UNIVERSITY of GREENWICH

Understanding molecular mobility of pharmaceutically important materials/systems – current knowledge and challenges

Milan D. Antonijević

Overview of presentation

Challenge 1

- Molecular mobility studied by TSC
- Examples (amorphous, polymorphs, co-crystals)

Challenge 2

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

Challenge 3

- Consumers care

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

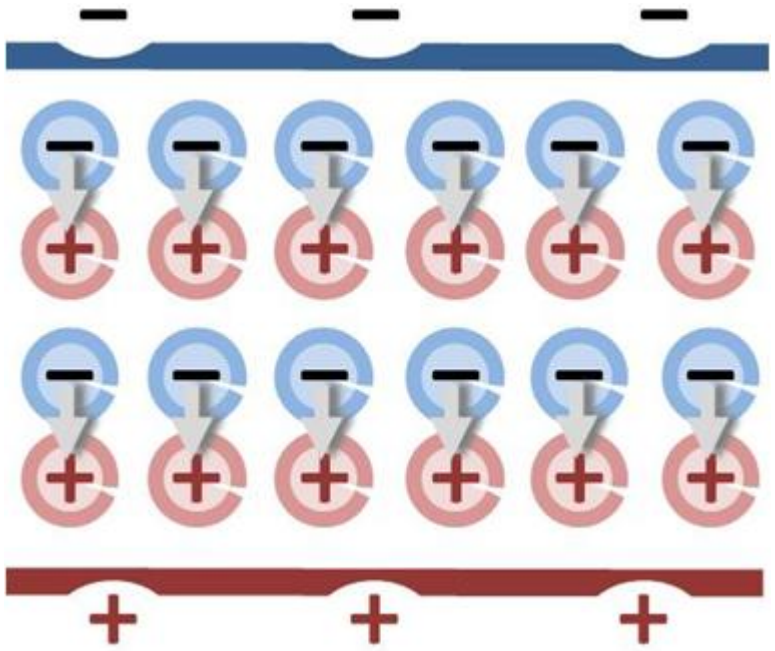
Challenge 1

"1 in 5000 drugs makes it from the lab to FDA approval"

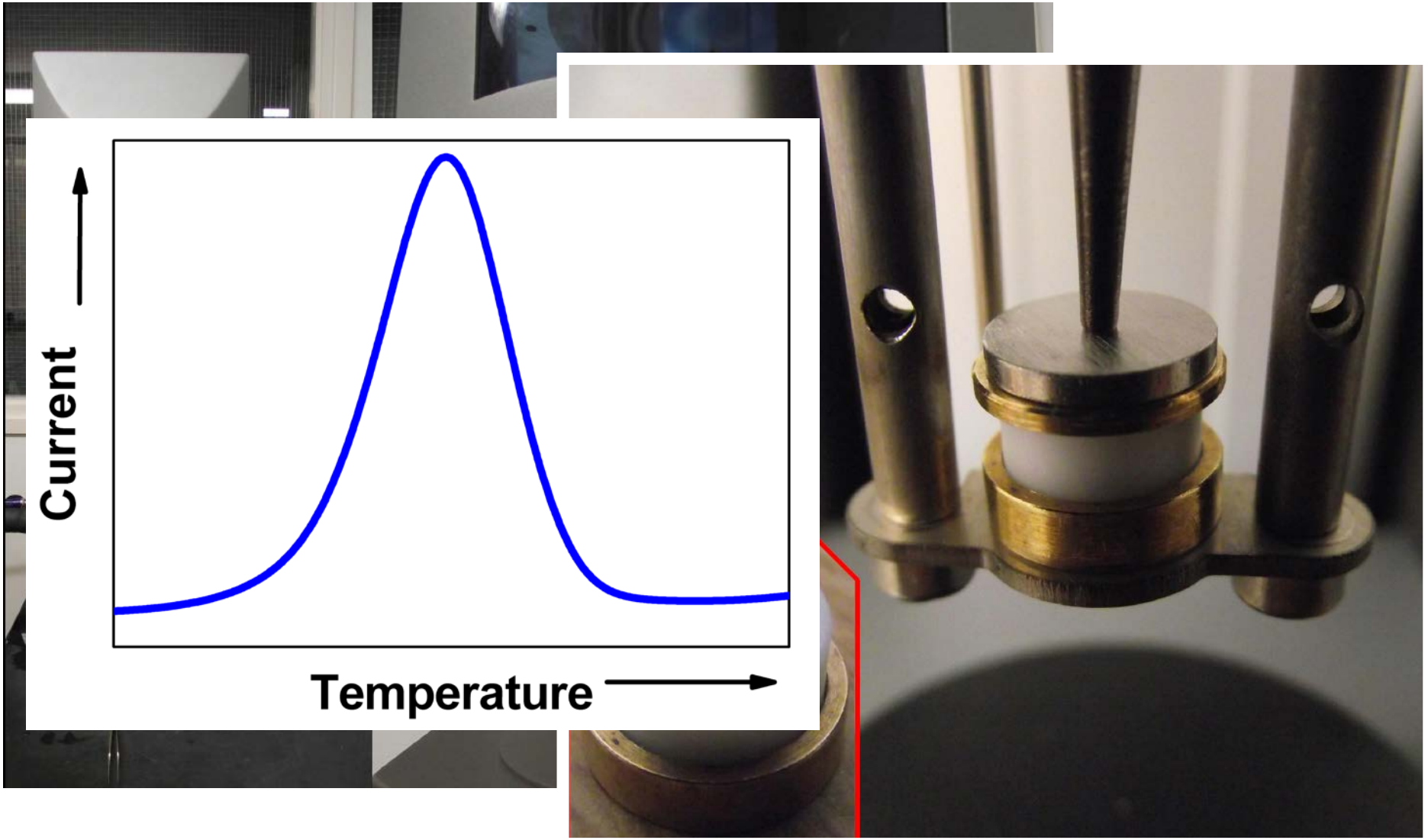
TSC is a general term applied to the measurement of current generated by temperature-activated relaxation of molecular dipoles in response to the application of a static electric field

- 1936, Frei and Grotzinger

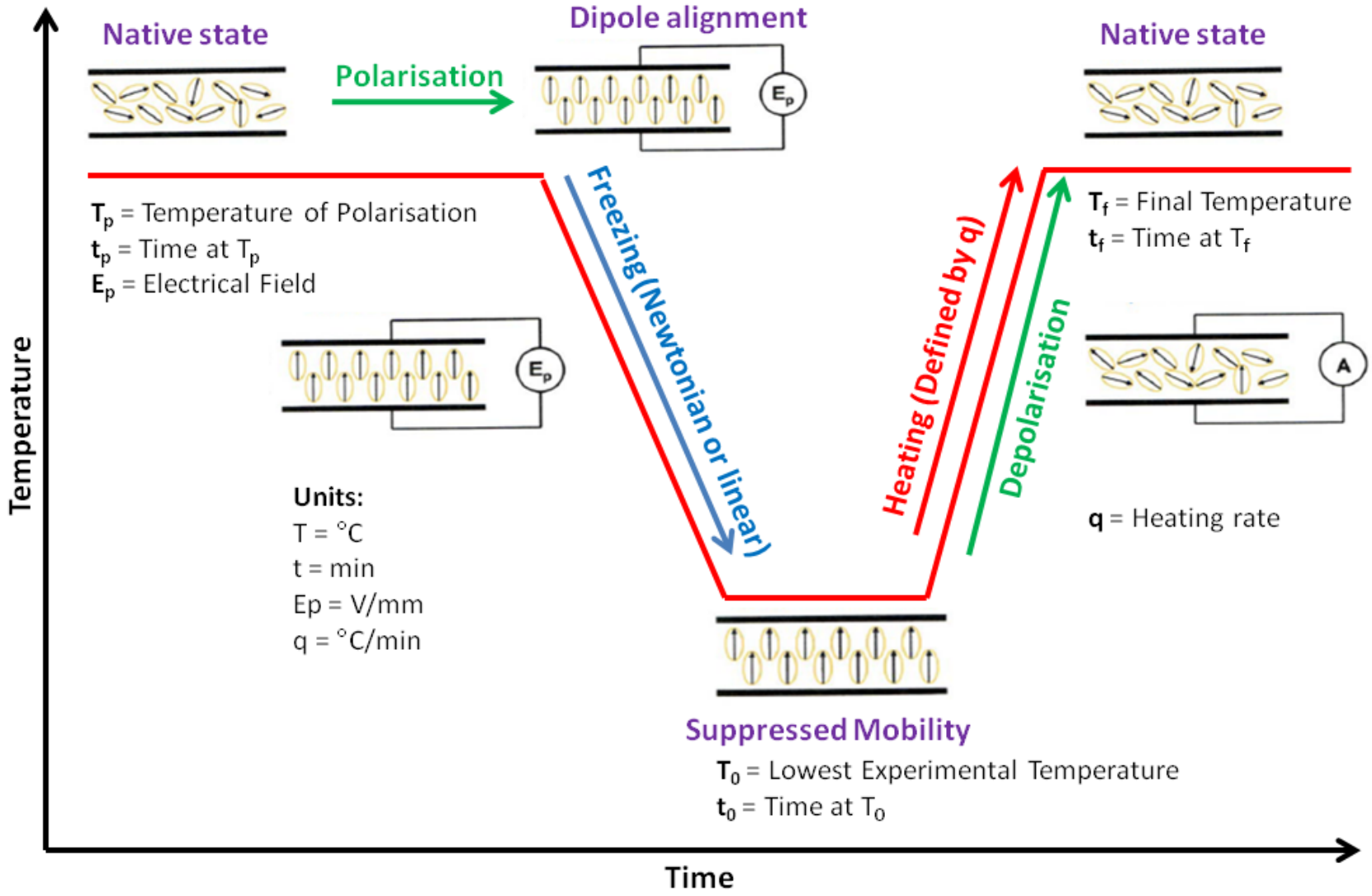
- electrets, ionic crystals
- waxes, resins
- ceramics, plastic
- small organic molecules



