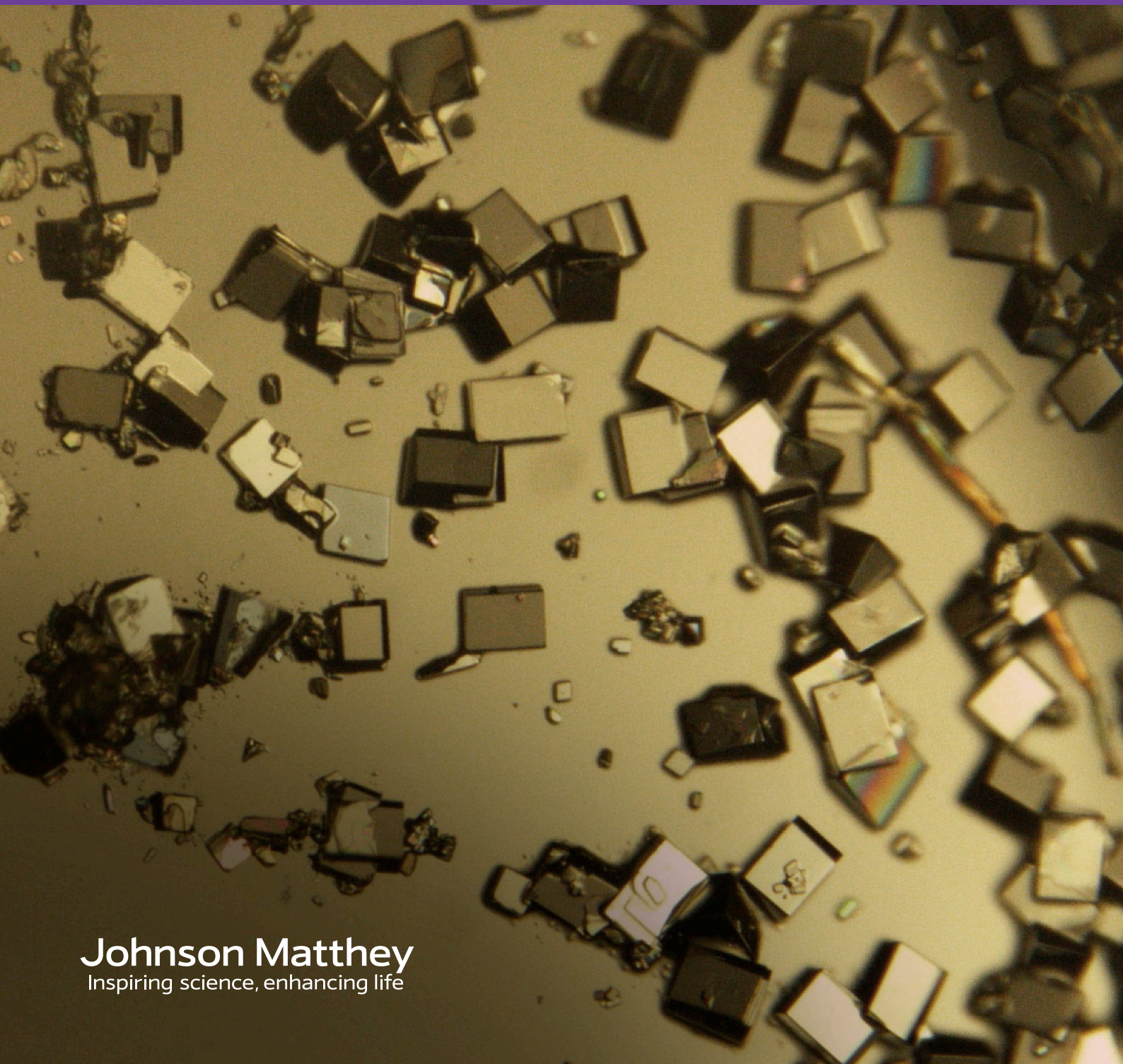


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Understanding solid form and crystallisation:

Webinar question and answers session





Distinguishing an ideal solid form of an API early in drug development is vital for improving the pharmacokinetic profile and increased stability. As such, it is always best to conduct a thorough search to identify as many forms (polymorphs, salts and co-crystals) as possible to allow you to select the one with the preferred physical/chemical properties and for IP. In this webinar, Dr Thomas Kendall, solid form scientist at Johnson Matthey, examines how solid form and particle technologies are providing drug manufacturers with powerful tools to improve the physicochemical properties of an active pharmaceutical ingredient (API), and address its aqueous solubility.

