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Setting Dissolution Specifications

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Introduction

Setting a specification for dissolution testing is an important part of the development of a new pharmaceutical. All drug products are required to remain within specifications registered with the regulatory agencies of the countries in which these products are sold, and they must remain so throughout their shelf life. The use of stability studies to predict potency over time is a well-established approach for setting the shelf life of a product, but a high percentage of product recalls also involve failure to remain within limits for dissolution. Using a rational, data-driven approach to setting the dissolution specification can reduce uncertainties about product quality and shelf life.

A dissolution specification can be set using tolerance limits applied to data from batches of drug product, provided these batches are drawn from clinical or stability studies used to support the new drug application. We show that statistical tolerance and confidence intervals can be used to set control limits for unit and pooled sample dissolution testing on batch data. Through simulation, we can also generate unit and pooled sample acceptance probability curves to directly set the control limits by inspection.

Guidelines

For immediate release products, a dissolution method should conform to one of the several methods currently specified for the dissolution requirement in USP 23. Certain guidelines should be followed in preparing the method and setting the specification (1). The specification "should be stated in terms of the minimum quantity of drug substance dissolved within a standard time interval;" typical specifications should range from 70% to 85% at dissolution times between 30 and 60 minutes; specifications in excess of 85% are inappropriate since allowance must be made for assay and content uniformity of the formulation. Times earlier than 30 minutes fall below typical disintegration times and should only be chosen on the basis of a particular need; times later than 60 minutes imply that the formulation is no longer of an immediate release nature. The specification should be practical to apply and efficient in terms of laboratory resource requirements; it should be an indicator of the quality of product with regard to its release properties.

Three types of specifications are distinguished when a drug article is tested: expiry, release, and control limit (2). The dissolution specification generated by our methodology is analogous to the control limit, and should fall inside the release specification. If it fell outside the release specification, there would be no clear distinction between results that are merely unusual, and those that are clearly unsatisfactory. "In such cases, a manufacturer [would] have to reject, retest, and rework batches simply because of the inherent variability of an in-control process (3)." In what follows, we present a set of simulated dissolution data, generate control limits for this data, and illustrate approaches for selecting a specification.

Demonstration Dissolution Data

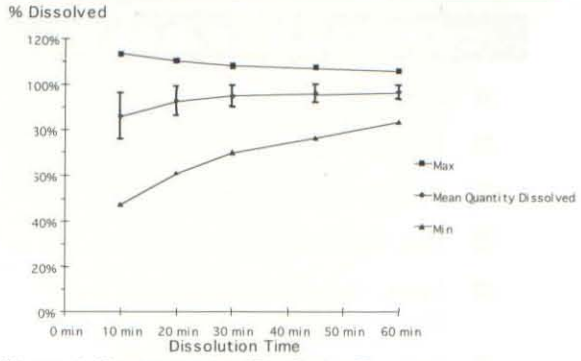

Figure 1. Demonstration Dissolution Data. Maximum observed unit result profile [Max]; minimum observed unit result profile [Min]; and average unit result profile for the entire population [Mean Quantity Dissolved] as a function of dissolution time.

Figure 1 shows dissolution data derived from the simulated observation of 250 unit results (from individual dissolution vessels) at

dissolution times of 10, 20, 30, 45 and 60 minutes. A profile of the mean quantity released for the entire population of unit results with error bars representing the standard deviation of these units is shown. Also shown are the maximum and minimum observed unit results for dissolution at each of the time points in the profile.

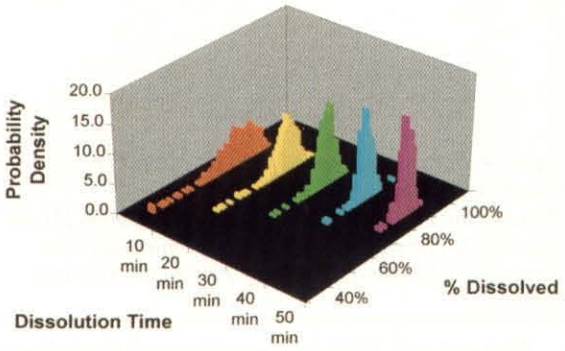

Figure 2. Demonstration Dissolution Data having a Non-Normal Distribution.

