Predicting physical stability of amorphous drugs

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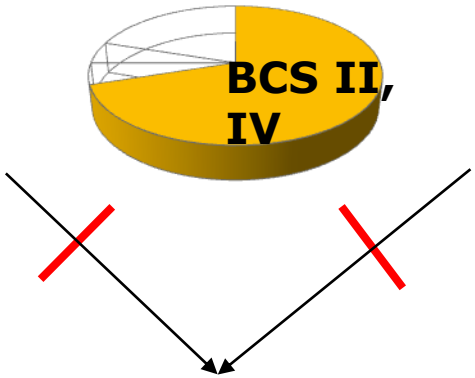
Outline

- **Introduction to amorphous drugs**
- **Linking transition temperatures in physical stability of neat amorphous drugs**
- **Linking transition temperatures to drug loading in co-amorphous systems.**

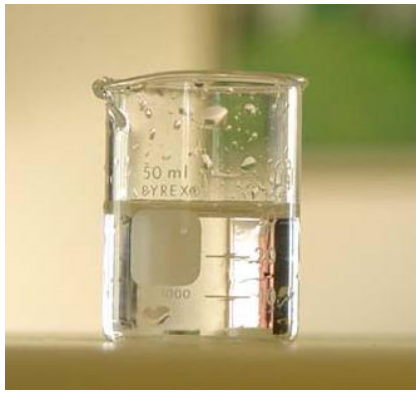
Poorly water-soluble drugs

HYDROPHOBIC ≠ LIPOPHILIC



"brickdust"

"greaseballs"



