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White Paper

Considerations for Dosing Accuracy in a New Carrier for Dry Powder Inhalation

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Inhalation drug delivery methods are attractive, noninvasive routes when rapid onset of action, minimal side effects and excellent bioavailability are desired. However, not many drugs are administered this way and accurate dosing can be a challenge.

What makes dosing problematic is the very small amount of dosage and a variety of forms of active pharmaceutical ingredients (APIs) that may be inhaled. Liquids carrying dissolved or suspended APIs may be atomized into small droplets for delivery to the lungs using metered dose inhalers. Solid APIs may be converted to fine powders by mechanical micronization for delivery by dry powder inhaler (DPI) devices.

Formulating for DPI delivery is challenging. API particle sizes affect absorption and must fall within the range of 1-5 µm. Because powders this fine tend to cohere, they are often combined with solid excipient carriers to improve drug stability and dose control. During inhalation, however, the API and carrier particles must separate so that only the API is delivered to the lungs.

Currently, most powder blends for DPI formulations are based on lactose monohydrate as an excipient carrier. Despite the widespread use of this carrier, microdosing these blends into pre-metered DPIs is still a critical step. Furthermore, as a carrier, lactose presents several challenges.

Because of the Maillard reaction, reducing sugars such as lactose are a major threat to the stability of peptides, biomolecules and small-molecule APIs with primary amine groups. Additionally, a significant number of patients are lactose intolerant.

A new, engineered, inert mannitol excipient

Recently, a new carrier based on an inert mannitol (Parteck® M DPI excipient) has become available to improve the flow and release characteristics of APIs in drugs delivered via dry, inhaled powders. Unlike mannitol itself, which – according to pharmacopoeia – still contains up to 0.10% reducing sugar impurities, the Parteck® M DPI excipient is physiologically inert and will not compromise API integrity. A lower specification limit (0.05%) for reducing sugars – with even lower actual values (see Figure 1) – greatly reduces the Maillard reaction's effect on sensitive APIs. The material's low water content and non-existent hygroscopicity also reduce the risk of API hydrolysis, promote reliable flow and help minimize bioburden. Its bulk and flow properties are well-suited for optimal blend homogeneity, API delivery to the lungs and constant dose uniformity. Lastly, it is a viable alternative for patients with lactose intolerance and is of non-animal origin.

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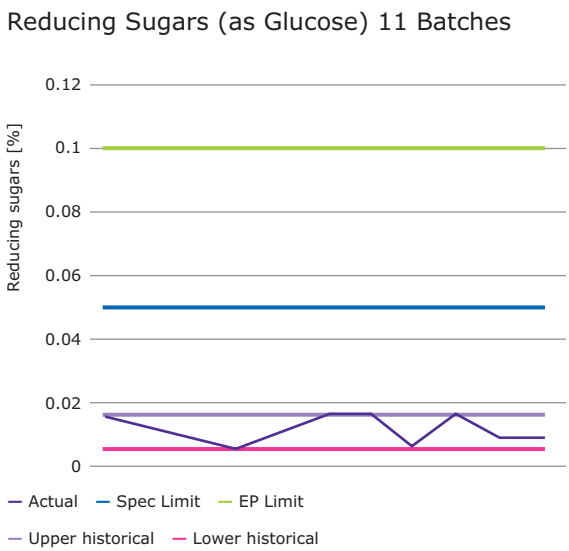
Impurities
Example: Reducing sugars in Parteck® M DPI batch to batch

Figure 1:

Exemplary measurement results of reducing sugar levels as measured in Parteck® M DPI batch to batch reinforce its suitability as an inhaled excipient.



Batch	Reducing Sugars
1	0.014%
2	0.011%
3	0.008%
4	0.005%
5	0.011%
6	0.015%
7	0.016%
8	0.006%
9	0.015%
10	0.008%
11	0.008%

What we know so far about Parteck® M DPI excipient's behavior

To date, our studies of Parteck® M DPI excipient have produced a number of useful findings. Compared with lactose, its structured surface demonstrates improved mixture homogeneity, with similar fine particle fractions. At the same time, the API load can be increased to much more than 15%. A broad particle size distribution (PSD) has demonstrated better fine particle fractions (FPF) than more monodisperse PSD fractions on the same surface, while the addition of a fines fraction offers no improvement.

