Drug Dissolution Testing-Deficiencies and Some Suggestions for Improvement

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Drug dissolution testing is a quantitative analytical technique for assessing drug release from pharmaceutical products, in particular solid oral dosage forms such as tablets and capsules. The reason for conducting the test is that generally for a drug to be absorbed, usually from the gastrointestinal tract, the drug should be in solution form. Thus evaluation of dissolution becomes useful and necessary.

There is ample evidence in the literature to indicate that drug dissolution is critical for drug absorption into the systemic circulation ("bloodstream") or human body in general [1-3]. In this respect, one may consider a dissolution test as a surrogate marker of availability of drug for systemic circulation. Commonly, this availability of drug in the body is known as bioavailability and is defined as, the rate and extent of absorption of a drug into the systemic circulation [4]. The rate and extent of drug absorption are generally represented by maximum observed concentration (C_{max}) of a drug in blood and area under the drug concentration verses time curve (AUC), respectively. In general, drug dissolution results are compared to these *in vivo* parameters.

Describing and comparing these *in vitro* and *in vivo* relationships of drug release are generally referred to as *in vitro-in vivo* correlations (IVIVC) and are conceptually valid and widely accepted [5-6]. However, commonly IVIVC appears to imply that there is a true quantitative aspect of such relationships, which may be reflected from its definition, i.e., a predictive mathematical model describing the relationship between an *in vitro* property (e.g. rate or extent of drug dissolution) and a relevant *in vivo* response (e.g. plasma drug concentration) [7].

There appears to be some confusion in the pharmaceutical community which tends to differentiate between formal (quantitative) IVIVC relationships from semi-quantitative or qualitative assessment (eyeballing) [8]. In reality both are very similar. It is only the extent of relationships which differentiate these, without any distinct separation line. Therefore, it is reasonable to assume that conclusions drawn from dissolution studies should always be a reflection of *in vivo* behavior, whether established qualitatively or quantitatively. Even tests which are considered as quality control tests, including those commonly described in pharmacopeial monographs, to establish batch-to-batch consistency in drug release characteristics of products are in reality applied as a surrogate for *in vivo* performance. The inter batch consistency in dissolution results implies similar consistency *in vivo* and corresponding bioavailabilities. In addition, with the concept of surrogate marker, it is recognized that in limited cases and without any formal IVIVC, that *in vitro* dissolution results should be sufficient *in lieu* of *in vivo* studies to establish equivalence of pharmaceutical products with respect to safety and efficacy of the products [9].

Such confusing and conflicting views, i.e. separating quality control tests from bio-relevant tests, hinder conducting useful and physiologically relevant dissolution studies and in fact have resulted in test procedures with arbitrary choices of apparatuses, media, stirring/mixing rates, etc. [10-11]. Thus, results obtained from such studies may be of limited relevance to pharmaceutical and particular physiological attributes of the products. This appears to be the current ambiguity of drug dissolution testing. The purpose of this article is to highlight issues which may be causing the confusion and to offer some suggestions for potential solutions.

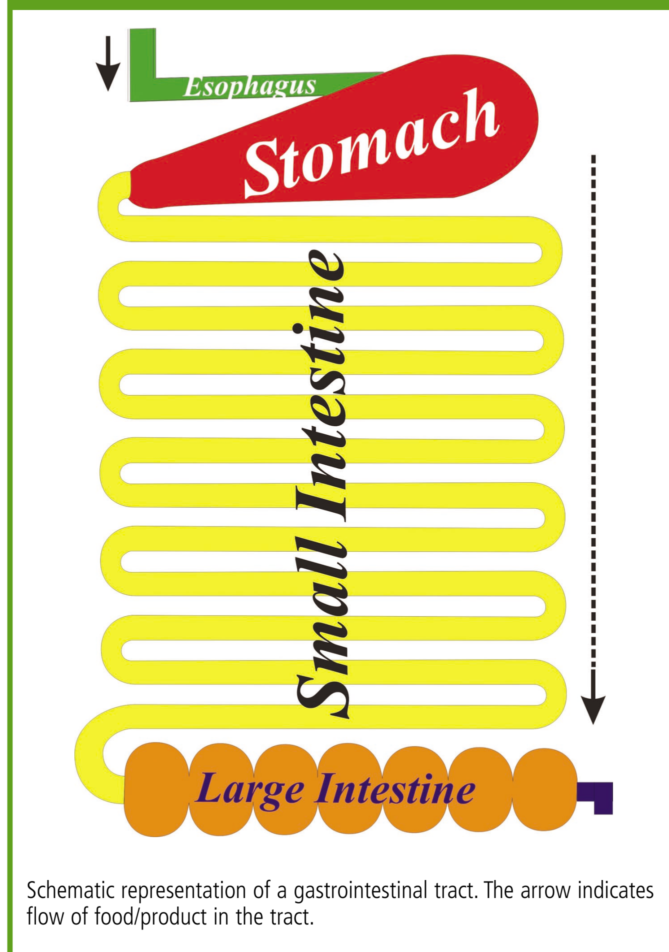
Dissolution testing is considered as an analytical chemistry technique. However, it would be described better if it were considered as a part of biopharmaceutics, a science of studying drug release characteristics of pharmaceuticals in the human body. The primary focus should be on the physiological aspects and the test should be conducted with matching analytical conditions required to simulate the physiological behavior.

