SCIENCE

UNIVERSITY of GREENWICH

What we know and what we would like to know
new developments in characterisation of pharmaceutical materials

Milan D. Antonijević

Overview of presentation

Part 1

- Introduction to Thermally Stimulated Current Spectroscopy (TSC)
- Examples (amorphous, polymorphs, co-crystals)

Part 2

- Thermal Analysis by Structural Characterisation
- Thermal Dissolution Analysis (TDA)
- Conclusions

Acknowledgments

PhD students:

Samuel Owusu-Ware

Anthony Cherry

Colleagues:

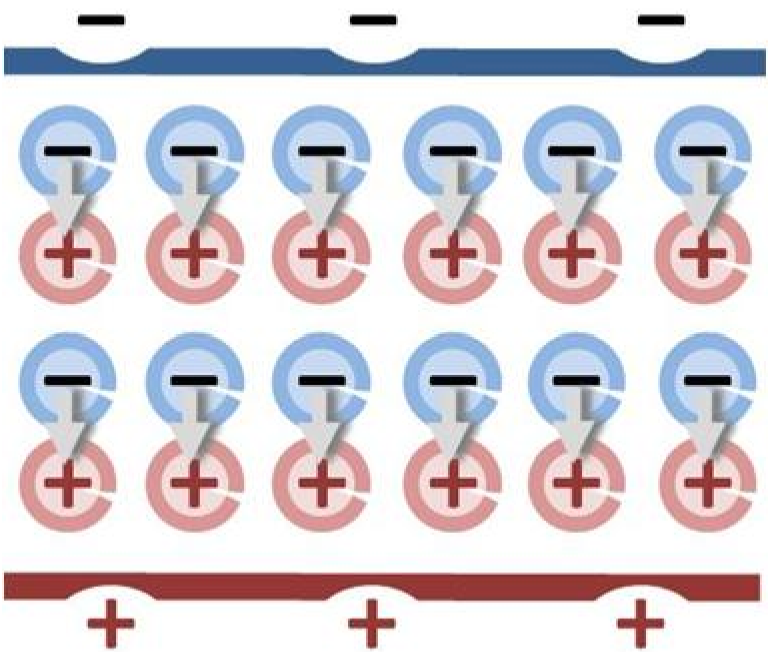
Mike Reading, Cyversa
Michael Morton, Cyversa
Andrew Lacey, Heriot-Watt University
Dave Grandy and Douglas Hourston, Loughborough University

Potential drugs

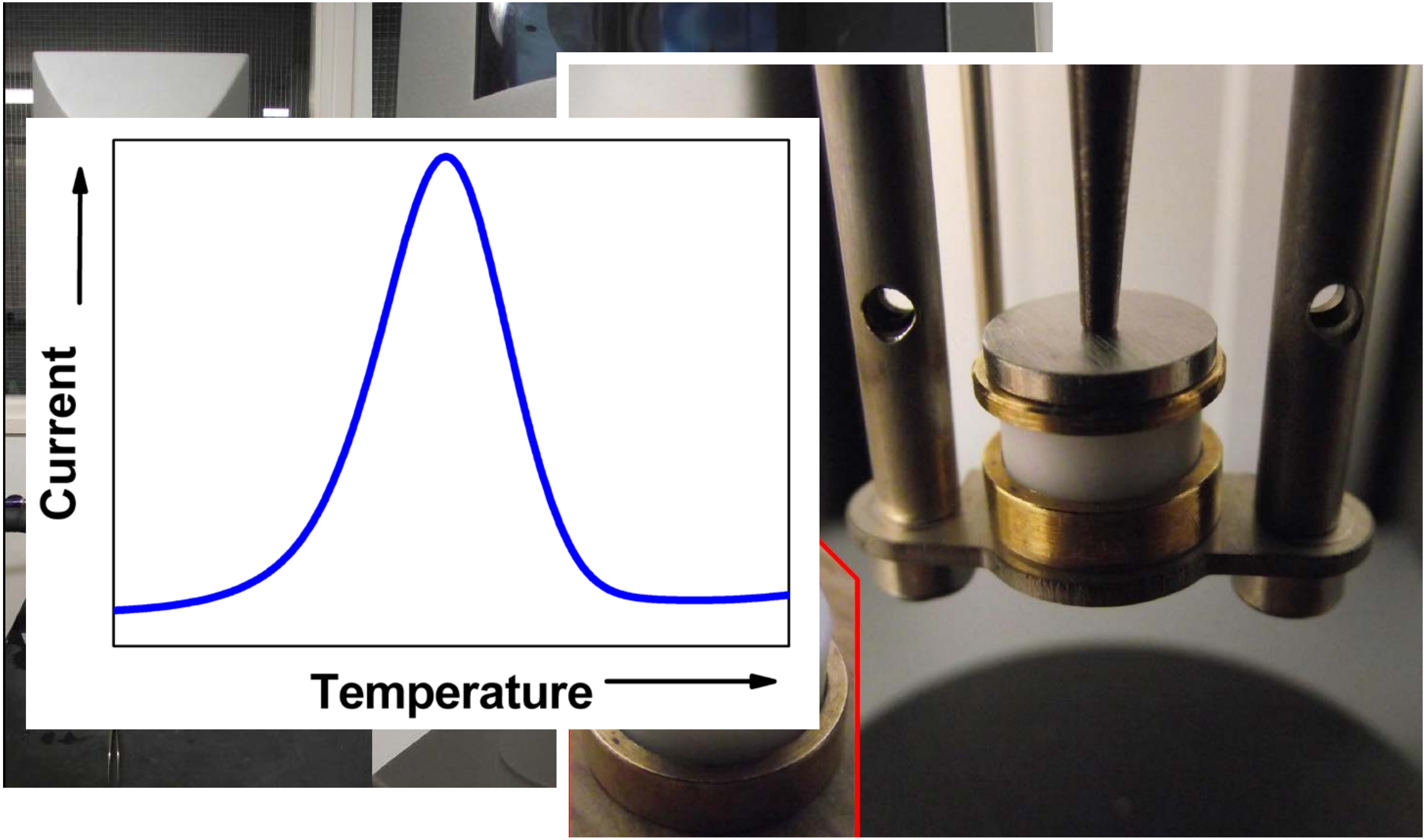
TSC is a general term applied to the measurement of current generated by temperature-activated relaxation of molecular dipoles in response to the application of a static electric field

- 1936, Frei and Grotzinger

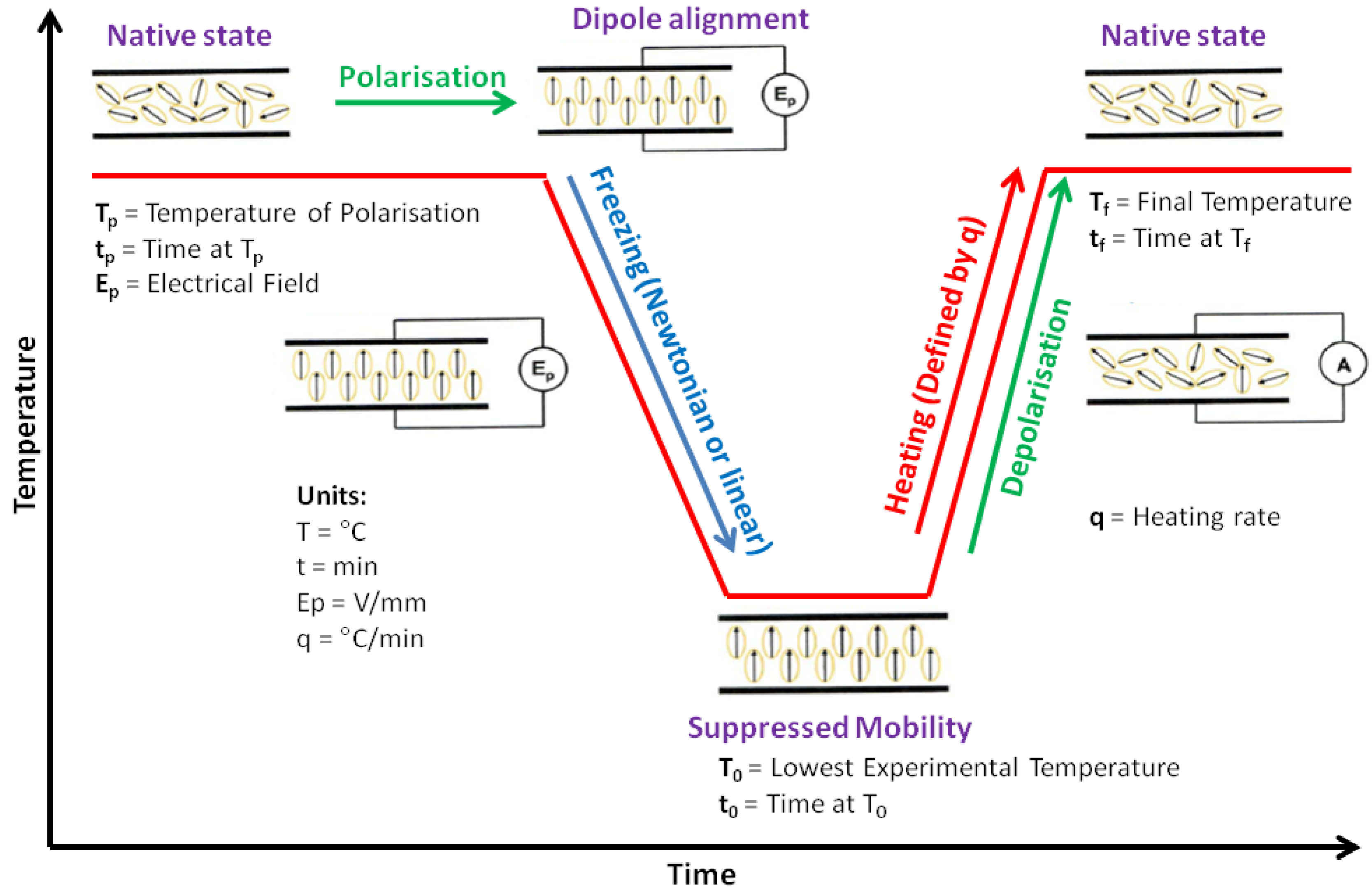
- electrets, ionic crystals
- waxes, resins
- ceramics, plastic
- small organic molecules



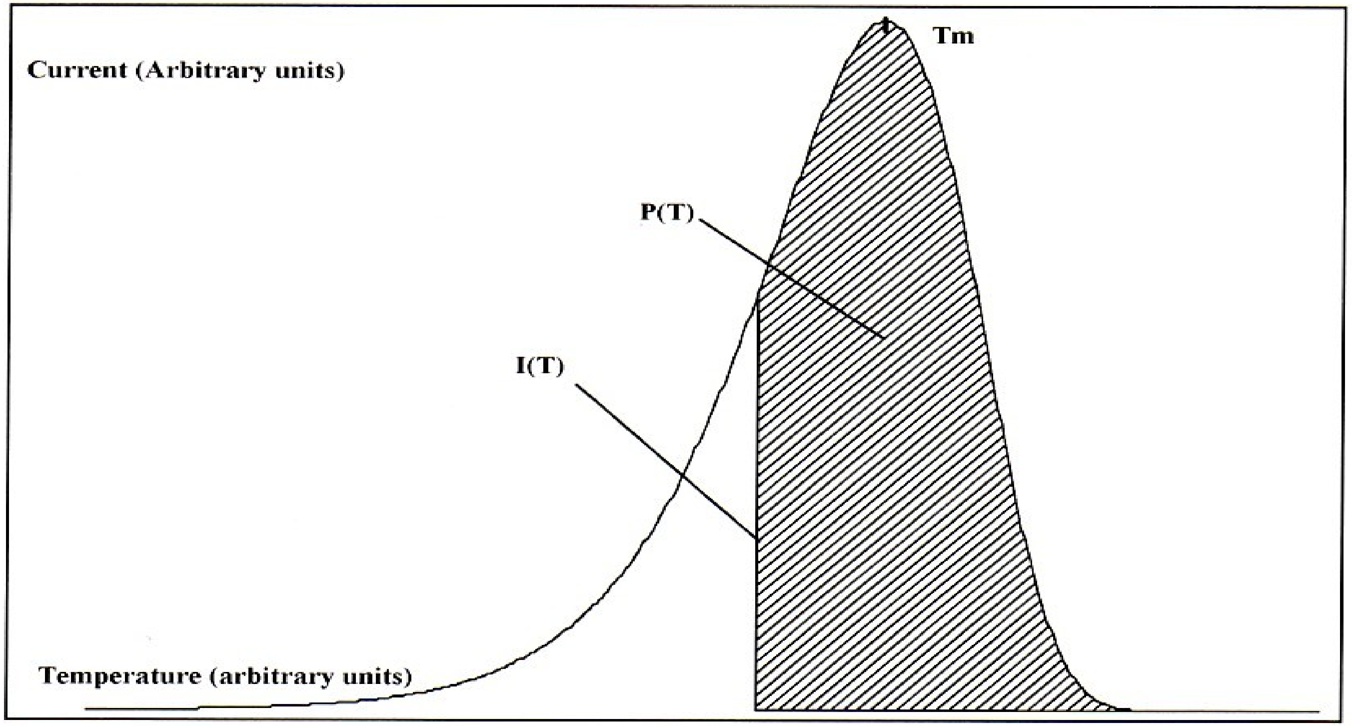
Introduction to TSC



Introduction to TSC



TSC Theory



$$J(T) = \frac{P(T_P)}{\tau_0} \exp(-\frac{E}{kT}) \exp\left[-\frac{1}{q\tau_0} \int_{T_0}^{T} \exp(-\frac{E}{kT'}) dT' \right]$$

