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Composite Method to Quantify Powder Flow as a Screening Method in Early Tablet or Capsule Formulation Development

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Michael K. Taylor[1*], Jeri Ginsburg[2], Anthony J. Hickey[3], Ferdous Gheyas[3]

[1]Drug Delivery and Disposition, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599
[2] GlaxoWellcome, Five Moore Drive, PO Box 13398, Research Triangle Park, NC 27709
[3] Schering Plough Research Institute, Kenilworth, NJ 07033

ABSTRACT The flow properties of typical tablet and capsule formulation excipients, active compounds, and representative formulation blends were tested with current and novel flow measurement techniques to identify a reliable bench test to quantify powder flow as a screening method in early tablet and capsule formulation development. Test methods employed were vibrating spatula, critical orifice, angle of repose, compressibility index, and avalanching analysis. Powder flow results from each method were compiled in a database, sorted, and compared. An empirical composite index was established and powder flow was ranked in accordance with formulator experience. Principal components analyses of the angle of repose, percent compressibility, and critical orifice of the powder materials were also performed. The first principal component accounted for 72.8% of data variability; scores associated with this principal component score can serve as an index of flowability. Data generated from vibrating spatula and avalanching methods were not reproducible and were inconsistent with formulator experience and cited vendor references for flow. Improvements of test instruments and further studies are necessary for better assessment of these approaches.

KEYWORDS: Principal components analysis, Critical orifice, Powder flow, Avalanching, Angle of repose, Compressibility index

***)Corresponding Author:** Michael K. Taylor, School of Pharmacy, University of North Carolina, Chapel Hill, NC, 27599; email: mkt5496@glaxowellcome.com

INTRODUCTION

In response to bulk material flow problems encountered in the mining and chemicals industry, the initial characterization of the flow properties of solids was conducted in the seminal works of Carr [1] and Jenike [2]. Carr evaluated interparticulate cohesive properties with angle of repose measurements and studied the effects of packing geometry of solids with bulk and tap density measurements. He found that density of a powder depends on particle packing and that density changes as the powder consolidates. The degree of consolidation is unique to the powder and ratio of these densities is related to interparticulate friction. This ratio, percent compressibility, was used as an index of flow. Jenike investigated adhesive/cohesive forces of particles as they relate to flow behavior by examining normal and shear stresses on powder beds. A shear-cell apparatus was developed to measure shear stress at different values of normal stress. A "flow factor" can be derived from a curve of unconfined yield stress and maximum normal stress and used as a measure of powder flow.

Augsburger and Shangraw may have been the first to address the need to determine powder flow for pharmaceutical formulations [3]. They identified a need for determining flowability indexes that were applicable to actual pharmaceutical production, after recognizing that the main objective in a tablet-compressing operation should be the maintenance of a uniform tablet weight. With that objective, they proposed the coefficient of variation of the average tablet weight as the flowability index, a dynamic

method of powder flow measurement unlike the static methods described in the previous paragraph. Other dynamic methods can be as simple as measuring the rate at which powder discharges from a hopper. Typically, a slide valve is opened and the time for the powder to completely discharge from the hopper is recorded and the mass flow rate calculated. Another dynamic method, which is gaining popularity, is the critical orifice diameter. This measurement device uses a cylinder with a series of interchangeable base plate discs that have different diameter orifices. The diameter is the size of the smallest orifice in a base plate disc through which powder in a cylinder will discharge. This test has many direct flow applications in the production setting. Goia [4] has investigated the use of this technique as a simple test to predict powder flowability in a capsule-filling operation.

More recent sophisticated dynamic flow characterization approaches include vibrating spatula [5] and avalanching methods [6,7]. These analytical techniques derive fractal dimensions from the dynamic behavior of their respective systems to quantify powder flow.

The importance of powder flow has also been recognized in less obvious pharmaceutical applications. For example, tablet and capsule blend sampling to ensure quality and meet content uniformity specifications have received significant attention. Sampling devices and techniques are critical to the procurement of representative blend samples. Garcia et al have compared the performance of two sample thieves (plug and grain) to determine content uniformity of a powder blend [8]. Relative standard deviations for blend samples taken with the plug thief were approximately half of those obtained using the grain thief. The inferior grain thief performance was attributed to the poor flow properties of the blend in the vicinity of the exposed grain thief sample chambers. On the other hand, the plug thief does not require powder flow into a sample chamber to obtain samples. The authors recommended that the selection of a bulk powder sampling thief should be made on a case-by-case basis, with a consideration of blend flow properties.

