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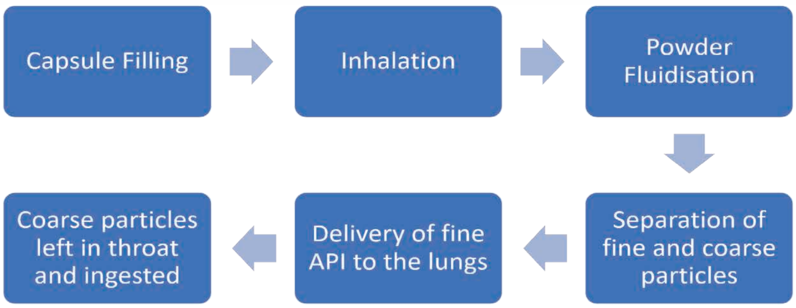
Applications of the FT4 Powder Rheometer® for Dry Powder Inhalers

Dry Powder Inhalers (DPIs) are used to deliver a controlled dose of active pharmaceutical ingredient (API) to the deep lung. An excipient, for example lactose, typically carries the fine particles of the API from the device before being stripped away as the API continues to the lungs. The coarser excipient is usually trapped in the throat and subsequently swallowed. However, the properties of the excipient will significantly influence performance, from the initial filling through to dosing and drug delivery.

Identifying the properties of a powder or blend associated with optimised performance allows compatible formulations to be developed, without the significant financial and time implications associated with running samples through the process.

A significant majority of DPIs are passive. This means that the energy available for fluidisation and delivery of the drug to the lungs must be supplied by the patient inhaling. A key goal for formulators, therefore, is to ensure that the energy required for fluidisation is sufficiently low making the product suitable for patients with reduced lung function.



An upper boundary limit of five microns is usually applied when determining fine particle dose (FPD), the mass of fine particles which on basis of size are likely to deposit in the lung. Due to this small particle size, the attractive forces between particles are relatively strong, and so the powder tends to be highly cohesive. Such powders do not usually flow freely and are often prone to agglomeration. One of the core problems facing DPI formulators is how to deliver particles within the required size range when the properties of such powders can make both dosing and dispersion problematic. Determining which properties of the powder are key to defining process performance is vital to DPI formulators.

Existing techniques such as Angle of Repose testing, Flow through a Funnel, and Bulk Density measurements, generating Hausner Ratio and Carr's Index, are well-documented. However, these methods were developed without the benefits of modern technology and lack the sensitivity to reliably identify subtle variations between powders that behave differently in process or application.

The FT4 Powder Rheometer® is a universal powder tester that provides automated, reliable and comprehensive measurement of bulk material characteristics. This information can be correlated with experience to improve processing efficiency and aid quality control. Specialising in the measurement of dynamic flow properties, the FT4 also incorporates a shear cell, and the ability to measure bulk properties such as density, compressibility and permeability, enabling comprehensive characterisation of a powder in a process relevant context.

Geometry-related Filling Performance

The performance of four excipients (S1, S2, S3 & S4) was evaluated in two filling configurations, A and B, shown in Figure 1. In both configurations, powder flows down a channel, into a pocket within a rotating wheel.

As the wheel rotates, powder is transferred into a receptacle. The wheel then rotates back around to the filling position. In both geometries, the volume of the pocket is the same, however Configuration A has a narrower feed channel, which is closely matched to the opening of the pocket in the wheel, while Configuration B has a wider feed channel.

Regardless of geometry, the aim is to achieve an efficiently filled pocket and receptacle. Process performance was described using a process-capability index (C_{pk}), derived from the weight-variation of the doses produced.