Furthermore, the material has been found to work equally well with various delivery methods, including reservoir type and single dose devices. In reservoir type inhaler devices, the new excipient has already demonstrated very good dosing behavior due to superior flow properties. In the case of single dose devices, doses are prefilled in capsules or blister units by machine. This dosing equipment must be highly accurate at low dosage amounts (10-15 mg). Since this accuracy is dependent upon the properties of the load, we needed to learn more about the behavior of the Parteck® carrier in this context.

The aim of this study was to assess the dosing performance of Parteck® M DPI excipients with typical equipment used in DPI manufacturing, and to examine how the carrier's PSD affects this performance.

Comparison of Parteck® M DPI excipient samples with different sized particles

Two sets of samples were tested. One, called M 100, contained the carrier mannitol (Parteck® M DPI excipient, Merck KGaA, Darmstadt, Germany) with a median diameter D(50) of 100 µm. The other, M 200, contained the same carrier but with a D(50) of 200 µm. Particles were dispersed dry at 0.5 bar (RODOS/L) and size distribution was measured using laser light diffraction (Helos/BF).

Micronized lactose monohydrate (Lactohale LH300, DFE Pharma, Goch, Germany) was chosen as the Model API and added to the mannitol carriers at 5%. The mixture was forced through a 1 mm sieve to eliminate agglomerates and then homogenized for 20 minutes at 23 rpm using a Turbula® blender Type T2A.

Bulk and tapped density were measured according to European Pharmacopoeia Ph. Eur. 8.0 (2.9.34, Method 1).

Studies were then carried out on the samples as follows:

Powder flow properties

An FT4 powder rheometer with a 25 mm test cylinder was used to measure:

- Basic flowability energy (BFE), determined by measuring the axial and rotational forces acting on a blade as it rotates down through the sample
- Compressed density (compressibility), determined by measuring the volume change effected by applying a defined normal force (15.0 kPa) with a vented piston

Results are shown in Figures 2 and 3.

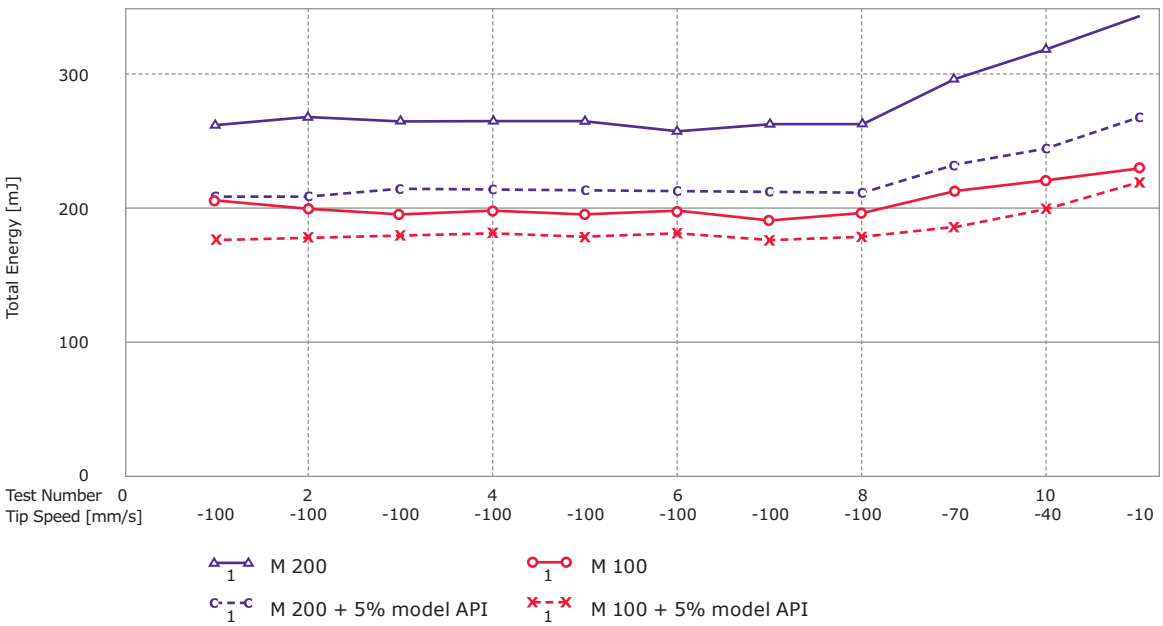


Figure 2:

