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Development of a robust procedure for assessing powder flow using a commercial avalanche testing instrument

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Abstract

The objectives of this work were to develop a robust procedure for assessing powder flow using a commercial avalanche testing instrument and to define the limits of its performance. To achieve this a series of powdered pharmaceutical excipients with a wide range of flow properties was characterized using such an instrument (Aeroflow, TSI Inc., St. Paul, MN, USA). The experimental conditions (e.g., sample size, rotation speed) were rationally selected and systematically evaluated so that an optimal standard-operating-procedure could be identified. To evaluate the inherent variability of the proposed methodology samples were tested at multiple sites, using different instruments and operators. The ranking of the flow properties of the powders obtained was also compared with that obtained using a conventional shear-cell test. As a result of these experiments a quick, simple, and rugged procedure for determining the flow properties of pharmaceutical powders in their dilated state was developed. This procedure gave comparable results when performed at four different testing sites and was able to reproducibly rank the flow properties of a series of common pharmaceutical excipient powders. The limits of the test method to discriminate between different powder samples were determined, and a positive correlation with the results of a benchmark method (the simplified shear cell) was obtained.

Keywords: Powder flow; Powder avalanche; Shear cell; Aeroflow

1. Introduction

Cohesiveness and poor flow of pharmaceutical powders is a common problem, and can cause difficulties in material blending and transfer operations (e.g., rat-holing, bridging) [1]. A relatively new technique called "powder avalanche testing" has the potential for use as a routine cohesivity test for pharmaceutical powders [2–4], and it has recently been reported that commercial avalanche testing instruments can indeed distinguish between poorly and freely flowing powders, blends, and granulations [5–7]. The principle of powder avalanche testing is

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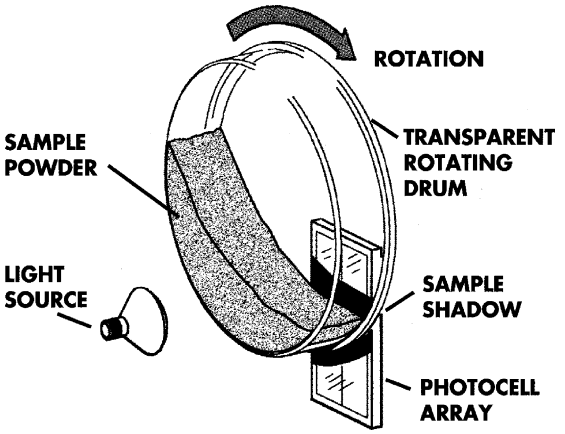

Fig. 1. Schematic of powder avalanche testing instrument (rotating-drum configuration) (image used with permission of TSI Inc.).

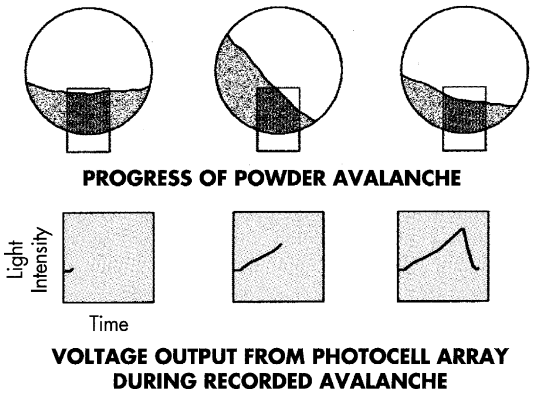

Fig. 2. Detection system employed in rotating-drum type instrument (image used with permission of TSI Inc.).

very simple. A simple stress (e.g., vibration, rotation) is applied to the sample powder until the powder shears and an avalanche occurs. Typically a known stress (e.g., fixed vibrational frequency or rotation speed) is used and the frequency at which avalanches occur upon repetition of the stress is monitored. In some cases the mass or volume of the avalanched powder is also monitored. The most common example of a commercial powder avalanche tester is the Aeroflow® device (TSI, St. Paul, MN) which consists of a slowly rotating clear plastic drum and an optical sensor system to detect the powder avalanches as they occur (Fig. 1). Avalanche events are characterized by discrete decreases in the detector output as the powder cascades between the light beam and the detector (Fig. 2). Analysis of the raw data from such an instrument (a powder avalanche frequency or mass distribution) can be achieved in a number of ways, however a method that is meaningful for the characterization of pharmaceutical powders has not yet been reported. For such an analytical approach to reach widespread acceptance in the pharmaceutical materials science community a robust experimental testing procedure that provides reproducible results when performed at multiple sites by different operators is required. The development of such a procedure, based on a fundamental understanding of the powder behavior during testing, is the subject of this article.

2. Materials and methods

2.1. Materials

Five common powdered pharmaceutical excipients were selected for use as test materials in this work. They were selected based on their wide range of physical properties (particle morphology, density, particle size distribution) and their flow properties when characterized using a simplified shear cell (see later). Single lots of each excipient were used for all the work reported and they were used as received. The excipients were: ascorbic acid USP (20–80 mesh grade, JT Baker Inc., Phillipsburg, NJ), citric acid USP (fine granular grade, Spectrum Inc., Gardena, CA), croscarmellose sodium NF (Ac-Di-Sol grade, FMC, Philadelphia, PA), hydroxypropyl cellulose NF (Klucel EXF grade, Hercules Inc., Wilmington, DE) and lactose anhydrous NF (200# grade, Quest International, Hoffman Estates, IL).