Physico-chemical properties
determine formulation approach

Salt formation

Co-solvents

Prodrugs

Molecular level

Cyclodextrins

Strategies to improve solubility

SMEDDS

SEDDS

Colloidal level

Micro-emulsions

Lipid solutions

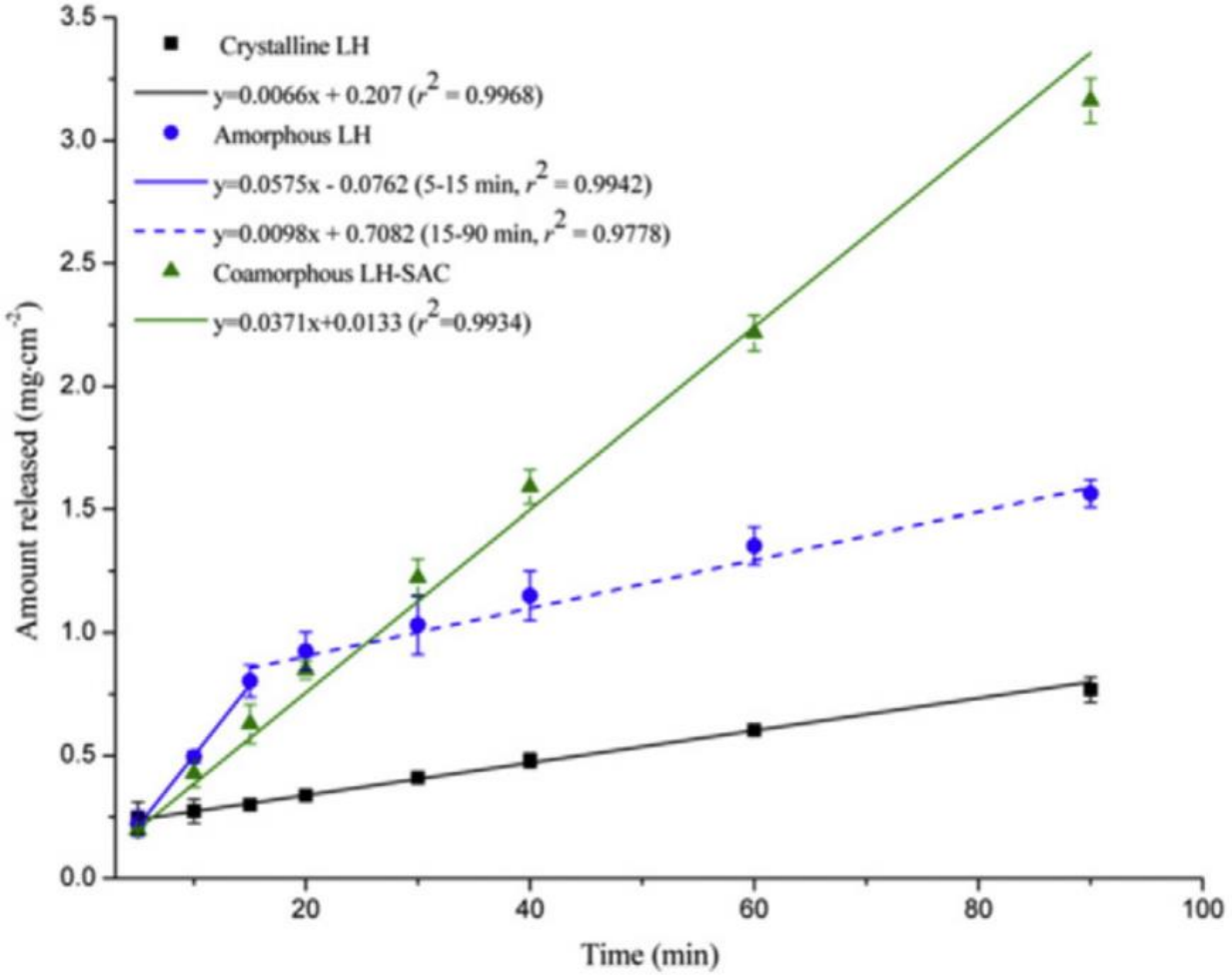
Emulsions

Particulate level

Metastable polymorphs

Amorphous systems

Particle size reduction

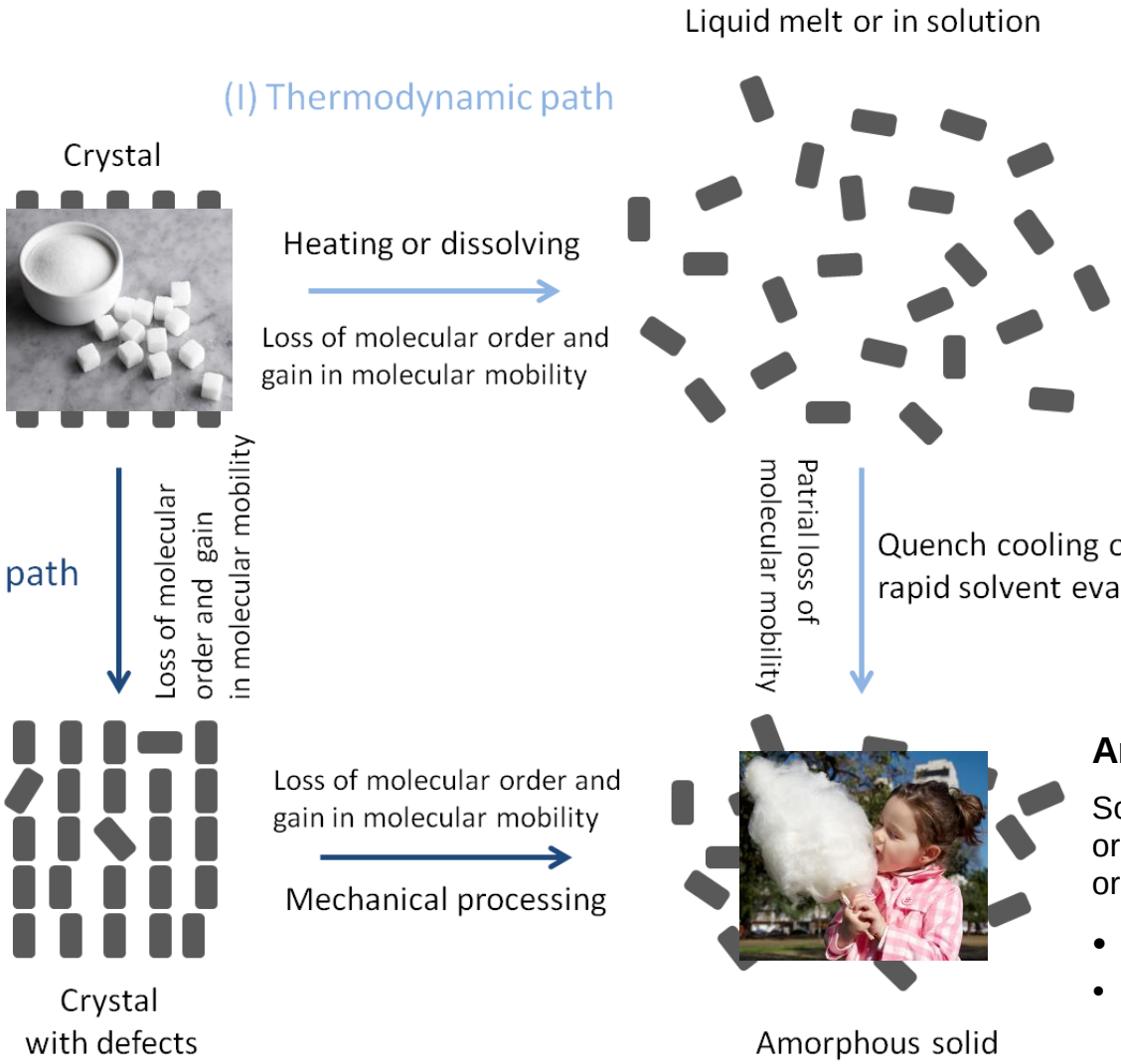


Qian et al. Cryst. Growth Des. 15 (2015).

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**
- instable

Marketed Product

Amorphous APIs

Accolate® (zafirlukast)

Ceftin® (cefuroxime axetil)

Accupril® (quinapril hydrochlorid)