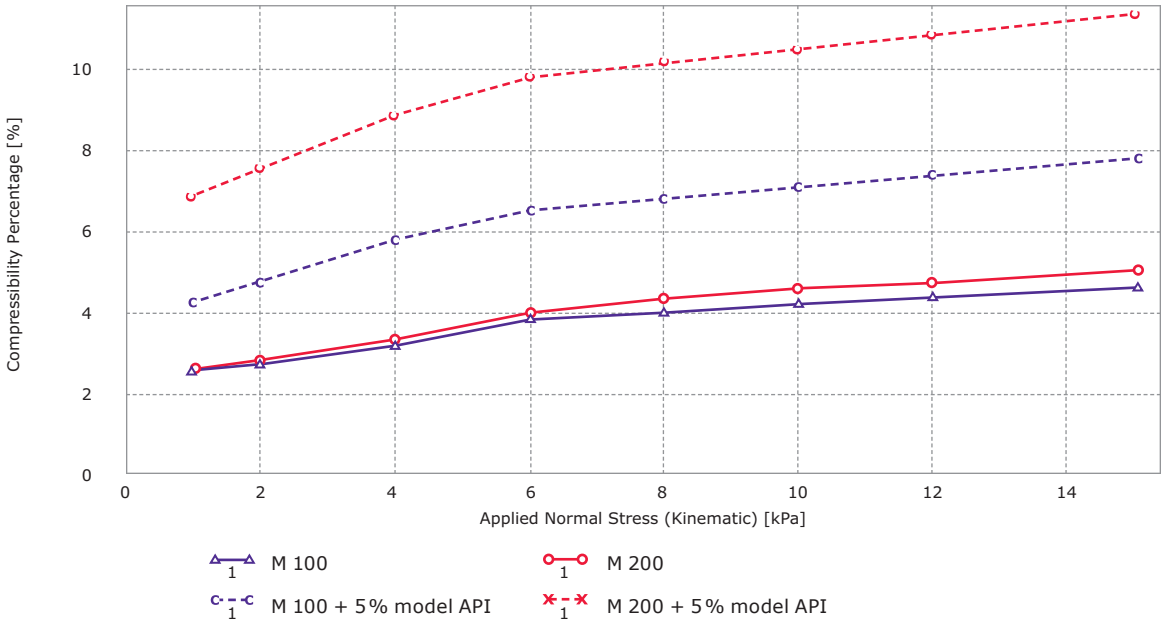
Basic flowability energy (BFE) – a lower energy input requirement predicts greater dosage accuracy

The measurement of total energy input by flow rheometer FT4 shows significantly lower energy input is needed for the finer grade carrier. Also, the addition of the fine-grade model API reduces the energy input. Lower energy input – as with the smaller particle-sized carrier – predicts better dosage accuracy.

These measurements demonstrate slightly higher cohesivity for the finer grade carrier material and for carriers mixed with fine-grade model API.

Figure 3:

Compressed density – higher compactability means better dosage system performance



The compactability of carriers with different particle sizes shows a significant improvement if fine-grade model API has been added to the carrier granulate. The finer grade carrier shows a better response to this addition than the coarser one, even though the carriers performed similarly without the model API.

Because a certain degree of compactability is needed for dosage systems operating with compaction or vacuum, to keep the dosage in a cavity for transfer, dosing performance is expected to improve with the addition of the fine-grade model API.

Compactability is not to be confused with compressibility – an expression used in the process of tableting. The parameters are based on totally different mechanisms. In compactability, we are only interested in the behavior of the free flowing powder.

Powder dosing

Two types of commonly used dosing technologies (Harro Höfliger, Allmersbach i.T., Germany) were tested.

- Dosator: ModuC LS capsule filler with interchangeable dosing modules (dosator size 5, piston height 6.0 mm, powder bed height 13 mm, machine speed 50 cycles/min)
- Vacuum drum: ModuC MS capsule filler with interchangeable dosing modules (vacuum drum system dosing chamber volume 22.5 mm^3, vacuum -400 mbar, machine speed 100 cycles/min)

Results are shown in Figures 4 and 5 a/b.