2.2. Methods

2.2.1. Powder characterization

The particle morphology of each material was assessed by microscopy using either an Olympus SZX12 optical microscope (Olympus Inc., Melville, NY, USA) or a Jeol JSM 5800 scanning electron microscope (Jeol USA Inc., MA, USA). The true densities of the samples were determined with a helium pycnometer (Quantachrome Inc., FL, USA) operated

at 20 °C according to the instrument manufacturer's recommended methods. The particle size distribution of each powder was determined using a Sympatec Helos/Rodos laser diffraction particle size analyzer (Sympatec Inc., NJ, USA) with dry powder dispersion capability. The powder dispersion pressure was 2.0 bar with direct feed into the dispersion funnel. The optical concentration was maintained in the range 8–12%.

2.2.2. Avalanche testing

A commercial powder avalanche tester (Aeroflow®, TSI Instruments, St. Paul, MN) was used for all evaluations, and was operated according to the manufacturer's instructions. The instrument consists of a plastic sample drum (∼125 mm diameter, ∼25 mm wide) mounted on a central horizontal drive shaft, and a light source coupled to an optical detector for detecting the movement of the powder in the drum as it rotates (Fig. 1). These components are enclosed in a light proof enclosure to prevent external sources of light from interfering with the avalanche detection system. The standard drum configuration was used for this work, with a coarse stainless-steel mesh insert fixed to the inner surface of the drum. This provides a rough surface on the inner wall of the cylinder and minimizes slippage of powder at the powder-wall interface. The drum assembly was cleaned before each use with alcohol and an anti-static cleaning fluid. After loading the powder the drum was rotated at a rate of either 100, 145 or 200 s per revolution (0.60, 0.41, or 0.30 rpm). These rotation times were chosen based on the capabilities of the instrument and on the basis of some simple geometric calculations (see later). As the drum rotated the time between successive powder avalanches was recorded by the optical detector and an avalanche frequency distribution was generated. The time for data collection was at least 1200 s (20 min), and this duration was selected to ensure a sufficient number of data points for analysis even for the poorest flowing powder being tested at the slowest rotation rate. Details and rationale for the sample size and data analysis methods used are provided in the discussion section of this paper. All tests were performed in duplicate and mean results are reported.

The reproducibility and robustness of the powder avalanche testing procedure results were assessed by repeating all of the experiments at three additional laboratories, using different instruments and different operators. The three new instruments used were from the same vendor and of the same model, and the materials used were from the same sources and lots. No attempt was made to control the environmental conditions during the powder avalanche testing procedures and the prevailing temperature and relative humidity varied slightly from experiment to experiment. The ambient conditions for sample storage and testing at each location were recorded so that the influences of normal fluctuations in these parameters could be evaluated.

2.2.3. Shear cell testing

Shear cells are considered by many scientists to be the preferred instruments for measuring powder flow and cohesivity [8]. However, such instruments have many features that make them unsuitable for the routine characterization of pharmaceutical powders. For example, their use can involve labor intensive and time consuming test procedures. In this work a simplified shear cell was used as the 'gold standard' to determine the powder flow characteristics of the test materials for direct comparison to the apparently faster and more robust powder avalanche testing procedures. It was hoped that such a comparison would help to establish if the ranking of the sample flow behavior using the two testing techniques was equivalent. The shear cell used was of a simplified design that has been described on several previous occasions [9,10]. It consisted of two flat parallel plates, one stationary and the other movable and connected to a load sensor. The plates were roughened on their surfaces to minimize slippage at the plate-powder interface, and the experiments were conducted at 22 ± 2 °C and 50 ± 5% relative humidity. Sample powder beds were prepared on the stationary plate by very carefully filling a cylindrical mould (8 mm thick, 82.5 mm diameter) with powder. After removal of the mould the upper plate was positioned on the top surface of the powder bed and a static normal load applied using brass weights. A shear stress was gradually applied to the upper plate until a steady state shearing condition was reached. The procedure was conducted in duplicate using normal stresses of 75.6 and 104.9 g cm^{-2} and the effective angle of internal friction calculated from the slope of the normal stress versus shear stress plot.

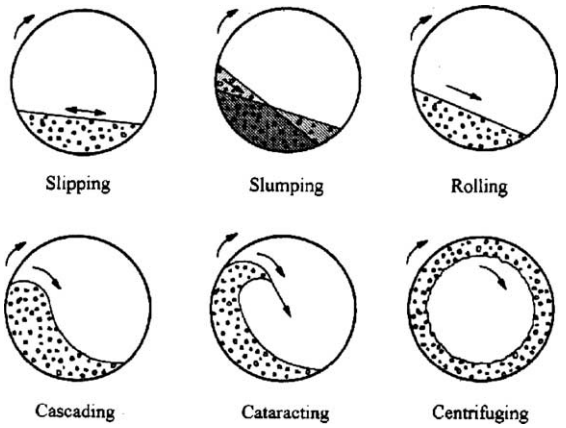

Fig. 3. Regimes of powder flow (adapted from [11]).

