Application of Ring Shear Testing to Optimize Pharmaceutical Formulation and Process Development of Solid Dosage Forms

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ABSTRACT

This study investigates how shear and wall friction tests performed at small stresses can be applied to predict critical flow properties of powders, such as flow patterns and arching tendencies, in pharmaceutical manufacturing operations. The study showed that this approach is a promising method for pharmaceutical process development.

INTRODUCTION

One of the most well-established process design and characterization approaches for bulk solids is the design procedure supported by the shear cell measurements developed by Jenike in the 1960's[1]. With the shear cell, internal friction and powder-wall adhesion (i.e. wall friction) of powders can be measured. Based on these measurements, the flow patterns of powders flowing in hoppers can be determined, that is either mass, funnel flow or borderline cases (Figure 1). Since funnel flow often leads to segregation, degradation and erratic flow, this type of flow has to be avoided from a process and quality perspective. In addition, the tendency of powders to form arches in mass flow hoppers is another challenge that has to be avoided[2].

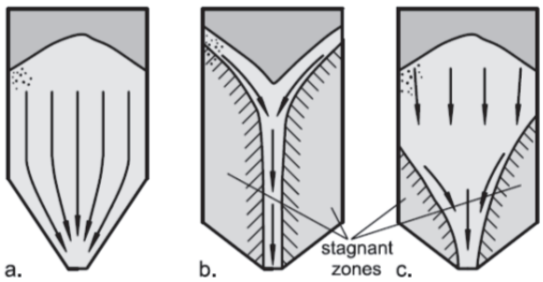

Figure 1. Flow patterns. A: Mass flow. B: Funnel flow. C: Mixed flow[2].

In the pharmaceutical industry, shear testing has been used for more than three decades now – in many cases for correlating the flowability, $ff_{c,}$ to tablet weight variation[3,4,5,6,7] Nonetheless, several studies still applies the shear tester as a mere flowability tester, i.e. the flowability of different powders is evaluated by comparing the measured ff_c of the powders – often without taking in to consideration the level of consolidation present in the process[8]. In addition, the principles used for silo and equipment design does still not seem to be applied in pharmaceutical process development unlike in other related industries[2,9]. Instead the trial and error approach still seems to dominate. The reason for this might have been that earlier commercial shear testers were unable to measure at the small stresses relevant to pharmaceutical processing which typically is performed in a smaller scale than in other industries. Recently, a new ring shear tester has been launched that enable shear testing at very small stresses[10]. This might provide the technical foundation for using Jenike's silo design procedure for smaller process equipment. Clearly, this has to be verified experimentally.

The aim of this study was therefore to investigate if shear and wall friction tests performed at small stresses can provide accurate predictions of critical flow properties of powders, such as flow patterns and arching tendencies, in small scale operations.

MATERIALS

Two pharmaceutical excipients commonly used in blends for direct compression of tablets were used as model powders, also named bulk solids, in this study. The two powders had identical compositions but different particle sizes. The nominal medium value of the particle size distribution, D_{50}, of excipient 1 (EX1) and excipient 2 (EX2) were 100 µm and 180 µm, respectively.

The powders were conditioned at 21±1°C and 40±3%RH for two days prior to the study, as other studies have shown that flow properties depend of the moisture level of the powder[2,11,12]. Otherwise, the materials were used as received form the supplier.

METHODS

Wall friction testing

The wall friction tests were performed with a Schulze ring shear tester (RST-XS.s, Dr.-Ing. Dietmar Schulze Schüttgutmess-technik, Wolfenbüttel, Germany). Each test was carried out using a 20 mL XS-WM cell with a wall material sample made from 316L/1.4404 stainless steel (Ra/Rz = 0.03/0.5µm). The test program consisted of five points of measurement at these wall normal stresses, σ_w: 1000, 800, 600, 400 and 200 Pa (one test cycle). The test started with the largest σ_w followed by the lower stresses in the order shown above. The test cycle was repeated three times for each excipient.

