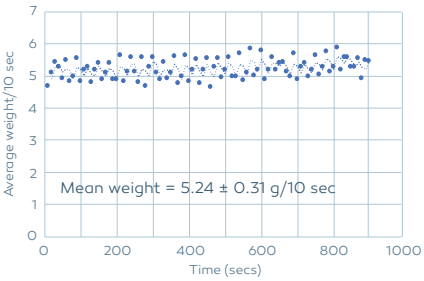
Pharmacel® 101



- Flowing excipient
- Low density
- Constant mass flow

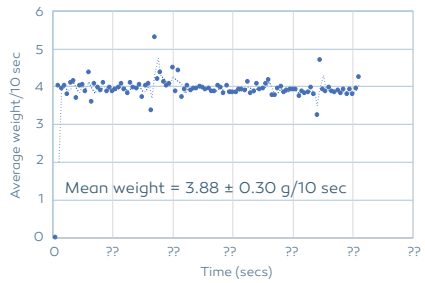
Result of feeder excipient behaviour – Constant hopper fill

SuperTab® 21AN



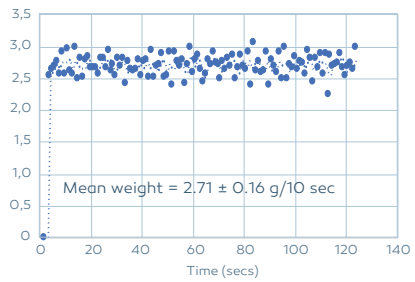
- Free flowing excipient
- Highest density
- Constant mass flow in time

Pharmatose® 200M



- Flowing excipient
- Medium density
- Constant mass flow

Pharmacel® 101



- Flowing excipient
- Low density
- Constant mass flow

	Varying hopper fill Mean weight	Constant hopper fill Mean weight
SuperTab® 21AN	5,61 g/10s	5,24 g/10s
Pharmatose® 200M	3,92 g/10s	3,88 g/10s
Pharmacel® 101	2,75 g/10s	2,71 g/10s

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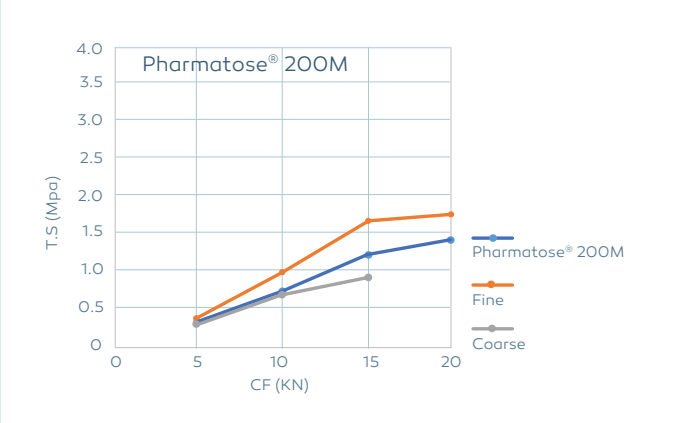
We know that the more controlled the particle-size distribution (PSD) of the excipients used, the more reliable the CM process. Understanding this has been a key factor in DFE Pharma's proud record on PSD consistency.

The effect of PSD consistency was demonstrated by our twin screw wet granulation study in which we altered our standard product, Pharmatose 200M, to create excipients that had finer and coarser particle size, and measured the effect on continuous unit operation.

After extrusion of the granules, we found differences in mean particle sizes, and these translated into varying levels of tensile strength in the resulting tablets. Ultimately, finer lactose produced harder tablets, whereas coarser excipients led to softer ones.

