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RESEARCH PAPER

# Investigating the Effects of Excipients on the Powder Flow Characteristics of Theophylline Anhydrous Powder Formulations

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## ABSTRACT

Pharmaceutical excipients may have a great effect on properties affecting tablet production. To determine if formulations containing theophylline anhydrous would have properties allowing them to be easily tableted, functional parameters affecting powder flow were evaluated. The Carr Flowability Indices were used for this evaluation. Formulations to be studied include theophylline anhydrous as the active ingredient, hydrous lactose and dicalcium phosphate dihydrate as diluents, polyvinylpyrrolidone as a binder, and fumed silica as a flow promoter. The effect of each component on powder flow is discussed.

*Key Words:* Powder flow; Carr indices.

## INTRODUCTION

Powder flow is defined as the differential movement of powder constituent particles when subjected to external force. Flow is an important property in tablet and capsule production, because an adequate level of powder flow is needed to ensure a constant fill of the tablet die or the capsule shell during production. The absence of acceptable flow would lead to weight variation and content uniformity problems based on the nonuniform fill of the die or shell.[1]

### Influences That Affect Powder Flow

Pharmaceutical powders may be categorized as cohesive or free-flowing. A number of factors affect powder flow properties, including changes in particle shape, size, density, electrostatic charge, and adsorbed

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moisture.[2] Changes in these factors may be a result of processing or formulation procedures.

Particle shape is an important factor in powder flow. Powders consisting of spherical particles tend to have better flowability as the spherical shape reduces interparticle friction.[3]

Powders composed of large particles tend to flow better than those composed of small particles. With particles less than 10 μm, powder flow is restricted because the cohesive forces between particles are of the same magnitude as gravitational forces. For this reason, if a powder contains a large portion of small particles or "fines," it may be beneficial to remove the fines or adsorb them onto the larger particles.[4]

Particles with high-density and low-internal porosity tend to possess free-flowing characteristics. For this reason, powders that are porous a of a low density are often densified by slugging or granulation.[5]

Adsorbed moisture may also lead to powder flow problems because of the formation of liquid bridges between the particles.[6,7] The powder then flows poorly on standing and caking may develop. Drying the particles or adding a moisture adsorbent, such as fumed silica, reduces the cohesiveness and allows the powder to flow.[4]

### Methods for Powder Flow Measurements

Because of the importance of powder flow in the drug development process, preformulation powder flow studies are routinely conducted to qualitatively assess the pharmaceutical consequences of each process improvement and provide direction for the drug development team. A number of tests have been used in the pharmaceutical industry for this reason.[1] Powder behavior is, however, multifaceted, and no single test method has been found to adequately characterize the flow properties of pharmaceutical powders.[8]

Flow rate data are difficult to compare to literature values, because it is critically dependent on the method used to measure it. Several factors affect the results obtained. These include the diameter and shape of the orifice, the type of container used to contain the powder (cylinder, funnel, or hopper from production equipment), the material the container is manufactured from (metal, glass, or plastic), and the diameter and height of the powder bed. The method of measuring powder flow rate may also be a factor. Typically, flow rate is measured continuously using an electronic balance with some sort of recording device, but discrete samples may also be measured. In this case, the measurement would be either the amount of time a given amount of material would take to pass through the orifice, or the amount of material that could pass through in a given amount of time.[8]

Angle of repose is determined by a relatively simple technique and is used for measuring resistance to particle movement. Angle of repose is defined as the maximum angle that can be obtained between the free-standing surface of a powder heap and the horizontal plane, and gives a qualitative assessment of the internal cohesive and frictional effects of a powder under low levels of external loading. Such situations include powder mixing, tablet die, and capsule shell filling operations.[9] Rougher and more irregular powders have higher angles of repose because of the frictional increase caused by the irregular surface.[10] Angle of repose is not universally considered a good method of measuring powder flow. Experimental difficulties arise because of segregation of material and consolidation or aeration of the powder as the cone is formed. Angle of repose is still considered useful by many, but is highly dependent on method used because it is not an intrinsic property of a powder.[8]

The compressibility index and the related Hausner ratio have recently become popular methods of predicting powder flow characteristics. Carr proposed using the compressibility index as one measure of flow evaluation based in part on the influence many properties that affect flow have on the compressibility index. He considered the compressibility index to be an indirect measure of these properties, which include bulk density, size and shape, surface area, moisture content, and cohesiveness of the material.[8,11]

