Particle-Size Distribution II: The Problem of Sampling Powdered Solids

Harry G. Brittain

All methods for the determination of particle-size distribution have absolutely no value unless the composition of analyzed samples is representative of the bulk from which they were removed. Obtaining a representative sample from a static powder bulk is difficult and may not even be possible. For instance, although it is widely believed that the use of sample thieves is an adequate method for good sampling, this seems to be an improperly held view. The general consensus is that only sampling from a bulk powder while it is in motion can yield the desired representative sample. These procedures present their own range of difficulties, but equipment exists that permits one to sample from moving powder beds on a variety of suitable scales. It is probably true that the use of a rotatory sampling device, or spinning riffler, is the best instrument available for the subdivision of powders that have heterogeneous particle-size distributions.

Harry G. Brittain, PhD, is the director of the Center for Pharmaceutical Physics, 10 Charles Road, Milford, NJ 08848, tel. 908.996.3509, fax 908.996.3560, hbrittain@earthlink.net.

The first article of this series outlined some of the general precepts of particle size and shape (1). One might have thought it appropriate to move into discussions of some of the most important experimental methods used to deduce that type of information, but those topics cannot be addressed until the procedure for obtaining a proper sample for analysis is discussed (2,3). Although one may use extraordinary care and technical skill while performing a given method for the deduction of the particle-size distribution of a powdered solid, the results will have absolutely no value unless the sample used for the analysis is indicative of the bulk from which it was taken. Nowhere else is the phrase "garbage in, garbage out" more appropriate.

Because it is never practical to test the entire bulk of a powdered solid (leaving none for its intended application), one must remove appropriate samples from the bulk to obtain inferences as to the composition of the entire ensemble. *Samples* are therefore defined as the units upon which a program of testing is conducted. The purpose of measuring or observing a property of a sample is to obtain information about the ensemble from which the sample was drawn and hence the need for the drawn samples to be genuinely representative. The degree of difficulty associated with the implementation of a sampling procedure will depend on the exact nature of the experimental situation.

For most pharmaceutical materials (and especially in the sampling of powders), a number of factors must be considered when devising a sampling scheme. These factors include the nature of the ensemble from where the sample is to be drawn, the cost of the sampling and associated assay(s), convenience, and the degree of precision required in the final result.

The goal of any sampling program is not only to obtain representative samples, but to avoid any bias in the selection of these samples. Independent samples are obtained when the selection of one particular sample does not affect the selection of any other sample. Bias in sampling will result when the selection of a sample changes the way in which other samples are taken. Randomization and blinding are ways to overcome bias, but, as this article discusses, these factors can be eliminated only through the adoption of rigorous procedures.

The structure of a sampling program consists of a number of decision points. The analyst must determine how many samples are needed to represent the bulk material and the size these will be. The analyst also must decide how the various samples are to be analyzed (e.g., pooled to yield a common sample or each to be characterized individually) and the required degree of accuracy in the results. The variability of the bulk material being sampled, the size of each individual sample, the number of samples taken, and the method in which these samples are prepared for analysis will determine the accuracy of the sampling program.

Probability sampling

Sampling procedures may be classified as either nonprobability sampling or probability sampling. Nonprobable methods typically are procedures of convenience and are chosen because the alternatives are deemed too difficult to implement. This type of sampling is also known as *judgment* or *authoritative* samplings. Samples often are chosen using the expertise of those who have a feel for the process and believe that they intuitively know when and where to obtain a representative sample. Nonprobability samples often contain hidden biases, and statistical methods for the estimation of precision cannot be applied.

On the other hand, probability sampling ensures that the sampling scheme is developed in such a manner that will yield samples that are highly indicative of the properties in the bulk ensemble. It goes without saying that although probability methods are more complicated than nonprobability methods, their use is infinitely more desirable.

Sampling methodologies

Although a considerable number of probability-sampling procedures can be used, this article describes the four most common approaches.

Random sampling. In random sampling, each of all possible sample units has an equal chance of being included in the sampling procedure. To obtain a random sample, a number is conceptually assigned to each potential candidate, and numbers then are selected at random to identify the units to be sampled. Alternatively, samples are selected during random time periods during a production run to obtain a pseudorandom sample. For instance, consider a process used to manufacture a material that is eventually packaged in 10,000 bottles containing 100 g of powdered solid in each. Each bottle in the run is assigned an identification number during the processing, and a random-number generator is used to select 10 bottles from the production run. The entire content of each bottle should be used to conduct the analysis, unless this is impractical for the type of measurement to be conducted. In that case, one must execute a further random procedure to select the sample for analysis.

