Assessing and Generating Useful Drug Dissolution Profiles – A Practical and Bio-relevant Approach

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

This article provides a discussion based on data presented in literature that a direct comparison of dissolution results (profile) with blood levels (C-t profiles) can lead to misleading interpretation. For a more appropriate comparison dissolution results should first be converted to C-t (plasma drug conc.-time) profiles. Examples are provided for converting dissolution profiles, using convolution techniques, to C-t profiles which provide improved evaluation of dissolution results. The article also presents an argument, that for proper reflection of bio-relevancy of dissolution results, the tests require higher agitation (or product/medium interaction) relative to what is provided by the paddle apparatus at 50 and 75 rpm.

The quality of a drug product, such as tablets and capsules, depends on its ability to deliver the expected amount of drug, and in a consistent manner, into blood (systemic) circulation. This delivery of drug in turn depends on the release/dissolution of the drug from the product in the GI tract, in particular the intestine. The dissolution in the GI tract, or in vivo, is evaluated by an in vitro dissolution test. As direct measurement of the in vivo dissolution is very difficult, if not impossible, it is indirectly measured based on primarily plasma (representing blood) drug concentration-time (C-t) profiles. Therefore, to evaluate the quality of a drug product based on in vitro drug dissolution characteristics, one requires equating or comparing the in vitro dissolution profiles to the C-t profiles. A schematic representation of these in vivo and in vitro approaches is shown in Figure 1.

A quantitative comparison of the in vitro and in vivo profiles is highly desirable and, indeed, there have been tremendous efforts to develop methodologies for comparing the profiles based on a practice known as IVIVC (in vitro-in vivo correlations). However, such attempts have not been successful. Therefore, one often resorts to qualitative comparisons (eye-balling), i.e. if the in vitro drug dissolution profiles show some rank order similarity to the C-t profiles then it is considered a success as well e.g. a level C, IVIVC. Unfortunately, even the qualitative approach seldom works which obviously adds to the frustration in legitimizing the use of a dissolution test or its practice. In this regard, an example is presented here from literature highlighting the difficulties in assessing dissolution profiles or characteristics. Furthermore, this article provides a different approach for improved development and quantitative evaluation of the dissolution profiles.

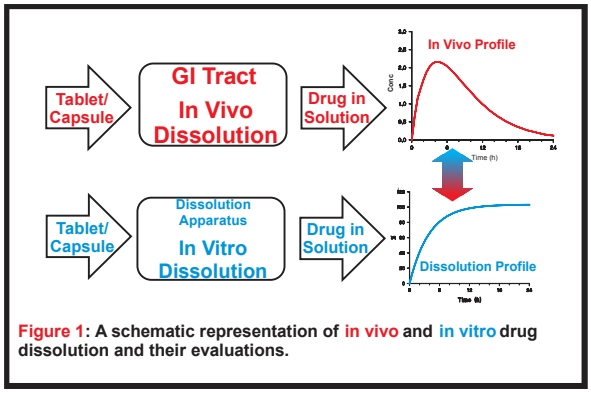

Figure 1: A schematic representation of in vivo and in vitro drug dissolution and their evaluations.

In the study from literature [1], referred in this article as *"the publication"*, dissolution characteristics of four IR deoxycycline hyclate (capsule/table) products from German market were analyzed using the WHO and US FDA suggested methods. The methods are recommended for bio-waiver applications and are based on testing products using media having a pH 1.2, 4.5 or pH 6.8. However, for simplicity and brevity, discussion here is limited to the results obtained using phosphate buffer (pH 6.8) only. In addition, it may be argued that the use of a medium having pH of 6.8 may be the most relevant as it represents the intestinal environment where mostly the drug absorption occurs. The suggested methods require the use of USP paddle apparatus. The only difference between the methods is of the paddle rotation speed, which is 75 rpm for the WHO suggested method while 50 rpm for the US FDA

one. The dissolution profiles are reproduced here (Figure 2) from *the publication* for the convenience of the readers. It is important to note that these products are available on the German market as equivalent based on their human bio-equivalencies evaluations, the results of those evaluations are also provided in *the publication*. However, based on the significant differences in dissolution characteristics (Figure 2) it is obvious that these products do not appear to reflect dissolution characteristics of bio-equivalent products.

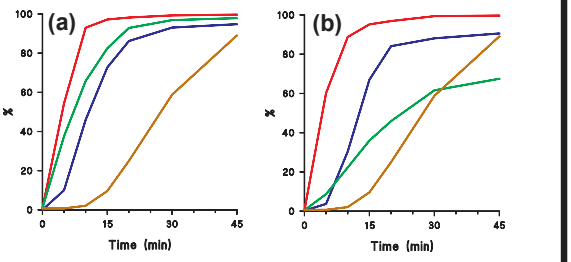

Figure 2: Dissolution profiles of IR doxycycline hyclate products in phosphate buffer (pH 6.8) using USP Paddle Apparatus set at (a) 75 rpm (WHO method) and (b) 50 rpm (US FDA method).

