


# CORRELATION BETWEEN POWDER RHEOLOGY DATA AND PROCESSABILITY IN SOLID DOSAGE FORM MANUFACTURING

**Erik Skibsted**
Principal Scientist, Oral Protein Formulation, Novo Nordisk

**The Quality by Design (QbD) paradigm is being introduced to more and more R&D and manufacturing units in the pharmaceutical industry. There are many good reasons for this, e.g. clear scientific development routes, high product quality, focus on safety and efficacy, economy and increased process and product knowledge. Most often, there is a large focus on identifying the critical process parameters (CPP) that influence the product quality and should be controlled to consistently produce the same quality, but just as important a component in a QbD development strategy is characterisation of raw materials and to understand how variations in raw materials influence the manufacturing process and the critical quality attributes (CQA) of the drug product.**

This article will show some preliminary results from powder characterisation and how the data correlates to process performance and drug product quality in solid dosage form development projects. Data from two development studies will be shown. The development and manufacturing of solid dosage forms relies heavily on powder material. API and tablet excipients are most often handled as a granular material. The powders are mixed and compressed to form a tablet. It is essential to characterise the mixing, flow and compression properties of the powders in order to be able to produce a high quality drug product. Traditional powder characterisation relies on static methods e.g. angle of repose, density and tapped density, but new techniques are emerging in the pharmaceutical R&D laboratory, for example, quasi- and dynamic techniques like compression methods and flowability tests performed under different conditions e.g. compression or aeration. By subjecting the powders to different environments during testing, the test results are more relevant when correlating them to process observations.

> "Key to understanding powder flowability is characterising the forces acting upon and between the particles"

Key to understanding powder flowability is characterising the forces acting upon and between the particles. A generalised depiction is shown in **Figure 1** on page 32. Each particle is affected by the gravity and the cohesive forces between the particles. The cohesive forces are Van der Waal forces. If particle one should be able to flow away from particle two and three, the gravity acting on particle one needs to exceed the cohesive forces between the particle and the neighbouring particles.

$$m_1 g > f_{coh\,a} + f_{coh\,c}$$

### Study 1: investigating optimal mixing times for powders with different cohesiveness

A very important unit operation in solid dosage form is powder mixing. This process can be performed in many different types of equipment and controlled by various factors like speed and duration. In order to obtain a homogeneous blend, the powder must have sufficient flowability. The flow properties are highly dependent on the cohesive forces acting between the particles. In this study, the mixing

behaviour of three powders with different flow and cohesiveness was investigated.

The flow properties were measured by using a FT4 Powder Rheometer (Freeman technology, UK). With the FT4 instrument, a 25 millilitre powder sample was placed in a glass cylinder. A specially engineered blade is forced through the sample in a downward spiral movement with a constant tip speed. The energy required to move the blade from the top to the bottom of the sample was recorded. As the blade is moving, a stress transmission zone is created in front of the blade (**Figure 2**). For a cohesive powder, the stress transmission zone is small and transcends only a short distance in front of the blade. This is because a cohesive powder contains a lot of entrapped air that is removed when the blade is moved downwards. A small stress transmission zone means that a small amount of energy is required to move the blade at a constant speed to the bottom. For the non-cohesive powder, a large stress transmission zone is established during blade movement and a higher amount of energy is required. The non-cohesive powder has a small amount of air entrapped.