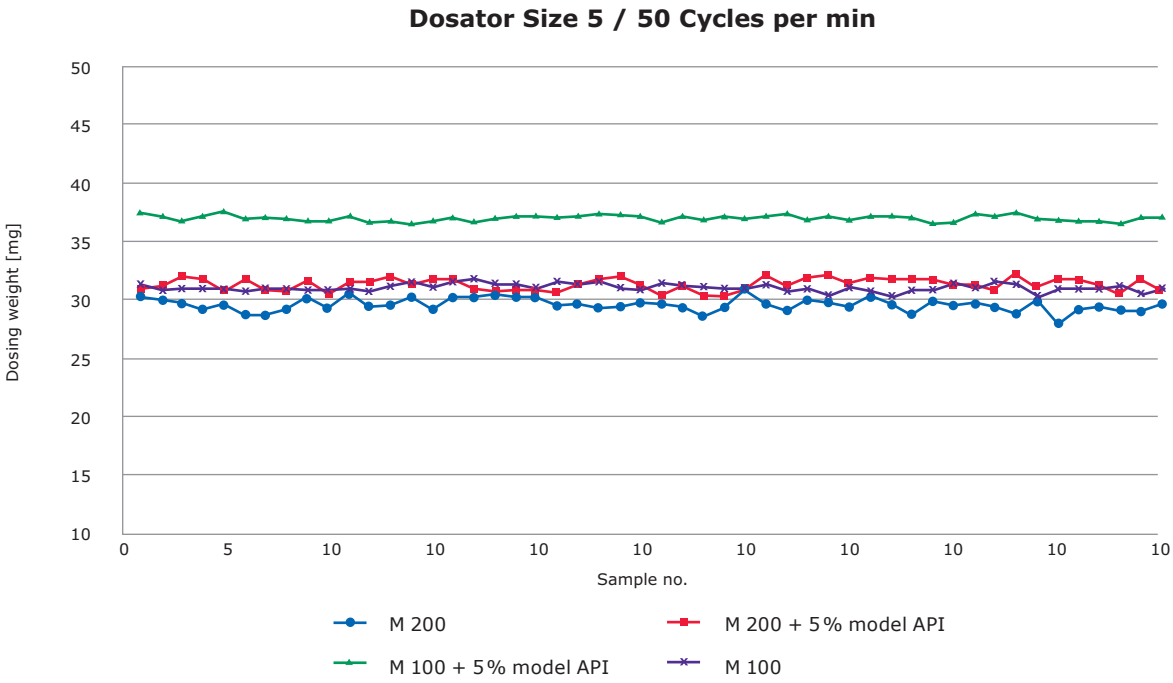


Figure 4:

Dosator behavior is reasonable for both sample types with and without the fine API

In a practical trial with a dosator module using both carrier powders of different particle sizes, with and without the model API, all powders and blends exhibited good reproducibility and a reasonable relative standard deviation (RSD) of less than 2%. The finer grade carrier showed even better results, with an RSD of less than 1%. The addition of 5% model API resulted in greater accuracy in both cases. The higher weight of dosage in the finest sample (M 100 + 5% model API) is most likely related to its higher compactability.

These results indicate that a dosator device can succeed at commercial scale with all tested powders. Performance improves with the progression from coarse to finer particle-sized carriers and through the addition of fine-grade API particles. These results confirm the predictions from the flow rheometer findings.

