

# Segregation of Powders during Gravity Flow through Vertical Pipes

Elizabeth D. Liss, Stephen L. Conway, James A. Zega, and Benjamin J. Glasser\*



Associated segregation can compromise the dose uniformity of a drug product. In this study, the authors examined the physical mechanisms that can lead to segregation during the gravity-driven flow of powders. Experiments were conducted to quantitatively determine the effect of a vertical drop through pipes on the segregation of powder mixtures.

**Elizabeth D. Liss, PhD**, was a doctoral student at Rutgers University when this work was conducted and is currently a senior research chemical engineer at Merck Research Laboratories (Westpoint, PA).

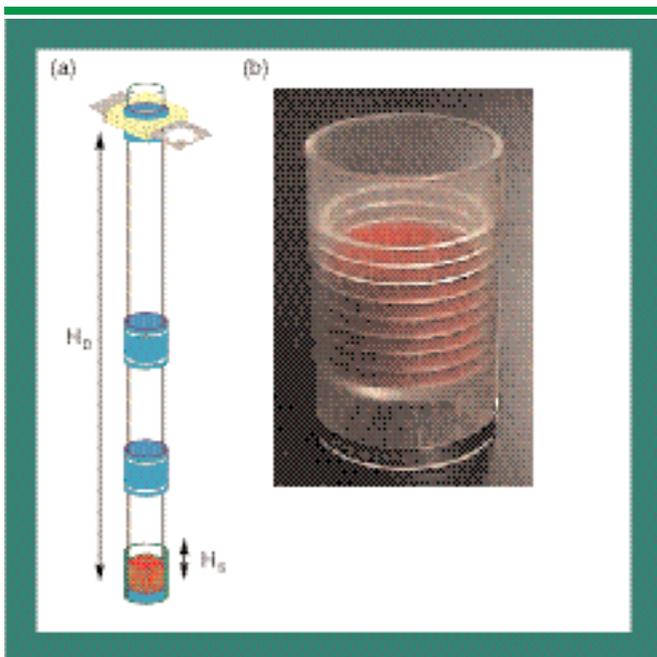
**Stephen L. Conway** is a doctoral student at Rutgers University on educational leave of absence from Merck Manufacturing Division (Somerset, NJ). **James A. Zega, PhD**, is a senior research fellow at Merck Research Laboratories. **Benjamin J. Glasser, PhD**, is a faculty member and associate director of the Pharmaceutical Engineering Program in the Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ 08854, tel. 732.445.4243, fax. 732.445.2581, [bglasser@soemail.rutgers.edu](mailto:bglasser@soemail.rutgers.edu).

\*To whom all correspondence should be addressed.

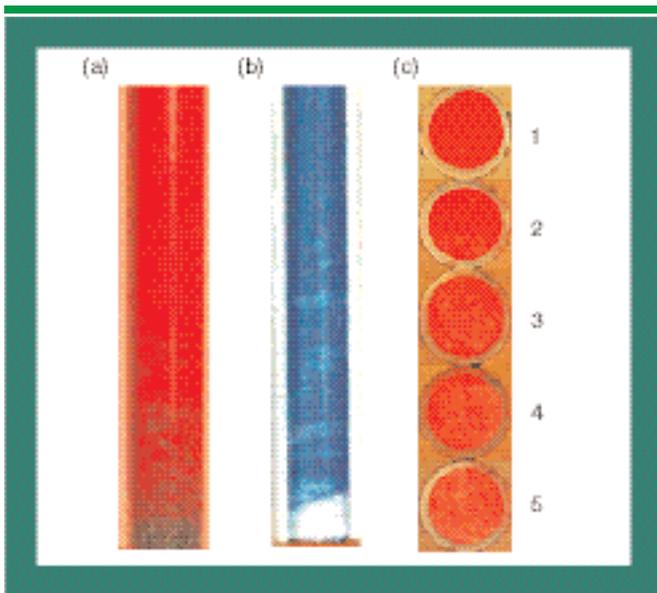
**B**ecause the majority of active ingredients and excipients in drug products are powders, advances in pharmaceutical technology will be driven by improving the industry's understanding of granular-material processing. In many cases, small amounts of active-drug crystals must be blended with large amounts of excipients with rather different physical properties. This leads to many challenges in achieving and maintaining blend uniformity, possibly owing to problems associated with the implementation and scale-up of the blending operation as well as the occurrence of segregation during transport of the powder mixture (e.g., discharge from the blender). In this study, the authors examined segregation during sedimentation, or dropping, of a powder through a vertical pipe. The resulting sediment was sampled using a collection unit designed to allow a specific property to be profiled as a function of height. For model cohesionless materials and weakly cohesive excipients, marked segregation occurs for drops on the order of a few feet, whereby the mass fraction of the fines is greatest at the top of the sediment. A quantitative framework for understanding such segregation was developed by varying physical and process parameters such as particle-size ratio, pipe diameter, and drop height. The results are consistent with a segregation mechanism based on differential particle-gas drag forces. Methods to control segregation during gravity-driven drops of pharmaceuticals are also discussed.

## Background

Granular flows can be extremely complex and in general are not well understood (1,2). Rheological properties cannot yet be fully predicted, and phenomena that have been observed include the formation of stable arches, convection under vibration, and cluster formation during fluidization. These occurrences have led to production problems and inefficient or ineffective equipment. Researchers are developing an understanding of the flow of granular materials and have found that many of the complexities in these flows come from the effect of various boundary conditions, the influence of local structure formation, and the role of the interstitial fluid (3). Mixtures consisting of multiple components and broad particle-size distributions pose even greater difficulties in predicting flow properties (4). When these mixtures of materials are



**Figure 1:** a) Experimental apparatus depicting relevant length scales. b) Close-up photograph of acrylic collection unit containing sediment.



**Figure 2:** Photograph of the collection unit after the completion of an experiment: (a) Sediment of a 50 wt% mixture of green 480  $\mu\text{m}$  and red 90  $\mu\text{m}$  glass beads after dropping 8 ft in a 0.5-in. diameter pipe. (b) The sediment of a 50 wt% mixture of white dicalcium phosphate (150–425  $\mu\text{m}$ ) and blue microcrystalline cellulose (53–90  $\mu\text{m}$ ) after dropping 8 ft in a 0.5-in. diameter pipe. (c) Individual layers of material contained by the collection rings at various heights after a 50 wt% mixture of white 310  $\mu\text{m}$  and red 90  $\mu\text{m}$  glass beads after dropping 68 in. in a 2-in. diameter pipe. Numbers refer to ring vertical position (see text).

