Mechanistic Modeling of Lipid Based Drug Delivery Systems for Oral Drug Delivery

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Purpose
To enable quantitative prediction, through mechanistic studies and mathematical modeling, of the effect of lipid-based drug delivery systems on drug transport in the intestinal lumen, and ultimately oral bioavailability.

Methods
A broad range of lipid-based drug delivery formulations (self-emulsifying drug delivery systems (SEDDS)) were designed using 3³ factorial design considering oil structure, surfactant hydrophilic lipophilic balance (HLB), and surfactant-to-oil ratio. Key processes occurring post-lipid ingestion: digestion, drug release/partitioning, and drug absorption, were studied \textit{in vitro}. Theory-based mass transport and mass action expressions were developed for these processes and incorporated into a systems-based model explicitly describing, for the first time, parallel drug transport processes in the intestinal lumen post lipid-ingestion (Figure 1). This model was solved numerically using experimentally estimated rate constants for key processes, enabling quantitative prediction of overall absorption enhancement achievable with SEDDS based on drug and formulation properties.

Results
Measured rate constants, reflecting function of lipid-based delivery systems, strongly depended on formulation design. Regression modeling successfully predicted functional kinetic constant dependence on formulation design parameters ($R^2=0.897$). Mechanistic model predictions for simultaneous formulation digestion, drug release, and absorption agreed favorably with \textit{in vitro} experimental results, supporting the validity of the model and associated assumptions. A pharmacokinetic model was incorporated to predict drug plasma concentration profiles. Exploration of sensitivity to lipid-based drug delivery system properties indicated an inverse correlation between rate of digestion and overall absorption, whereas surprisingly, drug release constant had minimal effect on overall drug absorption. For example, a 20-fold decrease in digestion rate constant (experimentally measured formulation design parameter) from $1.92 \times 10^{-4}$ to $0.096 \times 10^{-4}$ mol/min*cm$^2$ resulted in a 10% increase in predicted overall dose absorbed. Predicted impact of SEDDS relative to oral solid drug dosing indicated a strong dependence on dose. For example, improvement in oral absorption was observed with SEDDS at 600mg but not 200mg drug load.

Conclusion
A systems-based mechanistic model incorporating simultaneous dynamic processes occurring upon dosing of drug with a lipid-based drug delivery system enabled quantitative prediction of impact of lipid-based drug delivery systems on plasma drug concentration profiles, and thus bioavailability. This model will facilitate rational SEDDS formulation design.

Figure 1: Schematic representation of intestinal environment upon oral dosing of a lipid-based drug delivery system.