Modeling of Mixing-Sensitive Pharmaceutical Drug Substance Processes in Batch Reactors

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Abstract

Manufacturing of pharmaceutical drug substances involves chemical unit operations that are dependent on effective mixing, particularly reactions and crystallizations. Poor mixing can cause uneven distribution of chemical species in stirred tanks, leading to impurity formation and decrease in selectivity during reactions, and localized supersaturation, uncontrolled nucleation, impurity entrapment and agglomeration in crystallizations. These issues can be minimized by the optimization of process parameters, reactor configuration and mixing conditions, such as agitation rate, reactant feed rate and reactor configurations in batch reactors. COMSOL Multiphysics® software provides a platform to study the effect of mixing in these processes and to optimize the mixing conditions for better control of the final drug substance quality. In the present work, evolution of flow patterns, chemical species transport and mixing attributes in fed-batch reactors over time are examined using COMSOL® Rotating Machinery Reactive Flow interface to identify the critical geometrical components and process parameters that can impact the reaction selectivity, crystallization behavior and ultimately, final drug substance qualities.