Towards an Accurate Shear Testing Method for Characterizing Pharmaceutical Particulate Systems

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ABSTRACT

When using shear testing to determine wall friction of pharmaceutical particulate systems, it is crucial to measure at the correct wall normal stress. By comparing data obtained at a wall normal stress of 1000 to 200 Pa, the effect of the applied stress on the accuracy and precision of the method was assessed.

INTRODUCTION

When powder flows under gravity from a hopper, it follows one of two patterns, mass flow or funnel flow, Fig 1. Funnel flow is a persistent challenge when processing pharmaceutical bulk solids. Segregation and stagnant zones with uneven density and composition at the hopper outlet during production are common problems associated with funnel flow[1].

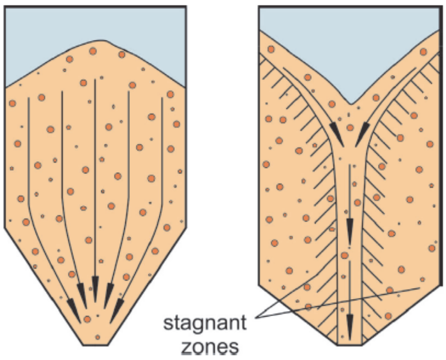

Figure 1. Mass flow (on the left) and funnel flow (on the right) [1].

Shear testing is a well-established method for determining mechanical properties of bulk solids[2-6]. Applying shear testing for determining the mechanical properties of pharmaceutical systems can help to predict in-process flow patterns. Especially, the powder-wall adhesion of the bulk solid, i.e. wall friction, affects the flow pattern of the powder system. This property can be determined by shearing a bulk solid against a wall material sample which is representative of the hopper wall. The wall friction angle at a given wall normal stress is a measure used to quantify the wall friction. By applying Jenike's method[7], the flow pattern from a hopper with a given wall inclination can be assessed based on the properties of the powder examined, Fig 2.

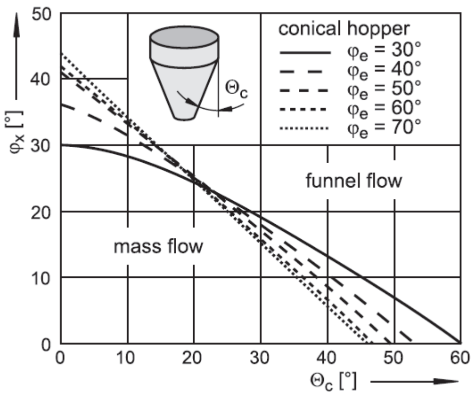

Figure 2. Mass flow diagram for a conical hopper, based on Jenike's method [7].

From Fig 2, it is evident that at a wall inclination in the area of 20-23º to the vertical axis, the wall friction angle, φ_x, is the major parameter affecting the flow pattern of the bulk solid. Factors affecting wall friction include hopper surface roughness, wall normal stress and bulk solid properties as moisture, temperature and storage time at rest[8]. Within the pharmaceutical field, the hopper dimensions and its surface roughness are fixed in most cases. However, adjusting the bulk solid properties is to some extent possible in early development through formulation design. Since the wall friction angle increases non-linearly with decreasing wall normal stresses[7], it is important to measure at wall normal stresses similar to the ones typically occuring in pharmaceutical processes in order to establish an accurate method. Wall friction has almost exclusively been measured at stresses above 1000 Pa[9,10]. Theoretical calculations based on Jansen's equation[7] show that wall normal stresses are lowest, i.e. the wall friction angle is highest, at the hopper outlet, Fig 3.

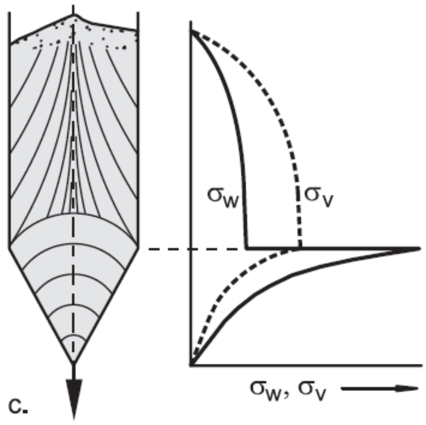

Figure 3. Wall normal stress, σ_w, and major vertical stress, σ_v, against the height in the conical hopper with an infinitely small outlet opening [7].

A rough estimate of the vertical stress at a hopper outlet can be calculated from:

$$\sigma_v = 0{,}2 \cdot g \cdot \rho_b \cdot d \quad (1)$$

Where d is the outlet diameter in a conical hopper. Assuming σ_v is equal to σ_w at the hopper outlet, (1) can provide an estimate of wall normal stresses present during processing. Therefore, if the wall friction is measured at stresses in the same magnitude as σ_w at the hopper outlet, this will provide a more accurate wall friction angle. The aim of this study was to assess the impact on precision from measuring wall friction at low stresses versus the gained accuracy of the method.

