A recent bioavailability study raises questions about the universality of the permeability enhancing effect of chitosan on poorly permeable drugs. 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 aequous 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 mechanically explain absorption, distribution, and clearance mechanisms. The kinetic parameters (Km and Vmax) for alcohol dehydrogenase (ADH1) mediated metabolism were obtained from literature (Km) or fitted (Vmax) to intravenous (IV) and oral (PO) formulations. The model utilized 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.

**RESULT(S)**

The control acyclovir Peff was 3.07×10⁻³ 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 (Fig. 2). The results from a mechanistic oral absorption modeling support a hypothesis that 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).

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