ADVANCING DROPWISE ADDITIVE MANUFACTURING OF PHARMACEUTICALS BY INCORPORATING CONTINUOUS PROCESSING, NOVEL DOSAGE FORMS, AND INDUSTRY 4.0 CAPABILITIES

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Abstract

In recent years, the pharmaceutical industry has embarked on an extensive program to modernize its manufacturing resources. Recognizing the limitations of traditional mass manufacturing, the industry is now focused on developing new production systems that can deliver high-quality medicines with enhanced efficiency, flexibility, agility, and reliability. To realize this vision, innovations in three key areas are being pursued: continuous processing, personalized medicine, and Industry 4.0.

This thesis contributes towards the industry's goal by focusing on the development of an advanced system to manufacture solid oral drug products. This system is centered around a pharmaceutical additive manufacturing technology called drop on demand (DoD) printing. This technology is highly effective in making personalized drug products, which allow for customizing dose attributes such as drug loading, release behavior, formulation type, and dosage form, based on patient requirements. To develop the DoD printer into an advanced production system, technologies such as end-to-end continuous processing, real time quality assurance, and automated operation need to be incorporated into it.

The studies presented in this thesis implement different aspects of these technologies in the printer. To enable end to end operation, a novel solvent switch process called three phase settling is developed, that can integrate the DoD system with upstream steps for synthesizing the active ingredient. To facilitate automated processing of formulations with different active ingredients, excipients, and particle concentrations; a model framework is developed to recommend operating conditions for the DoD platform that can deliver on-spec printer operation. To expand the range of personalized dosage forms offered by the system, the manufacturing of a new category of drug products, called mini-tablets, is demonstrated. To provide reconfigurability and quality assurance

capabilities in the platform, modular design and process monitoring tools are implemented. Lastly, to aid optimization and control of drug production processes, a digital twin is developed by combining the models developed for DoD, solvent switch, synthesis, and crystallization operations.

The research presented in this thesis lays the foundation for developing the next generation of manufacturing systems for drug products. Incorporation of scalability, autonomous operation, and real time release prediction are critical steps in facilitating the next phase of its development – deployment in real-world manufacturing scenarios.