Introduction to TSC



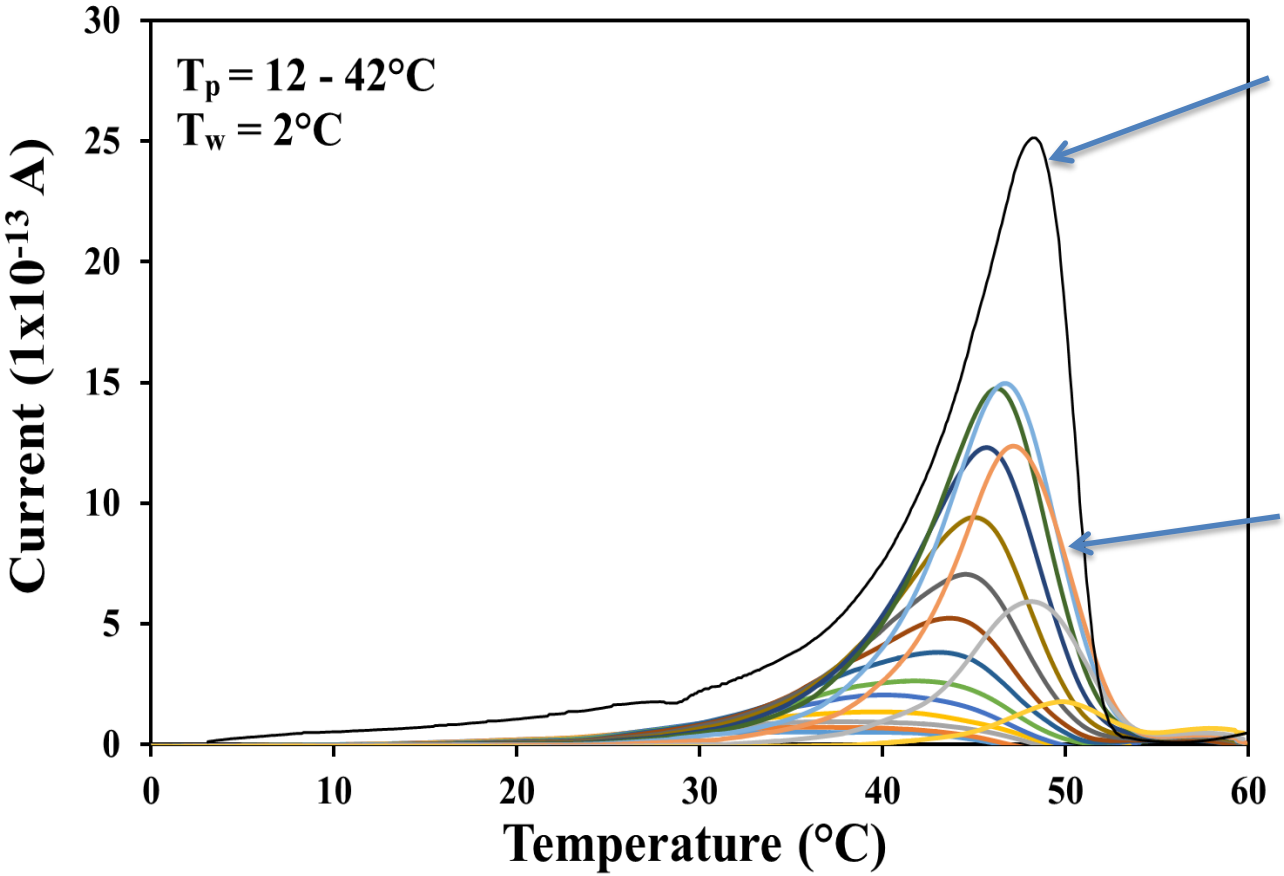
Introduction to TSC



Pharmaceutical Applications

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

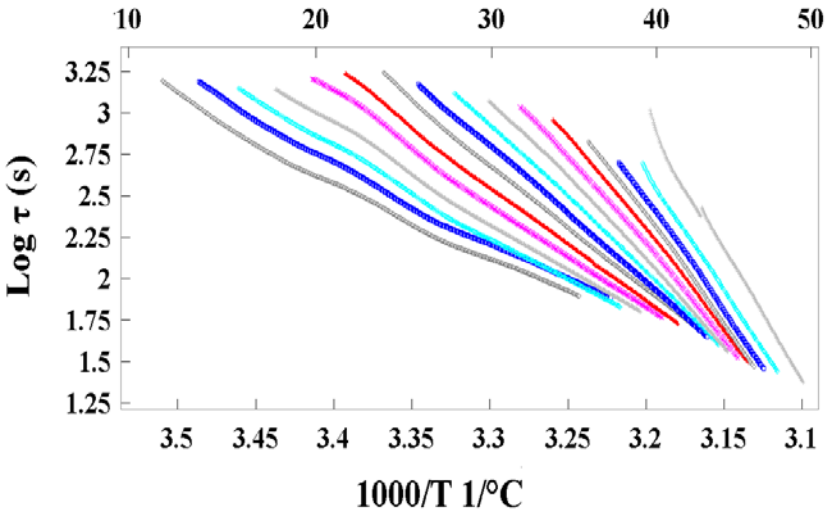
TW outputs



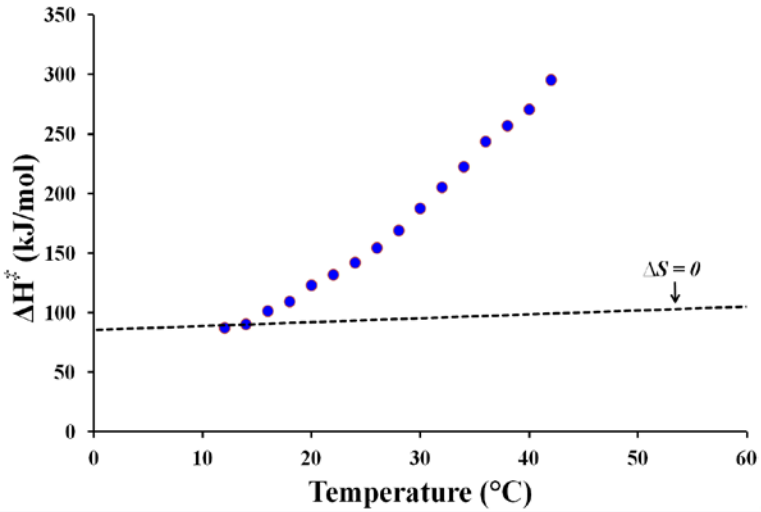
Global glass relaxation process

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

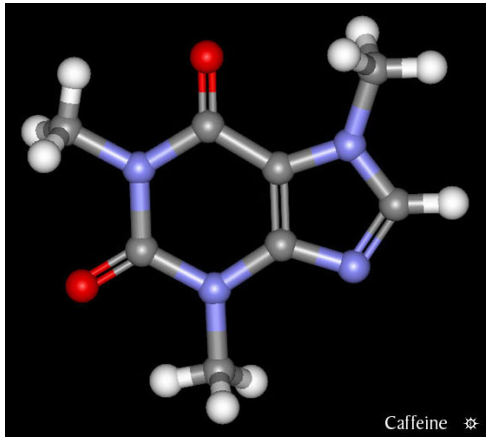


$$Fragility\ Index\ (m) = \frac{1}{2.303}\left[1\frac{E_a\ (Tg)}{RT_g}\right]$$

Pharmaceutical Applications

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

Caffeine



Exists in two polymorphic forms:

Form I, unstable at room T, Trigonal

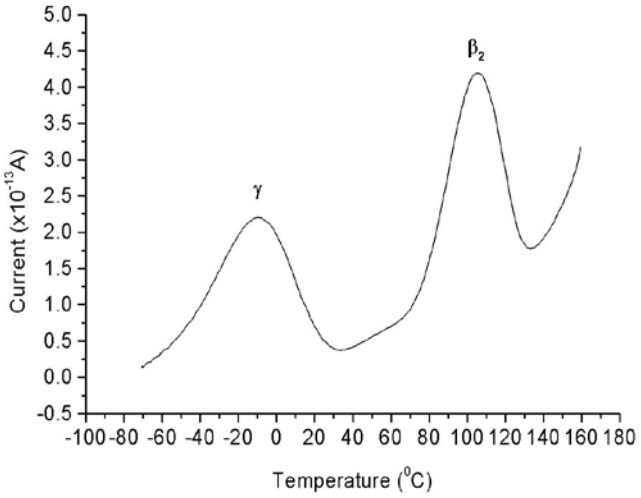
Form II, stable at room T, Monoclinic

Transition point: 141 ± 2°C

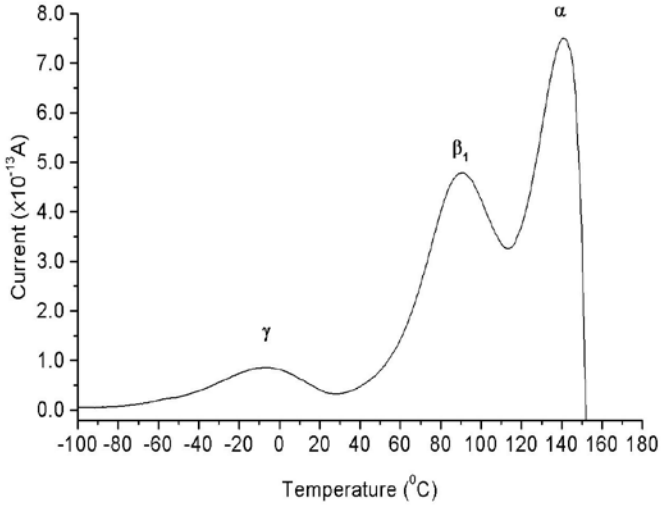
Melting Point: 236 - 243°C (British Pharmacopoeia)

Caffeine - TSDC Results

Form I



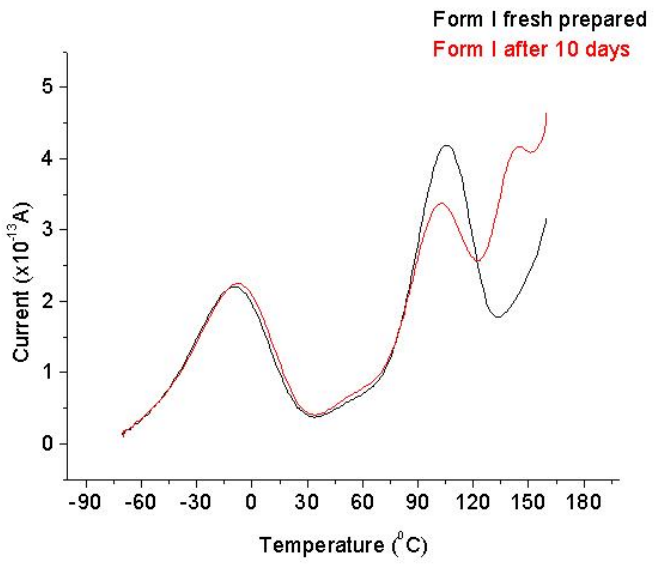
Form II



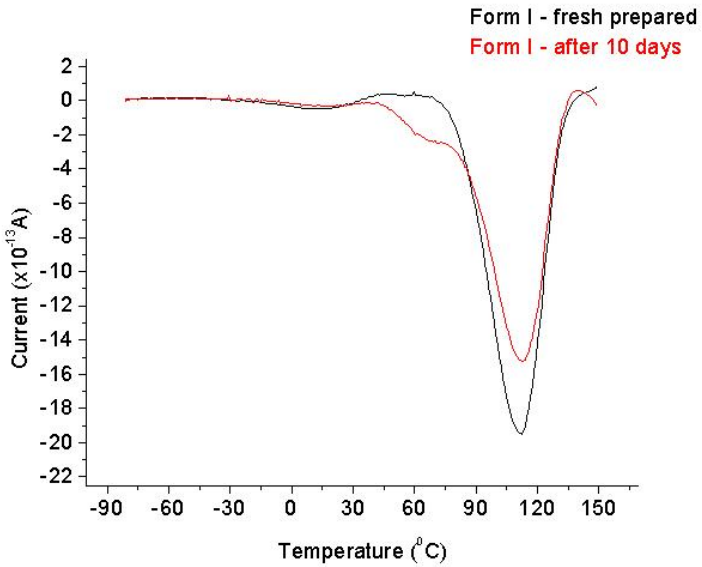
α-process 139ºC Form II only - *polymorphic transition*
γ-process -8ºC Forms I and II - *orientation of side group*
β_1-process 91ºC Form II
β_2-process 107ºC Form I - *orientation/mobility of sub-unit*

