

Research papers

## Sampling practices in powder blending

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### Abstract

Blending and sampling of granular materials are discussed in the context of pharmaceutical operations. Several experiments are used to compare the state of the art with regulatory expectations, especially those highlighted in a recent court ruling generally known as the ‘Barr Decision’. It is shown that samples obtained using thief probes can exhibit considerable errors, possibly leading to misleading results. The effects of sample size and number of samples are examined using an alternative characterization technique in which a powder mixture is solidified through infiltration with a polymer solution, sliced, and examined using image analysis. It is shown that number of samples is the most important parameter controlling the accuracy of the characterization. While a homogeneous mixture can be accurately characterized using just 30 samples, poorly mixed systems require hundreds of samples. It is also shown that an accurate characterization of a mixture inside a blender may not be indicative of the final state of the mixture after additional processing steps. © 1997 Elsevier Science B.V.

**Keywords:** Powder blending; Powder sampling; Mixing; Barr decision; Thief sampling

### 1. Introduction

Efficient blending and sampling of powders is of critical importance in the manufacture of a wide variety of pharmaceutical solid doses such as tablets and capsules. These products are manufactured from powder blends, granulated powders,

and extruded pellets. In a typical process, powders, granules, and pellets are blended, discharged to a tote or drum, emptied into a hopper on a press or encapsulator, and divided into the final dosage form. Inadequate mixing somewhere along the production sequence can result in rejection of finished product due to poor quality. Hence, achieving and maintaining homogeneous blends of powders and granules is of critical importance,

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especially in formulations involving small amounts of high potency components.

In many systems, the components requiring blending are powders of different size, density, shape, and cohesiveness. Since such materials often display a considerable tendency to segregate, ultimate mixture homogeneity cannot be taken for granted; quite the opposite, unless blending and handling processes are properly designed and controlled, the result is often a mixture with significant composition fluctuations throughout the powder bed (Fan et al., 1990; Poux et al., 1991). Inhomogeneities in the powder blend can result in increased variability in the contents of potent components in tablets, leading not only to decreased therapeutic value but also to direct health risks due to toxicity in super-potent tablets.

Hence, a thorough understanding of blending processes is highly desirable. Unfortunately, blending of granular materials is largely an art rather than a science, and at the present time the ability to design and accurately evaluate the performance of a mixing process for a high potency drug is limited. This problem has recently received considerable attention by the FDA. Quantitative validation of blending processes is increasingly becoming a central requirement of the regulatory agency, which has risen its expectations and initiated legal action to challenge industrial practices it now deems inadequate.

The best known example is described in a published court ruling (US vs. Barr Laboratories 812, F. Supp 458, D.N.J. 1993) herein referred to as the 'Barr Decision'. This ruling brought into sharp focus the need to understand, predict, monitor, and control the performance of blending processes. The court identified defective testing practices as one of the reasons for the litigation, and also made several statements concerning blending and sampling:

- The sampling technique should be representative of all portions.
- The blending process should not generate weak and/or hot spots in the blend.
- For assay tests, large samples are acceptable, but for content uniformity, sample size must be at most 3 unit dosages.

- Concerns that mixtures may declassify upon handling can be dealt with through particle size distribution studies.
- A time of mix study should be included in a prospective validation program.

Unfortunately, current regulations do not offer much help regarding how to achieve the goals put forward in such statements. In reviewing the Barr Decision, a number of issues remain unclear: (i) How should uniformity be assessed? Where should samples be taken, and how many samples are needed, to achieve 'representativeness'? (ii) What is the scientific foundation for the requirement that sample size be limited to at most 3 unit dosages? (iii) What are 'hot' and 'weak' spots, how does one find them, and what can one do to prevent them from forming? Moreover, two essential issues received minimum or no attention:

1. Sampling errors. The most common technique for obtaining samples is to use a thief probe. Such sampling devices can introduce large errors in sample composition. This issue is not even mentioned in the Barr Decision.
2. Segregation. It is well known among practitioners that powder mixtures often segregate (unmix) upon handling. In the Barr Decision, this concern is set aside by stating that such problems can be dealt with through particle size distribution studies. In fact, however, segregation can be a major problem in any process involving dry powders. The proposed solution, i.e., to control the particle size distribution, can be very difficult to achieve with current technology and might lead to conflicts with other performance objectives (such as dissolution) that also require specific particle size values.

A variety of experiments are used in this paper to clarify some of these issues. Section 2 provides a brief review of current blending and sampling practices in the pharmaceutical industry. The theoretical characterization of ideal mixtures is discussed in Section 3. Practical characterization of real mixtures is discussed in Sections 4 and 5. Segregation phenomena during processing are addressed in Section 6. Finally, conclusions and directions for future research are the subject of Section 7.

## 2. Blending of pharmaceutical powders: industrial practice<sup>1</sup>

The strict regulatory requirements for fully validated blending processes collide head-on with the state of the art in equipment design and performance prediction. While regulations require fully characterized, controllable, and predictable blending performance, available equipment is unreliable, poorly characterized, and far from controllable.

The two most common types of blenders used for pharmaceutical products are tumbling blenders and convective blenders. These two types of devices are based on very different operating principles. In a tumbling blender, the powder is confined within a vessel that is attached to a shaft. The shaft rotates, imparting an overall rotational motion to the entire vessel. The powder fills only a fraction of the vessel volume (optimum filling varies between 40% and 75% depending on vessel geometry). As the vessel rotates, the powder ‘tumbles’ downward, following a cascading motion. Powder flow patterns can be quite complicated even for the simplest vessel geometries. For example, for a cylindrical vessel rotating with respect to its axis, the powder flow shows two distinctive regions: a tightly-packed region undergoing upwards solid-body rotation, driven by the motion of the vessel walls, and an expanded region undergoing downwards cascading flow at the upper boundary of the powder bed. The position of this cascading region depends on both the rotational speed of the cylinder and the mechanical properties of the granular material. For low rotating speeds and free-flowing materials, the cascading region is planar and is inclined at an angle close to the angle of repose of the material. For fast flows, the cascading region develops curvature. If the material is even mildly cohesive, the position of the cascading region fluctuates with time and

shows widespread formation of avalanches. There is also some slip between the powder and the vessel. The amount of slip depends on axial position (Wightman et al., 1995), further complicating motion patterns.

Many types of tumbling blenders are commercially available, including cylindrical kilns, V-blenders, off-center V-blenders, cross-flow V-blenders, double cones, slanted cones, rotocubes, tote blenders, etc., etc. A thorough quantitative comparison of all of these designs has never been performed. Some partial comparative experiments have been carried out (Coulson and Maitra, 1950; Adams and Baker, 1956; Greathead and Simmons, 1957; Gray, 1957; Bannister, 1959; Kaufman, 1962; Lastovtsev and Khvalnov, 1963; Cahn et al., 1965; Campbell and Bauer, 1966; Harnby, 1967; Miles and Schofield, 1968; 1970; Orr and Shotton, 1973; Williams and Khan, 1973; Parrott, 1974; Harwood et al., 1975; Carstensen and Patel, 1977; Lai and Hersey, 1981a; Wong and Pilpel, 1988) but the characterization techniques used in all of these studies were limited to obtaining just a few samples using invasive techniques. Many of these blenders share certain limitations; for example, particles tend to move in re-circulating flow patterns, becoming trapped inside ‘dead regions’ and sometimes taking a very long time to blend with the remainder of the system (Carley-Macaulay and Donald, 1962; Cahn et al., 1966; Fan et al., 1972; Hogg and Fuerstenaue, 1972). Moreover, vessels with planes of symmetry orthogonal to the axis of rotation (such as V-blenders, double cone pans, and cylindrical kilns) often exhibit slow axial mixing. An example is shown in Fig. 1 for a V-blender of conventional design. Fig. 1a shows the initial condition of an experiment in which blue glass beads (Jaygo, Union, NJ) are loaded in one arm of a V-blender, and red beads are loaded in the other arm. The beads have a size range of 490  $\mu\text{m}$  to 700  $\mu\text{m}$  (nominal 600  $\mu\text{m}$ ) and a density of 2.55  $\text{g/cm}^3$ . The total filling level is 50% of the total vessel volume. Fig. 1b shows the state of the system after 5 min of rotation at 16 rpm. Almost no mixing has occurred. Fig. 1c shows the state of the system after 50 min. Even though this mixing time is much longer than the usual mixing times

<sup>1</sup> Blending practices have been reviewed in many textbooks on pharmaceutics, for example, Lantz and Schwartz (1981). Somewhat more comprehensive reviews discussing practices common to many industries have also been published (Fan et al., 1990; Poux et al., 1991; Fan et al., 1972; Harnby, 1992). Hence, only a brief review is provided here.

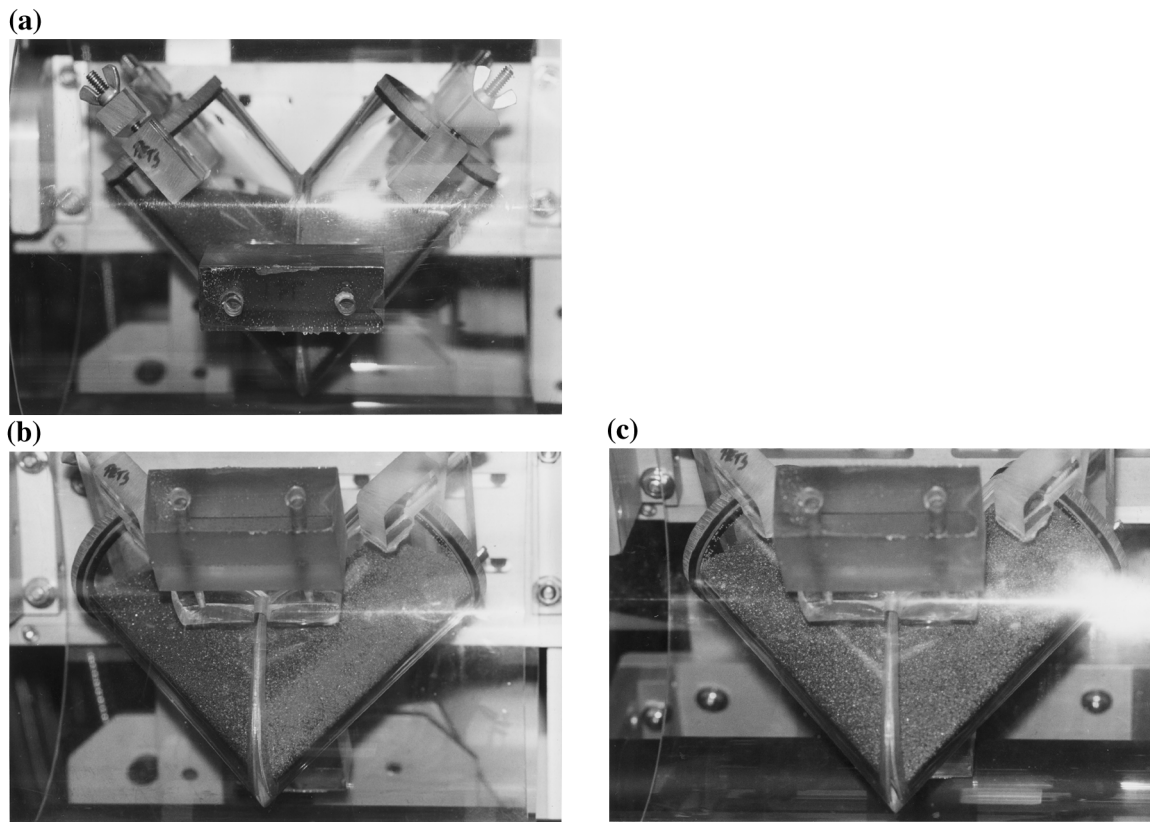


Fig. 1. Mixing in a V-blender. (a) Initial condition, (b) after 5 min of rotation at 16 rpm, and (c) after 50 min of rotation at 16 rpm.

used in industrial processes (typically in the order of 10 min), considerable heterogeneity can still be appreciated in the figure.

The other main type of blending equipment are convective blenders. These blenders are widely used in industrial operations. They are composed of a stationary vessel and a rotating impeller that stirs the powder. The main mechanism for mixing is the convective motion imparted by the impeller. The most common type is the ribbon blender, which is basically a rectangular container with a cylindrical bottom and a helical ribbon impeller affixed to a horizontal axle. Many versions of ribbon blenders are commercially available, each showing a slightly different ribbon or vessel design. Another common type of convective blender is the Nauta mixer, which is a vertical conical vessel with a screw impeller that both rotates and precesses. These mixers have been largely ignored

in the scientific literature. They have been discussed in some reviews (Weidenbaum, 1958; Fan et al., 1990; Williams, 1990), but the information is by-and-large qualitative and hard evidence about their comparative performance is unavailable.

Hence, it should be concluded that the state of the art in designing powder blending processes is largely unsatisfactory. In general, blenders are designed by trial-and-error, aided by cumulative experience and anecdotal evidence. One of the main reasons for this lack of rigorous design procedures is that the physics of powder flow is poorly understood. While some authors have proposed continuum approaches that can be used to predict powder flow patterns in some simple situations (Jenkins, 1986; Edwards, 1990; Johnson et al., 1990), generally accepted constitutive equations describing the relationship between forces

and velocities during powder motion are not available. Poor understanding of powder mixing processes translates into severe technical limitations:

- Equipment design and optimization must be approached on a case-by-case basis.
- Rational criteria for comparing mixing performance in different types of equipment are unavailable. Replacement of a given blender by another of different design often entails additional experimentation to ensure that product characteristics remain constant.
- Rigorous scale up procedures for blending processes have not been developed. Once homogeneous blending is successfully achieved in small scale batches, the practitioner lacks the means for ensuring *a priori* that similar results will be achieved in large scale equipment.