Stratified sampling. In stratified sampling, the ensemble to be sampled is divided into subsets, and random samples are taken from each subset. This method is best applied when the subsets themselves are very different in their properties, but objects in individual subsets are equivalent. To apply the method, samples are taken in a random manner, but only within specified time intervals. For example, consider a process used to manufacture a powdered solid at the rate of 5 kg/h that is scheduled to run for 10 h. To perform a stratified sampling procedure, one might sample 50 g of powder during each hour of operation. At the end of the production run, the 10 50-g samples are combined into a single 500-g sample, and this constitutes the sample that is subjected to analysis.

Systematic sampling. In systematic sampling, a definite sampling schedule is followed to obtain the units for testing. In other words, every *n*th sample is chosen during a production run to ensure regular sampling through the process. The time at which the sample is taken is not regulated, merely its position in the run. One should note, however, that systematic sampling only works when the ensemble is homogeneous. If the process happens to be cyclic or periodic in nature, then this procedure can lead to serious errors. As an example of systematic sampling, consider a process used to manufacture a powdered solid at the rate of 5 kg/h that is scheduled to run for 10 h. To perform systematic sampling, the operator pulls a 50-g sample exactly midway through each hour of operation. At the end of the production run, the 10 50-g samples are combined into one 500-g sample, which constitutes the sample ultimately subjected to analysis.

Cluster sampling. In cluster sampling, the ensemble is divided into groups or clusters, each of which contains subsets. Clusters are chosen at random, and all the elements in a cluster are included in the sample. This method is used when there are many primary units, each of which can be sampled. The subsamples from the clusters make up the sample taken for analysis. For a cluster sampling example, consider a process used to manufacture a material that is eventually packaged in 10,000 bottles containing 100 g of powdered solid in each. The primary units are the bottles, and the subsample units will be subdivisions of the bottle contents. To perform cluster sampling, one randomly selects 10 bottles from the stock produced and then randomly selects a 25-g sample from each bottle. After all the subsamples are properly combined, the resulting 250-g powder mass constitutes the sample to be analyzed.

Static powder sampling methods

Various methods can be used to obtain samples that are purportedly representative of the bulk from which the samples were drawn. The most common of these are scooping off the top surface and pouring and quartering. More-sophisticated methods include the use of a grain thief, a sample splitter–reducer, or a rotatory sample divider. Unfortunately, a general rule of thumb that has emerged is that the simpler the sampling method, the less likely it is to yield an acceptable sample.

Scooping from the top. It is almost painful to mention the most widely used method of sampling, namely that of using a spatula to scoop off some powder from the top surface of its bulk. Although this is by far the easiest method for sampling a powdered solid, there is no doubt that scooping off the top is less effective than the least desirable method that could be imagined. Leaving aside questions of chemical degradation at the upper layer, it is well known that particle segregation will result in the top layer of a powdered solid becoming enriched in its coarse-particle fraction (4). As a result, sampling this top layer would bias the particle-size distribution toward larger particles. Shaking the powder may not solve the problem because one may induce even more segregation in this process. Because the composition of the upper surface