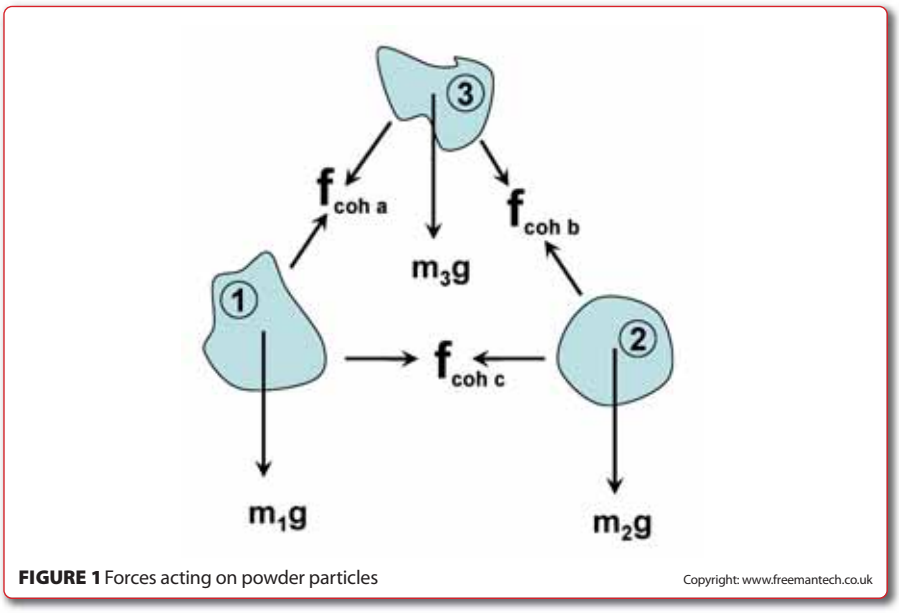



**FIGURE 1** Forces acting on powder particles



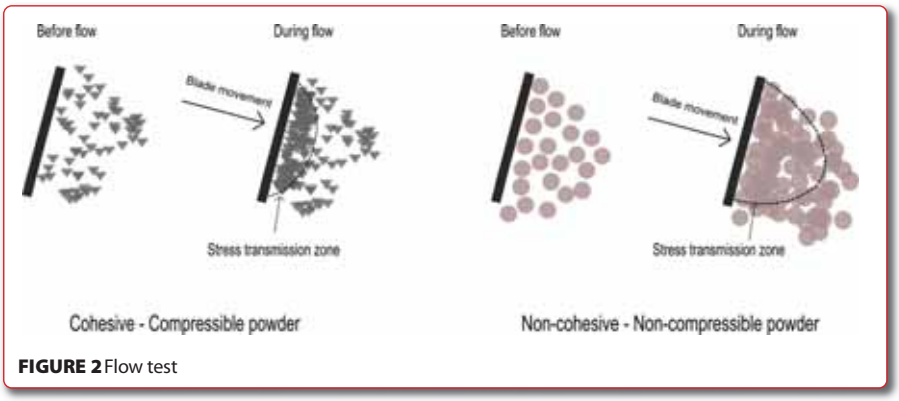



**FIGURE 2** Flow test

In this study, the flow properties of three commonly used pharmaceutical excipients were characterised, i.e. micro-crystalline cellulose (MCC), hydroxypropyl methyl cellulose (Methocel) and Lactose. The test was carried out seven times using a constant tip speed of 100 mm/second (stability test). Then the test was performed four times using different tip speed i.e. 100, 70, 40 and 10 mm/second (variable flow rate test). MCC and Methocel were tested in triplicate and Methocel was tested once. The test results are depicted in **Figure 3**. It was clear that Lactose was the most cohesive powder followed by MCC and finally Methocel as the least cohesive powder.

> **" A small stress transmission zone means that a small amount of energy is required to move the blade at a constant speed to the bottom "**

To investigate the mixing performance, three different experiments were performed. Experiment A: 16.8 w/w % Lactose (high cohesiveness) mixed in MCC (middle cohesiveness), Experiment B: 16.8 w/w % Lactose (high cohesiveness) mixed in Methocel (low cohesiveness) and C: 16.8 w/w % Methocel (low cohesiveness) mixed in MCC (middle cohesiveness). Each experiment was performed in triplicate. The mixing experiments were carried out in small glass vials that were fixated in a rotary laboratory mixer. The vials completed 120 rotations and at 20 different time points (number of rotations), the mixer stopped, the vials were removed and placed on a near-

