Potentially Incorrect Interpretation of In Vitro Dissolution Characteristics of Products – Glimepiride

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Often I have written about the deficiencies (flaws) of the Paddle and Basket apparatuses in obtaining relevant and useful dissolution results. The underlying cause of these deficiencies is a poor stirring and mixing environment within dissolution vessels. However, as a long held tradition, these apparatuses are recommended and used for dissolution testing. As the apparatuses do not provide a relevant in vivo environment, obviously in vitro results would not be relevant to in vivo characteristics of drugs and their products. However, ***to maintain the status quo, the dissolution results obtained are rationalized as legitimate and useful***. Considering practice of rationalization of dissolution results and noticing numerous queries in this regard about a drug glimepiride, I came across a publication (link) which may help in explaining the current dilemma of an analyst in dealing with in vitro drug dissolution testing.

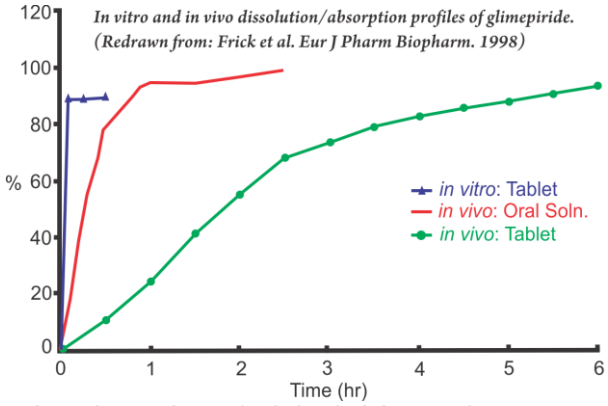
The publication describes in vitro drug dissolution testing of glimepiride products along with two other drugs. The discussion here, however, is restricted to only glimepiride product. The reported dissolution tests were conducted using a Paddle apparatus (75 rpm) with phosphate buffer (pH 7.8).

The in vivo dissolution profiles were calculated by means of numerical deconvolution using the glimepiride plasma concentrations from a bioavailability study. These profiles are shown in Figure 3 of the publication, which is redrawn here for the convenience of the readers. The in vivo dissolution results show a prolonged release profile where more than 80% of the drug is dissolved (released) in approximately 4 hours.

The conclusion drawn from this study as described in the publication is as follows: "*In contrast to in vivo dissolution, glimepiride is dissolved in vitro very rapidly after 15 min (80%). No correlation exists between in vitro dissolution (80% after 15 min) and in vivo dissolution (80% after 4 h)* ***because of the pH dependent, low solubility of the drug*** (emphasis is mine)".

It is not clear how this conclusion was drawn that the lack of correlation was due to the low solubility and pH dependent behavior of glimepiride. One can argue that this lack of correlation could be due to the mismatch of in vitro and in vivo environments. For example, it is highly unlikely that a drug/product would have seen a pH of 7.8 in the small intestine where most of the absorption occurs. In this region, pH is usually less than 7. Thus, if in vitro dissolution test would have been conducted at pH 7 or lower say 6.8, then the in vitro dissolution rate would have been significantly lower and could be nearer to the in vivo rate. In addition there is also a strong possibility that 75 rpm may have provided higher agitation than needed which may also have caused the faster dissolution in vitro.

The point being that for an appropriate in vitro-in vivo comparison one should first ascertain that both environments are similar. It is, however, a common practice that people assume that some arbitrarily selected set of test conditions using Paddle/Basket apparatus with 50, 75 or 100 rpm and a buffer having any pH should provide bio-relevant results. Obviously, it will not be possible. For bio-relevant testing, the in vitro testing environment has to be as close to the in vivo environment as possible.



The mismatches of stirring/mixing environment and the pH between in vitro and in vivo may very well be the cause of lack of bio-relevant results. A thought which should be kept in mind when planning for future studies in this regard.

The bio-relevancy aspect aside, glimepiride is a drug which is frequently noted for its problems in drug dissolution testing. In this regard, common explanations or rationalization of such problems are that of pH dependency and low solubility of the drug. Seeing the figure again, only from the in vitro aspect, using commonly recommended dissolution testing conditions, one should not expect problems from the drug dissolution testing. The product shows a dissolution behavior of a highly soluble drug product. Then, why are problems often encountered and suggestions are sought for addressing these problems?

The problem is not that of the drug (glimepiride) itself, it is the problem of testing of the ***low content products***. Similar problems of unpredictability and high variability in results, thus potential failures, have been reported for other low content products e.g. glibenclamide/glyburide, USP Prednisone Performance Verification Tablets. The reason being, Paddle/Basket apparatus provides unstirred area/pocket, thus there could be very high variability in results from tablet to tablet or lab to lab. It is quite possible that if one uses a different vessel or set of vessels, differences in curvatures of the vessels ***even within specifications*** can significantly increase or decrease dissolution results. It is an inherent problem of using Paddle/Basket apparatus, in particular Paddle, which is almost impossible address using these stirrers. Therefore, please keep these thoughts in mind when evaluating drug products in particular with low content. High variability and unpredictability in results, thus failures, are to be expected. Do not blame yourself or your product.