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Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 79–84
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
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Probability of passing dissolution acceptance criteria for an immediate release tablet

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Received 18 September 2006; received in revised form 24 January 2007; accepted 25 January 2007
Available online 3 February 2007

Abstract

During development of solid dosage products, a pharmaceutical manufacturer is typically required to propose dissolution acceptance criteria unless the product falls into Biopharmaceutics Classification System (BCS) class I, in which case a disintegration test may be used. At the time of filing the new drug application (NDA) or common technical document (CTD), the manufacturer has already met with regulatory agencies to discuss and refine dissolution strategy. The dissolution acceptance criteria are based on stability and batch history data and are often arrived at by considering the percentage of batches that pass United States Pharmacopeia (USP) criteria at Stage 1 (S_1), when in fact, the product is deemed unacceptable only when a batch fails USP criteria at Stage 3 (S_3) [H. Saranadasa, Disso. Technol. 7 (2000) 6–7, 18 [1]]. Calculating the probability of passing (or failing) dissolution criteria at S_1, S_2, or S_3 can assist a manufacturer in determining appropriate acceptance criteria. This article discusses a general statistical method that was developed to assess the probability of passing the multistage USP test for dissolution and how it was applied to an immediate release tablet formulation. In this case, acceptance criteria were set and the analysis was conducted to assess the probabilities of passing or failing based on this acceptance criterion. Whether the acceptance criteria were relevant to the product was also considered. This mathematical approach uses a Monte Carlo simulation and considers a range of values for standard deviation and mean of historical data.

Keywords: Dissolution; Probability; Acceptance criteria; Monte Carlo simulation

1. Introduction

Dissolution testing of drug formulations was introduced in the 1960s and has evolved into a test that pharmaceutical manufacturers hope will better predict the *in vivo* performance of drug products. In addition, the reliability and discriminatory capabilities of dissolution methods for immediate release (IR) products has gained much attention in recent years. The most widely used dissolution tests for IR products use 900 mL of an aqueous medium with USP apparatus I (basket) or apparatus II (paddle) at agitation rates of 100 or 50 rpm, respectively [2]. It is desirable to have an *in vitro* dissolution method that is sensitive to formulation factors that affect the dissolution process and in consequence bioavailability.

In vitro dissolution testing provides useful information throughout the drug development process. It can help select a suitable formulation, confirm batch-to-batch reproducibility of the product, and demonstrate that the product performs consistently throughout its use period or shelf life [3]. Formulation scientists use the test to assess the dissolution properties of the drug itself and thereby select appropriate excipients for the formulation. Dissolution can also aid in the selection of the most suitable dosage form. Clinicians correlate dissolution results with drug absorption profiles and establish *in vivo–in vitro* correlations (IVIVC). Where appropriate, regulatory scientists use the test to evaluate the biopharmaceutical implications of a product change, rather than to require a bioequivalence study [4].

If a dissolution method is required of a product because of its BCS classification, acceptance criteria are also required. USP <711> [5] provides a guideline for acceptance criteria at three stages of testing. S_1 takes into account the results from six tablets. S_2 requires testing of six additional tablets. Finally, S_3 requires that 12 additional tablets are tested. A batch is

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doi:10.1016/j.jpba.2007.01.047

Table 1
USP <711> dissolution acceptance criteria

Stage	Number tested	Acceptance criteria
S_1	6	Each unit is not less than $Q+5\%$
S_2	6	Average of 12 units (S_1+S_2) is equal to or greater than Q, and no unit is less that $Q-15\%$
S_3	12	Average of 24 units ($S_1+S_2+S_3$) is equal to or greater than Q, not more than 2 units are less than $Q-15\%$, and no unit is less than $Q-25\%$

considered unacceptable only after it fails S_3 criteria, but manufacturer acceptance criteria are typically set based on S_1 and/or S_2 criteria. Furthermore, initial acceptance criteria used during development are almost arbitrary for an IR product. A common acceptance criterion of $Q=75\%$ at 45 min is often used as a default until sufficient product information becomes available. This may evolve as stability data becomes available and as batch size increases toward a proposed commercial target. By the time ICH batches are manufactured a sufficient amount of stability and release data are available to set Q and/or calculate the likelihood of passing dissolution criteria in future batches.

