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## RESEARCH PAPERS

# EXAMINATION OF COMPONENTS OF VARIANCE FOR A PRODUCTION SCALE, LOW DOSE POWDER BLEND AND RESULTING TABLETS

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## ABSTRACT

A study was performed to quantify the contributions of the different components comprising the total variance term observed following the analysis of content uniformity testing of powder blends and tablets. A full scale (400 kg) blend study was performed on a low dose tablet formulation (drug content = 0.13%). Content uniformity samples were pulled from throughout the blender using a pocket type probe thief in a manner which allowed the blend to be assessed for both homogeneity and sample to sample variability at a given location. Tablets were compressed from the batch and assayed for content uniformity. Sampling error accounted for approximately 75% of the variance observed following analysis of drug content in the powder blends. The estimated total variance for the powder blend was approximately twice that observed for tablets compressed from the mixture. The analytical contribution to the total variance term was minor. The difference between the estimated total variance terms for powder blend and tablets was attributed to the superior sampling efficiency of the tablet press versus the sample thief. The results of the study support the use of wider specifications for powder blends than the tablets compressed from the mixture.

## INTRODUCTION

The demonstration of process control is critical in the manufacture of solid dosage forms. Extensive validation testing

is performed at various stages of the manufacturing process to show that various unit operations accomplish what they are purported to do. The validation of blending operations is a critical aspect in the manufacture of tablets. Without uniform blends, problems inherently arise with the drug content of the tablets compressed from the mixture.

During the development and manufacture of tablet dosage forms, it is common for blend samples to possess greater variation in drug content than that observed for tablets compressed from the same blend. Many explanations have been offered for this common occurrence, ranging from sampling bias to mixing in the feedframe of the tablet press. Harwood and Ripley (1) identified various sources of error associated with thief probes used for sampling powders. They found that the shape of the thief probe tip and the physical characteristics of the powder to be sampled significantly affected the composition of the resulting sample. Carstensen and Rhodes (2) have stated that the use of small thieves (which retrieve blend samples equivalent to the weight of the dosage unit) can cause mechanical separation and bias the content uniformity results. Stagner, et al. (3) utilized a propagation of error formula to examine the effects of tablet weight variation, blend heterogeneity and assay imprecision on dose variation.

It is critical that sampling bias be accounted for when setting content uniformity limits for powder blends and tablets. Additional factors such as analytical method variability can also contribute to the overall observed error. Otherwise, one takes the risk of performing additional (unnecessary) development work or rejecting an acceptable batch of product.

The primary objective of the following study was to quantify the various components of the total variance observed for content uniformity data from low dose powder blend and tablet data. The total variances for both the blends and tablets were separated into their analytical, processing and sampling components. The information gathered from this analysis was then utilized to set meaningful specifications for powder blend and tablet content uniformity. Because it is a commonly recognized measure of homogeneity, the first stage USP Content Uniformity limits of 85.0 - 115.0% with an %RSD value ≤ 6% was used as a benchmark to define the boundaries of adequate mixing.

## METHODS

### Materials

The formulation used to conduct the blend study contained the drug substance at a level of 0.13% W/W. The remaining components of the formulation were: Lactose Anhydrous NF,

Microcrystalline Cellulose NF, Pregelatinized Starch NF, and Magnesium Stearate NF. The study was performed on a full scale (400 kg) batch size.

Manufacture of the Powder Blend

A premix was prepared to disperse the drug into a portion of the Microcrystalline Cellulose NF prior to the main blending operation. The premix was manufactured in a high shear mixer (PharmaMatrix 150, Niro-Fielder, Columbia, MD) with the main impeller and granulator operating at low speed for 10 minutes. The premix and remaining excipients (with the exception of the Magnesium Stearate NF) were then added to a 1338 liter bin (Buls Cube, Matcon Limited, Moreton-In-Marsh, England) in a manner such that the premix was sandwiched between layers of the other excipients. The powders were blended for a total of 20 minutes at 17 +/- 1 RPM.

Sampling

Using a single compartment probe (pocket) thief with a pointed tip, the powder blend was sampled (target weight = 240 mg) according to the scheme identified in Figure 1. Triplicate samples were pulled from each location following 12.5 minutes of mixing to estimate the variability of drug content between multiple samples pulled from the same location. [The triplicate samples were taken following 12.5 minutes of mixing, which was the mid-point for additional work performed during this study to obtain a blending profile, which is not addressed in this publication.] Caution was exercised during this sampling exercise to minimize blend disturbance at the sampling site between replicate samples. The thief was carefully inserted through the same channel in the bed with minimal contact with the sides of the cavity to a constant depth at each location. The samples were pulled from the top levels first, to minimize bed disturbance in the lower regions of the blender prior to their sampling. Each sample was placed into a prewieghed numbered centrifuge tube. The material was then mixed for an additional 7.5 minutes (total mixing time = 20 minutes). Another set of samples were pulled from the blend (1 sample/location), to determine the degree of blend homogeneity. All samples were analyzed using an HPLC assay, and the quantity of drug substance was normalized to the target weight and reported as percent label claim.

