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A PBPK model of the negative effect of chitosan on acyclovir absorption: The mucus-chitosan interaction

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PURPOSE

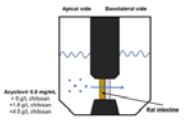
A recent bioavailability study raises questions about the universality of the permeability enhancing effect of chitosan on poorly permeable drugs1. Unexpectedly, chitosan reduced the bioavailability of acyclovir. The purpose of this study was to establish a hypothesis that could be tested using a mechanistic oral absorption model to help establish a possible mechanism for this result. .

METHOD(S)

Experiments were conducted *in vitro* to measure permeability through rat intestinal tissue and changes in pig mucus viscosity and rheology in the presence of chitosan. Effective permeability (Peff) values were incorporated into a PBPK model, and the aqueous diffusion coefficient (D) of acyclovir was varied according to viscosity observations. A mechanistic PBPK model for acyclovir was developed using GastroPlus™ 9.6 (Simulations Plus, Inc.) Advanced Compartmental Absorption and Transit™ (ACAT™) model and PBPKPlus™ module to mechanistically explain absorption, distribution, and clearance mechanisms. The kinetic parameters (K_m and V_{max}) for alcohol dehydrogenase (ADH1) mediated metabolism were obtained from literature (K_m) or fitted (V_{max}) to intravenous (IV) and oral (PO) formulations. The model utilized an all tissue permeability-limited model with active renal secretion mediated by two transporters: 1) organic anion transporter 2 (OAT2) on the basolateral membrane and 2) multidrug and toxin 1 (MATE1) on the apical membrane. The model was developed using IV and PO data from oral administration in the absence of chitosan. The model was further validated by comparing simulated and observed plasma concentration-time profiles for acyclovir obtained from clinical studies in the presence of two concentrations of chitosan.

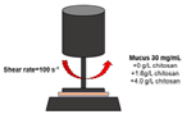
METHOD(S) CONT.

1) ACYCLOVIR PERMEABILITY (P_{eff})



Scheme 1: Ussing-type chamber.

2) MUCUS RHEOLOGY



Scheme 2: Rotational rheometer.

3) MODELING

$$Peff = Ptran + Ppara \quad (1)$$

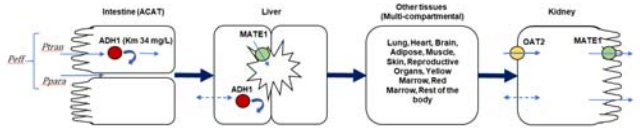
$$Ppara = \frac{\varepsilon_i \cdot D \cdot F\left(\frac{r}{R_i}\right)}{\delta} * \frac{K_i}{1 - e^{-K_i}} \quad (2)$$

$$Ptran = \frac{dM}{dt} = ka' * \left(C_{(t),lum} - C_{(t),ent}\right) \quad (3)$$

Table 1: Summary of ACAT model parameters

Intestinal Compartment	ASF (cm^{-1})	pH	Transit Time (h)	ADH1[a] expression
Duodenum	2.74	6.0	0.26	0.31
Jejunum 1 and 2[b]	2.68 - 2.69	6.2 - 6.4	0.94 and 0.74	0.11
Ileum 1, 2 and 3[b]	2.64, 2.60 and 2.53	6.6 - 7.4	0.58, 0.42 and 0.29	7.0×10^{-3}
Caecum	0.02	6.4	4.36	0.23
Ascending Colon	0.05	6.8	13.1	0.35

a: Converted by ImageJ[2]. b: Relative expression at each sub-segment.



Scheme 3: PBPK model used for acyclovir simulations[2,3,4,5,6]

RESULT(S)

The control acyclovir Peff was 3.07×10^{-5} cm/s ; chitosan decreased acyclovir permeability to 1.95×10^{-5} and 2.38×10^{-5} cm/s at 1.6 and 4.0 g/L, respectively. Mucus viscosity increased in the presence of those chitosan concentrations by approximately 4 and 64 times, respectively (Fig.1). Rat jejunum Peff was incorporated in the absorption model to predict the chitosan effect previously observed in clinical studies in healthy subjects[1] (Fig. 2). The results from a mechanistic oral absorption modeling support a hypothesis that a chitosan-mucus interaction might be responsible for a reduction in acyclovir paracellular permeability by decreasing the effective diffusion coefficient of acyclovir *in vivo*. The model accurately predicted acyclovir's bioavailability and the chitosan effect by considering both Peff and D (see Figure 2).

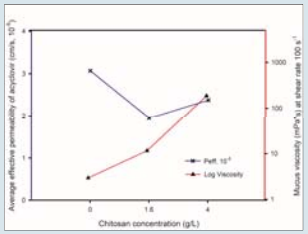


Figure 1. Chitosan effect on acyclovir permeability and mucus viscosity. The viscosity experiments in this graph were conducted using a mucus concentration of 30 mg/mL and a shear rate of 100 s^{-1}. Permeability is shown as a black line with (x) symbols according to the left axis. Viscosity is shown as an orange line with (triangles) symbols according to the right axis.

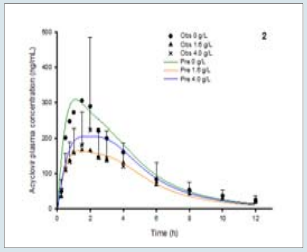


Figure 2. Observed and predicted plasma concentration vs time profile after PO administration of acyclovir 200 mg. Observed plasma concentration profiles were extracted from Kubbinga et al. at 0 (triangles), 1.6 g/L (circles) and 4.0 (squares) g/L of chitosan[1]. Predicted profiles are shown as simulation outputs at 0 (green line), 1.6 g/L (orange line) and 4.0 g/L (blue line) of chitosan.

RESULT(S) CONT.

Table 2. Mechanistic absorption at different Peff and D conc.

Peff (cm/s, 10^{-5})	3.07		1.95	
D (cm^2/s, 10^{-5})	0.97	0.45	0.97	0.45
Enterocyte Uptake (%)	31.5	45.5	9.31	28.1
Fraction metabolized (%)	23.4	30.7	8.40	21.6
Transcellular absorption (%) = Enterocyte uptake - Fraction metabolized	8.1	14.8	0.91	6.5
Paracellular absorption (%)	10.5	4.7	11.6	5.2

Acyclovir enterocyte uptake followed the ranking: jejunum > duodenum > ileum. However, both the regional ADH1 expression and enterocyte concentrations of acyclovir lead to the transcellular absorption ranking: ileum > jejunum > duodenum. In presence of chitosan, both the enterocyte uptake and metabolism remained roughly the same. Peff and D reductions lead to a decrease in paracellular absorption.

CONCLUSION(S)

The absorption and pharmacokinetics of acyclovir in healthy subjects were modeled using *in vitro* and *in silico* data. The model was successfully applied to capture the gut and liver metabolism of acyclovir by ADH1, and renal elimination mediated by secretory influx and efflux transporters. The application of a mechanistic oral absorption/PBPK model helped to identify the critical parameters that can explain the anomalous decrease in AUC induced by chitosan which is normally considered to be an excipient that enhances the absorption of poorly permeable drugs.

FUNDING/REFERENCE

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Reference:

[1] Kubbinga M, Nguyen MA, Staubach P, Teerenstra S, Langguth P. The influence of chitosan on the oral bioavailability of acyclovir—a comparative bioavailability study in humans. Pharm Res. 2015;32(7):2241-2249.