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RESEARCH PAPER

The Development of a Blend-Sampling Technique to Assess the Uniformity of a Powder Mixture

Thomas P. Garcia,[1,*] Simon J. Wilkinson,[2] and Jerry F. Scott[2]

[1] *Pfizer, Incorporated, Eastern Point Road, Groton, CT 06340*
[2] *Glaxo Wellcome Limited, New Product Introduction—Pharmaceutical Technology, Temple Hill, Dartford, Kent, UK DA15AH*

ABSTRACT

This article discusses the challenges overcome during the development of a blend-sampling technique and the successful validation of the blending operation for a tablet dosage form containing 2% active ingredient. Content uniformity results are discussed for three pilot-scale (15-kg) and seven commercial-scale (150-kg) batches of tablets. Blend and core content uniformity data from the pilot-scale batches were acceptable. For the initial commercial-scale batches, although the tablet core content uniformity data were acceptable, the blend uniformity results were poor. The blend data for these batches had very high mean values, but acceptable relative standard deviations (RSDs). This suggested that the drug was being preferentially sampled by the thief, but in a consistent, reproducible manner. Extensive testing was performed on a commercial-scale development batch to identify potential causes of sampling error. The results of this testing helped define the blend-sampling technique and strategy used to validate the mixing operation.

KEY WORDS: *Blend sampling; Content uniformity; Sampling bias; Static charge.*

* Corresponding author.

INTRODUCTION

One of the most challenging aspects encountered during the process development of tablet dosage forms is identifying an acceptable technique that can be used to obtain nonbiased, representative blend samples capable of assessing the true content uniformity of the powder mixture. A number of articles have recently been published identifying issues and sources of bias associated with sampling powder blends (1–11). Differences in the particle size, shape, density, and electrostatic charge of the excipients and active substance are examples of variables that can have an impact on the quality of blend samples withdrawn by sampling devices. Depending on the physical properties of the components of the powder blend, sampling bias may be very difficult to overcome. Recently, regulatory guidance documents have been issued that advocate blend uniformity as a routine in-process test during commercial manufacture (12). As a result, the responsibility to demonstrate blend uniformity has never been more critical as its ramifications could extend beyond process validation. It is critical that development scientists understand the properties of their powder blends and take the time to develop robust sampling techniques that are capable of generating nonbiased, representative data.

This article summarizes experiences encountered during the development of a sampling technique to demonstrate blend uniformity during the development, transfer, and validation of a tablet dosage form. Three pilot-scale (15-kg) and 7 commercial-scale (150-kg) batches of tablets containing 2% active ingredient were manufactured throughout the course of product development and transfer into production. The pilot- and commercial-scale batches utilized the same formulation and manufacturing process. In addition, the environmental control (temperature and humidity) for the pilot and commercial manufacturing sites were comparable. Table 1 describes each batch of tablets discussed in this article.

Blend and core content uniformity data for the pilot-scale batches were acceptable, justifying progression with the scale-up and transfer of the product into production. Three commercial-scale stability batches (batches 4–6) were manufactured at the production site, yielding blend data with high mean values, but low relative standard deviation (RSD) values. A commercial-scale development batch (batch 7) was manufactured and extensively sampled to identify potential cause(s) of the poor blend uniformity data and further refine the sampling procedure. The results obtained from this batch were incorporated into the blend-sampling technique used to sample the validation batches (batches 8–10) successfully.

This article chronicles the activities and key learning obtained from the blend and core content uniformity data for the above batches of tablets as an acceptable sampling procedure was developed for the product.

MATERIALS AND METHODS

Product Composition and Manufacture of Powder Blend and Tablets

The formulation for the tablet blend discussed throughout this article primarily consisted of 2% drug dispersed in a lactose, anhydrous NF/PhEur and microcrystalline cellulose, and PH102 NF/PhEur diluent. The remaining excipients constituted less than 3% of the formulation. All excipients were tested to ensure compli-

Table 1

Description of Batches Discussed in Study

Batch Number	Size (kg)	Use	Site of Manufacture
1	15	Stability	Pilot plant facility
2	15	Stability	Pilot plant facility
3	15	Stability	Pilot plant facility
4	150	Development	Production facility
5	150	Development	Production facility
6	150	Development	Production facility
7	150	Development	Production facility
8	150	Validation	Production facility
9	150	Validation	Production facility
10	150	Validation	Production facility

ance with both NF and PhEur specifications. For all pilot- and commercial-scale batches, the blend was prepared by mixing the drug and excipients (excluding the lubricant) in a low-shear blender (similar design and operating principle for both scales of manufacture) for 30 min. The lubricant was added to the blender, and the contents were mixed for 2 min. The blend was transferred to a rotary tablet press and compressed into tablets (target weight 100 mg).

