ABSTRACT

Içten, Elçin. Ph.D., Purdue University, May 2016. Manufacture of Individualized Dosing: Development and Control of a Dropwise Additive Manufacturing Process for Melt Based Pharmaceutical Products. Major Professors: Zoltan K. Nagy and Gintaras V. Reklaitis.

The improvements in healthcare systems and the advent of precision medicine initiative have created the need to develop more innovative manufacturing methods for the delivery of individualized dosing and personalized treatments. In recent years, the US Food and Drug Administration (FDA) introduced the Quality by Design (QbD) and Process Analytical Technology (PAT) guidelines to encourage innovation and efficiency in pharmaceutical development, manufacturing and quality assurance. As a result of emerging technologies and encouragement from the regulatory authorities, the pharmaceutical industry has begun to develop more efficient production systems with more intensive use of on-line measurement and sensing, real time quality control and process control tools, which offer the potential for reduced variability, increased flexibility and efficiency, and improved product quality.

In accordance with the changes observed in health care systems towards more innovative personalized therapies, this dissertation presents a novel technology for small scale, distributed manufacturing of individualized dosing. A dropwise additive manufacturing process for melt-based solid oral drug production is developed, which utilizes the drop-

on-demand (DoD) printing technology for predictable and highly controllable deposition of active pharmaceutical ingredients (API) onto an edible substrate, such as a polymeric film or placebo tablet. This manufacturing method has tremendous potential in individualized dosing because through a combination of drop size and number of drops, the dosage can be precisely and reliably controlled to match the prescribed amount for a patient.

The real-time process management (RTPM) strategy is developed for the dropwise additive manufacturing of pharmaceutical products (DAMPP). The automation program assures synchronous operation of process units, while monitoring process parameters and maintaining process control. The automation program is integrated with the Knowledge Provenance Management System (KProMS) to record and make accessible the data provenance of each and every dosage produced via DAMPP.

For the dropwise additive manufacturing system, the critical process parameters (CPP) are controlled to achieve the desired critical quality attributes (CQA) of the dosage forms. The effect of the CPPs on the final drug property is investigated and it is shown that implementation of a supervisory control system on the process is essential for producing individual dosage forms with the desired CQAs. A polynomial chaos expansion based surrogate model is developed to predict the dissolution profile of the solidified drug deposition given the temperature profile applied on the substrate. Using this model, a hierarchical control system is implemented by monitoring the drop size on-line and predicting a temperature profile to achieve the desired dissolution profile for the dosage forms created. The process control strategy effectively mitigates variations in the dissolution profiles due to variable dosage amounts, hence enabling the application of the DoD system for the production of individualized dosage regimens.

A crystallization model based on non-isothermal Avrami kinetic equation is developed for the cooling temperature dependent solid-state transformation of the melt-based solid oral dosages produced using the dropwise additive manufacturing process. Using the model, a mean crystal size can be achieved which would lead to the desired product quality, such as dissolution.

The DAMPP process is a viable method for on-demand production of various formulations. Melt-based dosage forms containing crystalline API and self-emulsifying drug delivery systems with amorphous API forms are produced and analyzed to demonstrate reproducibility of dosages and their dissolution behaviors.

The prototype system offers great promise as a tool for advancing personalized medicine by allowing the precise production of convenient solid oral dosages tailored to the patient on site at hospitals, clinics and even pharmacies. Future directions are suggested to further advance dropwise additive manufacturing of pharmaceutical products and lead to commercialization of this technology.