

Solubility Curve and Metastable zone Width using Lasentec FBRM & PVM

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Overview

Present a technique to determine both the solubility curve and Metastable Zone Width (MSZW)

Experimental results for 2 simple solute/solvent systems
(1 inorganic, 1 organic)

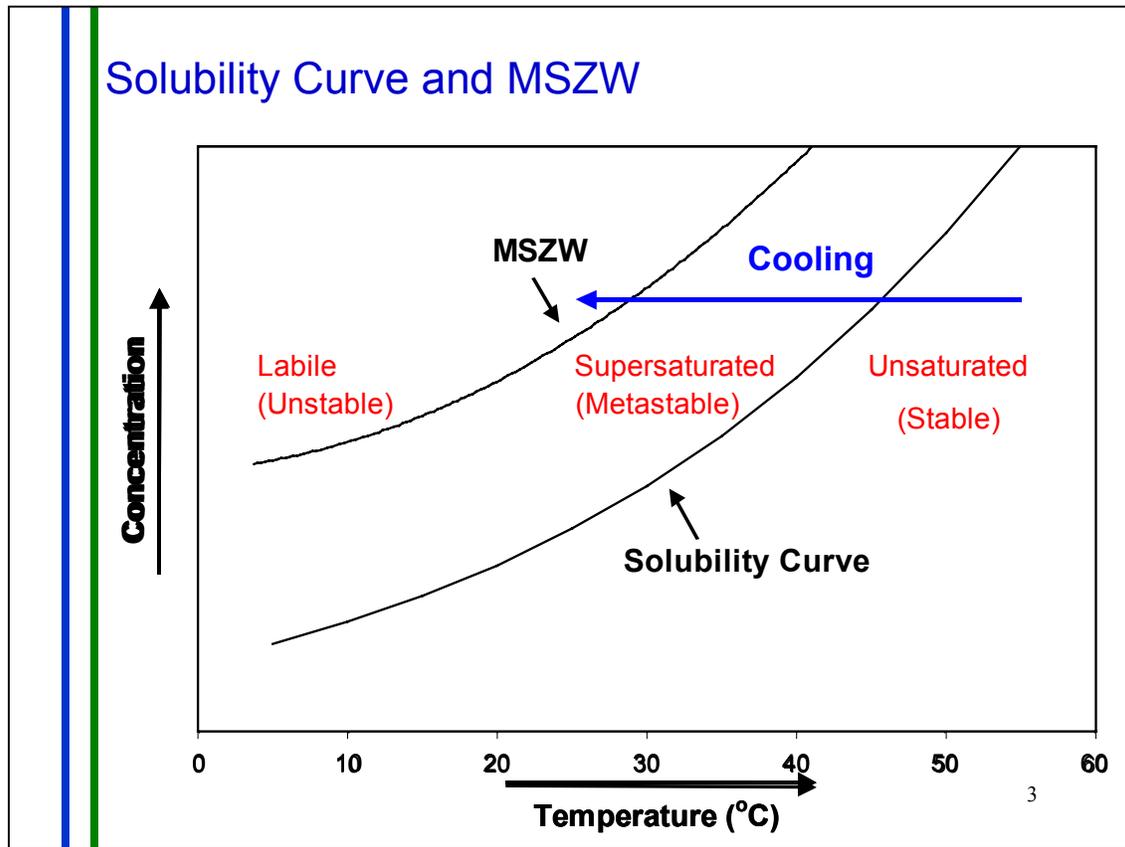
Potash Alum / Water & D-Mannitol / Water

Discussion of factors affecting the MSZW

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A successful industrial crystallization typically requires the development of a robust process in the laboratory. Knowledge of the solubility curve and the stability of the solution in the vicinity of the equilibrium point, as indicated by the metastable zone width (MSZW), are essential to the successful development, optimisation, and scale-up of a crystallization process.

Use of the Lasentec Focused Beam Reflectance Measurement (FBRM) system to detect the point of disappearance during dissolution trials and the point of nucleation during successive cooling experiments on aqueous potash alum and D-mannitol solutions is demonstrated. Results from these experiments indicate that the solubility curve and metastable zone width can be determined using FBRM. Several key factors affecting the MSZW are also investigated.



A solute will remain in solution until a sufficiently high level of supersaturation has been developed to induce spontaneous nucleation. The extent of this supersaturation is referred to as the metastable zone width. It will typically be influenced by a variety of process parameters including saturation temperature, rate of supersaturation generation, impurity level, mixing, and solution history. It is therefore important to characterize the metastable zone width under a specific set of operating conditions that relate closely to the conditions of the final scale crystallization.

Importance of Solubility

Effects Yield

Method of supersaturation generation

Importance of MSZW

Knowledge of the MSZW can help in the selection of the optimum rate of supersaturation generation to avoid excessive secondary nucleation

Help identify seeding regime

Can help identify a process that will scale up well

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The solubility curve is essential for the design of a crystallization process as it helps indicate yield, the type of crystallization process to perform, and the rate of supersaturation generation. The solubility curve is typically constant for a given solute/solvent system (assuming impurity levels are not changing).

The MSZW is governed by the kinetic phenomena of nucleation, so is not fixed for a given solute/solvent system. It can be influenced by a variety of process parameters such as rate of desupersaturation and mixing conditions. However, knowledge of the MSZW is essential to help determine seeding regime and optimum operating supersaturation levels throughout the process. It can also help identify a process that will scale up well.

Characterizing the MSZW: Literature overview

Nyvt, J. (1968) Kinetics of nucleation in solutions,
Journal of Crystal Growth, 3-4, 377-383



Mersmann, A., Bartosch, K. (1998) How to predict the
metastable zone width, Journal of Crystal Growth,
183,240-250

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There is a wide variety of information available in the literature on both nucleation and the MSZW and solubility curves.

Simple Outline of Experimental Procedure (Polythermal Method)

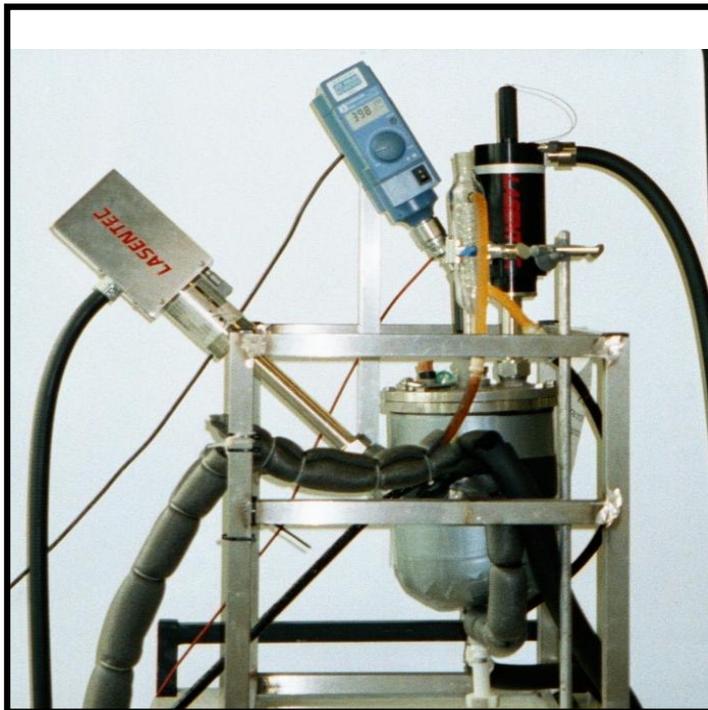
Charge mass of solute (Potash Alum) to
crystallizer

Add known mass of liquid (water)

Seal vessel and fit condenser

The polythermal technique (Nyvlt, 1968) is well established for determining the MSZW. The experimental protocol for this work is described in the following slides.

