International Journal of Pharmaceutics 418 (2011) 265–272

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

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

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ARTICLE INFO

Article history:
Received 16 February 2011
Received in revised form 28 April 2011
Accepted 16 May 2011
Available online 23 May 2011

Keywords:
Content uniformity
Sampling
Hopper
Segregation
Discrete element method

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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doi:10.1016/j.ijpharm.2011.05.042

[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

Table 2
Definitions for "Readily Pass" and "Marginally Pass" (Boehm et al., 2003).

When	Status
All batches have dosage unit weight corrected means for each location of between 90 and 110% of target, RSD of less than or equal to 4%, and all individual results are between 75.0 and 125.0% of target potency. $N \geq 60$	Readily pass
As above except that at least one batch has RSD between 4 and 6%	Marginally pass

exact number and identity of particles in a sample), it is possible to vary each parameter independently (which is very difficult to achieve experimentally), sample-to-sample size variation can be controlled much more closely than during experiments thus eliminating the potentially confounding effects of dosage form weight variation, the initial potency can be set to be exactly 100%, and the initial blend state can be set to be a uniform mixture. Thus, this type of study should provide insights into the relative importance of the sampling parameters on the assessment of product uniformity for a typical batch of tablets or capsules without any of the practical difficulties associated with taking samples from a real powder.

2. Materials and methods

Particulate discharge from a 3-D, conical hopper as shown in Fig. 1 is modeled in this work using the discrete element method (DEM). While complete details of the simulations have been reported previously (Ketterhagen et al., 2007, 2008; Ketterhagen and Hancock, 2010), a summary is presented here. The system consists of $N = 126{,}300$ binary, spherical particles with a size ratio $\Phi_D = 1.93$ and an active (fines) fraction of $x_f = 5\%$. The particle diameters are selected from one of two Gaussian distributions with mean values of $d_c = 0.224$ cm and $d_f = 0.116$ cm and coefficients of variation 4.5% and 7.8%, respectively. The particle density is held constant and is set to $\rho = 2.5$ g/cm^3. This density is within the range reported for typical pharmaceutical materials (Hancock et al., 2003), and is not expected to impact the segregation behavior of the powder blend as it is the same for both the large and small particles. The hopper diameter and outlet diameter are $D = 12.5$ cm and $D_o = 2.5$ cm, respectively, and the hopper half angle is fixed at $\theta = 15^\circ$ (measured from vertical).

The particle contact forces in the normal direction $\mathbf{F}_N$ are modeled with the Walton–Braun (Walton and Braun, 1986) hysteretic spring model

$$\mathbf{F}_N = \begin{cases} k_L \delta \hat{\mathbf{n}} & \text{for loading} \\ k_U(\delta - \delta_0)\hat{\mathbf{n}} & \text{for unloading,} \end{cases} \quad (1)$$

where k_L and k_U are the loading and unloading spring constants, respectively, δ is the overlap between particles, δ_0 is the overlap at which the unloading force is zero due to plastic deformation of the particles, and $\hat{\mathbf{n}}$ is the unit normal vector directed between the two particle centers. The tangential force, $\mathbf{F}_S$, is modeled with a Coulombic sliding friction element in series with a linear tangential spring (Matuttis et al., 2000):

$$\mathbf{F}_S = -\min(\mu \left|\mathbf{F}_N\right|, k_T \left|\boldsymbol{\xi}\right|) \frac{\boldsymbol{\xi}}{\left|\boldsymbol{\xi}\right|}, \quad (2)$$

where μ is the coefficient of sliding friction, k_T is the tangential spring stiffness, $\boldsymbol{\xi} = \xi \hat{\mathbf{s}}$ is the total tangential displacement, and $\hat{\mathbf{s}}$ is the unit tangential vector pointing in the direction of the tangential relative velocity. The total tangential displacement is given by

$$\xi = \left(\int_{t_0}^{t} \Delta \dot{\mathbf{x}}(t') dt' \right) \cdot \hat{\mathbf{s}} \quad (3)$$