Viracept® (nelfinavir mesylate)

Amorphous solid dispersions

Cesamet ® (nabilone – PVP)

Gris-PEG® (griseofulvin – PEG)

Kaletra® (lopinavir/ritonavir – PVP/vinyl accetat copolymer)

Sporanox® (itraconazole – hypromellose)

Intelence® (etravirine – hypromellose)

Zelboraf® (Vermurafenib-HPMCAS)

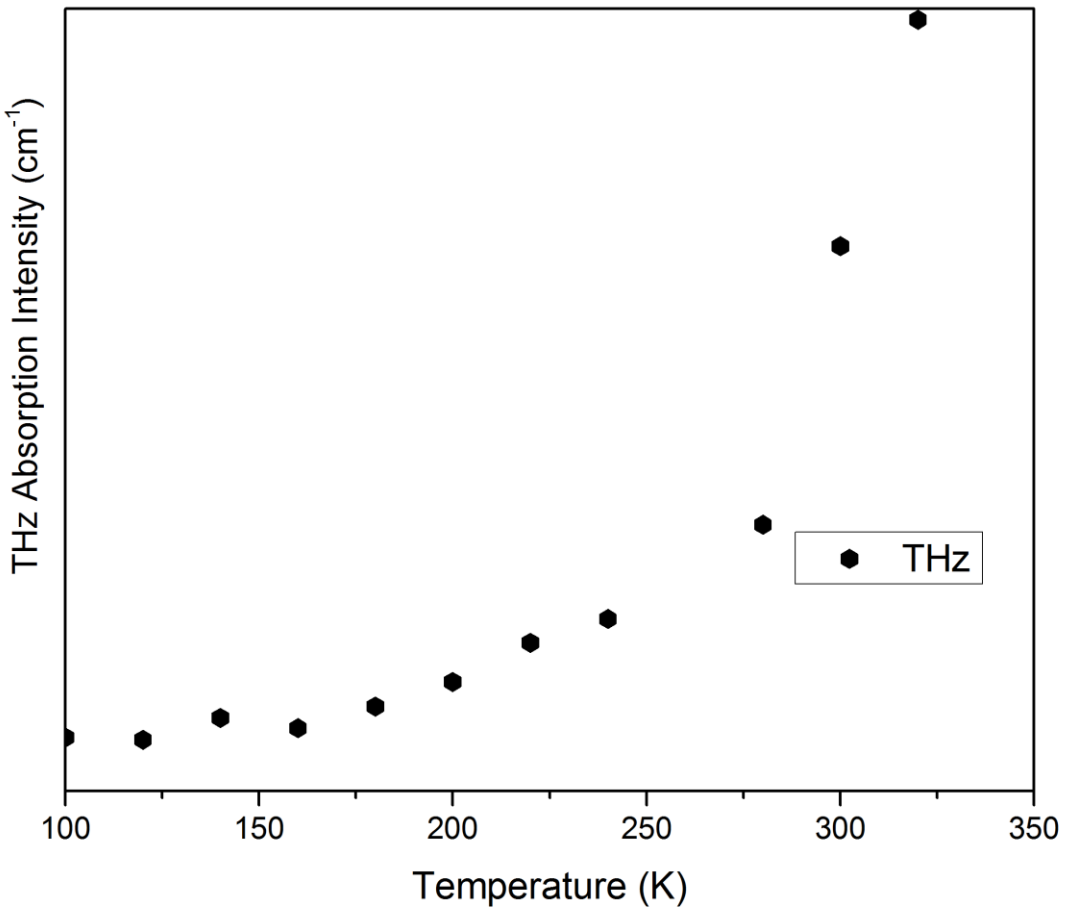
Challenge with amorphous formulations

- Lack of fundamental understanding on the reverting from the amorphous to crystalline form
- No model to predict the time it takes for the reverting process
- No model to predict how much drug can be stabilized with excipients
- FDA regulations