3. Results and discussion

3.1. Identification of the optimal test conditions

Several authors have described the different regimes of powder flow when mixed in cylindrical blenders and dryers (Fig. 3) [11,12]. Ideally the flow of pharmaceutical powders needs to be tested under conditions that correspond to the "rolling" or "cascading" state in order for meaningful data to be obtained with the type of instrument used in this work [7]. It is also well known from the literature on powder blending that the fill volume of rotating cylindrical blender can have a significant impact upon the type and rate of powder motion within that device [13–15]. Likewise the speed of rotation can markedly alter the dynamics of powder motion in the blender [16,17]. These variables (fill volume and rotation speed) were thus given close consideration when designing the test procedures to be used in the current work.

A review of the relevant blending literature revealed that too large a fill volume can result in "dead" (unmixed) regions in the powder bed contained within a cylindrical mixer [15,18]. Obviously too small a fill volume would prevent the current instrument from working correctly because insufficient material would be available to block the light beam from the detector. Based on these observations, and the recent reports of Metcalfe et al. [13], a fill volume of ~15% was selected to provide maximal turn-over of the powder bed, as well as a sufficiently large sample size to minimize wall effects and any test-to-test differences due to sampling. The resulting sample size (~50 ml) is reasonable for most pharmaceutical applications (e.g., prototype formulation characterization, quality control testing of a blend), especially since the test is non-destructive and samples can be recovered for additional analysis (e.g., potency testing) if required.

Careful consideration of the operating principles of the instrument was required to determine the appropriate range of rotational speeds and test durations for use in this work. Since the raw data is an avalanche frequency distribution a sufficient number of discrete avalanche events needs to be detected for a meaningful distribution to be constructed. It was considered that fifty individual data points (discrete avalanches) was the minimum number that was acceptable for meaningful statistical analyses to be performed. For a very poorly flowing powder there might only be three or four avalanche events per revolution of the sample drum, and thus at least 17 revolutions would be required to obtain the required number of data points. Thus, the ratio of the time for one revolution and the test duration ideally needs to have a value of greater than seventeen. This can be readily achieved either by running long experiments or by using a fast speed of drum rotation, however, there are disadvantages to both of these approaches. Increasing the speed of drum rotation may cause the powder avalanches to begin to merge together and not be discernable by the detection system (the instrument sampling rate is fixed at one data point every 0.2 s). This approach may also shift the predominant powder flow behavior away from the desired rolling and cascading regimes (Fig. 3). Minimally such an approach will shorten all of the avalanche times and compress the avalanche time distribution into a very narrow range, making it more difficult to distinguish the responses of similarly flowing materials. Long experiments are not desirable because of the time it would take to test multiple samples and because some powders could sorb water vapor or otherwise change over the course of a lengthy experiments. Thus, it is clear that there is an optimal experiment duration as well as an optimal speed of drum rotation. For the experiments described in this work three speeds of drum rotation were used (100, 145 and 200 s per rotation), in combination with a fixed experiment duration (1200 s). Assuming a worst case of four avalanches per rotation for the poorest flowing mate-

rials then these conditions would result in avalanche time distributions with between 24 and 48 data points. Whilst this is probably not sufficient for meaningful statistical analyses to be performed in all cases, it was considered to be sufficient to enable the ranking of the flow performance of all the powders relative to one another.

3.2. Identification of the preferred method of data analysis

The raw data produced by the commercial avalanche testing instrument is the detector response (in millivolts) as a function of the experiment duration (in seconds). A plot of these data can be readily analyzed to identify the large changes in detector output that correspond to individual avalanche events (e.g., Fig. 4), and the time between successive avalanche events can then be determined. The software that is provided with the commercial instrument permits an avalanche time frequency distribution to be displayed from this data and the mean, maximum, and standard deviation ("scatter") of the distribution to be calculated. It also allows the data to be displayed in the form of so-called "strange−attractor" plots [3]. The relevance of these plots to the powder flow problems encountered by pharmaceutical powder technologists is not obvious, so an alternate approach to analyzing the data was adopted for this work, based loosely on the work of Iacocca and German [19].

Initially, all samples were observed during testing to determine the type of powder flow that occurred during the testing procedure. Typically materials exhibited either rolling or cascading behavior, but the worst flowing powders did exhibit some tendency to slip and slump at the slowest rotation rate. The data sets were analyzed to determine if the avalanche behavior for each powder was consistent over the duration of the testing procedure. This was achieved by plotting a cumulative count of the avalanche events versus the testing time (e.g., Fig. 5). In all cases the powder performed consistently throughout the course of the experiment, and no indication of changing powder properties (e.g., agglomeration of primary particles) was detected by this method or by visual observation. Based on these observations it was concluded that the raw avalanche data for the different materials and test sites was suitable for further analysis and comparison.

