

APPLICATION NOTE

Lactose Powder – Rotational Rheometry

Interaction of a Lactose Powder with the Powder Cell

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Introduction

Compaction is defined as the “formation of a solid specimen of defined geometry by powder compression” [1]. The compaction of a pharmaceutical powder into a tablet consists of three different steps. First, the powder containing the active ingredient and the different excipients is filled into the die. In a second step, the powder is compressed. Finally, the tablet is ejected and can be packed.

The efficiency of processing, particularly in the first step, depends on the flowability of the formulation [2]. In turn, many factors influence the flow behavior of powders: particle size and particle size distribution, moisture content, temperature, interactions of the excipients with each other, interactions between the active ingredient and the excipients, etc.

Formulations used in the pharmaceutical industry for the production of tablets are a mixture of different powders that can interact and affect processing of the tablet. In the following, we study the impact of magnesium stearate on the interaction of spray-dried lactose particles.

Materials

Two commercial samples were subjected to rheological analysis:

- Spray-dried α -lactose monohydrate, consisting of 10% to 20% of the amorphous phase and 90% to 80% of the crystalline phase
- Magnesium stearate

Method

Sample Preparation

Spray-dried lactose and magnesium stearate were measured as received. Three mixtures of spray-dried lactose with 1% (w/w) magnesium stearate were prepared and measured under the same conditions as the pure substances. The mixtures were prepared just prior to the measurements.

The powders were manually tapped 10 times in order to obtain a volume of 31 ml, which corresponds to 20 g of lactose and lactose-magnesium stearate mixture or 9.5 g of magnesium stearate.

Rheological Measurements

A Kinexus ultra+ Prime equipped with a cylinder cartridge was used to perform the measurements. A cup with a diameter of 37 mm was introduced into the cylinder cartridge and a 2-blade metal paddle (diameter: 32.5 mm, stainless steel 1.4404) was used as upper geometry.

A volume of 31 ml of the powder was placed into the cup. The upper geometry was introduced into the cup at a constant angular speed of $5 \text{ rad}\cdot\text{s}^{-1}$ and lowered at a constant speed of $1 \text{ mm}\cdot\text{s}^{-1}$ until an absolute gap of 5 mm was reached.

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Fluidization

Each sample was subjected to a fluidization step consisting of a shear viscosity ramp between 100 s^{-1} and $3,000 \text{ s}^{-1}$ followed by a 5-minute rest. During this step, interactions between the particles are reduced [2] and the influence of the sample history is deleted.

Powder flowability is very sensitive to different factors, e.g., sample storage and preparation. After the fluidization step and some minutes at rest, all materials had been subjected to the same preparation and had the same history.

Amplitude Sweep

After the fluidization step, an amplitude sweep was performed on the powder at a controlled temperature of 25°C and a controlled frequency of 1 Hz . During the measurement, the shear stress was varied from 0.01 Pa to 50 Pa . Each material was measured three times with a new loading.

Method for Determination of the Cohesion Energy Density, E_c

The cohesion energy of the powder denotes the energy required to separate two particles in contact. The cohesion energy density, E_c is the ratio of the cohesive energy and the volume of particles. [3]

It can be determined as the area below the curve of shear stress versus shear strain that is measured in the linear viscoelastic region (LVR) of an amplitude sweep (see also figure 1).

$$E_c = \int_0^{\gamma_{(critical)}} \sigma' \cdot d(\gamma) \quad (1)$$

$\gamma_{(critical)}$: shear strain at the end of the linear region
 σ' = Elastic shear stress