where $\Delta \dot{\mathbf{x}}$ is the relative velocity at the point of contact, t_0 is the time at which the particles make initial contact, and t is the current time. In addition to the tangential force, particle rolling friction is also included to reduce the tendency of the model spherical particles to rotate, and bring their behavior more inline with most real particles that have some degree of non-sphericity. This rolling friction is modeled as a torque (Zhou et al., 2002):

$$\mathbf{M} = -\mu_R \left|\mathbf{F}_N\right| \frac{\boldsymbol{\omega}}{|\boldsymbol{\omega}|}, \quad (4)$$

where μ_R is the coefficient of rolling friction with units of length and $\boldsymbol{\omega}$ is the angular velocity. The values of the material properties and contact parameters are selected based on previous work (Ketterhagen et al., 2007, 2008) and are summarized in Table 3. For the purposes of this work, all particle properties, hopper dimensions, material properties, and contact parameters have remained fixed.

It is recognized that the model system described above is simpler than a real pharmaceutical powder blend (for example, no cohesion, spherical particles, smaller number of particles, etc.). However, these conditions have been shown to result in hopper

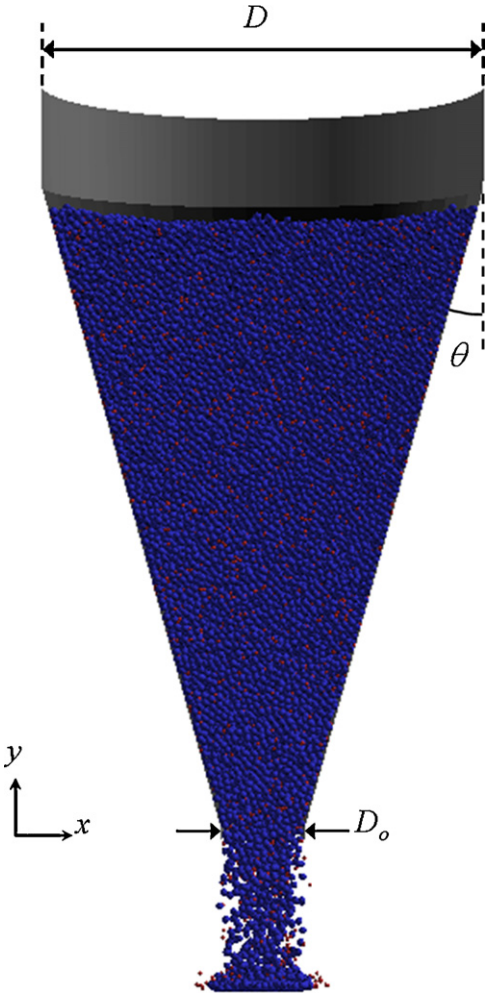

Fig. 1. A cross section of the 3D conical hopper computational domain.

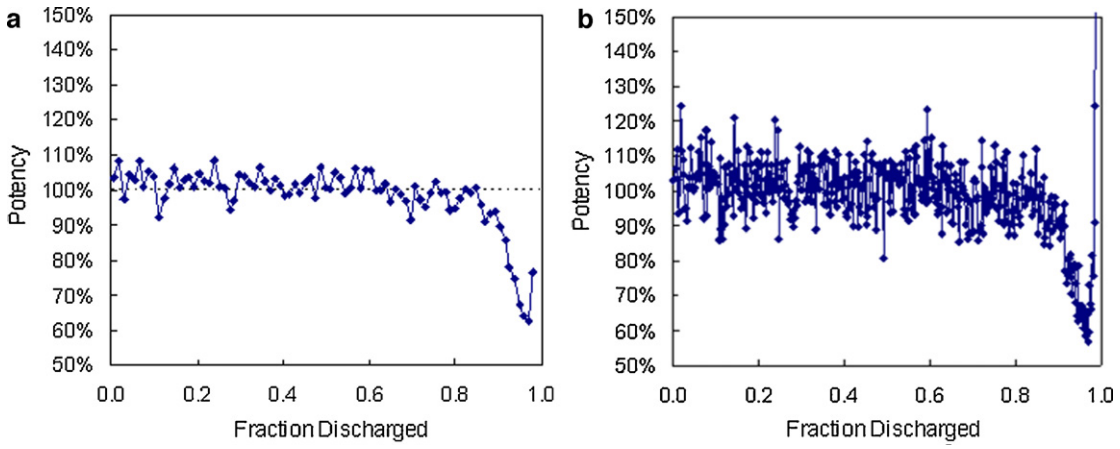

Fig. 2. Tablet potency as a function of fraction discharged for (a) all "large" tablets consisting of ~4400 particles and (b) all "small" tablets consisting of ~880 particles.

