

## Segregation Properties of Heart Healthy Medication

### 1.0 Segregation – An Introduction

There are two uses for segregation data. Engineers may use segregation data to optimize product design, creating a product with minimal segregation tendency. Engineers may also wish to modify the processing to minimize the effect of segregation in their plant packaging process or handling facility. In either case, the segregation pattern, segregation mechanism, and magnitude of segregation are key parameters required for process or product design.

Segregation occurs through several mechanisms. Identification of the primary segregation cause and the segregation pattern produced through handling is critical to prevent de-mixing of the final detergent mixture during handling and packaging. Any property difference between materials can cause separation of critical material components. However, there are five common causes of segregation problems in typical handling systems.

#### Sifting:

Fines may sift through a matrix of coarse particles during handling. This mechanism requires that the void space between adjacent particles be large enough to permit fine particle to pass through. Generally, this requires a particle size difference of about 3:1. Inter-particle motion is also required to provide a means of exposing empty void spaces to fine particles. The fines must also be free flowing enough to prevent arching between adjacent particles and the void spaces must be empty enough to accept fine particles. In general, this type of segregation produces a radial pattern as material forms a pile in process equipment. The fines accumulate near the pile charge point and decrease in concentration toward the edge of the pile.

#### Angle of repose differences:

Two materials may have different angles of repose. Thus, when these two materials flow down a pile they essentially create overlapping piles where the material with the steepest

repose angle accumulates near the top of the pile while the material with the flattest repose angle accumulates near the pile edge. Generally, there is a distribution of these two materials along the pile's surface. Repose angle differences of about 2 degrees can result in significant segregation. Material of different particle sizes can possess sufficient difference in repose angles to cause this type of segregation. However, particle size difference is not a prerequisite angle of repose segregation and materials of the same size can separate via this mechanism. In addition, your process must also generate piles during handling or processing to cause this type of segregation.

#### Air entrainment:

The mixture may contain fines that are small enough to be carried by air currents in the handling system. These fines drop out of the air stream when gas velocities decrease below the entrainment velocity. This causes separation of fines and coarse in handling systems. The fines generally deposit near the container walls. This type of segregation requires a source of air currents in process equipment. This source of air can come from free fall of a compressible material. When the falling stream impacts the material level, the entrained air is pushed out of the interstitial pores and carries the fine particles in the resulting dust cloud. This segregation typically causes a radial pattern during pile formation, but the fines are at the bottom of the pile and not the top.

#### Impact fluidization:

If the mixture is fine enough, then air trapped in the interstitial voids can cause material to fluidize. As a large particle drops into this fluidized layer, momentum causes the large particles to penetrate this fluid layer, resulting in a top-to-bottom segregation of fine and coarse particles. This mechanism requires a source of air and the ability of the bulk material to hang onto entrained air for a moderate amount of time.

## Percolation:

A fluidized layer of material can lose its entrained air as it sits stationary in a container that was just filled. Percolation forces air up through the bulk material. Generally, this process forms fissures in the bulk material where the gas escapes. The local velocity in these fissures is relatively high and can entrain fine particles in the process, causing top-to-bottom segregation. This results in the size separation of fluidizable material with wide particle size distributions.

It is critical to identify the cause of segregation to avoid processing that will induce the problem. It is also necessary to know the pattern of segregation in order to provide a means of re-mixing material, if required. Understanding the segregation mechanism will also help in determining what must be done to the material to create a product that is less likely to segregate.

## 2.0 Segregation Testing Results – Background

In the past researchers have fed bulk materials onto a pile, sectioned a conical pile into annular sections, and performed chemical or size analysis on the material collected in each annular section. This is a long and tedious method which results in only a very few measurements collected along the pile. Plant personnel often use thieves to sample piles in process equipment. This method also yields only a few measurements along the pile and disturbs the surface, thereby changing the segregation pattern. Other researchers measure the segregation pattern by placing material in a funnel flow hopper and then discharging the hopper, collecting the output stream and measuring the quality of the mixture by chemical composition or particle size. This method convolutes the segregation with the flow pattern from a particular hopper or bin. Unless the bin design in the tester is precisely the same as the bin design in the process, there is no guarantee that the composition during discharge from the tester will be similar to that found in the actual process. In addition, the cohesive properties of the bulk material can impede flow from the segregation tester hopper, even though hang-ups may not occur in the process with the same material.

One problem with current segregation testers is that they do not relate well to the process. Any two or three materials can segregate if there is a difference in properties and the mixture is subject to enough external stimuli. For example adding enough fluidization gas will separate materials of different densities, even though these extreme conditions

may never occur in the actual process. The real question to be answered is: will the mixture segregate when exposed to a feed behavior similar to that present in the process? Therefore, any measurement of segregation tendency should have three key elements. First, the feed should be controlled so as to allow the measured segregation to be scalable to process conditions. Second, the pattern of the segregation should be included as part of the measurement in order to predict the expected concentration leaving process equipment. Finally, the magnitude of the segregation should be quantified to provide guidance in determining if the mechanism is actually a potential problem in the process. Ideally we would like the concentrations based on chemical components in the mixture.

