

Granulation and Drying: the Choice of Excipients Matters

Relevant for: excipients, solid dosage forms, pharma, powder rheology, particle size analysis, BET surface area, density, powder rheology, powder flow, flowability, compactability, compressibility

Solid dosage forms are made of active pharmaceutical ingredients (API) and excipients which influence the powder processing and the quality of the final dosage form. The success of multiple step processes such as tableting and capsule filling mostly depends on instrument parameters and powder handling in intermediate steps like granulation (wet, dry) and drying. This application report examines the moisture uptake capacity of the excipients milled and sieved lactose and methylcellulose in order to estimate their behavior during wet granulation. The same excipients were also tested at different temperatures to reproduce the drying effect. It was investigated how the amount of moisture adsorbed during wet granulation and the temperature effect during the consecutive drying have an impact on the flow and compression characteristics.

1 Introduction

Solid dosage forms such as granules, tablets, capsules and sachets may not be as appealing as some of the novel drug delivery forms of recent years, but they will remain far and away the most prevalent dosage form on the market. They consist of a mixture of active pharmaceutical ingredients (API) and excipients. The excipient type or the excipients combination can impact important properties of the final powder like flowability, compactability, and compressibility, which may change attributes of final dosage forms (content uniformity, dissolution rate in the body). The optimization of mentioned properties strictly depends on intermediate process steps like granulation where small particles gather together to form particle enlargement by agglomeration. In this way, granules are produced that flow and compress better than starting materials.

Granulation processes can be divided into two types: wet and dry granulation. The first requires water or a binding solution (water and binding agents), where the water is consecutively removed by drying (e.g., fluidized bed dryer). Dry granulation is performed by mechanical compression or compaction and does not require liquid.

In this application report, different relative humidity, temperatures and durations were used to reproduce the wetting and the consecutive drying step of the wet granulation. Based on the moisture uptake of the excipients and the intermolecular forces built after

drying, it was possible to estimate the suitability of excipients to wet or dry granulation and the consequent impact on tableting or capsules/sachet filling processes.

Parameters like surface area, density, particle size and cohesion can be measured with Anton Paar instruments. Knowing these characteristics provides vital information about the most appropriate excipients to use in order to avoid defects which can cause the discharge of the batch at the end of manufacturing. The overview of the principal steps of solid dosage forms manufacturing and the corresponding parameters is presented in Figure 1.

1.1 Flowability

Good flowability ensures the appropriate filling of capsules or the die cavity during tableting. In this way, dosage forms with the consistent weight and uniform strength can be produced.

The measurement of particle size, and values estimated using the Hausner Ratio and Carr Index after granulation can be used to define the change in the powder flow behavior. The flowability can be directly determined with the flow function, which gives the tendency to flow in dependence of an applied stress. In addition, the determination of the unconfined yield strength and cohesion strength allows investigation of the resistance of granules to failure and cracking during compression or compaction.

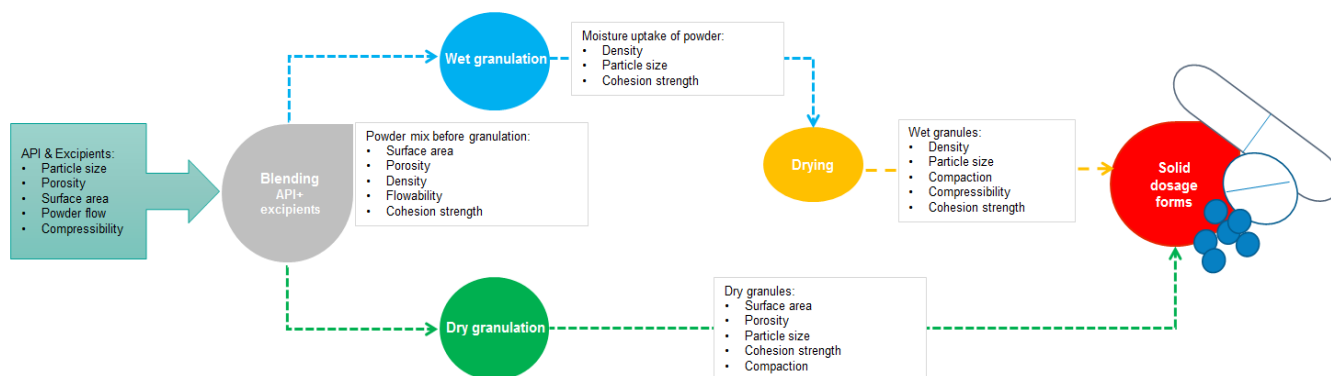


Figure 1: Schematic overview of principal steps for the manufacturing of solid dosage forms

1.2 Compactability and compressibility

In solid dosage form manufacturing, the granulation step helps to improve the compression and compactability. Tablets can be formed that remain intact, stable and compact when stress is applied. In the case of capsules, a better compaction during filling guarantees high weight uniformity. In fact, density, porosity and particle size distribution of granules influence the optimization of the packing before tablets compaction and in the filled capsule. These characteristics also contribute to increasing the consolidation stress applied during tableting. At the end of the granulation step, tablets with lower porosity and higher tablet strength as well as capsules with better content uniformity can be produced.

