Characterization of powder properties using a powder rheometer

Søren Vinter Søgaard[1], Mette Bryder[2], Morten Allesø[2] and Jukka Rantanen[1]

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

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

Introduction

Powder properties are critical material attributes that affect pharmaceutical powder processing and therefore the quality of the final product. During processing, powders are subjected to several physical environments requiring different behavioral properties[1,2]. Thus, characterization of powder properties using only one traditional single index methods, e.g. Carr's Index or flow through a funnel, is insufficient for screening of excipients and prediction of in-process performance of powders[2]. Instead a multiple approach should be applied in which powders are tested by several methods each evaluating different powder properties relevant to manufacturing. Recently, Dumarey*et al.* have shown how an FT4 Powder Rheometer can describe how raw material attributes affect a roll compaction process and thus the final tablet quality[3]. The FT4 Powder Rheometer is designed to characterize powders under various conditions in ways that resemble large-scale production environments[4]. The rheometer provides a comprehensive series of methods that allow powder behavior to be characterized across a whole range of process conditions. The methods include rheological, torsional shear, compressibility and permeability tests which can be performed using small bulk samples, i.e. 1, 10 or 25 ml depending on the test in question. The basis for all these methods is a bench-top rheometer with a built-in balance and a PC, a set of test vessels besides an aeration control unit used for aeration tests.

The rheological principles of the rheometer have previously been evaluated[5]. The objective of this study was therefore to evaluate the remaining methodologies provided by the FT4 Powder Rheometer, i.e. the compressibility, permeability, shear and wall friction tests. This was performed using eight commonly used pharmaceutical excipients.

Materials and Methods

Materials

Table 1 summarizes the information and the particle size distribution of the pharmaceutical excipients used in this study. The particle sizes were obtained as triplicates by laser diffraction (HELOS, Sympatec GmbH, Clausthal-Zellerfeld, Germany). Except for the sample division and acclimatization (see below), the excipients were not subjected to any further treatment prior to testing.

Table 1. Characteristics of the raw materials including particle size distribution.

Sales Name	*Generic Name*	*Supplier*	*Particle size distribution (µm)*		
			D_{10}	D_{50}	D_{90}
AvicelPH-101	Microcrystalline Cellulose	FMC BioPolymer, Philadelphia, USA	21	63	136
Avicel PH-102	Microcrystalline Cellulose	FMC BioPolymer, Philadelphia, USA	34	119	238
Avicel PH-200	Microcrystalline Cellulose	FMC BioPolymer, Philadelphia, USA	67	192	340
FlowLac® 100	Spray-dried α-Lactose Monohydrate	Meggle, Wasserburg, Germany	51	133	235
Parteck® M 200	Mannitol	Merck, Darmstadt, Germany	55	192	539
ProSolv® SMCC 90	SilicifiedMicrocrystalline Cellulose	JRS Pharma, Rosenberg, Germany	34	120	256
SuperTab® 21AN	AnhydrousLactose	DMV-FonterraExcipients, Nörten-Hardenberg, Germany	15	159	353
SuperTab® 22AN	AnhydrousLactose	DMV-FonterraExcipients, Nörten-Hardenberg, Germany	71	222	404

Sample preparation

The test samples were prepared in the following manner:

In attempt to obtain a bulk sample that is representative of the entire bulk material in the container from which the samples were taken, the portions of powder were removed from five different regions of the bulk, i.e. four regions in the periphery and one region in the center of the container. These regions included both the bottom, intermediate and surface layer of the powder. Powder samples consisting of approximately 100 ml were collected from the abovementioned regions with a powder sampler until a total bulk sample of 900 ml powder was obtained. The 900 ml bulk sample was then blended in a jar and divided into eight portions of 112.5 ml powder using a spinning riffler with eight divisions (Retsch PT100, Retsch GmbH, Haan, Germany). Each of these eight 112.5 ml pseudo-samples were further divided into eight portions resulting in total 64 test samples consisting of 14 ml. 12 of these 14 ml samples were randomly selected for testing in this study, while the remaining samples were used for purposes not included in this study.

After the sampling procedure, the test samples were acclimatized for more than two days in an in-house-built humidity control chamber with a fixed relative humidity at 50±5 % and a temperature at 21±1 °C. Then, the test samples were sieved through a 0.7 mm mesh to break down any agglomerates that might have formed during the acclimatization.

