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Sampling and characterization of pharmaceutical powders and granular blends

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Abstract

We use a variety of experimental results to illustrate issues and challenges involved in the sampling and characterization of pharmaceutical mixtures. Accurate and reliable characterization of granular mixtures is hindered by both the complexity of granular systems and the lack of validated and reliable sampling technology and techniques. Both sampling tools and sampling protocols are critically important for accurate characterization. Using cohesive and free-flowing powders and four thief probe designs, we reveal a large potential for extremely misleading results as well as severe disturbance of the granular bed. We also discuss results from several experiments designed to test the validity of various sampling protocols by varying parameters such as sampling location and frequency of sampling. These experiments illustrate the importance of effective sampling procedures to achieve the best and most efficient results.

Keywords: Powder blending; Powder sampling; Mixing; Thief sampling

1. Introduction

Blending of granular and powder materials is a vital component in the manufacture of many industrial and consumer products including foodstuffs, ceramics, fertilizer, and plastics. More than three-quarters of all pharmaceuticals are delivered as tablets or capsules that are manufactured using powder blends. Nevertheless, the dynamics involved in the processing of granular materials and methods for characterizing the homogeneity of a granular blend remain underdeveloped and minimally understood. Currently, it is extremely difficult to accurately measure mixture composition in an efficient and non-destructive fashion. In the pharmaceutical industry, this limitation greatly complicates the design of production cycles and can result in both the rejection of acceptable quality batches and the release of product containing potentially dangerous amounts of active ingredients in individual doses.

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In the past decade, blending issues have received substantial attention, in particular following a well-known court case (US vs. Barr Laboratories 812, F. Supp 458, D.N.J. 1993). Unfortunately, the pharmaceutical scientist confronted with out of specification blend uniformity results still cannot answer the most basic question: 'is this poor blending or inaccurate sampling?' It is highly ironic that the industry is strongly encouraged to validate blending practices using thief sampling, which is, in essence, a non-validated method. Many questions remain unanswered concerning the comparative accuracy of various sampling tools, the effects of powder cohesion and repeated sampling, and the location and number of samples needed to characterize a blend. In this article, we attempt to present rational methods for answering these questions by addressing aspects of both sampling technology and sampling procedures.

2. Background: blending and sampling—a review of the 'state of the art'

The nature of motion and mixing in granular materials is only partially understood. Powders are devoid of Brownian motion; effective mixing requires agitation to blend constituent powders. Most powder-based pharmaceutical products are mixed in either tumbling or convective blenders (see Poux et al., 1991; Fan et al., 1990 for a general review of blender types). Tumbling blenders consist of a hollow vessel of different geometries attached to a rotating shaft. Three of the most common vessel designs are the tote blender, the double cone blender, and the V-blender. Baffles and intensifiers are often mounted inside the vessels to disrupt periodic flow and increase shear. Convective blenders consist of a stationary vessel and a stirring mechanism such as a rotating impeller. Common convective blenders include the ribbon blender (a cylindrical vessel with a helical ribbon impeller mounted to a horizontal shaft), the paddle blender (similar to a ribbon blender with paddles instead of a helical ribbon) and the Nauta blender (a vertically oriented conical tank swept out by a rotating and precessing screw impeller). Furthermore, unlike tumbling blenders, which typically have an unobstructed mixing chamber (or a single baffle/impeller), convective blenders have impellers present in the mixing region, making thorough and uniform sampling difficult.

The type of agitation must be carefully selected because granular materials of different characteristics (e.g. density, size, shape, resiliency, etc.) can segregate when allowed to flow, resulting in poorly mixed final products. The tendency to segregate must be accounted for throughout the manufacturing cycle as initially well-mixed granular blends can unmix during post-mixing processing. In addition to inducing segregation, inappropriate agitation may cause a variety of undesirable effects including attrition (grinding the powder into finer particles), agglomeration (accretion of smaller particles into larger clumps) or intense heating of the powder, leading to carbonization or caramelization. The wide range of equipment available to blend granular materials further complicates the selection of a mixer. Most powder mixers have been only minimally characterized, if at all, and are often difficult to control or scale up (Weidenbaum, 1958; Carley-Macauly and Donald, 1962, 1964; Fan et al., 1972, 1990; Poux et al., 1991; Muzzio et al., 1997; Alexander et al., 2002).

The lack of accurate and reliable experimental data about the performance of powder mixers is a result of the difficulty involved in reliably characterizing granular mixtures. Powder mixtures are typically analyzed by removing discrete samples from the bulk mixture and analyzing these samples for their statistical properties. The most common techniques use a thief probe (also referred to as a thief sampler, or simply a thief). These devices extract a quantity of material from the bulk mixture, which may then be subdivided into smaller samples and analyzed for content.

Sampling techniques must avoid making several potentially dangerous assumptions about the powder mixture. Granular materials tend to mix slowly and can spontaneously segregate, leading to spatial variability within the mixture. Many statistical measures and sampling protocols assume a completely random distribution within the mixture (see examples in Poux et al., 1991). This assumption can lead to the erroneous conclusion that these

blends can be accurately characterized by sampling at only a few positions. Another invalid assumption made by most current analyses is that a sample obtained with conventional thief sampler is truly indicative of the composition of the mixture at that location. In several of the experiments presented here as well as in previous work (Poole et al., 1964; Schofield, 1976; Harwood and Ripley, 1977; Gopinath and Vedaraman 1982; Berman et al., 1997; Muzzio et al., 1997, 1999), we show that material from other parts of the bed contaminates the sample during acquisition. These issues must be addressed when developing and evaluating sampling and characterization techniques.