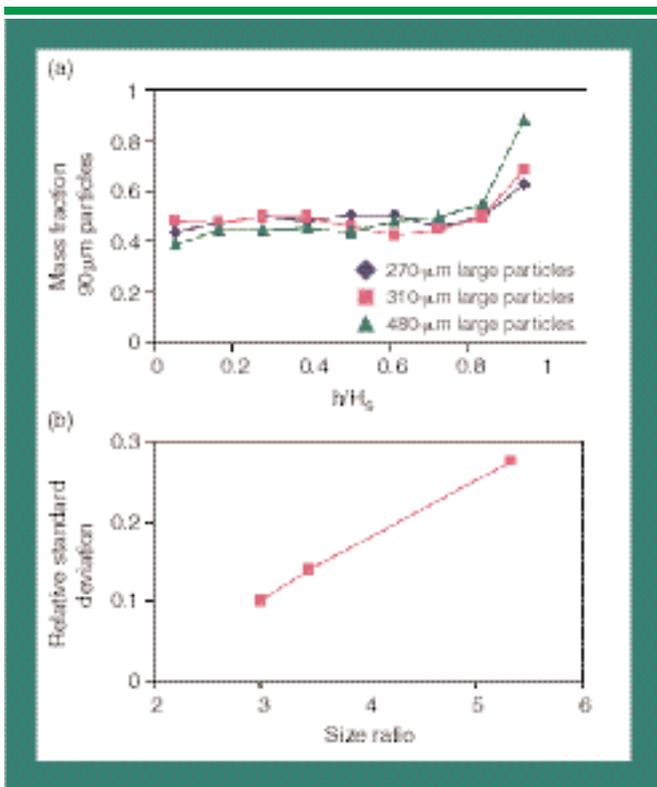
agitated or deformed, for example by pneumatic conveying or gravity-driven transfers, the well-known tendency to segregate can occur when individual grains differ from each other in terms of size, density, surface characteristics, and shape (5–9).

Size differentiation has been the predominant driver for segregation and is the subject of this study (10). If uncontrolled, size segregation can lead to dose variability in the final drug product and inhibit production. Segregation occurs even in the simplest powder flows including discharge from a bin (11–14), flow through a chute (15), heap formation (16,17), and in rotating drums (18). This work shows that powder sediments formed after a drop on the order of 1–2 ft also can exhibit significant segregation. An understanding of this fundamental process can lead to methodologies that can minimize segregation in this and more-complicated flow situations.

In typical pharmaceutical operations that require small percentages of active ingredients to be blended with much larger quantities of excipients, often with disparate properties, the maintenance of dose uniformity typically is the key quality requirement. For example, during direct compression of a blended formulation into tablets, segregation may occur when an initially homogeneous mixture is transferred from a blender to a compressing machine (13). The seriousness of such postblending segregation has prompted regulatory agencies to require assurance that blend quality is maintained “by design.” Historically, this has been difficult: scale-up of powder transport processes often introduces additional opportunities for segregation, even if care is taken to use the same blender and compressing machine types in both piloting and manufacturing (19). The appropriateness of test methods to ensure uniformity is a subject of debate between FDA and manufacturers (20). Although this highlights the need for a better physical understanding of underlying mechanisms, heuristic rules (e.g., avoiding solids transfers in long, inclined chutes and limiting the size ratio of particles in a mixture) currently remain the best practical methods for avoiding segregation (21).

Much of the initial segregation research focused on defining specific flow situations that promote or hinder segregation (6, 7,10,22–24). These works defined several flow mechanisms responsible for segregation, including sifting, surface velocity differences, dynamic effects, air entrainment, and particle entrainment in an air stream. Sifting, also known as *percolation*, is probably the best understood mechanism (10,25). Small particles can spontaneously move through the spaces between larger particles if the following conditions exist: a fairly large difference in particle size, a sufficiently large mean diameter, free-flowing properties (e.g., lack of cohesion), and the presence of inter-particle motion. Under the influence of gravity, sifting can leave large particles at the top of a powder bed.

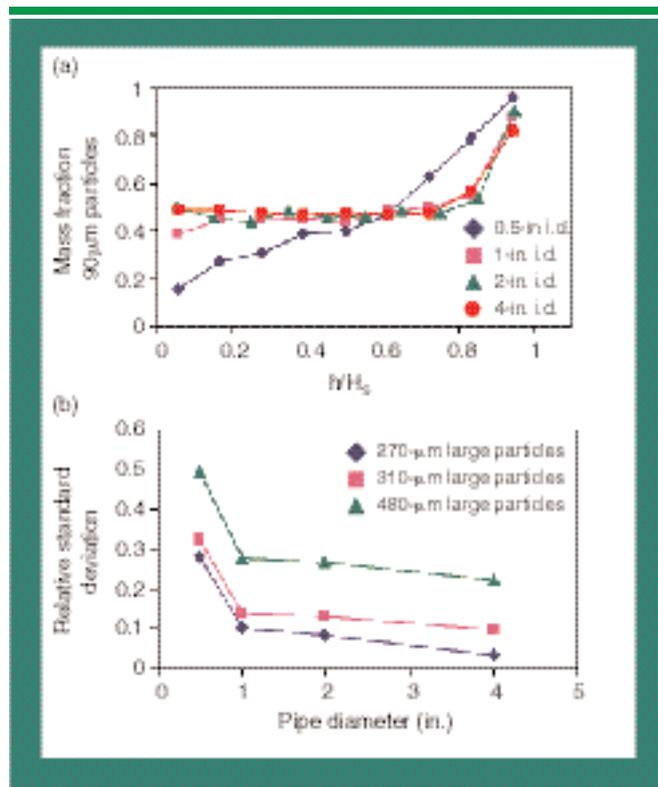
Researchers recently discovered another means of segregation that showed similar effects to sifting but occurred much more rapidly (26). Convection cells, which can carry all particles to the surface of a powder bed in a granular current, can be set up in materials subject to vibration. These currents tend to move downward in thin shear bands nearest walls, too narrow for large particles to fit into. Large particles thus are trapped at the free surface. Segregation by surface velocity differences refers to the specific situation in which particle properties affect the particle’s motion on a surface. Particles that are small or irregularly shaped have a higher frictional drag on a surface than do large, more-spherical particles. Other dynamic char-



**Figure 3:** Results for a mixture containing 50 wt% 90  $\mu\text{m}$  fine particles dropped 68 in. in a 1-in. inner diameter pipe. (a) Mass fraction of fines as a function of the dimensionless height within the sediment. (b) RSD as a function of size ratio.

acteristics of a material such as resilience and inertia also may cause segregation, although this is reportedly less common. Finally, air-entrainment segregation, also known as *fluidization segregation*, occurs because small particles have a lower permeability than do coarse particles and tend to retain air in the void spaces longer (10). Segregation as a result of the entrainment of particles in an air stream may occur when fine particles remain suspended in air longer than coarse particles or when secondary air currents deflect airborne particles from their intended path. Air resistance has a greater effect on small particles and their free-fall terminal velocity will be lower than that of coarser particles. The latter two segregation mechanisms both depend heavily on the underlying drag force exerted during particle motion. In the present work, air drag is shown to be a significant cause of segregation during a vertical drop.

