Use of thermal analysis as primary tool for generation and assessment of complex co-amorphous mixtures.

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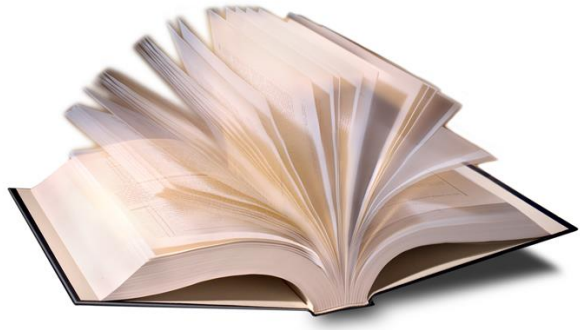
Overview of presentation

- Rational/Aims
- Introduction to amorphous and co-amorphous materials
- Methodology
- Results and Discussion
- Conclusions
- Future work



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Solutions

- Improve existing drugs and engineer new drug candidates
- Active component
  - Physical modification
    - Amorphous
    - Crystalline
  - Chemical modification
    - Hydrates
    - Salts
    - Co-Crystals
- Dosage form
  - Many innovative ways
    - HME, Lyophilisation, Buccal drug delivery, 3D printed medicines etc.

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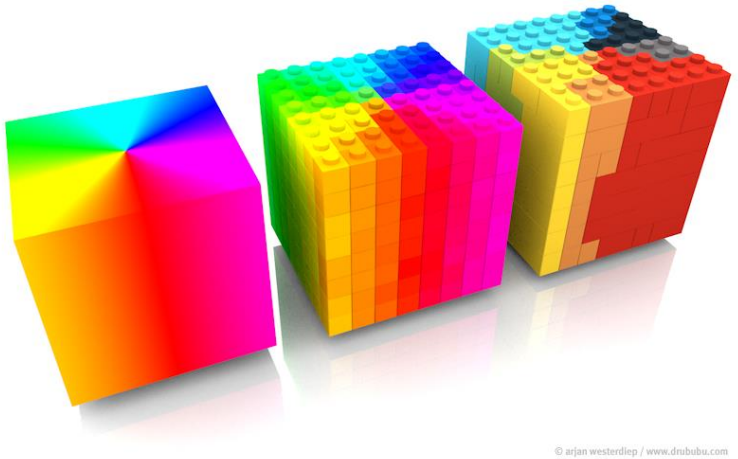
Amorphous vs Crystalline

- Non-periodic molecular arrangement.
- Better apparent solubility and dissolution rate then their crystalline counterpart.
- Thermodynamically unstable, stability issues.
- Glass transition (Tg) vs Melting point (Tm)



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Co-Amorphous

- Co-amorphous mixtures are homogeneous single-phase dispersions of amorphous materials.
- A co-amorphous system is primarily identified by one glass transition (Tg) indicating that the components are interacting.
- Higher glass transition temperatures indicate increased stability.
- Improved dissolution rates over single component amorphous systems.
- Not all materials can be converted into amorphous phase

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Aims

- Identify whether a three component co-amorphous system can be generated by Newtonian cooling from melt
- Determine how the properties of an amorphous material are altered by the addition of a compound with the propensity to form an amorphous or crystalline material.
- Learn how to manipulate Tg (stability) by altering composition
  - Pharmaceutical formulations are often multicomponent systems
  - Small amounts of impurities may have impact on quality of product

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Method

Mettler Toledo FP90 Central processor with FP82HT Hot Stage.

Q2000 DSC (TA Instruments, UK)

Q5000 IR TGA (TA Instruments, UK)

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DSC method

- EQUILIBRATION -80°C
- HEATING TO 180°C AT 10°C/MIN
  - Erase previous thermal history of sample and improve interactions between mixed components
- COOLING TO -80°C AT 20°C/MIN
  - Cooling at 5°C/min was also tested
- HEATING TO 180°C AT 10°C/MIN
  - To analyse the solid state of the product, generated by melt quench method

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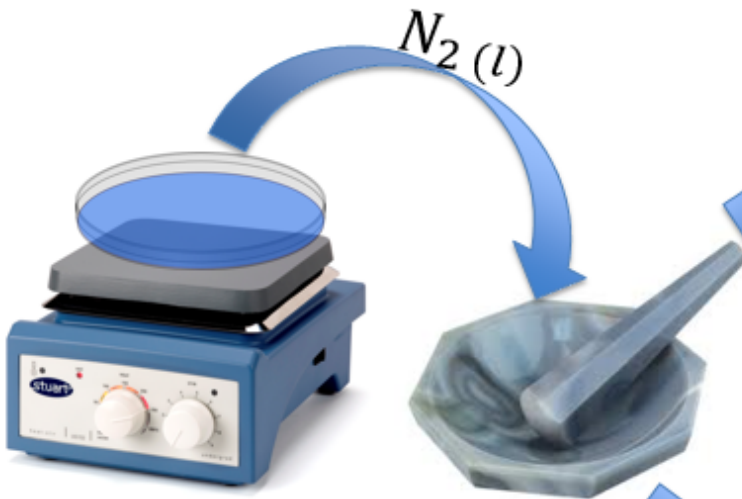
Generation of co-amorphous outside the DSC



1

XRD patterns were recorded using a D8 Advance X-ray Diffractometer (Bruker, Germany) with CuKα radiation over the interval of 2° to 40° (2θ).

2

FTIR spectra were recorded on Perkin Elmer Spectrum Two with ATR attachment within 4000–650 cm-1.