METHODS

Five samples of microcrystalline cellulose (Avicel PH102, FMC Biopolymer, Philadelphia PA, USA) were sampled with an automated sample divider. Wall friction angle was determined for each sample at wall normal stresses ranging from 200-1000 Pa (n=4), by using a wall material sample consisting of stainless steel, type 1.4404 (Ra/Rz = 0.05/0.3 μm). The measurements were conducted with a Schulze ring shear tester (RST-XS.s, Dr.-Ing. Dietmar Schulze Schüttgutmesstechnik, Wolfenbüttel, Germany) using a 20 mL Type WM cell. Shear testing was performed in accordance with the RST-XS.s user manual. The cycle of measurements were performed in decreasing order and repeated consecutively four times, so that there was no handling of the powder in between the cycles. All the samples were conditioned for two days at 21±1ºC and 50±5% relative humidity, and subsequently measured under the same conditions. Particle size distributions of each sample were analysed by laser diffraction (n=3) (HELOS/Br, Sympatec GmbH).

RESULTS

It was found that the wall friction angle increased non-linearly with decreasing stresses. Furthermore, it is clear that the variance, both within and between the samples, was greater at low stresses, Fig 4.

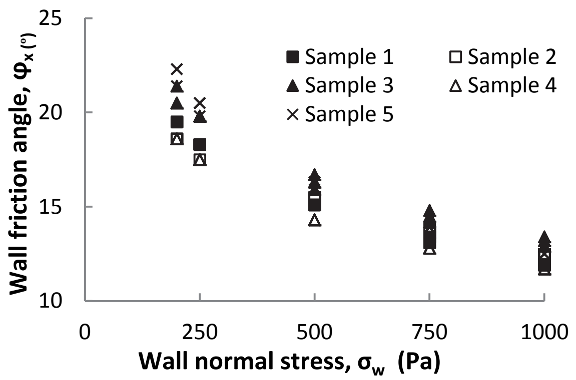

Figure 4. Measured wall friction angles in the range 200-1000 Pa.

To evaluate the data, an analysis of variance was made at each stress by comparing variance within each sample with variance between samples. At each stress, variance between samples were greater than variance of the repetitions, i.e. $S^2_{between} > S^2_{within}$. Furthermore, the variance was broken down into variance attributed to sampling and variance attributed to measuring, Table 1.

Table 1, wall friction angle ± SD (%RSD)

Stress (Pa):	200	1000
Wall-friction angle (°)	19.86 ± 1.44 (7.25%)	12.34 ± 0.56 (4.56%)
S^2_{within}	0.095	0.012
$S^2_{sampling}$	1.98	0.31
$S^2_{overall}$	2.07	0.32

Sampling constituted 95.2±2.4% of the overall variance at each stress, which illustrates the importance of testing a representative sample of the bulk solid, Table 1. The variance between samples can be due to differences in particle size distributions of the fractions collected from the sample divider. Though the mean particle diameter did vary between samples ($p=0.006$), no correlation between wall friction angle and mean particle diameter were found.

Equation (1) was used to determine the wall normal stress at a hopper outlet with a diameter of 47 mm. A density of 339 kg/m^3 for the excipient, measured at 249 Pa in a previous study, was used. Equation (1) yields a stress of 31 Pa present at the hopper outlet. This indicates that measurements performed at 200 Pa increases the accuracy of the method compared to wall friction tests performed at higher stresses. Even though the variance at 200 Pa is greater than at 1000 Pa ($p=7.3 \cdot 10^{-5}$), the wall friction angle at 200 Pa is a better match to the wall friction angle at the theoretical stress, table 1. When applying a 95% confidence interval to the average of the measurements, it is clear that the lowest value at 200 Pa is still greater than the highest wall friction angle at 1000 Pa. This confirms that wall friction tests performed at low stresses provide a more accurate measure of the actual wall friction being present in small scale hoppers, Fig 5.

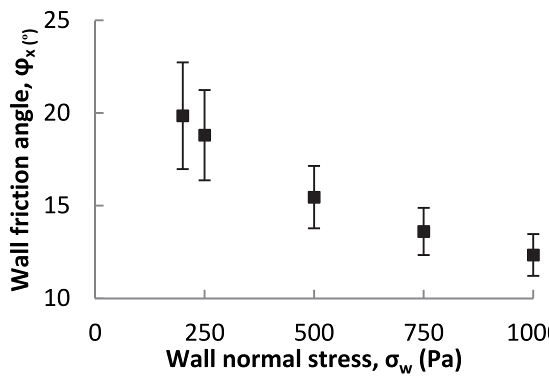

Figure 5. Average of measured wall friction angles with applied 95% confidence error.

When using mass flow charts to predict the flow pattern of a system, Fig 2, it is important to include the uncertainty of the method to ensure a correct prediction. Using the lowest value obtained at 200 Pa in this study would predict mass flow in a hopper with a wall inclination of 20 degrees to the vertical axis, whereas using the highest value predicts funnel flow.

CONCLUSION AND PERSPECTIVES

The accuracy of the wall friction method was increased by measuring at lower stresses; however variance was greater at lower stresses.

To ensure mass flow when designing a silo, it is common practice to add in a safety margin by subtracting 2-3 degrees of the wall inclination[7]. This approach could be applied when using wall friction test to determine mechanical properties of pharmaceutical bulk solids during development.

ACKNOWLEDGEMENTS

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