In considering physiological related aspects of drug dissolution, there are two important processes of gastrointestinal tract, (1) mechanical and (2) chemical [12]. For the mechanical aspect, the human gastrointestinal tract may be considered as a long multi-segmented tube, having different diameters and shapes, which is packed into small space. There are four distinct segments of the long tube comprising; (1) esophagus, (2) stomach, (3) small (narrow diameter) intestine, (4) and large (wide diameter) intestine. A schematic representation of the gastrointestinal tract is shown in Figure 1. The esophagus and large intestine, generally play limited roles in drug absorption, and may be considered as the segments which facilitate in transporting (esophagus) food/product to and excreting (large intestine) the waste from the absorption area. For drug absorption purposes, stomach and small intestine segments are important and will be referred to as GIS.

Generally, most of the absorption of drugs from products occurs in the small intestine because it has the large surface area available and longer resident time than in the stomach. The stomach may be considered mainly as an area for storage and preparing food/drug for the absorption phase. Therefore, when a drug is taken orally, it spends a short duration in the stomach where disintegration of the products usually occurs along with the mixing of the content of stomach. The non-disintegrating type tablets are stored and pushed into the small intestine.

For the chemical aspect, the GIS may be considered as a flowing

Figure 1.



Schematic representation of a gastrointestinal tract. The arrow indicates flow of food/product in the tract.

stream of an aqueous-based slurry ("soup"), at constant body temperature, with varying pHs usually between 1 and 7.The movement through the GIS is facilitated by peristaltic waves which also help in the mixing of the drug for efficient absorption. Drugs along with other food-related ingredients are absorbed through the wall of GIS tissue. Therefore, three variables; body temperature (~37°C), aqueous based environment with pH range of 1 to 7, and peristalsis for mixing and stirring appear to be important from the perspective of absorption of drug through the GIS. In the case of the dissolution media, while maintaining the pH range, some solubilizing agents, e.g. sodium lauryl sulphate, are added to facilitate dissolution of low solubility drugs [13]. The addition of such solublizing agents mimics the presence of *in vivo* solublizing agents such as bile salts.

Indeed these are the three variables which are used for conducting dissolution tests *in vitro* to simulate the *in vivo* environment. Thus, dissolution tests are conducted at 37°C, in aqueous based media having pH in the range of 1 to 7, with or without solublizing agents, and with a stirring and mixing environment.

The nature of mixing and stirring in the GIS is generally described by peristalsis with some sort of "churning." However, *in vitro* various stirring approaches are used and essentially these form the basis of different dissolution apparatuses. The most widely used apparatus is known as the USP Paddle and is shown in Figure 2 [10]. The stirring in the Paddle Apparatus is achieved with a T-shape stirrer, commonly spinning between 50-100 rpm. The product is placed (dropped) in the medium which is contained in a glass beaker with a round-shaped bottom.

Fundamentally, the concept of dissolution testing is sound and relevant to drug absorption through the GIS. By its nature, it should offer a predictable approach in assessing potential bioavailability of drugs in humans. However, in reality, obtaining bio-relevant dissolution results has been a frustrating experience from the beginning [14]. Even from very controlled studies, conducted with the support of the US FDA, it was observed that despite products with large differences in dissolution profiles, *in vivo* profiles were the same and equal [15]. Obviously this led to the concerns and frustration as to why a sound concept of dissolution testing is not reflected *in vivo* behavior of products.

To address the issue of lack of bio-relevancy of dissolution results, one needs to establish the source of the problems or deficiencies as to why a conceptually strong and relevant test does not provide the expected results. Only finding the source of the problem and then correcting it, will lead to the development of a predictable and useful test. In addition to the lack of bio-relevancy of results, unpredictability and lack of reproducibility of dissolution results are also frequently reported in the literature [16-18].

Recent reports in the literature highlight flaws of *in vitro* hydrodynamics as a potential cause of the problem [19-22]. The hydrodynamic environment within the GIS is generally characterized by intense mixing, churning and spreading (dispersing) [12]. On the other hand, hydrodynamics in a dissolution vessel (apparatus) lack most of these characteristics. In a dissolution vessel, hydrodynamics may be considered as laminar with constant angular velocity but decreasing linear velocity (Figure 2a). This type of flow provides limited mixing/stirring and also will produce a potentially un-stirred zone at the bottom of the vessel. Therefore, because of gravity and laminar flow, the product and its disintegrated aggregate tend to accumulate at the base of the vessel, especially in the case of denser particles/aggregates. This accumulation of particles at the bottom is a commonly observed behavior known as "cone" formation (Figure 2b).

With such hydrodynamics, which produce variable- and/or unstirred zones in the vessel, drug dissolution results are expected to be highly variable. The drug dissolution results appear to correspond to the settling position of the tablets and spread of the aggregates. Slight off-centred tablets and/or slight increases in the spread of aggregate have been shown to provide an increase in results in excess of 40%.

