UNIVERSITY of GREENWICH

Detection and characterisation of previously unreported molecular mobility of pharmaceutically important molecules by Thermally Stimulated Current (TSC) Spectroscopy

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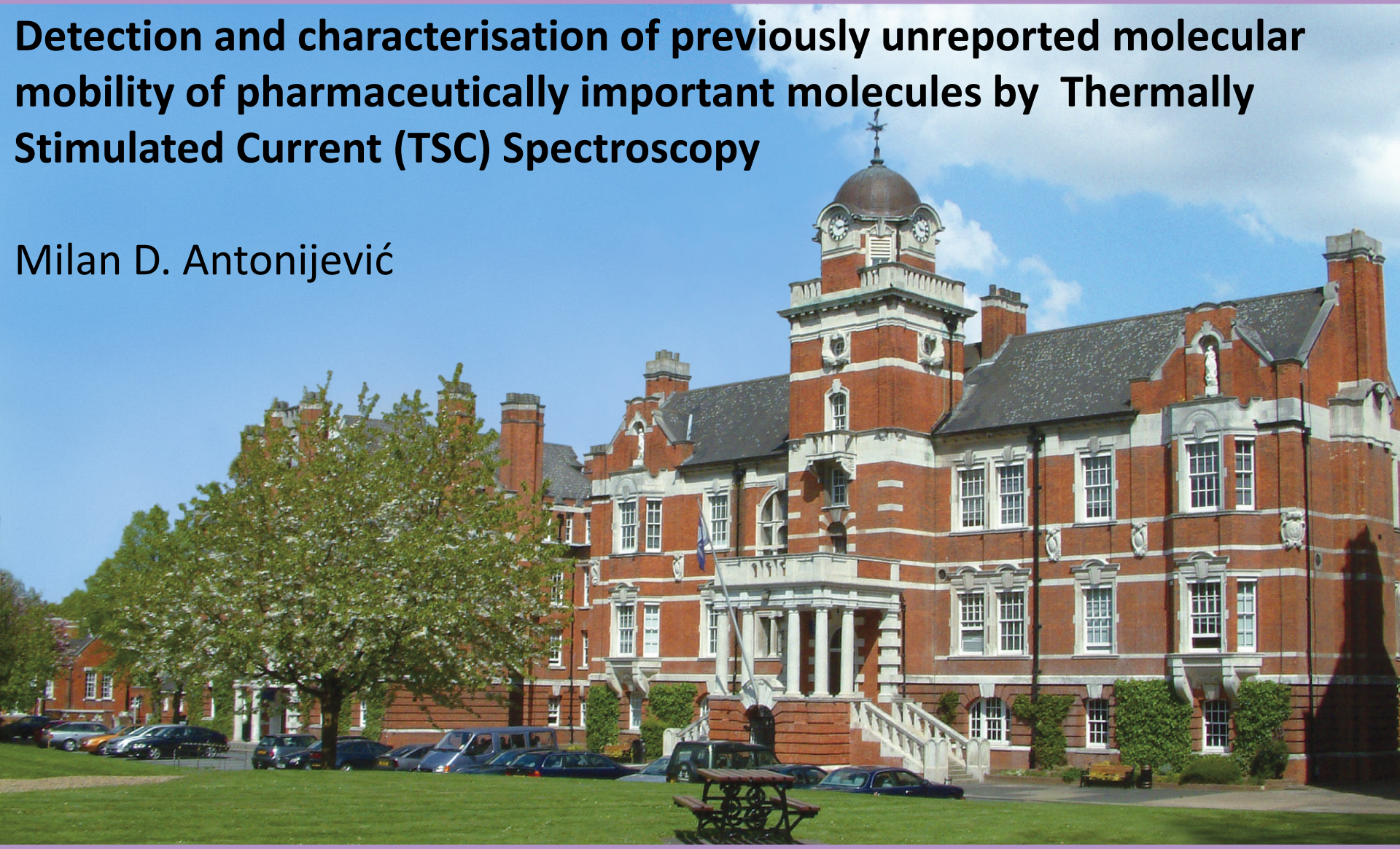