$$\tau(T) = P(T) / J(T)$$

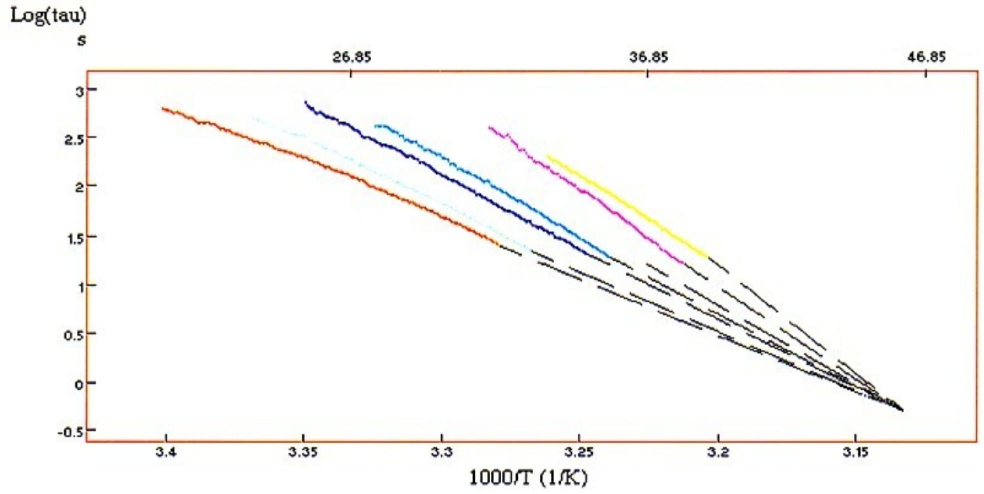
$$\tau(T) = P(T)/J(T)$$

Arrhenius equation

$$\tau_i(T) = \tau_{oi}\exp\left(\frac{E_{a\,i}}{kT}\right)$$

Eyring equation

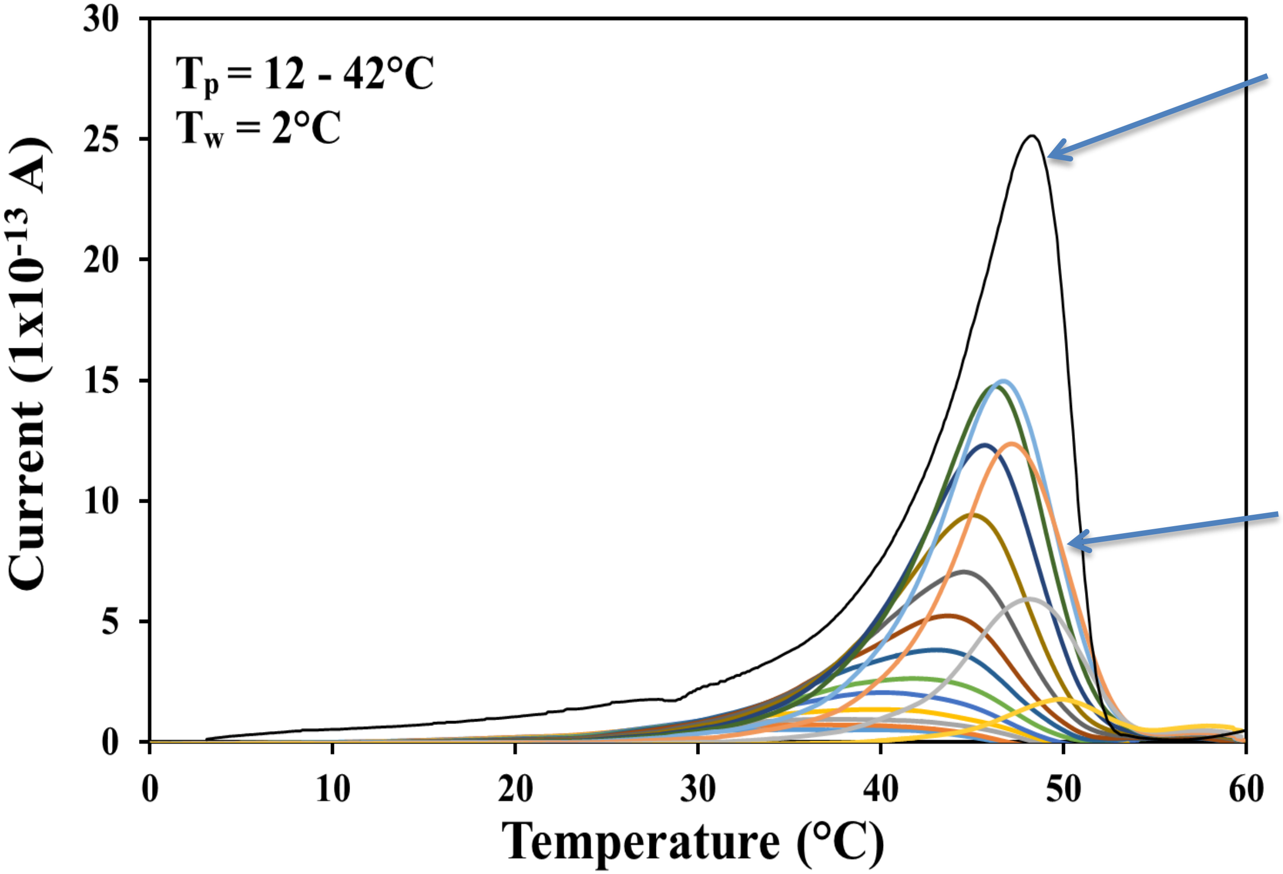
$$\tau_i(T) = \frac{h}{kT}\exp\left(\frac{\Delta G_i}{kT}\right) = \frac{h}{kT}\exp\left(-\frac{\Delta S_i}{k}\right)\exp\left(\frac{\Delta H_i}{kT}\right)$$



Pharmaceutical Applications

- **Amorphous materials**
- Polymorphs
- Batch-to-batch control
- Co-crystals

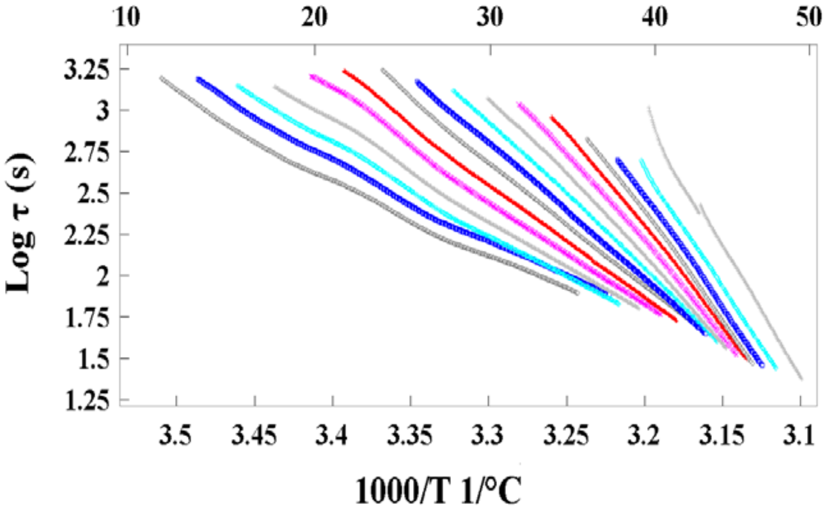
TW outputs



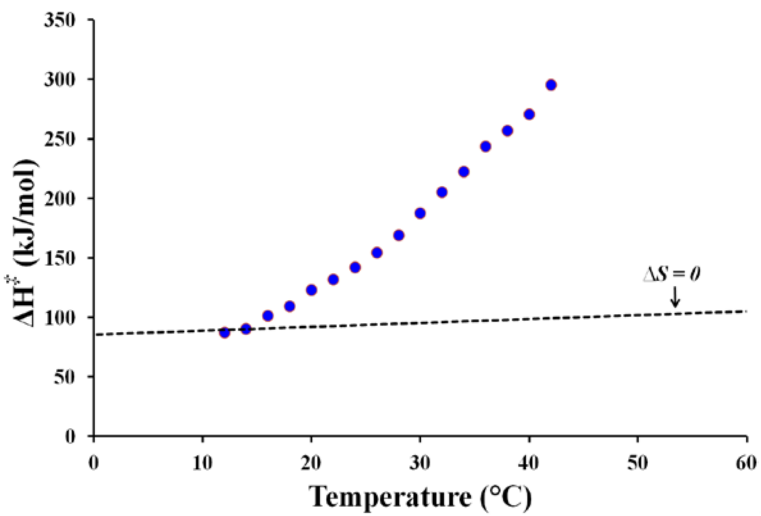
Global glass relaxation process

Different relaxation modes contributing to overall process

Defining E_a - (TW)



Tp(°C)	Tmax(°C)	Ea (kJ/mol)	ΔH‡ (kJ/mol)
12	35	90	87
14	37	93	90
16	38	104	101
18	39	112	109
20	41	126	123
22	42	135	132
24	43	145	142
26	43	157	154
28	44	171	169
30	45	190	188
32	45	208	205
34	46	225	222
36	46	246	244
38	47	259	257
40	48	273	270
42	50	298	295



$$Fragility\ Index\ (m) = \frac{1}{2.303}\left[1\,\frac{E_a\,(Tg)}{RT_g}\right]$$

Fragility - Indometacin

	Integration window (K)	T_{max} (K)	E_a (kJmol^{-1})	m
TSDC (T_p = 303 K)	20	314.4 (0.1)	138.8 (1.0)	23.1 (1.0)
	10	314.4 (0.1)	178.3 (1.8)	29.6 (1.9)
	5	314.4 (0.1)	232.3 (1.0)	38.6 (1.0)
TSDC (T_p = 313 K)	20	314.3 (0.1)	139.8 (1.5)	23.2 (1.5)
	10	314.3 (0.1)	180.2 (1.2)	30.0 (1.2)
	5	314.3 (0.1)	244.4 (2.3)	40.6 (2.3)
TSDC (T_p = 323 K)	20	314.5 (0.1)	141.2 (1.5)	23.4 (1.5)
	10	314.5 (0.1)	183.6 (2.5)	30.5 (2.0)
	5	314.5 (0.1)	251.5 (1.4)	41.8 (1.4)

$$m = \frac{1}{2.303}\left[\frac{E_a(T_g)}{RT_g}\right]$$

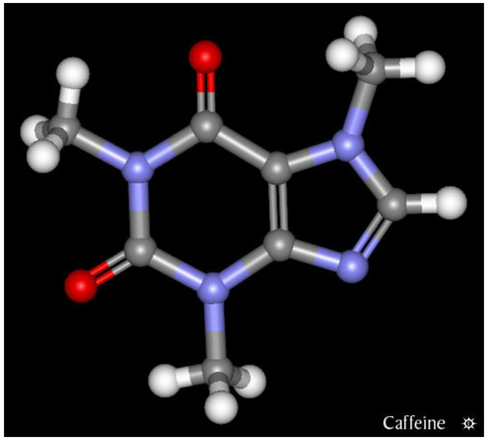
Integration window 2 K

	T_m (K)	E_a (kJmol^{-1})	τ (s)	m
TSDC (T_p = 303 K)	314.4 (0.1)	376.0 (3.3)	59.3 (9.0)	62.4 (3.3)
TSDC (T_p = 313 K)	314.3 (0.1)	388.3 (4.0)	54.8 (8.0)	64.5 (4.0)
TSDC (T_p = 323 K)	314.5 (0.1)	385.8 (3.2)	51.4 (7.4)	64.1 (3.2)

Pharmaceutical Applications

- Amorphous materials
- **Polymorphs**
- Batch-to-batch control
- Co-crystals

Caffeine



Exists in two polymorphic forms:

Form I, unstable at room T, Trigonal

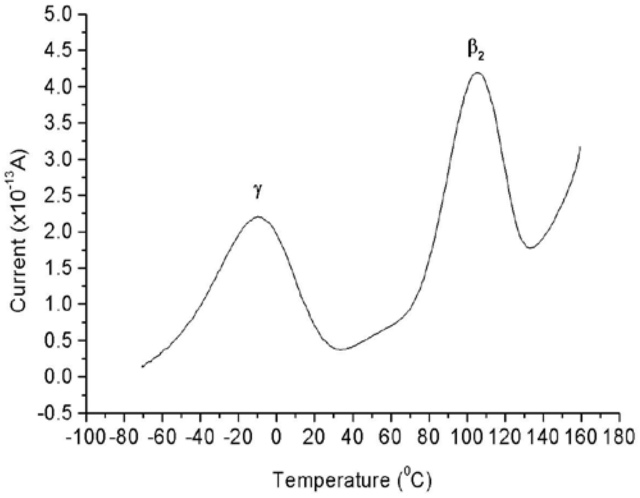
Form II, stable at room T, Monoclinic

Transition point: 141 ± 2°C

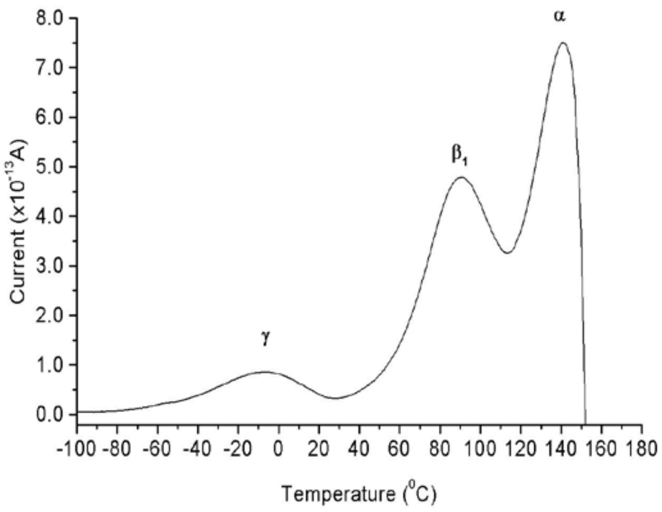
Melting Point: 236 - 243°C (British Pharmacopoeia)

Caffeine - TSDC Results

Form I

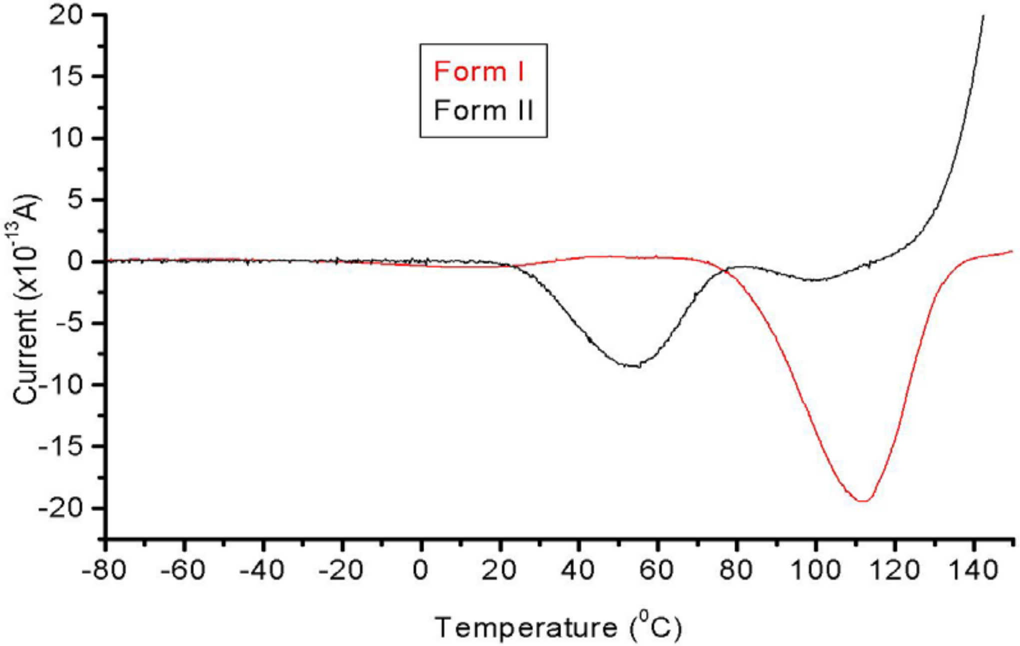


Form II



α-process 139ºC Form II only - *polymorphic transition*
γ-process -8ºC Forms I and II - *orientation of side group*
β_1-process 91ºC Form II
β_2-process 107ºC Form I - *orientation/mobility of sub-unit*

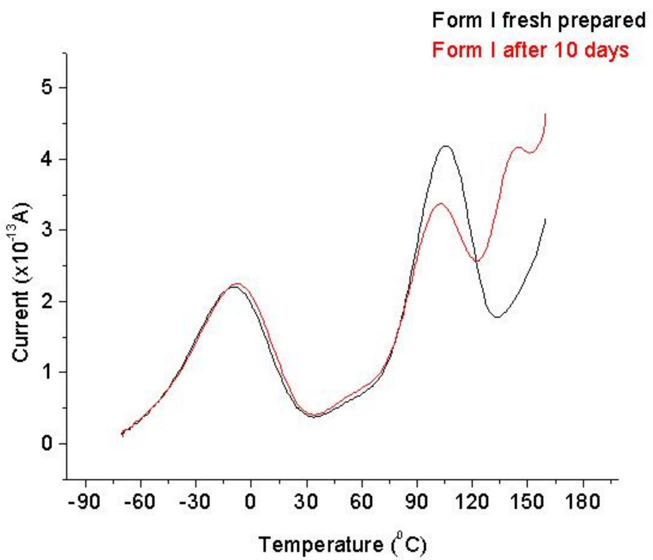
Caffeine - SDC Results



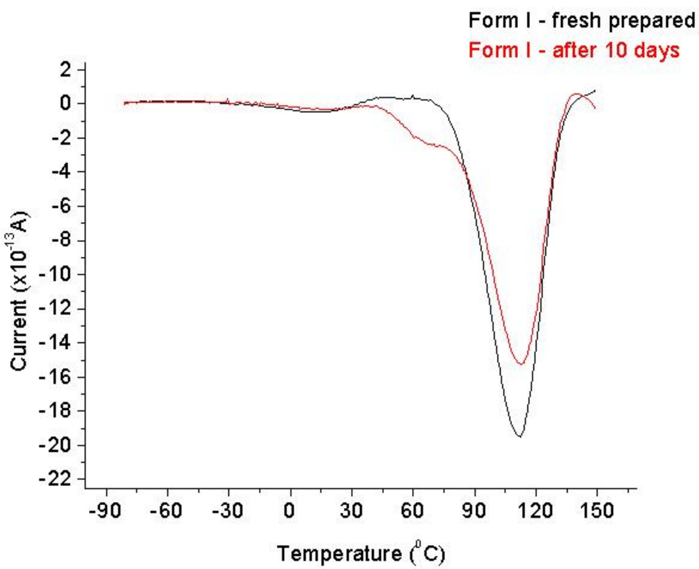
Form I - negative peak at -8°C and 112°C
Form II - negative peak at 52°C