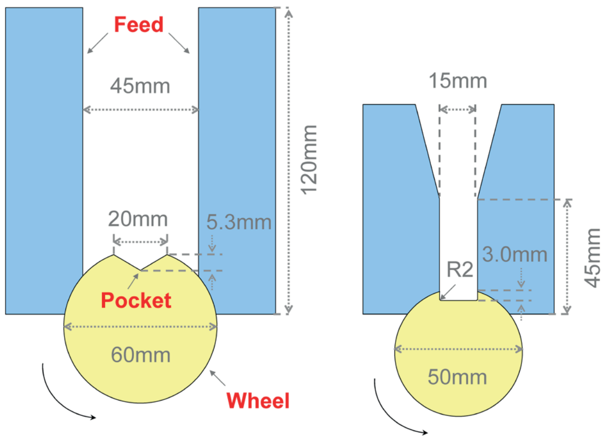


Figure 1: Filling geometry Configurations A (left) and B (right).

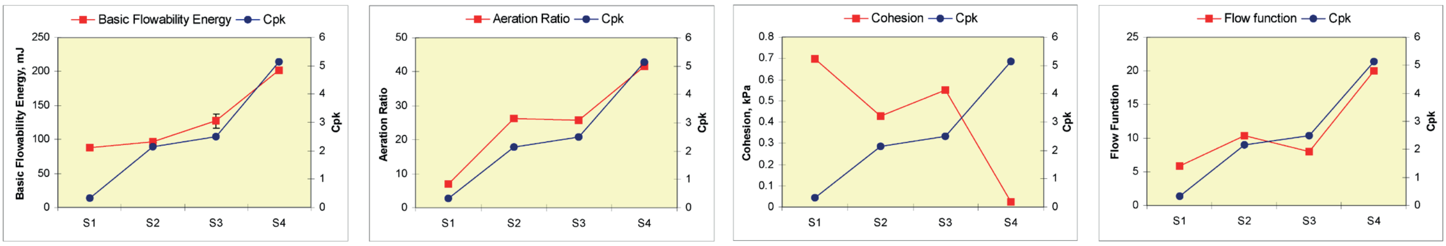


Figure 2: Correlations between filling performance (C_{pk}) and powder properties in Configuration A.

The four excipients were characterised using the FT4 Powder Rheometer. Dynamic testing was used to measure Basic Flowability Energy (BFE) and Aeration Ratio (AR). BFE is defined as the energy needed to establish a flow pattern of a twisted blade traversing downwards through the powder bed along a helical path. AR is the ratio of the BFE and the energy required for the blade to follow the same path while air is passed through the powder at a constant flow rate. Shear Cell testing was used to determine Cohesion and Flow Function.

S4 exhibited the least cohesive behaviour, characterised by high BFE, AR, and Flow Function values, and a low Cohesion value. In contrast, S1 was the most cohesive of the four samples.

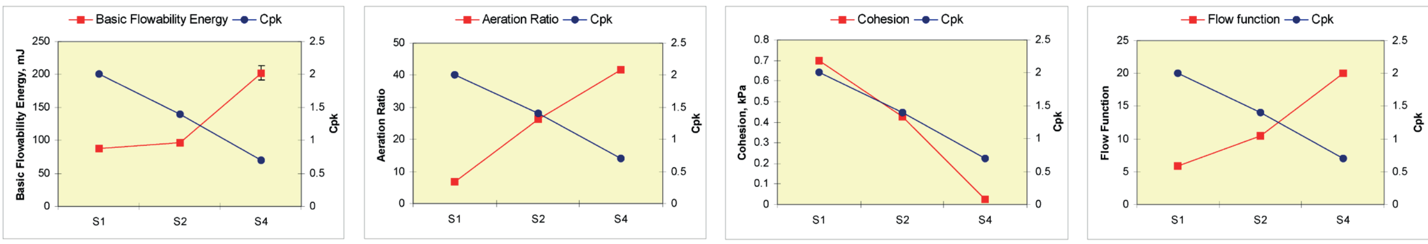


Figure 3: Correlations between filling performance (C_{pk}) and powder properties in Configuration B.

Figures 2 and 3 show the correlations between powder properties and filling performance in Configurations A and B respectively. Note that S3 was not intended to be processed in Configuration B.

For Configuration A, less cohesive materials performed better in the process. This indicates that for this configuration the powder needs to be able to flow freely down the channel and into the pocket to achieve optimum performance.