Kinetic Parameters - TSC Method

TSDC



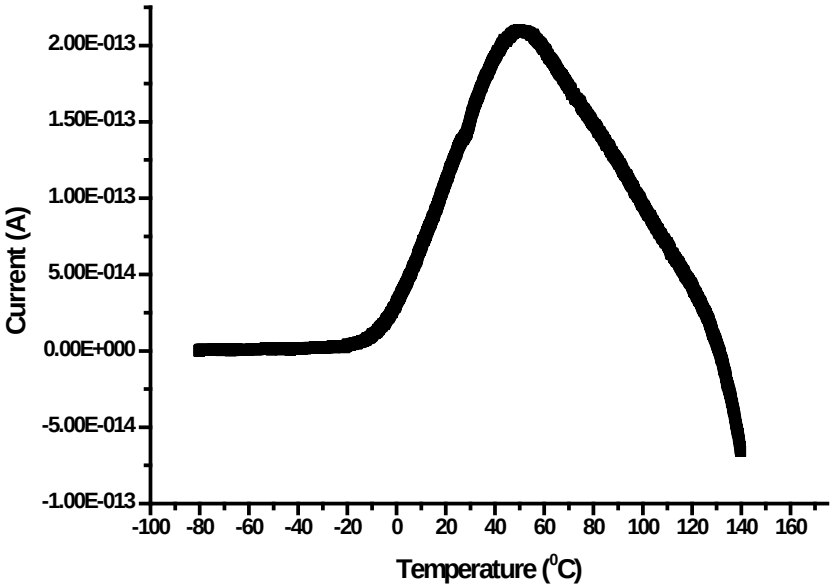
SDC

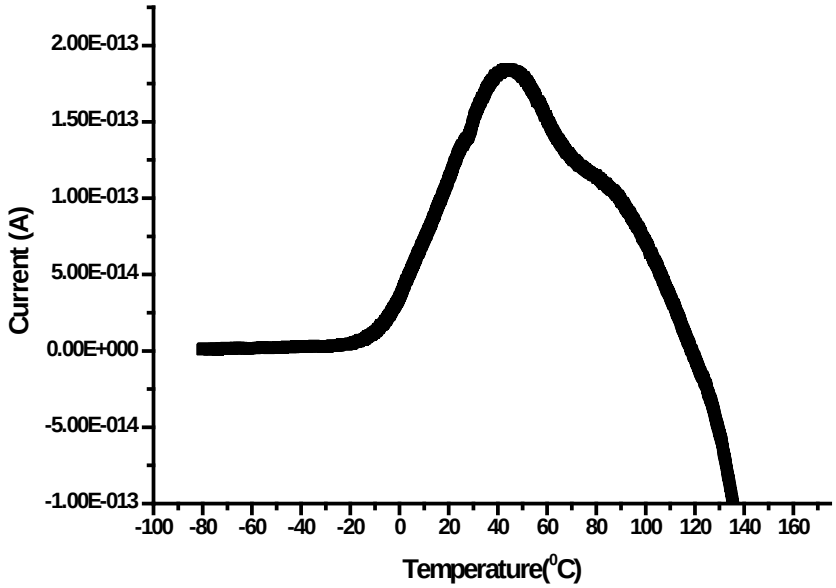


Pharmaceutical Applications

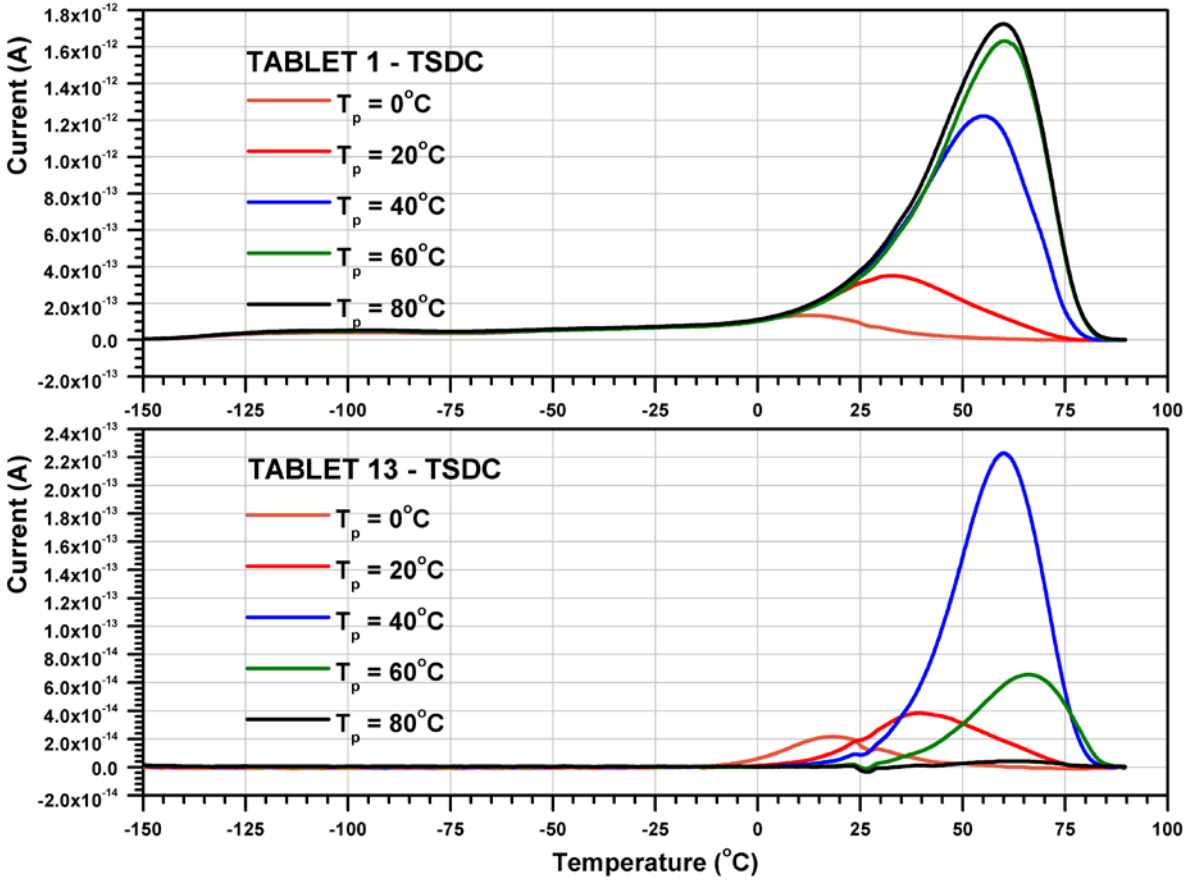
- Amorphous materials
- Polymorphs
- **Batch-to-batch control**
- Co-crystals

Batch to Batch variations





Batch to Batch variations

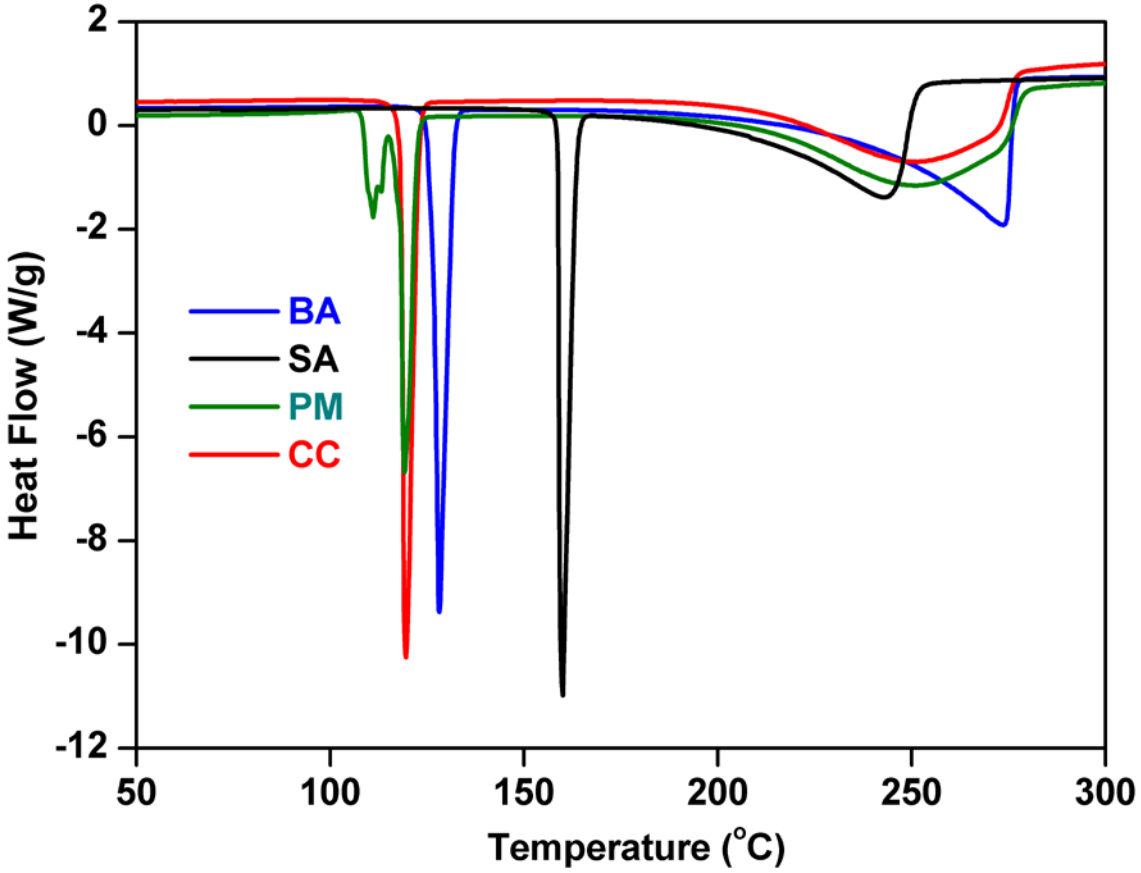


Pharmaceutical Applications

- 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:

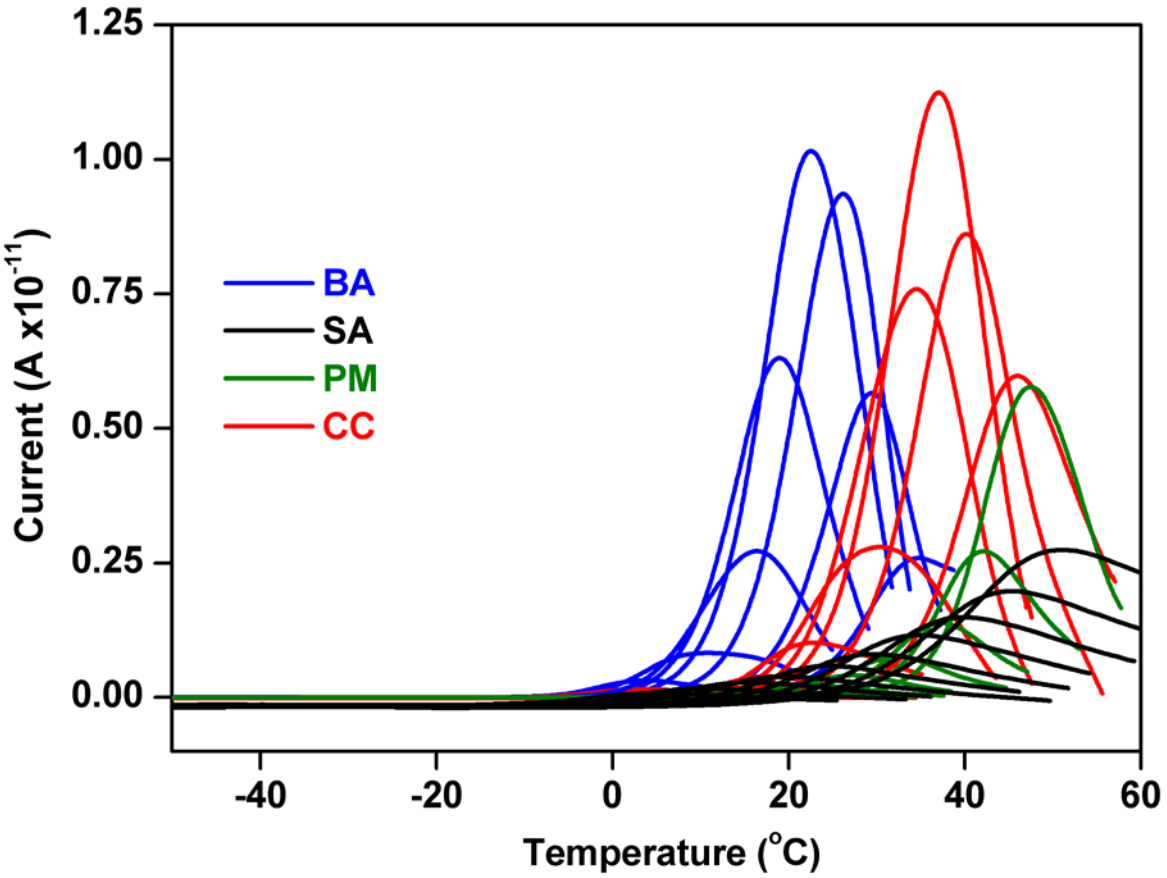
BA = 128°C

SA = 159°C

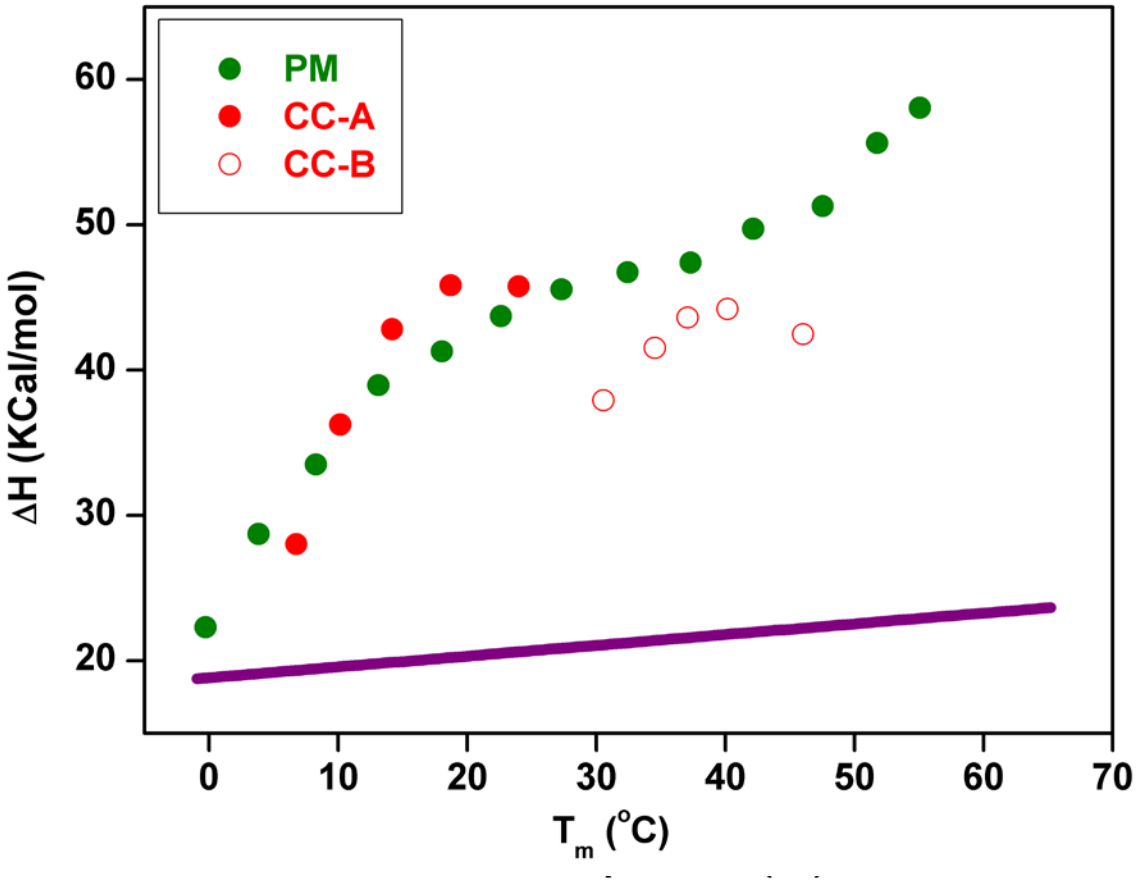
CC = 119°C

PM = 110°C

SA/BA co-crystal system



SA/BA co-crystal system



T_c:

CC-A = 125°C

CC-B = 119°C

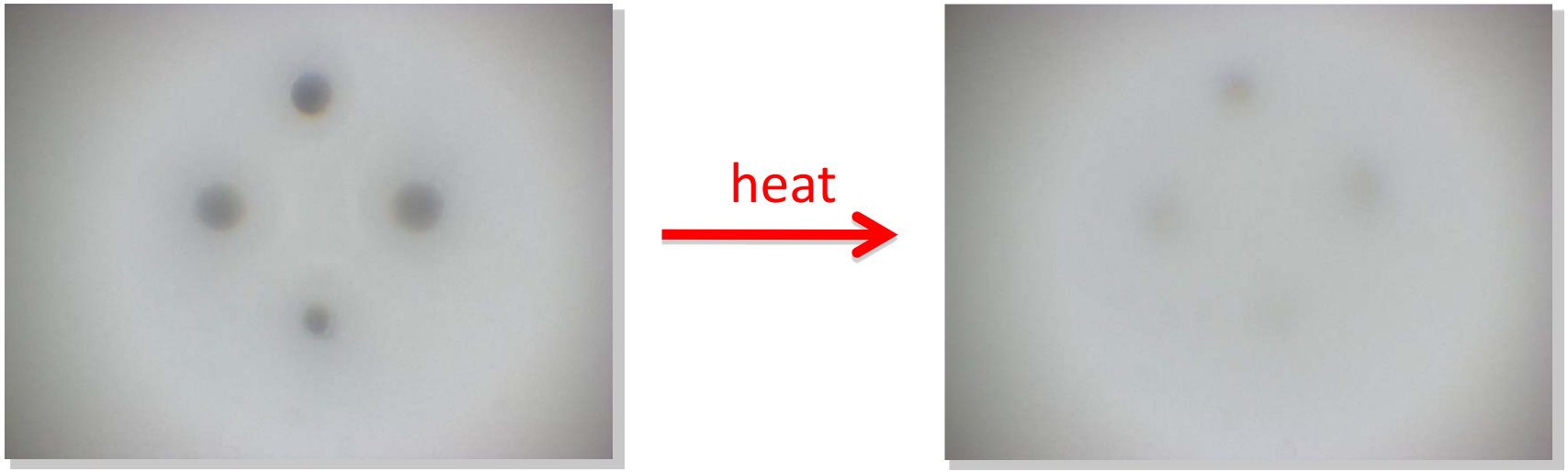
PM = 110°C

Challenge 2

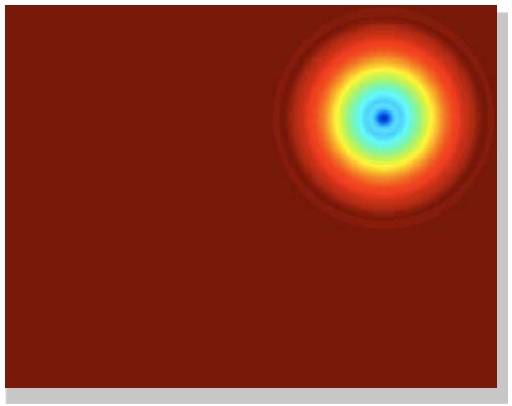
- **Thermal Analysis by Structural Characterisation (TASC)**

- **Thermal Dissolution Analysis (TDA)**

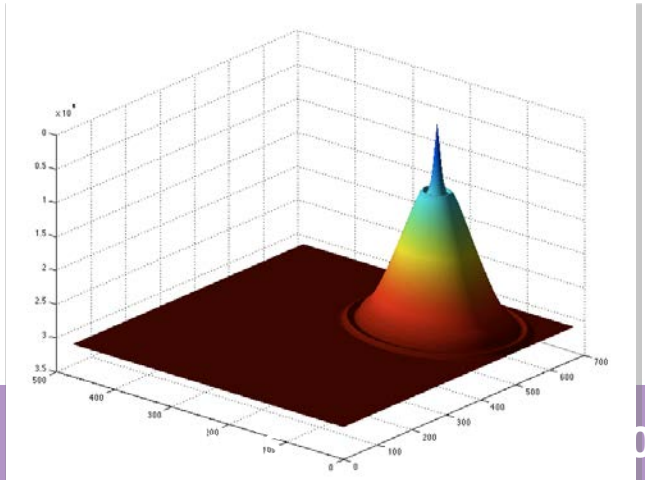
TASC consists of imposing a pattern on the surface of a sample or exploiting pre-existing structure, then characterizing how that pattern changes as the sample is heated; in this case Optical Microscopy was used but it can be applied to other forms of microscopy such as electron microscopy and Atomic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

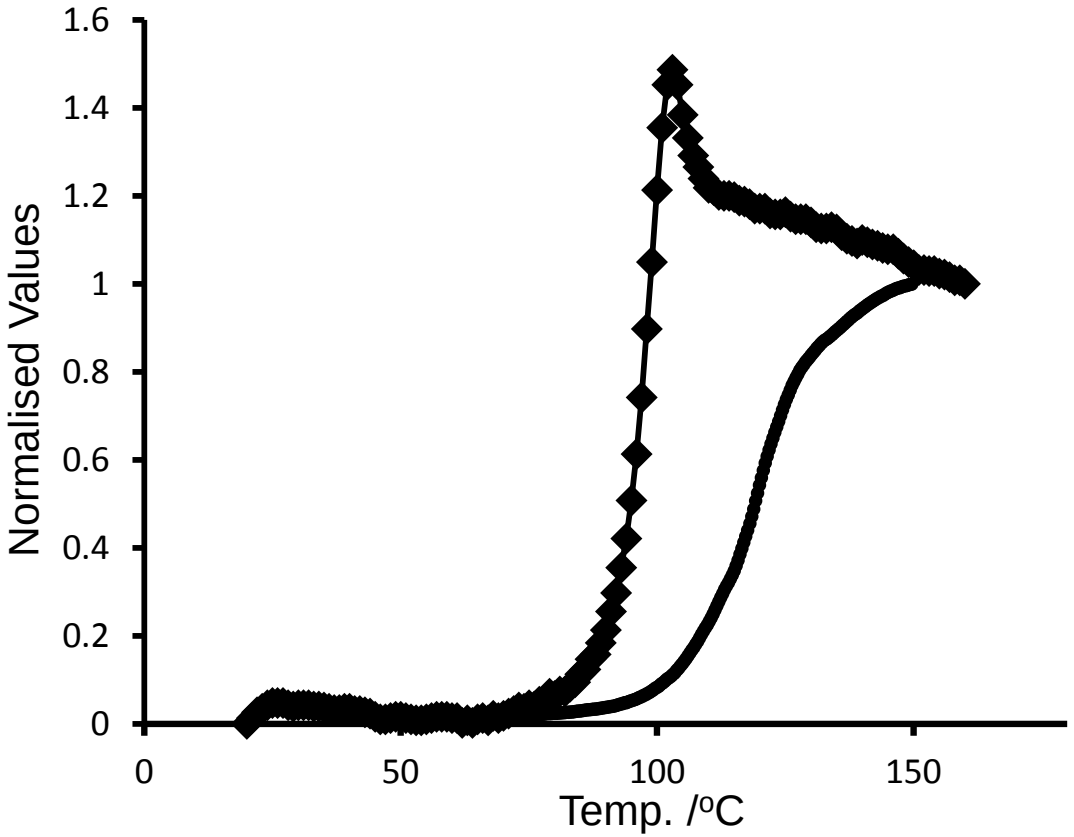


The TASC algorithm scans an area and tries to identify whether a designated structure exists and where it is located. **Top right** there is a schematic of an indentation, underneath this is the result of a TASC analysis.

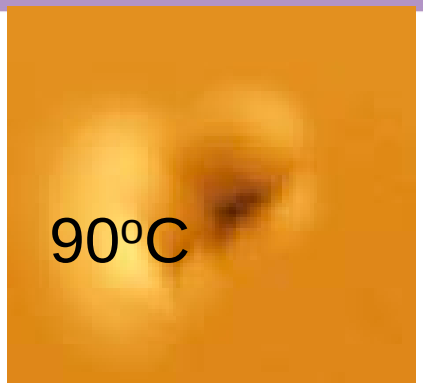


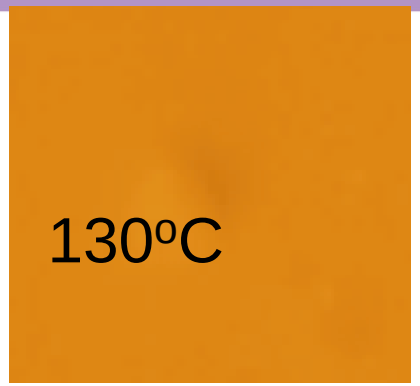
Right is a 3D representation of the output of the TASC analysis. The apex of the cone provides the location of the feature



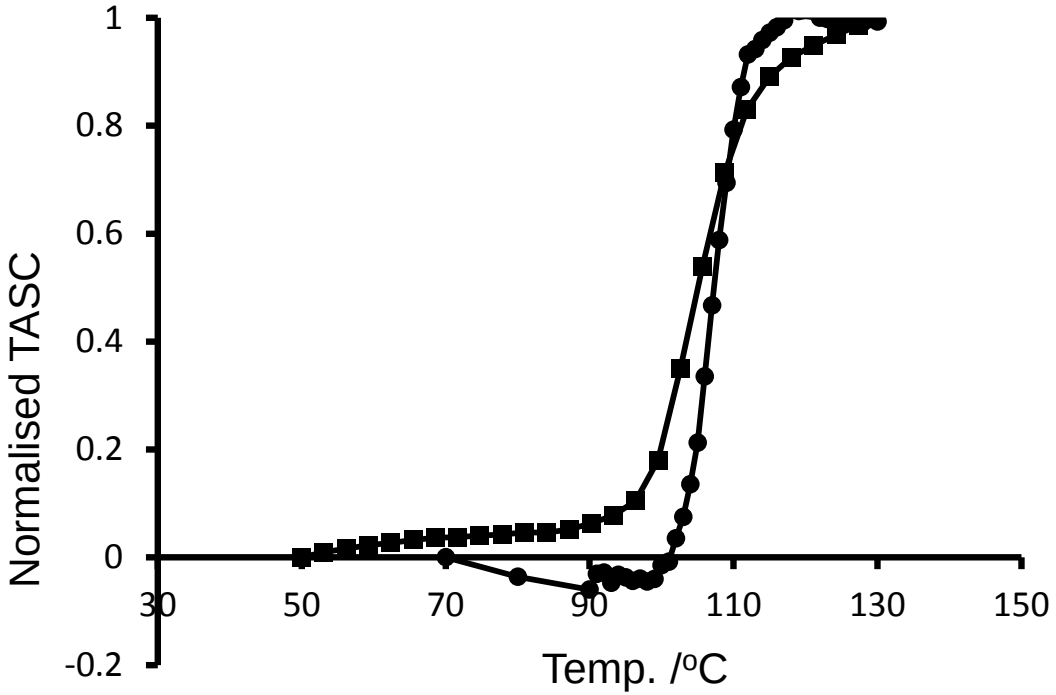


This is graph showing a co-plot of DSC and TASC data. The flow event happens after the glass transition as measured by DSC as expected.





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 200µm in diameter (squares).

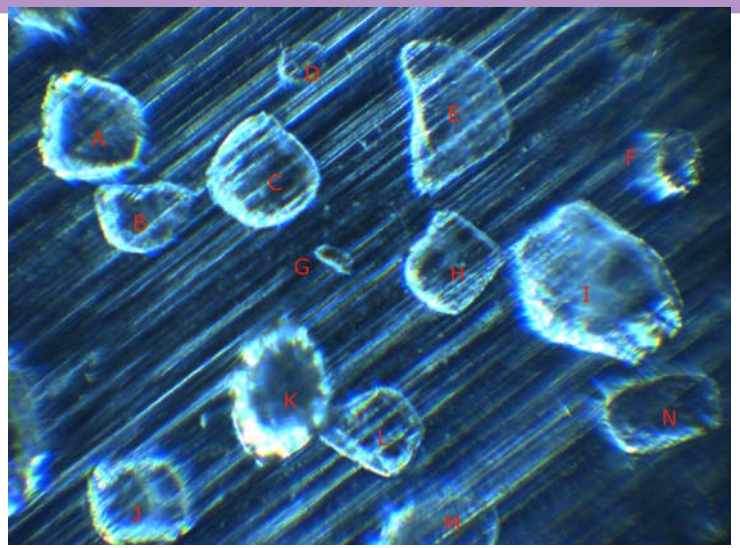


Part 2

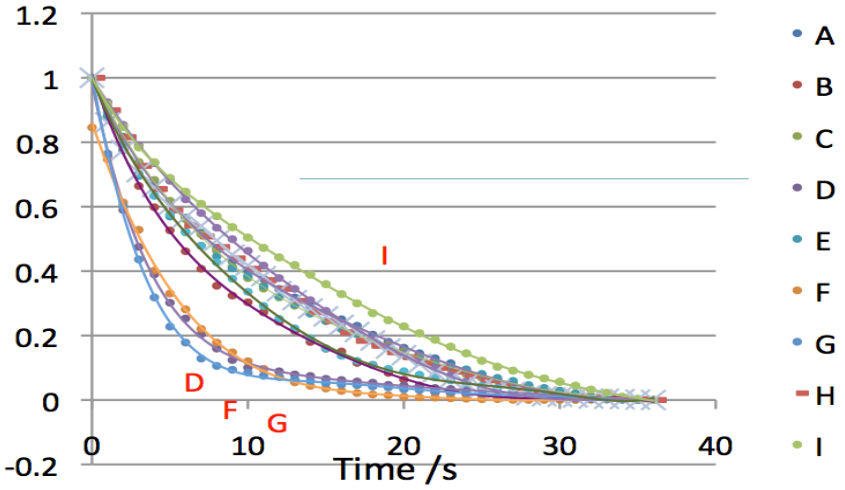
- Thermal Analysis by Structural Characterisation (TASC)

- **Thermal Dissolution Analysis (TDA)**

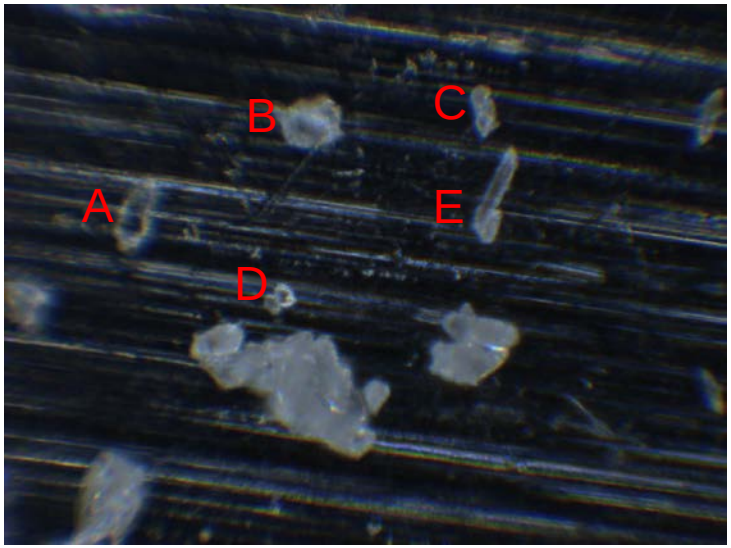
Right is an image of a collection of sugar crystals in water in a DSC crucible. The TASC algorithm can follow their disappearance.