At first, one might think powder flow in vertical pipes is one of the least complicated situations to examine because of the simple geometry and stationary boundaries. However, surprisingly little is known about the phenomena that occur, even for a single component. Previous studies have revealed that monodisperse granular flow in ducts or pipes can be a complex process, and simulations in the absence of an interstitial fluid have predicted that inelastic collisions between particles can lead to the formation of clusters and density waves (27–32). Experiments also have shown that these inhomogeneities readily form in pipes and may be compounded by the presence of air

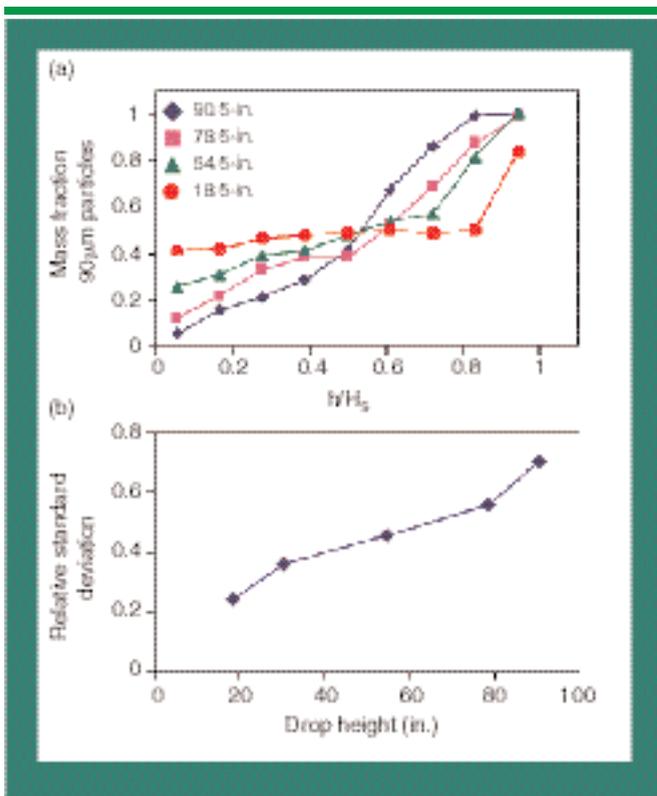


**Figure 4:** Results for a mixture containing 50 wt% 90  $\mu\text{m}$  fine particles by mass dropped 68 in. (a) Mass fraction of fines as a function of the dimensionless height within the sediment for a mixture containing 480  $\mu\text{m}$  large particles. (b) RSD as a function of the inner diameter of the pipe.

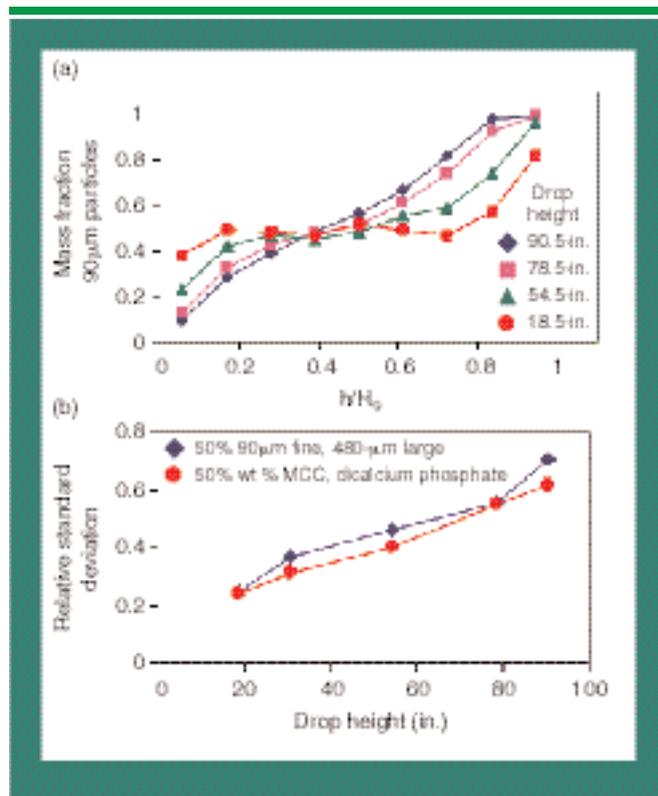
(29,33–38). Horikawa et al. reported that density waves may be present when an air-control valve at the bottom of a pipe is completely open but not when half closed. It has been suggested that constricting both particle and air flow creates a back-flow of gas, thereby promoting the formation of density waves (33). Moriyama et al. later confirmed that the interstitial fluid can play an important role in the creation of density waves by sealing their pipe-flow apparatus and regulating the amount of air allowed to escape (35). They observed that when large out-flows of air were permitted, the flow of particles and air through the pipe did not exhibit density waves. Upon limiting the amount of air escaping from the system, waves were observed. Although the nonuniformities inherent in monodisperse systems must be recognized, the interest of this study is the additional segregation effects seen in binary mixtures in the presence of an interstitial fluid and gravity.

### Experimental setup and procedure

The authors performed experiments to measure the degree of segregation that occurs when a fixed mass of a binary mixture of different-sized particles are dropped in a vertical pipe. Once the powder had come to rest at the bottom of the pipe, it was analyzed for segregation as a function of height within the sediment. Figure 1 shows the apparatus used, which consisted of a clear acrylic tube with a knife-valve and feed section open to the air at the top and a sealed collection unit at the bottom. This



**Figure 5:** Results for a mixture containing 50 wt% 90  $\mu\text{m}$  fine particles and 480  $\mu\text{m}$  large particles by mass dropped in a 0.5-in. inner diameter pipe. (a) Mass fraction of fines as a function of the dimensionless height within the sediment. (b) RSD as a function of drop height.



**Figure 6:** Results for a mixture containing 50 wt% microcrystalline cellulose (53–90  $\mu\text{m}$ ) and dicalcium phosphate (150–425  $\mu\text{m}$ ) dropped through a 0.5-in. inner diameter pipe. (a) Mass fraction of fines as a function of the dimensionless height within the sediment. (b) RSD as a function of drop height.

resembles the free-fall segregation tests of Chowhan (23), but in this study the authors extended the degree and ease at which samples were taken after a drop and constructed four systems using 4-, 2-, 1-, and 0.5-in. inner-diameter piping. This enabled an investigation into the effect of pipe diameter on segregation. Modular construction allowed drops from 6 in. to 8 ft to be accomplished. There were two important heights of interest:  $H_D$ , the height of drop, which was measured from the floor to the feed valve, and  $H_S$ , the height of the sediment (see Figure 1).

With the valve closed, test material was loaded to achieve a “well-mixed” condition, meaning that the material was mixed to a characterized level of uniformity. Initial investigations determined an appropriate initial condition for the experiments described in this work. Unfortunately, the same mechanisms that cause segregation in this system make mixing particles of various sizes extremely difficult. Even if complete mixing can be accomplished, the act of pouring the mixture into the feed unit could cause segregation. The authors concluded from pouring the material directly into the collection unit and sampling that premixing several fractions of the material and then loading the apparatus in batches produced the most reproducible initial condition. With this method, one can ascertain that even if a premixed fraction segregates during pouring, on the scale of the premixed fraction the material has the appropriate composition, and the initial condition is determined to be “well-

mixed” on the scale of the experimental measurements considered in this work.