It may be of interest to note that a parameter, similarity factor or F2, is often used for the comparison of the dissolution profiles. The F2 is used for comparing the dissolution profiles **among** themselves, but it is not linked to the bio-relevancy or bioequivalency of the products. The analysts/formulators often struggle with this lack of clarity and interpretation of this parameter which often causes confusion and frustration.

A more appropriate approach to assess the dissolution profiles should be the one in which dissolution profiles are linked to the C-t profiles. Such a link can be made by converting dissolution profiles to C-t profiles and then these C-t profiles are compared between themselves or with the corresponding in vivo C-t profiles based on the commonly used C_{max} (highest observed concentration on C-t a profile from a bioavailability study or predicted from dissolution results) and AUC (area under the curves i.e. C-t profiles) parameters.

The method commonly used to convert dissolution profiles into C-t profiles is known as convolution. The convolution step requires relatively simple arithmetic calculations which can be performed using spreadsheet software such as MS Excel. Details about the calculation and underlying principle of convolution method are described in literature [link].

Using the convolution method, dissolution results from *the publication* were converted to C-t profiles as shown in Figure 3.

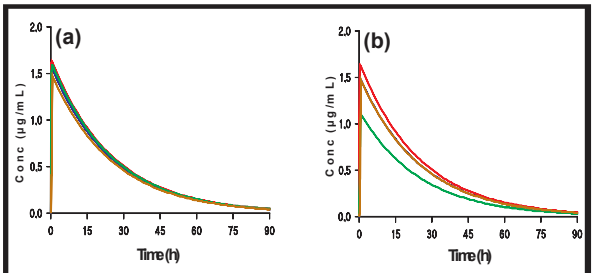

Figure 3: Predicted (estimated) drug concentration-time (C-t) profiles from the two sets of dissolution results as shown in Figure 1. (a) 75 rpm (WHO method) and (b) 50 rpm (US FDA method).

This conversion is based on single exponential elimination rate equation (one compartment model) for deoxycycline as suggested by Welling et al. [2]. The equation is based on an elimination half life of 17.4h. In addition, a bioavailability factor (F)=0.95 (or 95%) and volume of distribution (V_d)=57 L were used for the calculations. The values of half life and V_d represent averages from a number of studies as summarized by Saivin and Houin [3].

Figure 3(a) shows predicted C-t profiles obtained from dissolution results using the WHO method (75 rpm). The C-t profiles show very similar behaviour (profiles) of these products as one would expect from bio-equivalent products. So, what happened here? Significantly different dissolution profiles produced similar C-t profiles. Magic! Not really! The dissolution results are usually reported in percentages as obtained from the experiments, i.e. no data conversion or manipulation is involved. However, the body takes these percentages of dissolved drug and processes (eliminates) them using an exponential scale. Note that the

elimination step in pharmacokinetics does not follow linear but exponential (or log based) decay. In addition to exponential decay of the amounts of drug for each segment of dissolution, the remaining amounts from all previous segments are all added up. This data conversion or manipulation (logarithmic decay and addition) results in significantly dampening the differences of the dissolution results.

This discrepancy, because of scaling or data conversion can be explained with an analogy. For example, a company has 6 levels of salaries for its employees which are $1000, $2000, $5000, $10,000, $100,000 and $1,000,000. There is a 1000 times difference between the lowest and highest levels. To avoid the potential concern about such a large disparity in salaries, the company decided to report these levels based on a formula by taking the log of these numbers (3, 3.3, 3.7, 4, 5 and 6) and then adding to each number all the previous numbers obtained after the log conversion (with an explanation in small print only!). Therefore, these salary levels will become 3, 6.3, 10, 14, 19 and 25. Now, the "apparent" difference between lowest and highest salary is of about 8 times only, not 1000 times.

One can argue that if the body does not reflect the differences of the in vitro dissolution levels or profiles then one can ignore the variability in dissolution results testing, as the C-t profile appear to provide "similar" C-t levels. In this regard, it should be noted that differences in drug dissolution results are real, just like differences in salaries but masked by the exponential conversion and addition. It is a somewhat similar situation as with the measuring of pH where the difference of a single pH unit reflects a difference of a multiple of 10 in the concentration of hydrogen ions. That is why pH is to be measured or controlled in a small pH unit and not in percentages e.g. the allowed variability in pH for a dissolution medium (pH 6.8) is only 0.05 units. However, if a usual percent deviation of 5 to 10% in pH would have been allowed, then this allowance would be of 0.34 to 0.68 pH units, which would result in a very large allowance in variation of hydrogen ion concentrations. The point is, one should not compare different sets of results obtained using different scales. They will both have their own set of values and variation in their scaling units. However, they can be compared as usual where data is obtained using the same scale. Therefore, a direct comparison of results and/or variations in the results between dissolution results and plasma levels can lead to erroneous conclusions. The dissolution results should first be converted to C-t profiles and then these profiles should be compared among themselves and/or with those obtained from human bio-availability studies.