In the 1960s, Ralph Carr, Jr. proposed methods to compare the flow properties of various engineering materials and devised an index system by which to evaluate flow. Carr stressed the importance of using multiple measures of flow to properly evaluate a material because no single type of measurement adequately assesses all the factors that influence flow. The Carr index system was devised to assist the pilot-plant scientist in gaining knowledge on how various dry materials will flow in bins, hoppers, and feeders. This knowledge, in addition to allowing the engineers to properly evaluate the raw materials, may assist in the design of appropriate equipment for the materials they will be working with. The need for effective agitation, rotary valves to meter out material under control, and vent hoppers to remedy problems caused by air being forced into the hopper may all be anticipated based on the index parameters.[8,11–13]

In an effort to make obtaining data for the Carr indices more convenient for the pharmaceutical

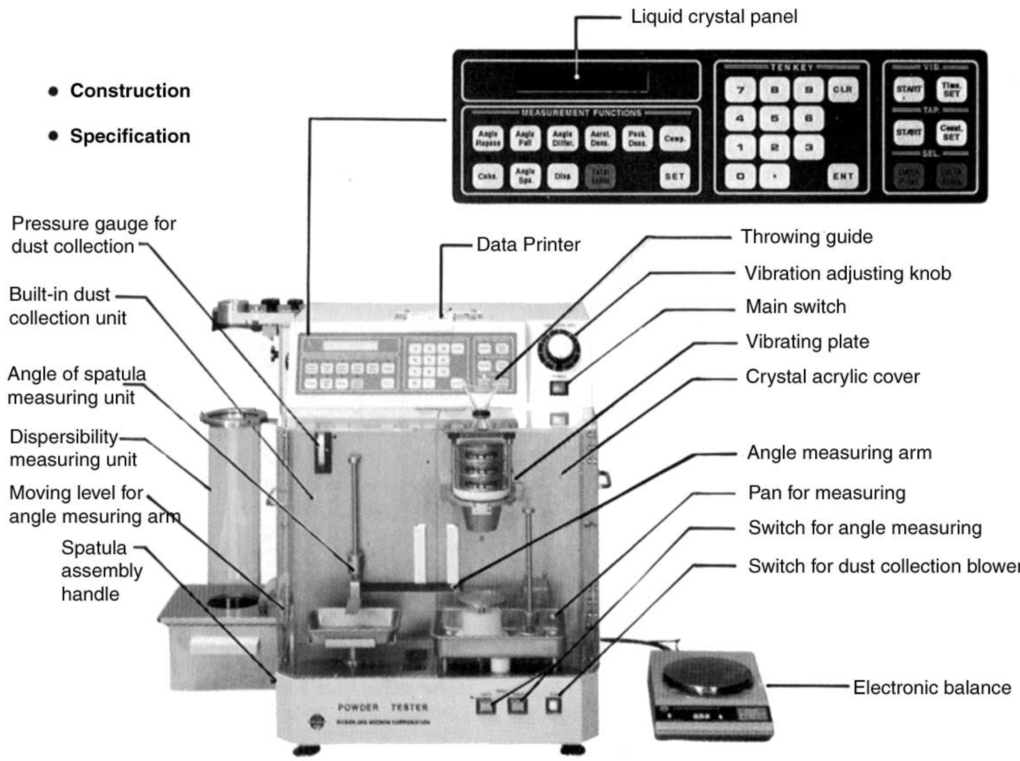


***Figure 1.*** Hosakowa micron powder characteristics tester. (Courtesy of Hosakowa micron powder systems.)

scientist, Hosakowa Micron recently developed the Micron Powder Characteristics Tester (Fig. 1). This instrument was designed as a rapid mechanical aid to quickly arrive at a "flowability index" for any powder, and measures or calculates the eleven parameters used to determine this index in a more convenient fashion than was previously possible.[12,14]

***Table 1.*** Ranges for pharmaceutical excipients in theophylline anhydrous powder formulations.

| Pharmaceutical excipient | Range in powder formulation |
|---|---|
| CABOSIL M5P | $0 \leq X_1 \leq 4\%$ |
| PVP | $0 \leq X_2 \leq 14\%$ |
| Lactose hydrate | $0 \leq X_3 \leq 60\%$ |
| Dicalcium phosphate | $0 \leq X_4 \leq 60\%$ |

## MATERIALS AND METHODS

### Preparation of Powder Formulations

The materials used in this study were theophylline anhydrous U.S.P. (Amend Drug & Chemical Co., Irvington, NJ), fumed silica (Cabosil M-5P®, Cabot Corporation, Tuscola, IL), polyvinylpyrrolidone (PVP; Kollidon-30®, BASF, Parsippany, NJ), lactose hydrous, NF grade (Sheffield Products, Norwich, NY), and unmilled dicalcium phosphate dihydrate (DI-TAB®, Rhone Poulenc Basic Chemicals Co., Shelton, CT). All materials were used as received.