The avalanche frequency distributions were observed to be quite varied in their form and included narrow and broad distributions, unimodal and bimodal functions, and symmetrical and skewed data sets (Fig. 6). Typically the form of the distribution was reproducible from run-to-run, and it was characteristic of the material being tested. It was noted that

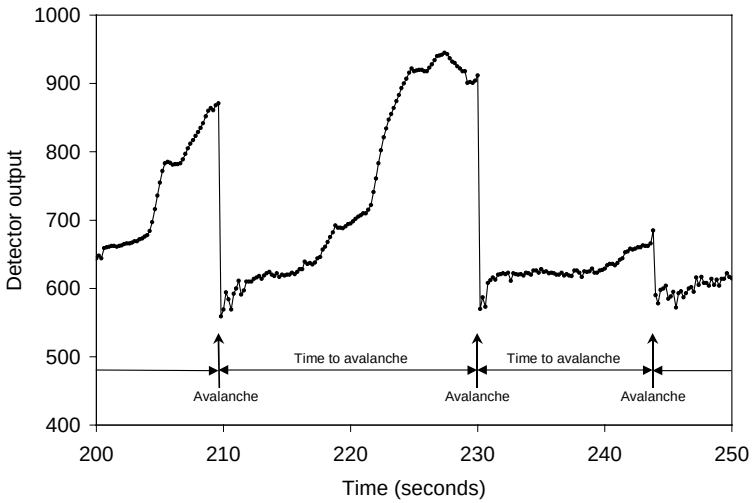

Fig. 4. Typical raw data from avalanche testing instrument.

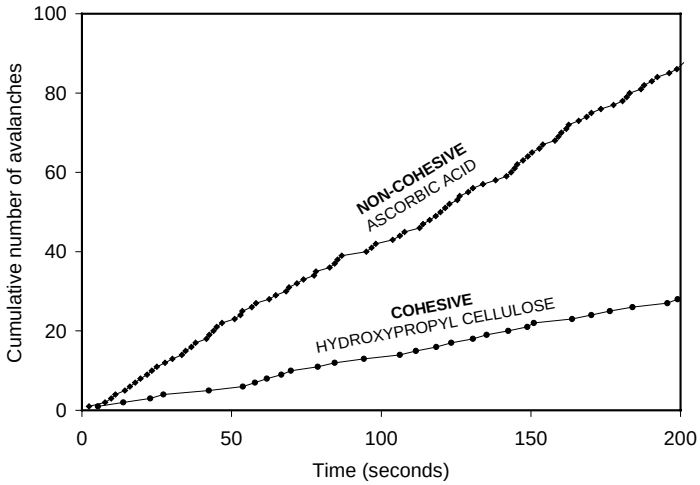

Fig. 5. Time-course of avalanche events for two powder samples.

the avalanche time frequency distributions were very similar to powder particle size distributions that are commonly encountered by pharmaceutical scientists. Therefore, similar statistical approaches were adopted for their analysis. The mean avalanche time and its coefficient of variation (standard deviation normalized by the mean, expressed as a percentage) were selected as pragmatic overall measures of the average and range of performance of the materials being studied and were calculated for use in further analyses. Obviously, this simplistic approach results in some loss in the discriminatory power of the data, but it does enable the flow performance of a very diverse range of pharmaceutical powders to be directly compared.

3.3. Consistency and reproducibility of data

The mean and coefficient of variation of the avalanche data sets for the four different testing sites and the five different powders are presented in Fig. 7a–e. Each plot is on identical axes so that the comparisons between different materials can be readily made. The most noticeable result is that the results for each material and testing condition are largely reproduced at each of the four testing sites, with site-to-site differences typically of the order of ±(1–2) s for the mean avalanche time and ±(10–20)% for the coefficient of variation. A more detailed statistical analysis of the mean avalanche times was conducted using an Analysis of Variance (ANOVA) approach and it was determined that the major influences on the avalanche time resulted from differences in the material type (∼57% of total variance) and changes in the testing speed (∼32% of total variance), whereas the testing location and interaction effects were relatively small (accounting for less than 10% of the total variance). When the data generated at each testing speed were considered separately it was determined that the differences in material type accounted for nearly all the observed variation (>85%) and the three testing speeds were comparable in terms of their overall variability. The ability to discriminate between different materials appeared to be very slightly better at the intermediate testing speed when assessed by comparing F-values. For some material–speed combinations it was possible to distinguish between the different testing sites using Tukey's Studentized Range Test, however, overall the results from the different sites were not significantly different from one another ($P < 0.01$).

A possible source of error between testing sites is the lack of control of the ambient temperature and humidity conditions for this work. The range of conditions that were encountered for each testing site is summarized in Table 1, and it is clear that the variation both within and between sites was quite small. The conditions were typical of those encountered in many pharmaceutical manufacturing facilities and in most