Experimental Apparatus



**Working
Volumes**

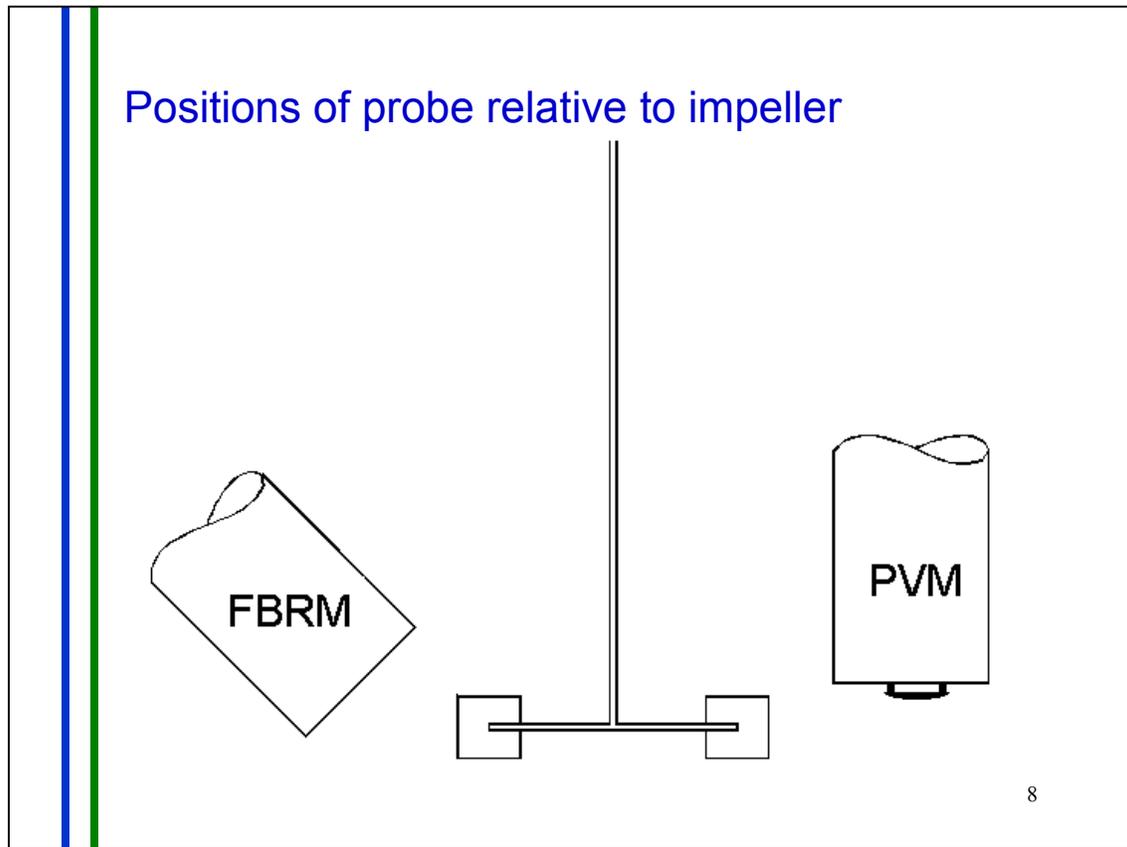
Maximum:
2 Litres

Minimum:
1 Litre

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The crystallization vessel had a maximum working volume of 2 litres, but the starting volume was about 1 litre. The agitated jacketed vessel had an inner diameter of 13 cm with a domed bottom and is equipped with a standard Ruston turbine with a diameter of 5 cm. The crystallizer has ports to accommodate the FBRM and PVM probes. The probes were positioned to ensure good flow against the probe windows, allowing a representative sample of the particle system to be measured.

For this work, the vessel was operated with four standard baffles, with the probes themselves offering additional baffling. An impeller speed of 400 RPM was employed for all experiments, which not only helped ensure adequate mixing, but also helped avoid excessive splashing in the vessel. The vessel was sealed and operated with a condenser at 10°C. Programmed cooling and heating profiles were implemented using a Julabo HP 50 Heating/Cooling system.



This schematic diagram illustrates the positions of both the FBRM and PVM probes relative to the radial flow impeller. The FBRM was mounted at a 45-degree angle to the horizontal. The PVM was used with the light-enhancement window attachment. The PVM probe was mounted straight down, allowing good flow through the gap between the probe window and the light-enhancement reflector.

Simple Outline of Experimental Procedure (Polythermal Method)

Heat until complete dissolution - monitor with FBRM

Heat 15°C above apparent point of dissolution

Hold for 1 hour

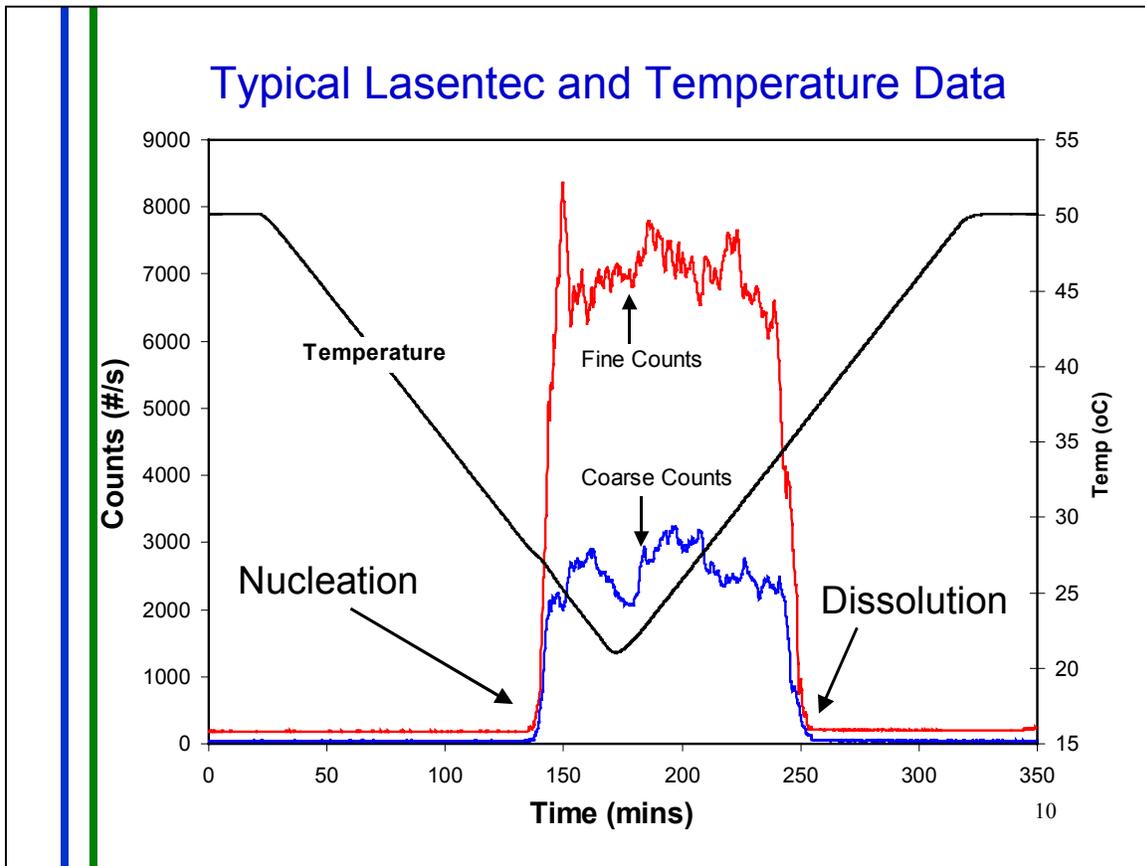
Cool at a fixed rate until nucleation

Track nucleation event with FBRM

Following nucleation – reheat at same rate

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To minimize the amount of material consumed and to help aid in future automation of the process, the same saturated solution was “recycled” batch to batch. A potash alum solution saturated at approximately 35°C was heated to 50°C and aged for one hour to help ensure complete dissolution. The solution was then cooled at a fixed rate. The nucleation event was tracked with FBRM. Following nucleation, the solution was reheated at the same fixed rate, to about 15°C above the apparent saturation temperature, and held there for one hour.



Initially, as the solution is cooled and becomes supersaturated, FBRM detects no particles and the count data indicate no change in particle number. However, as soon as nucleation occurs, crystals are formed, and there is a corresponding increase in counts in the FBRM data.

An advantage of using FBRM is that the measured count data can be split up into specific population regions, permitting isolation of the size range in which a change occurs. A ten-second measurement duration was used for all FBRM measurements. As the FBRM measures over a ten-second period, the number of counts in the 0 μm to 20 μm range was used as the indication of nucleation. Published growth data for potash alum predict that nuclei may grow by up to 15 μm in this ten-second period.