Once the material was loaded, the feed valve then was spring-loaded to allow for a reproducible operation that completely opened the valve in 1/30 of a second. In all cases, the time it took to open the valve was a small fraction of the total drop time. The apparatus was carefully clamped to ensure minimal lateral motion caused by opening the valve. Once the valve was opened, the material fell with typical drop times on the order of 1 s.

In this work, the authors examined both model systems of near-spherical glass beads and typical pharmaceutical excipients of similar dimensions. The former were chosen to isolate the effects of size segregation from more-complex particle interactions. However, for the excipients, one can expect that other characteristics such as particle morphology and cohesive forces will affect the results. As mentioned previously, historically, size-segregation mechanisms have dominated (39). The sizes of the particles reported in this article were averages determined using sieve analysis, with particle sizes distributed fairly normally around the mean. The pharmaceutical excipients examined were dicalcium phosphate and microcrystalline cellulose. To ensure reproducible results, all of the reported experiments were performed in an environmental chamber in which temperature and humidity were carefully controlled at 70 °C and 65% rela-

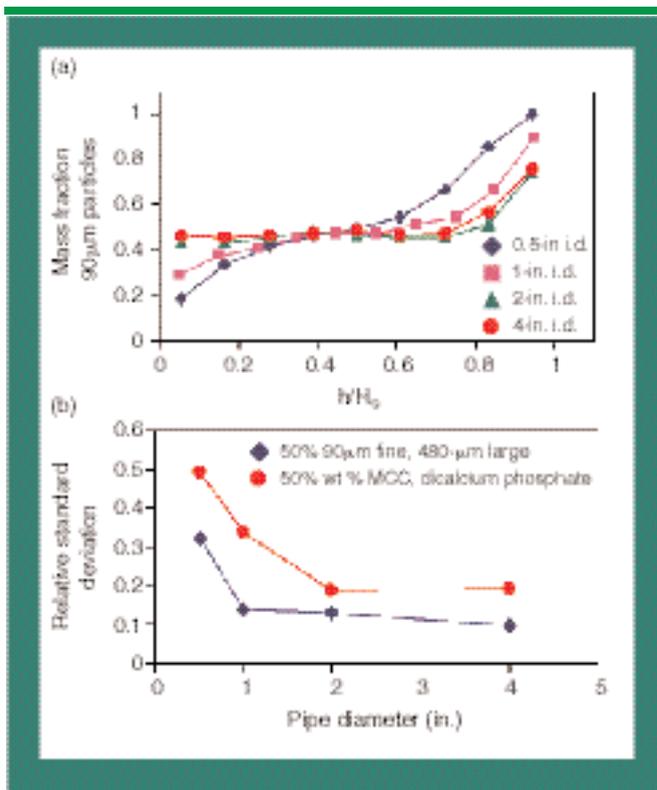


Figure 7: Results for a mixture containing 50 wt% fine particles dropped 68 in. (a) Mass fraction of fines as a function of the dimensionless height within the sediment for a mixture containing microcrystalline cellulose (53–90  $\mu\text{m}$ ) and dicalcium phosphate (150–425  $\mu\text{m}$ ). (b) RSD as a function of the inner diameter of the pipe.

tive humidity. These values were chosen to minimize the effects of cohesion (at higher humidity) and static electricity (significant at lower humidity).

Equal mixtures by weight of various-sized glass beads and pharmaceutical powders were dropped in each apparatus at a range of heights. Visual inspection of the sediments clearly shows sharp segregation (see Figure 2). Figure 2a shows the sediment of a 50 wt% mixture of green 480- $\mu\text{m}$  and red 90- $\mu\text{m}$  glass beads dropped 8 ft in a 0.5-in. inner diameter pipe. Particles of this diameter were chosen to be of comparable size with many pharmaceutical materials. This study also showed that these particles exhibited interesting settling behavior in air. In addition, the size difference between the two particle species was chosen to allow complete separation of the red and green using sieve plates. The glass beads of different sizes had the same true density, namely 2.5 g/cm<sup>3</sup>. Figure 2a shows that the bottom of the sediment consisted almost entirely of the larger green beads, the top of the sediment consisted almost entirely of the smaller red beads, and the composition varied consistently with depth.

Figure 2b shows that similar segregation occurred when a mixture of microcrystalline cellulose and dicalcium phosphate was dropped in a vertical pipe. The blue microcrystalline cellulose particles had diameters ranging from 53 to 90  $\mu\text{m}$  (representing a 70 wt% fraction of the commercial material). The

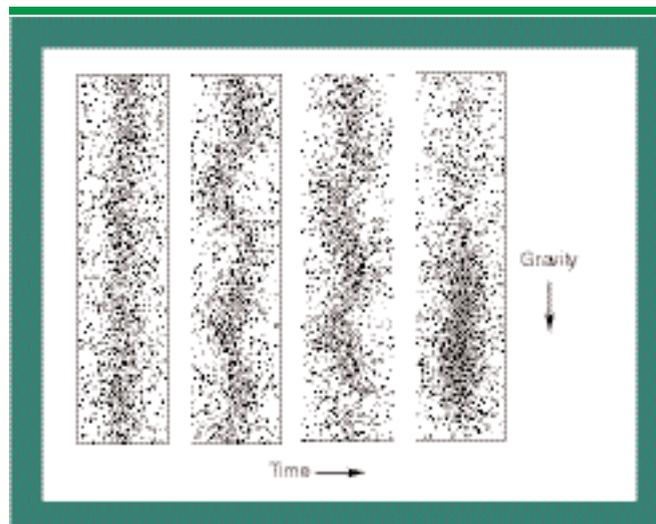


Figure 8: Particle dynamic simulation results for  $\sim 10,000$  cohesionless particles dropping under gravity in a two-dimensional pipe. Even in the absence of an interstitial fluid, density inhomogeneities such as plugs, waves, and clumps can form as a result of inelastic collisions between particles. For this system, pipe diameter =  $33.3 \times$  particle diameter, volume fraction = 0.31. (For details, see Reference 32).

white dicalcium phosphate particles had diameters ranging from 150 to 425  $\mu\text{m}$  (a 60 wt% fraction). The choice of these fractions was twofold: First, the fines were removed to alleviate dusting and hygiene concerns. Second, the two commercial-size distributions overlapped slightly, which meant that a mixture of the materials as supplied could not be perfectly separated on a sieve. Because the mixtures were to be separated with a sieve to quantify segregation profiles, only specific sieve fractions of each of the materials were used. The microcrystalline cellulose powder was sieved through a 90- $\mu\text{m}$  and then a 53- $\mu\text{m}$  sieve. Only the fraction that remained between these two sieves was retained (i.e., the fraction lying between 90  $\mu\text{m}$  and then 53  $\mu\text{m}$ ). The dicalcium phosphate powder was sieved through a 150- $\mu\text{m}$  sieve, and only the fraction that remained on the sieve was retained. Thus, the removal of a small fraction of each of the materials allowed the authors to perform the experiments with powders that could be readily analyzed for segregation. The microcrystalline cellulose and dicalcium phosphate had true densities reported by the supplier of 1.5 g/cm<sup>3</sup> and 2.3 g/cm<sup>3</sup>, respectively. Figure 2b shows that the larger white particles are clearly in excess at the bottom of the sediment, and the amount of the dicalcium phosphate decreases toward the top of the sediment. The opposite effect occurs in the case of the smaller blue particles.

