UCL SCHOOL OF PHARMACY
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Thermal Analysis of Pharmaceuticals:

New Approaches to New Problems

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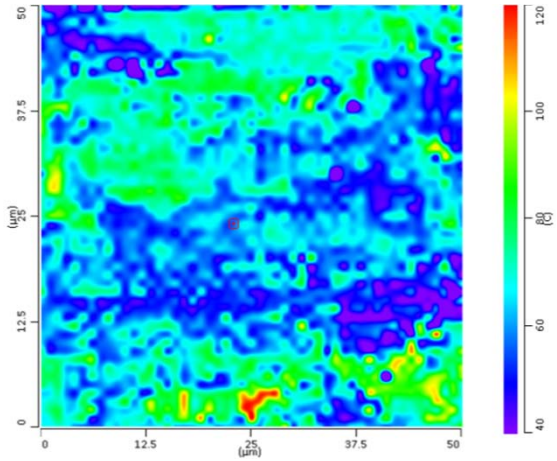

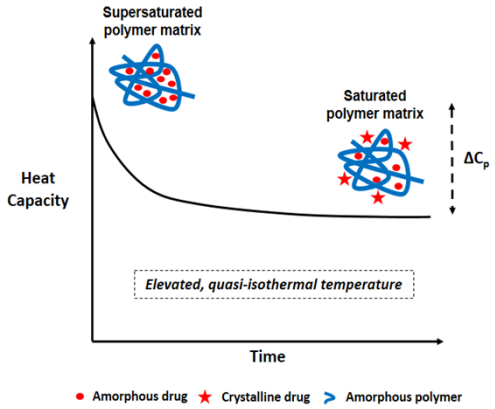

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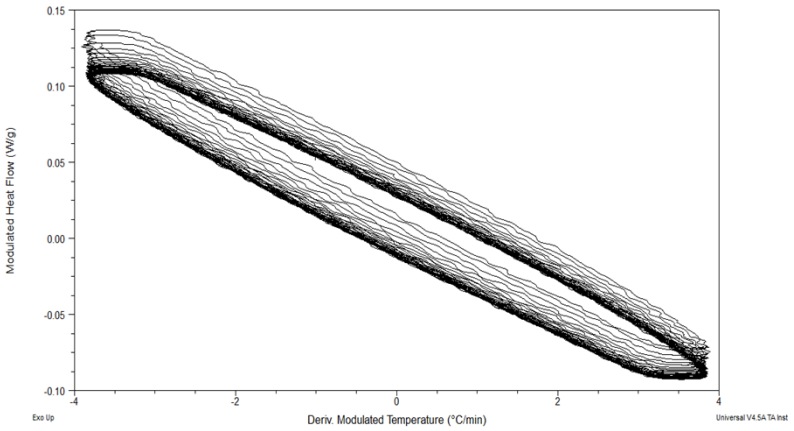
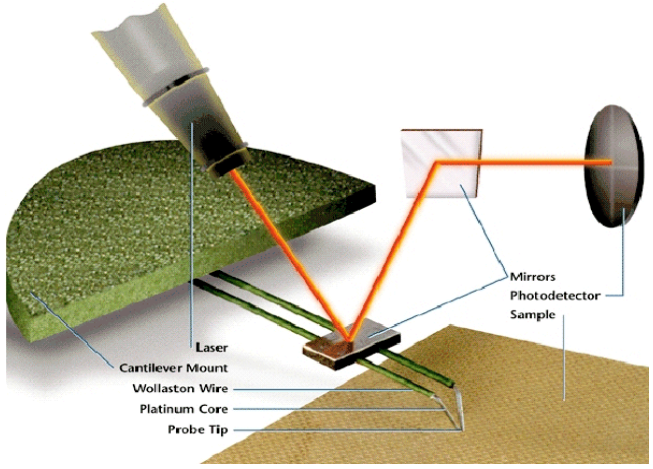
- Introductory comments – new solutions for old problems
- Measuring drug solubility in ASDs using quasi-isothermal DSC
- Transition temperature microscopy for thermal mapping of dosage forms
- Photothermal IR for spectroscopic mapping of materials
- New approaches to ASD requiring new analytical approaches



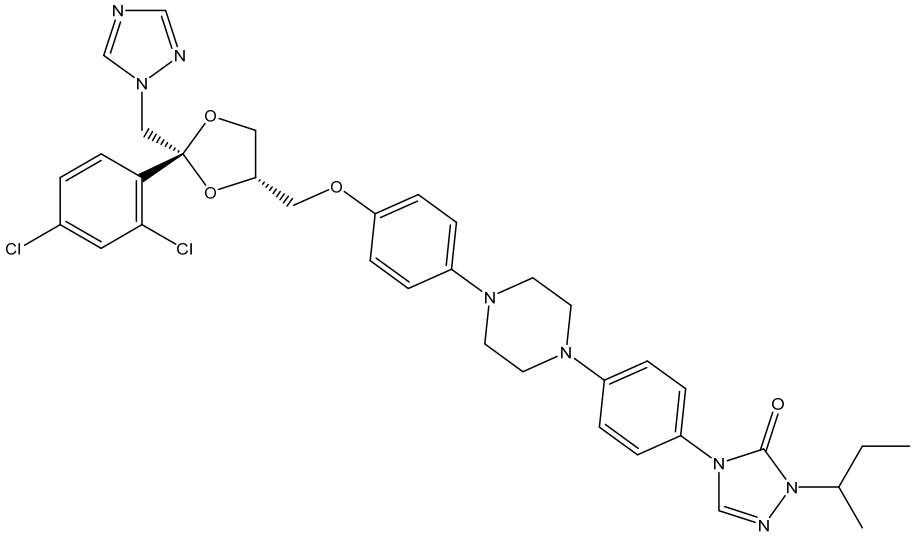


The problem of low drug water solubility

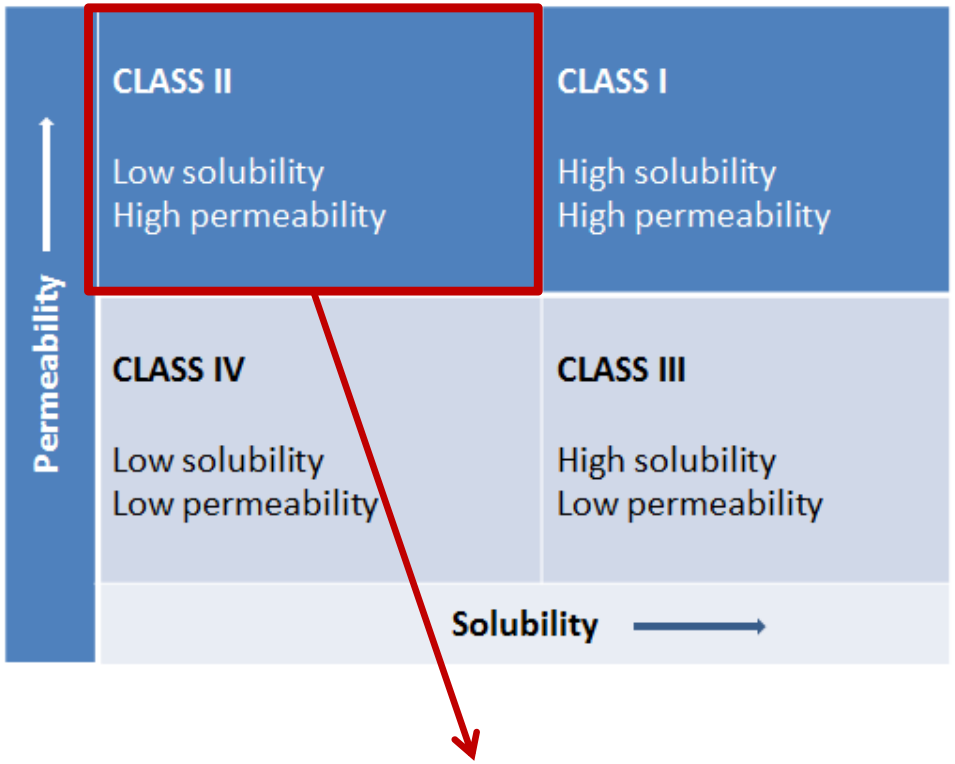
Drugs with low water solubility are predisposed to **low and variable oral bioavailability**

Itraconazole

MW: 705.64 g/mol

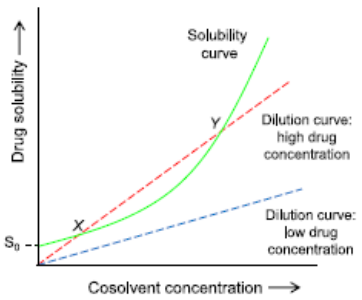


- broad spectrum **antifungal agent**
- **solubility**: ~1 ng/ml at neutral pH and ~4 µg/ml at acidic pH



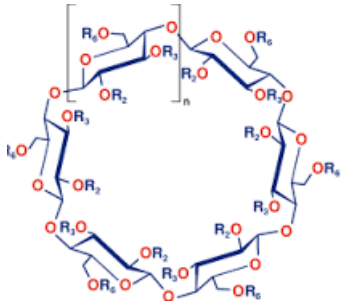
Oral absorption is **dissolution rate limited**


© Alamy

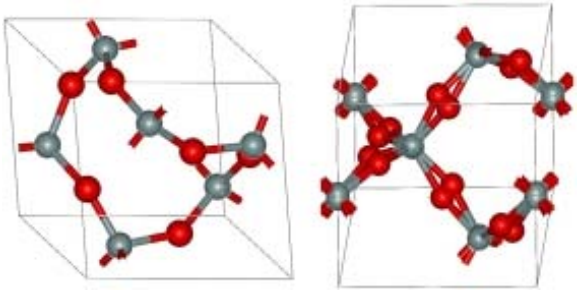


co-crystals

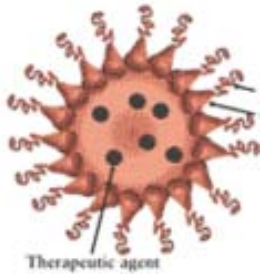
cyclodextrins



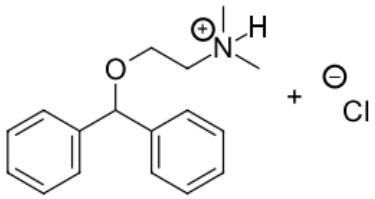
Common strategies to address low drug solubility



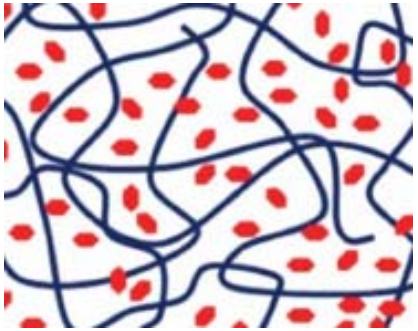
Lipid-based systems

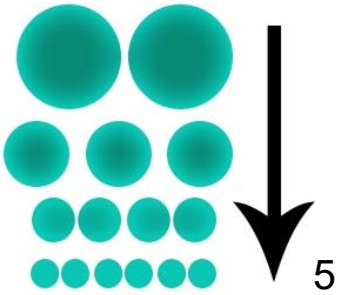


salts



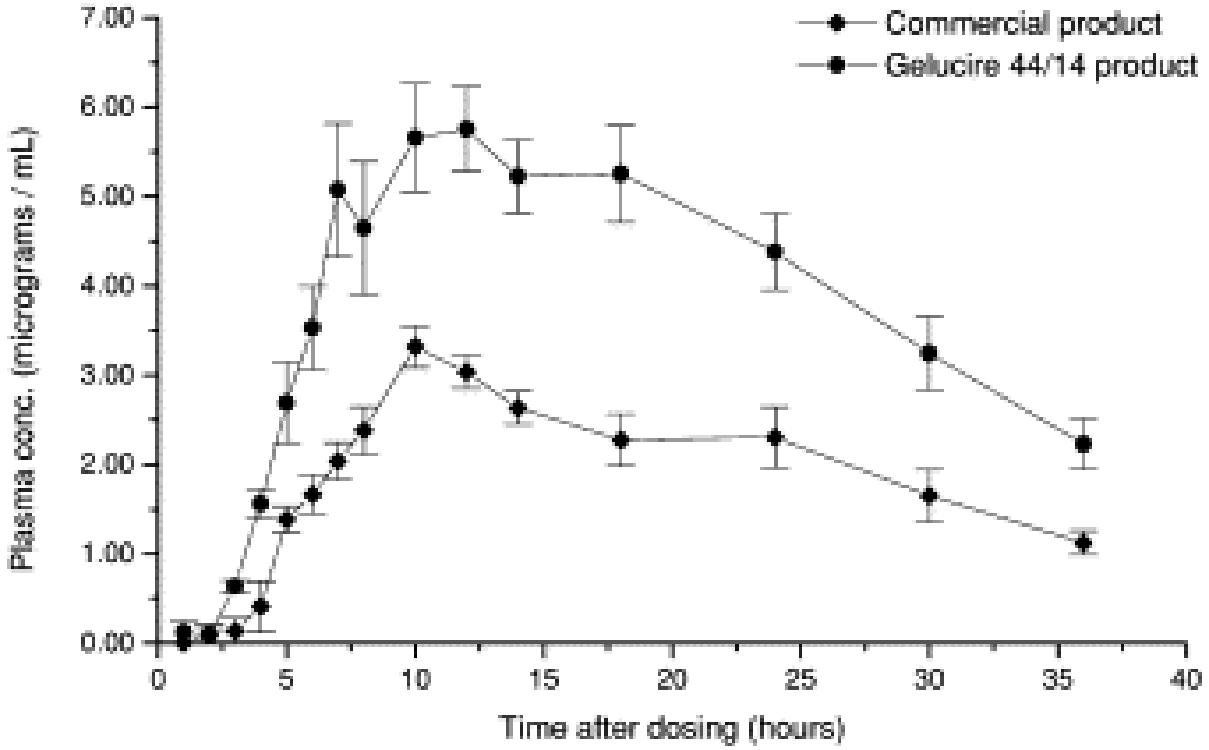
Amorphous solid dispersions





Solid dispersions of drugs in polymers

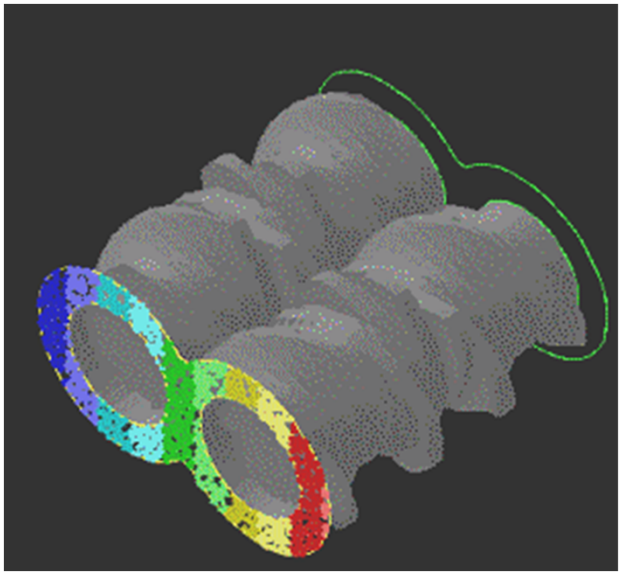
- Concept of dispersing a drug in a water soluble carrier (via a liquid intermediate)
- Remarkable increases in dissolution and bioavailability observed for many poorly soluble drugs