Simple Outline of Experimental Procedure (Polythermal Method) - continued

Cooling/heating-and-hold cycle is then repeated using rates of 0.7, 0.6, 0.5, 0.4, 0.3, 0.2 & 0.15°C per minute

To examine another Concentration a dilution is made to the system

- fixed mass of solvent (water)

Repeat temperature cycling process for new concentration

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The experimental protocol involved heating the solution to 15°C above the estimated point of solubility, holding for one hour, and then cooling at a fixed rate to 5-10°C below the detected point of nucleation. The solution was then reheated at the same fixed rate back to 15°C above the estimated point of solubility and again held for one hour.

This process is repeated for each of the temperature rates and the order in which they are performed is randomised. Each rate is repeated at least three times to ensure good reproducibility. FBRM and temperature data are recorded throughout this process at ten-second intervals. To obtain a new concentration, a dilution is made to the system, and the above protocol is repeated.

Nucleation Detection

Use FBRM counts in the region 0-20 microns

Why?

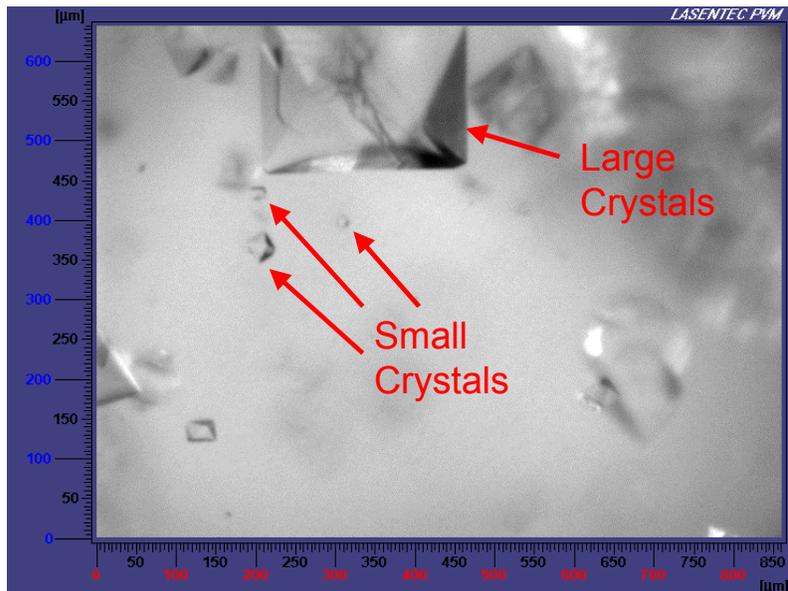
At supersaturation levels encountered at the point nucleation, one would expect (for this material) growth in the region of 10 microns in a 10 second period

(validated using measured and literature growth kinetics)

PVM Validation

Presence of large crystals and agglomerates shortly after nucleation event

50 Seconds After Nucleation

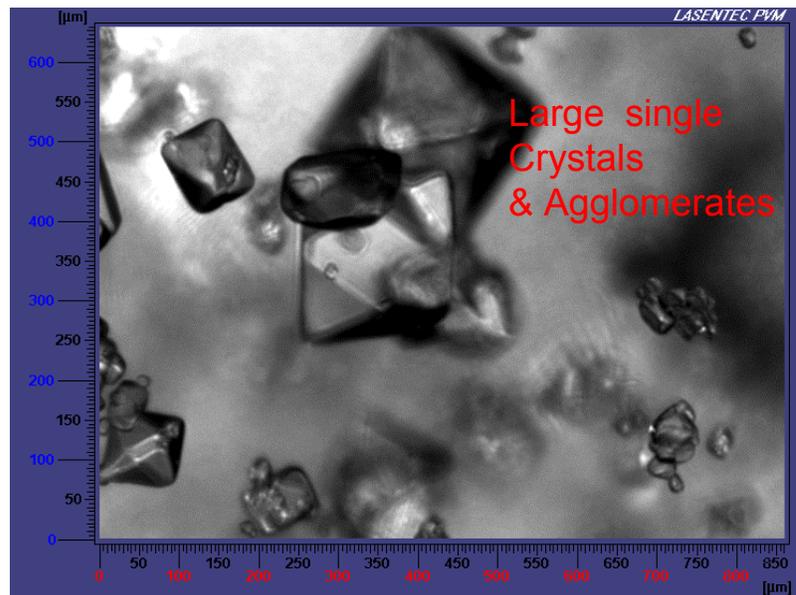


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Immediately following nucleation, the FBRM reports a rapid increase in coarse chord counts (Slide 10), indicating the presence of large crystals either through rapid growth or agglomeration.

PVM Validation

120 Seconds after nucleation event



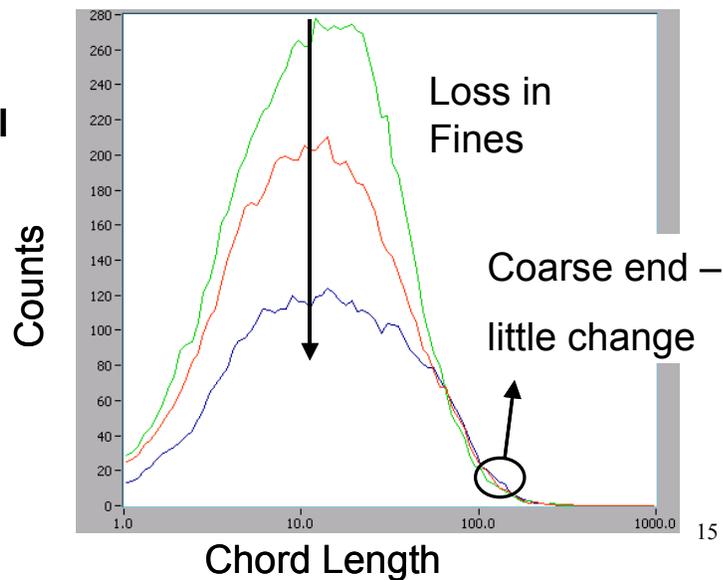
14

To validate this rapid increase in dimension, a series of PVM images were captured within the first few minutes of nucleation. The image shown here highlights the presence of both small and large single crystals and some agglomerates.

Tracking the point of Disappearance

During a dissolution process Fine particles dissolve at a faster rate relative to Coarse particles, due to their higher surface area to volume ratio

Experimental Verification:
FBRM Data during dissolution process

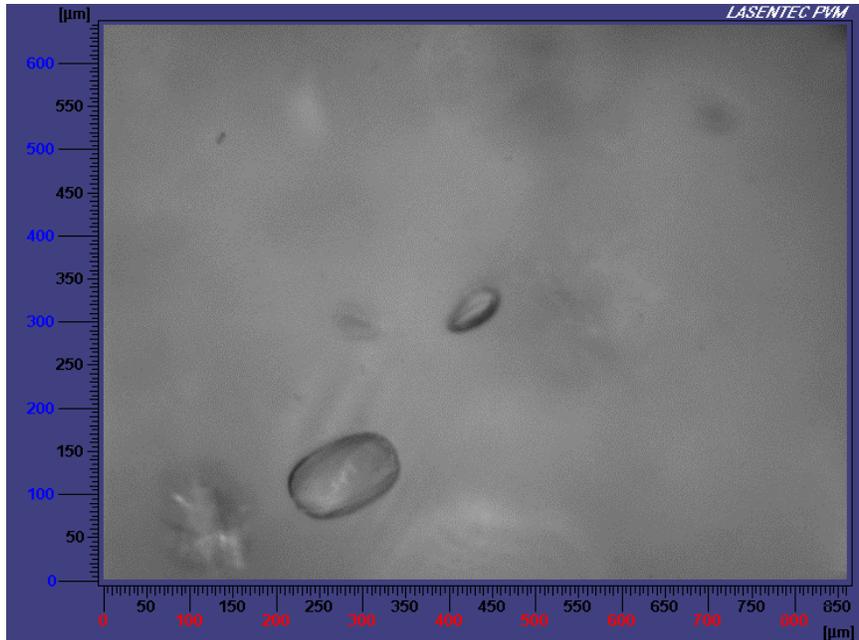


Fine particles have a high surface-area-to-volume ratio in comparison with coarse particles. By applying basic thermodynamic theory, these fine particles will have a tendency to dissolve at a faster rate relative to the coarser particles.

