Development and Validation of Drug Dissolution Methods – A Rational and Systematic Approach

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Abstract

Dissolution tests employed as quality assurance/control tests to monitor potential changes in product formulation and/or manufacturing attributes do not necessarily reflect drug release characteristics in humans, i.e. they may lack bio-relevancy. In such cases, observed deviation from expected drug release (dissolution) characteristics, even with possible (un)intentional changes in formulation/manufacturing attributes, would not indicate substandard drug release in humans. Therefore, such quality control tests may often result in false negatives. A more appropriate test would thus be one which is bio-relevant. This article provides a discussion on the difficulties in obtaining such bio-relevant tests and presents some suggestions for improved method development and validation approaches.

Keywords

Dissolution testing, method development, method validation, IVIVC, bio-relevance.

A dissolution test is an in vitro analytical test used for assessing expected drug release characteristics of pharmaceutical products in humans, in particular, of solid oral dosage forms, such as tablets and capsules. The rationale for conducting these tests is that, for a product to be therapeutically effective, the drug (active pharmaceutical ingredient or API) must be released from the product and should generally be dissolved in the fluids of the gastrointestinal (GI) tract. The API in solution form facilitates the absorption of the drug from the GI tract into the systemic (blood) circulation to reach its desired target (site of action) to exert its effect. Therefore, a dissolution test could be considered a critical step for assessment of quality of product batches, bridging to safety and efficacy aspect.

From both product development and quality control aspects, drug dissolution testing facilitates evaluation of the impact of formulation and manufacturing differences on drug release characteristics in humans. This link of dissolution test (in vitro) to anticipated or expected drug release characteristics in humans (in vivo) establishes the bio-relevancy of the test and is more formally known as in vitro-in vivo correlation or IVIVC. Commonly, in the literature, both terminologies, i.e. IVIVC or bio-relevancy, are interchangeably used. It is most important to note that bio-relevancy is a critical requirement for an appropriate dissolution testing procedure, whether at the product development stage or for its routine use as a QC test.

However, in the literature there has been some confusion, in which use of dissolution tests has been suggested to be based on two separate objectives, one for IVIVC supported and the other non-IVIVC supported [1]. Generally, IVIVC supported tests are considered as bio-relevant to be used to relate or predict bioavailability/bioequivalency characteristics of products. On the other hand, non-IVIVC supported tests are generally described as QC tests just to monitor or differentiate physical characteristics of the products, i.e. the tests should be capable of differentiating products having differences in formulation or manufacturing attributes.

Therefore, at present, these two dissolution testing approaches run in parallel, which may or may not overlap. These concurrent overlapping views of dissolution testing have created a confusing situation in the practice of dissolution testing. The purpose of this article is to present a discussion to highlight the issues and potential causes of this confusion and to make suggestions towards a coherent approach for dissolution method development and validation for improved product evaluation.

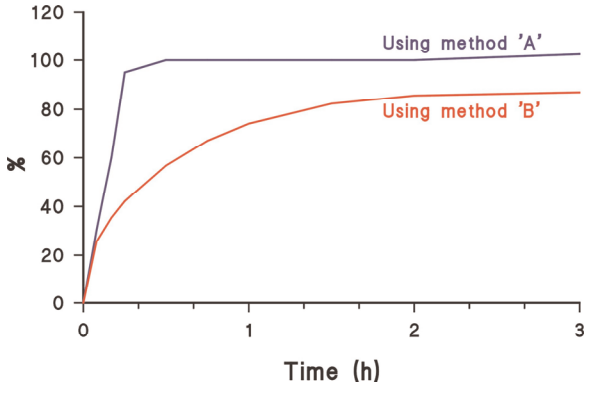
Often in the literature [1], from the method development and validation aspect, a dissolution method is treated like another analytical

procedure, such as spectroscopic or chromatographic (HPLC and/or GC). Therefore, method development and validation appear to be commonly based on such performance evaluation parameters as precision, linearity, repeatability, reproducibility, limit of quantitation, etc. Certainly, these are important and critical parameters for dissolution testing. However, surprisingly limited focus has been put on the relevance of dissolution testing itself for characterizing the product (formulation and manufacturing) and its bio-behavior. That is, how should a dissolution method be developed and validated to ensure bio-relevant dissolution results? This article will focus on the latter aspect towards developing and validating a dissolution method which would reflect products release characteristics that also provide bio-relevant results.

