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An Evaluation of a Unit-Dose Compacting Sample Thief and a Discussion of Content Uniformity Testing and Blending Validation Issues

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ABSTRACT

The ability of the unit-dose compacting sample thief to provide quantitative, precise, and reproducible sampling of powder blends has been demonstrated in five cases. The thief enables the pharmaceutical researcher to comply with Food and Drug Administration guidelines for unit-dose sampling of powders and granulations. Some issues regarding blending validation and content uniformity testing have been addressed.

INTRODUCTION

Whether the objective is to determine particle size distribution, moisture content, bulk density, composite assay, or content uniformity, powder blend sampling is an integral part for a valid assessment of mixture quality. When assessing homogeneity, the objective is to evaluate the active ingredient uniformity by sampling in different locations. Recently, U.S. federal agencies recommend that for blend content uniformity testing, the sample size should be no more than three times the run weight, and that the size of the individual sample analyzed should be equal to one dosage unit (1). This recommendation poses some difficulties for pharmaceutical researchers in sampling powder blends with accurate sample sizes using a conventional slit sampling thief, and it may require the use of several different slit sample thieves for powder blends with varying dosage and bulk densities.

The sample taken by a conventional slit thief still demonstrates a clear ability to segregate. In many instances, errors are further introduced to the assessment due to this segregation tendency, especially during weighing of the analytical samples. A unit-dose compacting sample thief, however, has been fabricated to eliminate segregation tendencies of various powders and granulations through its compacting mechanism. It has been used successfully during process validation and in-process testing to comply with Food and Drug Administration (FDA) guidelines for unit dose sampling of powders or granulations. This technical report describes the performance of the unit-dose compacting sample

thief and substantiates its use for blend uniformity sampling.

METHODS

Figure 1 illustrates the unique unit-dose compacting sample thief used in the study. A brief description of operational procedure for using the unit-dose compacting thief is also shown in Fig. 1. The device provides significant advantages over the conventional slit sampling thieves. Unlike the unit-dose compacting thief, conventional sampling thieves may not provide consistent, reproducible sample sizes of powders and granulations. Moreover, they cannot overcome electrostatic charges during sampling, which occasionally leads to inconsistent test results. Assaying the entire powder sample may eliminate the segregation during weighing but it cannot eliminate the adhesion of powder to the sample vial. The unit-dose compacting sample thief was used in the five cases as follows:

- Case 1: Compound W was blended with lactose, starch, and magnesium stearate using a 16-quart V-shaped blender. The drug load for the powder mix was 2.26%. After the mixing, the contents (2.2 kg) were discharged into a polyethylene-lined drum. Powder samples were taken randomly from the drum by using both a conventional slit thief and a unit-dose compacting thief.
- Case 2: One batch of powder blend (140 kg) containing drug N was prepared in a 10-ft^3 V-shaped blender with an intensifier bar and lubricated with magnesium stearate. The drug load for the powder blend was 16.7%. After the blending, the powder samples were taken from the blender using both a conventional slit thief and a unit-dose compacting thief.
- Case 3: One batch of powder blend at the full production scale (585 kg) containing drug A was prepared in a 40-ft^3 V-shaped blender and lubricated with magnesium stearate. The drug load for the blend was 13.3%. After blending, the powder blend was unloaded into nine drums and 27 powder samples were taken from three positions of each drum using the unit-dose compacting thief.
- Case 4: A 120-kg powder blend containing drug L was prepared using a 10 ft^3 V-shaped blender. The drug load for the powder blend was 33.3%. The powder mix was discharged into two drums. According to a specific sampling plan, 18 powder samples from each drum were taken using a unit-dose compacting thief.
- Case 5: A 130-kg powder blend containing drug L and drug H was prepared using a 10 ft^3 V-shaped blender. The drug load was 25% (20% for drug L and 5% for drug H). The powder blend was unloaded into two drums. According to a specific sampling plan, nine powder samples from each drum were taken using a unit-dose compacting thief.