Sampling Technique for the Plug Thief

Figure 1 contains a diagram of the plug thief, which was constructed of stainless steel. Blend samples were taken in triplicate by inserting the thief into the powder mixture to the desired location with the rod pushed through the tube such that its tip extended approximately 3/8 inch beyond the end of the tube. (Note that the tip of the plunger is round rather than flat to minimize the ploughing action of the thief as it penetrated the powder bed.) The plunger was withdrawn to the desired distance to obtain the proper weight of sample (target was 200 mg or 2× tablet weight), and the entire thief was pushed down to force a plug of powder into the vacated cavity. Caution was exercised to ensure that the rod did not move while the sample was being pulled to avoid excess weight variation or premature discharge of the sample. Once the thief was withdrawn from the blend, the powder plug was discharged directly into a suitable container, and the entire sample was analyzed for drug content. Prior to taking the next sample, the thief was wiped with either a low-lint cloth (pilot-scale batches) or antistatic cloth (commercial-scale batches) to remove any residual powder, except in instances otherwise noted. When sampling the commercial-scale batches, both the blending container and the thief were grounded.

Sampling Technique for the Pocket Thief

Figure 2 is a diagram of the pocket thief, which was constructed of stainless steel. Blend samples were taken in triplicate by inserting the thief in the closed position into the mixture to the desired location. The inner rod was rotated to align the sampling chamber with the opening in the outer sheath (open position), allowing powder (target weight 200 mg or 2× tablet weight) to flow into the thief. The thief was returned to the closed position and removed from the blending container. The powder sample was discharged directly into a suitable container, and the entire sample was analyzed for drug content. Prior to taking the next sample, the thief was wiped with either a low-lint cloth (pilot-scale batches) or antistatic cloth (commercial-scale batches) to remove any residual powder. When sampling the commercial-scale batches, both the blending container and the thief were grounded.

Sampling Schemes for Blends and Tablet Cores

Figure 3 contains the sampling scheme used for pilot-scale batches 1–3. Figure 4 contains the sampling scheme used for commercial-scale batches 4–10. Tablets were sampled from the press at defined intervals throughout the entire course of the compression process, including beginning and end-of-run samples.

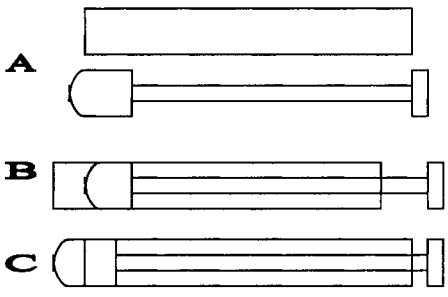

Figure 1. Diagram of plug thief: (A) disassembled; (B) open (sampling) position; (C) closed (insertion or sample discharge) position.

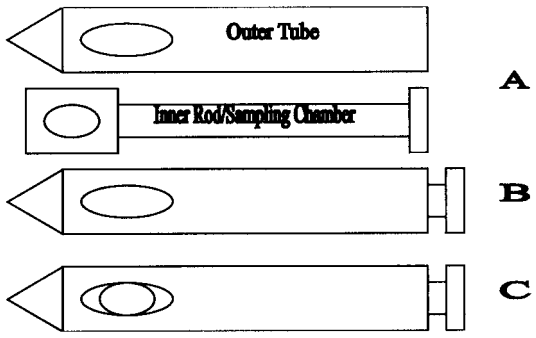

Figure 2. Diagram of pocket thief: (A) unassembled; (B) closed position; (C) open position.