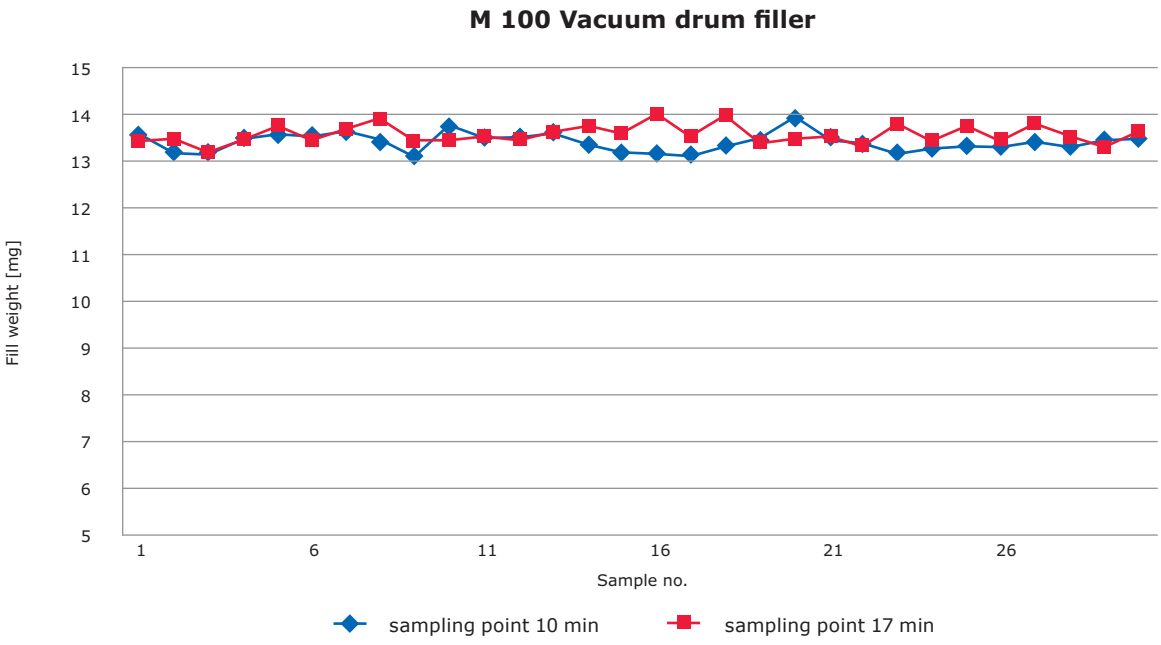


Figure 5a:

Practical trial with a vacuum drum filler using the carrier M 100 with 5% API added, demonstrates satisfactory dosing results

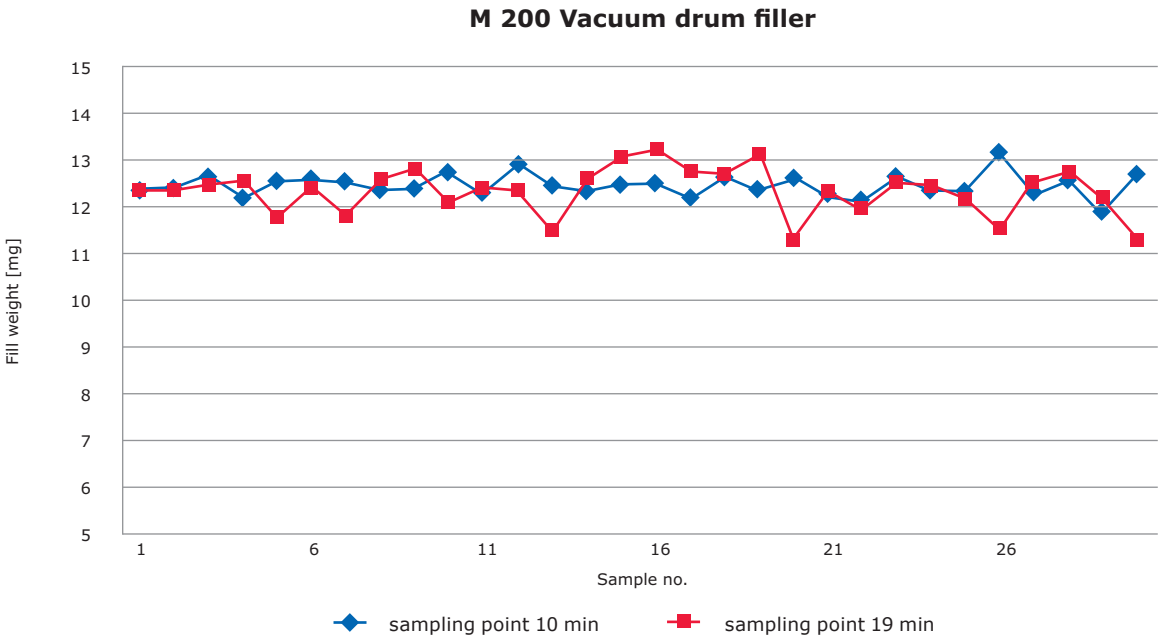


Figure 5b:

Practical trials with a vacuum drum filler using the carrier M 200, with 5% API added, demonstrates satisfactory dosing results

Dose fill weights achieved by the vacuum drum filler also represented good performance in all tested powder types. The better standard deviation, especially at the later time points, was seen with the smaller particle-size carrier. This consistency correlates to the smaller particle-size carrier's better compactability as measured by the powder rheometer.

Conclusions

This study has confirmed the suitability of FT4 powder rheometer evaluation for predicting the performance of powder blends in typical dosing technologies. Because additional components – in this case, the model API – can alter the powder properties significantly, the results also demonstrate the importance of evaluating the powder behavior of the final blends. While the PSD of such a carrier has some impact on dosing accuracy, this study shows that the newly available mannitol-based DPI carrier (Parteck® M DPI excipient) is suitable for commercial dosing systems commonly used for inhalation powders.

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