- Cohesion strength, unconfined yield strength and principal stress (consolidation stress)
- Surface area and true density
- Size and particle size distribution (PSD)

Temperature, time and humidity conditions used for the experiments are listed in Table 1.

Ambient conditions	20 °C, 30 %rH
Conditioning in climate chamber	
Moisture uptake	60 min, 35 °C at 45 / 65 / 85 %rH
Drying of sample previously conditioned for 60 min at 85 %rH at 35 °C	30 min, 20 %rH at 40 / 80 °C

Table 1: Overview of time, temperature and humidity conditions

2 Experimental setup

The analysis conducted in this application report focused on three excipients that are commonly used in solid dosage forms manufacturing: milled lactose (ML), sieved lactose (SL) and methylcellulose (MC). Lactose monohydrate is mostly used as diluent (fillers) in tablets or capsules/sachets filling to increase the weight and improve content uniformity. Methylcellulose acts as binder and contributes to the adhesion between the particles (e.g., API and excipients).

The aim of the investigation was to evaluate the suitability of the excipients to wet and dry granulation by reproduction of the wetting at different humidity conditions and drying behavior (e.g., fluidized bed dryer) at different temperatures. The following parameters were measured to characterize the powders in the raw and conditioned states:

- Bulk density and tapped density

The bulk density, cohesion strength and shear cell measurements were only performed for conditioning at 45 and 85 %rH (relative humidity). The surface area and true density were measured only for raw materials.

3 Instruments and results

3.1 Raw materials: before and after moisture uptake

3.1.1 Bulk density

The measurements were performed with a Modular Compact Rheometer (MCR) equipped with the powder shear cell (PSC). The measuring cell with a volume of 18.9 ml and the corresponding measuring system PSC43-21-0 (stainless steel attachment) were used for the tests (Figure 2). The results are listed in Table 2.



Figure 2: Measuring system PSC43-21-0 with three different attachments (stainless steel, aluminum, Teflon).

Bulk density (0 / 45 kPa)			
Sample	Raw	45 %rH	85 %rH
ML	0,487 / 0,808	0,460 / 0,833	0,518 / 0,804
SL	0,772 / 0,813	0,784 / 0,838	0,800 / 0,929
MC	0,373 / 0,400	0,359 / 0,389	0,350 / 0,380

Table 2: Bulk density of the excipients measured at 0 and 45 kPa before (Raw) and after moisture uptake (45 and 85 %rH).

Figure 3 shows the bulk density curve of the milled lactose in raw (red curve) and wetted (blue curves) condition.

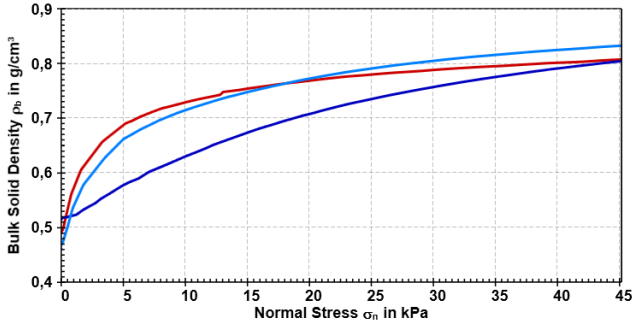


Figure 3: Bulk density of milled lactose
Red curve: ML raw; Light blue curve: ML 45 %rH; Blue curve: ML 85 %rH

3.1.2 Tapped density, Hausner Ratio and Carr Index

Tapped density was measured using an Autotap. Samples were tapped until the volume remains unchanged. The results are shown in Table 3.

Sample	Tapped density, $\rho(\text{g/cm}^3)$		
	Raw	45 %rH	85 %rH
ML	0.72	0.75	0.70
SL	0.87	0.87	0.90
MC	0.41	0.41	0.41

Table 3: Tapped density of excipients before (Raw) and after moisture uptake (45 and 85 %rH).

The Hausner Ratio (HR) and Carr Index (CI) were calculated from the tapped density measurements

according to Equations 1 and 2 and are given in Table 4.

$$\text{Hausner Ratio} = \frac{V_0}{V_f}$$

Equation 1: Hausner Ratio. V_0 = initial volume and V_f = final volume.

$$\text{Carr Index} = 100 * \frac{V_0 - V_f}{V_0}$$

Equation 2: Carr Index. V_0 = initial volume and V_f = final volume.

Hausner Ratio [-] and Carr Index [%]						
Sample	Raw		45 %rH		85 %rH	
	HR	CI	HR	CI	HR	CI
ML	1.73	42	1.82	45	1.65	39
SL	1.24	19	1.28	22	1.26	20
MC	1.32	24	1.36	27	1.31	23

Table 4: Hausner Ratio (HR) and Carr Index (CI) calculated from tapped density measurements.

