Predicting Blood Concentrations-Time (C-t) Profiles from Drug Dissolution Results without Developing an IVIVC – Validation

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Drug dissolution tests are conducted with an implicit or explicit objective to gain information about the potential drug release characteristics of a product in vivo, in particular in humans. As in vivo drug release is difficult to measure directly, dissolution results are compared with blood C-t profiles which are dependent on the in vivo dissolution of the drug.

The direct method to link the in vitro drug dissolution results to the in vivo results is to convert dissolution results into C-t profiles. This conversion step is known as convolution (link). In this regard, a spreadsheet based convolution method has been suggested (link). The procedure is quite simple and uses a few pharmacokinetic parameters of the drug. The values of these parameters can be obtained from the literature (e.g. see link), thus concurrent bioavailability studies are not required. The convolution approach is independent of the drug and the product type (IR/ER).

At present, the approach most often described in the literature to evaluate drug dissolution results is of in vitro-in vivo correlation or IVIVC, which requires the use of deconvolution technique to derive potential in vivo dissolution behaviour or profile of the drug. These derived in vivo results are then compared with the in vitro dissolution results to obtain a relationship. A must requirement for this approach is, therefore, to conduct one or more bioavailability studies using the test products. It is often stated that if one achieves this correlation (IVIVC), then the dissolution test method provides credibility and that it may be used to predict appropriately potential C-t profiles in humans for such products. It is important, and critical, to note that the deconvolution approach does not provide expected drug levels or C-t profiles. It only indicates that, if successful, then the particular dissolution method may predict the C-t profiles.

If one requires prediction of C-t profiles, as are necessary for the development and evaluation of pharmaceutical products, then the convolution technique is the only choice (link). There is no need for the development IVIVC as the convolution technique directly predicts blood levels.

The methodology of determining C-t profiles has been described earlier. However, this article provides validation of this approach based on a study described in literature. The objectives of this article are: (1) to demonstrate that if one is given dissolution results of different products, C-t profiles can easily be predicted from them; (2) to show that there is no need to conduct bioavailability studies, the needed pharmacokinetic (PK) parameter values can be obtained from the literature; (3) derivation and comparison of the AUC and C_{max} values of the predicted C-t profiles with those reported from the bioavailability studies ; (4) overall validation of the convolution technique based on comparison of results obtained from the bio-bioavailability studies.

The dissolution data (results) used in this article is obtained from a publication (Avramoff & Domb (2010), In-vitro and in-vivo characteristics of a modified-release double-pulse formulation for a water soluble drug. *Int J Clin Pharmacol Therapeut. 48:250-258* which will be referred in this article as *"the publication")* and is redrawn as shown in Figure 1. *The publication* provides both in vitro and in vivo evaluation of four diltiazem products, one of the innovator's and three in-house developed. To convert these dissolution profiles into C-t profiles the required PK parameters (bioavailability, volume of distribution and elimination rate equation) values are taken from the literature (link) and are the same used initially in developing the convolution approach.

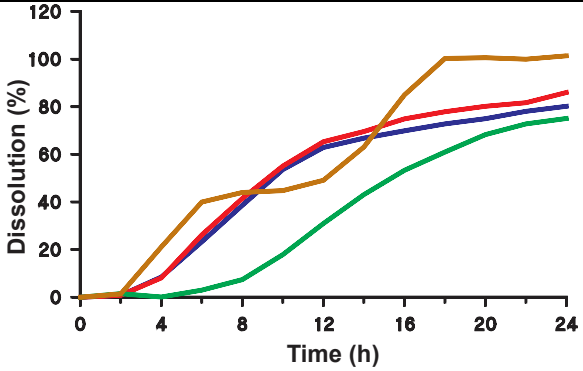

Figure 1: Drug dissolution profiles of four diltiazem products as described in the publication. See text for further explanation.

Predicting C-t profiles from dissolution results requires five steps: (1) Converting percent drug release values from a dissolution test into discrete amounts (doses, in mg etc) within every sampling interval; (2) multiplying this by the drug's bioavailability factor for converting into the amounts that will be available in the blood; (3) calculating decreasing amounts of drug in blood with time, separately for every dose/amount segments, using the drug's elimination rate equation; (4) Adding all the calculated drug levels (amounts) for every time; (5) Dividing amount in blood at every time by volume of distribution to calculate the blood concentration of the drug. This provides the predicted C-t profiles. These calculations can easily be performed using spreadsheet software (e.g. MS Excel). If it helps, a sample spreadsheet may be obtained by sending an email to moderator@drug-dissolution-testing.com.

