The science of drug dissolution testing: Testers or apparatuses, experimental conditions and interpretation of results - A systematic approach for learning.

Saeed A. Qureshi, Ph.D. (www.drug-dissolution-testing.com)

This article summarizes the principles of drug dissolution testing with an emphasis on the underlying scientific assumptions that are often not clearly described, or understood. It should be noted that the technique itself is extremely simple to use, however, current practices of selecting experimental conditions and the interpretation of dissolution results are seriously misunderstood, and require attention. To address these deficiencies, analysts should seek essential training in the areas of relevant physiology and pharmacokinetics. In the absence of such required training and knowledge of the subjects, it is highly unlikely that an analytical laboratory can generate relevant and accurate dissolution data, thus will fail in meeting the products development and evaluation objectives. Links to some articles on the subjects are provided which may help the analysts in improving their overall skills in these areas.

Drug dissolution testing at its heart is a simple analytical technique for determining the rate of appearance of drug in solution with time at 37 °C. To conduct such an experiment one would obviously require a vessel for the solvent, a stirrer for mixing the drug with the solvent and a controlled temperature (37 °C) environment. The combination of these three things will constitute a dissolution tester or apparatus. To minimize variability from multiple tests, however, an aggregate of 6 to 12 of these testers come as a unit, which is called a dissolution tester as well. The word "drug" has been used in defining the dissolution tester, but it could be any substance from pure common salt (NaCl) to a large Rock (crystalline) Sugar Candy. One can use this tester for determining dissolution characteristics of drug or non-drug products using a variety of solvents, stirring/mixing speeds and temperatures. The point being, it is a simple analytical test for the evaluation of the dissolution of solid products, thus named a dissolution test.

For drug product testing, however, the use of experimental conditions are linked to the human physiological environment, in particular, the GI tract. This physiological environment is represented by aqueous based solvent (e.g. water itself), temperature of 37 °C and some form of gentle mixing/stirring (which facilitate appropriate product/solvent interaction). Note that in the area of drug dissolution testing the solvent is commonly referred to as the "dissolution medium". At different times, samples are withdrawn to measure the amount of drug in the solution using any of the commonly used quantitation techniques such as spectrophotometric or chromatographic. The quantitation technique is not considered part of a dissolution tester, just like a printer or monitor may not be considered as a part of a computer but one is required to observe the output of the computing.

It is worth repeating that a dissolution tester is a tester having a combination of three parts: a vessel, a stirrer/mixer and an environment (water bath or otherwise) to maintain temperature. Considering common use and requirement of such testers for product development and evaluation, these are commercially available from a number of vendors and can be purchased in ready to use configurations. These testers are generally rugged and usually last a long time.

The training for operating the testers can be obtained from the vendors of the testers. It is important to note that dissolution tester training means, learning how to operate the instrument such as setting up the temperature, rpm, pouring the required amount of solvent into vessels and introducing the tablets/capsules followed by withdrawing samples using a syringe with a long needle at times. This is the precise description of the training for a dissolution tester. It is just like learning the operation of a TV or DVD player. No more, no less!

Again, it is very important to note that a dissolution tester is a combination of a vessel and a stirrer with a temperature controlled environment or mechanism.

The problems or complications starts when these simple apparatuses are considered or promoted as testers for monitoring the quality of drug products (for QC purposes) or for predicting plasma drug levels implying that the apparatus reflects or simulates the stomach or human GI tract. This is simply an inaccurate description and representation of a dissolution tester and this fact must be kept in mind. A dissolution tester should simply be considered a dissolution tester i.e. it can only provide dissolution results and nothing more. The results, however, may then be used for whatever purpose considered appropriate, independent of the tester.

The use of a dissolution tester can be explained with an analogy of using a chromatograph for analyzing plasma samples to determine drug levels in them. The analyst performs the chromatographic test and obtains the results. These results are used for developing a drug concentration-time profile which leads to the assessment of bioavailability (BA) and/or bioequivalence (BE) of a product. One does not consider a gas/liquid chromatograph a BA/BE or drug/product quality/efficacy tester. Similarly, a dissolution tester should not be called or considered a quality control tool, simulated stomach or BA/BE tester which would be an incorrect description, and misrepresentation of the reality! Such descriptions are often falsely used as marketing tools to promote training for dissolution testing.

