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Pharmaceutical Sciences Seminar

Wednesday, March 10, 2021
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4:00-5:00 pm

"New Insights into Oral Drug Products Formulation Design: A Physiologically Realistic Mass Transport Analysis"

Presented by:
Niloufar Salehi
Ph.D. Candidate

Abstract: *In vivo* and *in vitro* dissolutions are complex due to their dependency upon the physicochemical properties of drug product and GI physiological properties such as: pH, residence time, lumenal buffers, and intestinal motility both under fed and fasted conditions. The dissolution rate of an ionizable drug may benefit from manipulating *in vivo* variables such as the environmental pH using pH-modifying agents incorporated into the dosage form. A successful example is the use of such agents for dissolution enhancement of BCS Class II.b (high permeability, low solubility, weak-base) drugs under high gastric pH due to the disease condition or co-administration by acid-reducing agents (ARA) (i.e., proton pump inhibitors, H2-antagonists, and antacids).

We have developed a hierarchical mass transport model to predict the *in vitro* drug dissolution of formulations under varying pH conditions including high gastric pH. This model considers the effect of physical and chemical properties of drug and pH modifiers such as pK_a, solubility, and particle size distribution. This model also considers the impact of physiological conditions such as stomach emptying rate, stomach acid and buffer secretion, residence time in the GI, and aqueous lumenal volume on drug dissolution. The predictions from this model are applicable to *in vitro* multi-compartment dissolution vessels and are validated by *in vitro* experiments in the gastrointestinal simulator (GIS). This model's predictions can serve as a potential data source to predict plasma concentrations for pre-designed formulations.

This study provides a rational approach for selecting pH modifiers to improve monobasic and dibasic drug compounds' dissolution rate under high gastric pH dissolution conditions. Betaine chloride, fumaric acid, and tartaric acid are examples of promising pH modifiers that can be included in oral dosage forms to enhance the bioavailability of monobasic and dibasic drug formulations. However, selection of a suitable pH modifier is dependent on the drug properties (eg: solubility, pKa) and its interplay with the pH modifier pKa or pKa's. As an example of this complex interaction, for base drugs with high pK_a and high intrinsic solubility values, and large doses, a polyprotic pH modifier can be expected to outperform a monoacid pH.

This analysis provides an improved formulation design procedure using pH-modifiers through minimizing the experimental iterations under both *in vitro* and *in vivo* conditions.

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