Reporting and Analyzing Drug Dissolution Results:
A Systematic Approach

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Introduction

Dissolution tests are employed to establish drug release characteristics of solid oral products, such as tablets and capsules. In reality, dissolution testing may be considered as an extraction technique such as a Soxhlet extractor for extracting compounds from their matrixes or perhaps a simple shake-flask technique for solubility determination. It is not to say that dissolution apparatuses may be replaced or substituted by apparatuses for the two types of techniques mentioned, but highlighting the fact that these all work on the same principle but with different objectives. Following the extraction, as for the other techniques mentioned above, samples are withdrawn, filtered and quantified using any of the common techniques such as chromatographic/spectroscopic. The results are commonly reported as a percentage of the extracted/dissolved amount based on the total amount of the drug present in the product.

The preceding discussion is to emphasize the fact that drug dissolution testing is a relatively simple analytical technique. It should not require any more elaborate method development/validation steps or reporting of results than any other simple analytical techniques such as the two mentioned above. Such an understanding of the underlying principle of dissolution testing will help in critically evaluating current complex practices of reporting and evaluating the dissolution results, and hence simplifying them.

Reporting of Results From an Analytical Technique – In General

The outcome of any analytical technique is reflected by two parameters: a value, often a mean, and the observed variance. Without a variance value, the result may merely be considered as a value by chance. It is to be noted that the standard deviation (SD) value, which is the square root of the variance, is often used as a reflection of variance. Further, often relative standard deviation (RSD), also known as the coefficient of variation (CV), is used to express the variance. The use of %RSD (or %CV) is often preferred over the variance or SD, as %RSD provides a quick and intuitive answer of testing and its variability. For example, saying that a product provides a SD value of 3 while another 30, do not accurately reflect the quality of the test products. However, if these values are normalized based on the means, which is %RSD (SD*100/mean), then it would provide a quick intuitive evaluation of the products. In this case, if the strength (mean value) of the product is 30 mg, while for the second it is 300 mg. Then, the RSD in both cases will be 10%. i.e., both products have similar variability in testing and/or product quality.

It is critical to note that statistical evaluations of results are always based on SD, more specifically variance; however, for convenience as explained above, once appropriate comparisons/analyses of variances are completed, results are commonly reported as %RSD. Considering the relative simplicity of drug dissolution testing and the data one obtains from the tests, simple mean and SD or RSD values can be determined using any scientific calculator or computer spreadsheet software. Absence of such data analysis or reporting of results should be considered a great cause of concern.

With these thoughts in mind let us discuss the current practice of reporting results in drug dissolution testing and difficulties one would encounter.

Reporting Dissolution Results

Current Practices

There are a number of ways in which drug dissolution results are described. The most commonly described approach in literature is of that of the USP [1], also described in other pharmacopeias, which is range based. The dissolution results are expected to fall within a preset range or a value of not less than (NLT) a certain preset value. This preset value is commonly referred to as a *Q*-value. The *Q*-value based approach does not provide an upper limit. However, it is implied that the higher limit would not exceed the expected content or assay limit of 115% of labelled amount of drug in the product. Therefore, in reality the single *Q*-value based approach is indeed a ranged based criteria as well.

As explained above, both the *Q*- and ranged-based criteria are essentially the same, i.e. ranged based, and should not be considered different as commonly implied in the literature. Commonly, single point (*Q*-value) tolerances are described for fast or immediate-released (IR) products, while ranged based for extended- or modified-released (ER or MR) products. It should be noted that even for multiple sampling time analyses, the last sampling time values are usually similar to the *Q*-value type.

The interpretation of *Q*-based criteria, which is most commonly used, may be summarized as follows. The *Q*-based criteria are based on a combination of results from both single tablet as well as the mean from multiple tables. These are used in stages, i.e., if the test does not meet the criteria at a stage, it then provides an allowance of re-testing with further relaxed criteria to accommodate the failing results. As a first criterion, for a product having a *Q*-value of 80%, no tablet results, out of a run of 6 tablets commonly tested, should fall below *Q*+5% (known as Stage one). If this criterion is not met then, the testing moves to the second stage. In this case, mean values of 12 tablets including 6 from the previous stage, should not be below Q and no individual tablet result should be less than *Q*-15% (or 65%). If this criterion is not met, then testing should be continued to third stage. For the third stage, mean value of 24 tablets including 12 from the previous stages should not be below the *Q*-value and no two results be less than *Q*-15% (65%) or no result be less than *Q*-25% (55%) value.

In short, therefore, a product having a *Q*-value of 80%, the percent drug released value may vary from 55% to 105%. The value 105% is derived by considering that if a tablet gives 55% drug release then at least one other tablet should give a value of 105%, if not more, to provide mean value of 80%, to meet the mean value based criterion. Similarly, such a range would be 50% to 110% for a *Q*- value of 75% and still be wider for products that having *Q*-value lower than 75%.

