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OVERCOMING PARTICLE SEGREGATION IN THE PHARMACEUTICAL AND COSMETICS INDUSTRIES

by

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ABSTRACT

Segregation (separation) of particles in mixtures is a common problem in many industries. In the pharmaceutical industry such segregation is often of major concern when handling direct compression formulations prior to pressing tablets or capsules. The result can be unacceptable variations in tablet or capsule weights and/or assays. Similarly in the cosmetics industry, particle segregation can cause severe quality control problems.

Particle segregation can occur by one of five primary mechanisms, three of which are common in the pharmaceutical and cosmetics industries. Which mechanism is predominant in a given application depends on the physical properties of the material being handled as well as the type of equipment being used.

Each of the three common mechanisms will be described in detail. Then typical solutions will be presented for both retrofitting existing facilities as well as designing new plants. While it is not always possible to eliminate segregation, it can usually be minimized to the point that significant gains in product quality can be realized.

INTRODUCTION

Mixtures of solid particles often segregate (separate) while they are being handled in hoppers and conveying systems. This often results in costly quality control problems due to the waste of raw materials, lost production, increased maintenance and capital costs required to retrofit existing facilities.

Segregation problems occur in many industries and with a diverse range of bulk solids. However given the value of pharmaceutical and cosmetic powders, segregation in these industries can have more drastic economic implications than in almost any other industry. Consider, for example, a single batch of pharmaceutical powder which may have a value in excess of several hundred thousand dollars. Strict U. S. quality control standards dictate that some or all of the batch may have to be discarded if it is found that the amount of active ingredient or total weight of just five tablets in a batch varies outside narrow limits.

Segregation problems are particularly pronounced with direct compression formulations in which there is a wide range of particle sizes and the active drug is at one extreme of the particle

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size distribution (usually the finer end). Even wet granulation formulations can exhibit segregation problems if the batch is dry blended after granulation or if the individual particles in the granulation do not all have the same percentage of active drug.

SEGREGATION MECHANISMS

Five primary mechanisms have been identified as being responsible for most particle segregation problems [1]*. Of these five, only three typically occur with pharmaceutical and cosmetic powders. Each of these three will be described below along with conditions under which it occurs.

- **Sifting**

  Sifting is a process by which smaller particles move through a matrix of larger particles. From experiments [2] and actual field observations, it has been found that four conditions must be present in order for this mechanism to occur:

  A difference in particle size between the individual components. Sifting has been found to occur with particle diameter ratios as low as 1.3:1. In general, the larger the ratio of particle sizes, the greater the tendency for particles to segregate by sifting.

  A sufficiently large mean particle diameter. Below 500 microns (#35 U.S. mesh) the tendency to segregate by sifting decreases substantially. However, some sifting can occur down to and below a mean particle diameter of 200 microns (#70 U. S. mesh) for particle diameter ratios as low as 2:1.

  Free flowing material. In order for sifting to occur it is essential that no agglomerates are formed, either between particles of a given size or particles of varying size. This generally requires the mixture to have a low moisture content and little or no fine particles.

  Interparticle motion. If particles are stationary or moving with a uniform velocity they are essentially locked together and their tendency to segregate becomes almost non-existent, even for materials which are highly prone to segregation. Thus, a velocity gradient through the flowing material is required.

  It is essential that all four of the above conditions be present in order for sifting segregation to occur. If any one of the four is absent, the mixture will not segregate by this mechanism.

  Sifting segregation is common in pharmaceutical plants and, to a lesser extent, in cosmetics facilities. One place it often occurs is during filling of a bin or hopper. A concentration of fine particles develops under the fill point while the larger particles roll or slide to the periphery of the pile.

  Sifting segregation can also occur as a bin or hopper is being emptied. If a funnel flow pattern [3] develops, fines may percolate (sift) from the flow channel into the stagnant region.

- **Air entrainment (fluidization)**

  Fine particles generally have a lower permeability than coarse particles and, therefore, tend to retain air longer in their void spaces. Thus, when a mixture of coarse and fine particles is charged into a hopper, it is not uncommon to find a vertical segregation pattern develop, caused by the coarse particles being driven into the bed as the bin is filled while the fine particles remain fluidized near the top surface. Segregation by this mechanism can also occur when there is a source of air introduced into the hopper.