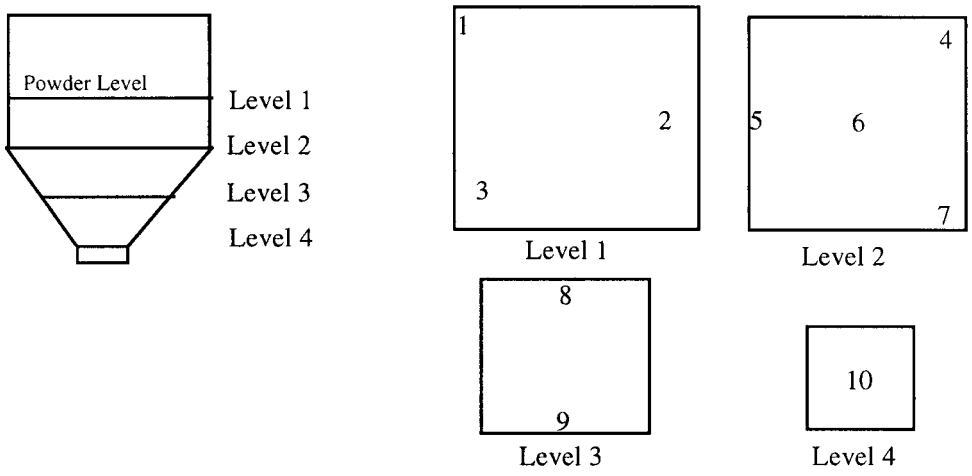

Figure 3. Sampling scheme used for pilot-scale batches

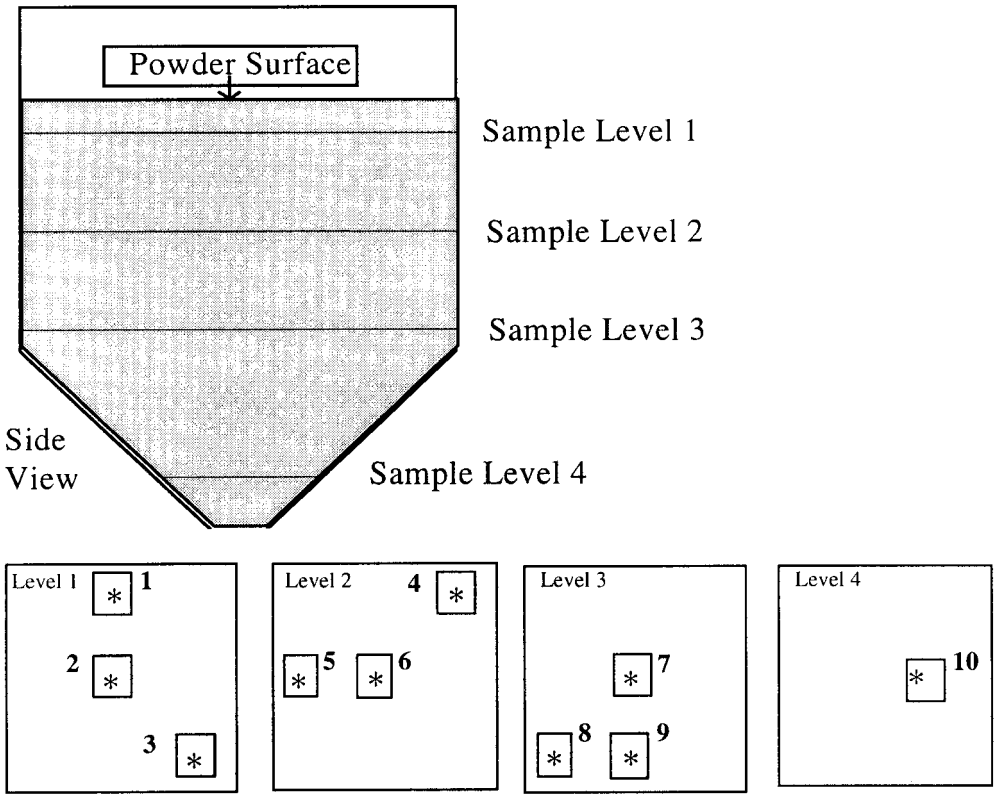

Figure 4. Sampling scheme used for commercial-scale batches.

Table 2

Content Uniformity Results for Pilot-Scale Batches

	Batch 1		Batch 2		Batch 3	
	Blend	Cores	Blend	Cores	Blend	Cores
Mean (%)	102.4	104.1	99.3	104.9	98.5	108.2
Minimum (%)	98.0	97.8	96.3	97.9	93.9	102.4
Maximum (%)	108.0	109.0	100.9	111.7	102.9	114.8
%RSD	3.8	3.0	1.7	4.0	2.7	3.8
n	10	15	10	15	10	15

RSD, relative standard deviation.