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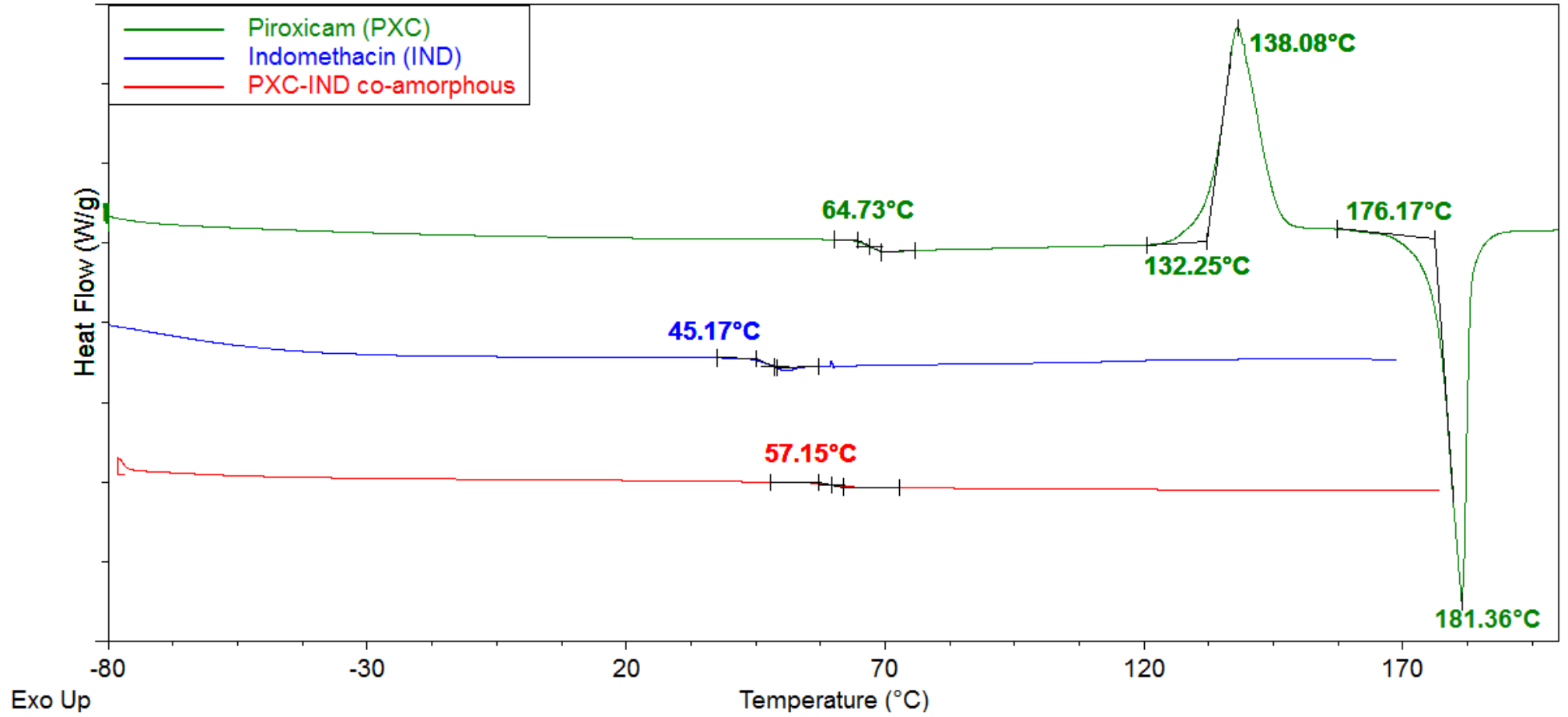
Selection of chemicals



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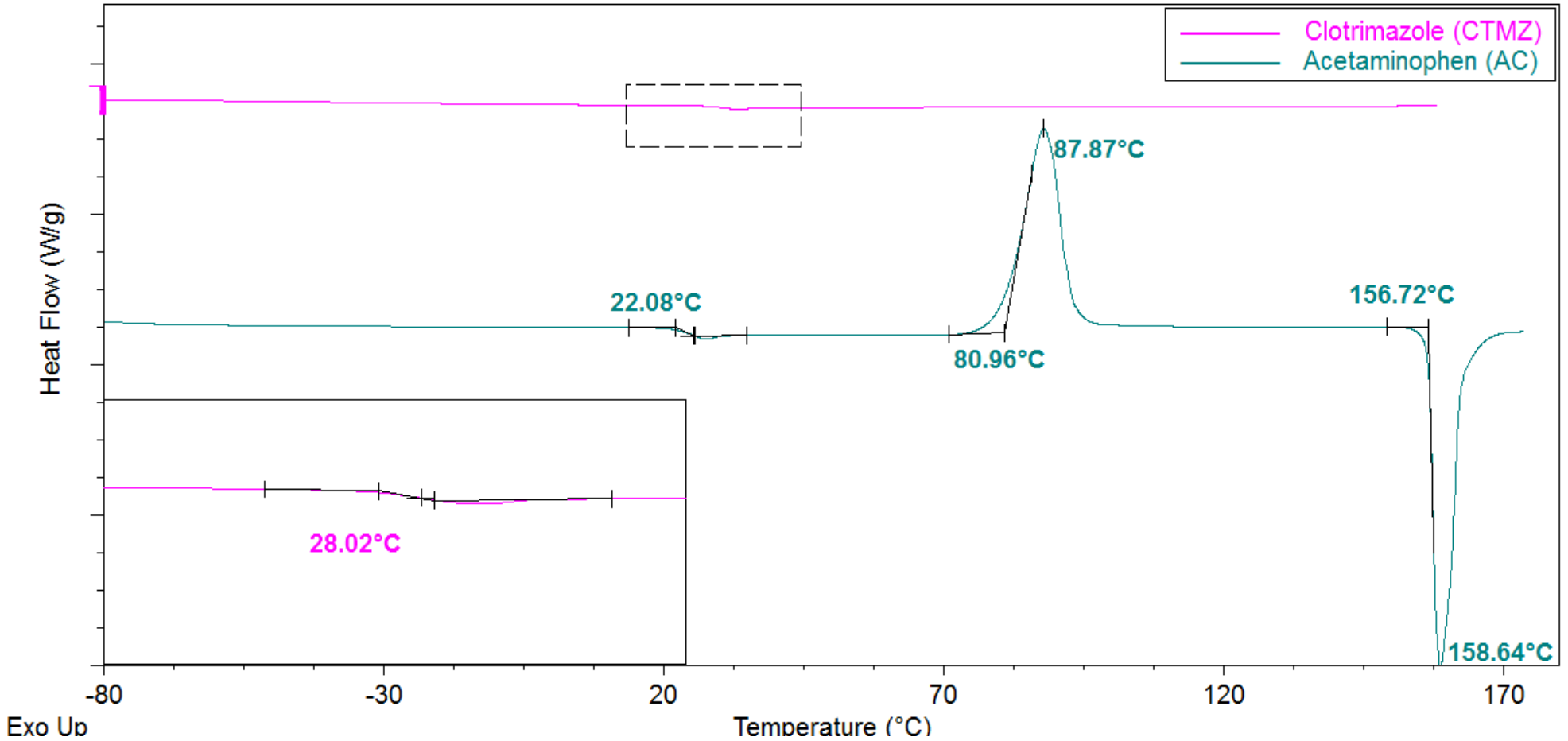
Selection of a third component



