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Evaluation of the vibratory feeder method for assessment of powder flow properties

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Abstract

The flow properties of pharmaceutical powders and blends used in solid oral dosage forms are an important consideration during dosage form development. The vibratory feeder method, a flow measurement technique that quantifies avalanche flow, has been adapted for measurement of the flow properties of common pharmaceutical powders used in solid oral dosage forms. The flow properties of 17 different powders were measured with the instrument, and the results are reported as a powder flow index (PFI). The PFI trends of the powders correlate well with flow properties reported in the literature. The flow properties of the powders were also measured with a commercially available avalanche instrument, the Aero-Flow™, and the results were reported as the mean time to avalanche (MTA). Since the two instruments analyze the avalanche by different algorithms, the results were compared with nonparametric statistical evaluation of ranked data, and they were found to be in excellent agreement. A recommended procedure for measurement of powder flow with the vibratory feeder is presented.

Keywords: Powder flow; Powder avalanche; Vibratory feeder

1. Introduction

Characterization of flow properties of drug substances, excipients, powder blends, and granules is important during development of pharmaceutical solid oral dosage forms, from preformulation through full development. Material flow impacts several unit operations such as mixing, milling, discharging, conveyance, and unit dose dispensing. The quality of solid material flow is influenced by physical parameters such as particle size and shape, bulk and true density, moisture content, crystal form, and surface charge. Various methods are commonly used to determine powder flow characteristics. These include the angle of repose measurement, Carr's index, Hausner ratio, flow through orifices of decreasing diameters, mass flow rates, and measurements using shear cells (Amidon and Houghton, 1985; Schweder and Shulze, 1990). Although these tests have been used for several years, none of the tests used alone completely captures the effects of all the physical parameters on powder flow, nor do they universally describe flow behavior in each unit operation (Amidon, 1998).

A newer approach to characterizing powder flow is dynamic in nature and is based on the deterministic chaos theory and fractal geometry of powders. Flowability determined using this approach is the re-

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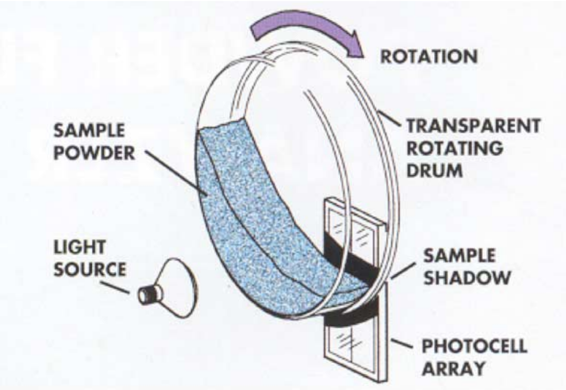

Courtesy: TSI Inc.

Fig. 1. Aero-Flow^{TM} instrument.

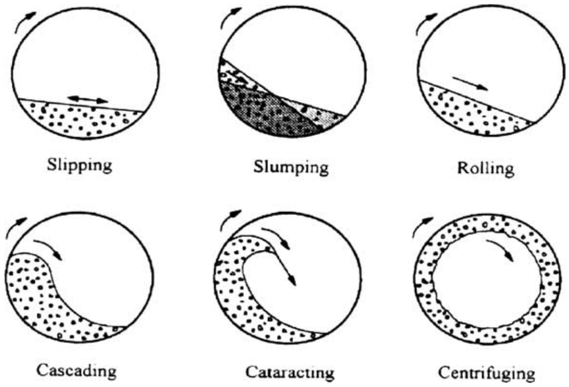

Fig. 2. Six types of flow in the Aero-Flow^{TM} instrument.

