The Interplay between Pharmaceutical Dissolution and Absorption in the Human Gut Studied with Computer Simulation

F. Behafarid, G. Vijayakumar, J. G. Brasseur
University of Colorado

Purpose

The absorption of drug across the intestinal epithelium can occur only after dissolution from clouds of drug particles of differing size followed by the transport of drug concentration to the mucosa by motility-forced intestinal fluid motions. During release and absorption the drug particles are transported as they reduce in size and dissolve. The relative timings of these interrelated dynamics depend also on drug solubility and diffusivity and wall permeability. These complex inter-relationships are difficult or impossible to quantify *in vivo* or *in vitro*. Here we integrate computer simulation with mathematical models to both quantify and develop deep insight into the inter-related dynamics underlying release, transport and absorption as polydisperse clouds of drug particles move and respond to hydrodynamic influences from peristaltic vs. segmental gut motility patterns. We focus on specific differences between drug release and absorption in the MMC phase III fasting state vs. the much larger bolus volumes and milder constrictions associated with the fed state.

Methods

We have developed computational fluid dynamics codes for high-fidelity 3D simulations of intestinal fluid motions predicted in response to specified time changes in luminal geometry (motility). We apply a 3D lattice-Boltzmann CFD method and the "momentum projection method" to transport and diffuse drug concentration fields. Polydisperse clouds of drug particles are transported by the predicted velocity field. A hierarchical extension of the "quasi steady state" dissolution model is incorporated to model the release of drug from diffusion and enhancements from hydrodynamic effects. The modeling allows for local heterogeneous changes in concentration from heterogeneous distributions of drug particles. For the fasting state simulation we incorporated a dual-grid strategy whereby a refined grid is placed in the highly occluded luminal segments. The codes are highly parallelized. We currently contrast fed and fasting states drug absorption under idealized peristaltic motility parameterized consistent with the human intestines with 936 ibuprofen drug particles in water with Gaussian particle size distribution with 100 micron mean diameter and 25 micron standard deviation. The bolus volume is 12 ml in the fed state and 3 ml in the fasting state simulation with occlusion ratio of 0.5 and 0.05, respectively. "Bolus dose" is the same in both simulations. For the current simulations we model high permeability by assuming immediate uptake of drug concentration at the surface. Finite permeability and segmental motility will be included in the near future.

Results

Figure 1 compares a prediction of drug released (blue), drug absorbed (red), and drug remaining (green) within the bolus for the fed state (solid) vs. fasting state (dashed), in moles. (The fasting state simulation is currently incomplete.) In contrast with the rapid release of drug molecules into the intestinal bolus, there is a delay in absorption as drug is released and transported to the luminal surface. Drug remaining (bolus concentration) reaches a maximum at a time that reflects rate of release vs. rate of absorption. At long times, all drug is absorbed, but an increasingly slow rate due to continually reducing bolus concentration. The time at which peak bolus concentration occurs is much shorter in the fasting state (27s) compared to the fed state (46s), as is the initial delay (5 s vs. 26 s). The ratio of time to peak concentration to total release time is 0.43 in the fed state and 0.66 in the fasting state. In Isocontour plots of the predicted concentrating fields show strong heterogeneity in drug concentration. We find that the heterogeneity is initially a result of large differences in particle size, given the much more rapid rate of dissolution in the smaller particles.

Conclusion

The details of the release and absorption of drug in the intestines results from balances between release and absorption rate. Peak bolus concentration, its value and the time at which the peak is reached, are similarly dependent on these balances. Due to the lower bolus volume in the fasting state, peak concentration is reached significantly earlier.