## 2.1 Relation of Test Results to Process

Let's identify the key attribute that must be controlled or measured to make segregation measurements scalable to process conditions. For simplicity, we will assume that material simply falls from a mechanical conveyor into the process vessel. Material entering the process typically free-falls from some fall height at some process velocity. It is important to note that, in this case, the dynamic effects caused by particle rebound or sliding down the pile scale linearly with the geometry of the process equipment (Figure 1). The same cannot be said of the case where gas is carried with the input stream. However, similar models can be created for this case and a scale law developed. For the purpose of this report, and because the segregation data is for simple comparison, we will assume little or no gas effects during the filling of a typical pharmaceutical process. The small scale segregation tester can then be run at a constant drop rate and fall height. We deposited material in a slice model, forming half a pile, at a rate of about 1 lit/min. The free fall dimension was set to be 0.57 times the diameter or width of the receiving bin. It is important to note that the full diameter of the receive bin in the process would correspond to twice the width of the slice mode bin in the tester since the slice model was filled on one side. For a typical 1.5-meter wide bin this would correspond to a drop of about 0.85 meters.

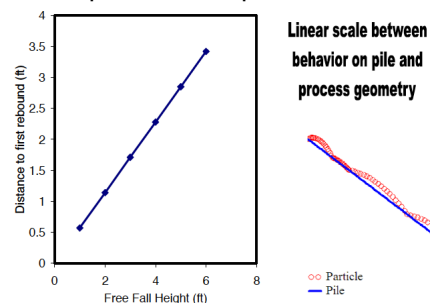


Figure 1. Typical rebound of free fall particles down pile surface

## 2.2 Segregation Pattern

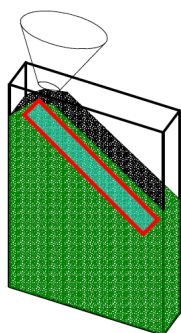
The pattern of segregation requires that segregation be measured by analyzing spatial concentration data. This spatial analysis always has a sample size or view port associated with it. It must be decided beforehand what volume of material represents a reasonable segregation basis. The view port must contain enough particles to be statistically relevant. If that volume occupies only one or two particles, then any segregation measurements are doomed to failure since the segregation measurement volume cannot represent an average sample. If that sample volume is the same as the bin size, then every segregation measurement will represent the global average concentration placed in the process vessel. The proper segregation volume should be chosen somewhere in between.

Obviously, these spatial segregation measurements require access to some spatial view of the material after it has segregated due to initial process filling. One way to gain access to the cross section of a pile is to fill a slice model with material and observe the segregation pattern through the side of the slice model using optical techniques (Figure 2).

Figure 2. Schematic of segregation tester

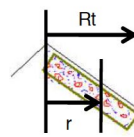
Dump material into box and observe the change in color intensity along the pile as measured just below the top surface of the pile (rectangle section).

These changes in color intensity are an indication of differences in either chemical composition or in particle size and can be used to estimate the segregation of key components in the system.



Observation of segregation through the sides of a slice model will be biased to the optical pattern that exists at the wall of the segregation tester. Therefore, care must be taken when loading the tester to assure a representative sample is visible through the side of the tester. Filling the tester across the width of the slice model will distribute the material to the tester wall, creating a uniform material across the tester. Limiting the thickness of the slice model will also help with the distribution of representative material to the tester wall. However, one should be aware that extremely thin slice models are subject to banding due to wall effects that would not be present in wider slice models. For typical materials, this limits the slice model to a minimum of approximately 25 mm thick.

Reflectance spectroscopic methods can be employed to measure subtle differences in color. Since we are dealing with a discrete particle system, multiple measurements are required to determine the average concentration within a given viewport. Segregation measurement is also a scale issue. The size of the chosen viewport should be large enough to contain a representative number of particles, yet small enough that differences in local compositions are not lost in the averaging scheme (Figure 3). We defined the tester view port area as 1.27 cm square and averaged 36 sample readings within the view port area. We moved the viewport to collect data at about 30 points along the length of the pile at a position that was about 1.27 cm below the top surface of the pile as indicated in the schematic in Figure 2.



Define the size of the view port and measure the spectra along the top of the pile. Adjacent viewports can overlap and tester can measure concentration at up to 50 locations along pile.



Figure 3. Measurement zone along pile top surface

If the spectra of the pure components are known, and the spectra of the mixture in different, view port boxes along the pile are known then pure component spectra can be used to compute the concentration of the components along the length of the pile. One drawback of this technique is that good data requires many spectral measurements collected at multiple points along the pile. Manually collecting this data is tedious and time consuming. Therefore, an automatic instrument was constructed to control the feed, obtain the pure component spectra, and measure spatial concentration profiles for spectral measurements (Figure 4).