discharge behavior and segregation patterns that are comparable to those seen in typical pharmaceutical manufacturing situations (Ketterhagen et al., 2007; Ketterhagen and Hancock, 2010). Frequently this is manifested as potency transients observed near the very end of the discharge of the batch from the hopper (Prescott and Garcia, 2001). This is shown in Fig. 2 where the potency for all the tablets created from the discharge stream is plotted as a function of the cumulative mass fraction discharged.

In previous work (Ketterhagen and Hancock, 2010), three replicate simulations each with $N = 126{,}300$ were conducted with different initial particle configurations to enable calculation of mean and standard deviation statistics. In the present work, each of these three simulation data sets are superimposed with one another with the start of discharge for each data set fixed at $t = 0$ s. This approach allows for three times as many particles $N = 378{,}900$ to be available for the sampling analysis and does not affect the segregation trends.

The cumulative discharge stream consisting of $N = 378{,}900$ particles is analyzed in the following manner. First, the stream is subdivided into "tablets". Second, these tablets are sampled using one of three protocols. Finally, the tablet "potency" and relevant statistics are calculated. Each of these is discussed in more detail in the following paragraphs.

The stream is subdivided into "tablets" by assigning each particle in sequence to a given "tablet" until the mass of that "tablet" differs from a specified target mass by less than the mass of a single particle. This approach ensures a negligible degree of tablet weight variability in the simulations. While this subdivision is completed on a mass basis, the tablet sizes are depicted on a particle number basis to facilitate comparison with typical numbers of particles in real tablets. In the analysis of the simulations tablets typically contain between 90 and 4400 particles for the smallest and largest tablet sizes, respectively, whereas a typical pharmaceutical tablet is expected to contain between 80,000 and 8×10^8 particles.[2] As part of this study we evaluate the impact of the tablet size (number of particles per sample) on the apparent tablet potency and potency variability.

The tablets are sampled according to one of three protocols intended to replicate possible experimental sampling procedures. In first protocol, *uniform sampling*, the prescribed number of samples are drawn at uniform intervals beginning with the first tablet and ending with the last tablet. This is the simplest experimental approach available. In the second protocol, *sigmoidal sampling*, sampling is concentrated at both the beginning and end of the batch with relatively few samples taken in the middle of the batch. This type of sampling approach has been used in the work of Howard-Sparks and Gawlikowski (2004) and am Ende et al. (2007), and conforms most closely with the PQRI BUWG guidelines. In the third protocol, *truncated sampling*, samples are drawn at uniform intervals between 10 wt% and 90 wt% discharged. Thus, any initial or final transients are not sampled. This sampling approach recognizes that tablets formed at the very beginning and end of manufacturing are often discarded. Initially this is due to adjustment of the press to achieve accurate tablet weights. Towards the end of the tableting run depletion of the powder in the press hopper can also interfere with tablet weight control and these tablets are frequently discarded in practice. The number of sampling locations $s = 10$ or 20 and the number of tablets sampled at each location, $n = 1$, 3, or 7 is selected based on the PQRI BUWG guidelines. The three sampling protocols are shown graphically in Fig. 3 (for the case where $s = 20$).

Finally, the potency (i.e. fines mass fraction) of each sampled tablet is determined after correcting for any tablet weight variability. Statistics over all of the individual sampled tablets including the mean, standard deviation, relative standard deviation, and minimum and maximum potency are then calculated. In addition, the same parameters are computed for each sample location. With these statistics calculated for each sampling protocol comparisons with the PQRI BUWG acceptance criteria (Tables 1 and 2) can then be made. To provide a baseline for comparison purposes the same parameters were calculated after sampling every tablet in the batch, and these results are shown in Table 4.

