TABLETS & CAPSULES
Solid Dose Digest
Insights, advice, and industry news about formulating, manufacturing, and packaging solid dosage forms brought to you by Tablets & Capsules *magazine*

More Questions and Answers

Q: How do you microdose APIs and excipients?

A: Roger Hultquist, Orbetron, says:

For the production of tablets and capsules, interest has been growing in how to feed individual or pre-blended ingredients at low rates, i.e., microdosing. If you're considering feeding at low rates, you must understand the challenge of designing the feeding equipment and how different features can affect the process. The lower your feed rate, the more challenging it is to produce drug products in a repeatable and consistent manner.

While every pharmaceutical manufacturer will have its own definition of microdosing, for discussion purposes, let's define it as feeding at rates as high as 200 grams per hour to less than 1 gram per hour.

When feeding at such low rates, you must consider three areas: the process, the material, and the feeder. Understanding those areas allows you to determine how best to incorporate microdosing feeding equipment into your process and gives you the best possible repeatability and consistency.

The process
The feed rate for microdosing differs depending on whether you operate in batches or continuously. For batch systems, you need to know the fill, mix, and release times. The fill time directly relates to the feeder's design. Let's say, for example, that you have four materials and each must comprise a fixed percentage of a 100-gram batch that needs to be filled in 20 seconds. In that case, your feeder must be fast enough to complete that goal.

For continuous systems, you must consider the complete range of feed rates that is required for each ingredient as measured in grams per minute or grams per hour, which means you need to know the minimum and maximum rates for each feeder to dispense. Then you size each feeder to feed at those rates, based upon the minimum and maximum desired output rates. Reviewing feed rates establishes the feeder's volume output requirements, the required volume per minute, and the disc or screw sizing.

The material
Material characteristics are the single most important consideration when feeding at low rates, playing a major role in designing the feeder and in determining the way in which you apply it to the manufacturing process. Most applications require material testing to confirm your material's characteristics and to determine if you can actually feed it at low rates.

The material's flowability—free-flowing, fairly free-flowing, or non-free-flowing—gives you a starting point in discussing a feeder's design. During material testing, you typically must define each material in more detailed language. For those materials that are APIs, you typically use a placebo for testing that is consistent with the actual material's characteristics.

Bulk density. You use both the initial density and the tapped density in sizing the feeder. We have found that over time, as material sits in a hopper, compaction of the material can occur, or if the materials are agitated, that the process can aerate the materials. Both have a direct effect on flowability. The compaction or aeration can induce variations that have a direct impact on the volume consistency of your output; thus, your feed accuracy can have wider variations.

Understanding the true bulk density allows you to define the disc or screw size to meet the minimum and maximum requirements for the feed rate of a specific material. As a rule of thumb, after you go below a bulk density of 8 pounds per cubic foot, the material becomes more difficult to feed consistently. You will need to look at different options to increase the bulk density, i.e., pre-blend materials if possible.

Size and shape. What is the shape of the material, e.g., is it a granulated fine powder? What is its milling level? Is the material blended prior to being fed into the process? You must ask all of those questions because some materials have a limit on their minimum feed time due to their actual physical size. With APIs and excipients that are primarily in powder form, I find that use of a consistently milled product can help in determining the design of the disc or screw to reach those low feed rates.

Static. How much static is associated with the movement of the material in the feeder? When reviewing the material during material tests, you must evaluate the static build-up, based on the specific material. If the static is built up due to refilling the feeder or during normal feeding, I advise the use of an antistatic solution. I find that a number of pharmaceutical materials can require static-neutralizing solutions. Lack of those solutions can reduce the accuracy of the screw or disc feeders.

The feeder. After defining the process parameters and determining each material's characteristics, you can establish the feeder sizing and design requirements for each material. The lower the feed rate, the more important it is to ensure that you have satisfied the requirements listed below because minor changes can have very large effects on the output of material.

Mounting. The mounting of feeders can be critical in ensuring that the material feeds into the process at the correct angle and location. Typically, the material should not fall onto the side walls of the mixing hopper. Such material can build up over time and create some inaccuracies at very low rates. Those inaccuracies can have a surging effect that could cause variations in overall material blends of 4-8 percent.

The requirements for the mounting configuration help you to decide what size of feeder is necessary to fit into a specific space. The configuration determines the volume of material that you can store and the required overall dimension of the feeder that feeds the material.

Hopper refill. For low rate feeders, hand filling is the most common method. The filling method can affect accuracy, based on the head pressure into the disc or screws. Determination of the filling process relates to the effects of variations in bulk density. When feeding at low rates, I find that I can directly relate feed accuracies by volume to the head pressure on top of the disc or screw. Typically, you must establish a recommendation for the minimum and maximum material levels to ensure the highest accuracy.

Motor and gear sizes. The feeding industry uses three basic types of motors—AC, DC, and stepper. For microdosing, I use a standard stepper motor because it has some advantages over AC and DC units. Small motors allow a more-compact feeder and the ability to count a defined number of steps per 360 degrees of rotation of the motor. This improves dosing accuracy as well as permits the use of stepper control software that can overcome material issues in feeding.

Disc/screw sizing. This choice involves some trial and error and is a good reason for actually reviewing your materials. For disc feeders, view the choice as identifying the disc for use with a discrete hole or for a volume consistently filled; I have found that concept to provide higher accuracy at the low rates of microdosing. I typically review screw feeders at rates above 200 grams/hour. Once again, I make those determinations based on my understanding of the materials' characteristics.

Determination as to whether you need flow aids. You must evaluate each material to determine if you must incorporate flow aids to ensure consistency of feeding. I typically install a flow aid if I determine that the material is not free-flowing. Flow aids can range from simple agitators to designs with a more direct mechanical discharge, located in the feed hoppers. Some software allows you to change the feeder's electrical conditions.

Determination of feeder accuracy. Each processor will have a recommended accuracy requirement for each ingredient that needs to be fed to ensure a consistent tablet or capsule. You must design each feeder to achieve an accuracy requirement based upon all of the material characteristics listed in the materials section. Through material testing with different feeder configurations and use of standard test criteria—like minimum sample size, minimum sample number, sample time interval, and statistical calculation of accuracy and repeatability—you can then establish if a feeder can achieve the accuracy that the manufacturing requires. I recommend that you determine the accuracy as a volumetric function. In microdosing, a feeder's design has to produce as consistent an output as possible. I also recommend that you ensure that the discharge of the material has no additional constraints that could impede the proper flow of material.

Integrating the feeder

After establishing the process parameters, evaluating the material, and determining the final design of the feeder, your processor and supplier can establish the best solution to batch or continuously feed the ingredients into the process. As manufacturers create new materials and as feeding technology continues to evolve, innovations will enable processers to feed or microdose materials at lower rates to reduce down time, cleaning, change overs, and the costs of production.

Roger Hultquist is the co-owner at Orbetron, Hudson, WI. The company supplies technology that ensures a consistent and repeatable feed of dry bulk solid materials.

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