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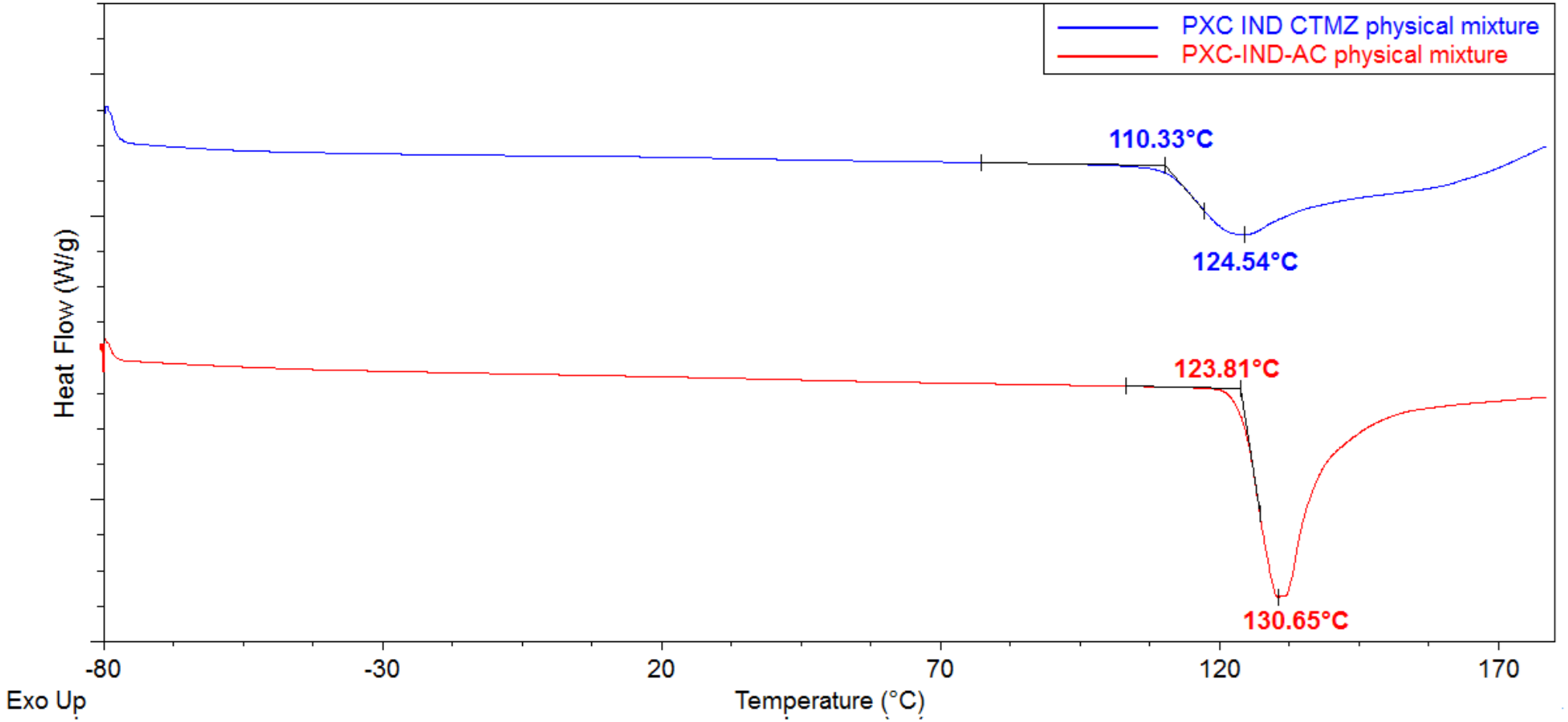
1:1:1 systems



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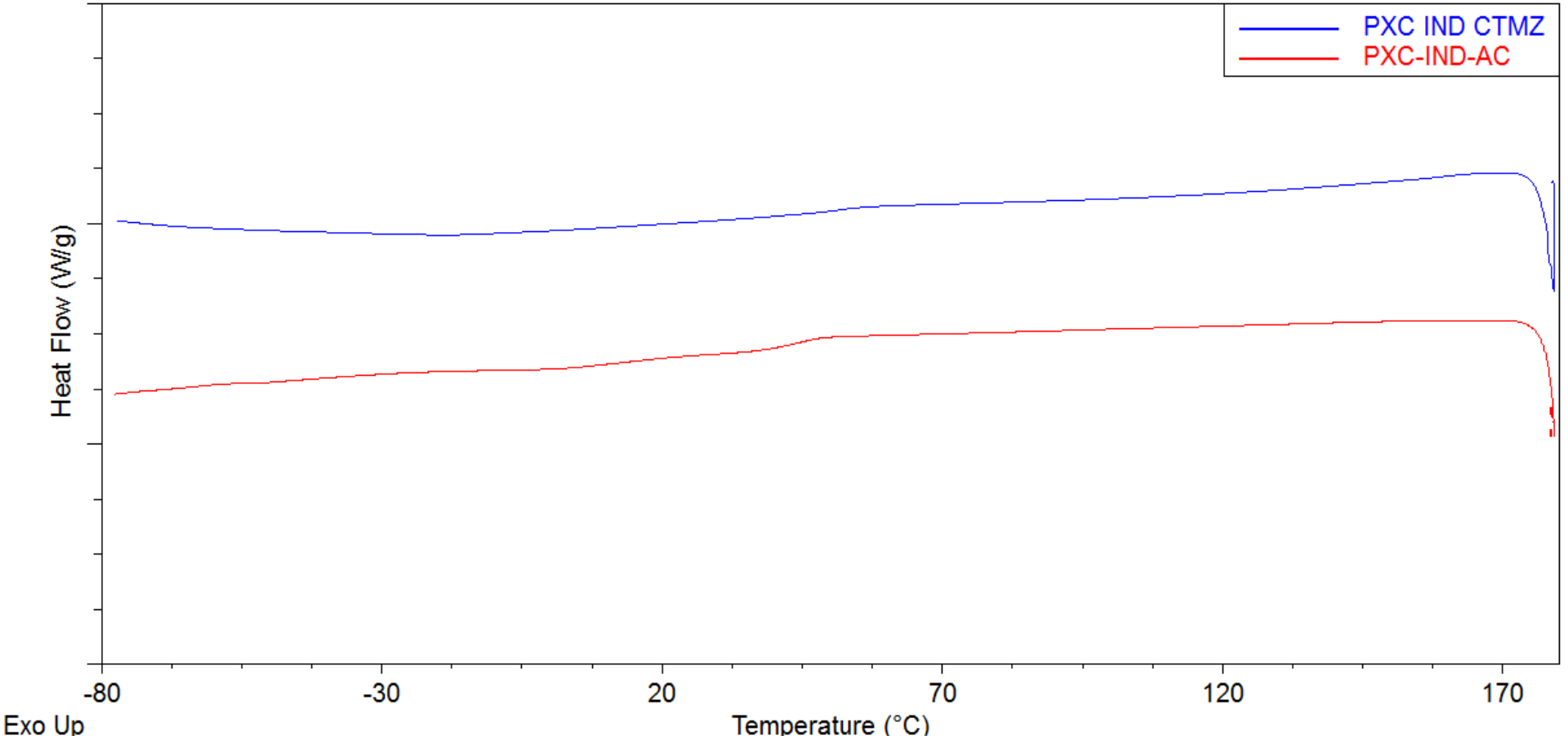
1:1:1 systems quench cooling after melting