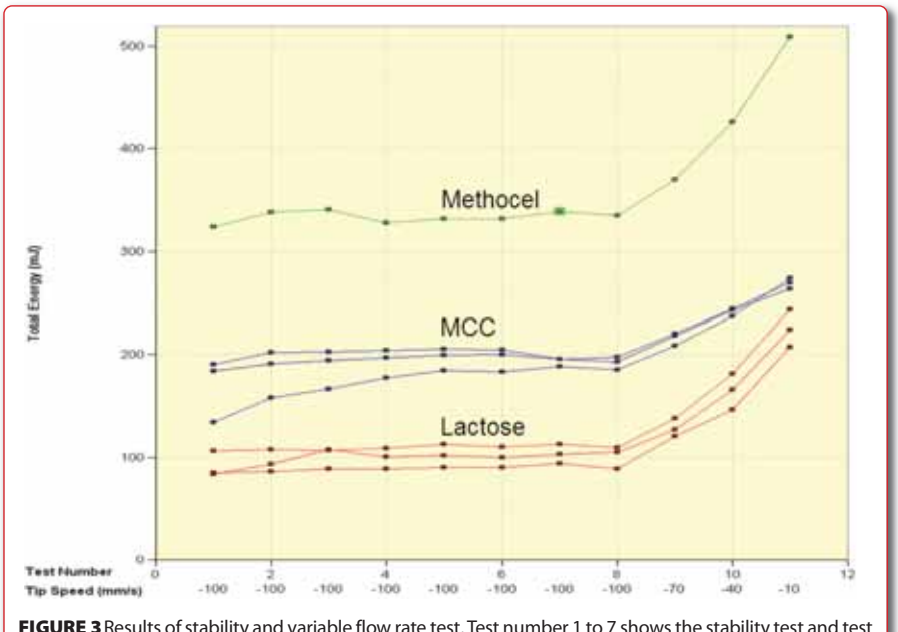



**FIGURE 3** Results of stability and variable flow rate test. Test number 1 to 7 shows the stability test and test number 8 to 11 shows the variable flow rate part

infrared reflectance measurement module (Bruker, FT-NIR MPA analyser) and a reflectance spectrum was measured through the bottom of the vial. Using built-in calibration models, the w/w % concentration of the minor component in the blend was predicted. By plotting the percentage versus number of rotations, mixing curves for each experiment were generated. When the mixing curve is stabilised on the target value, the blend is homogeneous. The average and standard deviation (N=3) for each of the experiment types is plotted in **Figure 4** on page 34. When mixing high cohesive Lactose in medium cohesive MCC, the blend was first homogeneous after 80 rotations. When mixing high cohesive lactose in low cohesive Methocel, the blend was homogeneous after 40 rotations. In the last experiment, low cohesive Methocel was mixed in medium cohesive

> "Samples of formulation excipients and formulation blends were characterised by five different tests using a FT4 Powder Rheometer"

MCC and this blend was homogeneous after 18 rotations. The mixing curves for Methocel in MCC was also much more stable compared to the two other experiments, indicating that it was truly homogeneous. The study shows how the cohesiveness of the powder components has a high impact on the mixing performance. Increasing cohesiveness requires longer mixing times in order to obtain a homogeneous blend.

### Study 2: Characterisation of formulation blends and process performance

When the powder blend is mixed homogeneously and ready to be applied in the tableting process, it is important that the powder can flow in a consistent manner from the hopper and into the dies in the tableting machine. This is important as non-optimal flow will affect the dose uniformity and up-scaling will be difficult.

In this study were two different formulations showing distinct different behaviour during tableting in pilot scale manufacturing. Formulation A showed bad flow properties during tableting as the blend was not flowing out of the hopper in a steady flow but was creating a 'rat hole' in the centre of the powder bed (**Figure 5C**, page 34). Formulation B showed nice flowability in the hopper during tableting (**Figure 5B**, page 34).

