Defining a dissolution tester and need for a reference product

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When one mentions or asks for a dissolution tester, immediately the following apparatuses come to mind: paddle, basket (rotating or reciprocating), and flow-through. The question is, why are these apparatuses known as dissolution testers? How do these apparatuses measure and describe a drug product's dissolution (characteristics)? Consider the question in another way. An analyst has a tablet product, e.g., of acetaminophen, and would like to determine the dissolution characteristics of the tablets. Can any one of these testers provide the answer? Not really. These apparatuses provide only an environment for interacting with a product (tablet/capsule) and the dissolution medium. The environment within a dissolution apparatus is no different than within a beaker or Erlenmeyer flask with a magnetic bar in it. Therefore, without some sort of associated and standardized experimental and operating conditions, one cannot obtain appropriate dissolution characteristics of the product. **Indeed, at present, what is lacking is a standardized set of experimental conditions. Thus, an analyst would not be able to determine the drug dissolution characteristics of a product.**

An apparatus to act as a dissolution tester requires a set of associated experimental conditions. Three experimental conditions are to be defined in this regard.

(i) Ability to provide space for an aqueous solution (water or buffer in the pH range of 5-7) and a product to interact freely and efficiently.

(ii) A mechanism to provide slow but thorough product and medium interaction, e.g., stirring.

(iii) Capability of providing i and ii at a constant temperature of 37 °C.

As most drug dissolution tests are conducted for products for human use, the choice of medium, temperature, and stirring are, therefore, dictated by the human GI tract physiology or environment. There is generally no argument about the temperature of 37 °C, which is accepted as a standard. With regard to dissolution medium, generally, there are no arguments about the nature. It is mostly water or an aqueous-based. However, the choice of the medium's pH creates confusion. It is generally suggested that as the pH of the GI tract ranges from 1 to 7 or 8, one may use any or multiple pHs to evaluate dissolution characteristics. Unfortunately, the choice of these pH values (single or multiple) is usually arbitrary and random. Current dissolution testing practice faces this arbitrariness and randomness, thus losing its credibility as a standard and relevant scientific technique.

However, the issue of this randomness can be addressed if one considers the location of drug absorption in the GI tract because dissolution would be required in this area. It is a generally well-established scientific fact that drug absorption mostly occurs in the small intestines,

where the pH ranges from 5 to 7. It is important to note that no discrete segments have specific pH values, but pH may vary from 5-7 from person to person, depending on the type of food one takes, race, gender, genetics, etc. Therefore, dissolution tests may be conducted using media having a pH within this range. Water, which by itself usually has a pH between 5 and 7, appears to offer this choice. A critical aspect is that the total expected amount of drug present in the product must be freely soluble in the volume available (commonly 900 mL) of the dissolution medium. If not, then a small amount of solubilizer is to be added to facilitate the solubility of the drug in the medium. Water (with or without solubilizer) appears to offer such a choice in this regard.

The third variable is agitation or stirring. Its nature and strength are a bit tricky to define. Often arguments are presented that it is not possible to establish a value for this variable. First, it cannot be determined accurately, and if determined, it changes drastically from person to person for the reasons mentioned above. So, rather than establishing an appropriate agitation standard, common practice is to choose any which should not be too soft or not too harsh. However, considering an intestinal environment and process of dissolution within, all that is required is the slow mobility of a product.

Any simple stirring mechanism may be used for such purposes.

Therefore, to summarize, transferring a product-medium interacting environment to a dissolution tester one requires fixing three parameters: (i) dissolution medium, 900 mL of water (with or without solubilizer); (ii) a stirrer set at a certain rotation speed, e.g., 25 rpm; and (iii) maintenance of the dissolution medium or test environment at 37 °C.

Fixing these experimental conditions still would not qualify an apparatus as a dissolution tester because an analyst would not be certain as yet if this combination of experimental conditions will indeed reflect the dissolution characteristics of a product in humans. **The results obtained using the described experimental conditions would be a set of values, not necessarily values reflecting dissolution characteristics of a product in the human GI tract.** One might need to make some adjustments, perhaps to the rotational speed of the spindle (rpm) or the dissolution medium, to link the in vitro environment to in vivo. How would one conduct these adjustments? Only by using a product whose in vivo dissolution value (characteristics) will be known. **Thus, one requires a reference product with dissolution characteristics established independently from the tester, most likely from a pharmacokinetic study.** Therefore, one has to have a product of known in vivo dissolution value to establish it as a dissolution tester. Unfortunately, there is no such (reference) product with associated dissolution characteristics available. Therefore, one cannot use the apparatuses for dissolution testing to assess the quality of the products for human use.