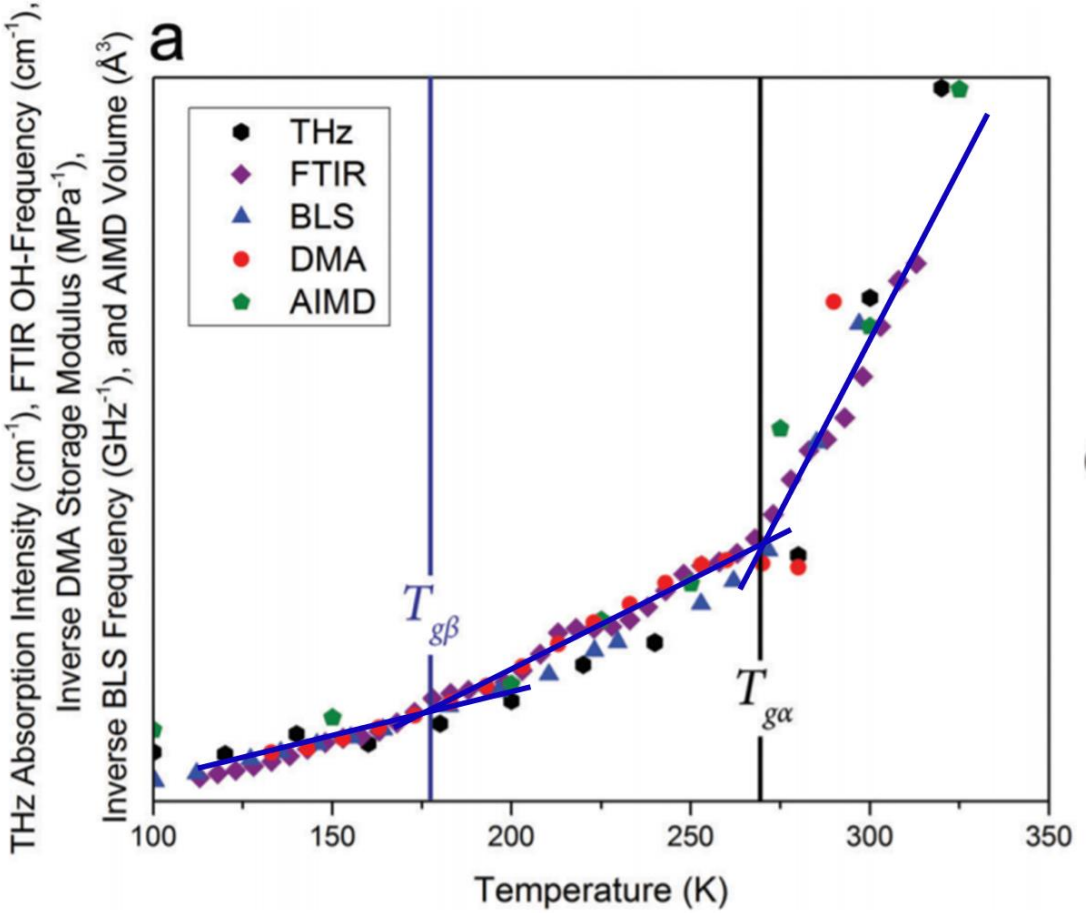
Outline

- Introduction to amorphous drugs
- **Linking transition temperatures in physical stability of neat amorphous drugs**
  - **Transition temperatures**
  - **Predicting physical stability**
- Linking transition temperatures to drug loading in co-amorphous systems