RESULTS AND DISCUSSION

Tablet Blend and Core Content Uniformity Results for Pilot-Scale Batches

Table 2 summarizes the content uniformity results for the pilot-scale batches. The blend was sampled using a pocket thief. The blend data demonstrated that the powder mixture was of acceptable uniformity prior to compression. All individual values were within the range 93.9%–108.0% of label claim. The content uniformity data for the tablet cores were also acceptable. This information provided confidence that the process produced tablets of acceptable uniformity and was ready for scale-up and transfer into the commercial site of manufacture.

Content Uniformity of Commercial-Scale Batches 4–6

Blend and Tablet Core Content Uniformity Results

Using a pocket thief, triplicate samples (target weight 200 mg) from each location were removed from the blender according to the sampling scheme defined in Fig. 4. One sample from each location was submitted for analysis. Table 3 summarizes the results of the blend and core content uniformity testing for batches 4–6. For each batch of blend sampled, the means were 12%–20% higher than label claim, but the RSD values were all $\leq$5.1. Batches 4–6 each had a number of individual values that exceeded the upper limit of 115% of the label claim, but no subpotent values. This implied that the sampling procedure was preferentially sampling drug particles over excipients, but in a consistent manner. The mean values for the tablet cores were much lower than the values obtained for the blends. RSD values for the core tablets were also smaller than the corresponding values obtained for the blends.

The core data demonstrate that the final product is of correct potency and acceptable quality. The larger range in individual values and elevated means for the blend data (compared to the tablet core data) suggest that the blend samples may have been biased by the sampling device and/or sampling technique. The tablet core data demonstrate that the blending operation produces a suitable dispersion of the drug and excipients, which when

Table 3

Blend Content Uniformity Results for Batches 4–6

	Batch 4[a]		Batch 5[a]		Batch 6[b]	
	Blend	Cores	Blend	Cores	Blend	Cores
Mean (%)	112.3	101.1	120.2	100.1	113.1	101.2
Minimum (%)	106.7	94.2	112.6	94.3	106.1	95.1
Maximum (%)	119.5	108.3	134.6	105.2	121.9	107.6
%RSD	3.8	3.1	5.1	2.6	5.0	3.3
n	10	15	10	15	10	15

RSD, relative standard deviation.
[a]Sampled with a grain thief.
[b]Sampled with a plug thief.

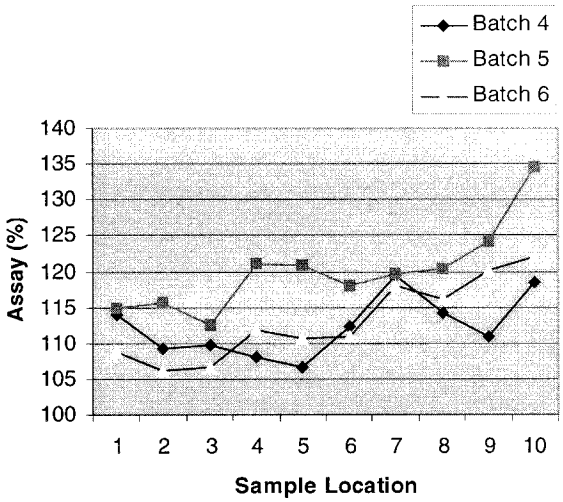

Figure 5. Blend content uniformity for batches 4, 5, and 6 as a function of sample location (pocket thief samples).

compressed, results in a product of acceptable content uniformity.

Effect of Sampling Location on Drug Assay

When the drug content was plotted as a function of location in the blender, a trend was observed for each batch (Fig. 5). As the sampling procedure progressed to locations deeper in the blender, the concentration of drug in the sample increased. Two possible causes of these discrepancies could be (1) differences among the particle size, shape, density, and flow of the drug and excipients and (2) electrostatic charge interactions.

Summary of Input Drug Substance Particle Size Distribution

Table 4 compares the particle size data for the input lots of drug substance that were used for batches 1–6.