To quantify the degree of segregation at various heights in the sediment, the material was dropped into a collection unit consisting of an outer supporting pipe and an inner pipe that had been cut into 0.5-in. tall rings (see Figure 1b). When the material settled, the outer supporting pipe was removed. The sediment layers in each ring were observed or collected by sliding off one ring, which left the remaining sediment intact. As each ring was removed, the material that was contained in that

ring discharged into a sampling pan for subsequent sieve analysis and mass-fraction determination. Figure 2c depicts the material contained in various rings. For a 50 wt% mixture of white 310- $\mu\text{m}$  glass beads and red 90- $\mu\text{m}$  glass beads dropped 68 in. through a 2-in. diameter pipe, segregation was observed by noting that the material in the top-most ring (ring 1) appeared nearly entirely red. For a ring from lower in the sediment (ring 5), the number of white particles had increased. Finally, Figure 2c shows that no observable radial segregation existed in the sediment.

## Experimental results

Figure 3a shows typical experimental results for an initially well-mixed powder of glass beads containing 50 mass percent fines that have an average diameter of 90  $\mu\text{m}$  and various-sized larger particles (270, 310, and 480  $\mu\text{m}$ ). The powder was dropped 68 in. through a 1-in. diameter pipe. Samples of the sediment were collected, and the mass fraction of fine particles was determined as a function of sediment height. The height of the sample from the base of the apparatus, defined as  $h$ , was nondimensionalized by dividing this value by the total height of the sediment, defined by  $H_s$ . These results confirmed the visual observations shown in Figure 2 and confirmed that mixtures of particles do segregate appreciably during vertical drops of typical heights encountered in common processing situations. This figure shows that for every size ratio, the upper-most layers of the sediment contain significantly more fine particles than do the rest of the sediment. (At the bottom of the sediment,  $h/H_s = 0$ .)

The shape of this segregation profile, referred to hereafter as segregation profile A, is significant. For this set of parameters, segregation does not occur consistently throughout the mixture. Two regions exist: one where the fraction of fines gradually increases through the sediment (i.e.,  $h/H_s$  between 0 and  $\sim 0.8$ ) and the other where there is a relatively large increase in the fraction of fines with height (above  $h/H_s = 0.8$ ). This figure also shows that as the size ratio of the particles increases, the fraction of fines at the bottom of the sediment does not change significantly but does increase appreciably at the top.

The relative standard deviation (RSD) characterizes the relative amount of segregation that occurs for each set of parameters and is defined as follows:

$$\text{RSD} = \sqrt{\frac{\sum_{i=1}^n (\mu - x_i)^2}{n - 1}} \quad [1]$$

in which  $n$  is the number of samples taken,  $m$  is the mean value of all the samples for the quantity of interest (in this case, mean mass fraction = 50%), and  $x_i$  is the value of the  $i$ th sample. Because RSD is a measure of the extent to which each data point varies from the mean, it increases with increased segregation. At the limits,  $\text{RSD} = 0$  for perfectly mixed sediment, and  $\text{RSD} = 1$  for completely segregated sediment. The squares in Figure 3b show the RSD value for each of the three experiments depicted in Figure 3a. This plot clearly shows that as the size ratio increases, the degree of segregation increases and that systems

with a wide range in particle size experience more segregation than those with a more narrow range. In addition, the dependence of RSD on size ratio appears to be linear.

Figure 4a shows the effect of pipe diameter on the segregation of a mixture of glass beads containing 50 wt% of fines that have an average diameter of 90  $\mu\text{m}$  and 50 wt% coarse particles that have a 480- $\mu\text{m}$  diameter. For drops of 68 in., the extent of segregation depends on pipe diameter. For 1-, 2-, and 4-in. inner diameters, the segregation profiles appear similar to those shown in Figure 3a in that the segregation is not consistent throughout the sediment and the mass fraction of fines increases sharply near the top of the sediment (i.e.,  $h/H_s > \sim 0.8$ ). The profiles of these three systems essentially are indistinguishable. However, the segregation profile within the 0.5-in. inner diameter pipe is significantly different. The degree of segregation in the 0.5-in. pipe occurs more consistently through the sediment height and has an S-shaped profile (referred to as segregation profile B). In contrast to profile A found in the larger-diameter pipes, profile B is symmetric. Figure 4b shows that the RSD value captures the dependence of the segregation behavior on the pipe diameter. The three curves in the figure represent experiments that were performed at the three size ratios. In all cases, the segregation behavior varied slightly when the pipe diameter decreased from 4 to 1 in., but a sharp transition occurred when the 0.5-in. diameter apparatus was used.

The effect of drop height on the extent of segregation was investigated. Varying the free-fall distance changed the duration that drag forces acted on the particles. Figure 5a depicts the experiments that were performed in the 0.5-in. pipe for a mixture of 90- and 480- $\mu\text{m}$  particles. The segregation profile changed dramatically as the drop height decreased from 90.5 to 18.5 in. The 90.5-in. drop had the features of segregation profile B, but the segregation profile for the 18.5-in. drop had the features of profile A. Thus, for the 0.5-in. diameter pipe, both segregation profiles were possible, and there was a smooth transition between them by means of an intermediate case. Figure 5b shows that the RSD value increased almost linearly with drop height. These results indicated that the degree of segregation and the shape of the segregation profile in the sediment depended both on the magnitudes of the drag forces and on the particles' time-of-flight (which allows the different velocities created by the drag forces to separate the particles).

All of the results described so far were conducted with glass beads. Experiments performed with a mixture of 50% wt/wt mixture of microcrystalline cellulose (diameter range 53–90  $\mu\text{m}$ ) and dicalcium phosphate (coarser and denser, diameter range 150–425  $\mu\text{m}$ ) are illustrated in Figure 6. When this mixture was dropped in the 0.5-in. diameter pipe, a segregation behavior similar to that for the glass beads occurs. Profiles shown in Figure 6a exhibit both type A and type B characteristics, and again, a smooth transition exists between these. Figure 6b shows the calculated RSD values for the pharmaceutical excipients and those presented in Figure 5b for glass beads. Both systems experienced nearly the same extent of segregation at the same drop height. However, as shown in Figure 7, the effect of pipe diameter on the segregation of pharmaceutical excipients differs from that for the glass beads because there is no longer a

sharp transition when the pipe diameter is decreased to 0.5 in. Instead, the results for 2- and 4-in. pipes are fairly similar, but RSD increased for pipe diameters <2 in. It is not surprising that quantitative differences exist between the results for the glass-bead system and the results for the mixture of pharmaceutical excipients. However, it is particularly noteworthy that the same general trends were observed for both mixture types.

