Limitations of Some Commonly Described Practices in Drug Dissolution Testing and Suggestions to Address These

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Introduction

Dissolution tests are employed to establish the quality of drug products, mostly tablets and capsules, based on *in vitro* drug release characteristics of these products. In reality, a dissolution test may be considered as a simple extraction step in a vessel with a stirrer. Most of the commonly used apparatuses in this regard are known as paddle and basket apparatuses, in which a round bottom vessel (1 L) containing a stirrer referred to as paddle (an inverted T-shaped bar) or small wired cage (known as basket), respectively, are used. These apparatuses are very well recognized and used around the world with the acceptance of regulatory and standard setting organizations. Detailed descriptions about these apparatuses may be found in any of the most commonly followed pharmacopeias such as United States Pharmacopeia (USP) [1].

As noted above, drug dissolution testing is a relatively simple technique, however, serious concerns and problems are often reported in the literature about it [2-5]. These reported problems often relate to: (1) failing of the performance evaluations of the apparatuses (calibration) and/or products; (2) lack of establishing the link between *in vitro* dissolution results and *in vivo* results, commonly referred to as *in vitro-in vivo* correlations or IVIVC; (3) lack of objectivity in setting or selecting experimental conditions for product evaluations (4) setting unreasonably wide tolerances based on complex and convoluted rationales. These wide spread concerns result in frustrations, within both regulatory and manufacturing environments, where objectivity and reliability of an analytical technique is of critical importance for establishing the standards for the assessment of quality of the drug products.

With such frustrations, it has been suggested that the dependence on drug dissolution testing should be eliminated [6]. As drug dissolution testing is an important and relevant step, the question obviously should be that what went wrong in the practice of drug dissolution testing rather than removal of the test that is mandatory [7]. This article will present a discussion as to why there are such concerns and describe some solutions to address these concerns.

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Background Information – Objective of Drug Dissolution Testing

The quality of an oral drug product (tablet and capsule) is based on the fact that the drug will be released from a product in a predictable and reproducible manner and dissolved in the fluid present in the human gastrointestinal (GI) tract, in particular, small intestine. Thus, this *in vivo* drug dissolution step, also interchangeably referred to as drug release, becomes a critical step for developing a product and later assessing its quality.

A drug dissolution test, or simply dissolution test, is conducted to mimic the above described *in vivo* dissolution behavior of the drug *in vitro*. It cannot be emphasized enough to highlight the fact that a drug dissolution test is a test to evaluate *in vivo* dissolution behavior of a drug product. There is no other objective or rationale for conducting this test. However, there is a common practice for describing and using the dissolution test, without its stated link to *in vivo*, for establishing batch to batch consistency of the product and this is referred to as a quality control (QC) test.

Unfortunately, this appears to be a misconception about the practice of drug dissolution testing and leads to current problems and concerns about the technique. If the link to the *in vivo* behavior is ignored, then the obvious question would be: what parameter/characteristic, or consistency thereof, a dissolution test reflects. In addition, what would be the basis of selecting experimental conditions to conduct a dissolution test? It is, therefore, important and critical to note that the only purpose or objective of dissolution testing is to assess the *in vivo* release behavior of a product. Keeping this objective in mind should also help and guide in defining experimental conditions for dissolution testing.

Evaluating and Relating to *In Vivo* Dissolution Behavior

Once the objective is set, as described in the previous section, then the question should be how one would relate the *in vitro* results to *in vivo* dissolution characteristics? This question should be answered in two parts. The first part addresses the fact that the dissolution test be conducted by mimicking, not necessarily duplicating, the *in vivo* or intestinal environment. The second aspect should be a comparison of the *in vitro* results to the *in vivo*. The discussion regarding the first answer is provided in the following section, however, discussion on the second aspect is provided in this section.