Overview of presentation

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

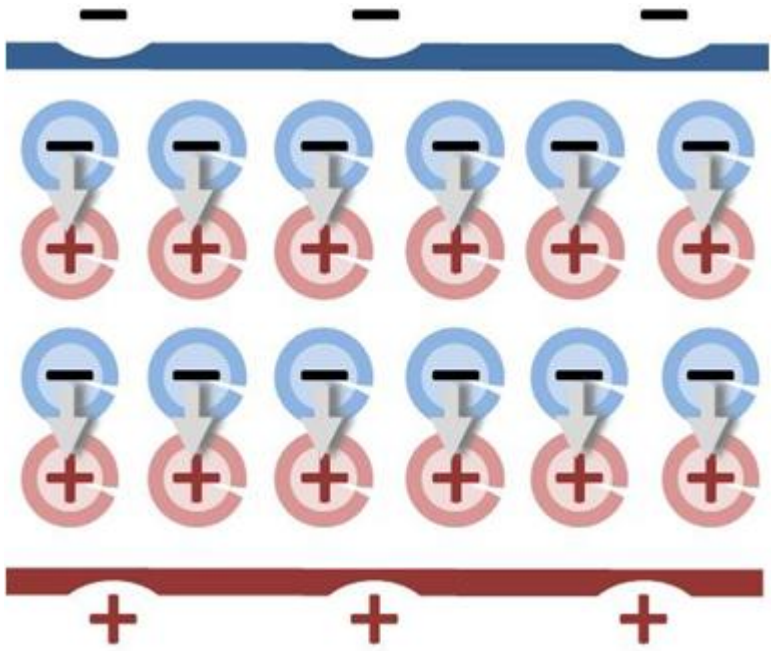
Potential drugs

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

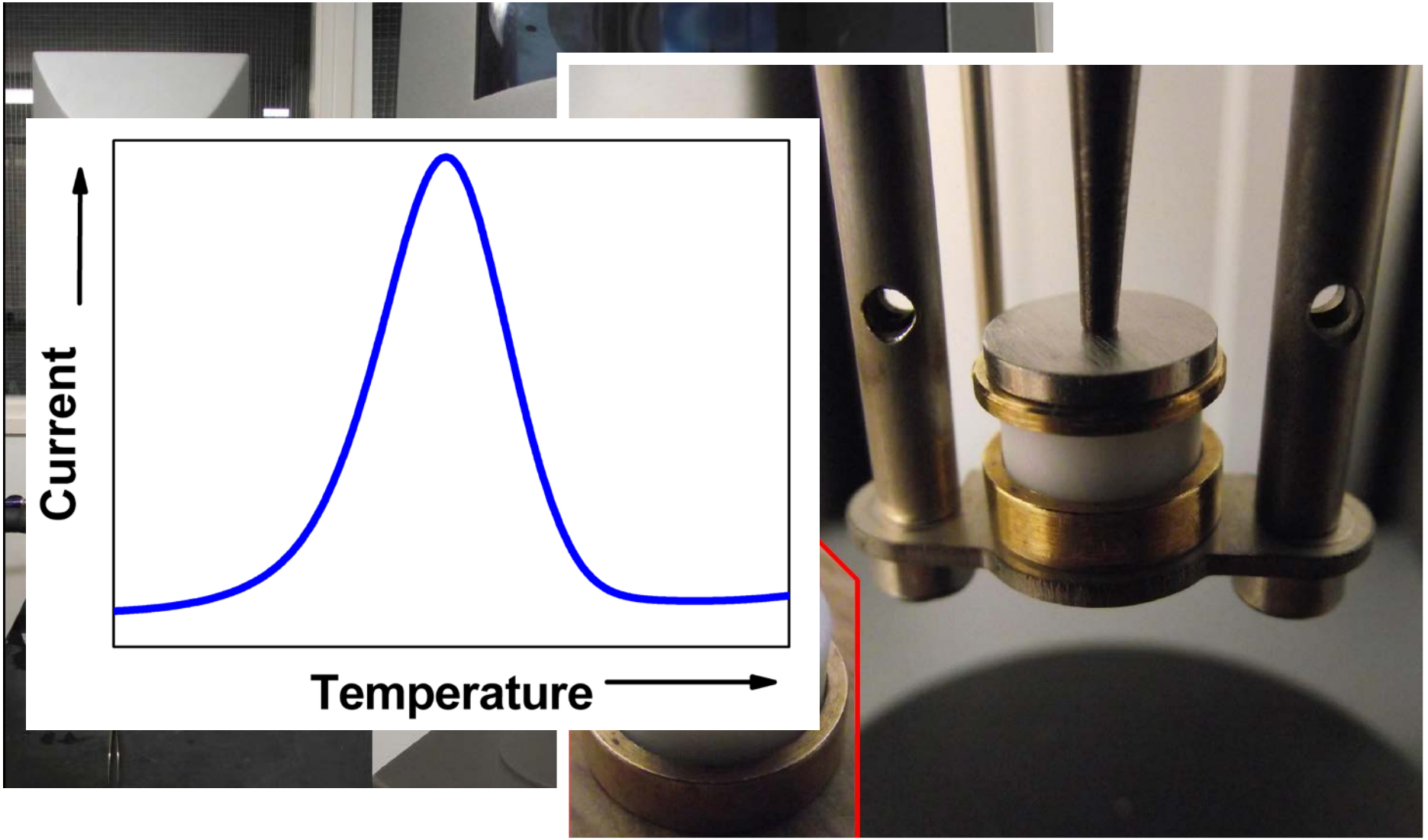
TSC is a general term applied to the measurement of current generated by temperature-activated relaxation of molecular dipoles in response to the application of a static electric field

- 1936, Frei and Grotzinger

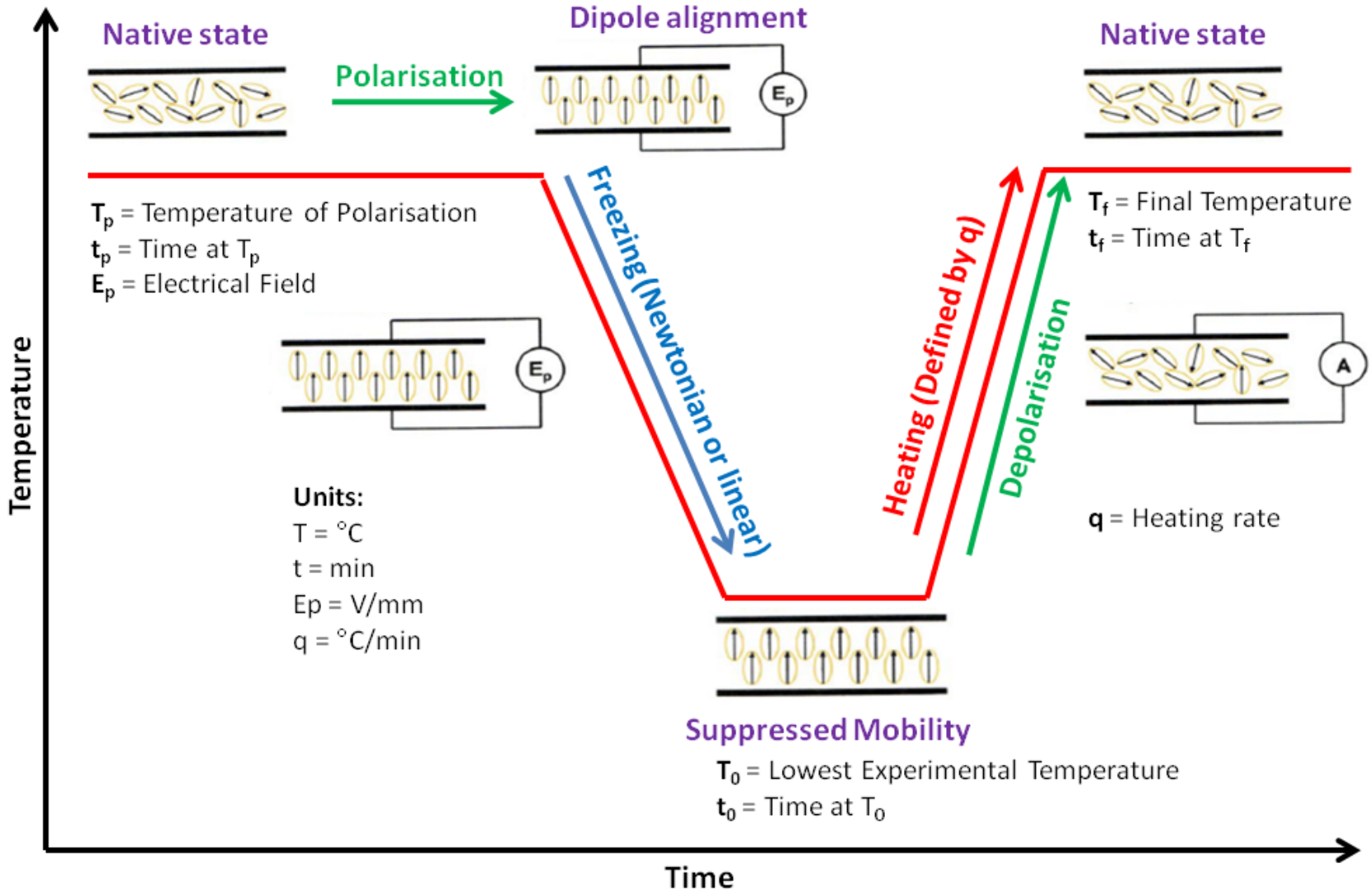
- electrets, ionic crystals
- waxes, resins
- ceramics, plastic
- small organic molecules