From a method development perspective one may describe the role of dissolution testing as depicted in Figure 1, in which two different drug dissolution or release profiles are obtained for the same product using two different testing approaches, which may be based on varied conditions such as different apparatuses, media or spindle rotation speeds, etc. The effective way to decide on an appropriate method would be based on drug release characteristics of the product observed in humans. Therefore, the testing technique, including procedure, must have a link to human drug release characteristics to provide bio-relevant results.

On the other hand, from a QC aspect, if a drug release profile deviates from the expected profile as shown in Figure 2, should the

Figure 1.



Schematic representation of drug release characteristics of a product using two different methods. In vivo drug release characteristics would be needed to establish which method would be the appropriate one.

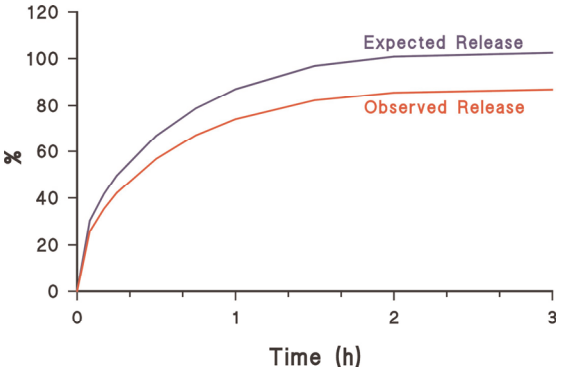
product/profile be considered as an expected variability or would it suggest substandard quality of the tested product? This can only be decided based on the observed release behavior of the product in humans. If both products are of acceptable quality, then differences in profiles would reflect tolerances for a QC standard. Otherwise, one of the products be considered of substandard quality. Therefore, even for QC purposes, the test is expected to relate to and predict the behavior of the test product in humans. Lot to lot, dissolution testing is done with the expectation that change in dissolution results will reflect potential change in formulation and/or manufacturing change, which may negatively affect the safety and efficacy of the product and thus quality. Therefore, even for QC purposes, a dissolution test must have a link to IVIVC. Thus, QC dissolution testing may be considered as part of IVIVC testing, not as a stand alone or independent test different from an IVIVC test.

In reality, therefore, there is only one objective of a dissolution test. The test should be capable of reflecting drug release characteristics of the products in humans. If a dissolution test is seen from this objective, it will become easier to develop and then validate an appropriate and useful dissolution test.

The next consideration is how to approach in developing a bio-relevant dissolution test. To achieve this objective, one would require a relevant analytical technique or apparatus. The critical word here is "relevant," i.e. how would one define a relevant technique for conducting a dissolution test. Again, one considers the environment in which the drug product will go through, i.e. in the GI tract. As stated earlier, that to exert a therapeutic effect, a drug must be released from the product and dissolved in the GI tract. Therefore, one needs to create a GI tract environment for dissolution testing.

It is important to note that drug dissolution testing only reflects drug release and dissolution in the GI tract. Absorption of the drug and

Figure 2.



Schematic representation of drug release profile of two different batches of the same product. In vivo drug release characteristics would be needed to establish whether the products are of similar/acceptable quality or not.

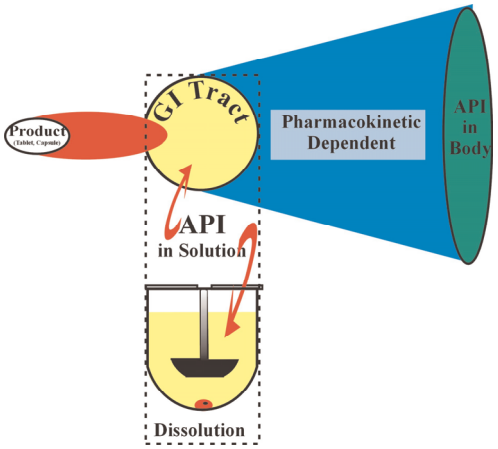
further pharmacokinetic steps, such as metabolism, elimination and degradation of drug in the GI tract, usually are not dependent on the drug dissolution. This principle is depicted in Figure 3, in which only the dissolution step is equated to dissolution in human GI tract, i.e. dissolution is a product characteristic while absorption is an API characteristic. If API characteristics (e.g. nature and strength) remain the same, then only absorption and bioavailability are dependent and directly linked to the dissolution rate. One can evaluate pharmacokinetic behavior of a drug (API) appropriately by administrating drug in solution, avoiding the dissolution step. However, for the evaluation of drug release characteristics of a product one needs to consider the dissolution step.

