Content uniformity is critical to the quality and performance of solid oral drug products. This article describes a study conducted to mitigate segregation of an example drug formulation during filling and discharge from a typical batch feeding process to ensure content uniformity of the final product. While the material and equipment discussed in this article are for a pharmaceutical application, the same principles apply to the nutraceutical, food, chemical, powdered metal, ceramic, and cosmetic industries.

Drug product developers carefully select excipients based on their function during the manufacturing process or in the final dosage form. Each ingredient must be present in the correct amount to ensure that the formulation adequately fills the tablet press die cavities or capsule filler tamping devices and does not stick to the tooling. Likewise, each finished tablet or capsule must contain the right mixture of ingredients to ensure that the product delivers the specified amount of active pharmaceutical ingredient (API) and dissolves at the appropriate rate and in the appropriate location within the patient’s body.
Because a formulation’s composition influences product quality and performance, achieving and maintaining content uniformity in the final product is critical. Content uniformity is expressed as a component’s actual concentration in a mixture divided by its desired expected average concentration in the mixture. In a perfect mixture, the content uniformity would be 100 percent. The limit on content uniformity is usually expressed as some percent deviation above or below 100 percent (± some percentage) and is considered the allowable percent change from the average.

For pharmaceuticals, the API typically must have a content uniformity between 95 and 105 percent for European products and between 90 and 110 percent for many US products. However, some US companies are beginning to adopt the European content uniformity standards. Excipients may have less stringent content uniformity ranges. To ensure that their products are within content uniformity limits for all important components or ingredients, drug product manufacturers must design their formulations and processes to minimize or mitigate segregation during production.

**Segregation mechanisms**

Segregation is a mechanistic phenomenon in which components of a blend separate by particle size, shape, density, or other characteristic. Understanding the magnitude, pattern, and cause of segregation is extremely important to mitigating its effects. If a material is relatively free-flowing, finer particles can sift down through a matrix of coarse particles, causing the fine particles to separate from the coarse particles during processing, packaging, and usage. If the fines are small enough, they may become entrained in air currents generated by free fall or pneumatic conveying during processing. These airborne fines can then be carried into the freeboard space of process equipment and deposited wherever the air velocity drops low enough for them to settle.

As a formulation fills a bin in a process, the material forms a pile with sloping sides. Particles with different characteristics such as size, surface friction, or shape can slide down the pile at different rates, causing segregation in the pile. Each segregation mechanism results in a unique pattern along the slope of the pile. With sifting segregation, fines tend to accumulate at the top of the slope, while air entrainment may cause fines to accumulate at the bottom of the slope. Each of these mechanisms may occur at different intensities in the same blend, and their combined effect for each component can give the overall magnitude of segregation on a component-by-component basis.

**Measuring segregation**

The first step to mitigating a segregation problem is to measure the mixture’s component segregation profile and component segregation intensity. You can do this by forming a pile in a slice box and then using near-infrared (NIR) spectroscopy to determine the concentration profiles of the key components measured just below the pile’s top surface, as shown in Figure 1.

With this concentration data, you can determine the segregation magnitude by computing the standard deviation of the concentration data for each component along the pile relative to the mean concentration. This gives a segregation intensity value that represents the percent deviation from the mean concentration of any one component.

Consider a fictitious piece of process equipment or bin in which material forms a pile that induces a radial segregation profile. If the process were to empty in such a way as to discharge the all the material just below the pile’s center first and then progress away from the center towards the perimeter of the pile, the time sequence concentration out of this fictitious process or bin would mimic the segregation pattern measured on the pile, with the material at the top of the pile’s slope exiting first and the material at the bottom of the pile’s slope exiting last.

However, no real process discharges in this manner. Even in a funnel-flow bin, the region just above the outlet empties and then the remainder of the material exits the bin by sloughing down the inverted conical pile that forms during the discharge event. Some mixing always occurs. This implies that, assuming no fluidization segregation or other additional segregation is induced during the emptying process, the measured pile segregation profile would be the worst-case scenario during a process-emptying step.

