Mechanistic Studies and Modeling of Self-Emulsifying Drug Delivery Systems for the Oral Delivery of Hydrophobic Compounds

The oral route for drug delivery is not possible for approximately 50% of currently marketed drug compounds due to low solubility in water. Lipid based drug delivery systems, and in particular self-emulsifying drug delivery systems (SEDDS), show great potential for enhancing oral bioavailability, as well as offering the advantage of minimal processing and inherent stability, but have not been broadly applied, largely due to lack of general formulation guidance and lack of knowledge of how these systems function to enhance bioavailability. It is hypothesized that a systems-based model incorporating key processes involved in oral absorption will enable prediction of the fate of compounds co-administered with self-emulsifying drug delivery systems.

In this investigation, in order to understand how formulation design influences physicochemical emulsion properties and associated function in the gastrointestinal environment, a broad range of SEDDS formulations was studied and used to develop a quantitative predictive model. Twenty-seven representative formulations were designed using 3^3 factorial design. Key functions of emulsion-based drug delivery systems, permeability enhancement, drug release, digestion kinetics, and lymphatic transport were studied separately in vitro and statistically related to three formulation properties — oil structure, surfactant hydrophilic liphophilic balance (HLB) values, and surfactant-to-oil ratio. Three surfactants with HLB values ranging from 10 to 15 and three structurally different oils (long chain triglyceride, medium chain triglyceride, and propylene glycol dicaprylate/ dicaprate) were combined at three different weight ratios (1:1, 5:1, 9:1). Strong influences of certain formulation parameters and interactions on emulsion function were observed. It was shown that regression modeling could be used to estimate key parameters reflective of performance of specific formulations such as digestion kinetics with high degrees of predictability (R^2=0.897).

A system-based model was constructed for the first time to enable quantitative prediction of overall absorption enhancement achievable with SEDDS based on drug and formulation properties. The model includes gastrointestinal mass transport processes of a drug orally administered with SEDDS using process kinetic constants and differential equations obtained from mechanistic studies. The following kinetic processes were considered building the model; formulation digestion, drug release from formulation and drug absorption. Simulation results for simultaneous formulation digestion and drug release were compared with combined in vitro digestion and release Electron Paramagnetic Resonance (EPR) experimental results. Close comparison between simulation results and experimental findings indicated the validity of assumptions made. The model was combined with a one compartment pharmacokinetic model to predict absorbed drug plasma concentration profiles. There was an inverse correlation between the rate of digestion and the amount of drug absorbed whereas surprisingly, there was no effect of variations in drug release constant on the amount of drug absorbed. Simulation results were further used to compare predictions of the extent of drug absorption in cases upon oral dosing in solid form versus within SEDDS, to assess enhancement (or not) in oral bioavailability due to SEDDS. Results demonstrate a strong predicted dependence of improvement in oral absorption on initial formulation loading; improvement in oral

absorption was observed with SEDDS with 400 mg load but not a 200 mg drug load. The model presented here would be of direct benefit to formulation scientists trying to achieve oral formulations of low solubility compounds with acceptable bioavailability.