sult of nonlinear interactions of many parameters such as powder grain size, shape, surface texture, moisture content, electrostatic forces, and adsorbed layers (Kaye, 1997). A commercially available instrument, the Aero-Flow^{TM} (TSI Inc., Shoreview, MN), is based on these principles. It detects avalanche events when a powder bed is slowly rotated at constant speed in a cylindrical drum (Fig. 1). The instrument analyzes the data through "strange attractor plots" to give the mean time to avalanche (MTA) and scatter results (Kaye et al., 1995). It has been suggested that this is indicative of cohesive flow (Hancock et al., in press). Recent publications indicate it can distinguish between good and poor flowing pharmaceutical powders and powder blends (Doherty et al., 1999; Trowbridge et al., 1999; Lee et al., 2000), and can be used to predict weight variation in a tableting operation (Trowbridge et al., 1999; Boothroyd et al., 2000). In order to give representative data, the flow type should be either cascading or rolling where avalanching occurs (Fig. 2). In other types of flow regimes, avalanche data is obtained but the results do not truly represent flow behavior. One group of workers extended the data analysis to derive parameters considered to be more useful to the development scientist. They determined the standard deviation of the MTA at each point on a series of increasing speeds, and use this analysis to calculate a "Flowability Index" as the mean of standard deviations. They also calculate a "Cohesion Index" from the MTA (Lavoie et al., 2002). While these parameters have potential utility in a development program, they significantly extend the test time and the amount of required material.

All of the above tests require a significant amount of material, ranging from 25 to 200 g, and they can be laborious. Since the availability of API and time to perform development experiments is limited during dosage form development, especially during the early stages of dosage form development, it is desirable to have a rapid and material sparing powder flow test.

An alternative means to measure avalanche flow is with a vibratory feeder (Kaye, 1989). It is a quicker method and uses less material, and has been reported to be useful for characterization of powder flow behavior (Hickey and Concessio, 1994). It is a dynamic method that measures fractal dimensions of powder flow rate profiles of powders to characterize flowability. We investigated the application of this instrument for characterizing the flow of common powder excipients used in solid oral dosage forms. Comparison was made to the commercially available avalanche instrument, the Aero-Flow^{TM}, in terms of powder flow results, the amount of material needed to perform the test and the time required to perform the test. This was done by assembly of a modification of the vibratory feeder instrument described by Hickey and Concessio (1994). The instrument was then used to characterize the flow behavior of 17 common pharmaceutical powders. From these measurements, the powder flow index (PFI) was calculated. These powders were also characterized with the Aero-Flow^{TM} and a nonparametric statistical comparison of the results obtained from the two instruments was carried out.

2. Materials and methods

2.1. Materials

Seventeen common pharmaceutical powders were evaluated on the vibratory feeder and the Aero-Flow™ Instrument (Table 1). Single lots of each sample were used. The materials were preconditioned by placing the powders in an open dish contained in a constant humidity chamber (25 °C/55% RH) for at least 24 h prior to flow measurements. The constant humidity chambers were prepared by placing a saturated sodium bromide solution in the bottom of a glass desiccator, and the samples were placed in open Petri dishes above the solution (Greenspan, 1977).

2.2. Methods

2.2.1. Vibratory feeder instrument

The vibratory feeder instrument set up is shown in Fig. 3. The vibrator used was a Syntron Magnetic Feeder (model FTO-C, FMC Corporation, Hoover City, PA, USA). Digital speed control was achieved with a Syntron Electric Controller (model CNDCTR DC15 FMC Corporation). The power supply to the vibrator was connected through an Uninterruptible Power Supply (model Smart-UPS, APC, Kingston, RI, USA) to ensure a stable voltage. A Mettler PG-203S balance (Mettler-Toledo, Inc. Columbus, OH, USA) was interfaced with a computer for data collection. The balance was placed on a marble block mounted on rubber pads to protect it from external vibrations. The glass shield on one side of the balance was removed to allow powder to be delivered from the feeder onto a pan on the balance; the pan was placed approximately 5 cm below the edge of the feeder. The sample was always introduced on to the same spot on the feeder through a glass powder funnel placed approximately 4 cm above it at a position approximately 22 cm from the discharge end. A HyperTerminal connection to the computer was enabled and the vibratory feeder turned on, to start data collection. The cumulative mass of powder delivered from the feeder was collected at a frequency of eight times per second. Data thus obtained was used to plot a cumulative mass versus time profile, which was used to construct a Richardson plot (Kaye, 1989) using the Matlab routine written by Crowder and Hickey (1999). Fractal dimensions (FD), defined as 1 + |slope|, were calculated from the plots. Initial experiments were analyzed with this method, and as explained in the following, the routine was then slightly modified to better fit this application. Better flowing powders have a lower FD (Crowder and Hickey, 1999). Although the FD obtained from the Richardson Plot has been commonly used, we found the PFI to be a more convenient numerical scale for comparison of powders. The PFI, was calculated from the FD (Eq. (1)).