Table 5

Comparison of Blend Uniformity Data for Samples Taken Using a Pocket and Plug Thief (Batch 5)

Batch	Plug Thief	Pocket Thief
Mean (%)	110.3	120.2
Minimum (%)	105.7	112.6
Maximum (%)	116.7	134.6
%RSD	3.6	5.1
n	10	10

Drug substance lots 4 and 6 had higher values for the ×90% and ×100% fractions. Lot 5 was comparable in particle size distribution to the lots of drug substance (1–3) used to make the pilot-scale batches. Larger particles generally possess superior flow characteristics compared to smaller particles. If the drug substance already possesses superior flow compared to the excipients (leading to drug-enriched samples), then larger particles could magnify the difference in flow between the active ingredient and excipients.

To determine if differences in the flow characteristics of the drug and excipients were responsible for drug enrichment in the blend samples, batch 5 was resampled with a plug thief (Table 5). The plug thief samples a stationary slug of powder from the blend in a manner that is independent of material flow. The plug thief samples produced a lower mean and RSD compared to the values obtained using the pocket thief. However, excluding the samples taken from locations 1 and 7, some evidence of a trend toward higher assay values at lower sampling sites in the blender was apparent (Fig. 6). This observation suggests that particle flow may not be the only factor that results in drug enrichment of the blend samples.

To verify that the higher drug assay values observed in the lower regions of the blender were an artifact of the

Table 4

Particle Size Distribution of Drug Substance

Drug Substance Lot Number	Drug Product Batch Number	X10% (μm)	X50% (μm)	X90% (μm)	X100% (μm)
378504A	Batch 1	31.59	88.79	172.44	305.0
378505A	Batch 2	35.85	120.97	198.23	305.0
378506A	Batch 3	30.51	96.99	177.60	305.0
453806A	Batch 4	23.02	94.01	216.84	365.0
453803A	Batch 5	34.00	101.71	198.04	305.0
453804A	Batch 6	51.90	140.56	240.96	365.0

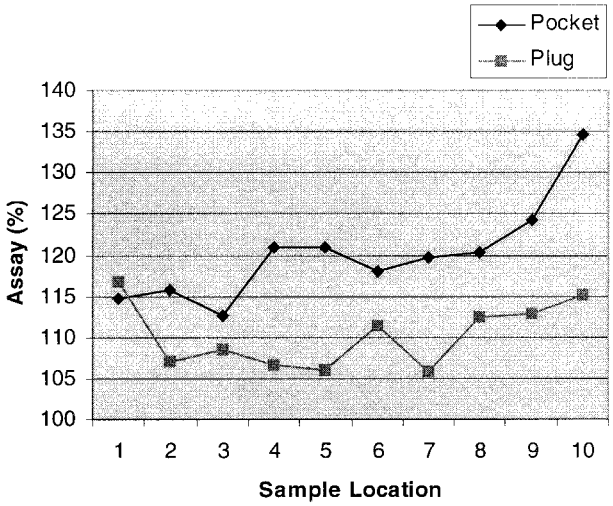

Figure 6. Drug content as a function of sample location using the plug and pocket thieves (batch 5).

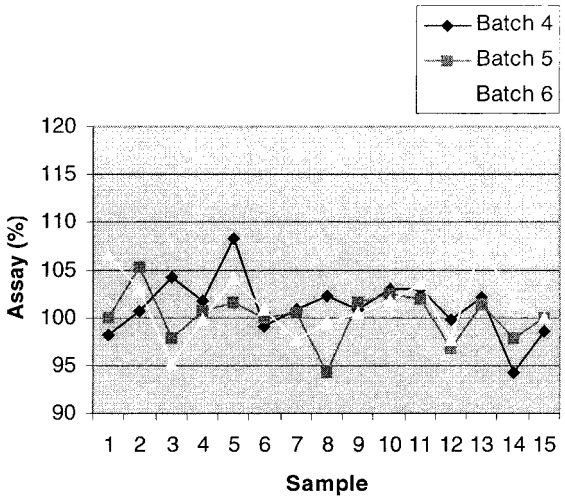

Figure 7. Tablet core content uniformity data as a function of sampling time.

sampling procedure, the drug content of the tablet cores as a function of sampling time during the compression run was assessed for batches 4–6 (Table 6, Fig. 7). Because powder at the bottom of the blending container is discharged onto the tablet press first, if that material was drug enriched, then tablets sampled at the beginning of the compression run would have higher assay values (approximately 115%–120%) than those sampled at the end of the run. Figure 7 demonstrates that such a trend does not exist. The core data are strong evidence that the content uniformity values obtained for the blend samples were falsely inflated and not representative of the true potency of the blend.

