Modelling Pharmaceutical Crystallisation Processes using Coupled CFD-Population Balance Approach

ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

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1. Introduction

- In the pharmaceutical industry, crystallisation process development and scale-up are generally carried out using experimental trial-and-error approaches, which can significantly affect the time-to-market
- A first-principle model based holistic approach using QbD principles has the potential to provide a step-change in the efficiency of work flows associated with the process development and scale-up in order to produce crystals of predefined attributes such as particle shape and size distribution .
- A CFD –PBM framework for modelling crystallisation processes is proposed to assess the effect of hydrodynamics, mixing and heat transfer on nucleation and crystal growth kinetics and hence in PS&SD
- This can provide a basis for multi-zonal modelling approach is suggested to predict CSD produced by batch cooling crystallisation in agitated crystallisers with the advantage of reducing extensive computational resources

2. Modelling framework

CFD model (ANSYS Fluent)
- *Eulerain-Eulerian* two-fluid model
- *Reynolds Stress model* for turbulence
- *Volume-of-Fluid* method for vortex formation
- Species & Energy transport equations

- Nucleation/growth kinetic parameters depend on operating conditions & scale
- These can be obtained from:
- Literature
- Direct measurements
- Crystallization process data using parameter estimation tool of gCRYSTAL

Two-phase CFD for hydrodynamics, mixing & heat transfer

Coupled via UDF

1D-Population Balance Model (PBM)

$$\frac{\partial}{\partial t}(\rho_s \alpha_i) + \nabla.(\rho_s u_i \alpha_i) + \frac{\partial}{\partial V}\left(\frac{G_v \rho_s \alpha_i}{V}\right) = \rho_s V_0 \dot{n}_0$$

Models for nucleation & growth rates: Power law, Classical Nucleation Theory (CNT), Two-step growth model…

Assessment of primary/secondary nucleation & growth kinetics using gCRYSTAL

Distributions of process parameters: velocity, concentration, supersaturation, temperature, shear rate, turbulent kinetic energy, energy dissipation rate, solid concentration…

Data for model validation & refinement

Multi-zonal Crystallisation Model
- Integrate CFD with the Multi-zonal modelling platform in gCRYSTAL
- Develop strategies for defining well-mixed zones
- Fluxes across the zone boundary
- Solve a 1-D PBM in each zone
- Implement a *Morphological Population Balance* model

Fig 1. Flow diagram summarising the strategy for the digital design of batch cooling crystallisation processes

3. Nucleation & crystal growth kinetics parameters estimation

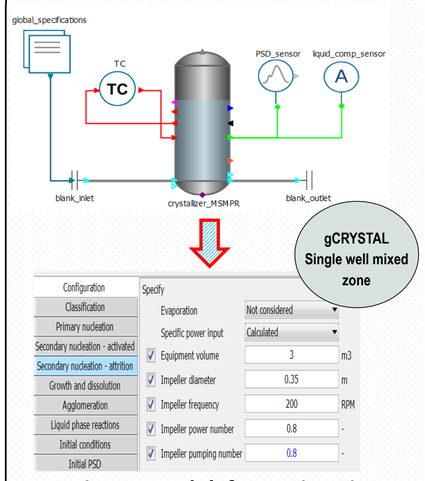


Fig 2. Model for estimation of crystallisation kinetics parameters in gCRYSTAL

$$J = k_B(\sigma)^b \qquad G = k_G(\sigma)^n$$

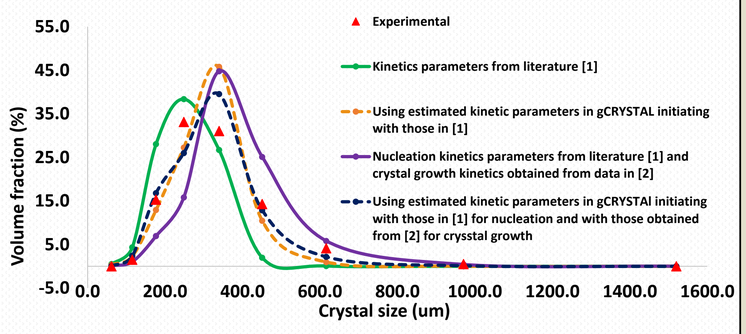


Fig 3. Comparative predictions of CSD using different sets of nucleation & growth kinetics parameters & comparison with experimental data