$$PFI = (FD - 1)1000 \quad (1)$$

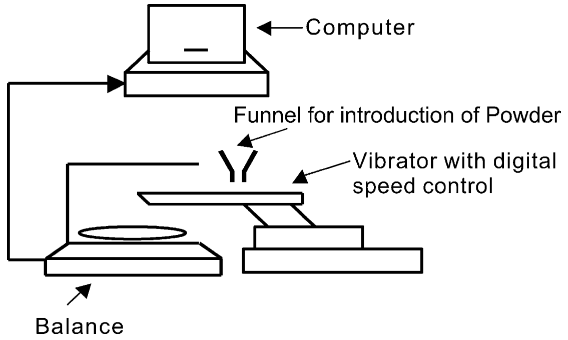

Fig. 3. Schematic representation of the vibratory feeder instrument.

Table 1
Materials used for comparative flow evaluation

Powder	Trade name	Manufacturer
Microcrystalline cellulose	Avicel PH 101	FMC
Microcrystalline cellulose	Avicel PH 102	FMC
Microcrystalline cellulose	Avicel PH 302	FMC
Citric acid	Citric Acid	Sigma
Crospovidone	Polyplasdone XL	ISP
Dicalcium Phosphate	Emcompress	Penwest
Dextrates	EMDEX	Penwest
Lactose monohydrate	Fast-Flo Lactose	Foremost
Lactose monohydrate	Lactose	Sheffield
Hydroxypropylmethylcellulose	Methocel E5	Dow
Silicified microcrystalline cellulose	SMCC 50	Penwest
Silicified microcrystalline cellulose	SMCC 90	Penwest
Silicified microcrystalline cellulose	SMCC HD 90	Penwest
Sodium starch glycolate	Explotab	Mendell
Pregelatinized starch	Starch 1500	Colorcon
Lactose monohydrate	Tablettose 80	Meggle
Sodium chloride	Sodium Chloride	Sigma

Sample quantity and vibrator speed were optimized using Fast-Flo Lactose. Each powder was measured three times using a fresh sample for each measurement. The temperature and humidity were recorded during each run.

2.2.2. Aero-Flow™ instrument

The Aero-Flow™ instrument (TSI Inc.) was used as received. Sample MTAs were determined as previously described (Hancock et al., in press) at a drum speed of 145 s per revolution for a duration of 20 min. The temperature, humidity, and flow type were recorded during each run. Each powder was measured three times using the same sample for each measurement.

2.2.3. Statistical comparison of the vibratory feeder and the Aero-Flow™

To accurately compare the instruments, data was collected in the following format. Each of the 17 powders selected, received a measurement from both instruments. This process was repeated three times. The data was then used to create three sets of ranked data for each powder on both instruments. Ranked data from the two instruments were analyzed statistically by a nonparametric procedure to determine if the powder flow evaluations from the two instruments were comparable. A direct comparison of the two instruments is not appropriate since the avalanche flows are measured and calculated by different methods.

Taking the vibratory feeder and the Aero-Flow™ to be independent judges, their equivalence was determined by the agreement between their ranks. The judges would be in agreement if the instruments return equivalent measurement rankings across all powders. In statistical terms, the two judges would be in agreement if they use the same probability distribution to select their ranks (Costello, 1983). To verify this, each judge ranks the three sets of measurement values for the same k objects, where k represents the 17 powders. Let $S_i = (S_{i1}, \ldots, S_{ik})'$ and $T_j = (T_{j1}, \ldots, T_{jk})'$ be the rank vectors assigned independently by each judge. Where $i = 1, \ldots, m$; $j = 1, \ldots, n$, and $m = n = 3$ represents the three measurements or judgments each instrument makes across all $k = 17$ powders. Thus, S_i and T_j make up two sets of observations where each set contains three measurement vectors of ranked data.