α-tocopherol in the lipid-based polymer Gelucire 44/14

Barker et al J Cont Rel 2003 91 477

- Huge resurgence of interest with the development of hot melt extrusion (HME)
- This provided a mechanism for producing solid dispersions in a scalable manner
- Highly intimate mixing at elevated temperatures
- Idea is that by producing a molecular dispersion, ultimate particle size reduction and no lattice energy to overcome
- This has led to focus on maintaining molecular dispersion characteristics
- Mechanism is open to challenge
- **Major concern is drug crystallization on storage – is there a safe limited of loading?**



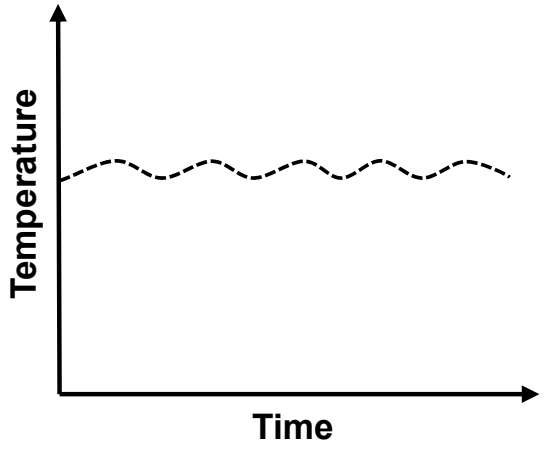
Measuring drug solubility in ASDs using quasi-isothermal DSC

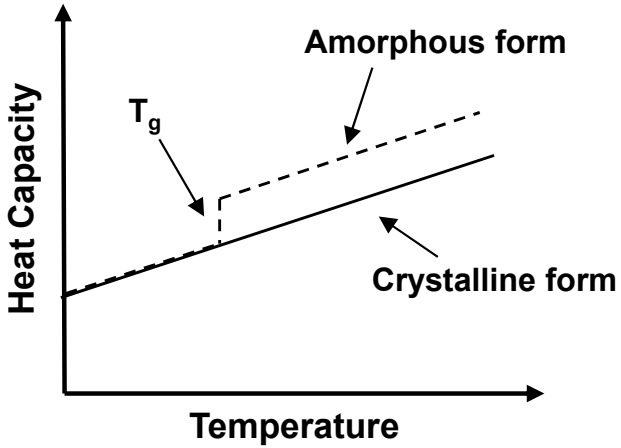
- Key question is what is the 'equilibrium' solubility of a drug in a polymer?
- In theory at drug loadings below this value the drug dispersion will be thermodynamically (and kinetically) stable
- The approaches used are broadly mixing methods (i.e. measuring the temperature at which the drug completely dissolves in the molten polymer)[1]
- Alternatively demixing methods may be used whereby the system is deliberately phase separated and the remaining polymer assumed to be saturated with drug[2]

1. Tao, J.; Sun, Y.; Zhang, G. G. Z.; Yu, L. Solubility of Small-Molecule Crystals in Polymers: D-Mannitol in PVP, Indomethacin in PVP/VA, and Nifedipine in PVP/VA. *Pharm. Res.* **2009**, *26* (4), 855–864.

2. Mahieu, A.; Willart, J. F.; Dudognon, E.; Danèide, F.; Descamps, M. A New Protocol to Determine the Solubility of Drugs into Polymer Matrixes. *Mol. Pharm.* **2013**, *10* (2), 560–566

Our approach is to use quasi-isothermal DSC as a means of assessing both solubility via heat capacity measurement and kinetic stability as a function of temperature simultaneously





- MTDSC with an underlying heating rate of zero
- Allows direct measurement of heat capacity as a function of time at an isothermal temperature
- Heat capacity = a measure of molecular mobility
- Crystalline and amorphous forms of a material have significantly different heat capacity above the T_g

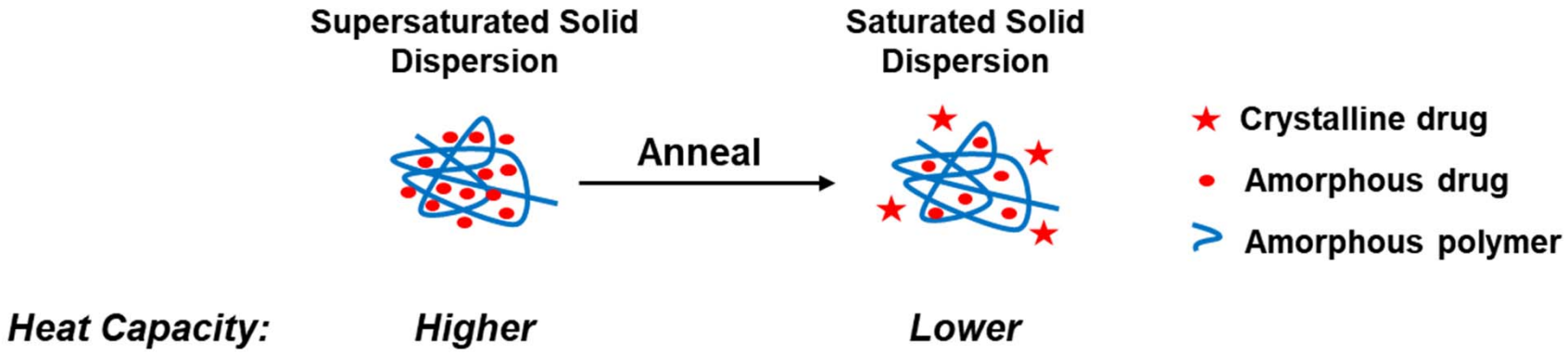
QiMTDSC: Exploiting C_p to measure drug-polymer solubility and crystallization kinetics

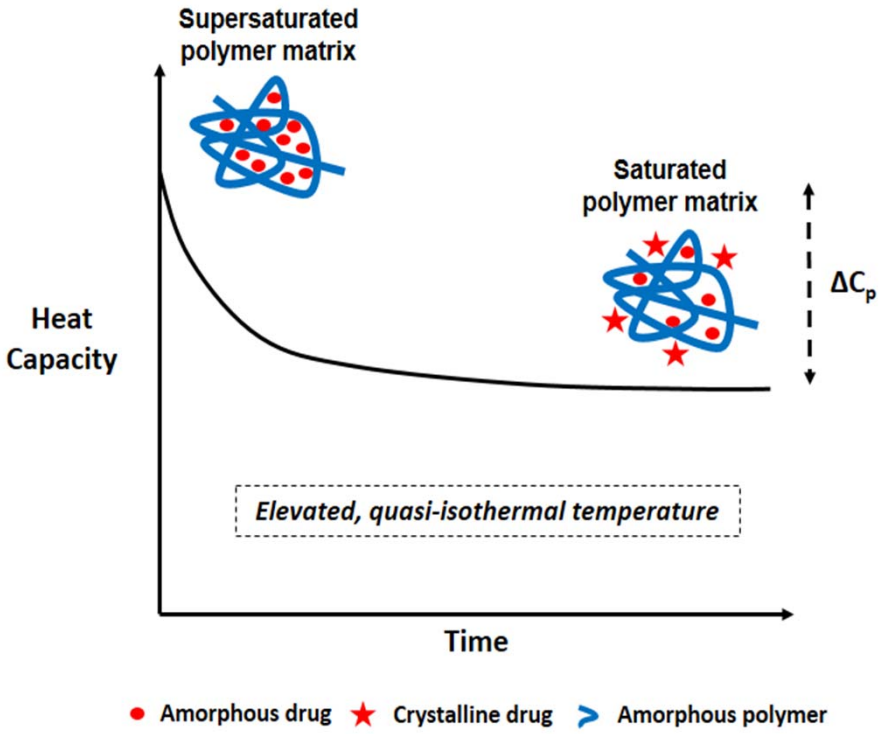
Theory:

1. Produce supersaturated drug-polymer solid dispersions

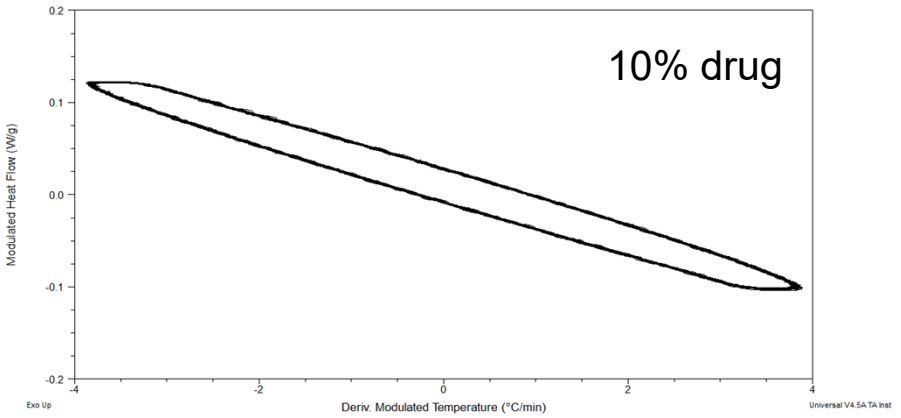
2. Anneal at set temperature with QiMTDSC to promote crystallization of excess drug

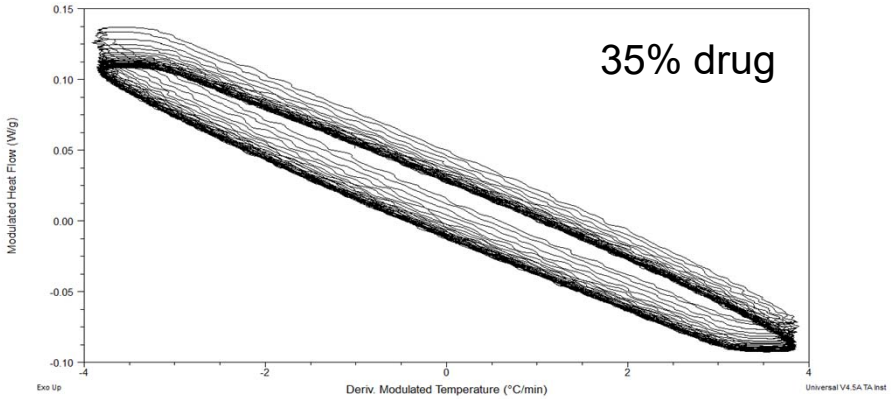
3. Use C_p to calculate the amount of amorphous drug remaining (solubility) and monitor the progress of crystallization (kinetics)