Granule and Tabletting behavior of lactose monohydrate



Granules N=3 batches N=5 tests	Bulk density (g/ml)	Tapped density (g/ml)	Practicle size (x50: micron)
Extruded material was dried and sieved over an 800 micron sieve			
Pharmatose® 200M	0.67	0.82	233
Fines added	0.63	0.80	208
Coarse added	0.70	0.96	244

Summary: *When feeding finer lactose monohydrate to a twin screw wet granulation line, harder tablets are produced, whereas coarser lactose monohydrate lead to softer tablets.*

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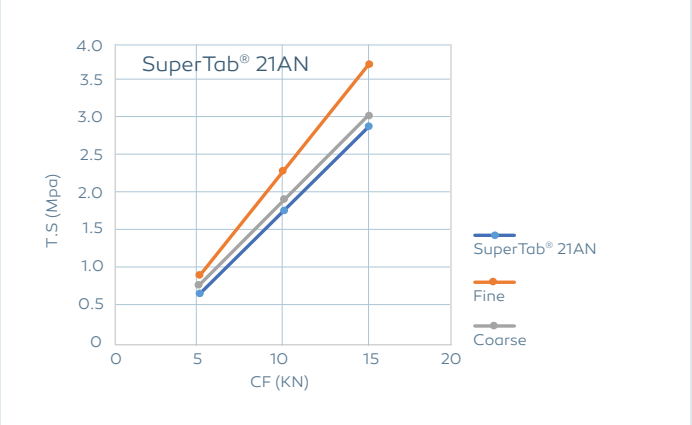
We were also able to show that compactability in anhydrous lactose is driven by beta-crystals. This experiment involved pressing tablets from anhydrous and monohydrate products, adapted to feature varying mean PSD, using increasing compaction force. The result was less variation in tensile strength of the tablets made from anhydrous than from monohydrate lactose, clearly demonstrating that the compactability of anhydrous lactose is driven by the beta crystals in the product, rather than the particle size of the material.

As these examples show, many factors – from flow to charging potential, particle size to compactability – influence the behaviour of excipients when they are applied to the CM process. The Certificate of Analysis (CoA), which focuses on the monographed parameters rather than functional characteristics, is not the whole story. Limiting variability without the need for labour-intensive, drawn out experimentation that impedes drug development pathways relies on a solid understanding of all of these factors.

Granule and Tabletting behavior of lactose anhydrous



Granules N=3 batches N=5 tests	Bulk density (g/ml)	Tapped density (g/ml)	Practicle size (x50: micron)
Extruded material was dried and sieved over an 800 micron sieve			
SuperTab® 21AN	0,64	0,72	510
Fines added	0,62	0,75	360
Coarse added	0,62	0,72	498

Summary: *The clear effects shown with Pharmatose® 200M were not visible with SuperTab® 21AN. This can be explained by the fact that the compctability of anhydrous lactose is driven by the beta-crystals rather than the particle size of the material.* *See page 9 for Phamatose 200M.*

3

Accounting for Variability: DFE Pharma's *'Stretch Batch Approach'*

Many organisations will assess the impact of excipient variability by testing multiple batches of excipients. However, this is a time-consuming, labour-intensive process that is not always executed diligently.

Instead, DFE Pharma advocate the use of multivariate data analysis (MVA) statistical techniques, which allow the simultaneous analyses of multiple variables to investigate patterns or clusters in the excipient dataset.

Our researchers work with our pharma partners to identify the major relevant sources of variation in the large, complex datasets, as well as noise variables that have no effect.

Batches near the Hotelling's T^2 95% confidence limit are then selected as a representative of a wide range of possible variation. Termed '***Stretch Batches***', these application-specific batches of excipients, based on DFE Pharma historical data, are truly representative of the possible variation, while remaining well within the specification limits of the CoAs.

The Stretch Batch Approach uses large data sets to enable MVA to identify major sources of variation, and facilitate a greater understanding of the relationships between all design inputs, from the desired quality attributes to process parameters and raw material attributes.

> "***The stretch batch approach*** is made possible by the wealth of historic and current data we hold and our understanding of what matters for the CM process. And it's important because using well-controlled excipients, designed for purpose, can reduce life-cycle risk in pharmaceutical development and production."

