The AAPS Journal (2019) 21: 36
DOI: 10.1208/s12248-019-0308-z

Research Article

Dissolution Edge Charts for Immediate Release Products and Their Applications: a Simulation Study to Aid the Setting of Specifications

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Received 27 November 2018; accepted 19 February 2019; published online 5 March 2019

Abstract. One of the most commonly used methods to establish the clinical relevance of dissolution is to align the dissolution specifications with pivotal clinical batches. The objective of the study was to create edge charts for the dissolution of immediate release (IR) drug products to quantitatively establish the bases for setting clinically relevant and discriminating dissolution specifications and to clarify which stage in the US Pharmacopoeia (USP) <711> acceptance tables should be targeted. The simulations of dissolution data were performed on a batch of IR products with 1,000,000 units. The desired acceptance criterion was $Q = 80\%$ of the label claim at 30 min. A total of 110 scenarios for IR data were generated, which included various combinations of two determinants: the batch mean and SD (standard deviation). For each scenario, the dissolution data were tested based on USP three-stage procedures to determine the pass/fail at each stage. This process was repeated 10,000 times. The failure rate at each stage for each scenario was calculated as the percentage of failed replicates across 10,000 trials. Contour plots, named edge charts, were created to demonstrate the relationship between the dissolution failure rates and the two determinants (mean and SD). The edge lines represent the failure rates for the given combinations of the mean and SD. The edge charts can provide a quantitative estimate based on the observed dissolution data and provide fundamental support for recommendations on using USP stage 2 as a target for setting the acceptance limit(s).

KEY WORDS: dissolution; dissolution specification; edge charts; simulation.

INTRODUCTION

Given its special characteristics and unique role, the drug dissolution test stands out among other quality indices in drug development and product quality control. It gets right at the heart of the equation between the *in vitro* release and the *in vivo* absorption, while being an independent test in the quality control package for evaluating the performance of solid oral dosage forms. Its importance has been generally recognized (1–7).

Underlying this quality index is the concept that the solid oral dosage forms directed to the systemic circulation must dissolve in the gastrointestinal (GI) tract prior to absorption. Due to this underlying concept, an indispensable feature for dissolution testing is its clinical relevance. Clinical relevance requires establishing *in vitro* acceptance criteria for dissolution, which controls against changes in product attributes that could influence *in vivo* performance, i.e., establishing an *in vitro*/*in vivo* correlation (IVIVC) or an *in vitro*/*in vivo* relationship (IVIVR). In fact, a dissolution test with demonstrated predictability for *in vivo* performance can be used to request a waiver of bioavailability/bioequivalence studies from regulatory authorities, thus significantly reducing development time and costs by avoiding lengthy and expensive clinical trials (1,3). Pharmaceutical scientists must understand the clinical relevance of dissolution and IVIVC or IVIVR to efficiently develop robust dosage forms and ensure that drug products consistently meet critical performance criteria. The IVIVR is most simply built by alignment of acceptance criteria against testing results obtained on materials used in pivotal safety and efficacy clinical trials (8). To obtain an appropriate alignment, setting dissolution specifications for product quality control is a key element.

In several surveys conducted recently, dissolution specifications were used as an evaluation tool and an important criterion to compare and differentiate the generic versions of products on the market, such as diclofenac sodium sustained release tablets (9), quinine sulfate tablets (10), albendazole (ABZ), mebendazole (MBZ), praziquantel (PZQ) (11), and levodopa/benserazide hydrochloride combination (12). In a study to compare different generic versions of clarithromycin on the market, a considerable number of the products tested fell short of the drug content and approximately one third of the generic products tested released less drug in 30 min

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compared with innovator tablets. However, the majority of these generic products met the dissolution specification (13), indicating that the dissolution specifications might not have adequate discriminating ability, and are not able to differentiate the low-quality product from the qualified product.

Although significant progress has been made since 1970, when the first compendial dissolution test (USP Apparatus 1) was introduced, appropriately setting dissolution specification to have adequate discriminating ability remains a practical issue and occasionally represents a challenge. One of the reasons for the inappropriateness may be attributed to the fact that there have been misunderstandings and/or confusions in the practices of setting dissolution specifications.

The US Pharmacopoeia (USP) provides a three-step procedure to determine whether the dissolution testing of a product batch meets the acceptance criteria. The Acceptance Table 1 in the USP general chapter <711> provides a three-stage approach for dissolution compliance for a product of IR solid dosage form. The dissolution limit required to be dissolved at a specified timepoint in terms of a specific percentage Q is based on the requirements in the individual USP monograph. The three-stage testing procedure is summarized in a flowchart, as shown in Fig. 1.

