

Development of a Reproducible Powder Characterization Method Using a Powder Rheometer

Søren Vinter Søgaard¹, Morten Allesø², Joergen Garnaes³, Stefania Baldursdóttir¹
and Jukka Rantanen¹

¹ Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark

² Product Development and Life Cycle, H. Lundbeck A/S, Ottiliavej 9, DK-2500 Valby, Denmark

³ Danish Fundamental Metrology A/S, Matematiktorvet 307, DK-2500 Kgs. Lyngby, Denmark

ABSTRACT

In this study, a powder rheometer was used to measure flow characteristics of two pharmaceutical model powders. Precise measurements were obtained for one of the model powders whereas the results were less precise for the second powder. In conclusion, further work is needed to increase the mechanistic understanding of powder rheological measurements.

INTRODUCTION

Modern pharmaceuticals are primarily manufactured by empirical approaches and batch-wise unit operations. However, regulatory authorities have started to require that future manufacturing schemes should be developed, monitored and controlled based on a mechanistic understanding of how material attributes and process parameters affect the performance of the final product^{1,2}. Yet, the mechanistic understanding of pharmaceutical powder processing is inadequate and generally relies on a few methods that are not very discriminative, e.g. flow through a funnel or Carr's Compressibility Index as defined in several Pharmacopoeia tests. New tools for studying powders are therefore needed in

order to increase the current understanding of underlying principles affecting powder behavior. The Freeman Technology 4 (FT4) bench-top powder rheometer, previously described elsewhere in the literature^{3,4}, might be such a tool due to the fact that it is designed to characterize powders under various conditions in ways that resemble large-scale production environments. In addition, the powder rheometer is able to measure several parameters related to process performance of powders. These methods include rheological, permeability, compressibility and torsional shear tests.

Within the recent years, several studies have been published using a FT4 powder rheometer to investigate and characterize different powder properties⁵⁻⁷. Though the FT4 rheometer does not provide direct in-process measurements of powder properties, it is indeed a promising tool for increasing the mechanistic understanding of powder behavior in lab-scale. The knowledge obtained in the laboratory can then be transferred and applied to large-scale processes. In 2011, Dumarey *et al.* showed how methods provided by the FT4 powder rheometer can be of great value to understand how raw material attributes

affect a roll compaction process and thus the final tablet quality⁶. Nonetheless, before such studies can be performed it is crucial to establish reproducible characterization methods, which is not a trivial task. Plenty of physical properties of powders, e.g. particle size and shape distributions, as well as environmental conditions in the laboratory, e.g. electrostatic charge, influence the measurements^{5,7}. These variables should be kept in mind when developing a powder characterization method.

A commonly used method in the previous mentioned studies is the stability and variable flow rate method (SVFR method), which is a powder rheological method. The objective of this study is to develop an experimental methodology based on the SVFR method, and subsequently evaluate it in order to obtain a reproducible characterization method. Furthermore, the relative standard deviation of the methodology is estimated using 16 replicates.

MATERIALS AND METHODS

Materials

The microcrystalline cellulose (MCC) was purchased as Avicel PH-200 from FMC BioPolymer, Philadelphia, USA. The anhydrous lactose (AHL) was a SuperTab® 21AN quality provided from DMV-Fonterra Excipients, Nörten-Hardenburg, Germany.

Sample preparation

An identical sample preparation procedure was carried out for both MCC and AHL: 896 ml of bulk sample was poured into an open container and placed in an in-house built humidity control chamber with a fixed relative humidity and temperature at 50±5% and 21±1°C, respectively. The bulk sample was left under these conditions for two days in order to make the water absorption on the powder material reach the equilibrium. After this the bulk sample was sieved through a 0.71 mm mesh

to break down any agglomerates that may have arisen during the acclimatization. The bulk sample was then divided into 32 identical samples of 28 ml using a spinning riffler with eight divisions (Retsch PT100, Retsch GmbH, Haan, Germany). This was performed by dividing the bulk sample into 8 portions of 112 ml. Every portion was then further divided into 8 sub-portions of 14 ml. The sub-portions were added together two by two taking sub-portions placed opposite one another at the spinning riffler with the aim of obtaining a representative sample division. Finally, the samples with a volume of 28 ml were placed in the humidity control chamber under the previous mentioned conditions for two days prior to the measurements. 16 of the 32 samples were randomly selected and measured. The remaining samples were applied for other purposes not included in this study.

Method

The measurements were carried out in the humidity control chamber with a fixed relative humidity (RH) and temperature at 50±5% and 21±1°C, respectively, in order to reduce the measurement error related to static electricity^{7,8}. The samples were measured using a modified programme based on the SVFR method, which is a standard method provided by the FT4 powder rheometer (Freeman Technology Ltd., Tewkesbury, UK) The default SVFR method comprises a stability method containing seven test cycles and a variable flow rate method containing four test cycles (Fig. 1). However, in order for the powders to reach a stable state, which is recommended by the manufacturer of the rheometer, the stability method was extended to contain 12 test cycles⁹. In that way, the modified SVFR method ended up consisting of 16 test cycles. The modified SVFR method was applied to measure the flow characteristics of each of the 16 replicates of AHL and MCC, respectively.