3. Thief experiments

The greatest obstacle encountered when trying to characterize a mixture using a thief probe is the large potential error associated with most available probes. Thief probes often exhibit large uncertainty and error due to the disruption of the powder bed by the probe and the uneven flow of different powder species into the probe. Only a few researchers (Harwood and Ripley, 1977; Gopinath and Vedaraman 1982; Berman et al., 1997; Muzzio et al., 1997, 1999) have attempted to quantify the errors caused by sampling powder beds with thief probes; however, interest has increased in recent years. Experiments performed by Berman et al. (1997) investigated the performance of two designs of side-sampling thieves using a blend of two common pharmaceutical materials of different sizes. Size segregation induced by the insertion of the samplers into the bed caused samples collected at different heights within the bed to display very different concentrations. Muzzio et al. (1997) compared three different sampling thieves using completely segregated granular beds composed of small, free-flowing glass beads. Visual analysis of the bed and comparison of the sample concentrations with theoretical values indicated that two commercially available samplers, the Globe-Pharma (also discussed here) and the slug thief, caused substantial disruption of the bed. These samplers dragged large quantities of material past the interface and led to the calculated concentration values far from the theoretical bed composition. The third thief, the tip sampler, was much less disruptive and produced more accurate results but still generated concentration values off by more than 10%.

We have extended the work of these researchers and seek to address some of the issues associated with thief sampling by experimentally comparing the performance of four different thief probes for sampling both free-flowing and cohesive powders. These probes are of two types: side-sampling and end-sampling. Side-sampling thieves (Fig. 1) such as the Globe-Pharma Probe (Fig. 1a and b) and the Groove Thief (Fig. 1c–f) are rod-like devices with a number of cavities located along the body of the probe. End samplers (Fig. 2) have single sampling cavities either mounted at the base of the thief, such as the End-Cup Probe (Fig. 2a and b) or extending the length of the thief, such as the core sampler (Fig. 2c–e). For more information on the core sampler, see Muzzio et al. (1999).

3.1. Globe-Pharma thief

This sampler consists of a hollow sleeve with several openings surrounding a rotating inner pipe (Fig. 1a) with several cavities that can be aligned with the outer pipe opening (Fig. 1b). Removable dies are fitted into the cavities to control sample volume. In all the tests described here, the upper cavity is filled with a solid die and only the lower cavity is used. The sampling cavities can be opened and closed by rotating the inner pipe. To use the thief, first seal the cavities and insert the thief into the powder bed to the desired depth, then rotate the inner pipe to allow powder to flow into the cavities. After sufficient material has flowed into the thief, seal the cavity and remove the thief from the bed. A limitation of this device is that only a few samples can be taken at a time.

3.2. Groove Thief

This device consisted of an outer hollow sleeve (1 in. in diameter) with an opening running the length of the pipe (66 in.) which surrounds a rotating inner pipe (Fig. 1c and d). This inner pipe

