



Diffusive mixing in antisolvent crystallisation.

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Projects aims

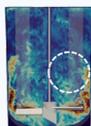
- To model diffusive mixing in multicomponent in highly non-ideal antisolvent crystallisation processes using physically correct driving forces
- Implement model to gain insight into the effect of both non-ideality and antisolvent choice on crystallisation outcomes
- Investigate the occurrence of liquid-liquid phase separation during the diffusive mixing process

Background Theory

- ❖ Driving force for crystallisation is supersaturation
- ❖ Addition of antisolvent generates supersaturation by lowering local solute solubility in solvent mixture
- ❖ Macro-mixing can be described by two sequential processes: bulk rearrangement of fluid elements & diffusive mixing

1. Macroscale Mixing

Fluid motion spatially rearranges fluid elements



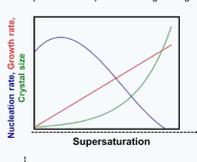
2. Microscale Mixing

Species exchange between elements occurs via diffusion



3. Effect on crystal properties

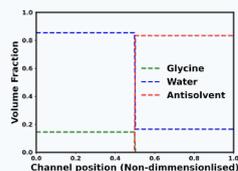
Crystal properties influenced by resulting supersaturation profiles during mixing



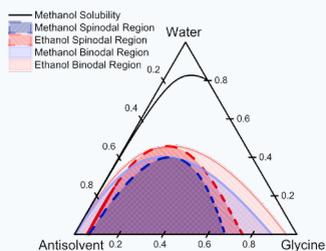
- ❖ At low length scales mixing becomes important consideration
- ❖ Antisolvent choice can impact diffusive mixing profiles and the resulting supersaturation profiles in strongly non-ideal solvent mixtures
- ❖ Crystallisation outcomes strongly influenced by supersaturation profiles [2]

Methods

Water/Antisolvent/Glycine ternary system



Initial volume fraction profile



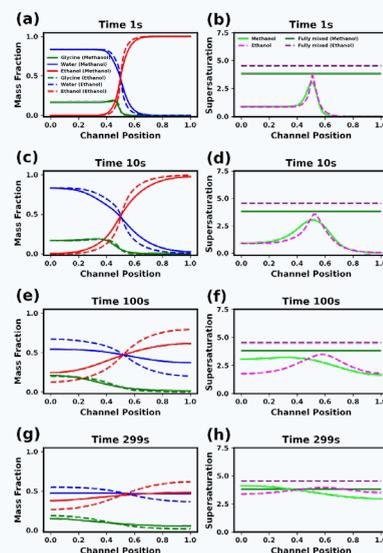
Predicted phase diagram

- ❖ Interdiffusion between fluid elements modelled as 'channel' filled with Aqueous glycine solution and antisolvent.
- ❖ Mixing modelled using the ternary component Maxwell-Stefan diffusion equation [3]
- ❖ Equations solved using finite volume approach
- ❖ Two antisolvents compared – methanol and ethanol
- ❖ Thermodynamic non-ideality predicted via Scatchard-Hildebrand approach [4]
- ❖ Activity model allows for calculation of phase diagram and correct driving force for diffusion based on activity gradients instead of concentration gradients

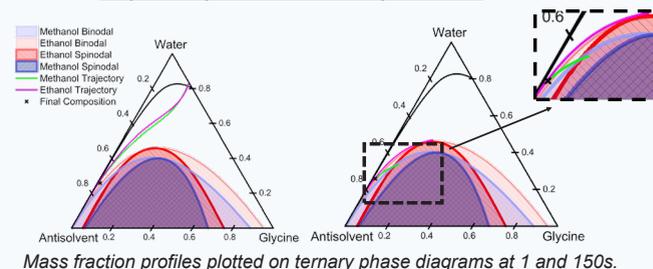
Results

Comparison of mixing profiles

- ❖ Comparison of mass fraction and supersaturation profiles for methanol/ethanol antisolvent systems
- ❖ Solid lines indicate methanol, Dashed depict ethanol
- ❖ Methanol system mixes quicker due to higher diffusivity
- ❖ Composition at peak supersaturation varies between systems
- ❖ Solute-solvent interactions effect crystal properties, such as morphology or shape



Liquid-liquid Phase Separation



- ❖ Localised liquid-Liquid phase (LLPS) separation spontaneously occurs when local solution composition enters spinodal region
- ❖ Complicates nucleation as co-existing phases have different solute concentrations, significantly affects crystal growth and nucleation
- ❖ Antisolvent choice influences occurrence of LLPS
- ❖ Composition profiles across channel shown below for the two antisolvent systems. 'channel' filled with 80% antisolvent and 20% aqueous glycine solution and pure antisolvent was used.
- ❖ Ethanol antisolvent results in local LLPS, as local composition enters spinodal region. LLPS does not occur in methanol system

Conclusions

- ❖ Diffusive mixing simulated for aqueous glycine solution with two different antisolvents with thermodynamically correct driving force for diffusion based on activity
- ❖ Supersaturation overshoots are artefacts of ideal Fickian diffusion models and do not occur in real non-ideal mixtures in antisolvent crystallisation
- ❖ The prediction of LLPS is influenced by antisolvent selection and offers a novel explanation for effects of various antisolvents on crystallisation outcomes

References: [1] Miller, R.; Sefcik, J.; Lue, L. Modelling diffusive mixing in antisolvent crystallization. *Cryst. Growth Des.* 2022, 22, 2192-2207
 [2] Mullin, J. W. J. W. Crystallization; Butterworth-Heinemann: Oxford, UK, 2001; p 594 [3] Krishna, R. Uphill diffusion in multicomponent mixtures. *Chem. Soc. Rev.* 2015, 44, 2812-2836.
 [4] Wilhelm, E. Mitigating Complexity: Cohesion Parameters and Related Topics. I: The Hildebrand Solubility Parameter. *J. Solution Chem.* 2018, 47, 1626-1709