3.1.3 Cohesion strength, unconfined yield strength and principal stress

The cohesion strength and shear measurements were carried out with an MCR (Modular Compact Rheometer). Two types of powder cells were used.

- Powder Flow Cell (PFC)
- Powder Shear Cell (PSC)

The main difference between these two measuring cells is that measurements that take place in the PFC can be performed in the stationary and in the dynamic state, whereas in the PSC the measurements are carried out in the stationary state only.

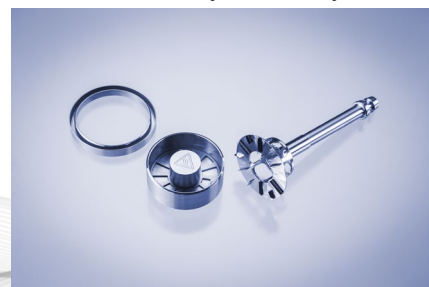


Figure 4: Measuring system PSC43-21-12 with shear cell.

Free-flowing powders such as sieved lactose and methylcellulose are ideal samples for measurements in the Flow Cell and cohesive powders such as milled lactose are well suited for measurements in the Shear Cell (Figure 4). Due to its cohesiveness, milled lactose could not be fully fluidized up to a maximum air flow of 15 l/min in the flow cell. Therefore, only the cohesion

strength of sieved lactose and methylcellulose were measured in the flow cell (Table 5).

Sample (Fluidization rate [l/min])	Cohesion strength [Pa]		
	Raw	45 %rH	85 %rH
SL (2.5)	139	161	125
MC (2)	255	200	186

Table 5: Results of cohesion strength for sieved lactose (SL) and methylcellulose (MC) before (Raw) and after moisture uptake (45 and 85 %rH).

Three cohesion strength measurements of methylcellulose are displayed Figure 5.

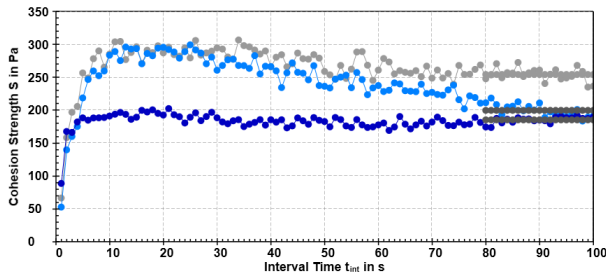


Figure 5: Cohesion strength measurements of methylcellulose. Grey curve: MC raw; Light blue curve: MC wetted at 45 %rH; Blue curve: MC wetted at 85 %rH

Some of the results which can be obtained with the shear cell - unconfined yield strength (σ_c) and the principal stress (σ_1) of milled lactose - are listed in Table 6.

Parameters	Raw	45 %rH	85 %rH
σ_c	4331	5541	6728
σ_1	9033	9936	9659

Table 6: Unconfined yield strength and principal stress of milled lactose before (Raw) and after moisture uptake (45 and 85 %rH) measured at 6 kPa.

Figure 6 shows a clear change in flowability at different humidity levels.

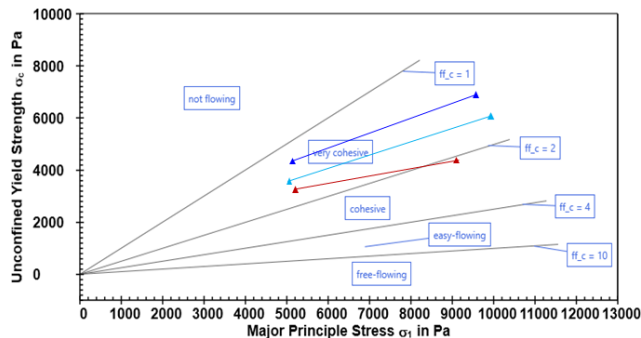


Figure 6: Flowability curve of milled lactose comparing raw and wetted material. Red curve: ML raw; Light blue curve: ML 45 %rH; Blue curve: ML 85 %rH

3.1.4 Surface area and true density

True density of the raw material was measured using helium gas with an Anton Paar UltraPyc 1200e. BET surface area was measured using a NOVAtouch instrument with N_2 gas at 77 K. Samples were dried under vacuum at 80 °C for 3 hours prior to the measurement. Because true density and surface area are reported per gram of dry sample, the study of these materials was limited to the untreated raw materials. The results are shown in Table 7.

Sample	BET surface area (m ² /g)	True Density (g/cm ³)
ML	2.43	1.55
SL	0.86	1.54
MC	0.65	1.26

Table 7: Surface area and true density of raw excipients.

3.1.5 Particle size distribution

The particle size distribution of the excipients was measured by means of laser diffraction in the PSA 1190. The measurements in dry dispersion were performed in Venturi and free-fall modes. The Fraunhofer approximation mode was selected. Figure 7 and Table 8 show the results and the corresponding measurement parameters used for Venturi mode.