Shear testing

The shear testing was performed with the ring shear tester mentioned above in the same manner for both excipients: A bulk sample of 70 mL was prepared in a XS-Lr0 shear cell. The sample was then sheared by using the stress walk program. The applied program included shear testing at two normal stresses at preshear, σ_{pre}: 250 and 375 Pa. At each $\sigma_{pre,}$ three shear to failure points were measured. These points were selected so that the normal stresses at failure were 20, 50 and 80% of the σ_{pre}. The procedure was performed in triplicates with three individual samples. In this way, two yield loci were obtained for each sample.

Discharge from a hopper

A 4.75L conical hopper from a Pressima AX tablet machine (IMA Kilian, Cologne, Germany) was applied for evaluating the two powders' flowability and flow pattern during discharge from a hopper. The hopper was constructed of the same material with a similar surface finish as the wall material applied in the wall friction test. The inclination of the hopper wall, Θ_c, was 22.6º to the vertical. The dimensions of the hopper are shown in Figure 2.

To evaluate the powders' flowability and flow pattern, the following discharging experiment was carried out: A spatula was placed beneath the hopper to block the outlet. Then the hopper was filled up with powder until 2 cm from the edge, i.e. a filling height of 34 cm. The spatula was removed from the outlet and the flow pattern and flowability was recorded by video.

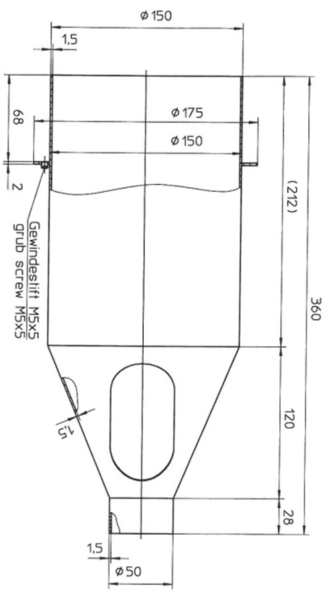

Figure 2. Hopper dimensions. The dimensions are stated in mm[13].

RESULTS AND DISCUSSION

Flow patterns

The average wall friction angles, $\varphi_{x,m}$, measured with wall friction test are shown in Table 1 for the wall normal stresses of 200 and 1000 Pa.

Table 1. Wall friction angles for EX1 and EX2 at wall normal stress of 200 and 1000 Pa.

	$\varphi_{x,m}$ at 200 Pa (°)	$\varphi_{x,m}$ at 1000 Pa (°)
EX1	19.4±0.0	11.6±0.0
EX2	16.4±0.0	10.3±0.12

Table 1 displays that the $\varphi_{x,m}$ for both powders increases as a function of decreasing wall normal stress. The data from Table 1 are plotted into a mass flow diagram for a conical hopper as shown in Figure 3. The $\varphi_{x,m}$ at 200 Pa as well as 1000 Pa predicts mass flow for EX1 and EX2 as shown on the mass flow diagram.

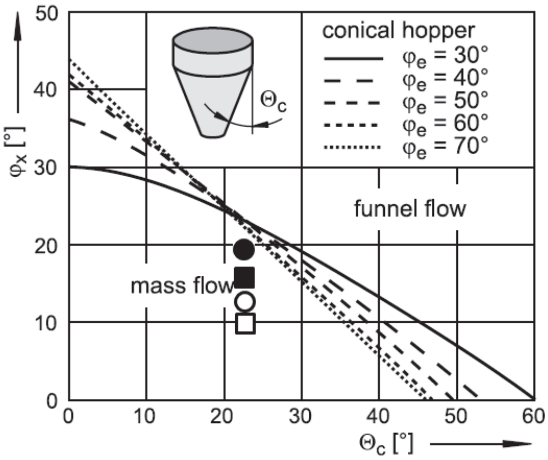

Figure 3. Mass flow diagram for a conical hopper[2]. The data from Table 1 are plotted into the diagram. EX1 is illustrated as circles, while EX2 is shown as squares. The solid and hollow symbols represent the wall friction angles at 200 and 1000 Pa, respectively.

