Effect of impurities on supersaturation control during batch cooling crystallisation of an organic compound

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Batch cooling crystallisation is used to produce a range of chemical products such as agrochemicals, fine chemicals and pharmaceuticals. These often require a certain crystal size distribution (CSD), achieved through control of the supersaturation as it is the main driving force for crystal nucleation and growth. Seeding is commonly implemented to control the crystal size, however unwanted impurities within the mother liquor can influence the crystallisation kinetics and potentially lead to an unexpected and undesirable product CSD. In this study, a model predictive control (MPC) strategy was developed for the control of supersaturation during batch cooling crystallisation of hexamethylenetetramine (hexamine) from pure ethanol solution. Using kinetic parameters available in literature [1], a digital twin describing the hexamine-ethanol crystallisation system was built using gPROMS Formulated Products software [2], solving 1D population balance equations to accurately predict the CSD evolution with time. With this first-principles based model, the time required to experimentally characterise a system's crystallisation kinetics and obtain necessary process data is reduced significantly compared to empirical models. The process model has been coupled with a control algorithm in PharmaMV software [3] to allow for supersaturation control both in-silico and on a physical 500 ml agitated jacketed crystalliser.

To characterise the effect of impurities on the performance of the MPC strategy, potential growth inhibitors for the hexamine-ethanol system were screened via seeded batch crystallisation at the 100 ml scale. Amongst three different inhibitors tested, citric acid was identified to have the strongest effect on crystal growth, with concentrations beyond 2 wt% citric acid/hexamine slowing the growth rate such that the supersaturation was driven beyond the metastable limit when cooling at -0.2 ˚C/min. At the 500 ml scale, concentrations up to 0.75 wt% citric acid/hexamine were found to reduce the growth rate without exceeding the metastable limit using the same cooling rate. A decrease in the number of solvent inclusions in hexamine product crystals was observed with increasing concentration of citric acid, which may have implied an inhibition of the agglomeration mechanism hexamine is known to exhibit [4]. The MPC strategy was found to be able to control supersaturation effectively even with the presence of citric acid impurities between 0.25-0.75 wt%. The mean supersaturation was found to be higher with increasing impurity concentration; the controlled variable became more sensitive to increases in the cooling rate, whereas it became difficult to reduce due to the significantly slower rate of crystal growth. From an industrial perspective, it should be noted that this was only achieved through a significantly reduced overall cooling rate, which lead to extended batch times that may be undesirable despite resulting in a consistent product CSD.

References

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