THE FLOWABILITY OF LACTOSE POWDERS TO OPTIMISE TABLETING PROCESSES

In this article, Aurélien Neveu, PhD, Particle Scientist at Granutools; Pauline Janssen, Product Application Specialist at DFE Pharma; and Geoffroy Lumay, PhD, Associate Professor at the University of Liege and Co-Founder of Granutools, discuss how new measurement methods can help gain a better understanding of the flowability of lactose powders – a necessary step for future improvement of oral delivery systems.

The processability of pharmaceutical powder plays a key role in the design and improvement of production processes for oral delivery systems (e.g. tableting, capsule filling). To control and optimise processing methods, material properties and the behaviour of bulk powder should be characterised.

Blending is one of the first steps in a direct compression process and is critical to achieve a homogeneous blend with uniform API loading. Good flow combined with density supports de-agglomeration of an API during blending (Figure 1).

Free-flowing powder has a relatively flat powder bed in a blender and tends to set up a "rolling" motion inside the powder bed. This results in ball milling of the API agglomerates, which is beneficial for the uniform spread of the API particles over the blend. Poor-flowing powder has a higher dynamic angle of repose and tends to avalanche. This results in less motion inside the powder bed and less ball milling of agglomerates. De-agglomeration of the API is beneficial to achieve good content uniformity in a pharmaceutical formulation, and this becomes more critical with a lower API dose.

Moreover, good flowing properties of a powder are also required for flow through the tableting system, resulting in uniform flow into the die cavities. Insufficient flow can lead to uneven filling of the dies, resulting in large weight and dosage variations of the final tablets. At high tableting speeds, the time to fill dies is reduced, making flow properties of the blend even more important. The particle properties, mainly size and shape, strongly influence the flowability of the powder and thus the critical filling velocity achievable in die filling.[1]

Pauline Janssen
Product Application Specialist
T: +31 6 2115 4579
E: pauline.janssen@dfepharma.com

DFE Pharma
Kleverstrasse 187
PO Box 20 21 20
47568 Goch
Germany

www.dfepharma.com

Dr Aurélien Neveu
Particle Scientist
T: +32 470 18 60 18
E: aurelien.neveu@granutools.com

Granutools
Rue Jean-Lambert Defrêne 107
4340 Awans
Belgium

www.granutools.com

Dr Geoffroy Lumay
Associate Professor and
Co-Founder of GranuTools
T: +32 43 66 44 21
E: geoffroy.lumay@uliege.be

University of Liège
Place du 20 Août 7
4000 Liège
Belgium

www.uliege.be

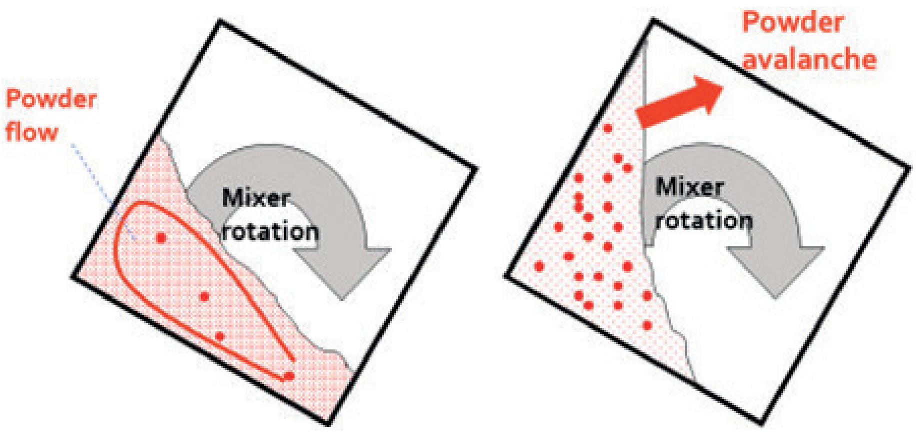


Figure 1: Free-flowing powders tend to set up a rolling motion inside the powder bed, resulting in ball milling of the API agglomerates. Poor-flowing powder tends to avalanche and results in less motion inside the powder bed and less ball milling of API agglomerates.

> "Good flow of a pharmaceutical formulation is critical to produce uniform dosage forms."

Consistent flow is also important for continuous manufacturing processes, which are gaining more and more interest from the pharmaceutical industry. Raw material feeding is usually one of the first units of operation in a continuous manufacturing line. The ability to feed powder consistently and continuously is regarded as one of the critical requirements for finished product quality and therefore stringent control on feeding is required.

