# POPULATION-BASED MECHANISTIC MODELLING OF ABSORPTION OF THE BCS/BDDCS CLASS II DRUG NIFEDIPINE: QUANTITATIVE PREDICTION OF FORMULATION-SPECIFIC FOOD EFFECTS.

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## Introduction

Assessing potential food effects (FE) on the rate and extent of absorption of orally dosed drugs is an important part of drug development. Significant FE is an added source of an inter-individual variability in drug exposure. The Biopharmaceutical Classification System (BCS) and the Biopharmaceutical Drug Disposition Classification System (BDDCS) can be applied to anticipate FE but such methods are neither able nor intended to predict the changes to AUC, $C_{max}$, $T_{max}$ *etc* and other kinetic parameters quantitatively. Moreover, they are not informative regarding population variability, which is an essential element of study design. Other approaches such as solubility/dissolution ratio in FeSSIF/FaSSIF do not consider the full range and interplay of physiological changes associated with FE. Classification systems cannot deal with the drugs near class boundaries and they are applicable only to Immediate Release (IR) formulations.

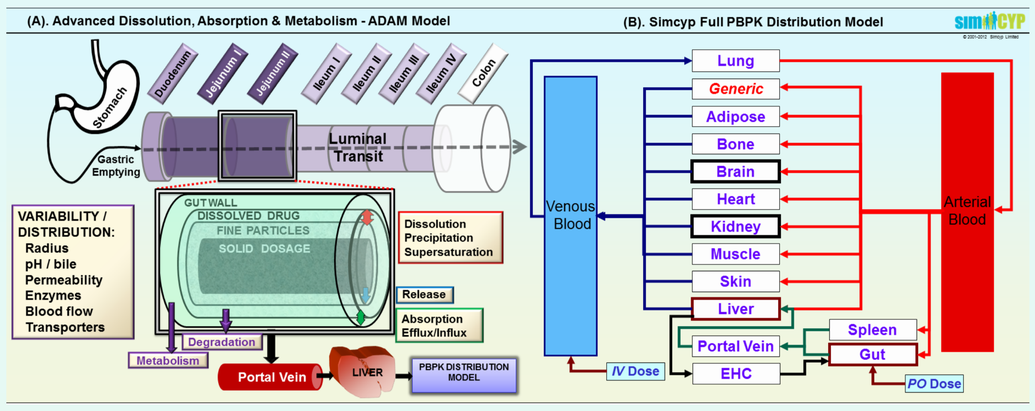


**Figure 1. (A)** Simcyp ADAM Model; **(B)** Simcyp Full PBPK Model

In contrast, with appropriate *in vitro* data, population-based mechanistic models are better able 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. However, to our knowledge, there are no reports both on the use of mechanistic models to predict FE on controlled release (CR) formulations and to predict formulation-specific differences in FE for BCS II drugs. Here we assess the use of the Advanced Dissolution, Absorption and Metabolism (ADAM) (Jamei *et al.*) model with the full PBPK model of the Simcyp Simulator (Fig. 1) to predict FE with IR and CR formulations of nifedipine (NIF).

## Methods

Aqueous solubility, including super-saturation parameters, *in vitro* metabolism and physicochemical parameters of NIF were obtained from the literature. Human intestinal permeability was predicted from experimental MDCK II permeability. Tissue:plasma partition coefficients were estimated from physicochemical parameters using the Rodgers *et al*. method. *In vitro* dissolution profiles of the CR formulation (Adalat OROS) were obtained from Schug *et al*. The clinical data for validation of the models were obtained from Reitberg *et al*. and Schug *et al*.

Simcyp version 11.1 (Simcyp Limited, Sheffield, UK) was used to simulate clinical studies. The Simcyp platform permits clinical trial designs to be simulated by enabling the selection of an appropriate ethnic, healthy or disease population, number of subjects, age range, gender, dosing regimen as well as the fasted/fed status. The Simulator has built-in population covariates where these are known to simulate realistic individuals /trials. In order to better account for potential statistical sampling issues each clinical study was simulated 10 times.

## Results and Discussion

The predicted plasma drug concentration (Cp) profiles of NIF IR and CR formulations were overlaid with observed values (Figs. 2 and 3). Respectively, 80 and 90% of the predicted Cp values were within 3-fold of observed Cp values for IR and CR formulations.

The over-estimation of Cp profiles may be due to the under-prediction of *in vivo* elimination from *in vitro* enzyme kinetic data and/or distribution to peripheral tissues. Models could be improved by adjusting (fitting) parameters based upon *in vivo* human data. However, the purpose of this study is to demonstrate the use of bottom-up mechanistic ADAM/PBPK models to predict FE so only *in vitro* data have been used as inputs without any fitted parameters.