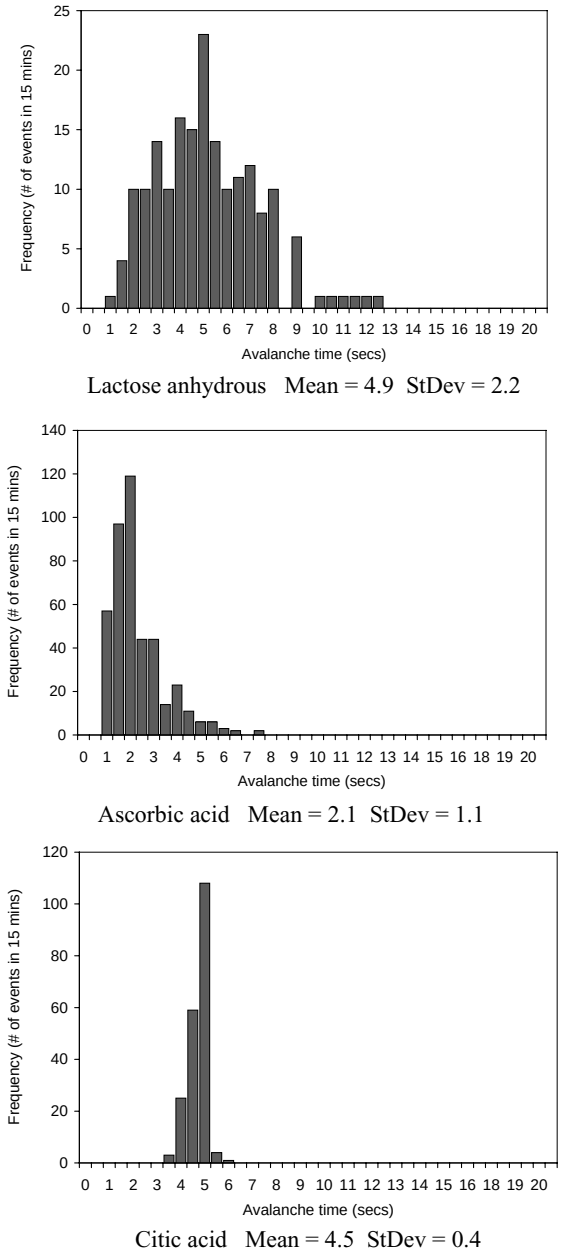

Fig. 6. Representative avalanche frequency distributions.

pharmaceutical research laboratories so any variation in the data that is due to differences in the ambient conditions at the four sites is probably representative of the effects of normal day-to-day fluctuations in conditions at a single site. Other possible sources of error between testing sites include differences in the skill level of the operators, differences in the condition of the instruments, and differences in the performance of the materials following shipping. Each of these influences can be considered to be normal sources of error for this type of analytical procedure and thus the variation in the data between sites in this study is probably typical of that which would be expected over the normal long-term application of this test procedure at any given location(s).

Table 1
Environmental conditions recorded during the powder avalanche testing conducting at the different testing sites

Site	Temperature mean and range (°C)	Relative humidity mean and range (%)
1	20 (18–21)	42 (29–47)
2	24 (19–25)	33 (30–41)
3	20 (19–20)	36 (34–38)
4	23 (22–24)	49 (45–53)

3.4. Effect of rotational speed

The effect of the drum rotation time on the avalanche frequency is as might be expected intuitively. That is, as the time for one rotation decreases the mean number of avalanches per second increases (Fig. 7a–e). For a halving of the time for one drum rotation the mean avalanche time is also reduced by approximately 50% indicating that the number of avalanches per revolution does not change significantly, and the type of avalanching behavior that is occurring (Fig. 3) is likely to be similar at each rotation rate for the materials studied in this work. This confirms what was reported qualitatively by the individual operators at each site. At the fastest rotation speed (100 s per revolution) there is only about 4 s separating the mean avalanche time of the extreme materials (ascorbic acid and hydroxypropyl cellulose), whereas this difference is nearer to 8 s at the slowest rotation speed (Fig. 8). Clearly a slower speed of rotation provides a larger ‘window’ in which to discriminate similarly performing materials (e.g., anhydrous lactose and citric acid), although experiments performed under these conditions will take proportionally longer to perform.

Perhaps most importantly for this work the rankings that were provided for the five different materials

