Modeling Impact of Ingested Lipids on Orally Delivered Drug Dissolution

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Introduction

Ingested lipids could offer valuable opportunities for enabling oral drug delivery, as approximately 40-70% of all new drug candidates have been estimated to have very poor water solubility[1] and are expected to exhibit low bioavailability when orally dosed. For hydrophobic drug molecules, the dissolution process in water is likely the limiting step of overall oral absorption. Therefore, the influence of ingested lipids on oral absorption has been associated with complex and poorly characterized interactions between drugs and several colloidal structures, which are naturally present in the gastrointestinal fluids after food intake[2]. In particular, emulsion droplets, micelles and vesicles influence dissolution kinetics, and they are able to maintain larger quantities of hydrophobic drugs in solution, increasing the solubilization power of the gastrointestinal (GI) tract contents. Furthermore, the distribution of drugs within oil, aqueous and micellar phases affects their absorption rate. However, despite the recognized capability of ingested lipids to impact several processes associated with the overall absorption of hydrophobic drugs[3], the fate of co-administered drugs remains unclear and unpredictable.

The aim of this study is to quantitatively investigate and model the effects of ingested lipids on dissolution and partitioning of orally delivered drugs by means of updated *in vitro* models incorporating simulated intestinal fluids. Kinetics of drug dissolution and partitioning between colloidal phases (oil, micellar, aqueous) have been studied by high performance liquid chromatography (HPLC) and electron paramagnetic resonance (EPR), respectively. The latter is a non-invasive technique that has the capability of detecting and quantifying radicals acting as spin probes. Since EPR spectra are highly sensitive to changes in environment micropolarity and microviscosity, the relocation of a selected spin probe within different phases can be monitored in real-time and quantified.

Model development

A film-equilibrium drug dissolution model[4] was developed and utilized to predict drug dissolution kinetics in simulated intestinal fluids with and without lipids. In the model, the influence of colloids interacting with drug on drug transport rates was explicitly taken into account. The model developed in the presence of colloidal particles assumes no net changes in colloid concentration, and that solute/colloid interactions occur rapidly enough relative to the dissolution process to be considered at equilibrium. Under the instant equilibration assumption between the free drug and the drug associated to colloidal species, the rate of dissolution is expressed by the equation reported in Figure 1.

$$\frac{dM_{diss}^{tot}}{dt} = \frac{S_p}{h}\left[D_s\left(C_{water}^{sat} - \frac{M_{water}}{V_{bulk}}\right) + \sum_i D_{ci}\left(C_{ci}^{sat} - \frac{M_{ci}}{V_{bulk}}\right)\right]$$

M_{diss} = total drug dissolved (mg)
S_p = surface area of N dissolving drug particle (cm^2)
D_s = drug diffusion coefficient in water (cm^2/s)
C_{water}^{sat} = drug solubility in water (mg/cm^3)
V_{bullk} = solution total volume (cm^3)
D_{ci} = diffusion coefficient of colloidal species i (cm^2/s)
C_{ci}^{sat} = drug solubility in colloidal species i (mg/cm^3)
M_{water}, M_{ci} = drug concentration in water and in colloid 'i' (mg/cm^3).

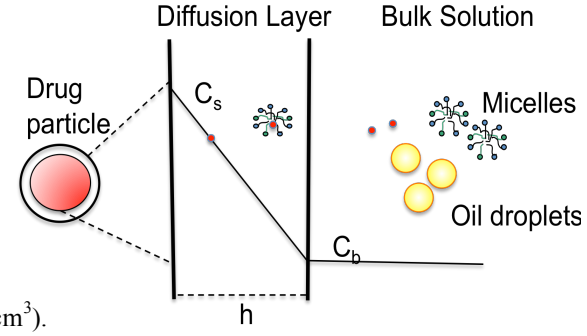

Figure 1: Stationary diffusion layer model for dissolution of solid compounds in colloidal solutions.

Experimental Method

The proposed simulated intestinal fluids consists of a bio-relevant medium, reflecting GI contents in the fed state[5], which was prepared in maleate buffer at pH 6.5 and included lecithin 4 mM and sodium taurodeoxycholate 12 mM as a model of human bile. Soybean oil was added (50 mM) to account for the lipid intake. Since only paramagnetic molecules are visible to EPR, the spin probe TEMPOL benzoate (TB), was selected as a model for poorly water-soluble moderately lipophilic drug. In dissolution experiments, samples were collected at specific time intervals, and analyzed for drug concentration by means of HPLC. In EPR measurements, TB was dissolved in the bio-relevant medium with and without lipids and tracked between phases in real time without any sample processing. EPR spectra of TB in separate environments (maleate buffer, bio-relevant medium, soybean oil) were recorded at 37°C and used to obtain simulation parameters for resolving EPR multi-component spectra of pre and post-lipolysis samples. Experimental dissolution and partitioning profiles were then compared with theoretical predictions according to the film-equilibrium drug dissolution model.

Results and Discussion

The kinetics of drug dissolution in maleate buffer, and in the bio-relevant medium with and without addition of lipids, was investigated by HPLC. The dissolution profile of TB in the bio-relevant medium showed 8-fold higher drug solubility and a faster dissolution rate with respect to the dissolution tests performed in maleate buffer. The presence of mixed micelle-forming species, bile salts and lecithin, greatly increased the solubilization power of the bio-relevant medium, in agreement to the predictions of the film-equilibrium drug dissolution model. However, the proposed theoretical model might fail in predicting dissolution profiles in the presence of lipids, most likely because of a different partitioning process occurring between the drug and oil droplets, which were further investigated by means of EPR. In order to determine the partitioning of the drug model TB between aqueous, micellar, and oil phases, real-time compound tracking measurements in simulated intestinal fluids at pH 6.5 and 37°C by means of EPR. The recorded EPR spectra represented complex spectra containing up to three different components (aqueous, oil, micellar), which were resolved and quantified by spectral simulation. In the EPR spectrum of TB dissolved in the bio-relevant medium, 85% of the TB molecules were associated with mixed micelles. After the addition of soybean oil, EPR spectra indicated increasing partitioning of TB into the oil phase (up to 30%), while the amount of TB associated with mixed micelles decreased to 67% over a time scale similar to that of drug dissolution (3 hours). Therefore, EPR studies showed that the slower partitioning of TB into the oil phase no longer satisfied the instant equilibration assumption required by film-equilibrium drug dissolution model, which had to be modified in order to take into account properly the contribution of lipids to drug dissolution.

This study represented an important step in the development of a systems-based model incorporating all the key processes involved in oral drug absorption – namely drug dissolution, drug partitioning, and lipid digestion. Such system-based models might enable prediction of the fate of orally administered drugs during the lipid digestion process and provide insight into their anticipated overall effect on oral absorption. The ability to predict the impact of lipids on oral drug delivery would shed considerable light on the “food effect” on oral drug absorption, a phenomenon of tremendous significance to the pharmaceutical industry and drug development.

References

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