Introduction to TSC

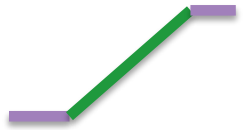


Introduction to TSC



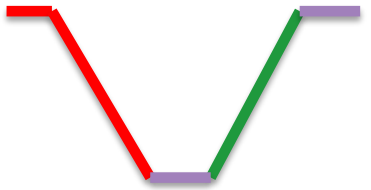
Introduction to TSC

- **SDC** (spontaneous depolarisation current) heating/cooling without an electrical field

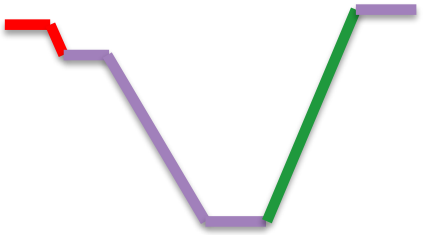


- **TSPC** (thermally stimulated polarisation current) heating/cooling utilising an applied static electrical field throughout

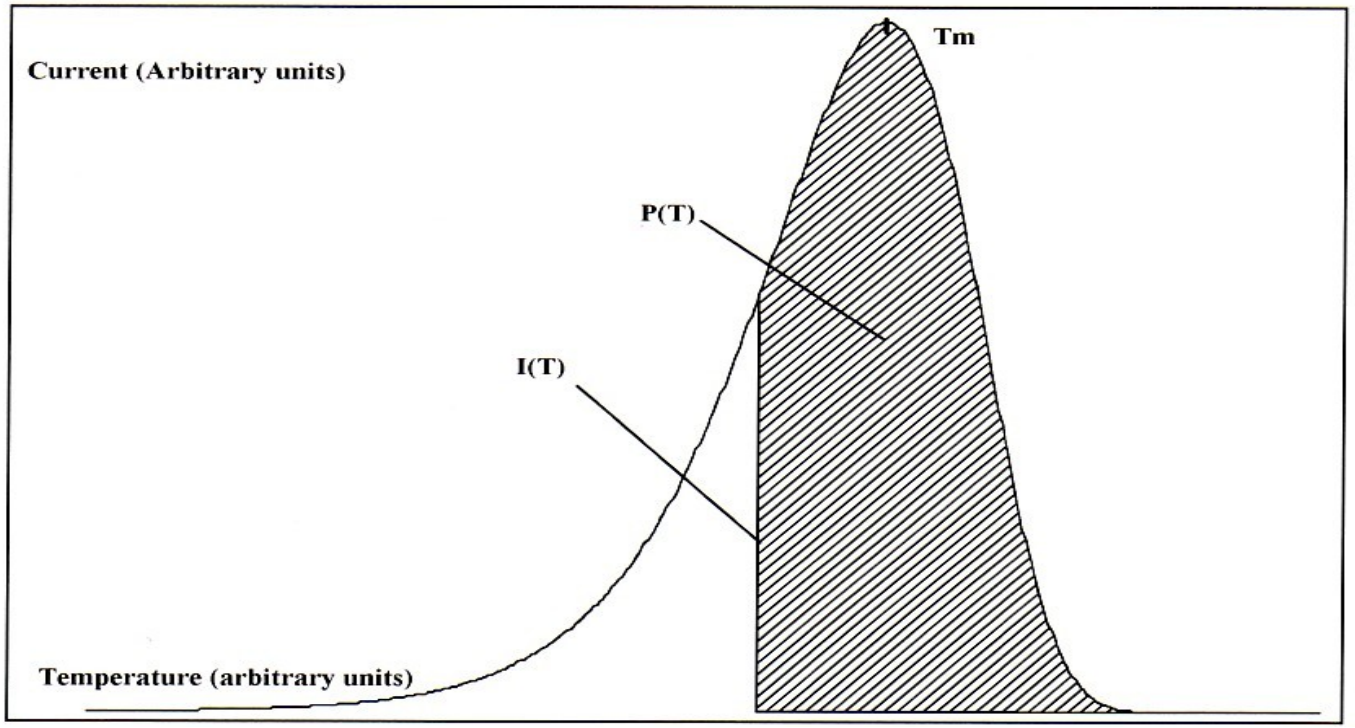
- **TSDC** (thermally stimulated depolarisation current) after the sample has been subjected to polarisation via a static electrical field



- **TW** (thermal windowing) uses a series of discrete temperature polarisation windows to experimentally deconvolute the global relaxation process into elementary relaxation spectra