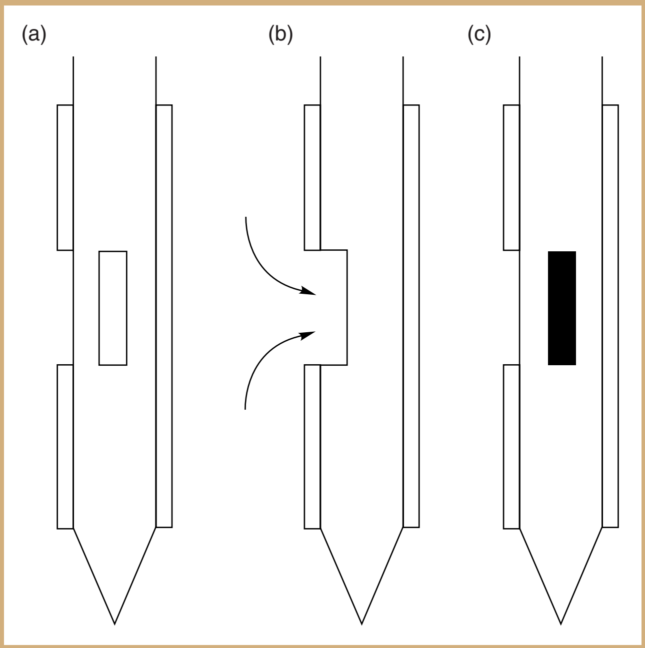

Figure 1: Operation of a sample thief. (a) The sleeve of the thief is rotated so that the interior compartment is isolated from the bulk powder. While in the closed position, the thief is plunged into the central mass of the powder. (b) Once the thief is at the desired position, the unit is rotated so that the interior compartment is now exposed to the bulk powder. Powder flows into the thief compartment of its own accord. (c) Once the interior compartment of the thief is filled, the sleeve of the thief is rotated so that the interior compartment is again isolated from the bulk powder. The thief is then withdrawn from the powder, and the sample is analyzed.

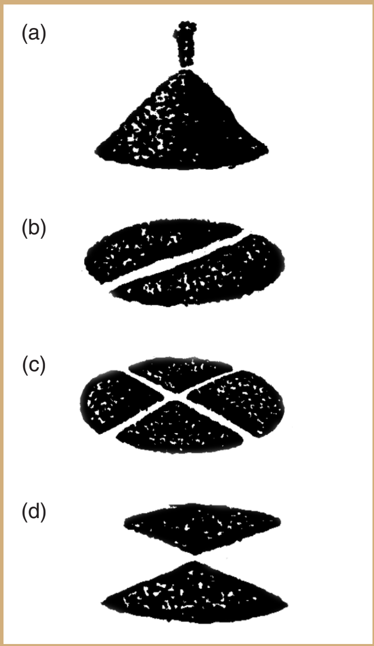

Figure 2: Performance of coning and quartering showing (a) pouring of the initial cone, (b) division of the flattened cone into halves, (c) further division of the flattened cone into quarters, and (d) removal of alternate quarters to define the subdivided sample.

of a bulk powder rarely is indicative of the bulk composition, this method of sampling is the worst possible way to obtain a sample.

Sample thief. A significant improvement in sampling can be achieved with the use of a sample thief, sometimes known as a grain thief for historical reasons. This device consists of two tubes, one fitting tightly inside the other, and with oblong holes cut through the tubes in corresponding positions. One end of the outer tube is fitted to a point to facilitate its insertion into a bulk powder. The sampling procedure, illustrated in Figure 1, consists of rotating the inner tube to close the holes, inserting the device into the powder, rotating the inner tube to open the holes, allowing the powder to enter the device, rotating the inner tube once more to close the holes, and finally removing the thief from the bulk powder.

Although thief sampling is a better method than merely scooping off the top of a bulk powder, it is still an inferior technique (5,6). Even though most thieves have relatively sharp ends, the very act of plunging the thief through the bulk powder must perturb the sample to some degree. A compressional force propagates ahead of the thief as it is pressed into the bulk, thus potentially changing the strata of the bulk and altering the wall of powder at the outer walls of the thief. Furthermore, because large particles will flow more easily than will small particles, an opened thief is liable to be filled preferentially with the coarse fraction of the particle distribution.

Coning and quartering. The main problem with scoop and thief sampling is that the samples are removed from a static powder bed, and there is simply no effective way to sample a nonmoving powder and obtain a representative sample. One procedure that attempts to address this problem is that of coning and quartering. For this procedure, one begins by pouring a cone of material, which is then flattened as evenly as possible. The material is then divided into quarters, whereupon two opposite quarters are discarded. The remaining two quarters are recombined and poured into another conical pile, which is then flattened and divided. The quartering process is continued until one is left with an amount of material that is the desired sample size (see Figure 2).

Great care must be taken when obtaining a sample by coning and quartering. When the initial powder sample is poured, it will undergo the full range of processes that result in segregation of particles according to their relative size. Because their flowability is the poorest, the finer particles will collect at the center of the cone, and the coarser particles will flow toward the edges of the cone. Hence, each wedge of a poured cone will become severely segregated by the act of pouring, making the process of subdivision and recombination critical. It is not unusual to ob-

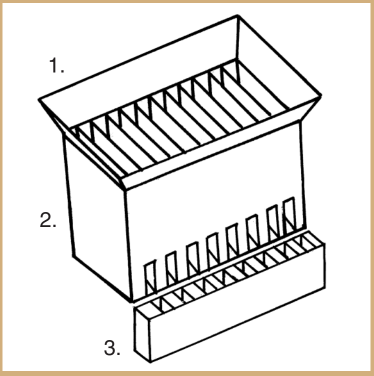

Figure 3: Schematic drawing of a chute sample splitter. Powder is fed through the upper baffles (1) and is discharged through the chutes (2) into the sample-collection tray (3).