For Configuration B, more cohesive powders, with lower BFE, Aeration Ratio and Flow Function values, and high Cohesion values, demonstrated better performance. It is likely that less cohesive materials did not maintain their position within the pocket as the wheel rotated.

The powders which were suitable for Configuration A were not suited for Configuration B (and vice versa) which highlights the need to match the properties of a formulation with the specific filling geometry to achieve desired performance.

Dosator Performance (Mass Consistency)

Dosing performance for a given dosator/powder combination, defined in terms of dose uniformity, can be influenced by process parameters, such as the magnitude of the applied compressive force, the initial height of the piston, and the depth of the powder bed, but also the powder's properties, for example the ease with which the powder bed flows and recovers following removal of a dose.

Five lactose powders, with decreasing particle size referred to here as Lactose 1 to 5, were processed through a lab-scale dosator (Lab Dosator, 3P Innovation, Warwick, UK) using outlets of progressively decreasing size from Dosator 1 to Dosator 4. All other process conditions were kept constant. The target was to consistently produce doses of 50 mg with a relative standard deviation (RSD) of <2%. The results of the trial in terms of RSD values for each lactose-dosator combination are shown in Figure 5. A range of dynamic, shear and bulk powder properties were measured for each of the lactose samples using a the FT4 Powder Rheometer to determine which parameters rationalised the performance observed.

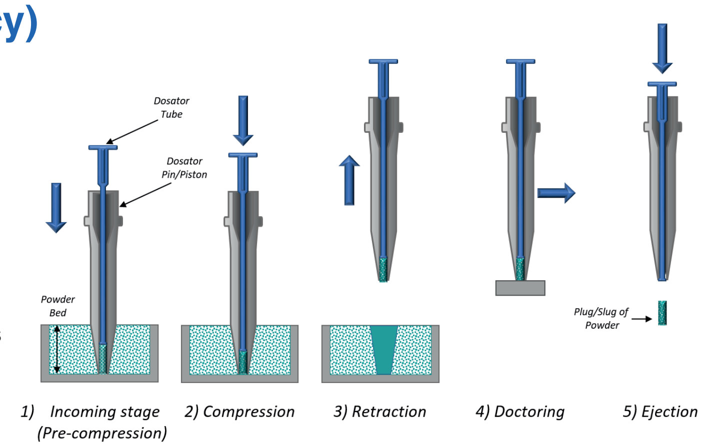


Figure 4: Dosator system used to pre-meter the dose of DPI formulations.

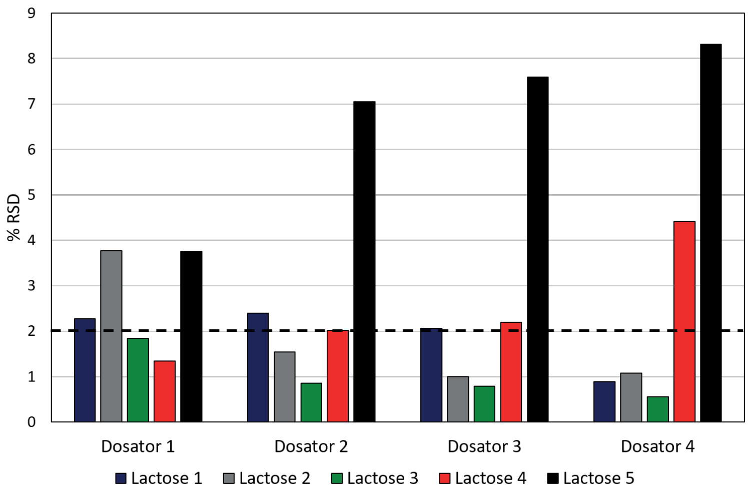


Figure 5: %RSD from Dosator 1 to 4 with Lactose 1 to 5.

