powder flow

Identifying and controlling segregation in tablet press feed systems

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This article describes the modes of segregation that can occur in tablet press feed systems and how to assess which mode dominates. It also provides design strategies to overcome segregation and uses a five-ingredient formulation as an example to illustrate the principles discussed.

Segregation can be a serious issue when a blend of multiple powders is fed to a tablet press, capsule filler, or other process equipment. This is especially true when the blend contains an API whose ratio must be maintained from the start to the finish of a tablet batch. In such cases, it is important to understand the blend's flow and segregation properties in order to design or select a tablet press feed system that minimizes segregation.

Solving a segregation issue from a process standpoint requires understanding four things and summoning the will to make changes. The first step is to measure the segregation potential of the blends of interest. When choosing the measurement methodology, seek tests that:

• Relate to actual processes in the production facility. Many test methods induce a stimulus designed to separate particles and then assess segregation behavior without considering whether the induced stimulus would typically occur in the process. Where possible, use segregation tests that relate to the type of flow behavior you expect during actual production.

• Reveal the segregation pattern (i.e., where each ingredient ends up spatially during filling or handling).

• Determine the magnitude of segregation ingredient by ingredient. This is typically done and reported as a standard deviation or variance relative to the mean concentration for each ingredient. In the pharmaceutical industry, this relates to the allowable range for acceptable content uniformity.

• Identify and quantify, to the extent possible, the root cause(s) of segregation. Segregation is a mechanistic phenomenon with multiple potential causes. Resolving a segregation problem requires understanding the specific cause in order to design a feed system that either avoids a stimulus that causes particles to separate or optimizes velocity profiles to remix segregated material during handling.

Second, review the fill and transfer operations that occur in the actual process after the blending step. The goal here is to identify stimuli that could induce particles to separate and—in conjunction with the segregation test results—compute or estimate the expected segregation pattern that could develop in a vessel after filling or after the blend is transferred. Sometimes the solution is to prevent or minimize a stimulus that causes segregation during filling. Thus, it's critical to understand where the different particles end up after filling.

Third, understand how flow properties and equipment geometry interact to generate flow profiles in the process. In this step, you must determine the expected velocity profile in the feed system in order to estimate at what point during the emptying cycle each segregating ingredient might leave the system. In many cases, mitigating segregation requires controlling velocity in the feed devices. Testing may reveal that a blend or ingredient shows moderate segregation, yet by designing the feed system to give the right velocity profiles, it's possible to remix the blend before it reaches the tablet press die.

Finally, modify the filling process and/or feed system geometry to eliminate or minimize each cause of segregation and, where the causes cannot be eliminated, design the feed system to create the velocity profiles that can handle the expected segregation pattern.

To better understand segregation mitigation, we'll use as an example a drug product blend of 10 percent API and several excipients: microcrystalline cellulose (MCC), lactose, glycolate, and magnesium stearate.

Segregation from powder transfers

The method used to measure segregation must generate stimuli comparable to those expected in the process that may induce particles to separate from each other. In a typical operation, once the powders are combined in a blender, they enter the feed system above the tablet press or are held in another vessel for later use. In either case, the material is transferred at least once from a blender to an empty vessel before it reaches the feed frame of the press and the die filling stations. Because mechanical constraints make transferring the blend directly to the feed frame difficult, almost all tablet press feed systems have a small to medium size receiving hopper. This arrangement raises two important questions about the blend's segregation behavior:

1. What type of behavior will be induced in the material when gas from an empty vessel attempts to vent up through the blender?

