Simultaneous DSC-synchronous XRD for understanding solid-state phase transformations

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Scope

• Background to physical forms, especially in relation to pharmaceuticals
• Physical form identification by DSC
• Methods that might aid interpretation
• Hyphenated DSC techniques
• DSC-XRD
• Summary
Physical forms in pharmaceuticals

- Probably the biggest decision after selection of the drug molecule itself
- Why?
- Affects everything from solubility to dissolution, bioavailability, stability and manufacturing
DSC for physical form characterisation

• Methodology simple
• Put sample in a pan, heat it then look for peaks!
• Tricky part is interpretation of the data

• No molecular information and different processes can give similar peaks
• How to interpret?
  – LOOK at whether events are exo- or endothermic
What's going on here?
DSC for physical form characterisation

- Methodology simple
- Put sample in a pan, heat it then look for peaks!
- Tricky part is interpretation of the data

- No molecular information and different processes can give similar peaks
- How to interpret?
  - LOOK at whether events are exo- or endothermic
  - Much can be gained from altering DSC method, *especially* by reheating sample and by changing heating rate
Reheating sample

Crystallization to Form I

First heating run

Second heating run

mp$_{II}$

mp$_{I}$
A metastable polymorph at two heating rates
Additional analyses

- Can help interpretation with additional analyses
  - TGA
  - Hot-stage microscopy
  - Evolved gas analysis
  - Raman
TGA in event of polymorph conversion
TGA in event of hydrate/solvate
Telford et al (2016)
10.1039/c6cc05006a

Paracetamol
• Data for glutaric acid
• The question is, to what events should the peaks be assigned?
DSC for physical form characterisation

- ‘Gold standard’ analysis is single-crystal or powder XRD
- Takes a long time to record diffraction pattern
- We wanted to confirm physical form with PXRD in real-time, in the DSC pan
- Best done with a synchronous X-ray source
DSC for physical form characterisation

- Problem comes in *absolute* confirmation of form
- Can use *in-situ* Raman or NIR, but usually single-crystal or powder XRD is required
- Takes a long time to record diffraction pattern
- We wanted to confirm physical form with PXRD in real-time, in the DSC pan
- Best done with a synchronous X-ray source

- We were able to record a powder pattern in 4s, with a 2s pause, so 1 pattern every 1 °C
How to interpret XRD data?
Glutaric acid:

Two enantiotropic polymorphs

Solid-solid conversion
From $\beta$ to $\alpha$

Clout et al, Anal. Chem. 10.1021/acs.analchem.6b02549
By selecting specific XRD reflections, can look at loss of β and creation of α.
Sulphathiazole:

Three enantiotropic polymorphs

Solid-solid conversion from a mixture of forms III and IV to form I
Again, can see loss of Forms III and IV and creation of Form I
Paracetamol
DSC of tolfenamic acid Form VII
Heating 10 °C/min
Summary

- DSC excellent for seeing phase transitions, but absolute assignment to physical forms tricky
- Simultaneous XRD capable of following change in form in real-time
- TA DSC is very easy to modify for this use
- Initial experiments have shown that solid-solid transitions occur without an intermediate liquid phase
- If you have systems of interest, contact us and we will schedule them on the Diamond Beam
Thanks to...

- Gareth Williams
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- Sally Price, Derek Tocher and Rona Watson
- Jas Mahey and TA Instruments
1949 version

Diamonds are a Girl’s Best Friend

Lyrics by Leo Robin
Music by Jule Styne

Recorded by Marilyn Monroe on M.G.M. Record 462

1949 version

2016 version

diamond is a DSC’s best friend