A number of papers [6–10] have been published proposing different approaches for setting a Q value. For example, Hauck et al. [7], proposed using a parametric tolerance interval approach on dissolution data generated from drug product development batches (i.e., batches used in clinical trials, bioavailability/bioequivalence studies, stability studies, etc.) to set Q, the dissolution acceptance criteria. Tolerance intervals based on historical data are used to determine the percentiles of the distribution of percent dissolution at a given confidence level. These percentiles are then used to set the Q value such that a certain percentage will pass S_1 criterion. Hauck's method is appropriate if the objective is to set Q. The method proposes a rigorous data based approach to setting Q so that the probability of passing S_1 dissolution criteria is known. Benefits of this approach include using actual dissolution data instead of a Monte Carlo simulation, controlling both the mean dissolution value and variance, and providing information on the width of the distribution of dissolution values.

The method outlined here for an IR tablet product, has a different objective. In this case, Q had already been established, and there was a desire to determine the probability of passing when historic data is measured against Q. Given Q then, an assessment of the discriminatory ability of the specification (method/acceptance criteria) was desired. The discriminatory ability was assessed based on the probably of passing the acceptance criteria. This approach benefits from its universal applicability; the probability contours based on Q and the percent dissolution population mean and standard deviation are data and product independent. Actual product data can then be overlaid on the plot to see how the actual data/product behaves relative to Q and the range of possible population means and standard deviations (a joint confidence region may be exploited to assess this). It is the conditional nature of the dissolution test, the fact that the probability of meeting acceptance criteria is dependent upon cumulative results from S_1 and S_2, which makes calculating the probability of passing or failing the test a subject of interest. If a statistical model shows that a product will pass dissolution criteria 100% of the time at these stages, it may appear that the test itself cannot detect manufacturing changes. Since it is important to have a test that can discriminate aberrant formulations, it is equally important to demonstrate that some production batches may fail S_1 or S_2 criteria for dissolution. Again, it is acceptable to fail S_1 and/or S_2 criteria as long as S_3 criteria are met.

For the IR tablets evaluated in this example, dissolution data from ICH stability lots were evaluated to determine the likelihood of passing S_1 dissolution criteria as defined in the USP. Because of a change in acceptance criterion to an earlier timepoint, lots manufactured prior to the ICH stability batches were not considered in the analysis. A general statistical method to assess the probability of passing the multistage USP test for dissolution was developed and applied. Monte Carlo simulation was used to calculate the probability of passing USP test for dissolution criteria. The simulation, which assumes a normal distribution for percent dissolved, calculates the probabilities of interest depending on Q and a set of population means and standard deviations. The results are graphed on a contour plot and the actual historical values are overlaid on the theoretical results.

2. Monte Carlo simulation

USP <711> *Dissolution* acceptance criteria as shown in Table 1 must be met at one of three stages, S_1, S_2, or S_3. Testing proceeds to the next stage unless the results conform at a previous stage. The probability of passing these acceptance criteria for a given product is a function of the %dissolution population mean and standard deviation.

Monte Carlo simulation, as outlined in Fig. 1, is employed to calculate the probability of passing S_2 and S_3 criteria, respectively. S_1 can be calculated by exact mathematical formulae so no simulation is necessary. Monte Carlo simulation may be used when an exact solution is mathematically intractable. In the case of S_2 and S_3, the conditional nature of the test makes for mathematically intractable solutions, i.e., S_2 criterion is tested *conditioned* on failing S_1, and S_3 criterion is tested *conditioned* on failing S_2. The utility of Monte Carlo simulation depends on The Strong Law of Large Numbers. This convergence law of probability guarantees an accurate probability assessment if the number of simulations is large [11].

2.1. For S_1

S_1 criterion is passed if all six units tested are $\geq Q+5\%$. This probability can be calculated directly as $P\{\text{Pass } S_1\}=p^6$, where