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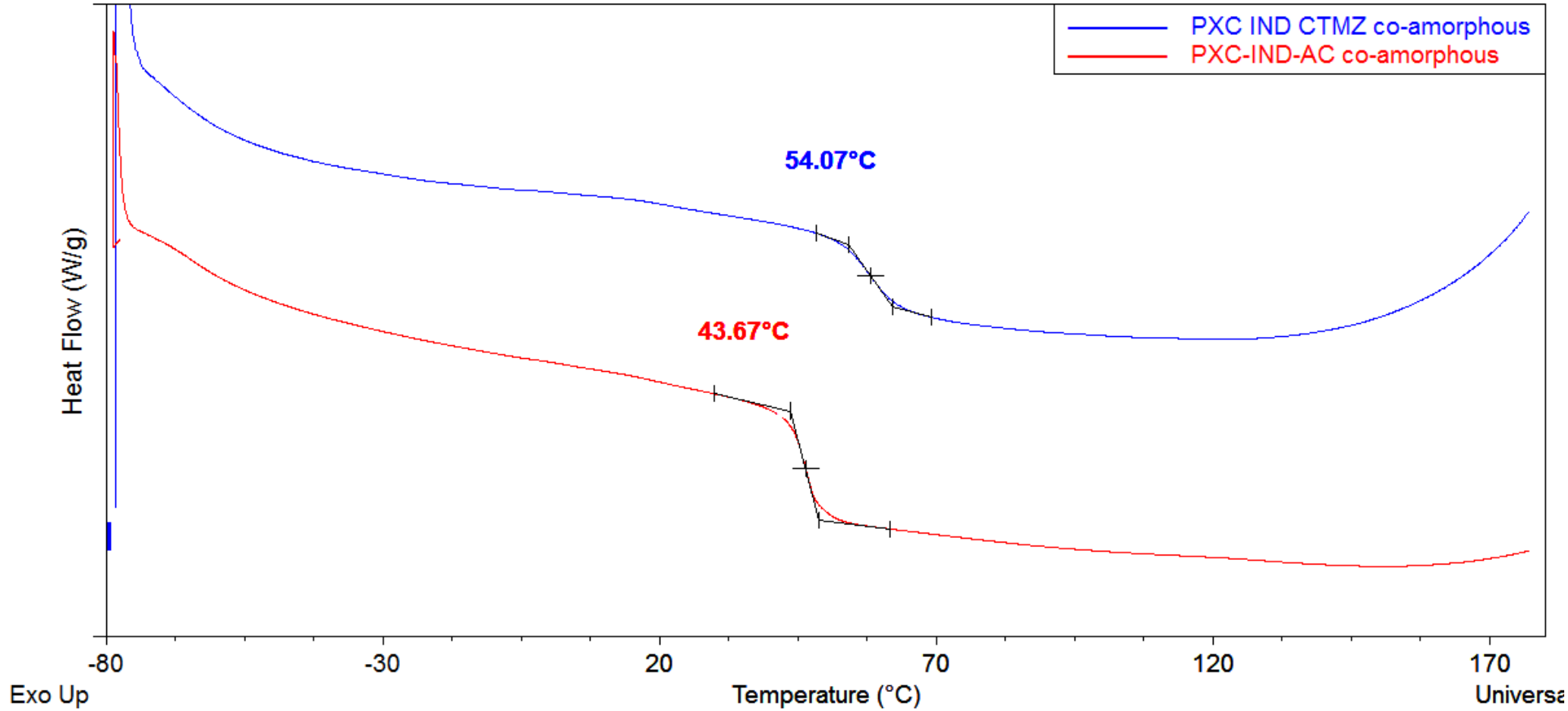
1:1:1 systems second heating



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Overview of the results

Chemicals	Melting point on initial heating (°C)	Crystallization on cooling (°C)	Thermal events on 2nd heating (°C)
PXC	203.1	-	Tg 64.6 Tc 138.1 Tm 181.4
IND	161.1	-	Tg 45.7
CTMZ	145.5	-	Tg 28.0
AC	169.8	-	Tg 22.6 Tc 87.9 Tm 158.6
PXC-IND	140.6	-	**Tg 57.6**
PXC-IND-CTMZ	129.3	-	**Tg 53.3**
PXC-IND-AC	130.7	-	**Tg 44.1**

[a] Tg – Glass transition, Tc – Crystallisation, Tm – Melting.

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Effect of different cooling rates

Chemicals	Thermal events on 2nd heating AFTER 20℃/MIN COOLING (℃)	Thermal events on 2nd heating AFTER 5℃/MIN COOLING (℃)
PXC-IND	Tg 57.6	Tg 53.3
PXC-IND-CTMZ	Tg 53.3	Tg 48.4
PXC-IND-AC	Tg 44.1	Tg 41.6