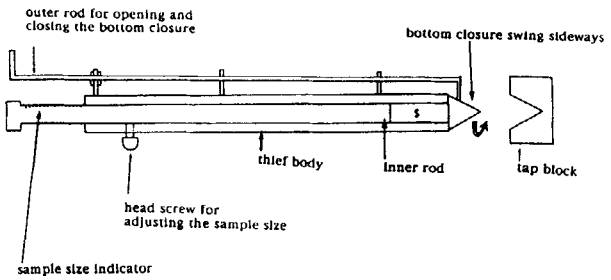

Figure 1. Schematic diagram for the unit-dose compacting thief. The procedure for using the thief has the following steps: (1) loosen the head screw; (2) raise the inner rod to an adequate position ("s" in the figure indicates sample port for the powder sample); (3) lock the inner rod to the position by using the head screw; (4) insert the thief into the powder blend at the desired location; (5) open the bottom closure by using the outer rod handle; (6) push the thief to sample the powder blend; (7) close the bottom closure by using the outer rod handle; (8) remove the thief from the powder blend; (9) put the thief onto the tap block; (10) loosen the head screw and tap the powder into a compact disk using a mallet; (11) open the bottom closure by using the outer rod handle and eject the compact disk. *Note*. US Patent Application 08/136,139, W. Wallace, I. Pinto, and G. Perez.

Content uniformity tests for all the samples were conducted using validated analytical procedures. Resampling was required to obtain approximately one dosage unit weight for the powder samples obtained by a conventional slit thief.

RESULTS AND DISCUSSION

A number of techniques and types of devices are available for powder sampling: cone and quartering, scoop sampling, chute sampling, spinning riffler, and sampling thieves. Sampling thief devices have a tendency to compact the powder bed by pushing the powder ahead of it, causing perturbation in composition due to segregation. In addition, sampling thief devices can

retain small particles within the sampling port and reduce the size of friable material between the inner and outer tubes. However, for blend content uniformity testing, the sampling thief is superior to other sampling techniques. Sampling thief devices, such as two concentric tube design and bottom closure swing sideways design, are useful for taking powder samples from a bulk quantity. But none in the market were precise, and variable sample sized thieves with compacting capability.

Table 1 shows a comparison of content uniformity data generated by using a conventional slit thief and a unit-dose compacting thief for in-process sampling of a powder blend for each of two active ingredients (drug W, case 1; and drug N, case 2). The results reveal mean values close to theoretical value (100% label claim) and show tighter RSD values for both compounds using the unit-dose compacting thief. Table 2 shows that the content uniformity data on powder blend samples for validating the blending process are consistently well within the recommended guideline (90–110% and RSD 4–5%) for blend uniformity by the Center for Drug Evaluation and Research (1). The intention of FDA's guideline using the sample size approaching one dosage weight is: (a) to have a direct comparison between blend quality and content uniformity of the drug product at the same scale of scrutiny, and (b) to prevent the unacceptable procedure of averaging out any nonuniformity, i.e., sample size much larger than individual dosage unit analyzed and additional mixing prior to the weighing for the blend assay. However, samples by a sample thief may not be representative of the real situation, due to the perturbation of the composition. Sampling thief technique also deviates from the so-called golden rules of sampling (2). In addition, the linear relationship between sample standard deviation and the square root of the sample size has been elucidated (3,4). Carstensen and Rhodes (3) point out the futility in attempting to obtain the standard deviation of a sample of unit-dose weight. Although end product testing is not sufficient to assure product quality, the content uniformity data for the finished product carry more significance for validating the blending process. The reasons for this are as follows:

1. Because the particles lose their mobility or the segregation is no longer important for the finished product, the data generated using the finished product exhibit less bias than those from the powder samples.
2. Blending is only one step in the manufacturing process. Many manufacturing steps can destroy

Table 1

Comparison of Content Uniformity Data Generated by Using a Conventional Slit Thief and a Unit-Dose Compacting Thief for In-Process Sampling of Powder Blends

	Case 1: Drug W		Case 2: Drug N	
Sample No.	Unit-Dose Thief (% Label Claim)	Slit Thief (% Label) Claim)	Unit-Dose Thief (% Label Claim)	Slit Thief (% Label Claim)
1	97.2	89.2	98.1	94.6
2	98.0	91.6	96.4	96.5
3	95.8	86.4	96.9	94.5
4	94.2	88.2	96.3	95.2
5	96.6	85.8	98.2	97.1
6	96.8	90.4	96.4	88.2
7	97.0	91.2	97.4	
8	100.4	84.4	97.0	
9	97.2	71.4	96.2	
10	96.0		96.9	
11	96.2			
12	96.6			
Mean	96.8	86.5	97.0	94.4
RSD (%)	1.45	6.74	0.74	3.4

