Investigating Differences in Solubility Between Crystalline and Amorphous Forms of Pharmaceuticals

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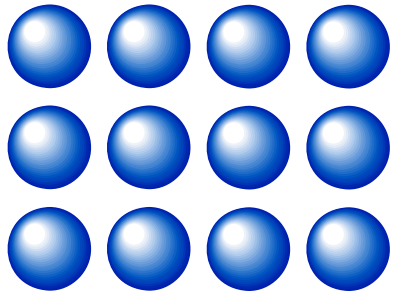
Aim

- To determine the differences in solubility between amorphous and crystalline forms of pharmaceuticals.
- To determine whether there are any trends between these differences.

Introduction: Why is the Solid-state Form Important?

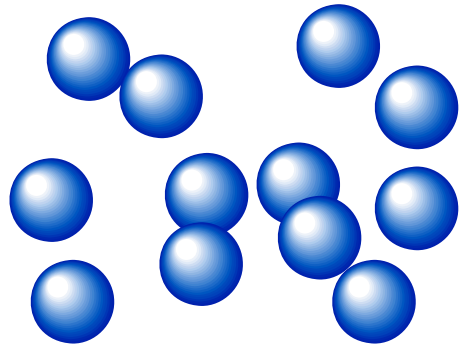
Thermodynamically Stable Crystalline Form



Molecules packed in a regularly ordered, repeating pattern

- More stable
- Lower solubility
- Lower risk

Amorphous Form

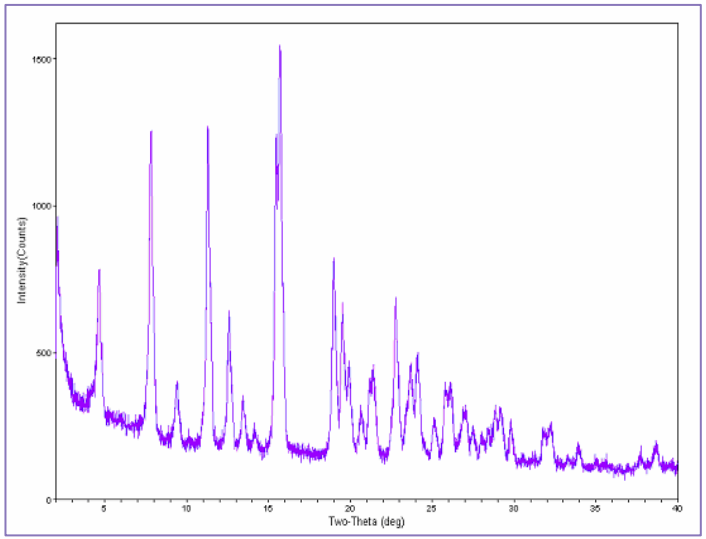


Molecules in a random arrangement.

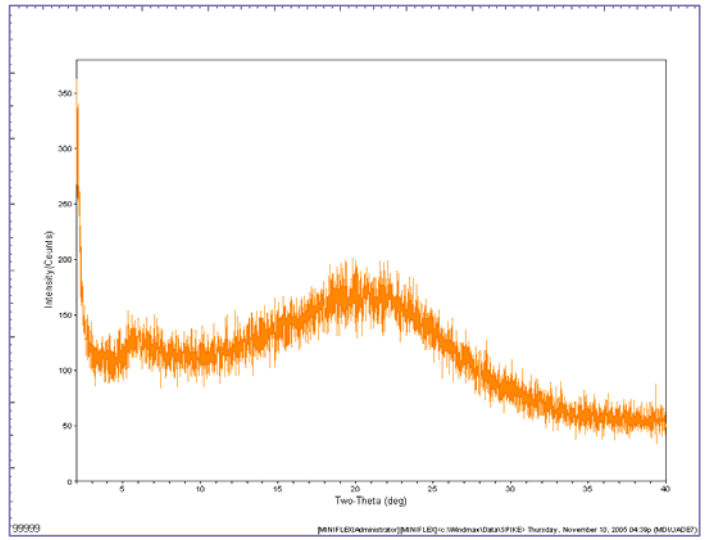
- Less stable
- Prone to crystallisation and degradation
- Higher solubility
- Higher Risk

Identifying the solid-state by XRPD

- X-ray powder diffraction is a powerful tool to determine whether a drug sample is amorphous or crystalline.