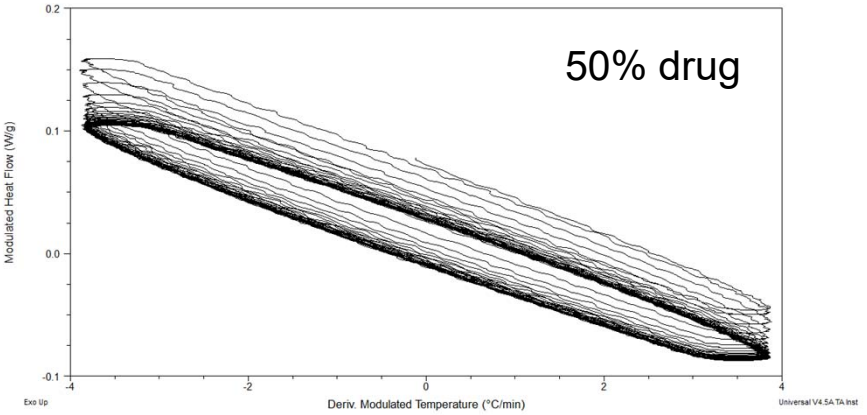




Hold and perform Q-isothermal measurements at different loadings

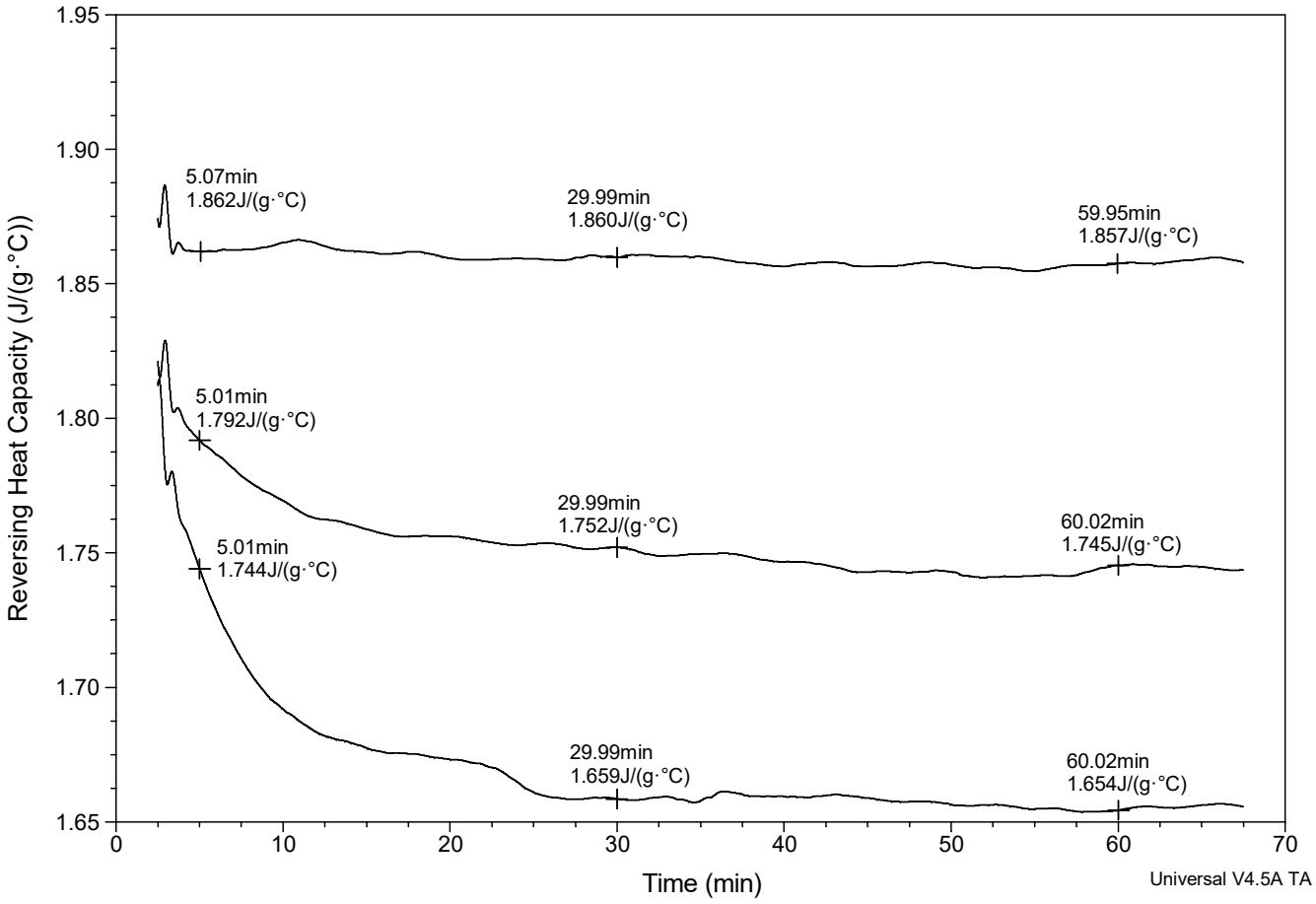






QiMTDSC: Measuring drug-polymer solubility

Three systems with increasing drug loading annealed at 90 °C (modulation: ± 1 °C every 100 seconds) to determine whether QiMTDSC could distinguish between the different levels of drug crystallization based on heat capacity



10% w/w olanzapine-PLGA

35% w/w olanzapine-PLGA

50% w/w olanzapine-PLGA

QiMTDSC: Measuring drug-polymer solubility

How can we determine amount of amorphous and crystalline drug following crystallisation?

- If make assumption that the heat capacities of the various components of the solid dispersion are additive then this is possible
- Measure heat capacity of the three components at temperature of interest (amorphous drug, crystalline drug and polymer)
- Solve the following equation to calculate weight fractions of amorphous and crystalline drug (x) following crystallisation

$$C_p^{total} = \phi\left[xC_p^{amorphous\ drug} + (1-x)C_p^{crystalline\ drug}\right] + (1-\phi)C_p^{polymer}$$

- The amount of drug that remains amorphous following crystallisation defines the drug-polymer solubility which can be calculated as follows:

$$Solubility\ (\%) = fraction\ of\ amorphous\ drug \times total\ drug\ fraction$$

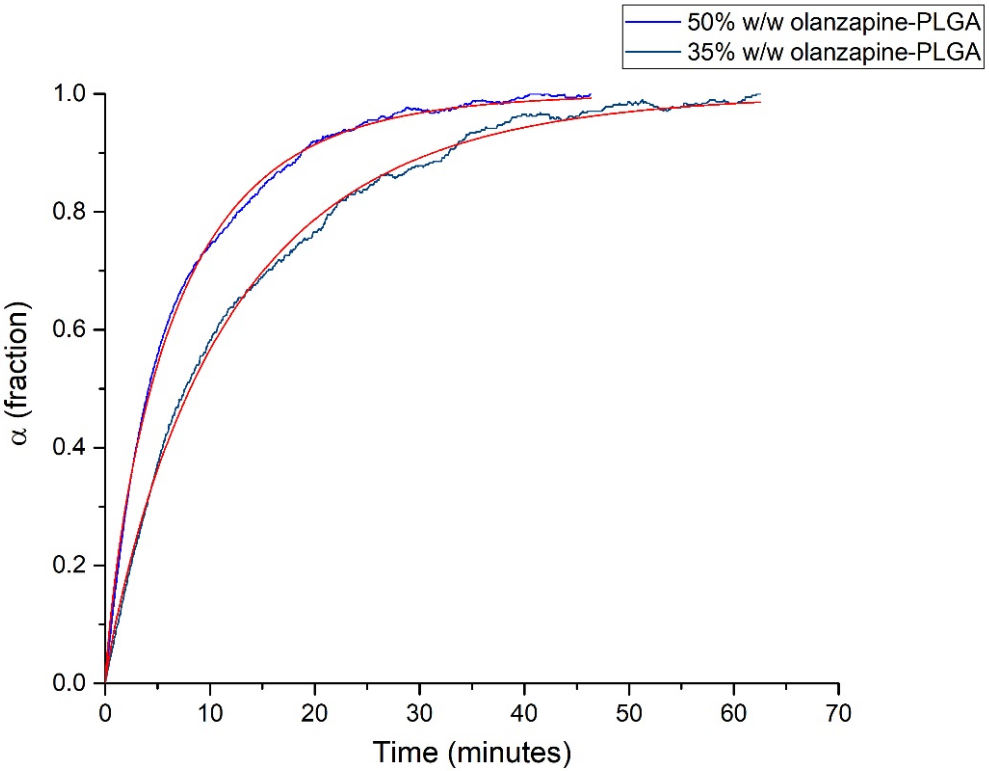
QiMTDSC: Measuring drug-polymer solubility

Method	Olanzapine-PLGA Solubility (% w/w)
Established DSC (T_g) method	21.4 ± 3.0
New QiMTDSC method	22.7 ± 6.3

- Successfully calculated amorphous drug fractions and therefore solubility values for this system from the QiMTDSC data
- When compared to established method (using T_g) found to be comparable which validates method
- Therefore, alternative method developed for measuring drug-polymer solubility based on heat capacity
- New method provides a rapid and simple method for measuring drug-polymer solubility which is a critical parameter for determining physical stability of solid dispersions

QiMTDSC: Measuring crystallisation kinetics

Measurement of heat capacity using QiMTDSC allows crystallization kinetics to be measured isothermally as change in heat capacity is directly related to phase change



$$\alpha = 1 - \exp(-kt^n)$$

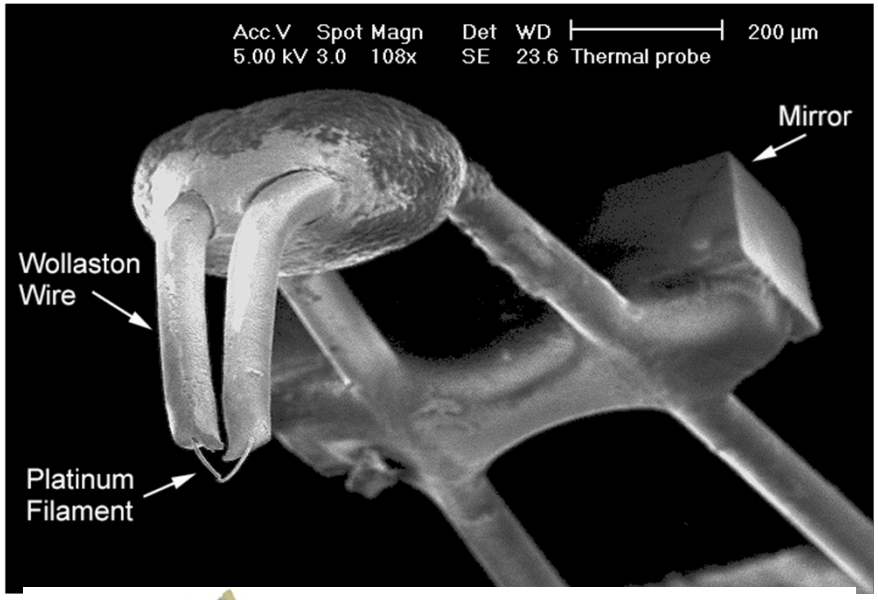
Avrami fitting – Crystallization kinetics at 90 °C

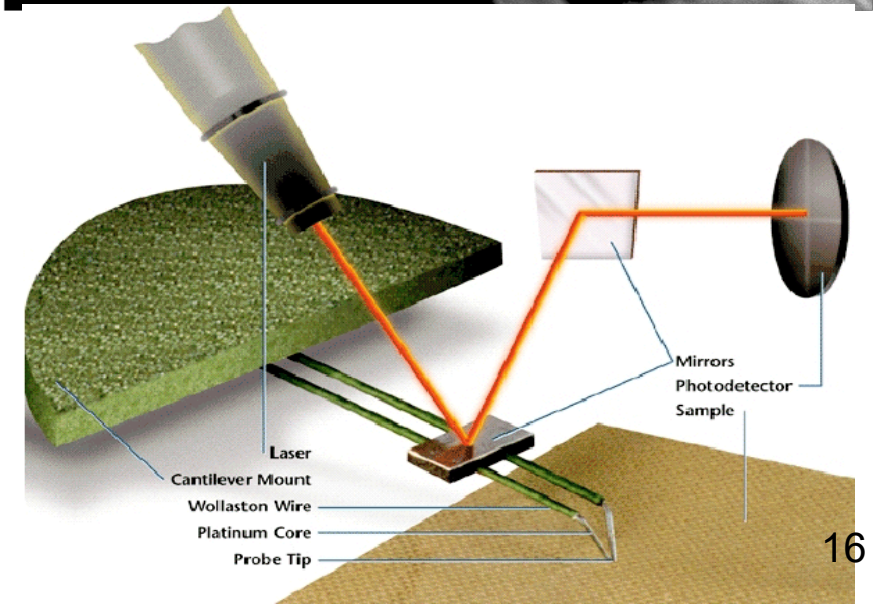
Solid Dispersion	k (min^{-n})	n	R^2
35% w/w OLZ/PLGA	0.108	0.890	0.997
50% w/w OLZ/PLGA	0.206	0.827	0.998

- Proof-of-concept that rate of drug crystallisation be measured within solid dispersions using QiMTDSC
- Useful for assessing the kinetic stability of amorphous solid dispersions

Transition temperature microscopy for thermal mapping of dosage forms

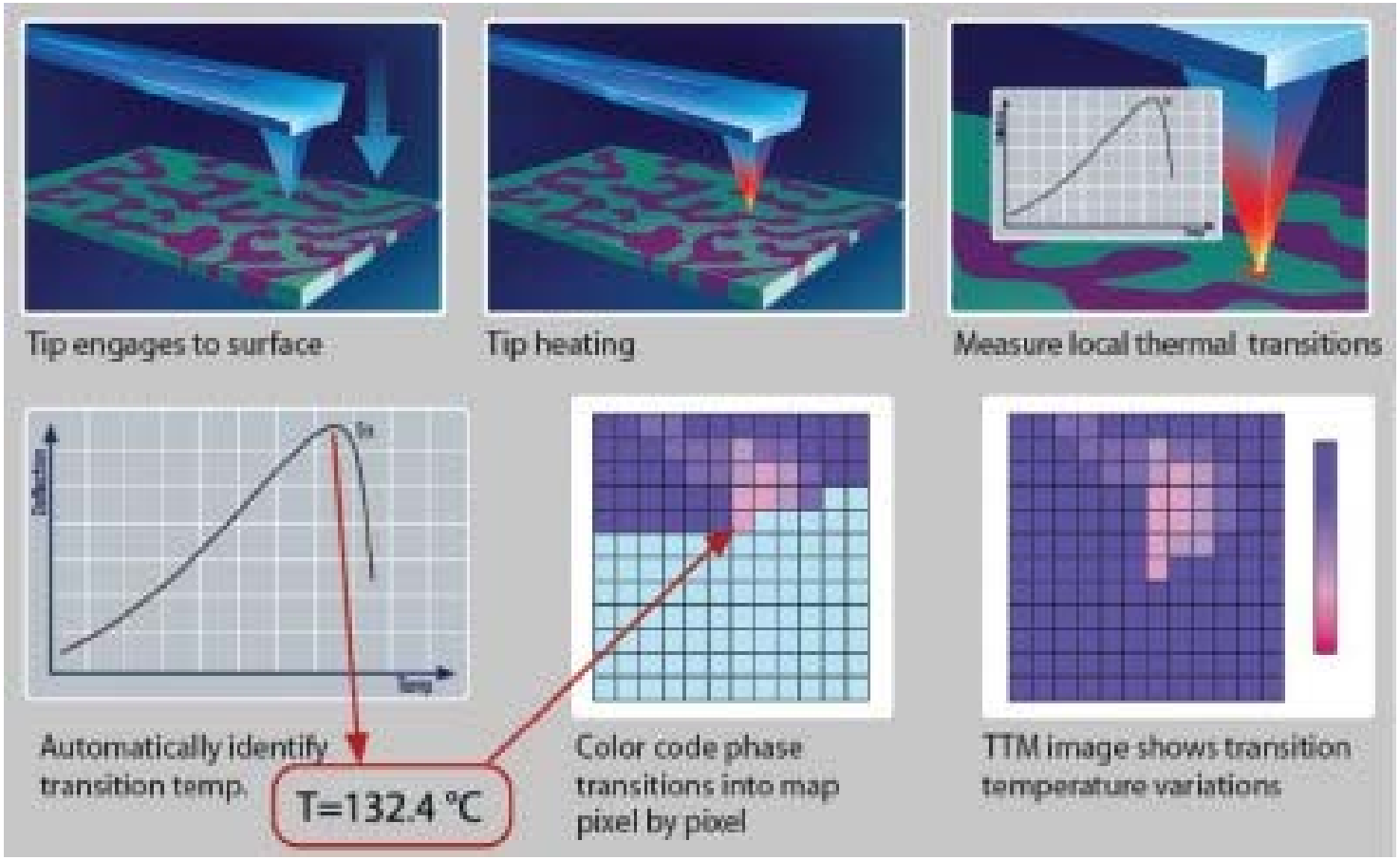
- ***Microthermal analysis***
- Method whereby tip of a conventional AFM is replaced by a thermal probe
- This allows analysis in a number of modes and also allows ***spatially resolved*** measurement



