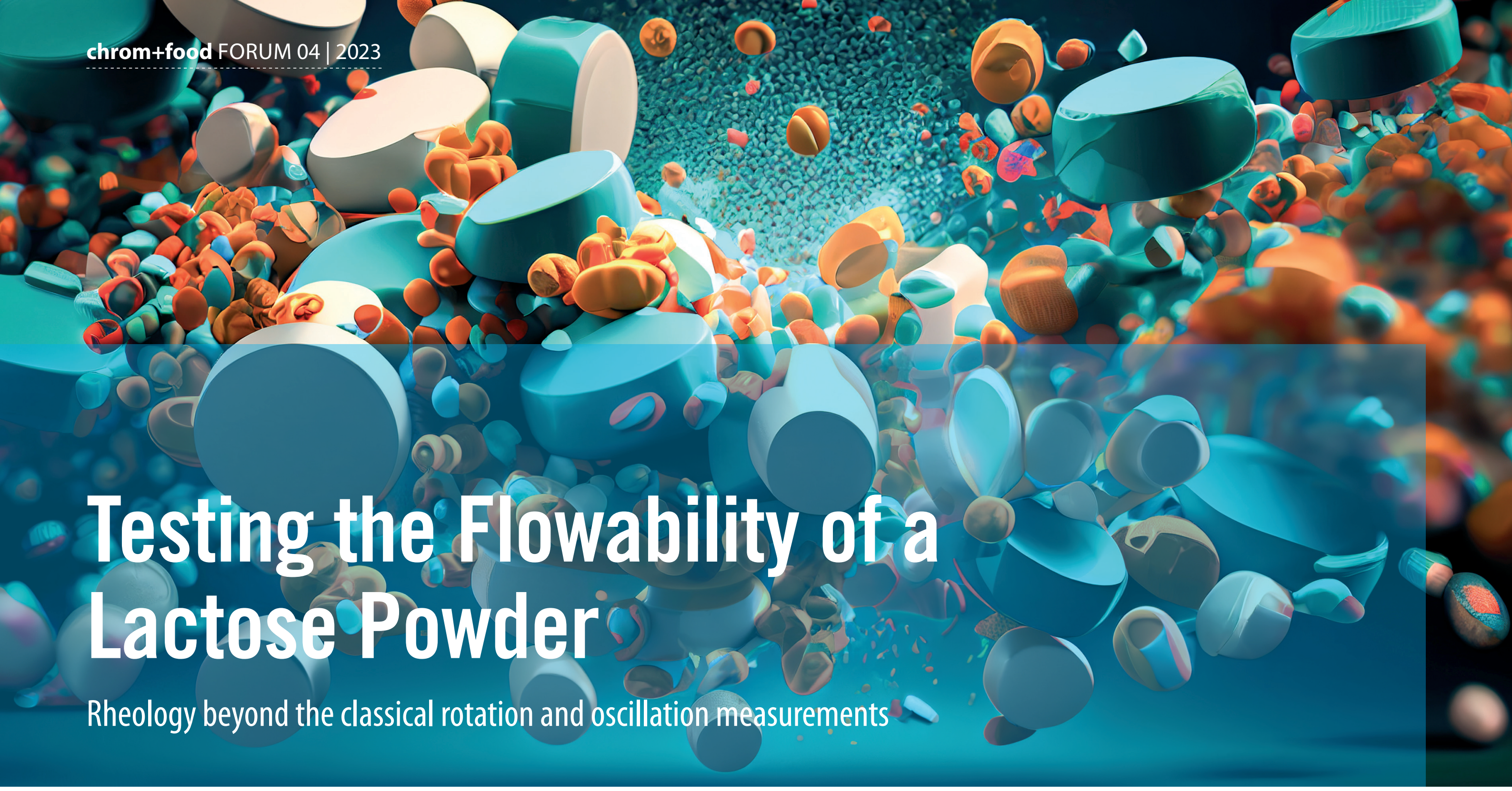

Testing the Flowability of a Lactose Powder

Rheology beyond the classical rotation and oscillation measurements

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Processing of a powder mixture for tableting is closely related to its rheological properties, particularly to its flowability. In the following, the influence of the addition of 1% magnesium stearate on the cohesion energy density of a lactose powder is investigated using the Kinexus rotational rheometer.

A medication is usually composed not only of the drug itself, but also of excipients that make its production and administration feasible. The excipients can be classified according to their function, and application in pharmaceutical formulation. Many of these substances may have more than one function in a dosage form, e.g., it can act as a lubricant, glidant, and anti-adherent. Among all administration routes, the oral route is the preferred way to administer medicines and tablets are the most common dosage form for oral administration [1]. Fillers, binders, disintegrants, and coating materials are also examples of excipient types for tableting.