Methods

The FT4 powder rheometer provides a large range of methods for powder testing. Furthermore, within each of these methods several options are available for adjusting the method to specific needs. In the case with the shear test and wall friction test, four standard programs with pre-consolidation levels of 3, 6, 9 or 15kPa, i.e. the normal stress applied to the bulk samples prior to testing, are available. In addition, three wall discs, made of 316 stainless steel, are available having a roughness average of 0.05, 0.28 and 1.2 µm, respectively. For each of these options, a choice has to be made based on which options that simulate the process in question, i.e. level of stress in the solid bulk in the process and roughness average of the equipment. However, based on the standard programs new programs can also be written if special requirements are needed.

In this study, the four standard programs shown in Table **2** were tested using the FT4 Powder Rheometer software version 4.0 (Freeman Technology Ltd., Tewkesbury, UK). The tests were performed under the same conditions as the sample preparation, i.e. in an in-house-built humidity control chamber with a fixed relative humidity at 50±5 % and a temperature at 21±1 °C, to eliminate the effect on the samples due to variation in the humidity.

Table 2. Methodologies applied in this study including their corresponding program files.

Methodology	*Program file:*	*Test vessel volume*
Shear cell test	25mm_Shear_9kPa.prs	10 ml
Wall friction test*	25mm_Wall Friction_9kPa.prs	10 ml
Compressibility test	25mm_Compressibility_1-15kPa.prs	10 ml
Permeability test	25mm_Permeability_1-15kPa-2mm-s.prs	10 ml

*roughness average of wall:0.28 µm.

The shear test measures the shear stress needed to obtain a failure of the powder, i.e. the powder particles start to move relative to one another, as function of the applied normal stress. This is performed for five levels of normal stress: 3, 4, 5, 6 and 7 kPa. In that way, five data points are obtained which can be plotted in two a dimensional coordinate system (the coordinates for a point are defined by one level of normal stress (σ) and the corresponding shear stress (τ)). The line passing through these five points is called the yield locus (Figure **1**) and is the basis of the parameters obtained during the shear test (Table**3**).

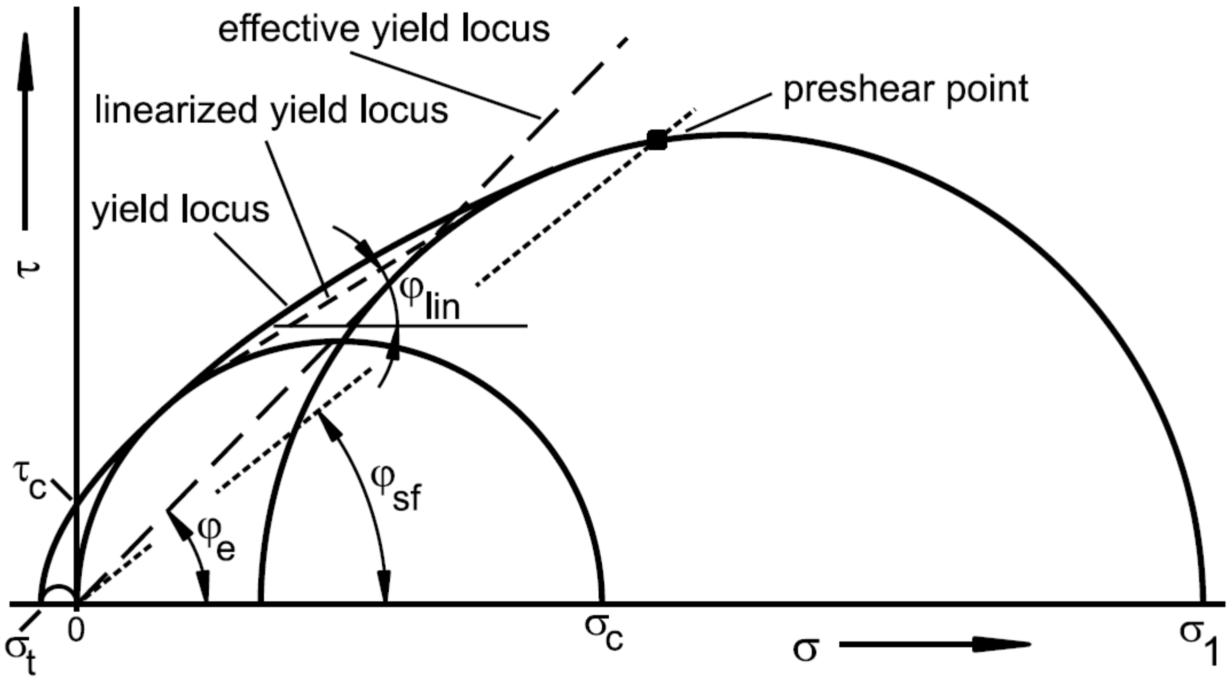

Figure 1. Yield locus and the flow properties that can be obtained using Mohr’s stress circles[6].

