



Content Uniformity and
Weight Variations in
Pharmaceutical *Solid Dosage Form*
Manufacturing



**JENIKE &
JOHANSON**

Bulk Solids: Science/Engineering/Design



HOW SEGREGATION
AND POOR FLOW
CAN WASTE PRODUCT
AND KILL PROFITS

THE COSTLY CONSEQUENCES OF PRODUCT VARIATION.

SEGREGATION CAUSED BY FLUIDIZATION

A direct compression blend consisted of a fine powder—the active ingredient—and coarser excipients. When fluidization occurred during the filling of the bin, the active ingredient became concentrated in a layer at the top, resulting in a product that failed content uniformity tests.

After measuring the blend's permeability and calculating deaeration times, we altered the bin filling method and optimized the flow pattern of the discharging material, eliminating segregation, resulting in a product that passed content uniformity tests.

Pharmaceutical manufacturing continues to move toward more direct-compression blends, highly potent active drugs with smaller particle sizes, faster manufacturing processes, and larger batches. These trends are leaving operations increasingly vulnerable to process problems caused by poor blending, sampling, segregation, and poor flow. Even if you haven't encountered these problems yet, it's likely that you eventually will. At Jenike & Johanson, our mission is to help you avoid or minimize the costly consequences of product variation and reduced productivity.

A single defective batch of product can cost several hundred thousand dollars in wasted material alone. Troubleshooting time, manpower, and paperwork can easily add tens of thousands of dollars more. Delayed time-to-market while seeking FDA approval can result in revenue losses of \$1 million to \$100 million or more over the life of your product - assuming your product is still viable and competition doesn't fill the market first.

More difficulties may be in store if a defective product reaches the marketplace. With insufficient active ingredient, the product will lack potency; with too much, it will cause side effects. Either way, dissatisfied customers mean lower sales and a poor company image—to say nothing of the health risks involved.

The need for high product quality is being demanded now more than ever. Increasingly discriminating blend and tablet uniformity techniques are more likely to reveal formulation and processing problems. The FDA is demanding companies to be proactive in addressing problems, saying “Manufacturers who choose to wait until FDA inspectors find violations rather than policing themselves will find they have made a poor and costly decision.”

If you're currently experiencing problems with content uniformity or poor flow, we can help you eliminate them. If you're developing a new product or production line, you can utilize our industry-leading technology to help you get off to a smooth start and avoid product variation headaches down the road.

ANALYZING AND CONTROLLING FLOW PATTERNS

When *mass flow* occurs in a bin or hopper, *all* of the material is in motion. If any material is stagnant, *funnel flow* is taking place. In general, mass flow is superior to funnel flow.

If the material is cohesive, arching and ratholing are common in funnel flow bins, resulting in erratic flow or no flow at all. Fine powders may fluidize as they fall through a rathole, which may cause significant bulk density (weight) variations. Mass flow addresses these problems.

Different mass flow designs produce different velocity profiles, because material in the center of a bin flows faster than material at the sides. Through numerical analysis, we can accurately calculate these profiles to either minimize segregation or maximize blending. Manipulating flow patterns and velocity profiles enables us to eliminate product variations.



Segregation—a real-world problem.

In an ideal material blend, any sample will have the same composition as any other sample from the same batch. But in real-world processing environments, materials tend to segregate when differences in particle properties exist.

Segregation can occur as material discharges from the blender into a container, such as a bin or a drum. Or as it travels from the container through the press feed chutes. Or as it goes from the press hopper to the press. As a matter of fact, segregation can occur at any point where material is moving.

And segregation means trouble.

We've observed that segregation of pharmaceutical powders is usually caused by one or more of these mechanisms:

Fluidization — The fine particles remain fluidized near the top surface.

Sifting — Fine particles move through a matrix of coarse ones.

Dusting — Fine airborne particles settle in regions within the bin.

Weight variation—and how it ruins production.

Although off-the-shelf portable bins and press hoppers work well enough for many materials, weight variation in a drug product formulation can be caused by erratic flow into the press or filler—or no flow at all. This leads to frequent stops and starts, painfully slow machine speeds, manual prodding of material, and forced check-weighing of each dosage unit. The flow pattern within the bin or hopper can make all the difference.

Call on the specialists.

At Jenike & Johanson, we've identified and solved problems in a wide variety of pharmaceutical manufacturing operations. We've assisted in blender selection and scale-up. We've implemented sampling plans to address thief sampling error. We've recommended equipment modifications to remedy segregation. We've updated presses and encapsulators to increase throughput rates while reducing weight variations. We've identified manufacturing steps that led to potency losses and reduced yield. We've steered formulation development towards the appropriate selection of active drug and excipient physical characteristics. And what we've done for these operations, we're ready to do for yours.

