TOWARDS CONTINUOUS, AGILE, AND DISTRIBUTED PHARMACEUTICAL MANUFACTURING SYSTEMS FOR ONCOLOGY MEDICATIONS

Ilke Akturk

The deficiencies in the pharmaceutical manufacturing supply chain during the COVID-19 pandemic highlighted the need for smaller-scale, decentralized facilities near raw material sources and hospitals. Meanwhile, although the move towards continuous processing and modeling has gained momentum, the seamless integration of unit operations into end-to-end drug manufacturing remains as an emerging area of development. Small-scale, distributed continuous manufacturing platforms combined with digital simulations can further enhance pharmaceutical production by reducing equipment footprint and processing time while increasing throughput. This research aims to develop such platforms, referred to as "MiniPharm", to ensure the availability and quality of essential medication.

The quality by design (QbD) approach is useful as it involves the systematic design of operating space using mechanistic models and design of experiments (DoE). The design space illustrates interaction of material attributes and process parameters while minimizing process variability and off-spec products. In this research, the critical quality attributes (CQAs) of active pharmaceutical ingredients (APIs) were identified, and systematic DoEs were performed to generate data spanning a broad operational space for each unit operation. To achieve this, experimental studies were supported with digital modeling and validated through modular platform demonstrations. The development and implementation of the mini-pharm end-to-end manufacturing platform were demonstrated on two commercial model compounds.

The first study focuses on lomustine, a chemotherapy drug, whose price was inflated by over 1500%. This research offers an alternative manufacturing process to enhance patient access by presenting the development and demonstration of a continuous, modular platform for end-to-end manufacturing of lomustine. The process was established through iterative development of both drug substance and drug product operations, including two-step API synthesis, continuous solvent-switch distillation (CSSD), crystallization-based purification, and drop-on-demand (DoD) formulation of capsules. The effect of process parameters, such as reaction temperature, reactant ratios, and concentration on the reaction kinetics, was explored. The operational range for CSSD

for effective separation of solvent-antisolvent was determined. A crystallization DoE was conducted to explore the effects of cooling rate and solvent-antisolvent ratio on crystallization which supported the design and development of the combined cooling and antisolvent crystallization process. Lomustine was successfully synthesized and purified with an improved yield through a continuous process that includes a two-step reaction, CSSD, and combined cooling and antisolvent crystallization. Integration of Omnibus automation and inline PAT facilitated robust real-time monitoring and safer operation. The platform has the capacity to meet the annual U.S. demand for Glioblastoma treatment that demonstrates the potential of modular continuous systems to be rapidly reconfigured for different products or scaled up via modular expansion.

The second case study investigates the solvent-mediated polymorphic crystallization of imatinib mesylate, a chemotherapeutic agent in two polymorphic forms influencing its manufacturability and process efficiency. The goal was to establish a structured strategy for batch to continuous polymorphic crystallization of imatinib mesylate. A systematic framework for crystallization process design was developed, integrating solvent screening, kinetically informed thermodynamic (KIT) design, and a batch cooling crystallization design of experiments (DoE). This approach enabled a robust process design, parameter estimation, and effective knowledge transfer to continuous operation. Using the MiniPharm purification module, a continuous crystallization process incorporating polymorphic transformation was successfully demonstrated for imatinib mesylate for the first time. This work introduces a novel approach to crystallization and offers valuable insights for optimizing target polymorph production while improving yield and sustainability metrics.

This research highlights the potential of MiniPharm platforms for on-demand, continuous manufacturing of high-value, low-demand oncology drugs and provides a systematic framework for continuous polymorphic crystallization development. The approach offers a flexible alternative to conventional batch manufacturing, enhancing efficiency and improving access to life-saving medications.