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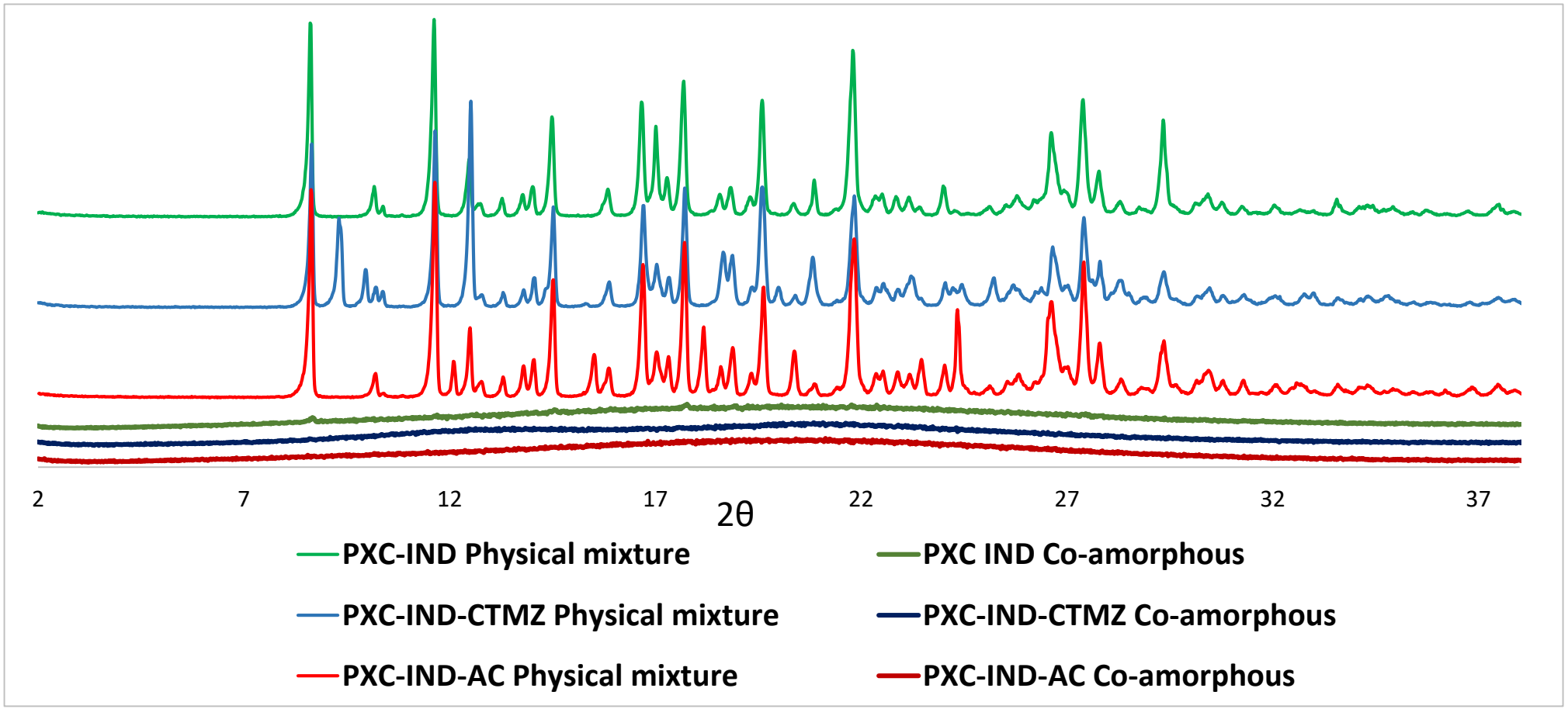
XRD



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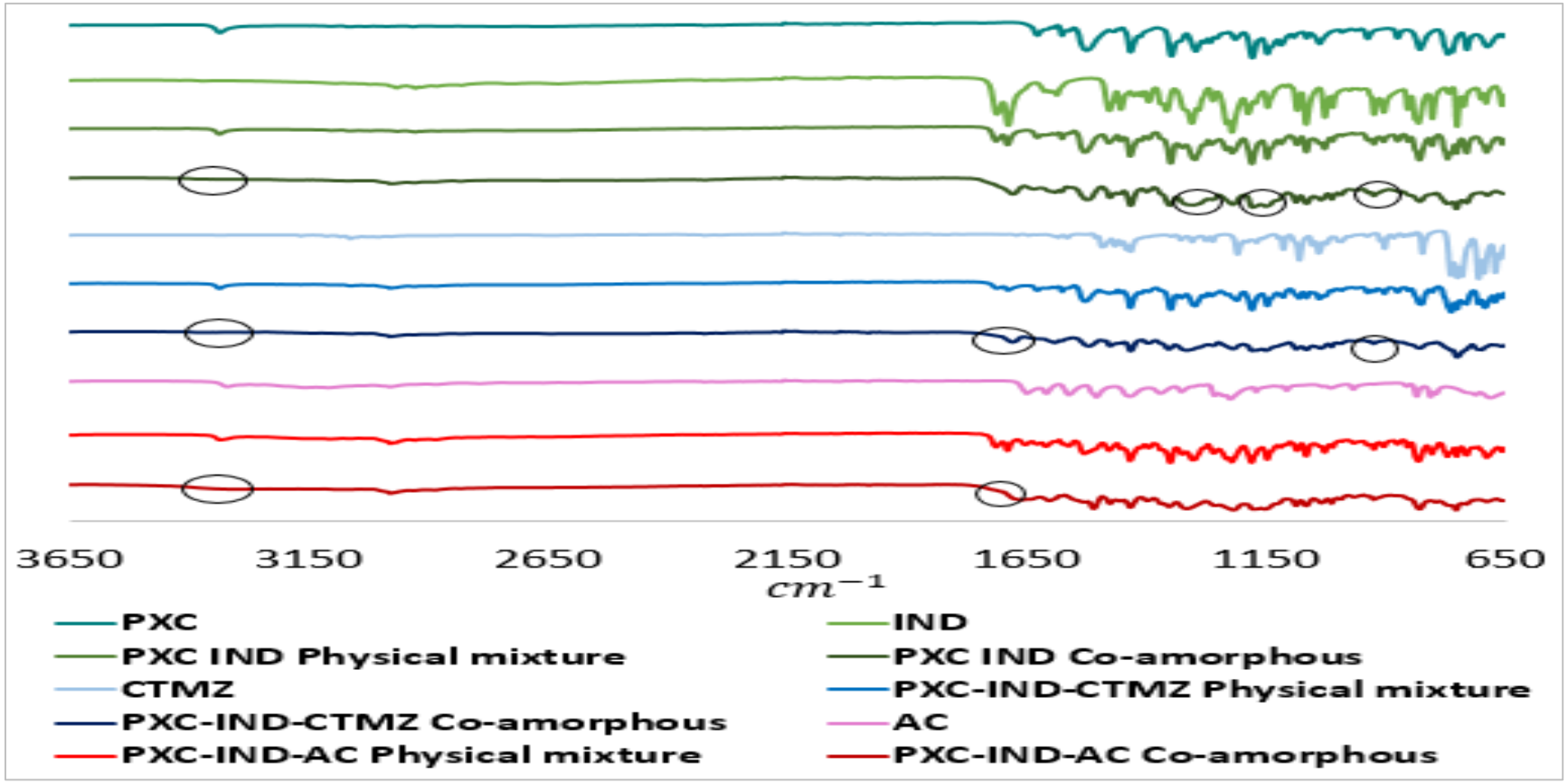
FT-IR



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STABILITY

SYSTEM	TIME (WEEKS)	Tg (°C)	SYSTEM	TIME (WEEKS)	Tg (°C)	SYSTEM	TIME (WEEKS)	Tg (°C)
PXC-IND	0	**57.6**	PXC-IND -CTMZ	0	**53.3**	PXC-IND -AC	0	**44.1**
	1	53.5		1	48.7		1	41.8
	2	52.0		2	47.1		2	41.1
	3	49.4		3	44.6		3	38.5
	4	**43.1**		4	**44.4**		4	**40.3**
ΔTg		**14.5**	**ΔTg**		**8.9**	**ΔTg**		**3.8**