The powder formulations studied consisted of combinations of drug, diluent, binder, and flow promoter. Not all formulations contained all components. Component combinations were generated by the extreme vertices statistical method of McLean and Anderson. All formulations contained theophylline anhydrous at 40% of the total formulation weight.[15] The use of fumed silica in ranges up to 4%, which is substantially higher than that typically used to enhance powder flow, is based on our previous work.[16] Percentages of other components may be found in Table 1. Powder formulations were prepared by placing the components for each powder formulation in a plastic bag (Tenneco Food and Utility Bag: 10″ × 8″) and blended by shaking for 5 min in a rotating manner. Samples were then screened through a 30-mesh wire screen.[16]

### Flowability Determination

Powder formulations were then analyzed for powder flow properties using a Powder Characteristics Tester (Hosakowa Micron Powder Systems, Summit, NJ). A battery of tests described by Carr were performed using this instrument, leading to the determination of flowability and floodability indices for the powder formulations in question. Descriptions of these indices and the parameters used to determine them are discussed in the following paragraphs.[11–13] The meaning of these parameters is described in the following manner. Precise means of calculation may be found in the literature.[11–14]

Angle of repose ($\Phi$) is defined as the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane, and is a simple method of measuring resistance to particle movement. The angle of repose gives a qualitative assessment of internal cohesive and frictional effects. Angles up to 40° indicate reasonable flow potential and those with angles greater than 50° exhibit poor or absent flow. Angle of repose measurements are sensitive to moisture content and may provide a means of monitoring batch-to-batch differences to this parameter.

Angle of fall is an angle of repose measured from a powder heap to which a defined vibration has been given, such as the dropping of a weight next to the cone produced when measuring the original angle of repose. This angle is generally smaller than the angle of repose, and a small number is indicative of a material that is free-flowing. However, materials that exhibit unstable, liquid-like flow also have small angles of fall. This situation is referred to as floodable flow and can be discontinuous, gushing, and uncontrollable. It occurs when a mass of particles become fluidized by air. When a powder contains air within its layers, the cone as a whole collapses during the measurement.[12]

Angle of difference is a calculated parameter. It is defined as the difference between the angle of repose and the angle of fall. A large angle of difference is characteristic of a material with a fluidizing problem.[12]

Density is defined as the ratio of mass to volume of a material. The powder flow analyzer measures two densities: the aerated or loose bulk density and the packed bulk density. Aerated bulk density is determined by allowing powder to flow from a hopper into a measuring cup, which is then leveled and weighed. Packed bulk density is obtained by placing the cup in an automatic tapping device. These parameters are used for further calculation.[12]

Compressibility is calculated from aerated bulk density ($A$) and packed bulk density ($P$). Compressibility above 20% indicates a powder that is not free-flowing and that has a tendency to create bridges in the hopper. Materials with compressibilities of 40–50% are particularly difficult to discharge from the hopper.[12]

Cohesion is a descriptive measure of interparticle forces based on the behavior of the material during sieving. Powders with higher cohesion percentages are less flowable, and care must be taken in designing feeders, hoppers, and other handling equipment.[9,12]

Angle of spatula is determined by measuring the angle of powder on a spatula lifted from a powder bed and averaging that number with the angle of powder remaining on the spatula after it falls from a set height. This parameter gives a relative angle of internal friction for a material. Angle of spatula is always greater than the angle of repose, and large numbers indicate poor flowability.[12]

Dispersibility is a measure of fugacity, dusting, and fluidizing characteristics of powder. Indexes higher than 50% indicate powders with high fluidizing characteristics.