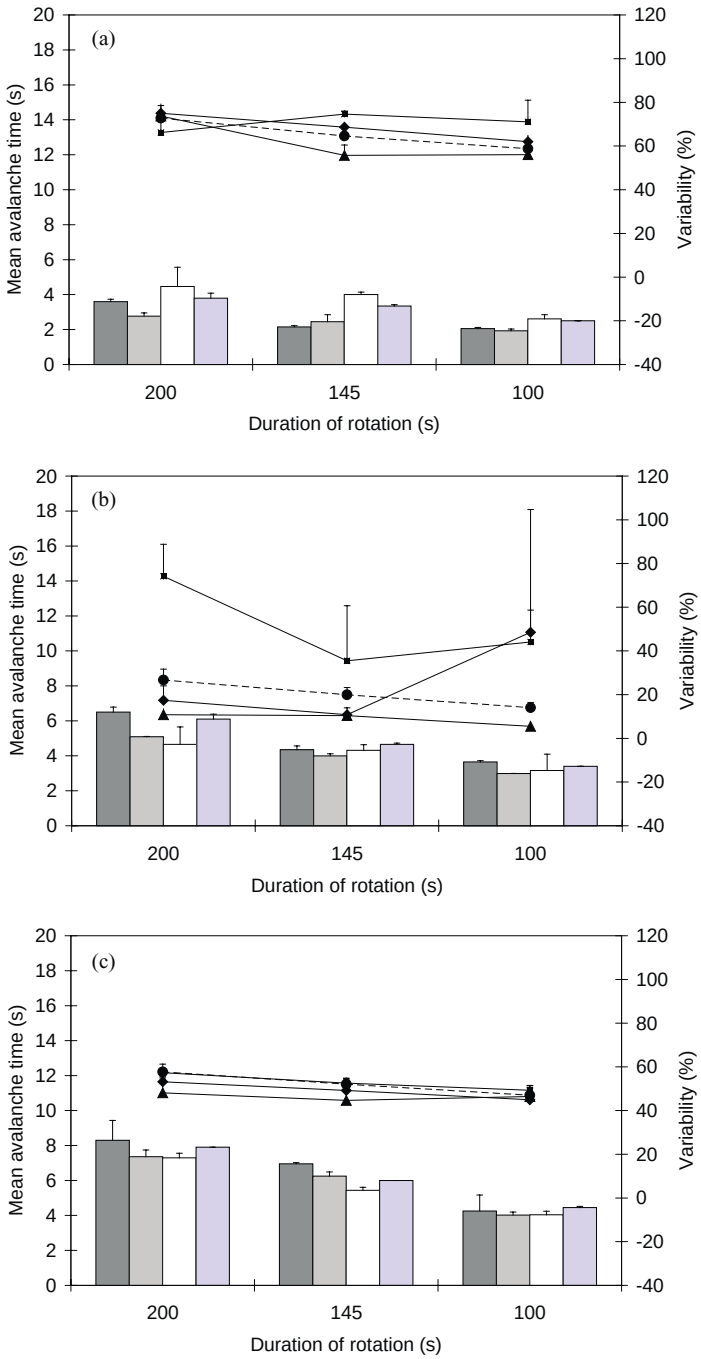

Fig. 7. Mean avalanche times and coefficients of variation ('variability') recorded at three different drum rotation durations ((a) ascorbic acid; (b) citric acid; (c) croscarmellose sodium; (d) hydroxypropyl cellulose; (e) lactose anhydrous) (from left to right: first column—mean, site 1; second column—mean, site 2; third column—mean, site 3; fourth column—mean, site 4. Triangle—variability, site 1; circle—variability, site 2; star—variability, site 3; diamond—variability, site 4).

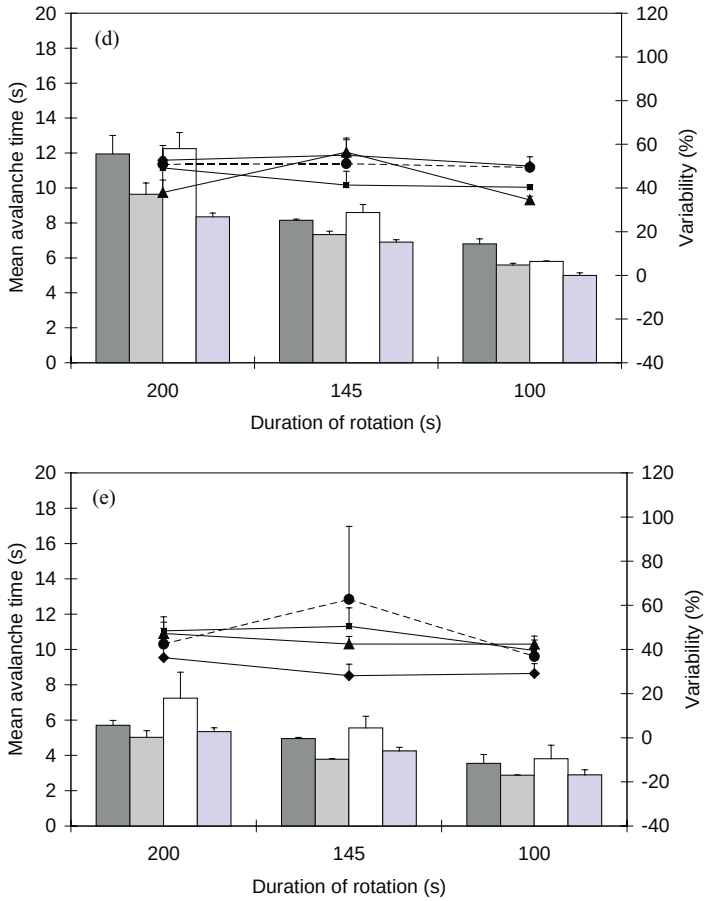

Fig. 7. (*Continued*).

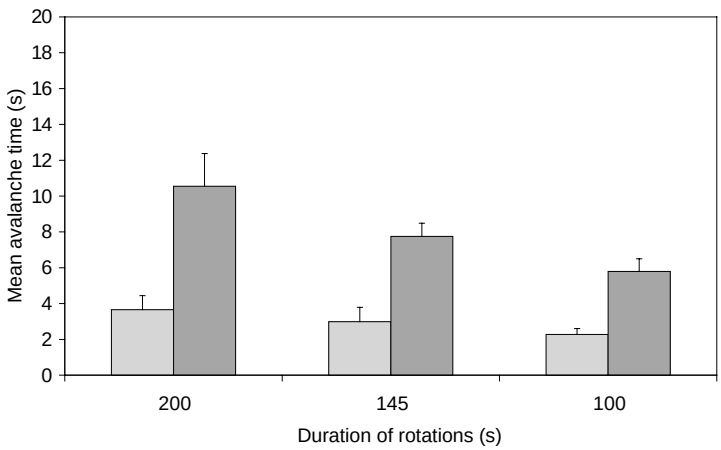

Fig. 8. Mean avalanche time comparison for ascorbic acid and hydroxypropyl cellulose (left column—ascorbic acid; right column—hydroxypropyl cellulose).