Figure 2 shows the actual observed distributions of these unit results at each time point where a small number of slow releasing units can be seen below the main body of the distributions. Although these units have little effect on the mean or standard deviation, they strongly affect the unit sample stage one acceptance probabilities. *Figure 3* shows the expected distributions of unit results if they were normally distributed with mean and standard deviation exactly the same as the observed distributions shown in *Figure 2*. Data simulated from these two types of distributions are referred to as the observed and normal data sets. In general, the distribution of observed unit result values is non-normal and skewed towards the lower range at early dissolution time points, but approaches normality at later time points.

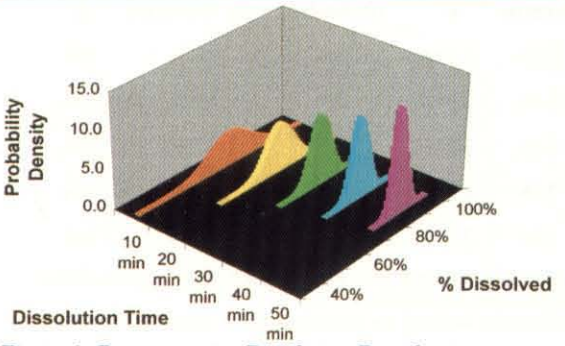

Figure 3. Demonstration Dissolution Data having a Normal Distribution.

Unit Sample Specifications

A tolerance limit on unit results is used to derive the stage one control limit for unit sample dissolution testing:

"A statistical tolerance limit furnishes a limit between, above, or below which we confidently expect to find a prescribed proportion of the individual items in a population [of observed data]."(3)

Associated with any tolerance limit is an expression of our level of confidence in its accuracy. The confidence level represents how often our method for selecting the tolerance limit (and therefore our control limit) will be accurate.

A **unit result** is defined as the release value obtained when testing a drug article in a single dissolution vessel. The **acceptance probability** for a unit result is the prescribed proportion of unit results that lie above or at the stated specification. Acceptance probabilities are also defined for the stages of the dissolution test: A

Setting Dissolution Specs... cont

stage one acceptance probability is the prescribed proportion of dissolution test results for a product that satisfy the stated USP stage one acceptance criteria, and this stage one acceptance probability can be expressed in terms of the unit acceptance probability for stage one (Equation 1). Similarly, acceptance probabilities can be determined for stages two and three using Monte Carlo simulation.

To set a control limit for this data using a tolerance limit approach, we only consider stage one, where six units are tested and each unit must not be less than five percent above the specification (Q). The probability of stage one acceptance (P) is the product of the six unit acceptance probabilities (p) since each unit result is an independent observation (4):

$$P = p^6 \quad (1)$$

To set a specification that will result in the acceptance of stage one of the test 95% of the time for a given data set, the unit acceptance probability must be 99.14%:

$$p = \sqrt[6]{P} = \sqrt[6]{0.95} = 0.9914 \quad (2)$$

Once the required unit acceptance probability has been determined, a control limit can be derived using a parametric or nonparametric approach.

Parametric Approach:

We select the desired unit acceptance probability (99%[1]) and level of confidence (γ=95%). Knowing the size of the data set at each time point, we consult a table that lists values for a factor (k) by which we multiply the standard deviation of the release values(s). We subtract this product from the mean release ($\bar{x}$), and arrive at a tolerance limit, which is five percent above the control limit for Q:

$$Q + 5\% = \bar{x} - k \cdot s \quad (3)$$

where k is tabulated as a function of p, γ, and n observations.

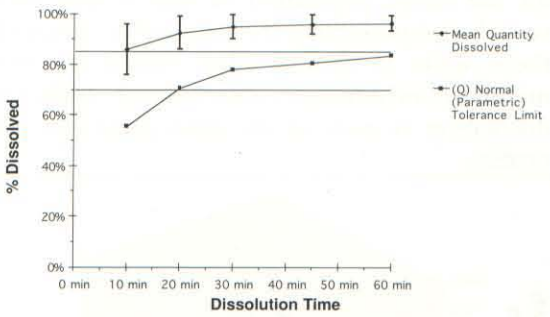

Figure 4. Parametric Control limit for Normally Distributed Data.
Average unit result profile for the entire population [Mean Quantity Dissolved] and control limit profile based on a parametric tolerance interval [(Q) Parametric Tolerance Limit].

