ABSTRACT

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Degree Received: May 2017
Title: Impact of Biologically Relevant Bile Salts on Solution Crystallization.
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With the increasing number of poorly soluble compound in the drug developmental pipeline, a variety of formulation strategies have been developed to address this issue. Although supersaturating formulations improve the bioavailability of therapeutic agents by providing a higher driving force for drug passive absorption across the gastrointestinal tract membrane, addition of a crystallization inhibitor is often required to maintain the solubility enhancement for biologically relevant timeframes. Besides polymeric additives, bile salts, which are endogenous surfactants, have been shown to inhibit crystallization of poorly soluble compounds. Due to the inevitable encounter of oral drug formulations with bile salts *in vivo*, it is imperative to evaluate the impact of bile salts on key attributes of supersaturated drug solutions.

In this work, the impact of various bile salts on the solution thermodynamics of telaprevir, a poorly soluble pharmaceutical compound, was revealed by determining the crystalline and amorphous solubility in the presence of monomeric and micellar bile salts. A side-by-side diffusion cell was used to determine the solute mass flow rate for telaprevir solutions in the absence and presence of bile salts as well as to provide an improved estimation of the crystallization driving force in complex media. At the same activity-based supersaturation, the impact of monomeric and micellar bile salts on telaprevir crystallization was investigated by measuring the induction time and crystal growth rate in

the absence and presence of monomeric and micellar biorelevant bile salts. An *in situ* common history seeding method was implemented to provide seeds that better mimic crystals formed from supersaturated solutions. It was found that all of the bile salts investigated in this work reduced the crystallization rates of supersaturated telaprevir solutions. However, the extent and kinetics of inhibition varied with structural differences amongst the bile salts as well as their aggregation level.

As bile salts exist in the gastrointestinal tract as mixed micelles with other biorelevant species, the ability of different combinations of bile salts and lecithin to maintain supersaturated telaprevir solutions was also evaluated. It was found that the crystallization tendency of telaprevir varied significantly between FaSSIF, the commercial recipe for simulated intestinal fluid which contains only one bile salt, and in mixed micelles with lecithin solutions; however, the impact of media composition was not observed when a highly effective polymeric crystallization inhibitor was present. This study provides detailed information on the crystallization of a poorly soluble drug in the presence of biorelevant bile salts as well as insights into formulation design.