Dissolution Testing: Is this the best we got? No, this is the worst which we are required to accept!

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A drug dissolution test is an analytical test of such significance that it is hard to imagine that any oral drug product such as tablet and capsule would be developed and manufactured without its use. The majority of the tests are conducted using testers commonly known as paddle and basket apparatuses. It is a well accepted, and implied, understanding that not using one of these apparatuses will require a long and unkind explanation for deviating from the "norms" resulting in potentially extensive and costly delays in bringing the products to the market. Therefore, the simple and logical choice is just to use these even though it is well described in literature that these apparatuses are not fit for their intended purpose [link, link].

Drug dissolution tests are conducted based on the principle that for a drug product to be effective, it must release its drug in the human GI tract where it should dissolve for its absorption into the blood stream [link]. The dissolution test is conducted to assess this in vivo or physiological drug dissolution. On the other hand, it should be noted that the test, using paddle and basket apparatuses, has never been validated for such a purpose [link]. Studies described in the literature clearly show that these apparatuses should not be used for such purposes as they do not provide an appropriate physiologically (GI tract) relevant environment (e.g. stirring and mixing) and/or results [link, link]. Therefore, results obtained from these tests will be of no relevance or use, let alone able to establish quality of the products.

Numerous official documents, using different acronyms such as SUPAC, BCS, IVIVC, bio-waivers and ICH, with increasing complexities, utilizing dissolution testing, are recommended for the assessment of safety, efficacy and quality of the drug products [link]. More recently, two new documents [link, link], perhaps even more complex and confusing than those previously described, have been introduced with the acronym Q*b*D (Quality by Design). Presumably, these documents are recommended for streamlining/improving manufacturing processes and their evaluation. These documents are also based on drug dissolution testing using the same flawed apparatuses and practices such as IVIVC [link, link].

An example of the implementation of the flawed concept or practice is a recommendation (official position) that bio-waivers may be granted for certain products based on just drug dissolution testing. However, as described earlier, it has never been shown that the dissolution tests using paddle/basket apparatuses provide bio-relevant results for such (IR) products [link]. Therefore, usefulness of the above mentioned recommendations and corresponding documentations is of questionable merit. Hence, these documents and respective recommendations need to be reconsidered on an urgent basis.

Another confusing, and scientifically even weaker case, at present is the use of these dissolution apparatuses/tests for quality control purposes i.e. as pharmacopeial tests. In this respect, it is often described that for a QC test, the dissolution test does not have to be physiologically relevant [link]. It is to be noted, and as described above, the dissolution test was introduced to assess physiological (GI) dissolution which leads to its use as a QC test. Without its physiological link, the test loses its credibility as a QC test, because then there are no grounds available for establishing experimental conditions and linking dissolution to product attributes. Hence, the experimental conditions and dissolution results become irrelevant. This is precisely what the current situation is i.e. dissolution test as QC tests described in pharmacopeias are based on arbitrary choice of experimental conditions and tolerances with no relationship to the quality attribute of the products [link]. Furthermore, the paddle/basket apparatuses have been shown to provide extremely variable and unpredictable results [link].

From a scientific perspective one of the main requirements for conducting an appropriate dissolution test is the use of a stirring and mixing environment in which the dissolution medium (solvent) and product are able to interact efficiently [link]. The suggested apparatuses (paddle/basket) do not provide this interacting environment. Experimental studies as described in literature have clearly demonstrated that these apparatuses probably offer the worst choice for the medium/product interaction or physiological simulation [link, link, link]. However, official documents persistently recommend the use of these apparatuses for QC testing (pharmacopeial) as well as for the physiological evaluations of the products (as per the above mentioned documents). Therefore, it would be safe to consider that this is the worst (apparatuses choices) the industry is required to accept.

The problem is not that options for addressing these flaws are not available, there are [see e.g. link, link], or that improved methods cannot be developed. It is, however, the implied insistence that dissolution tests should only be conducted using officially recognized apparatuses, even though they are known to be flawed. Therefore, one should be extremely cautious in following the recommended apparatuses/procedures, as invariably these tests will result in false conclusions regarding the quality of the pharmaceutical products.

The scientists/analysts/manufacturers/standard-setting-organizations in the pharmaceutical area should seek dissolution methods with sound scientific basis with link to pharmaceutical and physiological relevancy, if success is to be achieved in attaining the desired quality of the products.