Because the segregation intensity number is the standard deviation relative to the mean concentration, multiplying this number by 3 gives a practical approximate bound on the expected concentration limits for that component. For example, suppose the segregation test gave a segregation index number that was 3 percent. This would imply that 99.7 percent of all the measured points on the pile would fall between the mean value plus or minus about 9 percent of the mean.

In other words, a segregation intensity number of just over 3 percent would create a product that was always...
within the US content uniformity range for many pharmaceuticals. Therefore, if all of a formulation’s important measured segregation intensity numbers are lower than 3.3 percent, the risk of segregation is very low, and that formulation could be put into almost any process and generate a uniform product.

If the segregation test gives a segregation intensity number low enough, then no additional analysis is required. However, for formulations with segregation intensity numbers above 3.3 percent, before you can mitigate the segregation you will also need to know the segregation pattern as well as the mechanism.

**Analysis of an example formulation**

There are two ways to solve a segregation problem: The formulator can design the material so that it does not segregate, or the engineer can design the process so that the material is not segregated either in time or spatial dimension when it discharges from the process.

Consider a typical direct-compression (DC) tablet blend consisting of microcrystalline cellulose (MCC), lactose, sodium starch glycolate, magnesium stearate, and an API. Formulators often use MCC as a binder and diluent in DC tableting, it tends to have some disintegration properties and is relatively easy on tablet tooling due to its lubrication and compressibility properties. Lactose is also a diluent and is widely used in DC tableting because of its good binding and compression characteristics, though it is more abrasive on tablet tooling than MCC. Often, formulators will use a mixture of these two compounds for the diluent, which will make up the bulk of the formulation.

Sodium starch glycolate is often used as a disintegrant in DC tableting due to its ability to absorb water and expand. This disintegration property enhances the disintegration effect of MCC.

Magnesium stearate is used as a lubricant in DC tableting because it tends to reduce friction and adhesion between the formulation and the tablet tooling during compression. However, excess magnesium stearate can hinder the resulting tablet’s dissolution by forming a hydrophobic layer around the particles in the formulation.

The API is often one of the finest components in a formulation and is usually cohesive. In general, adding cohesion to a material that is prone to segregate will tend to reduce the segregation, but it may also change the segregation mechanism. Segregation is also a function of the concentration of key components.

Figure 2 shows the measured pile segregation profile for a formulation containing these ingredients with an API concentration of 2 percent. The segregation profile is plotted as a function of the dimensionless radius, with 0.0 representing the top of the pile and 1.0 representing the bottom of the pile. The MCC and lactose are mixed in a 1:1 ratio and, as the figure shows, their segregation patterns seem to be opposite from one another. When the

![Figure 2](image)

**Figure 2**

Segregation profile of example drug formulation (2 percent API concentration)

<table>
<thead>
<tr>
<th>Segregation intensity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC</td>
</tr>
<tr>
<td>Lactose</td>
</tr>
<tr>
<td>Glyco</td>
</tr>
<tr>
<td>Lubricant</td>
</tr>
<tr>
<td>API</td>
</tr>
<tr>
<td>MCC + lactose</td>
</tr>
</tbody>
</table>
concentration of MCC increases, the concentration of lactose decreases. In fact, the plot of the combination of these two components is nearly constant as a function of position on the pile.

It is awkward to express the concentration of all components on the same graph. However, if you compute the content uniformity (CU) of the segregation data along the pile surface, you can then compare all the concentration data directly. In this case, 100 percent would represent a component that is at the expected average concentration.

Using this technique, as Figure 3 shows, all of the components in the 2 percent API formulation exhibit CU outside the typical pharmaceutical limit of between 90 and 110 percent. This suggests that placing this formulation in a bin or hopper and forming a pile will induce regions in that bin that are segregated beyond allowable CU limits. If no remixing occurs to correct this before compression or encapsulation, there is a high risk that the resulting tablets or capsules will also show CU beyond the allowable limits.

