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Flowability Measurements of Pharmaceutical Powder Mixtures with Poor Flow Using Five Different Techniques

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ABSTRACT

Four different tablet formulations for direct compression with poor flow properties were tested regarding flowability using five different techniques: Hausner ratio, avalanching behavior, powder rheometer, uniaxial tester, and Jenike tester. In addition, the behavior of three of the formulations during emptying of the mixer and tableting was observed and compared to the results of the flowability measurements. The rank order correlation of the formulations was generally the same with all techniques. The flow properties measured by the different techniques reflected the behavior during processing of the powder mixtures.

Key Words: Flowability; Pharmaceutical; Poor flow; Uniaxial tester; Jenike tester.

INTRODUCTION

Pharmaceutical tablets are produced on a commercial scale by filling a powder mixture by volume. Consequently, the flow properties of the powder mixture are important to the uniformity of mass of the tablets.

Powder flows when the forces acting on the powder bed cause the resulting shear force to exceed the shear strength of the bed. Flow properties of powders are influenced by external conditions such as air content, state of compaction of the powder, and humidity, as well as particle surface, size, shape, and size distribution.

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A powder mixture consists of particles and air. Therefore, when testing the flow properties it is necessary to consider the air content and its distribution. To deal with this, powders may be preconditioned before testing to achieve consistent and reproducible packing.

There are several techniques for measuring the flow properties of bulk solids. Each technique utilizes different kinds of parameters for bulk solid behavior, and no single measurement fits all requirements. Nevertheless, different techniques can be taken into account to get a better insight of the material's behavior.

Poor flow properties of some powder mixture formulations for direct compression of tablets were investigated by different methods: Hausner ratio,[1] avalanching behavior,[2] powder rheometer,[3,4] uniaxial tester,[5] and Jenike shear cell.[6] These results were compared with the behavior during emptying of a double cone mixer and tableting in a rotary press. Measurements of the Hausner ratio and avalanching behavior were in-house methods at Pharmacia, Helsingborg. The powder rheometer and the uniaxial tester were also employed, as they represented new, interesting techniques. Measurements with the Jenike tester supplemented the uniaxial tester.

The objective of the study was to compare the results from different techniques for measuring flow properties of four similar tablet formulations with poor flowability with the behavior during processing.

MATERIALS AND METHODS

Formulations

Three different formulations (batches 1, 3, and 4) all containing approximately 15% of the active pharmaceutical ingredient (API), fillers, binders, and lubricant (2%)—were mixed in a 100-L double cone mixer. The degree of filling of the mixer was approximately two-thirds.

A fourth formulation (batch 2), also containing 0.33% of a glidant, colloidal anhydrous silica, was mixed in a Turbula mixer, with a degree of filling of approximately two-thirds. Batch 2 was otherwise similar to batch 1. Previous tests on a large scale indicated a tendency to picking due to the glidant in this specific formulation. Therefore, no tableting was performed with batch 2.

The proportions of the excipients differed between batches 1, 3, and 4. In addition, the particle size quality of one of the excipients differed for batch 1 compared to batches 3 and 4.

Measurement of Flow Properties

Hausner Ratio

Poured bulk density and tapped bulk density after 2500 taps was measured principally according to Ph.Eur.[7] The Hausner ratio is the ratio between tapped and poured densities.

Avalanching Behavior

This test was performed with TSI Aero–Flow automated powder flowability analyzer (TSI Incorporated Particle Instruments, St. Paul, MN) with 50 g of powder in the drum. The powder sample was placed inside the drum. As the drum slowly rotated during operation, the powder rotated with it, building up to an unstable condition until an avalanche occured. The avalanche was detected and measured photoelectrically. Each series of avalanches was analyzed to determine the time to avalanche, a function of the powder's flowability. The drum has an inner diameter of 13 cm and an inner width of 2.5 cm. A layer of sandpaper was placed around the internal rim of the disc to prevent the powders from slipping, and the disc was sprayed with antistatic spray to reduce the influence of electrostatic effects on the avalanching process. The drum rotation speed used was 120 seconds per rotation and data were collected for 900 seconds. Recorded data were the mean time between avalanches and the scatter (the standard deviation of the times between avalanches).