Figure 2 illustrates the three-stage dissolution testing procedure in a hypothetical case for a batch of IR products with a specification of $Q = 80\%$ at 30 min. The blue solid circles represent the dissolution values for individual units at 30 min, and the red triangles are the sample means. This batch does not pass stage 1, which requires each of the 6 units involved in stage $1 \geq 85\%$ ($Q + 5\%$, the green dashed horizontal line across stage 1). Thus, stage 2 testing is conducted with an additional 6 units. The batch does not pass stage 2 either due to the following two reasons: (1) the sample mean of the 12 units involved in stage 2 is $< 80\%$ (Q, the solid horizontal line across 3 stages) and (2) there is a unit $< 65\%$ ($Q - 15\%$, the dashed horizontal line across stages 2 and 3). Therefore, a stage 3 testing is needed with an additional 12 units. The batch passes stage 3 based on (1) the mean of a total of 24 units being $> 80\%$ (Q) and (2) no more than 2 units being $< 65\%$ ($Q - 15\%$), and (3) there is no unit $< 55\%$ ($Q - 25\%$, the dashed horizontal line across stage 3).

Although the three-step passing rule is applicable to determine whether the dissolutions pass or fail the acceptance criteria, it should also be considered when the dissolution acceptance criteria are set. The practices in considering these rules vary. Intuitively, targeting at stage 1 appears to be a natural choice with the intension for the product to pass the acceptance criteria on the first attempt. Whether this practice can appropriately control the product quality remains a question, which was the objective of the current study. Graphs named edge charts were developed to help appropriately set dissolution specifications.

Please note that dissolution specifications typically include two parts: the dissolution methodology/conditions and the acceptance criteria. Although this article is intended to concentrate on the acceptance criteria, the term specification is loosely used.

METHODS

To create edge charts and investigate which USP stage should be targeted when the dissolution specifications are set, dissolution testing through the three stages of USP <711> for IR dosage forms was mimicked. The general strategy was as follows: (1) generating batches, each having one million units (e.g., tablets, capsules, etc.) with different dissolution behaviors; (2) testing these batches with the three-stage procedures; and (3) comparing the ease of pass (failure rates) among these batches at different stages.

When the dissolution data were generated, two major influencing factors were considered: (1) the batch mean of the dissolution at a selected timepoint and (2) the variability at that timepoint expressed as standard deviation (SD) with the assumption that batches having similar dissolution means and SDs would behave similarly *in vivo*. Within a batch, the dissolution data were assumed to follow a normal distribution among the individual units based on the mean and SD using a function in the form of "rnorm(n, mean, sd)" in the R software.

For the IR solid oral dosage product, the desired acceptance criterion was set as $Q = 80\%$ of the label claim at a certain timepoint (e.g., 30 min). According to the three-stage procedure, a prespecified number of units was selected from the one-million-unit batch at each stage as outlined in Fig. 1. A total of 110 scenarios were examined, which included batches with various combinations of dissolution mean and SD values. The mean of the dissolution of the one million units in a batch varied from 79 to 89% of the label claim with a 1% increment (11 levels). For each level of the means, the SD varied from 1 to 10% of the label claim with a 1% increment (10 levels) as shown in Table I. For each of the 110 scenarios, 10,000 replicates were simulated based on the three-stage procedure. The failure rate at each stage for each scenario was calculated as the percentage of failed replicates in the 10,000 trials.

A contour plot, named edge chart, was generated for each stage to demonstrate the relationship between the failure rates and the two determinants (dissolution mean and SD).

Additional analyses were performed to categorize the reasons for failures. For each stage, the failure rates due to different reasons were compared with the total failure rates.

At stage 2 of the dissolution testing for products of IR dosage forms, the failures due to the mean less than Q and those due to individual units less than 65% (Q – 15%) were analyzed and plotted separately. At stage 3, the failures due to the mean less than Q, those due to individual units less than 65% (Q – 15%) and those due to individual units less than 55% (Q – 25%) were separately analyzed.

The simulations and analyses were implemented by several customized functions in R software (14) (version 3.4.0). In addition to the base R, packages of stats, grid, lattice, and latticeExtra (15) were used.

RESULTS

The edge charts created are presented in Fig. 3. As expected, the failure rate is dependent on the mean and SD values. The contour lines represent the failure rates (the edges) at given combinations of the mean and SD values. We define these contour lines as edge lines.

As shown in the edge charts, for an IR product batch to have 95% chance (5% failure rate) to pass stage 1, the mean dissolution value of this batch must be at least 88% with very low SD (less than 0.5%). If the SD is higher than 0.5%, the mean value must be at least 90% (left panel in Fig. 3).

Alternatively, if the mean dissolution value is 81%, the product batch will have 95% chance to pass stage 2 when the