TSC Theory



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

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

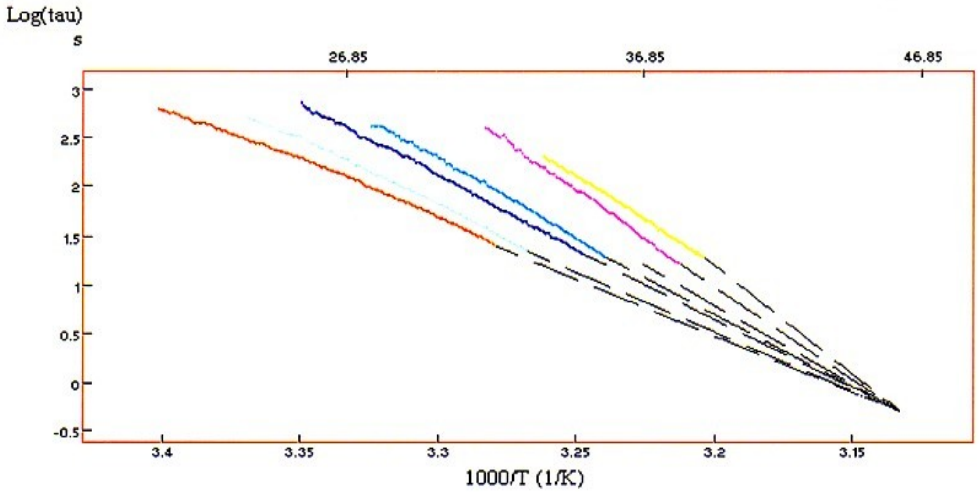
$$\tau(T) = P(T) / J(T)$$

Arrhenius equation

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

Eyring equation

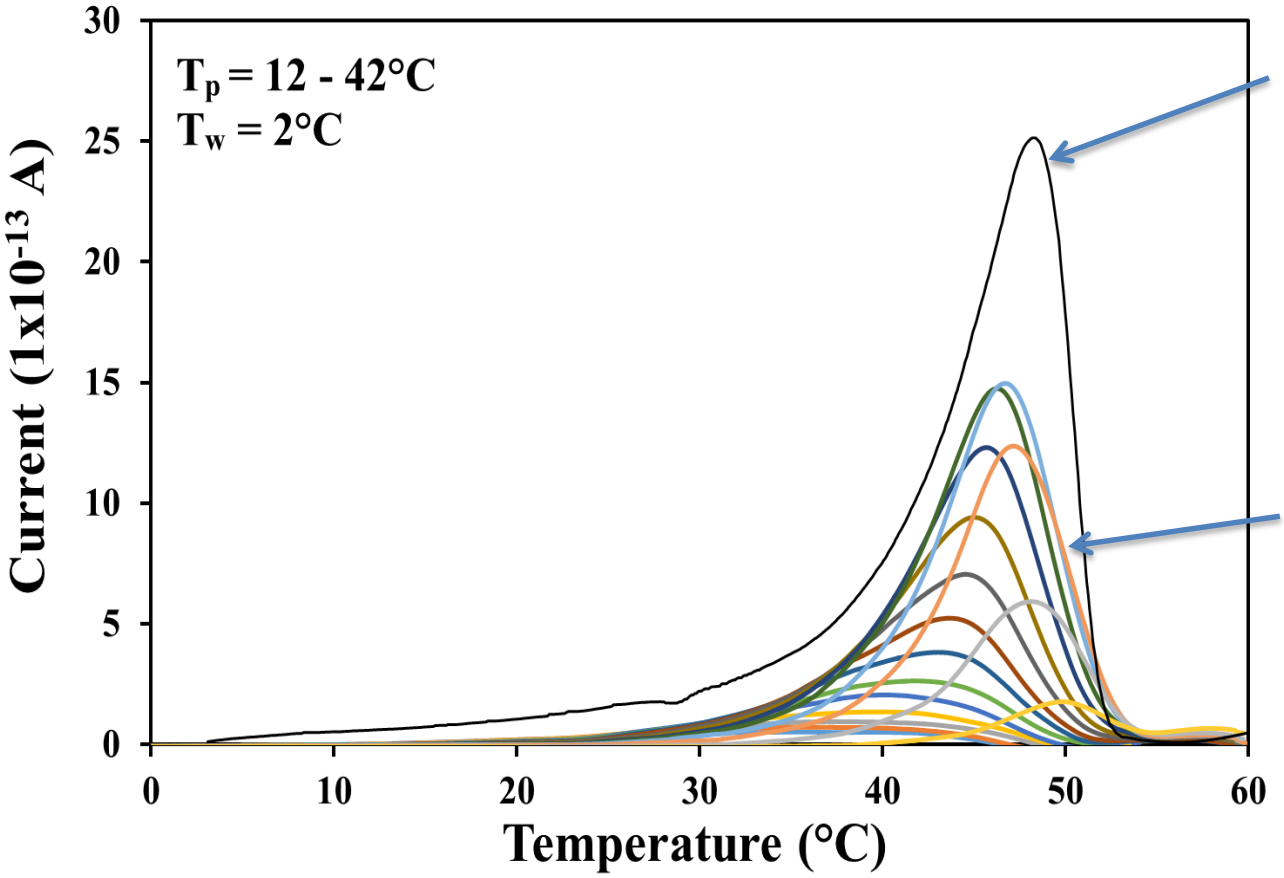
$$\tau_i(T) = \frac{h}{kT}\exp\left(\frac{\Delta G_i}{kT}\right) = \frac{h}{kT}\exp\left(-\frac{\Delta S_i}{k}\right)\exp\left(\frac{\Delta H_i}{kT}\right)$$



Pharmaceutical Applications

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

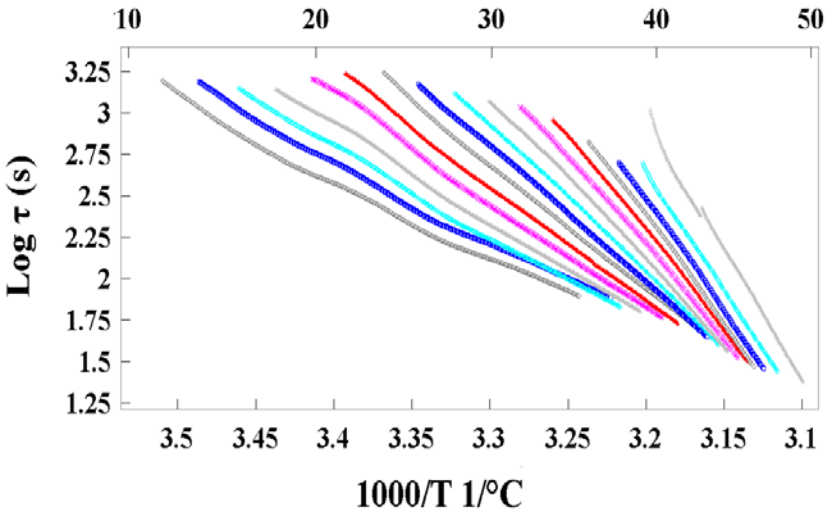
TW outputs



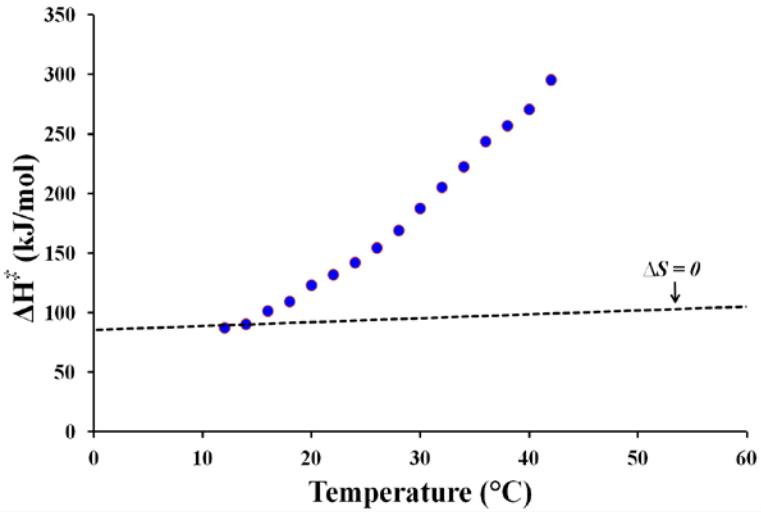
Global glass relaxation process

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**
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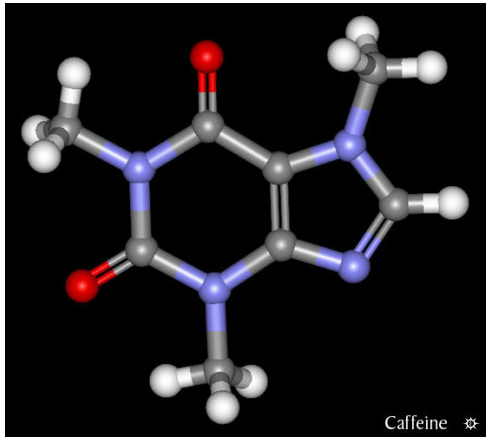
Caffeine



Exists in two polymorphic forms:

Form I, unstable at room T, Trigonal

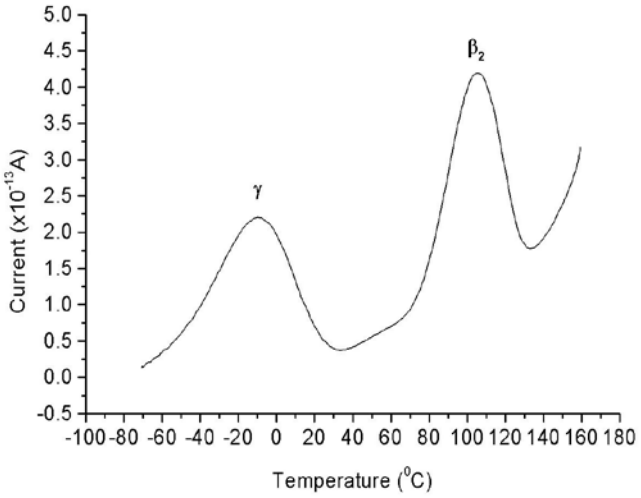
Form II, stable at room T, Monoclinic

Transition point: 141 ± 2°C

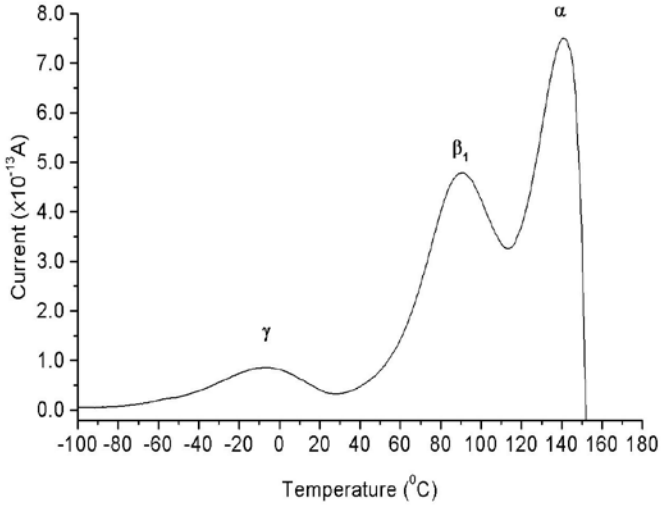
Melting Point: 236 - 243°C (British Pharmacopoeia)

Caffeine - TSDC Results

Form I

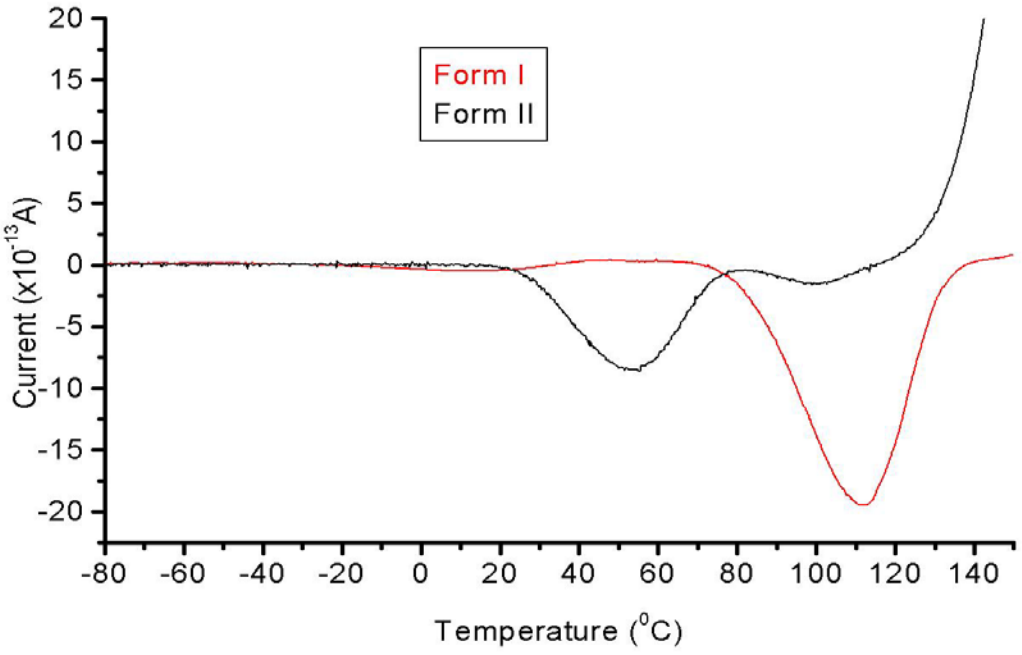


Form II



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*

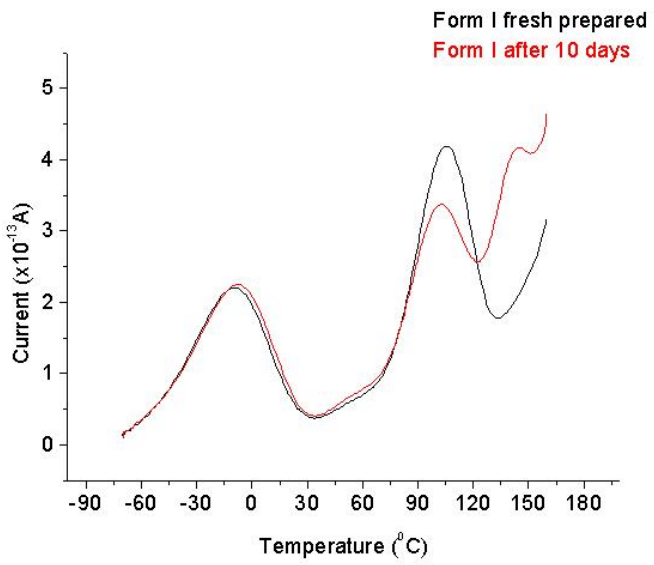
Caffeine - SDC Results



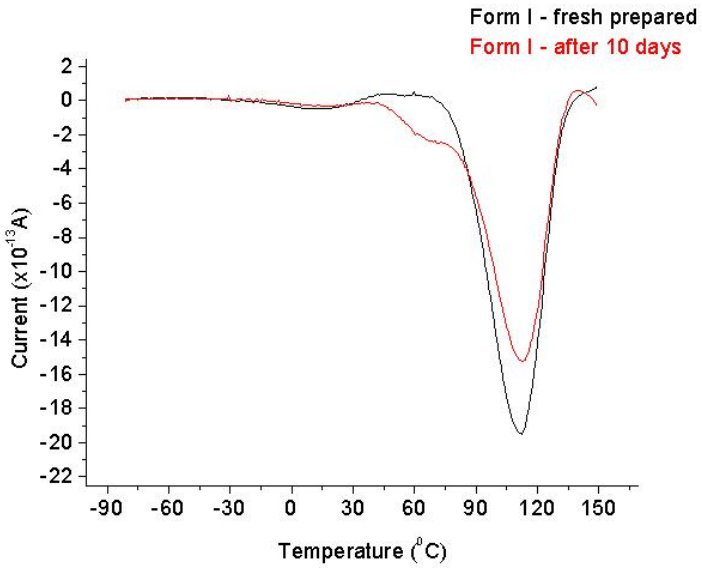
Form I - negative peak at -8°C and 112°C
Form II - negative peak at 52°C