  Segregation by air entrainment often develops with mixtures which contain a significant percentage of particles below 100 microns in size.

* *Numbers in brackets denote references at end of paper.*

- **Entrainment of particles in an airstream**

  The finer the particle size, the longer it may remain suspended in an air stream such as might be set up upon filling of a hopper. This effect starts to become important around 50 microns and is very common below 10 microns. Thus, secondary air currents can carry airborne particles away from a fill point into outer areas of a bin, scattering them in a way that bears no resemblance to the calculated trajectories.

SOLUTIONS TO SEGREGATION PROBLEMS

There are three main techniques that can be considered when segregation problems are present: change the material, change the process, or change the design of the equipment. Each of these will be addressed below.

- **Change the material**

  A common characteristic of most highly segregating materials is that they are free-flowing and, therefore, the particles easily separate from each other. Thus, one obvious change to decrease the segregation tendencies of a material is to increase its cohesiveness by, for example, adding water or oil. It must be recognized that this can be overdone since, if the cohesiveness is increased too much, flow problems such as arching or ratholing may develop and result in greater disruption to the process.

  Another technique that can be used is to change the particle size distribution. For example, if segregation is occurring by the sifting mechanism, lowering the particle diameter ratio below 1.3:1 or decreasing the mean particle diameter below 100 microns will reduce or eliminate it. If all of the particles are of a nearly uniform size, differences in fluidization and particle entrainment tendencies will be minimal as well.

- **Change the process**

  There is often little that can be done in a pharmaceutical or cosmetics facility in this area. However if the powder is being pneumatically conveyed into a hopper, it is generally preferable to use tangential entry into the side rather than going in at 90° to either the sidewall or the top. This will reduce the tendency for vertical segregation to develop.

  Another technique which has been used with success is to carry a pneumatic line into the center of a bin and then direct it upward to a deflector plate. This will decrease particle velocity and allow a symmetric pattern when particles fall from this surface.

- **Change the design of the equipment**

  The flow pattern in a mass flow bin is first-in, first-out flow, whereas in a funnel flow bin it is first-in, last-out [3,4]. Thus, if particles have segregated from side-to-side while filling a bin (e.g., by the mechanisms of sifting or particle entrainment), a mass flow pattern will tend to minimize segregation upon discharge, whereas a funnel flow pattern will make the segregation worse. Increasing the height-to-diameter ratio of the cylinder section of a mass flow bin above 1.0 usually results in a uniform velocity pattern across the top surface as long as the level is above one diameter in the cylinder. This lessens the effects of sifting segregation compared to using a short cylinder section or no cylinder at all.

  Mass flow will not correct segregation in which there are vertical striations in a bin. Such problems can only be overcome by first eliminating the vertical striations (e.g., by redirecting the entry of a pneumatic line). Then mass flow can be used if the resulting particle size distribution shows some side-to-side variation.

  An alternative to traditional mass flow bin design is to use a patented BINSERT® [5], which consists of a hopper within a hopper in which the velocity pattern is controlled by the position of the bottom hopper. It is possible to design such a system to provide a completely uniform velocity profile and thereby an absolute minimum level of segregation.

TABLE I.
EXAMPLE #1 PARTICLE SIZE DISTRIBUTION

U. S. STANDARD MESH	CUMULATIVE WEIGHT % PASSING
16	92
20	81
30	73
40	66
60	58
80	55
120	50
170	41
230	28

Alternatively, by changing the geometry at the bottom of the hopper, a velocity profile can be developed in which the center section moves faster than the outside, thus providing in-bin blending of the materials [6].

EXAMPLES OF SEGREGATION PROBLEMS

The following examples are all taken from the pharmaceutical industry. Since the powders and bulk solids handled in this industry are often more free-flowing than those handled in the cosmetics industry, more examples are available.

- **Example #1 (sifting segregation)**

This first example involves a direct compression formulation in a pharmaceutical facility in which the particle size distribution was as shown in Table I.

Obviously this material meets the first two criteria for sifting segregation. It was also a free-flowing material since its moisture content was low, so all that was needed for sifting segregation to develop was interparticle motion. This occurred as the material dropped from a twin shell blender into a portable hopper. During the filling process, the pile which formed had a concentration of finer particles directly under the fill point whereas the larger particles rolled or slid to the periphery of the hopper. As this hopper was discharged, it exhibited a funnel flow pattern since the converging hopper walls were not steep enough or smooth enough for material to slide along them. As a result, the fines came out first followed later by the coarse particles. Since the fines were high in active drug, severe quality control problems were evident at the tabletting press.