Kinetic Parameters - TSC Method

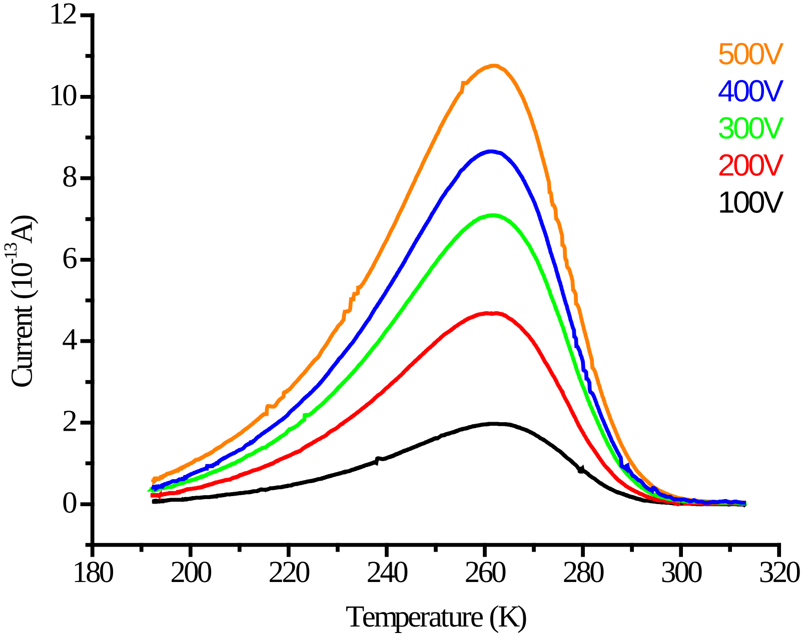
TSDC

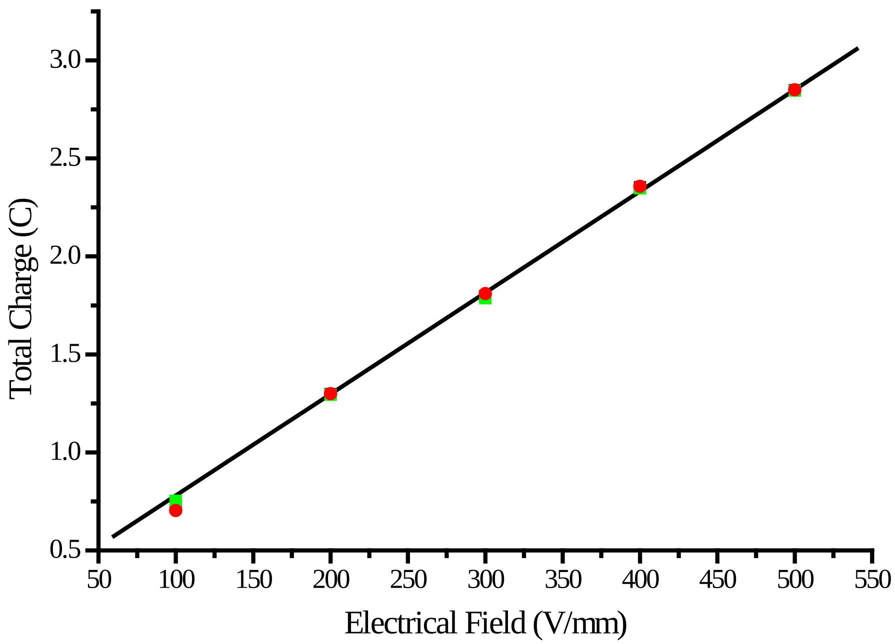


SDC



Sensitivity





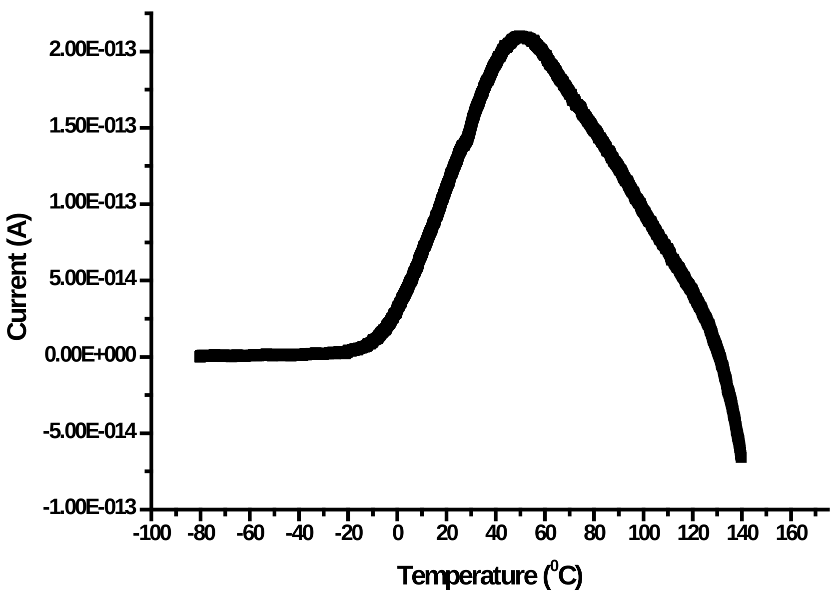
Pharmaceutical Applications

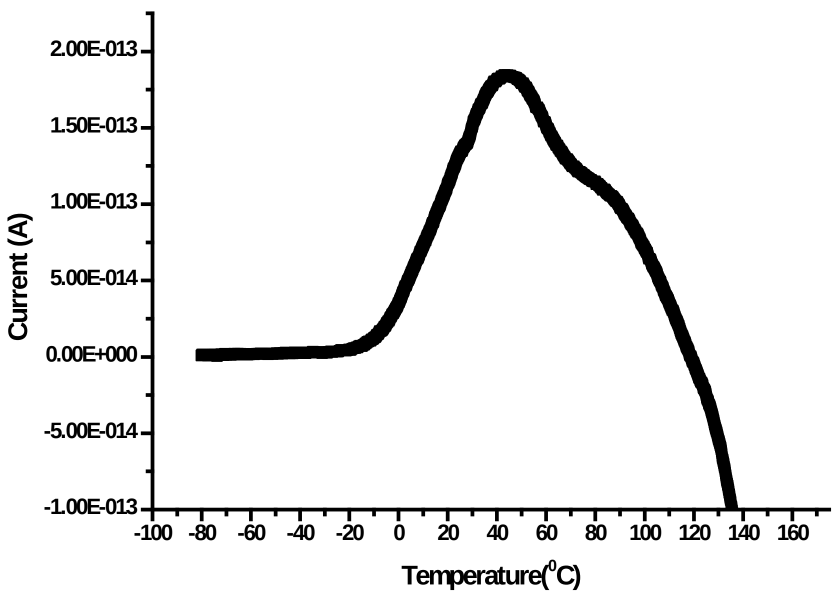
- Amorphous materials
- Polymorphs
- **Batch-to-batch control**
- Co-crystals

SCIENCE

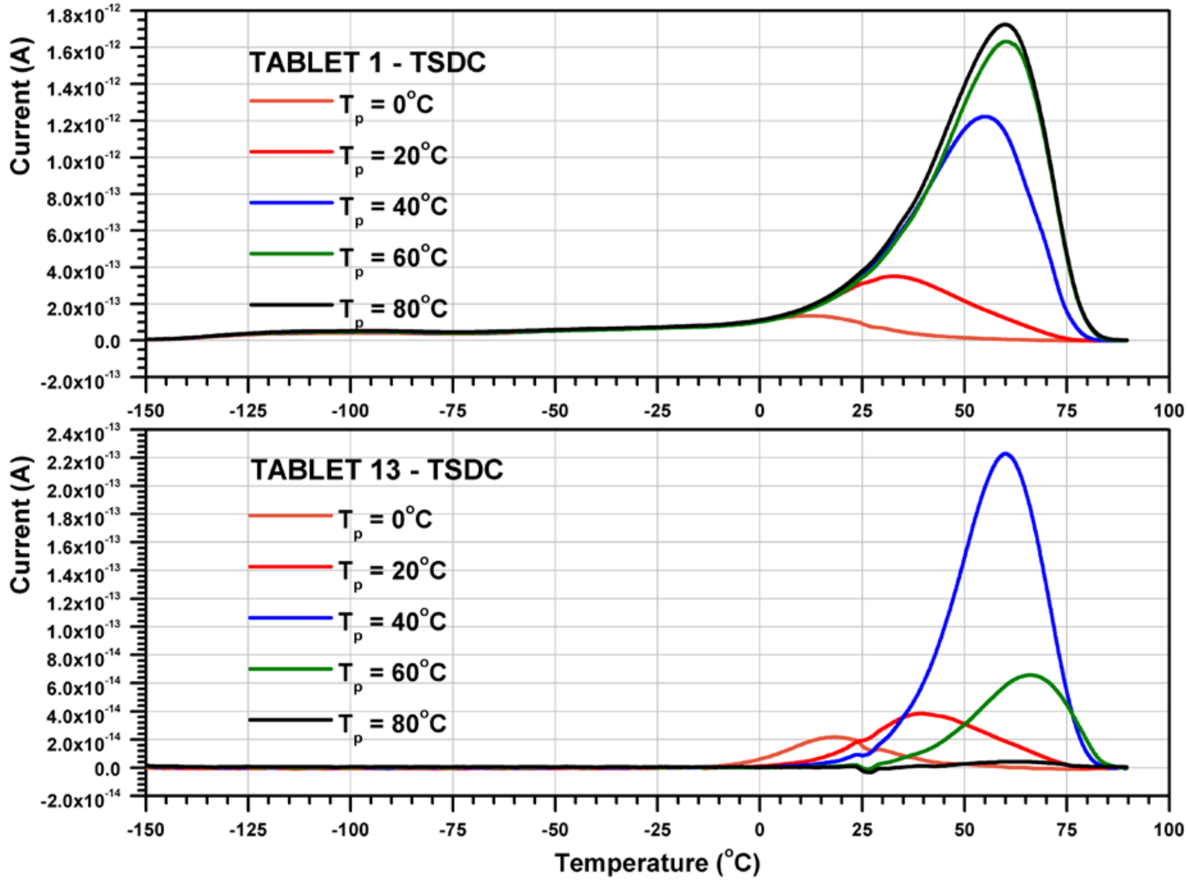
Batch to Batch variations

UNIVERSITY of GREENWICH





Batch to Batch variations

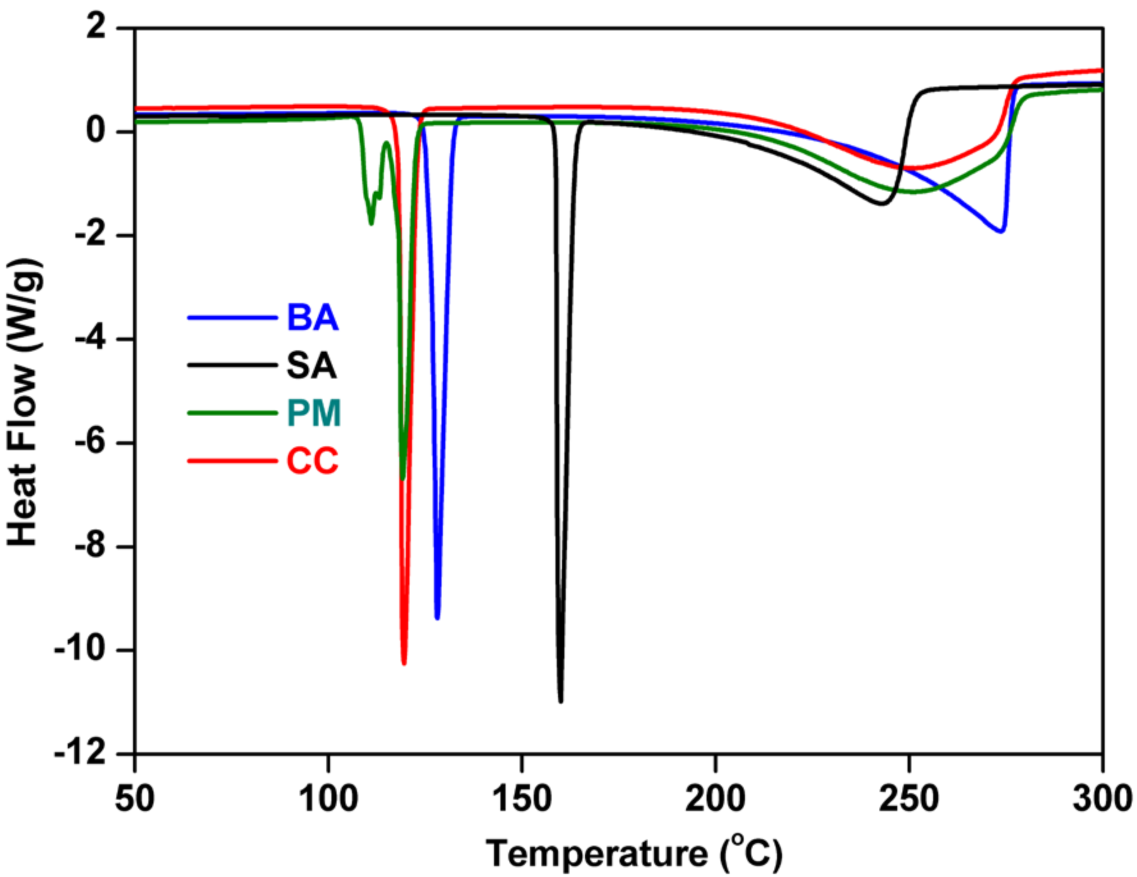


Pharmaceutical Applications

- Amorphous materials
- Polymorphs
- Batch-to-batch control
- **Co-crystals**

SA/BA co-crystal system

- 1:1 molar ratio co-crystal (CC) of salicylic acid (SA) and benzamide (BA)
- 1:1 molar ratio physical mixture (PM)



Primary transitions:

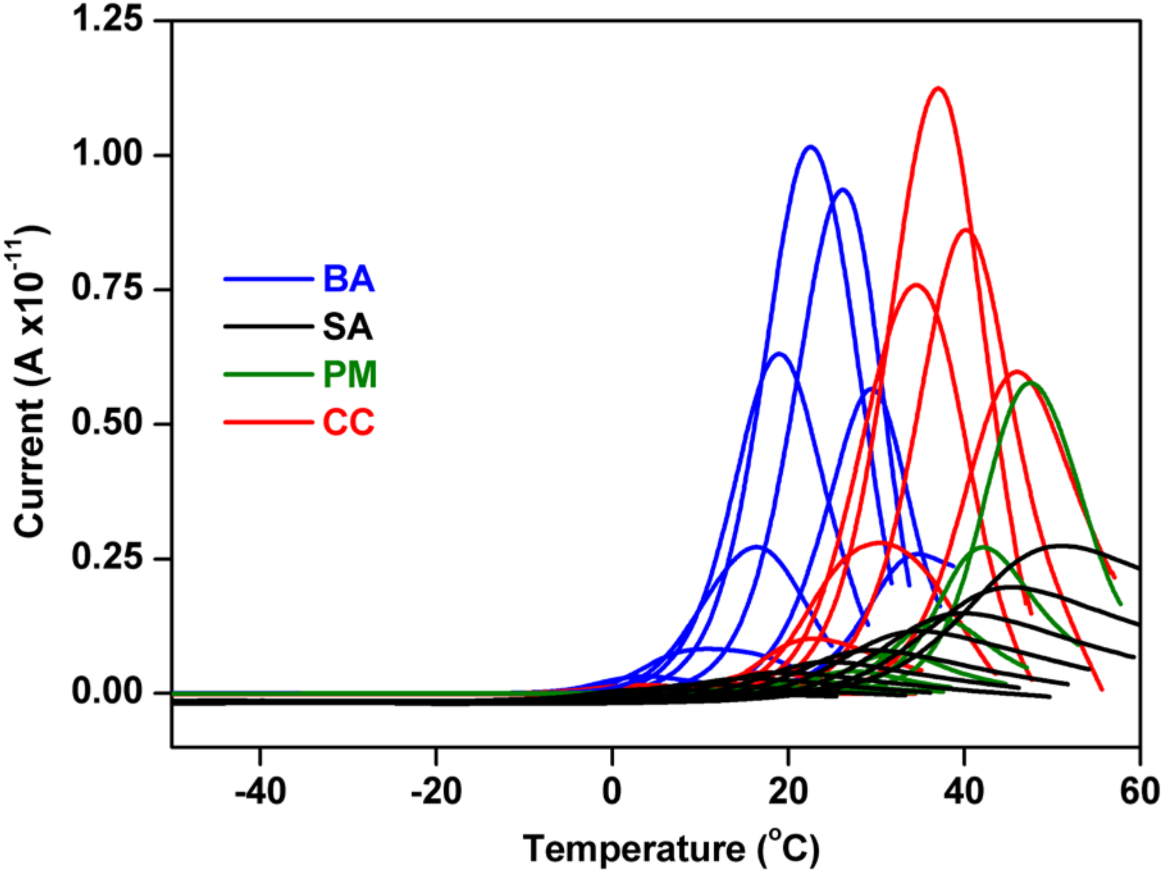
BA = 128°C

SA = 159°C

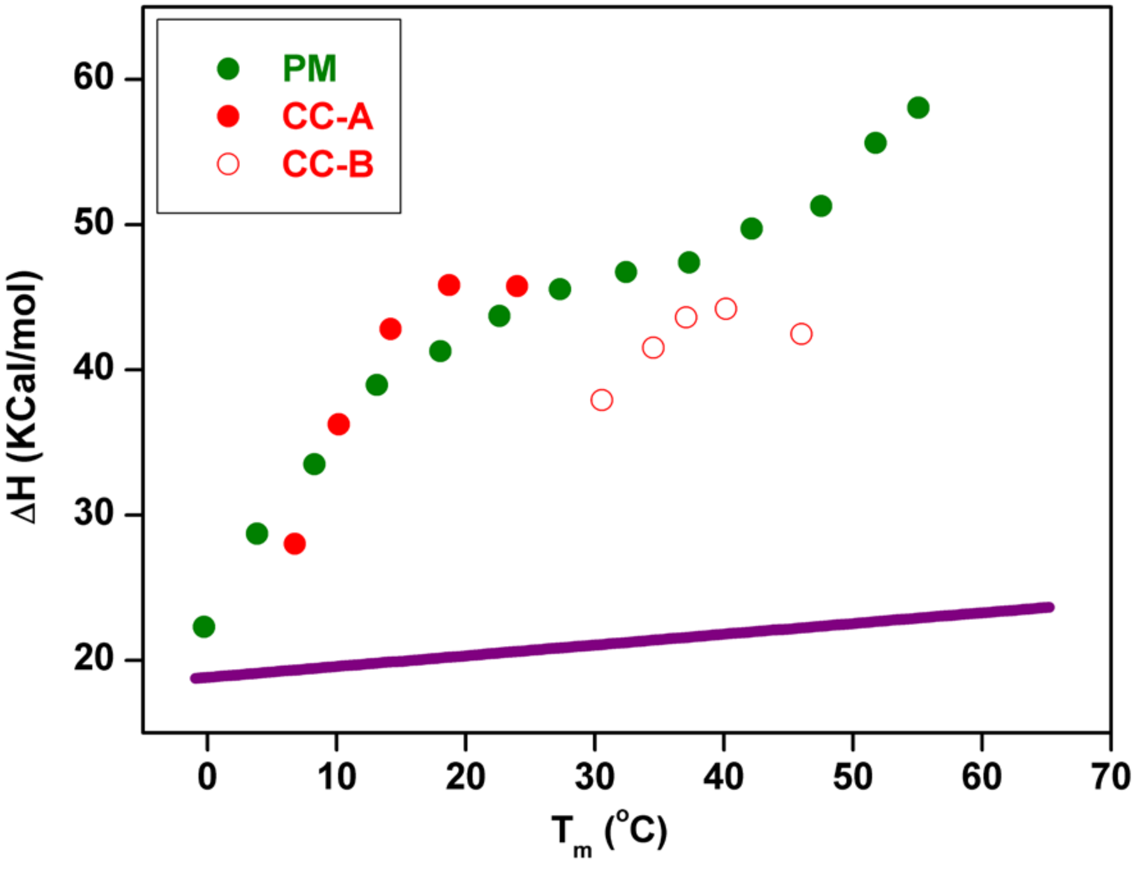
CC = 119°C

PM = 110°C

SA/BA co-crystal system



SA/BA co-crystal system



T_c:

CC-A = 125°C

CC-B = 119°C

PM = 110°C

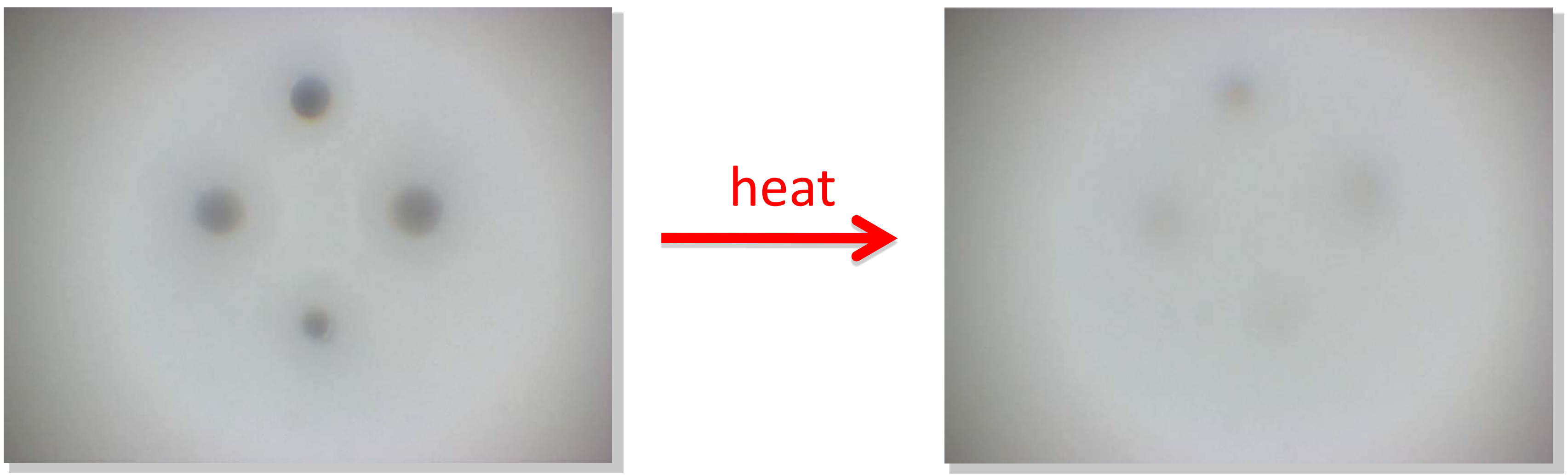
UNIVERSITY of GREENWICH

Part 2

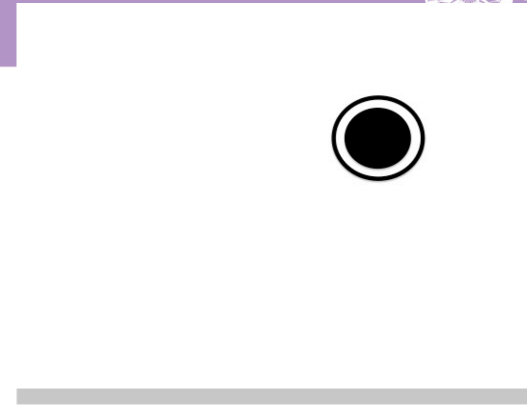
- **Thermal Analysis by Structural Characterisation (TASC)**

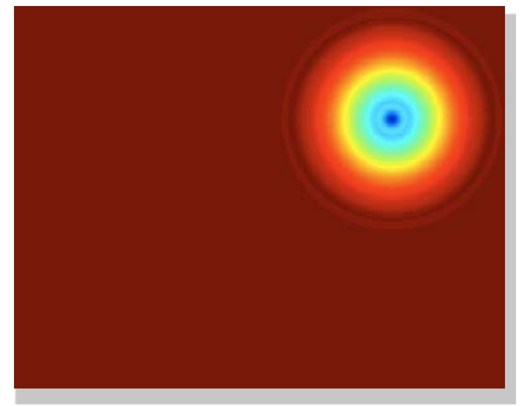
- Thermal Dissolution Analysis (TDA)

TASC consists of imposing a pattern on the surface of a sample or exploiting pre-existing structure, then characterizing how that pattern changes as the sample is heated; in this case Optical Microscopy was used but it can be applied to other forms of microscopy such as electron microscopy and Atomic Force Microscopy.

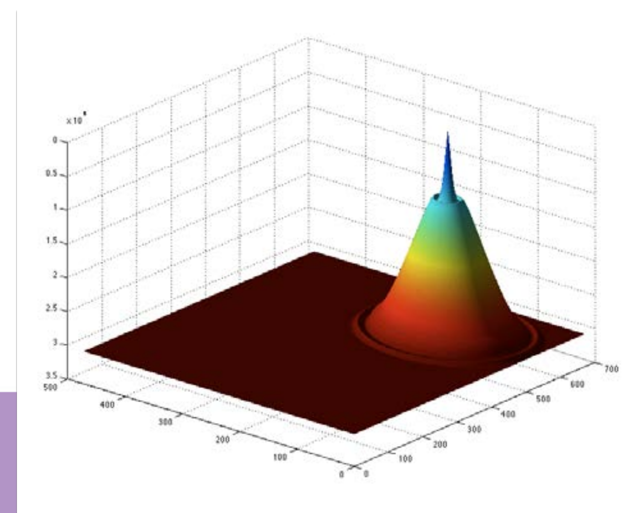


The TASC algorithm scans an area and tries to identify whether a designated structure exists and where it is located. **Top right** there is a schematic of an indentation, underneath this is the result of a TASC analysis.

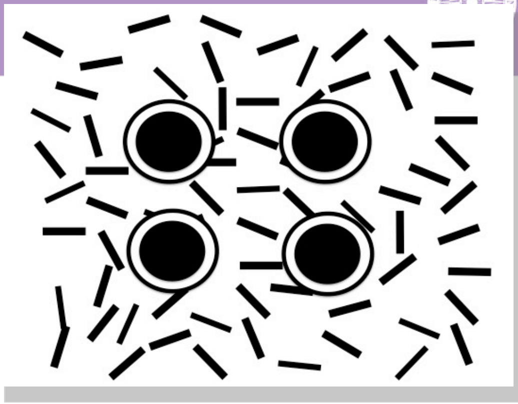


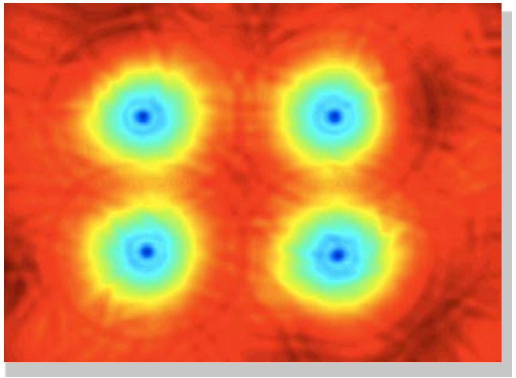


Right is a 3D representation of the output of the TASC analysis. The apex of the cone provides the location of the feature

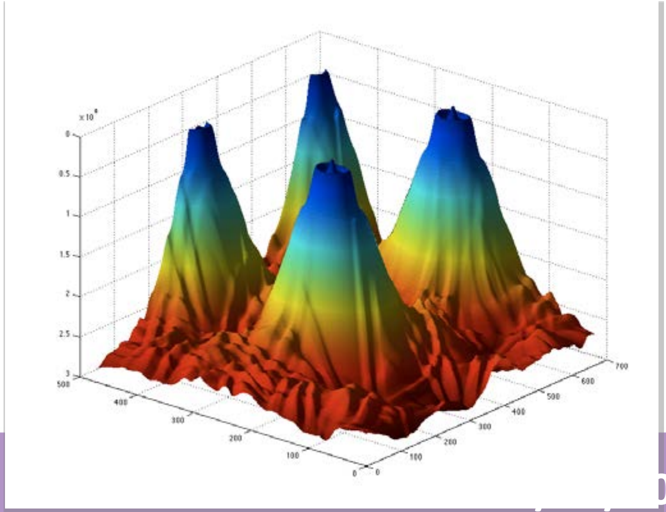


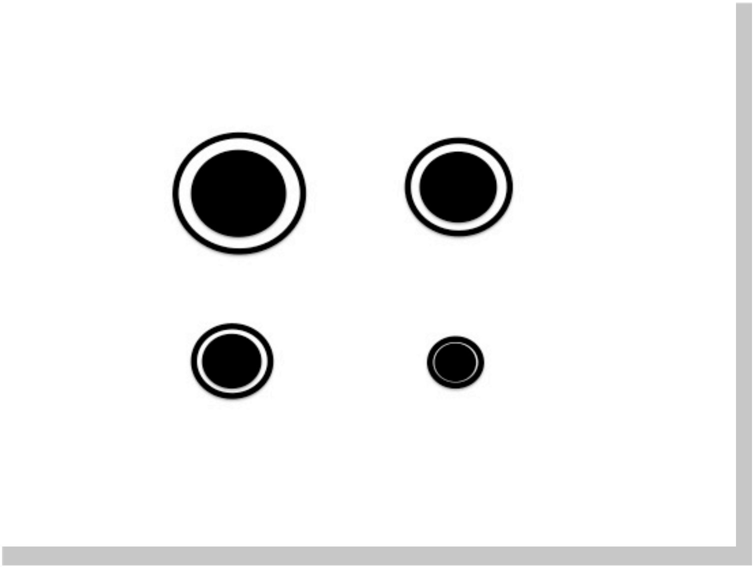
It is important that the algorithm is robust because it must deal with non-ideal samples. **Above right** there is a schematic of 4 indentations in a 'noisy' background. Below this is the result of a TASC analysis.

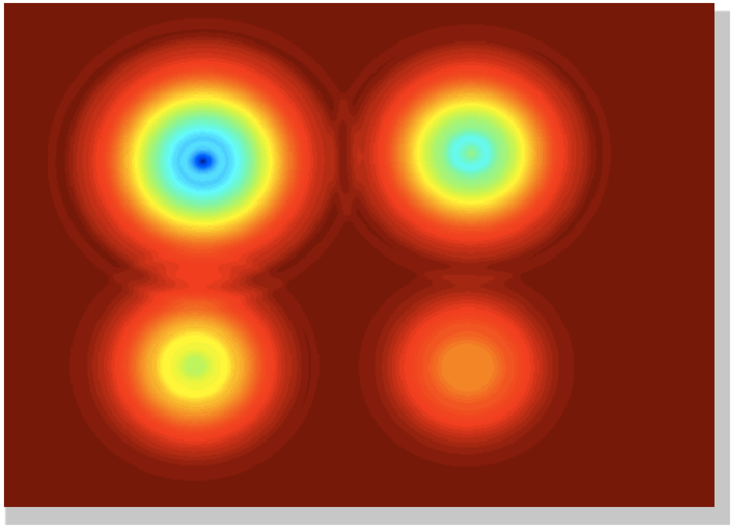




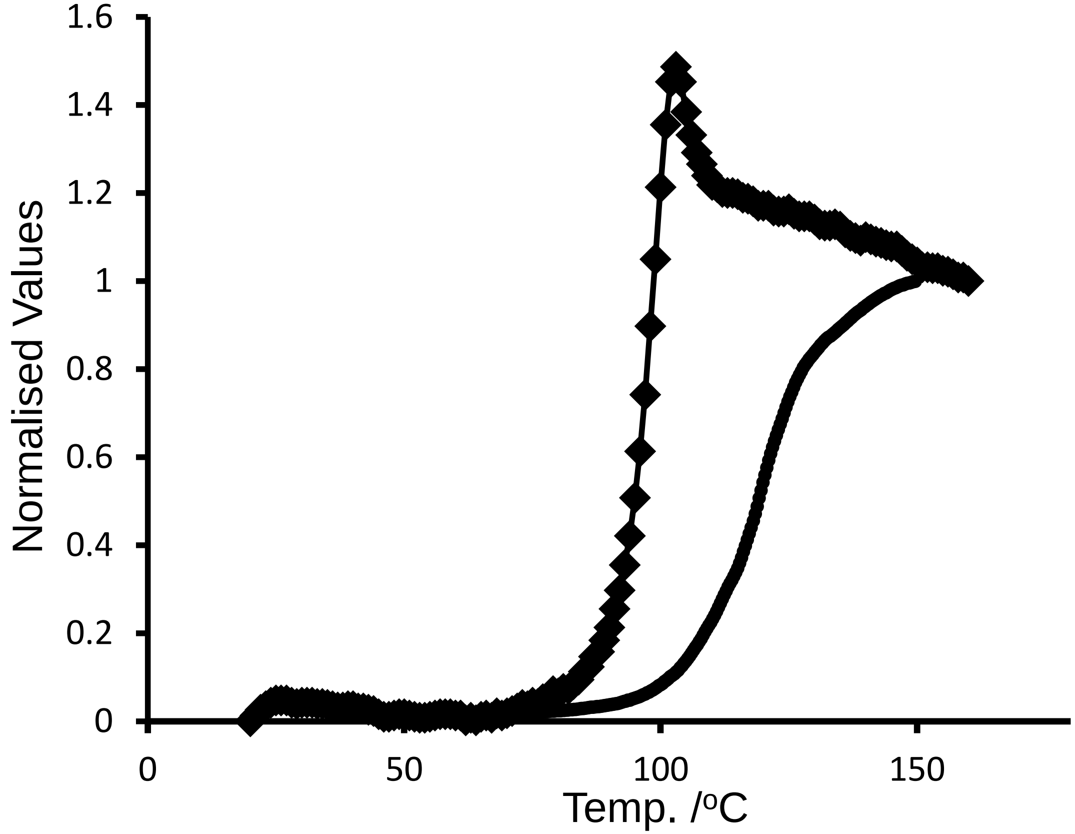
Right is a 3D representation of the output of the TASC analysis with the noisy background.



