COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Yitian Chen
Doctor of Philosophy

Ph.D. Dissertation Defense Seminar

"Cocrystals Mitigate the Negative Effect of pH on Solubility and Dissolution Behavior of Basic Drugs"

Wednesday, September 20, 2017 at 2:00pm
Weiser Hall, Room 170

DISSERTATION COMMITTEE:

Dr. Nair Rodriguez (Chair)

Dr. Gordon Amidon (Member)

Dr. Gregory Amidon (Member)

Dr. Adam Matzger (Member)

Pharmaceutical cocrystal is emerging as a useful strategy for enhancing solubility, dissolution, and bioavailability for poorly water soluble drugs. One of the most important properties of cocrystals is the fine-tunable solubility. This property enables a cocrystal to exhibit higher, equal, or lower solubility than the drug. Cocrystal solubility is the result of intricate chemical interactions between cocrystal constituents and solution environment such as pH and additives. Without the critical knowledge of cocrystal solution behavior and the underlying solution interactions, studying a cocrystal can become a time-consuming exercise of trial and error. This dissertation determines the mechanisms by which the cocrystal solubility is influenced by pH and solubilizing agents and investigates the relationship between cocrystal supersaturation index and conversion kinetics.

The objectives of this work are to (1) determine the effect of pH and solubilizing agents have on cocrystal solubility, supersaturation index, and dissolution, (2) derive mathematical equations that describe cocrystal solubility and supersaturation index behavior based on solution equilibria of cocrystal dissociation, component ionization, and component solubilization, (3) investigate the relationship between cocrystal supersaturation index and risk of solution-mediated conversion, and (4) assess the ability of cocrystal to generate and maintain supersaturation with respect to drug in solution.

Cocrystal solubility, supersaturation index, and dissolution behavior were investigated under physiologically relevant pH and surfactant conditions for three cocrystals comprised of a basic drug and acidic coformers. Mathematical equations that can quantitatively predict cocrystal solubility and supersaturation index were derived. Predictions made by the equations were found to be in excellent agreement with the experimentally determined values. Ketoconazole cocrystals used in this study were found to exhibit drastically different solubility-pH behavior compared to the parent drug. The cocrystals were found to have solubility transition points (pH_{max}), above which the cocrystals gain solubility and dissolution advantage over the basic drug. Supersaturation index was found to be a useful thermodynamic parameter for assessing the risk of cocrystal solution-mediated conversion to a less soluble form. Extremely high supersaturation index can cause rapid cocrystal conversion leading to no dissolution advantage. A moderate or low supersaturation index can help sustained drug supersaturation and may result in absorption enhancement.