### 3. Statistical characterization of ideal mixtures

‘Mixing theory’ is largely statistical in nature. One of the seminal papers on the subject is due to Danckwerts (1952)<sup>2</sup>, who proposed that the quality of a mixture could be quantified by computing the mixture’s correlation coefficient

$$R(\partial r) = \frac{\langle [C(r) - C_{av}][C(r + \partial r) - C_{av}] \rangle}{\langle [C(r) - C_{av}]^2 \rangle} \quad (1)$$

where  $C(r)$  is the composition of the mixture at a given position  $r$ ,  $C_{av}$  is the average composition for the entire mixture, and the symbols  $\langle \rangle$  imply that an average is taken over many locations. Danckwerts then derived two indexes, the linear scale of segregation  $S$  and the intensity of segregation  $I$ , respectively given by

$$S = \int_0^\infty R \partial r \quad I = \sigma^2 / \sigma_o^2$$

where,  $\sigma^2$  is the variance of the mixture composition and  $\sigma_o^2$  is the maximum possible variance

corresponding to an entirely segregated mixture. In a broad sense,  $S$  represents the average size of heterogeneous regions in the mixture and  $I$  represents the average magnitude of composition fluctuations throughout the mixture. Danckwerts’ study was followed by other statistical studies that used various mixing indices (Lacey, 1954; Ashton and Valentin, 1966; Shin and Fan, 1978) based on sample variances to characterize the degree of homogeneity of the mixture resulting from a given process.

Statistical mixing theory has been used to develop guidelines concerning the size and number of samples needed to achieve a given level of measurement accuracy in a random mixture. Such a random mixture is schematically depicted in Fig. 2a as a grid of mixture sub-units (naively, each box in the grid represents mixture subdivisions such as unit dosages). The values in such boxes can have any desired distribution (Fig. 2b), the only condition to describe such a system as a random mixture is that the value at a given location (i.e., the number at a given box) should be uncorrelated to the value at any other location (the number at any other box). The composition of samples obtained from such ‘random mixtures’ are readily predicted from statistical theory. A population of samples each equal in size to a unit box will exhibit a distribution (Fig. 2c) that becomes increasingly similar to that of the entire population as the number of samples increases (Fig. 2d). However, as predicted by the central limit theorem (Devore, 1982), if each sample is composed of several neighboring boxes, and the measured value assigned to such a sample is the average of the values in the boxes comprised in the sample, the distribution of values of the sampling population is different than the distribution of values in individual boxes (‘true distribution’). For a random mixture, the sampling population approaches a Gaussian distribution (Fig. 2e) with a mean equal to the mean of the distribution of individual boxes, but with a variance equal to the variance of the individual boxes divided by the number of boxes in the sample. This Gaussian distribution becomes more accurately resolved as the number of samples increases (Fig. 2f).

<sup>2</sup> Although Dankwerts’ discussion on characterization of mixtures is more than 40 years old, the language in his paper is uncannily current. This classical study is strongly recommended as required reading for any scientist with a genuine interest in mixing and blending processes.

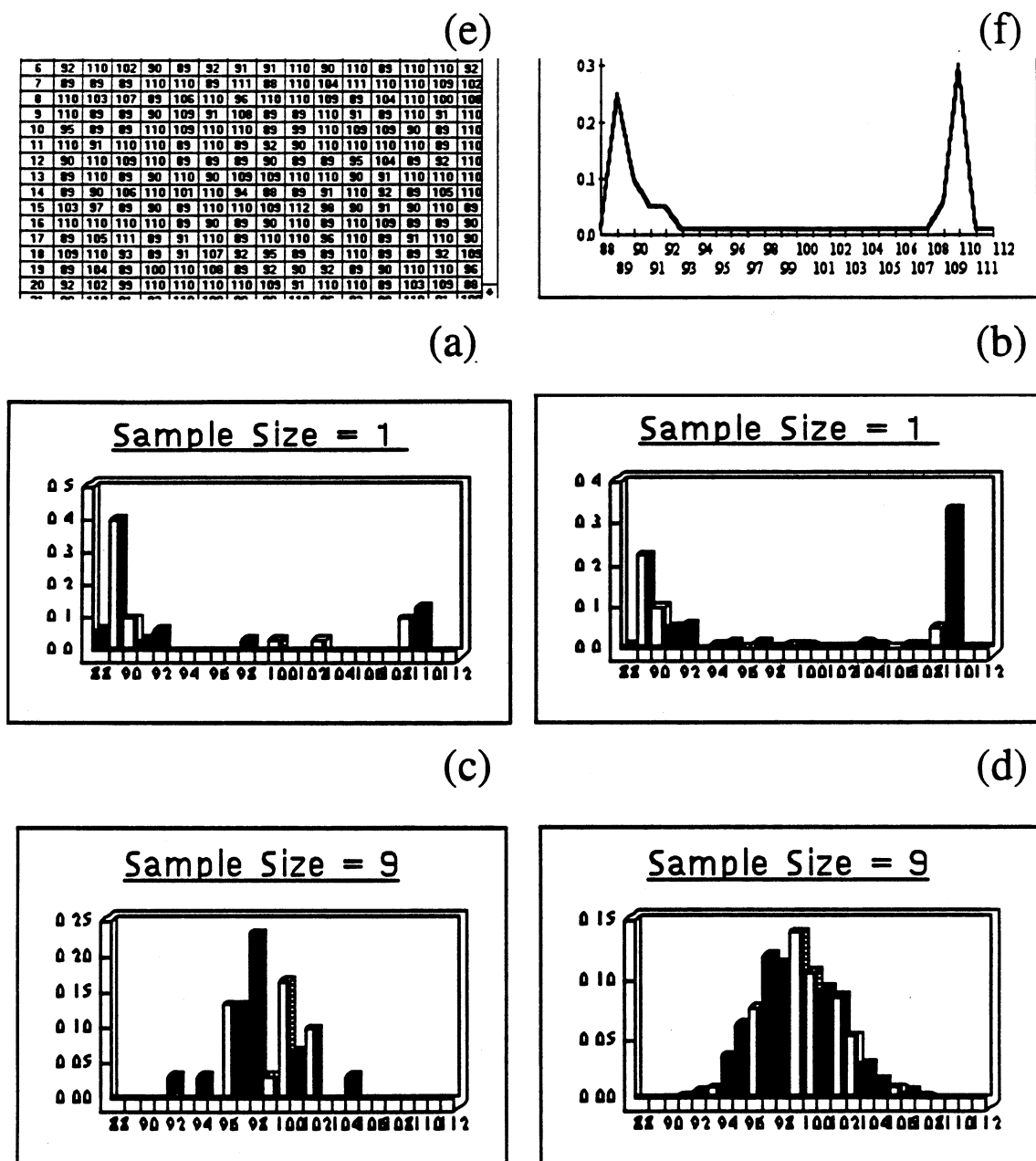


Fig. 2. (a) Schematic representation of a random mixture; (b) distribution of individual values in the random mixture; (c) estimate of the distribution of individual values for  $N = 30$  samples; (d) estimate of the distribution of individual values for  $N = 300$  samples; (e) estimate of the distribution of larger samples composed of  $9 (3 \times 3)$  adjacent boxes using  $N = 30$  samples, and (f) estimate of the distribution of larger samples composed of  $9 (3 \times 3)$  adjacent boxes using  $N = 300$  samples. In all cases, sampling was performed without removal, i.e., the same box can be sampled repeatedly by the process.

This averaging effect has provided the conceptual basis for the regulatory requirement that size of samples used for characterization of content uniformity be limited to at most three times the unit dose. However, underlying this requirement are three assumptions:

1. It is assumed that actual blends are random mixtures entirely devoid of spatial correlations and that a small number of samples is therefore sufficient to characterize the extent of variability in the system.
2. It is also assumed that a sample obtained by standard techniques is truly representative of the composition of the system at a given location.
3. It is further assumed that the state of the blend at a given stage of the manufacturing process predicts the final state of the blend at the end of the process. In other words, it is assumed that if a given degree of homogeneity (or heterogeneity) is demonstrated at an early cross-section of the process, such a characterization remains largely unchanged through further processing.

While in principle these assumptions might constitute a reasonable starting point in lieu of better evidence, experiments readily demonstrate that all three assumptions are violated even by simple materials under common processing conditions<sup>3</sup>. Such experiments are presented in the remainder of this paper.

#### 4. Characterization of real mixtures using thief probes

Characterization of mixtures in most industrial processes relies on taking and analyzing discrete samples. Parameters such as sample size ( $n$ ), number of samples ( $N$ ), and location of sampling

points can affect measurement values. As mentioned in the previous section, guidelines for selecting the number of samples (i.e.,  $N > 30$ ) have been proposed based on theoretical random mixtures with Gaussian distributions (Devore, 1982), but optimal values of sampling parameters are often unknown for real systems displaying incomplete mixing and non-ideal distributions.

In real mixtures, practical considerations and physical constraints of sampling mechanisms limit the number and size of samples and the locations where they can be obtained. Extensive sampling is often impractical; commonly, just a few samples ( $< 30$ ) are removed from a blender. The most common approach is to use a thief probe to withdraw samples from different locations in stationary powder mixtures. Thief samplers belong to two main classes: side-sampling and end-sampling. A typical side-sampling probe has one or more cavities stamped in a hollow cylinder enclosed by an outer rotating sleeve. The sleeve has holes that align with the cavities, allowing adjacent powder to flow into the cavities. An end-sampling thief has a single cavity at the end of the probe; such cavities can be opened and closed in a controlled manner. In both cases, the thief is introduced into the powder with its cavities closed. Once insertion is complete, the cavities are opened, allowing the powder to flow into them. The cavities are then closed, and the thief is withdrawn, removing samples from the mixture.

According to Allen, the two 'golden rules' of powder sampling are that: (i) a powder should be sampled only when in motion, and (ii) a sample should be collected uniformly from the entire process stream (Lantz and Schwartz, 1981). The use of thief probes violates both of these rules. Thief sampling is a rather laborious and cumbersome technique. Due to physical constraints, it is rarely practical to take more than 10 or 20 samples in production equipment, making it impossible to obtain a representative characterization of all regions of the blend. In any sampling scheme, the experimentally measured variance,  $\sigma_e^2$ , is actually a combination of the true variance resulting from the mixing process,  $\sigma_m^2$ , the variance introduced by sampling error,  $\sigma_s^2$ , and the variance resulting from chemical analysis,  $\sigma_a^2$  (Fan et al., 1990), i.e.

<sup>3</sup> In fact, some of the limitations of statistical characterizations were already identified by Danckwerts himself (Danckwerts, 1952), who indicated that two conditions needed for his approach to be valid were that (i) the size of the smallest particle be much smaller than the size of the sample, and (ii) the mixture be uniform in texture, i.e., be devoid of any large-scale segregation.

Table 1

Comparison of the thief probes used in the experiments reported in this paper

Thief	Globe Pharma	Slug	Rutgers
Type of probe	Side-sampling	End-sampling	End-sampling
Extent of disturbances near cavity	Significant	Significant	Minimal
Powder enters cavity while closed	Yes	No	No
Maximum sampling error	≈100%	≈30%	≈20%
Thief relies on powder flow to fill cavity	Yes	No	No

$$\sigma_e^2 = \sigma_m^2 + \sigma_s^2 + \sigma_a^2 \quad (2)$$

In an ideal situation,  $\sigma_s^2$  and  $\sigma_a^2$  are negligible, and  $\sigma_e^2$  (the variance subject to USP rules) is almost identical to  $\sigma_m^2$  (the true variance). Unfortunately, a thief probe can bias measurements to the point that sampling uncertainty should be expected to be a large fraction of the measurement (Ashton and Valentin, 1966; Schofield, 1976; Yip and Hersey, 1977; Lai and Hersey, 1981b). Two type of errors are often introduced by thief probes: (i) the mixture is extensively disturbed when the thief probe is inserted into the powder bed, and (ii) particles of different sizes often flow unevenly into the thief cavities. Side-sampling probes often have an additional problem: cohesive powders do not flow easily into thief cavities, sometimes resulting in samples that are smaller than desired.

Only a few studies have attempted to quantify the errors introduced by thief probes, mainly focusing on side-sampling devices (Gayle et al., 1958; Carley-Macaulay and Donald, 1962; Poole et al., 1964; Schofield, 1976; Gopinath and Vedaraman, 1982; Masiuk, 1987). Carley-Macaulay and Donald (1962) performed a comparison study between two types of side-sampling probes. One was a conventional probe (as described above); the other probe had cavities that were closed using a longitudinal slit. They took samples from a system composed of sand of two colors arranged in a layered structure. The conventional probe generated samples of a mixed color within a region of two aperture diameters (0.325 cm) from the layer boundary. In the longitudinal slit probe, sand particles tended to run down the slit, causing errors greater than the conventional side-sampling

probe. In both cases, errors occurred because the probe sampled locations that had already been disturbed by the insertion of the probe itself. Other studies reached similar conclusions. For example, in a study conducted by Williams and Khan (1973), although no quantitative data was reported, the authors concluded that a side-sampling thief gave totally misleading results in a segregating system. Orr and Shotton (1973) proposed that perturbations of the mixture structure were caused by friction along the length of the probe, and were independent of the profile of the tip. This suggested that an end-sampling probe would perform better than a side-sampling probe, because for an end-sampling probe the sample was taken from a relatively undisturbed region of powder beneath the tip of the probe. They developed such a probe for use with cohesive powders. Components sampled at depths of 1, 2, 4 and 6 cm through a 2-cm layer of charcoal powder qualitatively showed little contamination of the samples with charcoal powder. In a quantitative analysis, 20 samples of cohesive calcium carbonate were taken through a layer of cohesive lactose at a depth of 2 cm below an interface. The maximum amount of lactose found in the samples was 0.07% (Orr and Shotton, 1973).