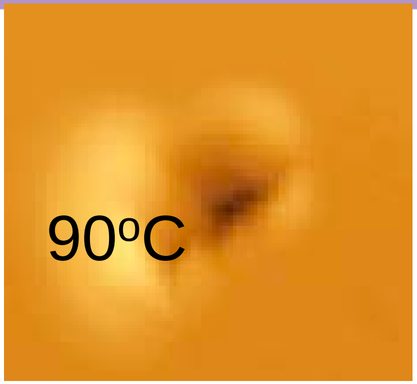


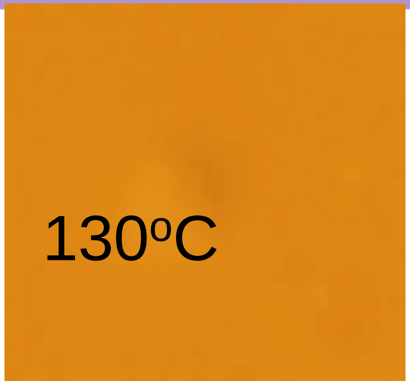


Above shows a series of schematic indentations of decreasing size. The degree of recognition by the TASC algorithm decreases as the size of the indentation decreases.

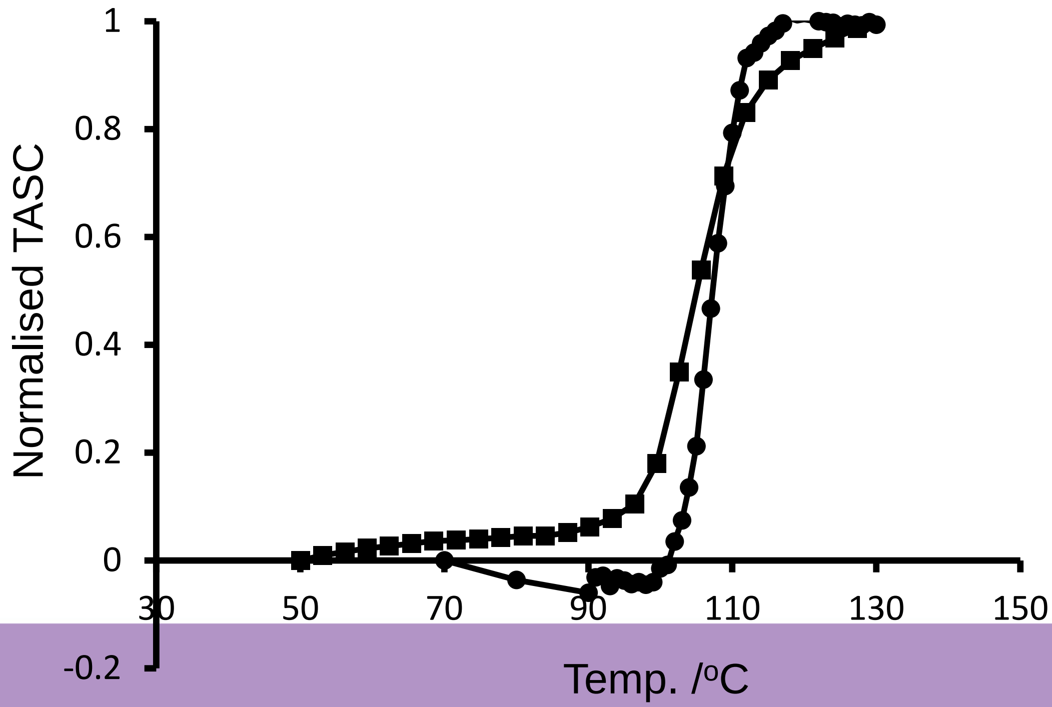


This is graph showing a co-plot of DSC and TASC data. The flow event happens after the glass transition as measured by DSC as expected.





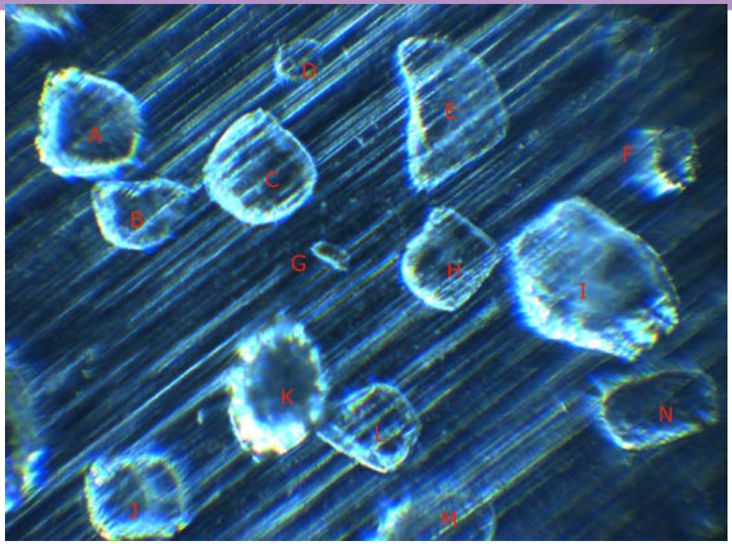
An ideal form of microscopy is Atomic Force Microscopy. Below is a comparison of an AFM result (circles), on an indentation 500nm in diameter with one obtained using optical microscopy on an indentation 200m in diameter (squares).



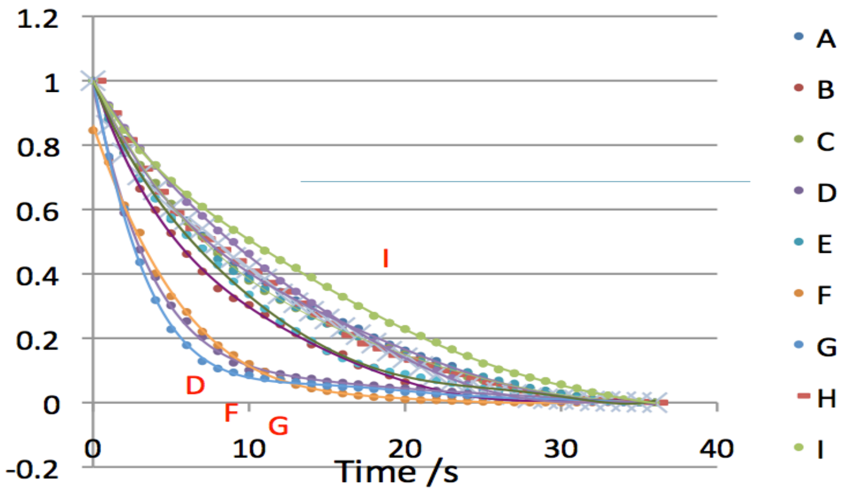
Part 2

- Thermal Analysis by Structural Characterisation (TASC)
- **Thermal Dissolution Analysis (TDA)**

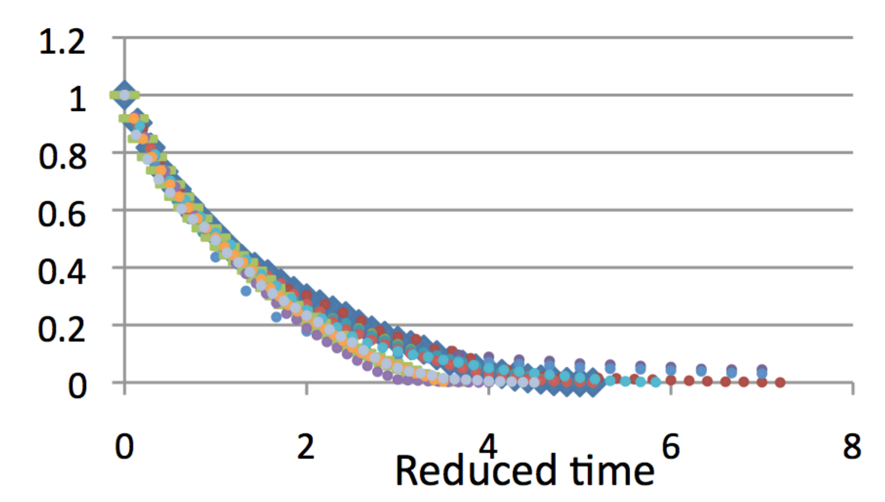
Right is an image of a collection of sugar crystals in water in a DSC crucible. The TASC algorithm can follow their disappearance.



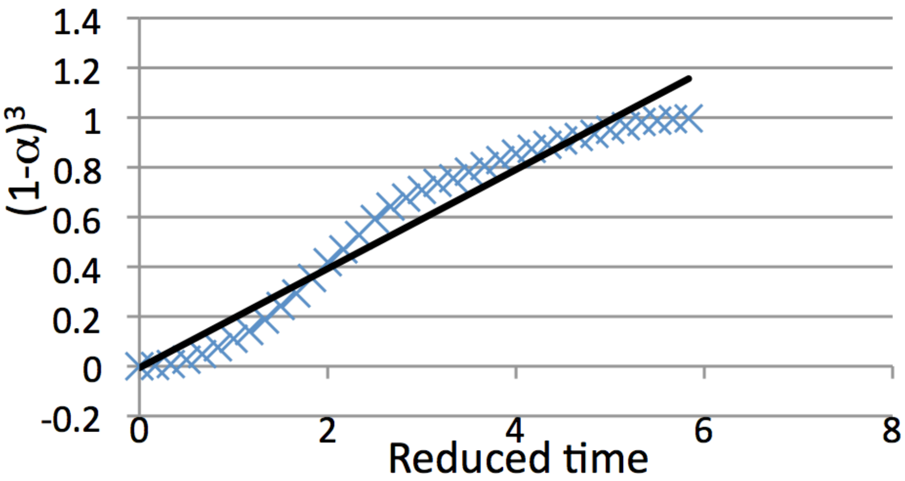
In the graph shown **right**; it can be seen that small crystals D, F and G disappear much faster than the large crystal I.



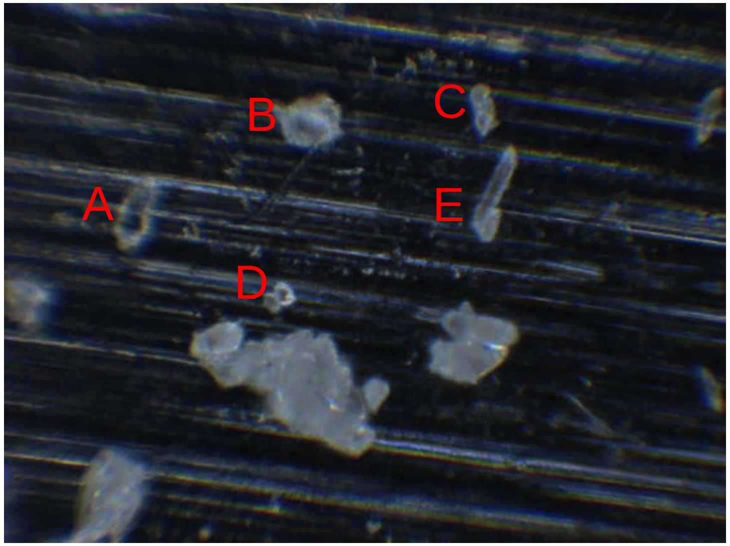
Right shows a reduced time plot of all of the crystals.

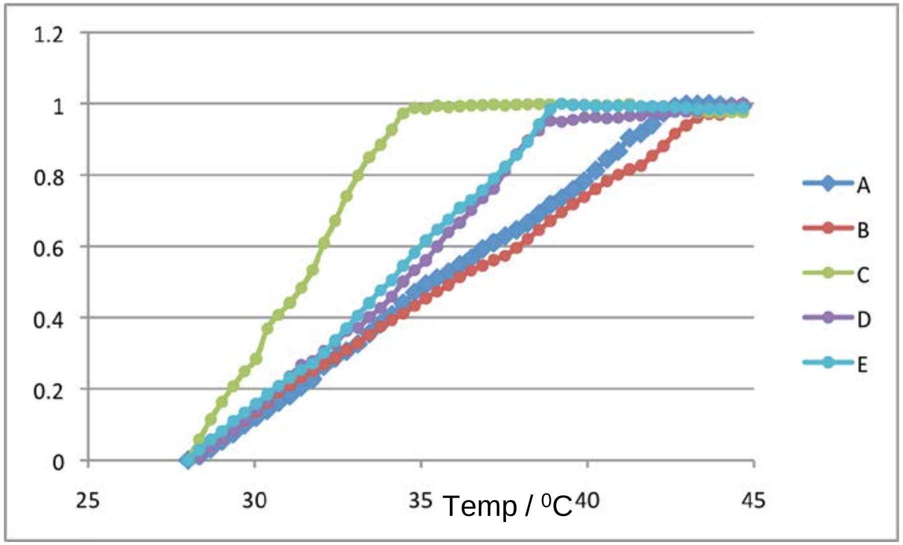


Right, averaged data are plotted against $(1-a)^3$, an approximately linear graph is obtained as would be expected for a shrinking 3D object.