Wall friction tests on a smooth stainless steel surface (2B finish sheet) showed that the conical hopper walls could be no more than 15° from vertical in order for mass flow to occur. Not only would this require more headroom than was available but segregation would not be eliminated if a straight, conical mass flow hopper were used. As the level dropped down in the hopper section, material at the center would flow faster than at the walls.

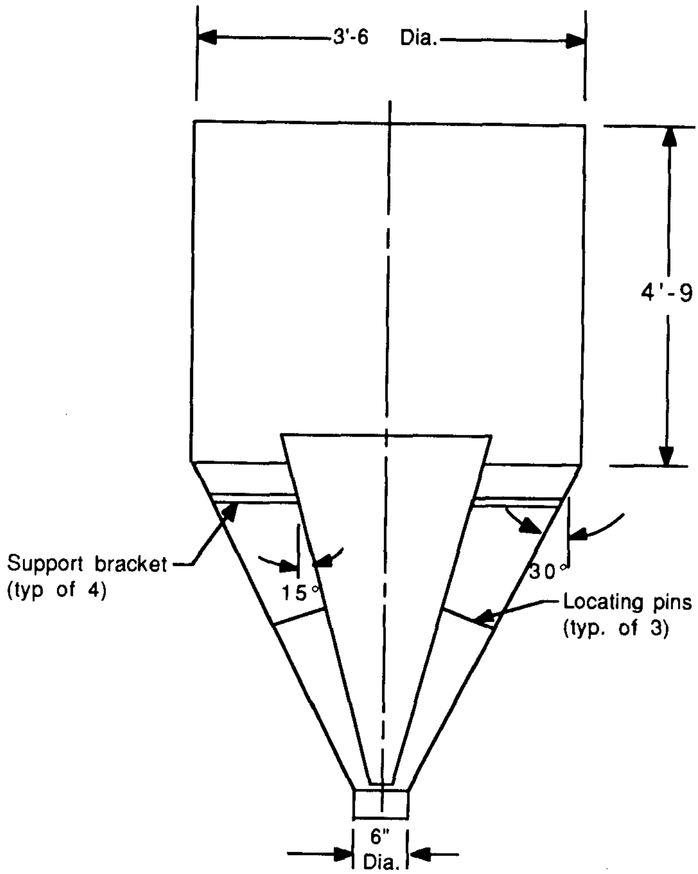

Figure 1. BINSERT® hopper - example #1

The most practical solution to this problem was to design the hoppers with a BINSERT® as shown in Fig. 1. This required no additional height or loss of volume. In addition it provided for a completely uniform velocity profile even as the level dropped well into the hopper section.

This set of portable hoppers has been in operation now for over six years and has produced excellent quality tablets.

- **Example #2 (air entrainment)**

An example of segregation due to air entrainment occurred in a feed bin for a pharmaceutical tabletting press which was being filled by a dense-phase pneumatic conveying system through a vertical downspout at the top center of the bin. (Fig. 2) The mixture consisted of a fine powder (the active ingredient) and inert filler materials consisting of larger particles. Because of fluidization during fill of the bin, the fine active ingredient became concentrated in a layer at the top, causing severe quality control problems when it exited the bin over a short period of time. The severity of this problem was lessened somewhat by the funnel flow pattern which developed upon discharge.