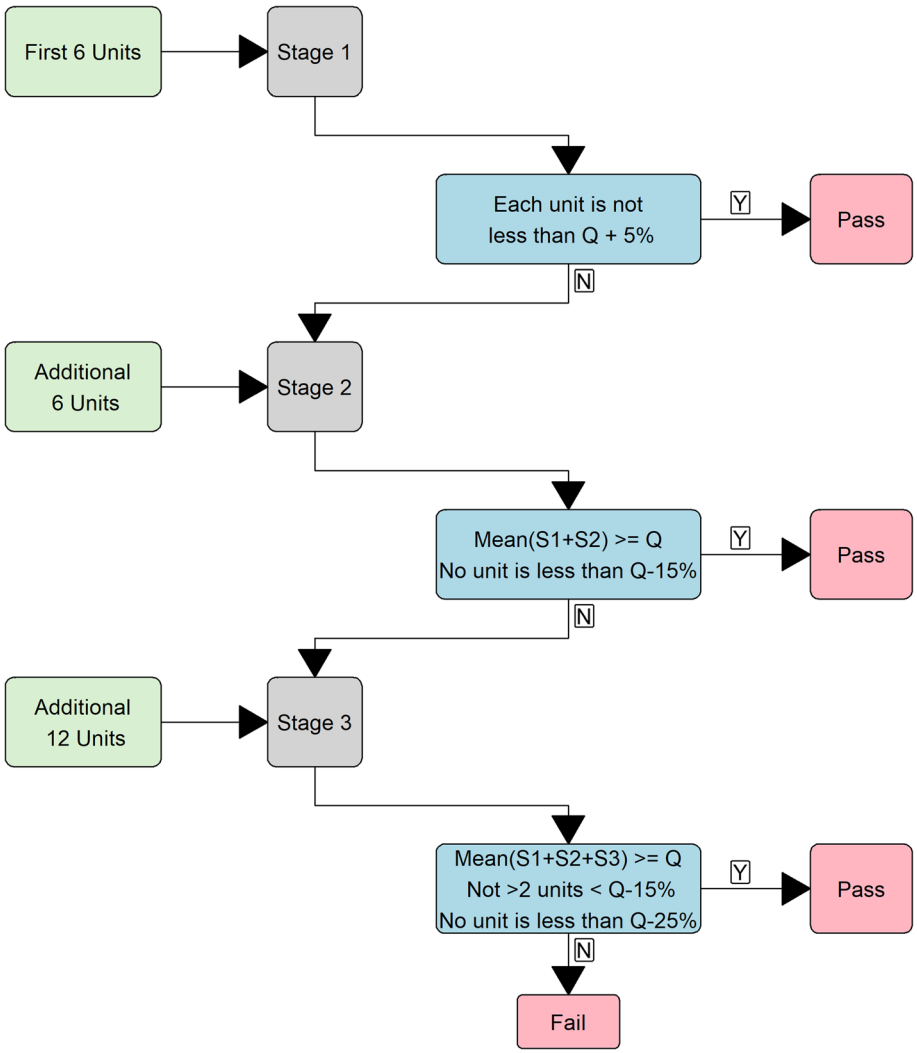

Fig. 1. A flowchart based on USP <711> Table 1 Acceptance table for immediate release dosage forms

SD was less than 2%. Even when the SD increases to 6% (approximately 7% CV), the batch will have 95% chance to pass stage 2 if the dissolution mean value is > 83% (middle panel in Fig. 3).

Therefore, it is apparent that passing stage 2 is much easier than passing stage 1. By similar comparisons, passing stage 3 is easier than passing stage 2, but the difference is not as dramatic as that between stage 2 and stage 1.

Figure 4 further identifies the edge lines due to different reasons in stages 2 and 3 for the products of IR dosage forms.

The edge lines for the failure rates due to mean values (less than Q 80%) are more vertical (panels b and e in Fig. 4) due to obvious reason: failures are mainly caused by the mean out of range. The edge lines around 50% failure rates are perpendicular to the x-axis, indicating that these failure rates are independent of SD. When the failure rate deviates from 50%, the edge line begins to have some dependence on the SD. Interestingly, the dependences of the edge lines for lower and higher failure rates progress in different directions, showing a stellated shape. The edge lines for the lower failure rates, such as those for 30% or lower, lean toward the right. This finding implies that if SD increases, the mean also has to increase to maintain the same low failure rate. However, the edge lines for the failure rates higher than 50%, such as the 80% edge line, lean toward the left. These results indicate that variability promotes failures, i.e., when SD increases, a high failure rate can be achieved even though the mean is slightly lower. In addition to the stellated characteristics, also note that the edge lines are squeezed together when the SD is low (< 2% at stage 2 and < 3% at stage 3), implying the failure rate is very sensitive to the mean. A small difference of the mean could produce a significant difference in failure rate. This is also true for the edge charts of total failure rates (Fig. 3). We define this region enclosed by the mean values of 79–81% and SD values of 0–2% (for stage 2) as "sensitive zone."

On the other hand, the edge lines for failure rates due to individual units out of limits are more horizontal (the panels c and f in Fig. 4), indicating these failures are mainly attributed by the variability (SD). However, the means also make certain contributions. In contrast to those failures due to means, these edge lines are almost parallel between different failure rates.

