Predicting Drug Concentration-Time (C-t) Profiles for Metoprolol Tartrate Tablet Products in Healthy Human Volunteers and a Sub-population Group

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The prediction of drug concentration-time (C-t) profiles in humans is highly desirable and needed for appropriate development of products and to establish their quality during production. A simple method to predict or estimate the C-t profiles, based on the convolution approach, has been suggested [link].

This article provides an application of the approach for the evaluation of metoprolol tartrate tablet products. Furthermore, it demonstrates that the approach can also be used to predict the C-t profiles for a sub-population as well.

To determine C-t profiles the analysts will require three common PK parameters of the drug which may be obtained from literature or the pharmacology/biopharmaceutic books. 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 PK parameters used for this article are 0.173 h^{-1}, 5.6 l/kg, and 38%, respectively. For further details and source of these values, please see the link. For procedural details of the convolution technique please see the following links (a, b, c).

The dissolution results used in determining the C-t profiles were obtained from a study described in literature [1] and are drawn in Figure 1.

The derived or predicted PK parameters obtained from the dissolution results were compared to the PK parameters obtained from bioavailability/bioequivalence study for the same products as reported in another publication in the literature [2]. The following summarizes the observations and their interpretations:

(1) Three products were prepared to have different in vitro dissolution characteristics (fast, medium and slow) compared to the reference (innovator's) product.

(2) Corresponding predicted C-t profiles, based on convolution technique, are shown in Figure 2. The C-t profiles show rank order similarity of C_{max} and T_{max} with dissolution profiles, as one would anticipate for products having different dissolution characteristics.

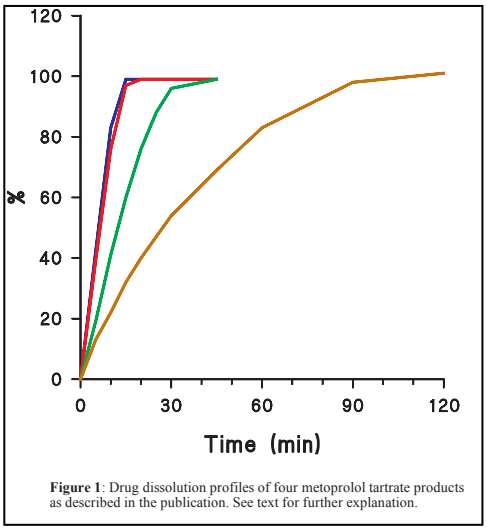

Figure 1: Drug dissolution profiles of four metoprolol tartrate products as described in the publication. See text for further explanation.

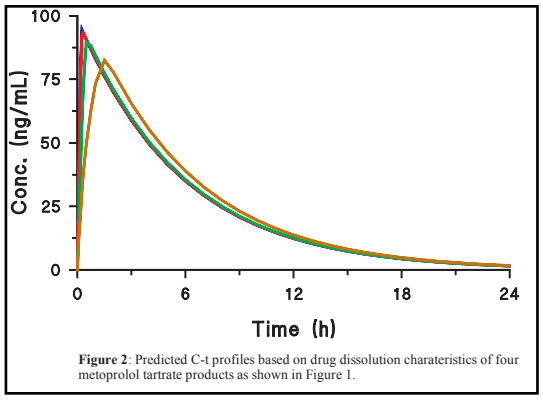

Figure 2: Predicted C-t profiles based on drug dissolution charateristics of four metoprolol tartrate products as shown in Figure 1.

(3) Although it was anticipated that vastly different dissolution results, in particular for the slowest release product, would show bio***in***equivaleny of the product against the innovator's product, this was not the case. All products showed bioequivalency to the innovator's product.

(4) As noted above, slight rank order differences are observed in the predicted C-t profiles. Considering the expected higher variability from the physiological environment, it can be

speculated that these differences may not result in bio***in***equivalency of the products.