Good flow properties are critical to the successful development of any pharmaceutical tablet or capsule formulation. It is essential that an accurate assessment of flow properties be made as early in the development process as possible so that an optimum formulation can be quickly identified. Costly, time-consuming studies of poor candidates can then be avoided. Although most of these simple tests are related to the flow of dry materials through bins, hoppers, and feeders, and are especially relevant to the formulation scientist, individual powder flow tests will challenge only one or two components of the complex phenomenon known as flow. Is it possible that a combination of flow tests might better characterize flow? If so, which are the relevant tests and how should they be weighted in any composite scheme? The aim of this study was to answer these questions.

MATERIALS AND METHODS

Materials

Excipients used in these studies were purchased from commercial suppliers in compliance with the relevant United States Pharmacopoeia/National Formulary, British Pharmacopoeia, or European Pharmacopoeia monographs. Particulars for active Glaxo Wellcome (GW) compounds will not be presented for obvious proprietary reasons. Some are under current development while others have been approved and are marketed as part of current GW product portfolio.

The group of excipients chosen for this study were purposely seeded with materials that have very different flow properties (Table 1). Other groups of excipients were chosen that have similar chemical properties but differing in physical properties, which would affect respective flow properties in a predictable manner. Examples include microcrystalline cellulose with material grades differing significantly only in particle size and distribution (Table 2) and lactose (Table 3).

Table 1. Physical Properties of Very Different Flow Property Excipients (as tested)

Grade	Particle Size Distribution (%) less than stated size			Bulk Density (g/cm^3)	Tap Density (g/cm^3)	Critical Orifice Index (mm)	% Compres	Angle Of Repose (degrees)	Composite Index	Principal Component Score
	75 µm	100 µm	150 µm							
Spress[1]	35%	57%	89%	0.63	0.74	4	18.0	22.0	93.3	-2.43
Ceolus[2]	4%	21%	48%	0.23	0.34	34	37.9	55.0	24.7	4.79
Supertab[3]	29%	48%	72%	0.67	0.81	4.5	17.7	21.0	93.6	-2.50

[1]Pregelatinized Corn Starch NF B820, Grain Processing Corporation, Muscatine, IA.;[2]Cellulose, Microcrystalline, NF, KG-801, FMC Corp., Philadelphia, PA.
[3]Lactose Monohydrate USP/NF, Spray Dried, FMC Corp., Philadelphia, PA.

Table 2. Physical Properties of Different Microcrystalline Cellulose Excipients (9)

Grade	Nominal Mean Particle Size (mm)	Bulk Density (g/cm^3)	Tap Density (g/cm^3)	Critical Orifice Index (mm)	% Compress	Angle of Repose (degrees)	Composite Index	Principal Component Score
PH 101[1]	50	0.320	0.386	19	21.4	38.0	63.7	0.552
PH 102[1]	100	0.307	0.370	15.5	19.2	36.0	70.4	-0.117
PH 200[1]	180	N.D.	N.D.	8.5	13.6	34.0	83.3	-1.39
PH 301[2]	50	0.38	N.D.	19.5	21.4	41.0	61.2	0.857
PH 302[2]	90	0.39	N.D.	14.5	17.2	43.0	68.2	0.230

[1] Handbook of Pharmaceutical Excipients, The Pharmaceutical Press, 1994 [2] FMC Pharmaceutical Division, 1735 Market St., Philadelphia, Pa

Table 3. Physical Properties of Different Lactose Excipients (from literature)

Grade	Particle Size Distribution (%) less than stated size			Critical Orifice Index (mm)	%Compress.	Angle of Repose (degrees)	Composite Index	Principal Component Score
	75 µm	100 µm	150 µm					
Supertab	29%	48%	72%	4	17.7	22.0	93.3	-2.43
Spray Dried[1]	15-45	35-75	-	8	9.20	31.0	88.8	-2.09
Anhydrous[2]	15-30	75-90	85-93	27	27.0	43.0	47.8	2.17

[1]Lactose Monohydrate, NF Modified Spray Dried (Fast-Flow Form 316). [2]Lactose, Anhydrous, NF, Direct Tablet Grade. Sieve Results from Handbook of Pharmaceutical Excipients, The Pharmaceutical Press, 1994.

Table 4. Physical Properties of Different Tablet Blends in Study – Compound F

Formu-lation #	% Glidant (wt/wt)[2]	% Lubricant (wt/wt)[3]	Lube Time (min)[4]	Critical Orifice Index (mm)	% Compress.	Angle of Repose (degrees)	Composite Index	Principal Component Score
Cmpd. F[1]-Blend 9	0.1	1	2	18	23.8	41.0	61.2	0.945
Cmpd. F-Blend 11	0.3	1	2	13	22.3	35.0	71.8	-0.138
Cmpd. F-Blend 5	0.1	0.5	5	15.5	23.5	39.0	65.6	0.532
Cmpd. F-Blend 7	0.5	0.5	5	9.5	15.7	37.0	78.8	-0.853
Cmpd. F-Blend 6	0.1	1.5	5	15.5	23.4	40.0	64.9	0.610
Cmpd. F-Blend 8	0.5	1.5	5	15.5	20.5	34.0	70.9	-0.176
Cmpd. F-Blend 10	0.1	1	10	20	23.7	42.0	58.4	1.19
Cmpd. F-Blend 12	0.5	1	10	13	19.9	39.0	70.7	-0.004

