

**Background:** The HEL polyblock system was used, in conjunction with the polythermal method, to create solubility and metastability design space information for two API compounds. By creating a solubility design space a fundamental understanding can be defined between the limitations for both cooling and anti-solvent crystallization processes. The resulting knowledge allowed crystallization process selection to be based on process benefits such as favorable yields and conditions which would be beneficial for crystal growth.

**Methods:** Known concentrations of API and solvent mixtures were prepared within the polyblock system and heated to dissolution. Variable cooling rates (between 0.1 °C/min to 0.6 °C/min) were used to quantify the shift in the metastable zone. Solubility information was assessed by heating the obtained slurries at a rate of 0.1 °C/min. Heating rates from 0.1 °C/min to 0.5 °C/min were examined, however the low heating rate of 0.1 °C/min was deemed adequate to prevent any over estimation of the saturation temperature.

Up to 8 different concentrations of API in solution were assessed for solubility. Differing solvent / anti-solvent composition were obtained automatically by the attached dosing unit to the polyblock. The outputted information was coupled with the Van't Hoff expression for solubility so the saturation temperatures, for different concentration, could be predicted over the entire design space. This information, in addition to the nucleation temperatures, were then inputted to a Matlab program which facilitated the production of the desired solubility and metastability design spaces.

### Solubility and Metastability Design Space

Shown below is the solubility design space for API x.

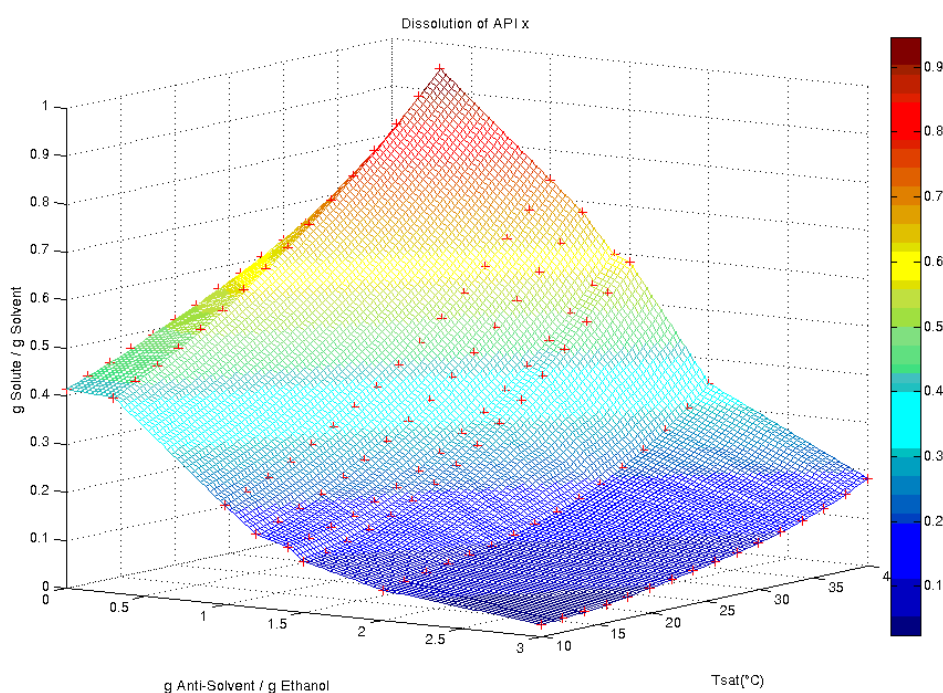


Figure 1: Solubility design space for compound x in variable solvent and anti-solvent compositions.

As shown on the right hand side of figure 1 the obtained temperature driven solubility curve is relatively flat. In turn it can be concluded that the product x is not very sensitive to temperature changes in the region between 40 and 10 °C. However, although this process may exhibit low process yields (0.18 g product x / g solvent) it would provide conditions that are favorable for particulate growth.