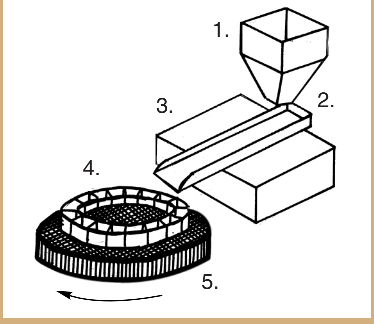

Figure 4: Schematic drawing of a rotary sample divider. Powder is fed through the hopper (1) into the delivery chute (2), expedited by the vibratory device (3). The subdivided samples are assembled in the collection tray (4), which is mounted on the rotary stage (5).

tain large standard deviations in particle-size results when the coning and quartering method is used to obtain a sample.

Dynamic powder sampling methods

There is little doubt that the superior methods of powder sampling entail procedures whereby the sample is removed from a moving powder bulk. Allen has contributed the two Golden Rules of Sampling that should be followed whenever possible (7):

- Rule 1: A powder should be sampled when in motion.
- Rule 2: The whole of the stream of powder should be taken for many short increments of time, in preference to part of the stream being taken for the whole of the time.

One method that has been developed to obtain more representative samples from bulk powders involves the use of sample splitters or sample reducers. These devices work by systematically rejecting segments of material flowing down a preset incline (see Figure 3). The sample is diverted from the main bulk and fed into a collection vessel. If the powder being divided has strong segregation tendencies, the powder flow must be rendered as homogeneous as possible to avoid bias. Only through homogenization of the powder stream will each subdivision of the bulk contain the same distribution of particle sizes as the mass from which it was taken.

The number of chutes necessary for a spitting device has been investigated (8). Increasing the number of chutes in the device may increase the efficiency of the system, but there are constraints on how this is to be accomplished. The chutes must all be of equal size, and their efficiency is improved when the size of the chute opening is reduced. However, when the system is appropriately designed and validated, its use can yield appropriately divided samples.

Arguably the best method for properly subdividing a powdered sample is through the use of a rotatory sample divider, commonly known as a *spinning riffler* and whose operation is illustrated in Figure 4. This device uses mechanical energy to provide a constant flow of material from its holder. The steady flow passes through a divider head operating at constant speed, thus minimizing segregation. Each sample from a rotatory sample divider can be analyzed separately or recombined to yield a representative sample. It almost goes without saying that the powder being tested must be free-flowing or it cannot be processed by the device.

A typical spinning riffler consists of three components. The powder hopper holds the bulk of powder that is to be subdivided, and its output is regulated by a feeding device. The most important part of the spinning riffler is the dividing head, which contains a number of sample collectors that are mounted on a rotating platform. During the rotation of the platform, the stream of powder emanating from the hopper is periodically cut into small portions. The riffler works best when the speed of rotation is relatively fast compared with the feed rate so that effects of flow segregation are minimal among each of the sample collectors. In other words, it is desirable that the powder accumulating in each sample collector is assembled from multiple samples of the powder in the hopper. Common sense dictates that the combined volume of all sample collectors must exceed that of the bulk powder volume in the hopper.

Conclusions

Regardless of how the sample is obtained, its composition must be representative of the bulk from which it was removed for analytical results to have any significance. Obtaining a representative sample from a static powder bulk is difficult and may not be possible even with the most thoughtful experimental design. Although it is widely believed that the use of sample thieves is an adequate method for good sampling, the literature seems to indicate otherwise. The general consensus is that only sampling from a bulk powder while it is in motion can yield the desired representative sample. These procedures present their own range of difficulties, but equipment exists that permits one to sample from moving powder beds on a variety of suitable scales. One can conclude that the use of a rotatory sampling device, or spinning riffler, is probably the best instrument available for the subdivision of powders having heterogeneous particle-size distributions.

Additional reading

1. C. Orr, *Particulate Technology* (Macmillan, New York, NY, 1966).
2. T. Allen, *Particle Size Measurement* (Chapman and Hall, London, 3d ed., 1981).
3. C.H. Murphy, *Handbook of Particle Sampling and Analysis Methods* (Verlag Chemie, Deerfield Beach, 1984).

