Prediction of plasma drug levels from dissolution results for OROS-based nifedipine products

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Drug dissolution tests are routinely conducted to evaluate drug release characteristics of pharmaceutical products such as tablets and capsules. It is highly desirable that these tests should be conducted to reflect in vivo drug release which in turn is reflected by the observed plasma drug conc.-time (C-t) profiles in humans.

In this regard, a simple convolution based method using spreadsheet software has been suggested to convert dissolution results into C-t profiles (*link1, link2*). This article provides another example describing estimation of plasma drug levels from OROS-based nifedipine products using the suggested convolution approach.

For this example, dissolution results are obtained, from literature [1-3], for two 60 mg and one 30 mg extended-release nifedipine (Adalat-OROS) tablet products. These products are extended release type using an osmosis-based drug release mechanism and are designed to release the drug at a constant rate over an extended time period, usually 24 hours.

For the convenience of readers of this article, the dissolution profiles are redrawn from the three publications [1-3] and are shown in Figure 1. Dissolution results were reported using media having different pHs, however, values used for this article are those obtained from using a medium having a pH of 6.8, which reflects the pH of the intestinal part of the GI tract where most of the drug absorption occurs.

The detailed theoretical and practical description of a procedure for converting dissolution results to plasma levels have been described earlier (*link1, link2*). Briefly, to determine C-t profiles the analysts will require three common pharmacokinetic (PK) parameters of the drug (nifedipine) which may be obtained from literature. These PK parameters are: (1) elimination rate equation, most commonly based on elimination rate constant (k_e) derived from elimination half-life ($t_{1/2}$); (2) volume of distribution (V_d) and; (3) oral bioavailability (F). The nifedipine PK parameters used for this article are 0.418 h^{-1}, 2.26 l/kg, and 45%, respectively. For further details and the source of these values, please see the *link*.

Converting dissolution results into plasma drug level profiles 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 these 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 individual times; (5) Dividing amount in blood at every time by volume of distribution to calculate the blood concentration of the drug which provides the predicted C-t profiles. The derived or predicted C-t profiles for the three nifedipine products are shown in Figure 2.

The values of PK parameters (C_{max}, T_{max}, AUC) from human bio-studies as reported in the publications [1-3] and calculated from the predicted C-t profiles are summarized in Table 1.

Results and conclusions:

(1) The suggested convolution approach predicted PK parameters' values fairly accurately.

(2) The observed differences in the predicted values and values from the bio-studies may not be reflective of prediction error, but a reflection of the high variability associated with the nifedipine pharmacokinetics in humans.

(3) Such differences in PK values may be observed even between human bioavailability studies (e.g. compare Study 1 vs study 2).

(4) In general T_{max} values are higher for the predicted values. This may be the result of poor/slower stirring and mixing environment using the paddle method. A faster and more rigorous stirring mechanism, such as the use of the crescent-shape spindle, may address this discrepancy.

(5) Overall the suggested convolution approach provides a simple, accurate, efficient and scientifically valid method for predicting C-t profiles for the development and evaluation of products.

References:

1. Schug, B.S., Brendel, E., Wolf, D., Wonnemann, M., Wargenau, M., Blume, H.H., 2002. Formulation-dependent food effects demonstrated for nifedipine modified-release preparations marketed in the European Union. Eur J Pharm Sci 15, 279–285.

2. Schug, B.S., Brendel, E., Wonnemann, M., Wolf, D., Wargenau, M., Dingler, A., Blume, H.H., 2002. Dosage form-related food interaction observed in a marketed once-daily nifedipine formulation after a high-fat American breakfast. Eur. J. Clin. Pharmacol. 58, 119–125.

3. Wonnemann, M., Schug, B., Anschütz, M., Brendel, E., De Nucci, G., Blume, H., 2008. Comparison of two marketed nifedipine modified-release formulations: an exploratory clinical food interaction study. Clin Ther 30, 48.

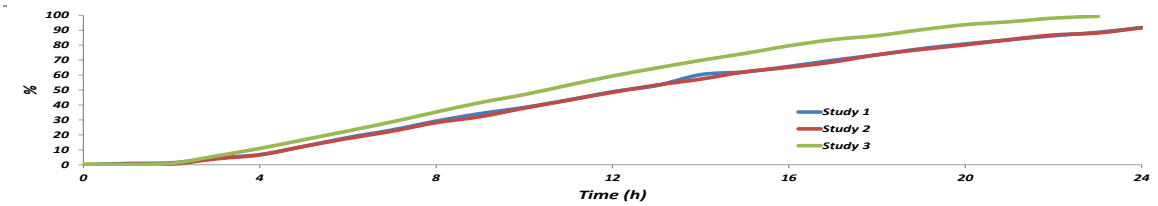

Figure 1: In vitro dissolution profiles of Adalat OROS tablet products using phosphate buffer pH 6.8 with Paddle apparatus [Source: reference 1-3].

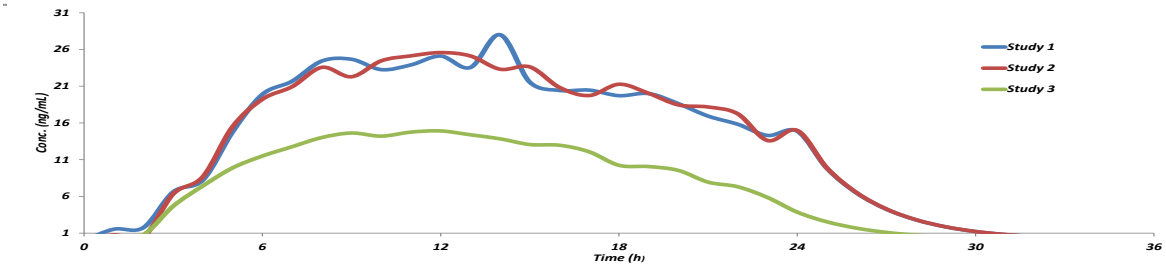

Figure 2: Predicted plasma concentration-time (C-t) profiles of nifedipine Adalat OROS tablet products

Table 1: PK parameters reported from human bioavailability studies [1-3] vs predicted from dissolution results

		From Human bio-studies		Predicted
		Fasted	**Fed**	
Study 1 (60 mg)	C_{max} (ng/ml)	23.2	27.4	28.0
	T_{max} (h)	9.0	9.0	14.0
	AUC (ng.h/ml)	321.0	357.3	421.9
Study 2 (60 mg)	C_{max} (ng/ml)	31.0	38.0	25.6
	T_{max} (h)	10.0	8.0	12.0
	AUC (ng.h/ml)	393.0	468.0	421.4
Study 3 (30 mg)	$C_{max(ng/ml)}$		19.2	14.9
	T_{max} (h)		10.3	12.0
	AUC (ng.h/ml)		361.3	238.9