Figure 4. SPECTester used in Segregation Analysis

## 2.3 Results of SPECTester Analysis

The segregation pattern and data is given in Figures 5 through 7. The concentrations are plotted as a function of dimensionless radius. A radius of 0 is the top of the pile and a radius of 1.0 is the bottom of the pile. This profile shows moderate segregation of the API and significant segregation of active B and inert C ingredients, as indicated by the segregation intensity (Figure 7). In the same Figure, active A and inert A ingredients show moderate segregation. Active A, active B, and inert C ingredients tend to accumulate at the top of the pile, while the inert A ingredient accumulates at the bottom of the pile (Figure 5). API tends to accumulate at the top of the pile and near the bottom of the pile. Measurements indicate that active B and inert C ingredients are the worst acting for segregation. Additionally, the API exhibits sufficient segregation tendency to be a real problem in production. This type of profile is indicative of angle of repose segregation. However, API may be segregating due to two mechanisms. Some of these inert ingredients that show significant segregation do not need to be well mixed with the mixture to maintain a good product. However, the API segregation is large enough that dry formation processes will need to be monitored carefully to ensure good (uniform) product formation. This mixture must be placed in a well designed handling system to assure that it remains mixed after the blending step before it is tableted.

Sometimes the segregation trend is easier to see if viewed from a cumulative concentration point of view. We can sum, or integrate, the fraction of any component along the pile and normalize it relative to the actual average concentration of that component along the pile (Figure 6). If there is no segregation, then this procedure would show a straight line passing through the point (0,0) and (1,1) when plotted against dimensionless radius. A positive deviation off this line indicates accumulation near the top of the pile. A negative deviation off this line indicates accumulation toward the bottom of the pile. An s-shaped curve indicated accumulation at both top and bottom. The magnitude of the deviation off this line indicates the percent deviation from the mean concentration for any one component. The reason for plotting segregation in this manner is to relate the segregation profile to the deviation from the mean or average concentration. These plot provide a quick way to view how bad the segregation is from a mean concentration point of view while giving you a feel of the type of segregation occurring.

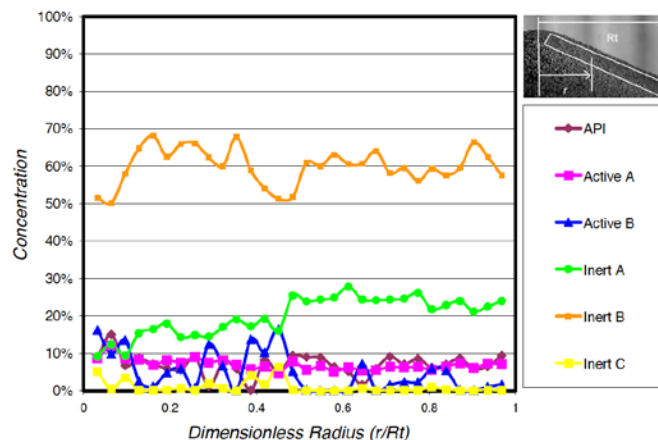


Figure 5. Radial segregation profile for Heart Healthy Medication

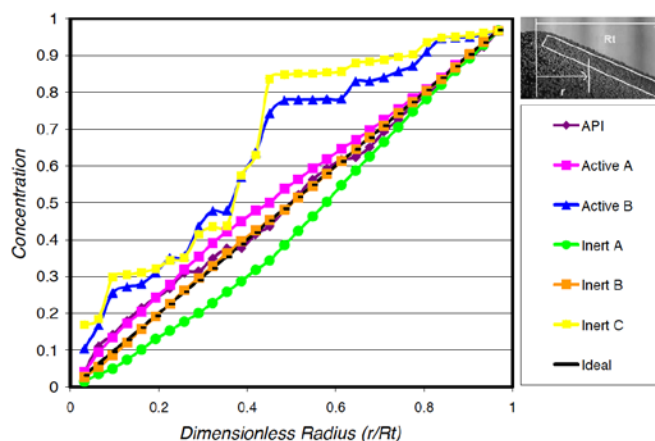


Figure 6. Cumulative radial segregation profile for Heart Healthy Medication

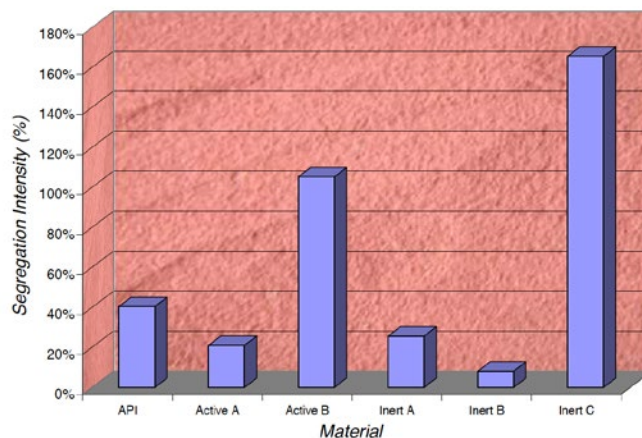


Figure 7. Segregation Intensity for Heart Healthy Medication