At the very least, the process should be evaluated to estimate the degree of segregation at discharge. A special mass-flow bin design would help to mitigate this segregation because, in mass flow, the material at the perimeter of the bin moves simultaneously with the material in the center of the bin, so the segregated pile is remixed at discharge.

Conversely, if the CU measurement of the pile segregation is within allowable limits and the formulation is not subject to segregation by fluidization, then any process can handle this material without significant segregation, and the process engineer does not need to worry about the final product’s CU.

Note that two of the components (MCC and lactose) segregating relative to each other implies that the other three components (API, glyco, and lubricant) also segregate relative to each other. This is common when describing the segregation behavior of multicomponent mixtures. In this case, the formulator can optimize segregation by focusing on two distinct systems.

For the API, glyco, and lubricant system, the segregation pattern indicates that the fine API and the lubricant accumulate at both the top and the bottom of the measurement zone in the pile, suggesting that at least two segregation mechanisms are occurring. The fine API and lubricant particles at the bottom of the measurement zone indicate that air currents are active during filling. Accumulation of the fines at the top of the measurement zone is likely the result of the fine API and lubricant particles sifting down through the coarser matrix of particles created by the MCC and lactose.

Figures 4 and 5 show the CU profiles for the same formulation but with API concentrations of 5 and 10 percent, respectively. The 5 percent API formulation showed

<table>
<thead>
<tr>
<th>Component</th>
<th>CU</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC</td>
<td>10.23</td>
</tr>
<tr>
<td>Lactose</td>
<td>10.15</td>
</tr>
<tr>
<td>Glyco</td>
<td>26.17</td>
</tr>
<tr>
<td>Lubricant</td>
<td>35.23</td>
</tr>
<tr>
<td>API</td>
<td>29.83</td>
</tr>
<tr>
<td>MCC + lactose</td>
<td>0.22</td>
</tr>
</tbody>
</table>
Figure 4

Content uniformity profile of example drug formulation (5 percent API concentration)

![Graph showing content uniformity profile with data points for MCC, lactose, glyco, lubricant, API, and MCC + lactose.]

Segregation intensity (%)
- MCC: 2.38
- Lactose: 2.16
- Glyco: 17.91
- Lubricant: 26.34
- API: 11.19
- MCC + lactose: 0.45

Figure 5

Content uniformity profile of example drug formulation (10 percent API concentration)

![Graph showing content uniformity profile with data points for MCC, lactose, glyco, lubricant, API, and MCC + lactose.]

Segregation intensity (%)
- MCC: 2.57
- Lactose: 3.70
- Glyco: 24.76
- Lubricant: 28.49
- API: 16.37
- MCC + lactose: 1.30
a significant reduction in the segregation of all components compared to the 2 percent API formulation, with the segregation intensity numbers for MCC and lactose within the 90 to 110 percent range (Figure 4). As Figure 6 shows, an API concentration of 5 percent seems to be optimal for this formulation.

The likely reason for the reduced segregation potential at higher API concentration is that the fine API particles are increasing the formulation’s cohesiveness and interparticle adhesion, making it more difficult for fines to percolate between coarse particles during pile formation. This highlights the positive influence a small amount of cohesion can have on segregation prevention.

**Changing the process to mitigate segregation**

At some point, mitigating segregation problems requires a change to the process. Further quantitative analysis of the active segregation mechanisms suggests that this example formulation is subject to 53 percent sifting segregation and 47 percent air entrainment segregation. This means that process engineers should look at places in the process where material free falls and minimize the free-fall height. Process engineers should also look for regions where piles and sifting can occur. Measuring or computing the material’s velocity profile through the process and coupling that data with the segregation pattern and magnitude allows you to minimize segregation as material leaves the process.

Part of the solution to sifting segregation is to create distribution chutes to minimize pile formation during filling. Mass flow vessels can help to minimize segregation of material as it passes through the system, but their steep velocity profiles may still induce segregation if they are used in a fill-and-then-empty mode of operation. Fill-and-then-empty operation mode generally causes more segregation than continuous operation mode, but it is often required in industries that rely on handling batches. Such cases may require special mass flow devices with a more controlled and uniform velocity profile.