2. What segregation may occur as a pile forms when the blend is transferred to a receiving vessel or feed hopper?

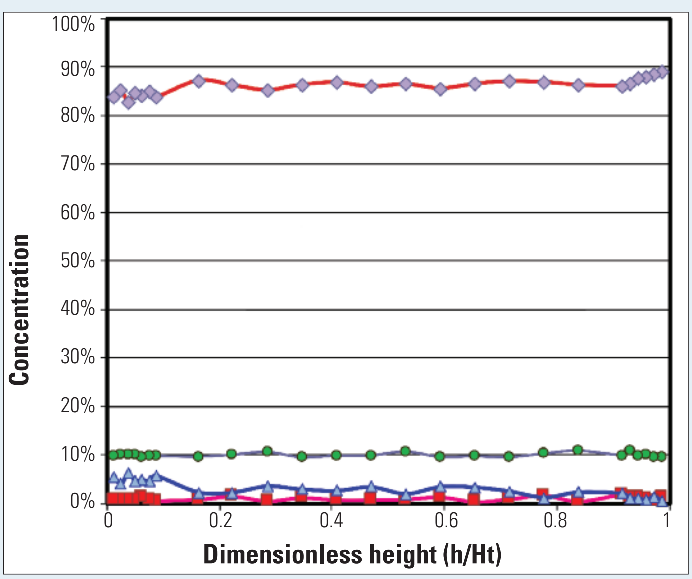
Gas fluidization of the blend

Powder flowing from the blender into a sealed feed hopper or holding vessel will cause the gas pressure in the vessel being loaded to increase until it reaches a critical value, after which a void or bubble will form at its inlet. This will induce a short-lived fluidization event and cause a "burp" to rise up through the blender. This may happen several times, and segregation could occur if fine particles are carried up with the gas. Thus, one segregation test protocol is to form a column of material and expose it to several short-lived fluidization events. A variety of test methods can be used to determine whether a given material is sensitive to segregation in a fluidized environment. The standard protocol is to fluidize the blend using gas for a long period and then measure the segregation concentrations. But that method wouldn't be effective in this case because the actual stimulus in the fill process is a very short-lived fluidization. Relying on the standard protocol would thus lead to erroneous conclusions.

Consider the segregation behavior of the API in a blend that, as it discharges in a column, is exposed to three short-lived fluidization events (Figure 1). In this case, the concentration profile of the blend was observed from the side of the column through a port after three fluidization

Figure 1

Key concentration of components in material after three distinct short-term fluidization events



Material	Segregation intensity (relative to mean)
MCC/Lactose	1.75%
Mag stearate	40.18%
Glycolate	54.86%
API	4.22%

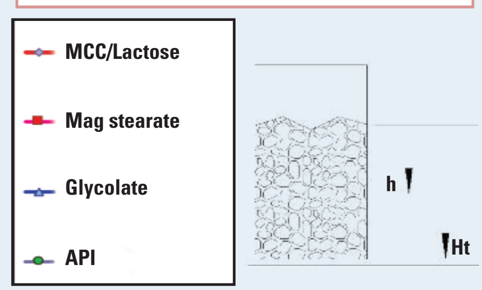
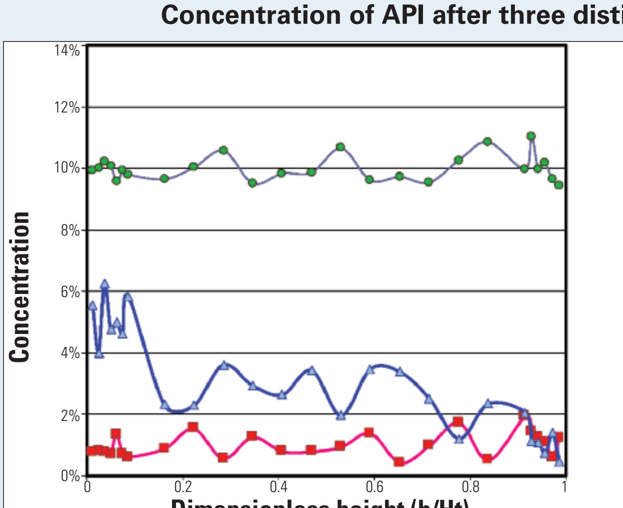


Figure 2

Concentration of API after three distinct short-term fluidization events



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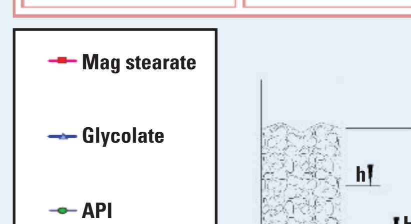


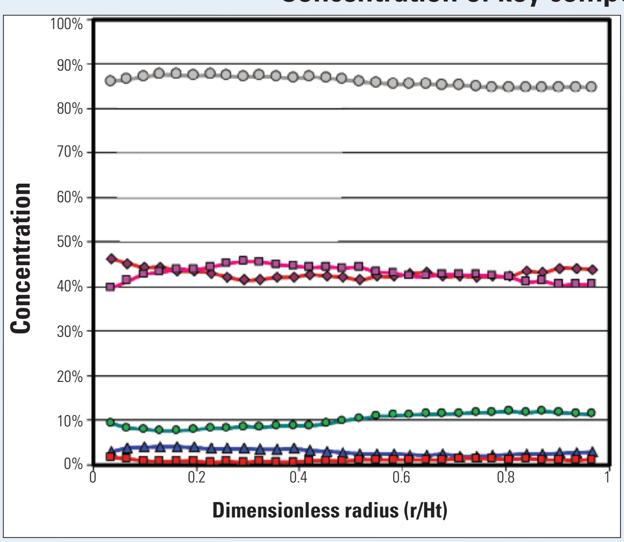
events. Next, the concentrations of the blend's five ingredients were determined using a spectroscopic segregation tester [1]. This automated tester measured 25 samples along the depth of the column. Because segregation due to fluidization events often occurs near the boundaries of the material, the data were biased to take more measurements at the top and bottom. Figure 2 shows the results.