Therefore, to successfully track when the material goes back into solution – the point of disappearance – counts in a coarse size range (100 μm to 1000 μm) are used and the point of disappearance is detected using these coarse counts in a similar manner to the nucleation work above. The FBRM distributions shown help emphasize the disappearance of the fines as the dissolution progresses.

PVM experimental verification

150 Seconds before dissolution

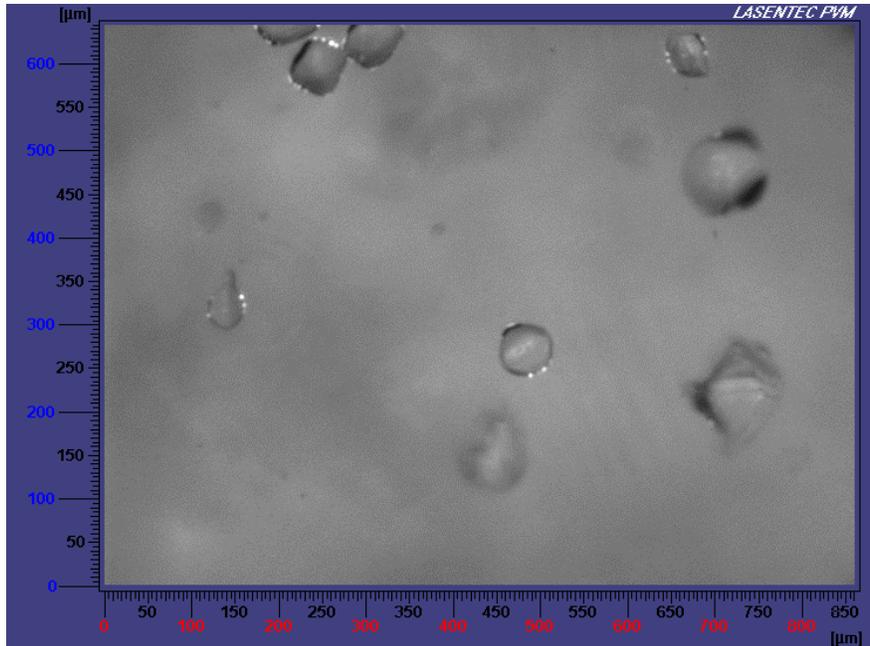


16

During this reheating process, the material will begin to dissolve. PVM images taken during this dissolution period give an indication of the complexities of the dissolution mechanism. There is a clear transition from the distinctive octahedral shape of the potash alum crystals to a more rounded structure.

PVM experimental verification

60 Seconds before dissolution



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It is evident from the PVM images that only large crystals are present and that the majority of fines have dissolved.

Determining Solubility Curve

During the heating process, as the point of saturation is approached, the rate of dissolution decreases

Fast heating rates – temperature measured at the point of disappearance may be significantly greater than the actual saturation temperature.

Slower heating rates – point of disappearance approaches saturation temperature

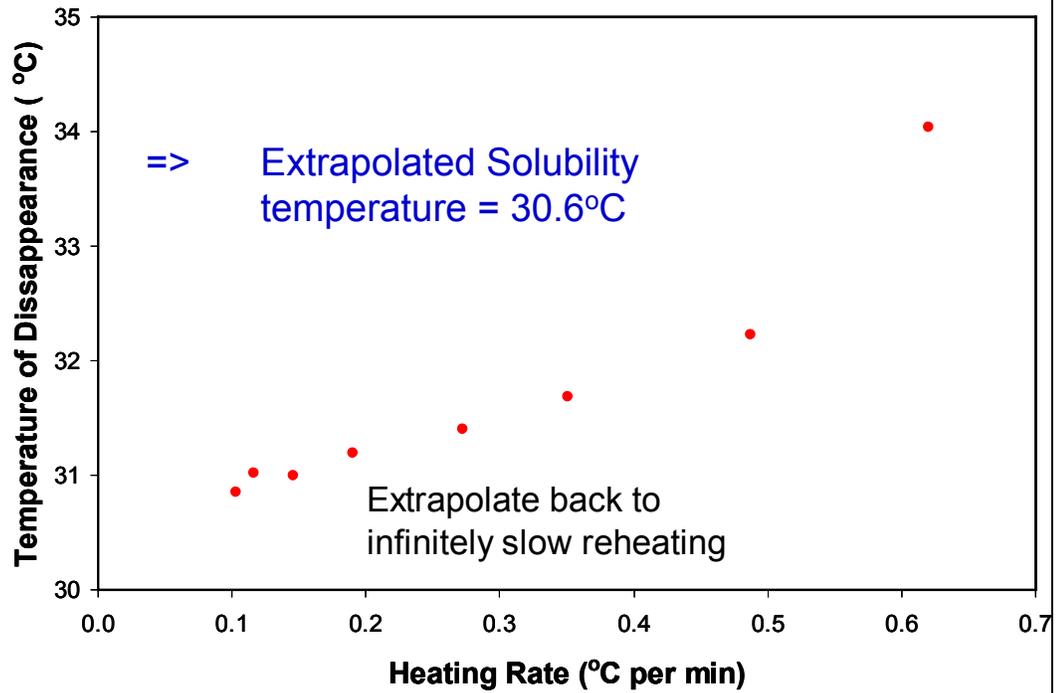
Measure 'point of disappearance' at a variety of heating rates & extrapolate back to an infinitely slow cooling rate

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During the heating process, as the point of saturation is approached, the rate of dissolution decreases. Therefore, for fast heating rates, the temperature measured at the point of disappearance may be significantly greater than the actual saturation temperature.

For this work, the point of disappearance is tracked using FBRM for a variety of different heating rates. As the heating rate is reduced, the temperature of the point of disappearance approaches the saturation temperature. Extrapolation of the data back to an infinitely slow heating rate will yield an estimate of the point of solubility.

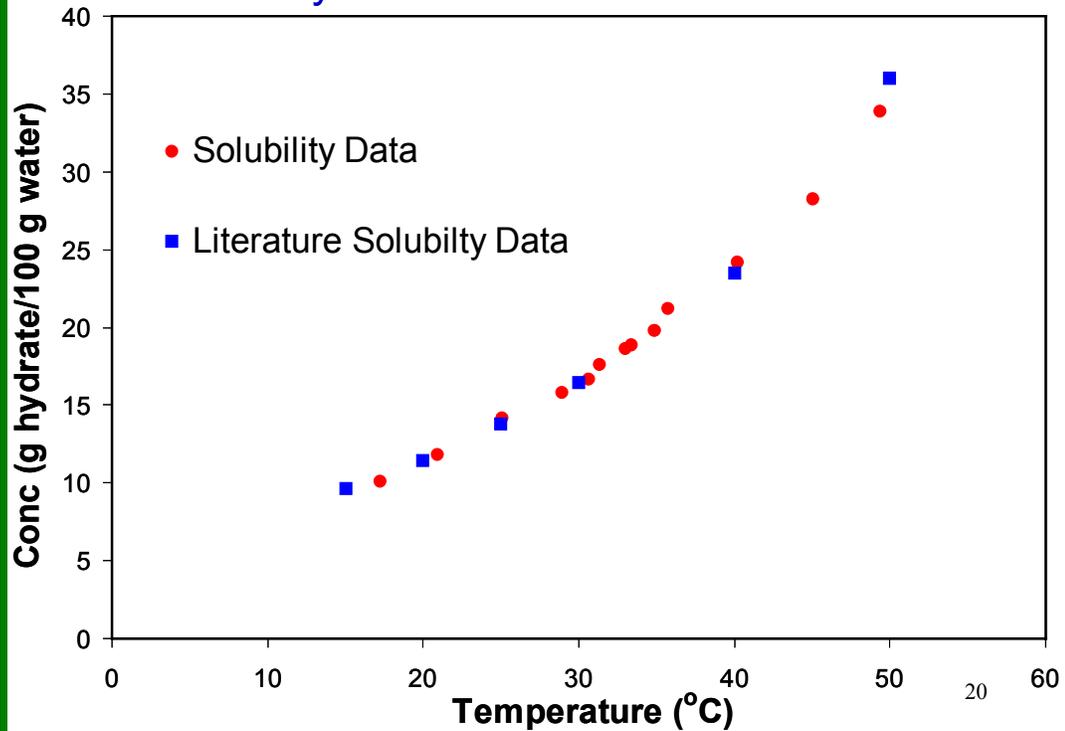
Demonstration of extrapolation technique



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This extrapolation process is demonstrated for some typical experimental data on the potash alum/water system.