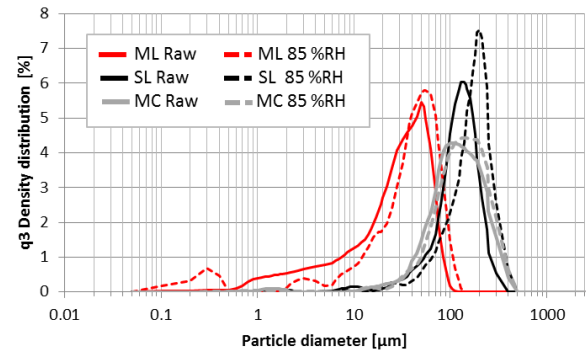


Figure 7: Particle size distribution (volume based) of milled lactose, sieved lactose and methylcellulose measurements in Venturi mode.

D values[μm]	ML			
	Raw material	45 %RH	65 %RH	85 %RH
D ₁₀	3.3	7.6	5.2	3.0
D ₅₀	28.5	39.7	40.5	38.6
D ₉₀	59.8	72.5	79.8	74.8
D[4,3]	32.0	42.5	44.2	41.6
	SL			
D ₁₀	50.8	50.2	57.6	68.4
D ₅₀	119.8	120.2	156.2	164.8
D ₉₀	193.8	195.7	248.9	248.7
D[4,3]	126.6	126.9	163.7	171.5
	MC			
D ₁₀	48.1	51.8	43	53.6
D ₅₀	111.5	117.7	109.3	125.5
D ₉₀	225.9	227.2	221.5	240.9
D[4,3]	132.0	136.2	127.8	145.2

Table 8: Volume weighted D-values measured in Venturi mode.

In Figure 8 and Table 9, the results of free-fall measurements are presented.

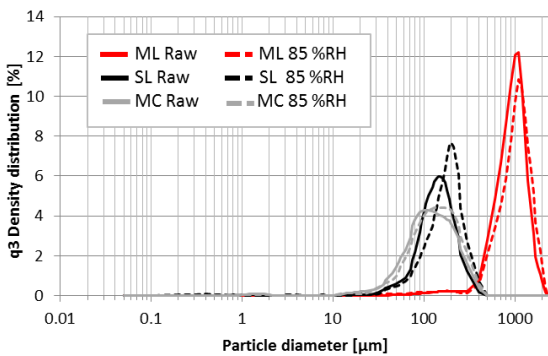


Figure 8: Particle size distribution (volume based) of milled lactose, sieved lactose and methylcellulose measurements in free-fall mode.

D values[μm]	ML			
	Raw material	45 %RH	65 %RH	85 %RH
D ₁₀	489.8	663.6	531.9	497.9
D ₅₀	890.1	1097.1	1120.5	980.9
D ₉₀	1340.1	1709.8	1728.8	1507.7
D[4,3]	953.7	1194.0	1165.7	1036.8
	SL			
D ₁₀	68.6	67.8	66.9	74.0
D ₅₀	133.2	134.4	153.9	166.6
D ₉₀	218.8	224.8	244.1	252.1
D[4,3]	144.8	147.2	163.3	174.0
	MC			
D ₁₀	44.7	50.8	45.1	48.9
D ₅₀	119.9	126.5	117.8	132.1
D ₉₀	233.8	235.5	232.6	243.3
D[4,3]	138.7	143.8	137.3	148.8

Table 9: Volume weighted D-values measured in free-fall mode.

3.2 After drying

The samples conditioned at 85 %RH and 35 °C for 1 h were then dried at 40 °C and 80 °C (20 %RH) for 30 minutes cf. (Table 1) and subsequently measured.

3.2.1 Bulk density

The same instruments and accessories were used as in the previous rheological measurements (Chapter 3.1.1). These results provide information on compressibility and compaction behavior. Table 10 gives an overview of the results.

Bulk density (0-45 kPa)				
Sample	Raw	85 %rH	40 °C	80 °C
ML	0,487/ 0,808	0,518/0 ,804	0,452/ 0,667	0,525/ 0,667
SL	0,772/ 0,813	0,800/0 ,929	0,740/ 0,828	0,726/ 0,809
MC	0,373/ 0,400	0,350/0 ,380	0,335/ 0,365	0,343/ 0,375

Table 10: Bulk density of the excipients measured at 0 and 45 kPa before (Raw) , after moisture uptake at 85 %rH and after drying at 40 and 80 °C.

The bulk density curve for milled lactose is shown in Figure 9.

