Mechanistic Surface pH Modelling Improves PBPK Prediction of a Weakly Acidic Drug: Case Study of Bempedoic Acid

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Explicit representation of surface pH using a mechanistic surface pH model which captures microenvironment acidification during the dissolution of weak acids, leading to improved prediction of in vivo release kinetics and plasma exposure of Bempedoic acid.

Background and Objective

Weakly ionisable drugs with pH-dependent solubility may substantially alter the local pH at the dissolving particle surface ($pH_{surface}$) which, depending on buffer capacity, can differ from the bulk intestinal pH. Published PBPK absorption models often assume that the $pH_{surface}$ is equal to the bulk fluid pH specifically for acids. Bempedoic acid (BA), a BCS Class II weak diprotic acid, exhibits pH-dependent solubility. For lipophilic weak acids dissolving in the small intestine, the $pH_{surface}$ can be significantly lower than bulk pH, limiting local solubility and dissolution rate[1-3]. Ignoring this "surface pH effect" can lead to overestimation of Cmax and underestimation of Tmax[4].

Objective

To assess the impact of applying a mechanistic surface pH model to predict dissolution-controlled absorption and overall pharmacokinetics of BA.

Methods

PBPK Model Development

A mechanistic PBPK model for BA was developed in the Simcyp Simulator v25.

Model parameterization was based on: Physicochemical properties (pKa, intrinsic solubility, permeability) and *in vitro* solubility and dissolution data across various pH. Distribution and elimination were represented using a minimal PBPK model that includes the gut, liver, and portal vein with combined distribution to the remaining tissues represented as a single adjusting compartment. Clinical pharmacokinetic data from single dose and multiple dose studies in different populations were available to validate the model.

Two approaches were evaluated:

Conventional approach: fixed regional gastrointestinal bulk pH as surface pH.

Mechanistic surface pH approach: dynamic (re)calculation of particle surface pH, accounting for interfacial acidification during dissolution using methods based on the approach of Ozturk et al.[1] The method accounts for buffer capacity and considers the impact of dissolved drug concentration in the bulk fluids (Figure 2).

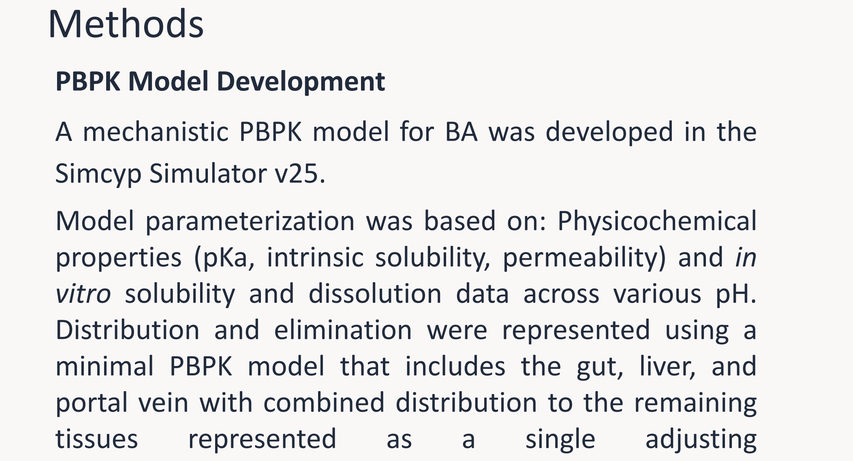

Figure 1: Modeling strategy & workflow

The model was verified against clinical data including single dose, multiple dose, different ethnic populations, and food effect studies[5-7]

Results

Ratios of predicted to observed geometric mean estimates for Cmax and AUC were well within the acceptable range i.e. 0.80-1.25 (Table 1 & Figure 3). The predictive performance of the PBPK base model was assessed against observed clinical PK from 1) IR tablets 180 mg Fasting (Table 2); 2) IR tablets 180 (Table 1) mg fed in healthy Caucasian population; 3) IR tablets 180, 120 and 60 mg in a fasting Japanese population (Table 1). Under fasting state, simulations without the mechanistic $pH_{surface}$ model resulted in rapid dissolution rates, leading to an overprediction of Cmax and early Tmax. Activation of the mechanistic $pH_{surface}$ model reduced dissolution rate, significantly improving predictions. For example, for 180 mg fasted IR predicted Cmax decreased from 19.5 to 16.3 mg/L and Tmax delayed from 1.6 to 2.7 h, better matching observed data (Table 2 & Figure 4). We also conducted simulations under fed conditions for BA 180 mg IR tablets, both with and without activation of the mechanistic surface pH model. As anticipated, no significant differences in the pharmacokinetic parameters were observed, which may be attributed to the higher buffer capacity in the fed state (results not shown here).