Experiments were recently conducted to assess the performance of three recently developed probes: a newly-released commercially available side-sampling probe (Globe-Pharma, Piscataway, NJ), an end-sampling 'slug thief' and an end-sampling thief designed at Rutgers University (Piscataway, New Jersey). A brief comparison of the three probes is provided in Table 1. The disturbances introduced by these probes were determined using two procedures:



(i) A qualitative assessment of the extent of perturbation of the granular structure was performed by inserting the thief probes into a system which consisted of several alternate 2.5 cm layers of white and red glass beads (Jaygo, Union, NJ) that had size ranges of 1400  $\mu\text{m}$  to 1600  $\mu\text{m}$  (nominal 1500  $\mu\text{m}$ ) and a density of 2.95 g/cm<sup>3</sup>. The granular beds were then solidified by infiltration with gelatin without removing the probes. The solidified beds were cut along the path of the probe and photographed.

(ii) Quantitative assessment of the errors introduced by each thief probe was carried out by sampling structures which consisted of two layers of 60  $\mu\text{m}$  beads (size ranges of 30  $\mu\text{m}$  to 103  $\mu\text{m}$ ) and 200  $\mu\text{m}$  beads (size ranges of 160  $\mu\text{m}$  to 250  $\mu\text{m}$ ) with a density of 2.46–2.69 g/cm<sup>3</sup> (Potters Industries, Parsippany, NJ). The layered structure consisted of a 76 mm top layer over a 102 mm bottom layer inside a cylindrical 152 mm diameter can. Two configurations were considered: 60  $\mu\text{m}$  beads on top of 200  $\mu\text{m}$  beads, and 200  $\mu\text{m}$  beads on top of 60  $\mu\text{m}$  beads. Samples were taken at known positions above and below the interface between layers, and the composition of such samples was compared with the theoretical composition of the material at the sampling depth. The number of samples taken during each experiment was limited by the diameter of the probe being tested. In each case, samples were taken at locations far enough apart (at least two probe diameters) so that the disturbances caused by previous insertions of the probe would not affect subsequent sampling.

The Globe Pharma thief (Fig. 3a) had the usual side-sampling design described above. The probe had two cavities. Removable dies were fitted into the cavities in order to control sample volume. In all of the tests reported here, the lower cavity contained a 0.2-ml die while the upper one was filled with a solid die. Experiments showed that insertion of the Globe Pharma thief created significant disturbances in the mixture (Fig. 3b). Particles from upper layers were dragged deeply into lower layers as the thief penetrated the granular bed. As a consequence of such disturbances, once the thief was opened, the sample flowing into the thief was contaminated with particles from all

positions along the path of insertion and did not necessarily reflect the true composition of the system at the intended sampling location.

The actual sample composition was compared to the theoretical composition expected from the sampling location for the Globe Pharma thief (Fig. 3c,d). Results were computed by measuring the fraction of the beads from the top layer that were contained in each sample. For most sampling locations, the sampling cavity was either entirely above or entirely below the interface, corresponding to a theoretical value of one or zero, respectively. When part of the sampling cavity was above the interface and part of it was below the interface, then the sample should have contained beads of both colors, corresponding to a theoretical value between zero and one. Results in Fig. 3c were obtained for 60  $\mu\text{m}$  beads on top of 200  $\mu\text{m}$  beads, and results in Fig. 3d were obtained for 200  $\mu\text{m}$  beads on top of 60  $\mu\text{m}$  beads. If the probe accurately sampled the desired location, the fraction of beads from the top layer should have been zero when the entire opening crossed the interface between the top and bottom layers. However, as shown in Fig. 3c,d, large sampling errors were incurred. For all sampling locations, the samples were composed almost entirely of particles from the top layer regardless of whether the top layer was composed of smaller particles (Fig. 3c) or larger particles (Fig. 3d). In addition, sample weight variability was considerable (R.S.D. = 34% of sample weight).

In order to identify the source of these errors, additional experiments were performed, in which the probe was introduced into the granular system and then removed without ever opening the cavity. Upon removal of the thief, it was observed that the cavity was partially filled with particles from the top layer. These experiments showed that free-flowing materials could enter the cavity even before the thief was opened. These errors could be magnified in industrial applications. In our experiments the thief was only inserted 10 to 15 cm below the upper surface of the granular bed, while in industrial sampling, depths of up to two meters are common. If particles flowed into the thief while the cavity was closed, the resulting sample would be a composite of the system along

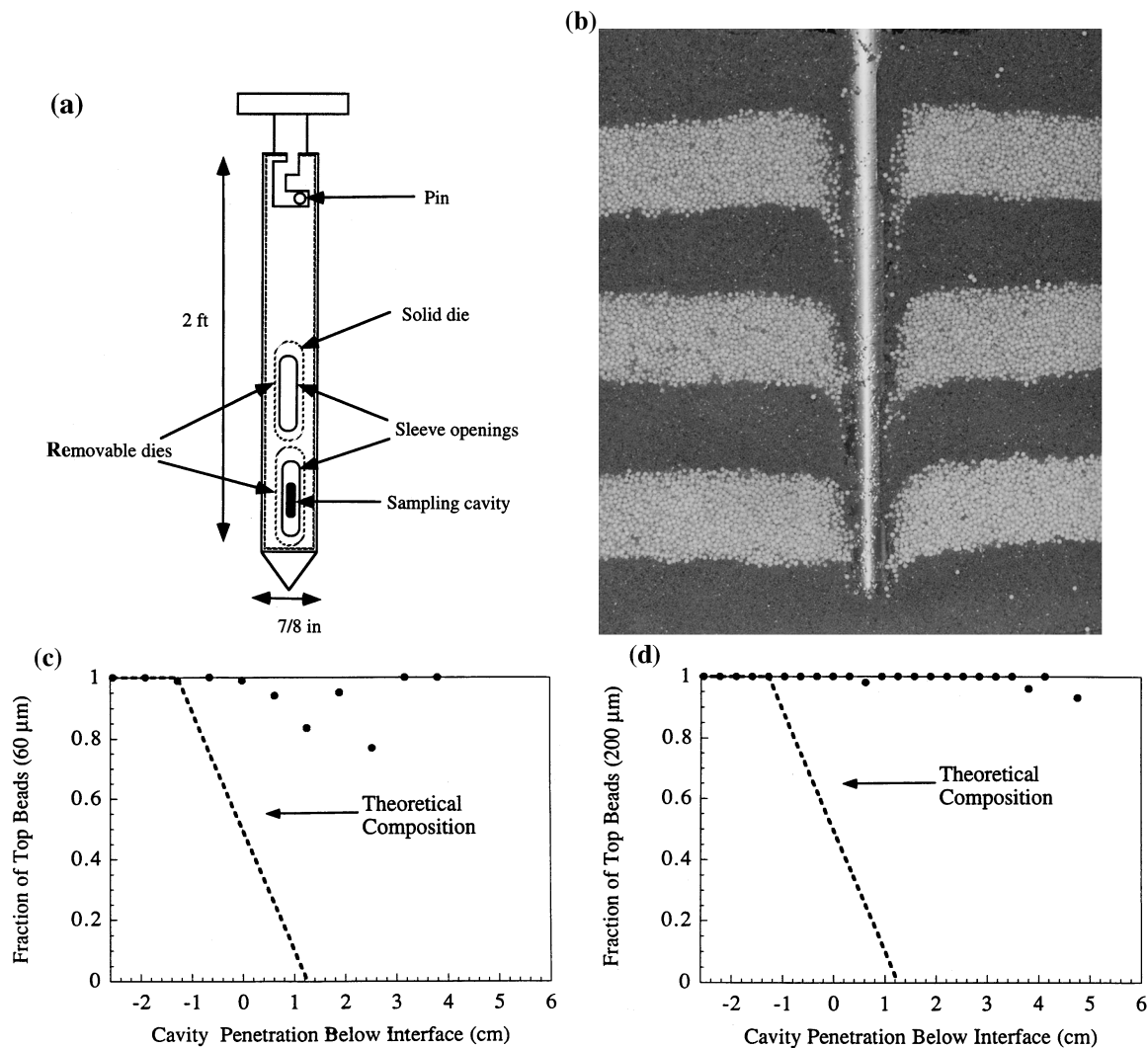


Fig. 3. Performance of Globe Pharma thief probe. (a) Schematic of the thief; (b) disturbances caused by insertion of the probe into particle bed; (c) comparison of theoretical (---) and experimental (●) results for 60  $\mu\text{m}$  particles over 200  $\mu\text{m}$  particle, and (d) 200  $\mu\text{m}$  particles over 60  $\mu\text{m}$  particles.

the path of penetration of the thief, rather than the true composition of the undisturbed system at the intended sampling location.

The second device tested, the 'slug thief', was an end-sampling device which consisted of a hollow tube with an internal plunger that could be positioned at variable heights in order to control sample size (Fig. 4a). A foot was mounted at the end of a shaft parallel to the hollow tube. The foot could be rotated to either open or close a

sampling cavity at the end of the hollow tube. The base of the foot was essentially flat with a small cone mounted on the end below the hollow tube. The slug thief was used as follows: (1) the plunger was adjusted to select the desired sample size, (2) the thief was inserted into the powder mixture, (3) the foot was rotated, opening the hollow tube, (4) the thief was inserted further into the powder bed, forcing particles to flow into the sampling cavity, (5) the foot was rotated closed, and (6) the thief

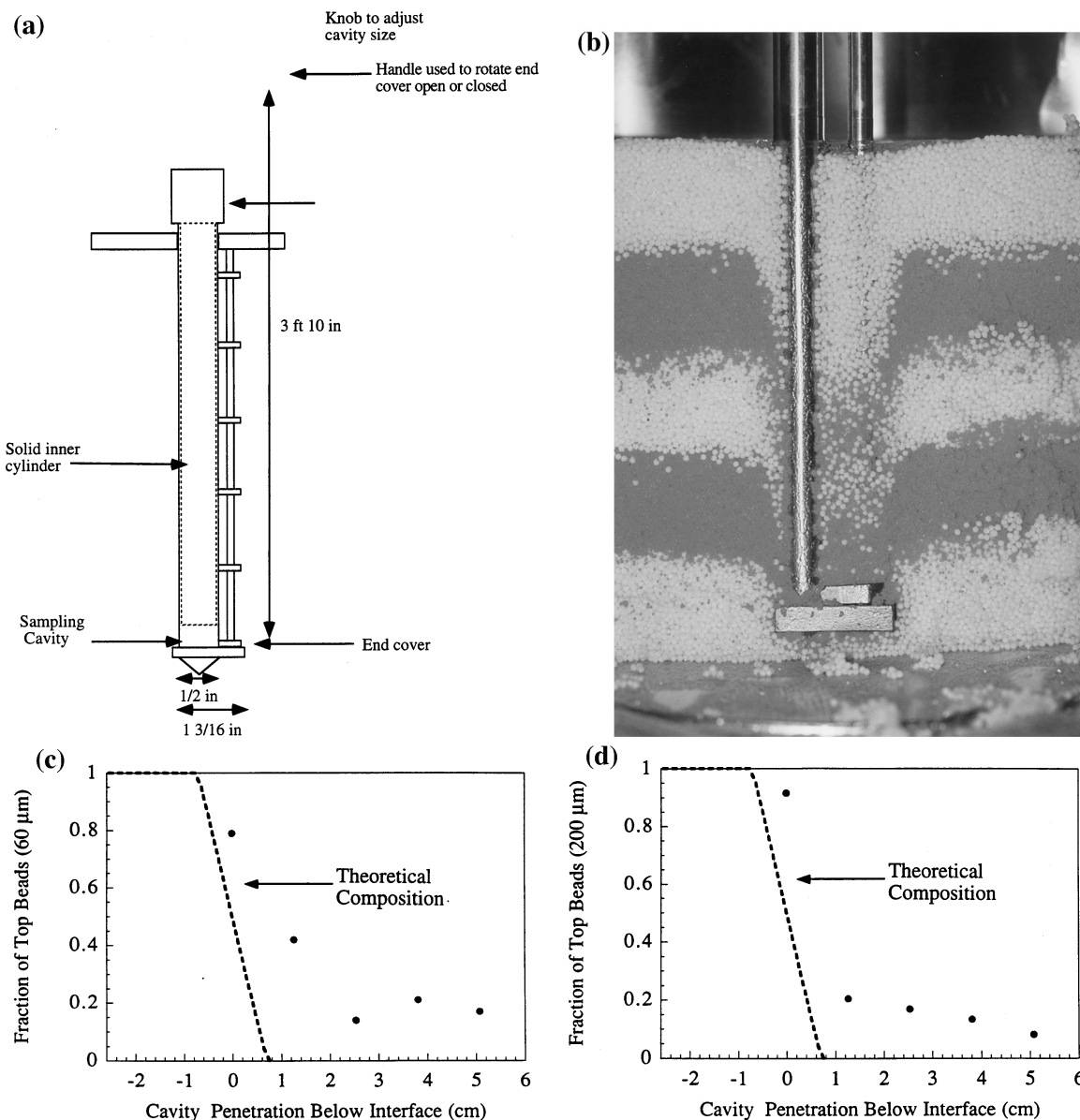


Fig. 4. Performance of slug thief probe. (a) Schematic of the thief, (b) disturbances caused by insertion of the probe into particle bed, (c) comparison of theoretical (—) and experimental (●) results for 60 μm particles over 200 μm particle, and (d) 200 μm particles over 60 μm particles.