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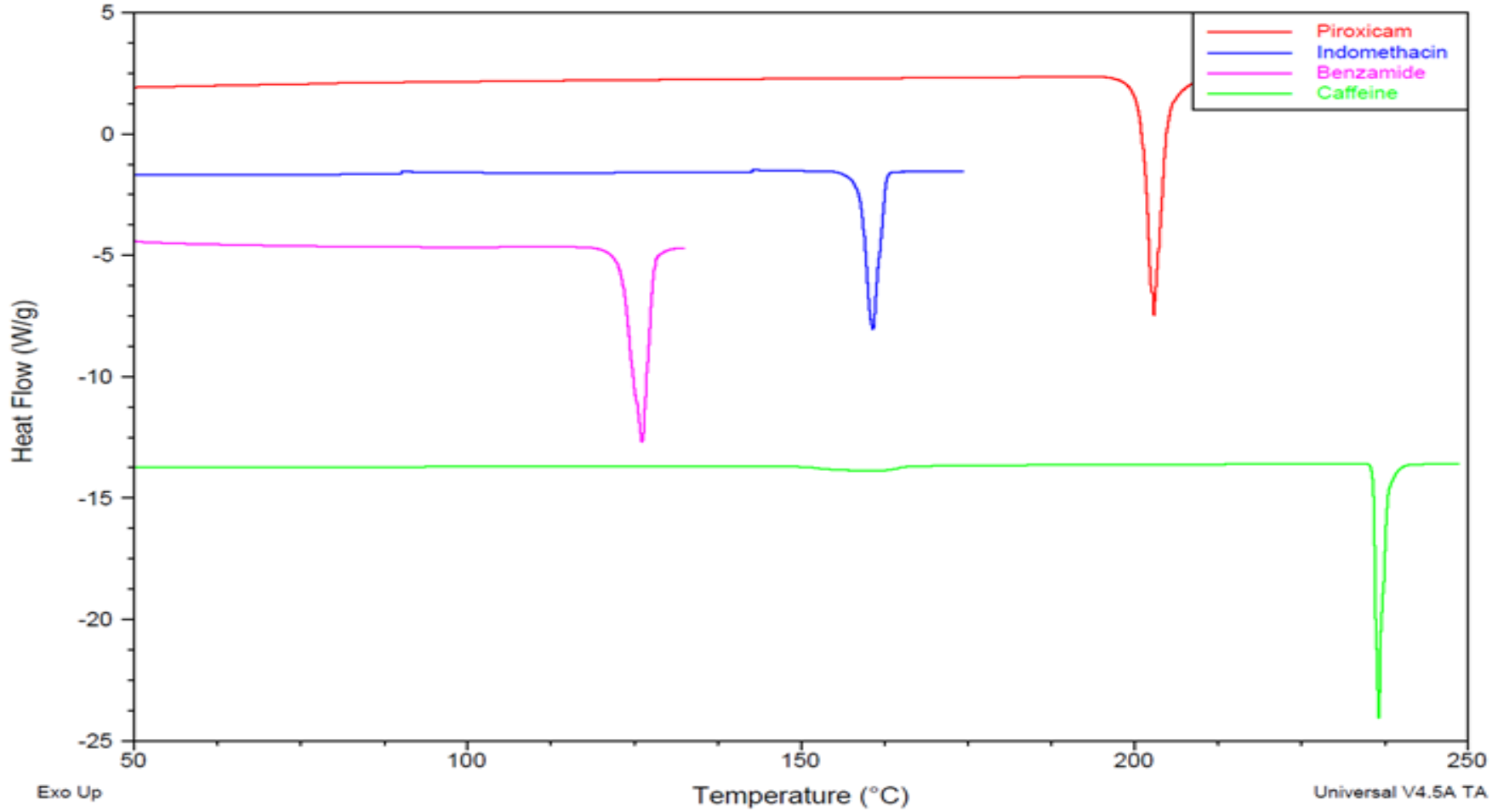
Selection of chemicals



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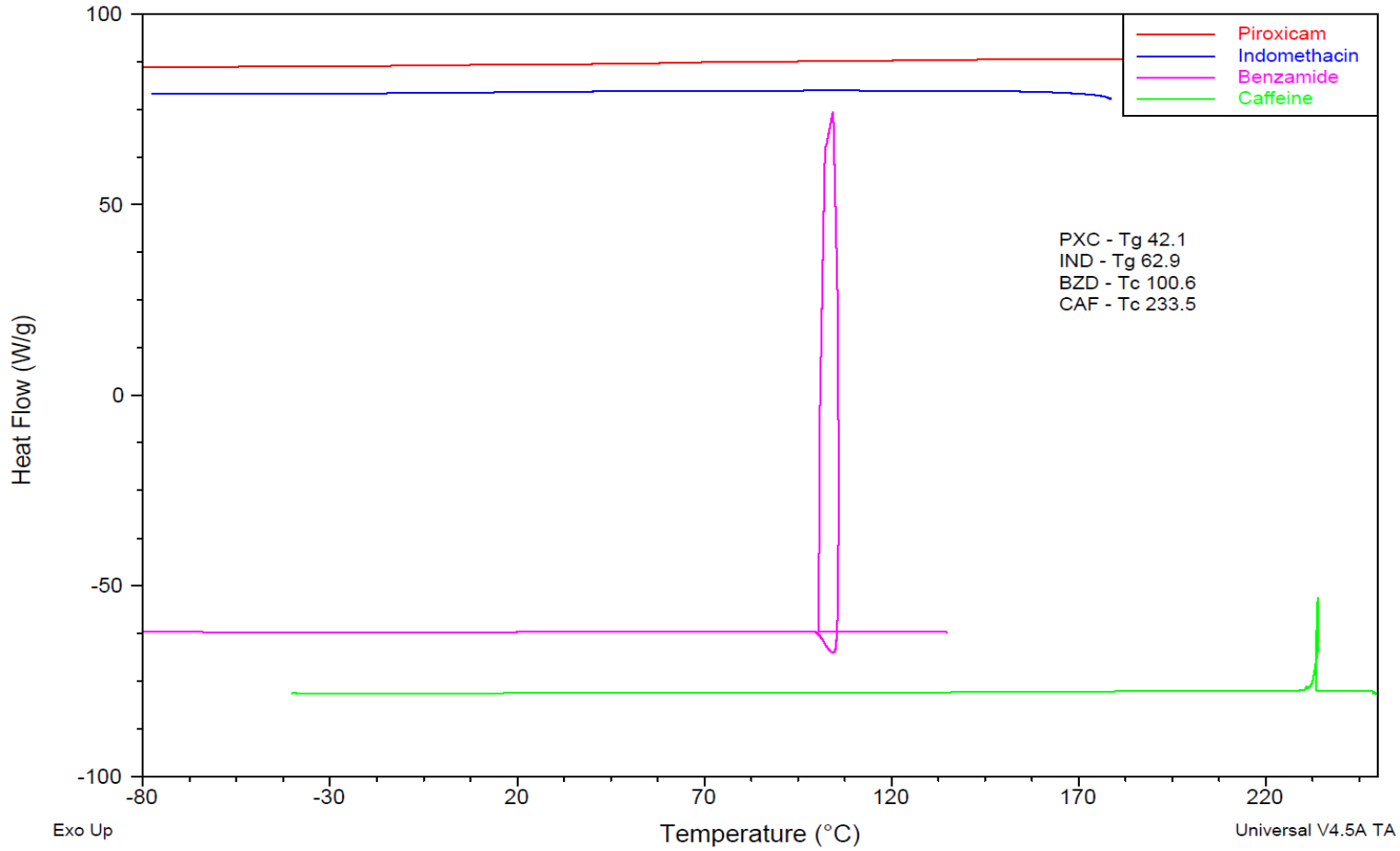
Selection of chemicals