Crystalline Diffraction Pattern



Amorphous Pattern: No diffraction.

Dispersive scatter of x-rays

Why is Solubility Important?

•Poor solubility, poor absorption of drugs into the body, poor bioavailability.

• Solubility is pH dependent, so is determined at physiologically relevant pH.

• Increasingly more drugs with poor solubility being made.

• Solubility determined early in the drug discovery process, to assess risks involved in progressing molecules.

Drug Discovery

- Early batches material used to assess solubility:

Limited quantity (only a few mgs)

Variable purity (often low)

Often amorphous/ semi-crystalline (not enough bulk to assess this)

- Later batches produced should be the crystalline, stable form to ensure no form changes during the development period or on storage.

Early solubility investigations are often performed on non-ideal material

Investigation Drivers

- Study investigates effects of a change in form (from amorphous to crystalline) will have on the solubility.

How much of an over-estimate are early solubility measurements?

- Literature describes the solubility increase from crystalline to amorphous material has been reported to be between 10 and 1600 fold.
- Selected 40 structurally diverse compounds with variable solubilities.
- Can this comparison help us to understand how crystallisation affects solubility?

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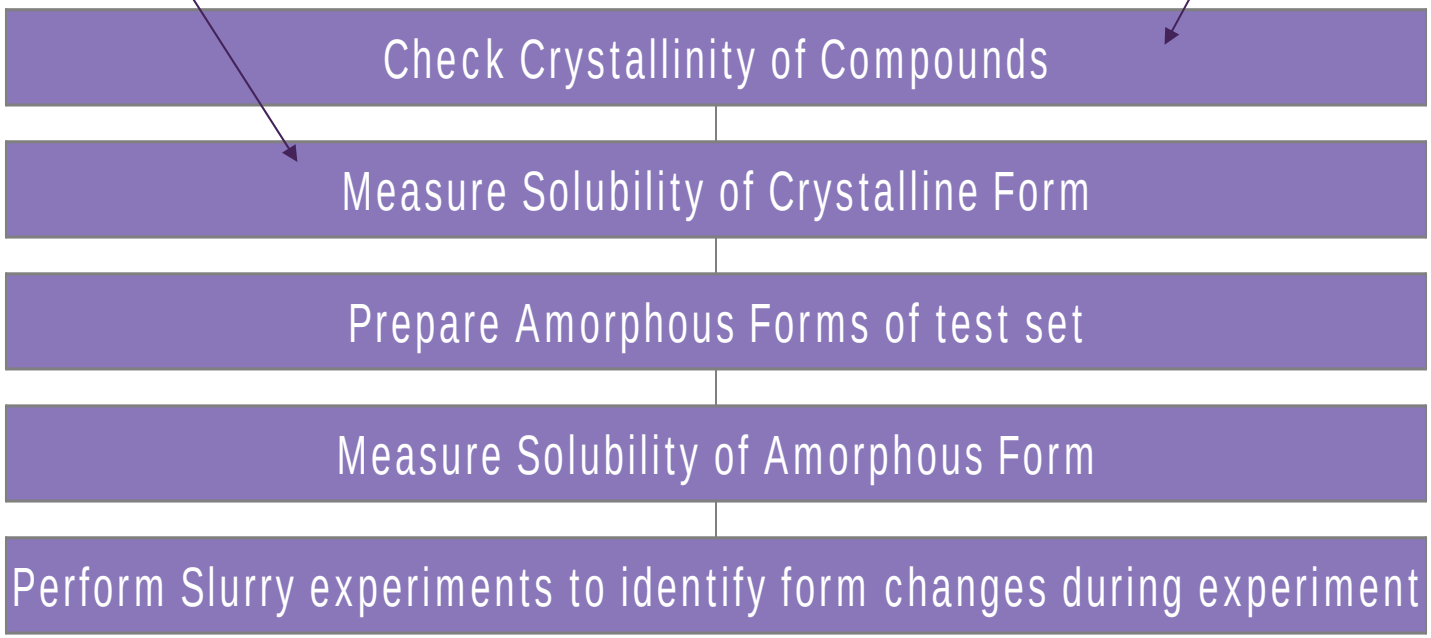
Experimental: Outline of work

2) In pH 7.4 buffer, 24 hour stirring, 25°C

Quantification by LC-MS

1) By XRPD



3) Making amorphous Compounds- The easy bit??