Flowability is determined by using the Carr flowability table (Table 2) and the values obtained for angle of repose, compressibility, angle of spatula, and cohesion. The measurements obtained for these four parameters are converted into index numbers using the table. These index numbers are then totaled to give the flowability index. High numbers (80–100) indicate that bridge-breaking measures are unnecessary. Numbers below 60 indicate that flowability is poor, and vibration or special apparatus and techniques may be required to get the material to flow through a hopper.[12]

Carr also expressed powder behavior in terms of floodability, a parameter based on: flowability, angle of fall, angle of difference, and dispersibility. High numbers indicate high floodability, which is characterized by liquid-like, unstable flow. Use of rotary seals or agitation of the hopper may be necessary with floodable materials to prevent bridge or arch formation.[12]

## RESULTS AND DISCUSSION

### Statistical Analysis of Powder Flowability Data

Statistical analysis of the powder characteristics data was determined by using JMP statistical

***Table 2.*** Parameters affecting the Carr flowability index.[12]

| Degree of flowability | Flowability index | Angle of repose (°) | Compressibility (%) | Angle of spatula (°) | Uniformity (no.) |
|---|---|---|---|---|---|
| Excellent | 90–100 | 25–30 | 5–10 | 25–31 | 1–5 |
| Good | 80–89 | 31–35 | 11–15 | 32–38 | 6–8 |
| Fair | 70–79 | 36–40 | 16–20 | 39–45 | 9–12 |
| Passable | 60–69 | 41–45 | 21–25 | 46–60 | 13–17 |
| Poor | 40–59 | 46–55 | 26–31 | 61–76 | 18–22 |
| Very poor | 20–39 | 56–65 | 32–37 | 76–90 | 23–7 |
| Very, very poor | 0–19 | 66–90 | >38 | >91 | >36 |

Oneway Anova

Summary of Fit

| | |
|---|---|
| RSquare | 0.803707 |
| RSquare Adj | 0.708727 |
| Root Mean Square Error | 3.182614 |
| Mean of Response | 46.75806 |
| Observations (or Sum Wgts) | 93 |

Analysis of Variance

| Source | DF | Sum of Squares | Mean Square | F Ratio |
|---|---|---|---|---|
| Model | 30 | 2571.3065 | 85.7102 | 8.4618 |
| Error | 62 | 628.0000 | 10.1290 | Prob>F |
| C Total | 92 | 3199.3065 | 34.7751 | <.0001 |

***Figure 2.*** Statistical analysis of the Carr Flowability Index for theophylline anhydrous powder formulations. Anova, analysis of variance; Adj, adjusted; Wgts, weights.

software. Triplicate measurements of each mixture were used in the statistical calculations. Analysis of variance testing yielded an $F$ ratio for each characteristic. If the observed $F$ ratio was greater than the critical $F$ value of 1.65, then the null hypothesis that all samples tested would have the same mean value for that characteristic was rejected, and the difference between the means was deemed statistically significant. The analysis of variance for flowability is found in Fig. 2. The $F$ ratio of 8.4618 is greater than the critical $F$ value of 1.65, leading to rejection of the null hypothesis. Flowability is therefore found to be statistically different among the sample formulations studied.

Sample formulations were next examined on the basis of whether they were binary, ternary, quaternary, or five component mixtures. By this method, the effect of an individual component on the flowability properties of sample formulations was more apparent. Composition of individual formulations may be found in Table 3. When tested individually, theophylline anhydrous and fumed silica exhibited extremely poor individual flow properties, and no Carr indices could be obtained for them. Carr indices could be obtained for the other components of the sample formulations, with PVP yielding a flowability index of 60.0, which would be considered passable, using Carr terminology. Dicalcium phosphate dihydrate exhibited good flowability (83.5), whereas

***Table 3.*** Composition of individual theophylline anhy-drous powder formulations.

| | % Present in formulation | | | | |
|---|---|---|---|---|---|
| Formulation | T | L | D | P | C |
| 16 | 40 | 60 | — | — | — |
| 17 | 40 | — | 60 | — | — |
| 18 | 40 | 46 | — | 14 | — |
| 19 | 40 | 56 | — | — | 4 |
| 20 | 40 | 42 | — | 14 | 4 |
| 21 | 40 | — | 46 | 14 | — |
| 22 | 40 | — | 56 | — | 4 |
| 23 | 40 | — | 42 | 14 | 4 |
| 24 | 40 | 26.5 | 26.5 | 7 | |
| 25 | 40 | 24.5 | 24.5 | 7 | 4 |
| 26 | 40 | 29 | 29 | — | 2 |
| 27 | 40 | 22 | 22 | 14 | 2 |
| 28 | 40 | 51 | — | 7 | 2 |
| 29 | 40 | — | 51 | 7 | 2 |
| 30 | 40 | 25.5 | 25.5 | 7 | 2 |
| 31 | 40 | 44 | — | 14 | 2 |
| 32 | 40 | 45 | — | 14 | 1 |
| 33 | 40 | 49 | — | 7 | 4 |
| 34 | 40 | 52 | — | 7 | 1 |
| 35 | 40 | — | 44 | 14 | 2 |
| 36 | 40 | — | 45 | 14 | 1 |
| 37 | 40 | — | 49 | 7 | 4 |
| 38 | 40 | — | 52 | 7 | 1 |