To statistically compare S_i and T_j for equivalence, information about their probability densities must be defined. Let Ω be the set of all permutations of $1, 2, \ldots, k = 17$ powders, and let P_1 and P_2 be discrete probability distributions on Ω. It is assumed that $S_1, \ldots, S_m$ and $T_1, \ldots, T_n$ are mutually independent and identically distributed with common probability distribution P_1 and P_2, respectively. Then the two groups of judges agree if and only if $P_1 = P_2$. Therefore, a test of equivalence can be defined by the following hypotheses: H_0: $P_1 = P_2$ versus H_1: $P_1 \neq P_2$. Using the following test statistic can test this hypothesis.

$$\text{Let } V = \frac{1}{k^3 - k}\sum_{h=1}^{k}(\bar{S}_h - \bar{T}_h)^2, \text{ where}$$

$$\bar{S}_h = \frac{1}{m}\sum_{i=1}^{m} S_{ih},\ \overline{T_h} = \frac{1}{n}\sum_{j=1}^{n} T_{jh},\ h = 1, \ldots, k. \qquad (2)$$

The results of the test statistic are compared to Costello and Wolfe (1985) critical value table to determine whether we accept or reject the null hypothesis. Costello and Wolf showed that Eq. (2) is bounded by $0 \leq V \leq 1/3$. Therefore, if all judges are in perfect agreement then $V = 0$ and $S_{ih} = T_{jh} = h$ for all possible values of i, j, and h. Otherwise, if complete disagreement exists between the two groups of judges then $V = 1/3$ and $S_{ih} = k - h + 1$ and $T_{jh} = h$. Furthermore, the results of the hypothesis test can be determined by calculating the P-value. The P-value is defined as $\underline{\alpha} = \sup_{p \in P} p(V \geq v)$, where P is the set of all discrete probability distributions on Ω and v is the observed value of V. In other words, the P-value is the probability of the test statistic V being equal to or greater than the observed value. In general, a small P-value (e.g. less than 0.05) is classified as strong evidence toward rejecting the null hypothesis of equivalence. Otherwise, a large P-value (e.g. greater than 0.2) provides strong evidence toward accepting the null hypothesis of equivalence.

3. Results and discussion

The minimum optimum sample size needed for a vibratory Feeder measurement was determined using Fast-Flo Lactose. Sample weights and vibration speed

Table 2
Results summary from sample weight and vibrator speed optimization experiments using Fast-Flo Lactose

Experiment number	Sample weight (g)	Vibration speed setting	Data points	PFI	Percent RSD
1	1.2	2.5	3385	9	0.06
2	1.2	3.3	236	22	0.26
3	1.8	2.9	884	7	0.25
4	2.4	2.5	7945	5	0.14
5	2.4	3.3	276	20	0.06
6	5.6	3.3	366	12	0.38
7	10.1	2.5	9885	8	0.46

settings (as determined from the feeder analog setting) were varied and the optimum sample size and speed setting were determined. The data from these experiments is summarized in Table 2. As evident from the data 1.2 g of Fast-Flo Lactose at a vibration setting of 2.5 resulted in a sufficient number of data points in the mass flow profile and the PFI values obtained were most reproducible. (A minimum of 1000 data points is required for the PFI calculation to be meaningful.) Insufficient data points were obtained at higher speeds (Table 2, experiments 2, 3, 5, and 6), where the powder flowed too fast (Table 2) and no powder flow was observed at lower settings. Very similar PFI results were obtained with higher masses of powder at the 2.5 speed setting (Table 2, experiments 1, 4, and 7) but the runs with 1.2 gm sample were the most reproducible (lowest percent RSD). Therefore, 1.2 g of sample were used per experiment. The digital speed control was acquired after the optimization experiments were completed. The equivalent vibrator speed setting on the digital speed controller was found to be 45.3 ± 0.5 and this setting was used for all subsequent measurements.