The data in figures 1 and 2 are presented as a dimensionless depth (h/Ht), where (h) is the distance from the top of the material and (Ht) is the depth at the bottom of the column. Point 0.0 represents material at the top of the column and 1.0 represents material at the bottom. The API shows only a minor segregation tendency but has three distinct increases in concentration at various column depths. These higher concentrations could have been caused by the three fluidization events. The glycolate shows major fluidization segregation, concentrating at the top of the column, and there appears to be interplay between the glycolate and two other excipients, MCC and lactose. This shows the importance of measuring the segregation profile of all ingredients in the blend. API segregation is within an acceptable range, but the other ingredients segregate relative to each other. This is a common occurrence when there are more than two ingredients. Most current literature—and less stringent segregation test protocols—deal with segregation in bimodal systems and pinpoint only one cause. Although it is possible to find measurements of simple bimodal materials, they offer little help in understanding the complexity of segregation in real blends. To be worthwhile, the test protocol should measure segregation in multi-ingredient blends after subjecting the material to a stimulus that is process-specific.

From this single segregation test, we learned that the API will not likely separate significantly when the blend is transferred to a receiving vessel. However, if the blend cannot be remixed before it gets to the die filling station, the amount of glycolate (a glidant) in each tablet may vary, and there may be flow problems during the tabletting run.

Figure 3

Concentration of key components due to formation of a pile



Material	Segregation intensity (relative to mean)
MCC	2.57%
Lactose	3.70%
Glycolate	24.76%
Mag stearate	28.49%
API	16.37%
MCC - Lactose	1.30%

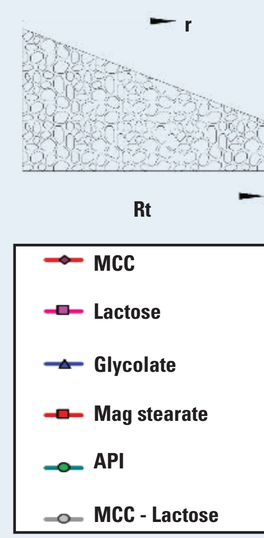
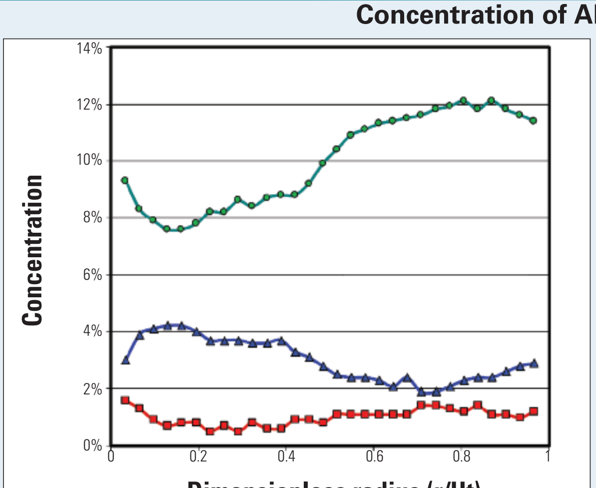


Figure 4

Concentration of API due to formation of a pile



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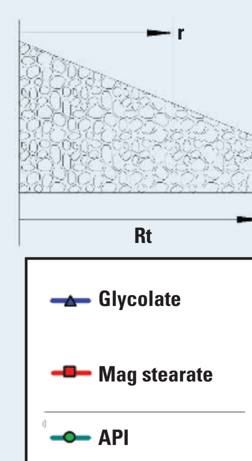


Segregation during pile formation

To assess how segregation occurs when the blend forms a pile, we need another segregation test protocol. To start, a thin slice of a bin or hopper is filled with material to form a pile. As the pile forms, a thin layer of material slides down the top of the pile's surface and creates zones where the powders exhibit a lot of inter-particle motion. There is a stagnant zone below this sliding zone. The fines could pass through the voids between coarse particles during sliding and get stuck in the void structure of the bulk material in the stagnant zone. This generally causes fines to accumulate at or near the top of the pile. In addition, air currents induced by the material freefalling into the vessel often carry fines to the vessel's edge, causing them to accumulate at the wall.

Differences in the frictional characteristics of the particles could cause some of them to slide faster down a pile, separating particles that have different repose angles. Differences in the coefficient of restitution of the particles could cause the more resilient particles to bounce farther down the pile, resulting in segregation due to the elastic properties of the particles. In a process, all these mechanisms can occur simultaneously. Therefore, the test protocol must simulate, to the extent possible, the expected behavior in the actual filling process. The protocol should provide data about the magnitude of segregation, its pattern, its intensity due to pile formation and, if possible, the root cause(s) of segregation ingredient by ingredient. Furthermore, by controlling the flow rate and drop height into the test equipment, you can correlate data obtained from the test to real process behavior.