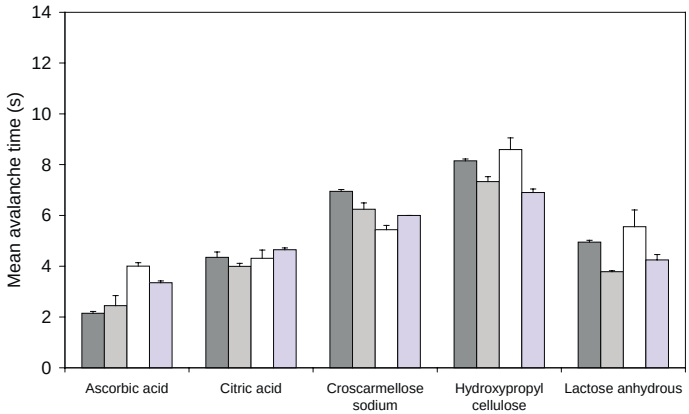

Fig. 9. Comparison of the mean avalanche time for five different materials (145 s per revolution) (columns from left to right: site 1; site 2; site 3; site 4).

at each of the three rotational durations were found to be similar, and thus data collected at a single speed could be selected for more detailed analysis. The data collected at a drum rotation duration of 145 s per revolution was chosen for this purpose because it represented a practical balance between the length of the experiment and number of data points collected.

3.5. Comparison and discrimination of materials

The mean avalanche times and the coefficients of variation (measured at the intermediate drum rotation duration) for the different materials are compared in Figs. 9 and 10 The ranking of the cohesivity of these materials based on the mean avalanche time was ascorbic acid < citric acid < anhydrous lactose < croscarmellose sodium < hydroxypropyl cellulose. This ranking was the same for all the individual sites except one (site #3), where the performance of the anhydrous lactose and croscarmellose sodium was effectively indistinguishable. A shorter mean avalanche time is taken to indicate that the powder flows more readily under the conditions of the test (i.e., low shear agitation in a dilated state). Thus, one might expect powders displaying a small mean avalanche time to be the easiest to blend in low shear mixers, such as in a twin-shell or 'V' blenders. Intriguingly the rank ordering of the powders' flow performance was different

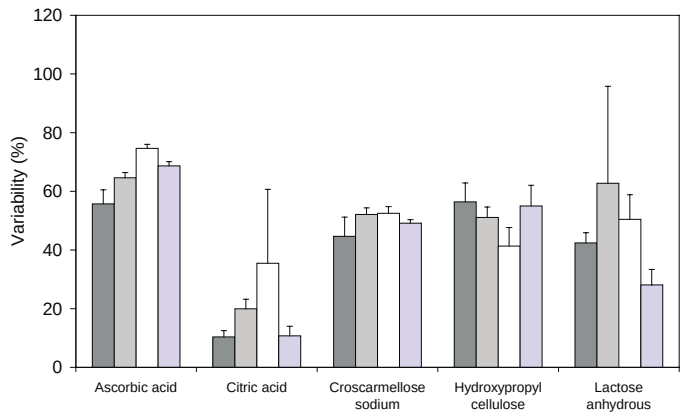

Fig. 10. Comparison of the coefficient of variation ('variability') for five different materials (145 s per revolution) (columns from left to right: site 1; site 2; site 3; site 4).

Table 2
Comparison of avalanche time and shear cell parameters for the five standard test materials

Material	Effective angle of internal friction[a] (degrees)		Mean avalanche time[b] (s)		Coefficient of variation[b] (%)	
	Value	Rank	Value	Rank	Value	Rank
Ascorbic acid	24.9	1st	2.2	1st	56.6	5th
Citric acid	29.6	2nd	3.8	2nd	29.4	1st
Croscarmellose sodium	38.0	4th	7.1	4th	44.4	3rd
Hydroxypropyl cellulose	44.7	5th	8.3	5th	53.3	5th
Lactose anhydrous	34.4	3rd	4.9	3rd	43.1	3rd

[a] A larger effective angle of internal friction (EAIF) is associated with poorer powder flow.
[b] Determined at 145 s per revolution for 1200 s.

when judged according to the range of their avalanche behavior ("coefficient of variation"). In this case the differences between replicate runs were slightly more pronounced (larger error) and it was more difficult to distinguish between the behaviors of the different materials. Using this parameter the samples were ranked: citric acid < croscarmellose sodium ≈ anhydrous lactose ≈ hydroxypropyl cellulose < ascorbic acid. The breadth of the avalanche distribution indicates the range of powder flow behavior that is encountered with any particular sample. Intuitively it might be expected that a material with a narrow distribution of avalanche times would flow more uniformly and be less likely to 'stop-and-start' during bulk powder conveying operations (such as discharge from a hopper or blender) than a material with a broad distribution of avalanche times. Thus, it is preferable to work with powders that not only have a short mean avalanche time, but also a relatively narrow distribution of avalanche times ("coefficient of variation"). Based on this conclusion the citric acid sample would be classified as having the best overall flow performance (low mean avalanche time and low coefficient of variation) of the five materials evaluated in this work.

3.6. Comparison with physical property and shear cell data

To provide additional insight into the information provided by the powder avalanche testing procedure a comparison with results from a simplified shear cell was performed. It should be recalled that the shear cell forces the powder to flow whilst under an externally applied compressive stress, whereas the avalanche tester causes the powder to flow after the random re-arrangement of its particles from a previous avalanche event. In both cases powder dilation is expected to be a prerequisite for flow, but the conditions under which the powder beds have been formed in each case are very different.