Powder Rheometer

An FT3 Powder Rheometer (Freeman Technology) was used to measure the flow properties of powders in terms of the energy required to make the powders flow.

The methodology used 25-mL powder samples that were tested in a 25-mm bore borosilicate glass cylinder. The powder was made to flow by moving a 23.5-mm-diameter twisted blade rotationally and axially so that it moved along a helical path through the test sample. Samples were prepared for testing by a conditioning process in which the blade caused gentle displacement of the powder to establish a consistent and reproducible packing density. The test cycle that followed moved the blade along a downward helical path (-5° at a blade tip speed of 100 mm/s), but in the opposite direction to impose compaction, thereby forcing the powder to flow around the blade. The axial and rotational forces acting on the blade during the cycle were measured continuously and used to derive the work done, or energy consumed, in displacing the powder. This energy is called the basic

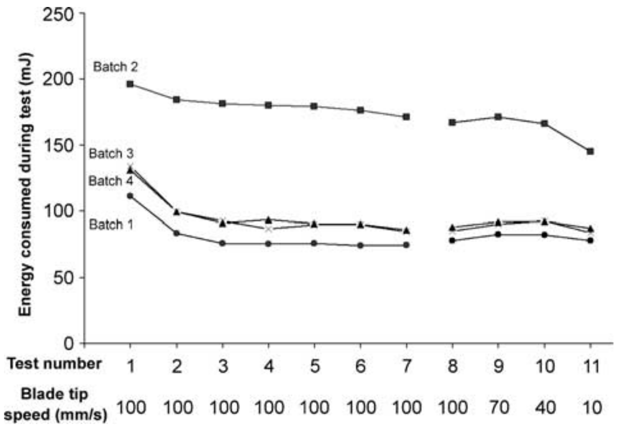

Figure 1. Flow energy as a function of repeated testing and flow rate (different blade speeds).

flowability energy (BFE) and is defined as the energy required to complete a standard test upon a conditioned powder (Test 7, Fig. 1). The BFE is regarded as a measure of the rheological properties of the powder when in a conditioned state.

Further tests investigated how this energy requirement changed in relation to:

Compaction: samples were consolidated prior to testing using two methods—direct incremental compaction to 20 kPa, and tapping 100 times. The standard test was then run (but without conditioning) to determine the increase of energy requirement. This increased energy figure was then divided by the BFE to determine the compaction index (CI).

Aeration: samples were aerated by supplying air to the base of the test vessel. The standard test was repeated at different rates of airflow to determine how the flow energy varied for various levels of aeration. The BFE was then divided by the measured energy required to fully fluidize the powder, to determine the aeration ratio (AR).

Other parameters measured included stability index (SI), flow rate index (FRI), and consolidation ratio (CR) (see Table 1 for definitions).

Uniaxial Tester

A small die with a volume of about 4 cm^3 was employed in all tests.[8] In the uniaxial tester, a sample is consolidated axially in the die by a piston. After consolidation, there is a relaxation for 120 seconds, an unloading of the sample before the die is removed, and a measurement of the unconfined failure strength. The unconfined failure strength at four different consolidation stresses from 5 to 40 kPa was measured. A higher stress level of 80 kPa was also chosen, although this stress is hardly relevant in bulk solids mechanics for gravity flow, but could be relevant to forced feeding of a tablet machine.

Jenike Tester

Jenike tests for a single-yield locus were carried out for all the four powder mixtures. In a yield locus, the shear stress causing shear failure along a plane in the powder is plotted as a function of the normal stress on that plane, for a given density of the powder, given by the preparation, including preshear. A complete number of 26 tests were carried out per batch. For preshear a normal stress of 3770 Pa was adjusted. For the shear step, three different stresses—1010, 1280, and 1840 Pa—were used. The parameters according to Table 2 were calculated.[9]

Table 1. Powder rheometer data.