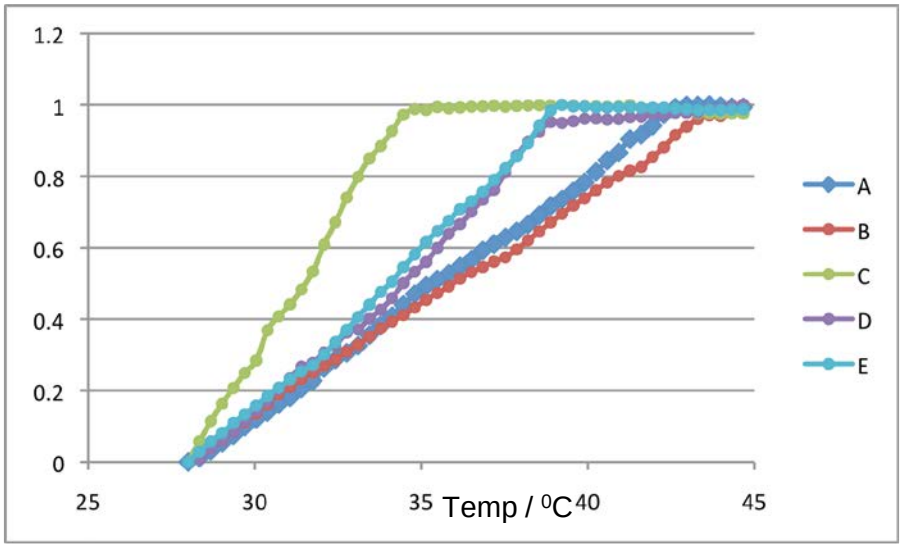


In the graph shown **right**; it can be seen that small crystals D, F and G disappear much faster than the large crystal I.

