Modelling and simulation of the effect of a permeability enhancer on the absorption of a poorly permeable compound

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Quotient Sciences

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PURPOSE

Compound A is highly soluble at physiological pH, highly bound to proteins (%PPB >99.9%) and has poor permeability (Caco-2 Papp < 1 nm/s). In dog, the volume of distribution is low (50 mL/kg), clearance is 0.835 mL/h/kg and a mono-exponential decline in plasma concentration is observed. An enteric coated solid oral dosage form of compound A was developed. Due to its negligible intestinal permeability, the permeability enhancer Salcaprozate sodium (SNAC) was incorporated into the formulation. One mechanism proposed to explain the action of permeability enhancers is the transient opening of intestinal tight junctions (during a time window of ~20 minutes), leading to a temporary increase of paracellular permeability [1].

The objective of this work was to develop a reduced PBPK model for the oral administration of compound A in dogs, focusing on the alteration of paracellular permeability caused by SNAC.

METHODOLOGY

A dog PBPK model for compound A was developed and verified in PKSim v10/MoBi v10 (Open Systems Pharmacology [2]) using dog plasma concentration profiles (Cp-t), comprising:

- IV bolus 1 mg/kg compound A
- Tablet A: 20 mg compound A + 600 mg SNAC enteric coated
- Tablet B: 20 mg compound A + 300 mg SNAC enteric coated

Table 1 shows the parameters used as input for the PBPK model. SNAC parameters were obtained with ADMET predictor v9.5.0.0 (Simulation Plus Inc, Lancaster, CA, USA)

Table 1. Inputs for PKSim PBPK model

Parameter	Compound A	SNAC
Intestinal permeability (transcellular)	1.02 x10^{-9} cm/min	1.14 x10^{-4} cm/min
Fraction unbound to proteins	0.001	0.06
Solubility	pH 6 = 9000 mg/L pH 7 = 9000 mg/L pH 8 = 9000 mg/L	pH 6 = 5656 mg/L pH 7 = 49059 mg/L pH 8 = 48622 mg/L
pKa	6 (B), 3 (A)	5(A)
logP	2.5	3

- As distribution of compound A was limited to plasma, endothelial permeability was set to zero.
- First order elimination was mediated by a non-specific enzyme in plasma and the clearance was adjusted using the IV data
  - Expression = 1 µmol/L, Intrinsic Clearance = 0.08L/min

A Weibull function was fitted to the experimental in vitro dissolution data (USP 2, 900 mL, pH = 6.8) and was used as dissolution input in the model (Figure 1):

- b (shape factor) = 1.6
- Dissolution time (50% dissolved) = 7 min

The model assumes that compound A and SNAC dissolve simultaneously and that the amount of SNAC does not impact the dissolution rate and extent.

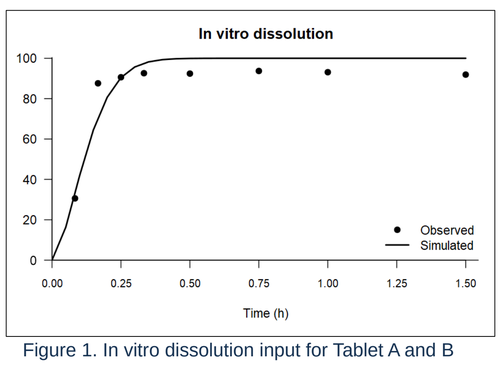

Figure 1. In vitro dissolution input for Tablet A and B

A dummy molecule named Excipient was created to allow the simulation of the enteric coated formulation. A simulation with the administration of compound A, SNAC and Excipient was created in PKSim v10 and exported to MoBi v10. The Excipient was used to simulate the enteric coat and trigger dissolution of the SNAC and compound A in the duodenum [4].