Lactose is one of the most widely used excipients in the pharmaceutical industry. There are many reasons for its popularity, the fact that lactose is largely inert, relatively inexpensive, safe, many different grades are available and it has a long history of usage in successful formulations worldwide. For direct compression processes such as tableting, lactose excipients can be used as a filler-binder to provide bulk density, compaction and flow to the formulation. Good flow of a pharmaceutical formulation is critical to produce uniform dosage forms.

In this article, we present how new measurement methods can help to gain a better understanding of the flowability of lactose powders, which is a necessary step for future improvement of oral delivery systems. Firstly, the well-known angle of repose is estimated to get a first screening of the cohesiveness of the powders. These results are then compared and extended to a vertical flow through an aperture, in a geometry closer to those encountered in die filling. Then, the effect of the process speed on the flowability – i.e. the rheological behaviour – is investigated with the rotating drum measurement method.

EXPERIMENTAL METHOD

Repose Angle (GranuHeap)

The GranuHeap instrument is an automated heap shape measurement method based on image processing and analysis. To create the powder heap, an initialisation tube with an internal diameter equal to that of the circular support (40 mm) is filled with 100 mL of powder. The tube then moves upward at a constant speed of 5 mm/s, allowing the powder to form a heap on the cylindrical support in a repeatable way. In the present study, 16 pictures of the heap, separated by a rotation of 11.25°, are taken and analysed by a custom image recognition algorithm to determine the position of the powder/air interface and compute the repose angle.

Flow through an aperture (GranuFlow)

The GranuFlow instrument is a laboratory hopper allowing the aperture size to be easily modified with a rotating device. The flow rate as a function of the aperture sizes D is measured with an electronic balance connected to a computer to obtain a complete flow curve. This flow curve is fitted with a theoretical model to extract the main parameters: the minimum aperture size (D_{min}) and the Beverloo parameter (C_b) related to the flowability of the sample.

Mass flow rate (F in g/s) was investigated for different hole size D (from 2–28 mm). The Beverloo parameter (C_b in g/mm^3) and the minimum aperture size to obtain a flow D_{min} are deduced from the regression with Beverloo law:

$$F = C_b \sqrt{g}\,(D - D_{min})^{2,5}$$

Dynamic Cohesive Index (GranuDrum)

The rheology of powders is investigated with the GranuDrum, an automated powder flowability measurement method based on the rotating drum principle. A small amount of powder (50 mL in this study) is placed in a horizontal drum with transparent sidewalls. The drum rotates around its axis at an angular velocity ranging from 2–60 rpm. Snapshots (40 images separated by 1s) are taken by a charge-coupled device (CCD) camera for each angular velocity. The air/powder interface is detected on each picture with an edge detection algorithm. Afterwards, the average interface position and the fluctuations around this average position are computed.

For each rotation rate, the dynamic cohesive index is measured from the interface fluctuations, which are solely due to the cohesive forces acting between the grains. The dynamic cohesive index is thus close to zero for non-cohesive powders and increases when the cohesive forces intensify. Furthermore, by varying the rotation rate, complex rheological properties of powders (shear thinning, shear thickening and thixotropic behaviour) can be investigated.

MATERIALS

Five lactose powders provided by DFE Pharma have been selected for this study, mainly differing in their production methods:

- Pharmatose® 450M: a fine-milled alpha lactose monohydrate
- SuperTab® 24AN: a granulated anhydrous lactose
- SuperTab® 30GR: a granulated lactose
- SuperTab® 21AN: an anhydrous lactose
- SuperTab® 11SD (EU): a spray-dried lactose.

Pharmatose® 450M is a milled lactose grade which is commonly used in wet and dry granulation processes. SuperTab® grades are high-end lactose grades specifically designed for direct compression processes and provide additional functionality in terms of flow and compression.

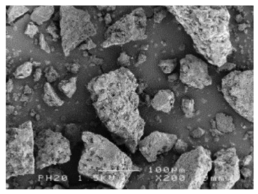
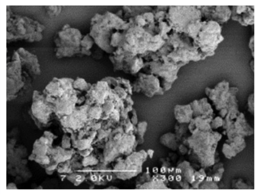
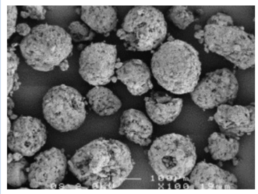
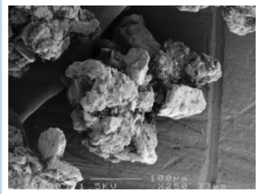
SuperTab® 21AN	SuperTab® 24AN	SuperTab® 11SD	SuperTab® 30GR	Pharmatose® 450M
				

Table 1: SEM images of the particles making up the powders.