Using the same spectroscopic tester [1] from the fluidization test, a pile is formed in a slice model test cell, and the segregation pattern is observed from the side. Next, NIR spectral techniques are used to measure the concentration profiles of all the ingredients down the pile. When analyzing the example blend, which contains 10 percent API, we observe a significant amount of it segregates (figures 3 and 4). This segregation concentration profile is expressed as a function of a dimensionless radius, where 0.0 represents the top of the pile and 1.0 represents the bottom. The pile segregation data suggest that the API concentration is moderately high at the pile's top, decreases halfway down the pile, and becomes high again at the bottom. This curious relationship suggests multiple segregation mechanisms may be acting on the material during pile formation.

The gycolate accumulates at the top of the pile, while its concentration is lower at the bottom of the pile. However, there is a slight increase near the bottom of the pile. The segregation behavior of the MCC and lactose, which are bulking agents, is interesting: When the concentration of one increases, it induces a decrease in the other's concentration, and this occurs in almost equal amounts. Because of this symbiotic relationship, the blend's total concentration of bulking agents is less prone to segregate.

Note how conducting these two simple segregation tests—fluidization and pile formation—provides sufficient information to get a very good idea of where different ingredients might end up in a typical tablet press feed system. The root cause(s) of the segregation, however, are not yet fully quantified. That requires additional information.

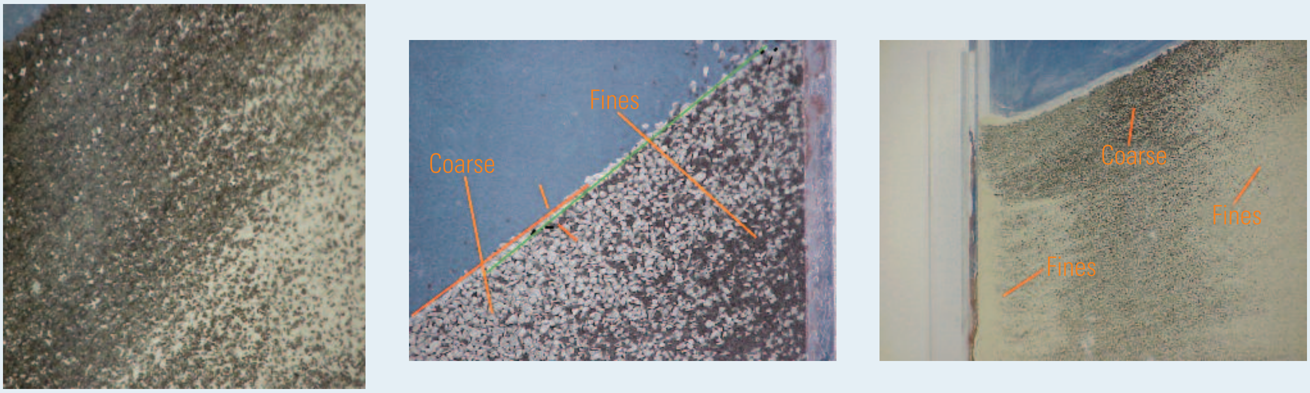
Other segregation mechanisms

Next, let's see what happens when the blend is subjected to each unique segregation mechanism. In sifting segregation, fines pass through a matrix of coarse particles. This type of segregation is driven by differences in particle size and the degree to which the voids between particles are filled with particles of sufficient size to prevent the passage of small particles (Figure 5a). When segregation arises due to a difference in repose angle, it is because ingredients with different frictional surfaces slide at different velocities down a pile (Figure 5b). Just 2 degrees of difference in this angle can cause significant segregation. The other segregation mechanism we will investigate is caused by fines being carried by air currents during the filling process (Figure 5c). In this scenario—air-entrainment segregation—particle size and the true density of the particles are the drivers.

Sifting segregation. In the ideal particle size distribution—which can exist—all voids are filled with particles

Figure 5

Typical patterns of segregation due to various mechanisms



Sifting segregation

Angle-of-repose segregation

Air-entrainment segregation

Figure 6

Particle size of components in mixture and driving force for sifting

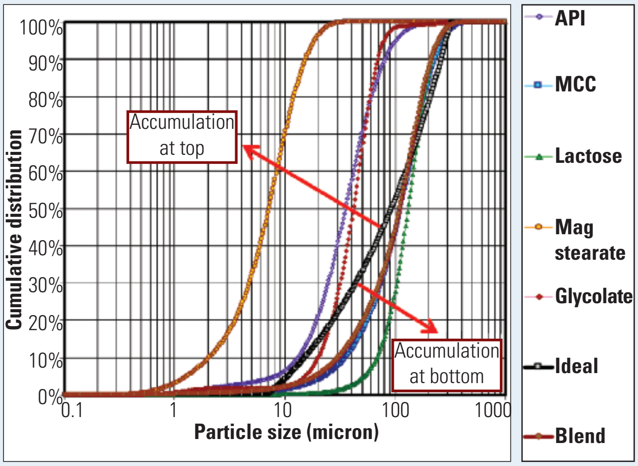


Table 1

Relative segregation variance for sifting

Material	Normalized sifting segregation variance (%)	Segregation direction (top or bottom of pile)
API	3.5	Top
MCC	5.3	Bottom
Lactose	5.0	Bottom
Mag stearate	72.6	Top
Glycolate	13.7	Top