Aim: Prepare amorphous forms of all 40 compounds

Solvent Approach

- Crash cooling, rapid addition of anti-solvent, evaporation at high temperatures.
  - Compounds tended to recrystallise rather than stay amorphous

Success = 1 compound!

Grinding / milling

- Mechanically disordered by grinding using a pestle and mortar and compacting.
  - Only small amounts of amorphous in predominantly crystalline bulk.

Success = 0 compounds!!

3) Making amorphous Compounds- The easy bit??

Freeze Drying

- Freeze a dissolved sample (acetic acid) and dry under vacuum. Hinders crystal growth.
  - Amorphous materials prepared, found to crystallise over time.
  - Some compounds not soluble enough to dissolve.

Success = 2 compounds!

Melting and rapid cooling with liquid nitrogen

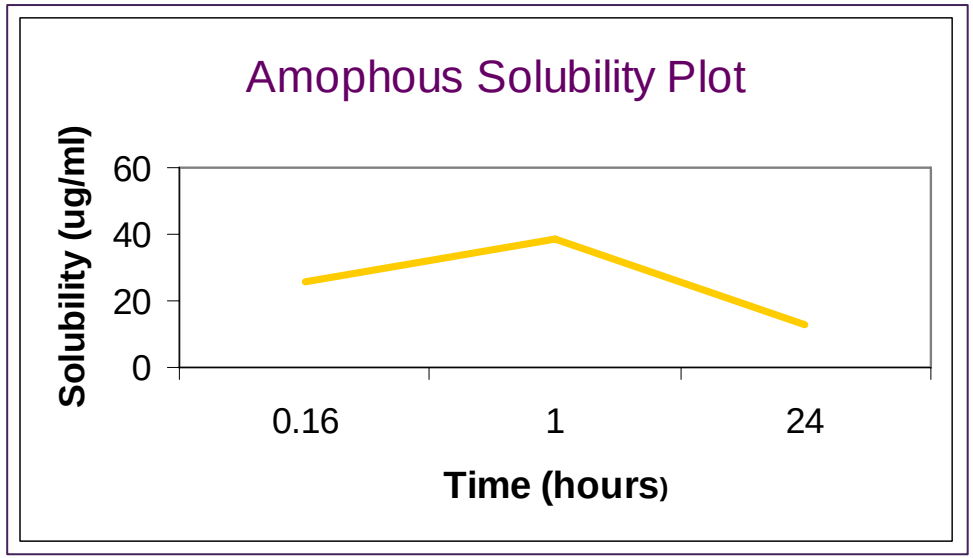
- Melt compound in pan and rapidly cool in liquid nitrogen.
  - Most sucessful technique, used as standard method of preparing amorphous.
  - However, many compounds found to decompose using this method.

Success = 20 compounds

4) Measuring Solubility of Amorphous

- Solubility of amorphous measured over 24h in phosphate buffer at pH 7.4.
  - Solubility measured at 10 mins, 1 and 24 hrs in excess solid.
  - Excess solid analysed by XRPD to determine form.