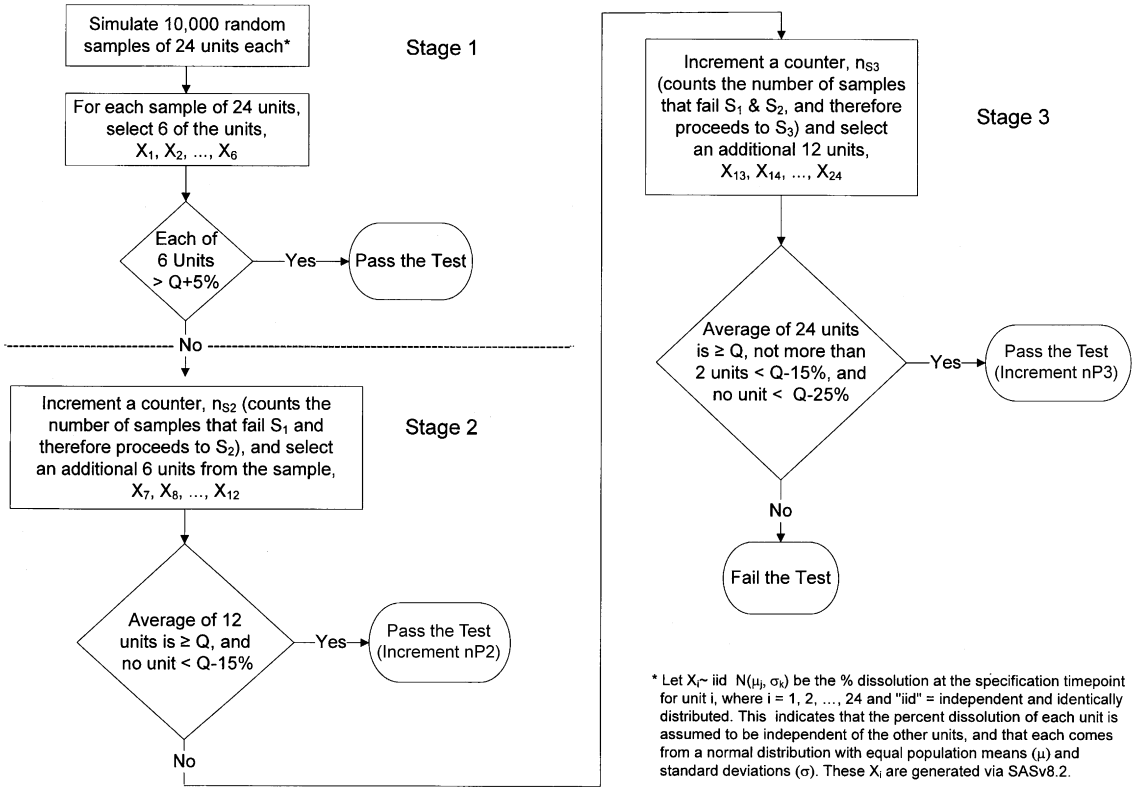

Fig. 1. Flow chart of the Monte Carlo simulation used to calculate the probability of passing USP <711> dissolution criteria.

$p = P\{X > Q + 5\}$ and $X \sim N(\mu_j, \sigma_k)$ for each (μ_j, σ_k) pair of interest. In other words, X = percent dissolution and is normally distributed, where $\mu_j = Q + (j - 1)$ is the jth ($j = 1, 2, \ldots, 26$) population mean percent dissolution, and $\sigma_k = k$ is the kth ($k = 1, 2, \ldots, 30$) population standard deviation.

2.2. For S_2 and S_3

Since calculating the probability of passing S_2 and S_3 criteria via mathematical formulae is not an option, simulation is used to assess these probabilities. This is accomplished by mathematically generating a sample ($n = 6$) of percent dissolution values from the distribution of interest (in this case, a Normal Distribution is assumed). This simulated sample is then compared against S_1 criterion. For those samples that fail S_1, a new sample of six is then generated and added to the sample so that the new sample now has 12 dissolution values. These 12 are then judged against S_2 criterion. Sampling/comparing continues in this fashion a large number of times (e.g., $N = 10{,}000$), and the proportion of these samples that passed S_2 criterion (and failed S_1) is the estimated probability of passing S_2. For those samples that fail S_2 criterion, another sample of 12 is added for a total of 24 dissolution values to be evaluated against S_3 criteria. The probability of passing S_3 is then estimated as the proportion of samples of size 24 that passed S_3 and failed S_2. This algorithm is formalized below.

For simulation n_{jk}, $n_{jk} = 1, 2, \ldots, N$, where N is very large ($N = 10{,}000$ in this case), $j = 1, 2, \ldots, 26$, and $k = 1, 2, \ldots, 30$.

1. Set $j = 1$, and $k = 1$.
2. Set the population mean $\mu_j = Q + (j - 1)$.
3. Set the population standard deviation $\sigma_k = k$.
4. Set $n_{jk} = 1$.

Let $X_i \sim$ iid $N(\mu_j, \sigma_k)$ be the % dissolution at the appropriate timepoint for unit i, where $i = 1, 2, \ldots, 24$ and iid = independent and identically distributed. This indicates that the percent dissolution of each unit is assumed to be independent of the other units, and that each come from a normal distribution with equal population means and standard deviations. These X_i are generated via SASv8.2.