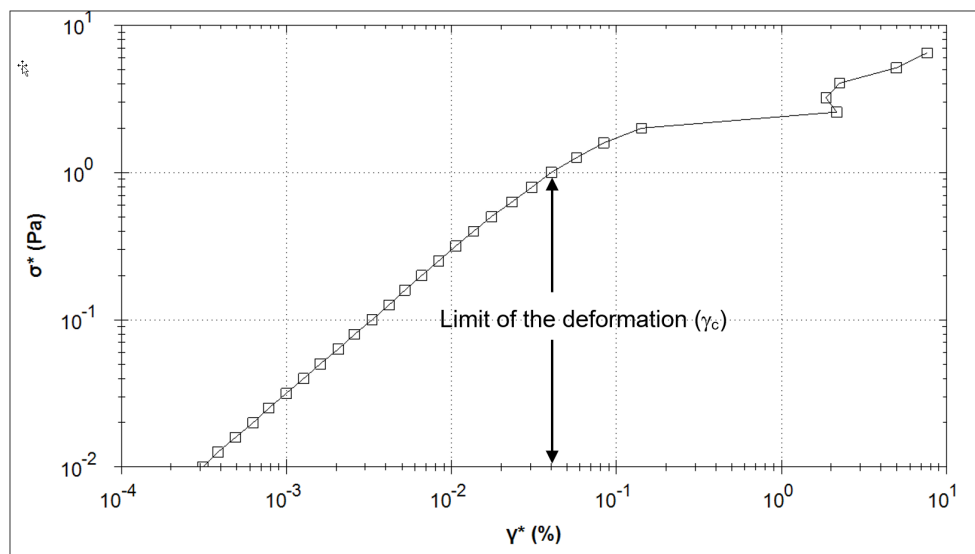
In the LVR, the following is valid: $G' = \sigma' / \gamma'$

So that (1) can be rewritten as follows:

$$E_d = G' \int_0^{\gamma_{(critical)}} \gamma' \cdot d\gamma = \frac{1}{2} G' \cdot \gamma_{(critical)}^2 \quad (2)$$

In a simplified way, the powder is represented as a viscoelastic material, which can itself be characterized as a combination of springs and dashpots. The stability of the material, in this case the cohesion of the powder, can be quantified with the elastic part (related to the springs) of the mechanical energy. The viscous part does not contribute to cohesion because the stresses imposed on the dashpots are not stored, but lost as heat.

Consequently, the cohesion energy density is calculated with the values of the elastic shear modulus during the LVR plateau and the strain at the end of the plateau.



1 Shear stress vs. shear strain during an amplitude sweep. The viscoelastic material is in the linear viscoelastic range as long as stress and strain are proportional.

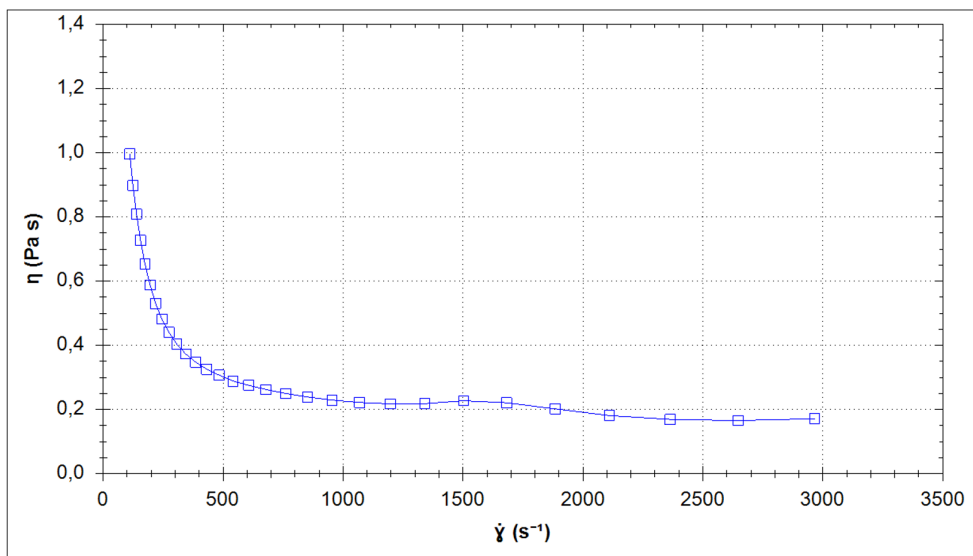
Measurement Results and Discussion

The apparent shear viscosity resulting from the fluidization step performed on spray-dried lactose is shown in figure 2. It decreases with increasing shear rates and reaches a plateau at 1000 s⁻¹. This independency of the apparent shear viscosity with respect to the shear rate in the high shear rate range shows that the applied shear rate was high enough to erase the sample history.