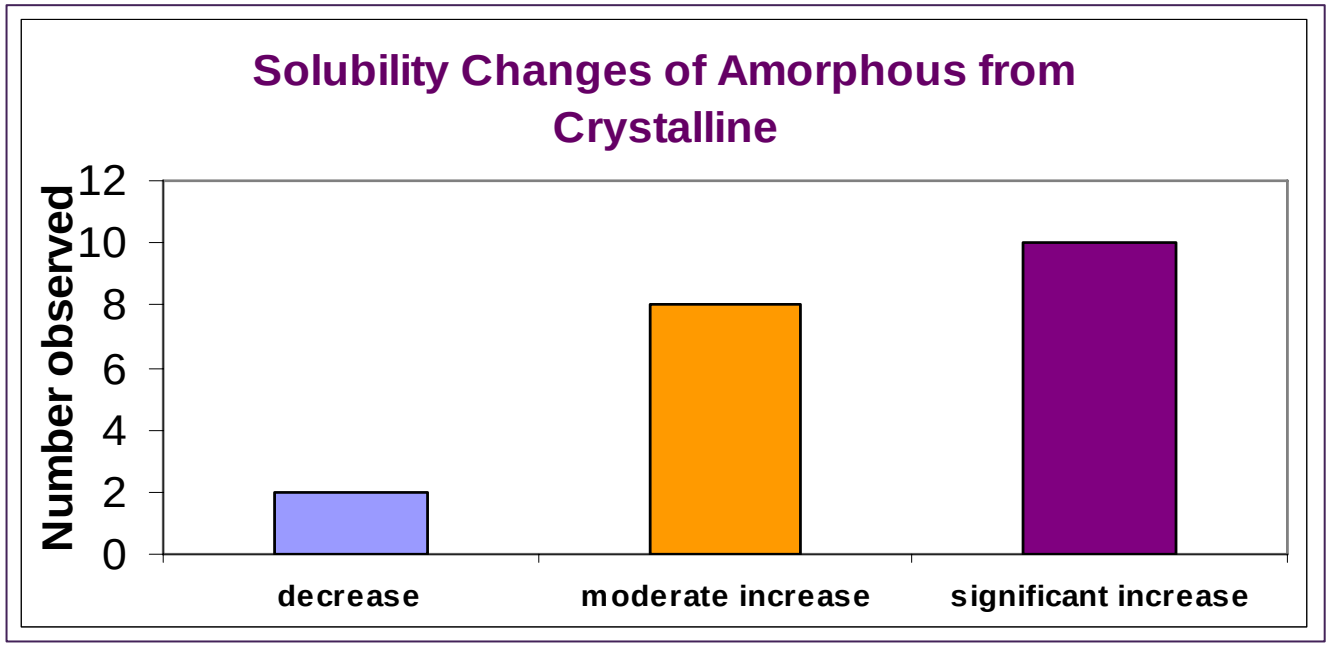
Amorphous solubility taken as the **maximum** solubility measured during experiment



Chlorpromazine

Results: Amorphous vs. Crystalline

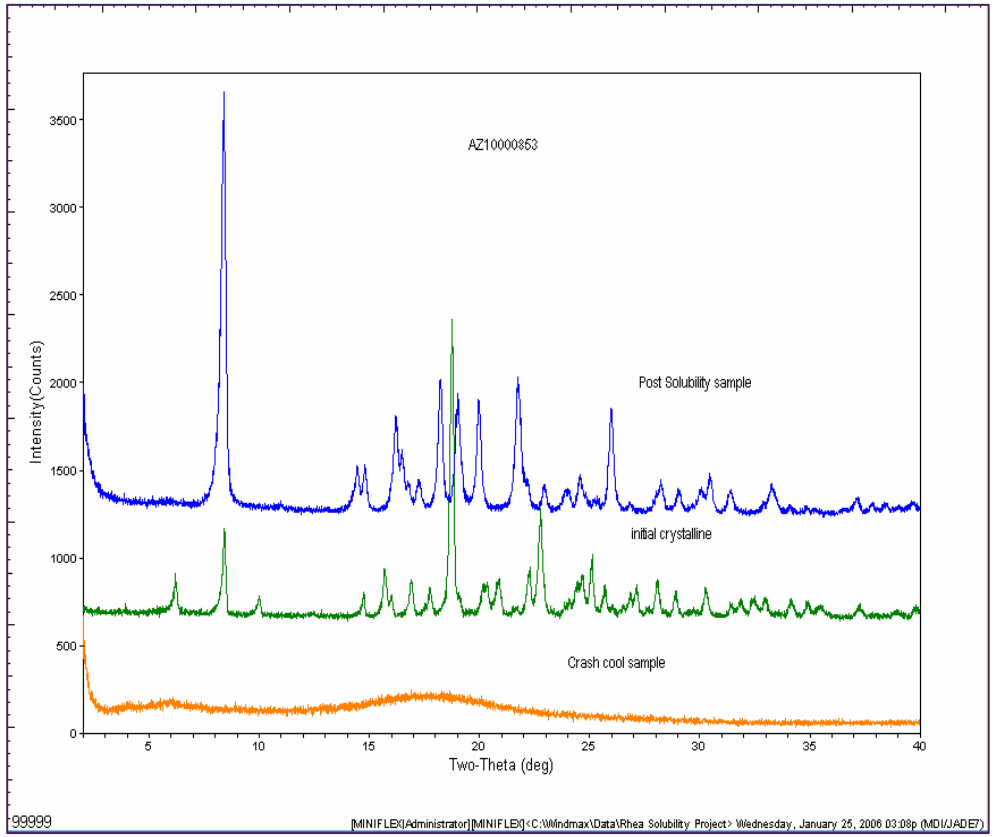
Comparing 24 hour amorphous and crystalline solubility