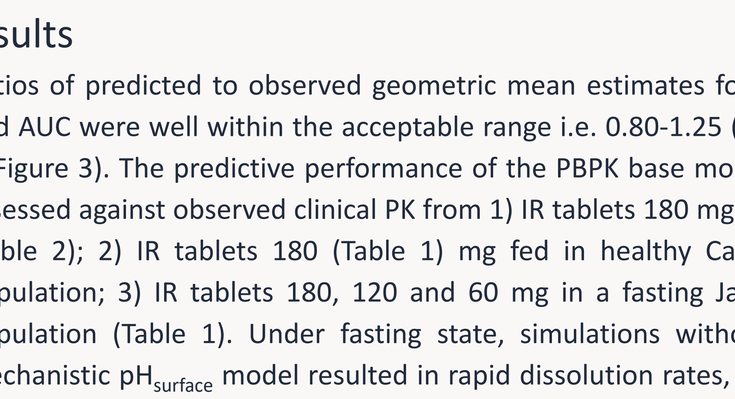

Figure 2: Mechanistic surface pH model schema.

Table 1: PBPK model verification- Model predictions of BA PK parameters compared with observed clinical PK for different studies.

Summary Statistics			
PK parameters	Tmax (h)	Cmax (mg/L)	AUC inf (mg/L.h)
Healthy Population			
Model development - Oral solution 240 mg	1.33	26.5	325.31
Observed oral solution 240 mg	1	27.2	297
P/O		0.97	1.1
Model Validation			
Predicted IR tablets 180 mg - Fasting	2.71	16.34	259.5
Observed IR tablets 180 mg- Fasting	3	13.5	225
Predicted/observed		1.21	1.15
Predicted IR tablets 180 mg - Fed	2.96	13.65	236.19
Observed IR tablets 180 mg - Fed	3	11.5	224
P/O		1.19	1.05
Japanese Population			
Predicted- IR tablets 180 mg	2.72	17.16	285.05
Observed- IR tablets 180 mg	2	17.8	280
P/O		0.96	1.02
Predicted- IR tablets 120 mg	2.64	11.69	190.28
Observed- IR tablets 120 mg	4	11.3	175
P/O		1.03	1.09
Predicted- IR tablets 60 mg	2.51	6.04	95.42
Observed- IR tablets 60 mg	2	6.17	66.2
P/O		0.98	1.44

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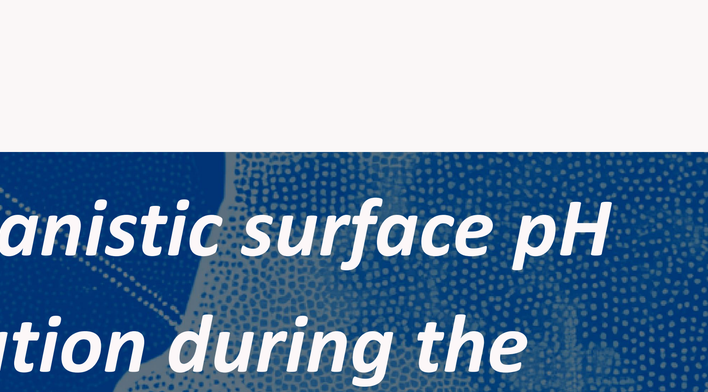

Figure 3: Observed vs Predicted Cp vs Time profiles for BA 240 mg oral suspension[5]

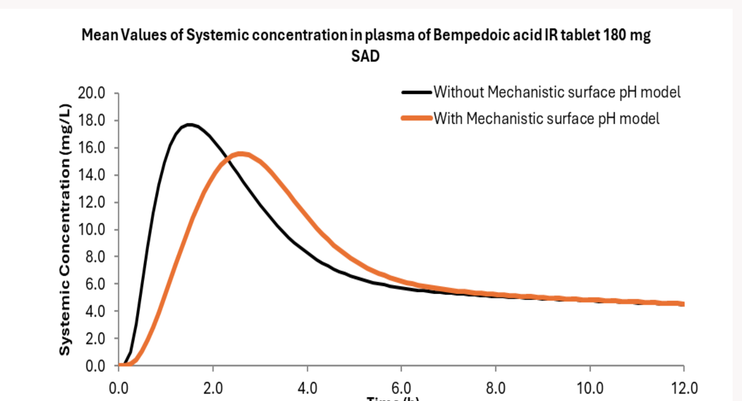

Figure 4: Simulated Cp vs Time profiles with and without applying the mechanistic $pH_{surface}$ model: BA IR tablets 180 mg, fasted state.

Summary Statistics			
	Tmax (h)	Cmax (mg/L)	AUC inf (mg/L.h)
Predicted without surface pH model	1.63	19.47	260.04
Predicted with surface pH model	2.73	16.34	259
Observed data	3	13.5	225
P/O- With surface pH model	0.91	1.21	1.15
P/O- Without surface pH model	0.54	1.35	1.15

Table 2: Observed vs predicted PK parameters of Bempedoic acid IR tablets 180 mg under fasting state with and without applying Mechanistic $pH_{surface}$ model.

Discussion

During dissolution, weakly acidic drugs can deprotonate and lower $pH_{surface}$, reducing local solubility and thence dissolution rate. Conventional film models fail to capture this interfacial acidification, leading to systematic overestimation of dissolution.

Conclusion

Mechanistic surface pH modelling can be essential for accurate prediction of the dissolution of poorly soluble weak acids with pH-dependent solubility and can support robust extrapolation across formulations, populations, and prandial conditions.

References

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