Effect of Blend Lubrication and Sampling Technique on Content Uniformity Results

To investigate the impact of the lubricant and sampling technique on the blend results, batch 6 was sampled with pocket thief prelubrication, plug thief prelubrication, plug thief postlubrication, and primed pocket thief prelubrication. It has been advocated that a primed thief (one that has been inserted into the blend and coated with the powder prior to sampling) could decrease sampling bias if the drug is attracted to the thief's surface (13). Table 7 and Fig. 8 summarize the results of the content uniformity data obtained for each of these sampling techniques. In each instance, a trend toward higher assay values at lower sampling sites in the blender was observed. Although still higher than label claim, the assay values produced by the plug thief were lower than those taken using the pocket thief. The use of a primed thief did not offer any significant benefit over one wiped with an antistatic cloth between samples.

Table 6

Summary of Tablet Core Content Uniformity Data for Batches 4–6

	Drug Content (% Label Claim)		
	Batch 4	Batch 5	Batch 6
Mean (%)	101.1	100.1	101.2
Minimum (%)	94.2	94.3	95.1
Maximum (%)	108.3	105.2	107.6
RSD	3.1	2.6	3.3

RSD, relative standard deviation.

Content Uniformity of Commercial Scale Development Batch (Batch 7)

Objective of Development Batch

Due to the difficulties encountered with the sampling of batches 4–6, a commercial-scale development batch was manufactured to gain further insight into the problems previously encountered and to develop an acceptable sampling technique that could be used for the validation campaign. To comply with current regulatory policy, the goal of the pharmaceutical scientist should be to develop a sampling technique capable of removing samples within the 1–3× range of the final dosage form. However, in situations when this is not possible, bulk samples (which are often less susceptible to sampling bias associ-

Table 7

Effect of Sampling Technique on Blend Content Uniformity (Batch 6)

	Pocket Thief, Pre-lubrication	Plug Thief, Pre-lubrication	Plug Thief, Post-lubrication	Primed Plug Thief, Prelubrication
Mean (%)	120.9	113.1	116.2	112.9
Minimum (%)	105.1	106.1	108.2	106.5
Maximum (%)	144.0	121.9	123.3	121.2
%RSD	9.7	5.0	4.5	4.6
n	10	10	10	10

RSD, relative standard deviation.

ated with lower weight samples) have been advocated to assess the uniformity of a powder mixture (13–15).

Because a concentration gradient was observed for the blend data from batches 4–6 but not for the core data, electrostatic charge was suspected to be contributing to sampling bias. Electrostatic charge could result in the preferential sampling of the drug if the particles and sample thief are oppositely charged. The deeper the thief is inserted into the blend, the greater the electrostatic charge it acquires, and the stronger is the affinity of the drug for the thief. As all sampling devices discussed in this article were made of stainless steel, this phenomenon would apply to blend samples taken using either the plug or pocket thief.

To investigate the above considerations, a commercial-scale development batch of tablets was manufactured to determine the effect of bin grounding time and sample size (200 mg vs. 2 g or 20× tablet weight) on the blend uniformity results. Following 30 min of mixing, the blender was grounded for approximately 30 min, and triplicate samples (target weight 200 mg) were taken from 10 locations (Fig. 4). The blending container was tumbled two revolutions to remove channels from the previous sampling procedure and grounded for approximately 30 min, and 10 bulk samples (target weight 2 g) were taken from the same 10 locations. The blender was tumbled 2 revolutions and grounded for approximately 24 h and resampled (target weight 200 mg). The blender was tumbled 2 revolutions and grounded for an additional 66 h (total grounding time approximately 90 h) and resampled (target weight 200 mg). All samples were taken using a plug thief, and both the thief and blending container were grounded during the sampling procedure.

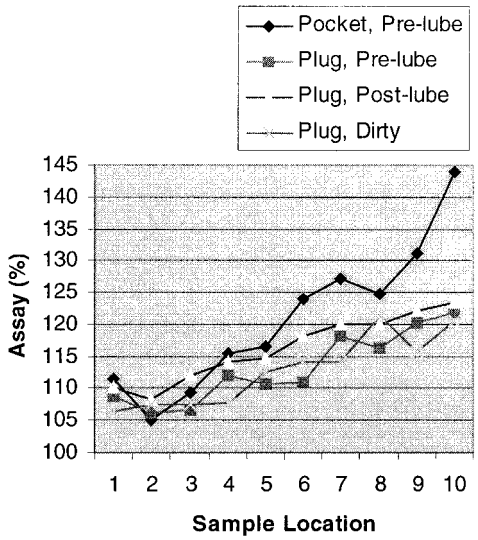

Figure 8. Effect of sampling procedure on blend content uniformity data (batch 6).