[1] Proprietary formulation blend containing actives GR109714X, GR63367X, 1592U89. [2]Glidant- Amorphous Fumed Silica. [3]Lubricant- Magnesium Stearate.
[4]Lubrication time in twin shell V-blender

Methods

Vibrating Spatula

The experimental setup included a vibrating spatula (Hierath Automated Systems Corp, ISO-G4107) or trough, which cascades powder onto a mass balance that has been interfaced with the vibrating spatula. Approximately 100 mL of powder is placed behind a removable gate 3 inches from the rear of the spatula, with the vibration amplitude set at 40%. The gate is removed and the mass of accumulated powder is recorded at 10-second intervals. Steeper slopes of mass accumulated vs time plots represent better flow.

Angle of Repose

Approximately 200 mL of powder is poured through a stainless steel funnel from a height of 6 inches onto a level bench top. The angle that the side of the conical heap makes with the horizontal plane is recorded as the angle of repose. Lower angle of repose values represent better flow.

Percent Compressibility Index

Approximately 100 mL of powder is gently poured into a tared graduated cylinder and the initial volume and weight of the material is recorded. The graduated cylinder is placed on a tap density tester and the final volume is recorded after 200 taps (Vanderkamp Tap Density Tester, VanKel Industries, 36 Meridian Rd, Edison, NJ, 08820). Lower percent compressibility values represent better flow.

Percent Compressibility Index = 100 × (Tap density – Bulk density)/ Tap Density

Critical Orifice Diameter

The bottom discharge port of the test device (Flodex Tester, Hansen Research Corp, 9810 Variel Ave., Chatsworth, CA, 91311) is fitted with an appropriate orifice diameter ring (typically 16 mm) and a cylindrical hopper is filled with sample powder to a height within 1 cm of the top by pouring the material through a stainless steel funnel. The material is consolidated for 30 seconds and then the shutter release lever is slowly turned to the open position. A test is deemed successful if an open cavity is visible through the bottom when viewed from the top on 3 successive tries. The flowability index is given as the orifice diameter of the smallest opening through which the powder falls freely. Smaller values indicate better flow.

Avalanching Methods

Approximately 20 g of material is loaded into a translucent rotating drum tester (Aeroflow® Device, Amherst Process Instruments, Mountain Farms Technology Park, Hadley, MA, 01035-9547; Figure 1).

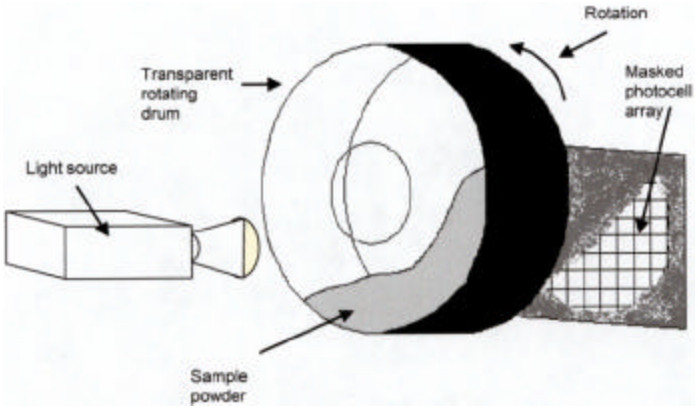

Figure 1. Aeroflow™ flow characterization instrument.

The drum is rotated slowly at a rate of 120 seconds/revolution. A photocell array detector measures total number of avalanches; the average time between avalanches is calculated. Lower average time between avalanches indicates better flow.

Principal Components Analysis

Principal components (PC) are specially constructed linear combinations of the original variables (ie, the different test method results). The first PC component explains the greatest variability in the original variables. The second principal component is orthogonal to the first and accounts for the largest remaining variability. Let x_1 and x_2 be the 2 original variables. Let us assume that these variables are centered and scaled (if the variables are centered, the principal components will go through the origin).

First PC score = $p_1x_1 + p_2x_2$ (Eq. 1)

The scores are calculated using Equation (1): p_1 represents the cosine of the angle between x_1 and the principal component; p_2 is the cosine of the angle between x_2 and the principal component.

In PC analysis, the original coordinate axes are rotated in such a way that the first principal component lines up along the direction of the most variability. The distance of each point (from the origin) along the principal component direction is the principal component score for that point (Figure 2).