Figure 4 and *Table 1* (parametric column) show the control limits obtained using the equation for each time point in the dissolution profile. Setting a specification above these limits would result in an unacceptable rate of batch rejection due to the inherent variability in the manufacturing and testing of the product. Considering this, and applying USP guidelines, we set specifications of 75% and 80% at 30 and 45 minutes respectively.

Table 1. Stage One Parametric Specifications for Unit Sample Dissolution Testing

Time Point	Mean Release	Standard Deviation	k[a]	Control Limit (Parametric)	Control Limit (by Simulation)	Stage 1 Q[b]
10 min	85.9%	10.0%	2.549	56%	57%	55%
20 min	92.4%	6.6%	2.549	71%	72%	70%
30 min	94.7%	4.6%	2.549	78%	78%	75%
45 min	95.7%	3.9%	2.549	81%	81%	80%
60 min	96.2%	2.9%	2.549	84%	84%	80%

[a] Factor for a 99% (γ = 95%) One Sided Tolerance Limit from Table A-7 (Factors for One-Sided Tolerance Limits for Normal Distributions) in reference 3.
[b] Release specification is established by selecting the nearest pentad of release specifications below the control limit.

Nonparametric Approach:

The preceding method for selecting specifications assumes that the data are normally distributed at each time point. Where this assumption is not correct, we must use a nonparametric approach in determining the

[1] 99% is approximately 99.14% for the purpose of looking up tabulated values of the confidence limit.

control limit. From the preceding discussion, the unit acceptance probability must be 99.14%. To apply the nonparametric approach, we order the unit result values from smallest to highest and select the m^{th} smallest value based on a table for one-sided distribution-free tolerance limits (3). The number (m) is tabulated as a function of unit acceptance probability (p=99%), level of confidence (γ=90%), and the number of observed release values (n). The control limit for *Q* is then set five percent below the tolerance limit as before.

In determining the value for m, we must use a level of confidence of 90% because 250 observations is insufficient for a 95% level of confidence using this table. So the control limit is higher than it would be, were we able to use a 95% level of confidence. The table requires us to select the smallest value in the range, so the control limit parallels the lower boundary of observed release values in the dissolution profile *(Figure 5)*. According to guidelines, we set specifications of 70% and 75% at 45 and 60 minutes respectively *(Table 2)*.

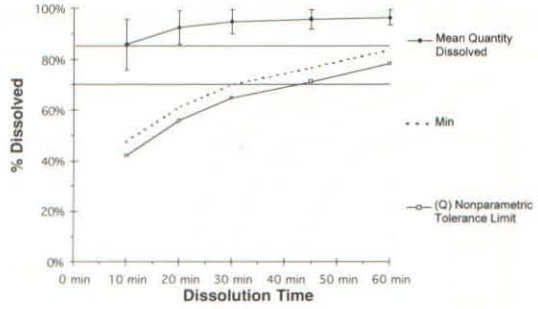

Figure 5. Nonparametric Control limit for the Observed Data Distribution
Minimum observed unit result profile [Min] and control limit profile based on a nonparametric tolerance interval [(Q) Nonparametric Tolerance Limit].

Comparison of the Parametric and Nonparametric Specifications:

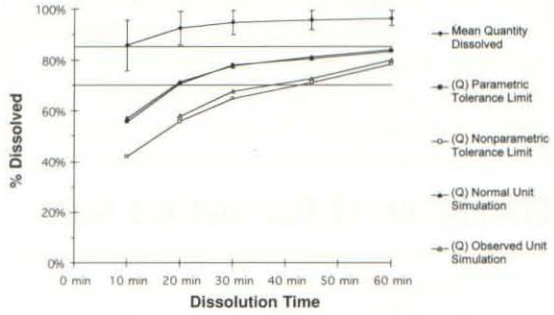

Figure 6. Comparison of Control limits for Unit Sample Testing.
Unit sample parametric and nonparametric limits compared with control limits derived by simulation. Simulated normal data [(Q) Normal Unit Simulation] and simulated observed data [(Q) Observed Unit Simulation].

Figure 6 compares the two control limits for *Q* and reveals that that the nonparametric limit is lower than the parametric limit at each time point. They differ most in the early stages of dissolution, but begin to converge at later sampling times. The nonparametric control limit is more conservative since it requires no assumptions about the distribution of data. By simulating the dissolution test as described in the next section, we will identify which approach yields the "best" control limit for these data.