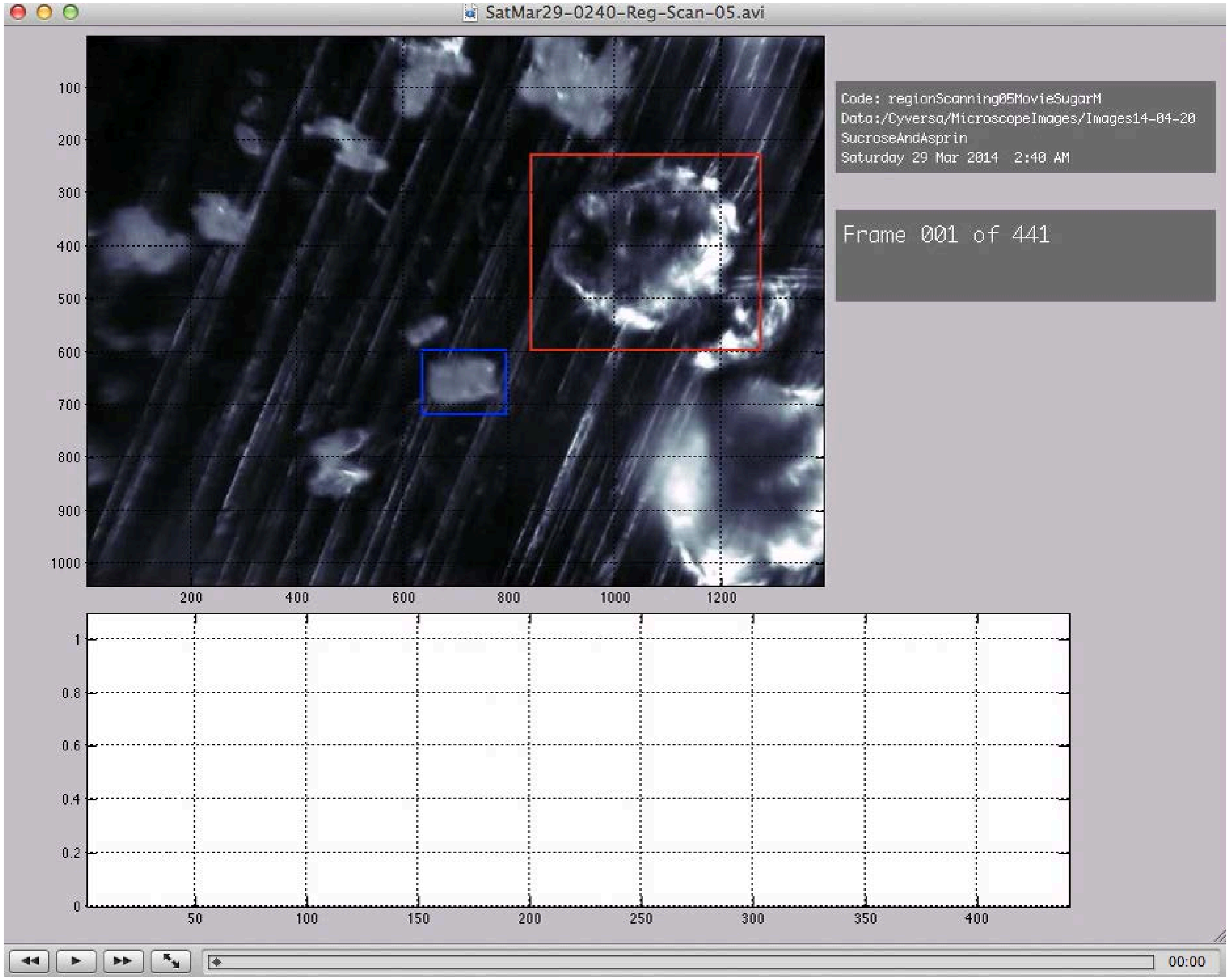
Thermal Dissolution Analysis

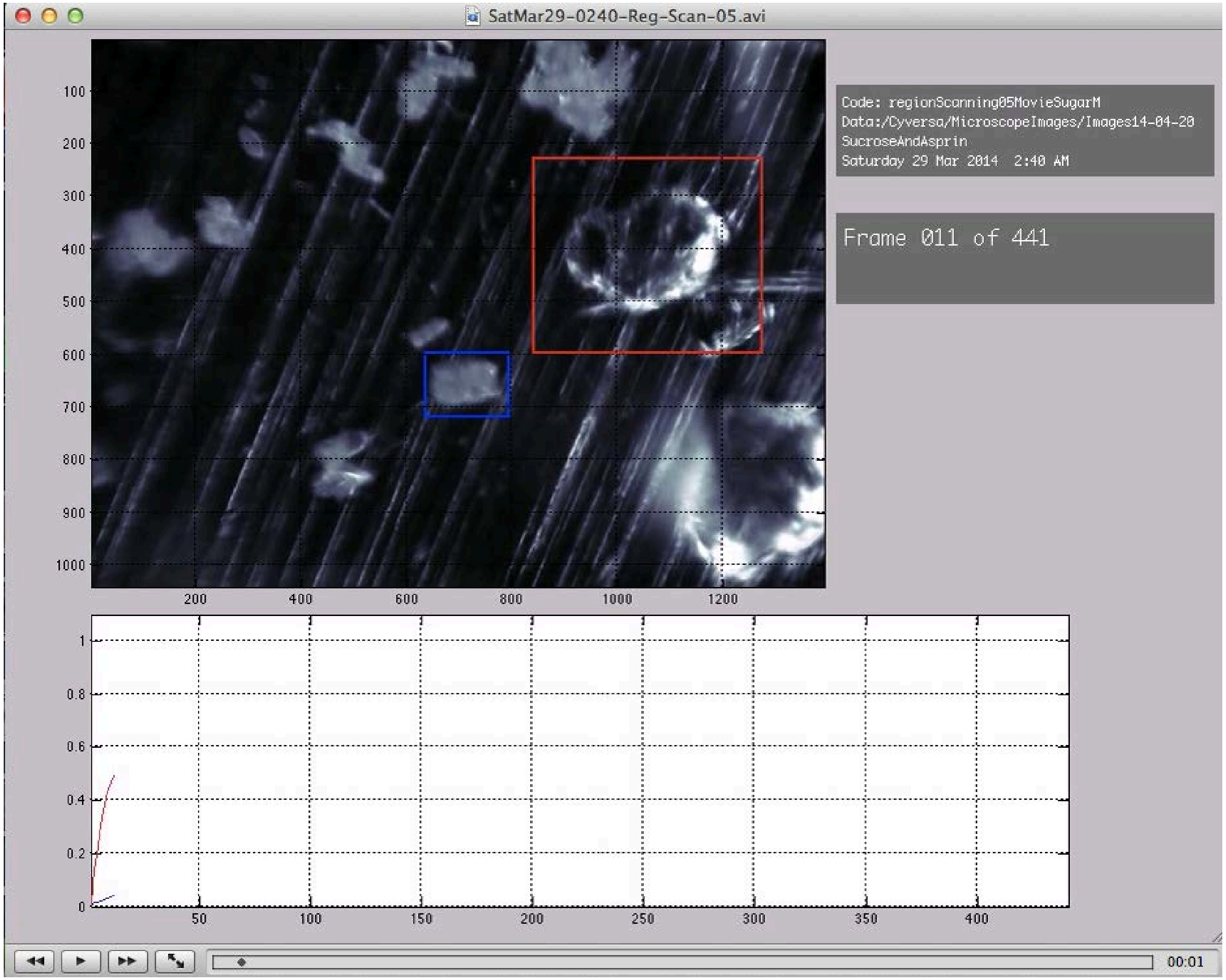


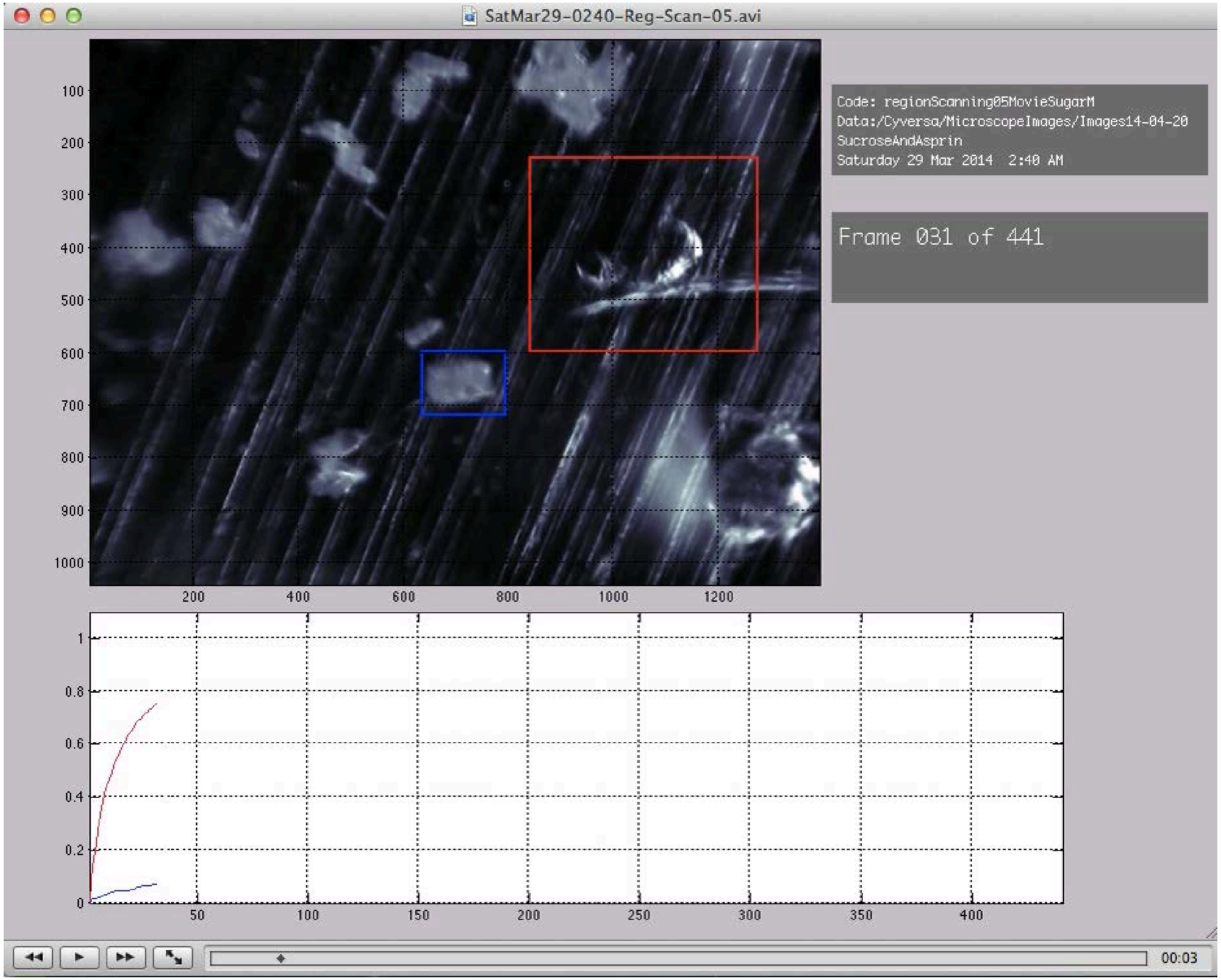


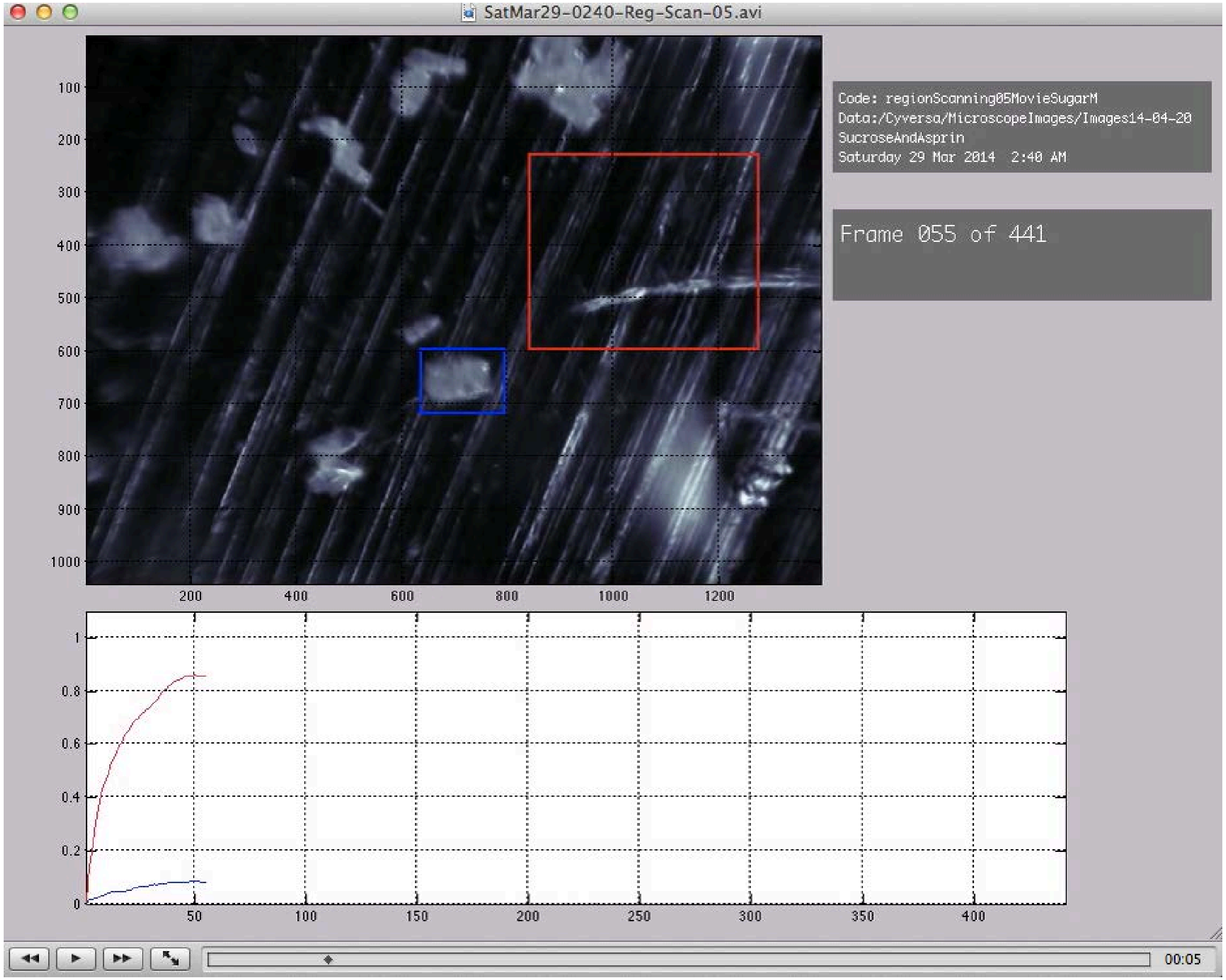
TASC is used to track the dissolution of the salicylic acid crystals in the field of view of the microscope. The temperature program was 5^{o}C/min.

