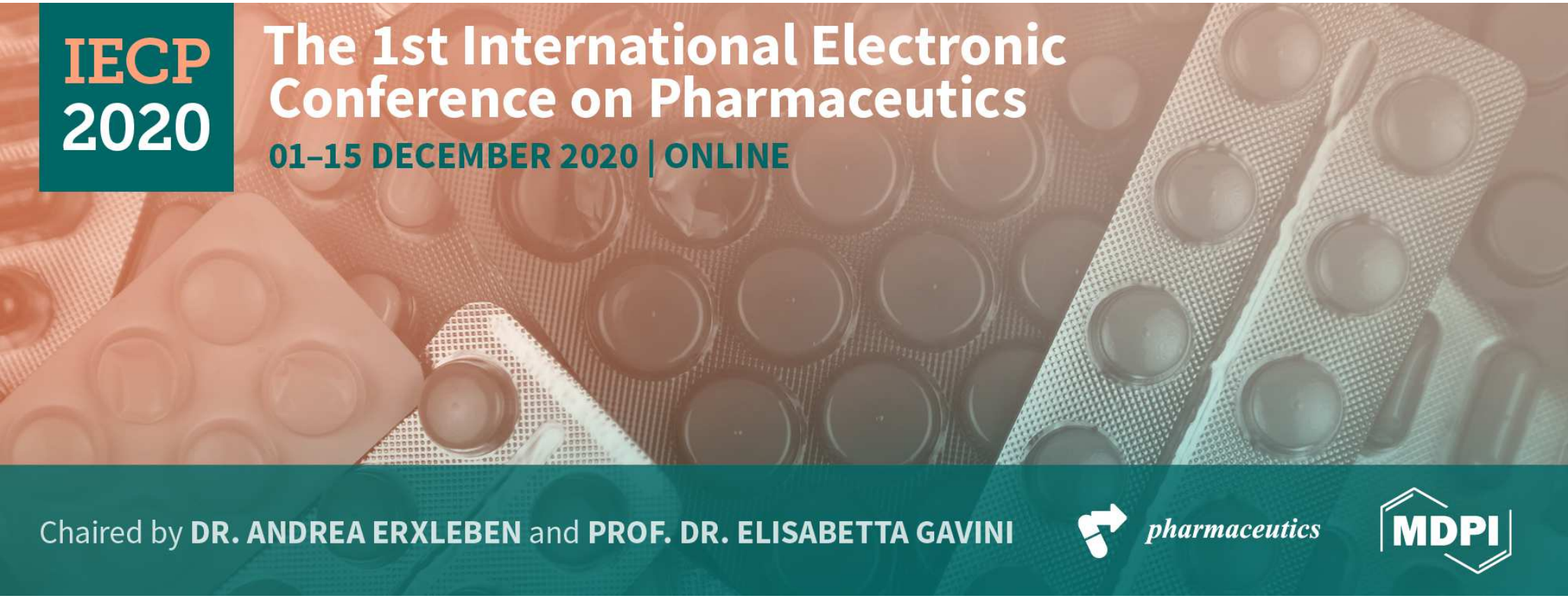


Investigating the optimal ratio between drug and co-former in co-amorphous systems

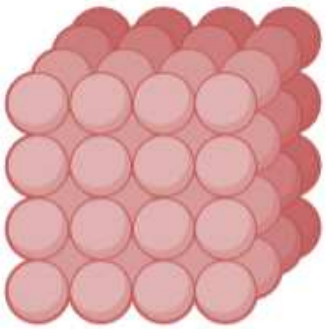
Prof. Dr. Dr. h.c. Thomas Rades

Research Chair in Pharmaceutical Design and Drug Delivery
Department of Pharmacy, University of Copenhagen, 2100 Copenhagen, Denmark
* Corresponding author: thomas.rades@sund.ku.dk

Crystalline Drug

Solid with orientational and positional long-range order in three dimensions.

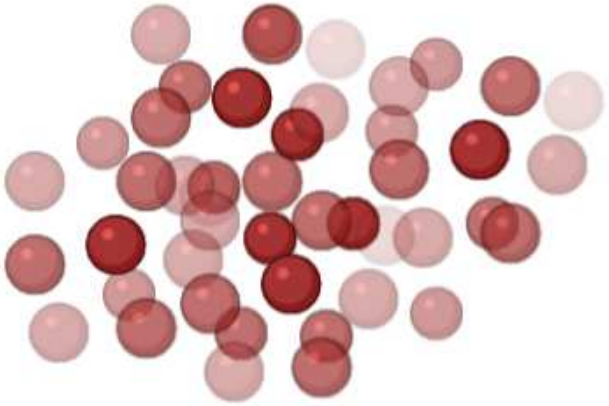
- Low solubility
- Stable



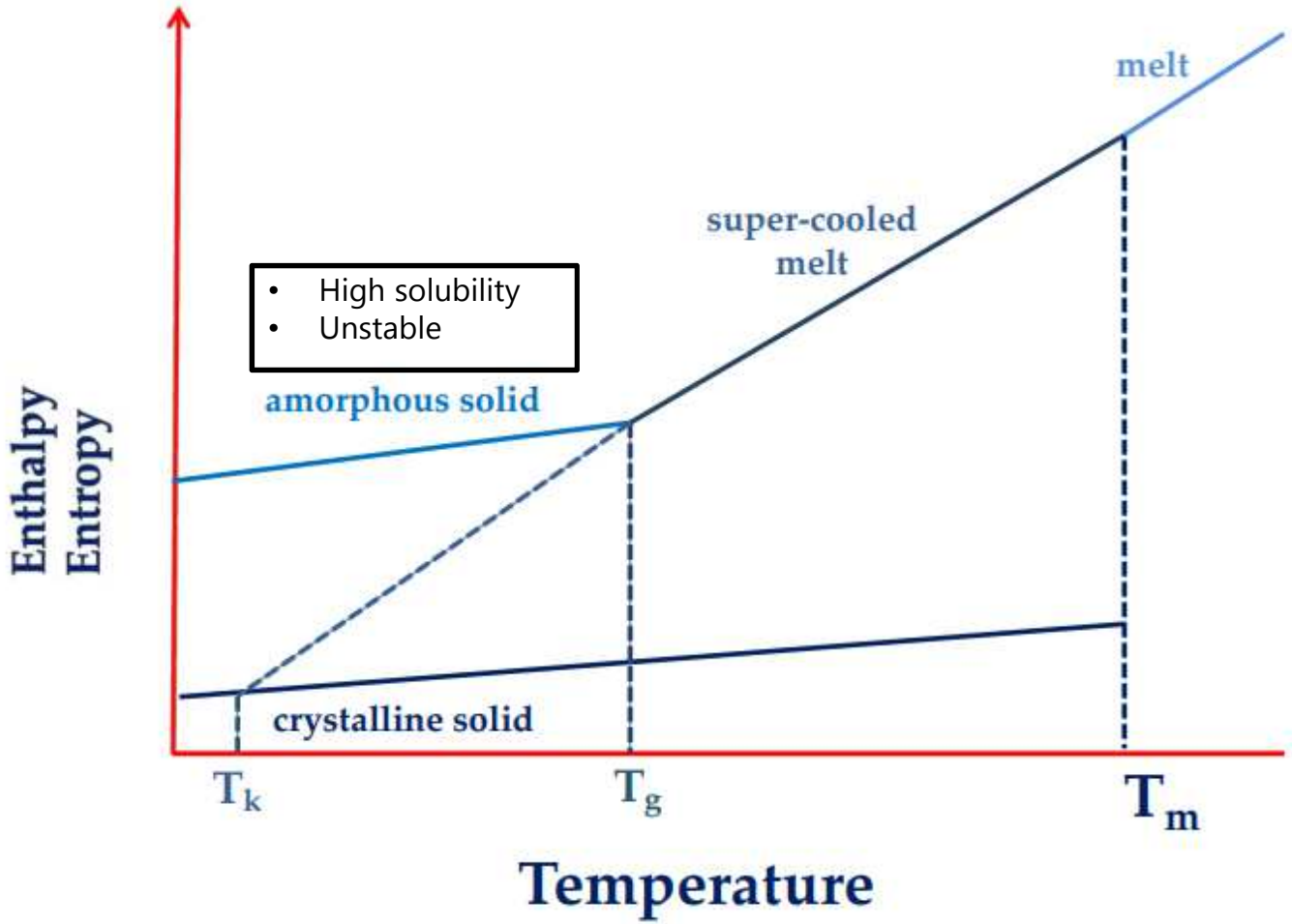
Amorphous Drug

Solid with no orientational or positional long-range order.

- High solubility
- Unstable



IECP 2020


melt
super-cooled
melt
• High solubility
• Unstable
amorphous solid
Enthalpy
Entropy
crystalline solid
T_k
T_g
T_m
Temperature

IECP 2020

Marketed Products

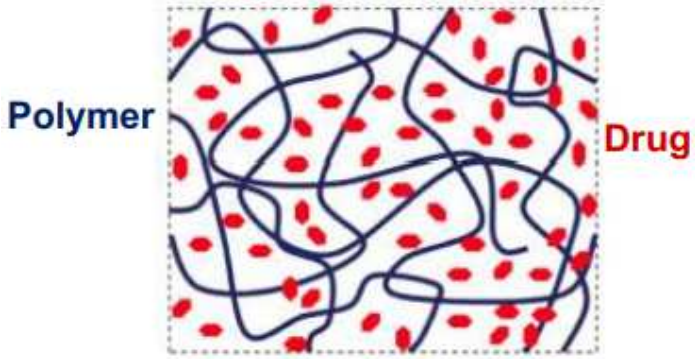
Amorphous APIs

- Accolate® (zafirlukast)
- Ceftin® (cefuroxime axetil)
- Accupril® (quinapril hydrochlorid)
- Viracept® (nelfinavir mesylate)

IECP 2020

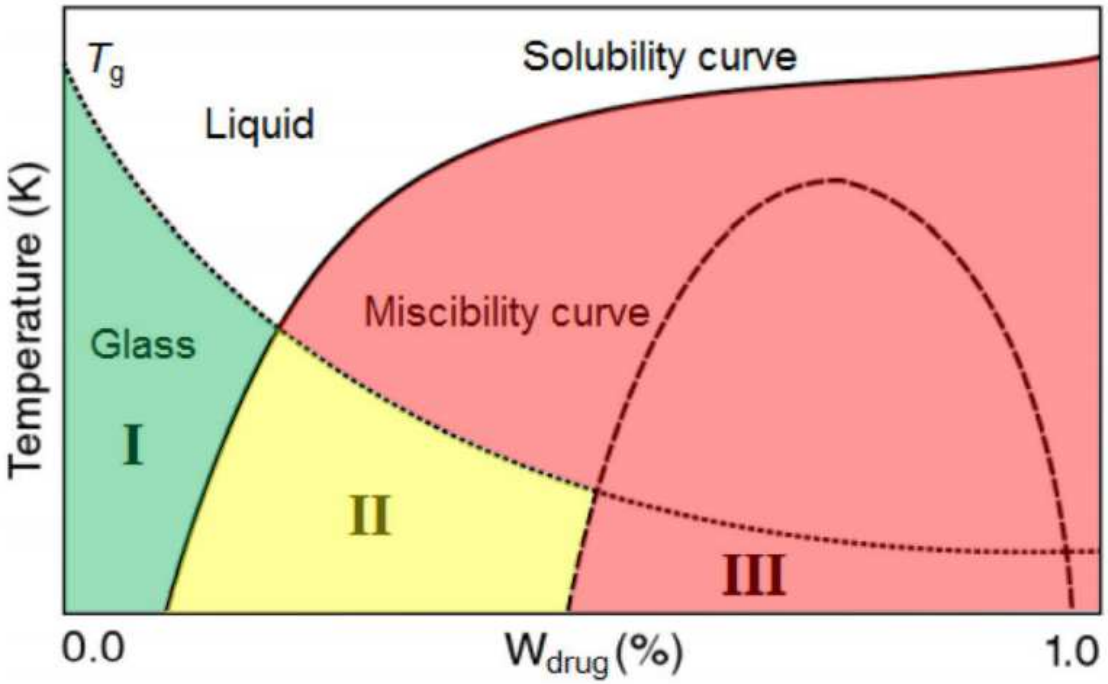
Amorphous solid dispersions

A polymeric amorphous solid dispersion is (ideally) a homogenous molecular dispersion of drug molecules in an amorphous polymeric matrix.