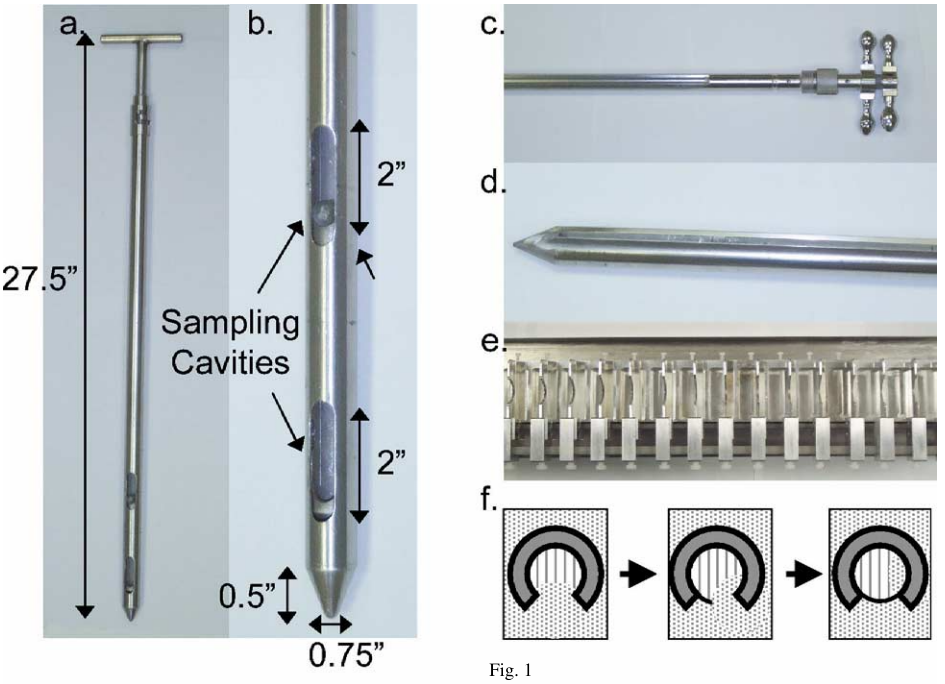

Fig. 1

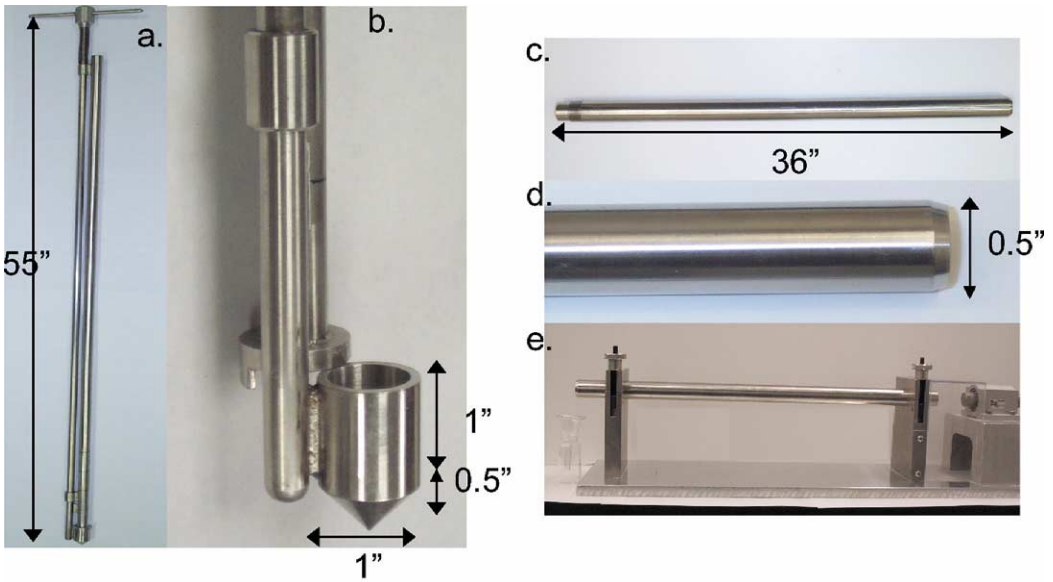

Fig. 2

Fig. 1. Two side-sampling thieves: (a and b) the Globe-Pharma Sampling Thief has an outer sleeve surrounding an inner pipe. Powder is sampled when openings in the sleeve are aligned with cavities of variable size in the inner pipe. (c and d) The Groove Thief has a sampling cavity that extends the length of an inner pipe, which is rotated by the handles. (e) After acquiring a powder core, the thief is mounted on divider supports and the material emptied into small trays for analysis. (f) The orientation of the rotating sleeve as the thief is sealed.

Fig. 2. Two end samplers: (a) The End-Cup sampling thief and (b) a close up of the open sampling cup. (c) The core sampler has a sampling cavity that extends the entire length of the thief. (d) The tapered end of the thief helps to minimize impact on the powder bed. (e) A core sampler mounted in an extruder, which separates the core into smaller samples.

is solid except for a sampling cavity running the length of the pipe. The cavity is 58 in. long and can be opened and closed by rotating the inner pipe. This sampler is inserted into the powder bed while open. A vertical core of material is trapped within the sampler by the rotation of the inner pipe (Fig. 2f). The sampler is then placed on a device designed to subdivide the core into a number of smaller individual samples. The thief is opened and the material is discharged into a series of small trays (Fig. 1e). In the experiments discussed here the trays are 0.75 in. in width and 2.5 in. in long but the sample size can be varied by using trays of different sizes. This ability to simultaneously acquire relatively large numbers of samples of roughly the same size is a strength of this device.

3.3. End-Cup sampler

This sampler consists of a pair of thin rods, one has a cup mounted at the end, the other is attached to a rotating cap aligned with the top of the cup (Fig. 2a and b). The cup is tapered to a cone to minimize the disruption of the powder bed during insertion. The sampler is inserted into the powder bed with the cup sealed until the desired depth is reached and the cap is rotated to allow powder to flow into the cup. The cup is then sealed by rotating the cap and the thief is removed from the bed. A major drawback of this sampler is that only a single sample can be acquired at a time.

3.4. Core sampler

The core sampler consists of a cylindrical tube, one end of which is tapered to a frustum (Fig. 2c and d). This sampler is inserted into the powder bed to a predetermined depth, isolating a cylindrical core of powder. Friction between the sampled material and the inner wall in combination with the cohesion between particles prevents material from flowing out of the sampler during extraction. The core sampler allows retrieval of a nearly undisturbed column of powder, which can then be subdivided into smaller samples for analysis. These devices can be fitted with a side-mounted rod with a cap that can be rotated to seal the sampler to prevent less cohesive material from flowing out of the core during extraction. Addition of the cap has the drawback of increasing the disruption of the powder bed as the thief is inserted. Another approach to help keep powder in the device is to treat the inside of the sampler with a surfactant solution to increase the frictional and cohesive resistance to flow. However, surfactant solution may contaminate the granular material and limit the analysis techniques that are available. Fortunately, neither technique is usually needed for pharmaceutical mixtures, since most materials of interest in pharmaceutical applications are sufficiently cohesive for clean extraction. In the sand bed experiments presented here, the cores were treated with soapy water.

Extracted cores are then subdivided into several ($\sim$5–30) individual samples using an extruder (Fig. 2e). The core is mounted on the extruder and material is pushed out of the sampler in predetermined amounts. In the cohesive system, the material was separated into samples of constant mass ($\sim$1.0 g) by weighing the material as it was expelled from the sampler. Material that occupied a constant 0.5 in. length (as measured by the extruder) in the core sampler was considered an individual sample for the free-flowing sand system.

4. Experimental systems

Microcrystalline cellulose (MCC, Avicel PH101 from FMC) and micromilled sodium chloride (NaCl) were used to create a cohesive powder system. A 1.5 in. layer of NaCl (mean particle size 56 μm) was loaded on top of a 6.25 in. layer of MCC (mean particle size 53 μm). The composition of the cohesive powder mixture was determined by dissolving each sample in 45 ml of purified water and measuring the conductivity of the resulting solution with an Accumet AB30 Conductivity Meter. While MCC is not soluble in water, NaCl completely dissolves. The conductivity varies with the amount of NaCl present in the sample. The meter was calibrated using measurement of the conductivity of solutions of known concentration of NaCl ranging from 0.01 to 1.0 g dissolved in 45 ml of de-ionized water.

Black and white art sand (mean particle size ~ 400 μm) was used as a free-flowing system. A 2.5 in. layer of black sand was loaded on top of 6 in. of white sand. The technique for determining the content of sand samples utilized image analysis: the individual samples were thoroughly mixed and photographed under exact conditions. The images were then analyzed for the distribution of black and white sand using standards of known composition. Both powder beds were layered in a plastic box (18 in. by 18 in. by 25 in. high), shown in Fig. 3.