Effect of Grounding Time on Content Uniformity Data

Previous in-house experience suggested that, for some powder blends, grounding the blending container for up to 7 days was necessary to allow static charge to dissipate from the mixture prior to sampling it for content uniformity. Table 8 demonstrates that, as the grounding time increases from approximately 30 min to 90 h, the assay values of the samples decrease and move closer to the label claim. The RSD values were not significantly affected by grounding time. It is also noted that the blend data obtained from samples following 30 min of grounding were comparable to those values obtained for batches 4–6, demonstrating that the development batch behaved similarly to the earlier commercial batches at this stage of sampling.

Figure 9 plots drug content as a function of sampling

Table 8

Blend and Tablet Core Content Uniformity Data (Batch 7)

	30-minute Grounding	24-hour Grounding	90-hour Grounding	Bulk Sample	Tablet Cores
Mean (%)	118.0	113.8	110.1	106.9	101.2
Minimum (%)	108.9	107.4	104.2	104.7	97.8
Maximum (%)	122.3	120.0	112.7	109.0	103.7
%RSD	2.6	3.6	2.6	1.6	1.5
n	30	10	10	10	15

RSD, relative standard deviation.

location and grounding time. Although the assay values decrease with grounding time, a trend in the data is still noted, with higher values being observed in the lower regions of the blender. As the sample thief is inserted into the blend, it could develop a static charge, which increases in magnitude as the probe is inserted lower into the blending container. If the drug substance possesses an opposite charge to that generated on the surface of the thief, it can have a higher affinity for the thief at lower depths in the blender, leading to drug-enriched samples.

An analysis of variance was performed on the data obtained following 30 min of grounding to determine the error associated with the sampling technique (Table 9). The total amount of variance was low (9.89), as expected based on the small RSD value (2.6%) for the data. The variance component estimate for location is three times that of the residual error (7.48 vs. 2.41), implying that there is little variability in the triplicate values pulled from the various locations, and the technique used to remove the blend samples is very reproducible. Although the samples are biased (resulting from the preferential sampling of the drug), they are being consistently enriched by the sampling technique.

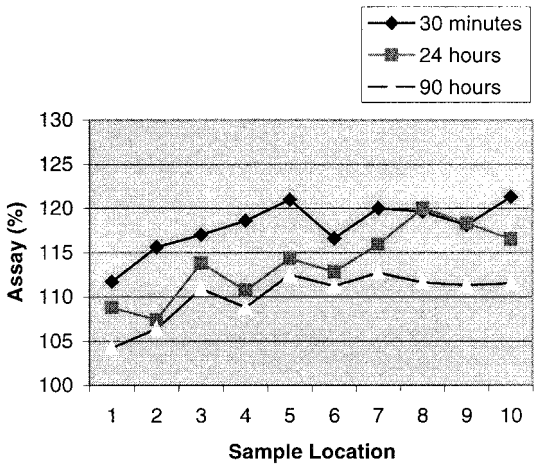

Figure 9. Drug content as a function of location and grounding time (batch 7).

Table 9

Analysis of Variance for Blend Data Following 30 Minutes of Grounding (Batch 7)

Total variance	9.89
Between location error	7.48
Residual error (within location error)	2.41

Another analysis of variance was conducted on the pooled data to determine if the difference in the drug content at each sampling location significantly changed as a function of grounding time (Table 10). The variance component estimates indicated that the residual error term, which in this instance accesses the variability between the three samples taken from a given location at the various grounding times, was 3 times greater than the location variance term (15.07 vs. 4.72). This implies that

Table 10

Analysis of Variance for Pooled Blend Data as a Function of Bin Grounding Time (Batch 7)

Total variance	19.79
Between location error	4.72
Residual error (within location error)	15.07

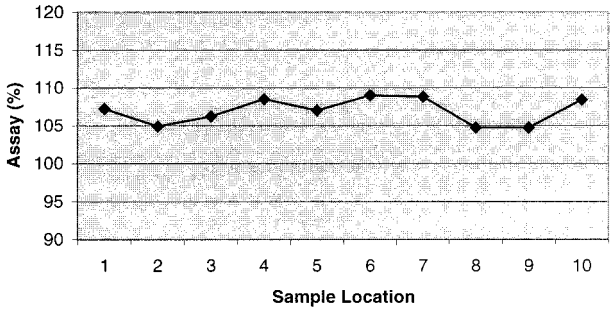

Figure 10. Drug content as a function of location for bulk blend samples (batch 7).

the assay results obtained from a given location are significantly different for samples taken following approximately 30 min, 24 h, and 90 h of grounding postmixing.

