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Discrete element method (DEM) simulations of stratified sampling during solid dosage form manufacturing

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ABSTRACT

Discrete element model (DEM) simulations of the discharge of powders from hoppers under gravity were analyzed to provide estimates of dosage form content uniformity during the manufacture of solid dosage forms (tablets and capsules). For a system that exhibits moderate segregation the effects of sample size, number, and location within the batch were determined. The various sampling approaches were compared to current best-practices for sampling described in the Product Quality Research Institute (PQRI) Blend Uniformity Working Group (BUWG) guidelines. Sampling uniformly across the discharge process gave the most accurate results with respect to identifying segregation trends. Sigmoidal sampling (as recommended in the PQRI BUWG guidelines) tended to overestimate potential segregation issues, whereas truncated sampling (common in industrial practice) tended to underestimate them. The size of the sample had a major effect on the absolute potency RSD. The number of sampling locations (10 *vs.* 20) had very little effect on the trends in the data, and the number of samples analyzed at each location (1 *vs.* 3 *vs.* 7) had only a small effect for the sampling conditions examined. The results of this work provide greater understanding of the effect of different sampling approaches on the measured content uniformity of real dosage forms, and can help to guide the choice of appropriate sampling protocols.

1. Introduction

From a patient or physician perspective, it is expected than every individual dosage form contains the intended amount of active pharmaceutical ingredient (API), and that this does not vary markedly between units. Hence, the uniformity of dosage units (aka content uniformity) for oral dosage forms is normally controlled within limits set in the various pharmacopeias (e.g., European Pharmacopeia). The pharmacopeial procedures generally rely on testing a number of individual units from a representative sample taken from the final batch of tablets or capsules and then comparing the mass or potency variation within that sample against some pre-defined criteria. Alternate approaches used for the non-pharmacopeial testing of content uniformity include the sampling of in-process materials (such as powder blends) (Garcia et al., 2001; Muzzio et al., 2003, 1997) and the analysis of individual dosage units taken from the outlet of the tablet press or encapsulator in a systematic manner over the entire course of the manufacturing process (so-called stratified sampling) (Prescott and Hossfeld, 1994). In 2003, the Blend Uniformity Working Group (BUWG) of the Product Quality Research Institute (PQRI) issued its final recommendation for the stratified sampling of blends and dosage units (Boehm et al., 2003), and this guidance has subsequently become the globally accepted non-pharmacopeial method for assessing the uniformity of solid oral dosage forms.

Ensuring that the API is equally distributed in all the dosage units that comprise a batch of drug product requires good initial powder blending and minimal segregation upon powder handling after blending. Even if the powder is uniformly blended, the blended powder must be discharged from the blender into and through the feeding system of the tablet press or encapsulator with minimal segregation. This is not always easy to detect and the best approach is to sample and test the dosage units periodically throughout the batch, as described in the PQRI BUWG guidelines. This avoids errors associated with using powder sampling thieves, utilizes samples of a realistic size, and enables the batch to be tested at the point at which the dosage form is being created. The PQRI BUWG stratified sampling guidelines have recommendations for sample location,[1] spacing, number and size based on theoretical statistical

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[1] The PQRI BUWG guidelines (Boehm et al., 2003) and other related literature use the terms location and spacing somewhat loosely in both the context of space and time. In terms of stratified sampling, location refers to the point in time when a sample is taken (e.g. at the beginning, middle, or end of a batch) while spacing refers to the period or interval of time between samples. Despite the potential for confusion, we elect here to continue to use the terminology in the same manner. However, to be more specific in this work, location is quantified using the cumulative mass fraction of material discharged from the hopper.

Table 1
Standard dosage form sampling and evaluation schemes proposed in the PQRI BUWG guidelines (Boehm et al., 2003).

Criterion	Dosage form
For process validation	Sample at least 20 locations with at least 7 dosage units from each location *Stage 1 testing* Assay 3 dosage units from each location & weight correct the result •Each location mean must be 90–110% •Each non-weight corrected result must be 75–125% •Overall RSD less than or equal to 4% = 'readily pass" •Overall RSD of 4–6% = 'marginally pass' *Stage 2 testing* Assay 4 more dosage units from each location and weight correct each result •Each location mean must be 90–110% •Each non-weight corrected result must be 75–125% •Overall RSD less than or equal to 4% = "readily pass" •Overall RSD of 4–6% = "marginally pass"
For routine manufacture of products that readily passed Stage-1 validation testing	Sample at least 10 locations with at least 3 dosage units from each location *Stage 1 testing* •Assay 1 dosage unit from each location & weight correct the result •Overall mean must be 90–110% •Overall RSD must be less than or equal to 5%
For routine manufacture of products that fail Stage-1 testing (above) and those that "marginally pass" validation testing	*Stage 2 testing* •Assay 2 additional dosage unit from each location & weight correct the result •Overall mean must be 90–110% •Overall RSD must be less than or equal to 6%