of the appropriate size (Figure 6). The difference in cumulative concentration between the ideal particle size curve and the blend's particle size curve enables us to rank the blend's tendency to segregate by sifting. We do not present the complete methodology here, but Table 1 shows the expected relative segregation tendency if sifting were the only cause. If we make that assumption, these data suggest that 3.5 percent of the total segregation would be due to the API, 5.3 percent due to MCC, 5.0 percent due to lactose, 72.6 percent due to magnesium stearate, and 13.7 percent due to glycolate.

Angle-of-repose segregation. It is possible to conduct a similar analysis for angle-of-repose segregation because the velocity of particles sliding down the pile is a function of the tangent of the repose angle. If the repose angle is large, then the velocity down the pile is low. If the repose angle is small, then the velocity down the pile is high. Furthermore, the deviation from the average repose angle provides a means of ranking the tendency for angle-of-repose segregation (Figure 7). The complete methodology is not presented here, but Table 2 shows the expected relative segregation tendency if angle-of-repose segregation were the only cause of segregation. If we make that assumption, then 34.6 percent of the total segregation would be due to the API, 2.1 percent due to MCC, 7.2 percent due to lactose, 10.1 percent due to magnesium stearate, and 46.0 percent due to glycolate.

Air-entrainment segregation. As stated above, air-entrainment segregation depends on both the particles' size and their true density. If the particles are light or small, they are carried further down the pile. Table 3 shows the expected relative segregation tendency when air

Figure 7

Repose angles of components in blend

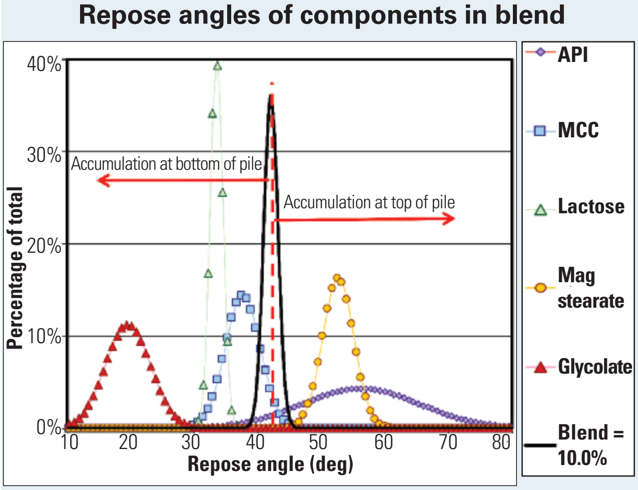


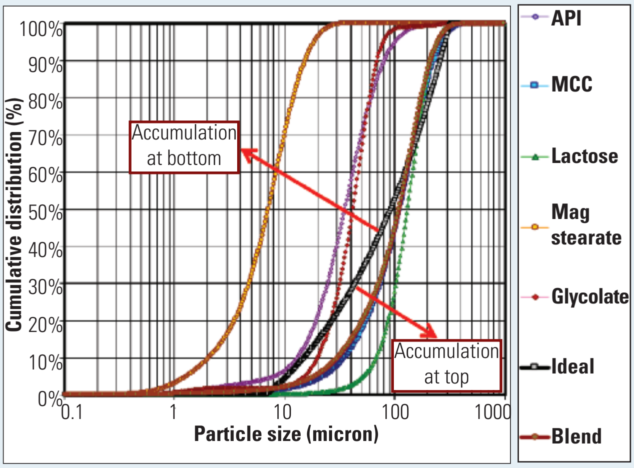
Table 2

Relative segregation variance for angle of repose

Material	Normalized angle of repose variance (%)	Segregation direction (top or bottom of pile)
API	34.6	Top
MCC	2.1	Bottom
Lactose	7.2	Bottom
Mag stearate	10.1	Top
Glycolate	46.0	Bottom

Figure 8

Particle size of components in blend and driving force for air entrainment



Material	True density (kg/m³)
API	1120
MCC	1570
Lactose	1540
Mag stearate	1090
Glycolate	1490

TABLE 3

Relative segregation variance for air entrainment

Material	Normalized angle of repose variance (%)	Segregation direction (top or bottom of pile)
API	0.3	Bottom
MCC	0.0	Top
Lactose	0.1	Top
Mag stearate	99.4	Bottom
Glycolate	0.2	Bottom

TABLE 4

Segregation intensity values for blend

Material	Measured segregation intensity (%)
API	16.4
MCC	2.6
Lactose	3.7
Mag stearate	28.5
Glycolate	16.4

TABLE 5

Quantification of segregation mechanism

Type of segregation	Percentage of total
Sifting	51.8
Angle of repose	8.2
Air entrainment	40.0

entrainment is the only cause. If we make that assumption, then 0.3 percent of the total segregation would be due to the API, 0.0 percent due to MCC, 0.1 percent due to lactose, 99.4 percent due to magnesium stearate, and 0.2 percent due to glycolate. The pattern of the magnesium stearate segregation indicates it accumulates at the top and bottom of the pile. This indicates that the sifting and air-entrainment mechanisms are dominant in this blend.