Table 2. Stage One Nonparametric Specifications for Unit Sample Dissolution Testing

Time Point	m[a]	mth Smallest Release Value	Control Limit (Nonparametric)	Control Limit (by Simulation)	Stage 1 *Q*
10 min	1	47.2%	42%	- 6b	40%
20 min	1	60.8%	56%	58%	55%
30 min	1	69.8%	65%	68%	65%
45 min	1	76.3%	71%	72%	70%
60 min	1	83.4%	78%	81%	75%7c

[a] Value of m such that at least 99% (γ = 90%) of the unit results lie above the m^{th} smallest value in the population of unit results. Taken from Table A-31 (Tables for Distribution-Free Tolerance Limits [One-Sided]) in reference 3.
[b] Generation of acceptance probabilities below 50% by simulation was not performed.
[c] *Q* = 80% using the acceptance probability generated by simulation.

Simulated Dissolution Testing

I developed a computer program for simulating the USP dissolution test given a population of unit results having an arbitrary statistical distribution. The simulation approach is briefly described in our recent evaluation of the test acceptance sampling

Setting Dissolution Specs... cont

procedure for pooled samples (6), and is an application of the well-known statistical computing technique of "Monte Carlo" simulation (7).

A simulated dissolution unit result is created from a mathematical model of the dissolution testing procedure. The model uses random variables, representing dissolution unit results, as input, and generates acceptance probabilities as a function of specification. Using the dissolution simulator, we can compute the probability that the dissolution test will be accepted based on the observed distribution of release data, and we can predict the acceptance rate at each stage in the test.

Simulation of Parametric Data

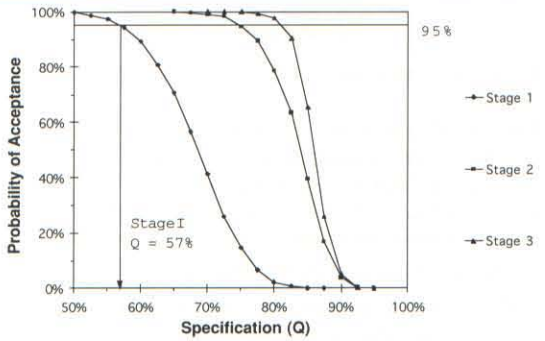

Figure 7. Acceptance Probabilities at 10 Minutes. Stage one acceptance probabilities [Stage 1]; Stage two acceptance probabilities [Stage 2]; and Stage three acceptance probabilities [Stage 3] as a function of specification.

Figure 7 shows the acceptance probabilities at 10 minutes for each of the three stages of the dissolution test under the assumption that these data are normally distributed. Setting a specification that yields a 95% acceptance probability for stage one is accomplished by drawing a horizontal line at 95% on the acceptance probability axis and dropping a vertical line from the point of intersection with the stage one acceptance curve to the specification axis. This specifies a control limit of 57% in 10 minutes for normally distributed data. We only consider stage one in setting the control limit since it is the first curve intersected. Applying this procedure to the acceptance probability curves for the other time points shown in *Figure 8* yields the control limits shown in *Figure 6* (Normal Unit Simulation) and *Table 1*. Comparing the parametric control limits with the limits derived by simulation reveals that the

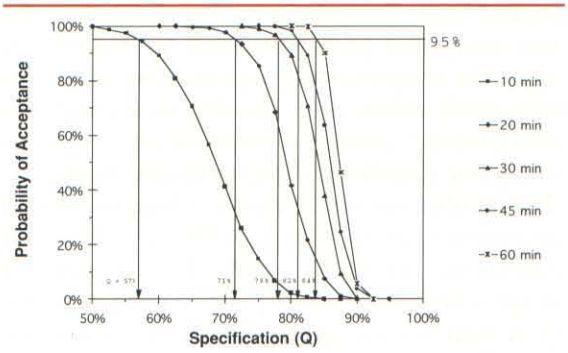

Figure 8. Stage One Acceptance Probabilities for Normally Distributed Data. Stage one acceptance probabilities as a function of specification for the 10, 20, 30, 45 and 60 minute dissolution sampling times.

two methods generate specifications that are in close agreement for this demonstration data set.