Table 3
Contact interaction parameters used in the present work.

Parameter	Interaction type	
	Particle–particle	Particle–wall
Coefficient of restitution, e	0.94	0.90
Sliding friction, μ	0.20	0.50
Rolling friction, $\mu_R l\, d_c$	0.045	0.045
Spring stiffness, loading, k_L (N/m)	250,000	250,000
Spring stiffness, unloading, k_u (N/m)	250,000	308,600
Spring stiffness, tangential, k_T/k_L (N/m)	2/7	2/7

[2] To estimate the approximate number of particles in a tablet, we assume a tablet mass of between 1000 and 100 mg and a particle diameter of between 100 and 10 μm. Further, particles are assumed to be mono-disperse and spherical, and the particle density is taken to be 2.5 g/cm^3 to match the value used in the model.

Table 4
Summary of statistics for all tablets.

Tablet size	Total number of tablets	Average number of particles per tablet	Mean	Standard deviation	RSD	Minimum	Maximum	Range
"Large" tablets	85	4400	98.2%	8.9%	9.1%	62.5%	108.4%	45.9%
"Small" tablets	428	880	100.1%	35.2%	35.2%	57.1%	784.9%	727.8%

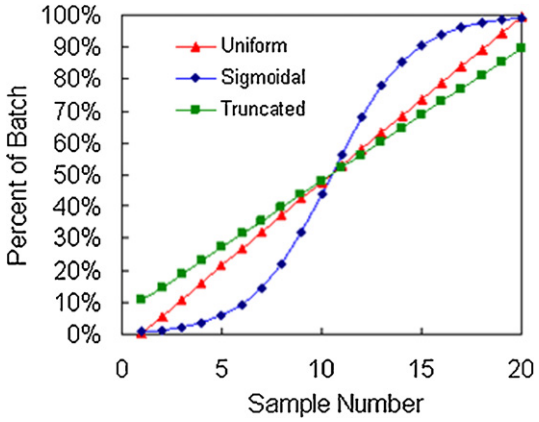

Fig. 3. A graphical representation of the three different sampling protocols for $s = 20$.

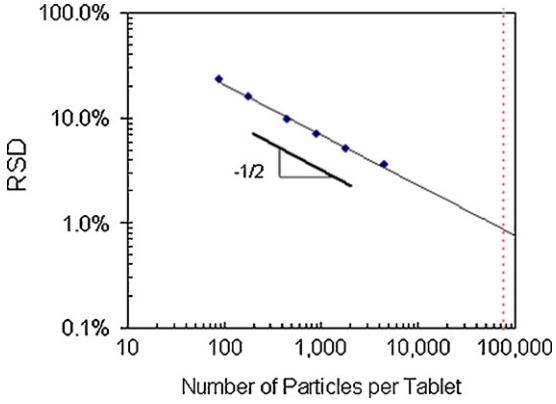

Fig. 5. RSD of all tablets between 10 wt% and 90 wt% discharged. The vertical dashed line indicates the approximate lower bound on the number of particles in a real tablet.

3. Results and discussion

3.1. Effect of tablet (sample) size

When a powder is discharged from a hopper under gravity, samples are taken at regular intervals as the powder is compressed into tablets or filled into capsules. Depending on the target fill weight of the tablet or capsule, the sample size can vary significantly and this could potentially impact the results of any potency or potency uniformity testing. To better understand the sample size effect, the particle stream from the hopper discharge simulations was subdivided into tablets of different sizes. These tablet sizes ranged from an average of 90 particles to an average of 4400 particles. The individual potencies, overall mean potency and overall potency variability across the portion of the batch between 10 wt% and 90 wt% discharged ('steady state conditions') were then calculated (Figs. 4 and 5).