Compression of the Powder Blend

After the blend samples were taken, Magnesium Stearate NF was added and the blend mixed for an additional 2 minutes. The powder blend was then discharged directly from the blender to a

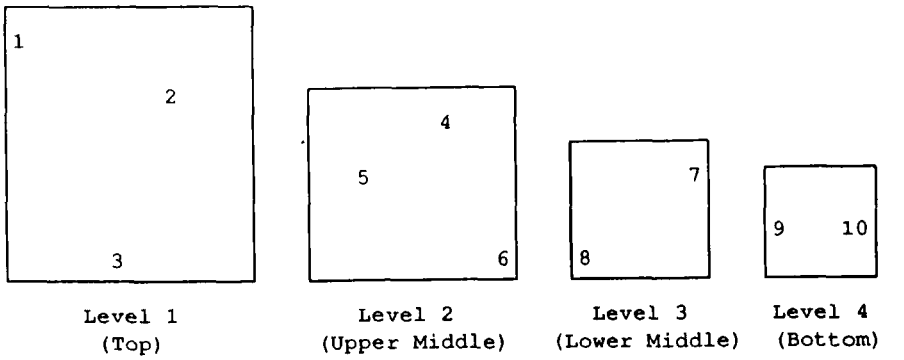


Figure 1

rotary tablet press (Courtoy R-200, Courtoy N.V., Halle, Belgium) for compression. A total of 30 tablets were sampled throughout the compression run and tested for content uniformity using the HPLC assay. The quantity of drug substance in each tablet was normalized to the target tablet weight and reported as percent label claim.

Preparation of Analytical Standard Samples

A mixture of the excipients was prepared using the same proportions as those utilized for the powder blend. Nine samples of the excipient blend were weighed into vials (target weight = 240 mg). A quantity of drug substance was dissolved in the mobile phase utilized in the HPLC analytical assay. A sufficient volume of this solution (equivalent to the tablet dose) was pipetted into the vials containing the excipient blend. [The small volume of mobile phase used to add the drug to the excipients did not significantly alter the concentration of the drug substance in the analytical sample following subsequent dissolution with additional mobile phase.] The samples were assayed according to the same HPLC method utilized for the blend and tablet samples.

## RESULTS AND DISCUSSION

Assumptions Made for the Blend Study

To obtain estimates of the various components of error, two assumptions were made to perform the analysis:

1. The concentration of drug at a given location was constant for each of the triplicate samples (taken following 12.5 minutes of blending) and was not affected by the repetitive insertion of the thief to the sampling location.

2. The degree of homogeneity in the blend was not significantly altered during the lubrication step, as the blender was discharged or in the tablet press feed frame. Therefore, the powder blend and tablets possessed the same degree of drug homogeneity.

Variability of Samples Taken From the Same Location

Table 1 contains the drug content values for triplicate samples taken from the same location following 12.5 minutes of blending. The fact that these samples were taken prior to the conclusion of the initial blend does not affect the interpretation of their results. The primary purpose of the samples was to quantify the degree of drug content variability in multiple samples taken from the same location, not to assess the homogeneity of the bulk blend throughout the mixer.

If one assumes that the blend is uniform in the immediate region in which the samples are taken, the values obtained for each of the triplicate samples should be the same. The least amount of variability occurred at location #1 (range = 96.0 - 97.4% label claim, RSD = 1.89%), while the greatest variability occurred for samples taken from location #9 (101.5 - 114.7% label claim, RSD = 16.70%).

A value slightly in excess of 115% was observed for the third sample taken from location #7 (115.4% label claim). This could be a cause of concern regarding the adequacy of the blending process, especially if a criterion such as the USP Content Uniformity Test was applied solely to the third set of blend samples. However, the significance of the high result becomes unclear in the context of the remaining two samples taken at that same location (which had drug content values of 102.7 and 108.8% label claim). If the assumption that blend homogeneity in the immediate sampling area is valid, the variability in the drug values is hypothesized to be due to sampling error.