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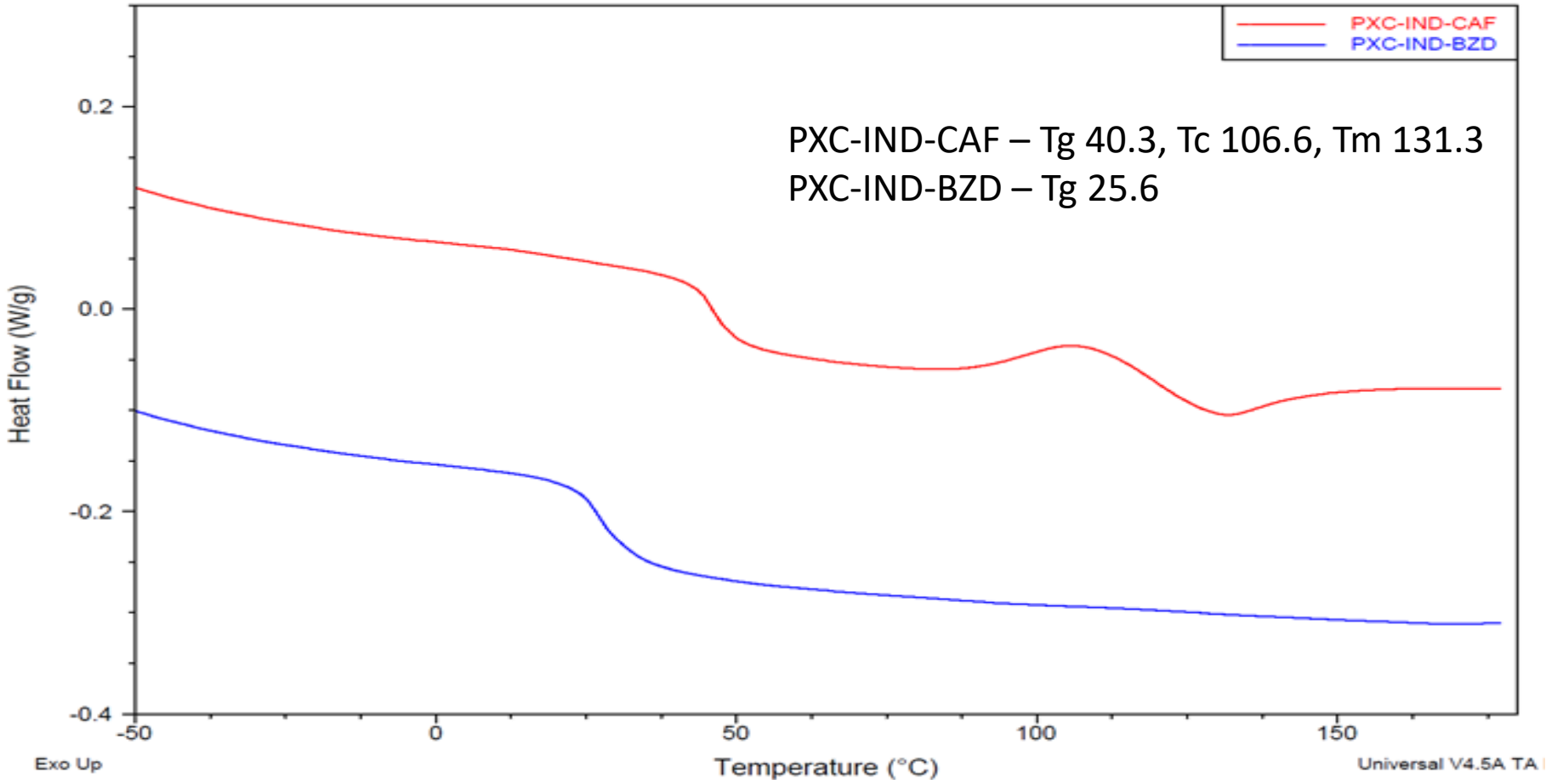
1:1:1 systems



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Temperature values of thermal events

Chemicals	Melting point on initial heating (℃)	Crystallization on cooling (℃)	Onset of mass loss in TGA (℃)
PXC	201.2	Tg 64.4, Tc 132.7, Tm 175.9	201
IND	158.8	Tg 42.7	199
BZD	123.7	Tc 101.6 (cooling), Tm 123.7	106
CAF	149.6 (enantiotropic transition), 235.8	Tc 233.3 (cooling), Tm 235.6	144
PXC-IND	**140.6**	**Tg 57.6**	**186**
PXC-IND-BZD	**130.7**	**Tg 25.6, Tc 90.0 (HSM), Tm 110.0 (HSM)**	**187**
PXC-IND-CAF	**129.3**	**Tg 40.3, Tc 106.6, Tm 131.3**	**184**

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XRD

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STABILITY

SYSTEM	TIME (WEEKS)	Tg (°C)	SYSTEM	TIME (WEEKS)	Tg (°C)	SYSTEM	TIME (WEEKS)	Tg (°C)
PXC-IND	0	**57.6**	PXC-IND -BZD	0	**28.8**	PXC-IND -CAF	0	**44.5**
	1	53.5		1	26.7		1	43.3
	2	52.0		2	26.1		2	42.0
	3	49.4		3	26.3		3	42.1
	4	**43.1**		4	**26.7**		4	**42.4**
ΔTg		**14.5**	**ΔTg**		**2.1**	**ΔTg**		**2.1**