An important consideration here is that, for dissolution testing purposes, the GI tract may be assumed to be a vessel (a tube with varying diameter). It is not necessary to duplicate human GI tract physiology in vitro to observe dissolution results, but a simple vessel capable of dissolving an API in vitro should suffice, as has been in use for the many years [2].

Apart from a vessel concept, there are some other biochemical properties of the GI tract that have to be considered for relevant drug dissolution testing. These are aqueous based milieu in the pH range of one to seven or eight maintained at 37 ºC. Also present are some bile salts which may facilitate dissolution of non-polar APIs with limited

aqueous solubility. Further, the GI tract provides a stirring and mixing mechanism to facilitate disintegration of products into fine particles with appropriate product and medium interaction.

Figure 3.



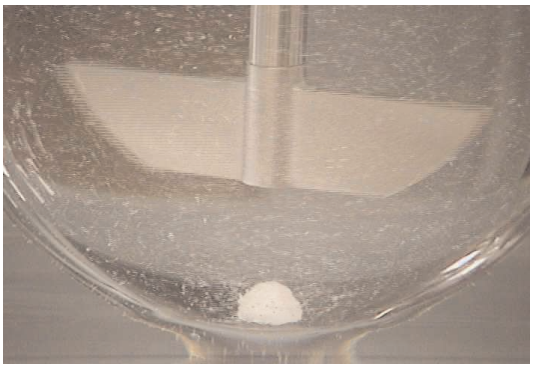
Schematic representation of in vivo and in vitro dissolution processes. For all practical purposes, the hollow tube of GI tract may be considered as a "pot," which is represented with a dissolution vessel for in vitro testing purposes. Given similar nature and strength of an API, its appearance (i.e. bioavailability) in the body would directly be linked to the rate of input of the API into solution, i.e. dissolution rate. This in vitro-in vivo link forms the basis of use of dissolution testing as a tool for product development and later as a quality control/assurance tool.

Therefore it is necessary that dissolution tests be conducted at 37 ºC, representing normal body temperature using aqueous based solvents in an efficient mixing and stirring environment. If any of the above described conditions are missing from the testing technique, then obviously it may not be possible to obtain bio-relevant results. In the end, the combined effect of the testing environment should be such that the drug release be reflective of drug release in humans with complete drug release from the product being within the dosing interval. That is, if a product is prescribed to be taken after every six, 12 or 24 hours, then complete drug release must be accounted for within six, 12 and 24 hour durations, respectively.

In short, for the development and validation of a dissolution test or procedure, the first and foremost requirement is to ascertain that the apparatus and procedure are capable of simulating an in vivo environment through which the product will pass.

At present, pharmacopeial (such as USP) apparatuses commonly referred to as Paddle and Basket are employed for the testing. Although, use of these apparatuses emphasizes using physiologically relevant test conditions, such as body temperature and aqueous-based dissolution mediums having pH values within expected physiological range. Surprisingly, the use of such apparatuses does not provide necessary product-medium interaction because of the lack of adequate stirring and mixing within the vessels. This lack of stirring and mixing appears to cause difficulties in developing appropriate dissolution methods. A pictorial representation of the result of the lack of product-medium interaction and stagnation of a product is shown in Figure 4. Therefore, developing bio-relevant dissolution tests using these apparatuses would be unlikely as has been reported in the literature [3].

Figure 4.



A pictorial representation of the lack of interaction between product and dissolution medium using the USP Paddle Apparatus. The environment within the vessel creates stagnation of product (disintegrated or non-disintegrated product). This lack of product and medium interaction and the stagnation in dissolution vessels represents dissimilarity of the in vitro-in vivo testing environment and thus appears to cause deficiencies in dissolution testing using current approaches, such as the USP Paddle Apparatus.

To address the artefact of the current practices, some alternate approaches are needed to perform dissolution testing, which would provide appropriate and efficient product-medium interaction, i.e. the apparatus should be capable of providing adequate stirring and mixing environment to mimic the physiological environment better.

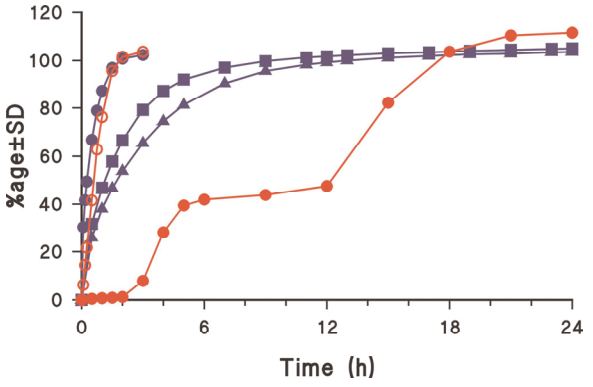
In order to achieve improved stirring and mixing or product and medium interaction, one approach is a modified spindle. There are a number of reports in the literature describing its use and superiority of the new spindle, known as crescent-shaped spindle, for dissolution method development and validation. The literature provides details of further information on the utility and relevancy of the crescent-shaped spindle [4-6].