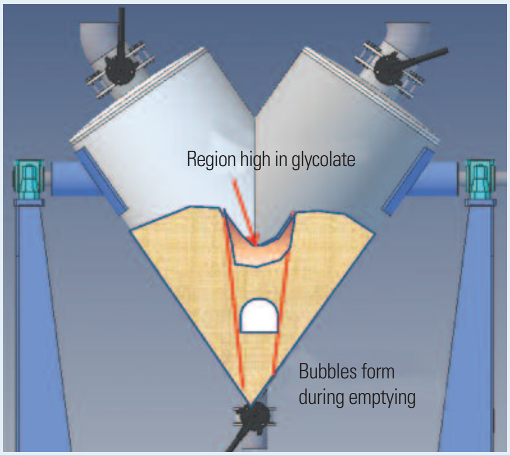
Using the measured segregation intensity (Table 4) and the normalized segregation variance for each mechanism, we can determine the percentage of segregation attributed to each segregation mechanism (Table 5). In our example, 51.8 percent of the segregation is due to sifting, 8.2 percent due to angle-of-repose effects, and 40.0 percent due to air entrainment.

FIGURE 9

Typical tablet press operation

FIGURE 10

Expected segregation in blender after initial charge of feed system



Process review

To illustrate how the process may affect segregation, we will assume that a V-type blender mixes the ingredients into a uniform blend and then discharges it to a tabletting operation below (Figure 9). Note that the transfer occurs in a closed system, with the blender connected to a sealed feed hopper. From the hopper, the blend moves through one or more chutes to the tablet press, where it enters the feed frame that fills the dies.

Blender. The blender discharges in a funnel-flow pattern, and as indicated by the fluidization segregation test, if the gas attempting to leave the feed hopper vents upward through the blender, a concentration of glycolate may rise to the top of the material remaining in the blender (Figure 10). Due to this funnel-flow discharge, we expect the active flow channel to empty first, with material sloughing in from the sides as the emptying cycle nears its end. This suggests that the concentration of glycolate increases by about 25 to 35 percent during the blender emptying cycle. Fortunately, the fluidization test indicated that the API will not undergo this type of segregation and should leave the blender with good uniformity.

We now have all the information needed to fully understand segregation associated with this blend. Zones where material flow generates inter-particle motion will induce sifting segregation. Since 51.8 percent of the segregation occurring in the material is due to sifting, zones of high inter-particle motion should be avoided. There are two distinct zones high in inter-particle motion in typical tablet filling systems. One zone is due to the flow behavior as material periodically cascades down a pile in a thin layer. This will create a significant velocity gradient across the flowing layer, and the sifting that occurs in this zone will result in fine particles accumulating at the top of any piles. Thus, filling the vessel without allowing piles to form or minimizing the piles will reduce sifting segregation. Angle-of-repose segregation will also be

FIGURE 11

Expected API concentration in feed hopper above press

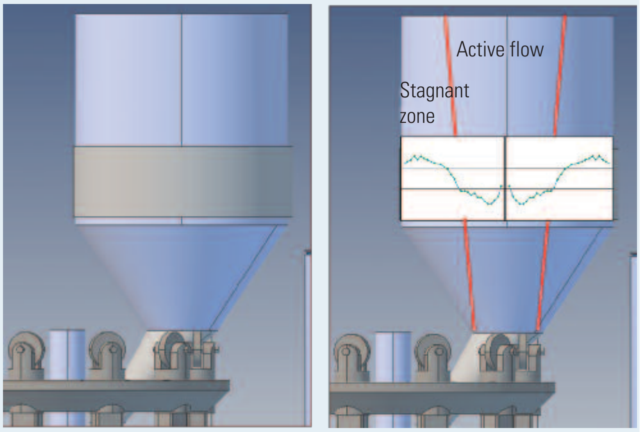
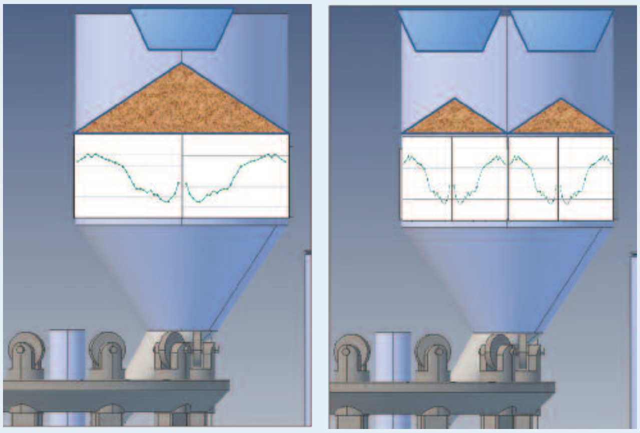