Comparison of the results of the two powder flow test methods was achieved by comparing the mean time to avalanche and the coefficient of variation with the effective angle of internal friction recorded for each material (Table 2). Despite the somewhat different shear conditions being applied to the powders during the two test procedures there was an identical ranking of the flow performance of the excipient powders by the effective angle of internal friction and the mean time to avalanche parameters. The coefficient of variability of the powder avalanche times did not appear to have any correlation to the data generated using the simplified shear cell. These results demonstrate that the 'average' ability of common pharmaceutical powders to flow under the conditions of the two tests is probably similar and either test method could be used for the purposes of determining the typical flow properties of such materials. This is an important first step toward demonstrating the validity of powder avalanche test methods for the routine characterization of powdered pharmaceutical raw materials, in-process intermediates (e.g., granulations), and formulated drug products.

The results obtained in this work can also be considered in light of the known physical properties of the material tested (Table 3). Typically, powders that are comprised of large and dense regular particles will flow more readily that those with particles that are small, irregular, or of low density [20]. Based on these general principles it would be expected that the

Table 3
Physical properties of the five standard test materials

	Particle morphology	True density ($g\,ml^{-1}$)	Median particle size (μm)	10th percentile size (μm)	90th percentile size (μm)
Ascorbic acid	Equant crystals	1.66	249	33	479
Citric acid	Equant crystals	1.60	388	196	585
Croscarmellose sodium	Elongated twisted fibres	1.55	42[a]	18[a]	114[a]
Hydroxypropyl cellulose	Fragmented fibres	1.21	85	12	247
Lactose anhydrous	Equant crystals	1.50	136	12	324

[a] Particle size parameters for this material are only approximate because of the elongated nature of the particles.

ascorbic acid and citric acid samples would be the most free flowing of the materials studied, and the croscarmellose sodium and hydroxypropyl cellulose powders would be the poorest flowing materials. This general trend is confirmed by the results of both the powder avalanche and the shear cell testing (Table 2) and provides additional confidence in the utility of powder avalanche testing for assessing the flow performance of common pharmaceutical powder samples.

4. Conclusions

A quick, simple, and rugged procedure for determining the flow properties of pharmaceutical powders using a commercial powder avalanche testing instrument has been developed. The experimental conditions were rationally selected and systematically evaluated so that an optimal operating-procedure could be identified. This procedure gives comparable results when performed at different testing sites and is able to reproducibly rank the flow properties of common pharmaceutical powders. The limits of the test method to discriminate between different powder samples have been determined, and a positive correlation with the results of a benchmark method (the simplified shear cell) has been demonstrated.

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References

[1] T.M. Crowder, A.J. Hickey, Pharm. Technol. (2000) 50–58.
[2] B.H. Kaye, I. Gratton-Liimalainen, N. Faddis, Part. Part. Syst. Char. 12 (1995) 232–236.
[3] B.H. Kaye, Part. Part. Syst. Char. 14 (1997) 53–66.
[4] B.H. Kaye, J. Gratton-Liimatainen, J. Lloyd, Part. Part. Syst. Char. 12 (1995) 194–197.
[5] S. Rastogi, G.E. Klinzing, Part. Part. Syst. Charact. 11 (1994) 453–456.
[6] R. Doherty, H. Sahajpal, R. Poynter, Y. Lee, J. Pharm. Pharmacol. 51 (1999) S323.
[7] E.M. Boothroyd, R.A. Doherty, R. Poynter, M. Ticehurst, J. Pharm. Pharmacol. 52 (2000) 174S.
[8] H. Ramchandruni, S.W. Hoag, J. Pharm. Sci. 90 (2001) 531–540.
[9] E.N. Hiestand, C.J. Wilcox, J. Pharm. Sci. 57 (1968) 1421–1427.
[10] B.C. Hancock, G.T. Carlson, D.D. Ladipo, B.A. Langdon, M.P. Mullarney, J. Pharm. Pharmacol. 53 (2001) 1193–1199.
[11] A.A. Boateng, P.V. Barr, Chem. Eng. Sci. 51 (1996) 4167–4181.
[12] J. Mellmann, Powder Technol. 118 (2001) 251–270.
[13] G. Metcalfe, T. Shinbrot, J.J. McCarthy, J.M. Ottino, Nature 374 (1995) 39–41.
[14] Y.L. Ding, J.P.K. Seville, R. Forster, D.J. Parker, Chem. Eng. Sci. 56 (2001) 1769–1780.
[15] J.L. Turner, M. Nakagawa, Powder Technol. 113 (2000) 119–123.
[16] K. Shinohara, B. Golman, Powder Technol. 122 (2002) 255–258.
[17] K. Kurihara, H. Kuno, in: Proceedings of the Fujihara Memorial Faculty of Engineering, Keio University, vol. 72, 1966, pp. 40–49.
[18] R.P. Behringer, Nature 374 (1995) 15.
[19] R.G. Iacocca, R.M. German, Powder Technol. 102 (1999) 253–265.
[20] G.E. Amidon, M.E. Houghton, Pharm. Manufact. 2 (1985) 20–31.