Dynamic Flow properties, particularly Aerated Energy (AE) and Specific Energy (SE), were found to correlate most strongly with performance. AE is the energy needed to establish a flow pattern while air is passed through the powder, at a given air velocity. AE at 2 mm/s Air Velocity (AE_2) was measured and the results shown in Figure 6. SE quantifies the resistance of particles moving relative to one another in an unconfined state. Particles of irregular shape and/or with rough surface texture tend to lock together and form temporary mechanical bridges. High SE values therefore indicate greater levels of mechanical interlocking reducing the ability to flow in an unconfined environment. Figure 7 shows SE values for the five lactose powders.

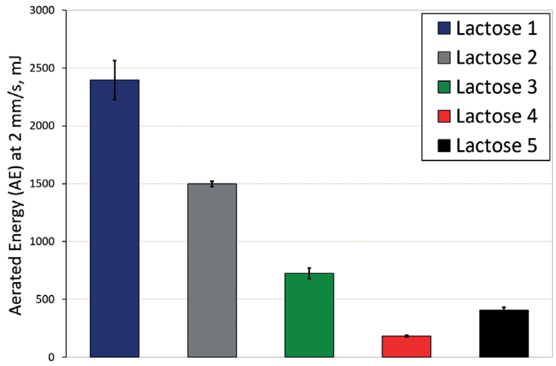


Figure 6: Aerated Energy at 2mm/s air velocity (AE_2) for Lactose 1 to 5.

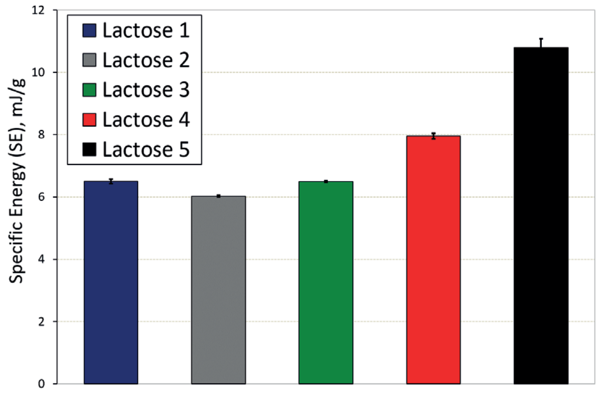


Figure 7: Specific Energy for Lactose 1 to 5.

Dosator 1 exhibits acceptable performance with Lactose 3 and 4, which both generate low AE_2 values. Lactose 5 also generates a low AE_2 value but its SE is high.

Dosator 2 and 3 perform well with Lactose 2 and 3 which generate moderate AE_2 values but also low SE values. Lactose 1 and 4 exhibit near acceptable performance but high AE_2 and SE values respectively appear to have a detrimental effect.

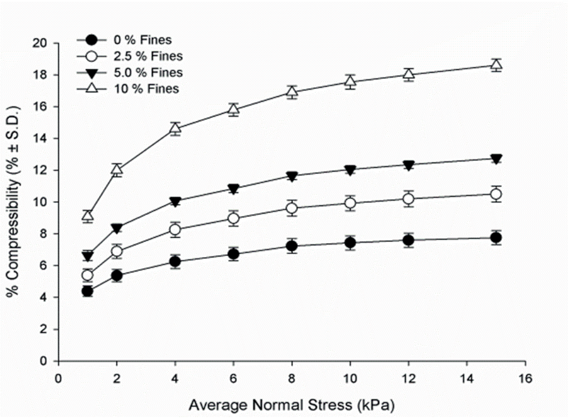
Dosator 4 works well with Lactose 1, 2 and 3 which all exhibit low SE values.

These results show that powders with a combination of low SE and low AE_2 perform best in all dosators. As outlet diameter decreases, AE_2 becomes less influential and the impact of SE increases. Larger dosators allow greater interaction with air at the outlet, reducing the impact of inter-particular interactions. In contrast, smaller outlets provide little opportunity for interaction with air and the physical interactions that define SE dominate performance.

Predicting Fine Particle Dose

The impact of fines on the properties of surface-etched lactose powder was experimentally investigated. Batches were produced containing 0, 2.5, 5 and 10% fines (Sorbolac 400, Meggle, Germany). Bulk Density, Permeability, Compressibility and Aerated Energy were all measured and evaluated with respect to performance within a DPI.