containing a sample was removed from the mixture. As shown in Fig. 4b, the slug thief created very large perturbations in the mixture structure, mainly due to the bluntness of its base. Similar to the Globe Pharma thief, particles from upper layers were dragged deeply along the path of

insertion of the slug thief. A quantitative comparison between theoretical and experimental sampling compositions is shown in Fig. 4c for a system of 60 μm beads on top of 200 μm beads, and Fig. 4d for a system of 200 μm beads on top of 60 μm beads. Very similar results were ob-

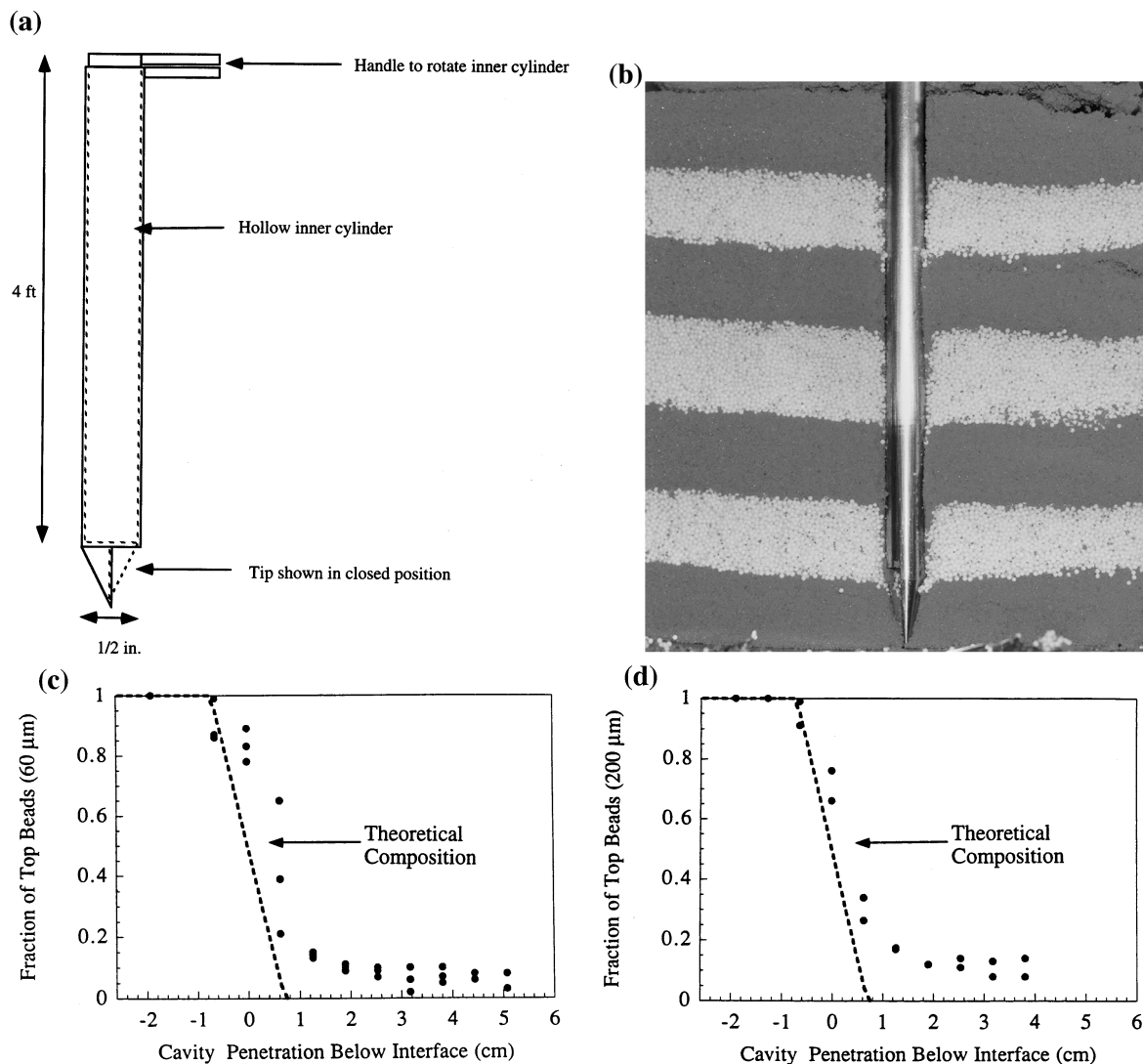


Fig. 5. Performance of Rutgers thief probe. (a) Schematic of the thief; (b) disturbances caused by insertion of the probe into particle bed; (c) comparison of theoretical (---) and experimental (●) results for 60  $\mu\text{m}$  particles over 200  $\mu\text{m}$  particle, and (d) 200  $\mu\text{m}$  particles over 60  $\mu\text{m}$  particles.

tained for both cases. Due to the large disturbances caused by the insertion of the probe, only five independent samples were removed during the each experiment. Sample weight variability (R.S.D. = 8% of sample weight) was considerably smaller than for the Globe Pharma thief. The agreement between theoretical and experimental data was better than for the Globe Pharma thief, mainly because particles did not enter the slug

thief cavity when it was closed. However, sample composition errors were still large (on the order of 20%).

The third thief tested was a new end-sampling probe designed and constructed at Rutgers University. The device consisted of two concentric hollow pipes, both ending in a pointed cone (Fig. 5a). Half of each cone was removed forming a sampling cavity which was opened and closed by

rotating the inner pipe; if the openings in both cones were aligned, the sampling cavity was open; otherwise it was closed. A gasket filling the space between the inner and outer cones prevented particles from entering the thief when it was closed. The thief was used in the same manner as the previous end-sampling device. Samples of consistent size were obtained by controlling the depth of insertion after the cavity was opened. Sample weight variability for this thief (R.S.D. = 6% of sample weight) was smaller than for either of the other two devices. As illustrated in Fig. 5b, this thief introduced much smaller disturbances of the granular structure than the previous two devices. While some disturbances along the length of the probe were observed, these disturbances were minimum near the tip of the probe where sampling took place. Particles did not penetrate the thief when the sampling cavity was closed. Quantitative comparison of theoretical and experimental sampling data is shown in Fig. 5c for 60  $\mu\text{m}$  beads on top of 200  $\mu\text{m}$  beads, and in Fig. 5d for 200  $\mu\text{m}$  beads on top of 60  $\mu\text{m}$  beads. In both cases, this thief performed much better than the previous two, but the average error was still large and in the range of 10%.

An additional source of errors in thief sampling is that particles of different sizes may flow unevenly into the thief cavity (Harwood and Ripley, 1977). This type of error was examined by performing extensive sampling of well-mixed systems composed of particles of distributed sizes. The Rutgers thief was chosen for this study due to its best overall performance in the other tests. A system composed of equal amounts of 60  $\mu\text{m}$ /200  $\mu\text{m}$  beads was homogenized by vibrating the system at 25 Hz for 25 min. Samples were then taken in groups of 20 at a time, analyzed by sieving and weighing, and then returned to the mixture to restore the original composition. Since the sampling process itself is known to cause segregation of the powder bed, the system was remixed between sample groups to avoid accumulation of sampling errors. A total of 12 groups of samples were analyzed. The number of samples that display a given weight fraction of large particles is shown in Fig. 6. The system showed a mean value of 46.7% with a relative standard deviation of

5.8% and a frequency distribution clearly tilted to the left (low concentration of large particles). In contrast, when the system was examined using mixture solidification and image analysis techniques, described in detail in Wightman et al. (1995), a nearly Gaussian distribution with a mean of 48.2% and an R.S.D. of 1.9% were obtained. While this difference in means (46.7% vs. 48.2%) at first seemed relatively small, a *t*-test immediately revealed that for the large number of samples used here ( $n = 240$ ), there was an extremely low probability that such differences could be due to chance, and strongly suggested that the 60  $\mu\text{m}$  particles flowed preferentially into the cavity of the thief (shifting the mean value to the left), generating also an artificially large measure of variance.

In summary, it must be concluded that samples obtained using thief probes are likely to contain significant errors. The insertion of a thief probe into a mixture causes extensive disturbances of the mixture structure, dragging particles along the path of insertion of the thief. The sample that is finally collected is likely to contain particles from all positions along the path. Even for an end-sampling thief of streamlined design, samples were contaminated by particles originally located as far as 5 to 10 cm away from the sampling location causing errors of 10% or more, i.e., considerably larger than desirable for an accurate characterization of mixture structure.

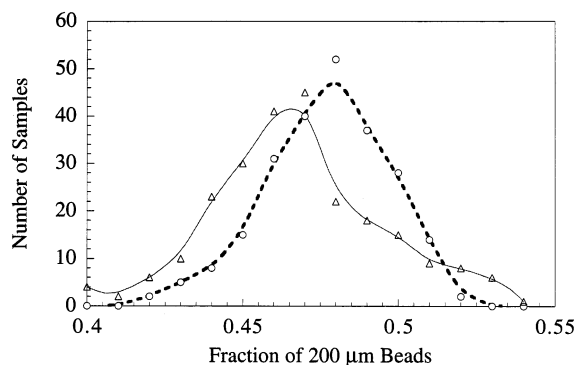


Fig. 6. Comparison of measurements for a well-mixed system of 60 and 200  $\mu\text{m}$  glass beads obtained using the Rutgers thief probe ( $\Delta$ — $\Delta$ ) and by freezing the mixture and using and image analysis ( $\circ$ — $\circ$ ).

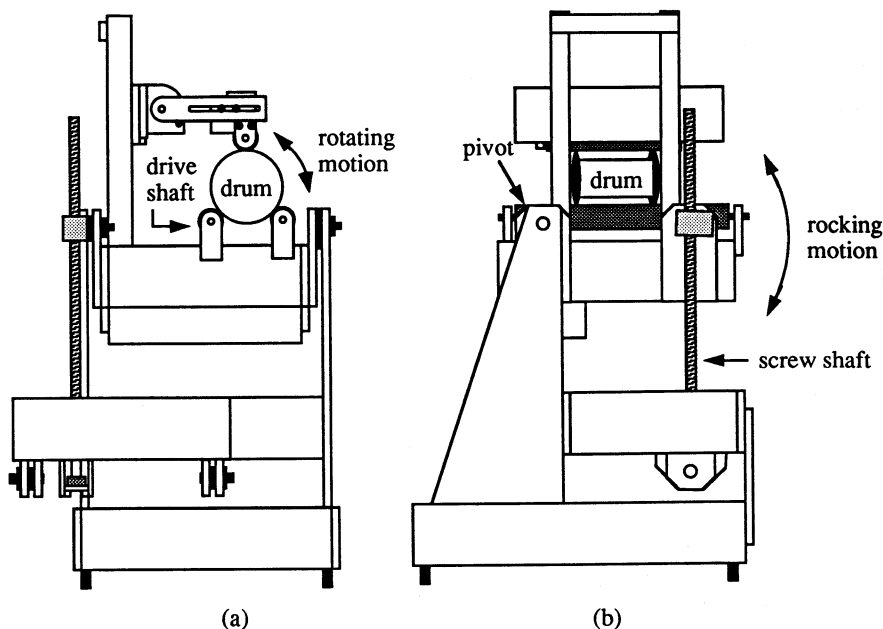


Fig. 7. Experimental mixing apparatus. (a) Front view and (b) side view.

### 5. Characterization of real mixtures: an image analysis approach

Given the limitations of thief sampling, an alternative approach was used in this paper to obtain a thorough quantification of undisturbed powder mixtures and to determine the effects of the sample size and number of samples on the accuracy of sampling measurements. The experimental method has been described in detail elsewhere (Wightman et al., 1995, 1997). Each experiment began with 60  $\mu\text{m}$  glass beads of two different colors (red and green) loaded in a disposable rotary-drum mixing vessel (103 mm diameter  $\times$  140 mm length). The interior of the vessel was pre-coated with sand to increase friction and minimize slippage of the glass beads at the cylinder wall. The cylindrical container was loaded so that the initial interface was at an axial position 70 mm from each end, i.e. beads of one color were loaded in the section of the mixer between  $-70$  and  $0$  mm, and beads of a different color were loaded between  $0$  and  $70$  mm, with respect to an axial coordinate with its origin at the center of the vessel. Equal volumetric amounts of beads of each

color were loaded to fill 30% of the vessel volume. The loaded vessel was placed on a mixer with two rollers (Syncro Motion Corp, Valley Forge, Pennsylvania), which imparted a rotational motion with respect to the vessel axis (Fig. 7a). The rollers also pivoted (Fig. 7b), which imparted a vertical rocking motion. During a rocking cycle, one end of the vessel was pivoted downward by  $10^\circ$  followed by an upward motion back to the horizontal position. The loaded vessel was rotated at a given rpm for a predetermined mixing time and rocking frequency.

At the end of each mixing experiment, the mixture was solidified in situ (i.e., inside the mixing vessel) to preserve the mixture structure in an undisturbed state. An opening was made at the top of the vessel, and a binder solution (Rave<sup>®</sup>, Chesebrough Ponds USA, Greenwich, CT) was slowly pumped on top of the mixture. The liquid gradually penetrated the bed of particles, filling voids and displacing air. As the solvent evaporated, the binder solidified at the contact points between particles, 'freezing' the mixture in an undisturbed state. The solid mixture was then extracted from the vessel and cut along the axis into slices 10 mm thick.