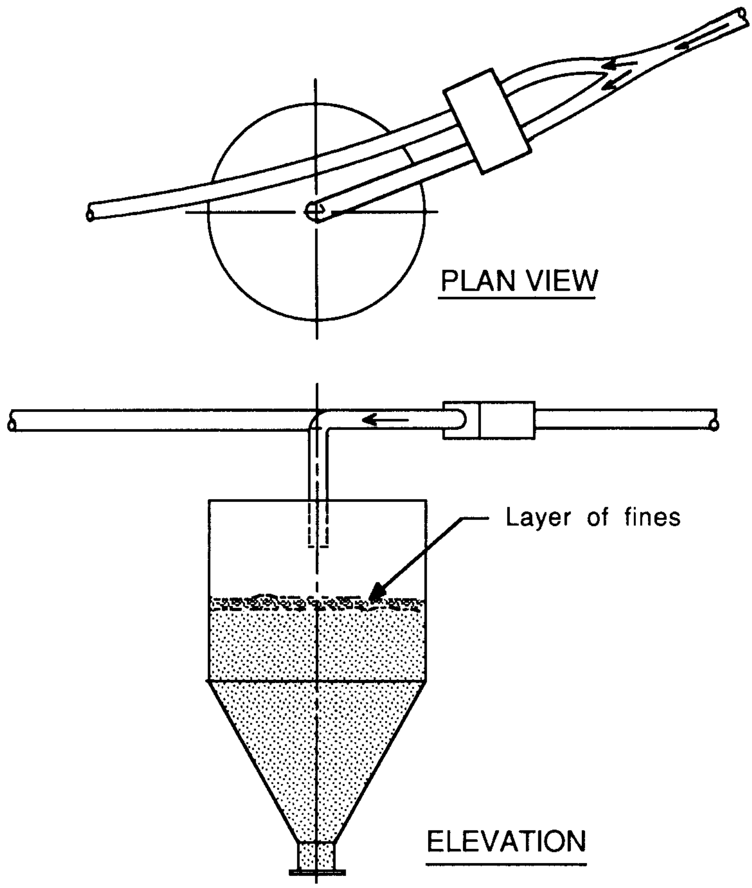

Figure 2. Original layout of system - example #2

This problem was corrected by orienting the pneumatic conveying line to enter the bin tangentially. (Fig. 3) In addition, a liner was installed on the hopper walls to provide a mass flow pattern since the tangential entry created some side-to-side segregation.

It is important to recognize that simply installing a liner to produce a mass flow pattern without correcting the entry problem would not have solved this segregation problem. Indeed whenever segregation consists of a vertical layering of particles, mass flow will always make the segregation more pronounced.

- **Example #3 (air entrainment)**

Another example of an air entrainment problem occurred in a pharmaceutical facility handling a wet granulation which was dry blended (in 1000 kg. batches) with a small amount of corn starch before being placed in a portable hopper. Because of the need to maintain complete batch integrity, the entire system including the Y-branch down to the tabletting press (see Fig. 4) was cleaned out between each portable hopper. The segregation pattern which developed was one in which the fines came out near the end of each batch. This was surprising since samples of the batch exiting the blender and in the portable hopper before pressing were found to be quite uniform. However, upon closer