## Discussion

In broad terms, the degree of segregation—as determined by the mass fraction height profiles—increases with the size ratio of glass beads. This correlation is consistent with previous theoretical and experimental findings for segregation driven by vibration or other driving forces (7,16). These earlier works have not typically quantified the rate of segregation as a function of exposure time or geometry of common unit operations, which, as has been shown, can determine the degree of segregation behavior. Although pharmaceutical formulations typically are more complex than bimodal mixtures, these results imply that the presence of fines among coarser particles leads to significant segregation rather rapidly, as is evident from this study involving relatively small drop distances.

Of the well-known mechanisms that lead to size segregation, only air (fluidization) entrainment or particle entrainment in air streams appears to be a significant factor. Visual observation showed that the powder mixtures become dilute during a drop and do not flow exclusively near walls. Thus the extent to which sifting, convection (phenomena requiring intimate particle–particle contacts and particle rearrangements), surface velocity differences, or dynamic effects can act is not obvious. Moreover, these mechanisms result in segregation patterns that have a greater number of large particles near the free surface of the sediment. In contrast, the results of the authors' experiments showed the greatest mass fraction near the base of the sediment layer. This leaves air (fluidization) or particle entrainment segregation as the remaining mechanistic candidates, both of which have been attributed to differential drag forces exerted on particles by the interstitial fluid. Changes in drop height clearly affect the extent of segregation. Therefore, one may intuitively conceive the existence of differences in air drag because as the particles drop, the air retards some particles more than others.

However, the existence of two distinct segregation height profiles cannot be so clearly explained. To help explain this, one must first consider the formation of the near-symmetric profile B, which can be accounted for if the relative migration of coarse particles (downward) and of fines (upward) occurs at a constant rate. If, for simplicity, one considers only the motion of a single particle in air and ignores the fact that each particle is surrounded by other particles (which would lead to a state known as *hindered settling*). The distance fallen  $x$  by one solid particle in air in time  $t$  is given by Equation 2 when the fluid density is sufficiently small compared with that of the powder material (40):

$$x = \frac{1}{2}gt^2 - \frac{4}{3}t^3 \sqrt{\frac{3g^3 \rho_f C_D}{4\rho_s D}} \quad [2]$$

in which  $g$  is the gravitational acceleration,  $\rho_f$  is the fluid density (in this case, air),  $\rho_s$  is the density of the particle of diameter  $D$ , and  $C_D$  is a drag coefficient, which is dependent on the shape and flow regime of the fluid passing around the particle. Because hindered settling effects are neglected, the drag coefficient is determined from correlations for a sphere moving in a fluid (40). Drag is a function of the Reynolds number characterizing particle flow in air. A separate Reynolds number also can be calculated for the flow of air in the pipe. In this case, both the particle and pipe Reynolds numbers are  $\ll 1$ , indicating that flow is laminar and governed by Stokes law. However, in principle, Equation 2 also can be used for turbulent flows with appropriate adjustment in the value of  $C_D$ .

The first term of the right side of the equation is the acceleration solely resulting from gravity, and the second term represents viscous or form drag. For constant physical properties,  $C_D$  decreases and  $D$  increases with particle size, so overall drag is inversely proportional to particle diameter. For one small particle on the scale of the glass beads or the excipients used in this study, one can show that soon after releasing a particle, the drag force grows to the same magnitude as the gravitational force, and the particle rapidly loses acceleration and reaches a terminal velocity. With a smaller relative drag, this terminal velocity is higher for larger particles. Similar arguments can be made even if one takes into account hindered settling as a result of the presence of a cloud of particles. Although in this case, the particle terminal velocity would be affected by the local volume fraction of particles (the additional “viscosity” provided by the presence of the particles would alter the value of  $C_D$ ). However, in both cases one may conclude that the large particles drop more rapidly, thereby resulting in a migration of large particles away from the smaller particles, and preferential accumulation of fines at the top of the sediment and coarse particles near the bottom. Given more time (i.e., for drops of greater height), this difference in velocity is amplified in the segregation profiles and one sees that all profiles eventually resemble profile B for the larger pipe lengths that have been used (see Figures 5a and 6a). However, before this effect becomes dominant, an initial period exists during which fines do not exhibit segregation behavior as shown by the type of profile obtained in shorter drops (profile A). This result also can be observed as the pipe diameter or size ratio increases (see Figures 3a and 4a).

One also can speculate that segregation as a result of differential degrees of particle entrainment is affected by another mechanism during the initial part of a drop. Consider the initial depth of packed powder just as the feed valve at the top of the chute is opened. Particles at the bottom of this bed begin to fall first because their underlying support has been removed, and drag effects will begin to act and encourage coarse particles to migrate downward. However, fine particles are prevented from migrating upwards because of the momentary presence of a dense powder above. In addition, there is no powder below

this material, so it accelerates rapidly into the air below, thereby leading to a relatively short time of flight and thus a short amount of time for segregation to occur. The degree of segregation is thus hindered for the lower part of the powder, which will go on to form the base of the sediment at the end of the drop. In contrast, once underlying powder has fallen away and the top of the initial packing starts to move and be acted on by drag forces, there is no interference to the upward migration of fines or the downward migration of coarse material. Because this part of the initial packing goes on to form the top of the sediment, this phenomena may explain why this region is more strongly segregated for short drops. (Again, for longer drops, the differences in velocities between small and large particles are thought to overcome the initial transients).

Another observation that deserves further discussion is the effect of pipe diameter. It is proposed that the dependence of the extent of segregation on pipe diameter is a result of a hydrodynamic instability in the flow. Hydrodynamic instabilities have been shown to lead to regions of clusters in many systems including gas–solid fluidized beds (41) and sedimentation of binary mixtures in viscous fluids (42–45).

As discussed, extensive work has been conducted recently on gravity flow of granular material through vertical pipes. Researchers have observed that the material does not flow homogeneously; regions of high solids fraction are surrounded by regions of lower-than-average solids fraction. For example, Figure 8 shows results of particle-dynamic simulations of a two-dimensional vertical channel with side walls, in which a variety of plug, wave, and clump structures can readily form for gravity driven flow owing to inelastic collisions between particles (32). These structures allow air to channel around particle clusters instead of passing evenly past all of the particles, exerting less total drag on average. The particles therefore descend more quickly and have less time to segregate. From hydrodynamic stability analyses of fluid-particle flows in wall-bounded geometries and observations of the effect of pipe diameter on segregation, the authors hypothesized that there is a critical pipe width at which this instability occurs. It appears that for the glass beads used in this study, the flow in the 0.5-in. diameter pipe is relatively uniform, and the drag force acting on the particles is on average greater than that in the larger diameter pipes (which are affected by channeling or gas bypassing), thereby causing the material to drop more slowly and allowing for the powder to segregate further.

Figure 7 suggests that density inhomogeneities also occur for the mixture of excipients, but in this case the critical pipe diameter is  $\sim 2$  in. The effect of air channeling on segregation could theoretically be investigated in more detail by the extension of multiphase computational fluid dynamics modeling approaches (46–47). For example, much research has been performed to investigate multiphase flows in fluidized-bed reactors by modeling fluid and particle phases as interacting continua (48). However, work remains to determine appropriate constitutive equations describing the collective motion of a mixture of particles as a function of flow properties.