	SuperTab® 21AN	SuperTab® 24AN	SuperTab® 11SD	SuperTab® 30GR	Pharmatose® 450M
Type	Anhydrous	Anhydrous granulated	Spray dried	Granulated	Milled
x10 (µm)	24	40	44	38	3
x50 (µm)	180	121	119	126	18
x90 (µm)	387	298	223	297	49

Table 2: Type and size distribution of the particles making up the five powders.

Table 1 provides scanning electron microscope (SEM) images of the powder's particles, revealing the shapes of the grains. Particle size distributions are summarised in Table 2.

RESULTS AND DISCUSSION

Repose Angle

Figure 2 presents the measured angle of repose for all powders. It appears that the Pharmatose® 450M and SuperTab® 21AN exhibit a similar angle of repose, higher than the other ones. Powders can then be classified in two categories with a threshold angle of repose around 55°, above which they are expected to have higher bridging propensity. Moreover, based on its lower angle of repose, the SuperTab® 11SD is expected to have the lowest bridging propensity, closely followed by SuperTab® 30GR and SuperTab® 24AN.

Pharmatose® 450M has the lowest particle size and thus it is not surprising it exhibits a higher cohesiveness and thus a higher angle of repose.[2] However, particle size is not the only parameter affecting flow, as it also depends heavily on powder morphology, as can be observed for SuperTab® 11SD which has a spherical shape.

Vertical flow

Figure 3 presents the mass flow rate versus the silo aperture for the three powders able to flow through the maximum tested aperture size (28 mm). First of all, only the SuperTab® 24AN, SuperTab® 30GR and SuperTab® 11SD were able to flow through the larger aperture size (28 mm) tested in this study, in coherence with the lower repose angle measured with the GranuHeap.

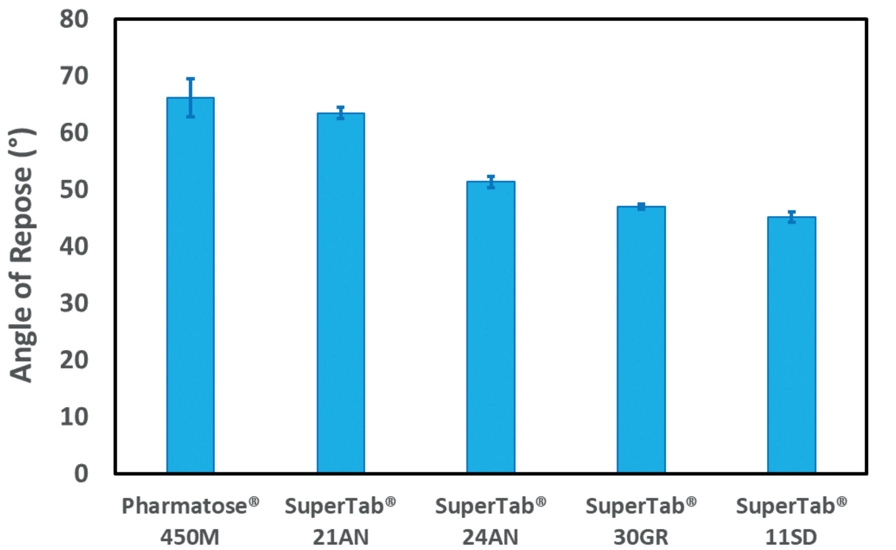


Figure 2: Mass flow-rate versus aperture for the three powders able to flow through the larger aperture (28mm).

> "The cohesiveness of a powder depends on the size of the particles that make up the powder: the smaller the particle, the higher the cohesion."

The SuperTab® 11SD has the highest Beverloo parameter and thus exhibits the best flowability through the silo aperture. This powder has also the lowest D_{min} and is thus able to flow though a smaller aperture than the other ones. It is then followed by SuperTab® 30GR and SuperTab® 24AN, in this order, in total accordance with the angle of repose measurements obtained with the GranuHeap.

The cohesiveness of a powder depends on the size of the particles that make up the powder: the smaller the particle, the higher the cohesion. However, other characteristics of the grains can play a role – such as the shape, the surface roughness or the chemical properties. For the powders we considered,