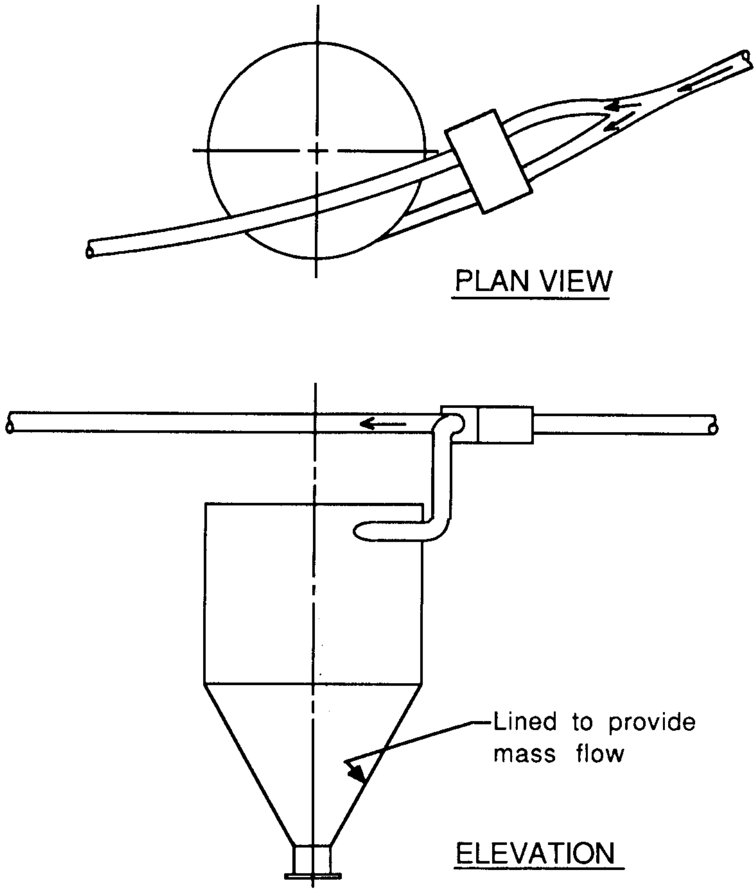

Figure 3. Revised layout - example #2

inspection we found that fines appeared on the top surface just after the butterfly valve at the bottom of the portable hopper was opened. This was caused by material dropping into the Y-branch which displaced the air. Since this was essentially a sealed system, the air had no place to go but up through the portable hopper. The fluidizing effect of this air carried some of the fines to the top surface causing a vertical pattern of segregation.

This problem was corrected by installing a vent line from the Y-branch to the top of the hopper so that most of the air could by-pass the hopper and not go through the material.

- **Example #4 (particle entrainment)**

An example of particle entrainment occurred in a surge bin used to store an excipient at a pharmaceutical facility. The material, a fine powder, was blown into the bin by a dilute-phase pneumatic line which entered the bin perpendicular to the side wall of the cylinder section. See Fig. 5. The particles were carried by air currents set up inside the bin during filling and dropped out of suspension at different rates. This resulted in a side-to-side segregation pattern in the bin with the coarser particles concentrated on the side opposite

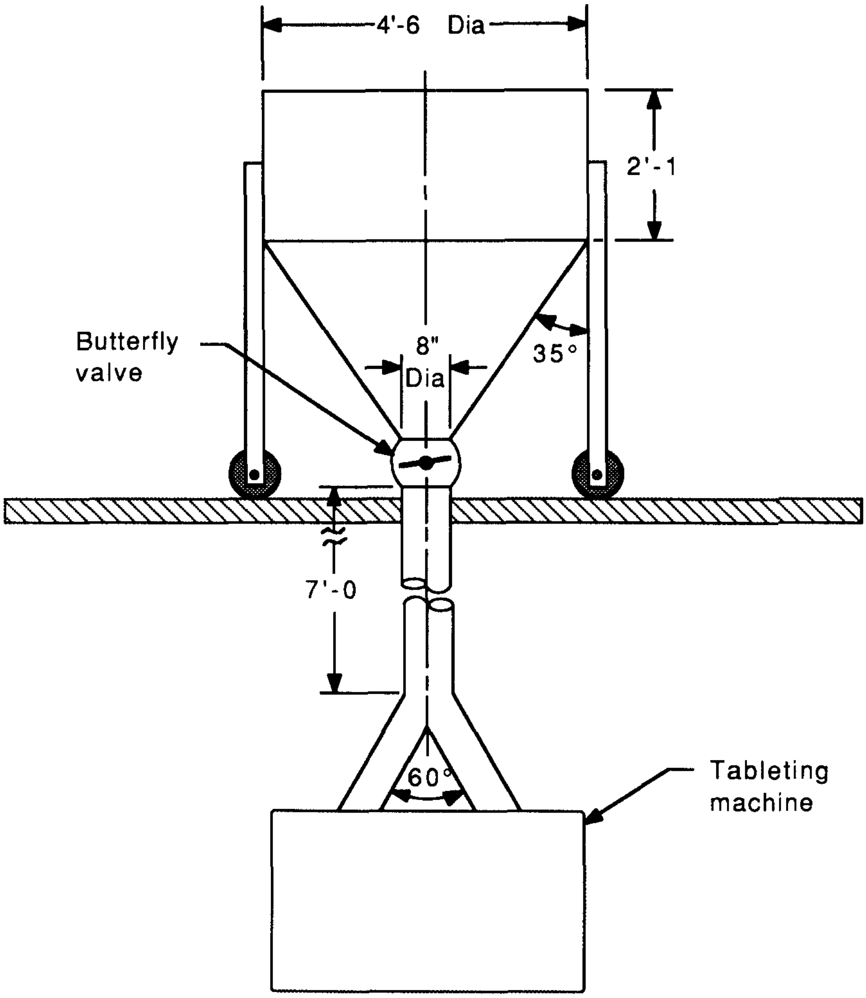

Figure 4. Original layout - example #3

the fill line. Even through the hopper walls were steep enough for mass flow, this segregation pattern caused a problem upon discharge since the outlet stream went through a Y-branch to one of two conveying lines.