After the experimental conditions were optimized, the Matlab routine was modified to better suit the intended application. The original routine is based on a method described by Higuchi (1988). At each stride length, the routine calculates the mean line length from multiple series, by stepping iteratively through the entire length of the profile. The routine was modified to calculate the line length from a single series for each stride length, thus ensuring that the point of origin of the profile was always included in the calculation. From the Richardson Plot obtained from these measurements, the slope was determined from the normalized stride length range 10^{-3} to 10^{-2}. The powder flow index was calculated using Eq. (1). Fig. 4 shows the mass versus time profile for Polyplasdone XL. Fig. 5 shows the Richardson plot derived from the profile.

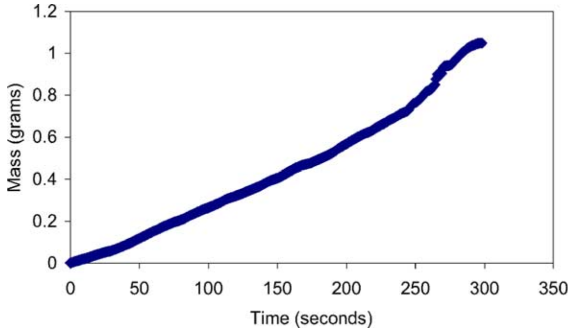

Fig. 4. Mass vs. time profile for Polyplasdone XL.

Data from the Aero-Flow™ instrument experiments was generated as a MTA as previously described (Hancock et al., in press).

3.1. Statistical evaluation

Data from the three sets of experiments were used to obtain three sets of ranks on the powders from each instrument. Table 3 summarizes the PFI and MTA data obtained on the powders. For the sake of simplicity, only the mean values and their ranges are shown in

Table 3
Mean ($n = 3$) PFI and MTA data from the vibratory feeder and Aero-Flow™

Powder	Mean PFI ± S.D.	MTA (s) ± S.D.
Fast-Flo Lactose	1.41 ± 0.05	2.61 ± 0.14
SMCC 50	10.35 ± 1.23	4.69 ± 0.08
Lactose	11.45 ± 1.27	6.55 ± 0.10
Explotab	12.26 ± 2.04	9.91 ± 0.31
Methocel E5	14.65 ± 1.29	10.29 ± 0.29
SMCC HD 90	2.5 ± 1.59	3.33 ± 0.09
Avicel PH 102	20.62 ± 1.7	5.77 ± 0.86
Avicel PH 101	24.28 ± 4.88	8.94 ± 0.20
EMDEX	3.04 ± 2.01	4.15 ± 0.13
Citric Acid	4.19 ± 1.18	5.52 ± 0.36
Tablettose 80	5.63 ± 0.48	4.54 ± 0.10
Emcompress	5.95 ± 0.38	3.44 ± 0.03
Starch 1500	6.17 ± 1.58	9.17 ± 0.15
SMCC 90	7.19 ± 5.94	3.43 ± 0.08
Sodium Chloride	7.83 ± 1.84	3.79 ± 0.04
Polyplasdone XL	8.36 ± 4.377	9.68 ± 0.16
Avicel PH 302	9.41 ± 5.69	5.72 ± 0.09

