DFE pharma

Understanding the differences between lactose grades in terms of powder flow

The pursuit of excipient excellence

1. Abstract

This paper presents the characterization of different types of lactose grades in terms of their physical properties related to powder flow. The flowability of powders and lactose grades in particular should be diligently assessed in relation to their function in a formulation or towards processing.

2. Introduction

With increasing differentiation of lactose grades being produced there is a need for the formulator to understand their handling and processing characters. Lactose grades are currently manufactured with a variety of physical properties.

The understanding of these flow related properties, eg particle size, density and flow is critical in the processing of excipients as is their intended formulations, processes and packaging. Milled lactose's are commonly (but not exclusively) used in wet and dry granulation processes where functional related characteristics of the lactose are the density rather than their flow, as a constant granulation bed height (volume) is key for the output of a granulation process.

Sieved lactose's are commonly used as diluents / flow aids in capsule filling and direct compression formulations. The Directly Compressible (DC) grades of lactose have been designed to provide additional functionality in terms of flow (requirement for DC), density and compression. The objective of this work is to measure the flowability and associated parameters of milled, sieved and DC-grade lactoses.

3. Materials and methods

Batches of Pharmatose® 80M, 150M, 200M, 350M & 450M as well as SuperTab® 11SD, 30GR and 21AN have been utilized. Particle size distribution measurements have been performed by laser diffraction using a Sympatec Helos dry powder method, in triplicate. Bulk and Tapped density was measured using an Engelsmann model A.-G. tapping device, in duplicate, using the poured powder density and tapped powder density after reaching equilibrium (USP <616>). Flowability was measured using an annular Brookfield PFT Shear cell tester. The flow function was derived by testing 3 yield loci and 5 points for each yield locus were obtained, tests were performed in triplicate.

4. Results and discussion

Milled lactose's are finer and have lower bulk densities than the sieved lactose grades (Table 1). The Hausner Ratio shows little to no differentiation between the milled lactose grades, while their particle size distributions do vary significantly. Reason for this is that de-aeration of fine (cohesive) powders is difficult and their 'ideal' packing cannot be achieved. All three DC lactose grades (SuperTab® 11SD, 30GR & 21AN) have medium (x50) particle size above 100 micron to ensure adequate flow and well as having poured (bulk) density values above 500 kg/m^3 enabling good API de-agglomeration in mixing processes.

Table 1: Summary of physical properties (particle size and density) of different lactose grades.

	Type	Particle Size				Density (kg/m^3)		
		x10 (micron)	x50 (micron)	x90 (micron)	Span	Poured density	Tapped density	HR
Pharmatose® 80M	Sieved	67.2±1.3	252±4	390±18	1.3	810	935	1.14
Pharmatose® 100M	Sieved	44.6±0.3	145±1	248±2	1.4	772	890	1.15
Pharmatose® 150M	Milled	6.5±0.2	54.8±0.3	206±5	3.6	660	885	1.34
Pharmatose® 200M	Milled	3.2±0.0	34.7±0.3	96.1±4.5	2.7	590	840	1.42
Pharmatose® 350M	Milled	4.1±0.0	28.6±0.4	77.1±3.0	2.5	565	788	1.39
Pharmatose® 450M	Milled	3.0±0.0	18.4±0.1	46.3±0.0	2.4	530	750	1.42
SuperTab® 11SD	Spray dried	45.9±1.5	118±2	226±4	1.5	601	716	1.19
SuperTab® 30GR	Granulated	41.8±0.8	140±4	294±6	1.8	548	668	1.22
SuperTab® 21AN	Anhydrous	12.2±0.1	159±1	339±1	2.1	710	896	1.26

The instantaneous flow functions (ffc) of the different grades of lactose, at 20±2ºC and 50±10%RH are presented show that the particle-particle flow of the sieved lactose grades is the highest (Figure 1). The SuperTab® lactose grades were not shown due to their overlap over the sieved lactose batches shown, data is presented in Table 2.

Shear cell testers are designed to show differences between cohesive to poor flowing powders, their accuracy for free flowing powders (ffc>10) is less. Pharmatose® 200M is better flowing than Pharmatose® 150M based upon the shear cell data. This appears to be in contradiction with the Hausner Ratio data (Table 1). These differences can be explained by their test methods, density being an indirect measure of flow based upon the particle packing ability and shear cell testing a direct measure of particle-particle flow. Also, the particle size distribution of Pharmatose® 150M is wider (span) than that of Pharmatose® 200M (Table 1). It is commonly understood that powders with a wider particle size distribution flow less than those with a narrow particle size distribution.

The flowability (flow function) of the sieved lactose grades is better than the milled lactose grades measured using a shear cell tester (Table 2), this is in alignment with the Hausner Ratio shown in Table 1. The data also shows that in terms of hopper dimensions the fine milled lactose grades (Pharmatose® 350M & 450M) need significantly large hopper outlet diameters than the coarser milled lactose grades (Pharmatose® 150M & 200M), while their flow function do not seem very different, being 3.0-3.2 and 3.7-4.5 respectively.

It may appear a surprise to find that SuperTab® 11SD has the smallest hopper outlet diameter with simultaneously the lowest flow function of the DC grades tested whereby all are considered free flowing. This is due to the fact that powder flow is a combination of density, angle of internal friction and wall friction. It is important to note that the calculated hopper dimensions are guides, typically a rule of thumb is that a 2º safety is applied to the hopper half angle and a 1-2 cm diameter addition to the outlet diameter to ensure mass flow. Also storing powders for a prolonged time in hoppers / solo's will result in consolidation of the powder, which may cause arching (no flow or ratholing).