Kinetic Parameters - TSC Method

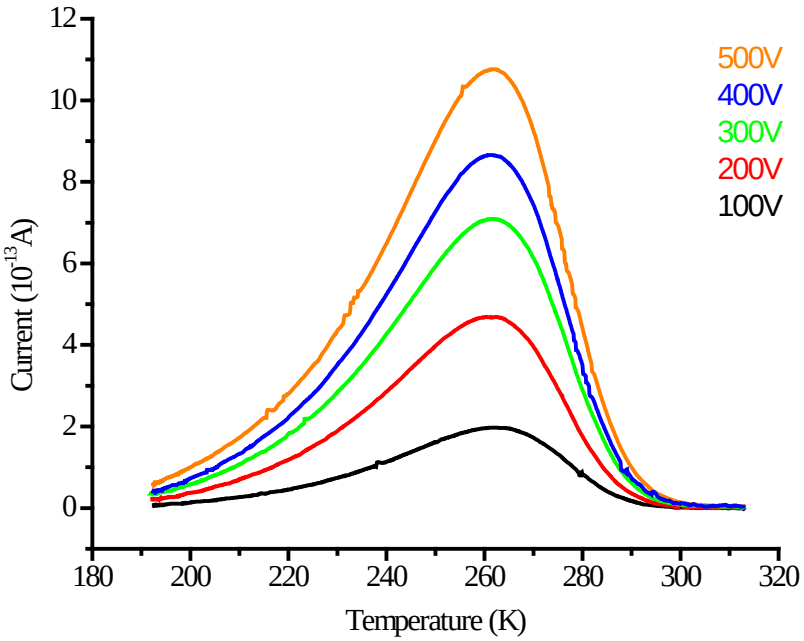
TSDC

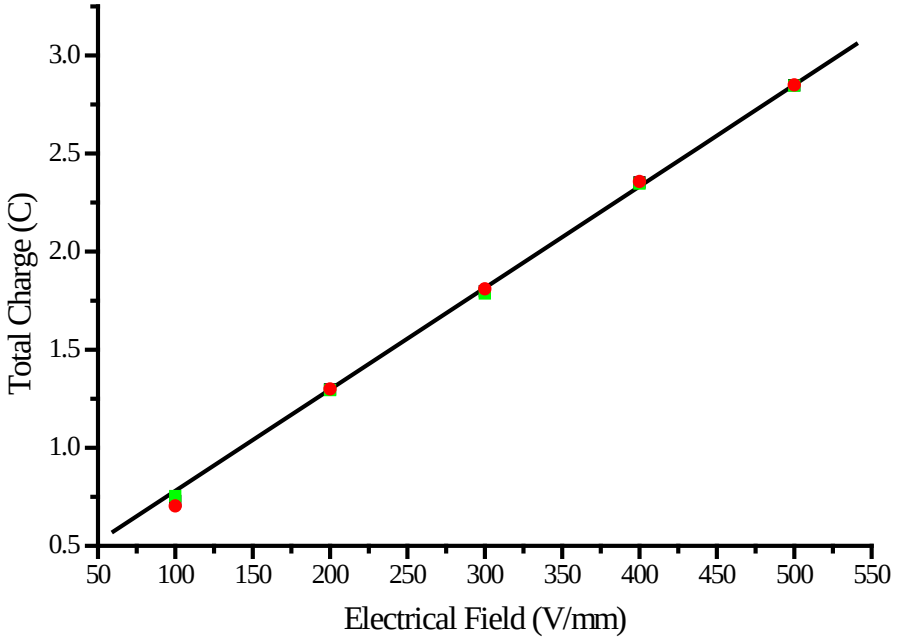


SDC



Sensitivity

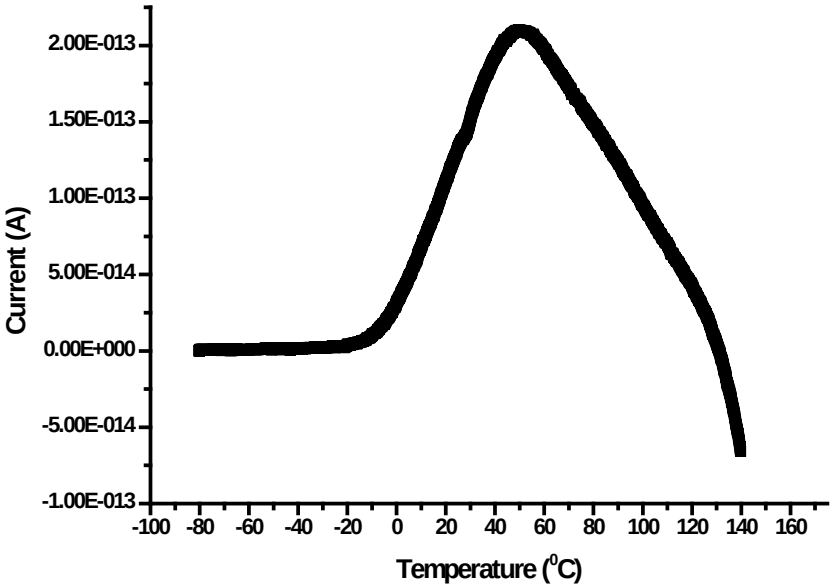


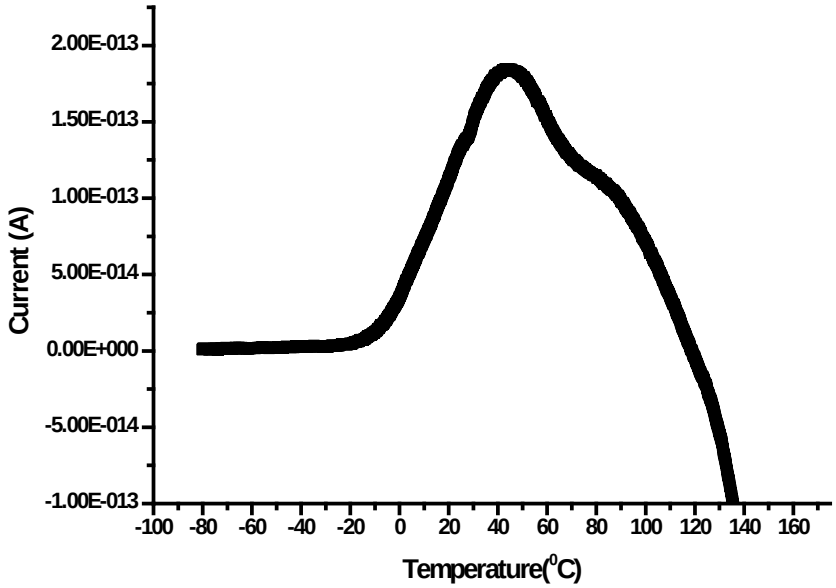


Pharmaceutical Applications

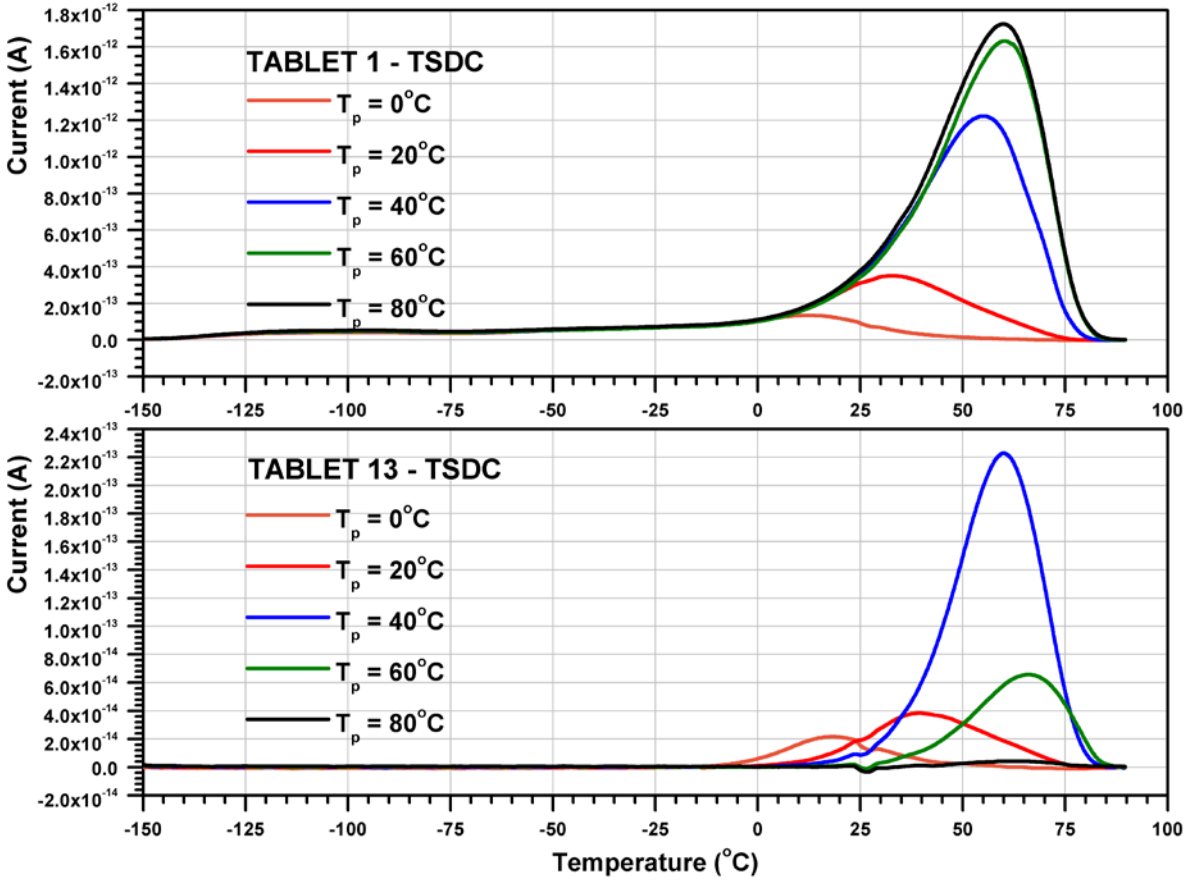