For S_2: If S_1 criterion is not passed for X_i, $i = 1, 2, \ldots, 6$, then increment a counter, n_{S2} (counts the number of simulations that fail S_1 and therefore proceeds to S_2), by one, and take X_i, $i = 7, 8, \ldots, 12$. Combine all of X_i, $i = 1, 2, \ldots, 12$ and check against S_2 criteria:

- If the Average of these 12 units is equal to or greater than Q, and no unit is less than $Q - 15\%$, then increment a counter n_{P2} (counts the number of simulations that pass S_2) by one. Otherwise do not increment n_{P2}.

For S_3: If S_2 criteria is not passed for X_i, $i = 1, 2, \ldots, 12$, then increment a counter, n_{S3} (counts the number of simulations that fail S_1 and S_2, and therefore proceeds to S_3), by one, and take X_i, $i = 13, 14, \ldots, 24$. Combine all of X_i, $i = 1, 2, \ldots, 24$ and check against S_3 criteria:

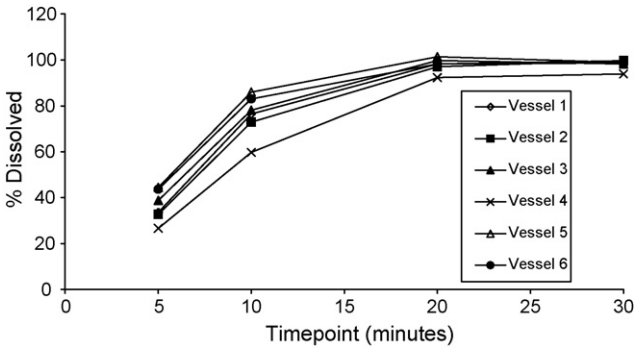

Fig. 2. Dissolution profiles of six individual immediate release tablets with specification criteria of $Q = 75\%$ at 20 min.

- If the average of these 24 units is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$, then increment a counter n_{P3} (counts the number of simulations that pass S_3) by one. Otherwise do not increment n_{P3}.

  Once all $N = 10{,}000$ iterations are complete for a given (μ_j, σ_k) pair, the probabilities of interest may be calculated by dividing the number of simulated dissolution results that pass a criteria of a given stage, by the number of simulated dissolutions that were tested against the criteria of that stage:

$$P\{\text{Pass } S_2\} = \frac{n_{P2}}{n_{S2}}, \quad P\{\text{Pass } S_3\} = \frac{n_{P3}}{n_{S3}}.$$

5. Then another (μ_j, σ_k) pair are generated and the simulation begins again for the new pair, and continues in the fashion until all $26 \times 30 = 780$ (μ_j, σ_k) pairs of interest are exhausted end the Monte Carlo simulation.

2.3. Practical Considerations for S_3

There are some practical limitations to be considered when calculating $P\{\text{Pass } S_3\}$. Even for very large N, n_{S3} (the number of units failing stages one and two, and therefore subjected to stage three testing) can be relatively small so that the probability calculation via simulation can be subject to unacceptably large simulation error. Increasing N can theoretically alleviate this issue, but even with modern computing speeds, increasing N enough to adequately increase n_{S3} can take a prohibitively long time when considering a wide range of μ and σ. This issue necessitates an approximation be made for $P\{\text{Pass } S_3\}$. A lower bound, LB, for $P\{\text{Pass } S_3\}$ then is given by [12]:

$$\text{LB} = -P\left\{Z < \sqrt{24}\frac{(Q-\mu)}{\sigma}\right\} + (276p_1^{22}p_2^2 + 24p_1^{23}p_2 + p_1^{24}),$$

$$p_1 = P\{X \geq Q - 15\},$$

$$p_2 = P\{Q - 25 \leq X \leq Q - 15\}.$$

The lower bound can be calculated for a range of μ and σ, then probability contours can be drawn to visually assess probabilities of interest.

3. Results and discussion

As discussed in the previous section, theoretical probabilities of passing acceptance criteria can be calculated for a set of potential population means and standard deviations. Historical, hypothesized, or potential dissolution results can then be overlaid on these theoretical results to give an accurate assessment of the probability of passing the acceptance criteria.

