Rheological Analysis of L-HPC and Suitability for Continuous Manufacturing

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Introduction

The characterization of the powder flow using traditional methods like Carr's index or flow through a funnel is as example insufficient to screen and predict the powder performances during the feeding step in a continuous manufacturing line, as the powders are undergoing several physical environments requiring different behavioral properties. [1,2]
During the development of formulations designed for a continuous process, looking into multi-functional excipients has several advantages. Besides the final functions of the excipients, it allows for a reduction of feeders needed. To compare different excipients, the pharmaceutical industry is looking for test methods which aid in the understanding of powder flow and feeding processes. One of these devices is the FT-4 Powder Rheometer, a widely used device for understanding powder flow behavior in the context of feeding and continuous manufacturing.
L-HPC having different particle sizes and shapes is an excellent candidate for taking first steps in rheology analysis. In this study, we demonstrate the flow properties of five different L-HPC grades measured with the FT-4 Powder Rheometer.

FT-4 Powder Rheometer

Materials and Methods

L-HPC (Low-Substituted HydroxyPropyl Cellulose) LH-11, LH-21, LH-31, LH-B1 and NBD-021 were sourced from Shin-Etsu Chemical Co., Ltd. The main differences between the powders are the particle size distribution and particle shapes. The chemical substitution level (HP-content) for each grade is 11%. The powder rheology of all L-HPC grades were measured with the FT4 Powder Rheometer. The methods we used in this study were mostly related to the feeding step and included stability and variable flow rate as dynamic methodology, and shear cell as shear methodology.[3] Shear cell data is more process-relevant for high stress environments (where the powder is compressed) and most specifically for discharge from hoppers, silos and feeders. To explore and predict flow in lower stress applications the focus should be on lower stress techniques like the dynamic measurements.

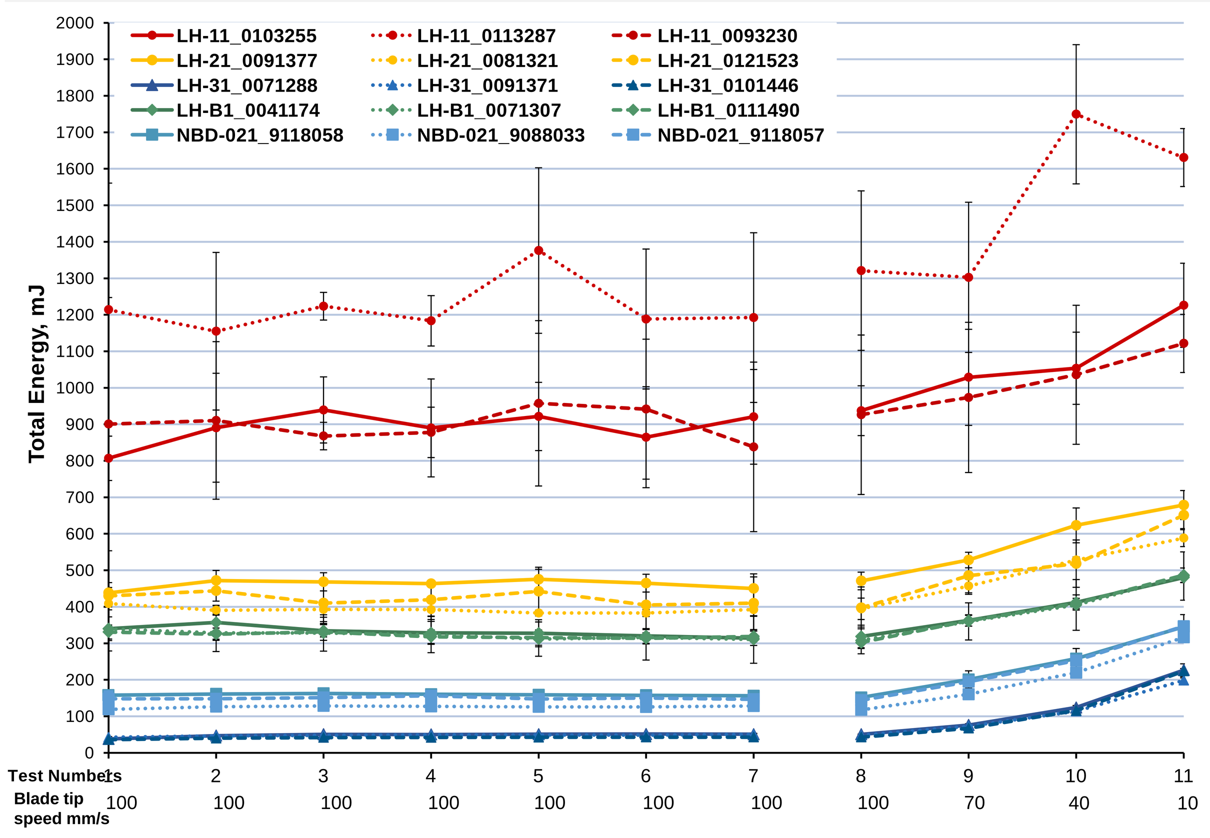
L-HPC (low-substituted HPC)