RESULTS

Fig. 2A and B show the measurements of the 16 individual replicates for AHL and MCC, respectively, which were obtained during the SVFR method. The measurements are expressed in total energy (mJ).

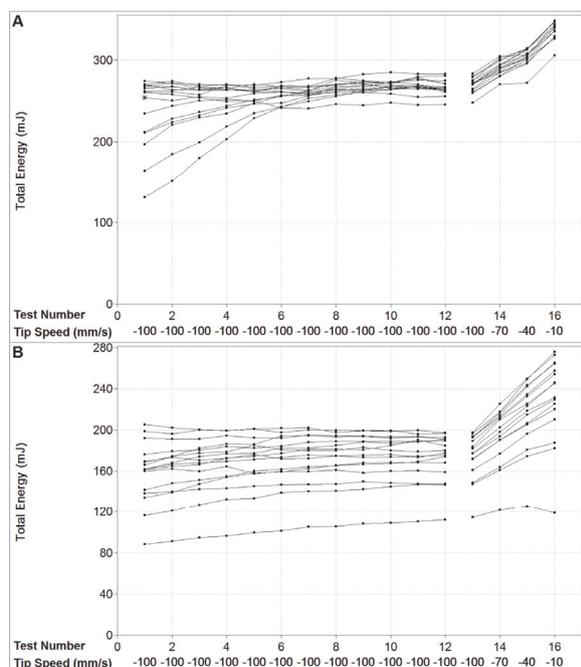


Figure 2. Measurements obtained from the stability and variable flow rate method. Test no. 1-12 constitute the stability method, while test no. 13-16 constitute the flow rate method. A: 16 replicates of anhydrous lactose. B: 16 replicates of microcrystalline cellulose.

Table 1 contains the flow characteristics and the bulk densities of MCC and AHL obtained by the SVFR method. The results are shown as averages with standard deviations (SD) and relative standard deviations (RSD).

DISCUSSION

The bulk densities shown in Table 1 prove that a very uniform packing state of both powder types is obtained after the splitting procedure. This means that the packing state of the replicates is very similar

prior to the first conditioning and test cycle for AHL and MCC. However, based on the bulk densities alone it cannot be assessed if the powders were homogeneous, i.e. the powders were not segregated.

Table 1. Flow characteristics of the powder samples obtained by the stability and variable flow rate method.

	Microcrystalline cellulose	Anhydrous lactose
CBD, g/ml	0.375 ± 0.002 (0.5%)	0.662 ± 0.004 (0.6%)
BFE (mJ)	174 ± 23 (13.2%)	266 ± 9 (3.6%)
SE (mJ/g)	5.25 ± 0.65 (12.4%)	5.11 ± 0.15 (2.9%)
SI	1.11 ± 0.10 (9.3%)	1.17 ± 0.27 (23.8%)
FRI	1.31 ± 0.09 (6.5%)	1.25 ± 0.03 (2.3%)

Average ± SD (RSD), n=16.

The BFE and SE obtained for AHL seems to be within a reasonable precision for powders, i.e. less than 5% RSD. In contrast, the same parameters obtained for MCC have much larger RSDs. The observation is also illustrated in Fig. 2 where the total energy obtained from the initial test numbers of both powders differs between the replicates. Nevertheless, the AHL replicates tend to stabilize at the same level of total energy whereas the MCC replicates reach different levels of total energy in the end of the stability method. This influences the BFE and SE (a measure of flowability and cohesivity, respectively), because these parameters depend on the measurements in the end of the stability method^{14,15} (Eq. 2 and 3). The same is the case for SI, which is a measure of how much the total energy for the sample is changing during the stability method (Eq. 4). Because all of the AHL replicates tend to end at the same level of total energy for the last test numbers of the stability method independent of the initial total energy, the SI of AHL has

a high RSD (Fig. 2A). On the other hand, the individual measurements of the MCC replicates elucidate that the individual replicates tend to start and end at the same level of total energy thereby obtaining SIs which are both closer to one and more precise than AHL. However, what the SI does not show is that the total energy obtained from the MCC replicates is spread over a large range of total energy (Fig. 2B).

Looking at the FRI, which according to the manufacturer of the powder rheometer is a measure of the powder's sensitivity to the flow rate, again shows that AHL obtains a more precise result than MCC. In general, the individual replicates of AHL and MCC shows that the replicates of MCC are wider distributed than AHL. Yet, the total energy in both cases increases when the flow rate, i.e. tip speed, decreases (Fig. 2).

The evaluation of the flow characteristics in the previous part shows that the parameters obtained for AHL overall are more precise compared to the parameters obtained for MCC. However, the SI results show the opposite although the SIs for AHL and MCC are fairly similar and in both cases above one. Since, test no. 1-12 are performed in the exact same way, this indicates that the measured total energy for the powders are increasing as a function of repeated testing. This could be caused by several phenomena. In the support documents of the powder rheometer, the manufacturer suggest that de-aeration, agglomeration, segregation as well as moisture uptake and electrostatic charge can cause this observation⁹. Since, the moisture level of the powders was fixed two days prior to and also during the measurements this cause can most likely be neglected. Additionally, electrostatic charges as a factor is also not plausible as the amount of electrostatic charge decreases with increasing relative humidity and is therefore barely present at 50 % RH⁷. The observation is therefore probably caused by either de-aeration, agglomeration or segregation.