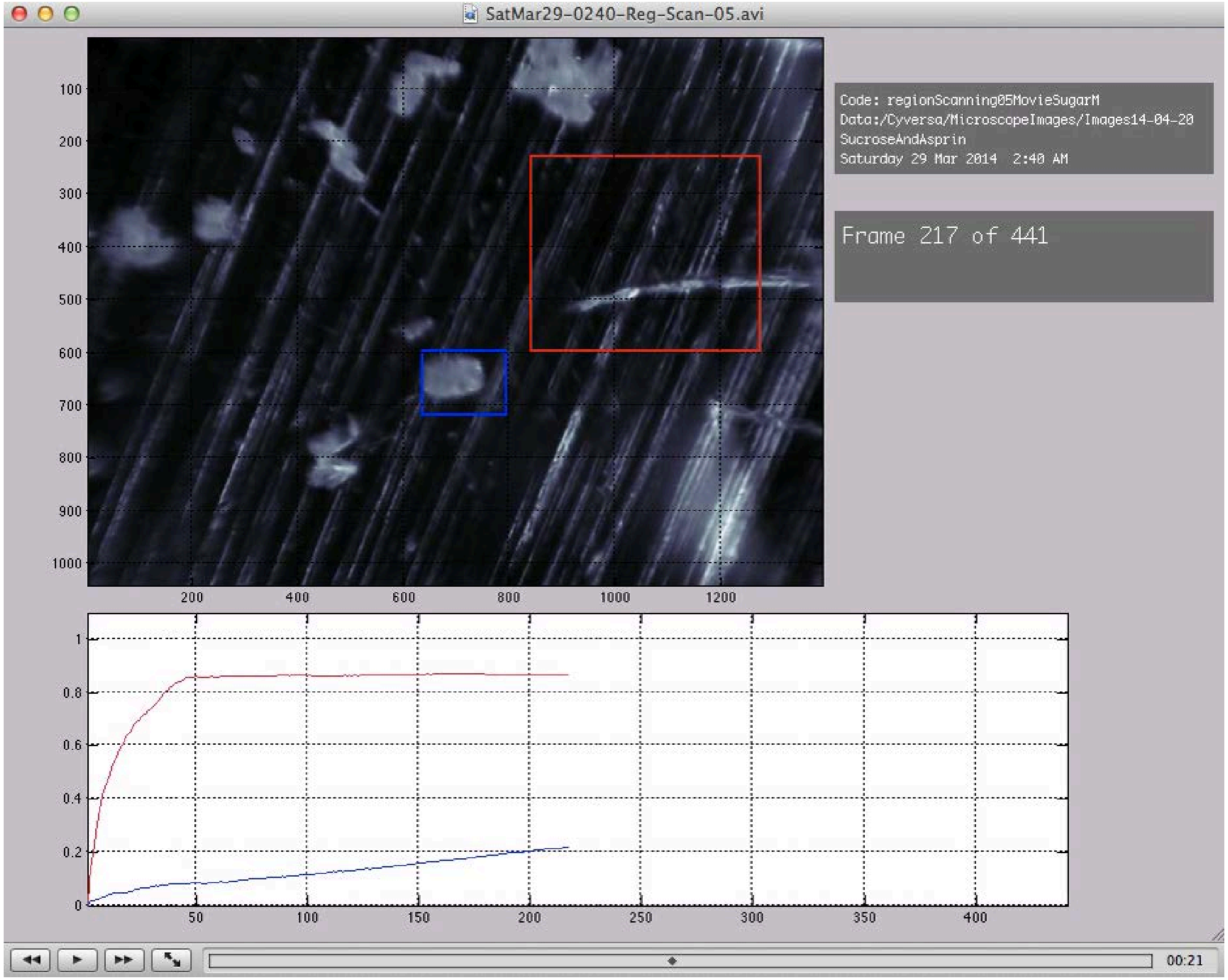
UNIVERSITY of GREENWICH

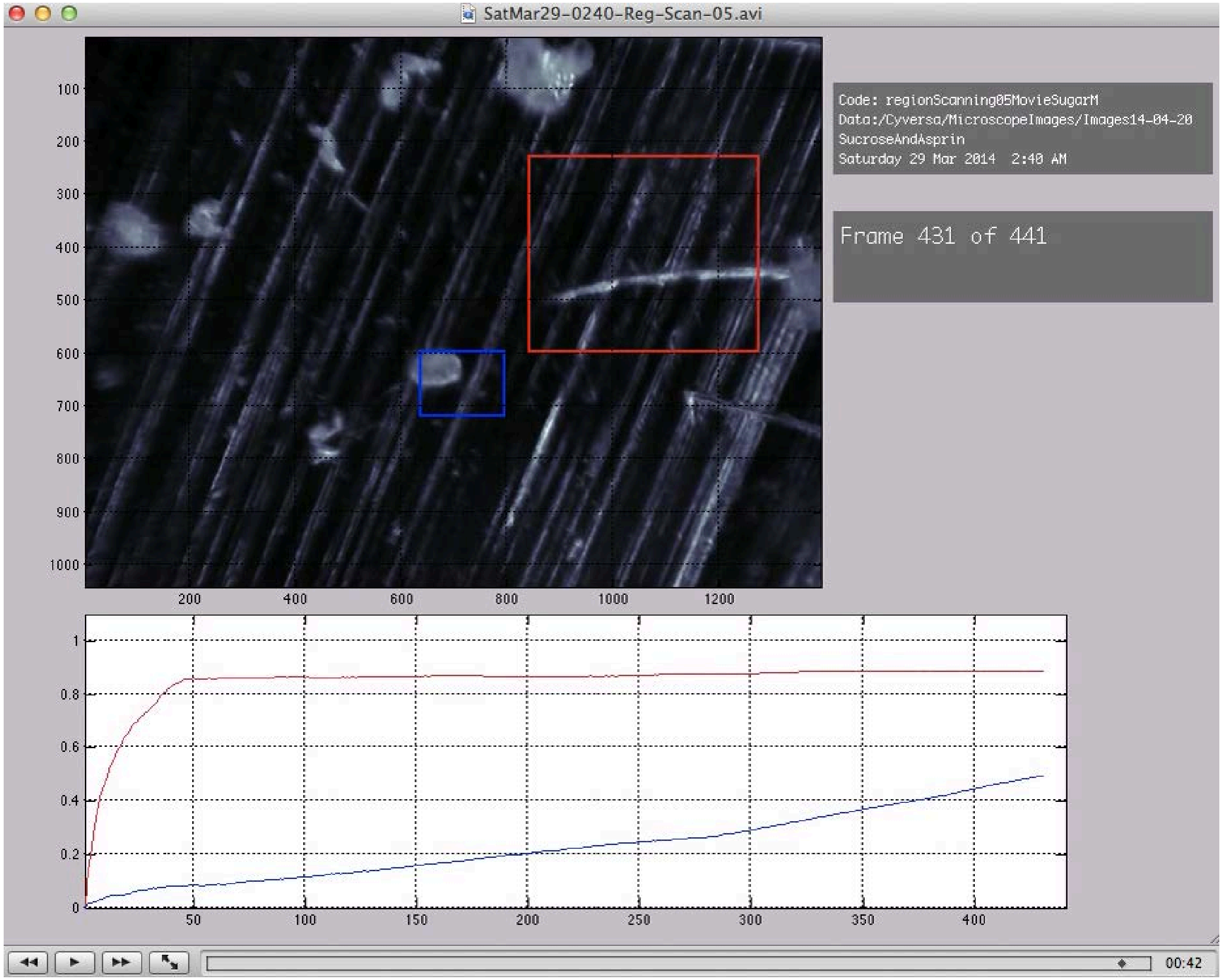



SatMar29-0240-Reg-Scan-05.avi
Code: regionScanning05MovieSugarM
Data:/Cyversa/MicroscopeImages/Images14-04-28
SucroseAndAsprin
Saturday 29 Mar 2014 2:40 AM
Frame 011 of 441
100
200
300
400
500
600
700
800
900
1000
200
400
600
800
1000
1200
1
0.8
0.6
0.4
0.2
0
50
100
150
200
250
300
350
400
00:01


SatMar29-0240-Reg-Scan-05.avi
Code: regionScanning05MovieSugarM
Data:/Cyversa/MicroscopeImages/Images14-04-20
SucroseAndAsprin
Saturday 29 Mar 2014 2:40 AM
Frame 031 of 441
100
200
300
400
500
600
700
800
900
1000
200
400
600
800
1000
1200
1
0.8
0.6
0.4
0.2
0
50
100
150
200
250
300
350
400
00:03

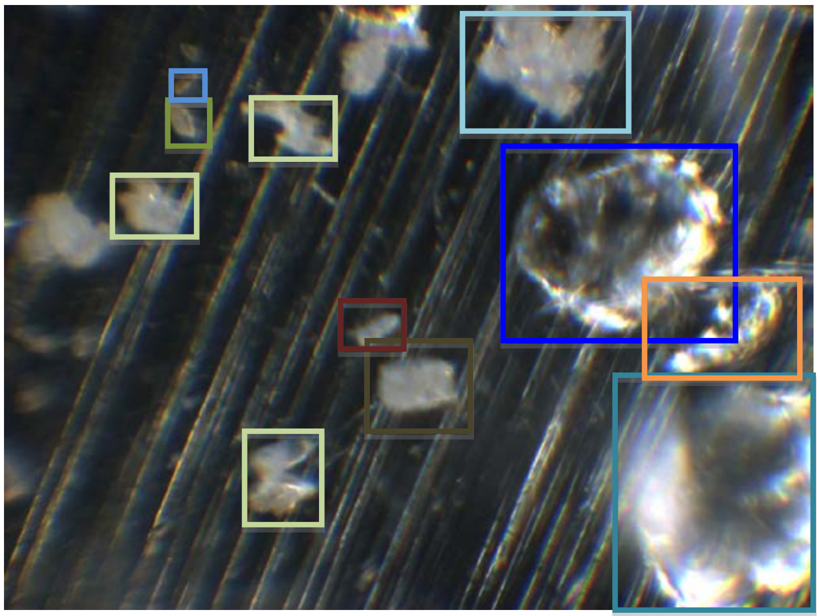

SatMar29-0240-Reg-Scan-05.avi
Code: regionScanning05MovieSugarM
Data:/Cyversa/MicroscopeImages/Images14-04-20
SucroseAndAsprin
Saturday 29 Mar 2014 2:40 AM
Frame 055 of 441
100
200
300
400
500
600
700
800
900
1000
200
400
600
800
1000
1200
0
0.2
0.4
0.6
0.8
1
50
100
150
200
250
300
350
400
00:05

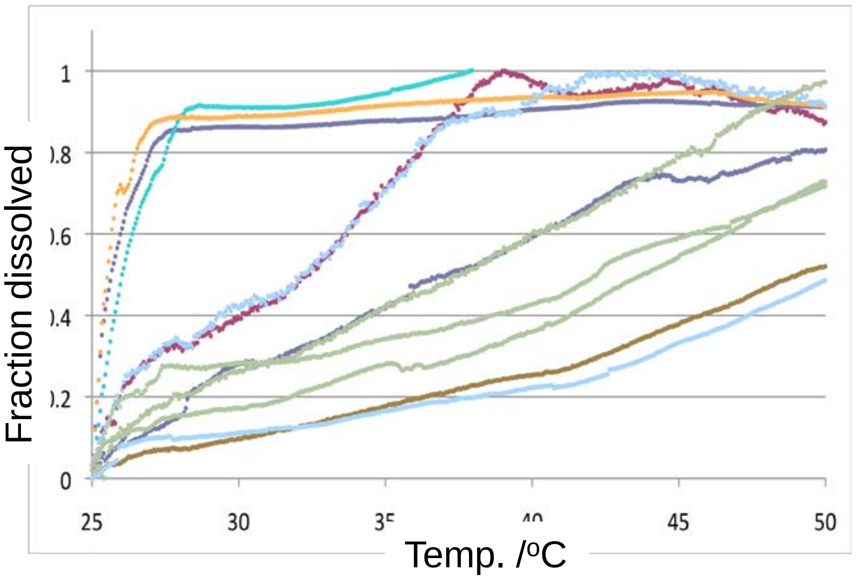

SatMar29-0240-Reg-Scan-05.avi
Code: regionScanning05MovieSugarM
Data:/Cyversa/MicroscopeImages/Images14-04-20
SucroseAndAsprin
Saturday 29 Mar 2014 2:40 AM
Frame 217 of 441
00:21


SatMar29-0240-Reg-Scan-05.avi
Code: regionScanning05MovieSugarM
Data:/Cyversa/MicroscopeImages/Images14-04-20
SucroseAndAsprin
Saturday 29 Mar 2014 2:40 AM
Frame 431 of 441
100
200
300
400
500
600
700
800
900
1000
200
400
600
800
1000
1200
1
0.8
0.6
0.4
0.2
0
50
100
150
200
250
300
350
400
00:42

Thermal Dissolution Analysis

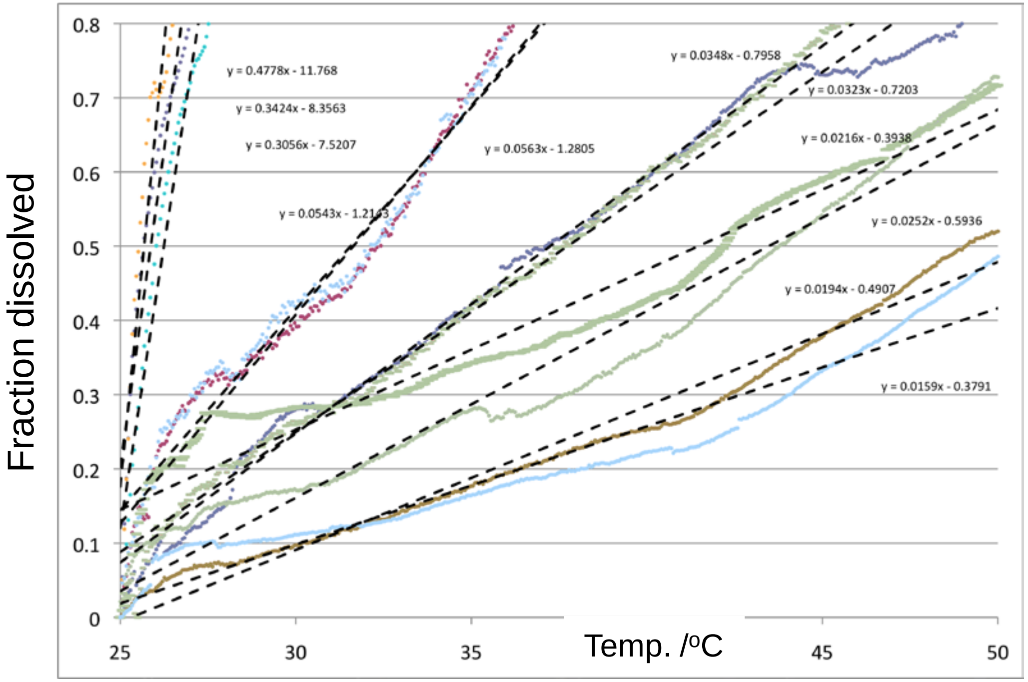
UNIVERSITY of GREENWICH

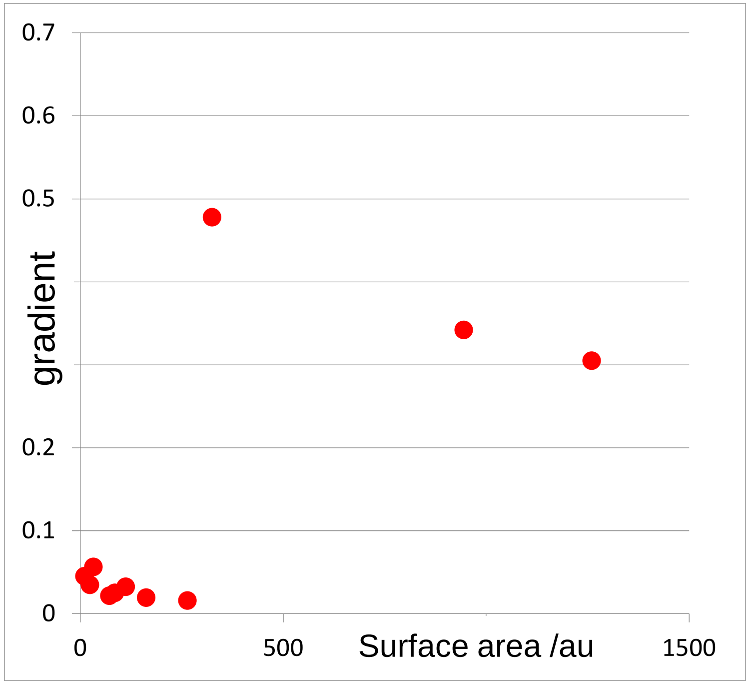




TASC is used to track the dissolution of the objects in the field of view of the microscope. The temperature program was 5^{o}C/min.

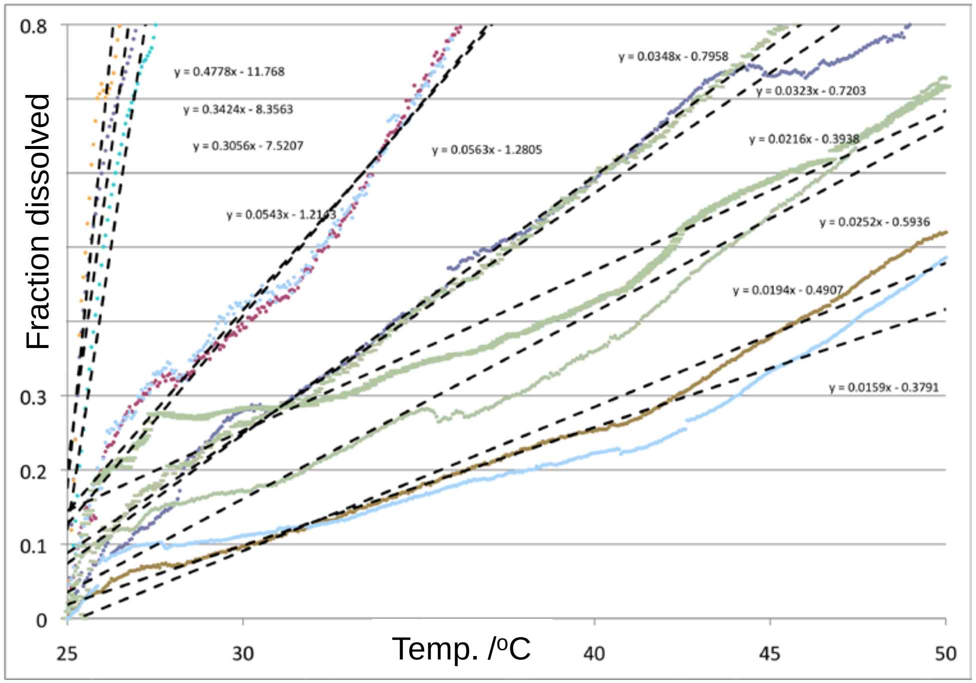
Thermal Dissolution Analysis

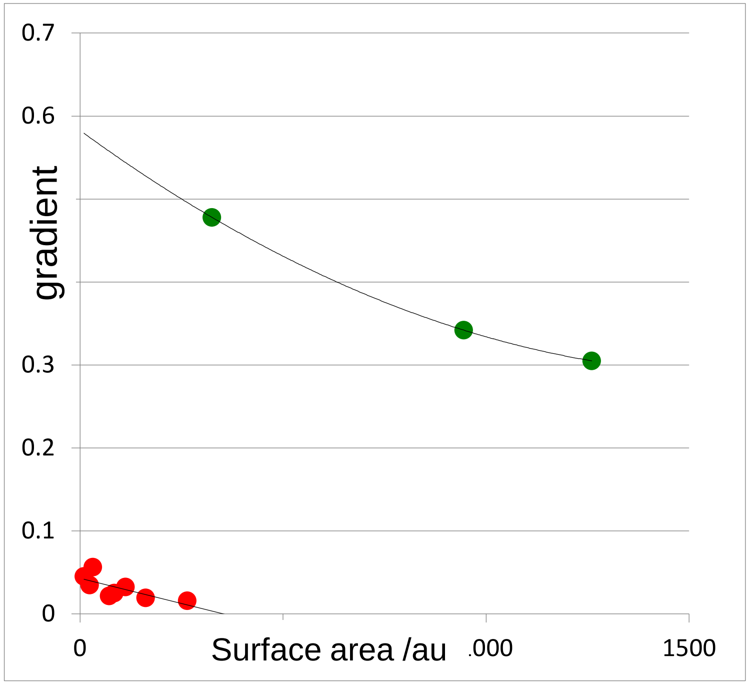




A line was fitted to the linear part of the dissolution curves and the gradients were plotted against the size of the crystals.