T, theophylline anhydrous; L, lactose hydrate; D, dicalcium phosphate dihydrate; P, polyvinylpyrrolidone; C; Cabosil M5P.

lactose hydrous showed very poor flowability (36.0). Formulations containing dicalcium phosphate dihydrate would therefore be expected to have better flowability than those containing hydrous lactose.

### Effect of Binary Mixtures on Powder Flow

Two binary mixtures were present in the formulations studied. Both contain theophylline anhydrous 40%, with the remaining portion of formulation 16 consisting of lactose hydrous, and formulation 17 containing dicalcium phosphate dihydrate.

Flowability indices obtained agree well with what would be expected, based on diluent used. A variety of properties lead to materials that flow steadily and consistently.[12] Lactose hydrous, which has poor flow properties, leads to a powder formulation with poor flow properties. Dicalcium phosphate dihydrate, on the other hand, exhibits much better flow, even when combined with an active ingredient with poor flow properties, such as theophylline anhydrous. This improved flow is likely because of the relatively smooth shape, small surface area (1–2 $g^2/m$), and nonhygroscopicity of dicalcium phosphate dihydrate, as well as the low amount of fines present in this material.[17,18] Conversely, hydrous lactose exhibits a much wider particle size distribution and a more irregular shape.[19] These factors contribute to the less optimal flow properties of formulations containing hydrous lactose and theophylline anhydrous. Flowability index values for formulations 16 and 17 are illustrated in Fig. 3.

Analysis of variance was not sufficient to determine if these formulations differed statistically from one another. The Tukey-Kramer multiple comparison test was used to gather this information and was applied to the entire group of formulations, with positive values indicating pairs of means that are statistically different. By this method, it was possible to determine that the flowability of formulations 16 and 17 do indeed differ statistically from each other.

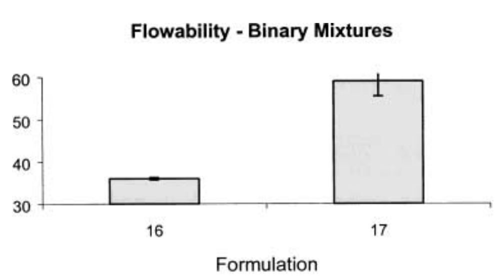


*Figure 3.* Flowability values for binary mixtures containing theophylline anhydrous and a diluent.

### Effect of Ternary Mixtures on Powder Flow

Sample formulations containing three components were also evaluated. Theophylline anhydrous was present at the same 40% level, while PVP 14% or fumed silica 4% was added to the formulation, with either hydrous lactose or dicalcium phosphate dihydrate as the diluent. The addition of other excipients into the mixture led to predictable results, which are illustrated in Fig. 4. Although fumed silica has poor individual flow properties, due in part to its extremely low-density and high-electrostatic charge, it is primarily used as a glidant in tablet formulations. It would therefore be expected to have a positive effect on the flow properties of the sample formulations.

The small particle size (approximately 25 μm) and large surface area ($200 \pm 25\,m^2/g$) of fumed silica make it an ideal glidant that may improve the flow characteristics of dry powders with which it is mixed by several mechanisms. The fumed silica may work to adsorb any moisture present on the surface of the particles being processed, preventing the surface tension of the water from binding the particles together and forming clumps.[20,21] A concentration of 1% fumed silica has been shown to effectively improve flow properties of such particles. Other mechanisms by which fumed silica exerts a positive effect on powder flow include its ability to coat particles and reduce surface irregularities. Particles that

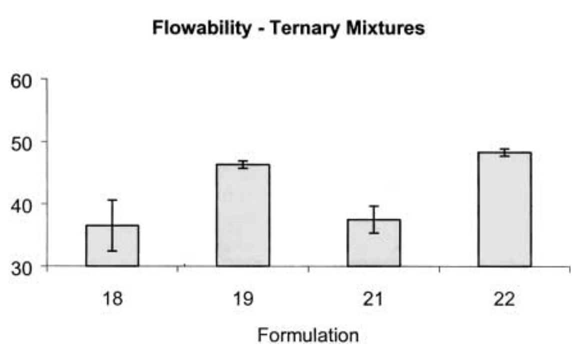


*Figure 4.* Flowability values for ternary mixtures containing theophylline anhydrous, a diluent, and PVP or fumed silica.

would otherwise exhibit poor flow because of surface roughness are able to slip past one another.[20,22] Friction between particles is thereby reduced.