Simulation of Nonparametric Data

The stage one probability of acceptance curves for data having the nonparametric

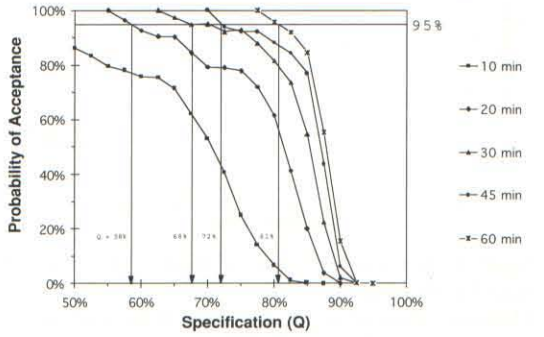

Figure 9. Stage One Acceptance Probabilities for the Observed Data Distribution.

observed distribution are shown in *Figure 9*. On the left, these curves are significantly lower than the corresponding curves for normally distributed data; this is entirely due to the presence of a small population (1% to 3%) of slow releasing dosage forms.

Overlaying the 95% specification line and dropping vertical lines from the intersections with the stage one curves yields the control limits shown in *Figure 6* (Observed Unit Simulation) and *Table 2*. Comparing these limits with the nonparametric control limits in the figure reveals a close concordance that supports the use of the nonparametric tolerance limit in setting control limits for this data.

Strategy for Setting Unit Sample Specifications

Figure 6 summarizes all control limits for unit sample dissolution testing. For this data, there is a strong concordance between the use of the parametric tolerance limit to set a control limit and simulation of the dissolution test under the assumption that the data is normally distributed. Likewise, there is a strong concordance between the use of the non-parametric tolerance limit to set a control limit and simulation of the dissolution test using the observed data distribution. Even though the deviation of this data from normality is modest, the results of simulation support the use of a nonparametric approach for setting the dissolution control limit.

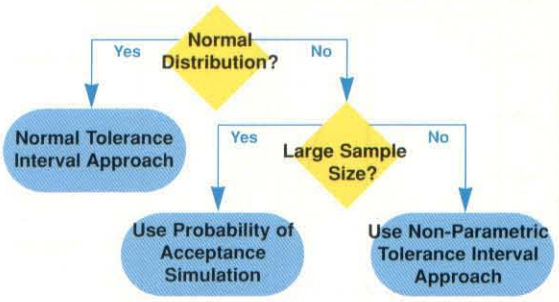

Figure 10. Which Approach to Take?

We therefore recommend the following strategy for setting a specification *(Figure 10)*: First determine whether or not you have normally distributed data. If the data are normally distributed, you may use the normal tolerance limit approach to derive a control limit. If the distribution is unknown or non-normal, then you cannot use a normal tolerance interval; the control limit will be set higher than it should be, and a larger than expected number of stage one failures will occur.

If the data are non-normal, determine if you have an observation set large enough to use the dissolution simulation approach. We recommend at least 200 unit result observations for data sets with moderate variability (<5%). If you have less data, you should use the nonparametric tolerance limit approach. This approach will result in the setting of a more accurate control limit, but will require more data than the parametric approach to increase the level of confidence. If your data set is fairly small, you may not be able to use confidence levels much above 70%.

Pooled Sample Specifications

The pooled sample dissolution test requires that unit samples be pooled before analysis, where the action of mixing the samples averages the unit results. The pool is analyzed and the test is staged according to the pooled sample acceptance table (5); the acceptance criteria are applied only to the pooled test results.

We use a confidence limit on unit results from the dissolution data to set a control limit for Stage 1 of the test (3):

> "A statistical confidence limit furnishes a range which will include, with prescribed confidence, the **true average** of the individual items in a set of data values"

As with the tolerance limit, the confidence limit has an associated expression of our confidence in its accuracy. This confidence level represents how often our method for selecting the confidence limit (and therefore our control limit) will be accurate.