5. Results and discussion

5.1. Globe-Pharma sampler

The Globe-Pharma sampler did not effectively sample cohesive powder systems. Several attempts were made to acquire samples from the cohesive bed but none gathered sufficient material for analysis. During insertion into the cohesive bed, the sampler displaced material and created a cylindrical hole. When the inner pipe of the thief was rotated to open the cavity, the powder at the wall of the cylindrical hole did not flow into the sampling cavity.The Globe-Pharma sampler will collect free-flowing material; however, the accuracy of these samples must be called into question by the great disturbances caused by insertion of the sampler into the powder bed and by the possibility that free-flowing particles may flow unevenly into the cavities. Material from the top region is drawn across the interface into the lower region and effectively surrounds the thief throughout the sampling region. Material flowing into the thief was contaminated with particles from all along the path of the insertion. This type of contamination is a major concern with invasive sampling procedures and in practice violates the intent of the '1X–3X' rule set forth by the Wolin decision (US vs. Barr Laboratories 812, F. Supp 458, D.N.J. 1993). The inability to accurately characterize the true composition is shown in Fig. 4a. Four samples were taken at different depths in the black/white sand bed and only the sample taken far above the interface accurately reflects the actual composition of the bed. In fact, until the probe is substantially below the interface (depth >2 in.), the experimental samples are entirely composed of material from the upper region (i.e. 100% error). The samples begin to reflect the content of the bed beyond this point but even at 4 in. below the interface, there is still more than 15% error in the analyzed sample.

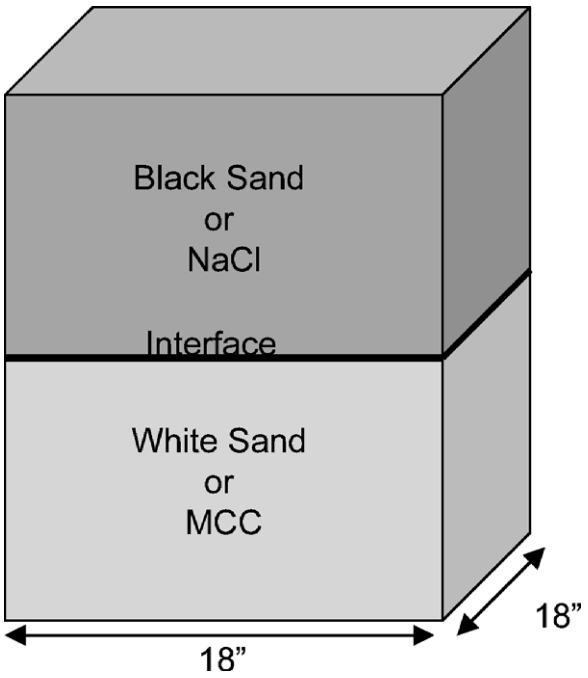

Fig. 3. Diagram of the experimental granular bed.

5.2. Groove Thief

In contrast to the Globe-Pharma thief, the Groove Thief generates much more accurate profiles of the two experimental powder beds. Fig. 4b shows the results from the cohesive system; all samples taken an inch or more beneath the interface are within 10% of the theoretical value. Reasonable results are also possible in free-flow systems as seen in Fig. 4c. Again, good agreement with theoretical predictions is achieved at sampling depths at least 1 in. below the interface, however, the spread is greater than in the cohesive case. It is apparent that material from the upper region is drawn into the lower region and this material

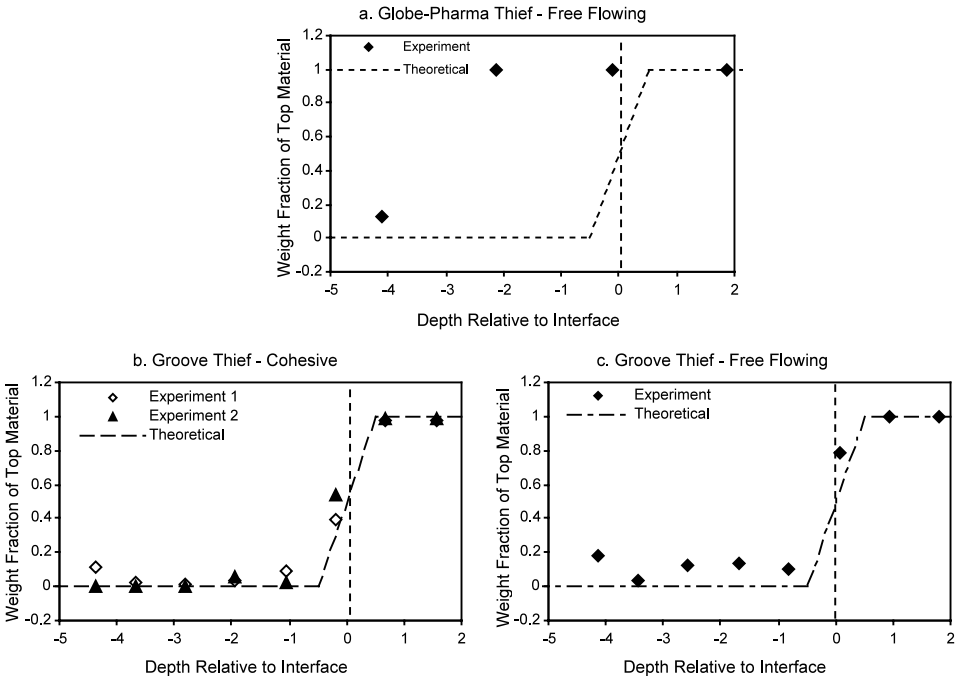

Fig. 4. A comparison of experimental and theoretical values for sampling performed using both side samplers. The dashed vertical line at 0 in each plot corresponds to the interface between the two components of the powder bed. The inability of the Globe-Pharma thief to distinguish between the free-flowing constituents is shown in (a), even well below the interface. The Groove Thief performs much better in both (b) the cohesive and (c) the free-flowing powder beds, accurately reflecting the composition of the bed above and below the interface.

penetrates the entire sampling region. The error at 1 in. below the interface is slightly higher than in the cohesive case, perhaps due to the fact that free-flowing material has more mobility than cohesive powders and can penetrate further into the lower bed.

This thief also permits much higher resolution of the bed than the Globe-Pharma as multiple samples can be taken with each insertion, which allows determination of concentration profiles along a core. Samples from the lower layer were still contaminated with material carried down from the upper layer during insertion into the bed, although this contamination is much less pronounced than for the Globe-Pharma Sampler. In addition to transporting material across the interface, the design of this device may result in additional adverse consequences. In a cohesive system, the act of rotating the outer sleeve to open the sampling cavity may move and partially collapse the powder adjacent to the probe causing materials from the upper part of the bed to contaminate the material below the interface. This may explain the large difference between experimental and theoretical values near the interface as well as the non-negligible differences even deep into the lower part of the bed. One further concern for the sampling of free-flowing materials is the ability of the material to flow into the space between the two concentric pipes during sampling. This material increases friction between the inner pipe and the outer sleeve and can damage the material as well.