It is interesting to note that these two types of edge lines (for failure rates either due to mean values or due to individual units) are more linear (panels b, e, c, f, and g in

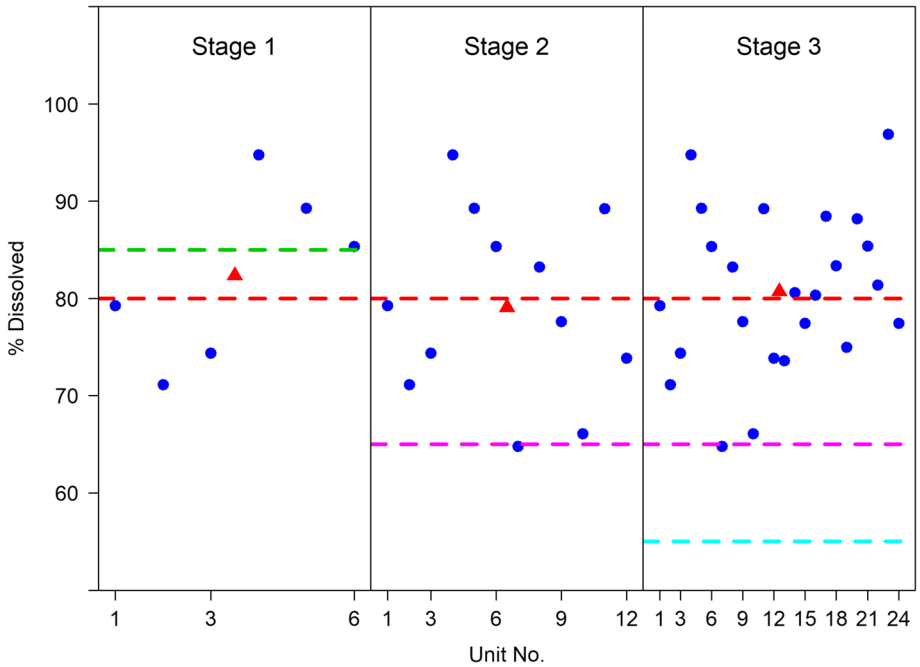

Fig. 2. A hypothetical case of three-stage dissolution testing for an immediate release product (for illustration)

Fig. 4) compared with those for total failure rates (panels a and d in Fig. 4). This linearity indicates that for the same failure rate, the contributions from the mean and the SD are constantly weighted, i.e., to compensate the increase of failure caused by variability (SD) increase, the required increase of mean is constant. For the edge lines due to the mean, this constancy is dependent on the failure rate, i.e., different edge lines have different slopes. For the edge lines due to individual units, the constant contributions are for all lines, regardless of the failure rates.

These two types of linear edge lines contribute to the syntheses of the edge lines representing the total failure rates for stages 2 and 3, which are more curved edge lines.

Of note, the edge lines for stage 1 (Fig. 3) are basically linear and the relative contributions from the mean and SD are dependent on the failure rates, as manifested by different slopes. The higher the failure rates, the steeper the slopes and the more the contribution from the mean. For lower failure rates, the lines are flatter, and the variability (SD) contributes more.

DISCUSSION

The Target Stage for Setting Dissolution Specification

One of the reasons for the stepwise USP dissolution passing rules is to offer the qualified product more opportunities to pass the acceptance limit(s). In the decision to pass/fail, "chance" plays an important role for a very small sample size of 6 (or 12, even 24) units out of one million or more. It is critical to note that this "chance" may reject the qualified product and pass the unqualified products, while the desired situation is to pass the qualified and reject the unqualified product batches. In this regard, the practice of setting acceptance limit(s) should involve every effort to create balance between providing the qualified product more opportunities to pass and rejecting low-quality products. Generally, among the broad spectrum, there is an optimum for the balance such as an edge separating the two sides. It is worthwhile to find this cutting edge when setting the acceptance limit(s).

To do so, it is important to choose the stage of the passing rule to target. In many regulatory submissions, it was deemed a quality problem if a production batch was not able to meet USP stage 1. Thus, USP stage 1 was thought to be the target for setting dissolution specifications. Targeting stage 1 is a natural (but incorrect) attempt, which is instigated by a misunderstanding or confusion regarding the three-step dissolution passing rules. It is necessary to make clarification and resolve the confusion.

The best way to clarify is to present quantitative evidence. The current study created the edge charts through surveying various scenarios in the three-step dissolution testing and recognizing overall patterns among the three steps to obtain insight into dissolution testing and its specification setting. The study also characterized the dissolution failure patterns attributed to different reasons within each step. These efforts provided quantitative bases for the

Table I. Simulation scenarios

Dosage form	Total units	Target specifications	Levels of mean (%)	Levels of SD (%)
IR	1,000,000	$Q = 80\%$ at 30 min	79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89	1, 2, 3, 4, 5, 6, 7, 8, 9, 10

