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ABSTRACT

In the pharmaceutical industry special care must be taken by companies to guarantee high quality medications that are free from byproducts and impurities. The development process involves various considerations including solvent selection, solubility screening, unit operation selection, environmental, and health impact evaluations. Traditionally, pharmaceutical manufacturing consisted of large, centralized facilities to meet pharmaceutical demands; however, there has been a recent shift toward distributed manufacturing. With distributed manufacturing platforms, rapidly changing supply chain needs can be met regionally in addition to supplying small-volume medications and personalized medicines to hospitals and pharmacies. To produce quality pharmaceuticals, distributed manufacturing platforms should integrate digital design, novel unit operations, and process analytical technology (PAT) tools for quality monitoring and control. In this dissertation, a process design and development framework is proposed and implemented for a small-scale pharmaceutical manufacturing platform: MiniPharm.

Various approaches to process design are detailed in this dissertation, which include heuristic-based and digital or simulation-based design. For heuristic-based design, the knowledge of the researchers was utilized to provide unit operation evaluation and screening of process alternatives. In cases when unit operations were highly complex, digital or simulation-based design was utilized to conduct sensitivity analyses and simulation-based design of experiments. With the implementation of simulation-based design, material and time needs were reduced while gaining knowledge about the system. The integration of various unit operations comes with increased understanding of start-up dynamics and operational constraints. What was found to be the most successful approach was the combination of heuristics and digital design to combine researcher knowledge and experience with the information gained from process modeling and simulation to create process alternatives that utilized system dynamics to reach desired process outcomes.

Additionally, MiniPharm was used for process model development at the small-scale. Various software packages have been made commercially available that focus on production scale; however, models for small-scale operations are not typically implemented in these packages. Models for unit operations were fit with collected experimental data to estimate model parameters

for small-scale synthesis, liquid-liquid extraction, and crystallization unit operations. The models were implemented to better capture the heat and mass transfer of the milli-fluidic scale platform, which consist of unit operations housed within microchannels. MatLab was utilized for estimation of parameters such as kinetic rate constants and overall mass transfer coefficients. These parameters were used for design space determination and process disturbance simulation. The exploration of the impact of various process parameters on quality attributes helps researchers gain a deeper understanding about the manufacturing process and helps to demonstrate how to control the process.

An important aspect of MiniPharm is the process development progress that has been demonstrated. With the construction of a modular and reconfigurable platform, various process alternatives can now be experimentally validated. The integration of unit operations operated at a decreased scale makes MiniPharm an example of process intensification. The implementation of integrated unit operations decreases handling time of intermediates and reduces the overall footprint for manufacturing. Designed to allow for increased flexibility of operation and decreased cleaning time at a low cost, perfluoroalkoxy alkane (PFA) tubing was used for synthesis and purification. The modular nature of the platform also allows for the investigation of individual unit operations for performance evaluation.

Finally, a novel continuous solvent switch distillation unit operation was designed and constructed along with customized reactor and crystallizers for process alternative screening for the synthesis and purification of two compounds: Diphenhydramine hydrochloride and Lomustine. Diphenhydramine hydrochloride is a low-value, high volume allergy medication commonly found in Benadryl and Lomustine is a high-value, low volume cancer medication used to treat glioblastoma and Hodgkin’s Lymphoma. The production of the compounds demonstrated the flexibility of the manufacturing platform to produce both a generic and specialty medication. A versatile platform is needed for distributed manufacturing because of quickly changing supply chain needs. Overall, this dissertation successfully demonstrates the process design, development, and simulation for small-scale manufacturing.