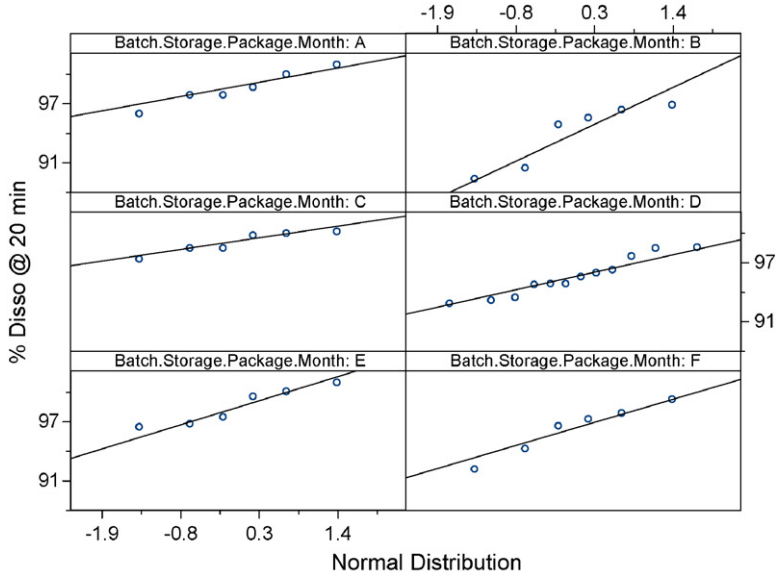

Fig. 3. Representative normal probability plots for percent dissolution at 20 min.

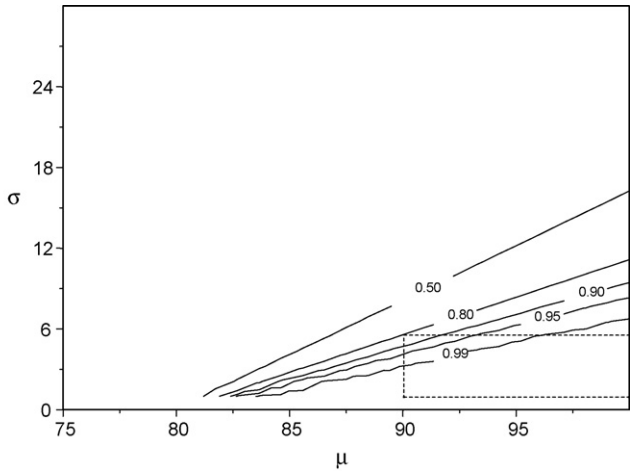

Fig. 4. Probability of passing S_1 criteria. Probability contours (50%, 80%, 90%, 95%, 99%) plotted as a function of population mean (μ) and standard deviation (σ) for S_1 based on the direct mathematical formulae. The boundaries of the box in the lower right of the plot represent the range of means and standard deviations calculated from historical data.

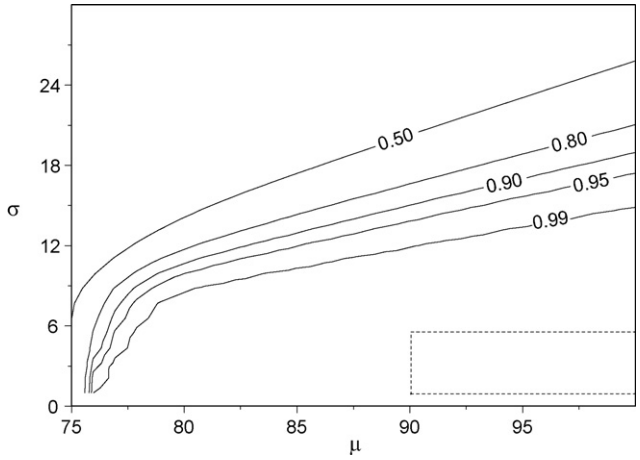

Fig. 6. The lower probability bounds of passing S_1, S_2, or S_3 criteria. Probability contours (50%, 80%, 90%, 95%, 99%) plotted as a function of population mean (μ) and standard deviation (σ). The boundaries of the box in the lower right of the plot represent the range of means and standard deviations calculated from historical data. These lower bounds are interpreted such that they provide a conservative probability assessment; i.e., each contour should be viewed as a "no less than" contour. For example, the 90% contour is actually the probability contour such that %dissolution with population mean-standard deviation pairs that fall along this curve provide *at least* 90% probability of passing S_3 dissolution criteria.