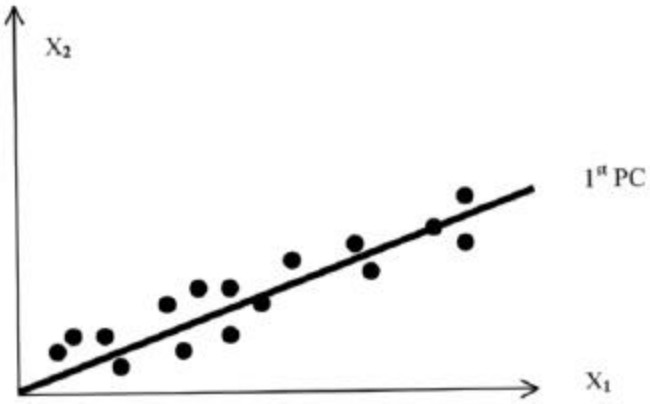

Figure 2. Representative schematic of first principal component.

RESULTS AND DISCUSSION

Results

Vibrating Spatula

Preliminary results with the vibrating spatula were encouraging, as slopes of mass accumulated vs time curves were significantly different for the initial excipients studied(Figure 3).

However, as bulk flow properties became more similar, a comparison of slope values was inadequate to differentiate flow profiles, so an enhanced data collection system capable of acquiring data at 150 millisecond intervals was utilized. This higher resolution introduced irregularities in the mass accumulated vs time plots including multiple regions of linearity (Figure 4).

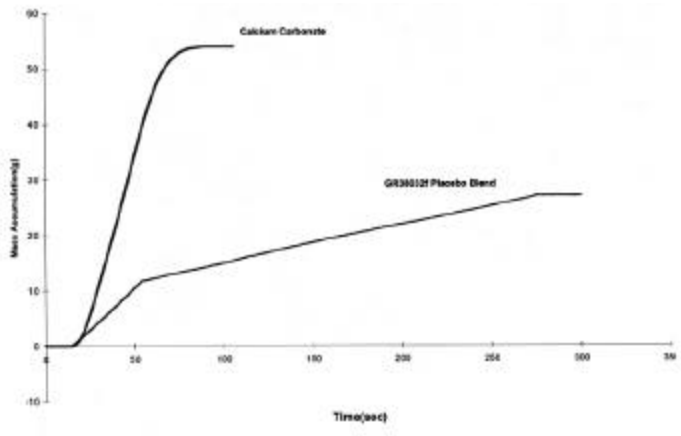

Figure 3. GR38032f placebo blend/calcium carbonate — mass accumulated vs time.

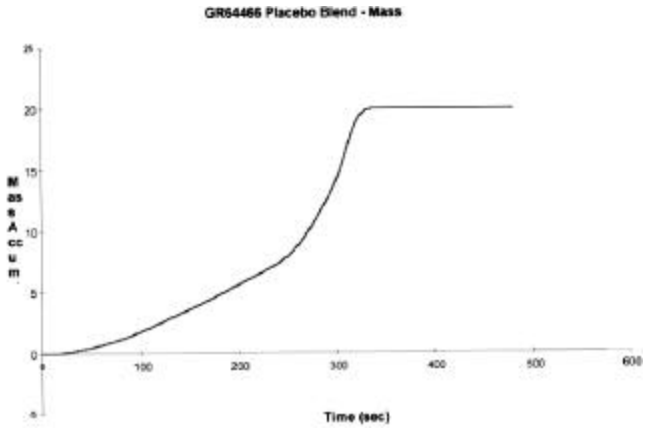

Figure 4. GR64466 placebo blend – mass accumulated vs time.

Efforts to standardize choice of linear regions and use of correlation coefficients of data points along the chosen linear portion of the mass accumulated vs time plots still failed to provide a discriminating method of analysis as all values > 0.999 (data not shown). Hickey and Concessio have demonstrated that it is possible to describe and characterize these flow irregularities from a vibrating spatula using fractal dimensions [5] Although this method could be used to quantify the uniformity of flow, it was not pursued further as it would involve a time-consuming and tedious analysis not suitable for a simple bench-top test.

Reproducibility of Individual Flow Tests

Measurements on 5 sets of Supertab, Avicel PH102, and Ceolus samples were recorded in order to study the reproducibility of the 3 flow tests. The estimated standard deviation of the experimental error associated with percent compressibility was 0.53 SD, 0.62 SD for critical orifice, and 1.1 SD for angle of repose measurements This suggests that percent compressibility and critical orifice tests are somewhat more reproducible than angle of repose.

