Selecting a Dissolution Apparatus – Some Practical Considerations

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A commonly asked question is how one should select a dissolution apparatus. It may be of interest to know that, such a question is often asked when a dissolution analyst gets frustrated with the unexpected or unanticipated dissolution behavior of a test product. Such a question is seldom asked at the beginning of the project as it is always understood or assumed that one will most likely use a paddle apparatus. Furthermore, the analyst will try some variations of rpm (50, 75 or 100) or medium (different buffers and pHs). If this does not work, then perhaps the basket apparatus will be tried with similar variations in rpms and buffers. In the end, the analyst usually settles with a test which will provide the ***anticipated/expected*** characteristics of the test product.

Most likely, then, the tested product will go to the bioavailability/bioequivalency testing. It is possible that the dissolution method may reflect bio-relevancy of the results (***a matter of chance***). However, in most cases, the bio results will disappoint the analyst, as they will be the opposite to what was anticipated. At this stage, the question would be what should be done? Suggestions are often made to try a different apparatus (USP 3 or 4) as the analyst already has exhausted testing ("playing") with the paddle and basket apparatuses.

Now let us consider this scenario a bit critically. The question is why did the analyst expect that the dissolution results will reflect the bio results? Is there evidence that these apparatuses (paddle/basket) are capable of providing bio-relevant results? Not really! Even the USP states that the dissolution test, only under some specified circumstances, may reflect the in vivo behavior of the product (link). Then why carry out this exercise? The reason is that traditions and worldwide regulatory expectations dictate that every manufacturer and laboratory has to go through this "ritual" of finding a test that matches bio-behavior of the test product. If not successful in obtaining bio-***matching*** results, the commonly held opinion is that one has not tried enough, otherwise some matching testing/experimental conditions would have been found to reflect bio-results. This is from where the question or suggestion of the use of other apparatuses originates!

Now the next questions are: why and how should the other apparatuses (USP 3, 4 or others) work or help? Are these apparatuses validated to provide bio-relevant results? Of course not! They even have shorter history of use/validation than paddle/basket apparatuses. They (USP 3 and 4) can certainly provide a different experimental environment, in particular, testing ability using multi media. Is it the lack of availability of multi media testing using the paddle/basket apparatuses which causes the observed lack of bio-relevancy in results? Probably not, there is no evidence available in support of this assumption. By the way, dissolution testing using multi-media (having different pHs such as 1.2, 4.6 and 6.8) is commonly conducted using paddle/basket apparatuses as well.

Is it not that one should first determine what could possibly be the reason that the paddle/basket apparatuses did not provide bio-relevant results. If the reason is not known then what is the point of trying, and investing large financial resources for a new technique or continue testing?

Let us theorize first the possible cause of the problem with an analogy as to why the dissolution testing might not have worked using paddle/basket apparatuses. The analogy is that a patient is given a two weeks supply of an antibiotic as a suspension taken orally to treat a condition. After a couple of days, the patient returns with a complaint that the product is ineffective. The physician asked the patient to bring the bottle back with the remaining medication. The physician observes that most of the medication is still present ("settled") at the bottom of the bottle. Obviously, the patient forgot the instruction of shaking and mixing the medication before taking it, thus lack of effectiveness. A similar situation exists with the dissolution testing, where most of the time results are based on the ***supernatants*** while the product is settled (stagnant) at the bottom of the dissolution vessel. Such a situation would obviously not occur in the physiological environment which a dissolution tester simulates. Obviously, the dissolution test will not reflect bio or physiological results. There is plenty of evidence in literature which shows that indeed this lack of mixing/stirring

within the dissolution vessel is the main cause of the problem. There have been incredible efforts, in the analogy of antibiotic suspension, in improving the quality of the bottle and product inside, however, until and unless thorough mixing, prior to administration, is not done the medication will be ineffective. Similarly, no matter how precise the dissolution apparatuses are and how controlled the experimental conditions would be, without stirring and mixing, it will not be possible that they will simulate the expected physiological environment.

It may also be important to note that the other apparatuses described in the pharmacopeia also suffer the same deficiency that they also do not provide thorough stirring and mixing of the content. Therefore, they will also suffer the same problem and most likely will not help in reflecting bio-relevancy of the results.

Therefore, rather than starting with a different or new piece of equipment which most laboratories may require to purchase, a more cost effective approach would be to modify the paddle or basket apparatuses itself so that they provide an improved stirring and mixing environment.

In this regard a new spindle is proposed which corrects this deficiency of the paddle/basket apparatuses (link). Details about the use of this spindle have been described in literature and on this blog. It is a simple and cost effective option to address the deficiency of currently used paddle and basket apparatuses.

So, in short, most commonly used apparatuses (paddle/basket) possess an inherent deficiency or flaw of not providing a stirring and mixing environment necessary to appropriately simulate bio or physiological environment. This mismatch of the environments will results in dissolution results which will not reflect corresponding bio-results. To obtain, bio-relevant dissolution results dissolution testers require an appropriate stirring and mixing environment. The use of the crescent-shape spindle appears to help in this regard by providing an improved stirring and mixing environment leading to bio-relevant results.