

Crystallization of Organic Compounds

An Industrial Perspective

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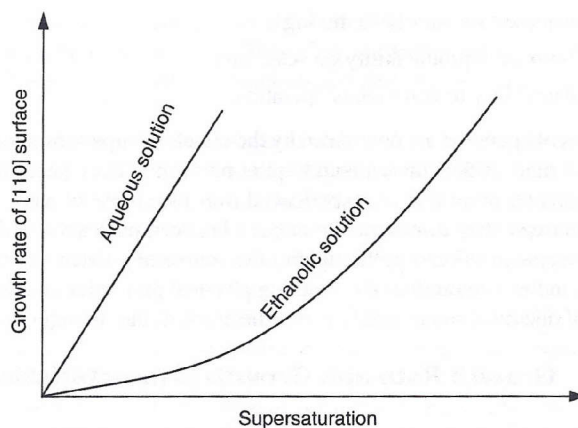


Figure 5-2 Comparison of the growth rate of hexamethylene tetramine crystals as a function of supersaturation in aqueous solution and in ethanol solution. (Reproduced with permission from Davey et al. 1982.)

Experimentation is required to evaluate these effects. The most useful experiments utilize spiking with known impurities when they can be isolated for this use. However, as is often the case, the number and possibly the low concentration of impurities often make this impractical. An experimentally simpler method is to recrystallize the compound with and without spiking of the mother liquors obtained from the process isolation. Differences in nucleation and growth may readily be observed by comparing photomicrographs of the resulting crystals. Both size and shape can be expected to be affected. If no significant differences are observed, the impurities from the process may not cause any nucleation or growth changes and the inherent properties of the compound may be assumed to prevail.

Ideal steps in determining growth potential include the following:

- purification to the highest possible extent (using chromatography if necessary)
- selection of a solvent with solubility < 50 gm/liter and some dependence on temperature
- preparation of a clear solution with low supersaturation
- aging of this solution with minimal or no mixing in the presence of some seeds, and/or
- subjecting the solution to heat/cool cycles (some fines dissolve during each heating cycle, and some growth may occur on slow cooling)

This procedure may show that growth is possible. A growth rate can then be determined by various methods, including the fluid bed method described in Chapter 4 using the crystals from the heat/cool experiments as seed.

5.4 OILING OUT, AGGLOMERATION/AGGREGATION

The most important property of a compound from a crystallization point of view may be its inherent growth characteristics. The critical question is: *will it grow?* A method to evaluate

operation, in order to be crystalline, nucleation must occur and the resulting nuclei are then assumed to grow to some limit in the nucleation phase. The question here is whether, after reaching this nucleation limit, further conditions of growth will or will not result in additional growth. While the authors have found that most compounds will continue to grow to some limit, depending on many process and inherent factors, there are some that do not exhibit significant growth beyond the 5–10 micron range.

A substantial-sized subgroup of those compounds which do not exhibit typical crystal growth, in which a repeated lattice grouping or crystal structure, is so difficult to achieve that the compound resembles a liquid as it emerges from solution. This is the phenomenon of oiling out, which is often accompanied by the additional complication of agglomeration/aggregation.

It is perhaps helpful to begin this discussion with the consideration of oiling out since it may be the first event in the pathway of crystallization or, in extreme cases, the operation may end with an oil, gel, or intractable gum or tar (Bonnett et al. 2002).

5.4.1 Oiling Out

Oiling out can be a critical factor in crystallization by any of the methods of creating supersaturation and becomes increasingly possible under several conditions, including

- high supersaturation
- rapid generation of supersaturation
- high levels of impurities
- presence of crystallization inhibitors even at low levels
- absence of seed
- inadequate mixing (high local supersaturation)

Oiling out is species dependent and may be more prevalent for low-melting compounds, although in many respects it resembles the solidification of high molecular weight compounds such as polymers. As discussed in Chapter 2, oiling out can be considered as a spontaneous phase split into two liquid phases. On a Gibbs free energy–composition diagram, it represents a system in which the overall composition has exceeded the critical composition for spinodal decomposition.