(5) It may be argued that differences in in vitro dissolution profiles, using current practices, may be poor indicator of products' biological or physiological characteristics. On the other hand, predicted C-t profiles provide more accurate and relevant product characteristics.

(6) The predicted C-t profiles overall compares well with those obtained from bioavailability studies as reported [2]. Thus, the convolution approach appears to provide a suitable approach for predicting the blood profiles.

(7) Values of the PK parameters from the reported bioavailability study and predicted profiles compared well and are presented in the Table 1. However, AUC values from the predicted C-t profiles appear relatively larger than observed from bioavailability study (see further discussion below).

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

Product	C_{max} (ng/mL)	AUC (ng.h/mL)	C_{max} (h)	AUC (ng.h/mL)
REF	94.5	552	89.4	445
Slow	82.5	565	80.3	408
Medium	89.5	550	88.6	417
Fast	93.2	553	96.2	463
	Calculated (using $t_{1/2}$ = 4h)		As reported from the bio-study[Ref. 2]	

(8) Dissolution tests were conducted in three media having pHs 1.2, 4.7 or 7.0 and using basket apparatus set at 100 rpm [2]. There were no significant differences observed between tests using different media. It was concluded that the products were independent of media effect.

(9) As bioavailability results do not relate to in vitro results, use of basket apparatus at 100 rpm, therefore may be considered as to provide bio irrelevant dissolution characteristics. Perhaps, significantly higher agitation intensity of stirring and mixing is required to overcome these exaggerated (false) differences in vitro results.

(10) To predict C-t profiles one requires values of the PK parameters which are obtained from literature. These values are often reported as ranges with considerable variations, often large. The most practical way to use these values for predicting C-t profiles is to use the average values, which work well. However, in some cases these average may not provide an accurate estimate of C-t profiles and their derived parameters, as it observed in this (metoprolol tartrate) case, the predicted values came out significantly larger (see Table 1).

Table 2: PK parameter values derived from the predicted C-t profiles shown in Figure 2 using $t_{1/2}$=3h.

Product	C_{max} (ng/mL)	AUC (ng.h/mL)	C_{max} (h)	AUC (ng.h/mL)
REF	94.0	421	89.4	445
Slow	78.7	432	80.3	408
Medium	88.3	419	88.6	417
Fast	92.3	421	96.2	463
	Calculated (using $t_{1/2}$ = 3h)		As reported from the bio-study[Ref. 2]	

(11) A close examination of the study design and pharmacokinetic of the metoprolol reveals that metabolism of metoprolol occurs at significantly different rate in a given population. The population is often divided into two subgroups i.e., extensive and poor metabolizers. The bio-study included only extensive metabolizers, i.e., only those volunteers were included in the study, which have high elimination rates or (shorter half life). The reported value of half life for metoprolol is 3 to 5 hours. For the routine calculations a half life of 4 (average of 3 and 5) was used. However, for the extensive metabolizers the calculations required a shorter half life of 3 hours. The results obtained using a shorter half life did not have much impact on the shape of the profiles, however, values of the PK parameter were reduced significantly and came closer to those reported for the bioavailability study. In reality, change in PK values reflects reduced bioavailability, which in essence would be the case with extensive metabolizers. Thus, it is concluded that the suggested convolution approach can also be used to differentiate different sub-populations.

References:

1. James E Polli, G. Singh Rekhi, Larry L Augsburger, and Vinod P Shah. 'Methods to Compare Dissolution Profiles and a Rationale for Wide Dissolution Specifications for Metoprolol Tartrate Tablets'. *Journal of Pharmaceutical Sciences* 86, no. 6 (June 1, 1997): 690–700.
2. Rekhi, G S, N D Eddington, M J Fossler, P Schwartz, L J Lesko, and L L Augsburger. 'Evaluation of in Vitro Release Rate and in Vivo Absorption Characteristics of Four Metoprolol Tartrate Immediate-release Tablet Formulations'. *Pharmaceutical Development and Technology* 2, no. 1 (February 1997): 11–24.