A linear relationship was established between the concentration of SNAC in duodenum and the paracellular permeability of compound A to simulate the process shown in Figure 2.

$$\boldsymbol{Paracellular\ permeability = SNAC\ conc\ duodenum\ lumen\ (\mu M) * 1.9x10^{-12}\ \left(\frac{cm}{min * \mu M}\right)}$$

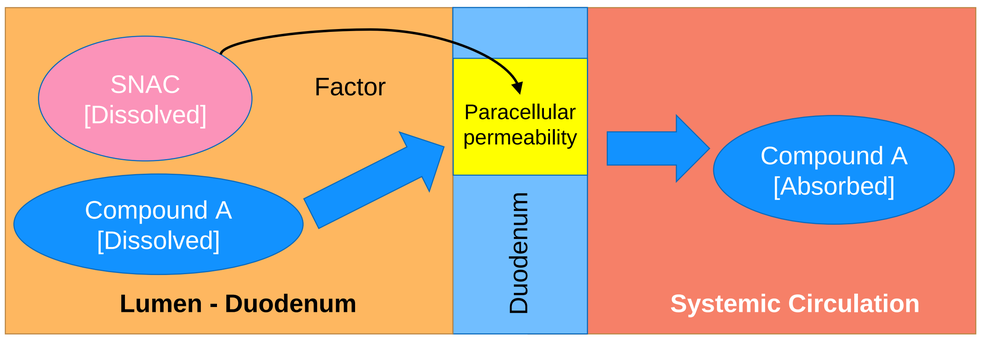

Figure 2. Paracellular absorption model relating to SNAC concentration in duodenum to absorption of Compound A implemented in PKSim v10/MoBi v10

This model was then used to verify the approach by simulating the Tablet B dog Cp-t.

RESULTS

The model predicted the distribution and elimination of the IV administration of Compound A to dog (Table 2)

Table 2. Observed and predicted distribution volume and clearance of Compound A after IV administration

	Vss (mL/kg)	CL (mL/h/kg)
Obs	45.7	0.835
Pred	52.1	0.836
%Dev	13.9	0.1

Observed data: Geometric means of individual parameters

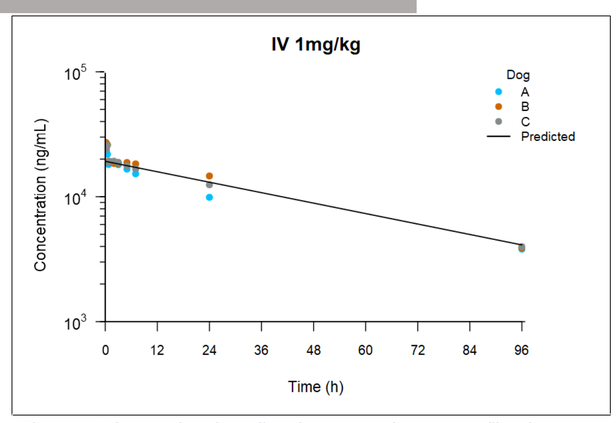

Figure 3. Observed and predicted compound A Cp-t profile after an IV 1 mg/kg administration to dogs

The model relates the concentration of SNAC in duodenum after PO administration of both tablets, to changes in Compound A paracellular permeability leading to its absorption (Figure 4).