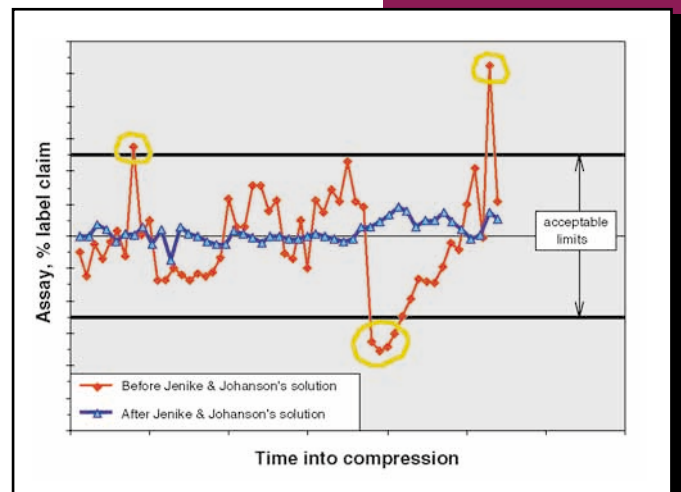
For over 30 years, we've specialized in solving bulk material handling problems for the pharmaceutical industry and many others. We will work with you through the entire system all the way to the final product. This means helping achieve content uniformity by eliminating segregation—wherever it may occur, development of a rational sampling program, and equipment design and supply. And it means helping you minimize weight variations by eliminating poor flow and production rate limitations.

Our method is not trial and error; it's scientific and systematic. If you're planning to implement a new system, we begin by evaluating your requirements. If you're trying to correct a problem in your existing system, we start by reviewing the steps you have already taken. To characterize the flowability of your material, we conduct tests—cohesive strength, permeability, wall friction, compressibility, and segregation—all of which we developed internally, but have become industry standards.

WEIGHT VARIATIONS CAUSING PRESS SHUTDOWN

A drug innovator developed a promising new product, which passed its clinical trials. To meet market demand and outsell the competition, the production rate had to double immediately. Unfortunately, the press was not able to operate at more than half its rated speed, as any increase resulted in severe weight variations that stopped the press. If the problem could not be solved, it would be necessary to buy a second million-dollar press, requiring a lead time of months.

After measuring the flow properties of the granulation and analyzing air/solid flow effects, we designed new portable bins and supplied them in weeks, not months—to say nothing of the cost savings over a new press. Upon startup, the new bins provided consistent flow, and the existing press was now able to run at the desired speed with acceptable tablet weights.



END THE COSTLY HEADACHES OF PRODUCT VARIATION.

SEGREGATION CAUSED BY SIFTING

In a bottle filling operation, a mixture of fine active drug and coarser excipients was developing a funnel flow pattern during discharge from the bin, causing severe content uniformity problems. Our analysis revealed that both a mass flow pattern in the bin and a uniform velocity profile were required.

Using our measurements of the mixture's flow properties, we computed velocity profiles in various possible geometries and optimized the geometry of the bin to achieve a uniform velocity profile using an insert. By manipulating the velocity profile, we dramatically improved content uniformity.

Our expertise covers not only testing but also the meaningful interpretation of test results. Rather than abstract comparisons, we provide practical data that's specific to *your* application. Depending on your needs, you can take advantage of any or all of these Jenike & Johanson services:

On-site consulting to troubleshoot and diagnose your problem. We'll visit your facility and discuss your requirements with both management and operators. We focus on gaining an understanding as to the root cause of observed problems.

Flow properties testing to predict your material's flow behavior. We draw upon the results of these tests, plus our experience with many applications, to help you achieve your objectives.

Design recommendations, based on flow property tests and our broad experience, to prevent or minimize product variation problems.

Detailed design engineering for our recommended designs.

Customized equipment to provide fast turnaround of a reliable high-quality solution.

Continued support, analyzing data from subsequent runs to ensure a smooth operation.

Education for providing an overview of equipment design plus formulation pitfalls and solutions.

This is the Jenike & Johanson method—and, as hundreds of pharmaceutical manufacturing operations around the world can attest, it gets results.

Material handling problems—if not identified and corrected quickly—can create a staggering drain on your budgets, your manpower, your time-to-market, and your revenues. At Jenike & Johanson, we have the experience and the expertise you need to avoid or eliminate product variation and its costly consequences.

If you're not experiencing product variation at the moment, you still need to be prepared for the possibility. If you *are* having product variation difficulties, you can't afford to wait another day. To get started, give us a call.



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