Parameter	Parameter definition	Batch 1	Batch 2	Batch 3	Batch 4
Conditioned sample volume (mL)		25	25	25	25
Sample mass (g)		10.5	11.5	10.5	10.5
Basic flowability energy, BFE (mJ)	Fig. 1, test 7	74.4	171	84.5	85.9
Stability index, SI (–)	Fig. 1, test 7/test 1	0.67	0.87	0.63	0.66
Flow rate index, FRI (–)	Fig. 1, test 11/test 8	1.00	0.87	0.99	0.99
Compaction index, CI (tapped 100 times) (–)	Energy of consolidated sample/BFE	6.80	4.61	6.51	4.92
Consolidation ratio, CR (tapped) (–)	Conditioned vol./consolidated vol.	1.35	1.25	1.35	1.35
Compaction index, CI (direct pressure of 0.2 bar) (–)	Energy of consolidated sample/BFE	2.57	1.91	4.21	2.91
Consolidation ratio, CR (direct pressure) (–)	Conditioned vol./consolidated vol.	1.31	1.14	1.31	1.31
Aeration ratio, AR (–)	BFE/Energy of fully aerated sample	12.2	59.4	10.9	7.9

Table 2. Parameters measured by the Jenike tester.

Designation	Parameter
σ_1	The major principal stress at stationary flow
σ_c	The unconfined failure strength
φ_i	The angle of internal friction
φ_e	The angle of internal friction at stationary flow
ρ_b	The bulk solids density
$ff_c=\sigma_1/\sigma_c$	The flowability factor

Mixing and Tableting

It was observed how the powder flows during discharge from the mixer. The tablet weight variation and compression force variation were recorded during the production of the tablets in a rotary press (P 1200 equipped with 24 stations, Fette, Germany) at 140,000 tabl/h and a force of 7–9 kN. One batch per formulation was tested.

RESULTS AND DISCUSSION

The four tested formulations were modifications of the same basic formulation, and the differences in their flow properties were caused by the proportions and the different particle sizes of the excipients.

Hausner Ratio

Two measurements per sample were performed and the mean value calculated. The variation in the two measurements was less than 1%.

From Table 3 it is evident that batch 2 had a lower Hausner ratio than the three other batches, due to the addition of glidant. Lower Hausner ratios of a material indicate better flow properties than higher ones. Consequently, batch 2 was expected to flow better than the other three batches. Of these, batches 3 and 4 are similar and with higher Hausner ratios than batch 1.

Avalanching Behavior

An index of the bulk flow of the material is provided by the time between avalanches. The scatter provides an index of the cohesivity, which is related to the irregularity of the flow. Short and reproducible times between avalanches, i.e., low mean time and scatter, indicate better flow properties. Only one measurement was performed per batch. Tests repeated three times with one of the components of the powder mixtures contributing to the poor flow properties indicated a variation in mean time of approximately ±5% for the particle size quality in batches 3 and 4, and about ±3% for the particle size quality in batches 1 and 2. The variation in scatter was larger, approximately ±15% and ±10%, respectively. It is obvious from Table 3 that batch 2 has lower mean time and scatter from the Aero–Flow measurements than the other batches. Batch 1 has marginally lower values and thereby better flow than batches 3 and 4.

Mixing and Tableting

According to Table 3, batch 1 had the best flow properties of batches 1, 3, and 4 when emptying the mixer and batch 3 had the worst flow properties. The addition of the lubricant improved the flow with batch 4.

Table 3. Hausner ratio, avalanching behavior, behavior during emptying of mixer, and variation of compression force and tablet weight.

Variable/batch	1	2	3	4
Aerated bulk density (g/mL)	0.45	0.47	0.46	0.45
Hausner ratio (–)	1.33	1.27	1.35	1.36
Aero–flow mean time(s)	4.72	3.17	4.97	5.34
Aero–flow scatter(s)	1.98	1.29	2.08	2.02
Tablet weight RSD[a] (%)	0.6–0.8	–	0.8–2.2	0.8–1.4
Compression force RSD (%)	3.1–3.6	–	3.3–3.8	2.8–3.3
Flow from mixer, without lubricant	Did flow, funnel flow	–	Did not flow without knocking	Did not flow without knocking
Flow from mixer, with lubricant	Did flow, funnel flow	–	Did not flow without knocking	Did flow, funnel flow

[a]RSD = relative standard deviation.