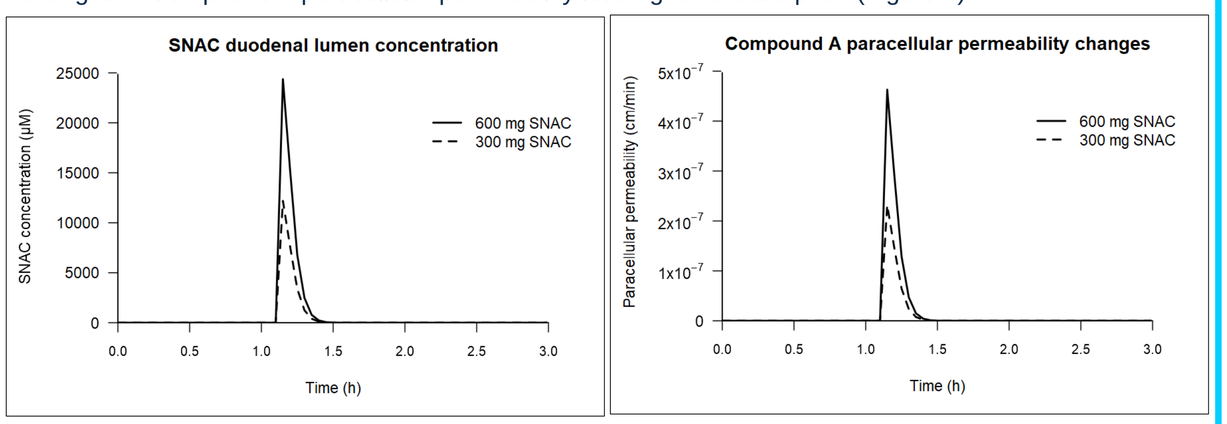

Figure 4. a) Predicted SNAC concentration in duodenum lumen corresponding to both tablets using the dissolution profile from figure 1. b) Predicted changes in paracellular permeability related to the concentration of SNAC in duodenum lumen

Oral dog pharmacokinetics of compound A were explained by changing paracellular permeability in the duodenum as a function of the predicted concentration of SNAC in duodenum for both tablets (Figure 5). The model was able to capture the ~2-fold increase in exposure when SNAC increases from 300 to 600 mg.

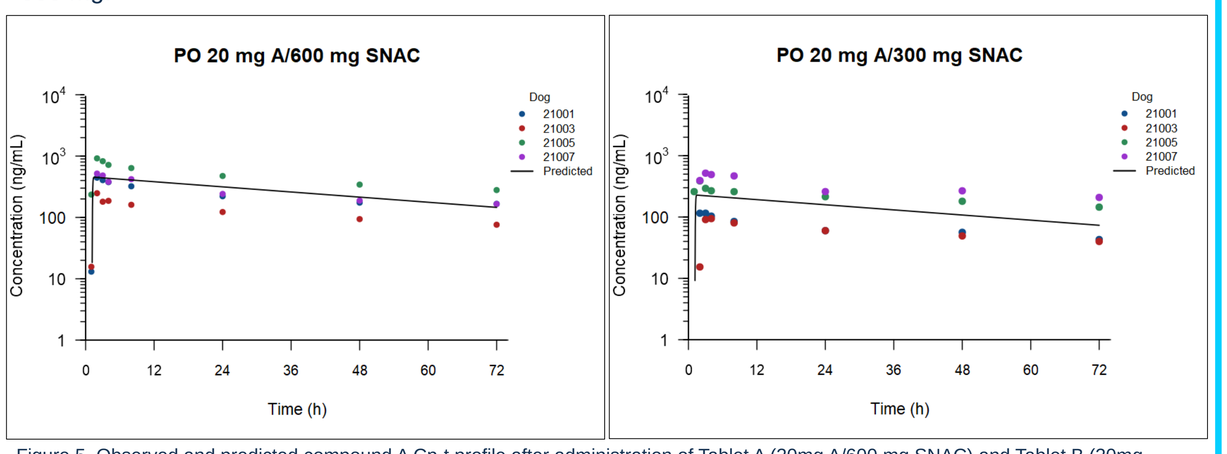

Figure 5. Observed and predicted compound A Cp-t profile after administration of Tablet A (20mg A/600 mg SNAC) and Tablet B (20mg A/300 mg SNAC)

Cmax, AUC0-t and AUC0-inf were all predicted within ± 20% deviation and the shape of the profile matched the observed data (Table 3). There is variability in the data that could be due to the intra dog variability and the performance of the formulation.

Table 3. Model performance evaluation

Administration	Cmax (ng/mL)			AUC0-t (ng*h/mL)			AUC0-inf (ng*h/mL)			Tmax (h)	
	Obs	Pred	%Dev	Obs	Pred	%Dev	Obs	Pred	%Dev	Obs	Pred
IV	-	-	-	957071	940046	-3.3	1197161	1196213	-0.1	-	-
Tablet A	478	452	-5.4	16212	19198	18	31379	28278	-10	2.0	1.5
Tablet B	216	227	5.0	8547	9655	13	17382	14222	-18	2.5	1.5

Observed data: Geometric means of individual subjects, except Tmax which is median

CONCLUSIONS

A PBPK model that predicts the PK of compound A based on the duodenal concentration of SNAC was developed for dog. This approach was developed for further use in clinical data. The principle of modifying intestinal permeability based on the concentration of the permeability enhancer in the intestine, can be used to model the effect of SNAC on other poorly permeable compounds.

REFERENCES

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