Although it does exhibit passable individual flow properties (60.0 Carr Index), PVP is a hygroscopic powder. Friction between particles is likely to lead to reduced flow characteristics when compared with formulations containing flow enhancers, such as fumed silica. Thus, lower flowability of formulations 18 and 21 (containing PVP) when compared with formulations 19 and 22 (containing fumed silica) is to be expected (Fig. 4). Improved flowability of the formulations containing fumed silica was statistically significant, as determined by the Tukey-Kramer multiple comparison test.

Another statistical comparison of ternary formulations may be made by comparing formulations containing hydrous lactose with formulations containing dicalcium phosphate dihydrate. Although formulations containing dicalcium phosphate dihydrate as the diluent would be expected to have improved flow characteristics, the formulations do not in fact differ statistically. In the case of formulations 19 and 22 (containing fumed silica), the possible explanation is that fumed silica was able to fill in hydrous lactose surface irregularities and improve the flow properties to a level comparable with the properties exhibited by the formulation containing dicalcium phosphate dihydrate. However, on closer inspection of the flowability data, it may be seen that whereas the flowability index of lactose formulation improved from an average of 35.67 to an average of 46.33, the index for the dicalcium phosphate formulation decreased significantly. Fumed silica is essentially hydrophilic and as such is compatible with hydrous lactose, which is also hydrophilic. Therefore, it is able to spread uniformly over the surface of the hydrous lactose and fill in rough areas, thereby improving flow properties. Dicalcium phosphate dihydrate, however, is practically insoluble in water. Fumed silica is thus not able to improve the flow properties of dicalcium phosphate dihydrate, because it does not spread well over the surface of the diluent. Results agree with those obtained by Varthalis and Pilpel[23] in studies of oxytetracycline and fumed silica.

## Effect of Quaternary Mixtures on Powder Flow

Figures 5 and 6 contain the flowability results for the more complex quaternary formulations, which contain theophylline anhydrous 40%, PVP, fumed silica, and either hydrous lactose or dicalcium phosphate dihydrate. Several of the formulations were repeated using a different lot of theophylline anhydrous. This lot was milled and consisted of much finer particles than the more needlelike theophylline anhydrous present in other sample formulations. Milled theophylline formulations are designated formulations 31-2 through 38-2.

In nearly all cases, the flowability index for the formulations containing the milled theophylline anhydrous was less than that of the unmilled theophylline anhydrous formulations. An exception was formulation 31, compared with formulation 31-2. However, although formulation 31-2 showed a slightly higher mean flowability index, the difference

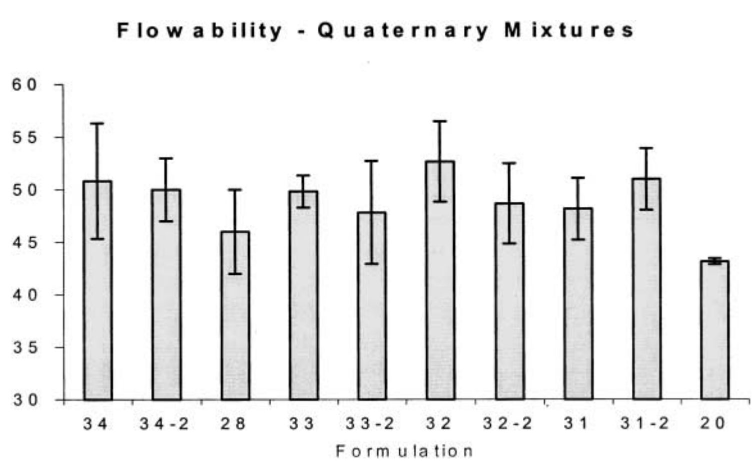


*Figure 5.* Flowability values for quaternary mixtures containing theophylline anhydrous, hydrous lactose, PVP, and fumed silica.