The tablet weight variation was acceptable with batches 1 and 4 but tended to be too high with batch 3. This was also reflected in the compression force variation, which was highest with batch 3.

Powder Rheometer

All results are represented in Table 1, where a brief definition of the flow parameters are also included. Figure 1 shows the primary test series where the initial seven tests determine SI and BFE and tests 8–11 determine the flow rate index.

Repeated test series using a new sample were only made with batch 1, which was tested twice. The variation was less than approximately 3% regarding all the measured parameters. Tests were repeated three times using new samples with one of the components of the formulations contributing to the poor flow properties. This resulted in a relative standard deviation of 1–3% regarding all the measured parameters.

The instability of these powders is evident from the seven repeated tests shown in Fig. 1. Except for batch 2, all powders reduce their flow energy requirement by about 40% after the first three or four tests, indicating their change of rheological behavior with working of the powder. This is attributed partly to the change of air content in the powder mass, but is also characteristic of the lubricant that continues to modify the rheological behavior with further agitation.

Batch 2 also has a higher bulk density, due to the 0.33% glidant that reduces the interparticle friction forces and allows closer nestling of particles. The BFE measurement for the batch 2 material is more than twice that of the other powders. This reflects its higher packing density and the higher forces required to cause the powder to flow under compaction.

All except batch 2 powders are insensitive to flow rate. This is probably due to the presence of lubricant that is likely to have reduced the flow rate index (FRI) from about 2 to unity. The batch 2 material with an FRI of 0.87 requires more energy to produce flow as the flow rate increases—a desirable characteristic not usually found in powders without flow additives.

All powders are readily consolidated by tapping. Their flow energy requirement increases. The batch 2 sample is marginally superior, having the lowest compaction index and the lowest consolidation ratio.

Direct pressure consolidation produces CR values of 1.31, except for the batch 2 material where it is 1.14. The resulting increases in flow energy do not correlate with CR, however, except that batch 2 has by far the lowest CR and CI values, both being good indicators. Batch 2 is less compressible and has the ability to unpack easily—hence the CI value of 1.9, which is a particularly low level of energy increase.

Aerating these powders resulted in the largest differences in flow performance with aeration ratio (AR), varying from 7.9 to 59.4. All materials readily aerated, but batch 2 reduced its flow energy requirement from 171 mJ (conditioned) to 3.4 mJ (fully aerated). This is the most positive indicator of good flowability, particularly when the powder is unconfined and able to aerate. The reason for this high AR value is likely to be that the glidant reduces bonding between particles so that the powder is able to fluidize, in which state it requires very little energy to promote flow.

To summarize, the batch 2 material is superior in regard to CR, SI, CI (tapped), CI (direct pressure), FRI, and most importantly, AR. It has the best all-around flow characteristics—being stable, free flowing when aerated, and able to recover readily from a consolidated state. Batches 3 and 4 have the lowest SI and AR, which suggests poor flowability.

Uniaxial Tester

The unconfined failure strength at the four desired stress levels from 5 to 40 kPa could not be measured because no self-sustaining specimen could be produced for unconfined failure tests in the tester. Therefore, a higher stress level of 80 kPa was also chosen to obtain valid data, although hardly relevant in bulk solids mechanics for gravity flow, this stress level could be relevant for tablet machines with forced feeding.

A failure test in the uniaxial tester generally consists of four steps, including consolidation, relaxation, unloading, and the failure test. Figure 2 shows a complete stress vs. time plot without the failure step. It can be seen that the consolidation is followed by a relaxation (constant volume, decreasing stresses) and the necessary unloading step before the failure test.

A minimum of two or three parallel measurements and sometimes more were carried out per sample. Averages of the results are given in Table 4. The scatter for all the parameters was up to 5%, except for the failure strength, which it was up to 15% of the average. Unfortunately, the samples were not weighed, but the densities of the samples in the uniaxial tester were only slightly less than those in the Jenike tester at the same consolidation stress levels based on experience.

Consolidation

Table 4 gives the deformation that is applied during consolidation between two stress levels: 10–80 kPa.