Insights gleaned from these stretch batches contribute to Quality by Design (QbD) by informing risk assessments and focusing the design of experiments on the most important parameters.

By effectively managing the variations that can impact on product performance, developers can slash the level of experimentation needed during product development and have all the information they need to quickly move up to commercial scale production.

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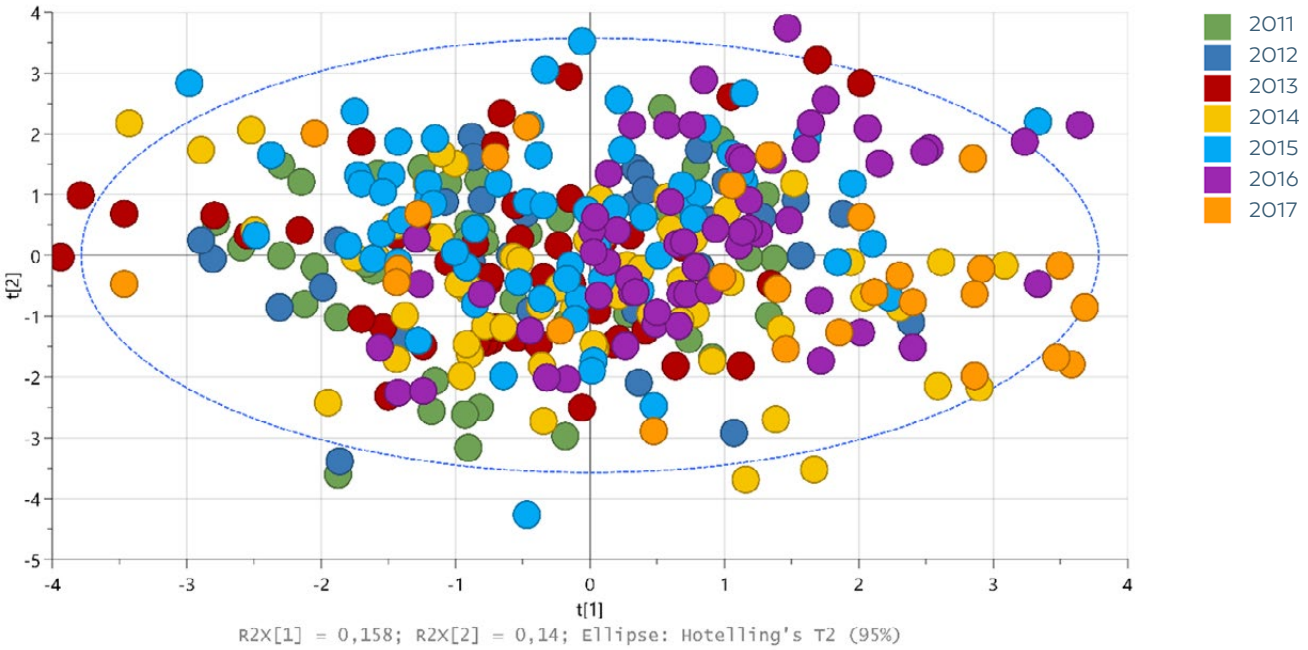
The industry can use the insights gathered from the Stretch Batch methodology to:

- look at how powder properties compare to the CoA
- run tests to find out which variations will impact on production processes or end- product quality
- design processes that account for a wide range of variability
- reduce the volume of experiments needed to account for variability
- demonstrate the safety and consistency of products to regulators
- avoid unexpected variation during the transition from development- to commercial-scale production

To learn more about what drives variation and how to account for it, visit the dfepharma.com/cm to read our study, ***Quality by Design: Using Multivariate Analysis of Batch-to-Batch Excipient Variation to Reduce Risk*** by Bastiaan Dickhoff.

Example of MVA scoreplot of SuperTab® 30GR (M2, PCA-X). Coloured according to year. No trend is observed in the data over the years. MVA is utilized to gain insights in variation and to select Stretch Batches, batches near the Hoteling's T2 confidence limit.