4. Modelling crystallisation of L-glutamic acid (LGA) in aqueous solutions

Experimental case
- Kilo-scale 20 L crystalliser with a single Beavertail baffle agitated by a retreat curve impeller
- Velocity data obtained using LDV at impeller speeds of 100, 150, 200 & 250 rpm[1]
- Unseeded batch cooling crystallisation of L-glutamic acid from aqueous solutions were performed[2] at:
  - Solution concentration: 45 g / 100 g (T_{sat} = 70 °C)
  - Cooling rate: 0.6 °C/min
  - Stirrer speed: 100, 150, 200 & 250 rpm

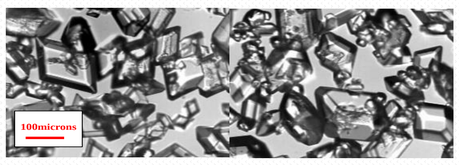


Fig 4. Microscopic images of α-form L-glutamic acid at 200rpm [3]

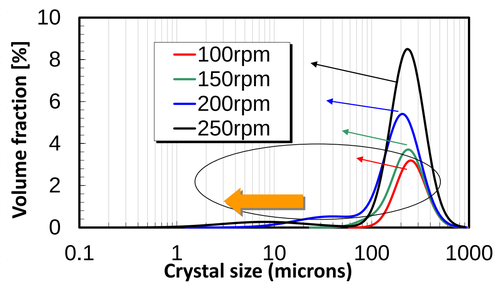
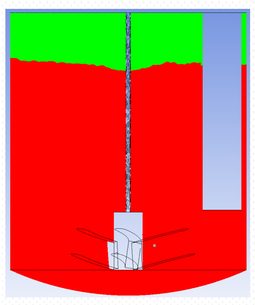


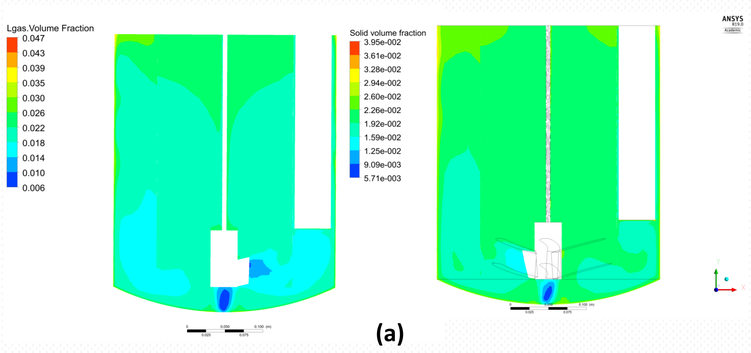
Fig 5. Measured LGA PSD at different impeller speeds [3]

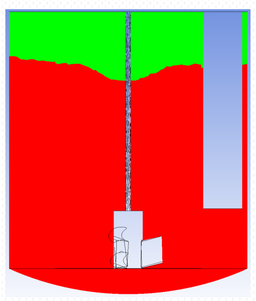
5. Two-phase CFD modelling (ANSYS Fluent)

CFD - Volume-of-Fluid (VOF) Approach

CFD - 1D-PBM simulations crystallisation of LGA in aqueous solutions







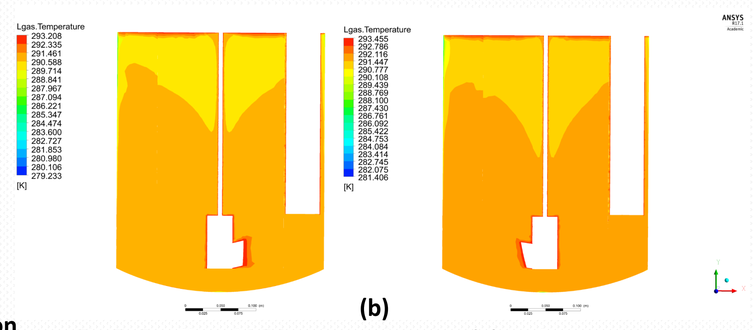


Fig 6. Predicted vortex formation for 100 and 150 rpm using VOF

Fig 7. Predicted LGA volume fraction (a) and temperature distribution (b) for 100 and 150 rpm