This is in comparison to the left hand side of the design space (g anti-solvent / g solvent), which allows anti-solvent crystallizations to be assessed. In this case the solubility curve is steep at isothermal temperatures. A notable increase in process yield is observed for the anti-solvent (i.e. 0.38 g product / solvent). Although high in yield the steep slope of the solubility curve indicates that the anti-solvent system would be an aggressive nucleator and in turn a reduction in particle size, when compared to the cooling technique, may be evident.

### Solubility Design Space for API y

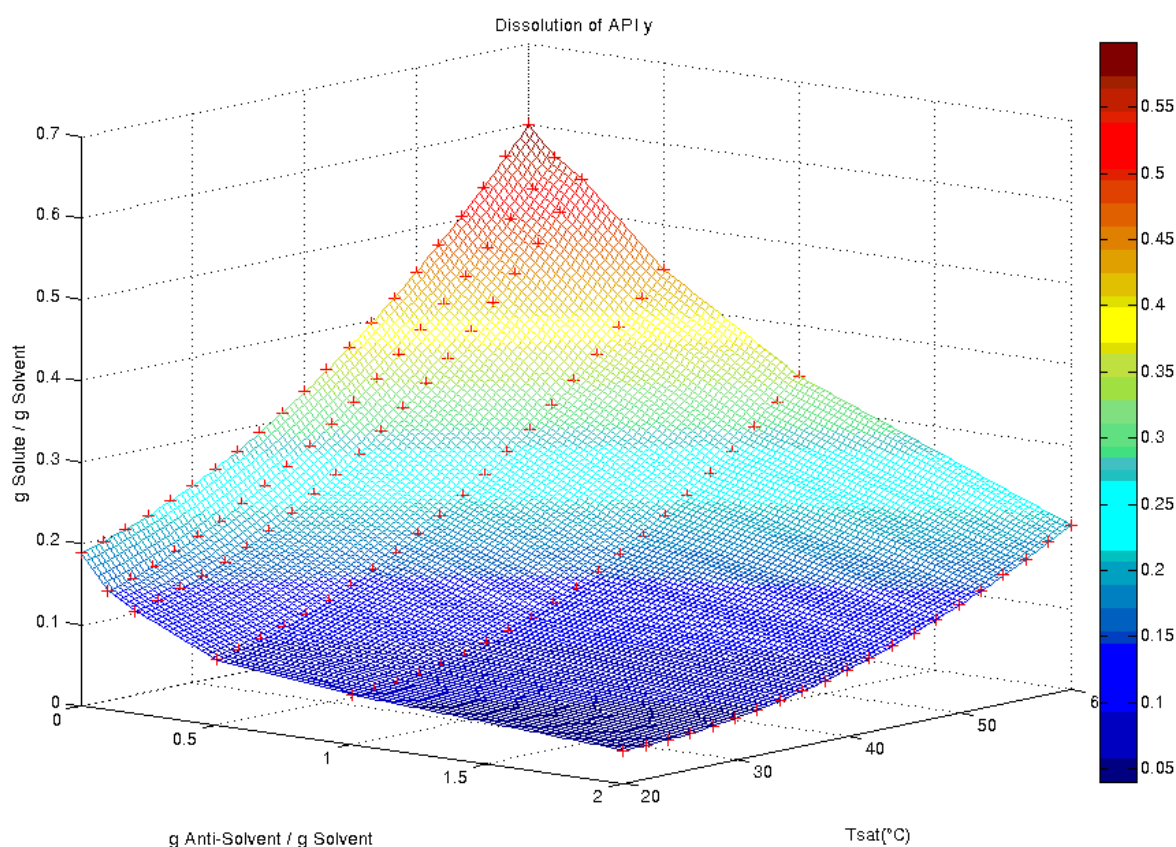


Figure 3: Solubility design space for compound y in variable solvent and anti-solvent compositions.

As shown the right hand side of the design space, which represents the solubility of the compound with respect to temperature (cooling crystallization), and the left hand side, which represents the solubility with respect to anti-solvent concentration (anti-solvent crystallizations), the solubility slope with respect to each crystallization technique is similar.

