Ph.D. Thesis Technical Summary

Continuous Processing of Multiphase Reactions for Pharmaceutical Applications

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With current needs to expedite new drug development, reduce cost and increase availability of existing drugs, and improve stability and safety of pharmaceutical manufacturing, the continuous flow synthesis has appeared as an attractive alternative to the conventional batch processes. Numerous technologies have emerged to facilitate the development of continuous flow chemistry, and the benefits of flow chemistry have been successfully demonstrated for many chemistries that would otherwise be challenging in conventional batch process because of demanding process conditions, hazardous intermediates, and limitations in mass and heat transfer. However, in contrast to single-phase reaction, transformation of multiphase reactions from batch to continuous flow still remains cumbersome due to complicated multiphase hydrodynamics, mass transfer, interfacial reaction kinetics, and potential clogging issues of solids.

This thesis aims at developing enabling strategies and solutions to make challenging multiphase reaction systems amenable in continuous flow system. For solid-liquid reactions with reactor clogging problems, a new modular miniature continuous stirred-tank reactor (CSTR) cascade is proposed to handle solid-forming reactions in flow, which serves as a robust strategy to study solid-containing reactions in small scale. For mass-transfer limited liquid-liquid systems, we have designed and demonstrated a high-performance miniature CSTR unit with magnetic coupling rotation mechanism, which decouples mixing and residence time to accommodate different reaction kinetics. To alleviate tedious scale-up procedure and safety concerns of catalytic gas-liquid reactions, we have provided a robust design of a thin-layer membrane reactor to safely and scalably perform catalytic heterogeneous hydrogenation and homogeneous aerobic oxidation, providing a superior alternative to conventional packed-bed reactors. For electrosynthesis involving electrode surface as a heterogeneous reaction surface, a cost-effective and scalable electrochemical flow cell is engineered for the N-hydroxyphthalimide (NHPI) mediated electrochemical aerobic oxidation of benzylic C-H bonds, and a microfluidic electrochemical flow cell is utilized to accurately control the lifetime of persistent and transient radicals in order to selectively generate cross-coupling products. The developed modular and plug-and-play reactors in this thesis offer additional tools to enable facile implementation of multiphase chemistries in flow.