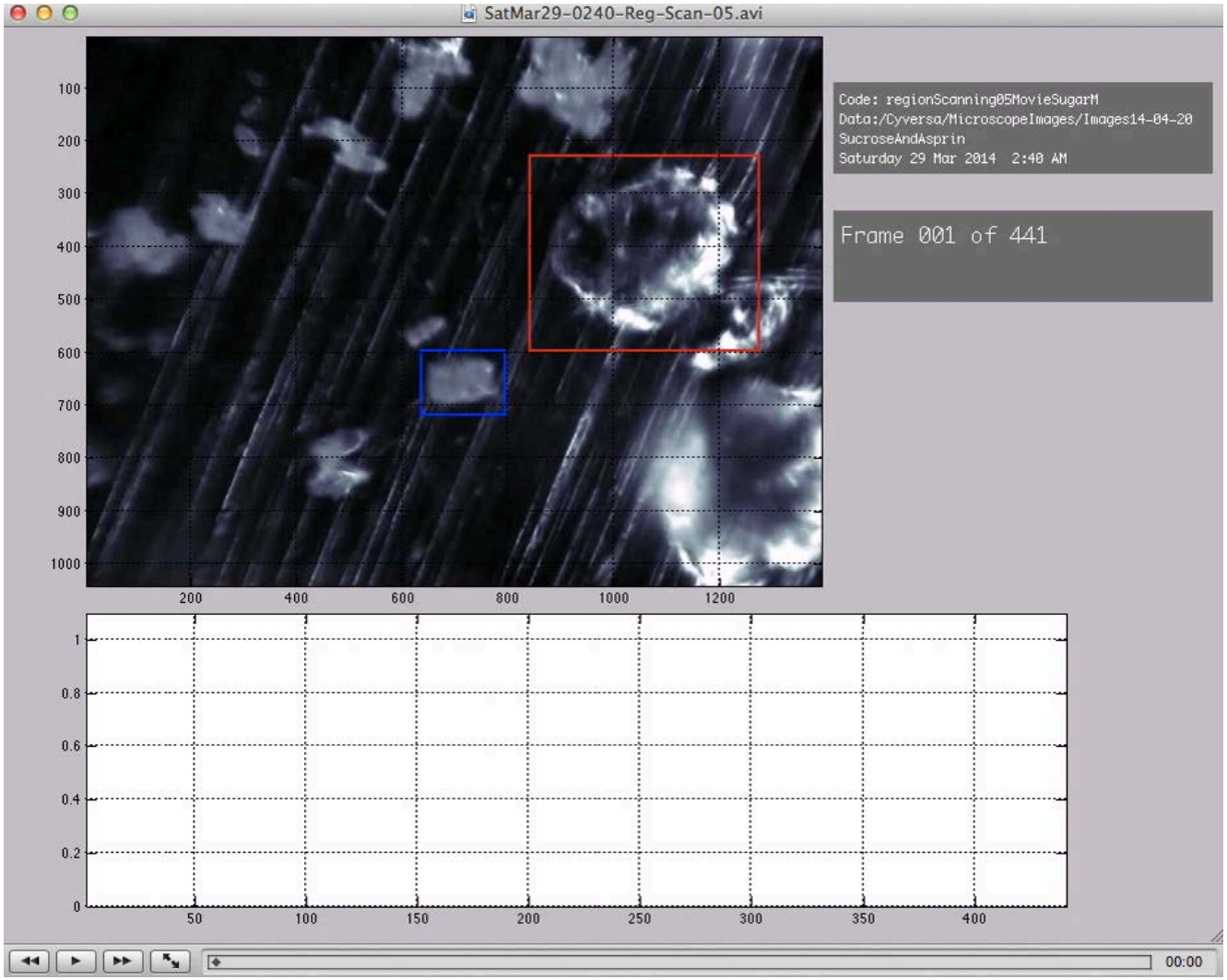


Thermal Dissolution Analysis





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°C/min.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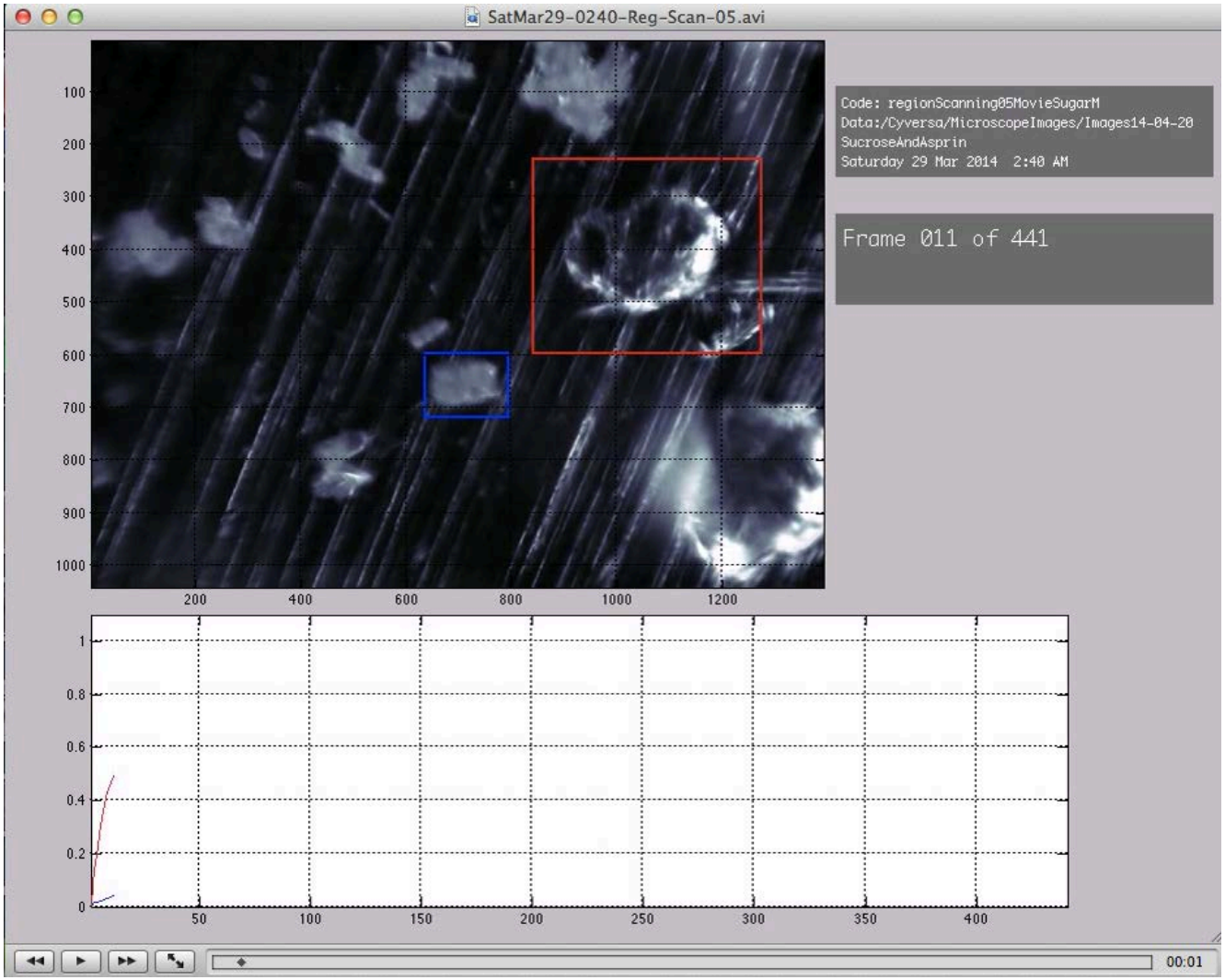
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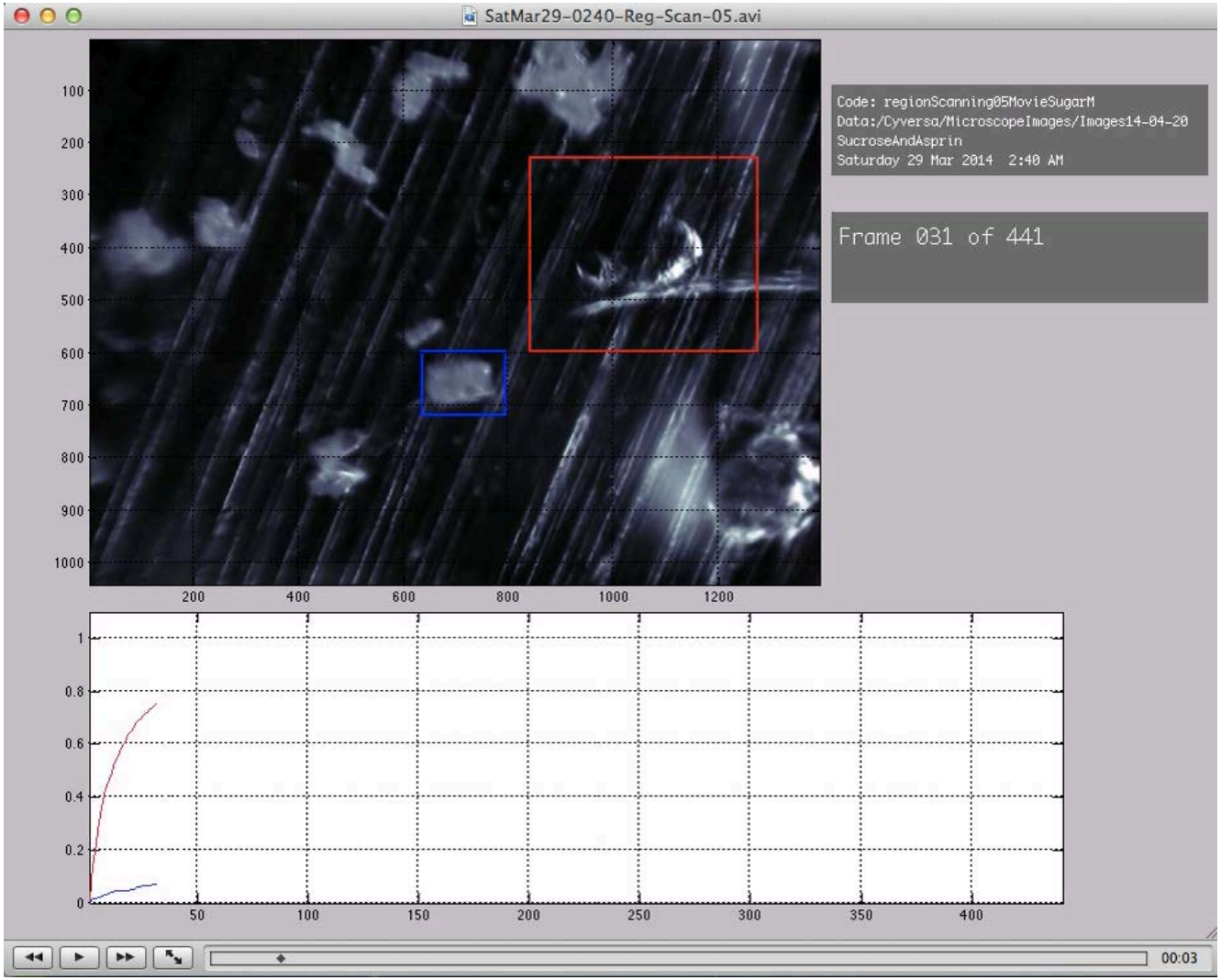
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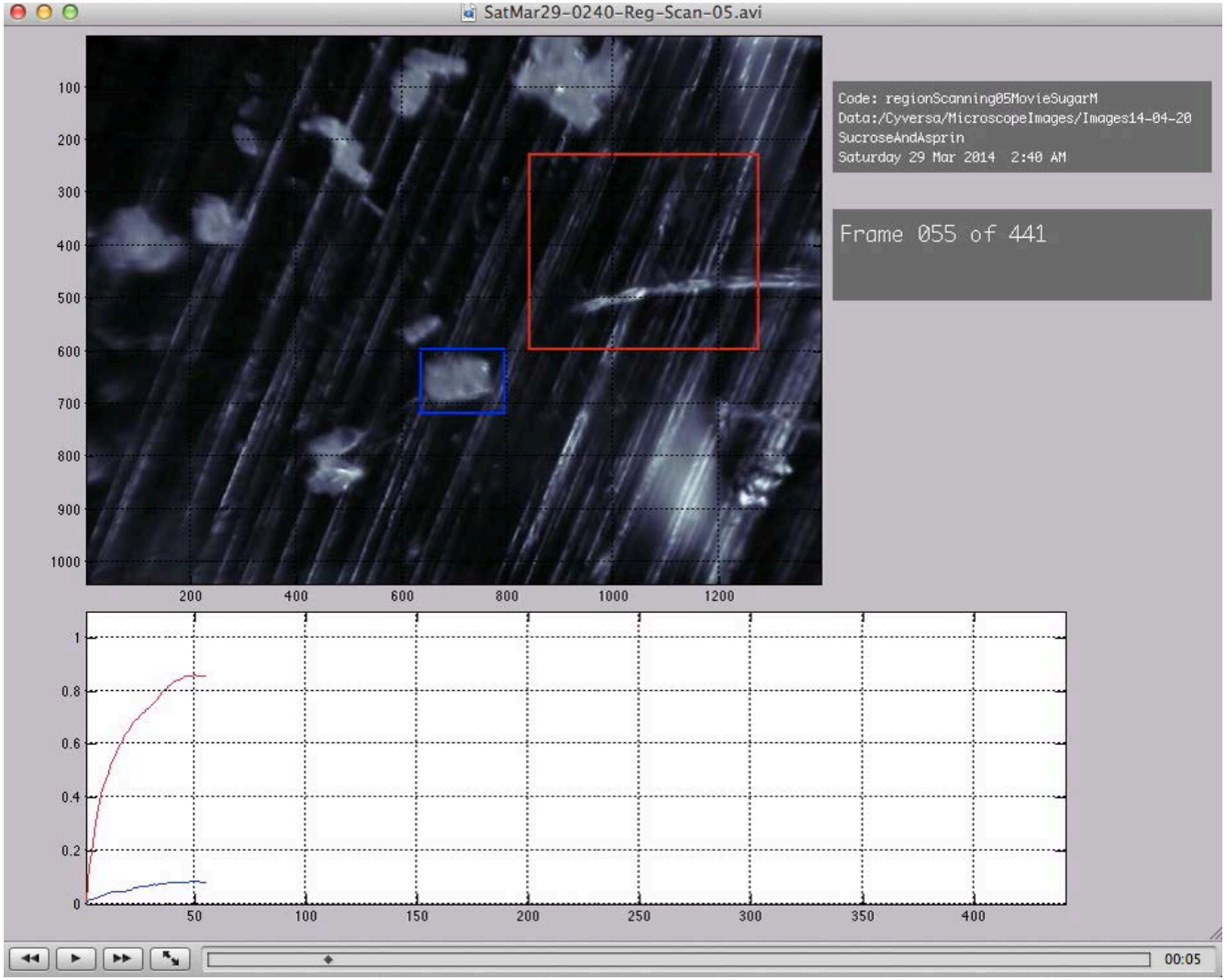
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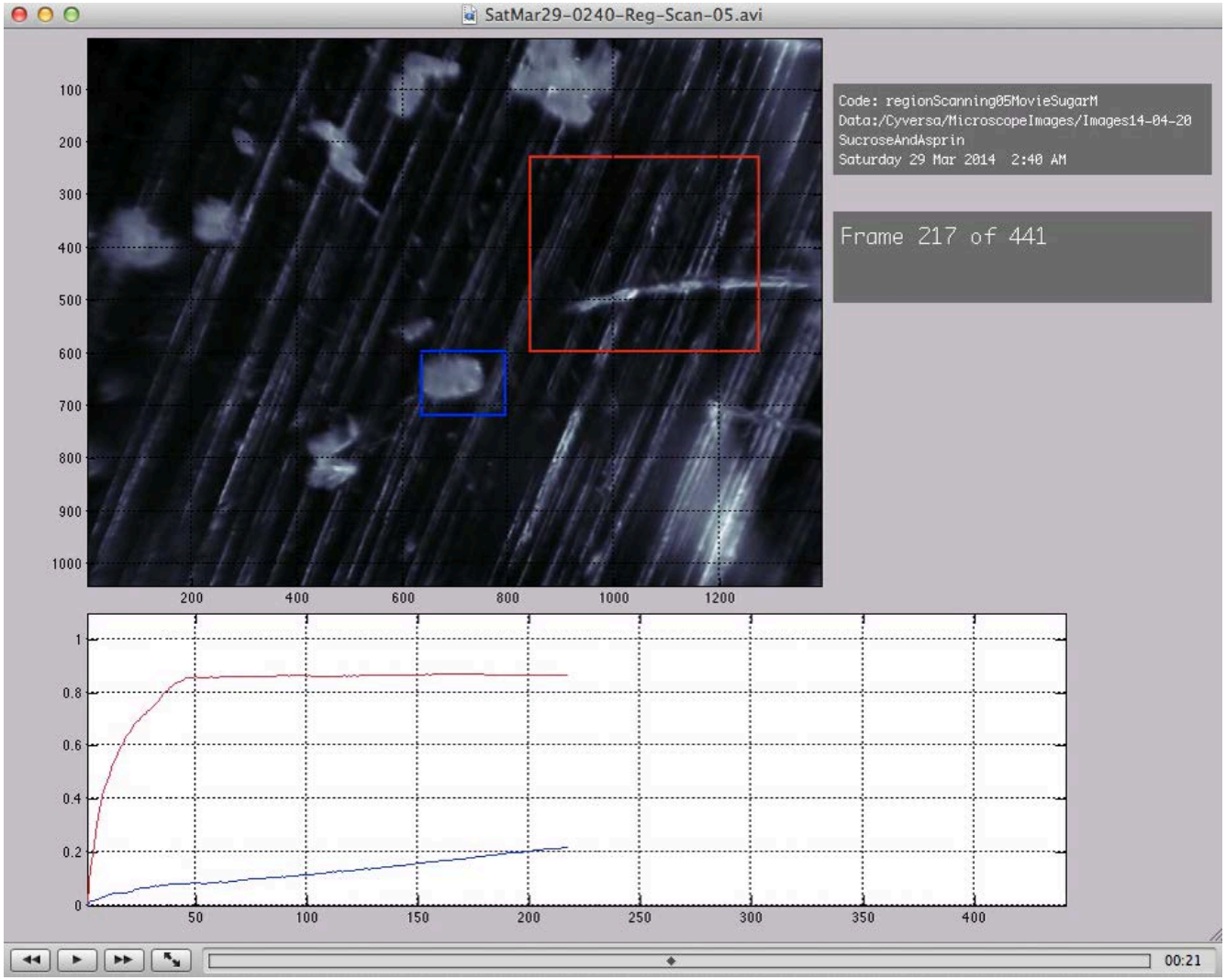
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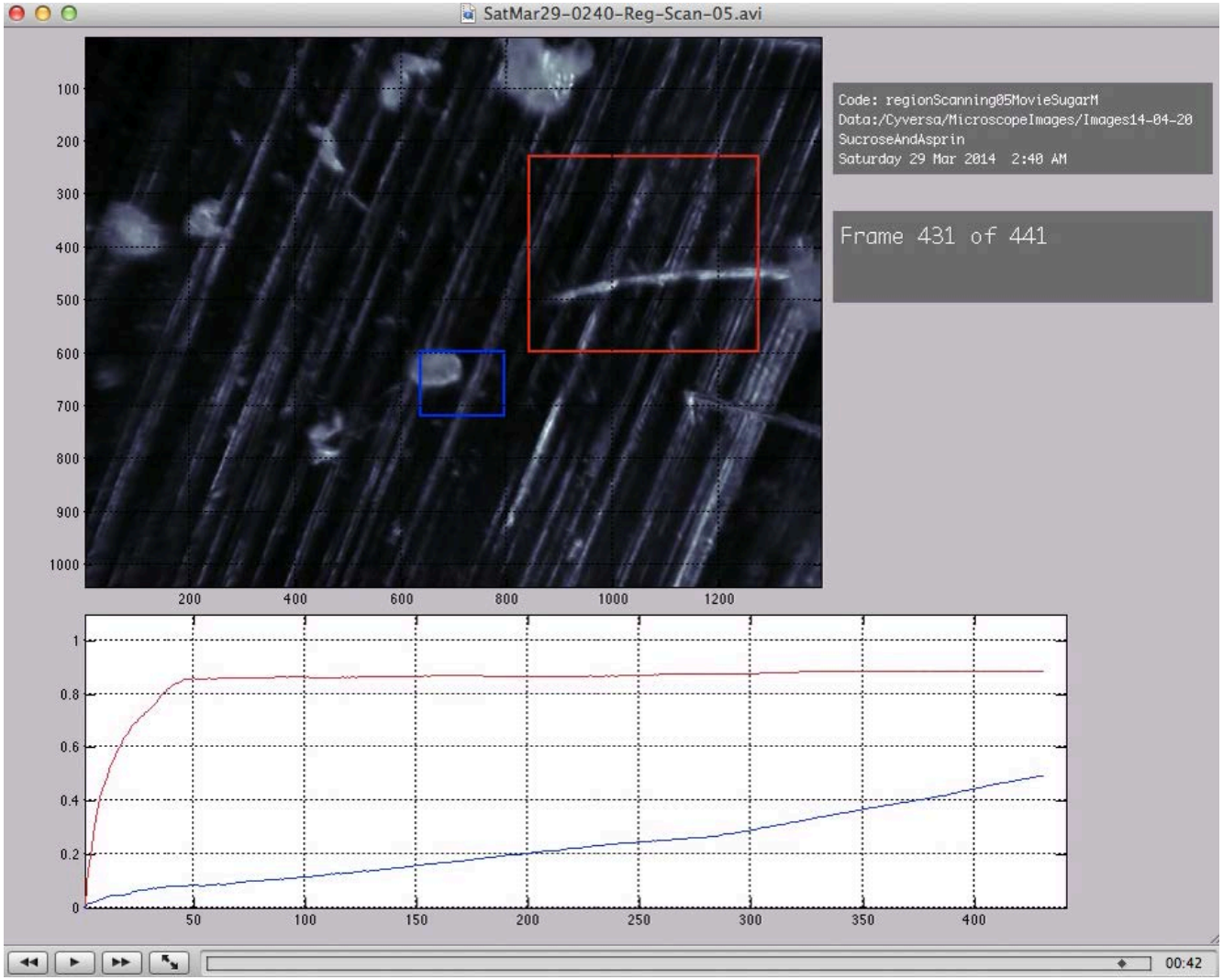
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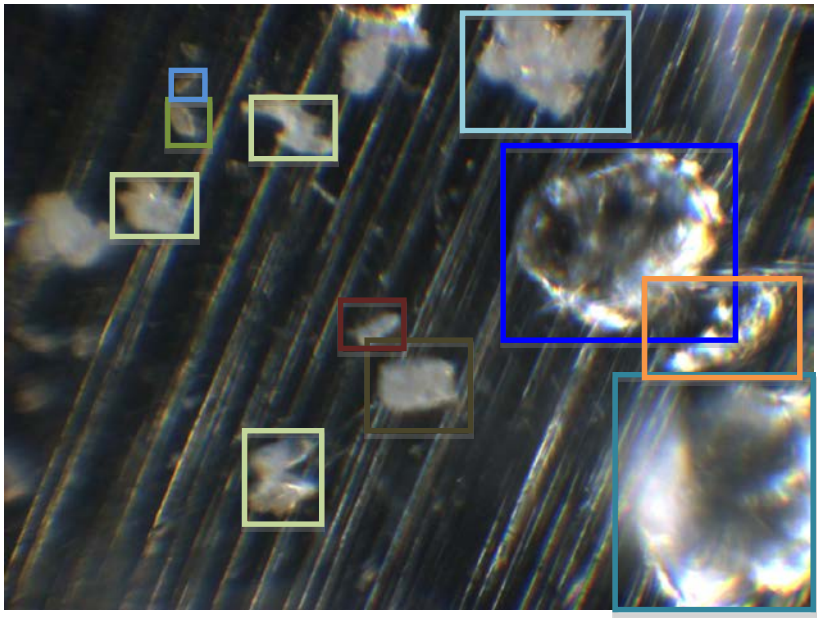
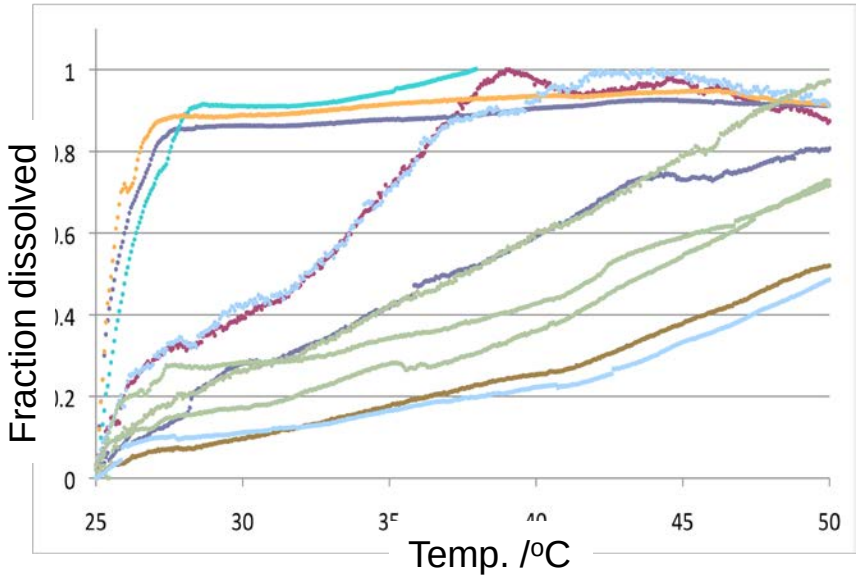
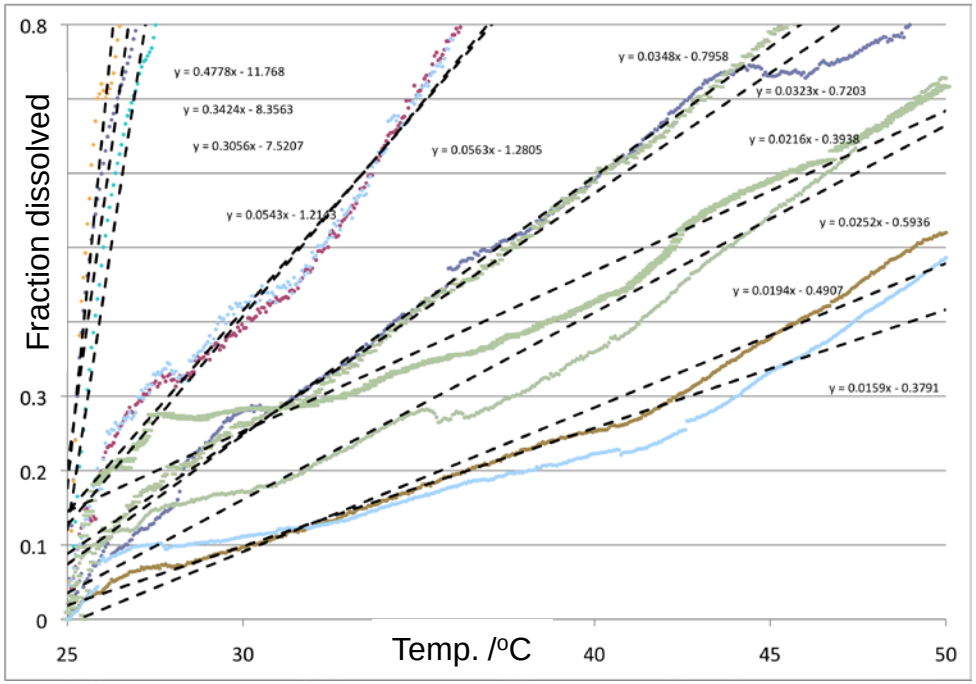
Thermal Dissolution Analysis