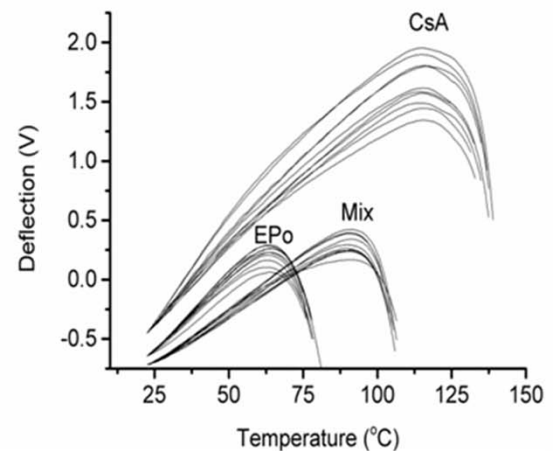


Related approach – **transition temperature microscopy**

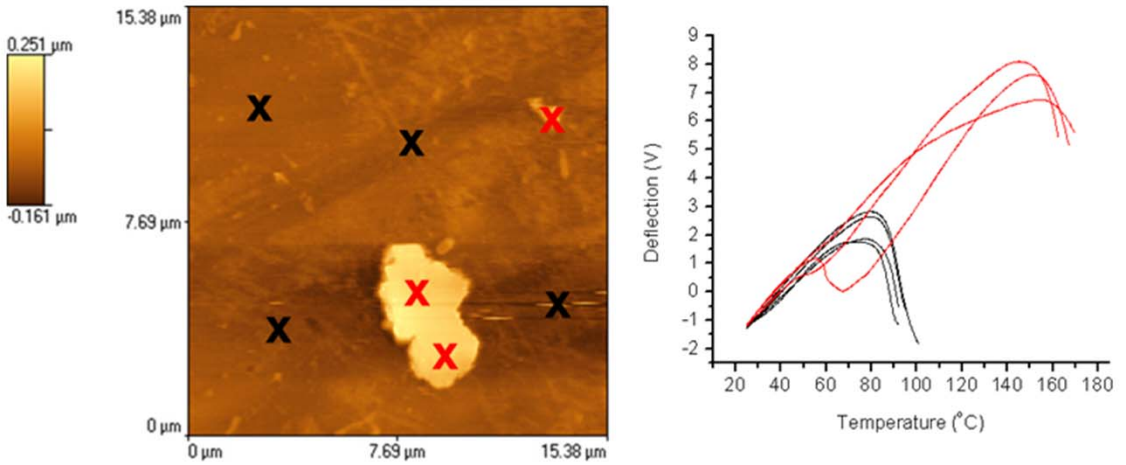
Surface scanned and components identified by their melting or softening point



Cyclosporin dispersions in Eudragit EPO

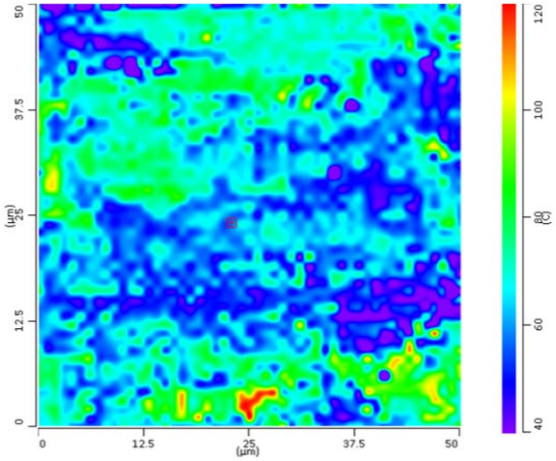


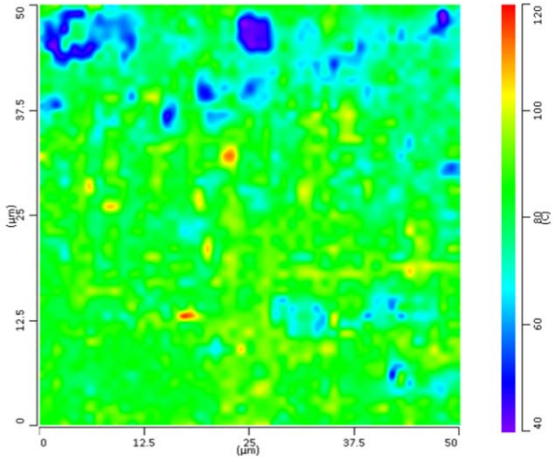
Localized thermal analysis – spin coated samples

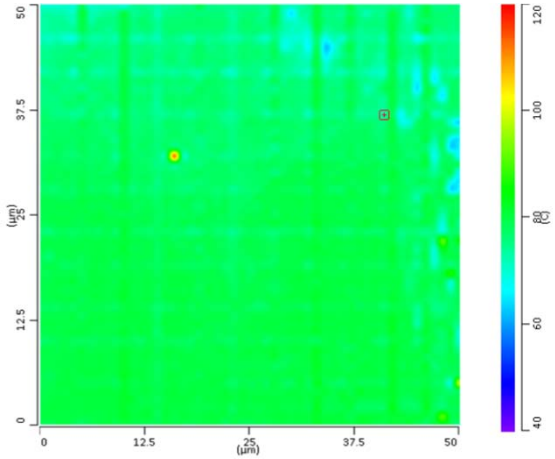


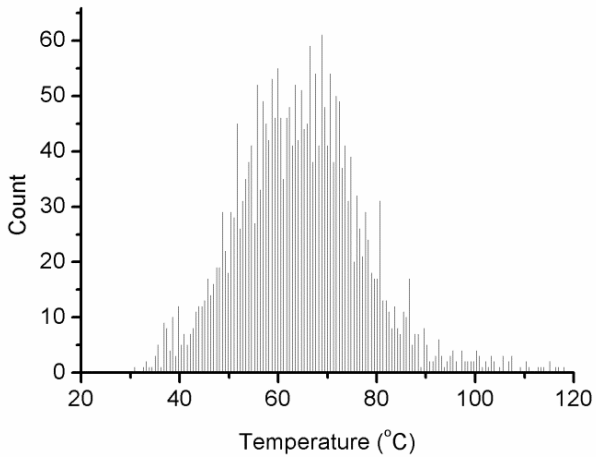
Localized thermal analysis – HME samples prepared at 150°C

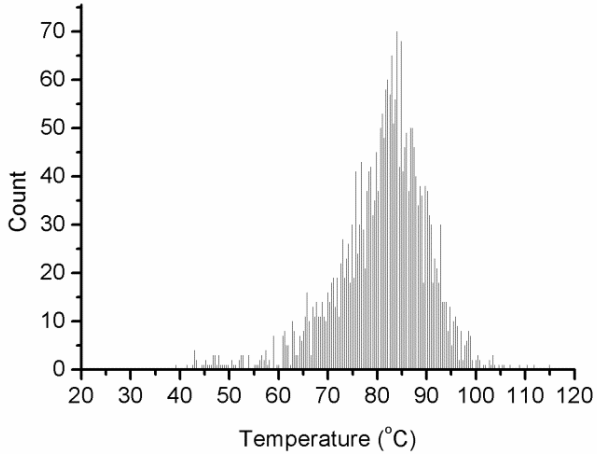
Moffat et al Pharm Res 31 1744 2014

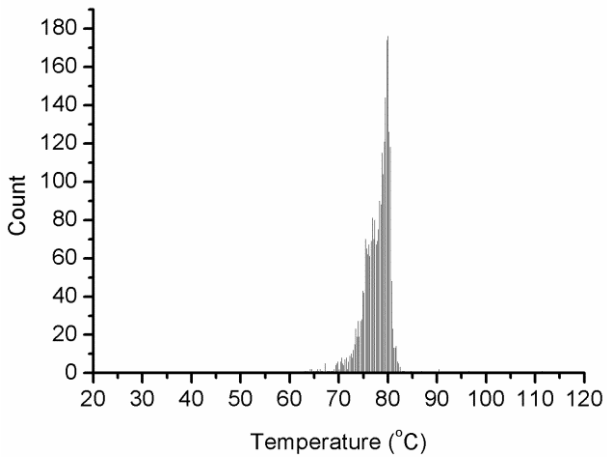










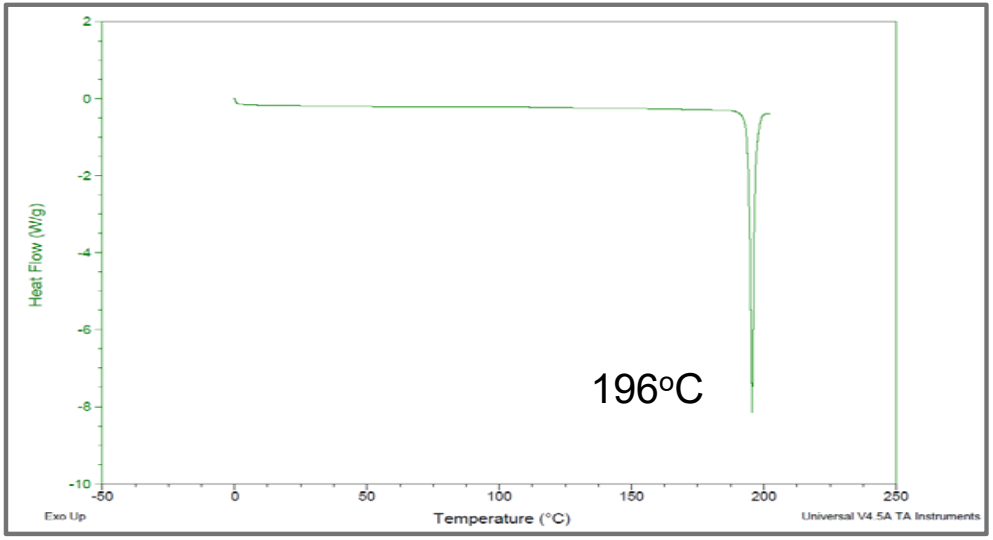


Dispersions prepared at residence time of
5 minutes/110 °C , 5 minutes/150 °C, 15 mins/150 °C

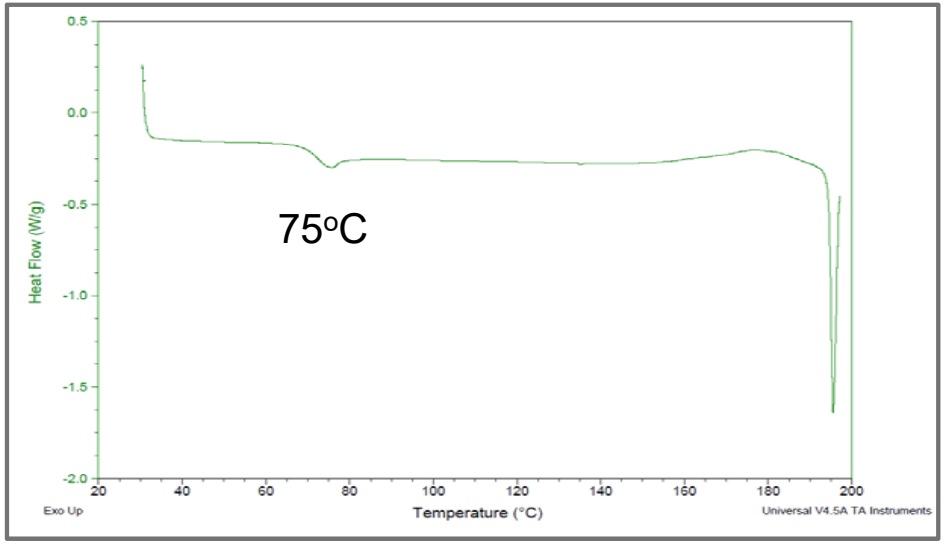
TTM mapping of compression-induced crystallization

More recently we have used the method to understand compression-induced changes in crystallinity

We studied the thermal behaviour of olanzapine in the crystalline and amorphous state