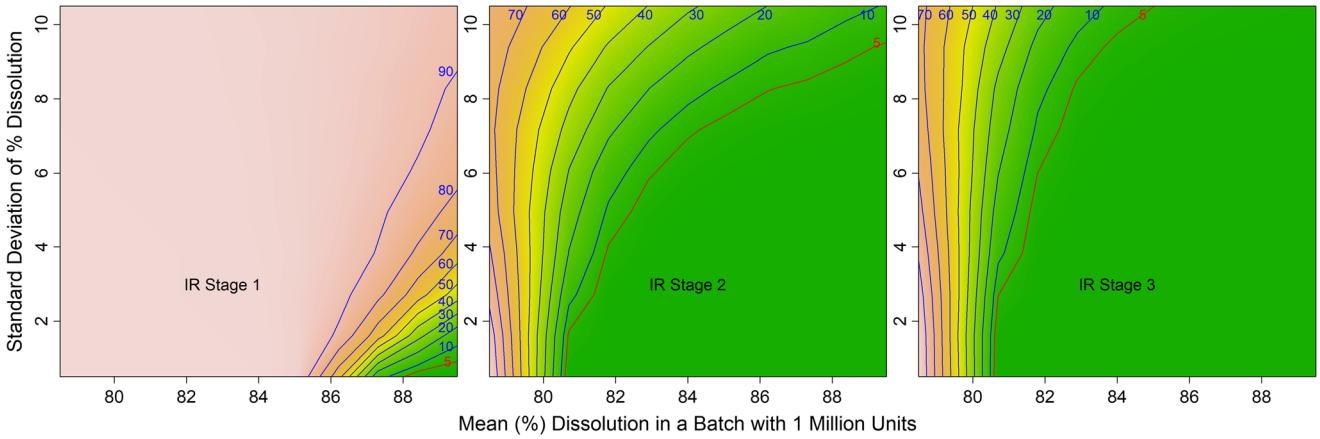

Fig. 3. The edge charts showing the influences of the dissolution sample mean and standard deviation (SD) on the failure rates at three stages of dissolution testing for a batch of an IR product with a specification of $Q = 80\%$ at 30 min. The edge lines represent the failure rates at certain combinations of two determinants: batch means and SD

selection of the target stage to set the dissolution acceptance limit(s) for products of IR dosage form.

Based on the edge charts, a significant difference in passing the acceptance limit(s) exists between stage 1 and stage 2. Due to the difference, if the acceptance limit(s) were set based on stage 1, the resulted specifications would be inappropriate. Figure 5 uses an IR tablet product as an example to illustrate two case scenarios: one using stage 1 and another using stage 2 as the target to set dissolution specifications. The data for the three batches involved in this example are listed in Table II. The example indicates that the specification based on stage 2 is more appropriate since it is likely to pass the qualified but reject the unqualified product batches. The practice targeting of stage 1 would result in acceptance limits that could provide an additional source of variability to the patient under the clinical setting, since such specifications would allow the release of batches into the market with significantly different release characteristics. It would also reward the manufacturers with poor process controls. The following question may arise: now that it is better to target stage 2 than stage 1, would it be even better to target stage 3? Again, the principle for setting specifications is to offer more opportunities to the qualified product and reject the unqualified product. When the specifications are set based on stage 3, although the unqualified products may be rejected more efficiently, the probability to reject the qualified products is increased.

The findings in this study are consistent with the current practice of the regulatory agency (FDA), who usually recommends, "Base the dissolution acceptance criteria on average *in vitro* multi-point dissolution data for each batch/lot under study, equivalent to USP Stage 2 testing (n=12)." (cited from a recent communication with the Agency). The results of current study provide a quantitative support for the recommendation.

Applications of Edge Charts

Beyond the intuitive fairness of the edge charts, their practical values are more prominent. As the example in Fig. 5 shows, edge charts can help to appropriately select the specification timepoint and set the acceptance criterion. The 5% failure rate edge line in stage 2 (middle panel in Fig. 3) provides a quantitative base and serves as the guideline for selecting specification timepoint(s) and acceptance limit(s) according to the observed mean and SD data. Familiarity with these edge lines will be helpful for setting the appropriate dissolution specifications.

Before outlining the general applications of the edge charts, it is beneficial to review the important principles related to the application. *Clinical Relevance.* Clinical relevance requires establishing IVIVC or IVIVR. In most cases, the relationship is simply built by alignment with the pivotal clinical batches. When using the edge charts to select the timepoint(s) and acceptance limit(s), the clinical batches, which demonstrated the efficacy and safety of the drug product, must be used. However, the pivotal clinical studies typically use more than one batch, and the differences between batches and within batch are commonly seen, which should be taken into consideration.

Discriminating Ability. Considering the inevitable variability, for the dissolution specification to have proper discriminating ability, it is essential to keep two concepts in mind. One is the "20% range" concept. As reported, the *in vitro* dissolution profile comparison using f2 similarity factor (16) generally matched *in vivo* bioequivalence criteria (17), which indicated that a 80–125% range (± 20%) *in vivo* is typically manifested *in vitro* by a dissolution range of 20% (± 10%). This has been the basis for the dissolution specification of an extended release (ER) product that is usually in the 20% range (mean ± 10%). The one-sided $Q = 80\%$ for the IR products also implies a 20% range (80–100%) since the maximum cannot exceed 100% (theoretically). Similarly, if the initial burst of an ER product is not high, the specification can be set one-sided as NMT (not more than) 20% and so can the last timepoint for an ER product as NLT (not less than) 80% with 20% ranges (0–20% and 80–100%, respectively). When the initial burst is high, a two-sided specification, for example, 10–30%, should be set to maintain the 20% range. According to this logic, the recommendation for the IR product to be NLT 75% (a 25% range 75–100%) seems