considerations (attachment 3 of guidelines). The guidelines also include flow charts with criteria for assessing the acceptability of the batch based on the results of the unit dose testing. However, to our knowledge, little research has been conducted to assess the impact of the various sampling parameters on the measured uniformity of a batch of tablets of capsules.

The various methods of sampling from blenders have received a lot of attention over the years, and the reader is referred to the literature in this area for more information (for example, Berman et al., 1996; Brittain, 2002; Allen, 2003; Venables and Wells, 2002). Blend sampling in this way is generally considered to be inferior to stratified sampling of the dosage form during production so we will not consider it any further. Rather, of primary interest in this work is the sampling of the powder at the point at which it is turned into a tablet or capsule. For simplicity, this study assumes that a randomly mixed powder blend is charged to the hopper of a tablet press or encapsulator and discharges under gravity directly into the dies of the tablet press or the dosing chamber of the encapsulator. Future work will address the influences of mechanical feeding systems that are used in some modern tablet presses and encapsulators.

Prescott and Hossfeld (1994) advocated that "tablets must be sampled at regular intervals during production to trace the variation to the segregation pattern within the batch" and commented that "if tablets are selected randomly after a batch is produced, tablet quality can be evaluated, but these data cannot be used to trace the source of the variability". While a regular sampling interval was suggested, they did not comment on the preferred number or size of samples. Prescott and Garcia (2001) (both members of the PQRI BUWG) advanced these initial ideas and created a solid dosage form and blend content uniformity troubleshooting diagram that allowed the pattern of dosage form potency variability during a manufacturing run to be related to the potential root causes of that variability. Twelve evenly spaced sample locations are shown with replicates at each location in their theoretical plots providing a mean value at each location and its associated error estimate. The PQRI BUWG guidelines (Boehm et al., 2003) published 2 years later recommend a tiered sampling scheme according to the amount of prior knowledge associated with any given product (Table 1). If little is known about the product and process being studied it is recommended that seven unique samples are taken from at least 20 locations during the manufacturing run, with the sampling locations focused where variability might be expected to be highest (for example, at the beginning of the run). The acceptance criteria presented in the PQRI guidelines consider the mean potency value, the relative standard deviation of the potency, and the range of individual potency values (all weight corrected) (Table 2).

Howard-Sparks and Gawlikowski (2004) were among the first to report data collected using the PQRI BUWG recommended procedures. In their study they concentrated the sample locations in the first and last half hour of the tableting process, and maximum and minimum results from triplicate samples taken at 23 different sample locations are reported. No comparisons are made with alternate sampling protocols. am Ende et al. (2007) reported stratified sampling data for a low dose dry granulated product as part of a process optimization study aimed at improving tablet content uniformity. They took samples at between 11 and 21 locations during the tableting process, with sampling being concentrated at the beginning and end of the tableting process. Again, they did not report any studies to elucidate the impact of the sampling protocol of the results. More recently Karande et al. (2010) utilized an in-line near infra-red measurement system to estimate the potency of tablets in real-time during a laboratory scale tableting process. They acquired data on the blend potency as it passed into the dies of the tablet press and by using an acquisition time of 100 ms for a 100-min run were able to acquire 10,000 raw data points (approximately one per tablet produced). Analysis of the results was restricted to just three locations (the "beginning", "middle" and "end" of the run) however. Despite this it is clear the additional information provided by a greater number of samples allowed greater process understanding to be achieved than would have been the case with standard pharmacopeial testing.

The objective of the current work is to use discrete element method (DEM) simulations to investigate the impact of sample size, number, and location on the apparent uniformity of a powder blend as it discharges from a hopper under gravity. DEM simulations are particle-based simulations that allow the position and velocity of every particle in a processing situation to be calculated and tracked. This approach to studying the uniformity of a product has several distinct advantages over other approaches. For example, virtual 'samples' can be taken without disturbing the powder or reducing the total amount of powder in the system, particle-level information can be easily obtained (such as the