As with example #2, this problem was also solved by orienting the pneumatic line to enter the bin tangentially. This reduced the amount of side-to-side segregation to a manageable level.

SAMPLING

When analyzing particle segregation problems, it is extremely important to collect representative and meaningful samples so that valid conclusions can be drawn. For example, it is not uncommon to find plant operators taking samples of a mixture in a blender to determine proper blend times, but then ignoring the de-mixing that occurs upon discharge from the

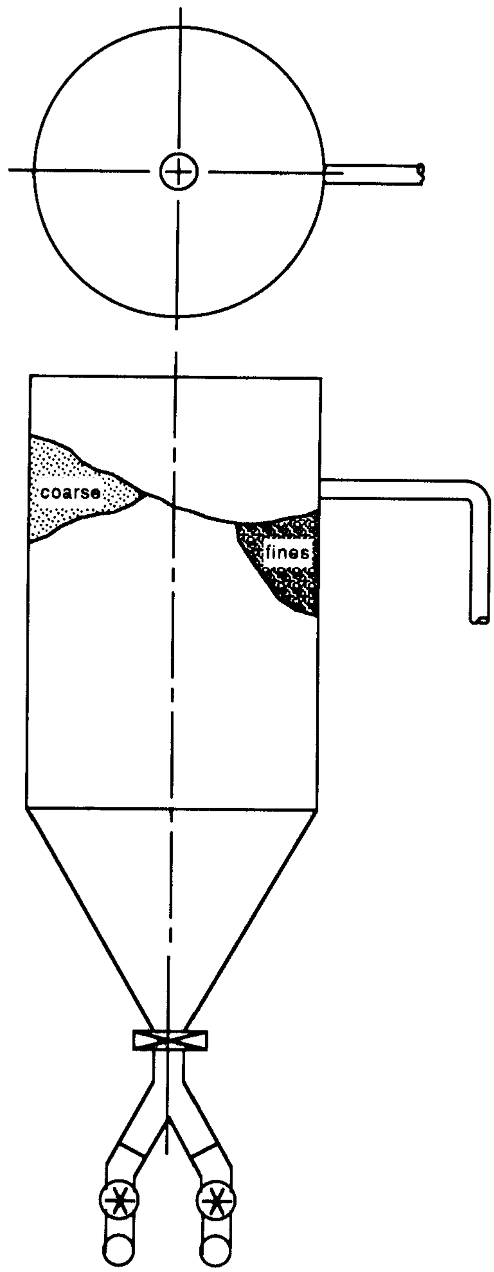

Figure 5. System layout - example #4

blender. It would be far more meaningful -- but unfortunately more time consuming -- to sample the discharge stream from a blender after various mixing times to determine what the correct mix times should be.

Another common mistake is to take a sample cut across a portion of a stream of material, ignoring the segregation which may be present within the stream. Only full stream width samples should be taken and then, if it is necessary to end up with a smaller sample for testing, split the sample using a riffler.

Testing in a pharmaceutical plant is often done by sampling tablets or capsules and checking for assay and weight. We have found it useful to average the results of individual tablets or capsules which have been produced at approximately the same time. Taking 10 or 20 tablets or capsules and then getting their mean and standard deviation values helps to see trends that might not otherwise be evident by looking at an individual tablet. Also, when considering assay values, it is important to separate out variations due to weight in order to determine whether or not the mixture is segregated.

Sometimes differences can be found on double-sided presses from one side to the other. Thus it is desirable to take separate samples from each side and analyze them individually.

REFERENCES

1. J. W. Carson, T. A. Royal, and D. J. Goodwill "Understanding and eliminating particle segregation problems," Bulk Solids Handling, Feb. 1986, pp. 139-144, Vol. 6

2. J.C Williams, "The segregation of particulate materials: A review," Powder Technology, 1976, pp. 245-251, Vol. 15

3. A.W. Jenike, Storage and Flow of Solids, University of Utah Engineering Experiment Station, BULLETIN No. 123, Nov. 1964

4. J. Marinelli, and J. W. Carson, "Preventing solids flow problems," Powder/Bulk Solids, Jan. 1986, pp. 23-25

5. "Blending apparatus for bulk solids," U. S. Patent 4,286,883, Sept. 1, 1981.

6. Jenike & Johanson, Inc., Flow-of-Solids® Newsletter, Vol 3, No. 1.