QUANTITATIVE PREDICTION OF FORMULATION-SPECIFIC FOOD EFFECTS FOR BCS/BDDCS CLASS II DRUG NIFEDIPINE AND POPULATION VARIABILITY OF ITS PHARMACOKINETICS USING THE ADAM MODEL WITHIN THE SIMCYP SIMULATOR

N. Patel[1], D. Turner[1], S. Polak[1,2], M. Jamei[1], A. Rostami Hodjegan[1,3]

n.patel@simcyp.com

[1] Simcyp (now Certara) Limited, Blades Enterprise Centre, John Street, Sheffield, S2 4SU, U.K.

[2] Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland

[3] School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, U.K.

Purpose

Assessing potential food effects (FE) on the rate and extent of absorption of orally dosed drugs is an important part of drug development especially for poorly soluble lipophilic drugs. Classification systems such as the Biopharmaceutical Classification System (BCS) and Biopharmaceutical Drug Disposition Classification System (BDDCS), FeSSIF/FaSSIF solubility ratio and QSAR based approaches have traditionally been used to anticipate FEs during early development stages. Such traditional approaches -

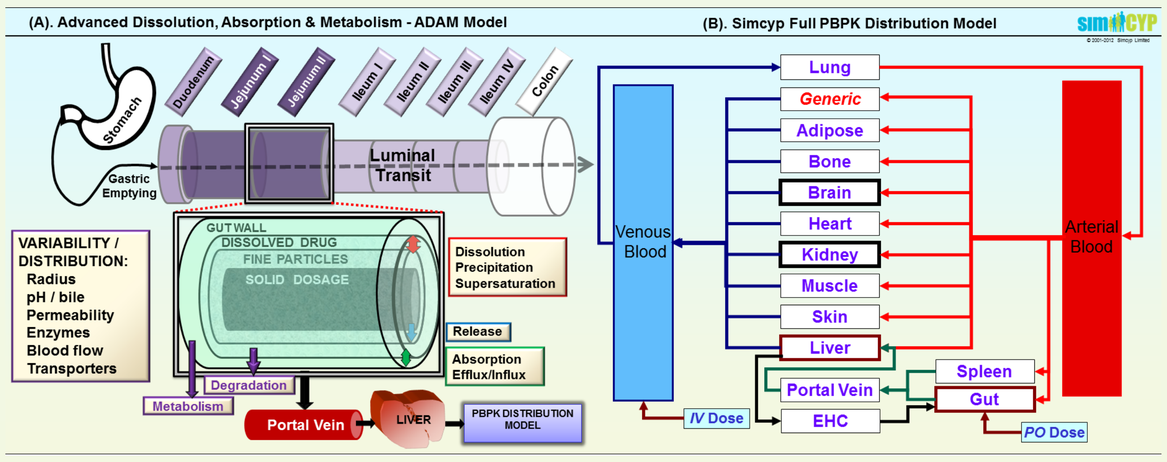
1. Do not consider the full scope and interplay of physiological changes postprandially
2. Cannot predict plasma concentration profiles in fasted and fed states
3. Cannot provide information about population variability
4. Are neither intended nor able to quantitatively predict the changes in AUC, C_{max}, T_{max}, etc.
5. Are only applicable to Immediate Release (IR) formulations and cannot predict formulation specific differences in nature and extent of FE.

In contrast, with appropriate *in vitro* data, population-based mechanistic models are more suitable to integrate all available physiological (*system*) data, and drug- and formulation-specific information. A wide range of food-related *system* changes can be incorporated, *viz.* blood flow, gastric residence time, luminal pH, bile salt concentrations and fluid volumes. Mechanistic models have been successfully used for the quantitative prediction of FE for IR formulations based upon measured bio-relevant solubility[1]. However, to our knowledge, there are no reports on either the use of mechanistic models to predict FE on controlled release (CR) formulations or to predict formulation-specific differences in FE for BCS Class II drugs. Here we assess the use of the Advanced Dissolution, Absorption and Metabolism (ADAM)[2] model with the full PBPK model of the Simcyp Simulator to predict FE with IR and CR formulations of nifedipine (NIF) and compare results with conventional methods.