- Amorphous materials
- Polymorphs
- **Batch-to-batch control**
- Co-crystals

Batch to Batch variations





Batch to Batch variations

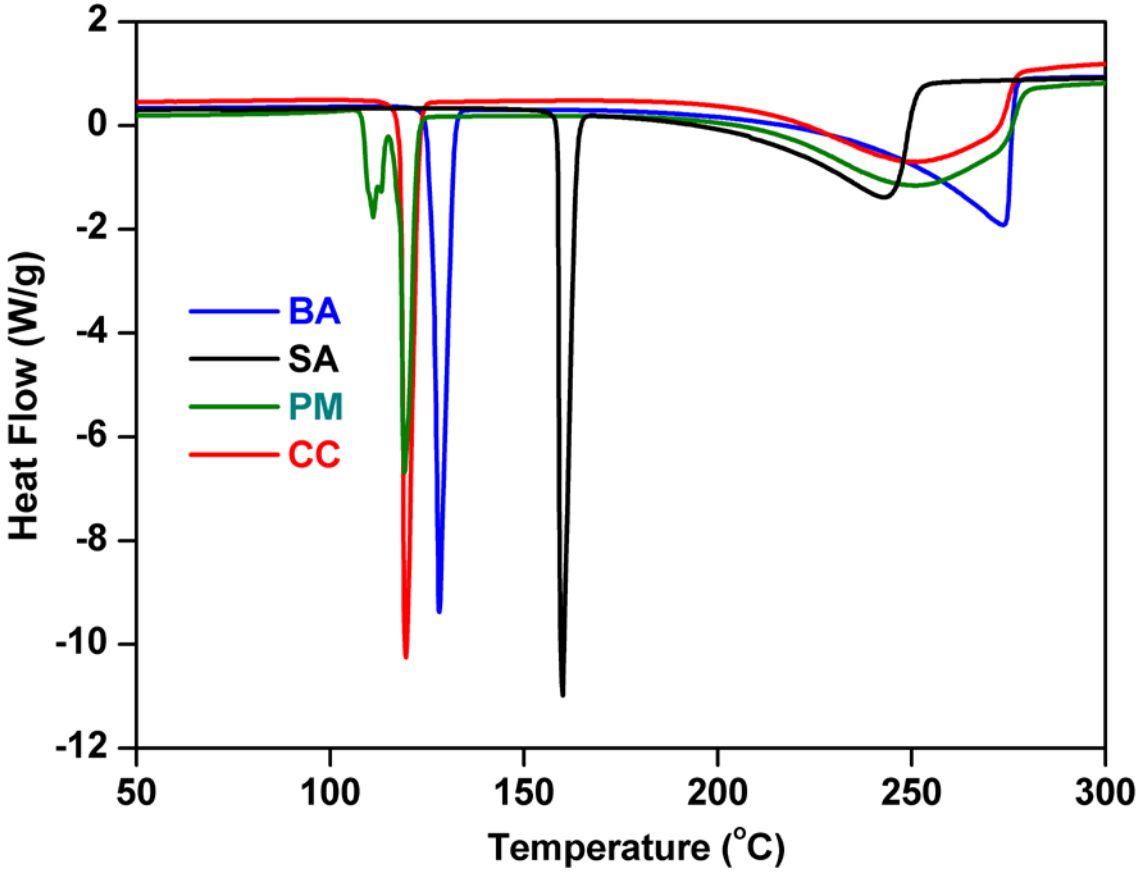


Pharmaceutical Applications

- 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:

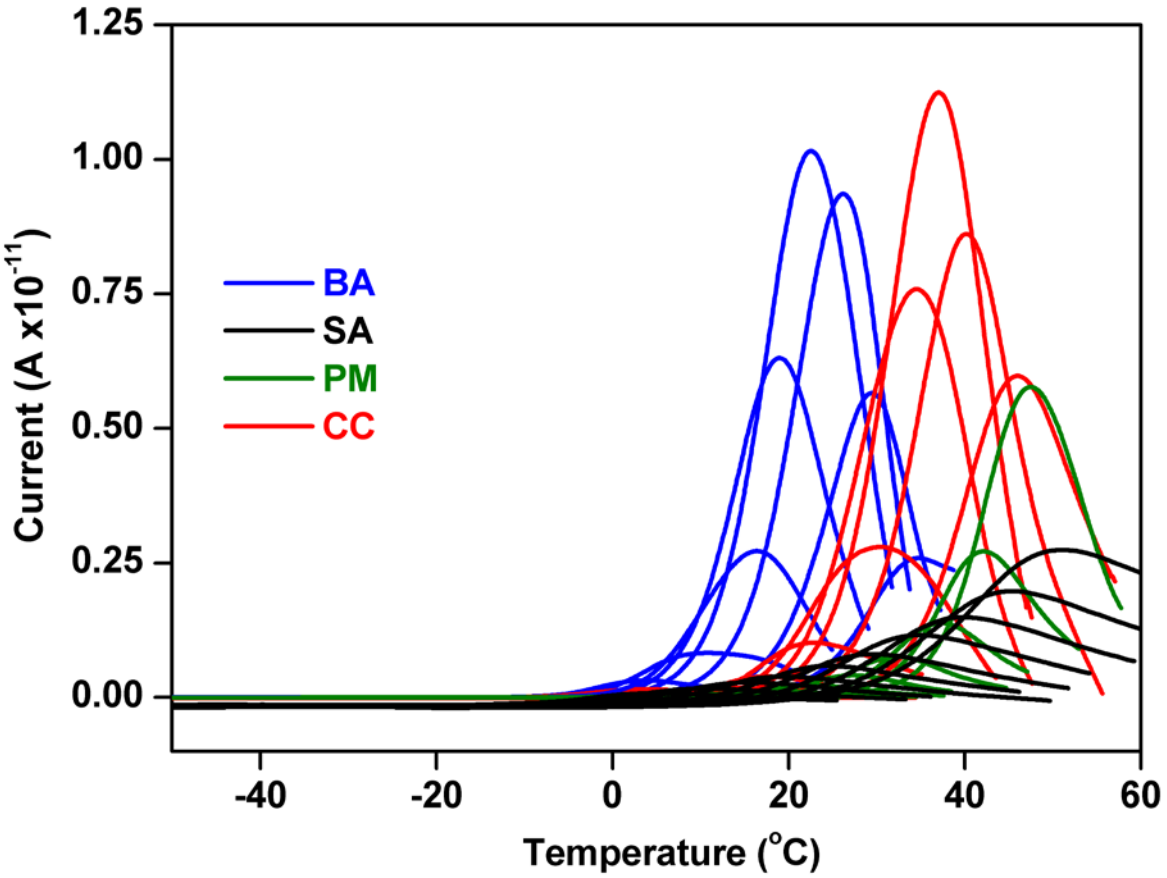
BA = 128°C

SA = 159°C

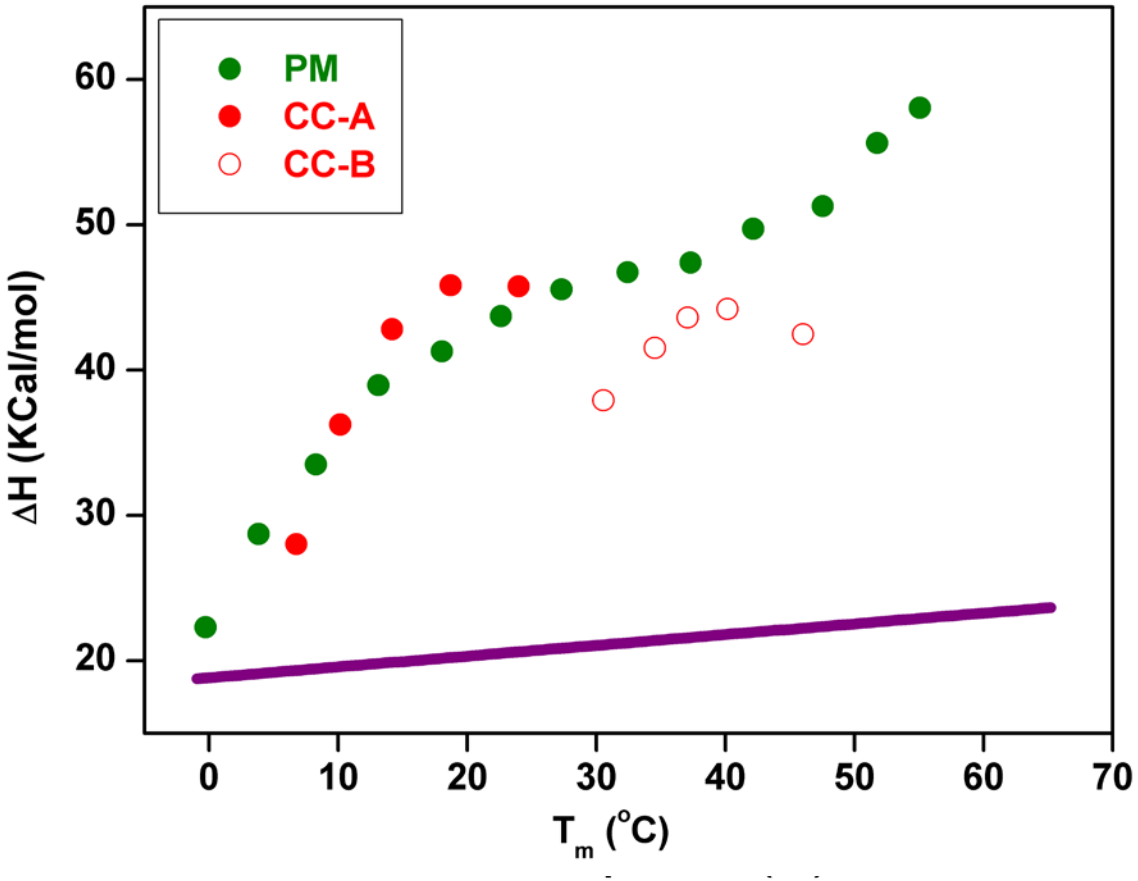
CC = 119°C

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

Conclusions

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

Acknowledgments

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Thank you for listening