

ABSTRACT

Radcliffe, Andrew J. PhD, Purdue University, August 2020. Development of Dropwise Additive Manufacturing with non-Brownian Suspensions: Applications of Computer Vision and Bayesian Modeling to Process Design, Monitoring and Control.
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In the past two decades, the pharmaceutical industry has been engaged in modernization of its drug development and manufacturing strategies, spurred onward by changing market pressures, regulatory encouragement, and technological advancement. Concomitant with these changes has been a shift toward new modalities of manufacturing in support of patient-centric medicine and on-demand production. To achieve these objectives requires manufacturing platforms which are both flexible and scalable, hence the interest in development of small-scale, continuous processes for synthesis, purification and drug product production. Traditionally, the downstream steps begin with a crystalline drug powder – the effluent of the final purification steps – and convert this to tablets or capsules through a series of batch unit operations reliant on powder processing. As an alternative, additive manufacturing technologies provide the means to circumvent difficulties associated with dry powder rheology, while being inherently capable of flexible production.

Through the combination of physical understanding, experimental work, and data-driven methods, a framework was developed for ink formulation and process operation in drop-on-demand manufacturing with non-Brownian suspensions. Motivated by the challenges at hand, application of novel computational image analysis techniques yielded insight into the effects of non-Brownian particles and fluid properties on rheology. Furthermore, the extraction of modal and statistical information provided insight into the stochastic events which appear to play a notable role in drop formation from such suspensions. These computer vision algorithms can readily be applied by other researchers interested in the physics of drop coalescence and breakup in order to further modeling efforts.

Returning to the realm of process development to deal with challenges of monitoring and quality control initiated by suspension-based manufacturing, these machine vision algorithms were combined with Bayesian modeling to enact a probabilistic control strategy at the level of each dosage unit by utilizing the real-time image data acquired by an online process image sensor. Drawing upon a large historical database which spanned a wide range of conditions, a hierarchical

modeling approach was used to incorporate the various sources of uncertainty inherent to the manufacturing process and monitoring technology, therefore providing more reliable predictions for future data at in-sample and out-of-sample conditions.

This thesis thus contributes advances in three closely linked areas: additive manufacturing of solid oral drug products, computer vision methods for event recognition in drop formation, and Bayesian hierarchical modeling to predict the probability that each dosage unit produced is within specifications.