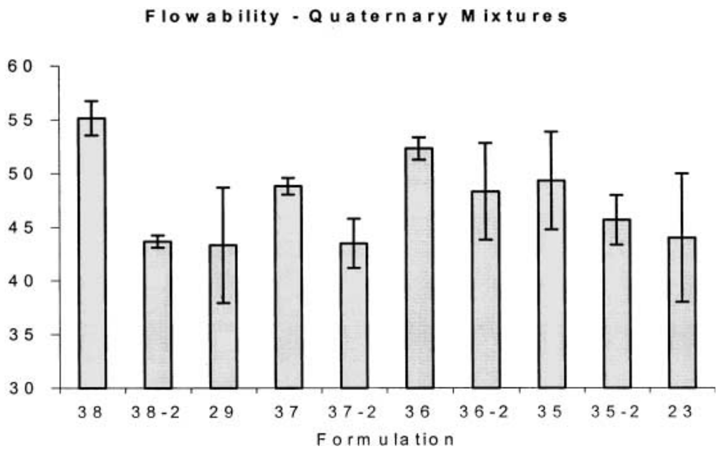


*Figure 6.* Flowability values for quaternary mixtures containing theophylline anhydrous, dicalcium phosphate dihydrate, PVP, and fumed silica.

was not statistically significant. In fact, all formulations containing hydrous lactose as the diluent gave statistically equivalent flowability indices.

Formulation 20, another quaternary formulation containing hydrous lactose as the diluent, was found to differ statistically from several of these sample formulations. As in ternary formulations involving hydrous lactose, significant statistical improvement in flowability is shown over the formulation containing just theophylline anhydrous and hydrous lactose. Fumed silica in amounts ranging from 1 to 4% of the formulation is sufficient to coat the surfaces of the hydrophilic powders present in the formulation and fill in surface irregularities to allow for improved flow.

Milled theophylline formulations containing dicalcium phosphate dihydrate exhibited lower Carr Flowability Indices than did their unmilled counterparts. Comparison of only the unmilled samples shows an expected trend. Samples containing only 1% fumed silica (formulations 36 and 38) show the highest flowability. Flowability decreases in formulations with higher percentages of fumed silica.

Figure 7 illustrates flowability data for a final pair of quaternary formulations. Both formulations contained equal amounts of hydrous lactose and dicalcium phosphate dihydrate as diluents. Formulation 24 also contained 7% PVP, whereas formulation 26 contained 2% fumed silica. Flowability was greater for the fumed silica formulation, and this difference was statistically significant. This would be expected because PVP would lead to somewhat decreased flow, whereas fumed silica is able to fill irregularities on the surface of hydrous lactose, improving the flow properties of that component of

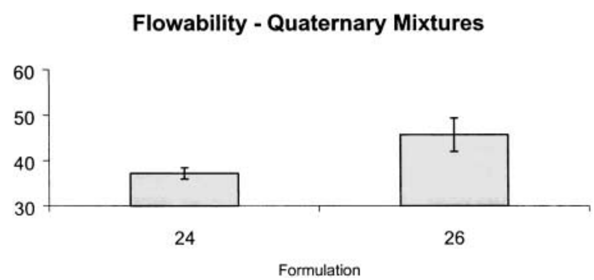


*Figure 7.* Flowability values for quaternary mixtures containing theophylline anhydrous, hydrous lactose, dicalcium phosphate dihydrate, and PVP or fumed silica.

formulation 26. It therefore exerts an effect on improving the flow characteristics of hydrous lactose in this formulation, whereas also impeding the flow of the hydrophobic dicalcium phosphate dihydrate.

## Effect of Five Component Mixtures on Powder Flow

Three formulations involved all five components studied. Flowability results are found in Fig. 8. Formulations 25 and 30 each contain 7% PVP, whereas differing in amount of fumed silica. Flowability was greater in the formulation containing a lower amount of fumed silica (2%) versus the formulation containing 4% fumed silica. This difference was statistically significant. The effect of fumed silica on impeding the flow of dicalcium phosphate dihydrate has a greater effect in this sample formulation than does its ability to fill irregularities on

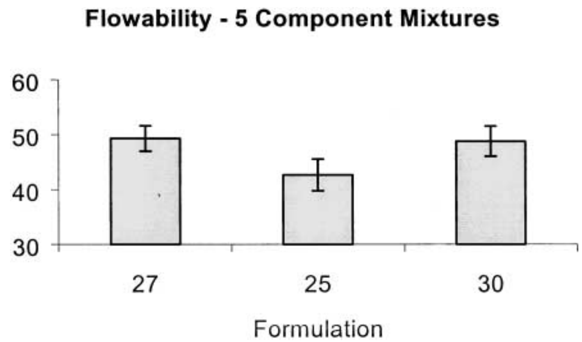


*Figure 8.* Flowability values for five component mixtures containing theophylline anhydrous, hydrous lactose, dicalcium phosphate dihydrate, PVP, and fumed silica.

the surface of hydrous lactose, thus improving the flow properties.