IECP 2020

Drug in polymer solubility



Stable zone

Metastable zone

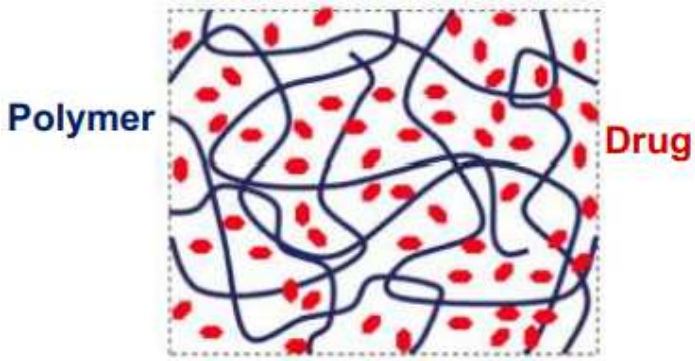
Unstable zone

Phase diagram of a drug-polymer mixture including the solubility curve (solid line), miscibility curve (dashed line) and the Tg curve (dotted line). **Area I** represents the thermodynamically stable amorphous solid dispersion (glass solution), **area II** represents a metastable amorphous solid dispersion where the mixture is kinetically stabilized due to low molecular mobility, **area III** represents a unstable amorphous solid dispersion in which phase separation occurs spontaneously.

IECP 2020

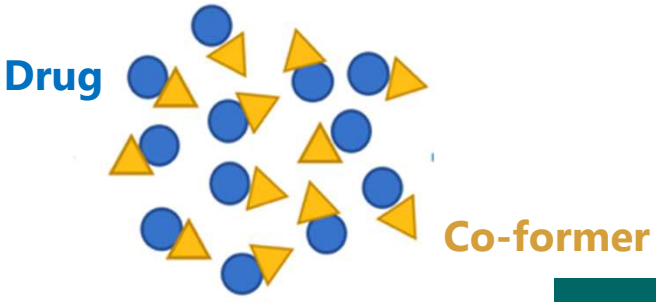
- Amorphous solid dispersions

  A polymeric amorphous solid dispersion is (ideally) a homogenous molecular dispersion of drug molecules in an amorphous polymeric matrix.



- Co-amorphous systems

  Co-amorphous systems consist of two low molecular weight, initially crystalline, materials that upon co-amorphization are mixed at the molecular level to form a single amorphous phase.

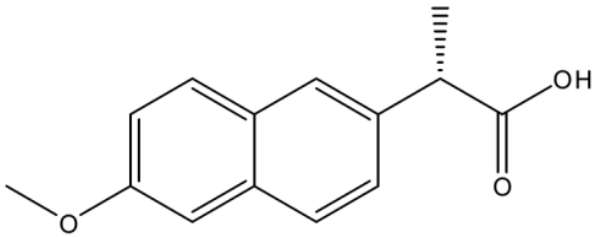


IECP 2020

Drug-Drug Combination

Naproxen

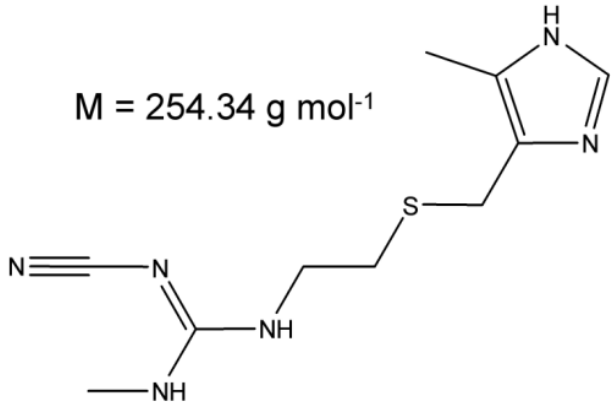
M = 230.26 g mol^{-1}



- BCS class II
- Non-steroidal anti-inflammatory drug (NSAID)
- Side effect: Gastro-intestinal disorders

Cimetidine

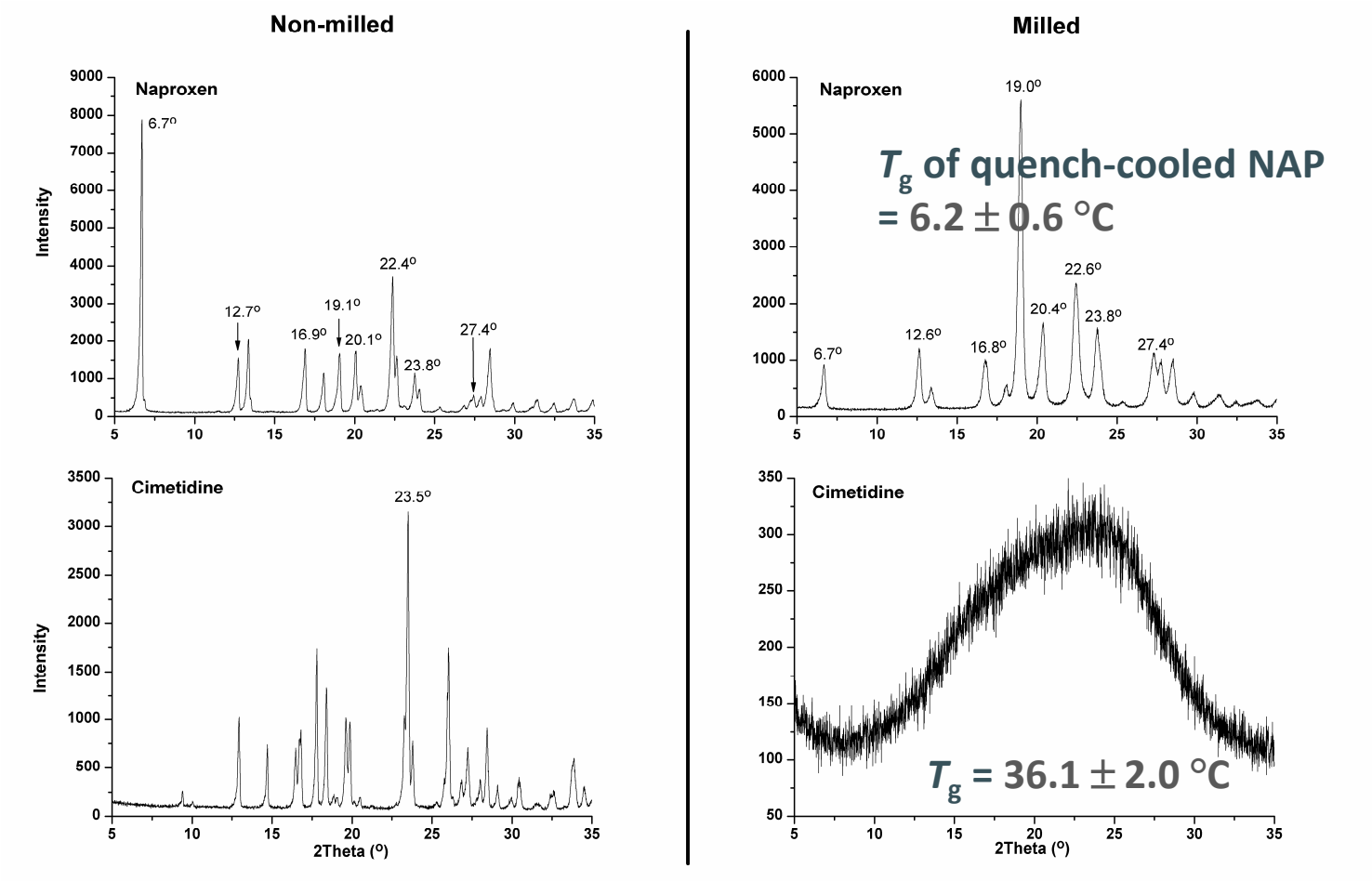
M = 254.34 g mol^{-1}



- BCS class III
- Used in the treatment of gastro-intestinal disorders
- similar dosing range for NAP&CIM

IECP 2020

Individual APIs before and after ball milling

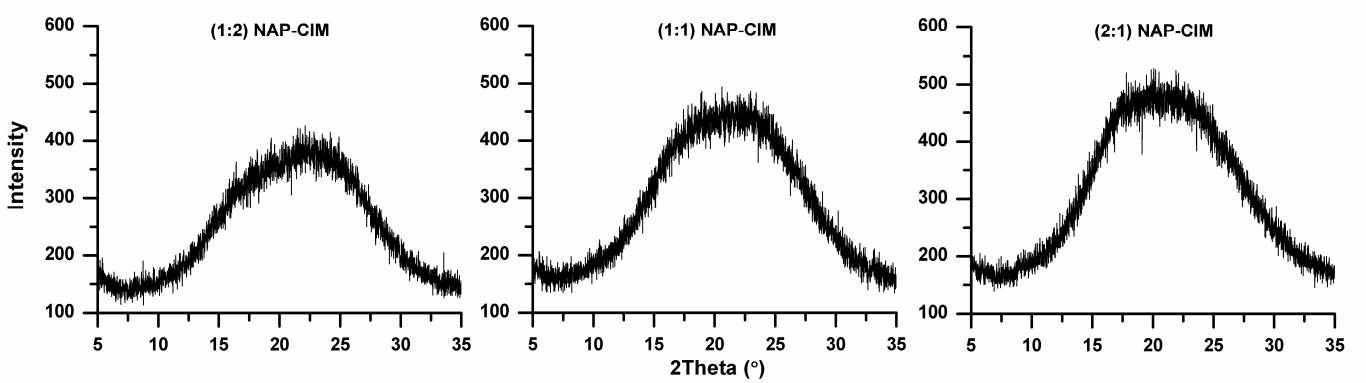


IECP 2020

Co-milled APIs at different ratios

- All drug-drug molar ratios resulted in X-ray amorphous mixtures
- No trace of crystallinity in DSC