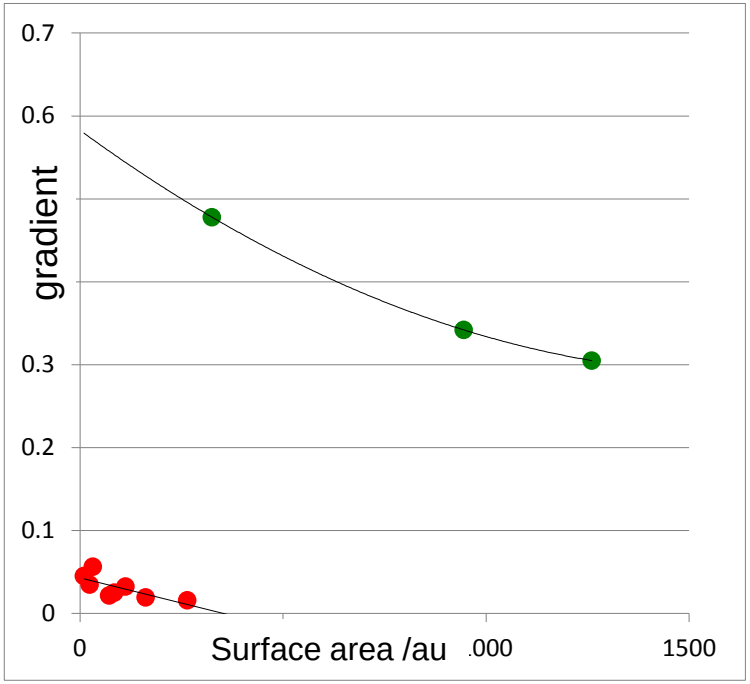




TASC is used to track the dissolution of the objects in the field of view of the microscope. The temperature program was 5°C/min.

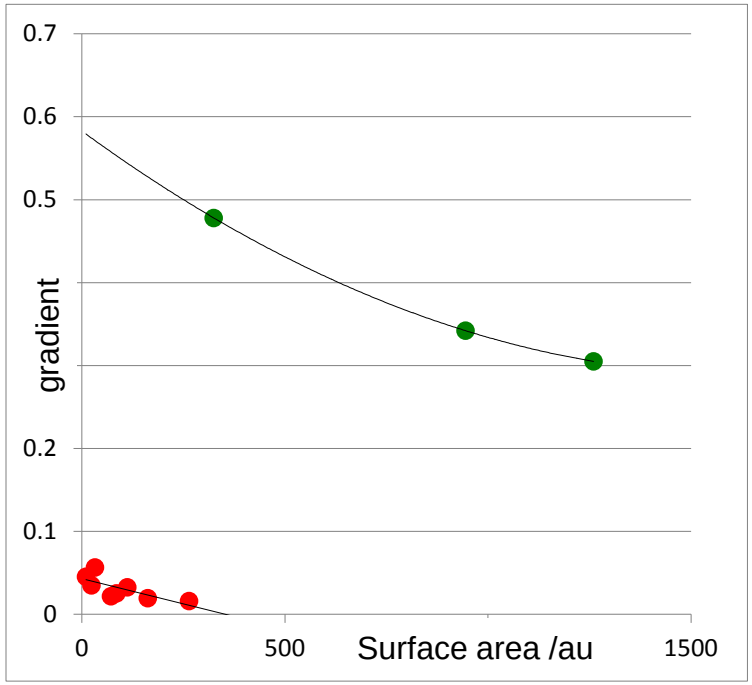
Thermal Dissolution Analysis

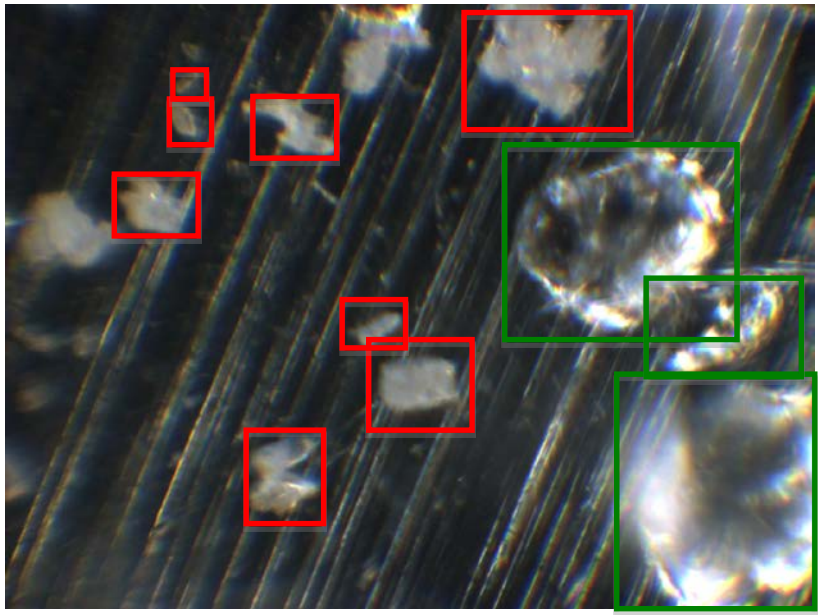




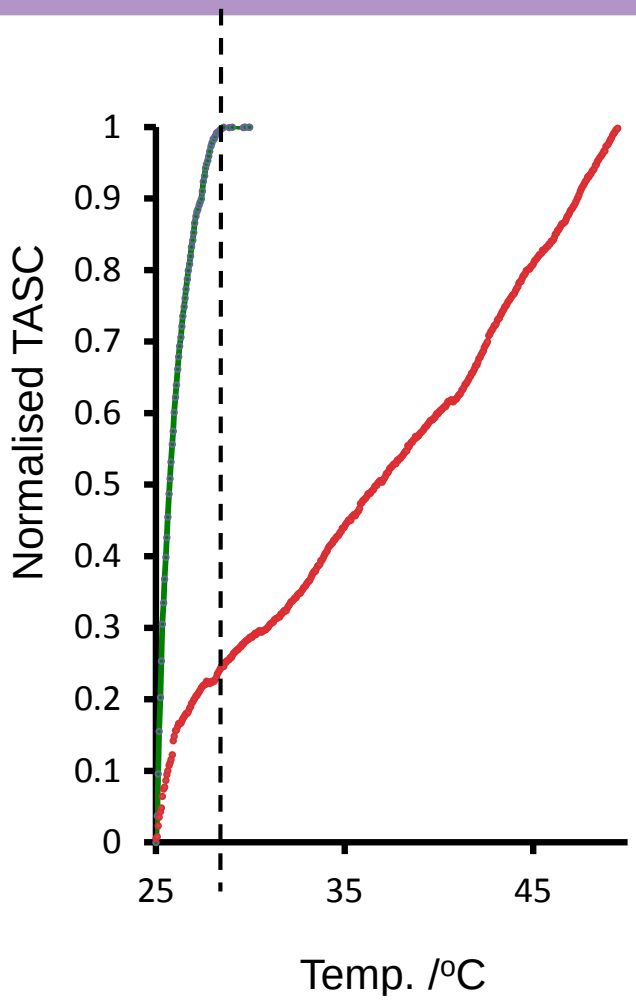
The dissolution behavior clears falls into two categories shown as red and green.

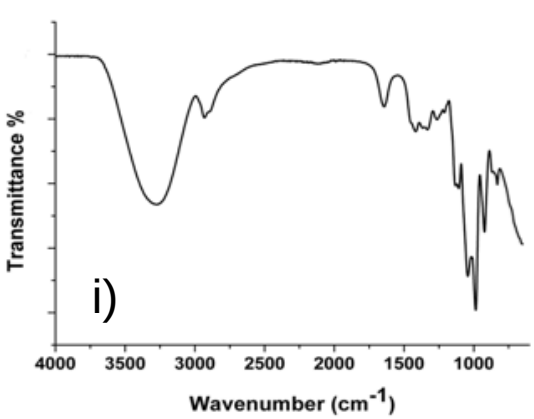
Thermal Dissolution Analysis

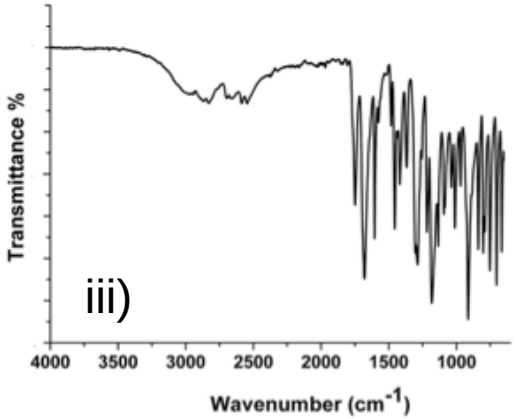


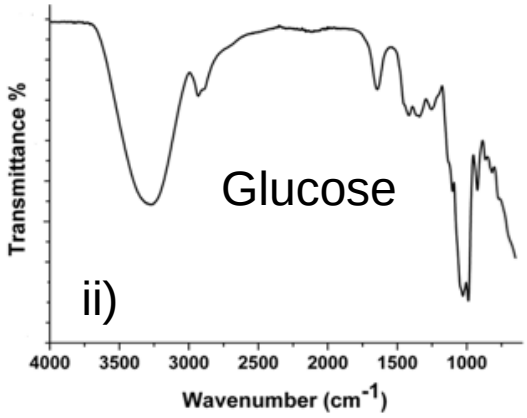


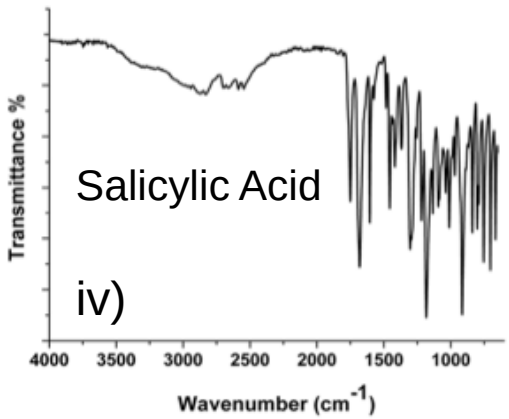
The objects in the field can be allocated to the two categories.