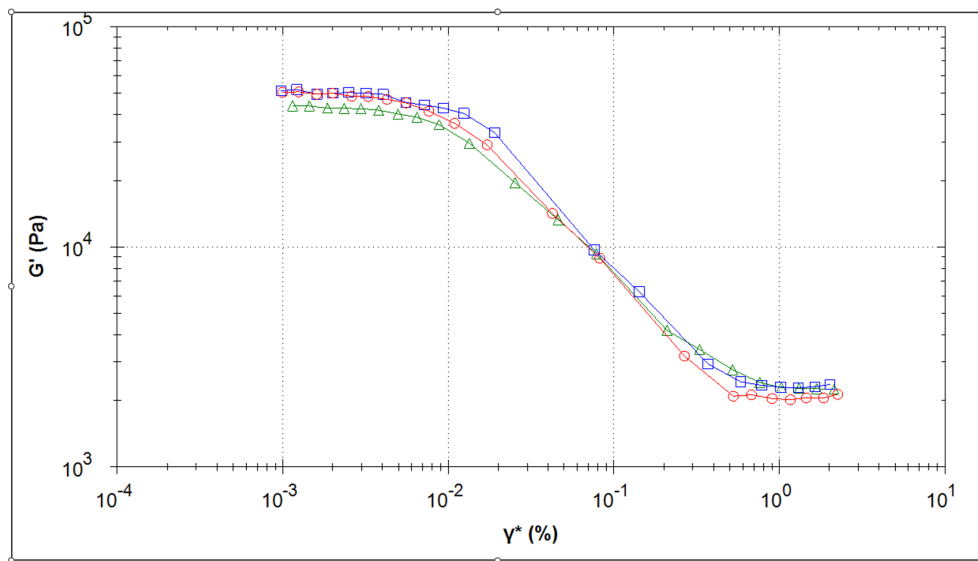
different loadings. The good repeatability of the curves confirms that the samples shared the same state after the preparation phase.

At low deformations, the curves remain constant: The powder is in the linear viscoelastic region, where the applied deformations do not lead to any structural breakdown and the applied shear strain is proportional to the resulting shear stress. At a strain of 4E-03 to 5E-03%, the material leaves the linear viscoelastic region. This means that for the timescale of the frequency used (1Hz), the powder begins to flow.

Figure 3 depicts the elastic shear modulus curves resulting from three amplitude sweeps carried out on spray-dried lactose just after the fluidization step, for three