It is clear from these results that the mean potency did not vary significantly over the range of tablet sizes studied, but the range of individual values (and thus the overall variability) changed markedly with sample size. As the tablet size, p, increased the overall RSD decreased with $1/\sqrt{p}$. Following this trend, the best-case RSD for real tablets (>80,000 particle per tablet; see footnote) (Fig. 5) will approach very small values, and can be assumed to be zero. Thus, a much lower RSD will be recorded for real systems as compared to a typical DEM simulation by virtue of the fact that a much larger number of particles per tablet are present.

An analogous sample size effect has recently been reported by Adam et al. (2011) for DEM simulations of powder blending, and it was explained by the early theoretical work of Lacey (1954) who calculated maximum and minimum variances for systems with different sample sizes. Fortunately, the discrepancy in the absolute RSD values caused by dissimilar sample sizes in experiments and DEM simulations does not alter the relative magnitude of the results within any given system. Hence, in this work we can still gain considerable insight from the RSD values calculated from the simulations provided we use a fixed tablet size throughout and focus on relative changes in the RSD values as we vary other parameters in the sampling protocols. To this end, the tablet size for all the data reported in subsequent sections of this manuscript will be fixed and will use the largest number of particles per tablet (~4400).

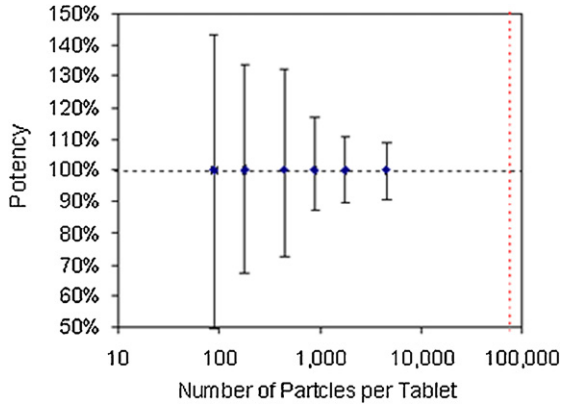

Fig. 4. Mean potency of all tablets between 10 wt% and 90 wt% discharged. The scatter bars indicate the minimum and maximum tablet potencies. The vertical dashed line indicates the approximate lower bound on the number of particles in a real tablet.

3.2. Effect of sample location, spacing, and number

Having fixed the sample (tablet) size, it is possible to examine the effect of sampling location, spacing, and number. The PQRI BUWG guidelines indicate that sampling locations should be concentrated in regions where content uniformity issues might be expected, such as during interruptions to the powder delivery system (that is, during events such as hopper changeovers). The minimum number of samples is explicitly stated (Table 1), but varies according to whether the batch is a validation batch or routine production, and according to prior manufacturing experience with the product. For processes that have shown little previous sign of potency variation the sampling can be considerably reduced. In this respect, it is both the number of sampling locations and the number of samples tested at each location that can be changed.