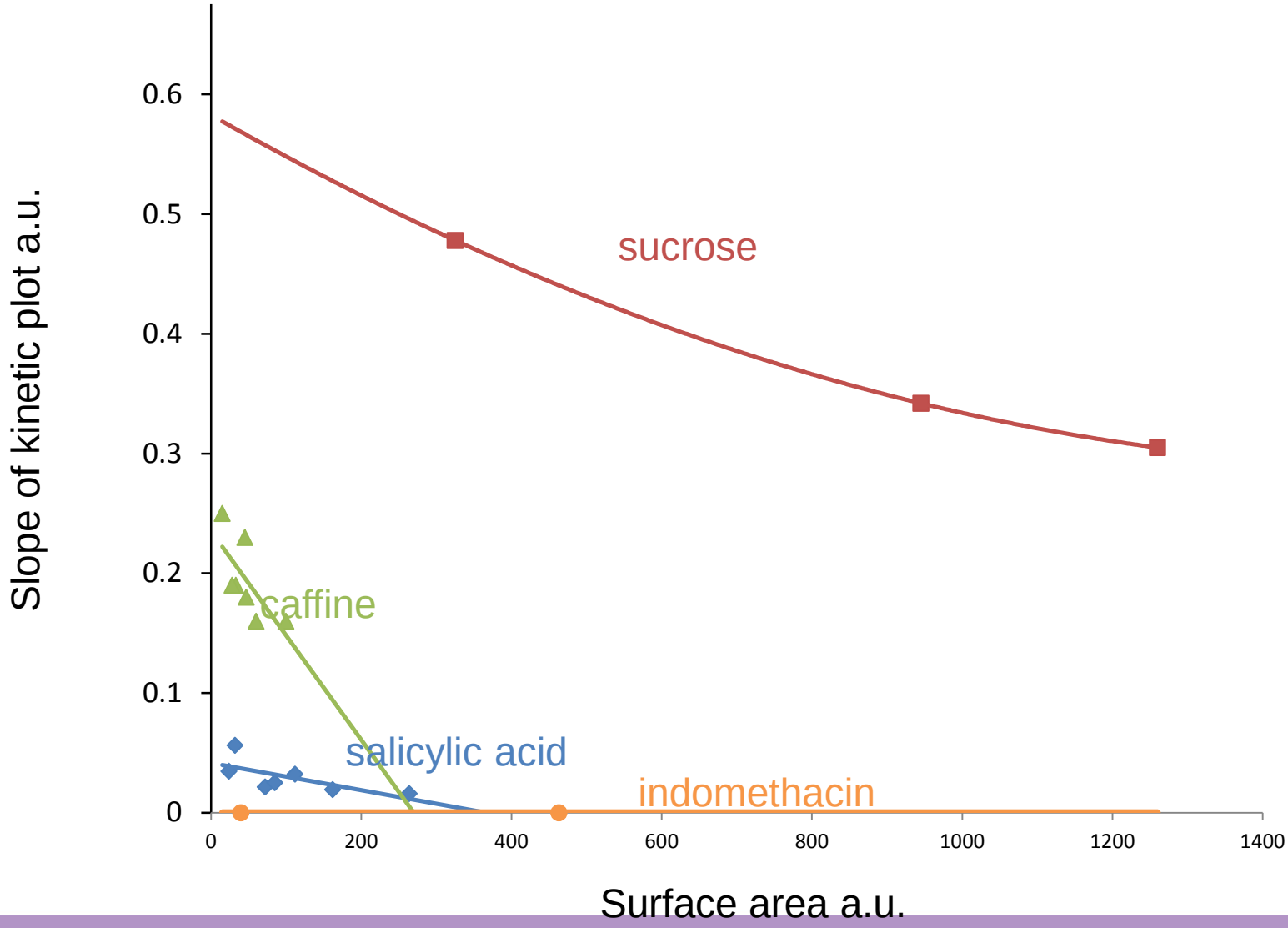




Filtered i) from solvent; iii) from residue

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

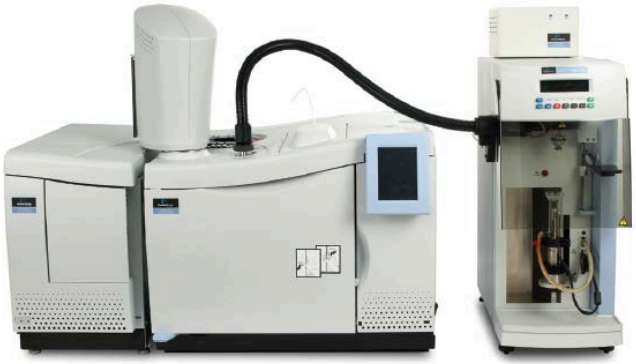


Figure 1: The Pyris 1 TGA coupled to the Clarus 600 C GC/MS gives the most sensitive method to identify evolved gases

Mass Loss

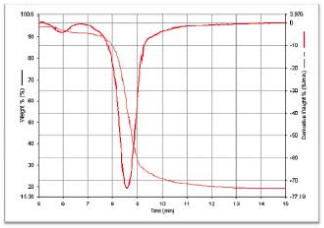


Figure 2: The TGA run of a sample of switch grass shows most weight loss occurs in one temperature range

Chromatography

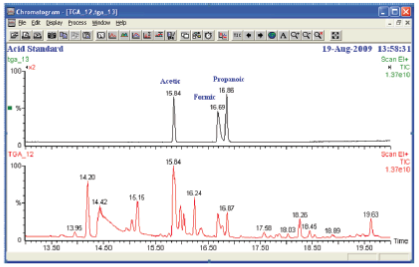
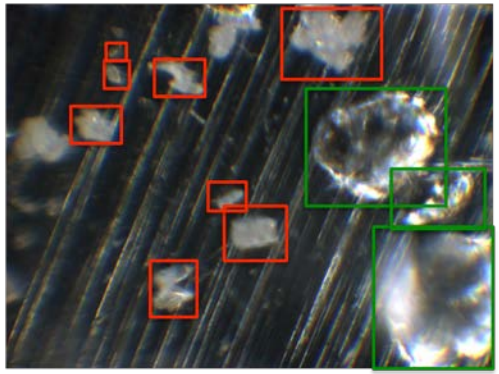
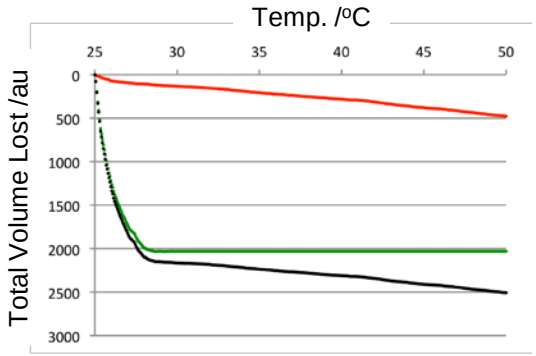


Figure 3: GC/MS on the gases evolved between 8 and 9 minutes and collected on the head of a GC column gave the chromatography seen on the bottom of the graph. MS analysis suggest that 15.8 is the acetic acid, which is confirmed above by running a standard of acetic, formic and propanoic acids

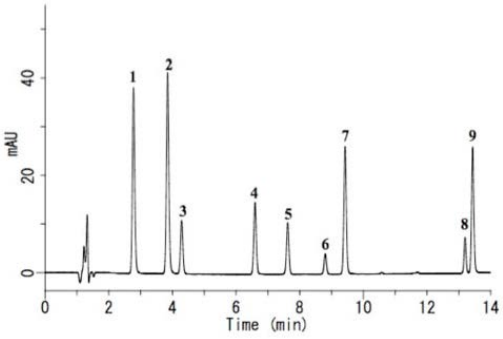
TDA-HPLC



'Volume' Loss



Chromatography



Challenge 3

Do customers get what they pay for?

SCIENCE

UNIVERSITY of GREENWICH

Evaluation of the dispensing efficiency of two commercially available emollient gels

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Aim

The aim of this study was to compare dispensing efficiencies of two commercially available emollient gels, Zerodouble gel (ZD) and Doublebase gel (DB), and to observe differences in the dispensing behaviour of these products.

Materials and Methods

Zerodouble gel evaluation
Each of six marketed 475 g packs (Lot No H134) was weighed prior to testing. During the evaluation, the bottles were held inverted with the cap at the base and gently squeezed to dispense the product out through the valve/cap. The amount of product dispensed was recorded during the trial and at intervals when an air-lock prevented the product from being dispensed.

If an air-lock occurred the bottle was tapped on the bench to allow the product to settle. Maximum effort was used to dispense as much of the product out of the bottle as possible. To achieve this goal, when the bottle was in an inverted position, additional taps on the bottom/ sides were applied to detach the gel that was adhering strongly to the bottle walls.

At the end, the bottle was washed and dried to enable pack weight to be determined.

Doublebase gel evaluation was based on the delivery of the gel as per the bottle design (through the supplied bottle/pump pack). The amount of product dispensed from six 500g bottle/pump packs (Lot No N1530) was recorded during the trial.

If an air-lock occurred, the bottle was shaken and tapped on the bench to allow the product to settle.
At the end of the testing when no further product could be dispensed from the bottle, the bottle was washed and dried to enable pack weight determination.

Results and Discussion

Table 1. Dispensing efficiency for Zerodouble gel (ZD) and Doublebase gel (DB)

Bottle	ZD 1	ZD 2	ZD 3	ZD 4	ZD 5	ZD 6	DB 1	DB 2	DB 3	DB 4	DB 5	DB 6	Average* ZD ± sd	Average* DB ± sd
Starting bottle and product weight (g)	526.10	525.11	525.70	526.65	525.55	526.41	588.57	592.84	586.45	586.80	592.48	589.23	525.88 ±0.63	589.56 ±3.03
Empty bottle (g)	44.81	44.64	44.98	44.57	44.67	44.66	87.96	88.65	88.16	88.74	88.22	88.48	44.70 ±0.16	88.45 ±0.26
Total quantity of starting product (g)	481.29	480.47	480.72	482.08	480.88	481.75	500.61	504.19	498.29	498.06	504.26	500.75	481.18 ±0.70	501.11 ±3.03
Total quantity of product dispensed by squeezing the bottle/pumping out (g)	409.06	417.68	417.75	418.88	419.73	417.58	486.97	490.47	486.27	488.86	494.40	489.05	418.32 ±0.95	489.81 ±2.98
% of product dispensed from bottle by squeezing/ pumping out from weight declared (475g for ZB and 500g for DB)	86.1	87.9	87.9	88.2	88.4	87.9	97.4	98.1	97.3	97.8	98.9	97.8	88.1 ±0.2	98.0 ±0.6

*Average calculations were based on 5 trials (2-6) as the first trial was used to establish and develop a correct dispensing technique

Upon examining the dispensing efficiency of two emollient gels (Zerodouble and Doublebase), it is evident that significant differences exist, as suggested from the results presented in Table 1.

The Zerodouble formulation had a great tendency to adhere to the walls of the plastic bottle (Fig. 1). Only 88% of the product could be dispensed even with repeated and vigorous tapping around the bottle. Air locking was observed during the second squeezing action and throughout the use of the product. Furthermore, a great deal of effort was needed to remove the remaining Zerodouble product from the bottle. Strongly attractive interactions between the formulation and the bottle prevented a greater amount of the product from being dispensed. It was noticed that the Zerodouble batch numbers were easily removed during bottle handling and washing.

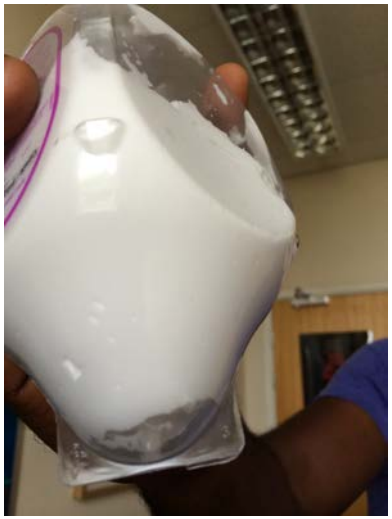
Figure 1. Images of Zerodouble and Doublebase packaging after maximum amount of product is dispensed

In the case of Doublebase gel, the trial revealed that 98% of the gel was dispensed from the original pump/bottle packaging. Air locking was infrequent and mainly observed towards the end, when a very small amount of the product was left in the bottle. The Doublebase bottles were easily washed. This suggests low interaction between the formulation and the bottle material, which was also evident during product dispensing.

Conclusion

There were significant differences in the dispensing efficiency between the two commercially available emollient gels. Zerodouble Gel, packaged in a 475 g squeezy bottle dispensed on average 88.1% of the declared weight, whereas Doublebase Gel, packaged in a 500 g pump dispenser, dispensed on average 98.0% of the declared weight.


Zerodouble
GEL
475g
A highly moisturising emollient gel for dry skin conditions



Bottle	ZD 1	ZD 2	ZD 3	ZD 4	ZD 5	ZD 6	DB 1	DB 2	DB 3	DB 4	DB 5	DB 6	Average* ZD ± sd	Average* DB ± sd
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Empty bottle (g)	44.81	44.64	44.98	44.57	44.67	44.66	87.96	88.65	88.16	88.74	88.22	88.48	44.70 ±0.16	88.45 ±0.26
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Conclusions

Challenges are all around us
some are new, some old

They are often complex

therefore

Thoughtful approach and joint effort, often involving innovative intellect, is required to solve them

Innovation often faces challenges and challenges in one area drive innovation in another


Keeping your attention was my challenge for today
Thank you!!!