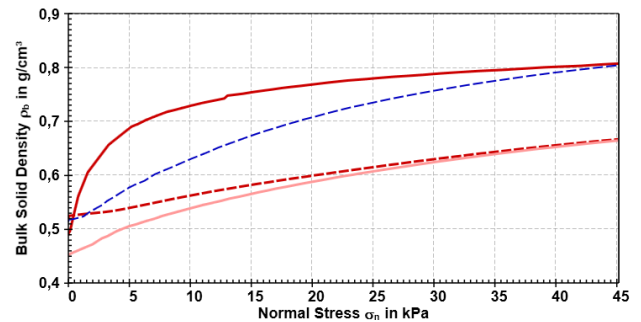


Figure 9: Bulk density of milled lactose. Red curve: ML raw; Blue dashed curve: ML at 85 %RH; Light red curve: ML dried at 40 °C; Red dashed curve: ML dried at 80 °C;

3.2.2 Tapped density, Hausner Ratio and Carr Index

The measurements were repeated after drying and the impact of temperature on tapped density (TP) was determined, along with the Hausner Ratio (HR) and Carr Index (CI) (Table 11).

Sample	TP (g/cm ³)		HR		CI (%)	
	40	80	40	80	40	80
ML	0.73	0.70	1.53	1.45	35	31
SL	0.89	0.89	1.29	1.35	22	26
MC	0.41	0.39	1.35	1.26	26	21

Table 11: Tapped density, Hausner Ratio, and Carr Index for dried samples.

3.2.3 Cohesion strength, unconfined yield strength and principal stress

The cohesion strength values of sieved lactose and methylcellulose granules after drying are listed in Table 12.

Sample (Fluidization rate [l/min])	Cohesion strength [Pa]			
	Raw	85 %rH	40 °C	80 °C
SL (2.5)	139	125	151	182
MC (2)	255	186	245	219

Table 12: Results of cohesion strength for sieved lactose (SL) and methylcellulose (MC) before (Raw), after moisture uptake at 85 %rH and after drying at 40 and 80 °C.

Figure 10 displays the cohesion strength curve of methylcellulose.

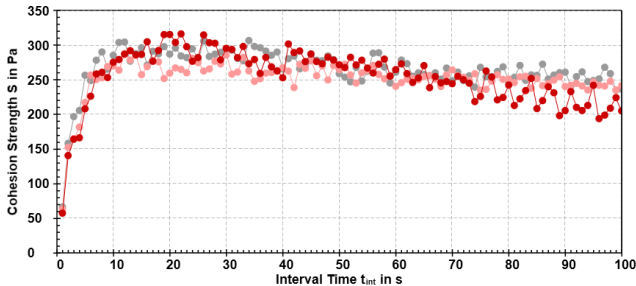


Figure 10: Cohesion strength measurements of methylcellulose after drying. Grey curve: MC raw; Light red curve: MC dried at 40 °C; Red curve: MC dried at 80 °C

The results of the shear cell for milled lactose granules are displayed in Table 13.

Parameters	Raw	85 %rH	40 °C	80 °C
σ_c [Pa]	4331	6728	8060	7982
σ_1 [Pa]	9033	9659	9813	10040

Table 13: Overview of unconfined yield strength and principal stress measured at 6 kPa before (Raw), after moisture uptake at 85 %rH and after drying at 40 and 80 °C.

3.2.4 Particle size distribution

The measurements were repeated after drying and the impact of temperature on granule formation was tested. Figure 11 shows the particle size distribution measured after drying at 80 °C in Venturi mode. Table 14 presents the overview of measurements after drying at 40 °C and 80 °C.

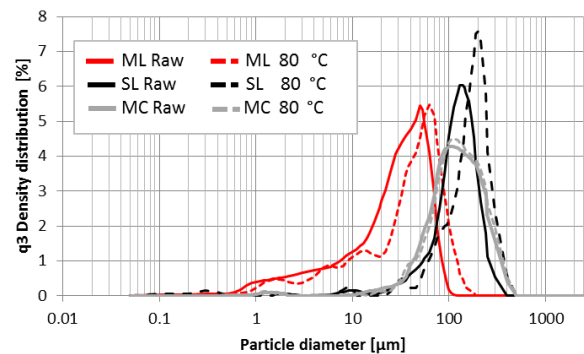


Figure 11: Particle size distribution (volume based) of lactose-milled, sieved and methylcellulose measurements in Venturi mode before (Raw) and after drying at 80 °C.

D values[µm]	ML			
	Raw material	85 %RH	40 °C	80 °C
D ₁₀	3.3	3.0	18.3	4.9
D ₅₀	28.5	38.6	46.3	40.7
D ₉₀	59.8	74.8	86.4	83.4
D[4,3]	32.0	41.6	52.5	45.1
	SL			
D ₁₀	50.8	68.4	62.6	60.7
D ₅₀	119.8	164.8	160.0	162.0
D ₉₀	193.8	248.7	248.3	245.2
D[4,3]	126.6	171.5	166.9	166.1
	MC			
D ₁₀	48.1	53.6	48.7	49.4
D ₅₀	111.5	125.5	118.5	117.4
D ₉₀	225.9	240.9	235.3	235.3
D[4,3]	132.0	145.2	138.6	138.6

Table 14: Volume weighted D-values measured in Venturi mode.

The analysis of agglomerates after drying was done by using the free-fall mode. The exemplary particle size distribution which was measured in free-fall at 80 °C is shown in Figure 12. The overview of all results obtained after 40 and 80 °C drying is displayed in Table 15.