XRPD



DSC

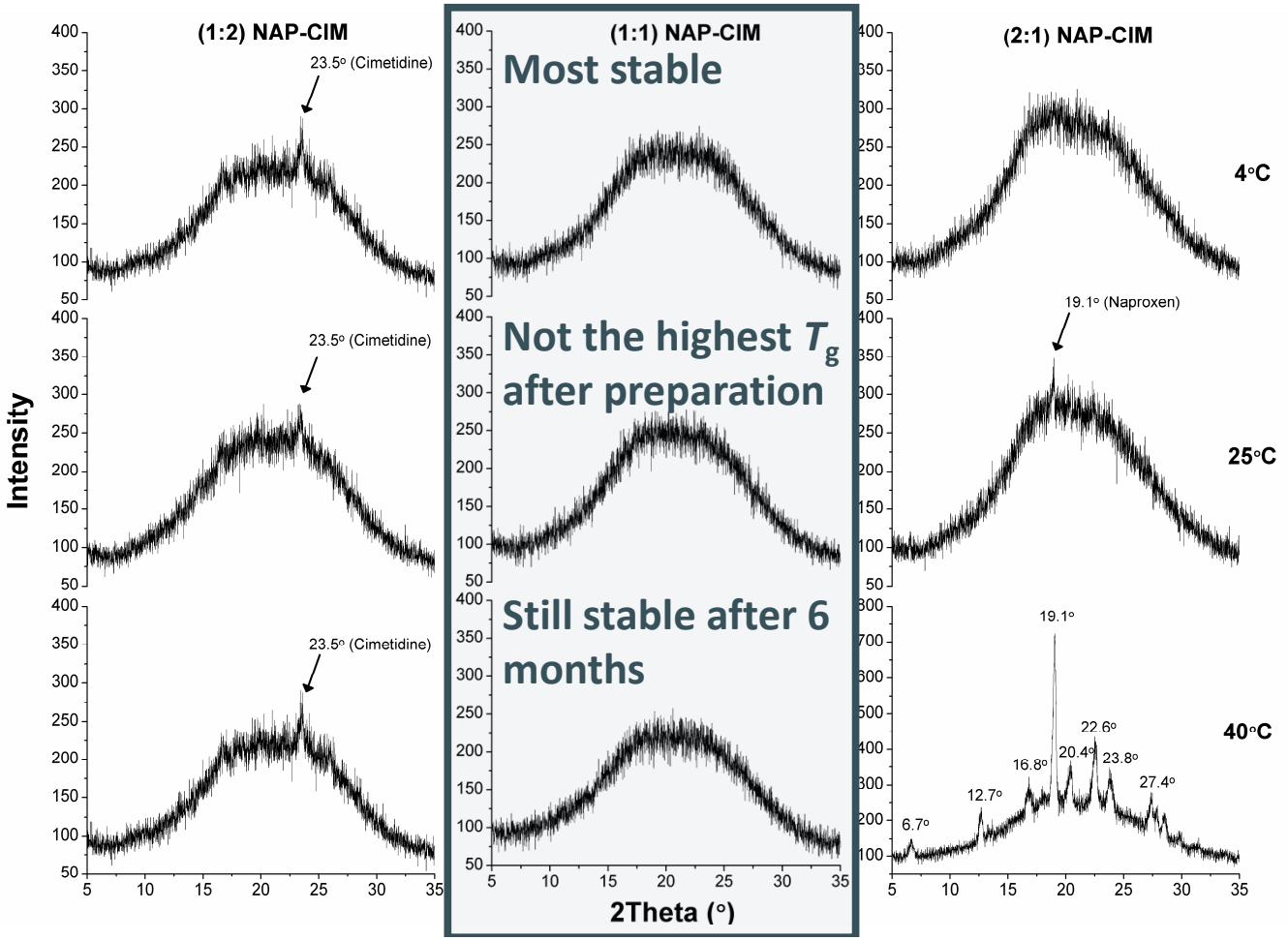
T_g= 40.2 ± 1.1 °C

T_g= 34.5 ± 0.3 °C

T_g= 31.5 ± 0.7 °C

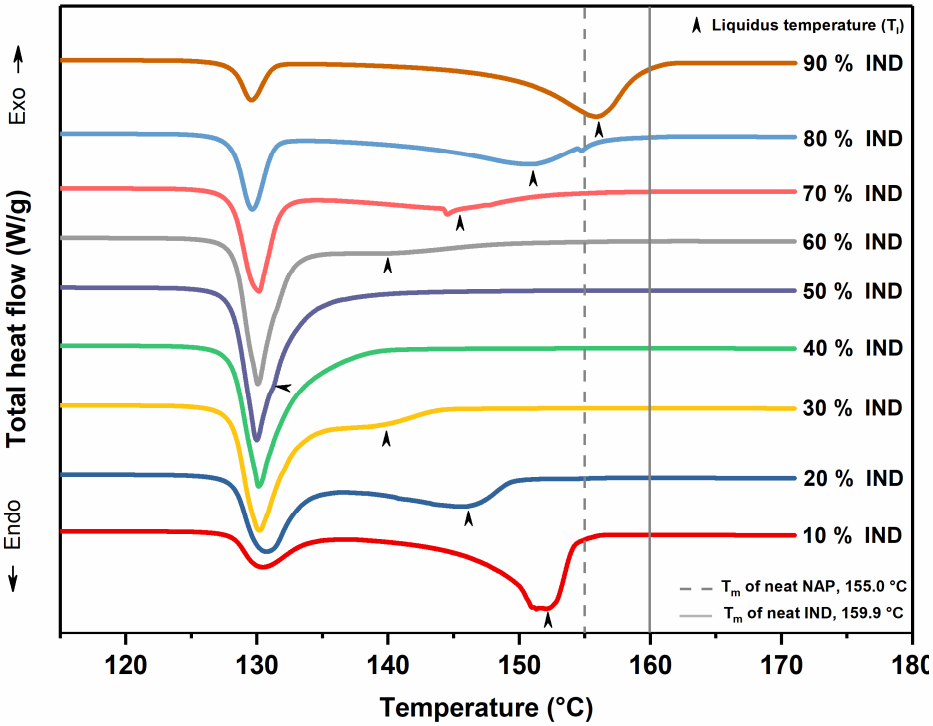
IECP 2020

Physical stability - 60-day storage at dry conditions

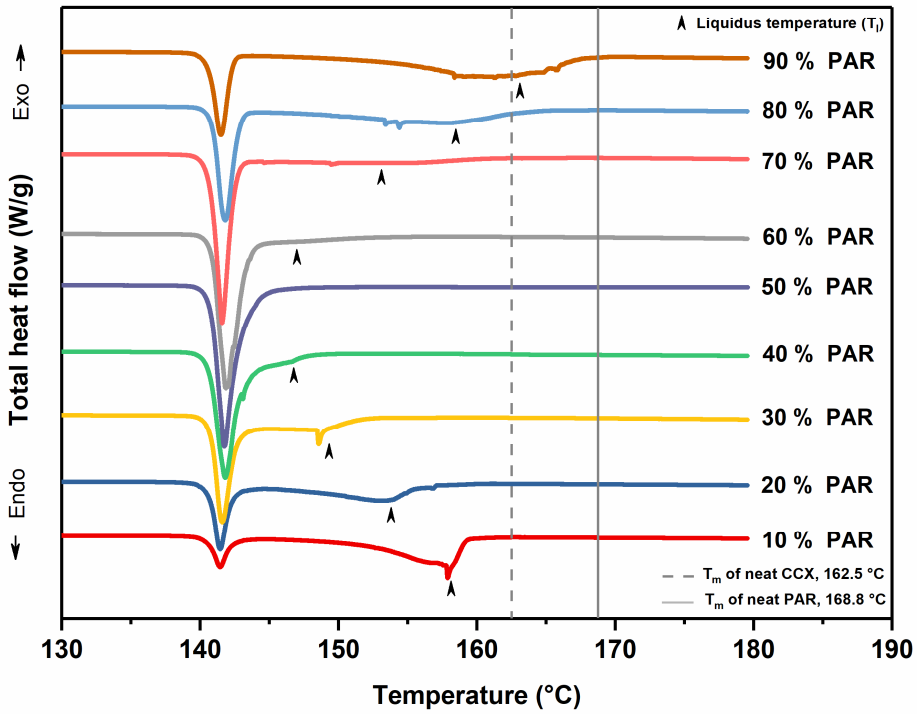


IECP 2020

Eutectic behaviour of co-amorphous drug-drug systems



Thermograms for Indometacin/Naproxen systems

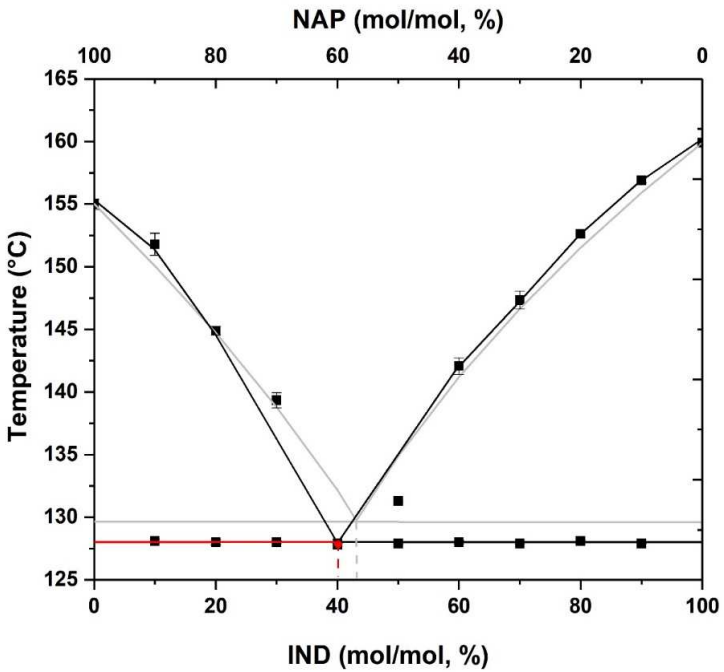


Thermograms for Paracetamol/Celecoxib systems

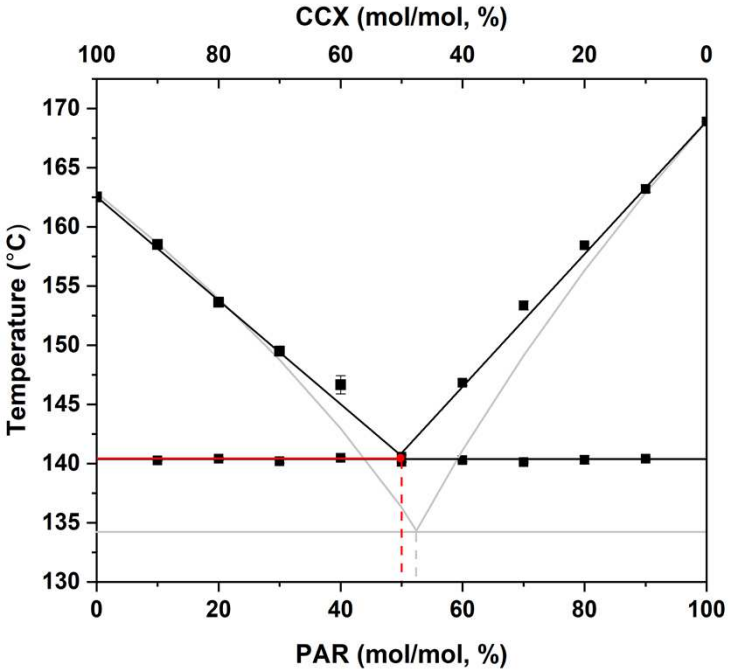
Kissi et al, Pharmaceutics 2019, 11, 628