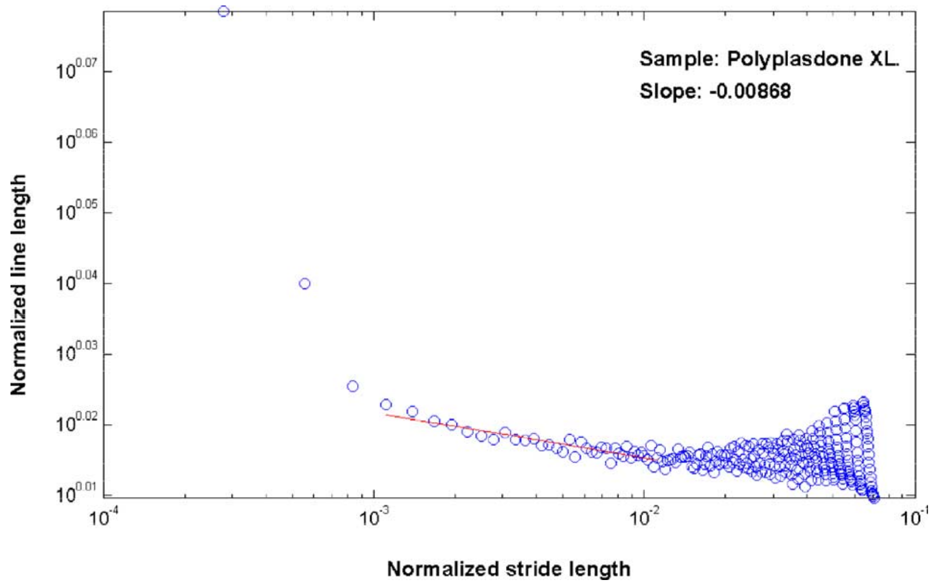

Fig. 5. Richardson plot for Polyplasdone XL.

the table. In actual statistical calculation, however, individual PFI and MTAs (and not the mean values) were used to rank the powders. Fig. 6 shows the comparative ranked data derived from the PFI and MTA data. Previous reports have shown that powders that flow well have lower values of FD (hence PFI) and MTA (Hickey and Concessio, 1994; Hancock et al., in press).

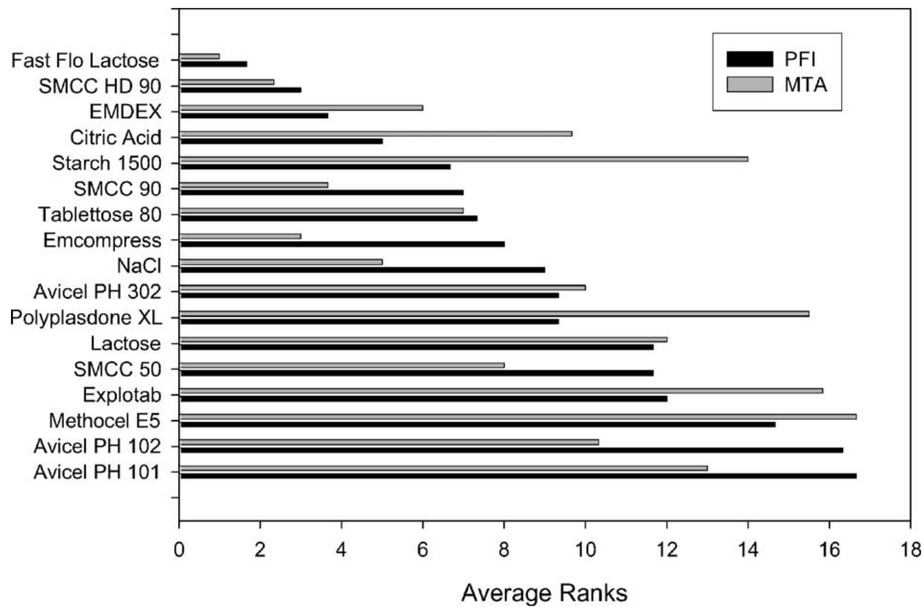

Fig. 6. Comparative PFI and MTA rank data.

Table 4
Comparison of flow characteristics obtained in this study with avalanche data from Doherty et al.

Excipient	Doherty et al., MTA (s)	This study	
		MTA (s)	PFI
Fast-Flo Lactose	2.80	2.61	1.41
Dicalcium Phosphate	4.45	3.44	5.95
Avicel PH 102	5.11	5.77	20.6
Avicel PH 101	7.26	8.94	24.3
Starch 1500	9.55	9.17	6.2

The Aero-Flow™ results of a subset from this study overlap with the study of Doherty et al. (1999) and they agree in rank ordering (Table 4). The flow ranking in both sets of measurements are Fast-Flo Lactose > Dicalcium Phosphate > Avicel PH 102 > Avicel PH 101 > Starch 1500. The quantitative differences between the two sets of numbers are not significant and can be explained in terms of differences in lot numbers, operator dependence on the measurement, measurement conditions, and material conditioning. Ranking of the vibratory feeder PFI results gives a slightly different ranking where Starch 1500 shows better flow in this test: Fast-Flo Lactose > Dicalcium Phosphate > Starch 1500 > Avicel PH 102 > Avicel PH 101. This could be due to the characteristics of the measurement techniques. In the Aero-Flow™ measurement, visual examination of Starch 1500 shows a slumping pattern, which, as indicated earlier, causes somewhat misleading results on the Aero-Flow™. Doherty et al. (1999) showed the importance of both visual and numerical characterization of Aero-Flow™ results.