Samples of formulation excipients and formulation blends were characterised by five different tests using a FT4 Powder Rheometer. From each test, the software calculated parameters that summarised the test results. In total, 33 parameters were calculated from the four tests. Seven blends with formulation A, seven blends with formulation B and six excipients were characterised by the tests creating a data matrix of 20x33 data points, each row representing a powder sample. The data matrix was imported into a software program for calculating multivariate statistical models (SIMCA 13, Umetrics). A principal component analysis (PCA) model was fitted to the data. Four principal components could describe 89 per cent of the original variation in the 33 parameters. When the score values for principal component 1 (PC1) and 2 (PC2) were plotted in a 2D score plot (**Figure 6**) it was clear that excipient samples 1, 2 and 3 that were used in Formulation A, and the formulation A blend samples were all

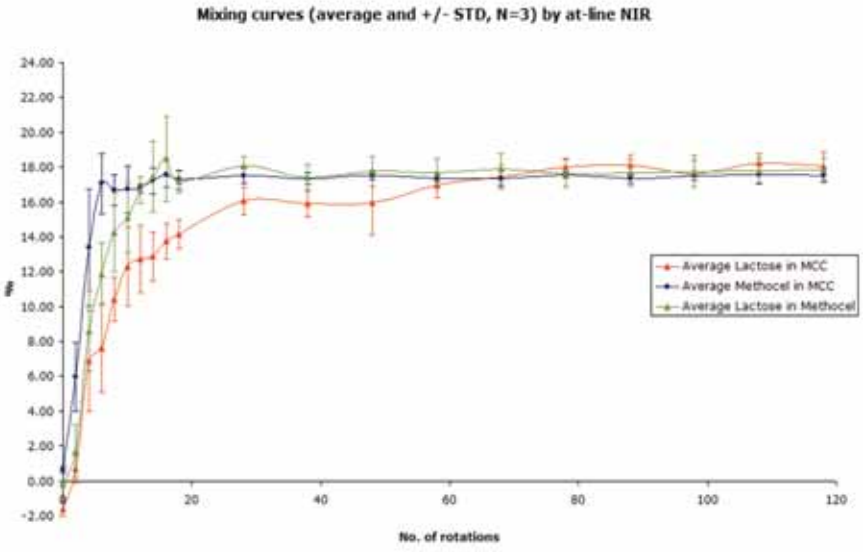



**FIGURE 4** Mixing curves

grouped in a cluster in the lower part of the plot. Excipient 4 and 5, used in formulation B together with formulation B blend samples, were all clustered in the upper part of the plot. Excipient 6 was clearly completely different from all other powder samples. Excipient 6 was magnesium stearate which is an extremely fine and highly cohesive powder that has very bad flow properties. By investigating the loading plots from the PCA model, it was found that it was the parameters from three of the five tests that discriminated the two formulation types i.e. a shear test, a flowability test and an aeration test.

> "The PCA model approach seems to be a useful tool to evaluate many characterisation parameters at the same time"

The PCA model approach seems to be a useful tool to evaluate many characterisation parameters at the same time. If more test parameters can be used to discriminate between good performing and bad performing powders, the combination of numerous test parameters and PCA modelling could have a higher discrimination power compared to using only one parameter from one test. When the PCA model is established, future samples can be analysed and their test parameter results can be projected onto the score plot. The relative position to the two clusters in the plot can be used to assess the process behaviour of the sample.