Results suggest certain changes can be made to reduce the segregation of pharmaceutical powders in vertical drops. Avoid-

ing long drops is well recognized as beneficial for ensuring uniformity (21). Decreasing the drop height does not eliminate the potential for segregation as a result of differential air drag, but it reduces the time available for this to take effect. For example, in direct-compression tableting it is common to attempt to minimize the drop height between the blender discharge and the compressing machine inlet hoppers. However, cases exist in which a finite drop height is unavoidable (e.g., use of nonstandard compressing machine, retrofit of an existing facility). The measurements show in Figures 5 and 6 provide representative rates of segregation evident in drops as high as 90.5 in. Less well known is the effect shown in this study of pipe diameter, where it may be feasible to offset the segregation expected in a vertical drop by increasing pipe diameters slightly. For example, Figures 4b and 7b indicate that reducing segregation by a factor of two is possible if pipe diameter is increased from 0.5 to  $>1$  in. Marginal reductions in segregation still can be obtained for larger diameters. Because a difference in air drag is the main size-segregation mechanism, reducing this drag should also help alleviate problems. This reduction can be achieved by venting the pipe to allow air to flow out the pipe rather than through the powder mass. Another possibility is reducing the pressure in the drop line. Johanson suggests that the addition of moisture to agglomerate particles can prevent air-current segregation, although the authors consider the application of this method in the pharmaceutical industry to be limited (49).

This study has been limited to a very small sampling of the materials one can expect in a pharmaceutical formulation. Although ultimately, the authors would like to be able to predict the relationship between measurable formulation properties, drop height, and geometry on the rate of segregation, the tests described in this article and in previous works such as Johanson (7) and Chowhan (23) can be used to test a new formulation at a relatively small scale. This test may reveal potential problems before piloting or full-scale manufacturing, in which subsequent modifications to processing facilities can be extremely expensive and time-consuming.

The current work involves the development of a model based on hydrodynamics to further investigate the segregation features in vertical drops. The initial work assumes a one-dimensional system in which variations in the vertical direction are modeled and wall effects are not considered (46,47,50). Initial results have verified that the magnitude of drag forces in a closed vertical pipe is large enough to cause significant segregation in drops on the order of a few feet. It is hopeful that such a model could be used as a predictive tool for the design of powder-handling systems. This work could be extended to account for walls in a two- or three-dimensional domain. Future work also could include examination of the bypassing of air and formation of particle clusters to suggest ways to minimize segregation in longer drops. We also have not closely examined the segregation of fines of diameter  $<50 \mu\text{m}$ , in which the effect of expected increases in cohesion may be significant for reducing segregation. This size range is important for many drug substances and warrants additional investigation. Progressing from a trial-and-error approach for prediction of seg-

regation to a more methodical quantification and design process is desirable for quality control purposes and is more amenable to process validation. Although assured blend uniformity usually takes precedence over other considerations such as equipment and material costs and operational concerns, it is obvious that understanding the rates of the various segregation mechanisms also benefits development and troubleshooting activities. Furthermore, as modern markets demand that production equipment be used for the widest range of products possible, there are advantages in avoiding major product-specific equipment modifications by discovering segregation problems early in development.

## Conclusion

An experimental apparatus was developed to measure segregation that occurs during vertical drops from 6 in. to 8 ft. The authors showed that significant size segregation can occur for dropping distances of a few feet. Four modular systems were constructed using 4-, 2-, 1-, and 0.5-in. inner diameter piping to investigate the effect of pipe diameter on segregation. The extent of segregation was quantified by measuring segregation profiles in the sediment as well as the RSD of a profile. Segregation for both cohesionless glass beads as well as typical pharmaceutical excipients was investigated.

Although one may hypothesize that a smaller system would have less propensity to segregate, this is not born out by the experiments conducted on pipe width. For drop height, the results were as expected: an increase in segregation was observed with an increase in drop height. Most results could be classified into two characteristic segregation profiles: a symmetric profile occurring in large-duration drops, characterized by equal rates of upward and downward segregation, and a profile with a higher degree of segregation at the top of the sediment, seen in large-diameter pipes and shorter drops. Arguments based on a differential air drag were used explain the profiles. Generally, segregation decreases as pipe diameter increases. Previous researchers have shown that density inhomogeneities can occur in wide pipes, and the authors conjecture that these lead to channeling of the gas, reduced total drag force, and thus less time for segregation. Pipe diameter is thus an important consideration in the design of feed frames to tablet presses, for example. Results suggest that for particle parameters and drop heights typical of pharmaceutical processing, segregation during gravity-driven drops must be properly considered in the maintenance of formulation blend uniformity.

## Acknowledgment

We thank C. Sutton, H. Guo, C. Gallop, F. Aslam, and J. Lowden for their experimental assistance. This work was partially supported by Merck Research Laboratories.