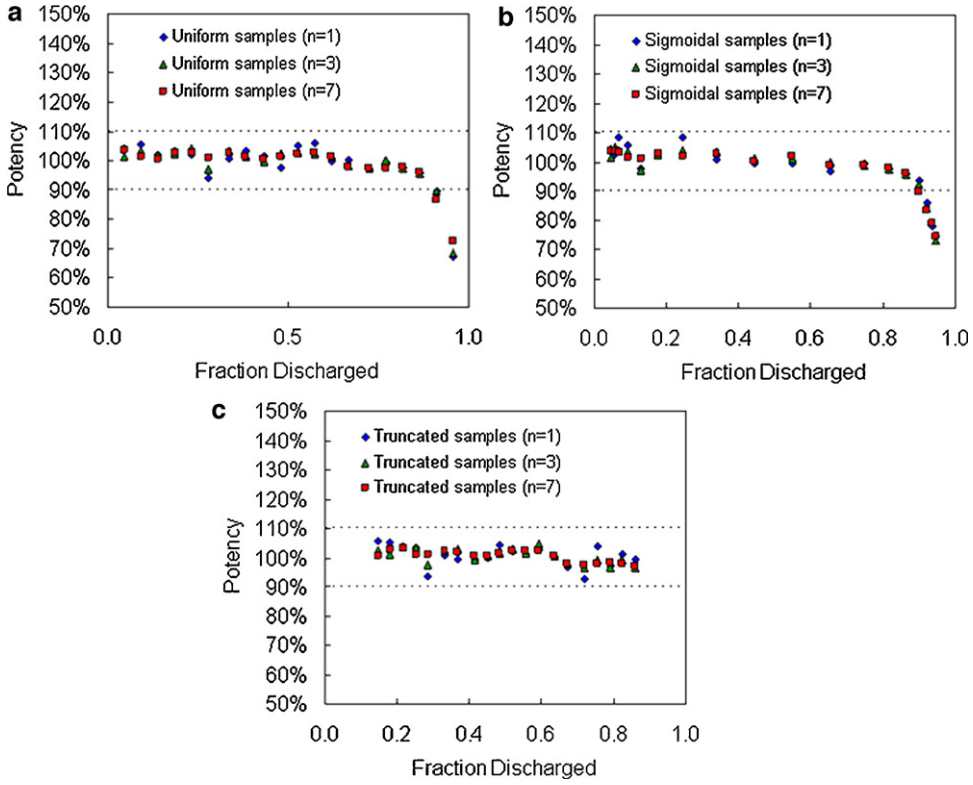

Fig. 6. Effect of sampling protocol on mean content uniformity trends for (a) uniform, (b) sigmoidal, and (c) truncated protocols (20 sampling locations; ~4400 particles per tablet).

First we will consider the case where samples are taken at 20 locations ($s = 20$). This is the most conservative approach described in the PQRI BUWG guidelines and is normally utilized when validating a process (that is, when relatively little experience exists with manufacturing the product and running the process). As described earlier (and shown in Fig. 3), we will consider three different sampling protocols: uniform, sigmoidal, and truncated.

Comparing these different protocols it is clear that the sigmoidal and uniform approaches best describe the true variation in potency at the hopper outlet over time (compare Figs. 2a, 6a, and b). In each case they capture the major drop in potency after about 90% of the batch is discharged. However, for the sigmoidal sampling the overall mean potency (~96%; Table 5) is lower than true value (98.2% for this sample size; Table 4) because samples are taken intensively in the potency trough region. For the truncated approach, the overall mean is higher than the true value because no samples are taken in the last 10% of the batch where the potency is lower than the target value. The overall RSD values also depend on the sampling protocol that is followed (Table 5). The RSD appears to be slightly overestimated in the sigmoidal sampling approach (>10% *vs.* ~9%; Tables 4 and 5) and markedly underestimated (<4% *vs.* ~9%) in the truncated approach. The range of individual values is high with both uniform and sigmoidal sampling approaches and close to the true value of 45% for this tablet, but significantly underestimated using the truncated approach. Thus, it is very clear that the choice of sampling locations can bias at least three of the parameters that are proposed as acceptance criteria in the PQRI BUWG guidelines.

In addition to the sampling location and spacing, the number of samples taken at each location n needs to be considered. As n increases the overall mean and RSD stay roughly constant within each sampling approach, suggesting no benefit of increasing n on the overall statistics (Table 5). As n increases from 1 to 7, the individual value range is better captured.

Finally, a comparison can be made between the results in Fig. 6 and Table 5 and the PQRI BUWG acceptance criteria in Tables 1 and 2. Using $s = 20$, the uniform and sigmoidal sampling approaches would result in the batch being discarded because none of the three criteria are met: location means outside the range 90–110% of target potency, low individual tablet potency values, and a high overall RSD. However, if sampling were conducted according to the truncated approach the batch could clearly "pass" even though significant segregation is occurring towards the end of the manufacturing run (Fig. 2a).