Comparison of Experimental and Literature solubility data for Potash Alum / Water



This extrapolation process is performed on a wide range of concentrations. The estimated solubility is plotted with literature data for the potash alum/water system. As can be seen from the graph, there is excellent correlation between the literature and experimental data.

Solubility Correlations

Variety of correlations available in the literature to fit curve to experimentally measured solubility data

Mullin, J. W (1993) Crystallization, Third edition, Butterworth-Heinemann, Oxford

Myerson, A. S. (1993) In A.S. Myerson Ed., Handbook of industrial crystallization, Butterworth-Heinemann, Boston

Grant, D. J. W., Mehdizadeh, M., Chow, A.H.L., Fairbrother, J.E. (1984) Non-linear van't Hoff Solubility – temperature plots and their pharmaceutical interpretation, International Journal of Pharmaceutics, 18, 25-38

Extrapolation of solubility curve can yield errors!

⇒ Measure solubility over operating temperature range

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Rather than simply fitting a curve to the solubility data, using some of the solubility correlations available in the literature is recommended. These should yield success when extrapolating the solubility curve over a wide range. However, it is recommended that the solubility curve be measured over the desired operating range to help avoid potential errors that are associated with extrapolation of solubility curves.

Solubility Correlations

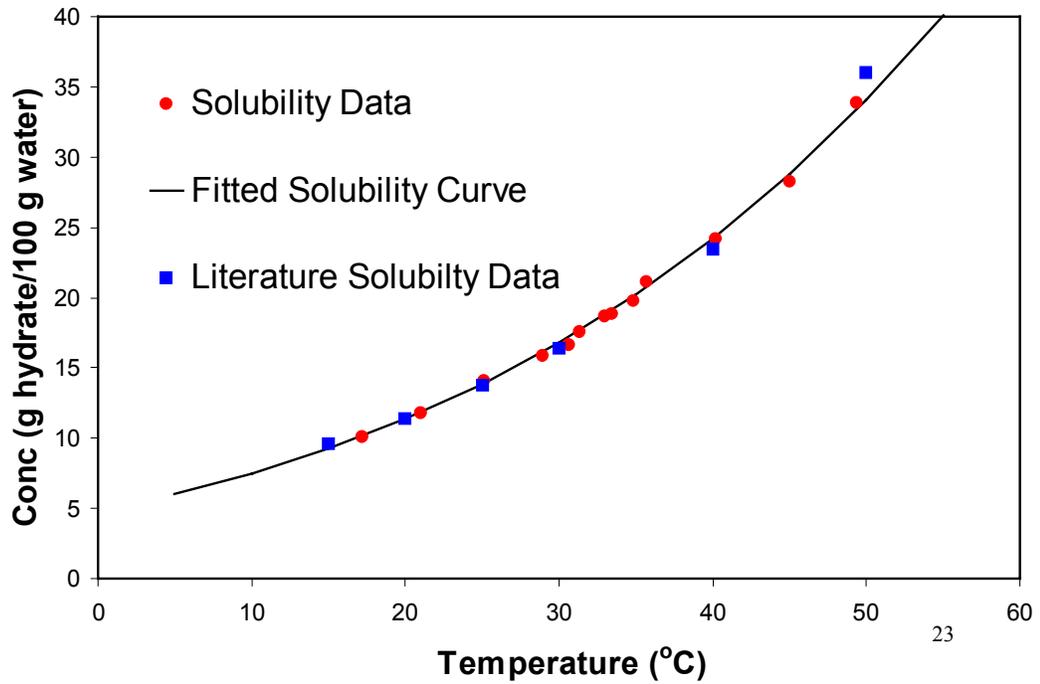
$$\ln(x) = \frac{A}{T} + B \ln(T) + C$$

x = Mole fraction of solute

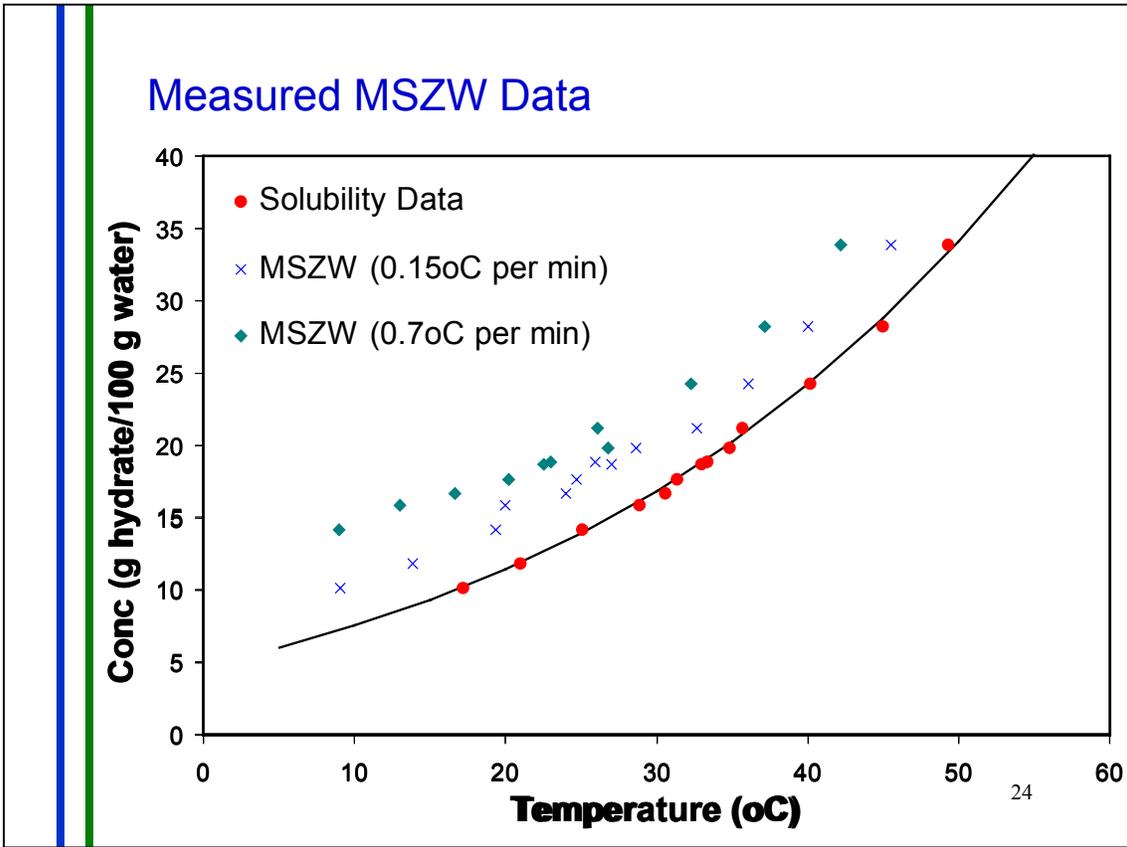
T= Temperature (K)

The solubility correlation fitted to this experimental data is given here. A non-linear regression is used to fit this equation to the experimental solubility data.