There is a potential alternative to this limitation in the absence of such a reference product with known in vivo dissolution values. This is based on the relative evaluation of dissolution

characteristics of two products of known in vivo characteristics, such as IR and ER products of a drug. IR and ER product differences are based on in vivo characteristics. If these are reproduced in vitro using a single set of experimental conditions, such criteria may be used to link in vitro testing to a known in vivo behavior. Such relative dissolution testing should not only differentiate between release characteristics of IR vs. ER products. Still, it should be able to provide a complete release of the drug, which should occur within prescribed dosing intervals of both IR and ER products. Therefore, in the absence of a reference product, such relative dissolution testing provides an alternative for establishing an apparatus as a dissolution tester. It is very important to note that once one has obtained a satisfactory set of experimental conditions, including agitation (stirring rpm), other products of unknown dissolution ***must*** be tested under these selected conditions.

One can simplify experimental conditions with a crescent-shaped spindle as (i) temperature maintained at 37 °C; (ii) dissolution medium 900 mL water (with or without solubilizer). The need for a solubilizer must be established prior to dissolution testing and is not related to a dissolution tester but the nature of the drug. (iii) 25 rpm, established based on the criteria of relative dissolution using IR vs. ER products of carbamazepine and diltiazem products.

Now, suppose a tablet/capsule product of a water-soluble drug is given to an analyst. In that case, they will be able to test it under these experimental conditions, i.e., 900 mL of water maintained at 37 °C with a crescent-shaped spindle at 25 rpm. Thus, the dissolution results would then potentially represent the product characteristics in vivo. If the results are not as expected, then an analyst has to alter the formulation/ manufacturing attributes but not the experimental conditions. The experimental conditions are linked to the GI tract, which is considered constant for dissolution testing. Under these circumstances, the apparatus using a crescent-shaped spindle will be considered a dissolution tester as it represents testing with experimental conditions developed based on their link to the in vivo behavior of the reference products.

Any old or new apparatus should meet such criteria to be defined as a dissolution tester.

Let us evaluate the most commonly referred dissolution apparatuses based on the abovementioned criteria.

<u>Basket and paddle or apparatus 1 and 2, respectively:</u> Both apparatuses require different experimental conditions for the evaluation of both IR and ER products. In fact, they require different sets of experimental conditions from product to product, particularly for ER products. Thus, they may not be considered dissolution testers. In addition, as stated above, the intestinal GI tract environment requires the mobility of a product and its disintegrants. Both paddle and basket apparatus provide significant stagnation of the products within vessels. Thus, these would lack relevance to the physiological environment leading to a lack of appropriate and relevant dissolution testing.

Reciprocating basket or apparatus 3: There is a lack of data on relative dissolution testing (IR vs. ER) for this apparatus using the same experimental conditions. Some studies have shown stagnation of disintegrants in this type of apparatus. Thus, its use as a dissolution tester may require caution.

Flow-through or apparatus 4: A study (link) shows testing of various release types of products under similar experimental conditions. Therefore, this apparatus might provide a dissolution tester status under those experimental conditions, and this aspect may be further explored. Further work may be required in establishing the use of an appropriate size of a flow-through cell and the corresponding flow rate.

Crescent-shaped spindle apparatus: This apparatus has been developed by addressing artifacts of the currently used apparatuses, particularly the paddle and basket. Using a crescent-shaped spindle provides mobility to the drug product and its disintegrants, thus reflecting in vivo behavior and a mechanism of efficient product-medium interaction. Standard and only one set of experimental conditions have been developed, facilitating simpler, efficient as well as drug and product independent testing. Comparative dissolution studies using a single set of experimental conditions have been described for products with different strengths of the same or different drugs in different release types (IR, ER) of products (e.g., see here).

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