LH-11 | **LH-21** | **LH-31** | **LH-B1** | **NBD-021**

Fibrous | Slightly Fibrous | Fine Powder (micronized) | Non Fibrous | Short Particle (optimized)

Sample name	Particle size D_{50}	LOD % (CoA)	Angle of Repose (°)	Bulk density (g/L)
LH-11	55	1.3	53.7	330
LH-21	45	1.7	49.7	380
LH-31	20	2.3	54.2	280
LH-B1	55	2.3	43.6	480
NBD-021	45	0.9	46.7	320

Stability and Variable Flow Rate Analysis Low stress Environment



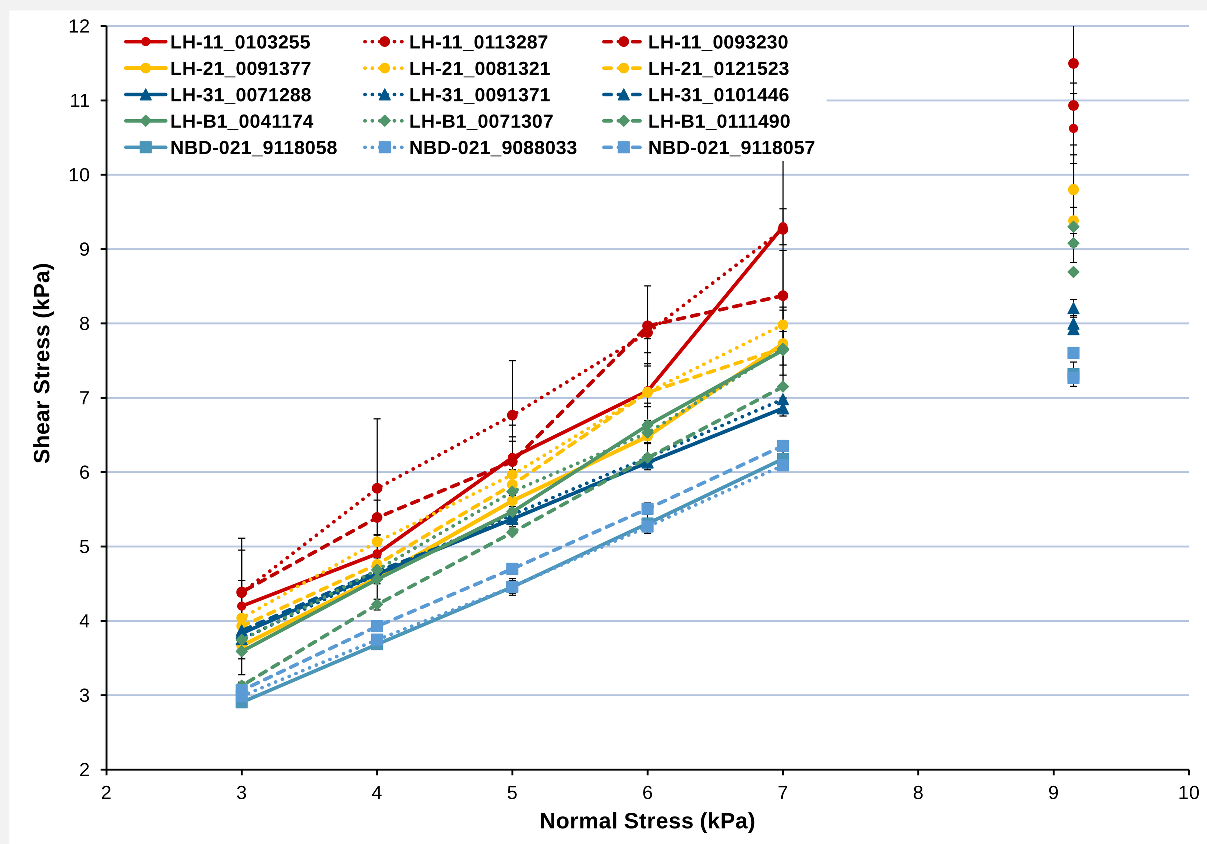
Two influences visible:
- Particle size: LH-11 needs more energy compared to LH-21 and LH-31, the coarser the sample the more energy is consumed to fluidize the powder: LH-11 > LH-21 > LH-31
- Particle shape: LH-11 and LH-B1 have the same PSD but different particle shapes, LH-21 and NBD-021 have the same PSD but NBD-021 has almost no long and more short fibers: means spherical and short fibrous particles need less energy to become fluidized