FIGURE 12

Expected API concentration in feed hopper above press after addition of baffles



minimized by the reduction of piles. These steps will eliminate 60 percent of the segregation problem. Minimizing pile formation, however, will have no effect on air-entrainment segregation, which could be mitigated by filling the feed system or receiving bin in a way that reduces freefall. Designing the feed system or receiving vessel to create a velocity profile that remixes material at the hopper outlet could also help.

Feed hopper. Next, let's consider the segregation pattern that may exist in the feed hopper above the tablet press. It typically has a funnel-flow design, so material will not flow along the hopper walls during discharge until material at the center discharges. Only then will material near the walls slough into the flow channel and discharge. The test for pile segregation suggests that a low concentration of API will form at the center of the bin and a high concentration will form at the side (Figure 11). Therefore, the API concentration will be lower than normal when the discharge starts and higher than normal when it ends. Now, suppose that baffles or other devices were added to produce multiple piles in the feed hopper. That would change the segregation pattern relative to the active flow channel (Figure 12), creating a more uniform average API concentration during discharge. This demonstrates that the filling mode can greatly influence segregation in this location.

As an alternative—or in addition—the press feed hopper could be modified to induce flow along the walls (mass flow). This is often touted by solids flow practitioners as the sole means of solving segregation issues, irrespective of the segregation mechanism. But if we were to apply mass flow to our example material, the conical hopper would need to be steeper than 25.6 degrees. Figure 13 shows the expected API concentration of the material as it discharges from the original funnel-flow feed hopper and from a hopper designed right at the mass-flow limit (25.6 degrees). With the original design, API concentration is low when discharging begins and grows higher when the hopper is nearly empty. For this feed hopper and material, funnel flow is a very bad choice. But a feed hopper at the mass-flow limit also results in a low API concentration at the beginning of discharge. Mass flow—flow at the walls—is important, but it may not be sufficient to solve segregation in a feed process. In this case, preventing segregation is all about velocity profile control.

The velocity within a mass-flow device or vessel must match the segregation pattern in the vessel. For example, if segregation in a feed device is present from top to bottom, it would be illogical to induce perfect plug flow (a type of mass flow with a uniform velocity profile) in it because that would preserve the segregation pattern in the discharge. The material on the bottom would empty first followed by the material at the top. That's why a non-plug-flow velocity profile is sometimes wanted, so long as all the material flows upon discharge. The non-plug-flow velocity will tend to blend material in different parts of the feed device, and the right mass flow velocity during discharge will help maintain uniformity. Indeed, sometimes both modes of segregation prevention—blending and uniform flow—are needed to minimize segregation. To illustrate this, Figure 13 also plots the expected API concentration profiles of material leaving the feed hopper if its mass-flow cone has a slope of 20 and 15 degrees.

Figure 14 shows the velocity profiles for four cones of different angles and the profile of the 25.6-degree cone is

FIGURE 13

Expected concentration of API as bin empties

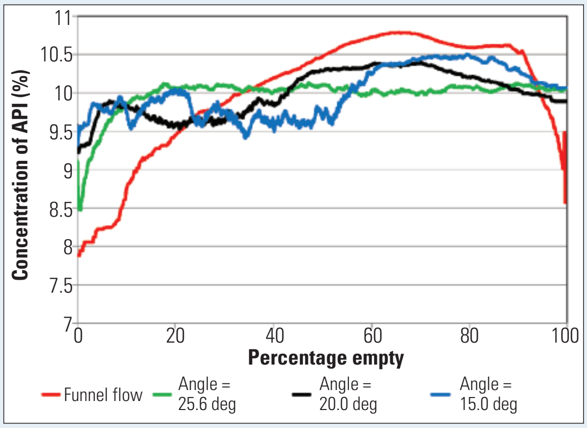
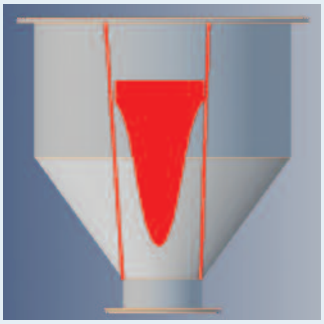
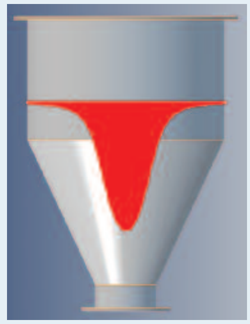


