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\text{max}, T\text{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. 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.

We here assess the use of the Advanced Dissolution, Absorption and Metabolism (ADAM)\textsuperscript{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\text{p}) profiles of the CR formulations (Adalat OROS and Nifedicon) were obtained from Schug et al.\textsuperscript{3} The clinical data of FE for IR product was obtained from Reitberg et al.\textsuperscript{4}

Physiologically Based Simcyp ADAM\textsuperscript{2} model for Prediction of FE:

![Simcyp Flowchart](image.png)

Conventional Methods for the Prediction of FE:

BCS/BDDCS Classifications:

- **BCS Class I**: High solubility, high permeability
- **BCS Class II**: Low solubility, high permeability
- **BCS Class III**: High solubility, low permeability
- **BCS Class IV**: Low solubility, low permeability

**QSAR Based on Solubility, Dose/Solubility ratio and LogP:**

| QSAR1: AUC\text{oral} | AUC\text{oral} - \text{FeSSIF} = 1.7709 \cdot \text{Sol} - 0.6979 \cdot \text{Sol} = \text{Aq} \cdot \text{Sol} | \text{mg} \cdot \text{ml}^{-1} \cdot \text{h}^{-1} | \text{mg} \cdot \text{ml}^{-1} \cdot \text{h}^{-1} |
|-----------------------|-------------------------------------------------|-----------------------|
| QSAR2: AUC\text{oral} | AUC\text{oral} - \text{FaSSIF} = 1.2836 \cdot \text{Sat} \cdot \text{Dose} | \text{mg} \cdot \text{ml}^{-1} \cdot \text{h}^{-1} |
| QSAR3: AUC\text{oral} | AUC\text{oral} - \text{FeSSIF} = 0.9048 \cdot \text{LogP} | \text{mg} \cdot \text{ml}^{-1} \cdot \text{h}^{-1} |

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.

![Graphs of Nifedipine IR and CR Formulations](image.png)

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

<table>
<thead>
<tr>
<th>FE Ratio</th>
<th>IR/CR</th>
<th>Simcyp Predicted</th>
<th>Observed</th>
<th>CR Formulation AUC IR/CR</th>
<th>Simcyp Predicted</th>
<th>Observed</th>
<th>CR Formulation AUC NIF/IR</th>
<th>Simcyp Predicted</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max}</td>
<td>0.74</td>
<td>0.77</td>
<td>NA</td>
<td>NA</td>
<td>1.23</td>
<td>0.90</td>
<td>NA</td>
<td>2.43</td>
<td>2.13</td>
</tr>
<tr>
<td>T\text{max}</td>
<td>1.1</td>
<td>1.54</td>
<td>↑</td>
<td>↑</td>
<td>0.80</td>
<td>0.96</td>
<td>NA</td>
<td>0.83</td>
<td>1.12</td>
</tr>
<tr>
<td>AUC</td>
<td>1.02</td>
<td>1.03</td>
<td>↑</td>
<td>↑</td>
<td>1.63</td>
<td>1.06</td>
<td>NA</td>
<td>1.31</td>
<td>1.23</td>
</tr>
</tbody>
</table>

NIF is one of the most extensively studied drugs in the clinic partly due to significant formulation-specific differences in FE\textsuperscript{4,9}. IR formulations are reported\textsuperscript{9} to have significant reduction in C\text{max}, increase in T\text{max}, and reduced to unaltered AUC when given with food while CR formulations show the opposite effect (increased C\text{max}, reduced T\text{max}, and increased/unaltered AUC)\textsuperscript{9}. 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\textsuperscript{7}. However, IR formulations are clinically observed to have negative FE on C\text{max} with no or negative effect on AUC\textsuperscript{4,9}. Thus, the simple rule-based or QSAR approaches are not predictive for NIF FE. The predicted values of the key parameters (AUC, C\text{max}, T\text{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\text{max} / increased T\text{max}) and CR (increased C\text{max} / reduced T\text{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