IECP 2020

Naproxen/Indomethacin systems



Celecoxib/Paracetamol systems

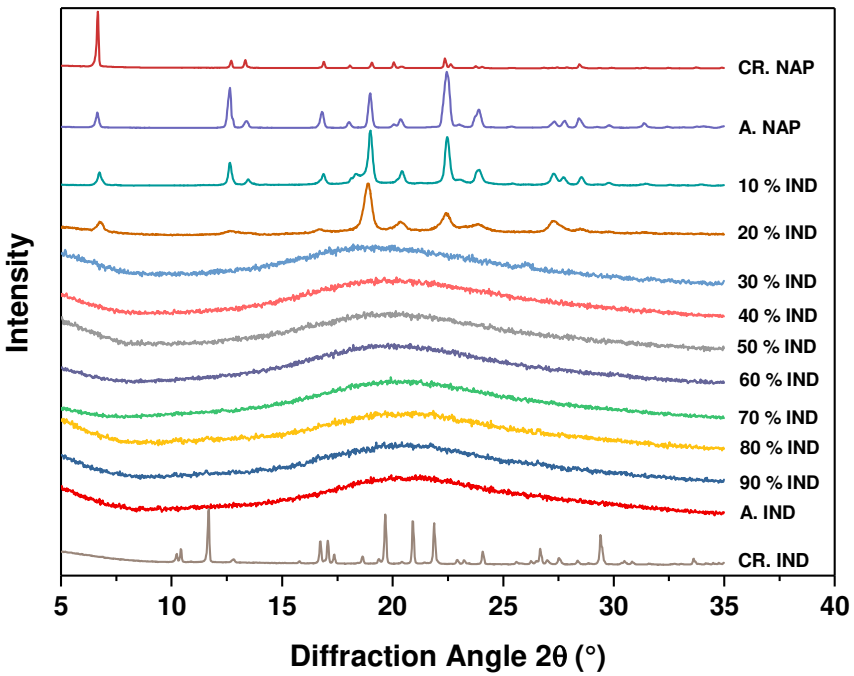


Kissi et al, Pharmaceutics 2019, 11, 628

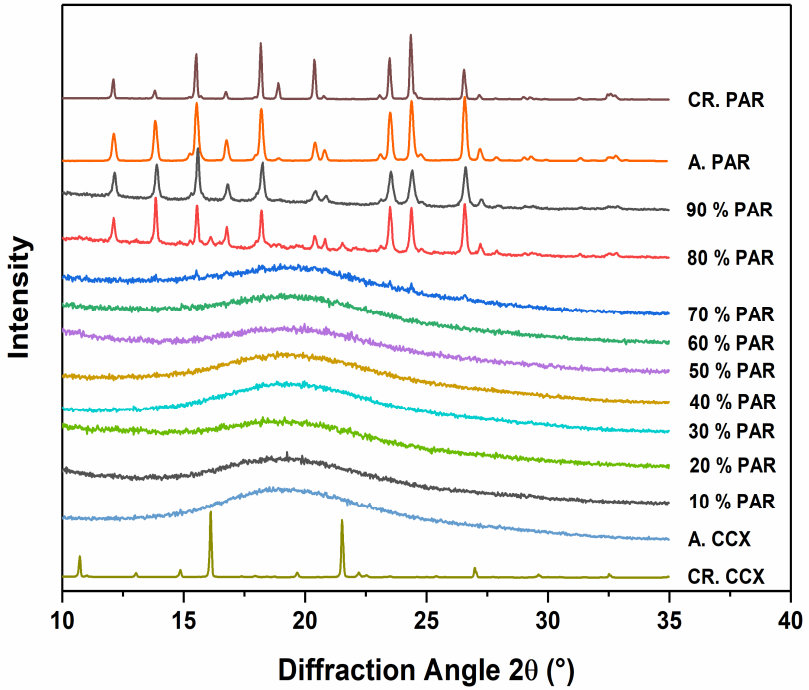
IECP 2020

Solid-state characterisation using XRPD

Naproxen/Indomethacin systems



Celecoxib/Paracetamol systems

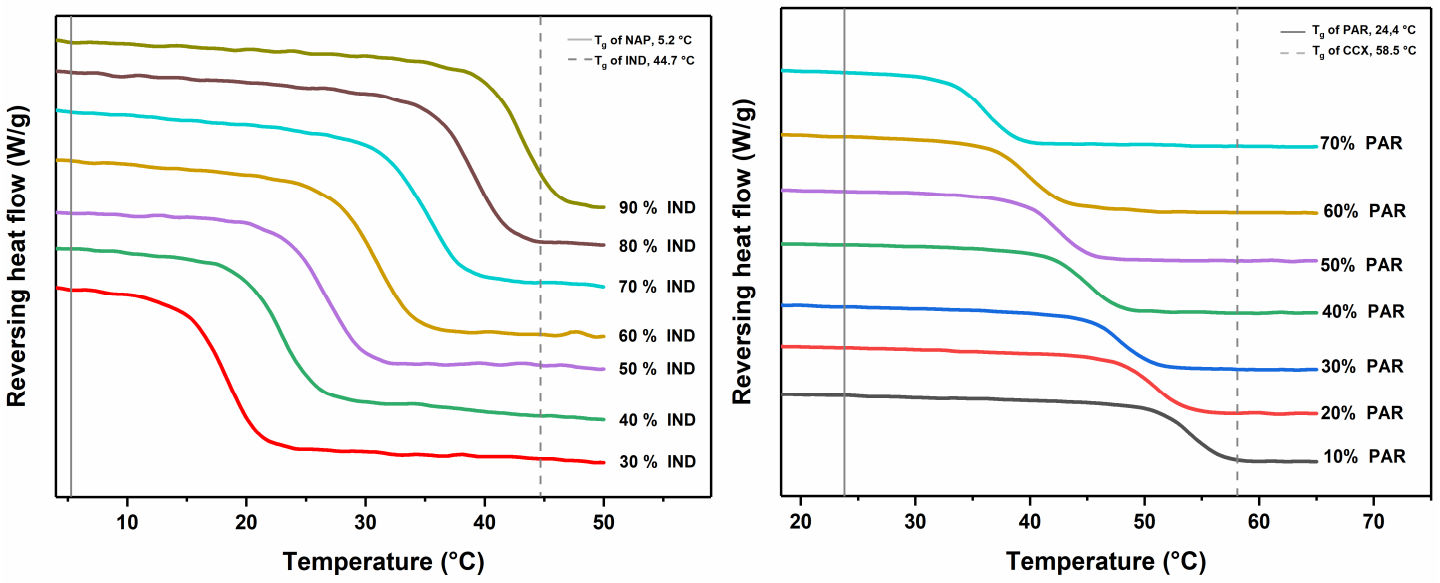


Samples that show crystalline peaks immediately after melting and cooling can be ruled out

Kissi et al, Pharmaceutics 2019, 11, 628

IECP 2020

Tgs for co-amorphous drug-drug systems



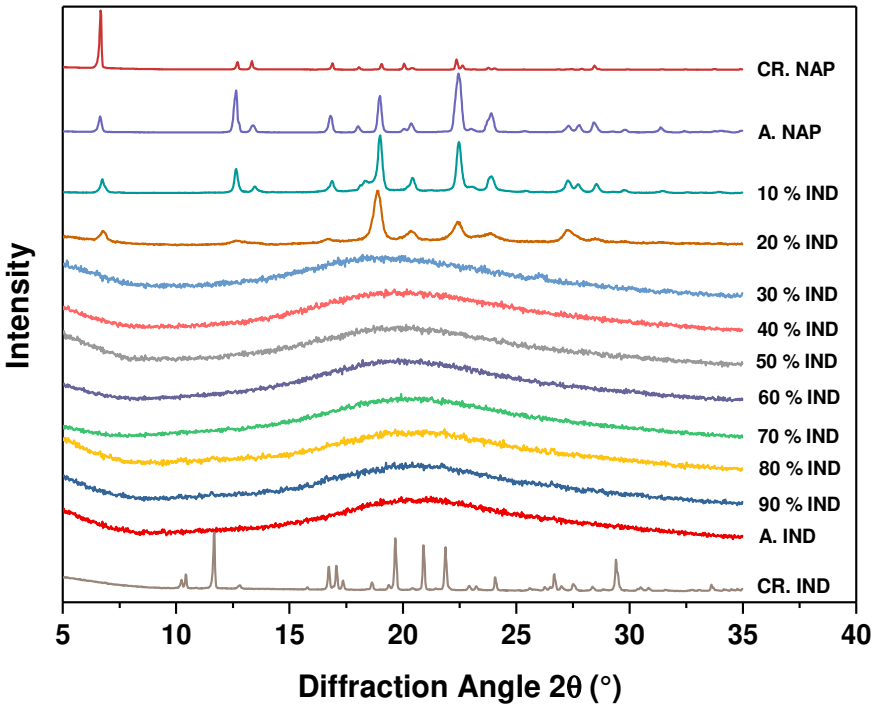
There is general decrease or increase in Tg with increasing or decreasing drug concentration.

Kissi et al, Pharmaceutics 2019, 11, 628

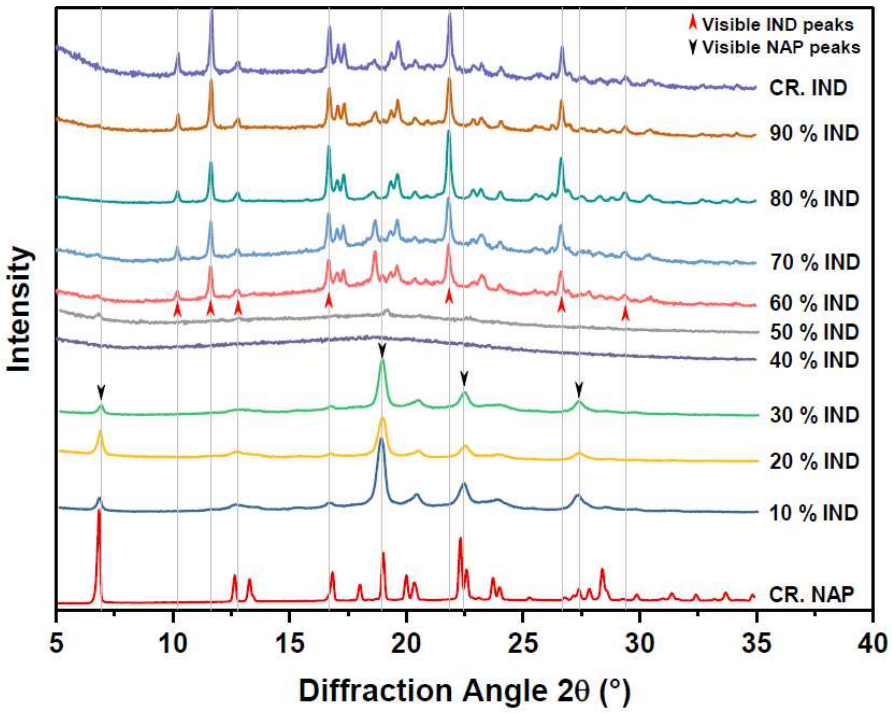
IECP 2020

Physical stability test

After preparation



After storage

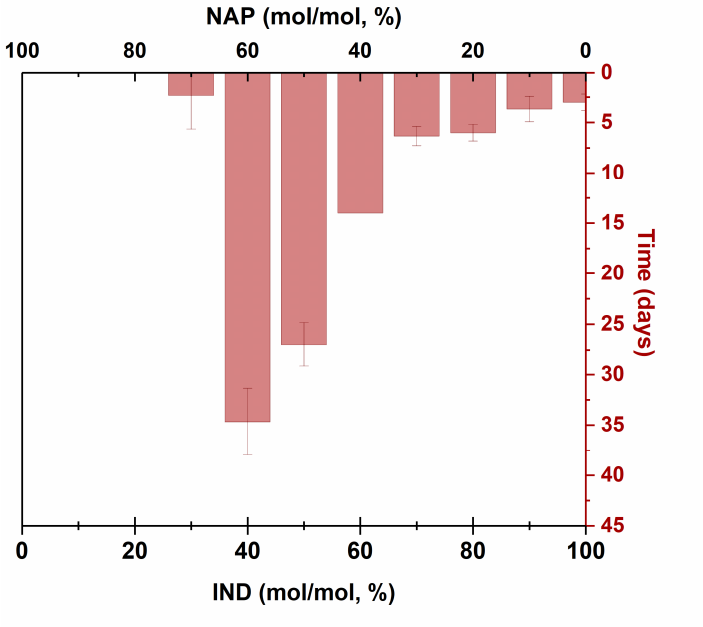


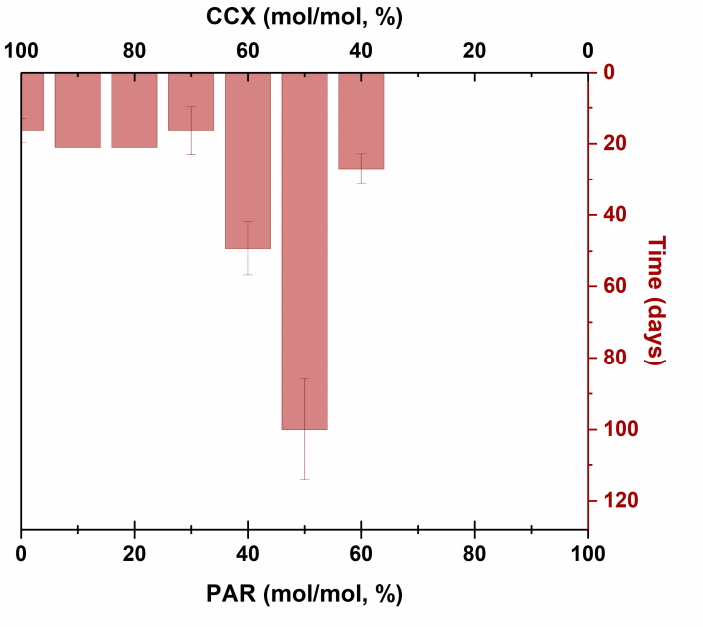
Test under dry conditions at room temperature