1 What criteria do you apply for starting and stopping crystal form screening?

Start

It is always best to start as early as possible. The polymorph is fixed from Phase 2b so the earlier you start, the earlier you can engineer the desired salt/co-crystal (if a possibility) and then polymorph thereof. The bulk of our clients are in preclinical, however, we are regularly working with more clients coming out of the discovery phase where solid form characterisation is used as part of the ranking criteria for candidate selection.

Stop

It's hard to say when to stop definitively. However, a typical workflow would usually take around six weeks. In that time, we would expect to undergo several screening crystallisation experiments covering cooling, anti-solvent, heat/cool, evaporative, etc., and several solvents. We would hope in these studies to identify two or three of the most thermodynamically stable and developable forms. It's reassuring to find several forms, including solvates and hydrates, and always a little worrying when you have a "monomorphic" material - although these do exist.

2 Could you suggest any reliable high-throughput method for thermodynamic solubility measurement?

For a reliable method, I would use Crystal 16. However, for a quick approximate measurement of solubility, you can do a gradual aliquot addition or gravimetric method. Additionally, solvent addition methods are applicable for approximate solubilities across a wide range of solvents.

Thermodynamic "shake-flask" may be performed at small scale followed by filtration, where the supernatant is analysed by HPLC assay for solubility value. It's always useful to analyse the recovered solid by XRPD to check for any solid form change.

3 What do JM offer in terms of hydrate screening and how do you do this?

For hydrate screening, it is important to assess the impact of water activity in a range of solvents in directing polymorph/hydrates. One method of doing this is similar to polymorphism screening, but we have additional detail on the volume of water present in our arrays and importantly the resultant water activity. You also need to consider the effect of temperature and concentration in such a screening array.

The design would be similar to the standard screen we would conduct, but using water and wet solvent (mixtures with water as well we would look at various humidities). Then we would prioritise Karl Fischer analysis to quantify water content.

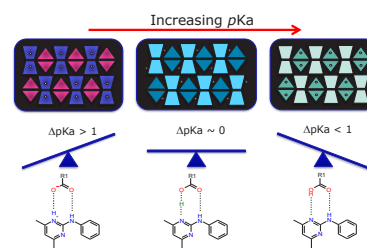
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What does delta_pKa mean in slide 9? As in, which two pKa's are being considered to calculate this delta?

The Delta pKa corresponds to the difference in pKa between the two molecules of interest (here pyrimethanol and acid). It should not be taken as a rule, but it is a good indicator of where you will form a salt or co-crystal.

Understanding Solid Form and Crystallisation: Slide 9

The salt/cocrystal continuum



- Salt is a new registered entity
- US FDA classify a co-crystal as polymorph with the same regulatory pathway as another polymorph

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Regarding anti-solvent crystallisation: Did you ever run into examples in which the anti-solvent would not be miscible with the "good solvent"? (So that you would have two liquid phases at some point in time)

Yes, ideally you would try selected solvents to avoid this problem. However, sometimes solvent changes are not possible. Dynochem has a spreadsheet that allows estimating of the miscibility of two or three solvents which can enable you to find the window of operation.

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Can you elaborate about finding the nucleation and growth rate from the expt measurements?

It initially models the growth based on assuming growth only from the de-supersaturation experiments using known growth equation. Then you can introduce nucleation, attrition and agglomeration again using known equations (e.g. Mullins etc.).

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When do you recommend continuous crystallisation?

Historically, this is best recommended when you are producing a lot of material for a long time, and do not have to worry about exclusivity. Although safety considerations also may come into play.

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How does Dynochem software calculation assist selection of right solvent for crystallisation?

There is a workbook from Dynochem that can aid in the prediction of solubility for a range of solvents and solvent mixtures based on the functional groups. Also, the heat of fusion and melting point of the molecule using UNIFAC regression which can aid in the selection of solvents. The crystallisation toolbox also predicts solvent and antisolvent mixtures to identify synergistic peaks and to control supersaturation.

Furthermore, there are several other solubility prediction packages, such as COSMO solv, which can help you get there quicker!

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How useful are the computer-based models for polymorph prediction?

We have had some experience with software in the past and in our dealings, these will always predict many more forms that you are likely to find experimentally. That said, it is good to see how predicted forms lie in their relative energies - is there a particularly stable form separate to all others? Does this correlate with actual experimental? This area of research is still an experimental science, which is good as we have a lot more to discover.

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Can the high-throughput crystallisation reactor be coupled with sono crystallisation technique?