Table 2

Content Uniformity Data on Powder Blend Samples for Validating the Blending Process

Sample No.	Case 3: Drug A (% Label Claim)	Case 4: Drug L (% Label Claim)		Case 5	
		Drum 1	Drum 2	Drug L (% Label Claim)	Drug H (% Label Claim)
1	100.2	99.4	97.6	96.9	94.2
2	101.5	98.5	96.4	98.8	94.2
3	99.8	97.0	96.2	96.9	96.0
4	102.6	97.9	97.3	96.2	100.1
5	100.8	98.9	98.2	99.6	100.3
6	101.5	98.1	97.2	98.3	95.9
7	98.8	98.0	97.4	96.2	95.7
8	99.6	97.9	97.1	97.3	94.8
9	100.8	99.3	97.9	99.7	96.6
10	98.6	98.2	98.6	101.7	98.6
11	101.2	97.4	98.0	95.3	94.4
12	99.7	98.0	97.8	94.9	96.3
13	99.6	98.3	96.1	100.5	100.7
14	102.4	98.3	98.7	89.8	94.1
15	100.6	98.4	97.5	95.9	96.6
16	100.9	98.5	98.5	98.8	96.0
17	102.2	98.5	98.4	91.8	92.1
18	99.1	98.8	97.9	96.6	95.0
19	99.9				
20	99.6				
21	99.8				
22	107.7				
23	100.6				
24	99.2				
25	99.4				
26	99.8				
27	100.8				
Mean	100.6	98.3	97.6	97.0	96.2
RSD (%)	1.8	0.6	0.8	3.0	2.5

Note. Using a unit-dose compacting sampling thief.

the quality of a mix that has been so carefully created. The content uniformity data have included all the impact of other processing steps on the finished product uniformity. The in-process powder blend uniformity data should be generated to develop a data base that could be used in future processing as a guide or a tool to discover uniformity problems and to pinpoint the part of the process where content uniformity problems arise.

The acceptance criteria for the USP content uniformity test assumes that the content uniformity results of the finished dosage forms follow a normal distribution. The application of statistical criteria to the content uniformity test is questionable as the samples do not have a normal distribution pattern (5). Furthermore, Orr and Sallam (6) suggested examination of the shape of the drug distribution curve. The presence of a skewed distribution could then be taken as an indication that the batch contained some tablets with relatively large doses of drug (6). Therefore, the FDA tends to request a demonstration of a normal distribution of the powder blend assay values and recommends a minimum of 10 samples to evaluate uniformity of powder blend (7). A

sample series of 10, however, seems insufficient to provide meaningful data and lacks statistical powder to detect any differences among standard deviations. Therefore, it appears that sample size used in the current USP content uniformity test is incapable of ensuring the dose within well-defined limits. For example, the individual assay of 10 dosage units is unlikely to detect the inhomogeneity of a batch of a couple million units.

The following will provide a more effective pharmaceutical content uniformity test method: Increase the sample size to allow greater confidence in estimating the true mean and standard deviation; and incorporate power function into content uniformity test method or incorporate the normality check, such as skewness, kurtosis, and normal probability plot.

CONCLUSIONS

The unit-dose compacting sample thief can provide quantitative, precise, and reproducible sampling of powder blends. The thief eliminates segregation tendencies of various powder blends through its compacting mechanism and enables the pharmaceutical researcher to comply with FDA guidelines for unit-dose sampling of powders or granulations. The thief also eliminates the need for additional manipulation of the sample and facilitates sample handling for the analyst. Due to the inherent invasive nature of any sample thief, bias is likely to be introduced. We suggest that the content uniformity data of the finished product carry more significance in validating the blending process. The in-process uniformity data should be generated to develop a data base that could be used in future processing as a guide or a tool to discover uniformity problems and to pinpoint the part of the process where content uniformity problems arise. The sample size for current content uniformity testing lacks statistical power in estimating the true mean and standard deviation. Increasing the sample size and incorporating the normality check or power function into the content uniformity test method provides a more effective procedure to ensure product quality and safeguard the public.

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