Table 2 shows the observations from the discharging experiments. As illustrated, EX1 is following a mass flow pattern as expected from the $\varphi_{x,m}$. In the case of EX2, the discharging result conflicts with the data obtained by the wall friction test, since a mixed flow was observed. Yet, by having a look at the $\varphi_{x,m}$ for EX1 at 200 Pa once again (Figure 3) it may be noted that the $\varphi_{x,m}$ are only 2-3° from the boundary distinguishing mass from funnel flow. EX1 might therefore be a borderline case, i.e. mixed flow (Figure 1), when it comes to flow pattern. This might not be fully detected by the wall friction procedure due to the uncertainty of the method. Furthermore, having in mind that sampling of bulk solids often can result in varying particle size distributions; this could also be the reason of the misleading prediction. In any case, it seems as if it would be necessary to add a safety margin of 2-3° to $\varphi_{x,m}$ in order to avoid borderline cases when dealing with pharmaceutical operations. This is a common approach applied within other fields handling bulk solids[2].

Table 2. Experimental observed flow patterns and flowability during discharge of EX1 and EX2 from a 4.75L hopper having an outlet diameter of 4.7 cm.

	Flow pattern	Arching
EX1	Mixed flow*	-
EX2	Mass	-

*Funnel flow with stagnant zones in the lower hopper part

The abovementioned results imply that wall friction tests performed at a normal stress of 200 Pa is a more accurate method for predicting flow pattern of pharmaceutical scale processing than wall friction tests performed at higher wall normal stresses, in this study 1000 Pa. The wall friction performed at 200 Pa simulates better the level of stress present in small scale processing.

Flowability

The data from the shear tests, i.e. stress walk data, are shown in Table 3 for EX1 and in Table 4 for EX2.

Table 3. Flow properties for EX1. YL: yield locus, σ_1: major principal stress, σ_c: unconfined yield strength, ffc: flowabity (σ_1/σ_c), ρ_b: bulk density, φ_e: effective angle of internal friction. 1.1 represents yield locus no. 1, sample 1, 1.2 represents yield locus no. 1, sample 2 etc.

YL	σ_1[Pa]	σ_c[Pa]	ffc	ρ_b[kg/m^3]	φ_e [º]
1.1	510	114	4.49	333	42.1
1.2	514	123	4.17	337	42.5
1.3	533	119	4.50	342	43.6
2.1	750	148	5.07	340	41.6
2.2	766	161	4.77	343	42.2
2.3	779	148	5.25	347	42.5

As the three replicates of each yield locus were obtained from three different samples, the variation of the replicates reflects the sampling error. Some variation must therefore be expected. Nevertheless, the EX1 and EX2 show significantly different flow properties according to the shear tests.

Table 4. Flow properties for EX1. YL: yield locus, σ_1: major principal stress, σ_c: unconfined yield strenght, ffc: flowabity (σ_1/σ_c), ρ_b: bulk density, φ_e: effective angle of internal friction. 1.1 represents yield locus no. 1, sample 1, 1.2 represents yield locus no. 1, sample 2 etc.

YL	σ_1[Pa]	σ_c[Pa]	ffc	ρ_b[kg/m^3]	φ_e [º]
1.1	482	48	10.09	375	35.7
1.2	478	44	10.88	381	38.0
1.3	479	44	10.98	375	38.1
2.1	684	57	12.11	379	36.7
2.2	690	63	11.03	385	36.6
2.3	694	43	16.17	379	37.1

In this case, with EX1 having a ffc of approx. 4.5 would be characterized as easy-flowing, while EX2 would be characterized as free-flowing due to a ffc > 10. Yet, in the following, it will be shown how other properties can be determined on the basis of shear testing.

To get a rough estimate of the major principal stress, σ_1, being present at the outlet opening during the discharge condition, Eq. 1 can be applied:

$$\sigma_1 = \frac{1+\sin\varphi_e}{1-sin\varphi_e} \cdot 0.2 \cdot g \cdot \rho_b \cdot d \qquad (1)$$

In which, φ_e and ρ_b is the effective angle of internal friction and the bulk density of the powder, g is the acceleration due to gravity (9.82m/s^2) and d is the diameter of the outlet opening stated in meters, i.e. 0.047 m for the hopper used in this study .