It should be noted that standard-setting agencies, including USP, provide a wide allowance of variability in drug dissolution testing to accommodate expected variability in dissolution testing as noted in the literature [2-4]. Setting tighter or narrower ranges for variability should be avoided as it may result in unnecessary out of specification results during product manufacturing.

The range-based tolerances follow a similar pattern as described above. A similar set of stage-based criteria are used at each sampling time. Thus, if testing requires four sampling times, then there will be four independent ranges to evaluate.

It should be noted that there is no requirement for evaluating and reporting variances, including SD or %RSD (%CV). This may cause significant difficulties in evaluating and reporting dissolution results, as discussed later in the article.

These standards are described in pharmacopeias (e.g. USP) and are commonly employed for routine quality control testing for evaluating batch-to-batch consistencies reflecting minor or no variations in product characteristics. Understandably, one would expect wider tolerances (ranges) where product composition/ manufacturing attributes are to be changed in order to accommodate these variations as well, such as during the product development stage.

When results from multiple drug dissolution samples at different times are reported, the outcome is commonly referred to a dissolution profile. The profiles fulfil the same purpose as that of reporting results in a tabular format. However, these profiles i.e., graphs of percent drug release with times, provide a visual and convenient read of the drug release characteristics of the test products. For the evaluation or comparison of these dissolution profiles, there is yet another criterion used, known as the similarity factor which is represented by f2. It is generally not used during routine testing such as pharmacopeial or QC testing. However, its use is more common in product development stages. This similarity factor is calculated using the formula as reported in the literature [4], which should provide a value between 50 and 100 to reflect similarity of two profiles or release characteristics of the two products, test vs. reference. The values of 50 or above reflect that, on average differences. in results from the profiles is less than 10%.

Limitations of the Ranged-based Criteria in Evaluating Dissolution Results

The foremost difficulty is that these tolerances are of a pass/ fail type, which would not provide for an appropriate comparative product evaluation, which is why dissolution testing generally conducted. Consider that when a lot is tested, one finds a mean value at 30 minutes of 80% dissolved. Then, the next batch provides results of 90% and third one 100%. If the Q-value for this product is 80%, obviously all these batches will meet the criteria. However, the question is, are these batches of equal quality? Under the current practices, it may be difficult to establish. Similarly, like any other analytical method including drug dissolution testing, one would require method validation. Suppose, two methods are evaluated based on a product having a Q-value of 80, and one gives results of 80% dissolved while another provides 90%. The question will be, are these two methods equal? If not, then which should be better or preferable? Such evaluations can only be established using the variance parameter. It is the variance value which will dictate the quality of a product or the method. Without the variance comparison it may not be possible to be sure about the accuracy and variability of the results. In fact, it may be argued, that without the availability of SD values, dissolution results should be considered of limited value and reliability.

The previous example reflects that one may not be able to make an appropriate or valid comparison without the availability of a variance component. Therefore, for appropriate standards or tolerances, not only is a mean value necessary but an associated variance around the mean is required and should be available for any compendial or other standards.

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With regards to f2 , this parameter differentiates profiles of two products having different formulation/manufacturing attributes based on a difference of 10% or less in dissolution results. This appears to be in conflict with other more commonly used pharmacopeial or regulatory standards. For example, as explained above, for a Q-value of 80%, the expected range of results would be 55 to 105 at the highest drug release level where variability is generally lower. On the other hand, at earlier sampling times as in case of extended release products, this range is usually even wider. Then, for both IR and ER products, f2 would differentiate products having similar drug release characteristics and may provide false negatives. Therefore, the use of f2 warrants caution in establishing similarity or dissimilarity of products.

Suggested Approach for Reporting and Evaluating Dissolution Results

Let us approach this issue purely from an analytical chemistry aspect for analyzing dissolution samples.

An analyst is given 4 racks, each containing 24 test tubes with liquid samples as a grid of 6x4, where a row of six tubes reflects replicates of the test and four columns represent four sets of samples. The analyst is provided with a validated method and asked to analyse the samples and to report results as a mean and %RSD for each set, a typical analytical protocol. The analyst is blinded to the nature and source of the samples. Let us assume that reported results are as follows: set #1: mean values of 10, 40, 80 and 100 with %RSD of 10, 8, 6 and 5, respectively; for set #2, respective values are 80, 85, 87, and 100 with %RSD of 5, 3, 4, and 2; for set #3; the values are 100, 95, 75 and 35 with %RSD values 5, 8, 12, and 25; for set #4, the values are 9, 45, 75 and 90 with %RSD 10, 7, 7, and 4.