In the case of the IR tablets evaluated here, the dissolution acceptance criteria was $Q = 75\%$ at 20 min. An assessment of the probably of passing this criteria was desired in order to help show that the method and acceptance criteria provided discrimination. Fig. 2 shows representative dissolution profiles for individual tablets of this product.

Based on historical data (in this case three stability lots, each with five different package configurations at 25 °C/60% RH and 30 °C/60% RH through 12 months on stability), tablet dissolution results at 20 min were approximately normally distributed as shown in Fig. 3. This normality assumption was exploited to generate probability contours (50%, 80%, 90%, 95%, 99%) as a function of population mean and standard deviation for S_1, S_2, and S_3 as shown in Figs. 4–6, respectively. For example, the 90% contour is actually the probability contour such that percent dissolution with population mean-standard deviation pairs that fall along this curve provide *at least* 90% probability of passing at S_3. Probabilities for passing S_2 criteria were simulated (via SAS v8.2). Probabilities for passing S_1 criterion and the lower probability bounds for passing S_3 criteria were assessed by direct mathematical formulae (no simulation necessary).

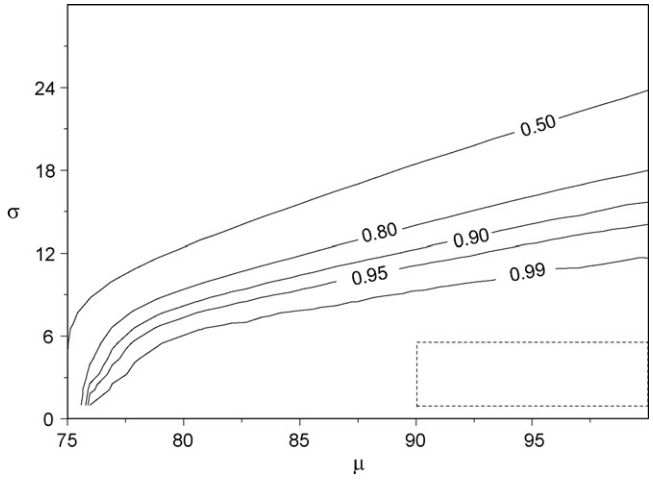

Fig. 5. Probability of passing S_2 criteria. Probability contours (50%, 80%, 90%, 95%, 99%) plotted as a function of population mean (μ) and standard deviation (σ) for S_2 based on the Monte Carlo simulation. The boundaries of the box in the lower right of the plot represent the range of means and standard deviations calculated from historical data.

The range of means and standard deviations calculated from historical data was plotted on each of the three probability contours. The box in the lower right of each of the plots in Figs. 4–6 represents this data. In Fig. 4, the box gives the range of means and standard deviations calculated from historical data. The choice of data to represent, ICH or other stability data, may depend on objectives. The contours are generated via direct mathematical formulae. Based on these data, there is at least an 80% chance of passing S_1 criteria. Fig. 5 assumes S_1 criteria were not met. The box on this plot also gives the range of means and standard deviations calculated from historical data. The contours are generated via Monte Carlo simulation. Based on these data, there is greater than 99% chance of passing S_2. Finally, Fig. 6 shows the lower probability bounds for passing the dissolution test. Again, the box is representative of historical data. These lower bounds are interpreted such that they provide a conservative probability assessment; i.e., each contour should be viewed as a "no less than" contour.

As demonstrated with this example, this model provides a straightforward approach to assessing the probably of passing acceptance criteria outlined in USP <711> *Dissolution*. As shown in Figs. 4–6, overlaying the actual data on the probably contours provides a simple visual assessment of the data.

An advantage of this method is that the probability contours are independent of dissolution data. They are dependent on the Q value and the curves shift along the x-axis based on the Q

value. Since this method, and hence the contour plots, is data independent it can readily be used for multiple projects to assess the probability of passing the various dissolution testing stages. In addition, this method can be used to assess data and help set a Q value for acceptance criteria if a certain probability of passing is desired.

4. Conclusion

A data independent statistical model was developed to calculate the probability of passing S_1, S_2, and S_3 dissolution criteria and was applied to an IR product. This model showed that the dissolution method did have discriminatory capabilities in that the probability of passing S_1 was not 100% and that the acceptance criteria were suitable. Since the model is data independent, it can be used for other products without having to run additional time-consuming simulations.

Acknowledgements

The authors would like to thank and acknowledge Amy Orce and J. Sean Space for generating a large amount of the dissolution results and Kim Vukovinsky for her help with the statistical analysis of the data.

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