Table 8 also contains the content uniformity data for the tablet cores compressed from the blend. As demonstrated for previous batches, the mean was much lower than that for the blend data, and the range of values was very tight, as evidenced by the low RSD value. Collectively, the above data are strong evidence that static charge biases the assay values obtained for the blend uniformity samples for this product.

Bulk Blend Data

Table 8 contains the results of content uniformity testing for bulk blend samples (target weight 2 g or 20× tablet weight) taken following 30 min of grounding. Individual values ranged from 104.7% to 109.0%, and the mean (106.9%) was much lower than that observed for the 200-mg samples. Figure 10 is a plot of drug content as a function of sample location for the bulk samples. Unlike the data for the 200 mg (2×) samples, a trend in higher assay values as the sampling location progresses to lower depths in the blender is not noted. Bulk blend samples are not as susceptible to the sampling bias affecting the smaller (2×) samples and are more reflective of the true uniformity of the tablet blend.

Blend and Core Content Uniformity Data for Validation Batches (Batches 8–10)

Based on the data and learning collected from the commercial-scale batches (batches 4–7), a technique was identified to sample the process validation batches. It was decided to ground the blending container for approximately 90 h prior to pulling the blend uniformity samples with a plug thief (target weight 200 mg). Stage 1 acceptance criteria were met if the drug content of 10 samples (target weight 200 mg) from 10 locations was within ±15% of label claim, and the RSD was ≤6.0%. If not more than one sample was outside the ±15% label claim range, but within ±25% label claim, then testing would progress to stage 2. Stage 2 testing consisted of assaying 10 bulk samples (entire sample assayed, target weight 2 g) from 10 locations in the blender for drug content. Stage 2 acceptance criteria were met if the drug content of the 10 bulk samples was within ±15% label claim, and the RSD was ≤6.0%.

Table 11 contains the content uniformity results for both the blend and tablet core samples for the validation batches. For each batch, the blend uniformity values were comparable to those obtained for batch 7 following 90 h of grounding. The blend data for each batch complied with stage 1 acceptance criteria (initial 10 samples within ±15% label claim, RSD ≤ 6.0%), eliminating the need to progress to stage 2 and testing the bulk samples. Tablet core content uniformity data were also acceptable and similar to values obtained for previous batches. Together, the blend and core data validated the blending and compression processes, demonstrating that these operations produced a product of acceptable content uniformity.

Table 11

Content Uniformity Data for Validation Batches

	Batch 8		Batch 9		Batch 10	
	Blend	Cores	Blend	Cores	Blend	Cores
Mean (%)	110.5	101.7	110.7	101.4	108.1	101.6
Minimum (%)	107.5	96.3	108.4	95.6	105.4	97.6
Maximum (%)	112.1	106.1	113.7	107.6	109.5	105.6
%RSD	1.3	2.5	1.9	3.1	1.3	2.4
n	10	15	10	15	10	15

RSD, relative standard deviation.

CONCLUSIONS

Through the series of batches and experiments described in this paper, a blend-sampling technique was identified that successfully validated the content uniformity of the tablet blend and cores. Although sampling bias was not evident for batches manufactured on a pilot scale, it was suspected for the initial commercial-scale batches as blend and core content uniformity data were not consistent. It was demonstrated that static charge make take days to dissipate from a powder mixture. Simply grounding the thief and the blending container at the time of sampling was not sufficient to dissipate the static charge from the blend. For this product, acceptable blend results could be obtained if the blending container was grounded for approximately 4 days prior to sampling. Alternatively, increasing the sample size from 2× to 20× also provided data that are more representative of the true assay and uniformity of the blend. By identifying the factors that contributed to sample bias, an acceptable blend-sampling technique was defined. This technique was then used to sample the process validation batches successfully.

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