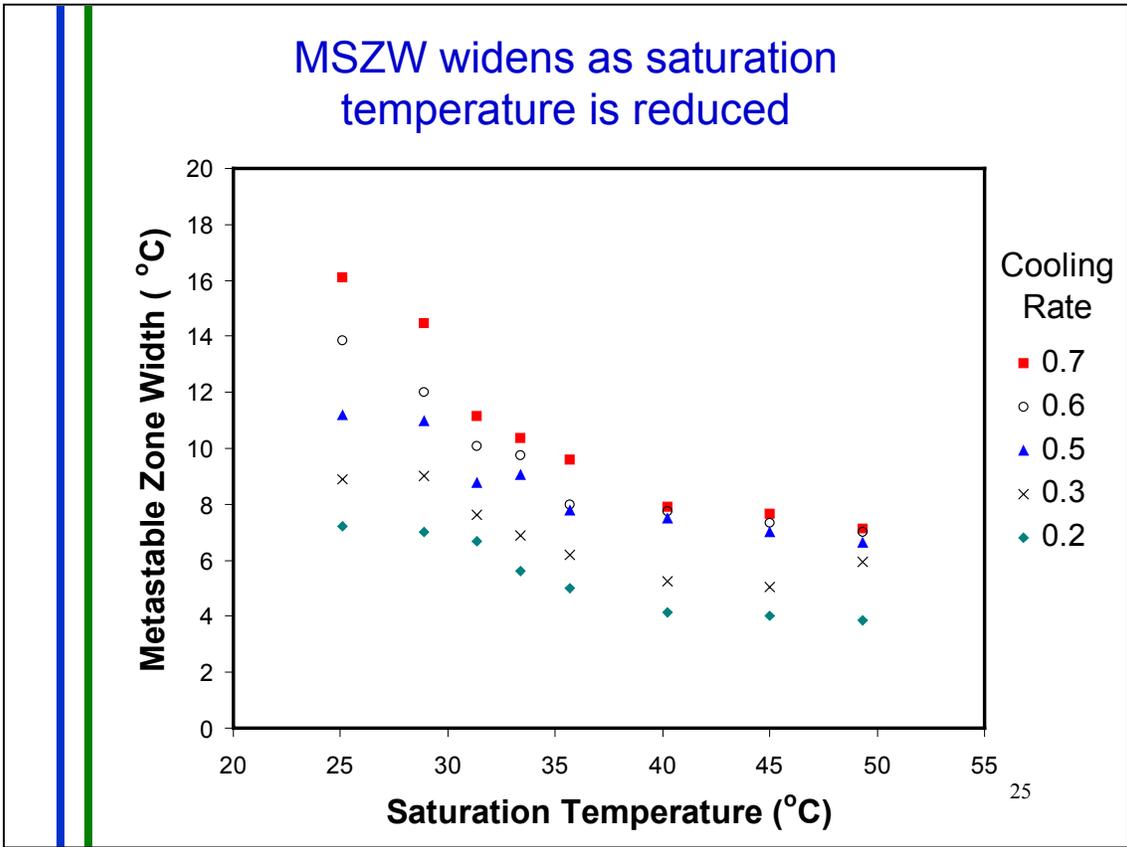
Curve Fitted to Solubility data



This again highlights the excellent correlation between the experimental and literature solubility data.



Experimentally measured MSZW data is plotted with the solubility curve. As expected, the MSZW widens with faster cooling rates.



This graph emphasises both the increase in MSZW as the cooling rate is increased and also as the saturation temperature is decreased.

MSZW widens as saturation temperature is reduced

This information can be used to generate kinetic expressions for the nucleation rate

$$B = k_N \Delta C^N$$

Nyvlt, J. (1968) Kinetics of nucleation in solutions, Journal of Crystal Growth, 3-4, 377-383

This information can be used to estimate the nucleation kinetics of the systems. Details of this calculation are given in the Nyvlt paper listed here. Estimating the nucleation kinetics in this manner should prove useful when comparing the nucleation behaviour of a solute in many different solvents.

Overview of Factors that may effect the MSZW

Solution History

'Recycling' or Heating/Cooling the same solution can have an impact on the point of nucleation

Overheating time (time held above saturation temperature) can also influence on the point of nucleation

Quantify this effect, if any:

Examine one heating and cooling rate several times – is there any effect on the temperature of nucleation?

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The technique for experimentally measuring both the solubility curve and MSZW is relatively straightforward. It should allow the quick and efficient evaluation of many solvents and assess their impact on both the solubility curve and metastable behaviour of the solution. However, to fully evaluate the behaviour of a solute in a given solvent, a variety of additional experiments should be performed.

It is reported that solution history can have an impact on the point of nucleation. Because the solution is "recycled" batch to batch for these experiments, it is desirable to quantify if this has an impact on the measured point of nucleation. To quantify this potential effect, one heating and cooling rate was repeated several times in a row and the point of nucleation was measured.

Quantifying the effect of solution History

Potash Alum solution saturated at 35°C

Heat and Cool at same fixed rate 8 times

Batch #	Nucleation Temperature (°C)
1	26.07
2	26.06
3	26.35
4	27.06
5	29.12
6	26.22
7	26.58
8	26.42

Mean = 26.4

standard
deviation = 0.34

1 outlier

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For this experiment, the recorded experimental data indicates that, apart from one outlier, the measured point of nucleation was very consistent batch to batch.

Effect of Mixing on the MSZW

“Liquids at rest can be supersaturated, as a rule to an appreciable extent. Up to a certain agitation intensity the region of metastability decreases”

Nyvit, J. (1971) Industrial crystallization from solutions, Butterworths, London

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Another important process parameter to consider is mixing and its effect on the point of nucleation. For example, water at rest will not freeze until about -5°C . However, with agitation, it will freeze at about -0.5°C .

Effect of Mixing on the MSZW

Mixing conditions can influence the temperature of nucleation

This effect may be exacerbated during process scale up, with different vessel and impeller configurations and typically a poorer mixing environment

Quantifying this effect in the lab can help identify if a process will scale up well

Assess the effect of impeller speed on the point of nucleation

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Mixing will be of importance to assess, particularly when the difference in mixing conditions between a laboratory and production vessel are considered. By identifying the impact of mixing speed on a laboratory scale, an insight into this effect on process scale up can be obtained. The effect of mixing on MSZW will be of particular importance to a process that is unseeded.

Effect of Mixing on the MSZW

D-Mannitol / Water - relatively wide MSZW

Solution saturated at 45°C

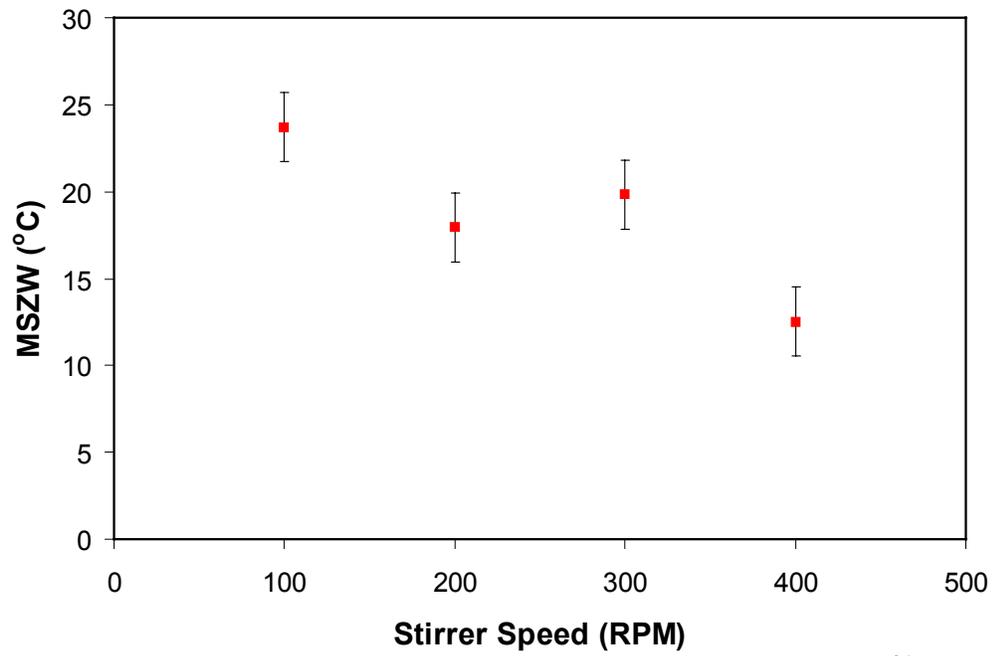
Cooled at a fixed rate of 0.15 °C per min

Stirrer speeds 100-400 rpm

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A solution of D-mannitol saturated at 45°C is chosen for these experimental trials. D-mannitol has a wide MSZW, representative of many pharmaceutical materials. Using a cooling rate of 0.15°C, a temperature cycling experiment is performed as before, but the impeller speed is changed for each batch.

Effect of Mixing on the MSZW



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It is clear from the experimental data that the mixing speed has had an impact on the MSZW.