Mixture slices were sequentially scanned and recorded as digital 8 bit gray-scale images, and analyzed using numerical image analysis algorithms. During the scanning procedure, a slice of the mixture was partitioned into 83 fields of view, and further subdivided into 5229 small rectangular areas ( $0.56 \text{ mm} \times 0.96 \text{ mm}$ ), called patches. The local composition was determined for each of these small patches using a calibration curve that transformed the mean gray level intensity of the patch to composition values (i.e., w/w % of particles of a given color). Patches were the smallest area evaluated in the experiments, i.e., the patch size determined the scale of examination in the mixing analysis. As discussed later, the scale of examination was varied (by changing the patch size) during the analysis to determine its effect on the statistics of the mixture. The image analysis procedure was repeated for each slice in the mixture, giving a detailed and accurate 3D-database of the system composition.

This 3D-composition database for each slice was configured into a matrix,  $M(i, j)$ , which consisted of 820 ( $i$ ) rows and 105 ( $j$ ) columns; each cell in this matrix corresponded to a patch. A large number of experiments (Wightman et al., 1997) demonstrated that the intrinsic error of measurement for each patch was at most  $\pm 4\%$ . This matrix, representing the entire mixture, was subjected to a random sampling process (as is done routinely in many industries). Patches were chosen using a random number generator to select both the row ( $i$ ) and the column ( $j$ ) coordinates. Each patch ( $i, j$ ) was selected only once. The random numbers for  $i$  and  $j$  had uniform probability in the intervals of  $[1, 820]$  and  $[1, 105]$ , respectively, thus accomplishing uniform volumetric sampling. The selected sample,  $M(i, j)$ , was considered the assay value of a sample of size equal to one unit (one patch). Samples of larger size were generated at the same location by averaging the assay value of multiple patches neighboring the randomly selected patch  $M(i, j)$ . A position in the matrix which had an assay value of zero was background, i.e., not part of the mixture. If one or more of the patches included in the sample equations had an assay value of zero, the location was discarded and a new random loca-

tion was selected. This rejection method avoided combining patches from different slices into a single sample, because the data for each slice was surrounded by cells that had zero values. This sampling process was repeated until the desired number of samples (i.e.,  $N = 30, 100$ , or  $1000$ ) was obtained.

A well-mixed system was obtained by rotating the mixture for 1000 revolutions at 5 rpm with a rocking frequency of two rocking cycles per revolution. As shown in Fig. 8a, the resulting mixture was very homogeneous. The slices were scanned and analyzed using the procedure described above. Fig. 8b,c show the effect of the number of samples and of the sample size on the estimated composition distribution of this well-mixed system. Each figure shows four curves. The first curve corresponds to a complete scan of each slice and therefore an exact measurement of the composition distribution  $F(c)$  for the selected scale of examination.  $F(c)$  was estimated as  $F(c) = dN(c)/d(c)$ , where  $dN(c)$  was the number of samples that had concentrations between  $c$  and  $c + d(c)$ . For a sample size  $n = 1$  patch, (Fig. 8b),  $F(c)$  was a broad, nearly Gaussian curve generated from  $\approx 68\,000$  samples. The following three curves correspond to  $N = 30, 100$ , and  $1000$  randomly selected samples. As shown in the figure, a poor estimate of  $F(c)$  was obtained for  $N = 30$  samples. The estimated composition distribution sometimes over-predicted and sometimes under-predicted  $F(c)$ . Closer estimates of  $F(c)$  were obtained using larger number of samples ( $N = 100$  and  $N = 1000$ ).

Since the mixture was homogeneous and close in nature to a random mixture, the effect of increasing the sample size followed the pattern predicted by Fig. 2 for a random mixture. Fig. 8c shows  $F(c)$  measured for 7500 samples of size  $n = 9$  patches. As the sample size was increased  $F(c)$  became narrower, while still preserving its Gaussian nature, demonstrating the averaging effect mentioned earlier in this paper. Estimates of  $F(c)$  obtained from  $N = 30, 100$ , and  $1000$  samples were all very close to the true distribution.

Clearly, if undisturbed samples could be obtained, a larger number ( $> 100$ ) of small samples will achieve the best approximation of the mixture distribution. However, if measurements are lim-

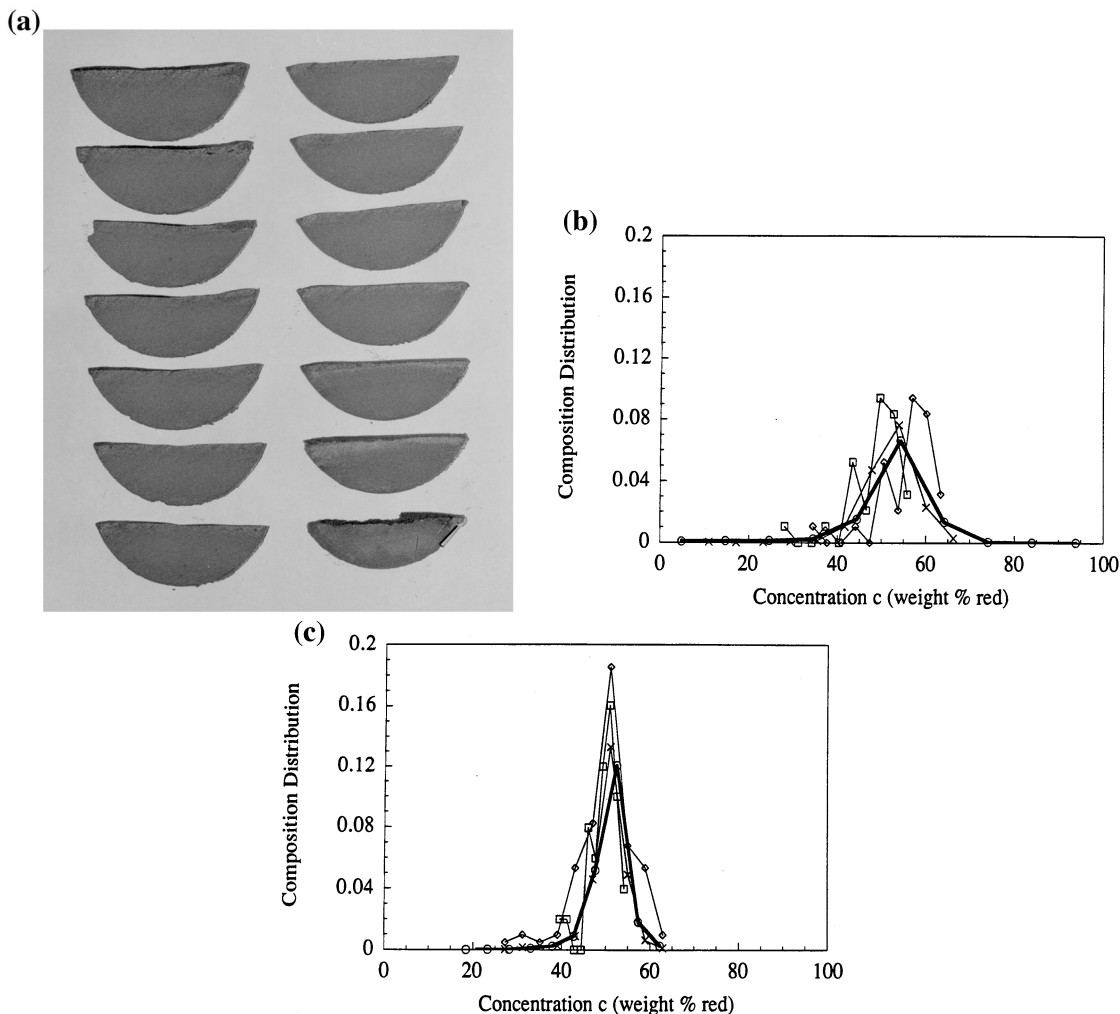


Fig. 8. (a) Slices from a well-mixed system obtained by rotating the mixture for 1000 revolutions at 5 rpm with a rocking frequency of 2 rocking cycles per revolution. (b) The composition distribution of the whole mixture,  $F(c)$  ( $\circ$ ), is compared to distributions generated for  $N=30$  ( $\square$ ), 100 ( $\diamond$ ) and 1000 ( $\times$ ) samples, for a sample size equal to  $n=1$  patch. (c) The composition distribution of the whole mixture,  $F(c)$  ( $\circ$ ), is compared to distributions generated for  $N=30$  ( $\square$ ), 100 ( $\diamond$ ) and 1000 ( $\times$ ) samples, for a sample size equal to  $n=9$  patches.

ited to a small number of samples (as is often the case in practical processes), larger samples give a more accurate estimate of the distribution corresponding to the proper scale of examination. A possible approach might be to (i) generate an accurate relationship between the variance and sample size for a well mixed system, (ii) accurately measure the variance corresponding to large samples, and then use this information to (iii) predict the variance corresponding to smaller samples.

The analysis described in Fig. 8 was repeated for a poorly-mixed system. This system was mixed for 20 revolutions at 5 rpm with a rocking frequency of two rocking cycles per revolution. Slices obtained using this procedure displayed a considerable degree of heterogeneity (Fig. 9a). As before,  $F(c)$  was measured from a systematic scan of each slice and also estimated for  $N=30$ , 100, 1000 (Fig. 9b,c). A broad, bimodal distribution was obtained for this poorly mixed system both



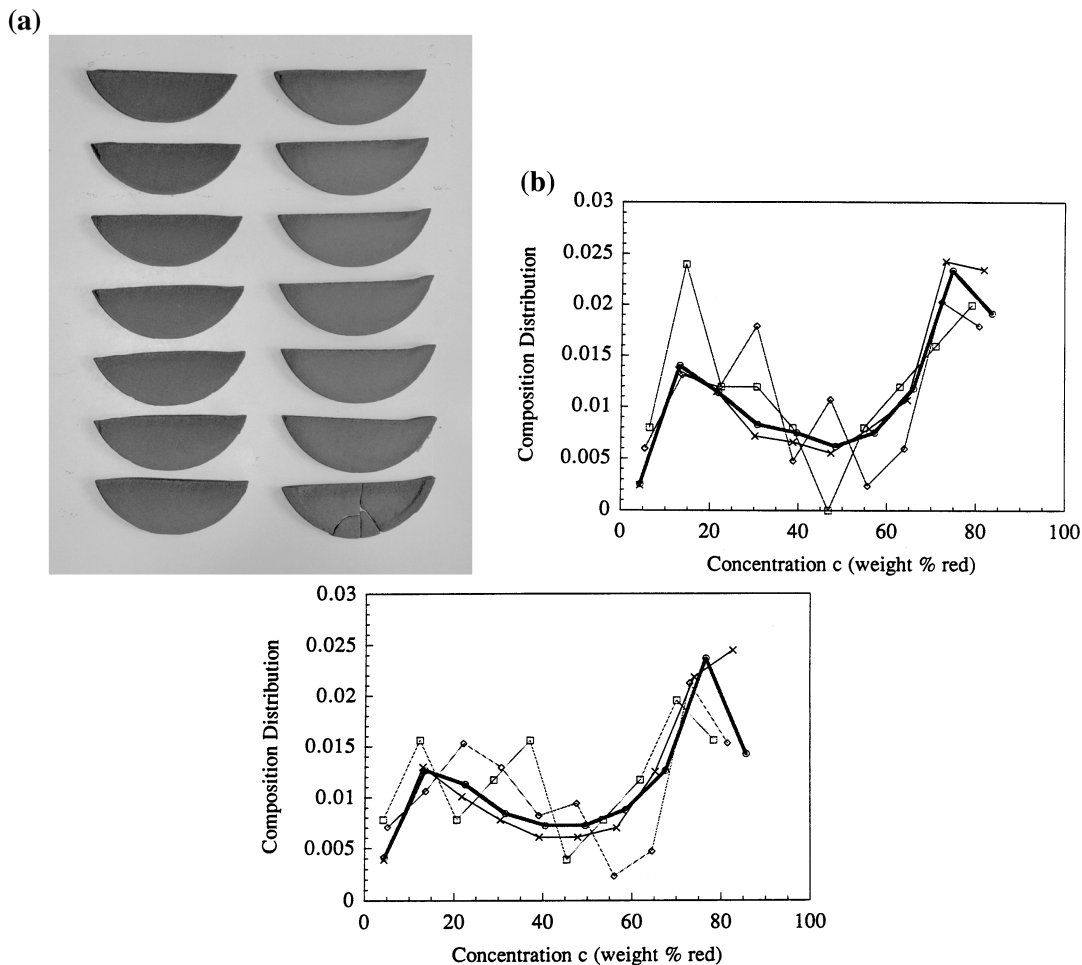


Fig. 9. (a) Slices from a poorly-mixed system obtained by rotating the mixture for 20 revolutions at 5 rpm with a rocking frequency of 2 rocking cycles per revolution. (b) The composition distribution of the whole mixture,  $F(c)$  ( $\circ$ ), is compared to distributions generated for  $N=30$  ( $\square$ ), 100 ( $\diamond$ ) and 1000 ( $\times$ ) samples for a sample size equal  $n=1$  patch. (c) The composition distribution of the whole mixture,  $F(c)$  ( $\circ$ ), is compared to distributions generated for  $N=30$  ( $\square$ ), 100 ( $\diamond$ ) and 1000 ( $\times$ ) samples for a sample size equal  $n=9$  patches.

