Mechanistic model predicting the role of ingested lipids in oral drug dissolution

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Introduction

Food is known to have an effect on the gastrointestinal (GI) absorption of oral drugs. However, its impact is not easily predicted, in part due to lack of a complete mechanistic understanding of the role of food in impacting drug absorption. Quantitative prediction of the food effect on oral drug absorption would facilitate rational design of effective drug delivery strategies. Considering that the majority of oral drugs in development and in the market have poor water solubility, lipids present in food, in particular, can significantly impact the absorption of such drugs. Ingestion of food triggers a cascade of processes that change the physical and chemical nature of the gastrointestinal milieu and directly affect the behavior of oral compounds in the GI tract and ultimately transport across the intestinal wall. Predictability of the effect of lipids on overall drug absorption is often elusive due to the multiple concurrent dynamic processes (e.g., drug dissolution, partitioning, lipid digestion, drug absorption) impacted by ingested food. Thus, understanding the underlying mechanisms of the effect of lipids on overall drug absorption and developing predictive quantitative models incorporating these dynamic processes may aid in predicting the lipid effect on oral drug bioavailability. For poorly water-soluble oral compounds, GI dissolution often becomes the rate limiting step for intestinal absorption. In this study, we have characterized *in vitro* and modeled *in silico* the parallel processes (dissolution, digestion, and partitioning) occurring in the GI tract upon co-dosing a model drug compound, carbamazepine, with a model lipid, triolein, commonly present in food to predict the impact of food-associated lipids on the dissolution of oral compounds in the intestine.

Materials and Methods

To simulate intestinal contents during food digestion, biorelevant medium consisting of 100 mM Trizma maleate, 65 mM NaCl, and 10 mM $CaCl_2*2H_2O$ at pH 6.5 was mixed with bile components (12 mM bile salts and 4 mM phospholipids) overnight at 37 ^oC and 300 rpm prior to use in experiments. To mimic *in vitro* lipid digestion, triolein was introduced at a 50 mM concentration along with pancreatic enzymes prepared as an extract using pancreatin from porcine pancreas. As simulated digestion proceeds the formation of fatty acids, one of the products of lipolysis, causes a continuous drop in pH. To maintain the pH steady at 6.5, 0.2 M NaOH was added as needed during the experiment. The experiment was performed under agitation at 300 rpm and maintained at 37 ^oC. Carbamazepine was dosed as a solid powder in the simulated intestinal solution and samples were collected at various time points for analysis of the dissolved drug concentration. Three processes have been proposed that describe the impact of ingested lipids on drug dissolution: i) the dissolution process itself, ii) partitioning, and iii) digestion (Figure 1 left). Each of these three process is modeled using first-principle equations

that describe system transport and kinetics ~~first principles~~. Kinetic parameters for each process are ~~obtained~~ determined by studying each process in isolation and fitting model equations to experimental data. The combined effect of lipids on drug dissolution is predicted by simultaneously solving the kinetic expressions for each process and is compared against *in vitro* experimental results.

Results and Discussion

The proposed mechanism and processes affecting oral drug dissolution along with respective equations for each process are shown in Figure 1 (left).

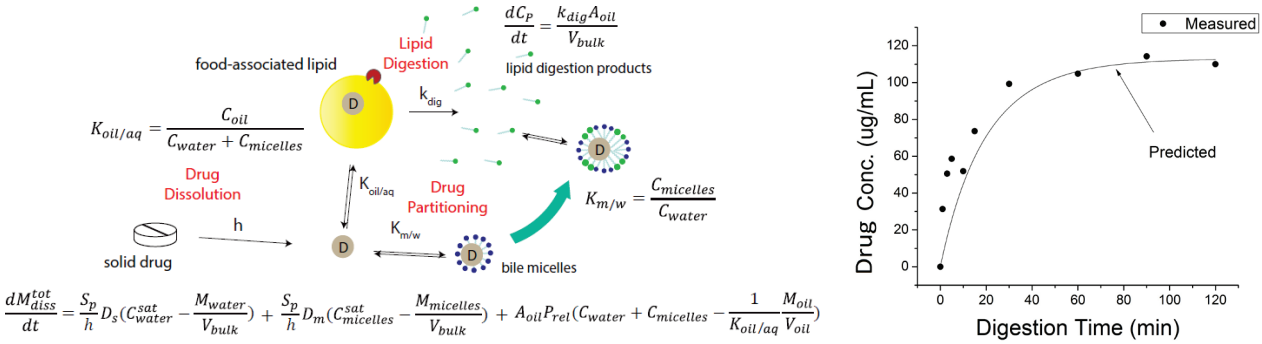

Figure 1: Left - Schematic of proposed mechanism of ingested lipid impact on drug behavior in the GI tract and respective equations. Right - Measured vs. predicted carbamazepine dissolution profile during a multi-process experiment including lipid digestion and drug partitioning.

Figure 1 (right) shows the measured vs. predicted (using equations shown in Figure 1 left) drug dissolution profile as the chemical and physical nature of the intestinal milieu changes during digestion. The predicted profile agrees reasonably well with *in vitro* observations, suggesting that the proposed mechanism of drug behavior in the presence of lipids correctly predicts the behavior of the chosen model drug compound.

Conclusions

The agreement between *in vitro* measurements and *in silico* simulation results validates the equations employed and thus the proposed mechanism of drug behavior in the presence of lipids in the intestine. Assessment of behavior of several different drugs of varying physicochemical properties is, however, needed to allow full validation of the mechanism proposed. Additionally, to ensure plausibility of the *in silico* model, it is critical to compare the overall pharmacokinetic model (including absorption, distribution, elimination) to the effect of food and lipids *in vivo*. Ultimately, this model could be exploited to develop more effective drug delivery strategies.

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