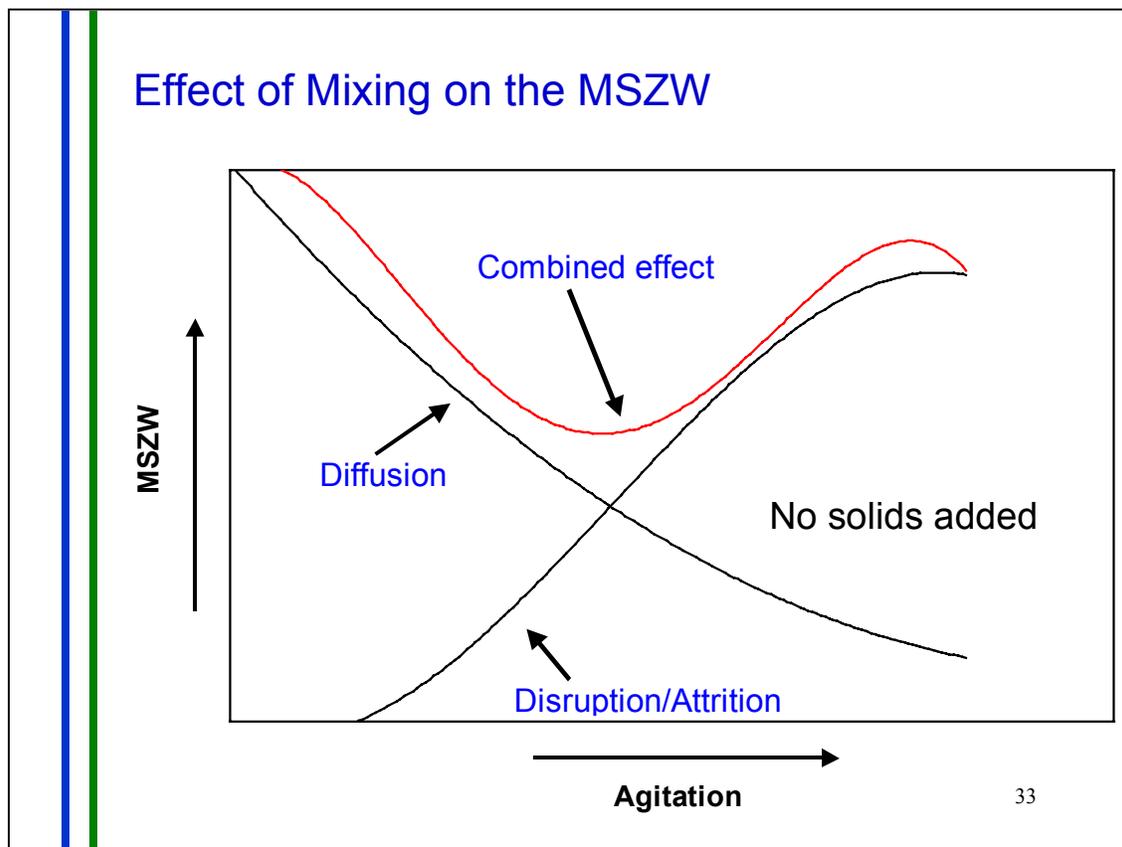
Effect of Mixing on the MSZW

Why does Mixing effect the MSZW?

Mullin, J.W., Raven, K. D., 1962, Influence of mechanical agitation on the nucleation of some aqueous salt solutions, *Nature*, 195, 35-38

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From the literature, there is a proposed basis for this observation. As the mixing speed increases, diffusion becomes significantly more efficient, reducing the MSZW. On the other hand, as the mixing speed is increased, it is proposed that there is a disruption/attrition type of mechanism due to micro- or meso-mixing, which can impact the molecule cluster size and interaction. These two factors combined give a profile similar in nature to those observed experimentally (see Slide 30).



It is obvious from this trend that if an unseeded process is designed in the laboratory, then due to mixing conditions, the production version of the process may nucleate at a different temperature. It is also possible that a seeding protocol designed in the laboratory may, in production, nucleate before the seeds have been added. It is therefore desirable to assess the impact of mixing on the MSZW in the laboratory, before the process scale up occurs.

Effect of solids on the MSZW

The presence of solids, even a tiny amount, can influence the point of nucleation, resulting in a narrower MSZW

Mullin, J.W., Chakraborty, M. Mehta, K. (1970) Nucleation and growth of ammonium sulphate crystals, Journal of Applied Chemistry, 20, 367-371

Why is this a problem?

Typically the MSZW is measured without solids present

Say for instance, the actual process is seeded, the presence of these seeds, can narrow the MSZW

May have seeded outside the 'solids present MSZW', which will result in high levels of secondary nucleation

The addition of crystals to a saturated solution, even a tiny amount, reduces the energy barrier for nucleation or, in other words, may reduce the MSZW. This is important if the seeding protocol of the process results in seed addition close to the MSZW. The very presence of these seeds may induce excessive amounts of undesirable secondary nucleation.

Effect of solids on the MSZW: D-Mannitol / Water

Solution saturated at 45°C

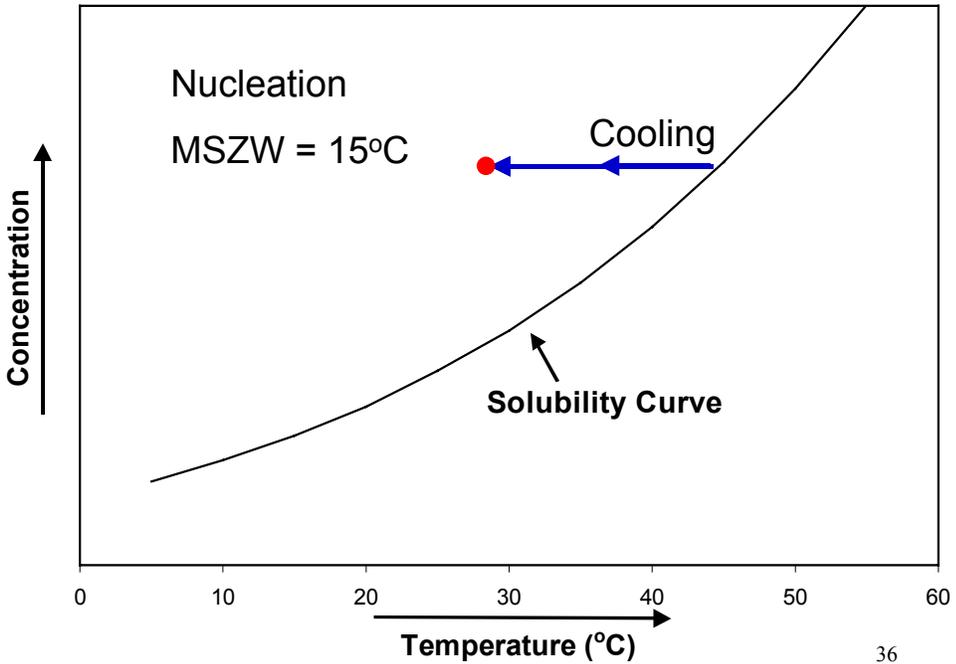
Cooled at fixed rate of 0.3°C per minute

Slightly supersaturated, a few small crystals added (0.025g)

