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Understanding the effect of diffusive mixing in antisolvent crystallisation

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Antisolvent crystallisation is a process widely applied within the pharmaceutical industry. It relies on the difference in solubility of a solute in two miscible liquids—the solvent and the antisolvent—to create the supersaturation required for crystallisation to occur [1]. The mixing process has a significant impact on the characteristics of the final product [2], since properties such as the crystal size distribution and the final crystal polymorph obtained are influenced by local supersaturation values. However, mass transfer in antisolvent crystallisation is not well understood, leading to the occurrence of unexpected and undesired phenomena such as oiling out (i.e. liquid/liquid phase split) or the formation of unwanted crystal phases.

Traditionally, the mixing of solute, solvent and antisolvent at the microscale has been described through Fick's law of diffusion. However, this model considers the driving force for mass transfer to be the gradient in concentration of the components, instead of the more physically accurate gradient in chemical potential. Therefore, it fails to explain non-idealities observed for certain systems including uphill diffusion [3], which is the diffusion of a component against its concentration gradient. The path of the system through the solubility phase diagram is dictated by mass transfer, and unwanted phenomena may occur when non-idealities lead the system to unexpected regions in this phase diagram. The development of a model that accurately predicts and describes these events is essential for their understanding and prevention.

In this work, we compare the performance of Fick's law against the Maxwell-Stefan equations in a system formed by water, ethanol, and glycine, in which the appearance of these phenomena has been reported. Since the Maxwell-Stefan framework considers the chemical potential as the driving force for diffusion, a better description of the mixing process is expected, including the prediction of non-idealities, as this model is more robust from a thermodynamical perspective. The simulation results are compared to experimental diffusion measurements obtained through Raman spectroscopy, with the expectation that the Maxwell-Stefan equations will adjust better to the experimental results.

This framework has the potential to greatly enhance our understanding of diffusive mixing processes not only in antisolvent crystallisation, but also in any other chemical process in which diffusion of non-ideal solutions takes place. Ultimately, this will lead to safer, more robust manufacturing of chemical and pharmaceutical products.

References

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