- When amorphous solubility, taken as maximum solubility measured, amorphous solubilities found to differ from crystalline between **0.3 and 6000 fold**

Results- The Crystallisation Problem

- Amorphous solid in contact with solvent can crystallise rapidly.
- Solubility measured may actually be that of semi-crystalline or crystalline material?
- Crystallisation after 24 hours.
- How rapidly does crystallisation occur in solution?
- Is it a feature of the ‘forced’ amorphous material?



Terfenadine

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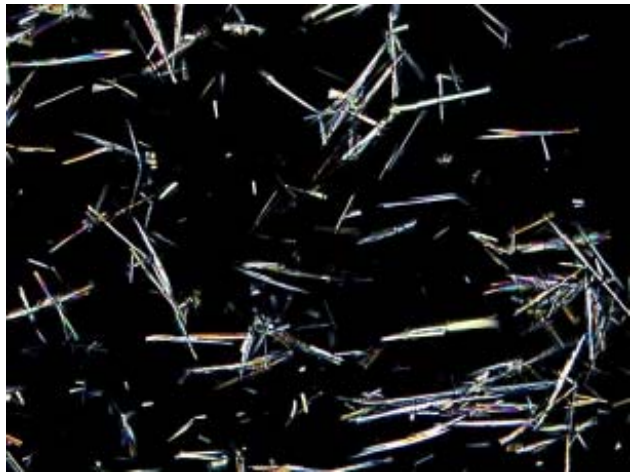
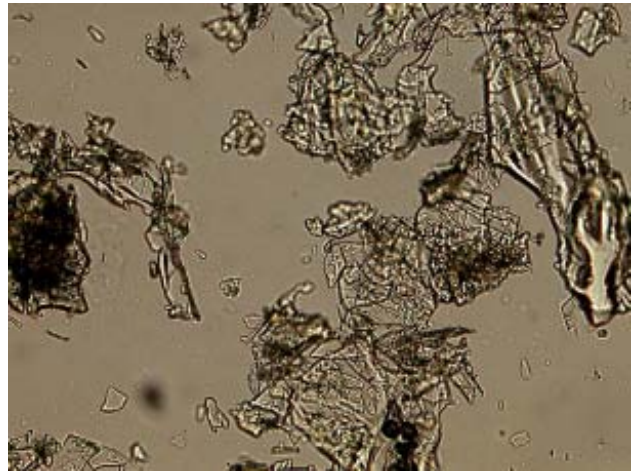
Polarised Light Intensity