Composite Index

On completion of the individual flow tests, a weighted composite index was generated to designate a single score for each material. As the relative contribution of each individual test to the "true" composite score was unknown, a decision was made to assign an arbitrary value of one third to each of the 3 methods and test the performance of the model against materials with "known" flow properties. Therefore, this empirical composite index was devised to yield a score of 100 for an optimum result for each of the 3 flow methods and each test result was transformed to a value between 0 and 33 1/3. These transformed values are summed to yield the composite flowability index. The raw data transformations are as follows:

Critical Orifice: Point Value = -1 1/9 * result + 37 7/9

%Compressibility: Point Value = -2/3 * % compressibility result + 36 2/3

Angle of Repose: Point Value = -2/3 * angle of repose result + 50

The blends and excipients were subdivided into 3 basic flow categories based on their respective composite flowability index scores. Tables 5, 6, and 7 show good, average, and poor flow materials, respectively.

Table 5. Excipients Demonstrating Good Flow Characteristics (Ranked best to worst by Composite Index)

Compound Name	Number	Critical Orifice Index (mm)	% Compress	Angle of Repose (degrees)	Composite Index	Principal Component Score
Super Tab[1]	1	4.5	17.7	21.0	93.6	-2.50
Spress® [2]	2	4	18.0	22.0	93.3	-2.42
Calcium Carbonate	21	4	8.8	32.0	92.8	-2.38
BWW-01C1 SR Gran A	3	5	18.0	24.0	90.9	-2.17
Lactose, spray dried	22	8	9.2	31.0	88.8	-2.09
Dibasic Cal. Blend	4	4	20.0	30.0	86.7	-1.55
GG818 Blend	23	7	14.4	33.0	85.1	-1.53
Avicel® PH200	8	8.5	13.6	34.0	83.3	-1.39
BWW-01C1 SR Gran B	5	4	19.0	33.0	85.3	-1.37
GR64466 Placebo Blend	6	6	14.5	36.0	84.1	-1.34
GR64465 Placebo Blend	7	5	19.0	34.0	83.6	-1.20
1592U89 Blend	9	5.5	18.6	36.5	81.6	-0.975
Cmpd. F[3]–Blend 7	10	9.5	15.7	37.0	78.8	-0.853
Avicel® PH102 Blend	11	14.5	26.0	28.0	72.3	-0.291
Anh.Lactose Blend	12	15	25.7	29.0	71.3	-0.188
Cmpd. F-Blend 1	24	11.5	23.1	37.0	71.6	-0.184
Cmpd. F–Blend 8	25	15.5	20.5	34.0	70.9	-0.176
Cmpd. F-Blend 11	41	13	22.3	35.0	71.8	-0.138
Avicel® PH102	13	15.5	19.2	36.0	70.4	-0.117
Cmpd. F-Blend 12	26	13	19.9	39.0	70.7	-0.004

[1]SuperTab® - Lactose Monohydrate USP, Spray Dried.
[2]Spress® - Pre-gelatinized Corn Starch NF.
[3]Proprietary formulation blend containing actives GR109714X, GR63367X, 1592U89.

Table 6. Excipients Demonstrating Average Flow Characteristics

Compound Name	Numbe	Critical Orifice Index (mm)	% Compressibility	Angle of Repose (degrees)	Composite Index	Principal Component Score
1555U88 Placebo	14	17	27.0	28.0	68.9	0.011
Avicel® PH302	27	14.5	17.2	43.0	68.2	0.230
Cmpd. F[1] –Blend 2	28	17.5	18.3	39.0	66.8	0.234
GI262570X	31	17.5	22.4	37.0	65.4	0.427
Cmpd. F –Blend 4	29	14.5	21.5	41.0	66.7	0.442
Cmpd. F – Blend 5	30	15.5	23.5	39.0	65.6	0.532
Cmpd. F – Blend 14	33	17.5	22.6	38.0	64.6	0.533
Avicel® PH101	15	19	21.4	38.0	63.7	0.552
Cmpd. F- Blend 6	32	15.5	23.4	40.0	64.9	0.610
Cmpd. F- Blend 3	34	17	25.0	37.0	64.2	0.619
Avicel® PH301	36	19.5	21.4	41.0	61.2	0.857
Cmpd. F- Blend 9	35	18	23.8	41.0	61.2	0.945

[1] Proprietary formulation blend containing actives GR109714X, GR63367X, 1592U89.

Table 7. Excipients Demonstrating Poor Flow Characteristics

Compound Name	Number	Critical Orifice Index (mm)	% Compressibility	Angle of Repose (degrees)	Composite Index	Principal Component Score
GR38032f Placebo Blend	37	24	19.7	36.0	60.6	0.648
Cmpd. F - Blend 13	38	19.5	25.1	39.0	60.0	1.01
Cmpd. F - Blend 10	16	20	23.7	42.0	58.4	1.19
BW509U81	17	28.5	13.0	46.0	53.4	1.30
GI275919X 25mg	39	23.5	30.0	35.0	55.0	1.44
BW248U74	18	22.5	29.0	41.0	52.8	1.79
Lactose, Anhydrous	40	27	27.0	43.0	47.8	2.17
GI275919X 100mg	19	24	34.7	40.0	47.9	2.35
Ceolus[2]	20	34	37.9	55.0	24.7	4.79

[1]Proprietary formulation blend containing actives GR109714X, GR63367X, 1592U89.