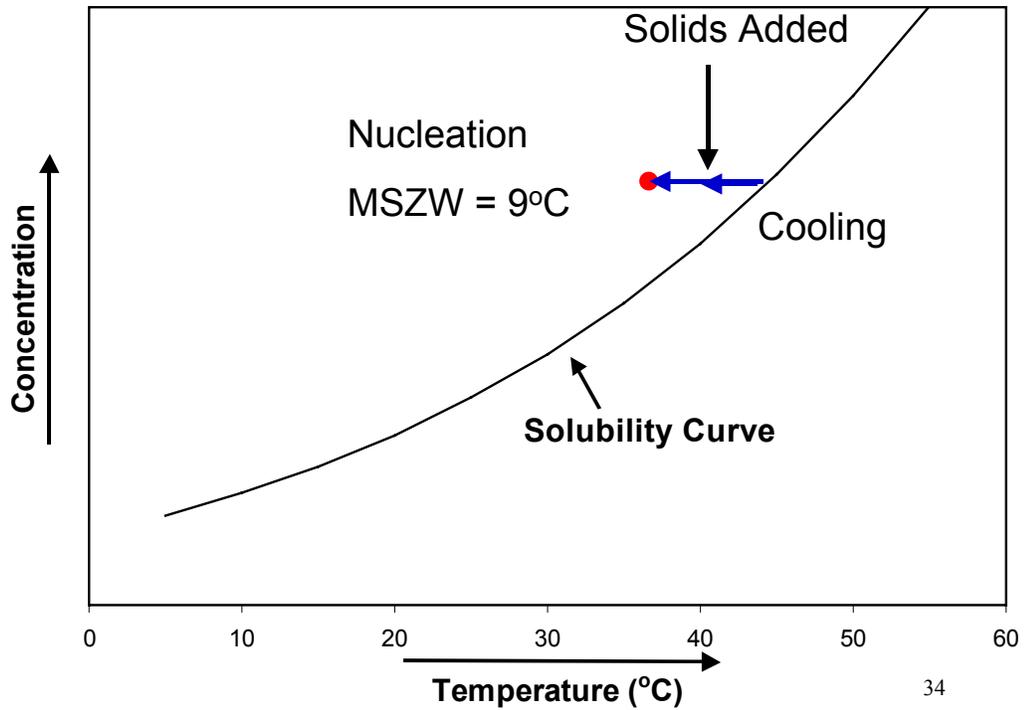
35

Designing a seeding temperature based on a MSZW determined without solids present could yield a seeding temperature that may in fact induce significant amounts of secondary nucleation. It is therefore advisable to also characterize the MSZW when solids are present, to determine a more appropriate seeding temperature.

Effect of solids on the MSZW: D-Mannitol / Water

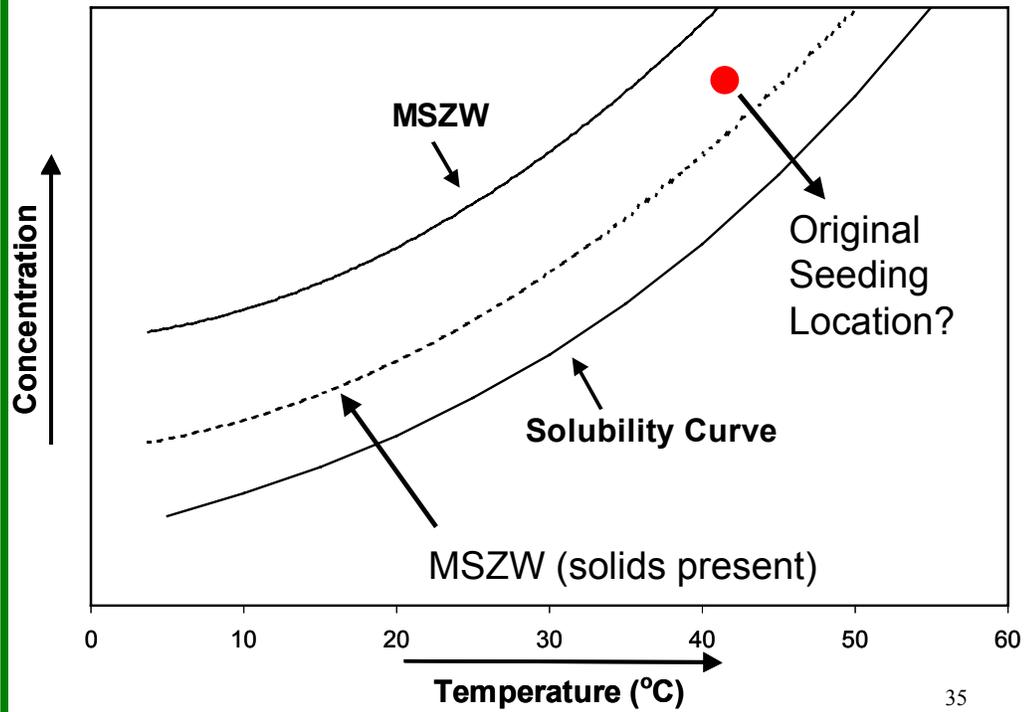


Effect of solids on the MSZW: D-Mannitol / Water



The same experiment as in Slide 33 was repeated. However, in this case, when the solution was only slightly supersaturated, a few crystals of D-mannitol (0.025 grams) were added, resulting in a nucleation event after 9°C.

Effect of solids on the MSZW



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The effect of solids on the MSZW is important, as it can help determine the position of the optimum seeding location to avoid excessive secondary nucleation.

Conclusions

A technique presented to determine the Solubility curve and MSZW

Scope for Automation – screen quickly and efficiently variety of solvents and solvent compositions

Experimental solubility results for an organic and inorganic system agree well with literature values

Can also assess future scalability of process:
Impact of solids, solution history, and mixing on the MSZW



Questions & Answers

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Q: When you found your metastable zone width, why didn't you do the same thing you did for finding your solubility curve – go back and extrapolate with your cooling? You would get a much narrower region.

PB: Yes, when the MSZW is determined you can, as with the solubility work, extrapolate back to an infinitely slow cooling rate which will “narrow” the MSZW region. However, this still does not address the difference one may expect to observe when there are solids present. It's advisable to investigate what happens when seeds are added – is there nucleation or growth?

Q: Does it matter how much solvent you have (i.e., the volume in the reactor)?

PB: As I illustrated in some of the slides, mixing can have an effect on the point of nucleation. Therefore, it follows that as the volume in the vessel increases due to dilution, the power per unit volume will decrease for a given impeller speed. This decrease is not as dramatic when the impeller speed is reduced from 500 rpm to 100 rpm. We saw no effect of liquid volume for the potash alum, and a slight effect for the D-Mannitol solutions.

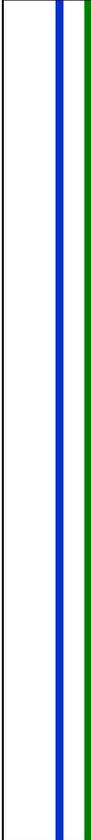


Questions & Answers

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Q: How would you go about monitoring nucleation and growth rate in a crystallization situation? For any system you are looking at where you want to track both nucleation and growth, what would be the approach?

PB: My approach would be to use a statistic to track the fine side for nucleation and the coarse side for crystal growth. PVM images can give important information about crystal shape, which can make FBRM data easier to interpret. To extract growth kinetic information directly from FBRM data is possible under certain conditions. I hope to present a paper on this next year.



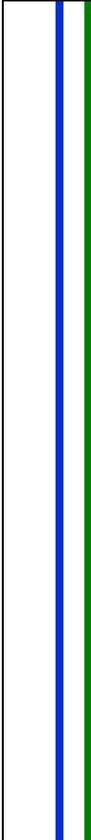
Questions & Answers

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Q: If you want to scale up, what is the ideal mixing speed?

PB: My goal for this presentation was to highlight that mixing conditions, and hence process scaleup, can effect the nucleation temperature. If you were relying on nucleation as the start of a crystallization, you could have problems in scaleup as the process may no longer be representative to what happened in the lab. You might be better off to do a seeded crystallization that relies on a nucleation event to start your batch.

There are a variety of correlations available to determine the optimum scale-up conditions – typically some function of power per unit volume, tip speed, and pumping capacity of the agitator. However, an industrial batch crystallization vessel is not going to be as well mixed as a lab vessel! The heat and mass transefer performance of the production vessel should be taken into consideration when designing a process in the lab, and the lab should be used to test the crystallization's sensitivity to temperature and concentration gradients. This makes the lab a useful tool for helping to develop and optimise a robust crystallization process.



Questions & Answers

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Kaz: The results you got used high-purity material for the solubility. When you measure the solubility curve, you don't want the solubility of the pure material because you are trying to crystallize an impure material. If you use your method, I think it would be a good idea to check the solubility by doing an isothermal slurry. Just take a sample of your slurry to check that the solubility you get with impure material corresponds to the solubility you got with pure material. Your method is okay, but because impurities would change the solubility of the material, you are measuring impurities as well, not just the solids you are interested in.

PB: I agree. Good point. But this leads to another possible application of the technique. If you know, for instance, that the impurity profile in your mother liquor may change as the quality of feedstock etc. changes during the process development, it may be worthwhile in the lab to investigate how both the solubility curve and MSZW change as a function of the impurity profile. Having this data early on and documented may save time later.