ABSTRACT

Hsu, Hsin-Yun. Ph.D., Purdue University, August 2014. Crystallization of Active Pharmaceutical Ingredient on Substrates. Major Professor: Michael Harris.

Due to the demand of individualized pharmaceutical formulation, the application of drop printing (DP) technology on manufacturing of pharmaceutical devices has received extensive attention. DP can provide precise dosage and distribution of the active pharmaceutical ingredient (API). By integrating DP into the manufacturing platform, development of formulations with predicable and highly controllable releasing behavior can be achieved. However, when a solution of API is deposited on the edible substrates, the surface can have a profound impact on crystallization of the API and may further affect its bioavailability.

Hence, the purpose of this study is to develop a more fundamental understanding of the effects of substrates on the crystallization of API. The influence of surface chemistry and degree of ionization of the substrates on the crystal growth rate and crystallization kinetics of acetaminophen (APAP) was studied. Additives were also employed to change the crystallization behavior of APAP. The interplay between additive, APAP, and substrates was investigated. Lastly, a setup of the printing platform was built, and solvent-based and melt-based solutions of API were printed to

make formulations. The physicochemical properties of the products were characterized.

It was found that films doped with more functional groups that can form hydrogen bond (H-bond) with APAP increased the crystal growth rate and the rate of crystallization. On the other hand, the ionization degree of the substrate did not have much effect on the crystal growth rate, but the time it took for APAP to get 50% crystallized (t_{50}) was less on films with higher extent of ionization. The smaller t_{50} is likely caused by the lower interfacial energy of the nucleus and highly-ionized film which can promote nucleation. When additives were introduced into the system, it was found that the additive-substrate is important in controlling crystallization at the interface; however, if crystallized without confinement, the additive-APAP interaction is more significant in determining the crystallization behavior. This study highlights the significant impact of substrates on heterogeneous crystallization and the complex interplay between additives, crystallizing molecules, and substrates. Finally, the characterization results of formulations built by the printing platform demonstrate DP is can be applied in pharmaceutical manufacturing.