Wet-mill Aided Continuous Cooling Mixed Suspension Mixed Product Removal Crystallizer

Wei Li, Brahim Benyahia, Chris Rielly

Department of Chemical Engineering, Loughborough University, Loughborough, Leics, UK LE11 3TU, UK
e-mail: w.li@lboro.ac.uk

Rotor-stator wet mills have been widely used in the manufacture of active pharmaceutical ingredients (API) to modify the size and morphology of crystal products, without the need to change solvent and without the use of additives, which may require further purification or cause bioavailability issues. Such wet mills have been used for size reduction and continuous nucleation (*in situ* seed generators) for many years. However, the process understanding about the latter mechanism is still very limited [1]. The isolation and handling of needle-shaped crystals with a high-aspect-ratio associated with many real API is one of the most important challenges in pharma. A wet-mill aided strategy is investigated here to tailor the desired size and shape distributions required for downstream processing and formulation.

This research is aimed at improving the process understanding about wet-mill aided crystallization processes. The integration of a wet-mill with an MSMPR crystallization platform is studied for the cooling crystallization of (i) paracetamol in isopropanol, which is subject to crystal agglomerated and (ii) lovastatin in ethanol, which results in very long needle-like crystals. Two types of wet-mill including internal and external setups are investigated. The wet-mill was applied as either an in-situ seed generator, i.e. as a nucleation stage, or as a crystal breakage device at the end crystallization. The wet-mill was incorporated in a recycle loop with a one-stage MSMPR. The wet-mill crystallization process was then experimentally investigated using factors such as wet-mill rotational speed, mean residence time and the time duration of milling. PAT were used to monitor the solute concentration, particle count, morphology and size. This integrated system demonstrated enhanced control over the CSD and morphology compared to the conventional cooling crystallization processes. Hence, enhanced control of the primary nucleation and reduced induction times were achieved by integrating a wet-mill.

gFORMULATE software was used to develop and simulate the mathematical model of the system, which utilized the finite volume method to solve the population balance equations. The kinetic parameters of crystallization model were estimated using experimental data from batch seeded and unseeded crystallization experiments. The experimentally validated model can then be used to optimise the operation of an integrated crystallization and wet-mill platform and enable enhanced control of crystal size and shape distributions.

[1] H.H. Tung, Industrial perspectives of pharmaceutical crystallization, Org. Process Res. Dev. 17 (2013) 445–454.

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