In this regard, the most commonly reported practice is that of developing or establishing an *in vitro-in vivo* co-relationship or IVIVC. The commonly cited definition of IVIVC from the US FDA guidance document is: "It defines IVIVC as a predictive mathematical model describing the relationship between an *in vitro* property of a dosage form (usually the rate or extent of drug dissolution or release) and a relevant *in vivo* response, e.g., plasma drug concentration or amount of drug absorbed" [8]. The preferred or desired IVIVC outcome is of level "A" which implies comparing point-by-point (time-by-time) *in vitro* dissolution results with *in vivo* dissolution results extracted from drug concentration-time profiles. Conversely, by comparing predicted drug concentration-time profiles obtained from *in vitro* dissolution results with the actual drug concentration-times profiles obtained from bioavailability/bioequivalence (BA/BE) studies. Apart from lack of clarity on the mechanics (procedure) of obtaining *in vivo* dissolution results or deriving blood levels from *in vitro* dissolution results, suggested IVIVC practices appear to have serious limitations. For example: As the name IVIVC implies that one is required to develop relationships between *in vitro* and *in vivo* results. However, in practice, conducting a dissolution test is never meant for establishing such a relationship as this relationship is considered to be always present. In fact, existence of this relationship (IVIVC) forms the basis of conducting of a dissolution test. It appears that there is serious confusion in the literature in this regard. The purpose of dissolution testing should be or has always been to evaluate characteristics (quality) of the product, based on the underlying principle that a dissolution test relates well to the product's *in vivo* dissolution characteristics.

Even when such a relationship is developed, as current practices require, by conducting both *in vitro* (dissolution) and *in vivo* BA/BE studies using single product or multiple products with different formulation/manufacturing variations, the question becomes what did one achieve from this practice. If one gets a perfect correlation then it would show that dissolution results are capable of predicting *in vivo* results. Is it not that a dissolution test is conducted based on this principle in the first place, i.e., a dissolution test is conducted to reflect potential *in vivo* behavior of a drug product. Then, why does the development of IVIVC have to be repeated with every drug and product?

There is another major flaw in the current practices of IVIVC. These practices of so called IVIVC seek a matching (rather than relationship) by adjusting experimental conditions so that *in vitro* results would match the *in vivo* outcome. Thus, in reality, the practice of IVIVC has become a practice of searching test/experimental conditions to match *in vitro* dissolution results of test product(s) to the *in vivo* results.

Furthermore, such "successful" IVIVC outcomes, which are rare, are hardly used in practice to evaluate the quality of drug products. The procedures which are used for the evaluation of the quality of products (such as pharmacopeial tests) are generally not based on these IVIVC evaluations. This obviously adds to the frustrations as to why IVIVC studies are to be conducted when it may not be useful in assessing the quality of the product.

The question would then be, what is the intended purpose of the IVIVC practice? The intended purpose of the practice of IVIVC is not to develop (co)- relationship but to predict, more accurately estimate, a potential *in vivo* outcome. The *in vivo* outcome which is often used in this regard is drug concentration-time (C-t) profiles obtained from the BA/BE studies. Therefore, the objective of any dissolution testing must be to estimate and evaluate the C-t profiles. A detailed discussion on the procedural detail about developing such C-t profiles and their evaluations are beyond the scope of this article. Readers are referred to the literature on this subject, where necessary concepts and methodologies, in this regards, are provided in detail [9, 10].

Choice of Experimental Conditions

As dissolution test are conducted to evaluate potential drug release *in vivo* i.e., in the GI tract, choice of experimental conditions are, therefore, dictated by the physiological environment. Basically there are three variants which are usually considered in this regard: (1) temperature, which is 37 ° C reflecting body temperature; (2) GI tract fluid which is reflected by water or aqueous solutions (buffers) having pH in the range of 5 to 7. If a drug is not expected to dissolve in water or buffers then a small amount of solubilizing agent may be added to enhance the solubility in the aqueous phase; (3) a mixing mechanism which is achieved by using a stirrer at a slow rotation speed. In short, water alone as a dissolution medium, or with small amount of solubilizing agent if the drug is of low aqueous solubility, maintained at 37 °C with a stirrer at low rotation speed of 25 rpm may be used for testing of the majority of drug products [11]. It is to be noted that experimental conditions are derived from the physiological environment which remains the same from product to product thus these have to be product independent. However, a quick review of the literature shows that most experimental conditions, except temperature, are product dependent. Conducting dissolution studies using product dependent experimental conditions clearly negate the basic requirement of the testing. This creates a serious concern about the relevancy and credibility of current practices of dissolution testing, thus results obtained from dissolution testing would be of questionable merit.