Now the case where the number of sampling locations s is cut to 10 should be considered. This may occur if the product has a history of satisfactory potency uniformity or during initial product development when analytical testing resources are scarce. In this situation the sigmoidal and uniform sampling approaches still better describe the true pattern of potency when compared to the truncated sampling approach (Fig. 7). However, the differences in the data are not as clear as with 20 sampling locations (Fig. 6). As was observed for $s = 20$, the overall mean is biased low for the sigmoidal approach (~96% *vs.* 98.2%; Tables 4 and 6) and biased high for the truncated approach (>100%). Another notable trend is that the overall RSD values are always higher for the case when $s = 10$ locations (*vs.* $s = 20$) even when $n = 7$ (Tables 5 and 6), although the size of this difference depends on the sampling protocol. Also, individual potency values fluctuate over a similar range to the $s = 20$ case, and, again, increasing n is beneficial in defining the true potency range. Finally, when comparing the $s = 10$ data to the PQRI BUWG acceptance criteria (Tables 1 and 2) the same conclusions would be drawn as for the case when $s = 20$. In summary, the use of $s = 10$ rather than 20 has only a small impact on the absolute values of the parameters obtained, has no impact on the qualitative trends in the data, and would not change the pass/fail assessment for this case according to the PQRI BUWG guidelines.

Table 5
Trends in potency data for 20 sampling locations (4400 particles per tablet).

Sampling protocol	*n*	Mean	Standard deviation	RSD	Minimum	Maximum	Range	Pass/Fail PQRI BUWG criteria
Uniform	1	98.6%	8.5%	8.6%	67.2%	106.0%	38.9%	Fail
Uniform	3	98.6%	8.2%	8.3%	64.0%	108.3%	44.3%	Fail
Uniform	7	98.6%	8.0%	8.1%	62.5%	108.4%	45.9%	Fail
Sigmoidal	1	96.5%	9.9%	10.3%	74.7%	108.4%	33.7%	Fail
Sigmoidal	3	96.4%	9.9%	10.3%	67.2%	108.4%	41.2%	Fail
Sigmoidal	7	96.2%	10.8%	11.3%	62.5%	108.4%	45.9%	Fail
Truncated	1	100.5%	3.5%	3.5%	92.7%	105.4%	12.7%	Pass
Truncated	3	100.6%	3.3%	3.3%	92.7%	108.5%	15.8%	Pass
Truncated	7	100.6%	3.5%	3.4%	90.5%	108.5%	18.0%	Pass

