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Modeling Dynamic Gastrointestinal Fluid Transit as a Basis for Dissolution and Absorption

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Purpose

Current mechanistic oral drug absorption models do not account for dynamic gastrointestinal (GI) fluid transport that impact drug disintegration, dissolution, transit, and absorption. Recent research has measured fasted state gastrointestinal fluid content via MRI in individuals given a 240mL water dose. The Dynamic Fluid Compartment Absorption and Transit (DFCAT) model is proposed as an approach that predicts gastrointestinal drug absorption and transit based on quantified GI fluid content.

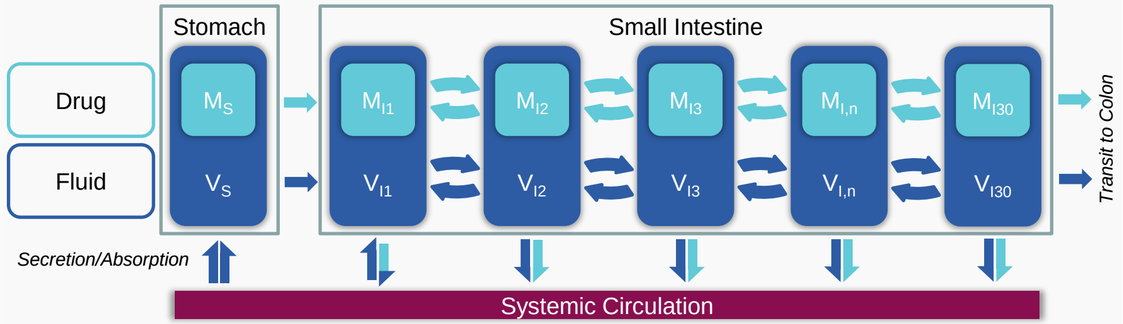
Model Design

Thirty fluid and drug compartments represent the small intestine with forward and reverse transit. Fluid secretion occurs in the stomach and duodenum. Fluid absorption approximated as a first order process with minimum volume. Design verification was conducted on individual and average basis. Total stomach and small intestine volume over time based on MRI fluid clinical study. Average small intestine transit condition is based on 199 min mean residence time. Pharmacokinetic evaluation is based on 100mg mesalamine solution dose. Simulations were executed on Matlab 2016a.

Results

The proposed DFCAT model was successfully verified with multiple sources of clinical observations. The average fluid content was well approximated in the stomach, small intestine, upper and lower small intestine. The model also exhibited a small intestine residence time similar to the CAT model. Phenol red dosing was not successfully verified but served as a calibration point for simulation mucosal volume which altered drug concentration. Individualized model could also be constructed using identical methods. Oral absorption data of 100mg mesalamine solution was manually fitted to establish pharmacokinetic parameters. Identical pharmacokinetic parameters were used for all simulations. Individualized DFCAT models predicted a highly variable plasma profile Cmax range of 1242 to 2122 ng/mL, a Tmax range of 18 to 46 minutes, and a AUC range of 1259 to 1562 nMh despite identical pharmacokinetic parameters. Additionally, double plasma profile peaks from certain fluid profiles were exhibited as a result of certain fluid transport profiles.

Model Overview



Conclusion

The model suggests the use of dynamic fluid concentration driven absorption approach better fits clinical observations (3 of 4) than the traditional mass driven CAT approach (2 of 4). Translation of individual fluid content behavior into simulation provides direct prediction of multi-peak or delayed absorption in a few individuals.

Continued investigation of modeling dynamic transport of GI fluid and characterizing individual GI fluid content provides an improving platform for future investigations to better predict drug absorption, dissolution, and transport.

Model Verification and Comparing Results