Thermal Analysis as a tool in Materials Science

Milan D Antonijevic
Materials Science

- Pharmaceutical materials science correlates physical properties of active compounds and pharmaceutical ingredients with the performance of the finished dosage product.

- Small molecules of pharmaceutical interest can exist in many different forms called morphs, which have different degrees of order at the atomic level.

- Detection, characterisation and quantification of amorphous, polymorphs and pseudo-polymorphs have been recent subjects of research globally.
Thermal Analysis (TA)

- TA has been extensively used to provide insight into structural changes on molecular level.

- It is the most important analytical tool for studying physico-chemical properties of materials.

- Amongst the most widely used thermal analytical techniques are thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and hot stage microscopy (HSM).

- Recently, differential mechanical analysis (DMA) and thermally stimulated current (TSC) spectroscopy draw attention to a new ways of monitoring motions and changes in the structure of materials.
Thermogravimetric Analysis (TGA)

- water content
- solvent content
- oxidation
- degradation pathway
- decomposition
- stability
Thermogravimetric Analysis (TGA)

- **Hyphenated techniques:**
  - TGA/DSC
  - TGA/IR
  - TGA/MS
  - TGA/DSC/IR
  - TGA/DSC/MS
Thermogravimetric Analysis (TGA)
Hot Stage Microscopy (HSM)

- phase transitions
- softening
- crystalline habits
- size distribution
- stability
Hot Stage Microscopy (HSM)
Amorphous Indometacin - HSM

Kings Hill 2009

the UNIVERSITY of GREENWICH
Amorphous Indomethacin - HSM

Kings Hill 2009
Differential Scanning Calorimetry (DSC)

- 1st- and 2nd-order transitions
- glass transition, polymorphic transitions
- crystallisation, melting
- degradation
- identity, purity
- co-crystals, pseudo-polymorphs
- excipient compatibility, stability
Differential Scanning Calorimetry (DSC)

Kings Hill 2009
Thermally Stimulated Current Spectroscopy (TSC)

- $\alpha$, $\beta$, and $\gamma$ transitions in materials
- Molecular motions over a wide temperature range (-160ºC to 250ºC)
- Cooperative and non-cooperative rearrangements
- Relaxation map analysis
- Calculation of activation energies for relaxation processes
- Stability prediction, excipient compatibility
Thermally Stimulated Current Spectroscopy (TSC)

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

Kings Hill 2009
TSC origin

Experimental variables:

- Temperature of polarization
- Time of polarization
- Polarization field
- Cooling rate
- The lowest temperature
- Time at lowest temperature
- Heating rate
- Final temperature
- Temperature of stabilization
TSC spectrum

Pharmaconference, Kings Hill 2009
Main parts of the instrument

- Thermostated sample holder
- Vacuum system
- Heating and Cooling unit
- DC generator
- Current detector ($10^{-4}$ to $10^{-16}$ A)
- Recording unit
Amorphous Materials

Glass transition is characterised by:

Heat capacity change (DSC)

Visco-elastic changes (TSC)
TW-TSDC

(a) T

(b) T

Current (x10^{-13} A)

Temperature (K)

TP=242K
TP=239K
TP=236K
TP=233K
TP=230K
TP=227K
TP=224K
TP=221K
Global TSDC

$T_p = 223$ K
$T_p = 220$ K
$T_p = 217$ K
$T_p = 214$ K
$T_p = 211$ K
$T_p = 208$ K
$T_p = 205$ K
$T_p = 202$ K
$T_p = 199$ K

Kings Hill 2009
Global TSDC

\[ T_p = 242 \text{ K} \]
\[ T_p = 239 \text{ K} \]
\[ T_p = 236 \text{ K} \]
\[ T_p = 233 \text{ K} \]
\[ T_p = 230 \text{ K} \]
\[ T_p = 227 \text{ K} \]
\[ T_p = 224 \text{ K} \]
\[ T_p = 221 \text{ K} \]
\[ T_p = 218 \text{ K} \]
TSC PEG 4000/6000/20000

delta_H(eV)

Tp(K)

1.16
1.14
1.12
1.10
1.08
1.06
1.04
200 205 210 215 220 225

delta_H(eV)

Tp(K)

1.4
1.375
1.35
1.325
1.3
1.275
1.25
1.225
1.2
220 225 230 235 240

Tp(K)

1.175
1.15
1.125
1.1
1.075
1.05
1.025
1
225 230 235 240 245 250 255

the UNIVERSITY of GREENWICH
Caffeine

Polymorphic transition
Form II is stable at room temperature
Form I is stable above 150°C
Xanthine alkaloid (theophylline, theobromine)
Both forms show no water content
Dehydration of monohydrate occurs rapidly at 40°C
Melting point was observed at 240°C
(change in slope from –1.6%/°C to –1.1%/°C)
Caffeine - TGA Results

Heating rate: 10K/min

Heating rate: 2K/min

Above 160°C sublimation become a fast process

Faster heating ramp can prevent loss of the caffeine during the examination

Kings Hill 2009
Caffeine Form II – DSC Results
Caffeine Form I – DSC Results

Integral: 444.91 mJ
Normalized: 3.000 mJ g^{-1}
Onset: 235.10 °C
Peak: 236.82 °C
Heating Rate: 10.00 °C min^{-1}

Kings Hill 2009
Caffeine - TSDC Results

Form I

- \( \alpha \)-process: 139°C - Form II only - *polymorphic transition*
- \( \gamma \)-process: -8°C - Forms I and II - *orientation of side group*
- \( \beta_1 \)-process: 91°C - Form II
- \( \beta_2 \)-process: 107°C - Form I - *orientation/mobility of sub-unit*

Form II

Kings Hill 2009
Kinetic Parameters - TSC Method

TSDC

Form I fresh prepared
Form I after 10 days

Current ($10^{-3}$A)

Temperature (°C)

SDC

Form I - fresh prepared
Form I - after 10 days

Current ($10^{-3}$A)

Temperature (°C)

Kings Hill 2009
Conclusions

- identity, purity
- water/solvent content
- amount of different amorphous and polymorphic form present
- co-crystals and pseudo-polymorphs
- secondary relaxations in materials ($\beta$ and $\gamma$)
- calculation
- stability prediction, excipient compatibility