Kissi et al, Pharmaceutics 2019, 11, 628

IECP 2020

Days these systems stayed amorphous

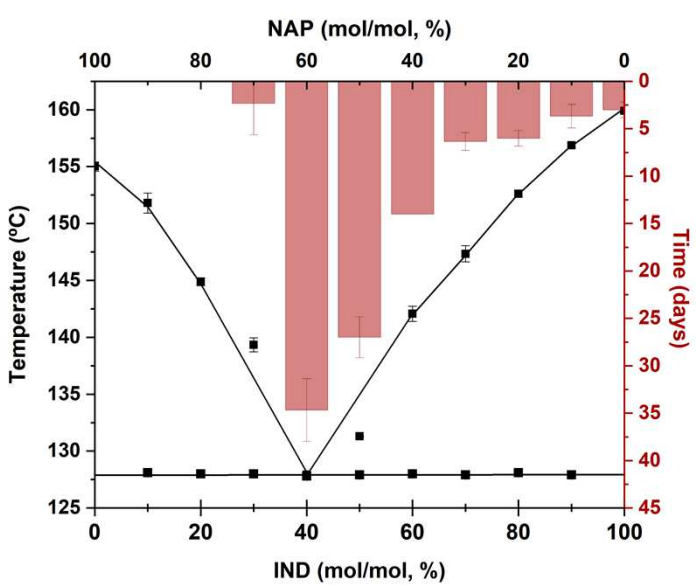


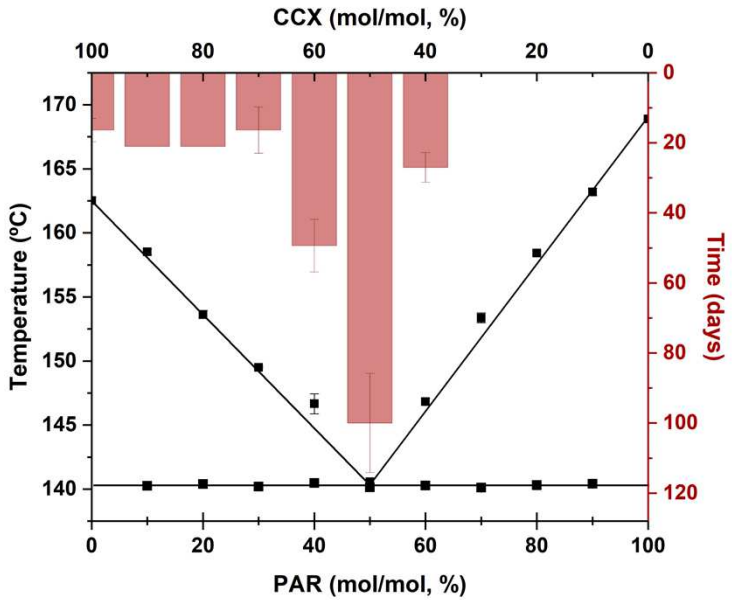


Kissi et al, Pharmaceutics 2019, 11, 628

IECP 2020

Superimposing eutectic behaviour and physical stability

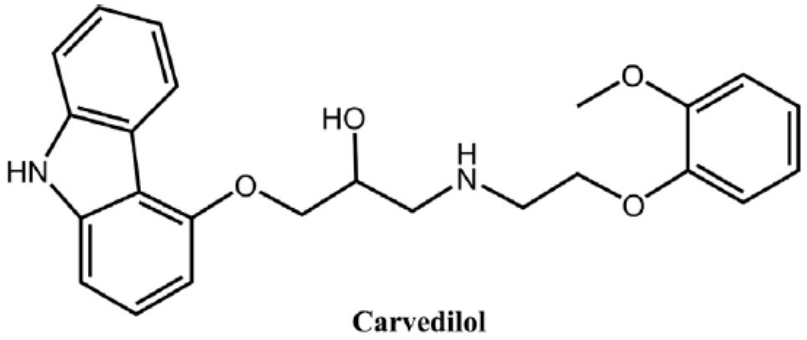




Kissi et al, Pharmaceutics 2019, 11, 628

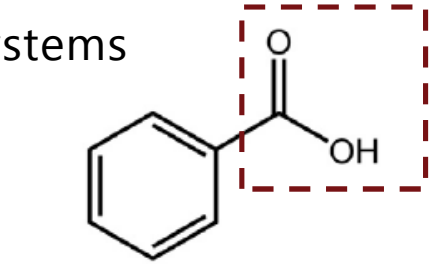
IECP 2020

Carvedilol-organic acids co-amorphous systems

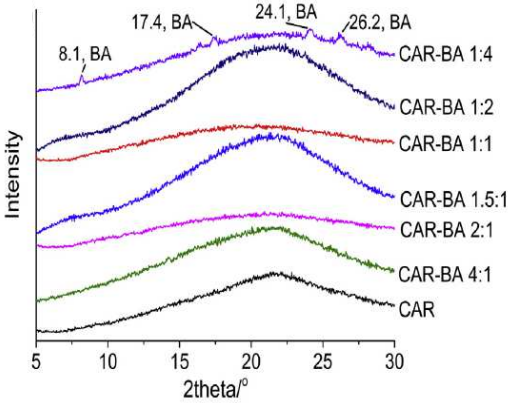


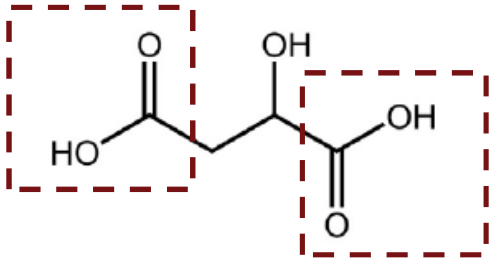
Carvedilol

<u>Molar ratios</u>: from 4:1 to 1:4 (CAR-OAs)
<u>Samples preparation</u>: Spray drying

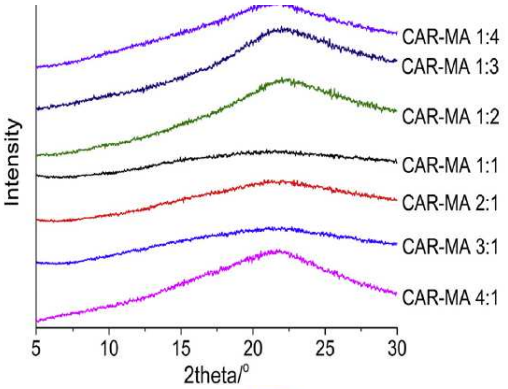


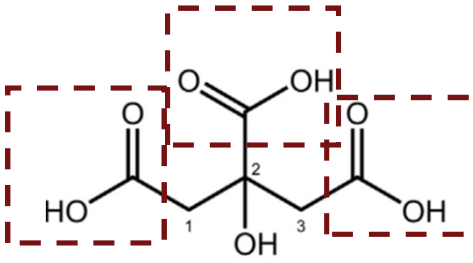
Benzoic acid



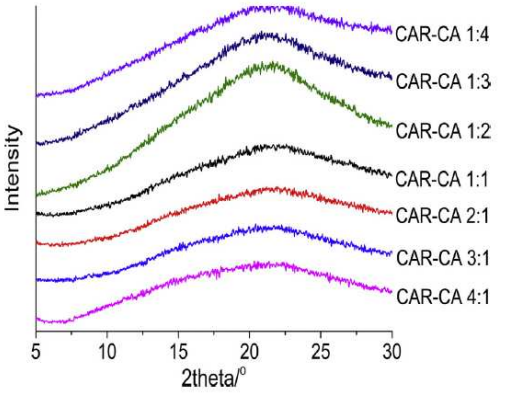


Malic acid





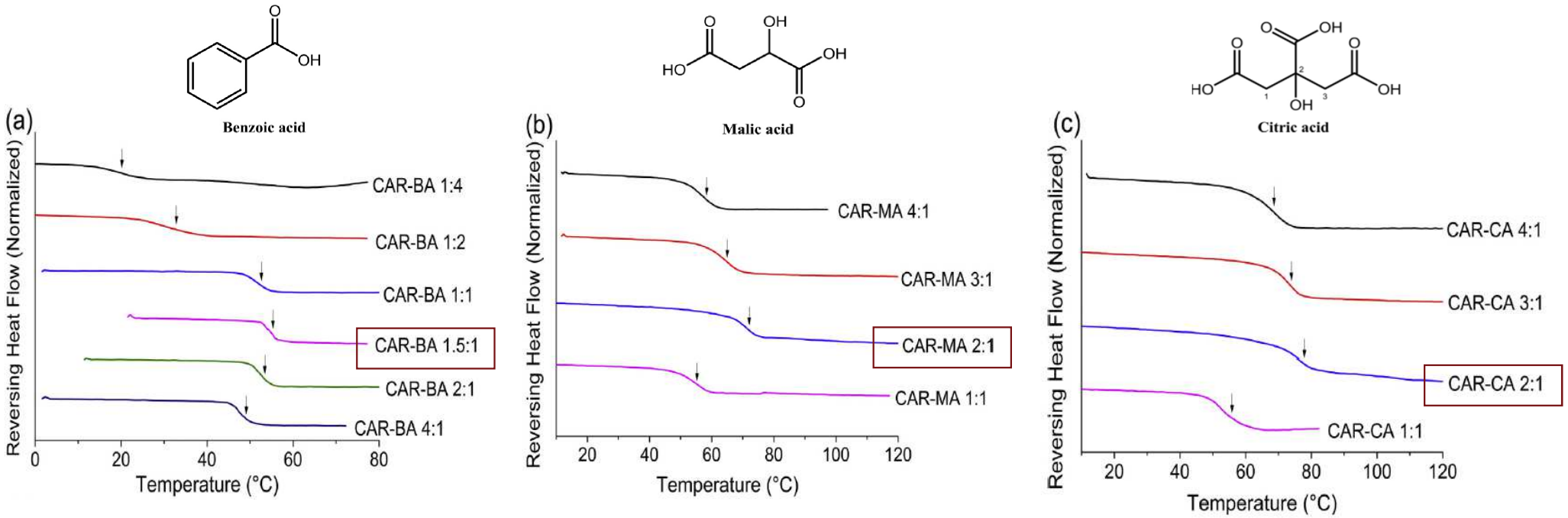
Citric acid



IECP 2020

Wu, W. et al., (2018). *European Journal of Pharmaceutics and Biopharmaceutics*, 131, 25-32.

Glass transition temperatures of CAR-OAs systems (mDSC results)

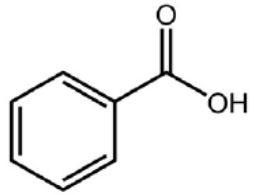


- Highest T_g values: CAR-BA 1.5:1, CAR-MA 2:1 and CAR-CA 2:1.
- In the case of CAR-BA and CAR-CA, the highest T_g was not found at the hypothesized ideal salt forming stoichiometric conditions (CAR-BA 1:1 and CAR-CA 3:1), but at molar ratios of CAR-BA 1.5:1 and CAR-CA 2:1.

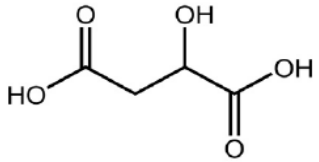
IECP 2020

Wu, W. et al., (2018). *European Journal of Pharmaceutics and Biopharmaceutics*, 131, 25-32.

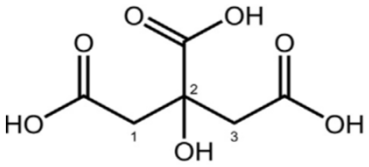
Physical stability of CAR-OAs systems (40℃, dry condition)