for  $n=1$  patch and for  $n=9$  patches. Moreover,  $F(c)$  was largely insensitive to the sample size; essentially identical distributions were obtained for both sample sizes. For a sample size  $n=1$  and for  $N=30$  (Fig. 9b), the estimated composition distribution was completely erratic; samples span the entire composition range but their relative frequency bore no resemblance to the true distribution  $F(c)$ . The same behavior was observed for  $n=9$  and  $N=30$  (Fig. 9c). For  $N=100$ , the estimates approximated the composition distribu-

tion more closely than for  $N=30$ , but they still had considerable error. It took as many as 1000 samples to obtain a reasonably accurate estimate of both the range and the bimodal shape of  $F(c)$ . Although the magnitudes of the ordinate were different, comparison of Fig. 9b,c with Fig. 8b,c indicated that a textured, poorly mixed system behaved very different from a homogenous random mixture. The number of samples (rather than the sample size) was the key parameter controlling the accuracy of the characterization of textured

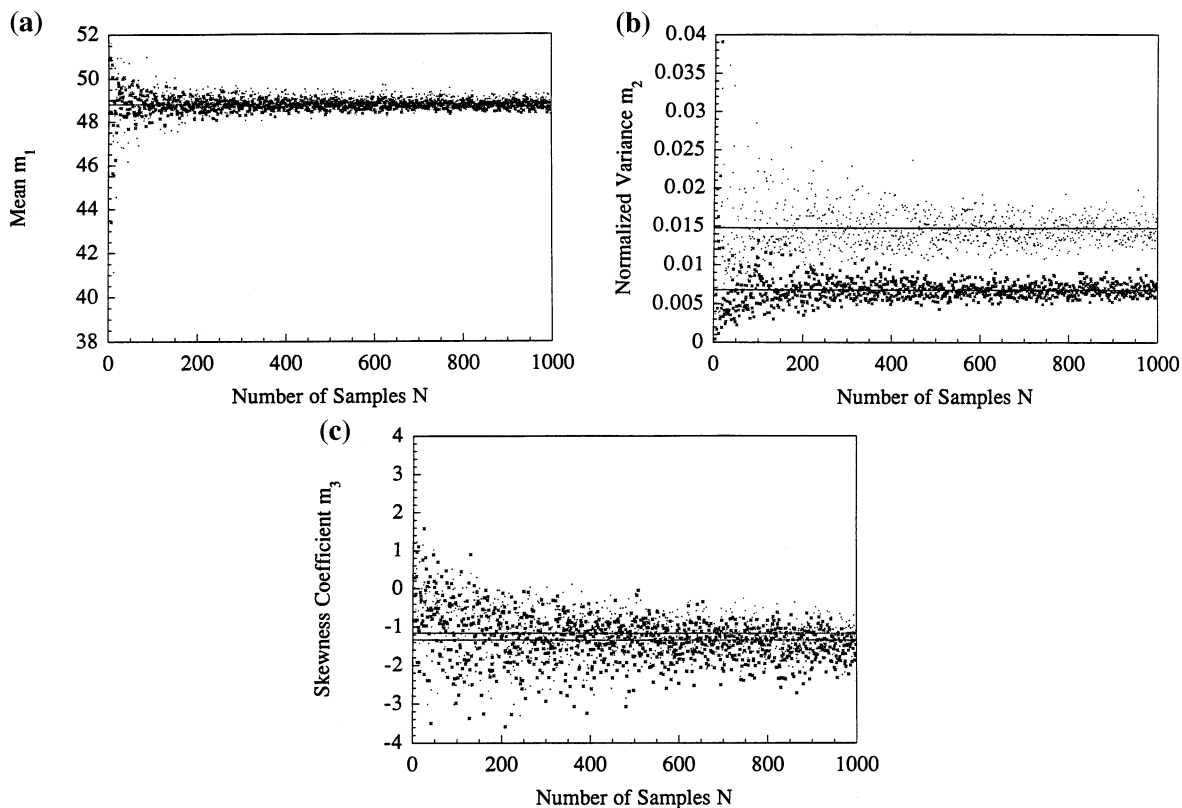


Fig. 10. The (a) mean ( $m_1$ ), (b) normalized variance ( $m_2$ ), and (c) skewness coefficient ( $m_3$ ) versus the number of samples and sample size ( $n = 1$  (●), and 9 (x) patches) for a well-mixed system obtained by rotating the mixture for 1000 revolutions at 5 rpm with a rocking frequency of 2 rocking cycles per revolution.

mixtures. In fact, the results shown in Fig. 9b,c exhibited no dependence on sample size. Invariance with respect to sample size was reasonable since the samples in Fig. 9b,c were all smaller than either the striations or the segregated regions within the mixture. Changing the sample size is significant only if the sample size is similar or larger than the scale of segregation between components (Danckwerts, 1952).

Most analyses of mixtures performed in industrial applications are carried out in terms of moments of the composition distribution. The effects of varying sample size and number of samples on the first three moments ( $m_1$ ,  $m_2$ , and  $m_3$ ) are examined in Fig. 10a–c and Fig. 11a–c. Fig. 10a–c shows the mean,  $m_1$  (Fig. 10a), normalized variance  $m_2 = \sigma^2/m_1^2$  (Fig. 10b), and Fisher's skewness coefficient  $m_3$  (Cochran, 1963)

(Fig. 10c) for the well-mixed system,  $n = 1$  and 9,  $N = 1$  to 1000. Each point in each of these figures is an estimate of the value of  $m_1$ ,  $m_2$ , or  $m_3$  based on a given number of samples ( $N$ ). As expected, both the mean (Fig. 10a) and the skewness (Fig. 10c) are independent of sample size; data overlap for different sample sizes. The variance (Fig. 10b), however, has a nonlinear relationship with respect to the sample size; the greatest difference being between a sample size of  $n = 1$  and  $n = 3$  (data not shown). Previous studies have suggested relationships between sample size and variance (Lacey, 1945; Carley-Macaulay and Donald, 1962; Williams, 1969/70; Kristensen, 1976; Yip and Hersey, 1977; Lai and Hersey, 1981a; Carstensen and Rhodes, 1993) that would allow one to predict the variance for smaller sample sizes. Such predictions would be

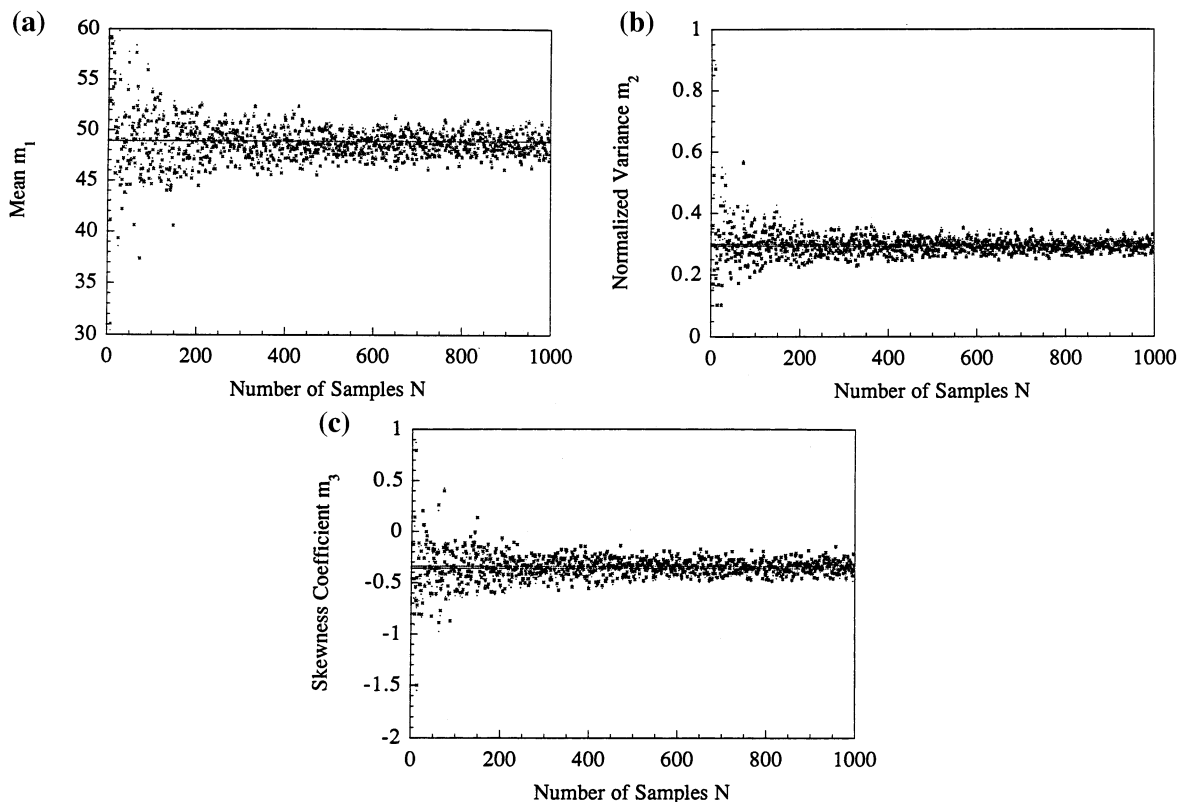


Fig. 11. The (a) mean ( $m_1$ ), (b) normalized variance ( $m_2$ ), and (c) skewness coefficient ( $m_3$ ) vs. the number of samples and sample size ( $n=1$  (●) and 9 (x) patches) for a poorly mixed system obtained by rotating the mixture for 20 revolutions at 5 rpm with a rocking frequency of 2 rocking cycles per revolution.

useful in pharmaceutical applications where sampling a large number of small samples ( $\approx 1$  unit dose) can be difficult. In practice, removing and testing a large sample (rather than a small sample) generates results that are much more reproducible. In addition, as shown in Fig. 10b, the larger sample size,  $n=9$ , has less noise in the measured variance compared to  $n=1$ .

As shown in Fig. 10, all three moments show a strong dependence on  $N$  (the number of samples). When  $N$  is small, all the curves oscillate widely as a function of the number of samples. The moments tend to level out for  $N > 200$ , but noise decreases very slowly as the number of samples increases; a significant level of noise remains even for  $N \approx 1000$ . Both the number of samples and

sample size have substantial effects on measured variance. There is no clear trend in the skewness with respect to the number of samples. Similar results are observed when the random sampling routines are repeated using different sets of random samples.

For the poorly mixed system, all three moments (Fig. 11a–c) are independent of sample size; in all cases, data for different sample sizes overlap onto a single curve. However, all three moments once again show a strong dependence on  $N$  (the number of samples). When  $N$  is small, values of all these moments oscillate widely as a function of the number of samples. Again, the values of the moments tend to level out for  $N > 200$ , but a significant level of noise remains even for  $N \geq 1000$ .

## 6. Significance of mixture characterization on quality of final product

So far, arguments presented in this paper have discussed characterization of mixtures inside a blender. However, in the pharmaceutical industry, blended powders often undergo several processing steps between blending and compression (or encapsulation). These processing steps may include discharge from the mixing vessel into a drum or tote, temporary storage, transport and/or tumbling of the drum or tote, pneumatic conveying, discharge from the drum or tote to a compressing or encapsulating machine, and feeding in the compressing or encapsulating machine. An important question is to what extent such processing steps affect the homogeneity and texture of a mixture. If significant changes do take place, even a highly accurate characterization of the mixture inside the blending vessel may not guarantee or even indicate the level of homogeneity at the time of compressing or encapsulating.

Previous work indicates that the mere action of discharging the mixture into a container can have a major impact on the texture of the mixture. Several studies have focused on the flow patterns of particles during discharge through a funnel or other discharge devices (VanDenburg and Bauer, 1964; Matthee, 1967/68; Theimer, 1969/70; Carleton, 1972; Samyn and Murthy, 1974; Levinson et al., 1977; Arteaga and Tuzun, 1990; Daniel et al., 1992). VanDenburg and Bauer (1964) focused on the segregation of free flowing powders flowing through a 60° cone. Samples were taken continuously as the material flowed out of the cylinder. The composition of an initially well-mixed system was found to vary as much as 30% as the cylinder was emptied. This experiment demonstrated that extensive segregation can occur for different sized particles when flowing through discharge devices.

The extent of change in mixture texture after discharge is demonstrated in Fig. 12. An initially segregated system composed of several horizontal layers of 1500  $\mu\text{m}$  red and 600  $\mu\text{m}$  blue glass beads (Fig. 12a) is discharged through a 60° funnel and collected into a 76 mm diameter cylindrical vessel (Fig. 12b). A funnel flow pattern

develops where particles from the top layer flow through a channel along the axis of the cylinder while the particles outside the channel remain stationary. The structure of the system is strongly altered as the mixture is discharged. Interestingly, a certain amount of mixing occurs during the discharge process, increasing the homogeneity of the mixture. In this case a detailed knowledge of the microstructure before discharge yields no useful information on the microstructure of the mixture after discharge. Moreover, as shown in Fig. 13, the structure of the segregated mixture (Fig. 13a) can depend quite strongly on the overall geometry of the discharge flow. Fig. 13a shows a horizontally segregated structure with the larger blue particles located predominantly on the right and the smaller red particles predominantly in the left side of a cylindrical container. This structure changes dramatically after it is discharged through the funnel, becoming segregated predominantly in the radial direction. As shown in Fig. 13b, the larger blue particles are now located in an annulus surrounding the smaller red particles. This structural change is reversible; when the system depicted in Fig. 13b is poured back into the funnel by lifting the lower container and inclining it sideways (therefore creating a horizontal flow), it segregates again in a pattern similar to its original horizontally-segregated condition (Fig. 13c).