The obtained shear testing data for EX1 and EX2 shown in the first lines of both Table 3 and Figure 4 can be used as inputs for Eq. 1. In that case, the σ_1 at the outlet are estimated as 156 Pa for EX1 and 132 Pa for EX2. This shows that very small stresses are present during discharging of powders in pharmaceutical unit operations compared to the stresses which are normally present in large bulk solids operations, i.e. several kPa[2]. Furthermore, this example explains why the wall friction tests performed at a wall normal stress of 200 Pa is more predictive than the test at 1000 Pa. The test at 200 Pa is simply more accurate in terms of mimicking the actual stress during discharging from the hopper.

Another property of bulk solids which can be a challenge during handling is arching, as it causes flow stop when powders have to flow under gravity, i.e. during dosing operations and in tableting machines. This phenomenon occurs when the powder's unconfined yield strength is greater than the stress existing in a stable arch in the hopper[2]. It is therefore important to be able to determine the risk of arching in a given hopper for a specific powder. This can be done for a conical hopper by calculating the critical outlet diameter to avoid arching, $d_{crit,}$ as shown in Eq. 2:

$$d_{crit} = \frac{H(\theta_c)\cdot\sigma_{c,crit}}{g\cdot\rho_{b,crit}} \qquad (2)$$

In Eq. 2, the factor $H(\Theta_c)$ is a function of the hopper geometry, g is the acceleration due to gravity (9.82 m/s^2) while $\sigma_{c,crit}$ and $\rho_{b,crit}$ is the unconfined yield strength and the bulk density, respectively, at the intersection of bearing stress and flow function. Similarly, $\sigma_{1,crit}$ is the major principal stress at the intersection of bearing stress and flow function. It is determined by linear extrapolation of the flow function to towards the smaller stresses, in order to find the intersection with the flow factor, ff, as described by Schulze[2]. The flow factor is determined from flow factor diagrams and depends on $\phi_{x,}$ ϕ_e and Θ_c. Based on these diagrams, an ff of 1.5 is applied in the calculations in this study.

Figure 4 illustrates graphically how $\sigma_{1,crit}$, $\sigma_{c,crit}$ and $\rho_{b,crit}$ are determined by extrapolation of the flow properties obtained by shear testing.

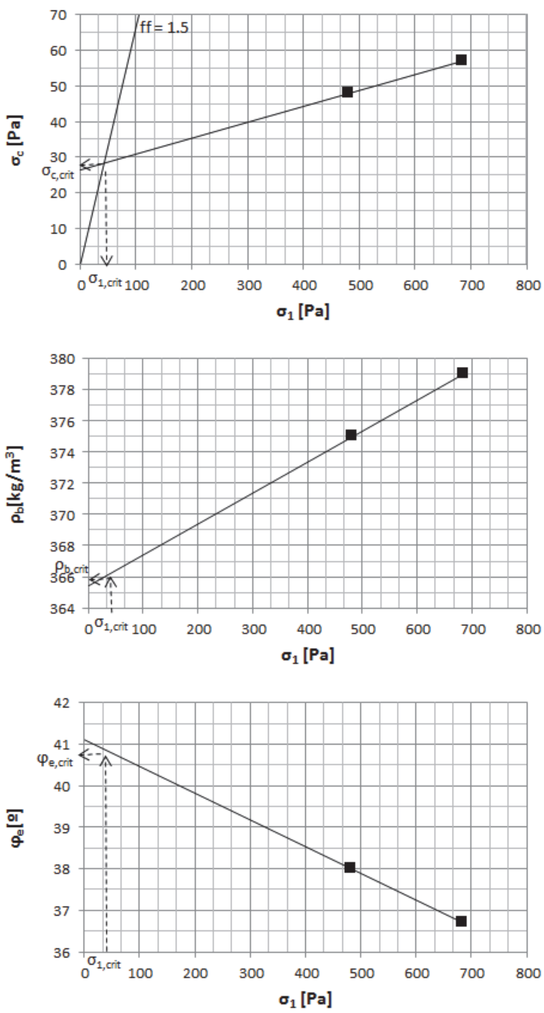

Figure 4. Diagrams illustrating flow properties for determination of the minimum outlet dimensions to avoid arching. The measured data are plotted as solid squares. The shown data is yield loci 1 and 2 for replicate 1, EX2.