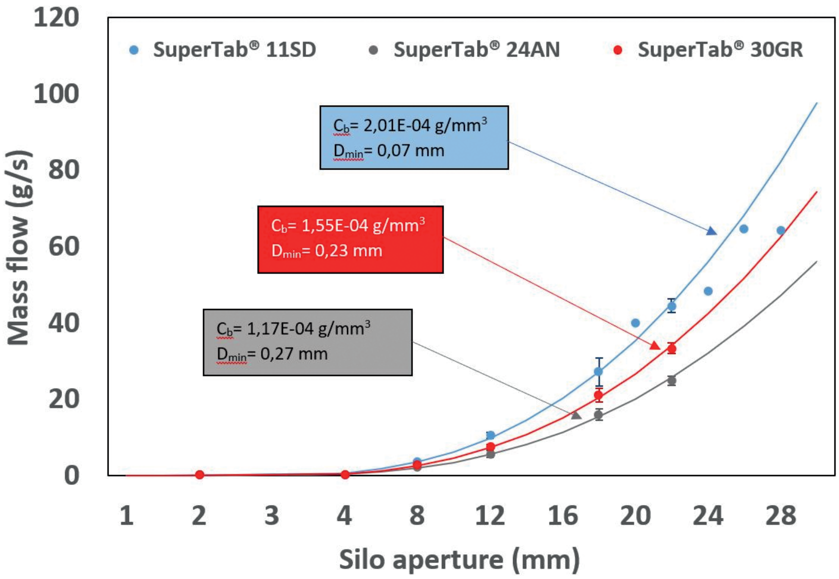


Figure 3: Mass flow rate versus aperture for powders.

it appears that the SuperTab® 21AN has the higher median particle size (x50=180 µm) but also a high bridging propensity, as it was not able to flow through the 28 mm aperture.

Considering the three powders that did flow through the 28 mm aperture (SuperTab® 11SD, SuperTab® 30GR, SuperTab® 24AN), the SuperTab® 11SD has the lowest particle size but also the lowest D_{min} and highest C_b. Therefore, the shape of the particles seems to be a more relevant characteristic to explain the flowability performance of these powders. Indeed, although the SuperTab® 11SD particles are smaller, they have a regular spherical shape which promotes the flow. The SuperTab® 30GR and the SuperTab® 24AN are granulated powders composed of agglomerates of slightly round shapes, explaining why they also exhibit a good flowability.

The more irregular shape of particles of the SuperTab® 21AN leads to increased bridging propensity due to interlocking effects. Pharmatose® 450M combines irregular particle shapes with the smallest particle size (x50=18 µm) – this powder is thus expected to have the lowest flowability.

The obtained results indicate the same ranking of hopper diameters for these lactose grades as shear cell measurements did before (SuperTab® 24AN was not considered in this experiment). With the previous shear cell measurements, the minimal required hopper dimensions in a conical hopper were predicted. Hopper outlet diameters were predicted to be the lowest for SuperTab® 11SD (15 mm), followed by SuperTab® 30GR (17 mm). SuperTab® 21AN was predicted to require a higher minimum hopper outlet of 96 mm, due to its relatively high wall friction. For Pharmatose® 450M, the predicted hopper diameter was 210 mm.[3]

Dynamic cohesive index

Cohesive index values as a function of the increasing rotating speed are presented in Figure 4. The observations and the classification obtained with GranuHeap and GranuFlow are consistent with the GranuDrum for equivalent stress state, i.e. at low rotating speeds. Moreover, the cohesive index gives another level of description as it allows us to distinguish the SuperTab® 21AN and the Pharmatose® 450M. It is evident that the Pharmatose® 450M exhibits the most cohesive behaviour, with a cohesive index much higher for the whole speed range. This is consistent with the significantly lower particle size of this powder (x50=18 µm).

Pharmatose® 450M, SuperTab® 11SD, SuperTab® 24AN and SuperTab® 30GR show shear-thickening behaviour, meaning that their cohesiveness increases with process speed. This decrease of flowability may limit the critical filling velocity achievable in oral delivery production processes. On the contrary, SuperTab® 21AN shows strong shear-thinning behaviour, leading to a cohesive index at high speed equivalent to those of the best flowing powders at low speed. Therefore, this powder is expected to perform the best at higher processing speeds. The larger particle size and irregular

> "The proper characterisation of powder flowability is a key step in understanding and improving manufacturing processes of oral delivery systems."