Discharge is not the only process that can affect the texture of a mixture after blending. A mixture may experience vibration when stored or transported from one location to another. Vibration also enters the process when a vibrator is placed on the compressing hopper, or even as noise in the factory floor. Vibration produces convective flows within the mixture (Ratkai, 1976, 1986; Ratkai and Toros, 1986; Savage, 1988; Rajchenbach, 1991; Gallas et al., 1992; Taguchi, 1992). Such flows are known to cause segregation of particles according to size. Large particles are expected to migrate to the top region of the mixture, and small particles are expected to collect in the bottom of the container (Williams and Shields, 1967; Campbell, 1973; Lai et al., 1981; Staniforth, 1982; Staniforth and Rees, 1982, 1983; Rosato et al., 1986, 1987, 1991; Jullien and Meakin, 1990; Popplewell and Peleg, 1991;

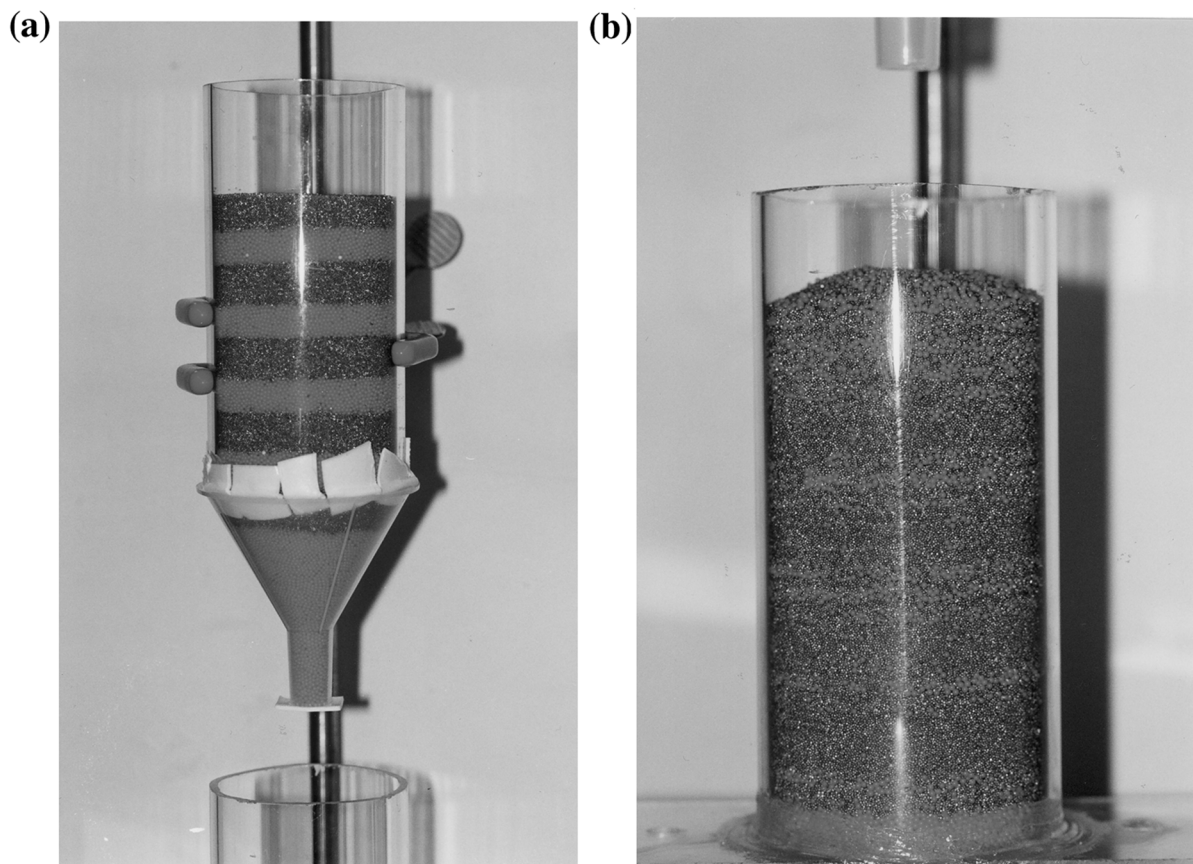


Fig. 12. Effect of discharge on mixtures. (a) Initial layered condition and (b) system after discharge through a funnel.

Meakin and Jullien, 1992; Jullien et al., 1992). However, understanding of this process is far from complete. As shown in Fig. 14, the final powder structure depends on the initial state and processing conditions. Experiments were performed using equal volumes of  $1500\ \mu\text{m}$  white and  $600\ \mu\text{m}$  red glass beads. The beds were housed in 102 mm diameter cylindrical cans, filled to a height of 127 mm. The containers were bolted to a mechanical vibrating table with a fixed amplitude of 3 mm. The structures were preserved by infiltration with gelatin at the conclusion of each experiment. An initially well-mixed system (Fig. 14a) becomes segregated (Fig. 14b) when vibrated at 14 Hz for 10 min. However, the horizontal layer anticipated from previous studies does not form; instead, a complex segregation pattern develops, with the smaller particles gath-

ering in a vertical column along the center of the container and larger particles migrating to the sides of the container. Unexpectedly, this segregation process is also reversible. Tendency to segregate depends strongly on the vibration frequency, and in general diminishes with increasing frequency. As shown in Fig. 14c, an additional 20 min of vibration at 20 Hz remixes the system. As before, this experiment shows that considerably more work is needed before a satisfactory understanding of the segregation behavior is achieved even for relatively simple flow processes.

## 7. Conclusions

Following the Barr Decision, the FDA has begun requiring that pharmaceutical companies

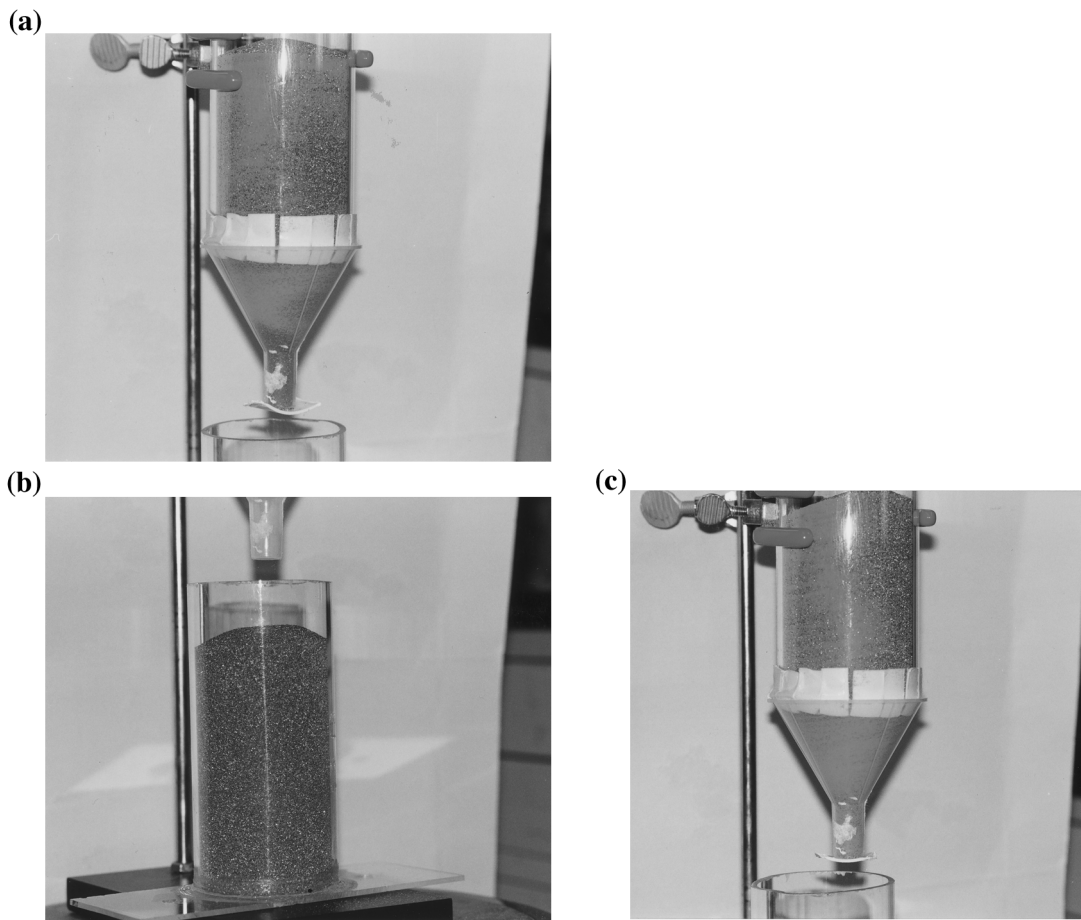


Fig. 13. Reversible segregation from discharge. (a) Initial segregated condition, (b) system becomes better mixed after discharge through funnel, and (c) returns to its original segregated condition after pouring into original container.

use small samples, no larger than three unit dosages, to assess blending uniformity in powder mixtures. As mentioned in Section 3, such guidelines contain several implicit assumptions. In the first place, when statistical theory is invoked to predict the effect of sample size on sample composition, it is assumed that actual blends are random mixtures entirely devoid of spatial correlations and that a small number of samples is sufficient to characterize the extent of variability in the system. The results reported in Section 5 demonstrate that for highly homogeneous mixtures, a few samples ( $\approx 30$ ) are indeed sufficient to characterize the state of a mixture. Results also show that the characterization of the mean content of well

mixed systems becomes more accurate as the sample size increases.

However, as is known from everyday experience and also from published reports, real mixtures can have considerable texture, either because the blending process is inefficient (as illustrated in Fig. 1) or because segregation occurs following blending (as illustrated in Figs. 12–14). Since these systems are most likely to present quality problems, one can easily argue that regulations should focus primarily on them. As was shown in Section 5 for poorly-mixed systems, the number of samples, and not the sample size, is the dominant factor in determining accuracy of the characterization. A small number of samples gives an

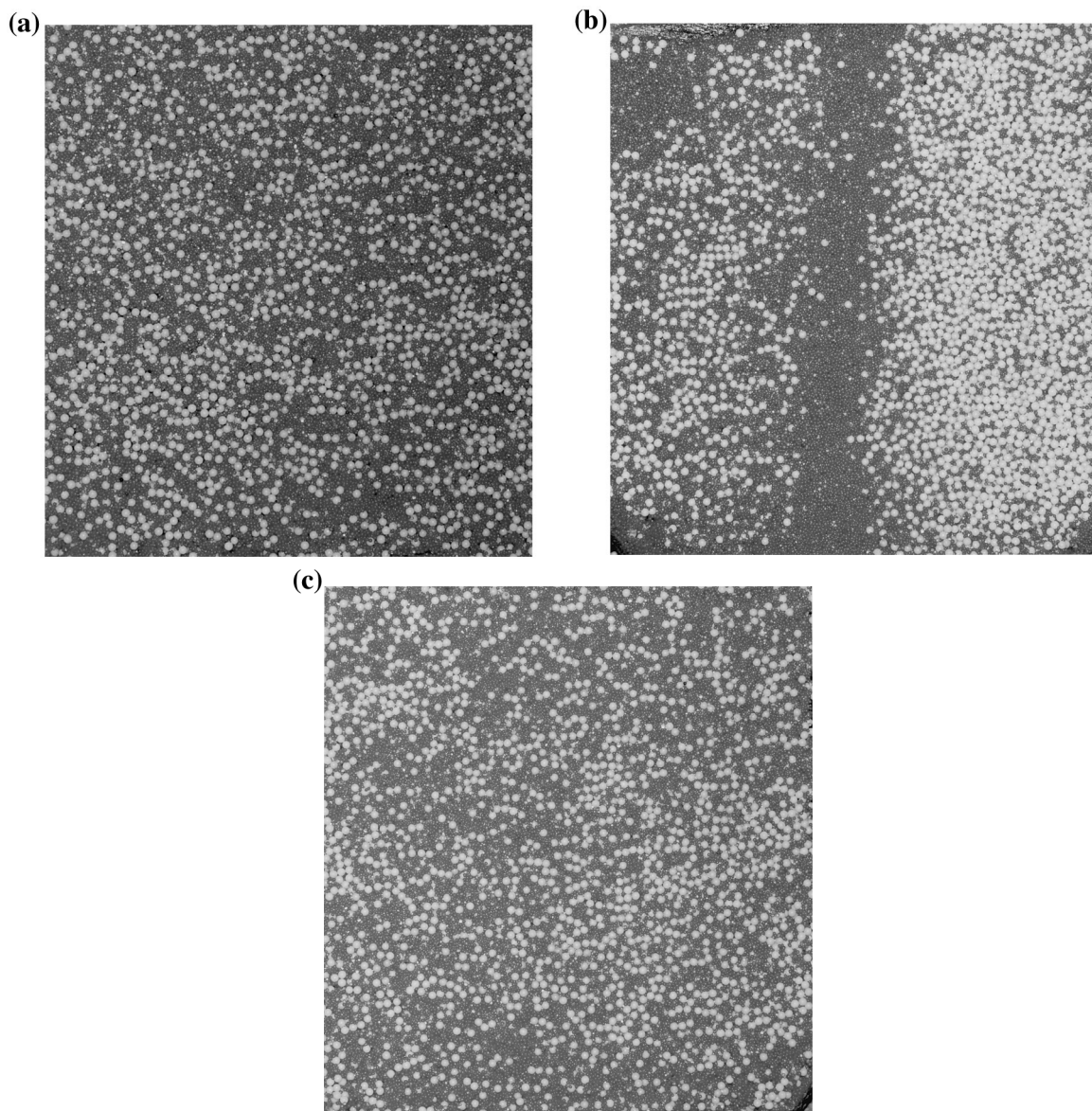


Fig. 14. Effect of vibration on mixtures. (a) Well-mixed initial condition, (b) after vibration at 14 Hz for 10 min, and (c) after an additional 20 min of vibration at 20 Hz.

inaccurate assessment of a poorly mixed system. Hundreds of samples are needed to obtain a reasonably good estimate of the distribution and its moments. Since sample size is only important if the sample size is of similar magnitude as the scale of segregation of the system, for poorly mixed systems the sample size is irrelevant and

has no effect on the characterization of the mixture.