The same approach as shown in Figure 4 was applied for the two remaining replicates of EX2 and all three replicates of EX1. The factor $H(\Theta_c)$ was set equal to 2.3 for Θ_c = 22.6º. In that way, the minimum outlet dimensions to avoid arching, d_{crit}, were determined. The results are shown in Table 5.

Table 5. Critical outlet dimensions to avoid arching, $d_{crit.}$ SD: standard deviation.

	EX1	EX2
YL	Dcrit (cm)	Dcrit (cm)
Replicate 1	4.3 cm	2.0 cm
Replicate 2	4.6 cm	0.1 cm
Replicate 3	5.3 cm	3.2 cm
Average	4.7 cm	1.8 cm
SD	0.5 cm	1.6 cm

Table **5** displays an average minimum outlet dimension, $d_{crit,m,}$ for EX1 of 4.7 cm, while for EX2, dcrit,m is 1.8 cm. In both cases, $d_{crit,m} \leq 4.7$ cm, which is the outlet diameter. According to these average predictions, arching would not appear during emptying conditions of the hopper. This is in accordance with the experimental results. Yet, the $d_{crit,m}$ covers some large variations between the individual d_{crit} calculated for each of the replicates. Especially for EX2, the results varies considerably (SD = 1.6 cm). This is due to that the same shear testing program was used for both powders in this study though the program is best suited for EX1. For estimation of $\sigma_{c,}$ the yield locus therefore has to be extrapolated to a greater extent for EX2 than for EX1 (not shown). This causes a more imprecise estimation of σ_c for EX2 which again causes an imprecise estimation of d_{crit} of EX2. However, this problem can easily be reduced by changing the shear to failure points in this way that the lower shear to failure point would be placed closer to the intersection of the yield locus with the minor Mohr circle. Still, if shear tests are performed similar to the procedure used in this study, where no precautions were taken towards sampling errors and where the same shear testing program were used for all the powders, the estimation of the minimum outlet dimension might only serve as a rough estimate of the outlet dimension of small scale hoppers. It is possible that a more uniform sampling, e.g. automated sample division, would decrease the variation of the measurements and thereby increase the predictive ability of the method for small scale equipment. This would have to be verified experimentally.

CONCLUSION

This study showed that shear and wall friction tests performed at small stresses, i.e. σ_1 and $\sigma_W \leq 1000$ Pa, can provide rough predictions of critical flow properties of powders, such as flow patterns and arching tendencies, in small scale operations.

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ABBREVIATIONS

d	diameter of the hopper outlet opening
d_{crit}	critical outlet diameter to avoid arching
$d_{crit,m}$	average critical outlet diameter to avoid arching
EX1	excipient 1
EX2	excipient 2
YL	yield locus
g	acceleration due to gravity, $g = 9{,}82 m/s^2$
Θ_c	Inclination of the wall of a conical hopper to the vertical
φ_e	effective angle of wall friction
φ_x	kinematic angle of wall friction
$\varphi_{x,m}$	average kinematic angle of wall friction
$H(\Theta_c)$	Factor which takes into account the hopper geometry, i.e. shape and wall inclination
σ_c	unconfined yield strength

ρ_b	bulk density
$\rho_{b,crit}$	the critical bulk density at the intersection of bearing stress and flow function
$\sigma_{c,crit}$	the critical unconfined yield stress at the intersection of bearing stress and flow function
σ_{pre}	normal stress at preshear
σ_1	major principal strength
$\sigma_{1,crit}$	critical major principal stress at the intersection of bearing stress and flow function
σ_w	wall normal stress

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