Mechanistic Studies and Modeling of Effects of Ingested Lipids on Oral Drug Absorption

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Ingested lipids, typically originating from food and potentially used as delivery agents, can in some cases enhance absorption of compounds by several hundreds percent. Yet, in other circumstances, they can have a zero or negative impact on absorption. The influence of lipids on compound absorption originates from colloidal structures they form, compound trafficking between these colloidal structures and aqueous medium, and effects on transport through the intestinal mucosa. However, these effects are typically documented through empirical, compound-specific observations, and are not predictable *a priori*. In addition, there is little quantitative understanding of the fate of the ingested lipids. Further results would have substantial implications on diet-related diseases. In previous works, the impact of lipid ingestion on co-administered compound absorption (compound solubility enhancement, change in intestinal permeability) was studied in isolation. Therefore, the interconnected processes taking place during the lipid digestion, and their dependence on dynamic system colloidal structure and composition, have not been studied in a comprehensive, integrated fashion that would enable further quantitative predictions.

The overall goal of this project is to provide new quantitative mechanistic insights about the influence of lipids in the gastrointestinal (GI) tract on compound absorption. The proposed research aims to thoroughly characterize and model kinetics of parallel processes occurring in the GI tract upon co-dosing a compound with lipids namely, compound dissolution, lipid digestion, compound partitioning into colloidal phases, absorption and to relate the kinetics to chemical composition and colloidal structure of intestinal contents. The result will be a systems-based model of the influence of ingested lipids on compound absorption, and an understanding of parallel lipid fate. It is recognized that lipid digestion and absorption are highly complex processes with multiple intricacies not cur-

rently possible to capture in mechanistic *in vitro* studies in a single project, the approach proposed is to start with a simplified system from which an experimental and theoretical framework will be developed, feasibility of quantitative prediction will be established, and considerable insight into complex effects of lipids on compound absorption will be gained. The resulting experimental and theoretical framework is expected to significantly transform study of orally ingested lipids, enabling systems-based consideration of gastrointestinal processes central to nutrition, drug delivery, and diet-related diseases.