Setting Dissolution Specs... cont

Confidence Limit Approach:

We select the desired level of confidence (γ = 95%) and consult a table of cumulative normal distribution values (z_p). The product of z_p with the standard error for the mean of six test units is subtracted from the population mean to arrive at a confidence limit, which is ten percent above the control limit for Q at stage one:

$$Q + 10\% = \overline{X} - z_p \cdot \frac{s}{\sqrt{6}} \quad (4)$$

Where:

$z_p \equiv z_{1-\alpha} = 1.645$ for $\gamma = 100 \times (1 - \alpha)\% = 95\%$ where:

$\alpha \equiv$ Level of Significance (0.05)

$\gamma \equiv$ Level of Confidence (95%)

s = Population Standard Deviation

$\overline{X} \equiv$ Population Mean

We use z_p instead of t_p (Student's t) since we are employing the observed mean, X, and standard deviation, s, of the entire population of unit results. For n = 250 these values are very good estimates for μ and σ, the actual mean and standard deviation of the observed data. Using z_p generally results in tighter confidence limits, and therefore higher control limits (3).

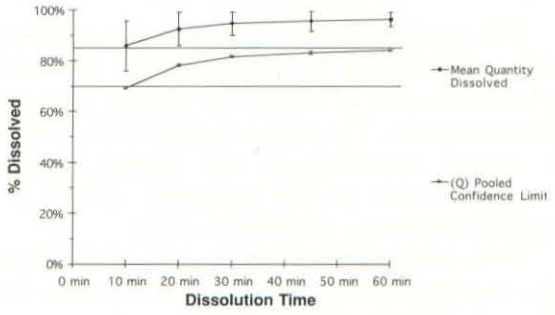

Figure 11. Control limits Based on the Confidence Limit Average unit result profile for the entire population [Mean Quantity Dissolved] and control limit profile based on the confidence limit [(Q) Pooled Confidence Limit].

Figure 11 and *Table 3* show the control limits determined from the lower confidence limit on the mean of unit results. Using the guidelines discussed above, specifications can be set at 75% and 80% for 30 and 45 minutes respectively. In contrast to the unit sample discussion of tolerance limits, there is no need to use a distribution free approach for setting a nonparametric control limit based on the confidence limit. From the central limit theorem, the distribution of the mean is approximately normal for moderately large sample sizes or data sets with minor departures from normality (3).

Simulation of Pooled Sample Dissolution:

I developed and implemented a model for simulating pooled sample dissolution using the Monte Carlo methodology described for simulation of unit sample dissolution testing. We used this model to generate stage one acceptance probability curves for the normal and observed

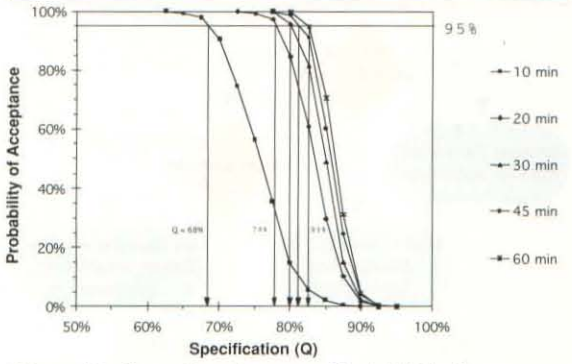

Figure 12. Stage One Acceptance Probabilities for Normally Distributed Data

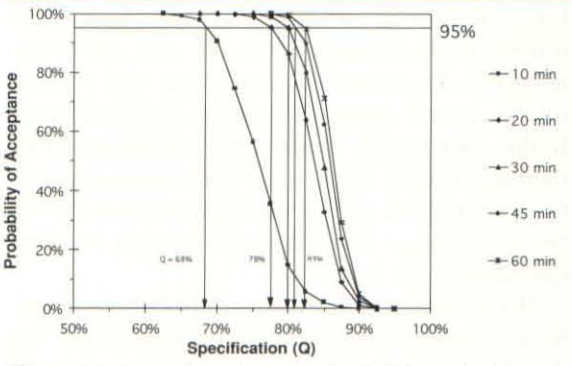

Figure 13. Stage One Acceptance Probabilities for the Observed Data Distribution

data sets shown in *Figures 12* and *13*. Applying the same procedure used for simulated unit sample testing, we determined and tabulated *(Table 3)* control limits at each time point. These control limits are shown for the normal and observed data sets in *Figure 14*.