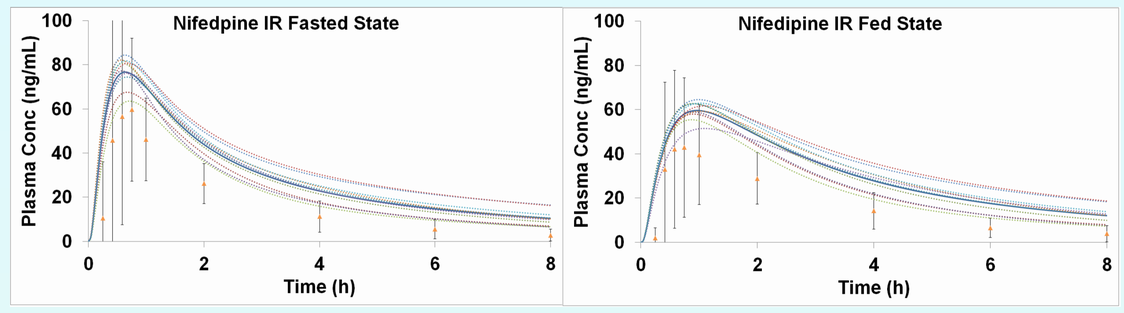


**Figure 2.** Predicted (Lines) and Observed (Markers) $C_p$ profiles of NIF IR Formulation under fasted and fed states

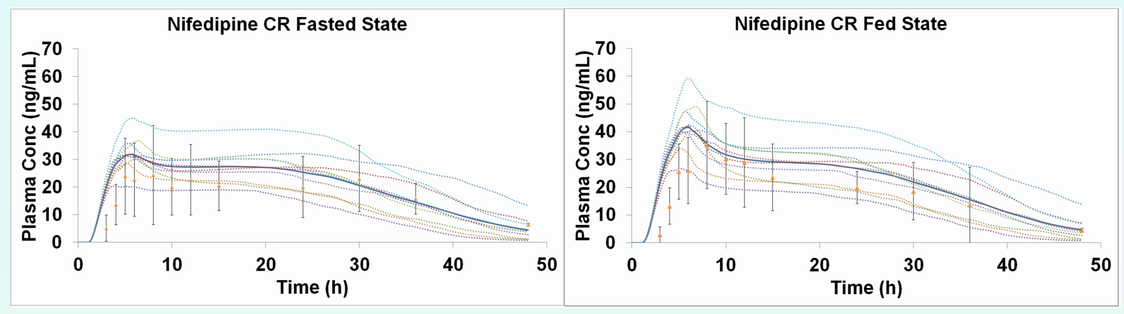


**Figure 3.** Predicted (Lines) and Observed (Markers) $C_p$ profiles of NIF CR Formulation under fasted and fed states

NIF is one of the most extensively studied drugs in the clinic partly due to significant formulation-specific differences in FE. IR formulations are reported to have significant reduction in $C_{max}$ and increase in $T_{max}$ when given with food while CR formulations show the opposite effect (increased $C_{max}$ and reduced $T_{max}$). Some CR formulations have also shown significant increase in exposure (AUC) with food. 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 (Custodio *et al*., Fleisher *et al*.). However, IR formulations are clinically observed to have negative FE on $C_{max}$, with no or negative effect on AUC (Reitberg *et al*., Hirasawa *et al*., Armstrong *et al*.). Thus, the simple rule-based approaches are not predictive for NIF FE.

| Immediate Release Formulation | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug Exposure Parameters | Fasted State | | | | | Fed State | | | | | Fed/Fasted Ratio | | | |
| | Observed | | Predicted | | | Observed | | Predicted | | | Observed | Predicted | | |
| | Mean | SD | Geo. Mean | Arith. Mean | Median | Mean | SD | Geo. Mean | Arith. Mean | Median | Mean | Geo. Mean | Arith. Mean | Median |
| $C_{max}$ | 78.9 | 42 | 70.39 | 79.36 | 73.73 | 58.70 | 31.3 | 54.22 | 61.93 | 59.37 | 0.74 | 0.77 | 0.78 | 0.81 |
| $T_{max}$ | 0.97 | 0.94 | 0.65 | 0.68 | 0.64 | 1.07 | 0.69 | 1.01 | 1.06 | 0.96 | 1.10 | 1.54 | 1.57 | 1.50 |
| AUC | 145.3 | 48.3 | 188.81 | 239.14 | 199.2 | 148.60 | 60.70 | 193.93 | 243.40 | 204.84 | 1.02 | 1.03 | 1.02 | 1.03 |

| Controlled Release Formulation | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug Exposure Parameters | Fasted State | | | | | Fed State | | | | | Fed/Fasted Ratio | | | |
| | Observed | | Predicted | | | Observed | | Predicted | | | Observed | Predicted | | |
| | Mean | SD | Geo. Mean | Arith. Mean | Median | Mean | SD | Geo. Mean | Arith. Mean | Median | Mean | Geo. Mean | Arith. Mean | Median |
| $C_{max}$ | 31 | 1.6 | 31.38 | 40.54 | 31.18 | 38 | 1.6 | 41.08 | 53.21 | 42.91 | 1.23 | 1.31 | 1.31 | 1.38 |
| $T_{max}$ | 10 | NA | 6.76 | 9.84 | 4.95 | 8 | NA | 6.19 | 8.00 | 5.25 | 0.80 | 0.92 | 0.81 | 1.06 |
| AUC | 707 | 1.7 | 640.57 | 950.83 | 673.4 | 730 | 1.70 | 703.08 | 1045.41 | 723.42 | 1.03 | 1.10 | 1.10 | 1.07 |

**Table 1.** Observed and Predicted Drug Exposure Parameters under Fed and Fasted States for IR and CR Formulations of NIF.

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 (Tab. 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. Fed-to-fasted ratio of all the three PK parameters were very close to the clinically observed data (Tab. 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 development.. The utilisation of such models for FE prediction for IR and CR formulations has been illustrated using NIF as an example. Further validation using a range of drugs with different biopharmaceutical properties is needed to improve confidence in and increase the acceptance of such an approach in advance of *in vivo* studies.

**References:** Jamei *et al*. *AAPSJ* 2009; Rodgers *et al*. *J Pharm Sci* 2005; Schug *et al*. *BJCP* 2002; Reitberg *et al*. *CPT* 1987; Custodio *et al. ADDR* 2009; Fleisher *et al. CP* 1999; Hirasawa *et al. EJCP* 1985; Armstrong *et al. EJCP* 1997.