Previous workers have shown by a variety of methods that silicified microcrystalline cellulose excipients (SMCC) flow better than microcrystalline cellulose excipients (Avicel) of the same particle size range (e.g. Sherwood et al., 1998; Cobb and Zeleznik, 2001; Hwang and Peck, 2001; Guo et al., 2002). The Aero-Flow™ and vibratory feeder from this study are consistent with this trend thus verifying the technique and the similarity of the two measurement techniques. When the comparison is done on the entire SMCC and Avicel sample population the rankings are very similar but are not identical: Aero-Flow™: SMCC HD 90 > SMCC 90 > SMCC 50 > Avicel PH 302 > Avicel PH 102 > Avicel PH 101; vibratory feeder: SMCC HD 90 > SMCC 90 > Avicel PH 302 > SMCC 50 >> Avicel PH 102 > Avicel PH 101. This slight difference between the measurement techniques could be to due to subtle differences in powder flow behavior in the instrument and the different data analysis basis. It was therefore decided to pursue a more rigorous statistical comparison of the data through a nonparametric analysis as is described in the next section.

3.1.1. Calculation of *P*-value

As mentioned above the *P*-value obtained from a test statistic helps to determine whether the null hypothesis should be accepted or rejected. For the current data set of 17 powders measured in triplicate on both instruments, the *P*-value was determined as follows. First, the test statistic V was determined by calculating the mean ranks of the powders from the vibratory feeder and Aero-Flow™ instrument measurements, per Eq. (2). The difference in mean ranks were then squared and divided by its corresponding numerator to obtain $v = 0.0519$. The observed test statistic value matches closest with Costello and Wolf's tabulated value of 0.1481 (Costello and Wolfe, 1985). The corresponding *P*-value found in the table is 0.2188. Statistically, our *P-value* was obtained as follows:

$$\underline{\alpha} = \sup_{p \in P} p(V \geq 0.0519) \geq \sup_{Q} p_{1/2,w}(V \geq 0.0519) \geq \sup_{Q} p_{1/2,w}(V \geq 0.1481) = 0.2188,$$

where $w = (w_1, \ldots, w_{17})$ is any element in Ω, the set of all permutations of $1, 2, \ldots, 17$, and Q is a subset of P, the set of all discrete probability distributions on Ω, including all distributions of the form

$$p_{1/2,w}(r) = \begin{cases} 1/2 & \text{if } r = w \\ 1/2 & \text{if } r = (18, \ldots, 18) - w. \\ 0 & \text{otherwise} \end{cases}$$

In other words, Costello and Wolfe were capable of reducing the dimensionality of P by letting Q be a subset of that space. This facilitates the ability to generate relevant tabulated *P*-values. Given that our observed test statistic value is not listed in Costello and Wolfe's table, linear extrapolation was used to determine the approximate *P*-value of 0.6246. Thus, given the two instruments are in agreement, there will be a 62.46% chance of getting an observed V value equal to or larger than 0.0519. Given the large P-value, the data supports the null hypothesis that the two instruments are in agreement in evaluating powder flow.

4. Conclusion

From the statistical evaluation performed using a nonparametric rank procedure, it is clear that the powder flow data obtained from the vibratory feeder instrument and the Aero-Flow™ instrument are in excellent agreement with each other. The vibratory feeder instrument therefore offers a rapid and convenient means of evaluating powder flow using small quantities of samples. An added advantage of the vibratory feeder method is that while the commercially available avalanche instrument is best suited for powders that exhibit cascading or rolling avalanching patterns, the vibratory feeder instrument does not have any minimum requirements in terms of flow quality.

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