5.3. *End-Cup sampler*

The End-Cup sampler caused substantial disruption of both experimental powder beds with correspondingly poor quantitative results (Fig. 5a and b). In fact, all of the experimental samples gathered below the interface contained substantial

amounts of the top material. The ability of this sampler to accurately sample material at a given depth is also hindered by the design of the sampler itself. This device collects material from above the position of the sampling cup. Since the powder bed structure has been perturbed by the insertion of the probe, any samples acquired do not necessarily characterize the true composition of the bed at that location. Two cohesive trials were performed for each sampling depth and there was pronounced disagreement between experimental and theoretical values (Fig. 5a). The sampler had to be inserted more than 4 in. below the interface before the amount of upper material was less than 50% of the sample. It is obvious that material from the upper layer has penetrated the interface and largely surrounds the sampler deep into the lower region. For the free-flowing mixture, the sampler caused even more severe disturbances in the bed. As shown in Fig. 5b, samples were almost entirely composed of material from the upper region until far below the interface.

5.4. Core sampler

There was very good agreement between experimental and theoretical values for both cohesive and free-flowing systems as seen in Fig. 5c and d. Bed disruption was minimal and experimental data closely matched the theoretical predictions to within 5%, even in the interface region. This device was clearly superior to the Globe-Pharma and End-Cup thief probes. The core sampler is also the easiest of the four thieves to use, requiring the least amount of effort to insert in the powder.

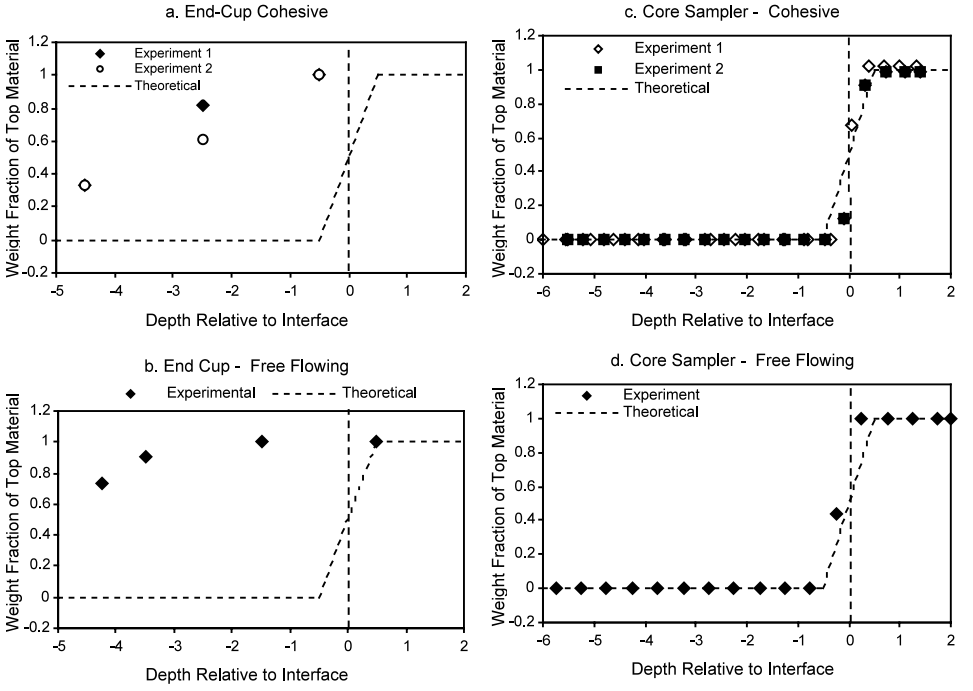

Fig. 5. A comparison of experimental results for sampling performed using both end samplers. The dashed vertical line at 0 in each plot corresponds to the interface between the two components of the powder bed. The End-Cup sampler causes substantial disruption in both powder beds and does not accurately sample material in either the cohesive (a) or the free-flowing (b) systems. By contrast, the core sampler accurately characterizes the composition of both (c) the cohesive and (d) the free-flowing powder beds, even in the interface region to within 5% of the theoretical value.

5.5. General results

Additional factors that affect the accuracy and utility of a given sampling technique include the number and size variability of the individual samples. A comparison of the number of acquired samples and the variability of the sample weight taken with each of the samplers for the cohesive systems was performed and the results are shown in Table 1. A major limitation of the End-Cup sampler is the inability to acquire more than one sample per extraction process. Any further samples will be extracted from the already disturbed bed, adding additional uncertainty to any analysis. There is also substantial variation in the size of a sample collected using the End Cup sampler, complicating the ability to generate reproducible results and further reducing confidence in this probe. The Groove Thief and the core sampler can gather many more samples from each extraction. This minimizes the disturbance of the powder bed, contributing to higher accuracy as well as reducing the time and effort required in sampling. The Groove Sampler exhibits a relatively large value for the relative standard deviation (RSD) of the sample weight; however, this value drops to 16% when the last sample acquired in each core is disregarded. This is plausible because these samples were consistently smaller than the rest of the samples and may not contain sufficient material for analysis and each core still produced seven or eight samples. The core sampler appears to be superior with the largest number of acquired samples and the least variation in the size of those samples.

6. Design of sampling procedures

How a powder blend is sampled is as important an issue as which tool to use. It can be difficult to sample representatively throughout the entire powder bed and during the entire mixing process, leading to inadequate or inappropriate sampling and increased uncertainty in the characterization. In this section, we discuss results from several experiments utilizing common sampling procedures that lead to wasteful effort or erroneous results. First, we discuss a case where a naive interpretation of common results early in a mixing cycle may result in extremely misleading conclusions concerning mixing performance. We then explore the effects of sampling position on mixing characterization, specifically how radial and axial sampling affect the analysis of mixing in a tumbling blender.

