Prediction of the *In Vivo* Behaviour of Modified Release Formulations of Metoprolol from *In Vitro* Dissolution Profiles Using the ADAM Model (Simcyp® V8)

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Objective

To predict plasma metoprolol concentration – time profiles after administration of different oral formulations from *in vitro* dissolution profiles.

Introduction

The Advanced Dissolution, Absorption and Metabolism (ADAM) model was developed to predict the rate and extent of intestinal drug absorption and metabolism and associated inter-individual variability [1]. The capabilities of the model have now been extended in Simcyp® V8 (www.simcyp.com) to handle modified release formulations, including up to four *in vitro* dissolution profiles per compound (incorporating gastric and intestinal release profiles in fasted and fed states).

Method

Metoprolol was used as a model drug to evaluate the ADAM model in predicting the *in vivo* performance of three different extended release formulations. Simcyp ® V8 library values describing the physicochemical characteristics of metoprolol and its elimination and distribution were used in the simulations. The volume of distribution value was assigned from published *in vivo* studies and the clearance was predicted from *in vitro* data obtained using human liver microsomes.

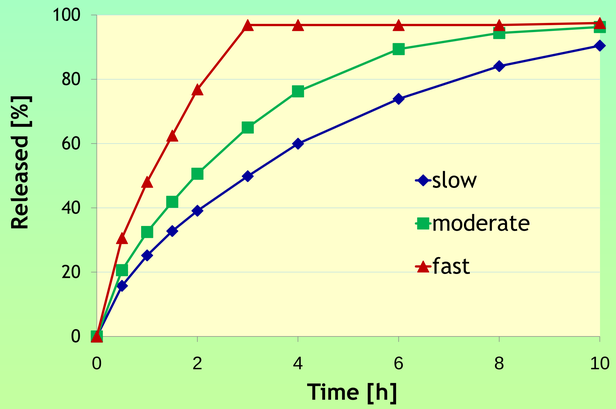

Figure 1: Extended release i*n vitro* dissolution profiles

The *in vitro* dissolution profiles for the 3 formulations (fast, moderate and slow release) were taken from reference [2] (Figure 2).

To mimic the clinical study [2], ten virtual trials with seven individuals (fasted state, CYP2D6 extensive metabolisers, male:female ratio - 4:3; age 33-47) were simulated. The subjects were each given a single 100 mg oral dose of metoprolol in the three different formulations. The ADAM model was used to predict values of t_{max}, C_{max} and AUC and plasma concentration - time profiles.

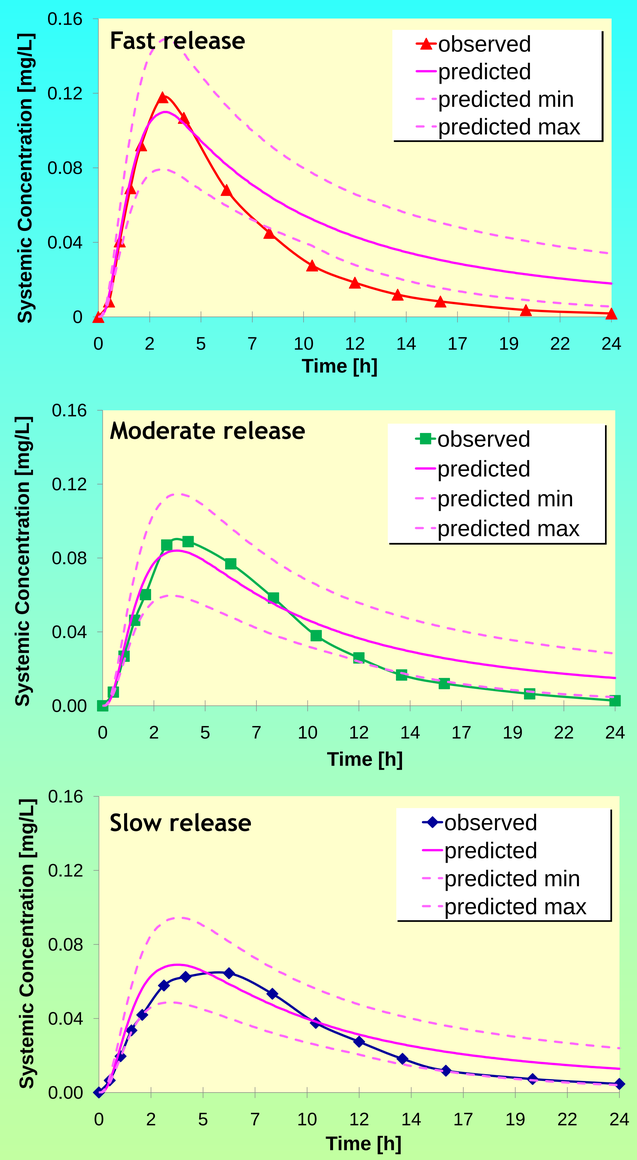

Figure 2: Mean, Max and Min *in vivo* predicted (n=70) and observed plasma metoprolol concentrations

Results

The predicted and observed data are shown in Figure 2 (a single simulation trial) and Table 2.

Table 1: Predicted *vs.* observed PK parameters

Formulation	t_{max} [h]		C_{max} [mg/L] (SD)		AUC [mg/L·h] (SD)	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
Slow	4.9	3.6	0.064 (0.014)	0.070 (0.015)	0.696 (0.17)	0.809 (0.69)
Moderate	3.6	3.5	0.086 (0.029)	0.084 (0.018)	0.812 (0.28)	0.959 (0.81)
Fast	3.1	3.2	0.108 (0.031)	0.110 (0.023)	0.791 (0.19)	1.171 (0.97)

Table 2: ratios of predicted and observed PK parameter ratios for different formulations

Formulations Ratio	Cmax [mg/L]		AUC [mg/L·h]	
	Observed	Predicted	Observed	Predicted
Fast/Moderate	1.26	1.31	0.97	1.22
Fast/Slow	1.69	1.59	1.14	1.45
Moderate/Slow	1.34	1.22	1.17	1.19

Conclusions

The ADAM model successfully predicted the plasma concentration profiles for all three modified release formulations, and was able to capture the differences between them based on the *in vitro* dissolution profiles. Thus it promises to be a useful tool for designing bioavailability and bioequivalence studies. As part of this, since the model also provides measures of inter-individual variability, it can be used to estimate the statistical power of *in vivo* studies.

References

1. Jamei M, et al. (2007). Novel Physiologically-Based Mechanistic Model for Predicting Oral Drug Absorption: The Advanced Dissolution, Absorption, and Metabolism (ADAM) Model. EUFEPS&COST Conference on Bioavailability and Bioequivalence: Focus on Physiological Factors and Variability. October 1-2, Athens, Greece.
2. Sirisuth N, Eddington N D (2002). The influence of first pass metabolism on the development and validation of an IVIVC for metoprolol extended release tablets. EurJPharm&Biopharm 53(3): 301-309.