4 QbD in action

DFE Pharma is working with a pioneering pharmaceutical company to actively trial the Stretch Batch Approach, to better understand the design space and embed QbD into their manufacturing processes.

As part of its continuous manufacturing design process, the company is exploring the full span of variation they could expect from the product it had previously purchased from DFE Pharma.

DFE Pharma explains:
"Our Stretch Batch Approach gives customers the data they need to de-risk their CM design process.

"They can use this information to study how the full span of possible excipient variability might impact on the final product, and fully understand any potential risks to later phase development. It's about providing confidence around the quality and consistency of the final product."

"Knowing up front, from entry into late development, what the potential variables are means the customer can decide if they need to study them in our operational setting, or if they can consider them to be low risk."

In this case, if the company was to rely solely on its own testing, then, there would have been a risk that greater variation in upcoming batches could unexpectedly influence process or formulation performance.

Deploying the *Stretch Batch Approach* to its historical dataset, DFE Pharma found that the client had received two "centre point batches".

Instead, DFE Pharma supplied product batches from all four quadrants of the MVA plot, representing the maximum range of variability, for use in their testing programme.

Through a deep dive into the variation, researchers were also able to provide full breakdowns of the excipients functional parameters, by flow, PSD and density, to inform their studies.

As the company sets about designing its first CM process from scratch, it aims to utilise the Stretch Batch Approach method to design robust, compliant processes that will ensure the quality and consistency of its products.

Commenting on the process, the R&D Team highlight:
"DFE Pharma can tell us the variation we can expect from their product, and how to visualise it, as well as share some of the origin of that variability. We will then take the information and study its impact on our CM processes.

"The transfer of information, that data connection, is very important because it gives us confidence that we know the design space, and that we won't get stuck in a lot of 'afterwork' once we have the processes up and running on the commercial plant."

Want to know more about how DFE Pharma's collaborations could help you?
Contact: cm@dfepharma.com

5 The Value of Expertise and Partnership

The pioneering companies making the FDA-recommended move to CM understand that while traditional processes such as direct compression, roller compaction, or wet granulation are used within the continuous lines, the role of excipients within them can differ from traditional batch processing. Pharmaceutical dosage form production requires a thorough understanding of all design inputs, from raw materials such as excipients and APIs, to formulations, processes or equipment. Without it, the design or quality of the end-drug is compromised.

DFE Pharma's heritage and understanding of excipient variability, built over 100 years of research and development, is key to helping the industry makes this inevitable transition. We have studied how the parameters of excipient variation within specification may impact processes such as continuous feeding, granulation and tableting and can provide valuable input to improving the consistency and quality of the manufacturing process. Additionally, we have a wealth of meaningful, historical data which we have used to devise the ***Stretch Batch approach***.

This novel technique can inform the efficient construction of compliant, Quality by Design (QbD), CM processes by potentially reducing the number of manufacturing-related experimental studies required during drug product development.

Robust drug development and successful CM starts with, and is dependent on, dialogue and collaboration between the pioneers and experts in their respective fields. Whilst excipients are but a small element of the overall drug development process, they are central to it.

At DFE Pharma, we are the excipient experts:

- we have insight over the variants of consistency
- we have the wealth of historical data and proven experience to share
- we have a proven knowledge bank through the ***Stretch Batch approach***.

At DFE Pharma, we care. We understand that realising the potential of CM can help bring life-changing, innovative medicines, that are affordable to all, to market as quickly as possible.

Let's talk.

DFE Pharma can support you with:

- Excipient expertise in selection of excipients for Continuous Manufacturing
- Excipient insights in variation (Score and loading plots using multi variate analysis (MVA))
- Excipient stretch batches of the (MVA) historical product space
- Multi-functional excipients designed for Continuous Manufacturing

For more information:

dfepharma.com/cm

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