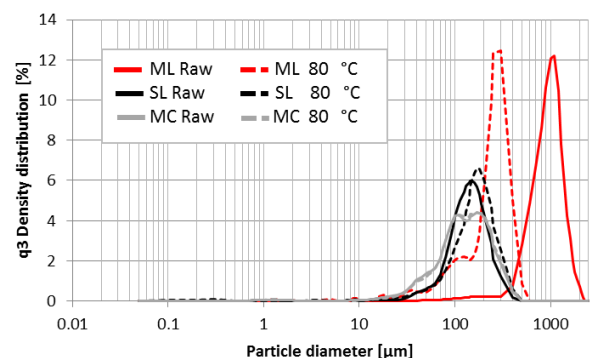


Figure 12: Particle size distribution (volume based) of milled lactose, sieved lactose and methylcellulose measurements in free-fall after drying at 80 °C.

D values[μm]	ML			
	Raw material	85 %RH	40 °C	80 °C
D ₁₀	489.8	497.9	80.0	77.0
D ₅₀	890.1	980.9	257.1	233.4
D ₉₀	1340.1	1507.7	418.4	345.0
D[4,3]	953.7	1036.8	279.6	240.4
	SL			
D ₁₀	68.6	74.0	72.0	63.7
D ₅₀	133.2	166.6	166.0	154.2
D ₉₀	218.8	252.1	255.0	247.3
D[4,3]	144.8	174.0	175.0	163.8
	MC			
D ₁₀	44.7	48.9	39.3	42.7
D ₅₀	119.9	132.1	112.2	117.3
D ₉₀	233.8	243.3	231.6	233.2
D[4,3]	138.7	53.6	132.7	136.6

Table 15: Volume weighted D-values measured in free-fall.

4 Discussion

4.1 Flowability

The effect of moisture uptake and drying on the flowability is discussed in this section.

4.1.1 Bulk density

Looking at the raw excipients, methylcellulose presents the lowest bulk density while sieved lactose the highest (Table 2). The moisture uptake causes an increase of the bulk density especially for milled and sieved lactose, where the adsorbed water fills the voids between the particles. Methylcellulose stays rather constant (Table 2). After drying, the most relevant changes can be observed for milled lactose (Table 10, Figure 9). The bulk density increase at 0 kPa is related to granule formation and the decrease of bulk density at 45 kPa is determined by the granule internal porosity that will favor the compactability and the compressibility (see paragraph 4.2.1)

4.1.2 Hausner Ratio and Carr Index

Table 16 shows the scale of flowability according to the Hausner Ratio and the Carr Index.

Hausner Ratio	Carr Index (%)	Flow Character
1-1.11	10	Excellent
1.12-1.18	11-15	Good
1.19-1.25	16-20	Fair
1.26-1.34	21-25	Passable
1.35-1.45	26-31	Poor
1.46-1.59	32-37	Very poor
>1.60	>38	Very, very poor

Table 16: Scale of flowability (1).

Raw excipients have different flowability:

- Milled lactose - *Poor* flowability
- Sieved lactose and methylcellulose - *Fair* and *Passable* flowability, respectively (Tables 4, 16).

For the milled lactose, the value of the Hausner Ratio and Carr Index increases after 45 %rH and decreases after conditioning at 85 %rH (Table 4). At low rH, the liquid bridges work as sintering medium between the particles and increase the cohesion. Therefore, the flowability decreases. At higher rH, such as 85 %rH, the excess water starts to dissolve the powder and acts as a lubricant slightly improving the flowability.

For the sieved lactose, the value of the Hausner Ratio and Carr Index shows a slight increase for both values in comparison to the starting material (Table 4). This indicates that water may contribute to the inter-particles adhesion.

For the methylcellulose, an increase of both parameters after 45 %rH was discovered, but after 85 %rH they decrease and reach a value close to the starting material (Table 4), indicating that methylcellulose, after conditioning, has still a passable flowability.

After drying at 80 °C, a significant improvement of flowability for the milled lactose, a slight change for the methylcellulose and a decrease of flowability for sieved lactose (Table 11) was observed. These data confirm that wet granulation of methylcellulose and sieved lactose would not have any additional advantage in terms of the flowability.

4.1.3 Cohesion strength, unconfined yield strength and principal stress

Sieved lactose and methylcellulose present a moderate cohesiveness in raw condition (Table 5) while milled lactose is very cohesive (Figure 6, Table 6). Sieved lactose undergoes an increase of the cohesion strength after 45 %rH and a decrease after 85 %rH (Table 5). This causes a flowability change, which can also be observed by the Hausner Ratio and Carr Index. Methylcellulose shows a decrease of cohesion strength and preserves a good flowability (Figure 5, Table 5). The cohesion of milled lactose continues to increase after wetting, as is indicated by the high value of the unconfined yield strength (Table 6).