As a result of this the crystallization process can be decided on based on process benefits and costs. In this example an anti-solvent crystallization may be favored due to the shortened time required to crystallize the batch or a cooling crystallization favored if anti-solvent cost are an issue.

In comparison to product x this product should exhibit more favorable attributes for the control of anti-solvent crystallization as its solubility, with respect to the chosen solvent, is relatively flat.

### Metastability Design Space for Product y

In addition to solubility information the polyblock was used to generate a metastability design space for API y as concerns were raised that product nucleation would require metastable zones up to and in excess of 25°C. To combat the negative nucleation attributes these driving forces would bring, the process was designed to minimize driving force while maintaining sufficient crystallization yields.

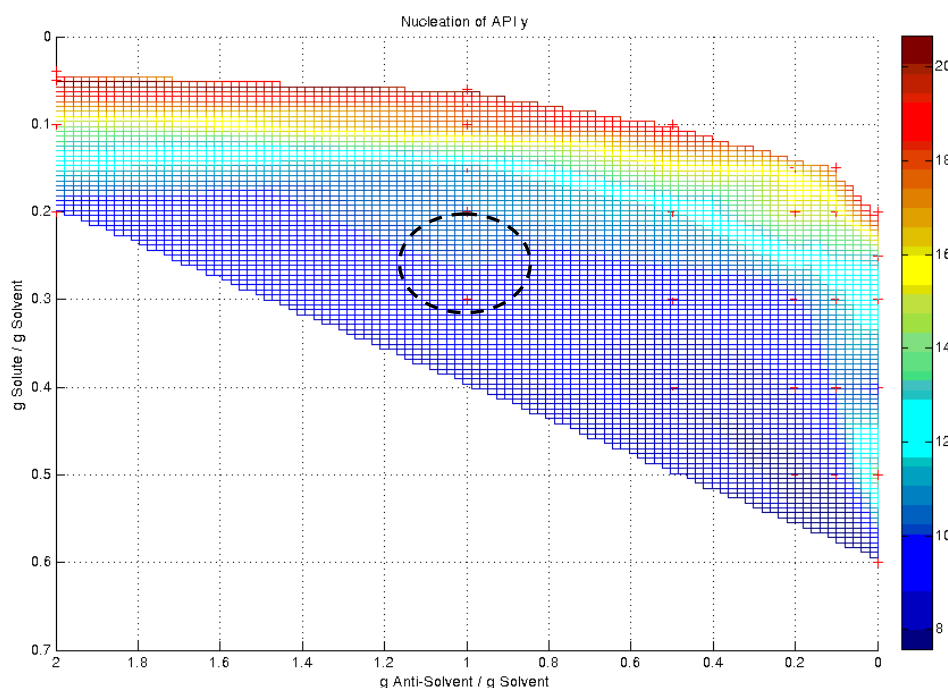


Figure 3: Metastability design space for compound y in variable solvent and anti-solvent compositions.

Shown above is the contoured plot for the metastable zone width for compound y with respect to various solute and anti-solvent concentrations. As shown the metastable zone, or driving force required to nucleate product y, is high at low solute concentrations (regions in red), with values in excess of 20 °C typically observed. On scale this driving force may be exacerbated with the reduction in turbulent mixing which is often observed on scale-up. In turn supersaturation values may in turn be high and lead to excessive product nucleation.

As a result of this analysis a concentration of 1 g anti-solvent / g solvent and 0.28 g solute / solvent was deemed adequate as the systems metastable zone is approximately 10 °C (see annotation in figure 3). Although seeding would be deemed favorable to prevent the exacerbation of the metastable zone on scale it was not permitted. In this case a slight increase in operating concentration from 0.12 g solute / g solvent to 0.25 g solute / g solvent was deemed adequate to control particle nucleation on scale.

## **Conclusions**

The HEL polyblock turbidity screening device, when combined with polythermal methods, enhances process understanding and enhances quality by design (QbD). By gaining a understanding of the limitations and benefits of a solubility and metastability design space a suitable crystallization technique can be designed.

## **Acknowledgements**

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