## Summary

When a QbD development strategy is being used it important to identify and control process factors that control drug product quality. But it is also as important to characterise material parameters and understand how their variability influences the processability of the materials as well as the drug product quality. In the two examples, presented powder characterisation with a modern rheometer was used to understand mixing performance as well as flow properties in two solid dosage form manufacturing studies

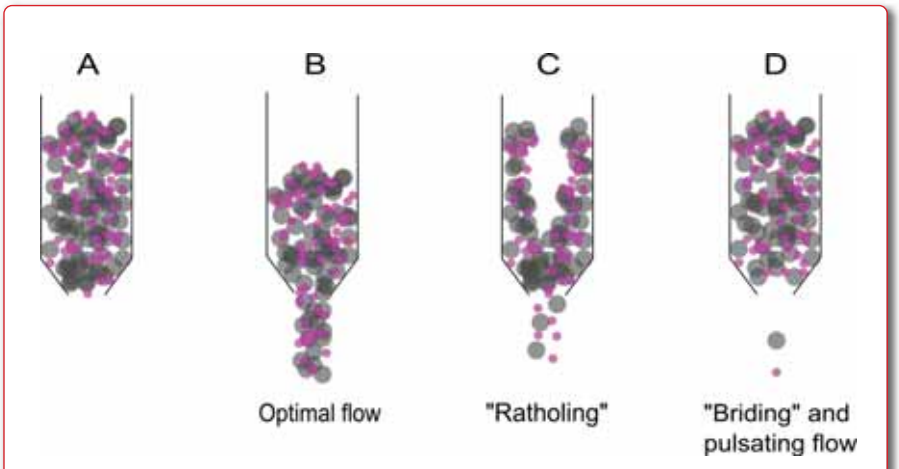



**FIGURE 5** An optimally mixed blend (A) can flow out of the hopper in an optimal flow (B) or if the blend flow properties are inferior 'ratholing' can occur (B) or restricted flow with bridging at the outlet (C)