The technique of drug dissolution testing can be divided into three distinct, but inter-linked, components: (1) Tester and its operation (2) Choice of experimental conditions (3) Interpretation of results.

(1) ***Tester and its operation***: A dissolution tester, as described above, is a mechanical apparatus for deteriming solution formation. In its operation, it is very close to a mixing setup such as a vortex mixer with a test tube containing some solvent or solution, or a flask with some solvent and a magnetic stirrer. One almost does not need training to operate a dissolution tester. However, as one cannot use a dissolution tester as a standalone, like a vortex mixer or flask with stirrer, but has to be used along with an analytical instrument, for quantitation, such as chromatographic (HPLC/GC) or spectrophotometer (UV) to measure the extent of solution formation, training is necessary. Therefore, a dissolution tester or testing is usually part of analytical chemistry group/practice, because to conduct an appropriate dissolution test one requires a good grasp of analytical instrumentations (HPLC, GC, UV etc) and methods (development, validation, etc). Often dissolution testing trainings and literature provide description/discussion of parameters such as specificity, calibration curve, precision, LOQ, etc, (see the USP General Chapter <1092>) which in fact are not part of dissolution testing but of analytical method development/validation common to any analytical method. Therefore, it is important to note that such trainings are not for dissolution testing per se but of general analytical chemistry with an emphasis on chromatographic and spectrophotometric methods. One should be aware of this confusion which exists in literature and the industry.

(2) ***Choice of experimental conditions:*** It is obvious that a dissolution tester by itself is not of much use unless it is used with the appropriate experimental conditions. An appropriate dissolution test requires a set of three experimental conditions (1) solvent or medium (2) stirrer or mixer, and (3) temperature. How should one decide what these should be? This is where the real/actual dissolution testing part starts. To answer this question one has to ask why a dissolution test is conducted. The answer is that a dissolution test is conducted to represent dissolution of a drug from a product (tablet/capsule) in the human GI tract, which is necessary for the absorption of drug into the body to provide its efficacious effects. Therefore, the choice of experimental conditions is linked to the GI tract physiology.

It is very important to note that it is quite common in the industry that a dissolution test is described as an in vitro test for quality control purposes or to monitor batch to batch consistency of a product, without its link to the physiological aspect. This is a simply untrue and false description of the drug dissolution testing that has been the cause of serious confusion and damage to the practice of drug dissolution testing.

On the other hand, to make the test legitimate, often references are made to the GI tract physiology in selecting experimental conditions. These references are often based on anecdotal views and not on the understanding of the necessary physiology. For example, as all drug products (IR and ER) go through a common physiological environment then why are so many, in the hundreds, product dependent experimental conditions or methods employed to represent the common and single physiological environment? The answer is that, at present, one does not deal with the true/actual GI tract physiology, but a GI tract physiology "designed" for the convenience of

the analysts, so that the use of currently recommended dissolution testers and practices of testing may be promoted and implemented (marketing!).

The point being, if one likes to decide on the choice of experimental conditions, it is highly recommended that one should learn from someone experienced in physiology (university teacher) or physiology literature. Experimental conditions should not be selected without some knowledge and understanding of GI tract physiology. In this respect, I have written a short and simple article on the physiology of GI relevant to drug dissolution test which may be useful (Link).

Interestingly, if one considers the underlying physiological characteristics, one leads to the conclusion that most drug dissolution tests can be conducted using distilled water as a dissolution medium, with the addition of some solubiliser if a drug has a limited aqueous solubility (Link). So, either employ water as the medium or select a more suitable medium but with a very clear basis of physiological reasoning.

Similarly, regarding two other experimental conditions i.e. temperature and stirring and mixing, commonly dissolution tests are conducted at 37 °C representing physiological (body) temperature. There is no argument about it, thus all dissolution tests should be conducted at 37 °C.