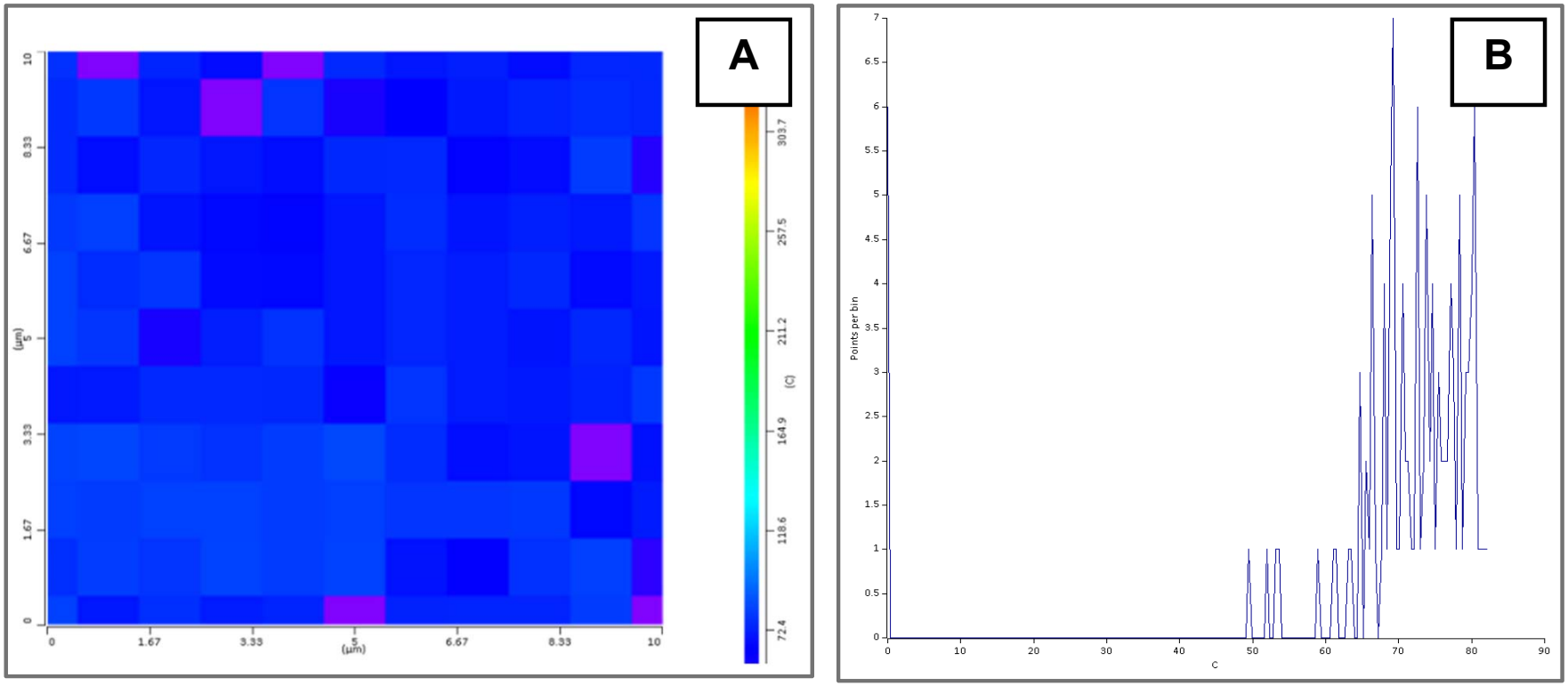
Crystalline olanzapine



Amorphous olanzapine

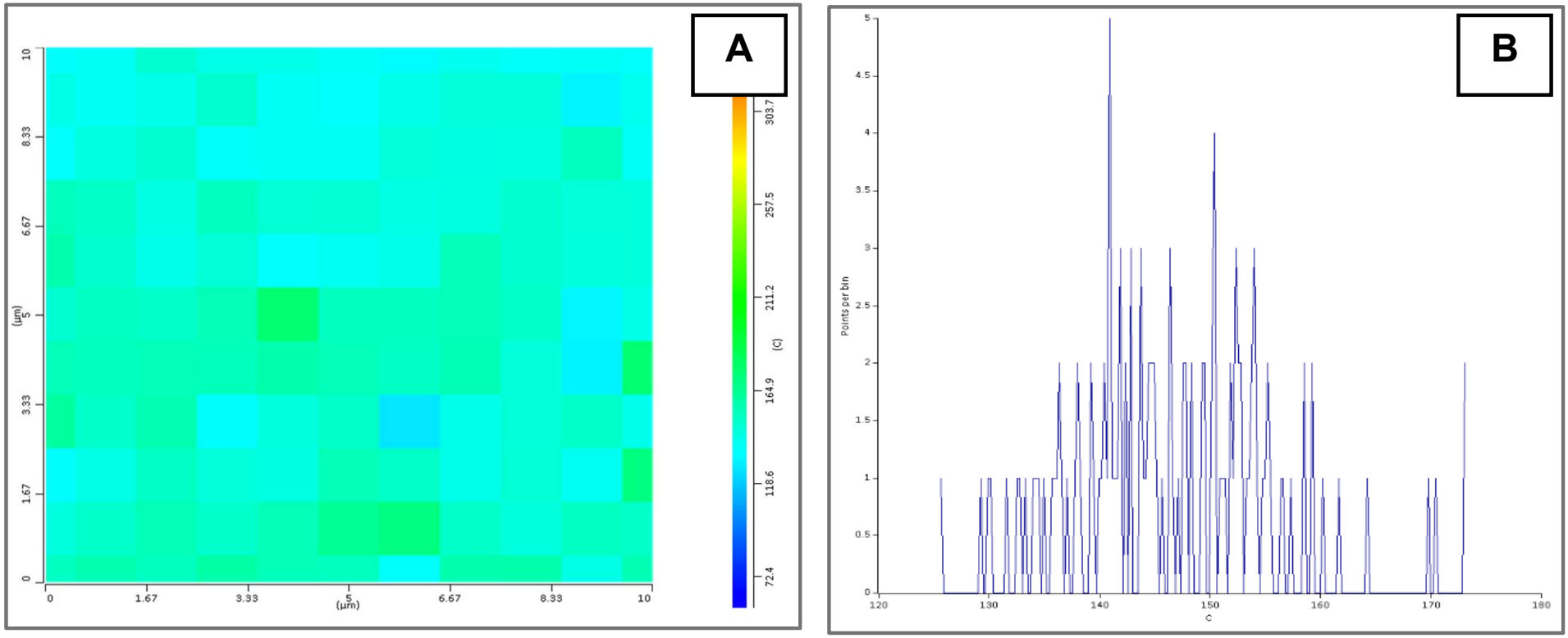
Ahmad Seyar Alkozi, Sean Askin, Susan A.Barker and Duncan Craig unpublished

Amorphous **Casts** of Olanzapine



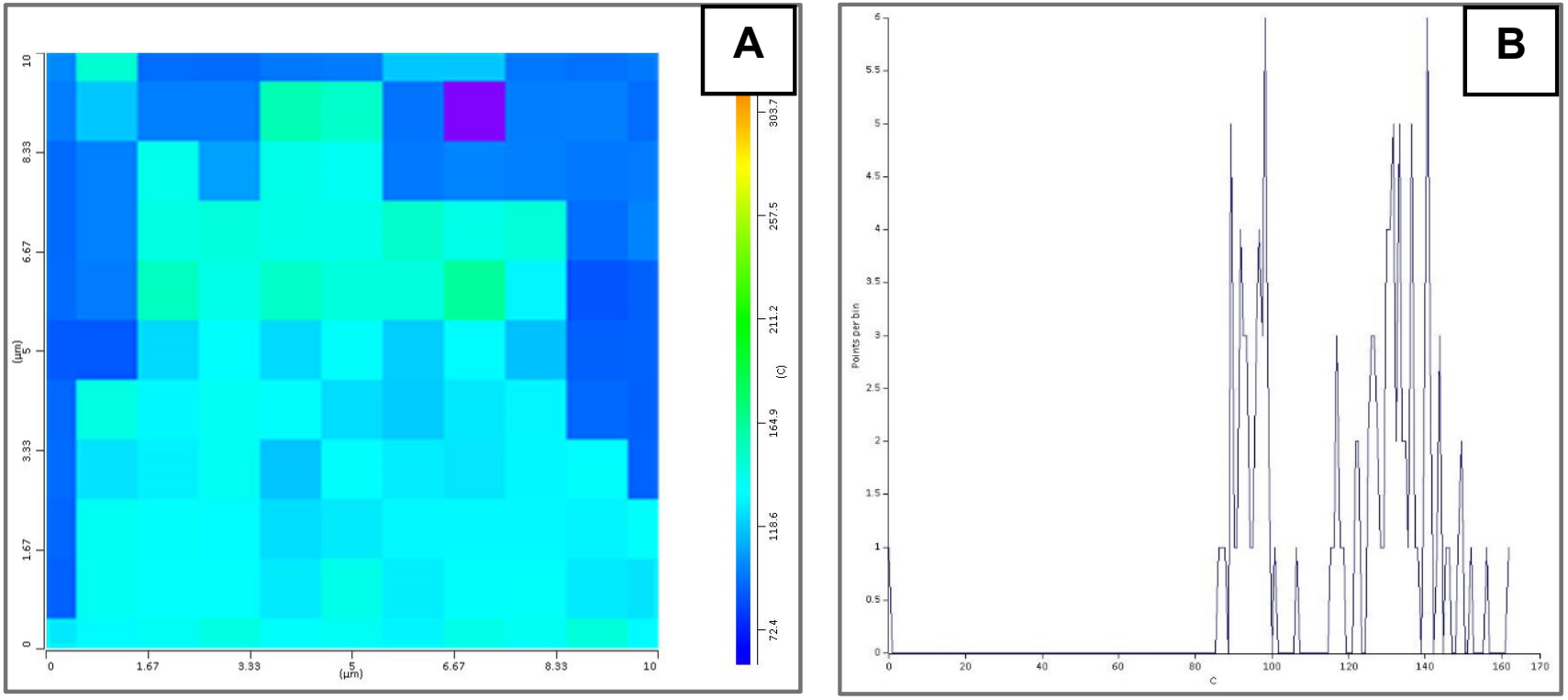
(**a**) TTM image of the amorphous glass showing the area scanned to be fully amorphous. (**b**) Histogram from the corresponding TTM image (left) showing the majority of transition temperatures are between 70-80ºC, across a range between 50-80ºC.

Crystalline **Compacts** of Olanzapine



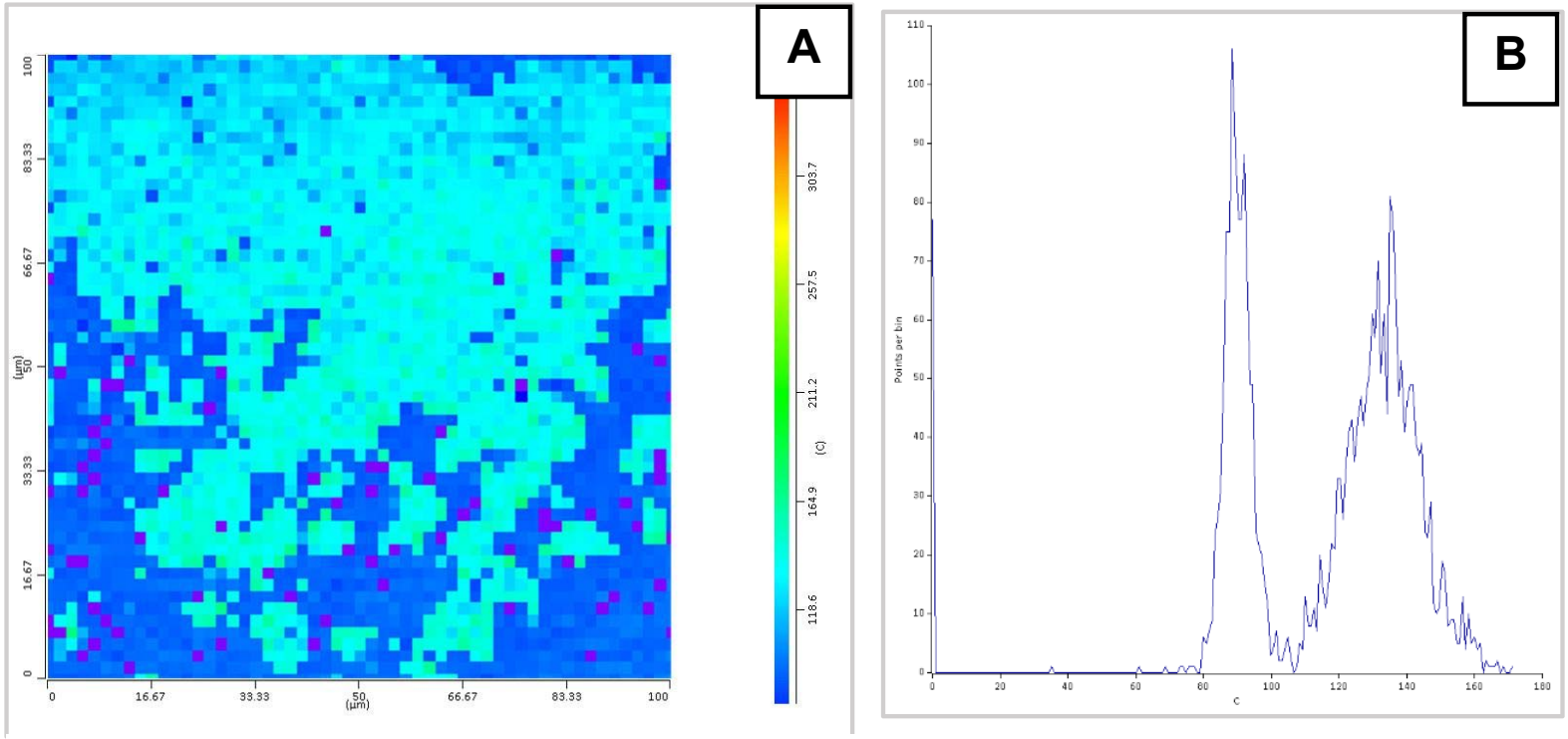
TTM image of the neat crystalline tablet surface showing the area scanned to be fully crystalline. (**b**) Histogram from the corresponding TTM image (left) showing most of transition temperatures are ~140ºC, across a range between 130-170ºC.