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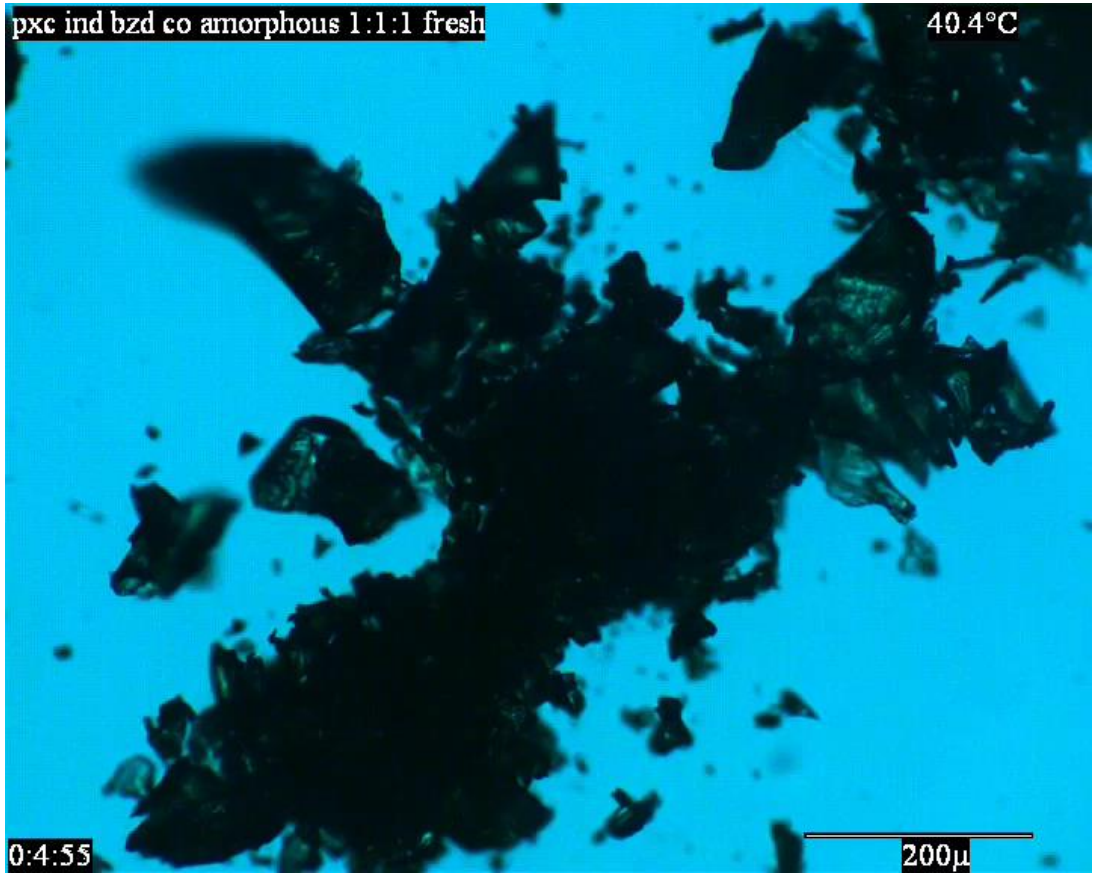
Hot-stage microscopy

PXC-IND-BZD



PXC-IND-CAF

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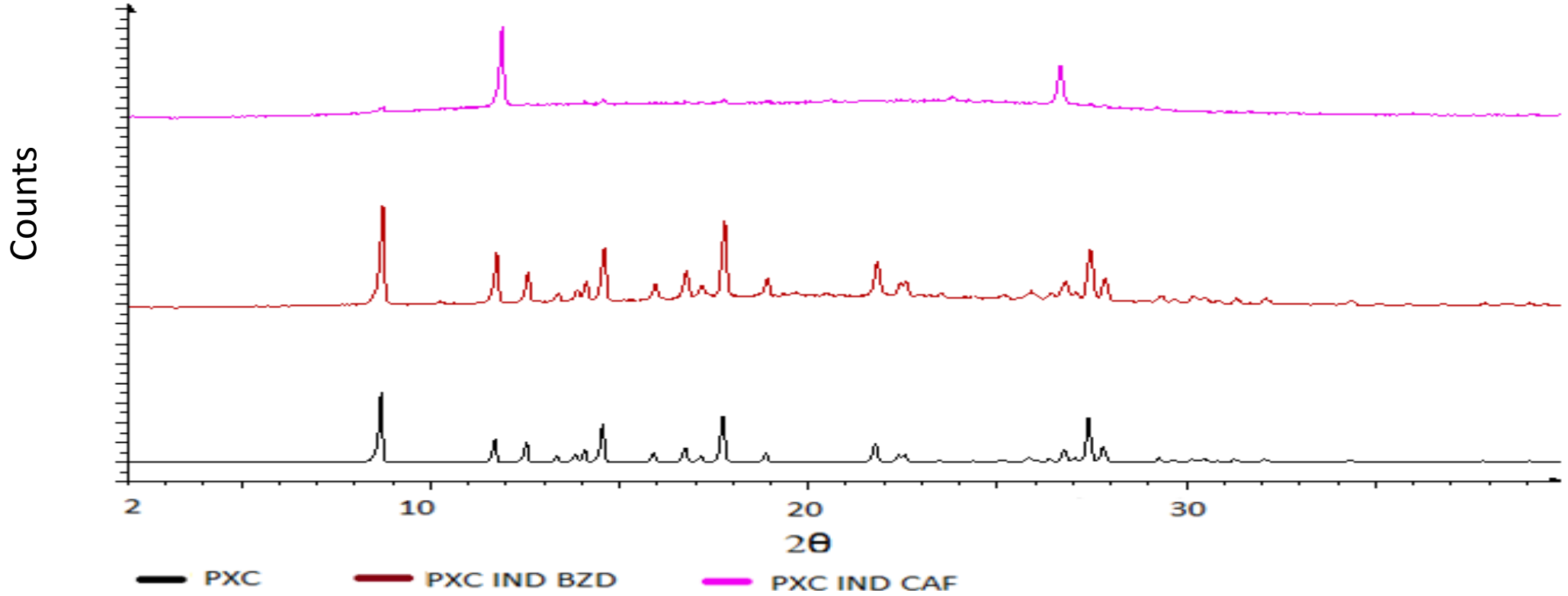
XRD OF COAMORPHOUS LEFT ISOTHERMAL AT THEIR CRYSTALLISATION TEMPERATURE



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Conclusions

It is possible to create a 3 component co-amorphous material via a melt quench method using either a crystalline or amorphous third component.

The addition of a third component has lowered the Tg in all cases.

Compounds that have propensity to crystallise generate more stable co-amorphous system (ΔTg – low)

The co-amorphous materials created using a crystalline component show less relaxation and a smaller deviation in Tg value upon storage (4 weeks).

Tg of co-amorphous system can be altered using appropriate 3rd component.

Physical parameters (ie. Tm and Tg) may not be sufficient, so knowledge of chemical interaction must be brought into equation when manipulating Tg.

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Future work

Determine the change in chemical environments that has occurred upon transformation to amorphous.

Explore influence of structural features on creation and stability of complex co-amorphous systems.

Analyse the influence of molar ration on properties of co-amorphous systems.

Define key parameters for design/management of co-amorphous systems.

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