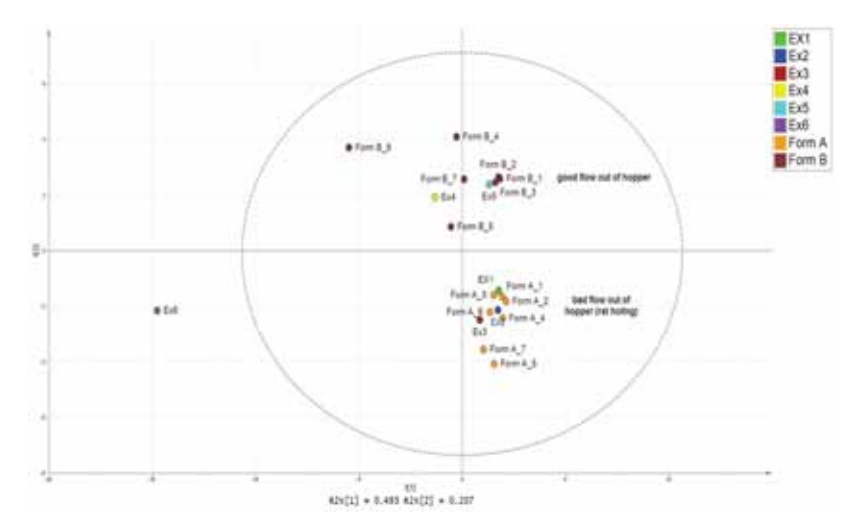



**FIGURE 6** Score plot of PC1 versus PC2. The dotted ellipse shows the 95 per cent confidence interval

## BIOGRAPHY

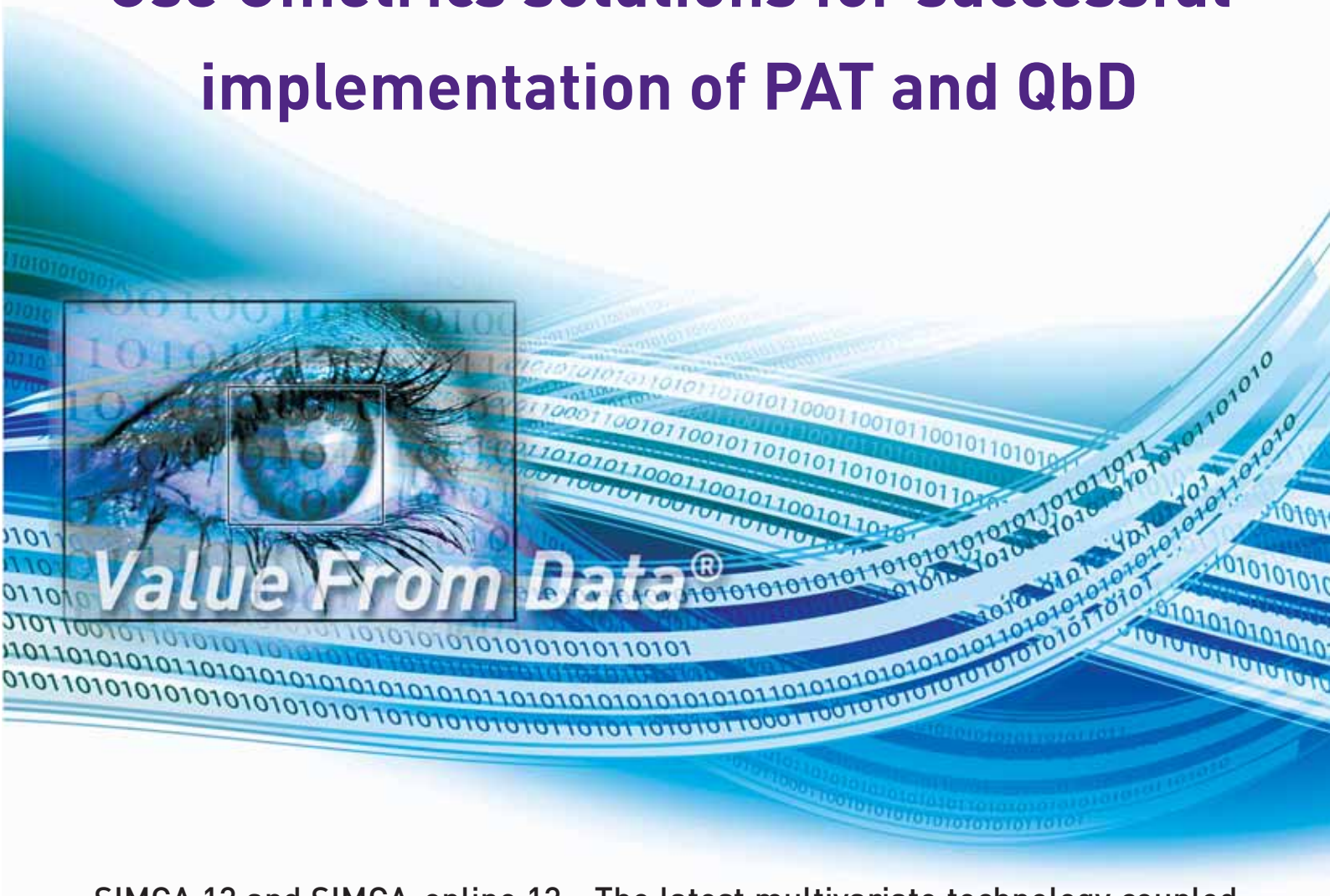
**Erik Skibsted** graduated with a Masters in chemistry from the Technical University of Denmark. In 2005, he joined Novo Nordisk as a research scientist working with spectroscopy, chemometrics and advanced trouble-shooting. After being appointed principal scientist in 2007, Erik became responsible for spectroscopy, chemometrics, quality by design and risk assessment in Oral Protein Formulation in 2009.

EXPLORE • ANALYZE • INTERPRET

MONITOR • PREDICT • CONTROL

UMETRICS

# Use Umetrics solutions for successful implementation of PAT and QbD




SIMCA 13 and SIMCA-online 13 - The latest multivariate technology coupled with powerful visualization tools. Making complex data analysis easy to use and implement. Modern, intuitive and flexible interface. Audit Trail for compliance with 21 CFR part 11. Developed in accordance with GAMP 5.

**Providing *Value From Data***

SIMCA® SIMCA-online®

www.umetrics.com