1:1 Physical mixes of amorphous and crystalline material (compacts)



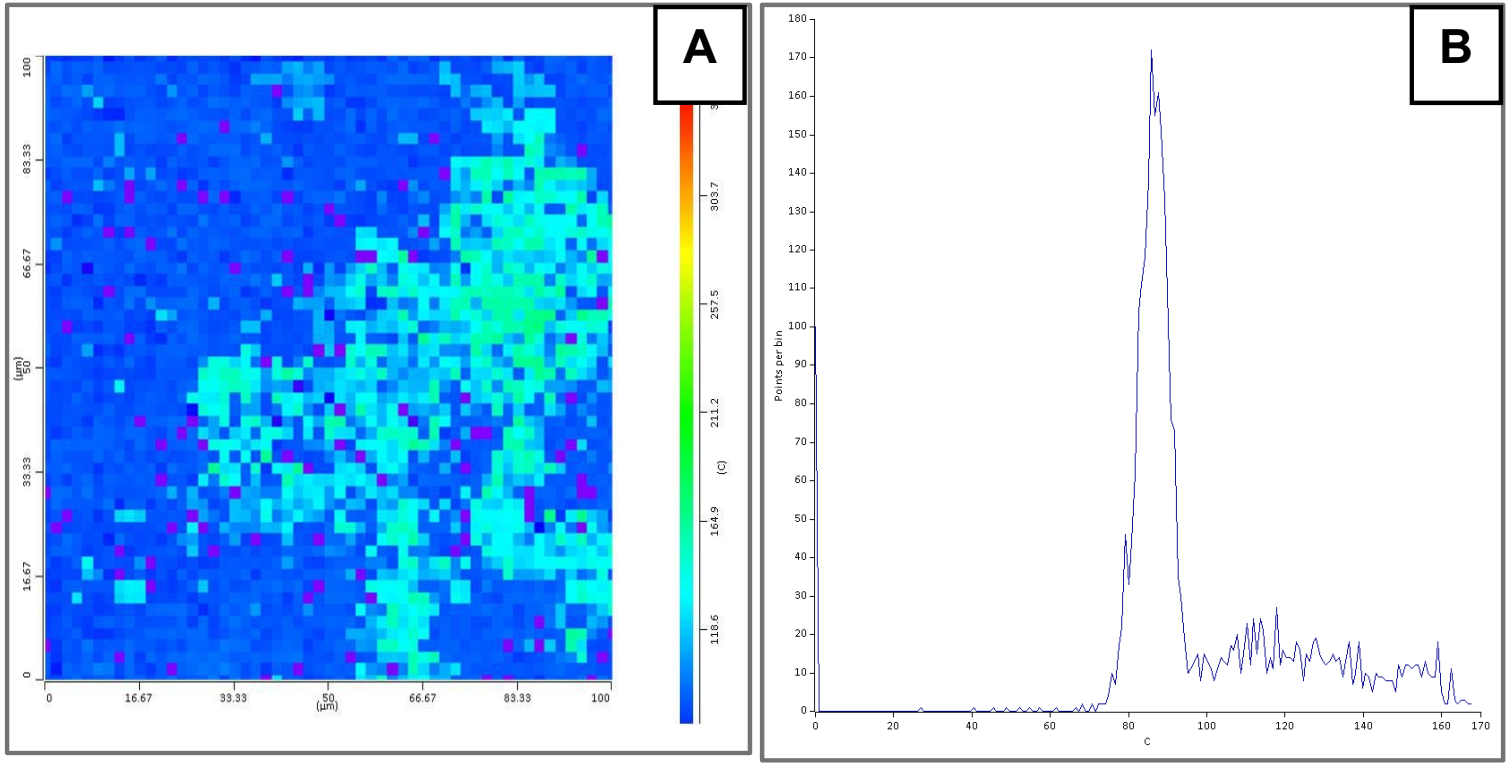
(**a**) TTM image of the amorphous-crystalline 1:1 mix tablet surface showing a crystalline segment (light blue/green) and an area of amorphous material (blue). (**b**) Histogram from the corresponding TTM image (left) shows transition temperatures of the amorphous regions between 80 and 100ºC, and transition temperatures of the crystalline regions are between 100 and 160ºC.

Amorphous compacts exposed to high temperature and RH



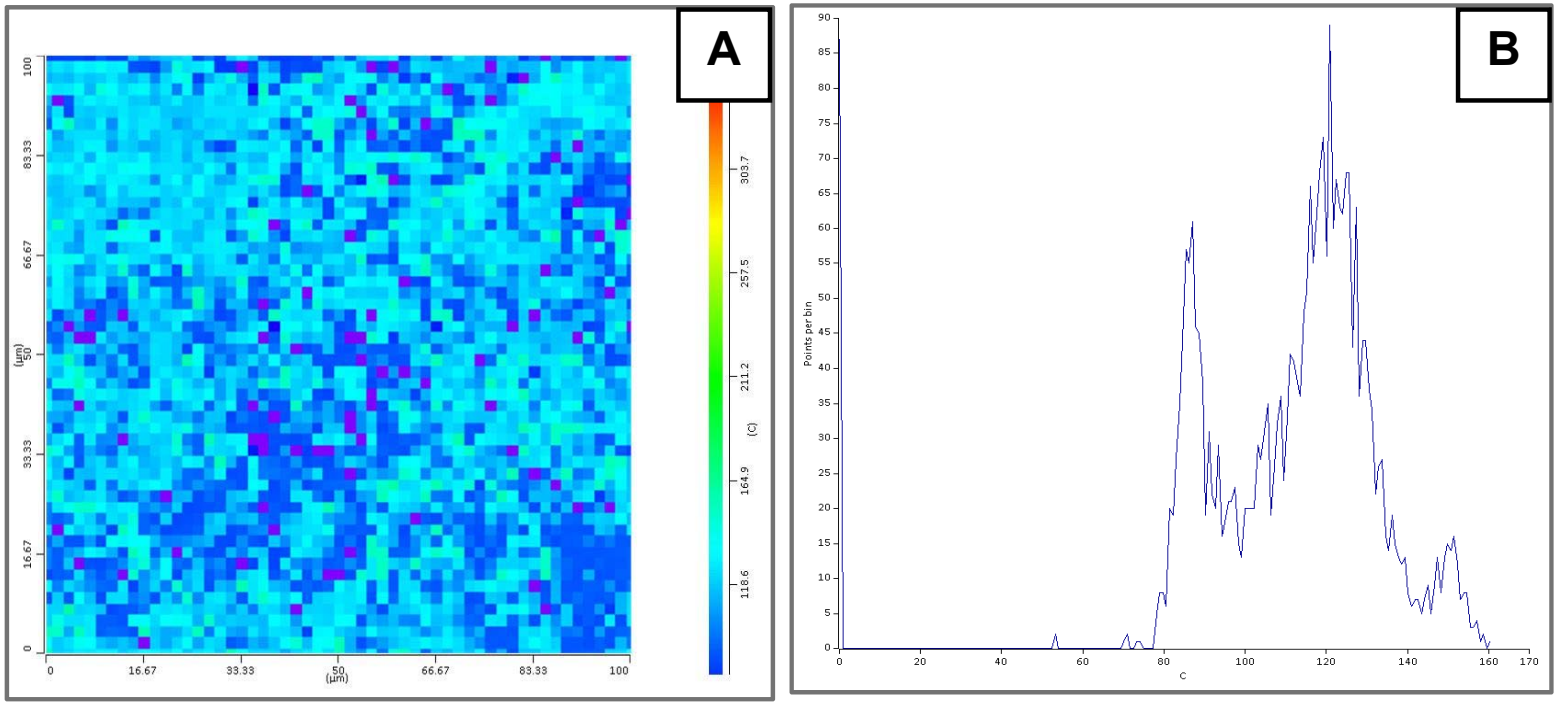
(**a**) TTM image of the amorphous tablet surface, stored at elevated temperature and RH, showing a crystalline region (light blue/green) intermingling with an area of amorphous material (blue). (**b**) Histogram from the corresponding TTM image (left) showing a bimodal distribution of transition temperatures at 90 and 130ºC, representing amorphous and crystalline OLZ regions, respectively.

Amorphous tablets – low compression



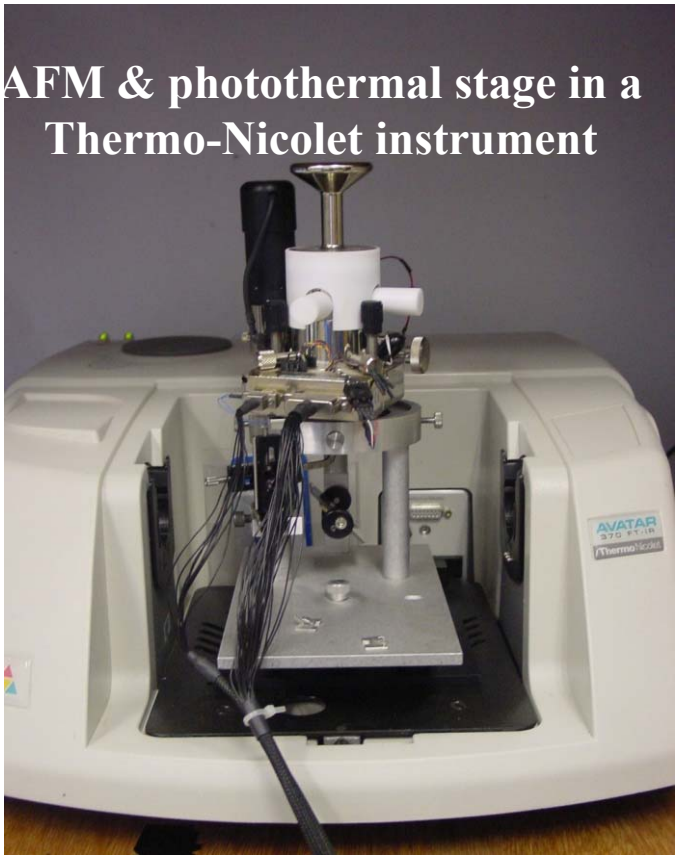
(**a**) TTM image of the fully amorphous tablet, compressed lightly, showing a largely amorphous surface (blue), with a smaller disperse region of crystalline OLZ (light blue/green). (**b**) Histogram from the corresponding TTM image (left) showing a mode of transition temperatures at 90ºC, with some up to 160ºC.

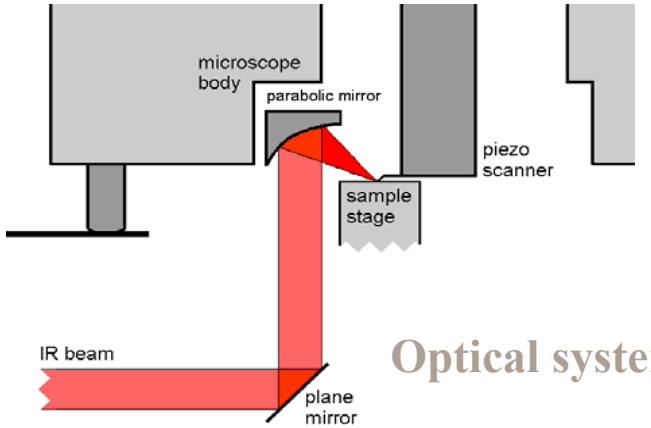
Amorphous tablets – high compression



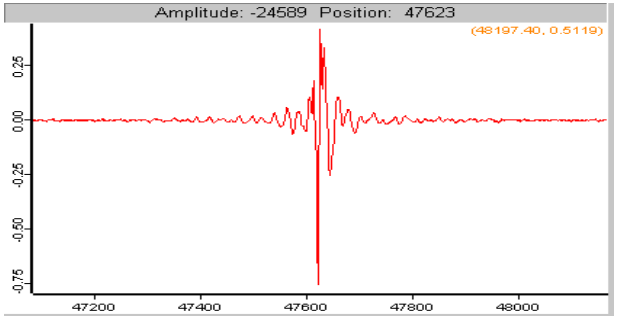
(**a**) TTM image of the fully amorphous tablet surface, compressed at highest pressure, showing a heterogeneous distribution of crystalline (light blue/green) and amorphous (blue) OLZ. (**b**) Histogram from the corresponding TTM image (left) showing the majority of transition temperatures at ~120ºC, with some at ~80ºC.

Photothermal IR for spectroscopic mapping of materials





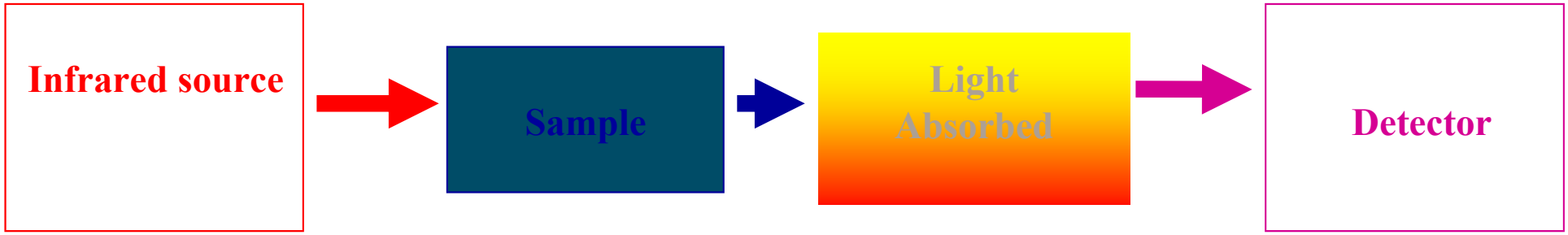
Optical system



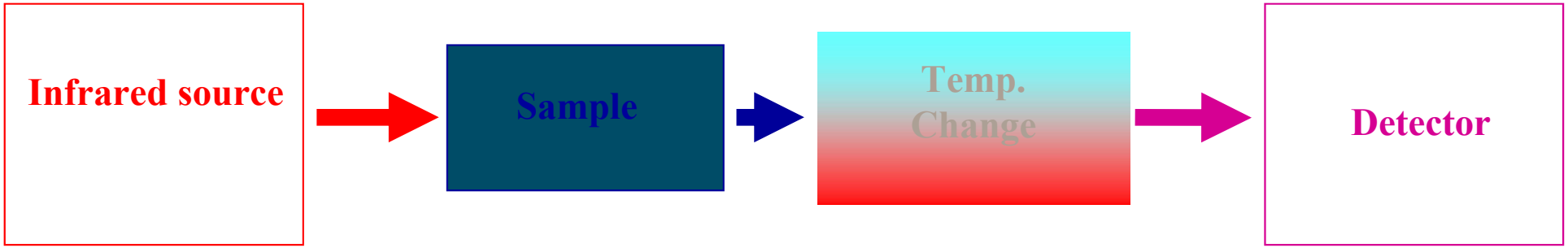
Interferogram

In brief, by focussing an IR beam on the sample or tip we can measure the energy absorption as a function of frequency

- Standard FTIR Spec.



- Photothermal – FTIR Spec.