6. Effect of kinetic parameters on predicted CSD

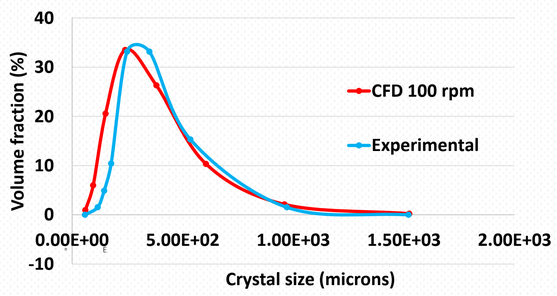


Fig 8. Comparison of experimental [3] and predicted CSD at 100 rpm using nucleation and growth kinetics from [1]

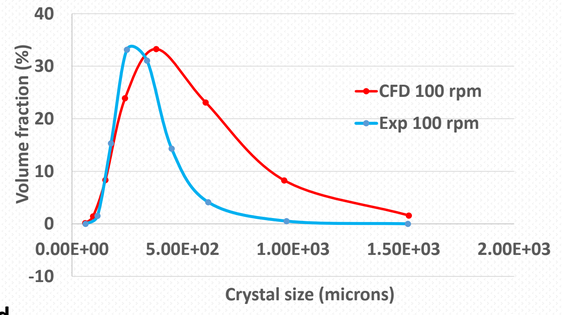


Fig 10. Comparison of experimental [3] and predicted CSD at 100 rpm using nucleation [1] and growth kinetics [2]

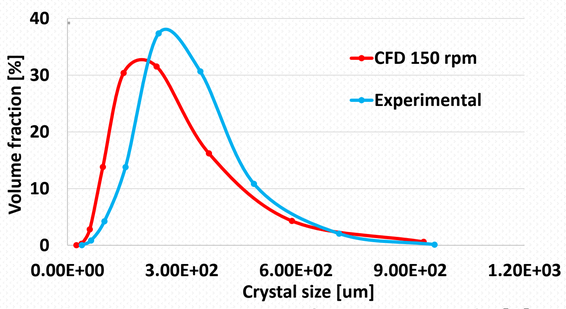


Fig 9. Comparison of experimental [3] and predicted CSD at 150 rpm using nucleation and growth kinetics from [1]

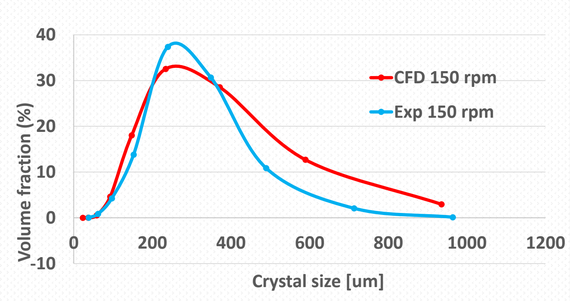


Fig 11. Comparison of experimental [3] and predicted CSD at 150 rpm using nucleation[1] and growth kinetics [2]

7. Conclusions

- Crystallisation process modelling methodology for accurate prediction of crystal size and shape distribution facilitates process development and scale up.
- CFD –VOF approach provides a detail insight of the hydrodynamics during batch cooling crystallisation process.
- Fully coupled CFD-1-D PBM model accurate predicts the effect of kinetic parameters on predicted CSD and the predictions are in good agreement with measurements.

References
[1] C.Y. Tai, W-L. Shei, Chem Eng Comm, 1993, 120, 139-152
[2] Penchev R. Y., 2007, PhD Thesis, University of Leeds, Leeds, UK
[3] K. Liang, PhD thesis, Department of Chemical Engineering, Heriot-Watt University, Edinburgh, 2002

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