4. K. Sommer, *Sampling of Powders and Bulk Materials* (Springer–Verlag, New York, NY, 1985).
5. M.J. Rhodes, *Principles of Powder Technology* (John Wiley & Sons, New York, NY, 1990).
6. N. Harnby, M.F. Edwards, and A.W. Nienow, *Mixing in the Process Industries* (Butterworth-Hienemann, Oxford, UK, 1992).
7. P. Gy, *Sampling for Analytical Purposes* (John Wiley & Sons, Chichester, UK, 1998).

References

1. H.G. Brittain, "Particle-Size Distribution Part I: Representations of Particle Shape and Size," *Pharm. Technol.* **25** (12), 38–45 (2001).
2. F.J. Muzzio et al., "Sampling Practices in Powder Blending," *Int. J. Pharm.* **155,** 153–178 (1997).
3. H.J. Venables and J.I. Wells, "Powder Sampling," *Drug Dev. Ind. Pharm.* **28,** 107–117 (2002).
4. J.W. Carson, "Overcoming Particle Segregation in the Pharmaceutical and Cosmetics Industries," *Drug Dev. Ind. Pharm.* **14,** 2749–2758 (1988).
5. J. Berman, A. Schoeneman, and J.T. Shelton, "Unit Dose Sampling: A Tale of Two Thieves," *Drug Dev. Ind. Pharm.* **22,** 1121–1132 (1996).
6. T.P. Garcia, M.K. Taylor, and G.S. Pande, "Comparison of the Performance of Two Sample Thieves for the Determination of the Content Uniformity of a Powder Blend," *Pharm. Dev. Tech.* **3,** 7–12 (1998).
7. T. Allen, *Particle Size Measurement* (Chapman and Hall, London, UK, 3d ed., 1981), p. 5.
8. T. Allen, *Particle Size Measurement* (Chapman and Hall, London, UK, 3d ed., 1981), p. 25. **PT**

Singla, continued from page 34

63. J. Pitha et al., "Hydroxypropyl-β-cyclodextrin: Preparation and Characterization; Effects on Solubility of Drugs," *Int. J. Pharm.* **29,** 73–82 (1986).
64. T. Loftsson et al., "2-Hydroxypropyl-β-cyclodextrin: Properties and Usage in Pharmaceutical Formulations," *Pharm. Ztg. Wiss.* **4** (136), 5–10 (1991).
65. H.O. Ammar, S.A. El-Nahhas, and R.M. Khalil, "Cyclodextrins in Acetazolamide Eye Drop Formulations," *Pharmazie* **53,** 559–562 (1998).
66. J. Szejtli, "Cyclodextrin Technology," *The Netherlands* **39,** 188–192 (1988).
67. T. Loftsson, B.J. Olafsdottir, and N. Bodor, "The Effects of Cyclodextrins on Transdermal Delivery of Drugs," *Eur. J. Pharm. Biopharm.* **37,** 30–33 (1991).
68. T. Loftsson et al., "2-Hydroxypropyl-ß-cyclodextrin in Topical Carbonic Inhibitor Formulations," *Eur. J. Pharm. Sci.* **1,** 175–180 (1994).
69. T. Loftsson et al., "Topically Effective Ocular Hypotensive Acetazolamide and Ethoxyzolamide Formulations in Rabbits," *J. Pharm. Pharmacol.* **46,** 503–504 (1994). **PT**

Gent, continued from page 66

deliverables with storage location of the validation documents. In other words, the validation testing report is a place to document what happened and how it happened for each validation test. In addition, the report captures all deviations and out-of-specification results.

Procedures and policies manual. A computer system can have all the bells and whistles that will help it comply with applicable regulations. However, built-in functionality and validation documentation does not make a computer system compliant. Policies and procedures are an enforcement tool that companies use to protect their computer systems from fraudulent use. These written guidelines provide a framework for specifying how the system will be used and managed, how data will be recovered, and what disciplinary actions can be taken for violations. Procedures should be written and implemented and should include security and data integrity, system operation, and system maintenance.

Team development

The activities of team development are an integral part of any development activity — validated or nonvalidated. The planning process helps the validation team implement a validated system. Standard documents are required to prove that a system is validated, and policies and procedures are necessary to implement and maintain a computer system in a validated state.

References

1. A. Dennis and B.H. Wixom, *Systems Analysis and Design: An Applied Approach* (John Wiley and Sons, Inc, New York, New York, 2000).
2. K. Wiegers, *Software Requirements* (Microsoft Press, Redmond, WA, 1999).
3. R. Budihandojo et al., "Validation of SAP R/3: A Conceptual Approach, Part 2," *Pharm. Technol.* **25** (3), 134–137 (2001). **PT**