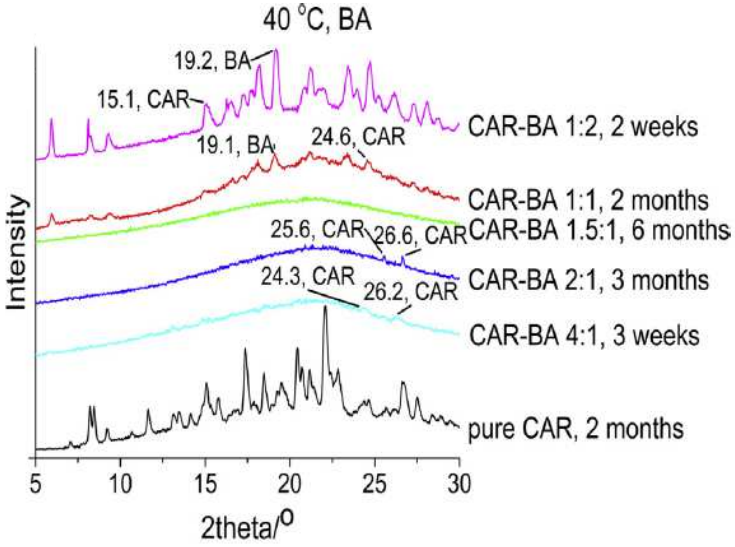
Benzoic acid

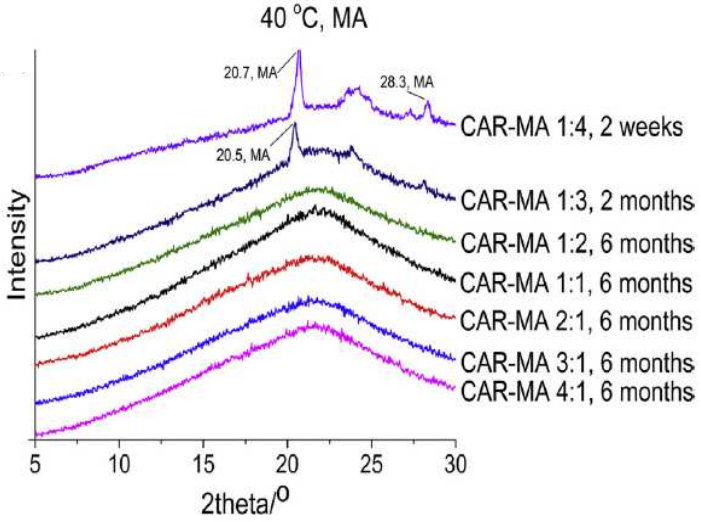


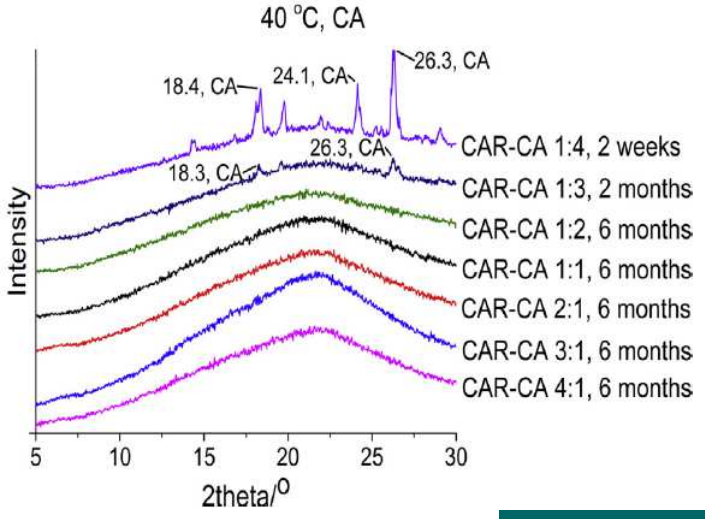
Malic acid



Citric acid







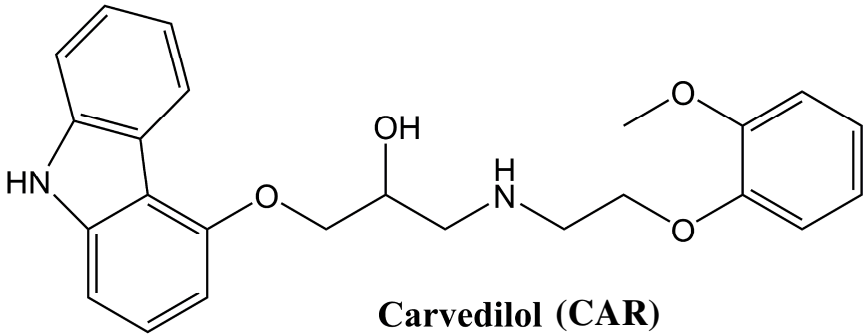
IECP 2020

Wu, W. et al., (2018). *European Journal of Pharmaceutics and Biopharmaceutics*, 131, 25-32.

Carvedilol-amino acid co-amorphous systems with strong interaction

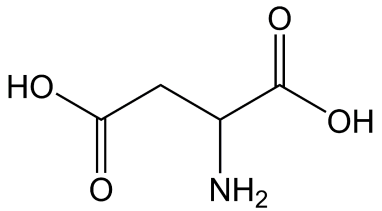
CAR to ASP molar ratios:
From 2:1 to 1:4

Sample preparation:
Spray drying



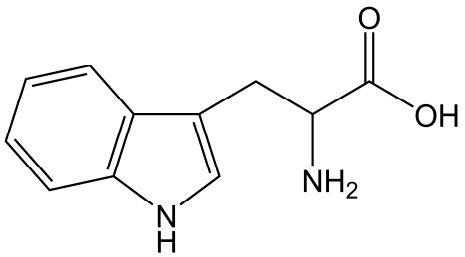
Carvedilol (CAR)

Strong interaction
(Salt formation)



L-Aspartic acid (ASP)

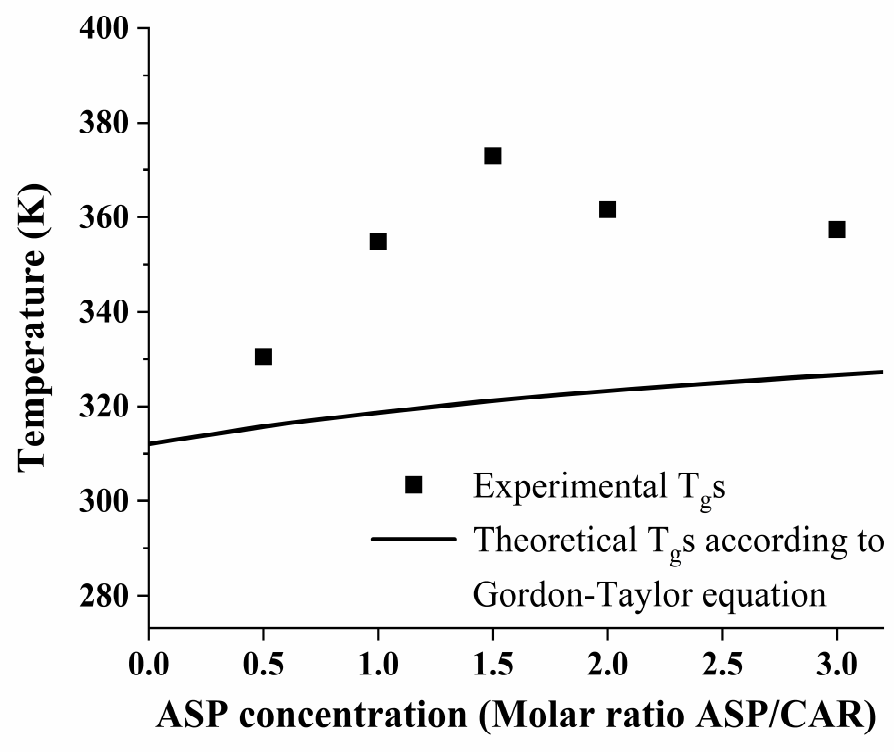
Non-strong interaction



L-Tryptophan (TRP)

IECP 2020

Comparison of experimental T_gs and theoretical T_g s



Gordon-Taylor equation:

$$T_{g12} = \frac{w_1 \cdot T_{g1} + K \cdot w_2 \cdot T_{g2}}{w_1 + K \cdot w_2}$$

$$K = \frac{T_{g1} \cdot \rho_1}{T_{g2} \cdot \rho_2}$$

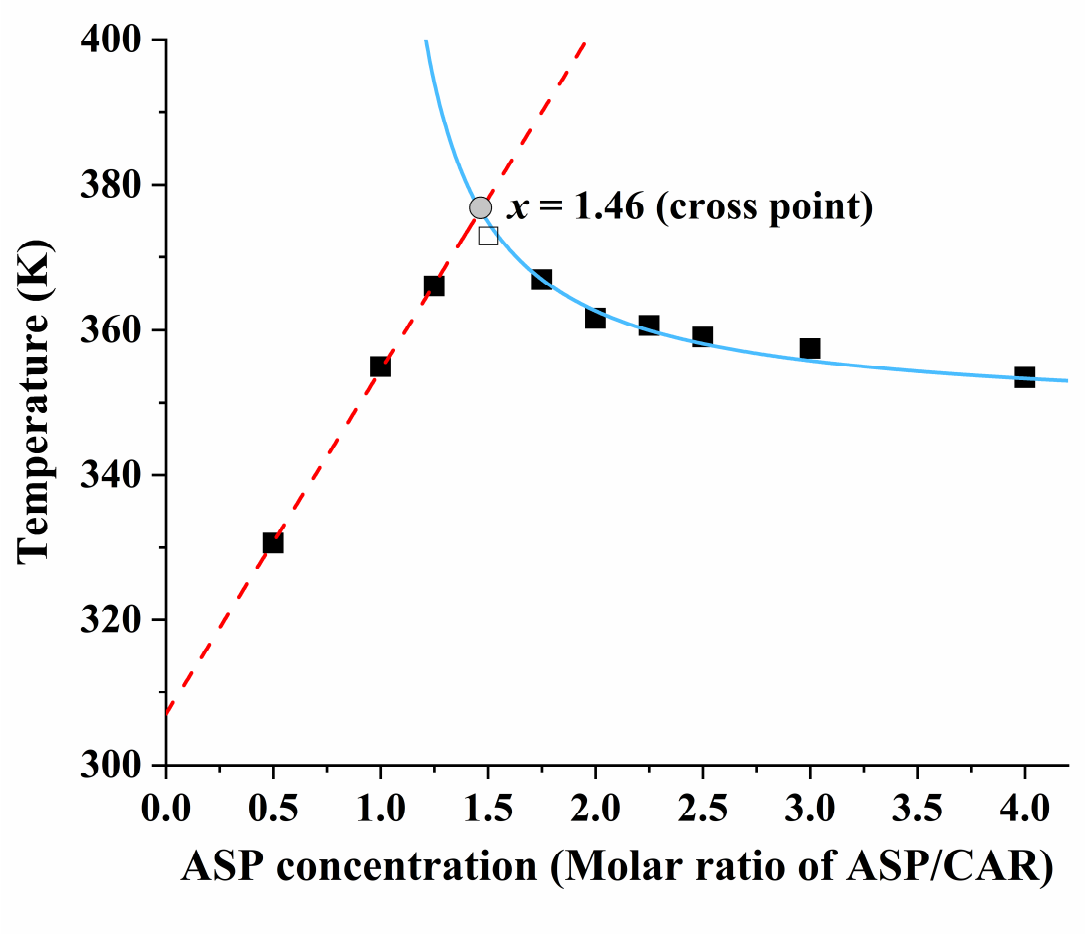
Component 1: Amorphous CAR

Component 2: Amorphous ASP

- All experimental values had a positive deviation from the theoretical T_gs
- Strong molecular interactions between CAR and ASP in co-amorphous systems
- The highest deviation was observed at the CAR-ASP 1:1.5 molar ratio (rather than at the 1:1 molar ratio)

IECP 2020

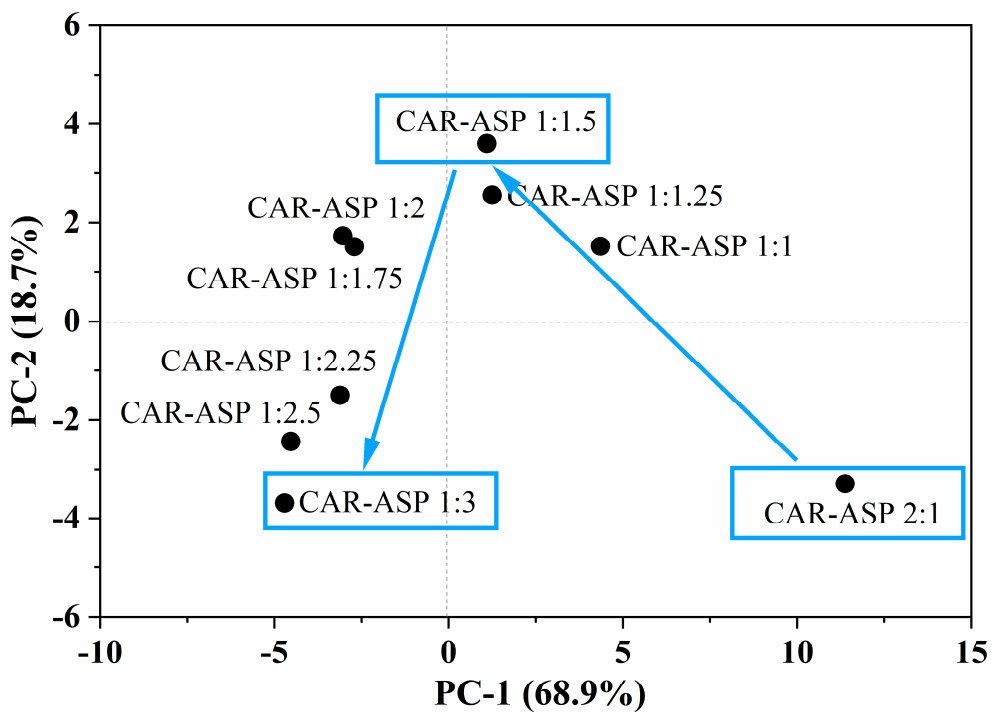
Liu, J et al. (2020). *Molecular Pharmaceutics*, 17(4), 1335-1342.