As fines content increases Conditioned Bulk Density (CBD) and Permeability also both decrease, and Compressibility increases (Figure 8). With more cohesive powders, the air retained in their relatively open structure is forced out when an external stress is applied. Less cohesive powders however are more efficiently packed, with little free volume, so are relatively unchanged by the application of stress. CBD and Compressibility data therefore suggest that the inclusion of fines increases cohesivity of the formulation.



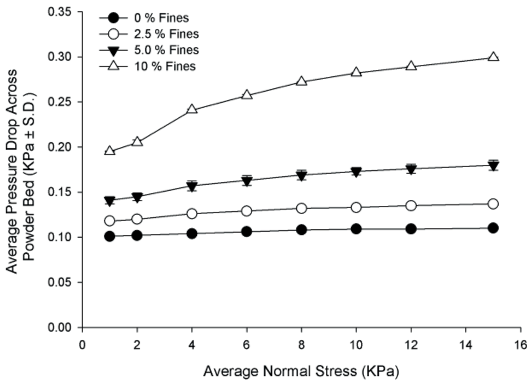


Figure 8: The impact of fines on Compressibility (left) and Permeability (right) of lactose powder.

More cohesive powders typically also exhibit lower Permeability; a greater resistance to the passage of air through the bulk. The combination of small void spaces and strong inter-particular forces makes it difficult for air to flow between individual particles creating a higher pressure drop across the bed. Permeability is directly relevant when considering fluidisation behaviour. These results suggest that batches with greater fines content are less easily fluidised, a trend reinforced by Aerated Energy measurements.

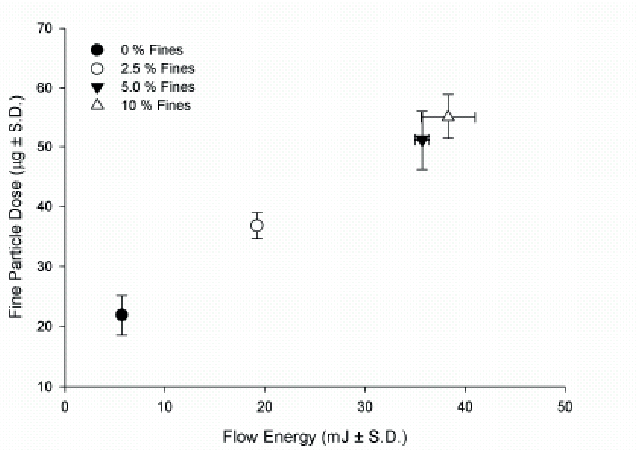


Figure 9: Correlating fine particle dose with the Aerated Energy (mJ).

As the fines content increased, Aerated Energy also increased (Figure 9). Interestingly, the relationship between fines content and FPD is not linear; doubling fines content from 2.5 to 5% has a much greater impact than raising it from 5 to 10%. However, the correlation between FPD and Aerated Energy is both linear and robust.

While multiple parameters highlight the trend towards greater cohesion with increasing fines, Aerated Energy uniquely and precisely reflects how this change affects the response to air, which is critical for drug delivery, emphasizing the value of dynamic powder characterization in this challenging application. In this example, a higher fines content results in improved performance, as indicated by the higher FPD. This is likely due to higher cohesive forces and lower Permeability which result in a more explosive dispersion of the dose.

Conclusions

Powder flowability is not an inherent material property but is more about the ability of powder to flow in a desired manner in a specific process or application. Successful processing demands that the powder and the process are well-matched. This means that several characterisation methodologies are required, the results from which can be correlated with process ranking to identify which parameters are most influential on performance, and produce a design space that corresponds to acceptable process behaviour.

These various studies illustrate how the FT4's multivariate approach can detect subtle variations in powders that are of direct relevance to their performance in both production and use of DPIs, and reinforce how more than one technique is required to fully describe powder behaviour. The FT4 can therefore support successful optimisation of DPI formulations, in a way that other measurement techniques cannot.

For further information, or to arrange a demonstration of the FT4, please contact:
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