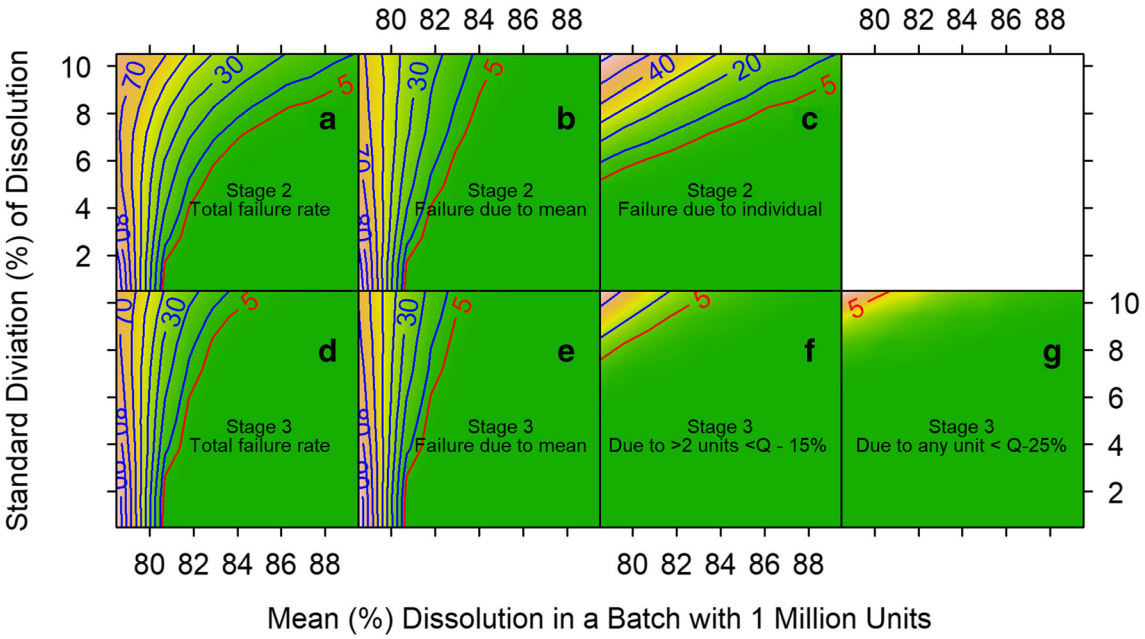

Fig. 4. The total failure rates and the failure rates attributed to different reasons for stage 2 and stage 3 of IR products

inadequate. Another essential is the "edge" concept, namely, the specifications should be as tight as possible if the clinical batches under foreseen situations could pass. This concept stems from the optimal balance between passing all qualified products and rejecting any unqualified products. The above two essential concepts are not always in harmony. A commonly seen case is the range obtained from the edge concept is less than that from the 20% range concept. A recommendation is to use the tighter range obtained from the edge concept as an internal limit and the other for regulatory submission. The rationale behind this recommendation is to use the range obtained from the edge concept as a "precursor" for any quality problems. Under normal conditions, the batches always fall within the internal limit. When it is out of the internal limit, a signal is sent that something is wrong or denotes the beginning of a quality drift, which warrants closer attention.

Sensitive Zone. Although the edge concept is useful for an adaptive approach, a special note for the IR dosage forms is to avoid the "sensitive zone" (mean < 81%, see "RESULTS" section) even if the variability (SD) of the clinical batch is very low, since an oversensitive specification does not benefit for product robustness.

Stability Data Consideration. To make the edge charts more informative, all available information should be taken into consideration, including the clinical batches for all pivotal studies. Although the stability data are generally not recommended to be included for setting the specifications, considering that the clinical trials do not always use freshly made product and the large clinical studies may last for years during which the patients may take aged product, certain stability data can be accounted for with reasonable justifications and convincing evidence.

Differentiation Between Worst Scenario and Outlier. Due to the amount of information and the uncertainty involved, the worst-case scenario from the clinical batches is considered as an edge. However, if one of the batches is apparently an outlier, the edge charts to differentiate the reasons for failure can be useful for seeking the source of the failure.

Shape of Dissolution Profile. The shape of dissolution profile plays an important role. Two points should be noted. First, the "edge" concept should be kept in mind, which not only maintains the discriminating ability but also avoids significant shape differences when the timepoint selected is pushed too far away from the "edge." Second, when the dissolution is very slow, one-point dissolution will not control the early release. To adequately control the shape of the release profile, for BCS Class II/IV products, a two-point dissolution specification, one at 15 min to include a dissolution range and the other at a later point (30, 45, or 60 min) to ensure complete release, should be considered (5).

Information Integration. Note that it is critical to integrate the information from the edge charts and other source into a rigorous process in an adaptive manner. It is this ability to deliver appropriate acceptance criterion with good risk–reward ratios that most highly commends the edge charts. Their general application is briefed below.

For the application of the edge charts, the first step is to obtain 12 units dissolution data at different timepoints for the clinical batches and calculate the mean, SD, and coefficient of variation (CV%) at each timepoint for each batch. For IR products, timepoints of 15, 20, 30, 45, and 60 min are generally selected. List the information in a table similar to Table II.