Also, vendor equipment often lacks the headroom for a proper mass flow design. In many cases, vendors incorporate funnel flow designs into their equipment out of simplicity rather than sound scientific basis, and plant production facilities must either redesign the vendor component or find ways to optimize segregation using available equipment. Sometimes this approach works, but process engineers need some guidance on how to approach this type of issue.

Tablet press configurations typically do not allow the formulation to be fed from a point directly above the die cavity, so vendors often use offset cones to feed the material to the feed frame and die cavity. Unfortunately,
many of these offset hoppers are not steep enough to induce flow along the hopper walls, creating a funnel flow pattern.

Likewise, process engineers are often forced to use metering devices to control or limit material flow into capsule filling machines or control the mass packaged into fill vials or packages. These devices often consist of a symmetric conical hopper with a central auger that extends through the outlet and controls the flow to the filling process below, as shown in Figure 7. However, these hoppers are generally funnel flow devices that use scraping blades and augers to promote flow along the hopper walls.

While scraping blades can break up stable ratholes, the material velocity in these devices is still very steep, and segregation can occur during discharge. Regardless of the exact configuration, the friction angles of typical formulations are often too high and the sloped walls of the hopper section too flat to create optimal mass flow, and these feed devices will have an active flow channel just above the outlet and poor flow along the hopper walls.

To complicate matters further, the gearbox and auger in such feed hoppers are at the center of the hopper, so the feed inlet must be located at or near the side of the vessel. Sometimes simply determining the optimal feed inlet location will be enough to mitigate the segregation. This potential solution is attractive because it is relatively simple and requires minimal modification to vendor designs. Superimposing the measured segregation pattern on the pile distribution pattern in the hopper, as shown in Figure 8, gives the initial distribution of key components in the equipment.
You can use the material’s flow properties and the feeder bin configuration to compute the expected velocity profile in the bin and then calculate the concentration of key components as material leaves the feeder bin during a complete fill-and-then-empty operation cycle, as shown in Figure 9.

To determine the optimal feed inlet location for the vessel shown, several positions were selected, and the expected concentration during the emptying cycle was computed, as shown in Figure 10. All dimensions are measured from the centerline of the hopper. A dimension of 230 millimeters is a position right at the hopper wall. Note that placing the feed inlet location right at the bin wall (purple line) causes some of the material exiting the bin to be outside the allowable CU of 90 to 110 percent. Placing the feed inlet location close to the
center (yellow line) causes even more of the material to be outside the allowable limits. However, placing the feed inlet location at some point between the center and the wall (blue line) causes 99 percent of the material to fall within the allowable limits.

The optimal configuration for the feed inlet location is summarized in Figure 11. This suggests that, for an API concentration of 10 percent, the best feed inlet location would be a point about 175 millimeters from the center-line of the feed hopper.

**Figure 11**

Optimal feed inlet location for metering feeder device (10 percent API concentration)

Measuring a formulation’s segregation profile can help formulators and design engineers determine if the material is prone to segregation in any feed process. If the standard deviation of these segregation measurements (the segregation intensity) for the key components is less than about 3.3 percent, the formulation can often be used in any process with minimal segregation problems. If the segregation intensity values are larger than 3.3 percent, some process modification will be required to mitigate segregation problems.

Ideally, processes should use proper mass flow bins with a velocity profile compatible with the material’s measured segregation patterns, enabling 100 percent of the final product to meet the allowable CU constraints. However, in some cases, small modifications to a less-than-optimal funnel flow hopper can reduce the segregation enough to keep the CU within allowable limits. 

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**Summary**

Dr. Kerry Johanson is chief operations officer of Material Flow Solutions (352 379 8879, www.matflowsol.com). He holds a PhD in chemical engineering from Brigham Young University and has more than 40 years of experience solving bulk powder and granule handling problems. The company specializes in material property testing and analysis and designing or retrofitting material handling systems to optimize production.