After drying, the cohesion strength of sieved lactose granules increases while methylcellulose granules are similar to the raw material (Figure 10, Table 12). It follows that there is no improvement of flowability for sieved lactose. This is confirmed by the change of particle size (Section 4.1.5) as well as by the Hausner Ratio and Carr Index values. Milled lactose granules, even with an increase in flowability (Hausner Ratio,

Carr Index, particle size), are still cohesive. In fact, the unconfined yield strength increases (Table 13) which indicates a higher resistance to cracking of granules when the mold used for the tablet press is removed. Figure 13 shows an example of the unconfined yield strength and the principal stress as would be acquired through a uniaxial test.

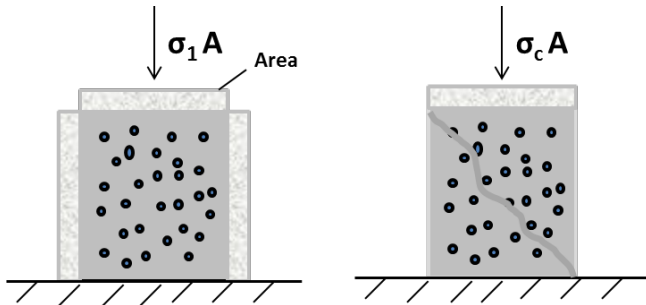


Figure 13: Example of the principal stress (σ_1) on the left and unconfined yield strength (σ_c) on the right.

4.1.4 Surface area and true density

In the case of low intraparticle porosity materials, such as those in this study, there is a direct correlation between surface area and particle size: The smaller the particle size, the larger the surface area (section 4.1.5). This correlation holds for the materials studied, where BET surface area of the lactose milled < lactose sieved < methylcellulose.

The porosity percentage can be calculated from the bulk density and true density by employing Equation 3. In the case of the samples studied, porosity is primarily interparticle porosity, as the low surface areas indicate a lack of pores inside these materials. According to the equation, milled lactose raw shows a higher interparticle porosity and this decreases the flowability and the particle packing. Porosity can be also related to the low bulk density, the small particle size and high cohesion.

$$\% \text{ Porosity} = \left(1 - \frac{\text{bulk density}}{\text{true density}} \right) * 100$$

Equation 3: Calculation of porosity from bulk and true densities.

4.1.5 Particle size and particle size distribution

The powder hygroscopicity affects the behavior during wet granulation and the tendency to water loss during drying. The investigation of the particle size distribution enables one to monitor the size enlargement due to water uptake and check the granule formation and the granule size after drying. In this way, powder agglomeration can be controlled to investigate possible caking and define the impact on flowability (2).

Among the tested excipients in the raw state, milled lactose shows the smallest size with a D50 of 28.5 μm

(Table 8), meaning that the surface area available for water adsorption is larger as indicated by the measured values (Table 7).

Due to this, the size increase of primary particles (Figure 7, Table 8) and agglomerates (Figure 8, Table 9) is more consistent for milled lactose.

The D-value, [4,3] which is the volume weighted mean sensitive to change in the coarse fraction, increases while passing from the raw condition to 65 %rH but decreases when the moisture goes up to 85 %rH (Tables 8, 9). In fact, at moderate rH such as 45 and 65 %rH, water molecules are adsorbed onto the particle surface and can form liquid bridges between particles. At this stage, due to liquid bridges, the size increase is consistent but the adhesion caused by the entrapped water reduces the flowability as is confirmed by the values of the Hausner Ratio and Carr Index. By increasing the rH, an event called deliquescence occurs to milled lactose. The particles start to dissolve in the water and therefore, the particle size of the solid fraction starts to decrease (2).

For sieved lactose primary particles and agglomerates (Tables 8, 9) show an increase of the D-value [4, 3] because liquid bridges start to build interconnections between the particles. The adhesion forces cause a slight decrease of flowability as is confirmed by the Hausner Ratio and Carr Index values.

As regards the methylcellulose, the particle size increase starts to be significant after 85 %rH treatment (Tables 8, 9). However, the water acts as a lubricant and because of particle size and adsorbed water, the excipient preserves a good flowability. This is also confirmed by the Hausner Ratio and Carr Index values as well as by the moderate cohesion strength.

After drying, granules are formed due to removal of water and the consolidation of particle interconnections through the creation of solid bridges.

The primary particles of milled lactose show a consistent increase in size after drying (Figure 11, Table 14) and the formation of granules is confirmed by the size of agglomerates with a D50 of 257.1 μm after 40 °C and 233.4 μm after 80 °C (Figure 12, Table 15). Therefore, the flowability of the powder is better than the raw material, as indicated by the Hausner Ratio and Carr Index values.

For sieved lactose, the size increase of primary particles suggests that solid bridges are formed which keep the particles together and promote their granulation (Figure 11, Table 14). However, Table 15 shows that after drying at 80 °C, the size of agglomerates (D50 = 154.2 μm) is close to that of agglomerates measured after 85 %rH (D50 = 166.6 μm). This could mean that after the drying step, the water was not completely removed and this could be an issue in wet granulation. The final flowability after wetting and drying is less than the raw materials, as is shown by the results of Hausner Ratio

and Carr Index calculations and the increase of the cohesion strength.