In the support documents, it is further mentioned that the BFE (or in general the measured total energy) is dependent on many physical powder properties, e.g. particle size/distribution, shape, density and elasticity⁸. However, how these physical properties influence the BFE quantitatively is not stated. Furthermore, it is mentioned that a low BFE in some cases represents a powder with good flow properties while a high BFE represents a powder with poor flow. Yet, it is also stated that the opposite might be the case⁸. The manufacturer claims that the reason is that the flow pattern is dependent on the powder's particle size. The shear zone in front of the blade is therefore not of constant size⁸. This complicates the comparison of BFEs obtained from different powders with different particle sizes. Therefore, it does not seem feasible to establish a direct correlation between BFE and flowability when comparing a large range of different powders. The same seems to be the case for the other parameter measured in this study.

In order for powder rheology to become a useful technique for powder characterization, the theoretical foundation of the technique needs to be increased. Especially, the geometry of the shear zone and the stresses within this zone needs to be elucidated in order to obtain a quantitative statement of flowability and consolidation during testing¹⁶. Based on the discussion above, methods which are well comprehended and based on bulk solids mechanics, e.g. shear testers, still seems to be a better solution than powder rheology for quantifying and predicting and in-process flowability of powders¹⁶.

CONCLUSION

In this study, two powders, anhydrous lactose (AHL) and microcrystalline cellulose (MCC), have been characterized using a powder rheometer. While the flow characteristics obtained for AHL in general were precise (RSD < 5%), the opposite was the case for MCC. The underlying principles of the powder mechanics, which are causing the variation of the rheological measurements, are not sufficiently understood. These principles need to be elucidated before powder rheology will be a useful characterization method for estimation of powder flowability.

ACKNOWLEDGMENTS

H. Lundbeck A/S, Danish Fundamental Metrology A/S and Drug Research Academy, University of Copenhagen are acknowledged for their collaboration and financial support of this work.

REFERENCES

1. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) 2005. Pharmaceutical Development Q8(R2)., Geneva.
2. U.S.Food and Drug Administration (FDA) 2004. Guidance for Industry. PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance.
3. Freeman RE, Cooke JR, Schneider LCR (2009), "Measuring shear properties and normal stresses generated within a rotational shear cell for consolidated and non-consolidated powders", *Powder Technology*, **190**, 65-69.
4. Freeman R. (2007), "Measuring the flow properties of consolidated, conditioned and aerated powders – A comparative study using a powder rheometer and a rotational shear cell", *Powder Technology*, **174**, 25-33.
5. Bharadwaj R, Ketterhagen WR, Hancock BC (2010), "Discrete element simulation study of a Freeman powder rheometer", *Chemical Engineering Science*, **65**, 5747-5756.
6. Dumarey M, Wikström H, Fransson M, Sparén A, Tajarobi P, Josefson M, Trygg J (2011), "Combining experimental design and orthogonal projections to latent structures to study the influence of microcrystalline cellulose properties on roll compaction", *International Journal of Pharmaceutics*, **416**, 110-119.
7. Léonard G, Abatzoglou N (2011), "Lubrication of pharmaceutical powder/wall interfaces and electrostatic effects", *Powder Technology*, **208**, 54-62.
8. Freeman Technology (2008), The Basic Flowability Energy W7030. FT4 Support Documents, Castlemorton Common, Worcestershire (UK): Freeman Technology Ltd. p 1-8.
9. Freeman Technology (2007) Stability Method W7011. FT4 Support Documents, Castlemorton Common, Worcestershire (UK): Freeman Technology Ltd. p 1-8.
10. Freeman Technology (2008) Getting Started W7001. FT4 Support Documents, Castlemorton Common, Worcestershire (UK): Freeman Technology Ltd. p 1-6.
11. Freeman Technology (2008), Dynamic Energy Calculation INF21. FT4 Support Documents, Castlemorton Common, Worcestershire (UK): Freeman Technology Ltd. p 1-2.
12. Freeman Technology (2008) Density W7007. FT4 Support Documents, Castlemorton Common, Worcestershire (UK): Freeman Technology Ltd. p 1-2.
13. Freeman Technology (2006) The Conditioning Process W7006. FT4 Support

Documents, Castlemorton Common, Worcestershire (UK): Freeman Technology Ltd. p 1.

14. Freeman Technology (2007), Stability & Variable Flow Rate Method W7013. FT4 Support Documents, Castlemorton Common, Worcestershire (UK): Freeman Technology Ltd. p 1-4.

15. Freeman Technology (2008), Specific Energy W7031. FT4 Support Documents, Castlemorton Common, Worcestershire (UK): Freeman Technology Ltd. p 1-2.

16. Schulze D (2007), Powders and Bulk Solids - Behavior, Characterization, Storage and Flow, 1 ed., Berlin Heidelberg New York: Springer.