At present there are two sets of variants in selecting experimental conditions for dissolution testing; media and apparatuses or stirrers. Commonly dissolution results are dependent on these two variants. In most cases, two types of apparatuses are used i.e., paddle and basket. These two types of apparatuses are similar in make and operation, expect for the stirring rods (or spindles). It is very well established, based on reports published in the literature, that these apparatuses are inherently flawed for dissolution testing because of poor hydrodynamics (mixing/stirring) within the vessels [2-4]. This flawed hydrodynamics results in serious deficiencies; such that the stirring provides limited product/medium interaction as well as creates unstirred and stagnant pockets. The physiological relevance of these apparatuses would thus be questionable as the intestinal environment provides thorough mixing and no stagnant pockets. Secondly, again based on the poor hydrodynamic characteristics, it has clearly been demonstrated that these apparatuses provide highly variable and unpredictable dissolution results unrelated to a product's characteristics. Therefore, results obtained using these apparatuses will always be suspect and of limited use. There have been numerous attempts and suggestions for improving the behaviors of the apparatus by tightening specifications [12], but with little success as the issue does not appear to be with the specifications (tight or relaxed) but the apparatuses themselves.

Furthermore, as the cause of the problems is poor hydrodynamics within vessel using paddles and baskets, then, it may not be possible

to make an appropriate choice of a dissolution medium using these apparatuses. The dissolution results obtained thus will always include high variability and unpredictability of the apparatuses. Unfortunately, instead of focusing on the issues of the apparatuses, there has been a tradition of supporting the use of paddle and basket apparatuses with weak rationales. The continued use of the paddle and basket apparatuses appears to be the major impediment of addressing the problems in developing appropriate dissolution tests [13].

Looking to the Future

The obvious question would be as to how these issues may be addressed. Obviously first and foremost is the need for recognition of the fact that unfortunately the recommended apparatuses (paddle and basket) are not appropriate for their desired purpose. There is strong experimental evidence in the literature regarding the deficiencies [5] as well as suggested solutions to address these [14]. However, there appears to be a lag in recognizing these developments. It is hoped that these new developments will provide impetus to re-evaluate the future use of paddle and basket apparatuses.

On the other hand, to accommodate the continued use of these apparatuses, at present, it has become a common practice to select arbitrary experimental conditions such as apparatus, rpm, dissolution medium etc. to achieve preconceived or expected dissolution characteristics of a product. The current practices of dissolution testing are therefore, in fact exercises of selecting/defining experimental conditions to obtain expected dissolution behavior rather than determining dissolution characteristics of the products. Hence, it would be safe to conclude that with the current recommended practices of dissolution testing one never determines the drug release (dissolution) characteristics of product.

In resolving the issue, it appears that there is a need for clearly defining and agreeing to the role of dissolution testing (evaluation of *in vivo* drug release) with an objective endpoint (developing C-t profiles). Such an objective and end point will facilitate the development/use of appropriate apparatuses and associated experimental conditions. One of the possible ways of achieving such an objective is through the availability of a reference product with known *in vivo* drug release characteristics. Such a reference product should be used in establishing the appropriateness of apparatuses and related experimental conditions. The use of such validated apparatuses and experimental conditions should be extended for other products. It is ironic that the drug dissolution community has been working for the past 3/4 decades and is expected to continue to work without a reference product. It is highly unlikely, if not impossible, that one will be able to get useful results from a technique/apparatus which has not be validated for its claimed propose. It is a critical deficiency which requires urgent attention.

In the absence of such a reference product, as well as for generating data towards developing a reference product, one may establish appropriateness of an apparatus and associated experimental conditions based on relative dissolution testing. The relative dissolution testing may be described as determining drug dissolution (release) characteristics of two products of the same drug (active ingredient) but having two different known drug release characteristics *in vivo* such as IR and ER products. The dissolution test conditions should reflect a physiological environment and must be such that while providing different release patterns, fast for IR and slow for ER product, provide complete dissolution to occur within the suggested dosing interval for the drug products. Once such a set of experimental conditions is established, this may be considered as reflecting/simulating *in vivo* environment and then be used for other test products. It is to be noted that using experimental conditions which are not observed *in vivo*, such as de-aeration of dissolution medium, use of sinkers etc., be avoided as these may invalidate the testing.

In conclusion, it may be argued that most of the deficiencies/problems of current practices of dissolution may be related to poor hydrodynamics within the paddle and basket apparatuses which also lack relevance to physiological environment. The dissolution testing may significantly be improved if its role may clearly and objectively be established that the tests are to be conducted only to reflect *in vivo* dissolution characteristics of a product. This clarity of objective will provide an improved basis for selecting appropriate apparatuses and associated experimental conditions. In addition, such an objective will also reduce significant work load by eliminating requirements of repeated IVIVC developments and other physiologically non-relevant testing.

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