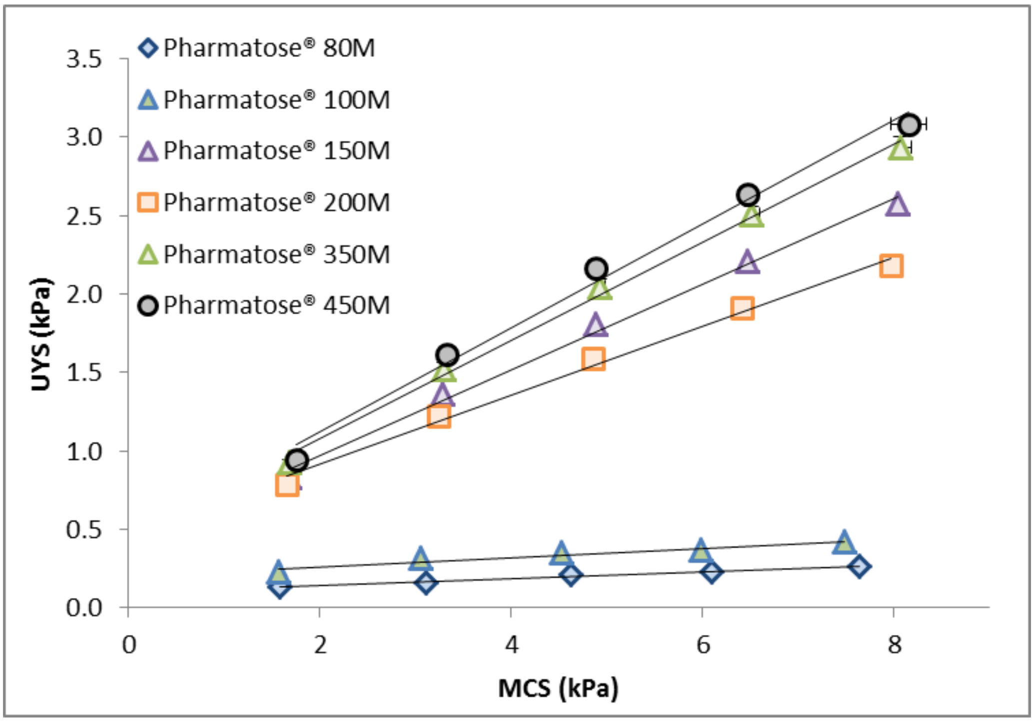

Figure 1: Instantaneous flow functions of the milled and sieved lactose grades tested, n=3 per product.
Table 2: The flow characterization and conical hopper dimensions for the lactose grades tested. Calculations of shown parameters are in accordance to Jenike [1] and Crowley et al., [2] principles.

	Flow Function	Classification	Effective angle of internal friction (º)	Angle of wall Friction(º)*	Hopper half angle for mass flow (º)	Hopper outlet for mass flow, D (cm)**
Pharmatose® 80M	44	Free Flowing	33.0	27.0	12.0	2.0
Pharmatose® 100M	34	Free Flowing	33.5	27.9	11.0	3.4
Pharmatose® 150M	3.7	Cohesive	36.8	28.0	12.0	4.2
Pharmatose® 200M	4.5	Easy Flowing	36.9	27.0	12.0	3.5
Pharmatose® 350M	3.2	Cohesive	37.2	30.2	13.0	20.0
Pharmatose® 450M	3.0	Cohesive	37.4	33.1	4.0	21.0
SuperTab® 11SD	13	Free Flowing	32.1	15.4	30.0	1.5
SuperTab® 30GR	40	Free Flowing	32.4	20.2	26.0	1.7
SuperTab® 21AN	18	Free Flowing	32.8	26.2	12.0	9.6

*Wall friction plate, stainless steel 304, 2B finish. **outlet diameter for conical hoppers.

The flowability of a pharmaceutical formulation is the combination of excipients and API used, as well as how these components are processed (eg low or high intensity mixing). Understanding the flow related characteristics is key for choosing and using the correct lactose grade for an intended formulation and / or process. In general it can be mentioned that for high speed tableting the formulation should have a good density and flow function above 6-8. C.C. Sun (2010) indicated that low density (<0.5 g/ml) powders having flow functions above 6.7 can be used for high speed tableting (=50.400 tablets per hour).

5. Conclusion

Characterisation of lactose grades regarding its flow properties is key towards their formulation and processing potential. These parameters are of importance to all formulators working with lactose and / or choosing their excipient(s) for complex formulations. Particle size and density of powders alone do not represent the flowability best, but should ideally be assessed together with shear cell data to be understood in relationship to their usage.

6. References

1. A.W. Jenike, Storage and flow of solids, Utah Eng Stn Bull 123 (1964), p. 1-194.
2. S.V. Crowley, et al., Influence of protein concentration on the physical characteristics and flow properties of milk protein concentrate powders, J. Food Eng. 135 (2014), p. 31-38.
3. C.C. Sun, Setting the bar for powder flow properties in successful high speed tableting, Powder Technology 201 (2010), p. 106-108.

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