No, the high-throughput reactor we showed is only really used for evaporations. But in theory, if you were interested in such a platform, it could be constructed.

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Is it possible the compound exists only in amorphous forms? And that no crystalline form can be identified?

While we agree from a theoretical standpoint, all amorphous material will eventually crystallise unless stabilised with additives. This is because the crystalline solids are the lowest energy form.

That said, there are well-known groups/moieties that notoriously retard crystallisation (e.g., five-membered saturated rings). Quite often and with significant effort, many "difficult to crystallise" compounds will eventually crystallise, but the output solid-form may not be that stable. In these cases, there are perhaps other avenues to explore, e.g. co-crystals.

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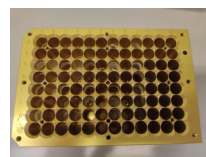
Can you run the XRPD directly using the plate, without scraping out the compound?

Yes, by running XRPD in transmission mode rather than reflection.

Understanding Solid Form and Crystallisation: Slide 15

Salt and co-crystal screening

- Reactor and XRPD plate in one
- 3-4 solvents and up to 9 counter ions
- 27 – 36 experiments using 5-7 mg per experiment 135 – 245 mg



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Can you elaborate on the advantage of using Crystal 16 comparing to the initial screening plate?

By measuring transmissivity, Crystal 16 gives better accuracy and reproducibility of a solubility point. It also allows you to determine the metastable zone, which is beneficial information in designing a crystallisation process.

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What is the better solution for oiling out?

Understanding your system, oiling out can be the result of solvent interactions with the compound. I would suggest stripping back to basics looking at individual factors until you identify what is causing it to oil out. Then conduct a DOE to find the window which is safe to operate.

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How to avoid agglomeration in crystallisation?

There is no "one size fits all" way of avoiding agglomeration. I would recommend investigating alternative solvents and cooling rates. If they are soft agglomerates (non-fused), then it is possible to break them then further disperse using ultrasound.

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How often do you get single-crystal X-ray studies on your polymorphs or screening? Or on your salts / co-crystals?

It is always desirable to provide a crystal structure of the solid form we recommend on a screening project. Also, we run our class-leading single-crystal service as a standalone service for many clients confirming structure and absolute stereochemistry where appropriate.

We have our in-house crystallographer at our site in Cambridge, UK along with two single crystal XRD instruments. One of these, we recently acquired - the state-of-the-art, dual-source X-ray diffractometer from Rigaku Oxford Diffraction. With the new equipment, we are now able to determine the chemical structure of even smaller crystalline samples and do it faster on a range of materials from organic pharmaceutical/ agrochemical type-compounds to inorganic transition metal oxides and other metal-organic complexes. To that end, if during a screen, if we see anything we think might give use good diffraction we will try and collect a single crystal.



X-ray diffractometer acquired from Rigaku Oxford Diffraction

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Given the move towards continuous / flow manufacture, how applicable is this to a continuous crystallisation processing?

In continuous crystallisation, you have to map the crystal journey as it moves through the system (multiple vessels or tubular) rather than controlling a fixed volume in a single vessel. Most of the underlying principles are the same and applicable, such as measuring and controlling solubility and supersaturation, monitoring in situ using PAT.

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Could you explain again why seeding windows become narrower upon scaling up?

On scaling up, the seeding window changes due to the decrease in the metastable zone. A sample will remain stable in the metastable zone until a nucleation event occurs. As you go up in scale, the control of mass and heat transfer decreases, increasing the probability of a nucleation event occurring.

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Do you use Visi-Mix like software for mixing considerations?

We use a combination of Dynochem and Visi-Mix. Dynochem is more geared for R&D and allows you to determine mixing condition for scaling between vessels and implants. Visi-Mix is more suitable for a larger scale.

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Will Blaze probe completely usurp the use of FBRM or does FBRM still have a place?

We have both in-house and both have their place. In particular, we like the multi-probe capability and flexibility that the Blaze offers us. The FBRM is still usable as a quick and cheap tool, but the Blaze is higher performance and spec.

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Is it possible to get more information about the antisolvent solubility and modelling them into Dynochem to predict the solubility at various solvent percentage?

The estimation of solubility is based on selecting the best regression equation. This is one that will fit the supplied data and the estimated data, to generate the extra figures based on the chosen equation.

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How can JM work with you

- Polymorph screening
- Salt screening
- Co-crystal development
- Amorphous dispersion
- Crystallography
- Physical and chemical analysis
- Chiral separations
- Crystallisation development
- Particle engineering
- Preformulation

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