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Solution crystallisation *via* a submerged liquid–liquid phase boundary: oiling out

P. E. Bonnett,[a] **K. J. Carpenter,**[a] **S. Dawson**[a] **and R. J. Davey***[b]
[a] *Process Studies Group, Syngenta, Huddersfield, West Yorkshire, UK HD2 1FF*
[b] *The Molecular Materials Centre, Department of Chemical Engineering, UMIST, PO Box 88, Manchester, UK M60 1QD*

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In many situations the process of crystallisation from solution is known to occur *via* metastable crystalline states (polymorphs or solvates). Here we present what we believe to be a novel example of small molecule crystallisation in which the initial separation of a solute rich liquid phase precedes the crystallisation event. We believe this occurs because a submerged liquid–liquid phase boundary is accessible within the metastable zone of the crystal nucleation process.

The technique of crystallisation is used extensively in the process, pharmaceutical and food industries as a method of isolation and highly selective purification[1] and as an advanced formulation technique.[2] The process allows thermally sensitive products to be separated to very high specifications from mixtures containing similar chemical species, *e.g.* enantiomers,[3] and it also allows control over crystal size and structure which is essential to down-stream processing and formulation of active materials. Overall, significant progress has been made in the last twenty years on issues surrounding crystal growth, morphology and polymorphic form, while the fundamental phenomenon of crystal nucleation remains, at least from a structural perspective, something of a mystery. Recent molecular dynamic simulations of the early stages of nucleation and crystallisation by Anwar and Boateng[4] for the nucleation of a 'Lennard–Jones' crystal from solution and by Gavezzotti and Filippini[5] for acetic acid both found a liquid-like state to precede crystal formation. In the context of Ostwald's Rule[1] such a supercooled liquid may be considered the most unstable metastable form available and hence it is, perhaps, not a surprising outcome of the simulations. Experimentally the separation of a liquid phase during a crystallisation process has indeed been directly observed in certain classes of macromolecular system such as proteins[6–8] and polymers.[9,10]

Early phase equilibrium studies conducted by Sidgwick and Ewbank[11] reported, for salicylic acid, a liquid–liquid phase separation prior to crystallisation but provided no direct evidence. Recently, Roberts *et al.*[12] have inferred the transitory appearance of a liquid phase from *in situ* monitoring of the crystallisation of citric acid from aqueous solution and Lafferrere *et al.*[13] have published evidence of an industrial pharmaceutical compound exhibiting similar phase behaviour. In the work presented here we report for the first time the direct observation of liquid phase separation during crystallisation of a small organic molecule from solution, define the composition of the liquid phases and record the transformation into a crystalline material. The underlying reasons for this phenomenon are discussed and its impact on the operation of a crystallisation process are highlighted.

We have studied the cooling crystallisation of methyl(E)-2-[2-(6-trifluoromethylpyridine-2-yloxymethyl)-phenyl]-3-methoxyacrylate (**1**) from a water–methanol solvent mixture. Briefly, a solution of mass ratio (1 : water : methanol) of 50 : 8.5 : 42.5 was heated to 70 °C in a stirred glass reactor, held under total reflux conditions until all the solute was dissolved. This was then left for an additional three hours to equilibrate (saturation temperature of the mixture composition was 55 °C). Samples of this hot solution were subjected to two experimental observations.

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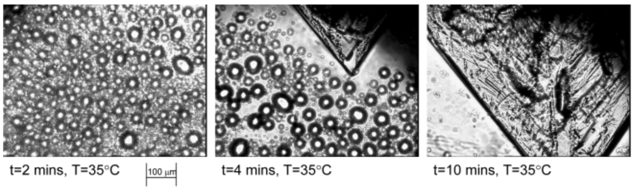
In the first, *in situ* microscopic examination was performed in a thermostated environmental cell. This cell comprised a rectangular, optical glass, capillary (volume approximately 50 ml) mounted on a hot stage (Linkam Th600) polarising microscope (Zeiss Optiphot) allowing the temperature to be controlled between 20 °C and 70 °C. This equipment enabled microscopic observations of the nucleation and crystallisation processes to be made as a function of temperature at a resolution of a few microns.

In the second, 10 ml samples, contained in quiescent, sealed, glass vials, were allowed to self-cool under ambient conditions to room temperature. Using a digital camera (SHARP VE-LC2) visual observations were recorded as these samples cooled and crystallized.