Materials and Methods

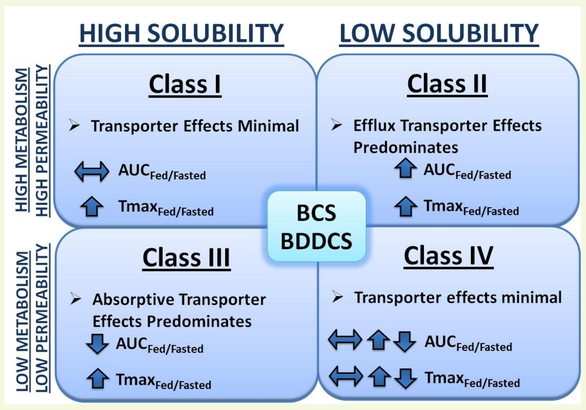
Aqueous solubility, *in vitro* metabolism, intestinal permeation and the required physicochemical parameters of NIF were obtained from the literature. *In vitro* dissolution and fasted/fed state human plasma concentration (C_p) profiles of the CR formulations (Adalat OROS and Nifedicron) were obtained from Schug *et al*.[3] The clinical data of FE for IR product was obtained from Reitberg *et al*.[4]

Physiologically Based Simcyp ADAM[2] model for Prediction of FE:



Conventional Methods for the Prediction of FE:

BCS[5]/BDDCS[6] Classifications:



QSAR Based on Solubility, Dose/Solubility ratio and LogP[7]:

QSAR1:

$$\frac{AUC_{Fed}}{AUC_{Fasted}} = 1.7709 * Sol^{-0.0697}, Sol = Aq\ Sol\ \frac{mg}{mL}$$

QSAR2:

$$\frac{AUC_{Fed}}{AUC_{Fasted}} = 1.2836 * SR^{0.0563}, SR = \frac{Dose}{Sol}, Dose\ (mg)$$

QSAR3: $\frac{AUC_{Fed}}{AUC_{Fasted}} = 0.9048 * e^{0.1085 * LogP}$

Results and Discussion

The predicted plasma drug concentration (Cp) profiles of NIF IR and CR formulations under fasted and fed conditions overlaid with observed values are shown in Fig. 1. Comparative performance of Simcyp with conventional methods in predicting formulation-specific FE is provided in Table. 1.