It should be noted that these could be any type of samples. However, as the subject under consideration is drug dissolution testing, the samples have the following description, unknown to the analyst. Set #1 represents results of samples from four different dissolution sampling times of a 100 mg strength product; the second set represents samples from four batches of the same product as in the first case; the third set represents four different formulation of the same (100 mg) product. Set #4 represents results from four different dissolution sampling times of the same 100 mg strength product but with changed formulation. Another way of saying this is that sets #1 and #4 represent a usual testing of a slow release product resulting in profiles, set #2 represents typical quality control samples from four lots, and set #3 represents the samples from a product development stage.

Point being, a simple and common approach can be used in reporting and analyzing the results. All that is required is a mean value and %RSD to evaluate the quality of the results with confidence (variance). As all analyses provide mean and variance values, a valid statistical comparison of any of the results can be made, resulting in an appropriate inference about quality of results and/or the test product(s). Thus, the approach, well established and commonly used for analytical testing, appears to provide a simple alternative to current practices.

The currently used approaches as described above appear confusing, complex, and lack statistical merit. Therefore, their use may be reconsidered or at least be debated to establish their usefulness against the well established mean and %RSD based evaluations.

Suggestions for Selecting Sampling Times

Another difficulty in dissolution testing is the selecting of sampling time(s) to define or establish characteristics of a product. Current practices do not appear to provide a systemic or standard approach in this regard, but appear to be empirical and subjective in nature.

The purpose of dissolution testing is to evaluate drug release characteristics of a product. These release characteristics are defined or established by two parameters: the extent and rate of drug release. The extent part is straight forward, i.e. the total amount (100% with an acceptable margin of error) of drug present in tablets or capsules, must be released. If release is less than 100%, say 80%, then the cause of this discrepancy must be determined and corrected, because prescriptions or use of drugs are based on 100% releasable drug. Often the use of apparatuses with poor hydrodynamics, such as USP paddle, shows lower dissolution results because of unstirred pockets. In such cases, the use of such apparatuses should be avoided. Similarly, if the cause is related to formulation/manufacturing attributes then those should also be addressed accordingly.

The second aspect of dissolution testing is the establishing of the rate of drug release. The rate of drug release depends on two things: the product and the stirring within a dissolution vessel, with all other things being equal. To determine product release rate, the stirring rate has to be fixed or constant. This is perhaps the most challenging aspect of drug dissolution testing at present, how to fix or establish the stirring rate. To establish this, one requires a reference product with known drug release rate in humans. Unfortunately there is no such reference product available at present and thus the setting of an absolute/reference rotation speed is not possible. In the absence of such a reference product or release rate, one possible alternate would be that the apparatus may be calibrated or standardized based on relative values. For such a relative approach, the stirring speed using two products having known different release characteristics, such as IR and ER products of the same drug, should be analyzed under the same experimental conditions, including stirring speed. The test results must differentiate these products as fast and slow release products and should also show complete drug release from both products within a suggested dosing interval in humans. Then, this stirring speed may be used for determining the release rate of the test product [6].

Next, the question would be to determine how to select the sampling time. One of the reasons one requires a release rate, in particular, is to avoid the possibility of dose dumping. The dose dumping term is used to characterize an unexpected and abrupt release of drug in a short period of time, usually during the initial phase of the extended release products. Such dose dumping must be controlled to avoid adverse drug effect which in some cases may be fatal. Although, there are no hard and fast rules about selecting sampling times, but perhaps a rule of thumb would be as follows:

First, analyst should conduct a test for an extended period of time, say 3, 6 or 24 hours with frequent samplings to establish 100% drug release using established experimental conditions of stirring and dissolution medium. From this test run, in the absence of any drug specific needs (e.g. for narrow therapeutic index drugs), three sampling times before maximum (100%) may be chosen to provide a defence mechanism in observing dose dumping. These three times should be around 25%, 50%, and 75% of the expected

drug release. These percentages do not have to be exact, but conveniently obtainable from dissolution testing, say with a plus or minus 5 to 10% difference. One may use many more sampling times to smooth out a dissolution profile, if so desired, for monitoring and controlling the drug release more precisely. For example, more sampling times may be added if a drug has a narrow therapeutic index and may require a more precise control and estimation of release rate.

For products where dissolution is designed and expected to be completed quickly, say in 30 minutes or less, then dose dumping becomes less of a concern. Multiple sampling becomes less valuable. Therefore, for efficiency and economic reasons, the so called "single" time point testing may be used with a sampling time where complete drug dissolution is observed.

In conclusion, current practices of evaluation of dissolution results based on ranges appear confusing, complex and lack statistical merits. Also, there appears to be a lack of a systematic approach in setting or choosing sampling times for dissolution tests. These difficulties may be avoided if results are analysed based on mean and variance values. Furthermore, the selecting of sampling times can be simplified and standardized, if the concept of dose dumping be considered as described in this article. **APR**

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