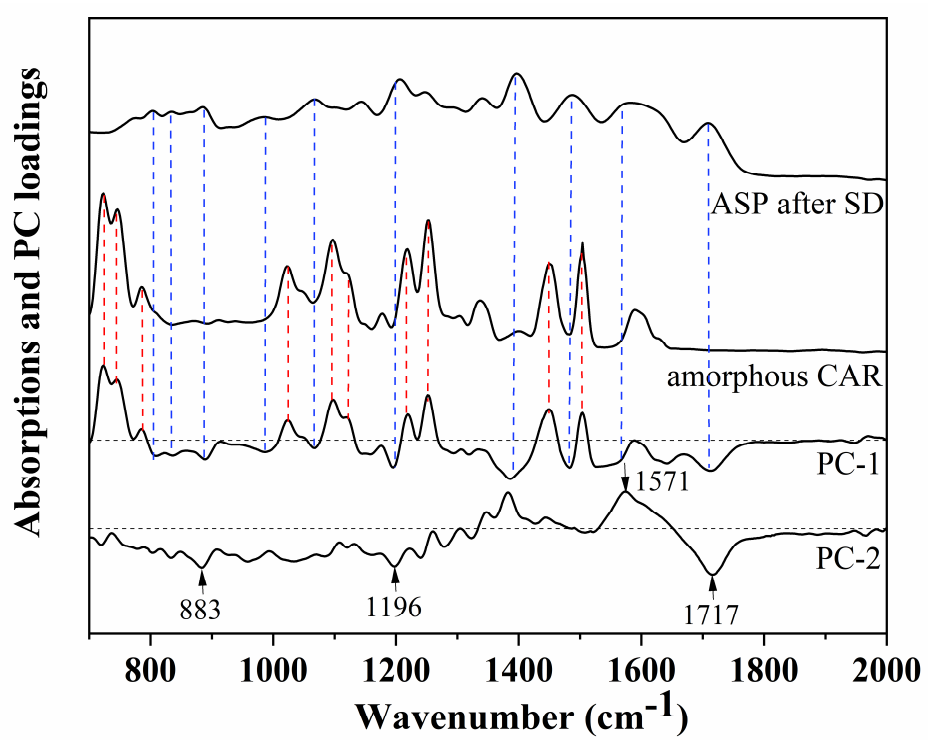


IECP 2020

Liu, J et al. (2020). *Molecular Pharmaceutics*, 17(4), 1335-1342.

PCA on FTIR data





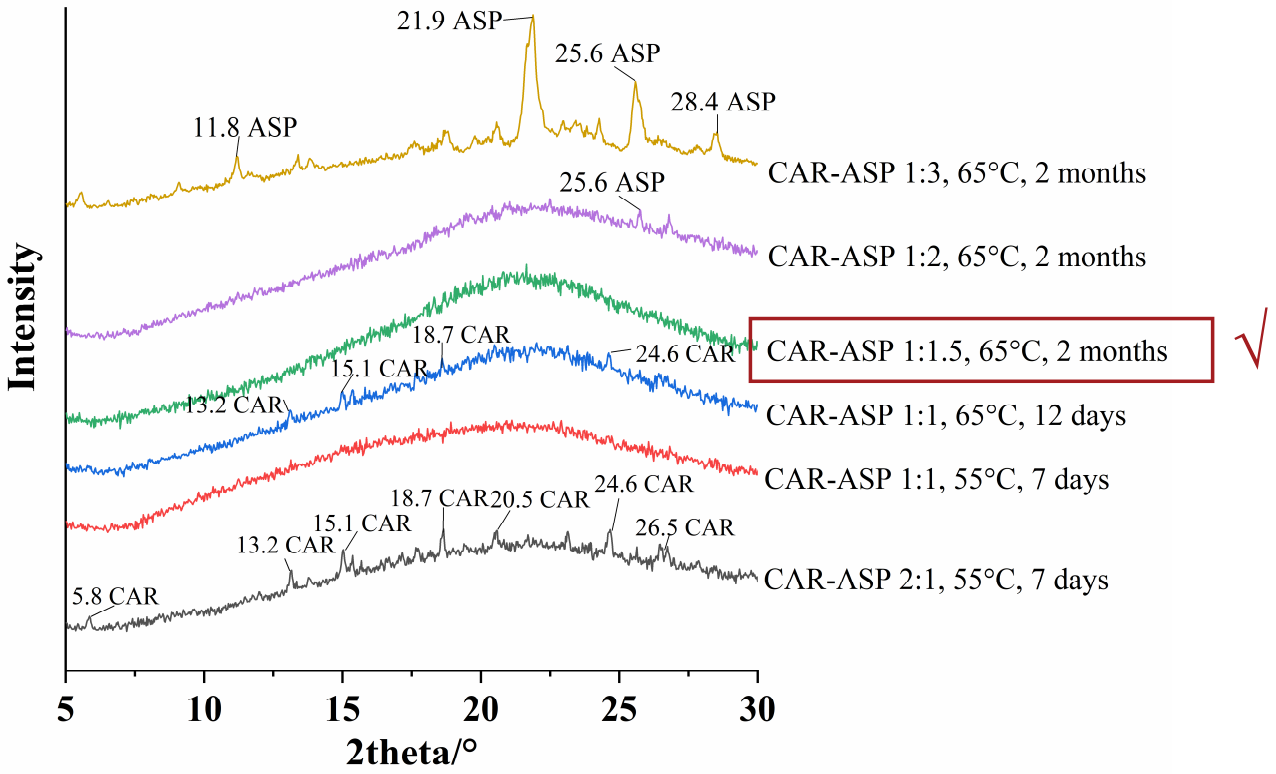
- PC-1: Varying molar ratios
- PC-2: Molecular interactions

- 1717 cm^{-1}: -COOH group of ASP
- 1571 cm^{-1}: Aromatic ring stretching of CAR

Liu, J et al. (2020). *Molecular Pharmaceutics*, 17(4), 1335-1342.

IECP 2020

Physical stability (under dry condition)



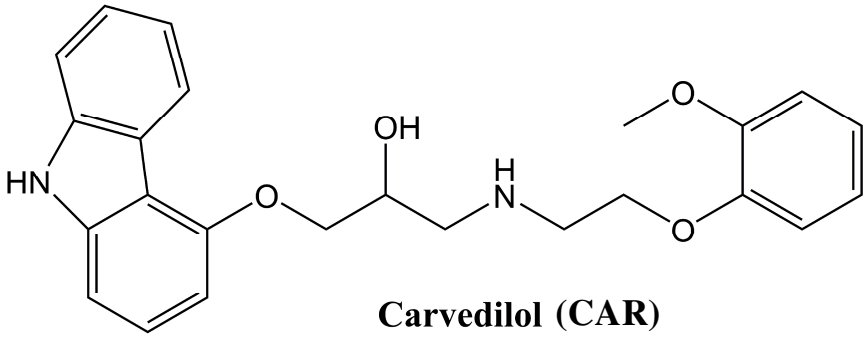
- The presence of an excess compound, relative to the sample at the optimal molar ratio (CAR-amino acids 1:1.5), resulted in re-crystallization of the excess component.

IECP 2020

Liu, J et al. (2020). *Molecular Pharmaceutics*, 17(4), 1335-1342.

Carvedilol-amino acid co-amorphous systems with non-strong interaction

Carvedilol-amino acids co-amorphous systems

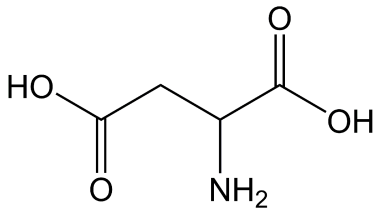


Carvedilol (CAR)

CAR to TRP molar ratios:
From 10% to 90%

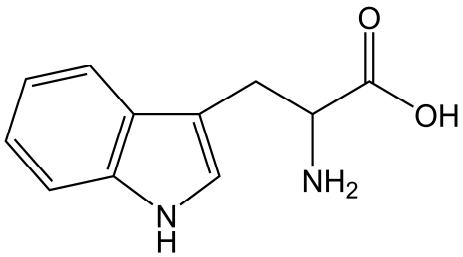
Sample preparation:
Ball milling

Strong interaction
(Salt formation)



L-Aspartic acid (ASP)

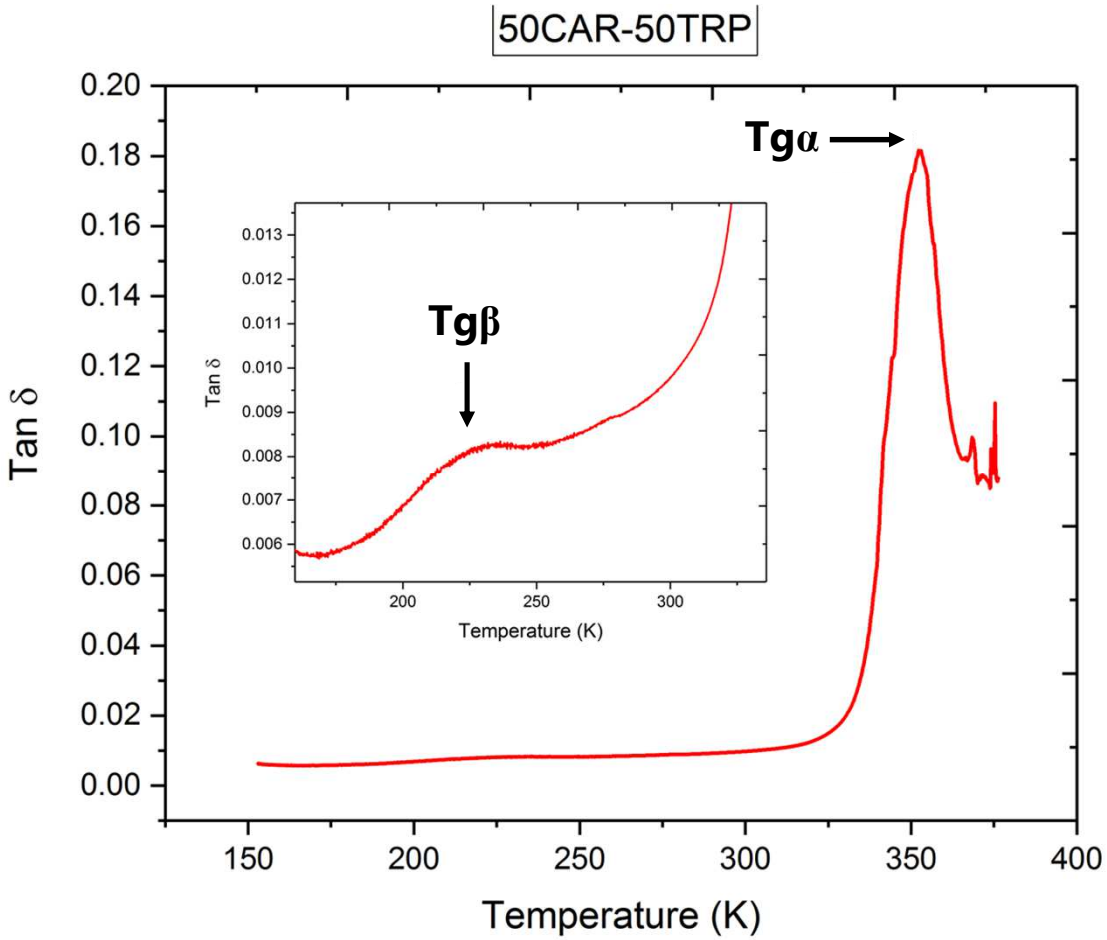
Non-strong interaction



L-Tryptophan (TRP)