[2]Ceolus – Microcrystalline Cellulose, NF, KG-801

Formulation Blends

Materials that exhibited good flow characteristics (Table 4) provide a representative example of the full scope of individual and composite method performances. A comparison of 2 tablet formulations that differ only in the level of glidant would predict that the formulation with higher glidant quantities would demonstrate better flow properties. Cmpd F-Blend 11 (0.3%-Table 4) does perform better than Cmpd F-Blend 9 when measured by critical orifice (13 vs 18), angle of repose (35° vs 41°), but the percent compressibility results (22.3 vs 23.8) are comparable. The composite index results for these compounds show a much greater resolution (71.8 vs 61.2). Considerable differences in flow properties would be anticipated with a 5-fold difference in glidant levels with Cmpd F-Blend 12 (0.5%) and Cmpd F- Blend 10 (0.1%) and these are confirmed by critical orifice (13 vs20) and % compressibility (19.9 vs 23.7) methods. However, the angle of repose (39 vs 42) may be too close given the larger random variability associated with results based on this method.

The composite index results do reflect the considerable difference in flow properties (70.7 vs 58.4). This pattern is repeated with another comparison of materials with a 5-fold glidant level difference: Cmpd F-Blend 8 (0.5%) and Cmpd F-Blend 6 (0.1%). Here, the percent compressibility (20.5 vs 23.4) and angle of repose (34 vs 40) results show some difference but the critical orifice results are identical (15.5). The best resolution is offered by the composite index (70. 9 vs 64.9).

Lactose

Another ranking type comparison was made with different forms of lactose used in pharmaceutical formulations. Spray dried (SuperTab® FMC Corp, 2000 Market St, Philadelphia, PA. 19103), modified spray dried (Fast-Flow® Form 316, Fast-Flo-Foremost McKesson Foods Group, Crocker Plaza, One Post St. San Francisco, CA 94101), and anhydrous lactose were tested with expectations that flow properties would decrease in that order, respectively. The reasoning was that the SuperTab® material showed a higher

distribution of larger particles and a narrower distribution than the Fast-Flow® material. Also, material manufacturers had conducted tabletting studies with these materials and the SuperTab® material demonstrated superior flow properties as measured by tablet weight coefficient of variations. Finally, both sphere-shaped spray-dried materials would flow better than the anhydrous lactose. Critical orifice and angle of repose measurements predicted flow as expected (Table 3) but percent compressibility results (17.7 vs 9.2 vs 27) suggest that the Fast-Flow® material flows better than the SuperTab® lactose. This is not surprising. The SuperTab® lactose manufacturer has engineered the material such that the interaction of amorphous lactose covering the surface of each lactose crystal acts as a binder increasing the bond strength between crystal surfaces during compaction, resulting in higher percent compressability results. Again, the ranking suggested by the composite index (93.3 vs 88.8 vs 47.8) was consistent with theory.

Microcrystalline Cellulose

The major difference between the 3 microcrystalline cellulose excipients (Avicel® PH 101, PH102, and PH200) was the mean particle size (Table 2). A comparison of microcrystalline cellulose materials' nominal mean particle sizes (see Table 2) would suggest that the rank order of flow properties would be Avicel PH200>Avicel PH 102>Avicel PH 101. Although all methods predict flow as expected with critical orifice and percent compressibility test results demonstrating good resolution, the relative difference in angle of repose results (34° vs 36° vs 38°) is not as discriminating as one might predict based on the large differences in the mean particle sizes of the materials.

Principal Components Analysis

As mentioned earlier, the weighting scheme for the generation of the empirical composite flow index was chosen arbitrarily. The validity of this composite index was assessed by comparison to an index provided by principal components analysis. The first Principal Components scores (PC) based on different measures were used as indexes of flowability.

x_1 = critical orifice diameter

x_2 = % compressibility

x_3 = angle of repose

Since different flow characteristics are measured on different scales (in different units), the data values for each flow property were transformed to have a mean of 0 and a standard deviation of 1. The first principal component accounted for 72.8% of the variation in the data.

$$score\ (1^{st}\ principal\ \ component\ ) = 0.637 \times \frac{x_1 - mean\,(x_1)}{std\ .dev\ .(x_1)} + 0.532 \times \frac{x_2 - mean\,(x_2)}{std\ .dev\ .(x_2)} + 0.558 \times \frac{x_3 - mean\,(x_3)}{std\ .dev\ .(x_3)}$$

(Eq. 2)

The coefficient of the critical orifice index term is higher than the coefficient of the other terms, (ie, the critical orifice term contributes most to the principal component scores).