6.1. Evolution of mean concentration value

A phenomenon that complicates efforts to characterize mixing was observed during a study of mixing of a model pharmaceutical formulation. There was an observable time-dependent variation in the average concentration of an active ingredient that reflected the overall state of mixedness in the system. This variation complicates the use of common statistical analysis techniques used to characterize the mixedness of a granular mixture and creates the potential for misinterpretation of concentration data as indicative of good mixing.

Batches of inert ingredients, lubricant (38% Avicel, 60% Lactose, 1% Magnesium Stearate)

Table 1
Comparison of individual sample weights from cohesive system for each sampler

	Globe-Pharma sampler	End-Cup sampler	Groove Thief	Core sampler
Minimum mass of sample (g)	Not valid for cohesive materials	2.33	0.24	0.99
Maximum mass of sample (g)		4.57	0.68	1.30
Average mass of sample (g)		3.89	0.50	1.02
Total number of samples from one sampling process (depth = 7.5 in.)		1	8–9	17–18
RSD of sample weight		19%	23%	5%
Sample weight controllable		No	Yes	Yes

and 1% active ingredient were used as a model formulation for seven blending experiments performed in a 56L GEI-Gallay Tote-Blender at 10 RPM. The materials were loaded in a top–bottom fashion (Lactose, Avicel, and Magnesium Stearate) at a 50% fill level. Experiments were run for 4, 8, 16, 32, 64, 200, and 400 revolutions. The mixed material was discarded after sampling and the blender thoroughly cleaned before loading material for the next experiment. Samples were gathered from 9 cores taken across the surface of the blender. The cores were extruded in a controlled manner to produce a large number of individual samples (each roughly 0.8 g), each core producing fifteen to 25 samples. These samples were analyzed using UV Spectroscopy to generate mixing curves and concentration profiles for this system. A mixing curve for this system is constructed by plotting the RSD vs. mixing time (Fig. 6a). It is evident from this plot that good mixing (illustrated by asymptotic behavior of the RSD) is only achieved after a long period of mixing (>200 revolutions). An interesting phenomenon can be seen from the concentration profiles for each core. Concentration profiles are plots of the active ingredient concentration in each sample vs. the depth in the powder bed and are useful in characterizing spatial concentration variability. Pockets of active materials, agglomerates, segregation, hygroscopicity, and blending mechanism are factors that may lead to variation in the concentration profiles.

An analysis of the concentration profiles revealed that, near the start of the mixing process, the measurements of the concentrations from each core were uniformly much higher (2–3-fold) than the expected 1% and had a relatively small spread of values. The spread narrowed and the values converged around the expected average concentration value as the mixing time increased. Fig. 7 shows two such plots, the first for a short time (Fig. 7a), the other after a long period of mixing (Fig. 7b). The values of the concentration appear to oscillate around a mean value in both cases. This behavior poses an interesting problem for assessing blend homogeneity and for quality control procedures. From the blending point of view, the bed may be naively assumed to be well-mixed, since it may be assumed that there is relatively little variance among the cores. One might assume that the mixture has homogenized and assign the difference in mean to 'sampling bias' or 'analytical bias'. One might then conclude that the blending process is efficient even though it did not reach the expected mean value. However, we know from the RSD plot and later concentration profiles that good mixing is only achieved after long times. Both the mean value and standard deviation of the active concentration approach values indicative of thorough blending with increasing mixing time (Fig. 6b and c).

The fact that the RSD slowly decreases with time and, most importantly, that the mean value of the concentration only eventually approaches the known mixture composition reveals an interesting phenomenon: in tumbling blenders, it takes a very long time to reach homogeneity in the axial direction. The early super-potency of the samples is entirely due to the fact that the active is added near the center of the vessel and remains there for long times. While radial homogeneity is achieved very rapidly (hence, the lack of a vertical gradient), axial homogeneity takes much longer. Since in general for vessels with upper hatches, one is only able to sample the center of the vessel, it is easy to miss the slow-mixing sub-potent regions at the axial extremes of the system and erroneously attribute this effect to analytical bias.

6.2. Radial vs. axial sampling in tote blenders

Two important features of any sampling protocol are determining sampling locations and the number of samples to collect. An understanding of both the basic dynamics of the blender in use and the limitations of powder sampling can greatly help in the design of an efficient procedure. Any effective and accurate sampling procedure must generate a sufficient number of samples to adequately characterize the powder blend while avoiding redundant samples and analysis. While greater numbers of samples usually leads to more accurate results, the object of any sampling scheme is to gather reliable results with the fewest number of samples. In industry, typical sampling practice dictates the extraction of unit dose samples