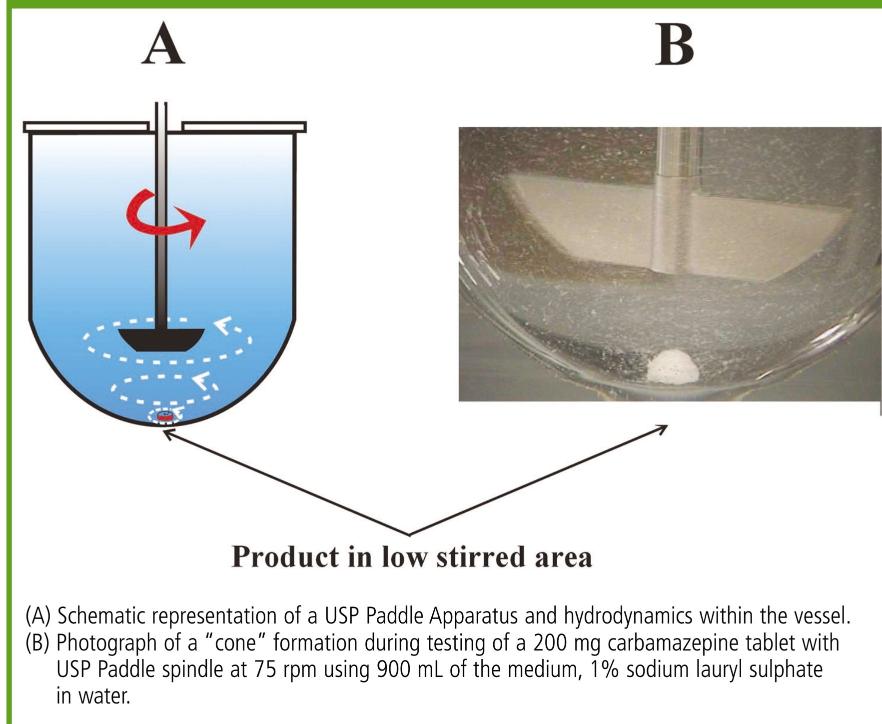
Further, because of the nature of the flow (laminar) and accumulation at the bottom, the product medium interaction will be limited. Thus products will tend to show lower drug dissolution than their true release properties, i.e. fast release products may appear as slow-release products. Such accumulation-based lower dissolution results may not be relevant to *in vivo* behavior as in the GIS significant mixing occurs and products are not expected to be localized at a single place. Therefore, in such cases, obtaining bio-relevant results would be highly unlikely.

Even with non-disintegrating type tablets where, because movement of medium beneath the tablets is generally limited, relatively slower drug dissolution will be observed than the release characteristics of the products [23]. Thus, the two different types (disintegrating and non-disintegrating) of products will give slower drug results than their true release characteristics and expected *in vivo*.

Therefore, not only should one expect high variability in dissolution results, one should also anticipate slower dissolution results than would be observed *in vivo*, thus explaining the lack of relevance to pharmaceutical attributes and IVIVC. In addition, one may also extend this observation by stating that as the settling properties dictate and differentiate dissolution behavior *in vitro* but not *in vivo*, products with different settling characteristics will show significantly different dissolution results but could be expected to show similar release behavior *in vivo*, and thus fail to generate IVIVC for comparative studies. Although such an *in vitro* discriminatory behavior is a common occurrence [15, 24-25], it is actually an artifact of the mixing and stirring technique.

In summary, high variability in dissolution results, slower drug release characteristics than are true of product attributes, and dis-

Figure 2.



(A) Schematic representation of a USP Paddle Apparatus and hydrodynamics within the vessel.
(B) Photograph of a "cone" formation during testing of a 200 mg carbamazepine tablet with USP Paddle spindle at 75 rpm using 900 mL of the medium, 1% sodium lauryl sulphate in water.

criminatory drug release *in vitro* for products with similar *in vivo* drug release, appear to be explained well based on the poor hydrodynamics in the dissolution vessels.

Recently, a new approach based on a new spindle design has been suggested [26]. In this case, a crescent-shaped brush type spindle is proposed to address the artifacts of using the current USP Paddle spindle. The new spindle provides turbulent rather than laminar flow, which does not allow the material to accumulate or to form a "cone," and by raking over the surface of the vessel it forces the material to spread or move around, in the case of non-disintegrating products. The suggested spindle appears to provide an improved alternative for interaction between product and medium and thus improved dissolution. Some applications of this new spindle are provided in the literature, highlighting bio-relevancy of the technique [26-27].

Further evaluation of this or similar approaches of more efficient stirring for improved product-medium interactions may be desirable to obtain improved and bio-relevant dissolution results.

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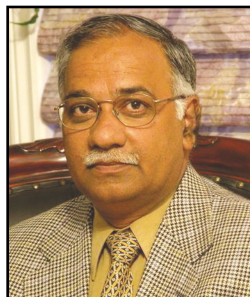

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