Fillers are used to increase the volume of the powder when making a tablet of a potent drug. Lactose is the most common filler for tablets and capsules. It is water soluble, but not hygroscopic, reacts with a limited number of other substances, and features good taste and high compactability. Depending on the production process, three different stable polymorphs are obtained: anhydrous α-lactose, anhydrous β-lactose, or monohydrate α-lactose. Although anhydrous and monohydrate lactose are directly compressible powders, the addition of small amounts of amorphous lactose enhances its compactability [2].

Compression of the powder into a tablet involves three steps: filling of the die, tablet formation by the punch entering the die and compressing the powder, and tablet ejection from the die. In these steps, glidants assure that the powder to be compressed flows homogeneously into the die, while lubricants lower the friction between the powder and the die walls, facilitating tablet formation and ejection. On the other hand, anti-adherents reduce adhesion between the powder and punch faces [1].

Magnesium stearate is a very fine, light white powder of low bulk density, consisting of variable proportions of magnesium stearate and magnesium palmitate. The hydrophobic character of magnesium stearate defines its primary use as a lubricant in the capsule and tablet manufacture at concentrations between 0.25% to 5.0% w/w. It has also anti-adherent properties [1,2].

Although magnesium stearate is considered a poorly flowing and cohesive powder, it is also a glidant in concentrations below 1% w/w. By adhering to the surface of the other components of the powder mixture, magnesium stearate fills in the surface gaps, creating smother particles with less friction and improved flow properties [3].

From Rotational Rheometry to Powder Flowability

In this study, we compare the flowability properties of pure α-lactose monohydrate and a mixture containing 1% magnesium stearate using the Netzsch Kinexus rotational rheometer. For the measurements, a cup (lower geometry) and a 2-blade paddle (upper geometry) were used (Fig. 1). A constant temperature was maintained by the cylinder cartidge, in which the lower geometry (cup) was introduced.

Since the results largely depend on the powder conditioning, it is crucial to prepare the different samples under exactly the same conditions: Same sample amount, same pre-conditioning parameters (e.g., a defined speed and time of rotation). Here, a fluidization step was performed prior to the actual measurement to achieve the same pre-conditioning. For this purpose, the paddle was immersed in the powder and rotated up to a shear rate of 3,000 s^{-1} using a shear rate ramp. Table 1 shows the measurement parameters.

Fig. 1: Cup and blade paddle

Tab. 1: Measurement parameters

	Pre-conditioning: Fluidization	Amplitude sweep
Device	Kinexus ultra+, cylinder cartridge	
Geometry	2-blade paddle	
Gap	1 mm	
Type of test	Rotation	Oscillation
Temperature	25°C	
Shear rate	100 to 3,000 s^{-1}	---
Shear stress	---	0.2 Pa to 40 Pa (Lactose) 0.1 Pa to 50 Pa (Mixture)
Frequency	---	

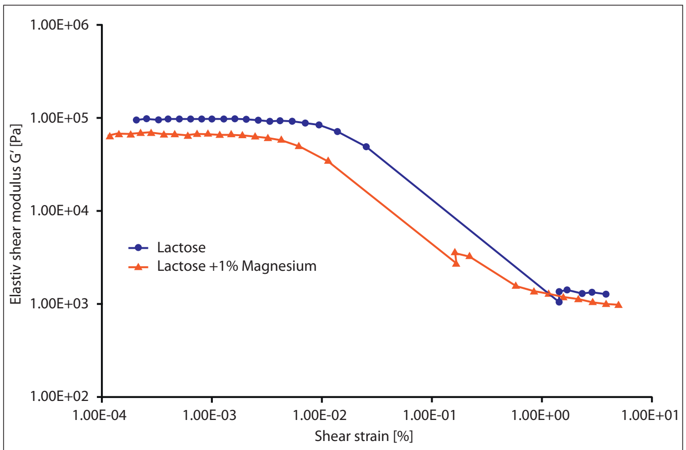


Fig. 2: Elastic shear modulus resulting from the amplitude sweep on lactose (blue) and on the lactose + 1% magnesium stearate mixture (orange).

Figure 2 depicts the elastic shear modulus curve (G´) resulting from the amplitude sweep measurements on lactose and on the lactose + 1% (w/w) magnesium stearate mixture. In the lower shear strain range, the elastic shear modulus remains constant. This plateau signifies the linear visco-elastic range (LVER), in which the applied stresses (or strains) are insufficient to cause breakdown of the structure. As long as the sample is in its linear visco-elastic range, its microstructural properties are being measured. For a powder, this is related to its cohesion properties. As soon as the powder structure breaks down, the elastic modulus begins to decrease.