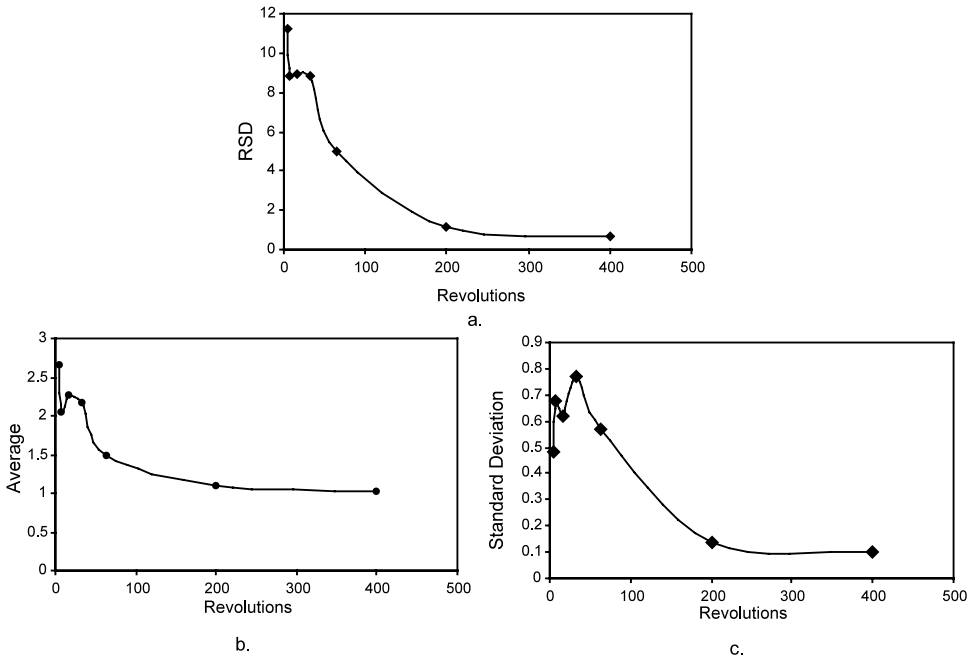

Fig. 6. Plots of the (a) RSD, (b) mean value and (c) standard deviation of the concentration of a 1% model pharmaceutical formulation blended in a tote blender. All three of these plots asymptotically approach reasonable values for long mixing times.

(typically between five and several dozen) that roughly attempt to cover the entire powder bed. This approach does not take into account either the loading method of the blender or the mixing mechanisms. Taking these factors into account can guide the experienced practitioner to the areas of the blender that require special scrutiny to expose expected variability in mixture quality.

For example, in a V-blender, the major inhibitor to mixing is the transfer of material across the plane of symmetry and sampling from only one shell of the blender would clearly not give accurate details as to the overall mixture quality. In the double cone blender, sampling in the middle of the blender (where the mixture is deepest) without looking at the outer regions (where the mixture is shallower) could present an extremely misleading picture if segregation had occurred (which has been shown to leave the outer areas rich in one component of the blend (Alexander et al., 2001). Another concern is the over-sampling of a blend. The extraction of redundant samples leads to longer analysis times and can cause both excessive disturbances in the mixture and underestimation of the RSD.

To illustrate some of these concerns, we examine experiments run in a 300L GEI-Gallay Tote-Blender. Material was sampled with 13 cores in the grid-pattern shown in Fig. 8a. Fig. 8b and c show abbreviated sampling schemes for which only a subset of the total number of probes was used to determine mixture quality. The blender was loaded top–bottom with a 50/50 mixture of colored art sand to 60% of capacity. This loading pattern creates an initial axial gradient in component percentages, as the top component is slightly richer near the sides of the blender and correspondingly deficient near the center. Previous work indicates that radial mixing in double cone blenders (which are geometrically related to tote blenders) is 10–20 fold faster than axial mixing (Brone and Muzzio, 2000). Hence, we expect that axial gradients in concentration would be the last to disappear and we should sample the blender accordingly. As seen in Fig. 8a, the total sampling scheme involves taking cores (consisting of 10–20 individual samples/core) throughout the mixture.

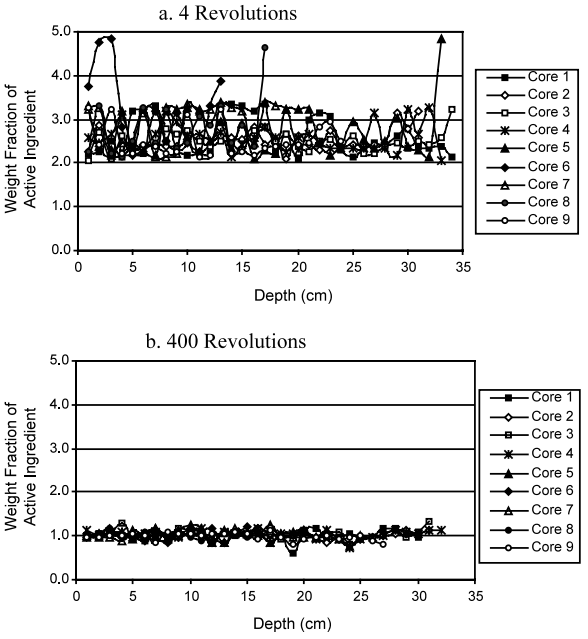

Fig. 7. Concentration profiles for a (a) relatively unmixed state and a (b) well-mixed state. Note that in the unmixed case the values cluster around 2.6 and have a wide spread, while in the well-mixed case the values are centered around the expected value of 1 and have very small spread. It may be possible to misinterpret the first set of data as being indicative of near thorough mixing as the concentration values cluster around a single value.

The modified schemes focus on extracting cores at axial and slightly off-axis locations. The results for the three sampling schemes are shown in Fig. 8d, which shows the decrease in variance from 4 to 32 revolutions. The modified sampling schemes show very good agreement when compared to the total variance from all the probes. The use of seven probes leads to an average of 3.0% difference in the estimated RSD between the results for all 13 cores and the use of only five probes has a 6.2% difference between the results for all 13 cores. Clearly, axial sampling is sufficient to determine mixture quality given these experimental conditions and further samples in the same axial slice (radial sampling) is redundant and provides no further information about mixture quality.

Similar results are found in two other mixing studies performed in tote blenders using common pharmaceutical components. In the first experiment, performed in the same 300L tote blender as the sand experiments, batches of 60% Lactose, 37% Avicel and 3% KCl (used to track mixing) were loaded horizontally at 60% fill level and sampled after 4, 8, 16, 32 and 64 revolutions at 10 RPM. Two different sampling patterns were used, identical to those shown in Fig. 8a (13 total cores) and c (five cores along the axis of rotation). RSD curves generated from this data are shown in Fig. 8e. The overall behavior of both curves is similar, showing large initial values for the RSD and asymptotic behavior (indicating well-mixed conditions) after long periods of mixing. After 64 revolutions, there is slightly more than 5.1% difference between the values calculated from each of the two sampling schemes. The second study monitored the blending of 1% MgSt in a 65% Avicel, 35% Lactose matrix in a 40L Bohle Tote Blender at 40% fill level. The Avicel and Lactose were premixed and then MgSt was spot injected in the center of the blender. The total and radial sampling patterns were the same as for the sand and salt experiments described above and total RSD and radial RSD curves are plotted in Fig. 8f. With the exception of the 80 revolution case (with an 8% difference), all of the radial RSD values are within 3% of the total RSD values. This effect appears to be robust for a wide variety of materials and provides a method to improve sampling protocols.