A mechanism for oiling out can be postulated as follows: When supersaturation is achieved rapidly such that the concentration is beyond the upper metastable limit—as can often be the case in a nucleation-based process—the substrate is forced to separate into a second phase by the creation of the resulting high solution concentration. However, crystallization is delayed by a slow crystallization rate. This combination may result in the creation of a nonstructured oil or possibly an amorphous solid. The rates of phase separation and nucleation are relative to each other such that “slow nucleation” implies only that nucleation was not fast enough to create discrete particles before oil separation.

Transition of an oil or an amorphous solid or a crystal can then occur. However, this type of operation can be difficult to control, and scale-up is treacherous because the oil droplets may coalesce into masses and/or form gum balls and increase in size to intolerable levels.

It should also be noted that the tendency to oil out and/or form an amorphous solid is generally increased for low-melting compounds because solvent association can effectively

reduce the melting point below its expected value, leading to melting—oiling. High molecular weight compounds are also subject to oiling and/or amorphous solid formation because of the increased complexity of molecular alignment in crystal formation. Oiling is, of course, also dependent on the solubility in the solvent and is particularly likely to occur on “reverse addition” of a solution to an antisolvent. An additional factor may be mutual solubility of the substrate and a component of the solvent mixture, in which case the oil may be a transient solution of the solvent and the substrate in the two-liquid phase, three-component nonequilibrium mixture.

Oiling out may be minimized or eliminated by control of supersaturation and seeding (Deneau and Steele 2005), as discussed below. Seeding has been proven to be essential to prevent oiling out in some systems because, although the oil may not be the thermodynamically stable phase, the transformation to crystals may be sufficiently slow and uncontrolled to cause severe processing problems, as discussed above.

The initial formation of an oil, gel, gum, or amorphous, solid conforms with the Ostwald step rule discussed in Myerson (2001, p. 39). This rule states that in any process, the state that is initially obtained is not the most stable state but rather the least stable state that is closest in terms of free energy change to the original one. It has been postulated that the initial state of crystallization processes is amorphous clusters and that the difference in time constants for the transformation to more stable crystalline states (nuclei) is a key determining factor in the course of the crystallization. It is difficult to distinguish between cluster formation, nucleation, agglomeration, and growth in the early stages (Mersmann 2001, p. 235). The following possibilities can be recognized qualitatively as determined by the time constants and the physical chemistry of the specific compound and system:

- Initial oil or gum that never transforms into a crystal and can agglomerate into large masses.
- Initial oil or gum that transforms into an amorphous solid and stops at that point—never crystallizes—but can form agglomerates.
- Initial oil or gum that transforms into crystals slowly enough that the amorphous form can be observed and can cause agglomeration before discrete crystals are obtained.
- Crystals once formed—either slowly or so rapidly that the amorphous form virtually does not exist—can transform into stable crystals.
- Transformation may continue into more stable polymorphs—if they exist.
- Transformation among polymorphs can be slow such that only the initial form is obtained or, at the other extreme, rapid so that the most stable form is the only one observed.

As is well known, some compounds have never been crystallized, and phase separation results in a stable oil or an amorphous solid. The search for solvents and conditions, or the introduction of foreign particle seeds (e.g., by scratching a glass test tube) to induce crystal formation for a new compound, becomes a matter of trial and error. Combinatorial techniques continue to be developed that can aid in this evaluation. A critical factor for success may be removal of impurities to achieve a very high level of purity, because the effect of even very low levels of impurities on homogeneous nucleation will not be known at this stage.

High supersaturation can lead to very small (nano-sized) particles and resultant agglomeration and gel formation. This phenomenon has been discussed by Mersmann (2001, p. 295) and Mullin (2001, p. 317). Although difficult to define or predict, one mechanism

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