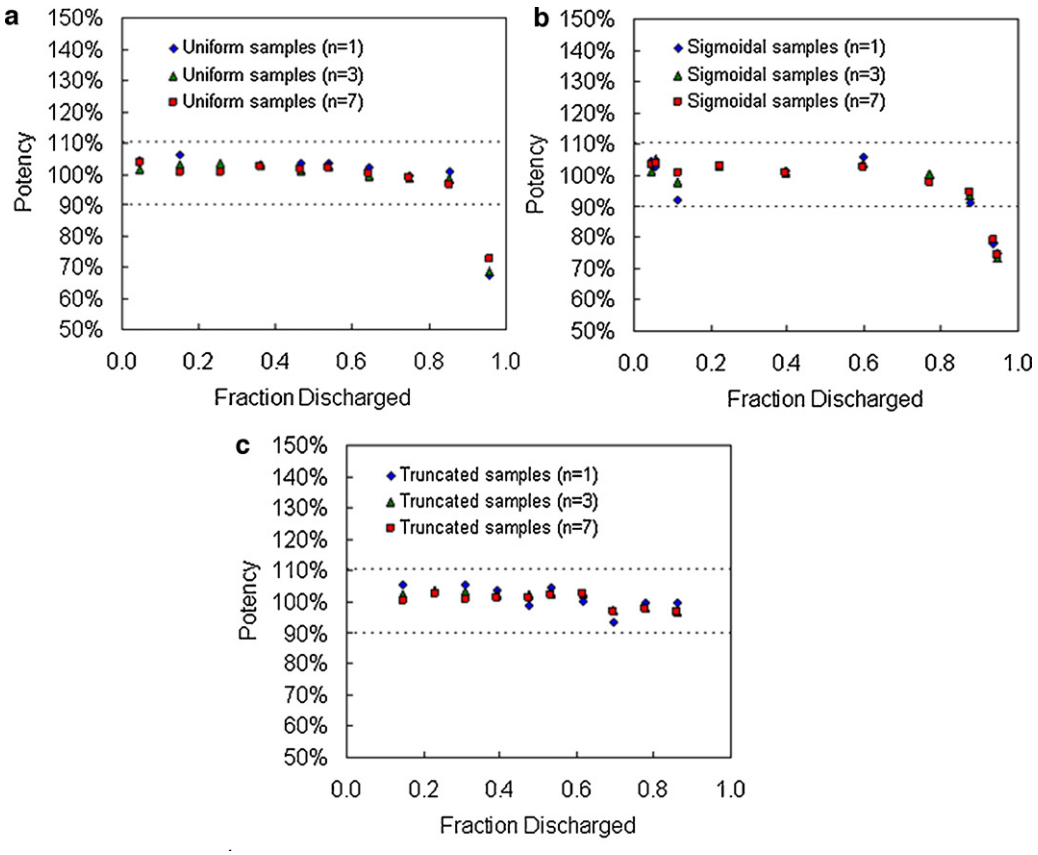

Fig. 7. Effect of sampling protocol on mean content uniformity trends for (a) uniform, (b) sigmoidal, and (c) truncated protocols (10 sampling locations, ~4400 particles per tablet).

Table 6
Trends in potency data for 10 sampling locations (4400 particles per tablet).

Sampling protocol	*n*	Mean	Standard deviation	RSD	Minimum	Maximum	Range	Pass/Fail PQRI BUWG criteria
Uniform	1	98.9%	11.3%	11.4%	67.2%	105.9%	38.8%	Fail
Uniform	3	97.9%	10.5%	10.7%	64.0%	108.3%	44.3%	Fail
Uniform	7	98.0%	9.5%	9.7%	62.5%	108.4%	45.9%	Fail
Sigmoidal	1	95.1%	11.1%	11.6%	74.7%	105.8%	31.1%	Fail
Sigmoidal	3	95.9%	11.0%	11.4%	67.2%	108.4%	41.2%	Fail
Sigmoidal	7	96.1%	11.5%	12.0%	62.5%	108.4%	45.9%	Fail
Truncated	1	101.2%	3.7%	3.7%	93.5%	105.4%	11.8%	Pass
Truncated	3	101.1%	3.4%	3.4%	93.3%	108.5%	15.2%	Pass
Truncated	7	100.3%	3.6%	3.6%	90.5%	108.5%	18.0%	Pass

4. Conclusions

The utility of DEM simulations to assess the impact of different sampling protocols on the predicted results of stratified sampling of solid dosage forms during manufacturing has been clearly demonstrated. This approach for studying potency fluctuations during pharmaceutical manufacturing operations has the advantage of eliminating the significant practical issues of sampling real powders in a laboratory or factory. Hence, it allows a focus to be placed on understanding the fundamental aspects of stratified sampling (such as sample size, location, and frequency) in a controlled yet practical situation.

For the type of particle segregation that commonly occurs during hopper emptying under gravity, it is clear that sampling location

has a very big effect. Sampling uniformly across the discharge gave the most accurate results. Sigmoidal sampling (as recommended in the PQRI BUWG guidelines) tended to overestimate potential segregation issues, whereas truncated sampling tended to underestimate them. The size of the sample had a major effect on the absolute potency RSD, but this could be understood based on previous theoretical calculations and was effectively controlled by maintaining a constant sample size in the analysis of the DEM simulations. The number of sampling locations (10 *vs*. 20) had very little effect on the final conclusions drawn from the data, and the number of samples analyzed at each location had only a small effect for the values of sampling parameters *s* and *n* examined here.

The results of this study provide insights that can enhance the design of sampling plans for use when manufacturing solid dosage forms. The PQRI BUWG guidelines are generally supported by the results of this study, although care should be taken when comparing results of studies with differences in sample size, sampling location, or number of samples. This appears to be quite common in practice (see for example, am Ende et al., 2007; Howard-Sparks and Gawlikowski, 2004) and its potential significance should not be underestimated. Future experimental work should be conducted with a range of pharmaceutical blends to test the conclusions drawn in this work, and to confirm their applicability to typical pharmaceutical materials.

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