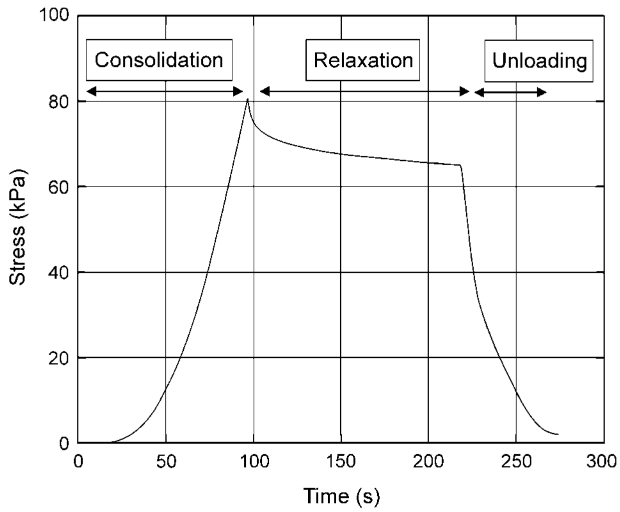

Figure 2. Stress vs. time for the test procedure in the uniaxial tester (without failure test).

The total amount of deformation from 0–80 kPa cannot be taken into account since some differences occur due to the sample preparation. That is why a considerable start stress level was chosen. It can be seen that for a consolidation range from 10–80 kPa the difference between batch 1 and 2 is small, and also between 3 and 4, whereas the difference in compressibility between the two groups is considerably larger. In general, the less compressible a batch is, the better it will flow. Table 4 therefore indicates that batch 2 flows better than batch 1, which flows better than batch 4, which in turn flows slightly better than batch 3. According to Table 2, the mixing and tableting tests resulted in the same ranking among the four samples.

Relaxation

Relaxation in the field of particulate solids means the decrease of stress while the deformation is kept constant (mechanical relaxation). A relaxation can be understood as a further very small movement of the particles. The conclusion is that good flowability increases relaxation and the amount of stress decreases. It can be concluded from Table 4 that batch 3 shows the smallest stress decrease because of a poorer flowability compared to the other batches. Furthermore, it is seen that the ranking of the four batches is the same as for the deformation during consolidation.

Unloading

Table 4 shows the stress decrease during the unloading stage for all batches. An unloading distance of 0.5 mm usually results in a complete disappearance of the stress. After an unloading distance of 0.5 mm a considerable stress remains for all four powders. It can also be seen that differences only occur between the groups with batches 1 and 2, and batches 3 and 4, whereas nearly no differences can be observed within these groups. Batches 3 and 4 show a higher elasticity (higher remaining stress after unloading) than batches 1 and 2, indicating poorer flowability. Again the ranking is the same as for deformation and relaxation, and the mixer and tablet machine.

Failure

Proper samples can be produced at high consolidation stresses far away from the stress levels relevant in bulk solids handling for gravity flow. Table 4 gives the values for the failure stress σ_c of the investigated powders after consolidation to 80 kPa. Since only a few samples were produced, these values are approximate. For batch 2 no sample, i.e., no coherent plug, could be produced. Batch 3 shows the highest failure stress, although this value is still very small. From these results it can be concluded that batch 2 is the powder with the best flowability and batch 3 is the powder with the poorest flowability, with batch 1 better than batch 4. Here the differences between the groups is about the same as within each group, but the ranking is still the same as that for the three other characterizations, and in agreement with the practical tests with the mixer and the tablet machine.

Jenike Tester

Since a high stress level (80 kPa), with of the relevance to in bulk solids mechanics for gravity flow,

Table 4. Deformation, stress decrease, remaining stress after unloading, and failure stress.

Parameter/batch	1	2	3	4
Deformation 10–80 kPa (mm)	1.51	1.33	2.35	2.09
Stress decrease after 120 s (kPa)	16.0	17.2	13.3	15.6
Remaining stress after 0.5 mm unloading (kPa)	12.4	11.8	36.6	35.4
Failure stress σ_c (kPa) at $\sigma_{1,c}=80$ kPa	0.1	–	0.3	0.15

Average of two or three tests, sometimes more. Scatter up to 5%, except for the failure strength, where the scatter was up to 15% of the average.