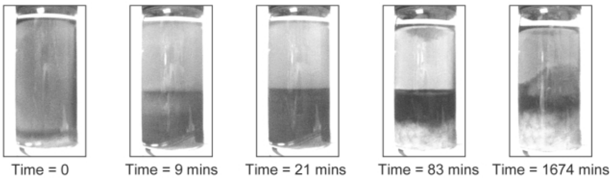
At both scales the initial event observed in the supersaturated solutions was the spontaneous formation of two liquid phases followed soon after by the appearance of crystals. Fig. 1 shows the micrographs of this process recorded at 35 °C. Liquid–liquid phase separation first generated dark, sub-micron droplets whose size increased with time due to coalescence (Fig. 1a). A few minutes later a crystal appeared in the field of view (Fig. 1b, 1c) and clearly grew at the expense of the dispersed drops. Solute is transported from drops to crystal *via* the continuous phase in a solvent mediated process in which the drops disappear as the crystal grows. This behaviour is identical to that observed in the crystallisation of emulsions.[14] The locus of the primary crystal nucleation event could not be determined because nucleation was always initiated outside the field of view of the microscope. On re-heating the sample cell, to effect dissolution of the crystals, and subsequent re-cooling the two-liquid phases were not regenerated confirming that the liquid–liquid system is always thermodynamically less stable than the crystal–solution.



t=2 mins, T=35°C t=4 mins, T=35°C t=10 mins, T=35°C

Fig. 1 Optical microscope images of liquid–liquid phase separation and subsequent crystallisation.

Observations at the 10 ml scale mirrored this behaviour (Fig. 2) with the initial appearance of a fine dispersion of droplets which gradually settled to leave a clear pale liquid in the top half of the vial and a dark bottom layer. The lower layer being the darker layer and more dense suggests that it is solute rich.

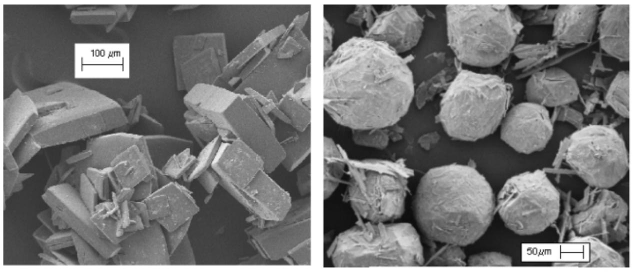


Time = 0 Time = 9 mins Time = 21 mins Time = 83 mins Time = 1674 mins

Fig. 2 Digital images of oiling out on 10 ml scale (non-agitated).

Subsequent sampling and GC compositional analysis confirmed this with approximately 70 w/w% of (**1**) in the darker layer and 7 w/w% in the lighter phase. In the vials nucleation appeared to occur in both phases but the predominant domain for crystal growth was generally the dark phase.

One of the macroscopic consequences of this behaviour is that if the system is crystallised in a stirred vessel then the droplets of the solute rich phase may eventually transform to crystals yielding a product with the spherical morphology shown in Fig. 3b. Comparing this to crystals grown from a single phase solution, Fig. 3a, the morphological change imposed by the dispersed phased is clear.



(a) (b)

Fig. 3 SEM image of crystals produced from a normal (a) and oiled out (b) crystallisation.

In seeking an explanation of this phenomenon two possibilities are considered. Firstly, it could be that the kinetic processes of crystal nucleation and growth are so hindered in this system that the solute finds a preferred kinetic route to crystallisation *via* an intermediate, undercooled liquid phase (Ostwald's Rule[1]). If this explanation were valid then it might be expected that this liquid would be equivalent either to an undercooled melt or have the composition an uncrystallised solvate. In fact, neither of these is true—the liquid has the composition 70% (1), 10% water, and 20 wt% methanol. It is also known that in other single component solvent systems (*e.g*. methanol, ethanol) at equivalent supersaturations, molecule **1** crystallises readily without liquid phase formation. These arguments effectively rule out a kinetic explanation based on Ostwald's Rule.

A second interpretation of these results lies in the phase diagram itself. With all crystallisation processes there is inevitably a metastable zone in which nucleation is unlikely and hence in which the supersaturated solution has significant stability. If, as seen in Fig. 4, a liquid–liquid phase boundary lies below the liquidus but just inside the metastable zone, then a supersaturated solution may be prone to liquid–liquid phase separation before the onset of crystal formation.[15] One of the liquid phases will be solute rich and one solute lean, however since they are in equilibrium with each other the solute chemical potential and hence the supersaturation for the solute in each phase should be identical. This is consistent with the observation that crystallisation can take place in either liquid phase and with the measured liquid phase compositions.

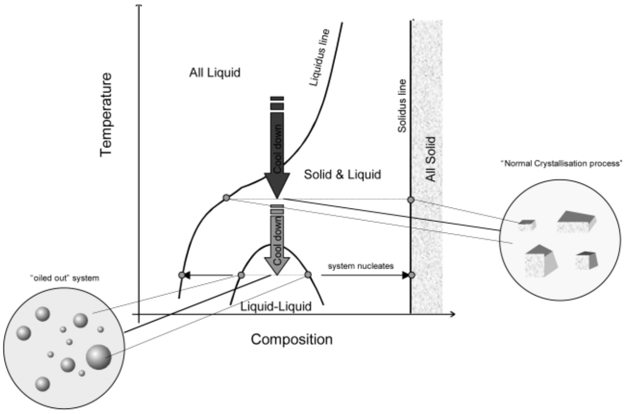


Fig. 4 Phase diagram for oiling out system.

The molecular basis for this effect is not clear. The solute, (**1**), is a small, amphiphillic molecule with RMM of 367 g mol^{-1}. Its solubility in the mixed solvent system shows an unusually strong temperature dependence (not shown here). To what extent such physical properties direct the observed behaviour will only be evident when more such cases have been reported.

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