If the replicate samples are biased in any way due to the repetitive insertion of the sample thief into the blend, different values could be expected for each sample. For example, if the probe contacts the side of the original channel when it is inserted for replicate samples, powder will be displaced into the sampling location. The chance of this phenomenon increases as the distance to reach the sampling location increases. [Note the

TABLE 1

Variability in Drug Content for Multiple Samples Taken from the Same Location After 12.5 Minutes of Blending

| Level | Location | 1st Sample | 2nd Sample | 3rd Sample | Average | %RSD |
|---|---|---|---|---|---|---|
| 1 | 1 | 97.4 | 97.1 | 96.0 | 96.8 | 0.76 |
| 1 | 2 | 95.4 | 93.8 | 94.8 | 94.7 | 0.85 |
| 1 | 3 | 95.3 | 101.0 | 93.7 | 96.7 | 3.97 |
| 2 | 4 | 97.6 | 97.1 | 105.6 | 100.1 | 4.77 |
| 2 | 5 | 103.2 | 96.2 | 98.2 | 99.2 | 3.64 |
| 2 | 6 | 101.7 | 99.1 | 103.4 | 101.4 | 2.17 |
| 3 | 7 | 102.7 | 108.8 | 115.4 | 109.0 | 5.83 |
| 3 | 8 | 110.7 | 107.4 | 101.4 | 106.5 | 4.43 |
| 4 | 9 | 101.5 | 114.7 | 110.1 | 108.8 | 6.16 |
| 4 | 10 | 107.1 | 104.8 | 103.4 | 105.1 | 1.78 |

larger degree of variability for samples pulled from lower levels in Table 1.] Therefore, to avoid biasing the sampling error term, the sampling component of the total variance was estimated only using the data obtained from the top two levels in the blender.

Evaluation of Components of Experimental Error

Equation 1 expresses the total variance as a function of its analytical, processing and sampling components:

$$\sigma_t^2 = \sigma_p^2 + \sigma_s^2 + \sigma_a^2 \quad (1)$$

where: $\sigma_t^2$ = total variance for the powder blend

$\sigma_p^2$ = variance due to processing

$\sigma_s^2$ = variance due to sampling

$\sigma_a^2$ = variance due to analytical methods

Estimates of the respective variance terms ($\sigma_i^2$) were obtained from their corresponding sample standard deviations ($s_i$) resulting from statistical analysis of the data. Since $s_i$ is an estimate of $\sigma_i$, $s_i^2$ estimates $\sigma_i^2$. In addition, by taking the square roots of the estimates of variance, each component's variability can be expressed in terms of standard deviation of percent label claim.

Each variance is composed of its own constituent components. For example, the analytical variance contains ruggedness (sample preparation) and precision (instrumentation) components. Table 2 summarizes the distribution of the blend data prior to lubrication. The total variance ($\sigma_t^2$) was obtained from the estimate of variance of the blend data. The combined sampling and analytical variances ($\sigma_s^2 + \sigma_a^2$) were estimated from the triplicate blend samples pulled from each location.

The analytical variance was estimated from the assays of the standard samples (Table 3). This value was then subtracted from the estimate of the combined sampling and analytical variances to obtain an estimate of the sampling variance. Processing variance, which is a measure of the degree of heterogeneity of the drug substance in the powder blend was calculated by subtraction using Equation 1.

The estimated total variance for the blend study following 20 minutes of blending was 12.28%. The pooled estimate of sampling and analytical variances was 9.36%, while the analysis of the standard samples indicated that the analytical component of the total variance was 0.13%. Therefore, approximately 75% of the estimated total variance term (9.23%) was due to sampling. By subtraction (from Equation 1), the estimated variance in drug content between locations ($\sigma_p^2$) was 2.92%.

Comparison of Blend and Tablet Content Uniformity

The final portion of the study involved compressing the powder blend and determining the content uniformity of the resulting tablets. The overall variance for drug content from the tablet data is expressed by Equation 2.

$$\sigma_{t*}^2 = \sigma_p^2 + \sigma_{s*}^2 + \sigma_a^2 \qquad (2)$$

where: $\sigma_{t*}^2$ = total variance of the tablets

$\sigma_p^2$ = variance due to processing

TABLE 2

Summary of Drug Content in Blend Samples After 20 min of Blending

| | |
|---|---|
| Mean (% label) | 99.3 |
| Minimum Value (% label) | 94.0 |
| Maximum Value (% label) | 106.5 |
| % RSD | 3.53 |
| $\sigma^2$ (%) | 12.28 |
| Number of Samples | 10 |

TABLE 3

Summary of Drug Contents for Standard Blend Samples

| | |
|---|---|
| Mean (% label) | 98.77 |
| Minimum Value (% label) | 98.42 |
| Maximum Value (% label) | 99.59 |
| % RSD | 0.37 |
| $\sigma^2$ (%) | 0.13 |
| Number of Samples | 9 |