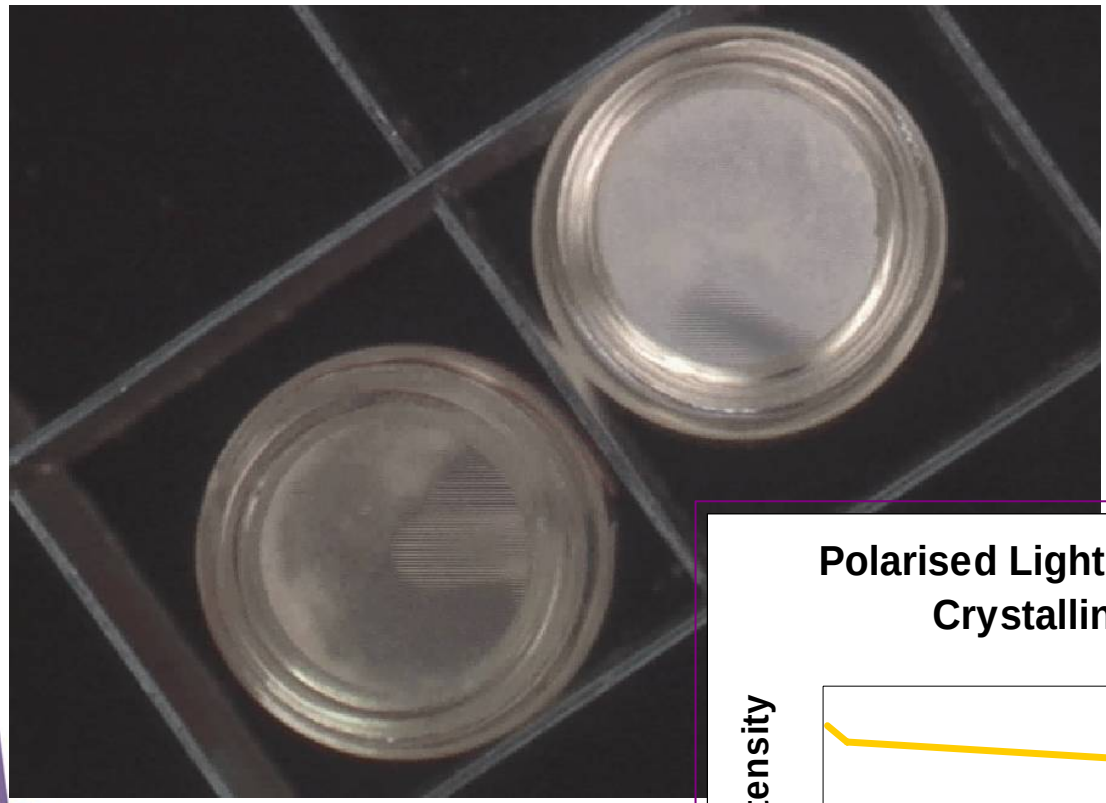
Crystalline

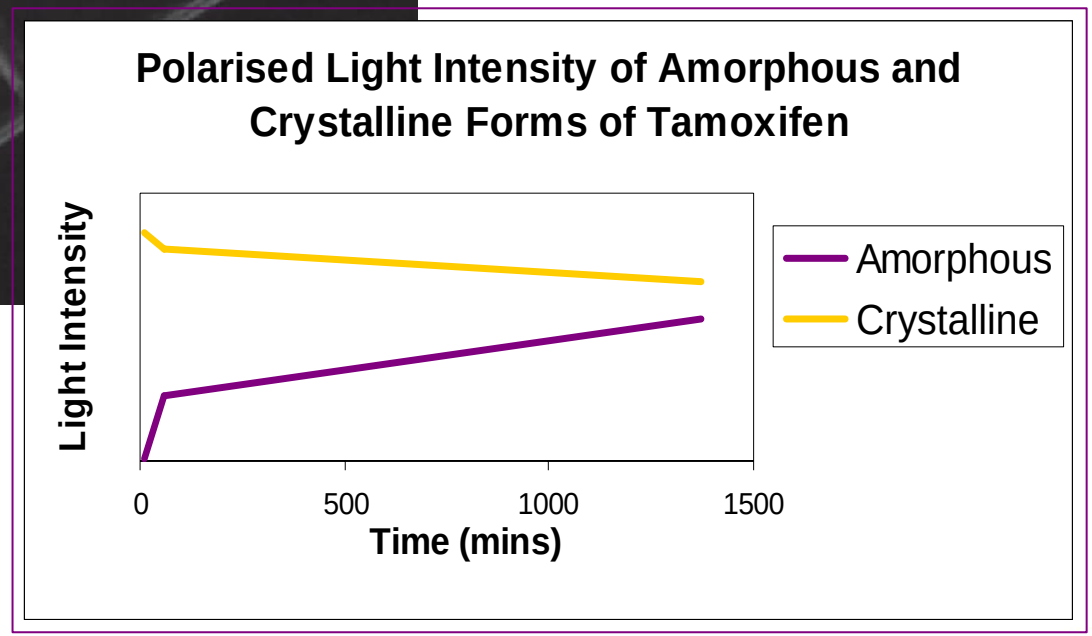


Amorphous



Polarised Light Experiment



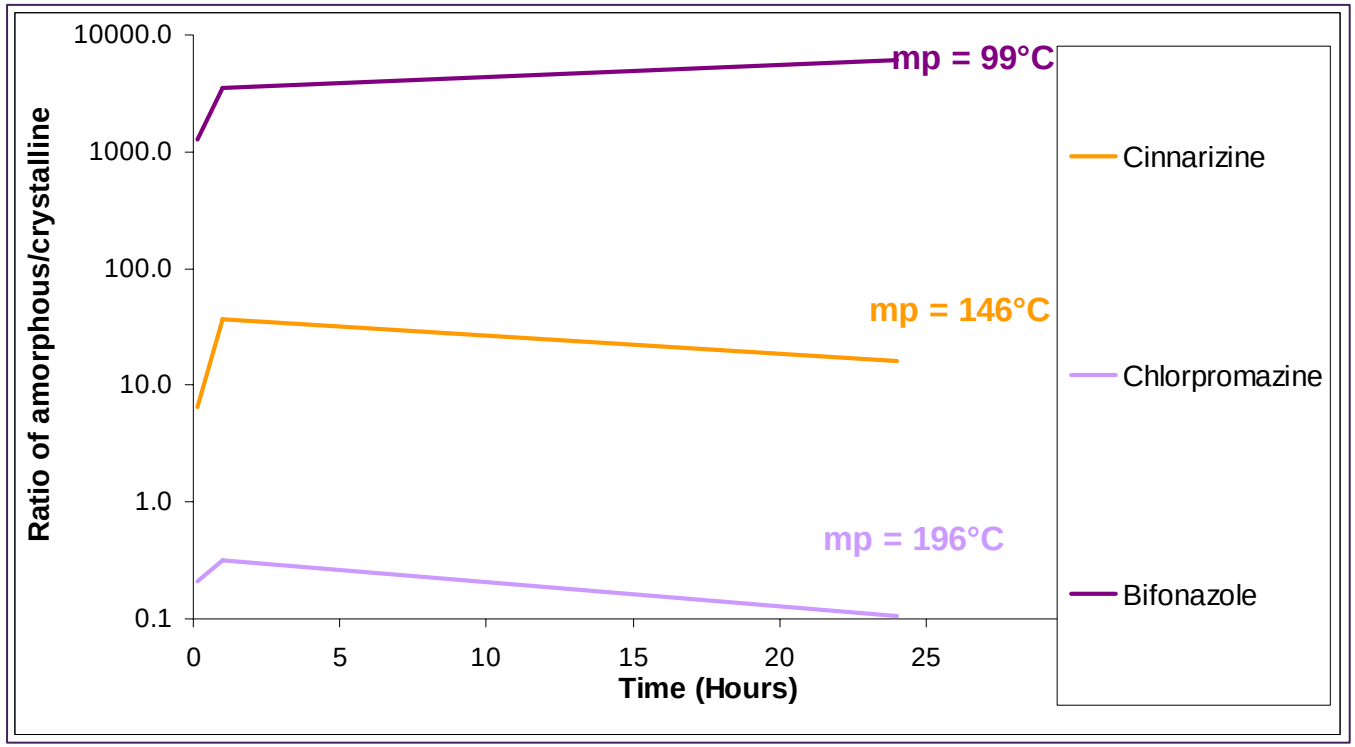


Looking for Trends

In theory.....

- Compounds with strong crystal lattices (high melting points) will readily crystallise in solvent hence the solubility benefit will be low.
- Compounds with weak crystal lattices (low melting points) are less prone to crystallise and therefore amount in solution will remain high. Greater solubility benefit.

Amorphous/Crystalline Solubility vs. Time



- Appears to be a correlation of high melting point compounds with a low enhancement of solubility and vice versa.

Conclusions

- Difficult to make amorphous compounds from crystalline.
- The tendency to degrade and/or recrystallise is very common.
- In the majority of cases, the amorphous form of pharmaceuticals are more soluble than the crystalline form.
- For half of the compounds the solubility increase remained for at least 24 hours.
- Physical properties e.g. melting point may indicate the enhancement of the amorphous solubility over that of the crystalline.

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Questions?

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