2 Lactose. Fluidization step.

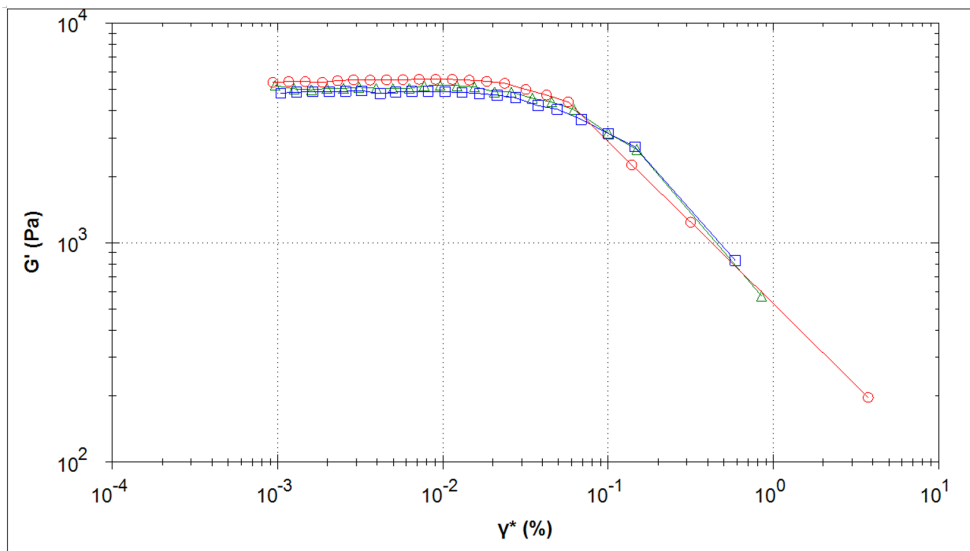


3 Spray-dried lactose. Amplitude sweep on 3 different loadings.

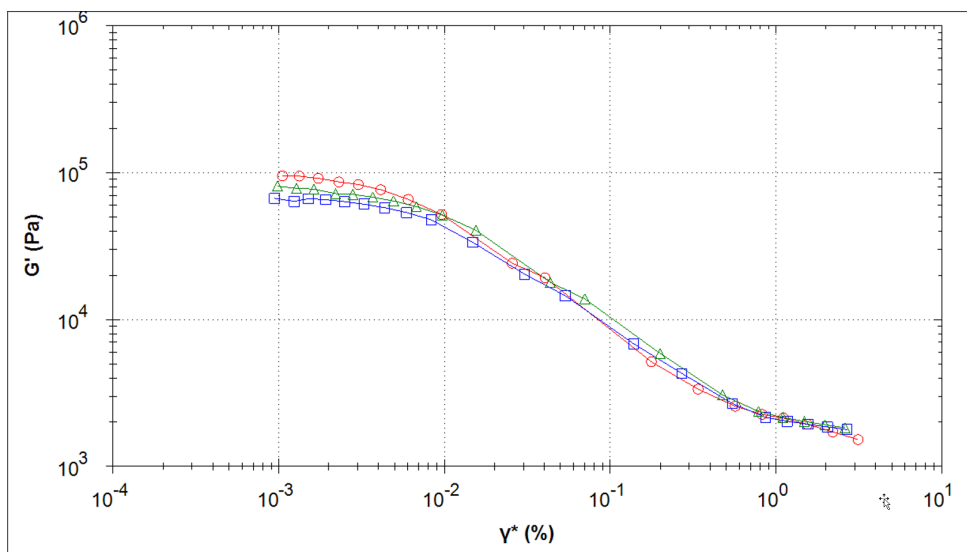
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Figure 4 depicts the elastic shear modulus curves resulting from the three amplitude sweeps performed on magnesium stearate. The elastic shear modulus value in the linear viscoelastic plateau is almost one decade lower than for the spray-dried lactose, while the plateau is broader.

Figure 5 displays the three curves obtained for the mixture. Obviously, the LVR plateau is shorter for this sample than for the lactose and the magnesium stearate taken alone.



4 Magnesium stearate. Amplitude sweep on 3 different loadings.



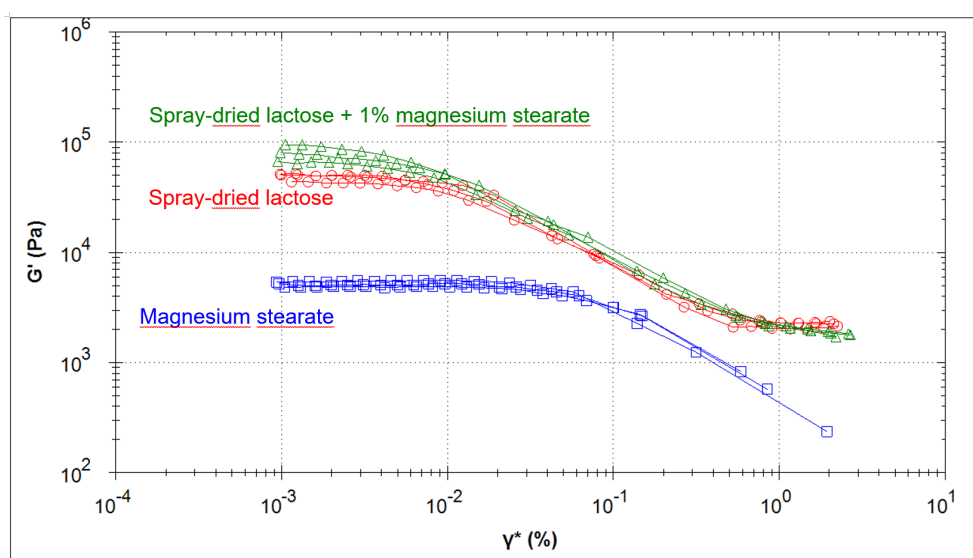
5 Mixture of spray-dried lactose and 1% magnesium stearate. Amplitude sweep on 3 different loadings.