Table 5. Results obtained from the Jenike tests, based on one yield locus per batch.

Batch/parameter	σ_1 (Pa)	σ_c (Pa)	ff_c (−)	ρ_b (kg/m^3)	φ_i (^{o})	φ_e (^{o})
1	7364	639	12	514	38	40
2	7789	572	14	496	37	39
3	7753	878	8.8	522	37	40
4	7199	864	8.3	520	36	39

had to be applied with the uniaxial tester, measurements were also performed with the Jenike tester.

The Jenike tester is more appropriate for investigations of flow properties at low stresses, although the time consumption is higher compared to the uniaxial tester.

The six parameters of Table 5 give a detailed characterization of the powder flow properties. Only one yield locus per batch was measured.

Between batches 1 and 2 a significant difference is observed (Table 5), the unconfined failure strength and the bulk density for batch 2 are smaller than for batch 1, while the flowability factor is higher for batch 2. Also, between batches 3 and 4 the difference is not that emphasized. In this group the flow properties are more or less the same, even slightly better for 3 than for 4 (higher flowability factor). Batches 1 and 2 also show lower bulk density, and the density of batch 2 is significantly smaller than for all the other powders. The angle of internal friction and the angle of internal friction at stationary flow (effective angle of internal friction) do not show significant differences. Batches 1 and 2 show better flowability than batches 3 and 4. It can be concluded that batch 2 is definitely the best flowing powder, and batches 3 and 4 are the poorest flowing powders.

The experience from the tablet production shows that the results obtained from measurements with the uniaxial tester can possibly describe the tableting characteristics better than the results from the Jenike tester, due to the additional information about the compaction behavior of a specific powder. The Jenike tests could not be expected to determine that batch 3 is the worst powder at tableting while batch 3 is definitely the outstanding powder of all four tested powders (Table 4).

CONCLUSIONS

Batch 2 was known to be the powder mixture with the best flow properties. This was confirmed by all the employed techniques—Hausner ratio, avalanching behavior, powder rheometer, uniaxial tester, and Jenike tester. Batches 3 and 4 had the worst flow properties according to all the employed techniques, and batch 3 was slightly worse than 4 according to the Jenike tests, and clearly worse according to the uniaxial tester.

The rank order correlation was similar with all the tested techniques.

Observations during emptying of the mixer and the tableting showed that batch 3 had the worst properties, and batch 1 the best, whereas batch 2 was not observed in these units, because previous tests had shown that this formulation had a tendency to picking during tableting.

The flow properties measured by the different techniques reflected the behavior during processing of the powder mixtures during emptying of the mixer and tableting.

REFERENCES

1. Hausner, H.H. Friction conditions in a mass of metal powder. Int. J. Powder Metall. **1967**, *3*, 7–13.
2. Kaye, B.H.; Gratton-Liitmatainen, J.; Faddis, N. Studying the avalanching behavior of a powder in a rotating disc. Part. Syst. Charact. **1995**, *12*, 232–236.
3. Podzeck, F. Rheological studies of physical properties of powder used in capsule filling. Pharm. Technol. Eur. **1999**, *11* (9), 16–24.
4. Podzeck, F. Rheological studies of physical properties of powder used in capsule filling. Pharm. Technol. Eur. **1999**, *11* (10), 34–42.
5. Maltby, L.P. *Investigation of the Behaviour of Powders Under and After Consolidation*; Dr. Ing. Thesis NTH/TMIH: Porsgrunn, Norway, 1993.
6. Williams, J.C.; Birks, A.H. The preparation of powder specimens for shear cell testing. Rheol. Acta **1965**, *4*, 170–180.
7. European Pharmacopoeia. *2.9.15. Apparent Volume*, 4th Ed.; Council of Europe: Strasbourg, France, 2001; 207–208.
8. Enstad, G. News on development of the uniaxial tester. Postec Newslett. **1998**, *No. 16*, 17–18.
9. *Standard Shear Testing Technique for Particulate Solids Using the Jenike Shear Cell*; The Institution of Chemical Engineers, Rugby: Warwickshire, England, 1989.

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