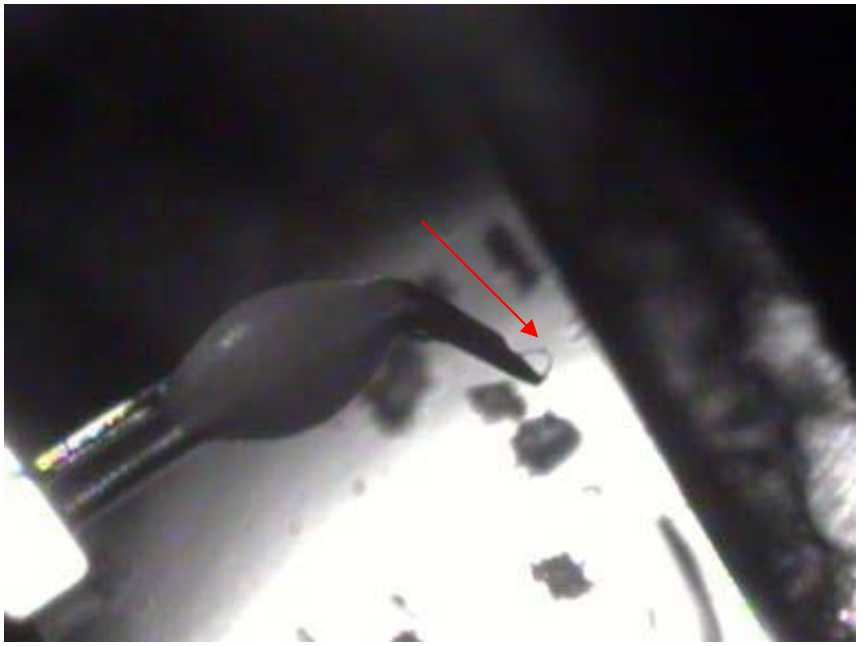


Single particle degradation

We are able to pick up individual particles on the tip and subject them to UV light

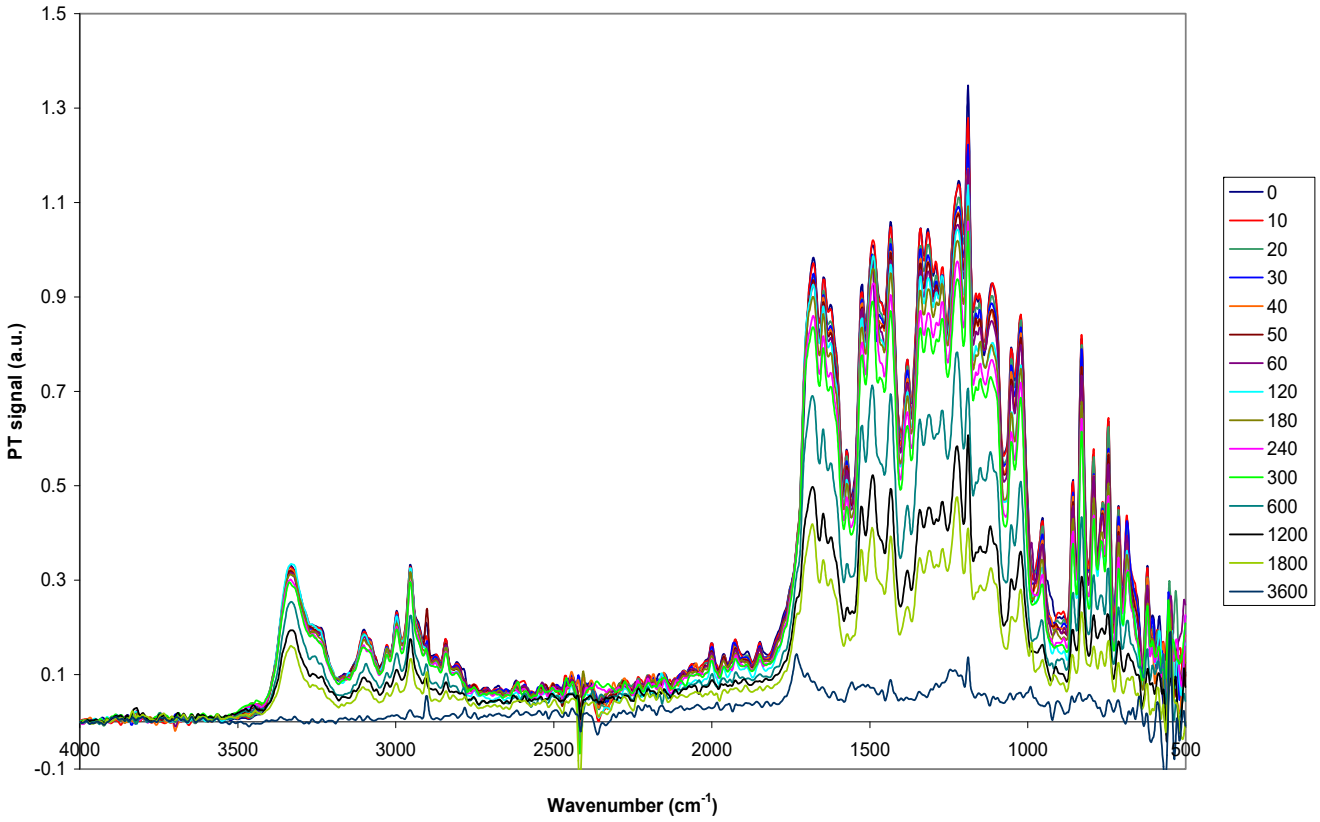
Image shows tip loaded with a 5µm particle of nifedipine

Sample was subjected to UV light for periods up to one hour and then analysed



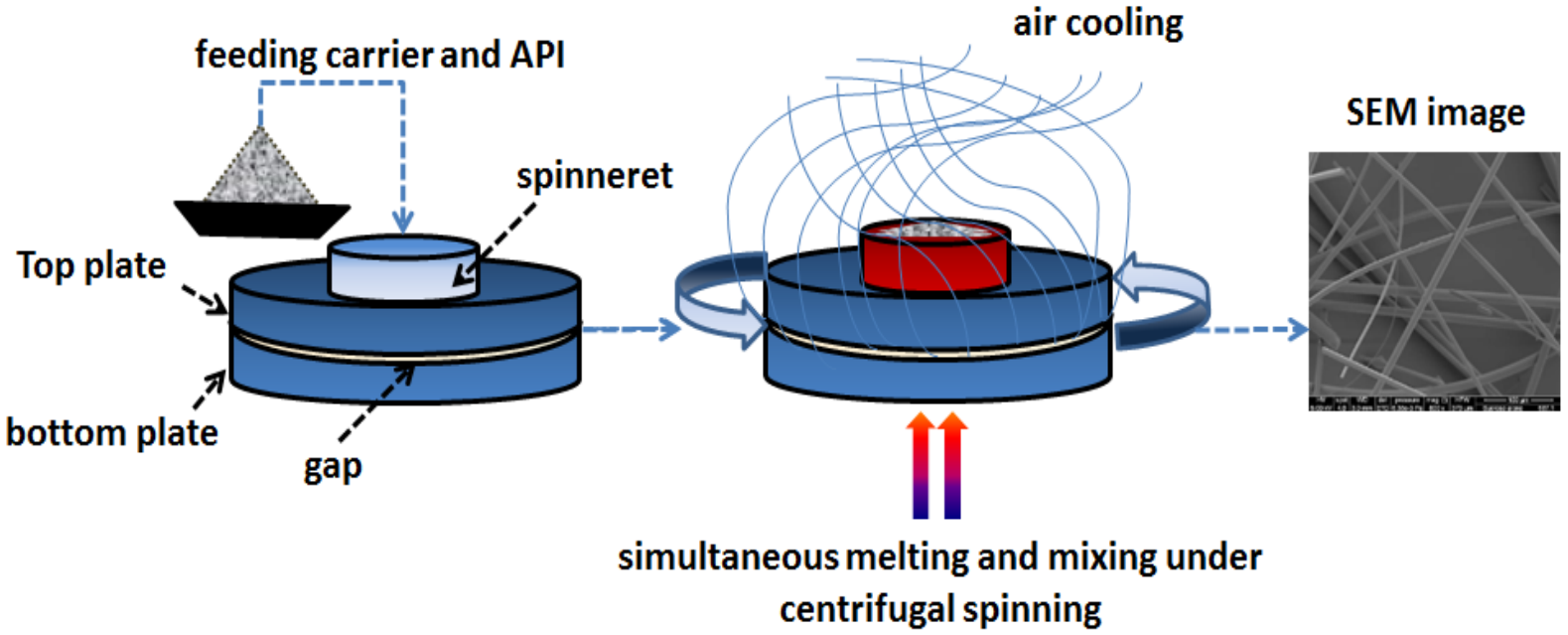
Moffat et al 2013 Analyst. 138, 2315-2322

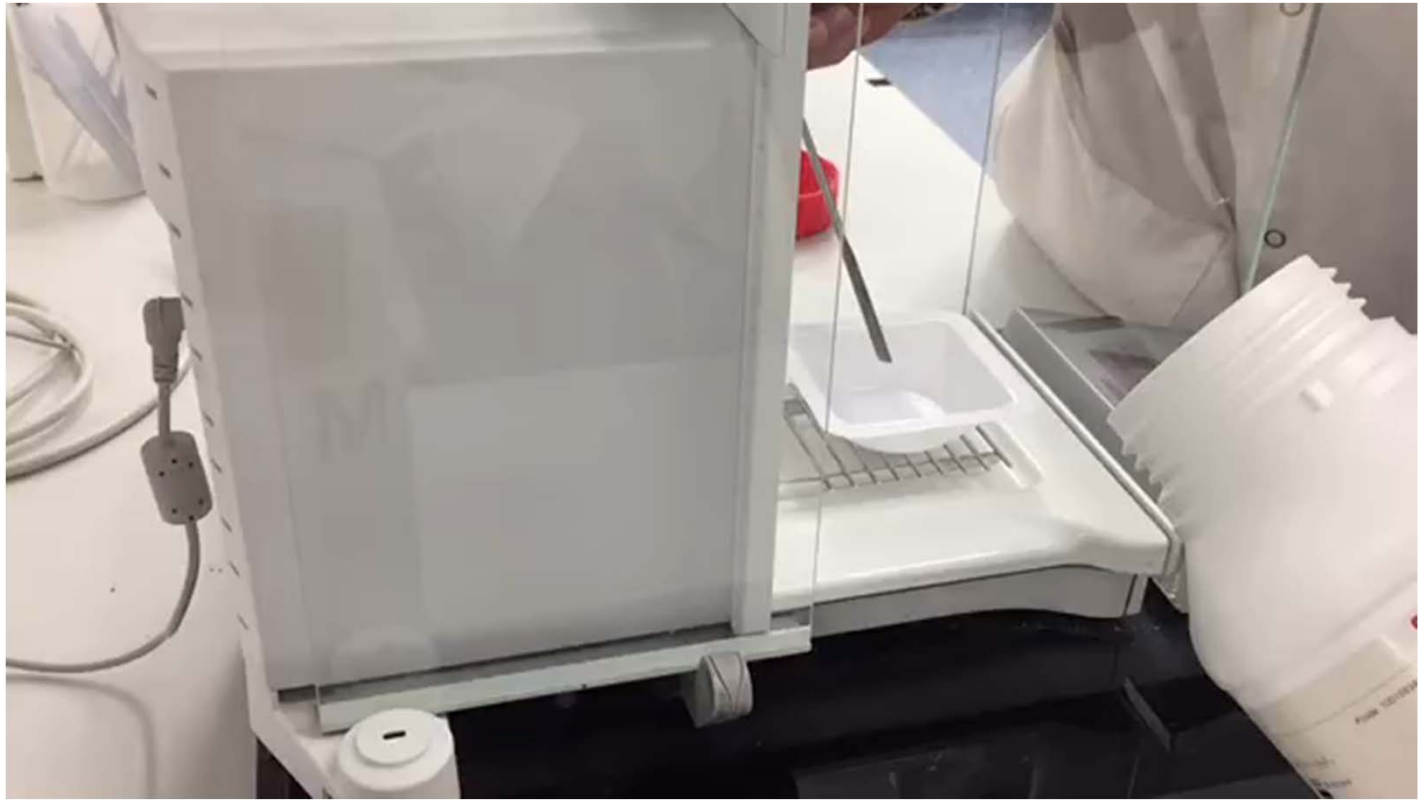
We can then monitor the FTIR spectra as a function of exposure time



Centrifugal spinning

- Alternative method of large scale fiber production which works on the basis of rapidly spinning molten carrier through a narrow gap
- Limited to materials that can withstand heat, but has advantage of no solvent removal
- Work driven by Stefania Marano, sponsored by BBSRC and Colorcon





Our Lab Scale Temperature-Controlled Centrifugal Spinning Device

Cotton candy floss machine

STEP 1: add voltage regulator

STEP 2: spinneret modification

Questions that arise include

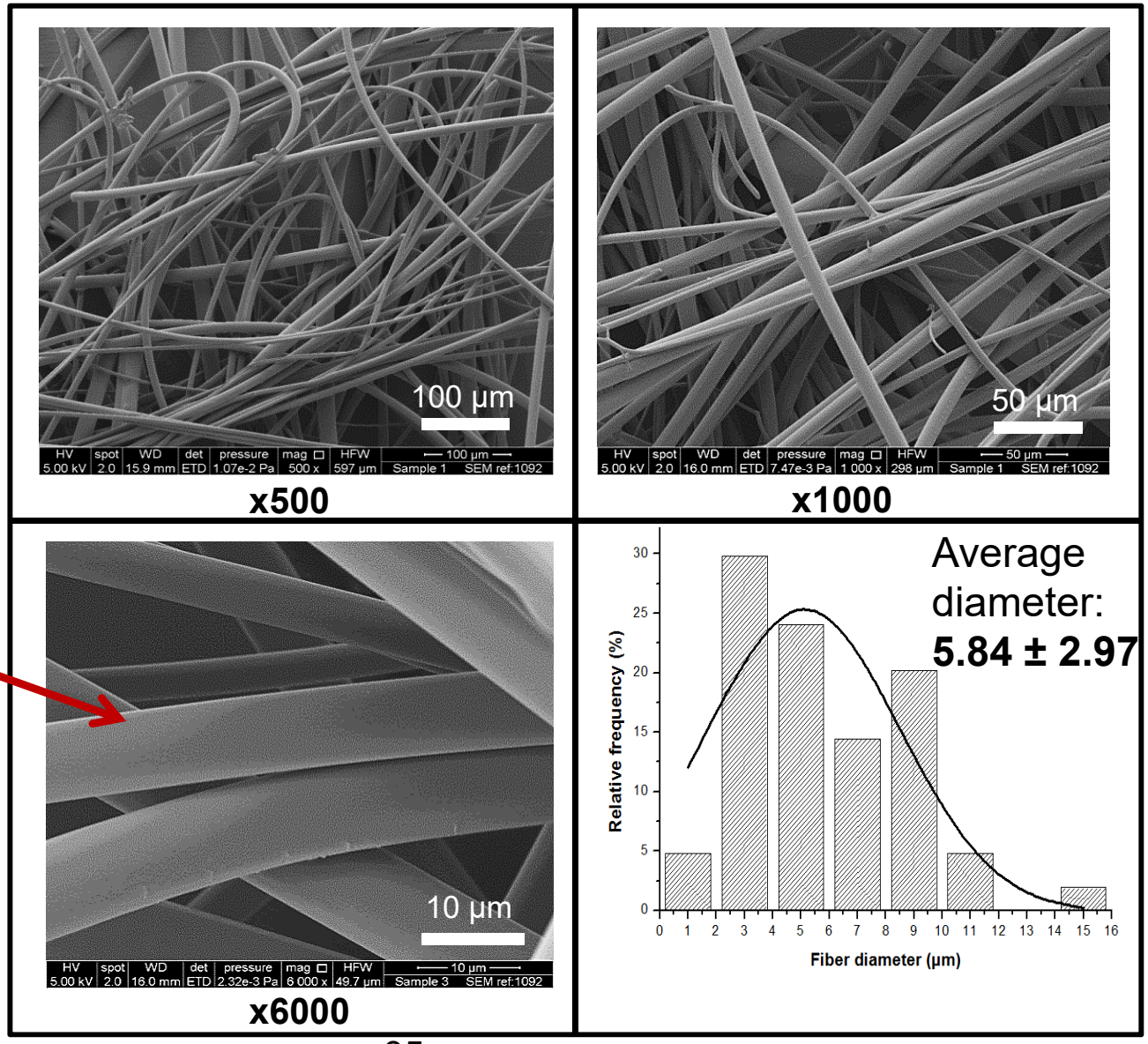
- How stable is an amorphous sucrose formulation?
- How acceptable is sucrose as an excipient especially for children?
- Could enhanced dissolution lead to lower dose requirement?

