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Crystal nucleation rates from induction time measurements and microfluidic devices.

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Introduction

Nucleation is one of the key processes in crystallization of pharmaceutical products as it determines various crystal product quality attributes such as crystal size distribution and crystal structure. Therefore, understanding the fundamentals of nucleation is key to attaining control over these properties. Nucleation refers to the generation of a new phase of nanoscopic clusters of molecules from a supersaturated mother liquor.

Microfluidic devices are a promising tool for the analysis of crystallisation kinetics due to their ability to create and control a large number of droplets of known composition in isolated, controlled conditions quickly.

Recent work within CMAC has shown that concentration is enhanced at interfaces, particularly oil/solution interfaces (McKechnie et al.). This is of particular significance for work in microfluidic devices, where crystallising droplets are in constant contact with oil and often have significantly greater surface to volume ratio. In this work nucleation rates were calculated from small scale (1 ml) induction time measurements using a technique developed by Jiang et al. These results are to be compared with those gained from micro scale nucleation measurements in a microfluidic device. This work endeavours to present microfluidics as a tool for simple, quick acquisition of nucleation rate data and analyse the effect of solution oil/interface on nucleation rate.

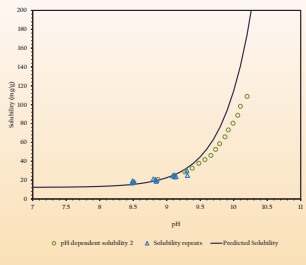
Assessing the effect of oil/water interfaces on crystal nucleation

Key Project steps.

1. Solubility determination
2. Induction Time measurements
3. Nucleation rate determination
4. Microfluidic Nucleation Rate

1. Jiang, S. and ter Horst, J.H. (2011). Crystal Nucleation Rates from Probability Distributions of Induction Times. *Crystal Growth & Design*, 11(1), pp.256–261.
2. McKechnie, D., Anker, S., Zahid, S., Mulheran, P.A., Sefcik, J. and Johnston, K. (2020). Interfacial Concentration Effect Facilitates Heterogeneous Nucleation from Solution. The Journal of Physical Chemistry Letters, 11(6), pp.2263–2271.

Solubility Model



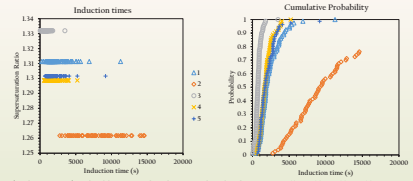
Experimental solubility determined in Crystal 16 at 20 °C. Modelled solubility as a line.

Solubility was initially determined experimentally in the Crystal 16 and was compared to a predictive model:

$$C = Ceq\ (1 + 10^{-pKa+pH})$$

This model is the starting point for solubility prediction. However, this model does not accommodate solution activity and assumes infinite anion solubility. To improve accuracy, solution activity must be incorporated and an upper limit given to anion solubility.

Induction time results



Expt	Supersaturation Ratio	Nucleation Rate (particles/m³/s)	Growth Time (s)
1	1.31	545	675
2	1.26	120	3450
3	1.33	1400	200
4	1.30	755	815
5	1.30	775	795

Left: Induction times of DL-Phenylalanine in pH adjusted water at isothermal conditions at S = 2.43 (1), 2.28 (2), 2.55 (3), 2.39 (4), 2.44 (5).
Right: Cumulative probability distribution P(t) of experimentally obtained induction time for DL-phenylalanine in pH-adjusted water.

The probability of forming a nucleus in a time interval is described by the Poisson distribution. The average number of nuclei formed in a certain volume at constant supersaturation over a time interval is linearly related to the nucleation rate. The probability that a nucleus is formed in a time interval is described by the equation (Jiang et al.):

$$P(t) = 1 - \exp\left(-JV\,(t - t_g)\right)$$

where J is the stationary nucleation rate, V is the volume and t is the detection time. The time taken for crystals to grow large enough to be detected is given by t_g.

Slight differences in pH caused by dissolution of amino acid lead to changes in supersaturation ratio which is the primary driver of nucleation.

Methods

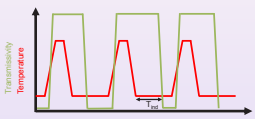
Solubility determination conducted through equilibrium concentration method. Vials of solution with excess DL-phenylalanine were brought to equilibrium, filtered and evaporated to determine solubility.

Induction time measurements taken at known supersaturation under isothermal conditions in the Crystal 16 multiple reactor system.

S - C / C* (C* is predicted from pH-dependent solubility model determined from fitting experimental solubility to predictive model)

Crystal 16 Multiple reactor system

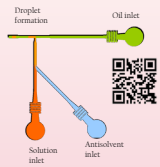
Representation of transmissivity of vials



Induction time experimental profile

Microfluidic work.

Microfluidics can be used as a tool for high throughput experimentation. Droplet microfluidics allows for the simultaneous production of hundreds of independent droplets of known solution composition that can be monitored simultaneously.



YT-junction design. Solution and antisolvent are mixed at the Y component into a supersaturated solution. Aqueous in oil droplets are formed at the T component and progress onward to the storage chamber. QR code: animation of Y junction

Droplets of supersaturated solution are formed at the YT-junction design element before being transported to a storage matrix where they can be observed for crystal nucleation. Droplets are of 0.5 nL volume.

Due to the linear relationship between nucleation rate and volume one would expect to require a significantly greater nucleation rate at these volumes. The main driver of nucleation being supersaturation ratio, one would expect to require a supersaturation ratio increased by orders of magnitude.

Future Work

Next steps are to fully develop the solubility model. As nucleation rate is a function of supersaturation, accurate solubility is essential to analysing nucleation rate. A comprehensive understanding of induction time across the pH range is necessary to accurately map the effect of supersaturation on nucleation rate. Microfluidic nucleation rate experiments will be performed to analyse the difference between the small scale, 1 ml induction time measurements and the nano-scale 0.5 nl experiments. This data will then be compared to assess the effect of the oil/water interface on nucleation.

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