Now the question is, why are these in vitro dissolution results so variable? The reason is, which is now commonly known, that this variability originates from the testing itself because of lack of proper stirring and mixing within dissolution vessels (see link1, link2). *The publication* provides an indirect support for this view as well. Compared to the dissolution results from 75 rpm, 50 rpm provides, Figure 3(b), a lower dissolution rate with wider variations between dissolution characteristics of the products. The stirring and mixing impact is so low at 50 rpm that one of the products only showed dissolution of around 60%. Authors of *the publication* reported that there was significant cone formation with 50 rpm, which is another way of describing the lack of proper product/medium interaction or stirring and mixing.

Authors of *the publication* suggested that for comparing the results with bio results, the choice of 75 rpm may be more appropriate as the results obtained represent bio-behaviour better ("closer dissolution results") than at 50 rpm. However, this argument can be further extended to a scenario in which if one would have done the testing at 100, 150 or higher rpm then the dissolution results may have been faster and even closer, reflecting even better similarity to C-t profiles. Point being, the data and physical observation (coning) suggest that a higher agitation (stirring and mixing) is required to represent the GI tract environment than provided by the paddle apparatus at commonly used speeds

of 50 and 75 rpm. An impact of simulated higher agitation and resulting C-t is shown in Figure 4.

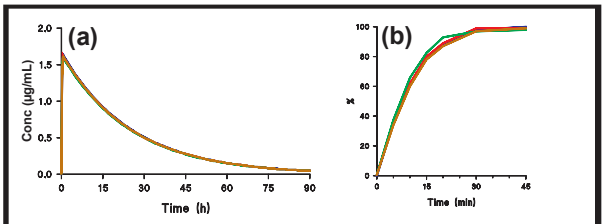

Figure 4: Predicted drug concentration-time (C-t) profiles (a) for the same four products shown in Figure 2, but with dissolution profiles (b) obtained with a higher simulated agitation.

It is important to note that it is not necessary that one has to use higher rpm, a different mechanism or approach (e.g. crescent-shaped spindle) can provide much improved product/medium interaction even at lower rpm. The critical aspect is the need of a higher level of agitation or product/medium interaction within a dissolution vessel.

Unfortunately, the dissolution community appears to have the mindset that if agitation were to increase then the discriminatory ability of the test will be lost and some "nonexistent" differences between products will not be observed. At present dissolution tests are conducted at lower agitation (rpm) knowingly that they provide irrelevant differences. However, higher agitation or different agitation mechanisms are not considered because of a fear of missing out on these differences. This is really an unfortunate situation with huge waste of human and financial resources, which should be controlled and mitigated.

Furthermore, current practices of dissolution testing leads to a related conflicting requirement. The testing requires similar dissolution profiles for products having similar blood profiles and at the same time dissolution test are expected to show differences in dissolution profiles between these products. It is like saying that a bioequivalence study should show products being bioequivalent and at the same time the study should also discriminate between these products. Obviously, not only is this logic flawed but also an unachievable objective. A dissolution test should be conducted using such experimental conditions, including agitation, that it should provide similar dissolution profiles for bioequivalent products.

As these products, as described in *the publication*, are bioequivalent but show differences in in vitro dissolution results or characteristics, it confirms that choice of experimental conditions are inappropriate for testing for bio-waiver purposes. The data presented in *the publication* clearly suggests that the experimental conditions require higher agitation or product/medium interaction, if relevant dissolution profiles are to be obtained i.e. similar dissolution profiles for bio-equivalent products.

Conclusions:

1. Direct comparison of dissolution results (profile) with blood levels (C-t profiles) can lead to misleading interpretation regarding the similarity/dissimilarity bio-behaviour (bioequivalency) of products.

2. For a more appropriate comparison dissolution results should first be converted to C-t profiles, using convolution technique, which then should be compared with the C-t profiles obtained from bioequivalence study.

3. To reflect appropriate in vivo dissolution behaviour of products higher agitation or product/medium interaction is required than what is provided by the paddle apparatus at 50 and 75 rpm.

References:

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3. Saivin, S, and G Houin. 'Clinical Pharmacokinetics of Doxycycline and Minocycline'. *Clinical Pharmacokinetics* 15, no. 6 (December 1988): 355–366.