Stretch objective – development of formulations for children containing itraconazole

In particular, itraconazole given prophylactically to children undergoing chemotherapy due to risk of invasive aspergillosis

Oral solution typically used, although this has associated taste problems and possibly vomiting

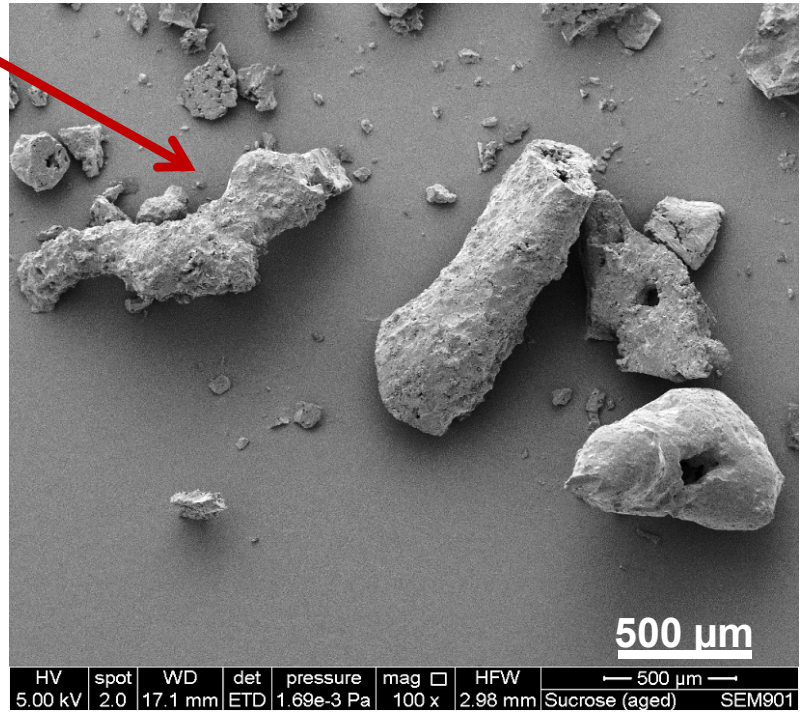
Scanning Electron Microscopy images of 10% itraconazole-loaded sucrose microfibers



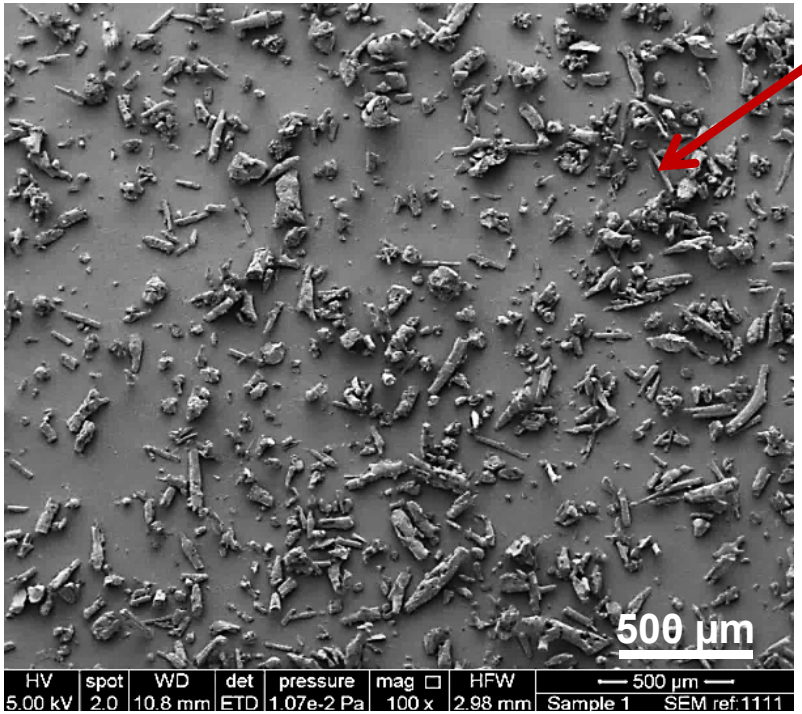
- Homogeneous morphology
- drug loading efficiency **(98 % ± 3)**
- No visible drug crystals

Scanning electron microscopy images of recrystallized sucrose vs recrystallized itraconazole-sucrose microfibers at 75% RH

Recrystallised sucrose fibers

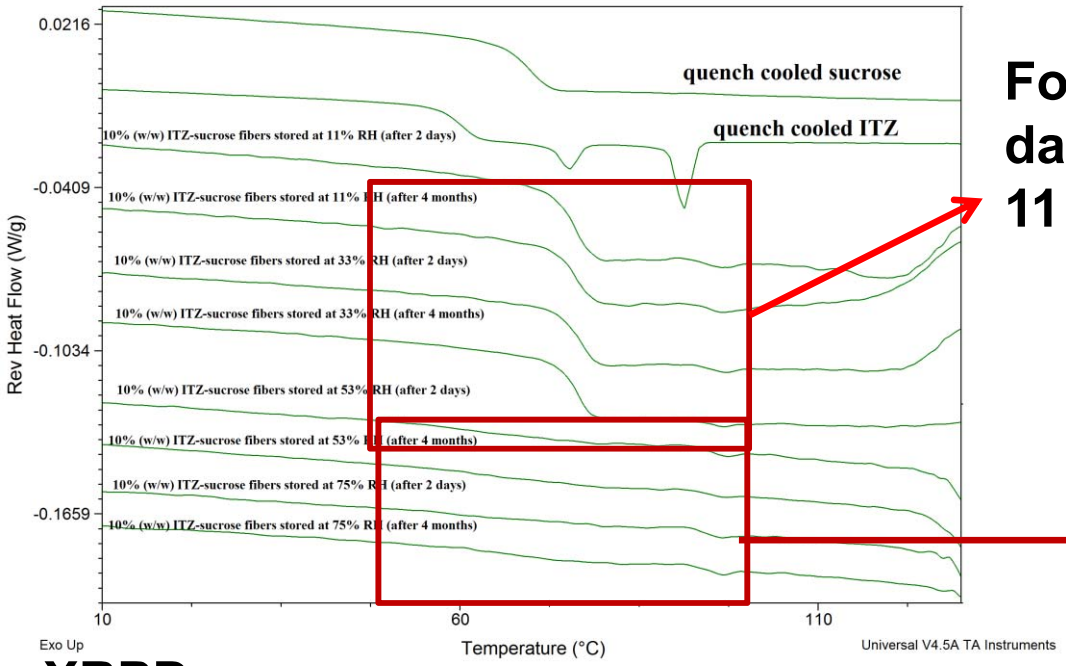


Recrystallised ITZ-sucrose fibers



Solid state characterization using MTDSC and XRPD

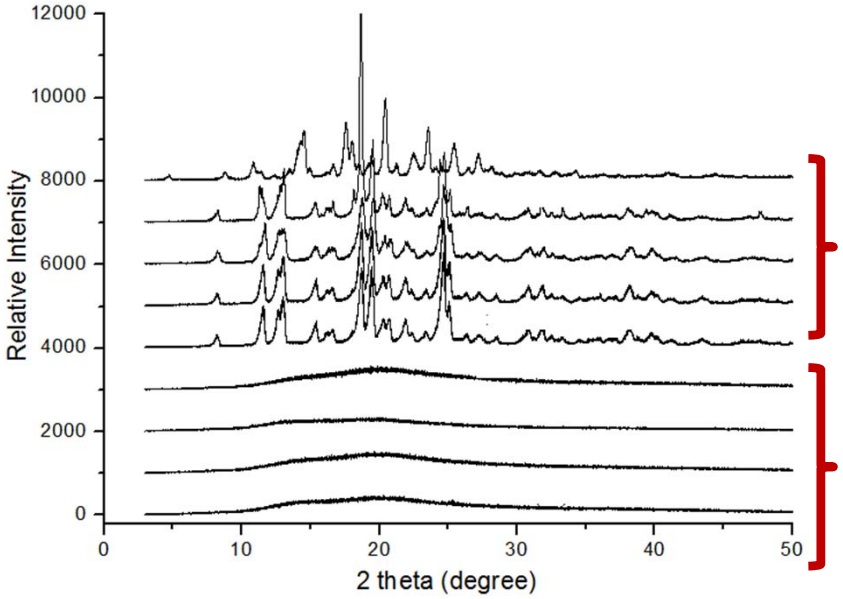
MTDSC



Formulations after 2 days and 4 months at 11 and 33% RH

Formulations after 2 days and 4 months at 53 and 75% RH

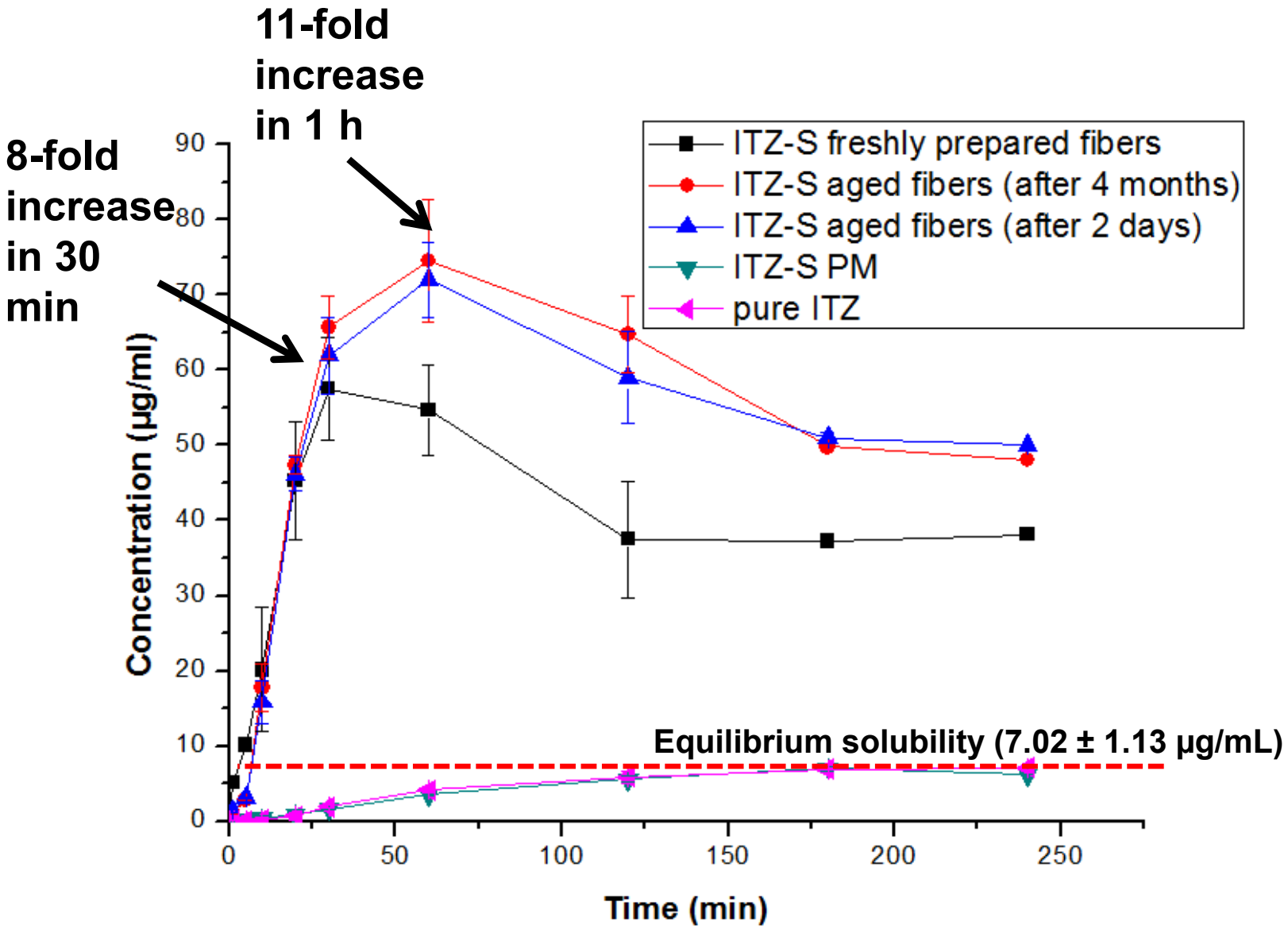
XRPD



Formulations after 2 days and 4 months at 53 and 75% RH

Formulations after 2 days and 4 months at 11 and 33% RH

Dissolution–supersaturation profiles obtained under non-sink conditions



Marano et al, Mol Pharm, just accepted

ACKNOWLEDGEMENTS

EPSRC
Pioneering research and skills

LCN
LONDON CENTRE FOR NANOTECHNOLOGY

Colorcon

BBSRC
20 Years of Pioneering
Great British Bioscience

UCL ENGINEERING

gsk GlaxoSmithKline

AstraZeneca

BASF
We create chemistry

EVONIK
POWER TO CREATE

…….and the people who did all the work