Table3. Shear test parameters[6].

Parameter	*Symbol*	*Description*
Unconfined yield strength	σ_c	The stress causing the consolidated bulk solid specimen to move
Major principal stress	σ_1	The largest of all normal stresses acting during steady-state flow in all possible cutting planes of the specimen
Jenike's flow function	ff_c	$ff_c = \frac{\sigma_1}{\sigma_c}$ (1) The larger ff_c, the better a bulk solids flow. When ffc< 1 the bulk solid is non-flowing, while it is free flowing when ffc> 10.
Effective angle of internal friction	Φ_e	Slope of the effective yield locus

During the wall friction test, measurements similar to the one in the shear test are performed. However, the output of the wall friction test is the kinematic angle of wall friction, Φ_x. This parameter quantifies the effort required to move a bulk solid across the surface of a specific wall material. The kinematic angle of wall friction is calculated by the following equation:

$$\varphi_x = tan^{-1}\left(\frac{\tau_x}{\sigma_x}\right) \quad (2)$$

Where τ_x and σ_x are the shear and normal stress at the wall material, respectively.

In the compressibility and the permeability test, the bulk density of the bulk solid, ρ, and the pressure drop across the powder bed, Δp, respectively, are measured as function of the normal stress. In both cases the following normal stresses are applied: 1, 2, 4, 6, 8, 10, 12 and 15 kPa. For the permeability test an air velocity of 2 mm/s is applied during testing. If needed an alternative permeability test is also available in which the air velocity is varied, while the normal stress is fixed at a certain level. However, this test was not tested in this study.

Data analysis

The raw data was treated and analyzed using the FT4 Data Analysis software version 3.01.0057 (Freeman Technology Ltd., Tewkesbury, UK).

Results and Discussion

Table 4 summarizes the results obtained by the shear and wall friction test. The results are shown as average values including relative standard deviation (RSD) based on three replicates. The table shows that σ_c in general have large RSD value, especially for the smaller σ_c. The problem in this case is that the tested excipients have very small unconfined yield strengths, i.e. only a small force needs to be applied to make the bulk solid flow. Since the unconfined yield strength is obtained by first extrapolating the yield locus and secondly drawing a Mohr circle tangent to the yield locus (Figure 1), the unconfined yield strength becomes more uncertain as the extrapolation increases. In this test, the smallest normal stress that was applied during testing was 3 kPa. The yield locus therefore had to be extrapolated over a long range to obtain the unconfined yield strength. However, this can be avoided by spreading the normal stresses applied in the test over a broader range, e.g. 1-7 kPa, with a fixed distance between the points. Consequently, a more precise unconfined yield strength should be obtained. The imprecise measurements of the σ_c further affect the ff_c (Eq. 1), which also has large RSDs. However, solving the imprecise determination of σ_c mentioned above will at the same time lead to a more precise estimate of ff_c. The remaining parameters are in general precise, i.e. RSD < 5 %, for most of the excipients. This is important as the parameters are often applied in calculation for prediction of the excipients in the process, e.g. flow pattern and rate[6].

To summarize, it should be possible to obtain parameters with a sufficient precision for both the shear and wall friction test if a few adjustments are made to the shear test. However, in 2010 Léonard and Abatzouglou presented results showing that the accuracy of the FT4 shear test was significantly different from the Jenike shear tester when applying a 85 ml test vessel[7]. While the similar results were obtained with Xylitol, the two shear tests gave significantly different results when microcrystalline cellulose (MCC) and dicalcium phosphate (DCP) were tested. The discrepancies could not be explained from a theoretical point of view since there was no systematic offset between the two shear tests. Yet, for both MCC and DCP, the FT4 shear test underestimated the shear properties compared to the Jenike results[7]. This phenomenon is often encountered with a torsional shear tester[8]. Nonetheless, the problem needs to be solved as underestimation of the shear properties might lead to large prediction errors of the bulk solids' in-process properties.

Table 4.Summary of the results obtained by the shear and wall friction test at 9kPa.The first four parameters from left are measured during the shear test, while the last parameter, Φ_x, are obtained by the wall friction test (Ra = 0.28µm)