The cohesion energy density of a powder is related to the value of the elastic shear modulus measured in the LVER plateau, and to the width of the LVER plateau. It can be calculated by means of the following equation:

$E/V = ½\, G' \times \gamma^2$

E/V: cohesion energy density [Pa];
G´: elastic shear modulus measured in the LVER [Pa];
γ: shear strain at the end of the LVER [%]

The curves clearly show that the lactose and magnesium stearate mixture has a lower elastic modulus value in the LVER as well as a shorter LVER plateau in comparison to the lactose powder. This indicates a lower cohesion energy density. This means that the 1% magnesium stearate leads to an increase in lactose flowability.

From Rheological Curves to the Quantification of the Cohesion Energy Density

The values of the amplitude γ and of the elastic shear modulus G´ at the end of the linear visco-elastic range (LVER) can be determined automatically in the Netzsch rSpace measurement and evaluation software as soon as the measurement is finished. To do this, the shear strain at which the elastic modulus decreases by 5% compared to the elastic modulus value in the LVER plateau is taken into consideration. Table 2 shows the evaluation.

As shown in Table 3, the addition of 1-% magnesium stearate greatly influences the cohesion energy density of lactose powder, as expected [3]. It leads to a 6-time lower cohesion, meaning an improvement in flowability of the mixture in comparison to lactose alone.

Each excipient entering the composition of a powder mix for tablet manufacturing may influence the properties of the mixture, e.g., its cohesion, compactability, adherence, etc. This, in turn, will influence its processing.

More than classical rotation and oscillation measurements on visco-elastic materials, the Kinexus rotational rheometer also provides first insights into powder rheology. The tests described here highlight the consequences of a small addition of magnesium stearate on the flowability of lactose.

Tab. 2: Shear strain and elastic shear modulus (G´) at the end of the LVER plateau

Action Name	Find value - Find stress and strain where G' drops by %5	Find value - Find stress and strain where G' drops by %5
Experiment Name	LVER determination	LVER determination
Sample Description	006-5-23-12 Lactose	006-5-23-10 Lactose and MgStearate AmpliSweep (1)
Phase angle (°)	4,52	6,30
Point Index	1	1
Shear modulus (elastic component) (Pa)	8,905E+004	6,054E+004
Shear modulus (viscous component) (Pa)	7,037E+003	6,672E+003
Complex shear strain (%)	6,54436E-003	3,16252E-003
Complex shear stress (Pa)	5,851	1,924

Tab. 3: Measurement parameters

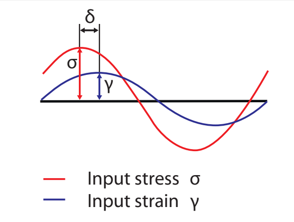
Sample	Lactose	Lactose + 1% (w/w) magnesium stearate
Elastic shear modulus [Pa]	8.9E+04	6.1E+04
Shear strain [%]	6.5E-03	3.2E-03
Cohesion energy density [Pa]	1.9	0.3

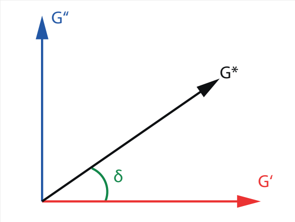
Functional principle of a rotational rheometer (oscillation measurement)

The upper plate oscillates with a defined frequency f [Hz] (or ω [rad/s]) and amplitude [%] (or shear strain γ [%]). The shear stress σ [Pa] required for this oscillation is determined and is split into an "in-phase" and an "out-of-phase" part.

The "in-phase" part is related to the elastic properties (➔ G´, storage shear modulus), the "out-of-phase" part to the viscous properties (➔ G´´, loss shear modulus) of the viscoelastic material. The phase angle δ ($\tan \delta = G''/G'$) is a relative measure of the viscous and elastic properties of the material. It ranges from 0° for a fully elastic material to 90° for a fully viscous material.

The viscoelastic properties of the sample are determined, in particular its complex stiffness G* and its complex shear viscosity η* [Pa·s]: $\eta^* = \frac{(G^*)}{\omega}$



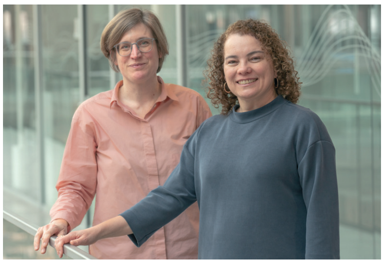


LVER – Linear ViscoElastic Range

The LVER is the amplitude range where strain and stress are proportional. In the LVER, the applied stresses (or strains) are insufficient to cause structural breakdown of the structure and hence microstructural properties are being measured.

Reference:

[1] Taylor, K.M.G., Aulton M.E., 6th edition, Elsevier.
[2] Rowe, R.C., Sheskey, P.J. and Quinn, M.E., 6th Edition, Pharmaceutical Press.
[3] Morin, G., Briens, L. AAPS PharmSciTech 14, 1158–1168 (2013).



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