Sample	Stability Index (SI) SI= Energy Test 7/Energy Test 1	Flow Rate Index (FRI) FRI=Energy Test 11/Energy Test 8	Specific Energy (SE) in mJ/kg
LH-11	**1.1** ± 0.2	**1.3** ± 0.2	**10.8** ± 0.8
LH-21	**1.0** ± 0.1	**1.5** ± 0.1	**8.7** ± 0.2
LH-31	**1.2** ± 0.1	**4.6** ± 0.2	**8.2** ± 0.3
LH-B1	**0.9** ± 0.1	**1.6** ± 0.1	**7.1** ± 0.4
NBD-021	**1.0** ± 0.1	**2.5** ± 0.0	**8.0** ± 0.2

– **Stability Index**: stable powders ≈ 1, powders with SI > 1 and SI < 1 are unstable
➢ With regards to the standard deviation, all powders are more or less stable
– **Flow Rate Index**: FRI values > 1 represent bigger resistance to flow when powder is made to flow more slowly
➢ Typical for powder is a FRI value between 1.5 and 3.0

➢ Highest resistance is shown by LH-31 which could be related to the highest amount of fine particles
– **Specific Energy** is a measure of how easily a powder will flow in an unconfined or low stress level and is primarily influenced by mechanical interlocking and friction between particles
➢ LH-11 is highly fibrous and shows the highest SE followed by LH-21. Long fibers could easily interlock between each other
➢ Lowest SE is shown by LH-B1 with the highest amount of spherical particles, the higher the amount of spherical particles the better the flow

Shear Cell Analysis (Pre-shear normal stress of 9 kPa) High Stress Environment



– Shear stress shows how easily a previously at rest, consolidated powder will begin to flow; the higher the shear stress for a given normal stress, the less likely the powder will yield and begin to flow if entrapped in a funnel or other vessel under a similar setting stress
– Differences between powders can be observed by determining the standard deviation: no overlap in the error bars = differences between the samples which can potentially change their process performance

– LH-11 shows the highest yield loci which results in a greater resistance to flow due to the high amount of long fibers
– Taking the overlapping error bars into account, all batches of LH-21, LH-B1 and LH-31 show more or less similar yield loci, despite the different PSD and shape
– Lowest yield loci measured for NBD-021
➢ lower Shear Stress values for all batches of NBD-021 indicate lower resistance to the onset of flow following compression.

Sample	Flow Function (FF)	Cohesion (kPa)
LH-11	**7.3** ± 3.3	**0.8** ± 0.2
LH-21	**7.0** ± 1.2	**0.9** ± 0.2
LH-31	**3.3** ± 0.2	**1.5** ± 0.1
LH-B1	**8.6** ± 2.6	**0.5** ± 0.2
NBD-021	**9.0** ± 1.0	**0.6** ± 0.1

– Flowability (Flow Function) defined as follows [4] :
  – < 1 hardened
  – 1< FF < 2 very cohesive
  – 2 < FF < 4 cohesive
  – 4 < FF < 10 easy flowing
  – > 10 free flowing
– According this definition, LH-31 is cohesive whereby all other products are easy flowing
– The same impression is given by the cohesion in kPa, LH-31 shows the highest value and thus is more cohesive then the other samples.
– LH-B1 and NBD-021 shows higher FF values and lower cohesion, means spherical particles of LH-B1 besides an optimized particle morphology of NBD-021, improves the flowability due to a lower cohesion affinity.

Summary

Both methods measure different characteristics of powder behavior. Almost all L-HPC grades, except LH-11 and NBD-021, behave in the same way when in a consolidated environment, during the initiation of flow, like in a feeder (shear testing data), but they have significantly different flow properties when moving dynamically in a process, as seen by the dynamic flowability measurement. L-HPC powders are likely to behave in a similar way in a feeder. Only the long fibers of LH-11 could result in feeding problems because of its interlocking behavior. In more dynamic, moderate, or low stress environments, such as mixing and filling processes, these powders are likely to exhibit different performance. By modeling a Continuous Manufacturing line, these different behaviors should be taken into account to guarantee a successful production of pharmaceuticals.

References

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