Given the state of the art in sampling technology, the second assumption, i.e., that the sample obtained by standard techniques is truly representative of the composition of the system at a given location, is even more problematic. As was shown

in Section 4, this assumption is likely to be violated when the sample is obtained following the usual practice of using a thief. Thief probes extensively perturb the structure of a powder mixture. Particles are dragged along the path of insertion of the thief, and as a result the samples are likely to contain particles from a large region along the sampling path. Given this 'mixing' effect, the rationale proposed in the Barr Decision for taking small samples, i.e., to avoid 'averaging' the sample composition over a large region of the system, is meaningless. In reality, regardless of whether the sample is large or small, a thief samples particles from a large region of the mixture. Moreover, thief probes can generate entirely misleading results. As demonstrated in Fig. 3, a segregated system can generate samples that are very uniform, possibly leading to acceptance of a poor quality mixture. As shown in Fig. 6, thief-sampling of a well mixed system can generate samples that are considerably different than the actual system because particles of different sizes flow unevenly into thief cavities. This observation is particularly troublesome because it suggests that, as it is often argued by industrial scientists, high quality mixtures can fail to meet specifications because of thief error. Hence it must be concluded that accurate characterization of the structure of a powder mixture using a thief is not feasible. Therefore, thief sampling should only be used to detect gross inhomogeneities in powder mixtures, and given the extent of sampling errors reported here, information obtained using thief probes should be considered with a healthy dose of skepticism. Data obtained using side-sampling probes should be interpreted with additional caution. Similar conclusions were recently presented by Berman et al. (1997), who performed a careful study of thief performance using pharmaceutical materials.

Finally, as shown in Section 6, to assume that the state of the blend at a given stage of the manufacturing process predicts the final state of the blend at the end stage of the process is a risky proposition. Even if a complete and accurate characterization of the state of a mixture inside a blender were feasible, such a characterization could fail to predict the degree of homogeneity of

the mixture as it is fed to a press or encapsulator, because mixtures can either mix or segregate extensively when discharged, conveyed, and vibrated. In the Barr Decision, it is stated that segregation problems can be solved by controlling particle size distribution. In reality, in processes such as crystallization, milling, and granulation, accurate control of particle size distribution can be very difficult. Moreover, the fact that homogeneity can increase during discharge has not been extensively investigated in previous studies. This observation could explain why uniform tablets are often obtained from largely inhomogeneous mixtures. Practitioners have long suspected that the cause for this well-known but poorly understood phenomenon is that mixtures become more homogeneous as they are conveyed from the blender to the press.

One overall conclusion of this study is that given the state of development of blending and sampling technology, the only reliable approach for characterizing the quality of a batch of tablets or capsules is to analyze the tablets or capsules themselves. Regulations mandating extensive analysis at earlier stages are misguided and are likely to result in misallocation of resources. If the goal is to assure that the process consistently generates a quality product meeting specific attributes (i.e., validation), this goal would be most effectively achieved by increasing the number of tests performed on finished products. Analysis at earlier stages are valuable only as coarse indicators of potential problems.

Another overall conclusion of this study is that pharmaceutical manufacturing processes in general, and blending and sampling technology in particular, need to be considerably improved if reliable prediction and tight control of product quality is likely to be achieved. This will require sustained research efforts in a wide range of areas. The fundamental phenomenology of granular systems needs to be better understood so that the flow and segregation behavior exhibited by particles can be related to particle properties such as (but not limited to) size, shape, density, and cohesiveness. Once the role of particle properties is understood, unit operations used to make and process particles need to be carefully examined in



order to gain the ability to make particles with desired properties. Accomplishing these goals will make it possible to develop optimally designed and accurately controlled processes for pharmaceutical manufacturing.

## 8. List of symbols

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$\sigma$	standard deviation
$c$	concentration (wt%) of red glass beads
$F(c)$	composition distribution of the a mixture
$M(i, j)$	3D matrix of composition data for a mixture
$N$	number of samples
$n$	sample size, i.e., the number of patches making up the sample

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## References

Adams, J. and Baker, A., *Trans. Inst. Chem. Eng.*, 34 (1956) 91.  
 Arteaga, P. and Tuzun, U., *Chem. Eng. Sci.*, 45 (1990) 205.  
 Ashton, M.D. and Valentin, F.H.H., *Trans. Inst. Chem. Eng.*, 44 (1966) T166.  
 Bannister, H., *Chem. Proc. Eng.*, February (1959) 53.  
 Berman, J., Schoeneman, A. and Shelton, J.T., *Drug Dev. Ind. Pharm.*, (1997).

Cahn, D.S., Healy, T.W. and Fuerstenau, D.W., *Ind. Eng. Chem. PD D*, 4 (1965) 318.  
 Cahn, D.S., F.D.W., Healy, T.W., Hogg, R. and Rose, H.E., *Nature*, 209 (1966) 494.  
 Campbell, A.P., *Trans. Inst. Chem. Eng.*, 51 (1973) 72.  
 Campbell, H. and Bauer, W., *Chem. Eng.*, September (1966) 179.  
 Carleton, A.J., *Powder Technol.*, 6 (1972) 91.  
 Carley-Macaulay, K.W. and Donald, M.B., *Chem. Eng. Sci.*, 17 (1962) 493.  
 Carstensen, J.T. and Patel, M.R., *Powder Technol.*, 17 (1977) 273.  
 Carstensen, J.T. and Rhodes, C.T., *Drug Dev. Ind. Pharm.*, 19 (1993) 2699.  
 Cochran, W.G., *Sampling Techniques*, Wiley, New York, 1963, p. 413.  
 Coulson, J.M. and Maitra, N.K., *Ind. Chem. Eng.*, 25 (1950) 55.  
 Danckwerts, P.V., *Appl. Sci. Res.*, A3 (1952) 279.  
 Daniel, J.C., Scrivens, B.G. and Michaelides, E.F., *Powder Technol.*, 72 (1992) 177.  
 Devore, J.L., *Probability and Statistics for Engineering and the Sciences*, Brooks/Cole, Monterey, CA, 1982, p. 640.  
 Edwards, S.F., *Rheologica Acta*, 29 (1990) 493.  
 Fan, L.T., Chen, Y.-M. and Lai, F.S., *Powder Technol.*, 61 (1990) 255.  
 Fan, L.T., Chen, S.J. and Watson, C.A., Solids mixing. In V.M. Weekman (Eds.), *Annual Review of Industrial and Engineering Chemistry, 1970, I&EC Annual Review*, Am. Chem. Soc., Washington, DC, 1972, p. 22.  
 Gallas, J.A.C., Herman, H.J. and Sokolowski, S., *Phys. Rev. Lett.*, 69 (1992) 1371.  
 Gayle, J.B., Lacey, O.L. and Gary, J.H., *Ind. Eng. Chem.*, 50 (1958) 1279.  
 Gray, J.B., *Chem. Eng. Prog.*, 53 (1957) 25.  
 Gopinath, S. and Vedaraman, R., *Res. Ind.*, 27 (1982) 321.  
 Greathead, J. and Simmons, W., *Chem. Eng. Prog.*, 53 (1957) 194.  
 Harnby, N., *Powder Technol.*, 1 (1967) 94.  
 Harnby, N., Characterization of powder mixtures. In N. Harnby, M.F. Edwards, and A.W. Nienow (Eds.), *Mixing in the Process Industries*, Butterworth-Hiemann, Oxford, 1992, p. 414.  
 Harwood, C.F. and Ripley, T., *J. Powder Bulk Sol. Tech.*, 1 (1977) 20.  
 Harwood, C.F., Walanski, K., Luebecke, E. and Swannstrom, C., *Powder Technol.*, 11 (1975) 289.  
 Hogg, R. and Fuerstenau, D.W., *Powder Technol.*, 6 (1972) 139.  
 Jenkins, J.T., Rapid flows of granular materials. In R.J. Knops and A.A. Lacey (Eds.), *London Mathematical Society Symposium Non-Classical Continuum Mechanics*, London Mathematical Society Lecture Notes Series 122, Cambridge University Press, 1986, p. 213.  
 Johnson, P.C., Nott, P. and Jackson, R., *J. Fluid Mech.*, 210 (1990) 501.  
 Jullien, R. and Meakin, P., *Nature*, 344 (1990) 425.

- Jullien, R., Meakin, P. and Pavlovitch, A., *Phys. Rev. Lett.*, 69 (1992) 640.
- Kaufman, A., *Ind. Eng. Chem. Fund.*, 1 (1962) 104.
- Kristensen, H.G., *Powder Technol.*, 13 (1976) 103.
- Lacey, P.M., *The Chemical Age*, August (1945) 119.
- Lacey, P.M.C., *J. Appl. Chem.*, 4 (1954) 257.
- Lai, F. and Hersey, J.A., *Chem. Eng. Sci.*, 36 (1981a) 1133.
- Lai, F. and Hersey, J.A., Mixing performance of a V-blender. In *Inst. Chem. Eng. Symp. Ser. No. 65*, The Institution of Chemical Engineers, 1981b, p. S1.
- Lai, F., Hersey, J.A. and Straniforth, J.N., *Powder Technol.*, 28 (1981) 17.
- Lantz, R.J. and Schwartz, J.B., Mixing. In Lieberman, H.A. and Lachman, L. (Eds.), *Pharmaceutical Dosage Forms: Tablets*, Marcel Dekker, New York, 1981, p. 1.
- Lastovtsev, A. and Khvalnov, A.M., *Br. Chem. Eng.*, 8 (1963) 626.
- Levinson, M., Shmutter, B. and Resnick, W., *Powder Technol.*, 16 (1977) 29.
- Masiuk, S., *Powder Technol.*, 51 (1987) 217.
- Matthee, H., *Powder Technol.*, 1 (1967/68) 265.
- Meakin, P. and Jullien, R., *Physica A*, 180 (1992) 1.
- Miles, J.E.P. and Schofield, C., *Proc. Eng.*, September (1968) 2.
- Miles, J.E.P. and Schofield, C., *Trans. Inst. Chem. Eng.*, 48 (1970) T85.
- Orr, N.A. and Shotton, E., *Chem. Eng.*, January (1973) 12.
- Parrott, E.L., *D&CI*, August (1974) 42.
- Poole, K.R., Taylor, R.F. and Wall, G.P., *Trans. Inst. Chem. Eng.*, 42 (1964) T305.
- Popplewell, L.M. and Peleg, M., *Powder Technol.*, 67 (1991) 21.
- Poux, M., Fayolle, P., Bertrand, J., Bridoux, D. and Bousquet, J., *Powder Technol.*, 68 (1991) 213.
- Rajchenbach, J., *Europhys. Lett.*, 16 (1991) 149.
- Ratkai, G., *Powder Technol.*, 15 (1976) 187.
- Ratkai, G.Y., *Chem. Eng. Sci.*, 41 (1986) 1351.
- Ratkai, G.Y. and Toros, R., *Chem. Eng. Sci.*, 41 (1986) 1345.
- Rosato, A., Prinz, F., Stranburg, K.J. and Swensden, R.H., *Powder Technol.*, 49 (1986) 59.
- Rosato, A., Strandburg, K.J., Prinz, F. and Swensen, R., *Phys. Rev. Lett.*, 58 (1987) 1038.
- Rosato, A.D., Lan, Y. and Wang, D.T., *Powder Technol.*, 66 (1991) 149.
- Samyn, J.C. and Murthy, K.S., *J. Pharm. Sci.*, 3 (1974) 370.
- Savage, S.B., *J. Fluid Mech.*, 194 (1988) 457.
- Schofield, C., *Powder Technol.*, 15 (1976) 169.
- Shin, S.H. and Fan, L.T., *Powder Technol.*, 19 (1978) 137.
- Staniforth, J.N., *Powder Technol.*, 33 (1982) 147.
- Staniforth, J.N. and Rees, J.E., *J. Pharm. Pharmacol.*, 34 (1982) 700.
- Staniforth, J.N. and Rees, J.E., *J. Pharm. Pharmacol.*, 35 (1983) 549.
- Taguchi, Y.-H., *Phys. Rev. Lett.*, 69 (1992) 1367.
- Theimer, O.F., *Powder Technol.*, 3 (1969/70) 235.
- VanDenburg, J.F. and Bauer, W.C., *Chem. Eng.*, 71 (1964) 135.
- Weidenbaum, S.S., Mixing of solids. In T.B. Drew and J.W. Hoopes (Eds.), *Advances in Chemical Engineering*, Academic Press, New York, 1958, p. 209.
- Wightman, C., Mort, P.R., Muzzio, F.J., Riman, R.E. and Gleason, E.K., *Powder Technol.*, 84 (1995) 231.
- Wightman, C., Muzzio, F.J. and Wilder, J., *Powder Technol.*, (1997).
- Williams, J.C., *Powder Technol.*, 3 (1969/70) 189.
- Williams, J.C., Mixing and segregation in powders. In M.J. Rhodes, (Eds.), *Principles of Powder Technology*, Wiley, New York, 1990, p. 71.
- Williams, J.C. and Khan, M.I., *Chem. Eng.*, January (1973) 19.
- Williams, J.C. and Shields, G., *Powder Technol.*, 1 (1967) 134.
- Wong, L.W. and Pilpel, N., *Drug Dev. Ind. Pharm.*, 14 (1988) 609.
- Yip, C.W. and Hersey, J.A., *Powder Technol.*, 16 (1977) 189.