Comments on a recent article

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I read a recent article published in the *American Pharmaceutical Review* titled "A Rational Approach to Development and Validation of Dissolution Methods" by G.P. Martin. In the article author suggested approaches one may take in developing drug dissolution testing methods.

It is unfortunate that the author ignored the current views and literature highlighting flaws of current practices of drug dissolution testing. Not only are the scientific approaches described in the articles are weak, more appropriately inaccurate, the logical thinking would also not support the arguments presented. For example, it is stated that:

1. "*The test will be performed using a standard compendial apparatus, …*". However, it is very well known that these apparatuses have never been validated and/or qualified for the intended purpose of evaluating dissolution characteristics of a product for human use. Therefore, use of these apparatuses will not assure accuracy of the test or dissolution characteristics of a product, thus quality of the products.

2. "*The dissolution results for most release samples will reach 80% within 60 minutes*." If such information is to be available, then there must already be a dissolution method available to indicate such dissolution characteristics. Then, what is the purpose of developing a new method, in particular using the test product?

3. "*The method will be discriminating with respect to significant manufacturing changes and/or changes on stability."* A dissolution test is conducted ***only*** to evaluate dissolution characteristics of a product, not to evaluate manufacturing differences. This view for method development for evaluating manufacturing changes is inaccurate. There are two reasons for that: (1) a dissolution test has no link to the manufacturing aspect just like a thermometer can only monitor body temperature but cannot determine the sources causing the changes in the temperature (2) Differences in manufacturing and their observance, in particular using dissolution testing, do not reflect poor quality of a product. Products manufactured using differences in manufacturing can be of equally good quality (e.g. generics).

4. *"Starting with the QC dissolution test, the first order of business will be to collect information. What is known about the dosage form? Is it intended to be an immediate release, extended release or delayed release oral product, or something different? This will help to identify the time scale for the dissolution test, and could influence other parameters of the test"*. If one is able to identify whether a product is of immediate release (IR) or extended release (ER) type, it could then be argued that what is purpose of developing a dissolution test. Furthermore, how would it be established in the first place whether the product is of IR or ER type. In actuality, the author is suggesting that one should first know dissolution characteristics and then select or propose experimental conditions which would reflect his or her perception about the dissolution characteristics of the product. Such an approach completely defeats the purpose of developing dissolution methods.

5. *"The preferred stirring speeds are 100 rpm for baskets and 50 rpm for paddles, making these good speeds for initial development experiments."* There is a lack of any scientific reason in choosing such RPM. In reality, it is a very well established fact that spindles (baskets/paddles) rotating at such RPMs provide very poor hydrodynamics within the dissolution vessel and often completely misrepresent the dissolution characteristics of a product.

6. *"Note: it is a good idea to avoid pH values around a pKa of the drug, where a fraction of the drug is ionized and the remainder is un-ionized, since this can lead to reproducibility issues"* This could be true for any pH, not necessarily at pH equivalent to pKa, where some drug will be ionized and remainder will be unionized. On the other hand, keeping in mind that drug dissolution occurs in the

intestinal part (where most of the drug absorption occurs), and the pH of the dissolution medium for in vitro studies should then be comparable to the pH of the intestine, in the range of 5 to 7. If the physiological aspect, or its pH ranges, are to be ignored then dissolution methods may be developed at any pH value including 8 and higher.

7. *"It is best to select a pH where the dissolution medium will be able to dissolve at least three times the amount of drug present in the vessel, since it is known that as a solution nears saturation, the rate of solubilization can slow down."* If that is the case, then should not one be able to choose pH 8 or higher? In reality, it is not the solubility and/or the sink condition which dictates the choice of the pH of the medium, but the physiological environment of the GI tract, where the required pH should be between 5 and 7.

8. *"With dissolution testing, it is possible to design many different test conditions which may give widely varying results; how do you know which is the most appropriate set of conditions? This question actually leads us to the possibility of different goals for a dissolution test."* In essence this means a single product can have different dissolution characteristics or values and one may chose the one which fits the purpose. Interesting! Following this with the analogy of using of a thermometer, one may say that one should have separate thermometers for healthy people and for the sick. Furthermore, by extension of this logic, one should also have thermometers depending on the nature of the sickness. Bizarre! It is important to note that a product can have only one dissolution value. Suggesting or obtaining different dissolution values for a single product is scientifically and logically invalid.

9. Although the title of the article includes the word "validation" of dissolution methods, the article content does not provide any suggestion as to how a method is validated. Interestingly, whole article does not contain the word validation with the exception of the title. It is important to note that for validation of a dissolution method (i.e. method is suitable for determining dissolution characteristics of a product) one would require a reference PRODUCT approved for human use which is not available at present. Therefore, the article content may not be considered reflective of the title.

In short, the article appears to have been written with poor and inaccurate scientific understanding of dissolution testing and its requirements. The readers of the article should be cautious in following the suggestions provided to avoid potential frustrations and unexpected outcomes from their studies.

PS: These comments have been shared with the author of the article, however, a response has not been received at the time of this posting.