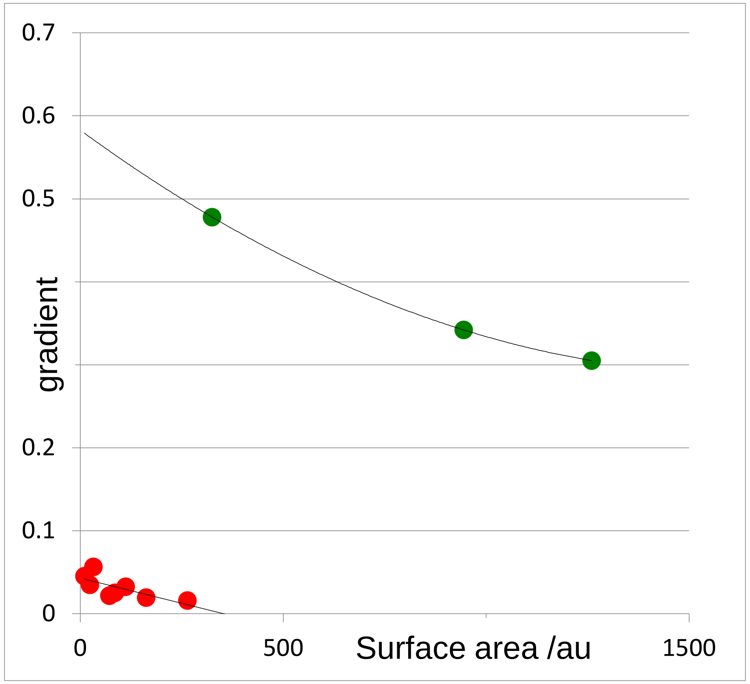
Thermal Dissolution Analysis

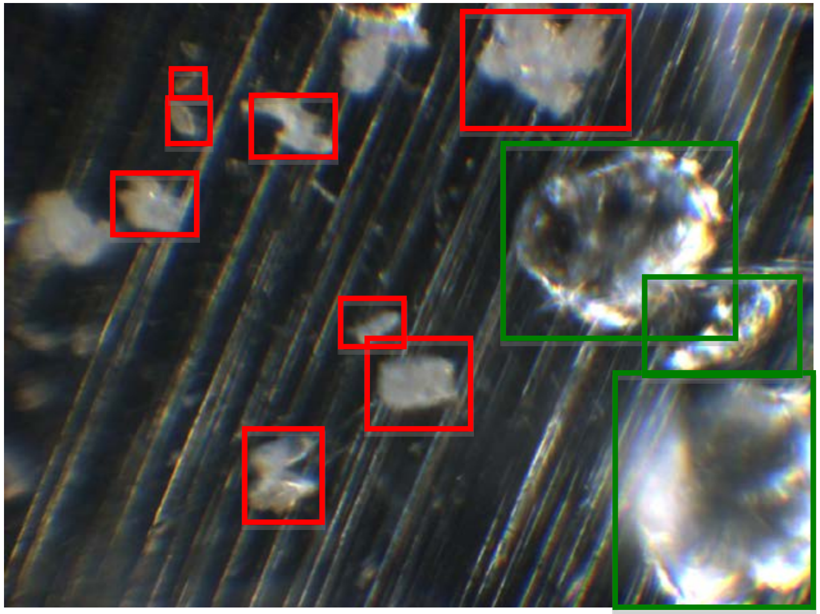




The dissolution behavior clears falls into two categories shown as red and green.

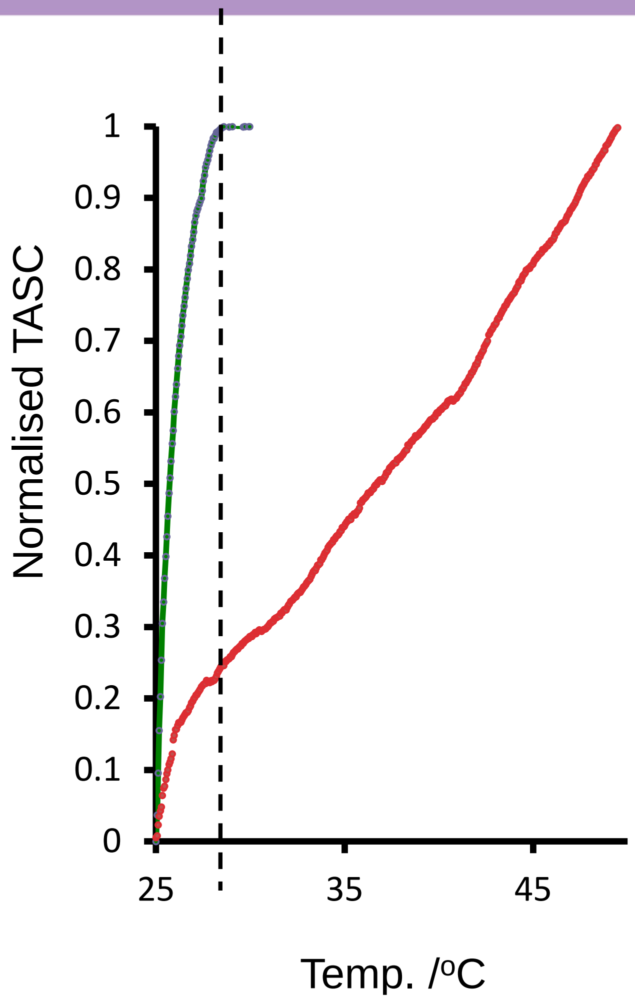
Thermal Dissolution Analysis

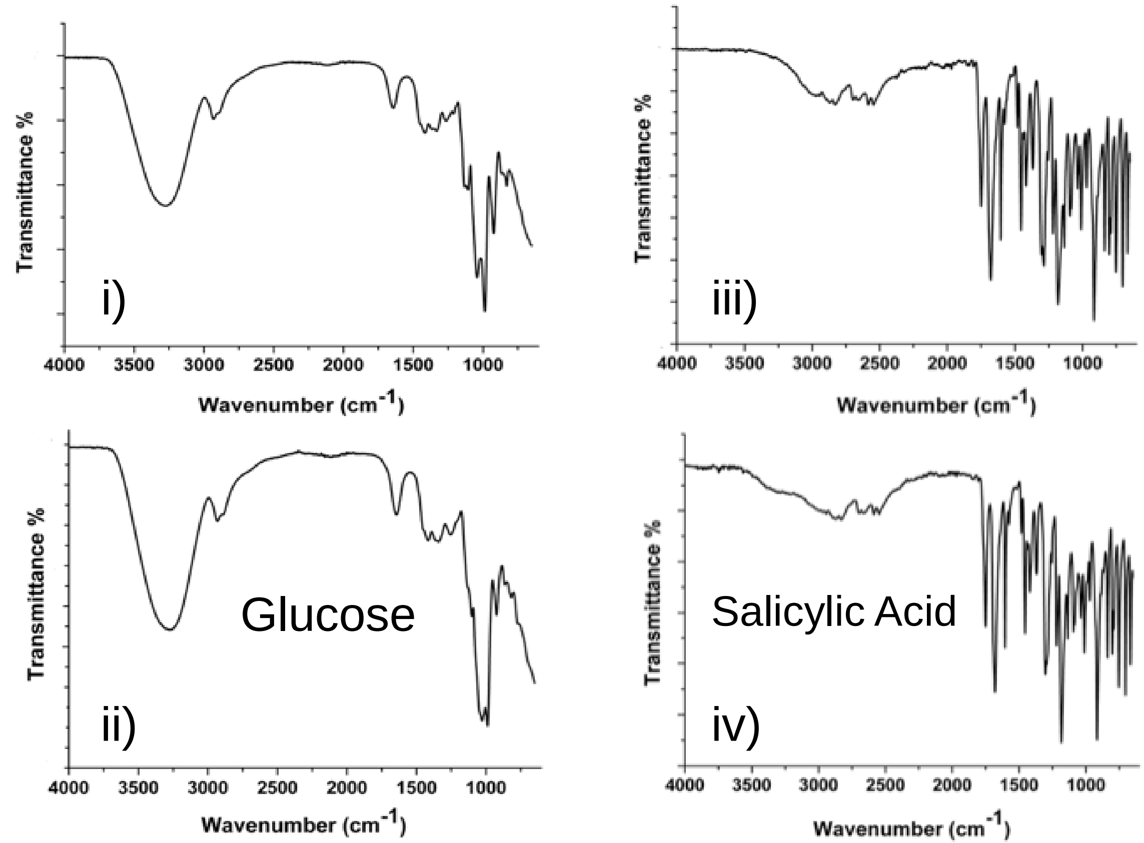




The objects in the field can be allocated to the two categories.

CIDA

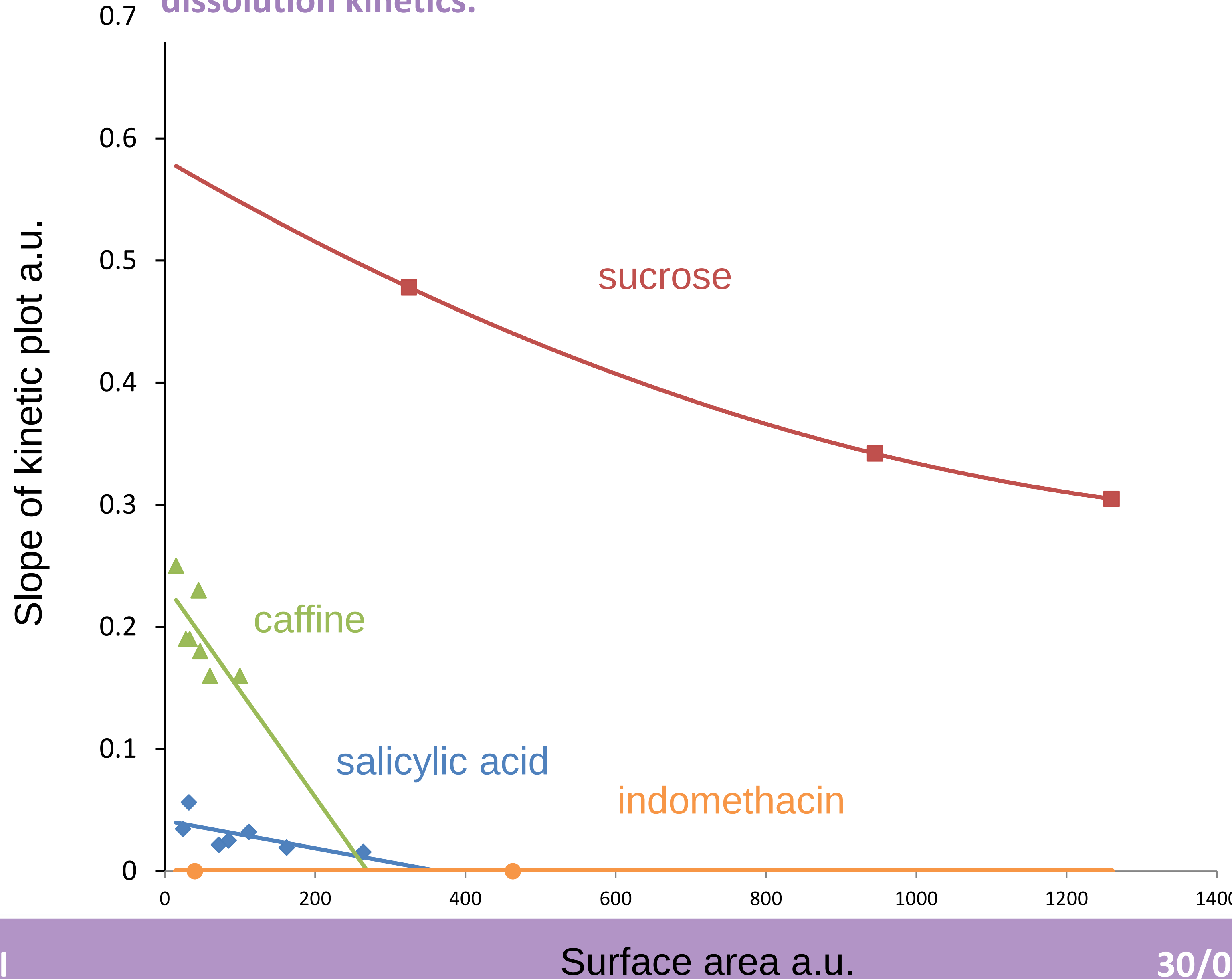




Filtered i) from solvent; iii) from residue

By appropriate chemical analysis the ‘red’ and ‘green’ materials can be identified.

It is typically the case that different material have different dissolution kinetics.



Thermal Dissolution Analysis

TGA-GC-MS

Figure 1: The Pyris 1 TGA coupled to the Clarus 600 C GC/MS gives the most sensitive method to identify evolved gases

Mass Loss

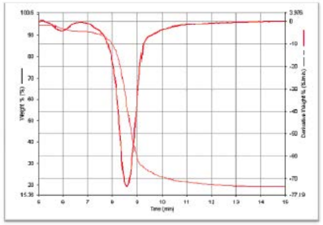


Figure 2: The TGA run of a sample of switch grass shows most weight loss occurs in one temperature range

Chromatography

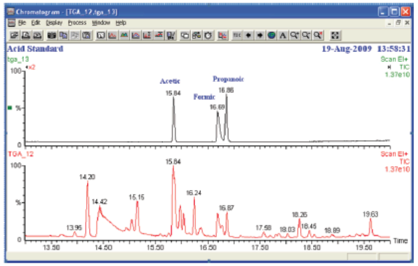
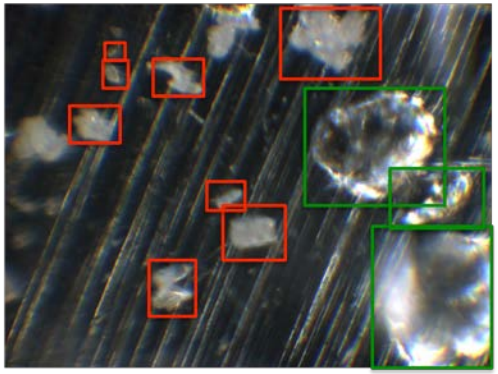
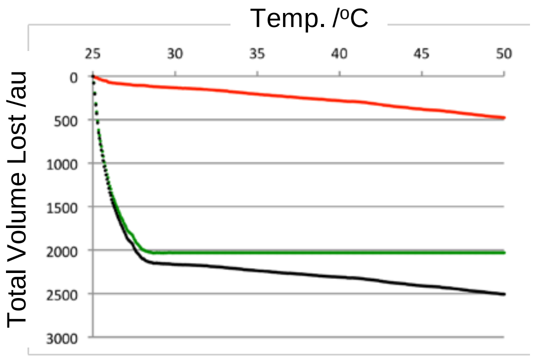


Figure 3: GC/MS on the gases evolved between 8 and 9 minutes and collected on the head of a GC column gave the chromatography seen on the bottom of the graph. MS analysis suggest that 15.8 is the acetic acid, which is confirmed above by running a standard of acetic, formic and propanoic acids

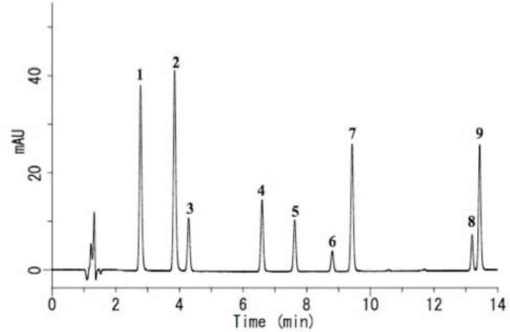
TDA-HPLC



'Volume' Loss



Chromatography



Conclusions

TSC

- Detection and characterisation of amorphous materials
- Characterisation (Kinetics) of polymorphic transitions and co-crystal systems
- Detection of beta and gama relaxation processes
- Links between secondary (beta and gama) and primary relaxation
- Batch to batch variations

TASC/TDA

- Molecular mobility at a micro and potentially nano scale
- Surface structural analysis
- Dissolution kinetics of different materials in different solvents


Thank you for listening