Table 3. Stage One Specifications for Pooled Sample Dissolution Testing

Time Point	Mean Release	Standard Deviation	Zp[a]	Observed Data Control Limit (Confidence)	Normal Data Control Limit (Simulation)	Observed Data Control Limit (Simulation)	Stage 1 Q
10 min	85.9%	10.0%	1.645	69%	68%	68%	65%
20 min	92.4%	6.6%	1.645	78%	78%	78%	75%
30 min	94.7%	4.6%	1.645	82%	78%	80%	80%
45 min	95.7%	3.9%	1.645	83%	80%	81%	80%
60 min	96.2%	2.9%	1.645	84%	83%	83%	80%

[a] Standard Normal Variable for a 95% (γ = 95%) One-Sided Confidence Limit from Table A-2 (Cumulative Normal Distribution—Values of z_p) in reference 3.

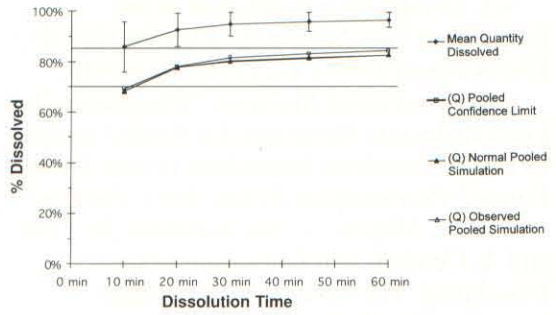

Figure 14. Comparison of Control limits for Pooled Sample Testing
Comparison of control limits based on the confidence limit with limits based on simulation of normal [(Q) Normal Pooled Simulation] and observed data [(Q) Observed Pooled Simulation].

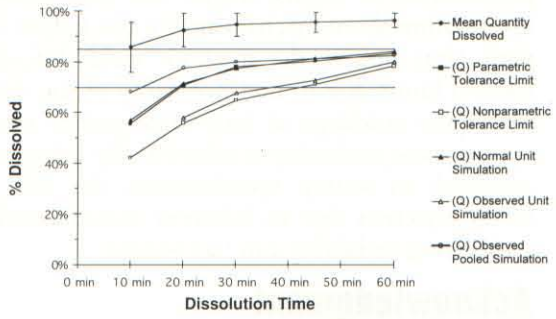

Figure 15. Comparison of Control limits for Unit and Pooled Sample Testing

Comparing the three control limits in *Figure 14* and *Table 3* reveals that the confidence band approach yields a similar but slightly higher control limit at all time points. Control limits derived from simulation of normal or observed data are practically identical; the shape of the distribution of dissolution results is unimportant since acceptance criteria are based on average results only.

Discussion

Unit Sample versus Pooled Sample Testing:

Figure 15 summarizes the control limits obtained for unit sample and pooled dissolution testing of the simulated dissolution data set. For unit sample testing, control limits based on normal or distribution-free tolerance limit are markedly different at early time points; at later time points, the control limits converge. Dissolution simulation shows that the distribution-free control limits are more realistic than those derived under the assumption that data are normally distributed. Pooled sample control limits are much higher than those found for unit sample testing, and we conclude that less stage one testing failures would be observed using this approach.

The unit sample dissolution test is very sensitive to the presence of "slow" releasing dosage forms at stage one whereas the pooled sampling technique is insensitive by design. The unit sample test should be used if their detection is important to the quality of product.

Simulated Dissolution:

The simulation approach is limited by the need to collect enough data to adequately determine the form of the distribution, but it has the advantage of being able to model data with complex behavior, (e.g. multiple sources of variation). Since it is difficult to define test acceptance in closed form for higher stages, the development of specifications for these stages requires that dissolution be simulated, and full simulation of the dissolution test yields the

Setting Dissolution Specs... cont

relative proportions of tests expected to pass at stages one, two, and three. This allows one to forecast the actual number of test failures expected not only at the stage one control limit, but at higher stages as well.

Conclusion

In summary, we have shown that you may use a tolerance limit on unit results to set a stage one control limit for unit sample dissolution testing, and a confidence limit on unit results to set a control limit for pooled sample testing. Simulation can be used to predict acceptance probabilities at higher stages, and can provide information about mechanisms for test failure. At early time points, the methods yield different control limits due to non-normality of the data; the limits converge at later time points when approximate normality is achieved. By using our approach to setting specifications, the risk of batch rejection due to inherent manufacturing and testing variability can be reduced.

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