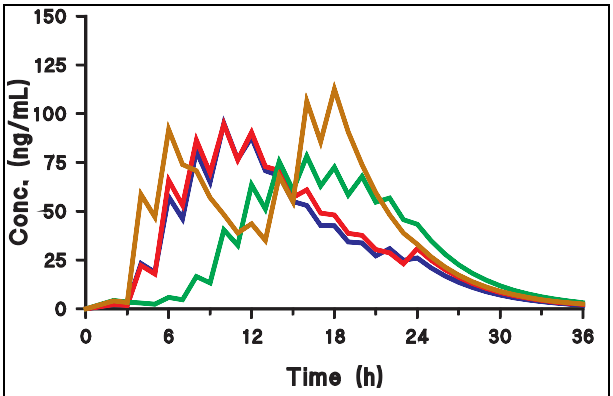

Figure 2: Predicted C-t profiles based on drug dissolution characteristics of four diltiazem products as shown in Figure 1.

The predicted C-t profiles are shown in Figure 2. The following summarizes the observations and their interpretations:

(1) The predicted C-t profiles show a similar pattern as those which are obtained experimentally from bioavailability studies as shown in *the publication*.

(2) The intent of the study described in *the publication* was to obtain a two phase drug release in the body, however, only a single phase was observed, but with extended-release characteristics, from the in-housed prepared formulations. The predicted C-t profiles from the in vitro dissolution results match the profiles as shown in *the publication*.

(3) Only the innovator product appears to provide a two phase drug release. A similar two-phase drug release pattern in humans is predicted from in vitro dissolution results using the convolution approach.

(4) The derived AUC and C_{max} values for three out of four products are similar to those reported in *the publication* from the bioavailability studies. One of the formulations (F1) provides higher predicted values. The reason for this discrepancy is unclear, perhaps because of high variability in the bioavailability data.

(5) It is to be noted that in general nominal values of AUC and C_{max} obtained from predicted C-t profiles (Table 1) are lower than those of the innovator's product. However, this discrepancy can be explained based on observed lower dissolution results of the in-house products. These lower dissolution results may be because of the deficiency of the paddle apparatus, where some drug usually remains in the unstirred (stagnant) areas within the dissolution vessels (link). Therefore, use of the paddle apparatus requires caution for such IVIVC evaluations. However, if normalized to 100% drug release, all products provide similar values for the AUC and C_{max}.

Table 1: PK parameter values derived from the predicted C-t profiles shown in Figure 2.

Product	%Dissolution	C_{max} (ng/mL)	T_{max} (h)	AUC (ng.h/mL)	C_{max} (h)	AUC (ng.h/mL)
F1	80	95	10	1164	119	1451
F2	86	95	10	1246	110	1449
F3	75	78	16	1083	104	1442
REF	101	113	18	1470	111	1450
	Obtained from predicted C-t profiles				Normalized to 100% dissolution	

(6) *The publication* also describes dissolution testing using water as a medium, but having a pH of 5.5. Although, the dissolution test show two-phase dissolution profiles using this

medium, it did not correlate well with the bioavailability results. The dissolution results obtained using phosphate buffer (pH 6.8) provided a more accurate reflection of bioavailability behaviour. This is an expected observation/behaviour as most of the drug absorption usually occurs in the intestine where the pH is generally higher than 5.5.

(7) The results described in *the publications* are based on a dose of 240 mg. The AUC and C_{max} values correspond to the respective values obtained from a 120 mg ER tablet product as reported earlier from our own laboratory (link). This is an indirect confirmation that even results from not only different products but also different laboratories can also be compared easily.

(8) The results from our laboratory were obtained using the crescent-shaped spindle. Therefore, agitation intensity/effect, not the hydrodynamics, of crescent-shaped spindle at 25 rpm and that of with the paddle at 50 rpm may be considered equivalent. However, unlike the paddle apparatus which requires multiple and product dependent experimental conditions, the use of the crescent-shaped spindle provides an added advantage that it uses a single common set of experimental conditions to test different strengths and types of products (IR/ER).

(9) The use of such a convolution technique may be beneficial in selecting sampling times for future bioavailability studies to establish shapes of C-t profiles and their parameters (e.g., C_{max} and/or T_{max}) more accurately, thus improved product development.

(10) Such a convolution approach may facilitate in differentiating sources of variability, product vs physiological, thus providing a tool to design improved products and their drug release characteristics.

In conclusion, the above described observations and interpretations clearly demonstrate and validate the fact that the convolution technique can predict C-t profiles accurately. The technique, as described, appears robust as it can be used in comparing data across products and laboratories.