7. Conclusions

This analysis of sampling technology and techniques illustrates some of the difficulties and challenges involved in accurate and efficient powder sampling. Many of the commonly used sampling devices have proven to be inaccurate and destructive to powder and granular mixtures. Sampling errors develop from a number of different issues: cohesive mixtures not flowing into sampling cavities, bed disruption during probe insertion and uneven flow into the sampler. Most of the available sampling ‘technology’ causes massive disruption to a powder bed during use and results in extremely inaccurate results. The core sampler produced the most accurate and

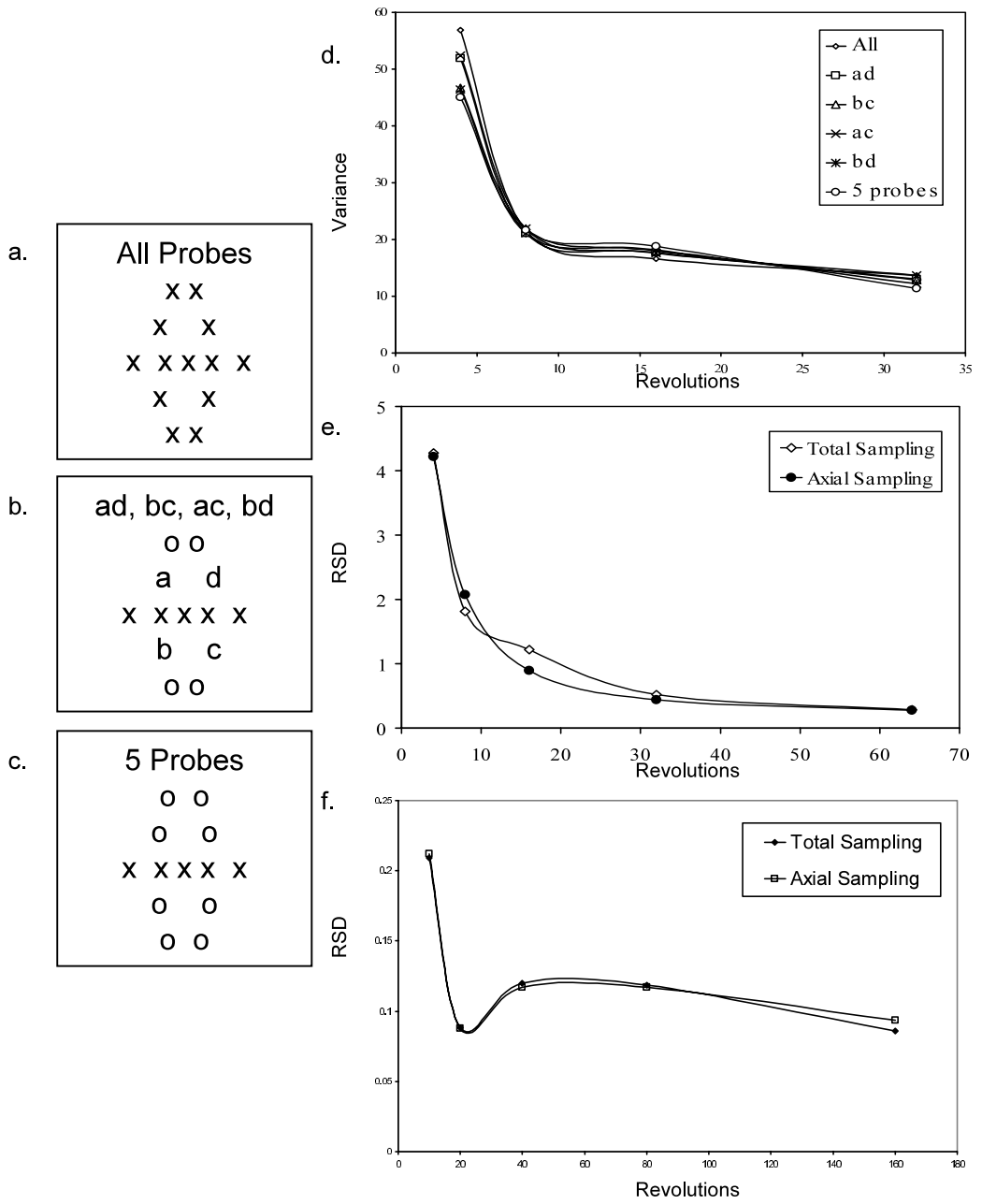

Fig. 8. (a–c) Three sampling schemes used to sample a tote blender, (a) covers the entire bed, both axially and radially while in (b), only seven probes are used, marked by 'x' and four different pairings identified by letters a, b, c and d and unused probes marked by a 'o'. Only the five probes along the axis of rotation are used in (c). The decrease in total mixture variance is plotted vs. the number of revolutions in (d) for the various sampling schemes shown in (a–c). There is only minimal difference in the results determined using each of the different sampling schemes. RSD data is show in (e and f) for two model pharmaceutical formulations: (e) Lactose, Avicel and salt; and (f) Lactose, Avicel and MgSt. These data demonstrate behavior similar to the experiments performed with colored sand. Sampling strictly along the axis of rotation appears to accurately characterize mixing throughout the powder bed.

reliable results but still may not be sufficiently accurate for industrial or regulatory requirements.

The act of sampling also has the potential to produce a variety of complications for accurate powder mixing characterization. Any sampling procedure must be designed to account for the dynamics of the mixing process while acquiring enough data points to produce accurate and repeatable results without over-sampling. Care must be taken in the interpretation of statistical data, as seen by the time evolution of concentration profiles in a generic mixing system. An understanding of the dynamics of a given blender is important in the development of efficient and precise techniques, such as those that concentrate on regions of poor mixing or sample along the prevailing composition gradient in a given blender. Both the technology and techniques used to sample and characterize powder mixing are extremely underdeveloped and need to be validated and improved to achieve the level of accuracy required from industry and by regulatory agencies.

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