## References

- C.S. Campbell, "Rapid Granular Flows," *Annu. Rev. Fluid Mech.* **22**, 57–92 (1990).
- L. P. Kadanoff, "Built upon Sand: Theoretical Ideas Inspired by Granular Flows," *Reviews of Modern Physics* **71** (1), 435–444 (1999).
- K. Hutter and K.R. Rajagopal, "On Flows of Granular Materials," *Continuum Mech. Thermodyn.* **6**, 81–139 (1994).
- T. Shinbrot and F.J. Muzzio, "Nonequilibrium Patterns in Granular Mixing and Segregation," *Physics Today* 25–30 (March 2000).
- H. Matthee, "Segregation Phenomena Relating to Bunkering of Materials: Theoretical Considerations and Experimental Investigations," *Powder Technol.* **1**, 265–271 (1967).
- J.N. Staniforth, "Advances in Powder Mixing and Segregation in Relation to Pharmaceutical Processing," *Int. J. Pharm. Tech. Prod. Mfr.* **3** (suppl.), 1–12 (1982).
- J.R. Johanson, "Solids Segregation: Causes and Solutions," *Powder and Bulk Engineering* 13–19 (August 1988).
- S.R. de Silva and G.G. Enstad, "Bulk Solids Handling in Scandinavia: A Case Study in the Aluminum Industry," *Bulk Solids Handling* **11**, 65–68 (1991).
- D. Stuart-Dick, "Segregation Affects Glass Quality," *Ceram. Eng. Sci. Proc.* **17**, 78–83 (1996).
- J.W. Carson, T.A. Royal, and D.J. Goodwill, "Understanding and Eliminating Particle Segregation Problems," *Bulk Solids Handling* **6**, 139–144 (1986).
- H. Matthee, "Segregation Phenomena Relating to Bunkering of Materials: Theoretical Considerations and Experimental Investigations," *Powder Technol.* **1**, 265–271 (1967).
- P. Arteaga and U. Tuzun, "Flow of Binary Mixtures of Equal-Density Granules in Hoppers: Size Segregation, Flowing Density and Discharge Rates," *Chem. Eng. Sci.* **45**, 205–223 (1990).
- J.K. Prescott and R.J. Hossfeld, "Maintaining Product Uniformity and Uninterrupted Flow to Direct Compression Tablet Presses," *Pharm. Technol.* **18**, 99–114 (1994).
- A. Alexander et al., "A Method to Quantitatively Describe Powder Segregation during Discharge from Vessels," *Pharm. Technol., Tableting & Granulation Yearbook* 6–21 (2000).
- S.B. Savage and C.K.K. Lun, "Particle-Size Segregation in Inclined Chute Flow of Dry Cohesionless Granular Solids," *J. Fluid. Mech.* **189**, 311–335 (1988).
- J.A. Drahn and J. Bridgewater, "The Mechanics of Free Surface Segregation," *Powder Technol.* **36**, 39–53 (1983).
- H.A. Makse and H.J. Herrmann, "Microscopic Model for Granular Stratification and Segregation," *Europhys. Lett.* **43**, 1–6 (1998).
- O. Zik et al., "Rotationally Induced Segregation of Granular Materials," *Phys. Rev. Lett.* **73**, 644–647 (1994).
- A.S. Hussain, "Blend Uniformity: PQRI Research," FDA docket presented at the Advisory Committee for Pharmaceutical Science (CDER, FDA, Rockville, MD, 8 May 2002), [http://www.fda.gov/ohrms/dockets/ac/01/slides/3804s1\\_05\\_hussain.ppt](http://www.fda.gov/ohrms/dockets/ac/01/slides/3804s1_05_hussain.ppt).
- Federal Register*, **67**, 96 (17 May 2002).
- C. Wibowo and K.M. Ng, "Operational Issues in Solids Processing Plants: Systems Overview," *AIChE J.* **47** (1), 107–125 (2001).
- Z.T. Chowhan, "Segregation of Particulate Solids, Part I," *Pharm. Technol.* **19** (5), 56–63 (1995).
- Z.T. Chowhan, "Segregation of Particulate Solids, Part II," *Pharm. Technol.* **19** (6), 80–94 (1995).
- J. Mosby, S.R. de Silva, and G.G. Enstad, "Segregation of Particulate Materials: Mechanisms and Testers," *KONA* **14**, 31–42 (1996).
- A.M. Scott and J. Bridgewater, "Interparticle Percolation: A Fundamental Solids Mixing Mechanism," *Ind. Eng. Chem. Eng.* **14**, 22–27 (1975).
- J.B. Knight, H.M. Jaeger, and S.R. Nagel, "Vibration-Induced Size Separation in Granular Media: The Convection Connection," *Phys. Rev. Lett.* **70**, 3728–3731 (1993).
- J. Lee and M. Leibig, "Density Waves in Granular Flow: A Kinetic Wave Approach," *J. Phys. I France* **4**, 507–514 (1994).
- G. Peng and H.J. Herrmann, "Density Waves of Granular Flow in a Pipe Using Lattice-Gas Automata," *Phys. Rev. E* **49**, R1796–R1799 (1994).
- T. Poschel, "Recurrent Clogging and Density Waves in Granular Material Flowing through a Narrow Pipe," *J. Phys. I France* **4**, 499–506.
- C.-H. Wang, R. Jackson, and S. Sundaresan, "Instabilities of Fully Developed Rapid Flow of Granular Material in a Channel," *J. Fluid Mech.* **342**, 179–197 (1997).

31. A. Valance and T. Le Penec, "Nonlinear Dynamics of Density Waves in Granular Flows through Narrow Channels," *Eur. Phys. J. B* **5**, 223–229 (1998).
32. E.D. Liss, S.L. Conway, and B.J. Glasser, "Density Waves in Gravity-Driven Granular Flow through a Channel," *Physics of Fluids* **14**, 3309–3326 (2002).
33. S. Horikawa et al., "Self-Organized Critical Density Waves of Granular Material Flowing through a Pipe," *J. Phys. Soc. Jpn.* **64**, 1870–1873 (1995).
34. T. Raafat, J.P. Hulin, and H.J. Herrmann, "Density Waves in Dry Granular Media Falling through a Vertical Pipe," *Phys. Rev. E* **53**, 4345–4349 (1996).
35. O. Moriyama et al., "Dynamics of Granular Flow through a Vertical Pipe: Effect of Medium Flow," *J. Phys. Soc. Jpn.* **67**, 1616–1624 (1998).
36. O. Moriyama et al., "Statistics and Structure of Granular Flow through a Vertical Pipe," *J. Phys. Soc. Jpn.* **67**, 1603–1615 (1998).
37. J.-L. Aider et al., "Experimental Study of a Granular Flow in a Vertical Pipe: A Spatiotemporal Analysis," *Physical Review E* **59**, 778–786 (1999).
38. J. Hua and C.-H. Wang, "Electrical Capacitance Tomography Measurements of Gravity-Driven Flows," *Ind. Eng. Chem. Res.* **38**, 621–630 (1999).
39. J.C. Williams, "The Segregation of Particulate Materials: A Review," *Powder Technol.* **15**, 245–251 (1976).
40. J.O. Wilkes, *Fluid Mechanics for Chemical Engineers* (Prentice Hall, New York, NY, 1999), p. 188.
41. J.C. Chen, *Clusters: Progress in Fluidized and Fluid Particle Systems*, D. King, Ed. (American Institute of Chemical Engineers, New York, NY, 1995) **92**, pp. 1–4.
42. R.H. Weiland, Y.P. Fessas, and B.V. Ramarao, "On Instabilities Arising during Sedimentation of Two-Component Mixtures of Solids," *J. Fluid Mech.* **142**, 383–389 (1984).
43. G.K. Batchelor and R.W. Janse van Rensburg, "Structure Formation in Bidisperse Sedimentation," *J. Fluid Mech.* **166**, 379–407 (1986).
44. R.G. Cox, "Instability of Sedimenting Bidisperse Suspensions," *Int. J. Multiphase Flow* **16**, 617–638 (1990).
45. P. Valiveti and D.L. Koch, "Instability of Sedimenting Bidisperse Particle Gas Suspensions," *Applied Scientific Research* **58**, 275–303 (1998).
46. Y.T. Shih, D. Gidaspow, and D.T. Wasan, "Hydrodynamics of Sedimentation of Multisized Particles," *Powder Technol.* **50**, 201–215 (1987).
47. Y. Zimmels, "Simulations of Nonsteady Sedimentation of Polydisperse Particle Mixtures," *Powder Technol.* **56**, 227–250 (1988).
48. Agrawal et al., "The Role of Mesoscale Structures in Rapid Gas-Solid Flows," *J. Fluid Mech.* **45**, 151–185 (2001).
49. J.R. Johanson, "Predicting Segregation in Binary Particle Mixtures Using the Flow Properties of Bulk Solids," *Pharm. Technol.* **20**, 46–57 (1996).
50. R.A. Williams and W.P.K. Amarasinghe, "Measurement and Simulation of Sedimentation Behavior of Concentrated Polydisperse Suspensions," *Trans. Instn. Min. Metall.* **98**, C68–C82 (1989). **PT**

**Please rate this article.**

On the Reader Service Card, circle a number:

**345 Very useful and informative**

**346 Somewhat useful and informative**

**347 Not useful or informative**

*Your feedback is important to us.*