Avalanching Methods

A comparison of avalanching flow determination results and principal components showed very little agreement in the ranking of flow materials. Twenty of the compounds were ranked according to flowability based on average time between avalanches and principal component scores with 1 the best and 20 the worst (Table 8).

The avalanching method ranked the microcrystalline cellulose materials different from all of the other methods, including the composite index. Perhaps the most significant difference was the poor flow ranking the method assigned to Super Tab ®, which all other methods ranked as one of the best flow materials tested. A comparison of the avalanching method results and principal components results shows no correlation (Figuzre 5, $R^2 = 0.342$).

These results would confirm visual observations made during test runs. As the powder drum rotated, the powder bed would often shift or cascade en mass as it climbed the drum outer wall. This event was not a true avalanche but would have been interpreted as such by the instrument.

Table 8. Avalanching Rankings vs Principal Component Score Ranking

Compound name	Com pound Number	Avalanching Method Rank	Principal Components Rank
Dibasic Cal. Blend	4	1	4
GR64465 Placebo Blend	7	2	7
1592U89 Blend	9	3	9
GR64466 Placebo Blend	6	4	6
BWW-01C1 SR Gran B	5	5	5
BWW-01C1 SR Gran A	3	6	3
Anh.Lactose Blend	12	7	12
Cmpd.F[1]- Blend 7	10	8	10
BW509U81	17	9	17
Avicel® PH102 Blend	11	10	11
Cmpd. F Form. 10	16	11	16
Spress®	2	12	2
Avicel® PH102	13	13	13
Avicel® PH200	8	14	8
Super Tab[2]	1	15	1
Avicel® PH101	15	16	15
1555U88 Placebo	14	17	14
Ceolus®	20	18	20
GI275919 100mg	19	19	19
BW248U74	18	20	18

[1]Formulation blend containing actives GR109714X, GR63367X, 1592U89.
[2]Avalanche method determinant used here is time between avalanches.

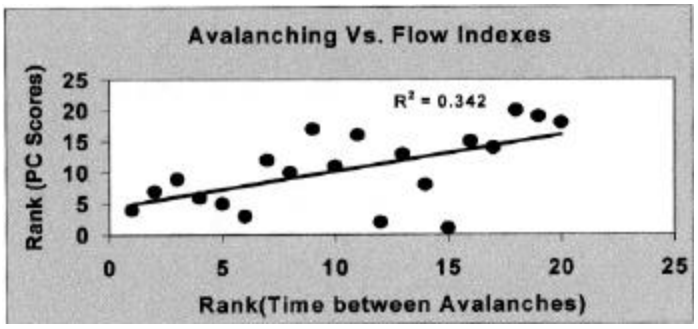

Figure 5. Avalanching ranking vs PC scores ranking.

Crowder et al have evaluated the avalanching method of flow characterization and suggest that the data may best be analyzed by a different approach than the time between avalanches [10]. These investigators propose that the variability in the size of powder avalanches represents a more discriminating method of determining flow properties of similar materials and the avalanche size standard deviation provides a quantitatve measure of the uniformity of flow.

The 41 powders tested have been sorted by flow properties (best to worst) as judged by principal component scores (Tables 5, 6, 7). Although the order suggested by composite index score reveals some minor differences, the two methods show good agreement. This observation is confirmed by a statistical comparison of the two indexes, which reveals an excellent correlation (Figure 6; $R^2 = 0.993$).

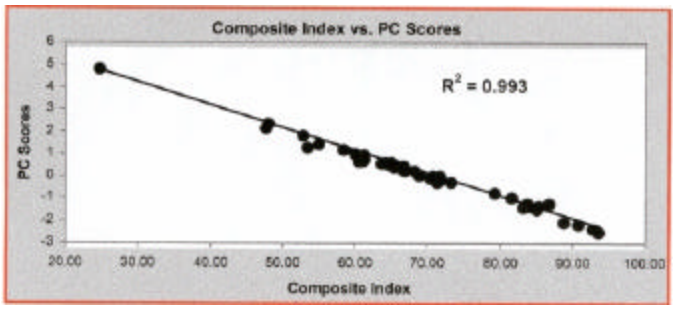

Figure 6. Composite index vs PC scores.

Principal component scores were also compared with individual method results to determine if any single test might predict flow properties better than others. A comparison of percent compressibility (Figure 7; $R^2 = 0.617$) and angle of repose (Figure 8; $R^2 = 0.679$) to principal component scores show a poor correlation.