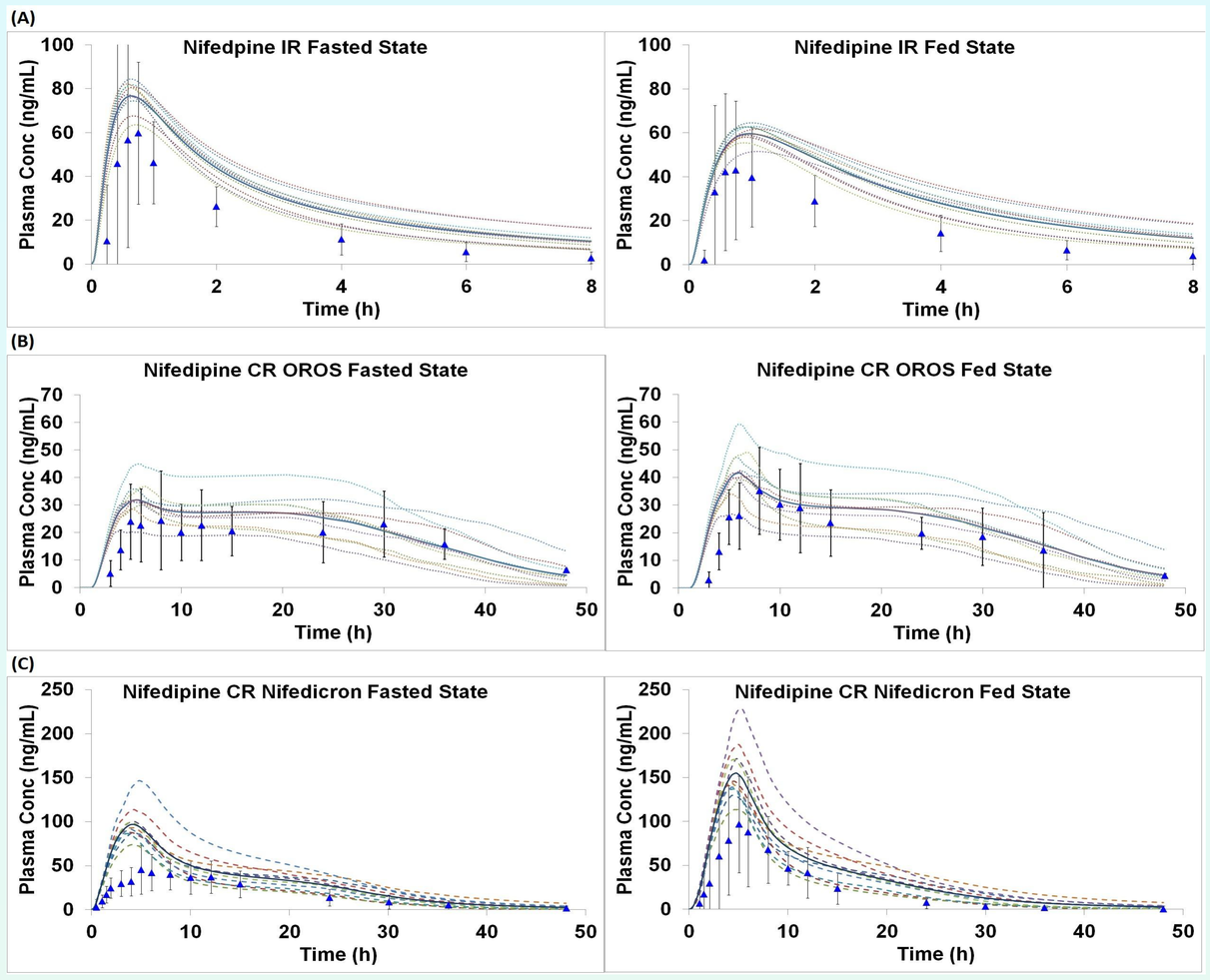


Figure 1. Predicted (Lines) and Observed (Markers) C_p profiles of NIF IR and CR Formulations

Fed/Fasted Ratio of Exposure Parameters	Immediate Release							CR Formulation Adalat OROS				CR Formulation Nifedicron			
	Observed	Predicted						Observed	Predicted			Observed	Predicted		
	Mean	Simcyp	BCS / BDDCS	FeSSIF/ FaSSIF	QSAR1	QSAR2	QSAR3	Mean	Simcyp	QSAR 1-3	BCS/ BDDCS	Mean	Simcyp	QSAR 1-3	BCS/ BDDCS
Cmax	0.74	0.77	↑/↓	NA	NA	NA	NA	1.23	1.30	NA	NA	2.43	1.73	NA	NA
Tmax	1.1	1.54	↑	NA	NA	NA	NA	0.80	0.96	NA	NA	0.83	1.12	NA	NA
AUC	1.02	1.03	↑	↑	2.33	1.82	1.21	1.03	1.06	NA	NA	1.21	1.23	NA	NA

Table 1. Observed and Predicted Fed/Fasted Ration of Drug Exposure Parameters for IR and CR Formulations of NIF

NIF is one of the most extensively studied drugs in the clinic partly due to significant formulation-specific differences in FE[3,4,8,9]. IR formulations are reported[4,8] to have significant reduction in C_{max}, increase in T_{max}, and reduced to unaltered AUC when given with food while CR formulations show the opposite effect (increased C_{max}, reduced T_{max}, and increased/unaltered AUC)[3]. NIF, a CYP3A4 substrate, is a BCS and BDDCS Class II drug with a FeSSIF/FaSSIF ratio of 2.54 (173/68 µM); thus, IR formulations are expected to exhibit positive FE[5-7]. However, IR formulations are clinically observed to have negative FE on C_{max}, with no or negative effect on AUC[4,8,9]. Thus, the simple rule-based or QSAR approaches are not predictive for NIF FE. The predicted values of the key parameters (AUC, C_{max}, T_{max}) for assessment of drug exposure under fasted as well as fed states for IR and CR formulations were within 2-fold of clinically observed values (Fig. 1). The ADAM model predicted the opposite FEs observed for NIF IR (decreased C_{max} / increased T_{max}) and CR (increased C_{max} / reduced T_{max}) formulations and also the difference in magnitude of FE between CR formulations. Fed-to-fasted ratio of all the three PK parameters were very close to the clinically observed data (Table. 1). Overall, the nature and magnitude of observed FE were recovered well by the Simcyp ADAM model.

Conclusions

Mechanistic absorption models such as ADAM are cost-effective and reliable tools to quantitatively predict the nature and magnitude of FE at early stages of drug development. The utilisation of Simcyp ADAM models for FE prediction for IR and CR formulations has been illustrated for NIF as an example.

References

1. Jones *et al. CP* 2006; **2.** Jamei *et al*. *AAPSJ* 2009; **3.** Schug *et al*. *BJCP* 2002; **4.** Reitberg *et al*. *CPT* 1987; **5.** Custodio *et al. ADDR* 2009; **6.** Fleisher *et al. CP* 1999; **7.** Singh *et al. DDR* 2005; **8.** Hirasawa *et al. EJCP* 1985; **9.** Armstrong *et al. EJCP* 1997.