There are a number of ways one may evaluate the bio-relevancy of a new method. One simple approach is that the developed method must not be product dependent, as on average human, the GI tract physiology remains the same and is product independent. Therefore, an in vitro method should also be product independent. This concept is highlighted and discussed by describing a dissolution method using a crescent-shaped spindle. The use of the modified spindle not only achieves this objective but also makes the method development and testing significantly simpler and useful. For example:

Dissolution profiles of carbamazepine and diltiazem products are given in Figure 5. Dissolution profiles were generated using the USP vessel apparatus but with crescent-shaped spindles at a rotation speed of 25 rpm. The media used was 900 mL water for diltiazem and 900 mL water containing 0.5 percent sodium lauryl suphate (SLS) for carbamezepine. Products tested were IR (60 mg diltiazem tablets and 200 mg carbamazepine tablets) and ER (120 mg diltiazem capsules, 200 and 400 mg carbamazepine tablets). It is to be noted that all of these products were tested using the same experimental conditions, except for medium, where SLS was added for carbamezepine to provide the needed sink condition. Therefore, testing with improved product-medium interaction using crescent-shaped spindle fulfills a necessary experimental condition that products should be and can be analyzed under similar experimental conditions. Under the suggested experimental conditions, all one has to do is to provide an appropriate dissolution medi-

um so that the expected amount of drug be soluble in the medium, obviously within physiological requirements [5-6].

Figure 5.



Drug dissolution profiles of multiple products using a vessel based apparatus with crescent-shaped spindle (25 rpm) in 900 mL of water (diltiazem) alone and water with 0.5 percent SLS (carbamezepine). The products tested were [5-6]: 60 mg IR diltiazem tablets (—O—); 200 mg IR carbamazepine tablets (—●—); 120 mg ER diltiazem capsules (—●—); 200 mg ER carbamezepine tablets (—■—) and; 400 mg ER carbamezepine tablets (—▲—).

It is to be noted that the same method is being used for different type of products, i.e. tablets, capsules, IR and ER products having high water solubility (diltiazem) and low solubility (carbamazepine). As these experimental conditions are commonly used and simple, thus method may easily be transferred to a QC test with a supported bio-relevancy of the testing environment. Therefore, such a method would also meet the requirement that both the bio-relevant method and the QC test will be the same.

The reason current practices of dissolution testing do not provide such single procedure appears to be due to a lack of an appropriate product-medium interaction which causes inefficient dissolution [6]. Generally, a dissolution procedure is set for an individual product to achieve certain desired dissolution behavior. For example, all products described above have their own testing methods for a total of five different methods [7-8]. Obviously, the GI tract physiology does not change with the products. Multiple methods would not be bio-relevant. Furthermore, it would be difficult to compare release characteristics of a slow versus fast release product. Moreover, these methods, which are described in the USP, are generally considered as QC tests, obviously for bio-relevant tests, other sets of experimental conditions may be needed. Another important point in this regard is that if a single method cannot be used to differentiate IR and ER products, which have relatively large formulation and/or manufacturing differences, then how would such a method be used for evaluating the impact of small changes within a product category? Thus, use of current procedures, such as those described in pharmacopeias, have become quite confusing in practice. However, it appears that improved dissolution methods may be developed by providing improved product-medium interaction. That is, by enhancing stirring and mixing.

In short, for developing appropriate dissolution methods, the methods should be linked to in vivo drug release characteristics of the products. If this principle is followed, then quality control tests and bio-relevant tests become one and the same thing, which would provide simplicity to method development. Further, simplicity would be achieved by developing tests using a product independent dissolution test environment reflecting the product independent in vivo environment. It appears that lack of efficient product-medium interaction in currently used apparatuses may be the cause of the confusing situation in dissolution testing. Efficient product-medium interaction appears to provide an improved and bio-relevant dissolution testing environment, thus methods.

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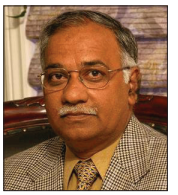

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