For methylcellulose, the results show that, after drying, the excipient retains the same structural properties of its raw materials. In fact, the particle size distribution of the raw material overlaps the one measured after drying (Figures 11, 12). This confirms the outcomes of the cohesion strength, Hausner Ratio and Carr Index calculations.

4.2 Compactability and compressibility

The following discussion is focused on the capacity of formed granules to compact and compress.

4.2.1 Bulk density and tapped density

The filling capacity of a capsule or a sachet as well as the tablet strength before cracking can be estimated by measuring the bulk density and the tapped density of raw materials as well as of final granules.

In the case of the investigated excipients, milled lactose granules at the end of the drying process show (at 45 kPa) a low bulk density while sieved lactose and methylcellulose do not have consistent changes in comparison with the raw materials (Table 10, Figure 9). However, the low bulk density of granules formed by milled lactose and methylcellulose will improve the compression during tableting as well as the packing in capsule filling. In fact, a lower bulk density is linked to an increased porosity of granules (3). Because of this, they will undergo a plastic deformation under compression, which increases the area of contact between particles (3; 4). At the end, tablets with lower porosity and higher tensile strength are produced. In the case of capsules, the voids can be filled by excipient or API of smaller size and the packing density can be improved, as well as the content uniformity (4). The results of the tapped density for the three excipients did not show significant differences after and before conditioning (Tables 3, 11). Nonetheless, sieved lactose shows a high tapped density, meaning that this excipient could be used to produce tablets with high tensile strength by means of direct compression or to improve the granule packing in the capsule filling process.

4.2.2 Cohesion strength and consolidation stress

The good flowability (Table 4) and the moderate cohesion strength (Table 5) of raw sieved lactose and raw methylcellulose make them suitable for dry granulation and direct compression. In fact, the results obtained in this analysis (Tables 12, 13) show that wet granulation would not favor the flowability (Section 4.1) or compressibility of these excipients. This is also confirmed by the bulk density, particle size change,

Hausner Ratio and Carr Index calculations. Contrary, after moisture uptake and consecutive drying, the principal stress of milled lactose granules increases (Table 13), indicating that the stress that can be applied during tableting or capsule filling can be increased without causing granule breakage.

4.2.3 Surface area

The high surface area of milled lactose (Table 7) and therefore the higher interparticulate interactions makes challenging the compactability or compression without wet granulation. Due to the low surface area and therefore, to the low attrition forces between particles, raw sieved lactose and raw methylcellulose are more suitable for dry granulation and direct compression.

4.2.4 Particle size and particle size distribution

Compressibility as well as compaction improves with increased particle size and decreases as the size becomes smaller. In fact, small particles have higher surface area and therefore, higher frictions. Because of this, they have less ability to lock together as it is explained in Section 4.2.3.

According to the results for the three excipients in this analysis, the granulation process could contribute successfully to the size increase of milled lactose (Figures 11, 12). Sieved lactose does not require wet granulation because the size of the starting powder is already promising for the compressibility.

Nonetheless, due to low cohesion strength, the combination with a binder excipient having a broader particle size distribution would enhance the strength of final tablets. It follows that sieved lactose is a useful excipient in the direct compression process or in capsule filling. This is also confirmed by its density, cohesion and raw surface area.

The size increase of methylcellulose in the wet granulation process is not significant as shown by the results of this analysis. The raw material has displays a distinct affinity for compressibility due to a discrete compressibility due to the broader particle size distribution and the moderate cohesion strength. For this reason, it can be used in the dry granulation and direct compression processes as a binder, mixed with other excipients such as sieved lactose.

5 Conclusions

As demonstrated by the results of this analysis, the raw excipients have different flowability and compressibility that can be influenced by granulation. Cohesion strength, Hausner Ratio, Carr Index, bulk density, particle size distribution and surface area values show that milled lactose is a cohesive, poorly

flowing powder while sieved lactose and methylcellulose are powders with medium flowability. However, the time, drying temperature and relative humidity have a different impact on handling and processing of excipients.

The moisture uptake is faster and more significant for milled lactose and the granules formed after drying at high temperature show a better flowability and compressibility than the raw material.

The wetting and consecutive drying process negatively impacted the sieved lactose flowability. The increase of drying temperature does not have any benefit on granule formation. Water is not completely removed after drying and the wet granules would result in fragile solid dosage forms. Therefore, sieved lactose would be more suitable as diluent in the direct compression process or in capsule filling.

Methylcellulose preserves its flowability and compressibility after conditioning. The parameter changes due to moisture and temperature are reversible, indicating that methylcellulose would be more appropriate as binder in combination with other excipients in dry granulation or direct compression.

The results of this analysis demonstrate that the choice of excipients and process parameters (temperature, relative humidity, time) can be defined and improved during the manufacturing steps before final dosage forms are produced.

6 References

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