Concerning the stirring mechanism and speed, definitely a large pool of confusing arguments exists in the literature. The cause of these arguments does not appear to be based on scientific/physiological reasoning, but on trivial and often invalid logics which can make dissolution testing almost a "voodoo science". Unfortunately, the choice of the most commonly used stirrers (basket/paddle) is perhaps the worst choice for the job (Link). These stirrers, not only lack physiological relevance, they often cannot even provide stirring or mixing at all. Therefore, if it is possible then the analysts should avoid these apparatuses as the results obtained will be of no use.

On the other hand, if one considers the underlying GI tract physiological characteristics, then it becomes clear that one requires a simple stirrer which could provide gentle but through mixing or interaction of the product and the medium. Based on this physiological consideration I have suggested a modified stirrer which provides much improved product/medium interaction, thus bio-relevant testing (Link). However, if one prefers to use one's own, make sure that stirrer should provide gentle and thorough mixing and must make physiological sense.

In short, the choice of experimental conditions is dependent on the underlying physiological environment. Therefore, for dissolution testing some familiarity with the physiology of the GI tract is essential.

(3) ***Interpretation of dissolution results:*** Dissolution results are often reported as percent drug dissolved at time. Suppose, one has done a dissolution experiment and obtained dissolution results e.g. 80% drug dissolved in 30 minutes. The question is what should one do with this number or numbers if one measures dissolution at multiple times? This number is exactly like a number an analyst obtains for the absorbance of a solution from UV spectrophotometer or peak height/area from a chromatogram. One cannot use this number (results) in any useful way until these numbers are linked to the objective of the test. What is the objective of the dissolution test? As stated above, a dissolution test is conducted to simulate or estimate dissolution of drug in the GI tract. So, if we have dissolution results from the GI tract, also known as in vivo results, then we can compare them directly and are done with the drug dissolution testing. However, unfortunately, one cannot measure the in vivo dissolution results directly, at least in most cases. These in vivo dissolution results are measured indirectly using plasma drug levels, so one has to know how this in vivo, and by extension in vitro, dissolution is linked to the plasma drug levels. Note that, this is purely a results/data conversion step. In my opinion, the job of a dissolution scientist is not completed until the scientist/analyst provides the simulated plasma drug levels calculated/derived from the dissolution results.

How should one convert dissolution results into plasma levels? For such a conversion, the analyst is required to know some basic principles of pharmacokinetics, the science of drug disposition in the bodies. It is exactly like that for selecting dissolution experimental conditions one has to know some physiology, similarly for data conversion one is required to learn some basic principles of pharmacokinetics. It is unfortunate that current practices often draw conclusions from the raw dissolution results (percent drug dissolved at times) concerning plasma levels and/or quality of products for human use, without linking the dissolution data to plasma levels. Therefore, this aspect of dissolution testing i.e. data interpretation, perhaps is the most confused and abused aspect of drug dissolution testing, at present.

One should seek a basic understanding of the pharmacokinetic principles through a university course or through literature, however, the analysts have to learn it. It is a requirement. To provide help in this regard, I have published articles describing the necessary principles of pharmacokinetics to predict/estimate plasma drug levels (Link 1, 2). It is important that the analyst should avoid interpreting raw dissolution results or drawing conclusion from them regarding plasma drug levels or profiles, or quality of a product because these interpretations/conclusions may invariably be incorrect.

In conclusion, a drug dissolution tester/apparatus is a simple form of a mixing/stirring arrangement, which practically does not require a training to operate. However, for conducting an appropriate dissolution test/study using relevant experimental conditions followed by pertinent interpretation of dissolution results reflecting plasma drug levels requires basic training in human GI tract physiology and pharmacokinetics. Thus, it may be prudent for an analyst in the area of drug dissolution testing to seek help from people who have a strong analytical chemistry background with sound training and understanding of relevant physiology and pharmacokinetics.

For further information on the topic and/or relevant available trainings, please contact moderator@drug-dissolution-testing.com