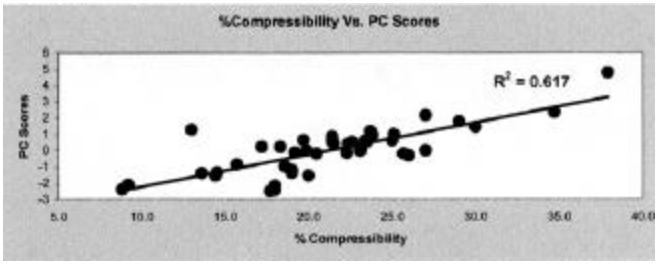

Figure 7. Percent compressibility vs PC scores.

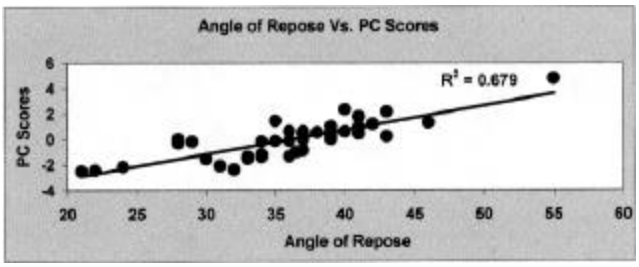

Figure 8. Angle of repose vs PC scores.

Alternatively, critical orifice results (Figure 9; R^2 = 0.887) demonstrate a higher correlation and may indicate that this method may be the best single flow indicator of the individual tests studied.

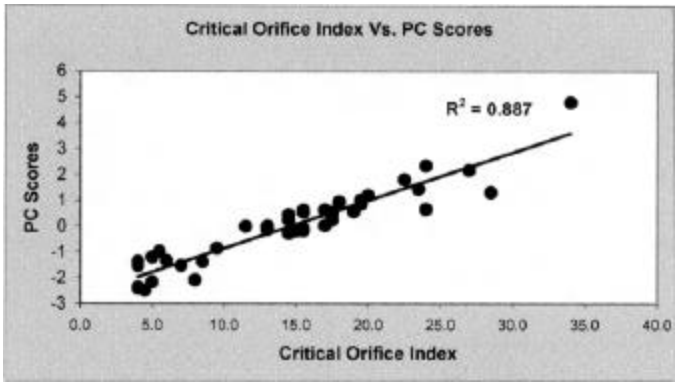

Figure 9. Critical orifice index vs PC scores.

Principal component analysis also corroborates the higher critical orifice coefficient term in the principal component score equation (Equation 2). These findings would confirm that the empirical composite flow index, composed of test methods with equal weights, provides a better prediction of flow properties than any single test alone. Further, the weighting assigned to test methods by the principal components analysis may represent an even more accurate composite index and a reasonable approach to the quantification of powder flow.

In general, for most of the methods, results for the 41 powders tested were consistent with formulator experience. However, each of the individual tests failed at some point to measure and rank the flow properties of the powders in accordance with theory or cited vendor references. Also, some of the methods could not detect small differences in flow between similar materials. This can be partially explained by variations in the mechanics of performing the flow tests or the interpretation of results. For example, the angle of repose can vary depending on the method used to form the cone and nature of the base of powder. Distortions in the peak of the cone are affected by the impact of the powder added. Also, the base of the powder can affect the angle of repose by altering the cone formation. . Although the compressibility index measurement is rather straightforward, several factors can influence final results, including the diameter of the cylinder used , mass of material tested, and rotation of the sample during the tap test. Flow through an orifice is also dependent on several variables in the test methodology. Type of container material, diameter and height of powder bed, as well as the diameter and shape of the orifice are important considerations that may affect test results. Amidon et al have recommended procedures for the measurement of flow properties with these methods [11].

The failure of individual tests to fully and accurately characterize powder flow is not unexpected as each method challenges separate components of flow. Carr proposed that the angle of repose was a valid characterization of flow because it provided an indirect measurement of the shape, size, porosity, cohesion, fluidity, surface area, and bulk properties of the material. He suggested that percent compressibility indicated the uniformity in size and shape, deformability, surface area, cohesion, and moisture content of the test materials [1]. The critical orifice diameter is a direct measure of powder cohesion and arch strength [12]. Clearly, powder flow is a complex phenomenon, which cannot be fully characterized by any single test methodology.

CONCLUSIONS

The results of this study demonstrate that a statistical index derived from principal components analysis of individual tests is a reasonable approach to the quantification of powder flow. This approach also provides a better characterization of powder flow than individual tests alone and is based on simple, reliable bench tests currently available to the formulation scientist.

Additional work is planned to further refine the composite index. The possibility of modifying current test methods will be evaluated as well as the need to modify raw data transforms. As the database of tested excipients and blends is expanded, additional principal components analyses will be conducted to determine if test method coefficients need to be revised. Practical applications of this work include the identification of minimal acceptable flow properties of new drug formulations and recommendations for selection of content uniformity sampling thieves based on characterization of blend flow properties.

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