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For better comparability, all curves are plotted in figure 6.

The end of the linear viscoelastic region was automatically determined by the measurement and evaluation software. For this, the points from a shear strain of 1E-03% were taken into account. The mean value of the elastic shear modulus in the LVR plateau was determined along with the shear strain at which the elastic shear modulus loses 5% of this mean value. Table 1 summarizes the results for the three measurements performed on each powder as well as the calculated cohesion energy density according to equation (2).

Spray-dried lactose has a lower cohesion energy density than magnesium stearate and thus better flowability properties. Magnesium stearate is normally applied as lubricant to facilitate a tablet's ejection from the die after powder compression. Although it is considered a cohesive powder, it has a glidant effect at low concentrations [4]. As expected, the results show that this component improves the flowability properties of the lactose powder if added in the small concentration of 1% weight. This behavior is due to its ability to adhere to the surface of the other components of the powder mixture, allowing it to fill in the surface gaps and create particles with less friction, thus improving flow properties [4].



6 Comparison of the curves

Table 1 Cohesion energy density determined on the three samples

Material	Measurement	Shear strain at LVER end [%]	Elastic shear modulus in LVER [Pa]	Cohesion energy density [Pa]	
				Individual values	Mean value
Spray-dried lactose	1	4.46E-03	5.03E+04	0.05	0.49 ± 0.01
	2	4.78E-03	4.24E+04	0.50	
	3	4.38E-03	4.91E+04	0.47	
Magnesium stearate	1	2.68E-02	5.45E+03	1.965	1.86 ± 0.01
	2	2.57E-02	4.86E+03	1.604	
	3	2.82E-02	5.06E+03	2.019	
Mixture of spray-dried lactose and 1% magnesium stearate	1	3.48E-03	6.35E+04	0.38	0.39 ± 0.01
	2	3.30E-03	7.20E+04	0.40	
	3	2.92E-03	8.78E+04	0.38	

Conclusion

The cohesion energy density of three powders was determined by means of measurements performed with the NETZSCH Kinexus rotational rheometer. The method uses a fluidization step followed by a rest time prior to the actual amplitude sweep. Cohesion of the powder is related to the shear strain at the end of the linear viscoelastic plateau and to the elastic shear modulus in the plateau. The higher the cohesion energy density resulting from the amplitude sweep, the poorer the flowability properties of the powder.

It was possible to investigate the influence of a small amount magnesium stearate on the flowability of spray-dried lactose with this method.

Sources

- [1] Aulton's Pharmaceuticals, Kevin M.G. Taylor and Michael E. Aulton, 2021
- [2] Characterization of flow properties of cohesive powders: A comparative study of traditional and new testing methods, M. Leturia, M. Benali, S. Lagarde, I. Ronga, K. Saleh, Powder Technology, Volume 253, February 2014, Pages 406 - 423
- [3] Predicting powder caking using cohesion energy density Karthik Salish, R.P. Kingsly Ambrose, Powder Technology, Volume 393, November 2021, Pages 312 - 322
- [4] Morin, G., Briens, L. AAPS PharmSciTech 14, 1158 -1168 (2013)