Formulation 27, which contains a higher level of PVP than the formulations just discussed (14%), along with 2% fumed silica, does not differ statistically from formulation 30, which contains the same amount of fumed silica. It does, however, show statistically higher flowability than formulation 25, which contains more PVP but a lower percentage of fumed silica. As PVP has been shown to lead to some decrease in flowability in previous formulations, it is apparent that fumed silica is exerting a greater effect on overall flowability than the PVP in these five component mixtures. The greater amount of fumed silica present in formulation 25 had a greater effect changing the flow of dicalcium phosphate dihydrate than higher amounts of PVP effect on the flow of formulation 27.

### Overall Effect of Mixture Components on Power Flowability

Flow properties of the mixtures studied were affected by a combination of factors, with overall composition being of prime importance. Although dicalcium phosphate dihydrate has much better individual flow properties than does hydrous lactose, the addition of other excipients can drastically effect a formulation, even if the amount added is small. Fumed silica, commonly used as a flow promoter, works as such when it is able to coat the surface of other hydrophilic materials, such as theophylline anhydrous, hydrous lactose, and PVP. When it is used in combination with hydrophobic materials, such as dicalcium phosphate dihydrate, however, this ability to improve flow properties vanishes and fumed silica instead leads to lessened flowability. PVP leads to lessened flowability because of its own poor flowability, which results from its hygroscopicity and tackiness, which lead to friction between particles. The effect of PVP on formulation flowability is, however, less than that of fumed silica.

## CONCLUSION

Formulation aspects must be considered when developing appropriate dosage formulations. The inclusion of diluents in this work allowed for formulations that more closely resembled the composition of a formulation used for tablet production. To determine if the formulations studied would have properties allowing them to be easily tableted, functional parameters affecting powder flow were evaluated. These parameters were used to determine the Carr Flowability and Floodability Indices. Formulations were compared based on a number of components present in their formulation.

When binary mixtures consisting of theophylline anhydrous and a diluent were evaluated, flowability indices obtained agreed well with what would be expected. Hydrous lactose is a poorly flowing powder, and its use in combination with theophylline anhydrous yielded a poorly flowing formulation. Hydrous lactose exhibits a wide particle size distribution and an irregular shape, both factors that contribute to poor flow. Conversely, dicalcium phosphate dihydrate exhibits improved flow, even when combined with a poorly flowing active ingredient, such as theophylline anhydrous. The relatively smooth shape and narrow particle size distribution of dicalcium phosphate dihydrate contribute to this improved flow.

Formulations containing more than two components have flowability that is affected by complex processes. Several general trends were observed:

1. While fumed silica has poor individual flow properties, due in part to its extremely low-density and high-electrostatic charge, it possesses characteristics ideally suited for a glidant or flow promotor. Formulations containing hydrous lactose and PVP show improved flow when fumed silica is added to the formulation. The small particle size of fumed silica acts to fill in surface irregularities of the other components of the formulations. Particles that would otherwise exhibit poor flow because of surface roughness are then able to slip past one another.[22,24]

2. Fumed silica does not always improve the flow properties of formulations in which it is a component.

Formulations using dicalcium phosphate dihydrate as a diluent show decreased flow when fumed silica was added. This may be explained by the hydrophilic nature of fumed silica, which is unable to spread uniformly over the surface of dicalcium phosphate dihydrate. It is thus unable to positively affect the flow properties of formulations in which dicalcium phosphate dihydrate is present.

3. PVP exhibits passable flow properties on its own, but can lead to decreased flow in formulations in which it is a component because of its hygroscopic nature. When fumed silica is also not included in formulations containing PVP, flowability is decreased because of friction between particles.

4. Formulations containing both hydrous lactose and dicalcium phosphate dihydrate as diluents exhibited the best flow when intermediate levels of fumed silica were present in the formulation. At intermediate levels, fumed silica was able to fill in irregularities on the surface of hydrous lactose, leading to improved flow. When levels of fumed silica were increased, the primary effect of the additional fumed silica changed to impeding the flow of dicalcium phosphate dihydrate.

Overall, the Carr indices aided in analysis of flow differences of the formulations studied.

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