Next, compare the mean profiles among different clinical batches by plotting them as the left panel of Fig. 6, where

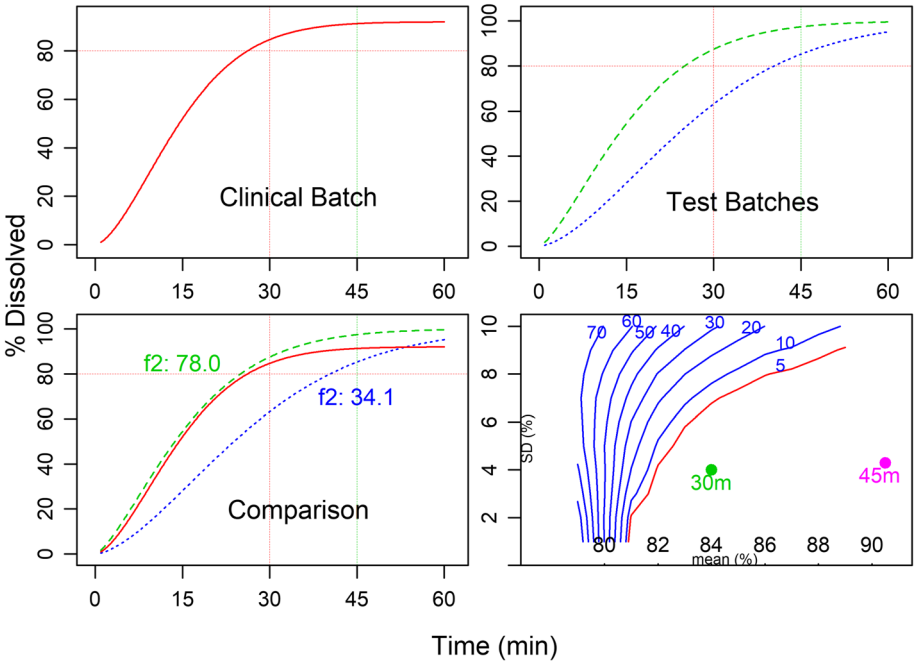

Fig. 5. An example for setting dissolution specifications. Data for clinical batch, qualified and unqualified batches are shown in Table II. **Scenario 1, targeting stage 1:** at 30 min, the first six tablets of the clinical batch (upper left panel) have less than 85% dissolved for most of the individual units. The batch would not pass stage 1 when Q is set as 80%. For this batch to pass stage 1, the timepoint extends to 45 min and thus the dissolution of the first six tablets are all greater than 85%. Accordingly, the specifications are set as $Q = 80\%$ at 45 min. This specification will not only pass a qualified batch but also pass an unqualified batch (upper right panel) at stage 2 with a mean of 85 ($n = 12$). However, the unqualified batch has significantly lower dissolutions. As shown in the lower left panel, compared with the clinical batch, the qualified batch has an f2 value of 78.0 while the f2 for the unqualified batch is 34.1. When the *in vivo* dissolution slowness of this batch reaches such an extent that significantly affects *in vivo* performance compared with that of the clinical batch, the effectiveness of this batch would be a problem. Under this case, the specification ($Q =$ 80% at 45 min) is not adequate. **Scenario 2, targeting stage 2:** at 30 min, the mean of the 12 units for the clinical batch is 84% with an SD of 4%. By checking the 5% edge line at Stage 2 of the edge chart for IR product (lower right panel), the probability for this batch to pass a specification of $Q =$ 80% at 30 min is greater than 95% (as shown by a solid circle labeled with "30m") while it would not possible to pass $Q = 80\%$ at 15 or 20 min. On the other hand, the solid circle labeled with "45m," representing a criterion of $Q = 80\%$ at 45 min, is too far from the edge line (scenario 1 above). In reality, when the specification is set to $Q = 80\%$ at 30 min, the qualified batch will pass stage 2, but misses stage 1. The unqualified batch will not pass stage 1, stage 2, and even stage 3 (data not shown)

there are three clinical batches. Among these batches, batch 1 represents the worst-case scenario.

The selection of the specification timepoints is the key step for IR. Pick up those timepoints with the mean above 80% as the candidates. In the case for the left panel of Fig. 6, the timepoints of 20, 30, and 45 min for batch 1 (the worst scenario) are selected. By drawing a horizontal line at 80% and a vertical line at 20 min, it seems possible for a

Table II. Dissolution (%) data for the example shown in Fig. 5

Batches	6 tablets at 30 min			Additional 6 tablets at 30 min*			6 tablets at 45 min			Additional 6 tablets at 45 min*		
	Units	Mean	SD	Units	Mean	SD	Units	Mean	SD	Units	Mean	SD
Clinical	80, 92, 84, 82, 82, 83	83.8	4.2	86, 90, 84, 85, 85, 81	84.0	4.0	87, 99, 90, 89, 89, 89	90.5	4.3			
Qualified	88, 92, 87, 87, 88, 84	87.7	2.6	83, 95, 87, 85, 85, 86	87.0	3.0	93, 105, 97, 95, 95, 95	96.7	4.3			
Unqualified	64, 68, 63, 63, 63, 60	63.5	2.6	59, 70, 62, 61, 61, 61	63.0	3.0	86, 90, 85, 85, 85, 82	85.5	2.6	81, 93, 84, 83, 83, 83	85	3.0