Material	σ_c	*RSD (%)*	σ_1	*RSD (%)*	ff_c	*RSD (%)*	Φ_e	*RSD (%)*	Φ_x	*RSD (%)*
Avicel PH-101	2.6	19	18.0	1.6	7	18	40.0	1.3	29.5	4.5
Avicel PH-102	0.6	22	15.6	1.6	28	24	34.5	1.1	27.8	3.1
Avicel PH-200	0.6	59	16.4	4.6	36	79	35.2	6.4	24.2	1.9
FlowLac 100	0.5	29	13.0	2.0	30	37	28.0	3.9	16.9	6.5
Parteck M 200	0.5	99	17.9	8.9	131	130	41.4	4.8	27.5	4.0
ProSolv SMCC 90	0.5	23	15.6	0.4	31	22	34.2	2.5	23.6	6.0
SuperTab 21AN	2.5	26	16.8	6.0	7	20	40.1	4.1	22.4	6.5
SuperTab 22AN	0.1	103	16.5	3.1	389	92	37.7	0.4	20.1	4.6

Mean and RSD, n=3. σ_c: unconfined yield strength,σ_1: major principal stress, ff_c: Jenike's flow function, Φ_e: effective angle of internal friction,Φ_x: kinematic angle of wall friction. The parameters are stated in units of kPa.

Table 5 shows the results from the permeability and compressibility test at 15 kPa. Yet, the two tests also provide information of the permeability and compressibility for the remaining normal stresses included in the tests, but for simplicity only the result for 15 kPa is shown. The permeability test tends to have slightly larger RSDs than the compressibility test. This is not surprising since the test is very sensitive to the packing state of the bulk solid. Nonetheless, if the data are to be used for calculations the test should be further investigated to reduce the variance in order to reduce the uncertainty of further calculations.

Based on the data in Table **5**, the compressibility test appears to be a precise measure. This is very important since the bulk densities are used in several calculations to predict flow properties. Yet, the data do not state if the result is accurate compared to the Jenike shear tester. One problem with the FT4 shear tester is that the test vessel has a height/diameter ratio of 0.8 (20 mm/25 mm). In order to reduce the influence of the friction in the test vessel, it have been mentioned in the literature that height/diameter should be less than 0.3[6]. This is especially important for the vessels constructed of stainless steel or similar due to the friction of these materials. However, the test vessel in the FT4 shear test is made from smooth surface borosilicate[9]. The friction of the borosilicate vessel might therefore have a much smaller impact of the compressibility result compared to regular test vessels. Still, the bulk densities obtained by the FT4 compressibility test needs to be compared to the Jenike test to assess the accuracy.

Table 5. Results from the permeability (left) and compressibility (right).

Material	*Δp(mbar) at 15kPa*	*RSD (%)*	*ρ (g/ml) at 15 kPa*	*RSD (%)*
Avicel PH-101	0.82	4.9	0.403	3.1
Avicel PH-102	0.44	6.0	0.403	4.3
Avicel PH-200	0.24	2.7	0.409	3.6
FlowLac 100	0.50	7.7	0.662	4.1
Parteck M 200	0.42	3.8	0.571	4.8
ProSolv SMCC 90	0.44	4.0	0.405	4.7
SuperTab 21AN	2.26	6.3	0.815	4.5
SuperTab 22AN	0.50	6.1	0.759	3.3

Mean and RSD, n=3. Δp: pressure drop across powder bed.

Conclusion

In this study, the permeability, compressibility, torsional shear and wall friction test of a FT4 powder rheometer using a 10 ml test vessel has been evaluated. It has been suggested how to modify the standard shear test program in order to design a program suitable for measuring pharmaceutical excipients and thereby obtain more precise shear test results. Though it seems possible to obtain precise results with the FT4 powder rheometer, the accuracy is still of concern. Studies have shown that torsional shear testers in general tend to underestimate the shear properties of certain bulk solids. However, this trend is not systematic, but only counts for certain bulk solids. The accuracy of the tests in this study therefore needs to be further investigated.

Acknowledgements

Financial and scientific support by H. Lundbeck is greatly appreciated.

References

1. Howard S 2002. Flow Properties of Solids. In Swarbrick J, Boylan J, editors. Encyclopedia of Pharmaceutical Technology, 2nd ed., New York: Marcel Dekker. p 1264-1285.

2. Prescott JA, Barnum RA 2000. On Powder Flowability. Pharmaceutical Technology60-85.

3. 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.

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. Søgaard S, Allesø M, Garnaes J, Baldursdottír S, Rantanen J 2012. Development of a reproducible powder characterization method using a powder rheometer. Annual transactions of the nordic rheology society (submitted).

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

7. Léonard G, Abatzoglou N 2010. Stress distribution in lubricated vs unlubricated pharmaceutical powder columns and their container walls during translational and torsional shear testing. Powder Technology 203:534-547.

8. Schwedes J 2003. Review on testers for measuring flow properties of bulk solids. Granular Matter 5:1-43.

9. Léonard G, Abatzoglou N 2011. Lubrication of pharmaceutical powder/wall interfaces and electrostatic effects. Powder Technology 208:54-62.