$\sigma_{s*}^2$ = variance due to sampling (by the press) during compression

$\sigma_a^2$ = variance due to analytical methods

Equation 2 is equivalent to Equation 1 with two exceptions. The total variance term ($\sigma_{t*}^2$) addresses the total variability observed for the tablets, while the sampling component term ($\sigma_{s*}^2$) represents the variation in the tablet press rather than

the sample thief (since an individual tablet is the sample). The HPLC method used to quantify the drug content of the tablets was the same as that used for the powder blend, so the value of $\sigma_a^2$ (0.13%) did not change. Processing variance was also assumed to be the same for the powder blend and tablets (2.92%). This assumption implies that the contributions of the mixing actions during the 2 minute lubrication step did not alter the overall homogeneity of the powder blend prior to compression. Previous product experience supports this assumption since comparable %RSD values have been obtained for blends prior to and after lubrication. This assumption also implies that neither mixing nor segregation occurred as the blender was discharged (onto the press) or within the feedframe, both of which are theoretically possible and could affect product homogeneity.

Table 4 summarizes the distribution of the content uniformity data for tablets. The estimated total variance for the tablets ($\sigma_{t*}^2$) is 6.10%. This term demonstrates that the drug content values for the tablets were less variable than those observed for the blends. By subtracting the estimated values for $\sigma_a^2$ and $\sigma_p^2$ obtained in the blend analysis from the estimated total variance for the tablets (Equation 2), the estimated sampling variance for the tablet press ($\sigma_{s*}^2$) was 3.05%.

If the tablet press was a perfect sampling device, the value of $\sigma_{s*}^2$ would be zero (since the sampling actions of the press would not introduce any error) and $\sigma_{t*}^2$ (for the tablets) would be equivalent to the sum of $\sigma_p^2 + \sigma_a^2$ (or 2.90%). Although it is not perfect, comparison of $\sigma_{s*}^2$ (3.05%) and $\sigma_s^2$ (9.23%) imply that the tablet press is a much more efficient sampling device than the thief used to determine blend content uniformity.

Additional factors could contribute to the observed differences between the sampling efficiencies of the thief and press. Violations of the assumptions that no additional mixing occurs as the Buls cube is emptied or in the feed frame of the press could lower the value of $\sigma_p^2$. If this assumption was inaccurate and additional mixing does occur, the estimate of $\sigma_p^2$ obtained in the above analysis would be inflated. Since $\sigma_{s*}^2$ is obtained by subtraction (using Equation 2), its calculated value would be conservative due to the lower contribution of $\sigma_p^2$ to the total variance term. Therefore, the actual difference between the blend and tablet sampling error could be less than that reported. Regardless of the accuracy of the previous assumption and the magnitude of the various components of the variance, the total variance term for the tablets (6.10%) was still less than the sampling component alone for the blend analysis (9.23%).

The difference between the estimated blend and tablet variances was 6.18%. The majority of this difference is

TABLE 4

Summary of Drug Content in Tablets

| | |
|---|---|
| Mean (% label) | 98.8 |
| Minimum Value (% label) | 93.5 |
| Maximum Value (% label) | 103.6 |
| % RSD | 2.49 |
| $\sigma^2$ (%) | 6.10 |
| Number of Samples | 30 |

attributed to sampling error. For the validation of the product and manufacturing process, this difference justifies having a broader specification (correlating to an additional variance of 6.18%) for powder blends compared to that imposed on the tablets.

Recent regulatory stances have suggested the use of tighter limits for powder blends than tablets. The rationale is that subsequent material transfers of the blend may produce segregation and demixing. However, this stance ignores sampling error which has been shown to be a greater source of variability on the blend uniformity results than that produced by material transfers (for this product). The above analysis quantifying the components of variance justifies broader limits for powder blends than for tablets. Depending on the active ingredient concentration and the physical characteristics of a particular formulation, the magnitude of the sampling error can be expected to vary from product to product and should be taken into account during development and validation activities.

## CONCLUSIONS

1. The range for drug content varied by as much as 13% for triplicate samples pulled from a single location in the blender.

2. The estimated total variance (experimental error) for the content uniformity of the powder blend was split into its analytical, sampling and processing components. The estimated

sampling variance was 9.23%, while the estimated analytical and processing variances were 0.13% and 2.92%, respectively. This analysis demonstrates that significant errors are introduced into the blend content uniformity results through the use of pocket type probe thiefs.

3. Tablets compressed from the blend study material had a total variance of 6.10%, versus 12.28% for the powder blend. This difference was attributed to the smaller sampling variance for the tablet press (3.05%) compared to the thief used to sample the blend (9.23%). Therefore, the tablet press is demonstrated to be superior to the thief as a sampling device. Broader limits for blend samples (compared to those imposed for tablets) are justified.

4. During process development, it is advisable to determine blend sampling errors prior to setting specifications and progressing to commercial validation.

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