FIGURE 14

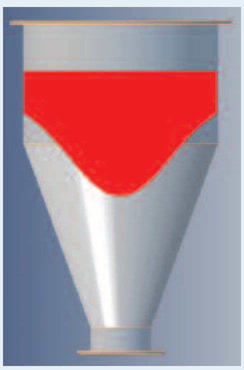
Expected velocity profiles in feed hopper



Funnel-flow bin (orignial hopper)



25.6-degree mass-flow hopper (at mass flow limit)



20-degree mass-flow cone

15-degree mass-flow cone

very steep, almost as steep as the funnel-flow profile. But the velocity profile in the 15- and 20-degree mass-flow cones is much less steep. One might think that the more uniform the velocity, the better the segregation prevention. However, as shown in Figure 13, the 15-degree hopper creates more variation in API concentration than the 20-degree hopper. This suggests that, for a given material, there exists a mass-flow design with just the right velocity profile to minimize segregation as the blend discharges.

Conical hoppers are not the only option for creating mass flow to solve a segregation problem. Cone-in-cone devices and plane-flow Diamondback hoppers can also achieve the right velocity profile for many materials (Figure 15). In fact, the cone-in-cone device is the most flexible mass-flow device because its inner-cone geometry relative to its outer cone can create many more velocity profiles to resolve segregation issues.

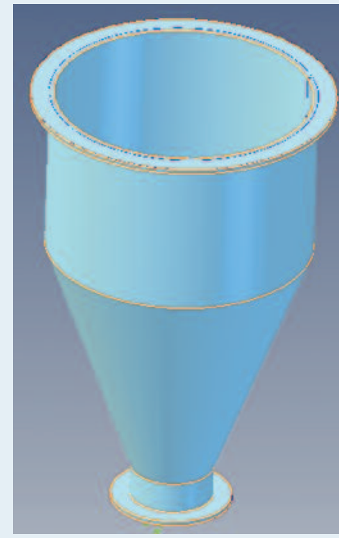
Summary

To resolve a segregation problem, it is critical to characterize the material, assess its flow properties, and measure its segregation tendencies relative to the expected stimuli in the process. This segregation measurement should account for, in detail, all the ingredients in the blend and reveal the segregation pattern, magnitude, and root cause(s). Ranking the types of segregation active in the material and feed system is helpful. This requires measuring key particle- or ingredient-scale properties.

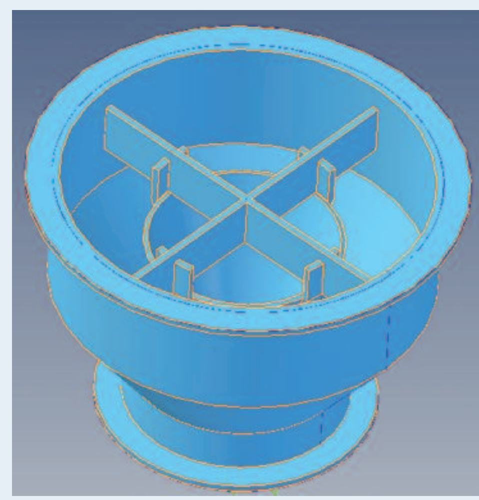
Any resolution of a segregation problem must also include a review of the entire process following the

FIGURE 15

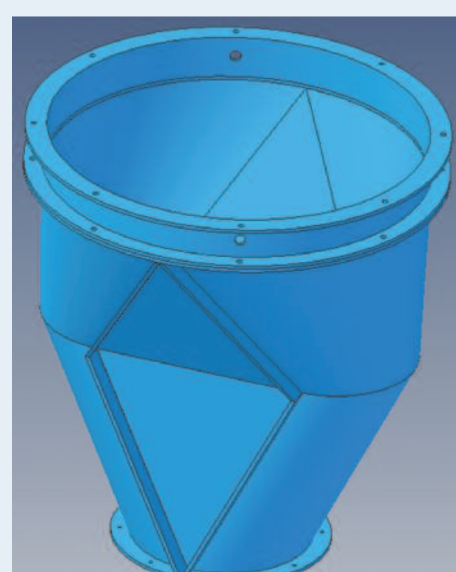
Mass flow hoppers that can reduce segregation effects



Conical hopper



Cone-in-cone



Plane flow (Diamondback)

blending step. The review should account for the blend's flow properties and segregation tendencies to identify regions where ingredients may concentrate. The assessment should also account for how the blender discharges material, which is often ignored. In addition, any design proposed to decrease segregation should either 1) attack the cause of segregation and reduce the segregation during filling and operation or 2) include velocity profiles compatible with the type and magnitude of segregation present in the blend. Mass flow is often important, but may not be the optimal method to prevent segregation. Rather, segregation prevention from a process point of view must center on controlling the velocity profile in the handling equipment. This will often require custom designs. Segregation prevention may also require modifying one or more process steps after blending. *T&C*

Reference

1. SpecTester from Material Flow Solutions, Gainesville, FL.

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