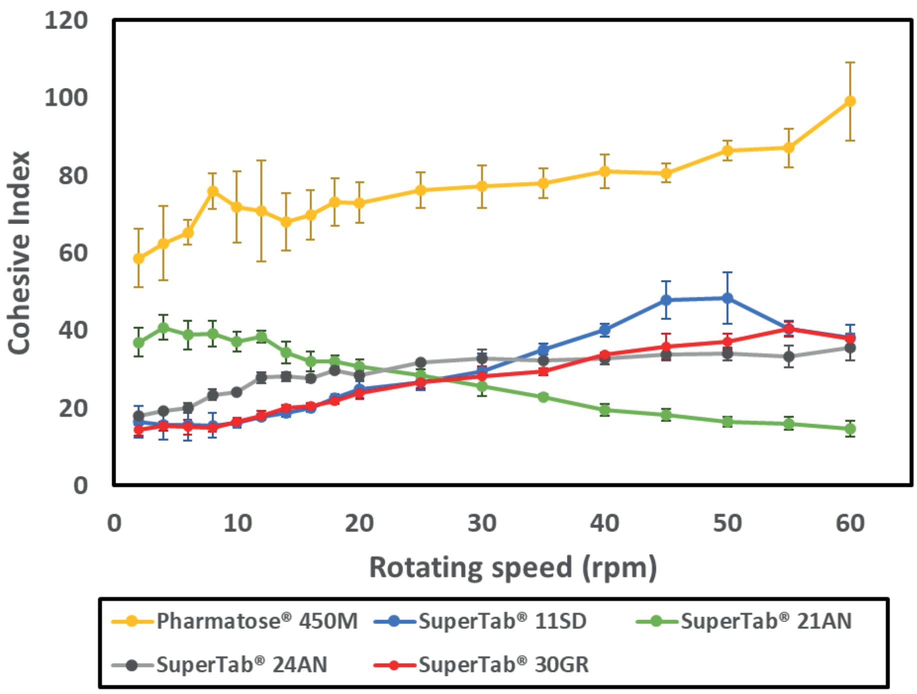


Figure 4: Cohesive index versus rotating drum speed. Shear-thickening behaviours are observed, except for powder SuperTab® 21AN, which exhibits strong shear-thinning behaviour.

particle shapes may explain why this powder differs strongly from the others.

CONCLUSIONS

The proper characterisation of powder flowability is a key step in understanding and improving manufacturing processes of oral delivery systems. For this reason, the flowability of five lactose powder grades was investigated. The SuperTab® 11SD, SuperTab® 24AN and SuperTab® 30GR showed the best flowability with GranuHeap, GranuFlow and GranuDrum instruments.

It appeared that SuperTab® 21AN did not exhibit the best flowability despite the large particle size of this lactose grade, explained by the irregular shape of the grains. The small particle size of Pharmatose® 450M led to a much higher cohesiveness and poor flowability compared with the other studied powders. Moreover, shear thickening is observed except for the SuperTab® 21AN which showed strong shear-thinning behaviour.

For inherently dynamic processes, especially in continuous manufacturing lines, this improved knowledge of rheological behaviour provides indispensable information to develop and select the most suitable powder.

ABOUT THE AUTHORS

Aurelien Neveu's research activities mainly focus on the understanding of granular materials at different scales. During his PhD he developed discrete numerical models to describe fragmentation mechanics of cohesive granular materials by taking into account the complex micro-properties of the grains. Dr Neveu then moved to study segregation in gravity-driven rapid flows as well as aeolian transport of granular materials, with huge implications for natural disasters. He is now working as a particle scientist at Granutools, performing research on powder characterisation.

Pauline Janssen is a Product Application Specialist in oral solid dosage (OSD) at DFE Pharma. She has been working on application development of excipients based on fundamental knowledge of excipients and powder physics. Ms Janssen joined DFE Pharma at the beginning of 2017 and worked as a product developer on multiple OSD and DPI projects. As an analytical expert, she supported the design of experiments to understand products and their usage.

Geoffroy Lumay is Associate Professor and Soft Matter Physics Chair at the University of Liege in Belgium. Dr Lumay is leading research projects in the field of soft matter physics at the intersection between fundamental sciences and industrial applications. He teaches both basic and advanced physics to students in pharmaceutical sciences, engineering and agronomy. Dr Lumay co-founded the company Granutools, which is developing, producing and commercialising a range of laboratory instruments dedicated to powder characterisation.

ABOUT THE COMPANY

Granutools combines decades of experience in scientific instrumentation with fundamental research on powder characterisation, to develop and manufacture instruments that measure physical powder characteristics such as flow, static cohesion, dynamic cohesion, tapped density and tribo-electric charge.

REFERENCES

1. *Zakhvatayevaa A, Zhonga W, Makrooa HA, Harea C, Wu CY, "An experimental study of die filling of pharmaceutical powders using a rotary die filling system". Int J Pharm, 2018, Vol 553, pp 84–96.*
2. *Boschini F, Delaval V, Traina K, Vandewalle N, Lumay G, "Linking flowability and granulometry of lactose powders". Int J Pharm, 2015, Vol 494, pp 312–320.*
3. *"Understanding the differences between lactose grades in terms of powder flow". Technical Paper, DFE Pharma.*