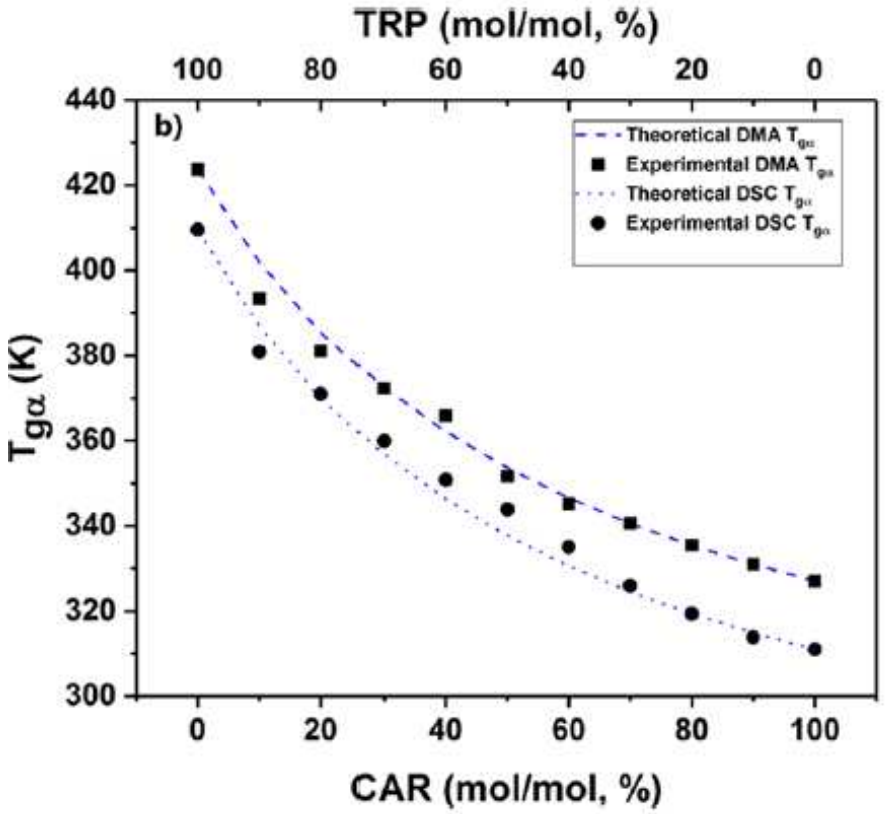
IECP 2020

Transition temperatures in co-amorphous CAR-TRP



IECP 2020

Transition temperatures in CAR-TRP co-amorphous systems

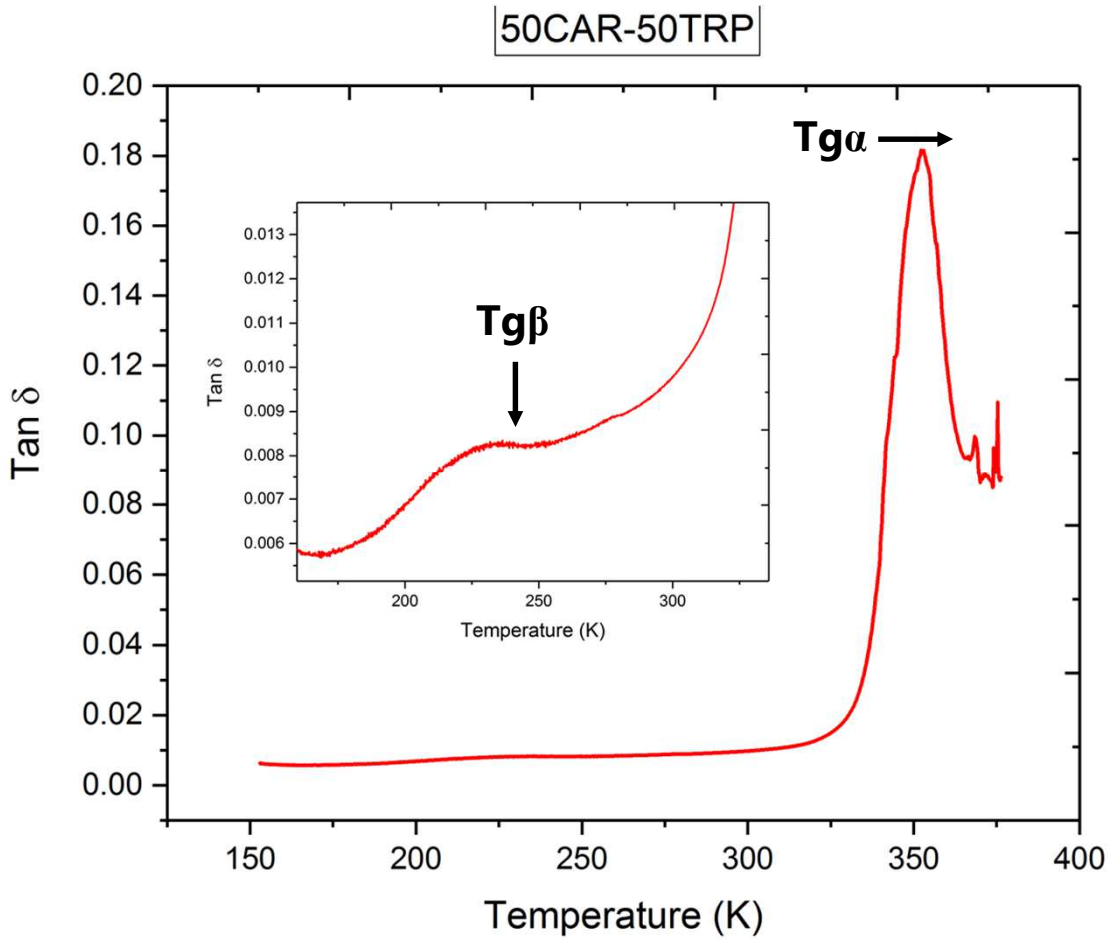


The experimental T_gs were consistent with the theoretical T_gs.

IECP 2020

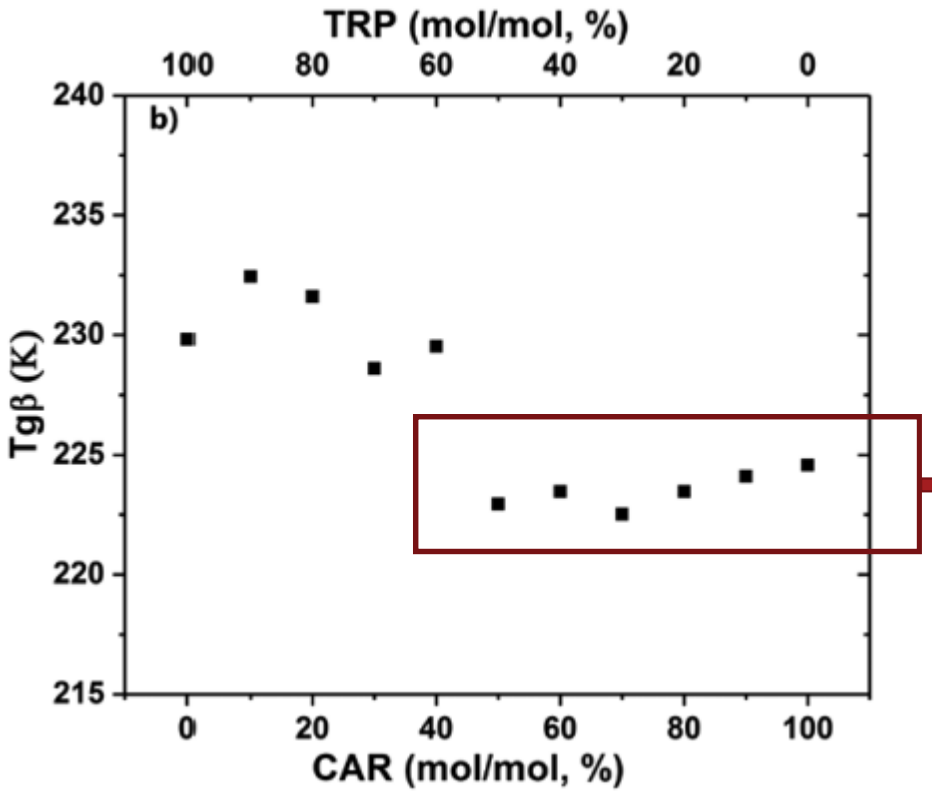
Kissi, E.O., (2018). *Molecular Pharmaceutics*, 15, 4247-4256.

Transition temperatures in co-amorphous CAR-TRP



IECP 2020

Transition temperatures in CAR-TRP co-amorphous systems

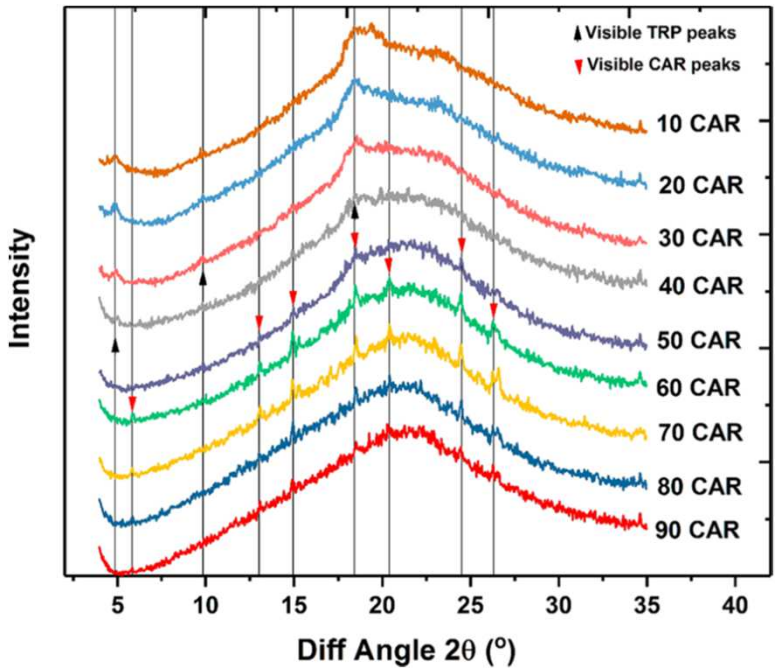


Similar $T_{g\beta}$ values over large concentration ranges of the drug (and amino acid) imply that these transitions originate from an excess component.

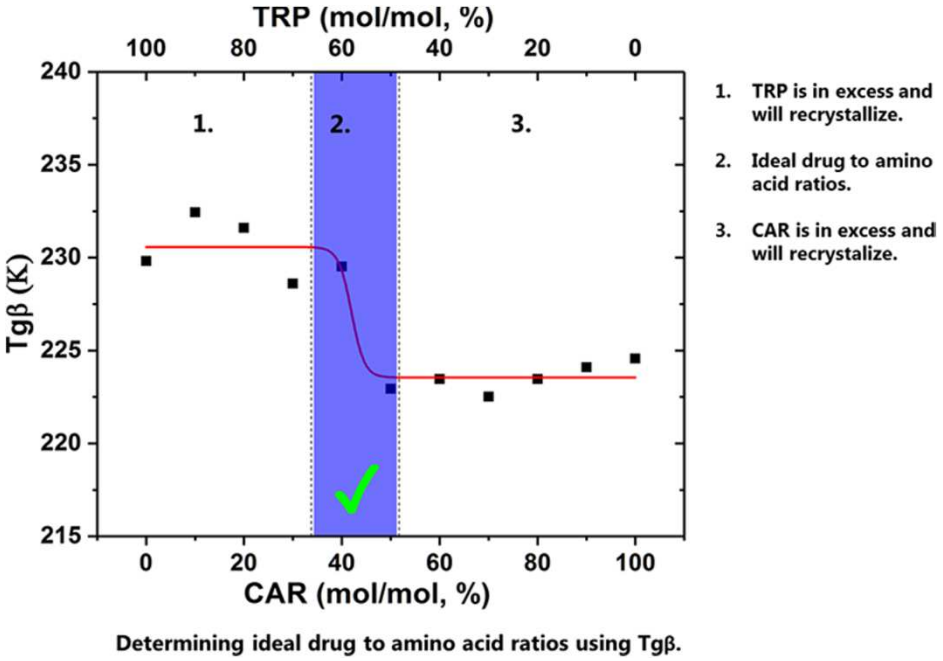
IECP 2020

Kissi, E.O., (2018). *Molecular Pharmaceutics*, 15, 4247-4256.

Physical stability and $T_{g\beta}$ of co-amorphous CAR-TRP



Diffractogram of the CAR–TRP samples after 62 weeks of storage under dry conditions at 40 °C.



Determining ideal drug to amino acid ratios using Tgβ.

IECP 2020

Kissi, E.O., (2018). *Molecular Pharmaceutics*, 15, 4247-4256.

Conclusions

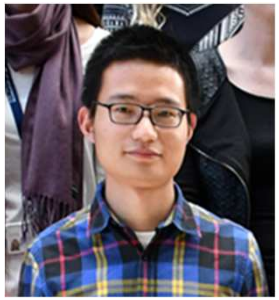
- In systems that can form eutectic mixtures the eutectic ratio is a good starting point for finding the most stable co-amorphous systems.
- In systems with strong interactions, it is not necessarily the stoichiometric molar ratio of the strong interaction that leads to the most stable system.
- In systems with weak interactions the beta relaxation values can be a good guide to find the most stable system.
- Current work looks at other methods to determine the ideal ratio of drug to co-former for systems with weak interactions…
- Current work looks at other methods to determine the ideal ratio of drug to co-former for systems at non-day storage conditions…
- …to be continued…

IECP 2020

References:

- Wu W et al. European Journal of Pharmaceutics and Biopharmaceutics 131: 25 – 32 (2018)
- Kissi E et al. Molecular Pharmaceutics 15: 4247-4256 (2018)
- Kissi E et al. Pharmaceutics 19: 628 (2019)
- Liu J et al. Molecular Pharmaceutics, 17: 1335-1342 (2020)

Thanks



Wenqi Wu

Eric Kissi

Jingwen Liu

IECP 2020

Thank you for listening!

IECP 2020