*The mean and SD are for a total of 12 units (first 6 + additional 6 tablets)

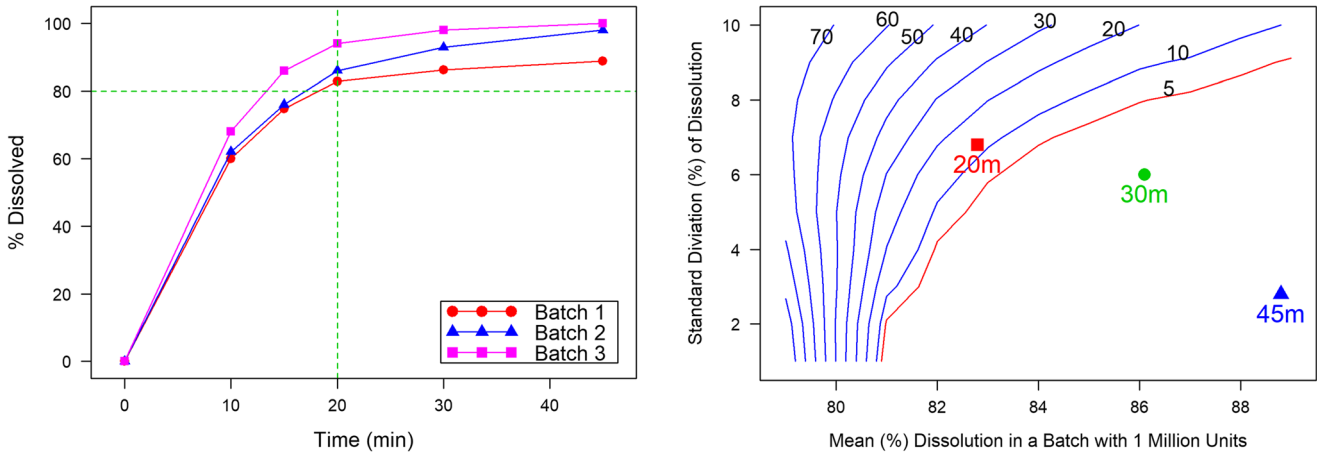

Fig. 6. The applications of edge charts

specification to be set as $Q = 80\%$ at 20 min. However, when putting a symbol for each candidate (using the mean and SD obtained in the first step) in the stage 2 edge chart as shown in the right panel of Fig. 6, the 20-min timepoint can be excluded because the failure rate is greater than 10% when such a specification is implemented. Compare the distances from those symbols located in the region with less than 5% failure rates (such as the symbols labeled with "30m" and "45m") to the edge line represeting 95% pass rate (5% failure) and the closest one (the 30-min timepoint) is selected.

An R function was created for the application of edge charts. The R script for the function is available by request.

Note that the applications of edge charts assume that the dissolution method and conditions used to obtain the data are adequate. If the method has not been optimized or the samples are not appropriately selected, edge charts do not help. In addition, the edge charts deal with normal cases. For special circumstances, such as high dissolution variability drug (CV > 10%), consultation to the regulatory authority is recommended.

The Goal Is Improvement of Product Quality

Although the probability plays a role as stated above, it should be emphasized that "chance" is not the only factor affecting pass/fail. The product quality itself is more important to consider. As the study results show (Fig. 4), the dependences of the failure rates on either mean or SD are basically linear, indicating that an IR batch with higher variability must have higher mean values or the batch with lower mean must have lower SD to pass the specification. To evaluate the performance of a product batch, both the mean and the SD are of concern. Ideally, high mean and low SD produce a high-quality IR batch. The more curved lines in stage 2, which are synthesized by the contributions from the mean and from the SD (Fig. 4), are better targets to rely on.

In this study, the traditional approach to the drug quality is replaced with a quantitative framework within which the product quality can be evaluated in a more rigorous manner, leading to rational decisions without misunderstanding or confusion. The goal is to turn scientific insights into high-quality evidence with the tool firmly footed in the understanding of product quality.

Inspired by the current study, the quantitative methods in biopharmaceutics are not only suitable for *in vitro* practices but also for *in vivo* practices. A consideration of setting the product specification(s) based on *in vivo* performance is more prominent (18); however, it is beyond the scope of the current study.

CONCLUSIONS

Using a data-driven, analysis-fueled, simulation-intensive, and risk-based approach, this study showed that the edge line with 95% pass probability at stage 2 in the edge charts (Fig. 3) serves as a guideline for setting dissolution specifications for the products of IR dosage forms. At the end of the edge chart story, it is the combination of the mean and the variability (SD) of the quality indices (such as dissolution) that best pave the way to a high-quality product. With this realization, edge charts like many useful tools are elegant in their simplicity, which not only characterize the influences of these two parameters on the product quality but also set edges that balance the reward/risk and allow the product manufacturers to understand their products better.

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