Transition temperatures on a wide range of techniques



Transition temperatures on a wide range of techniques



TAKE HOME MESSAGE

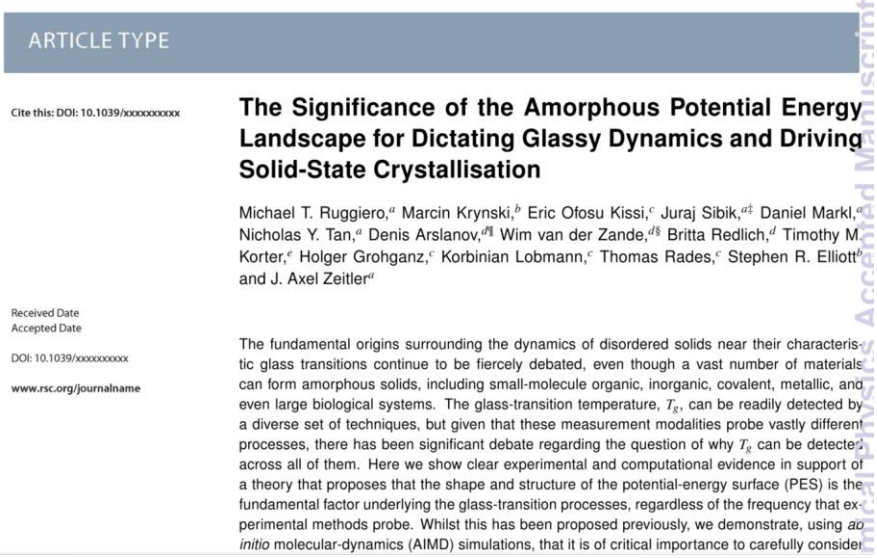
- **All these techniques can detect the glass transition temperature irrespective of the frequency they operate.**
- **Two modes are present Tgα and Tgβ**

Definition of Glass Transition Temperature

1. The glass transitions ($T_{g\beta}$ and $T_{g\alpha}$) represent temperature ranges at which there is sufficient thermal energy to overcome the potential barriers, leading to increased motion and thus increased molecular mobility

- Above $T_{g\beta}$, increased mobility increases the probability that two neighboring molecules will move into a favorable (crystalline) packing motif, which could set off a chain of crystallization events.

- Below $T_{g\beta}$, recrystallization is not possible for the disordered molecules



ARTICLE TYPE

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The Significance of the Amorphous Potential Energy Landscape for Dictating Glassy Dynamics and Driving Solid-State Crystallisation

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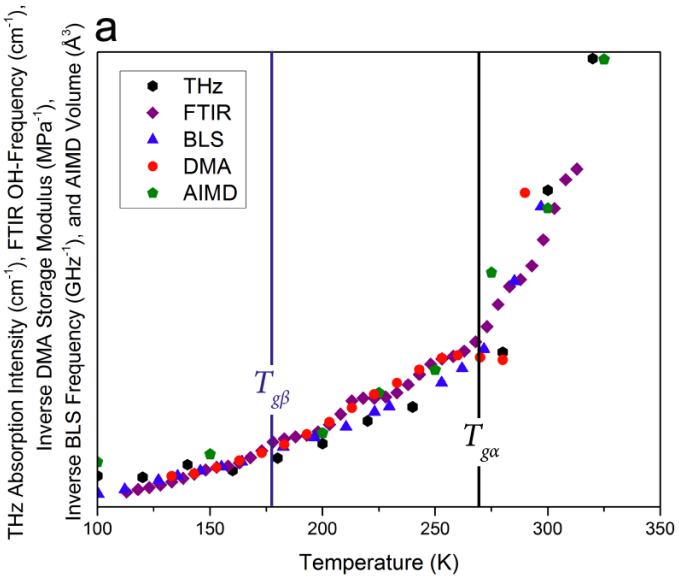
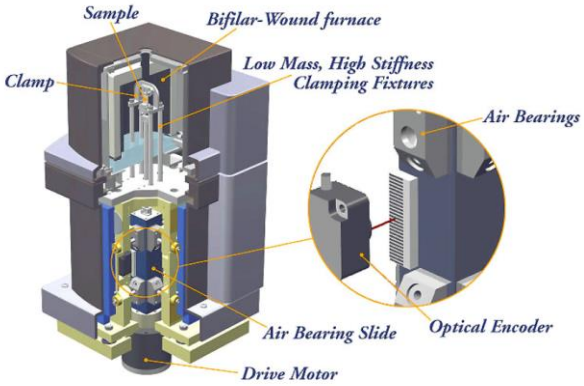
The fundamental origins surrounding the dynamics of disordered solids near their characteristic glass transitions continue to be fiercely debated, even though a vast number of materials can form amorphous solids, including small-molecule organic, inorganic, covalent, metallic, and even large biological systems. The glass-transition temperature, T_g, can be readily detected by a diverse set of techniques, but given that these measurement modalities probe vastly different processes, there has been significant debate regarding the question of why T_g can be detected across all of them. Here we show clear experimental and computational evidence in support of a theory that proposes that the shape and structure of the potential-energy surface (PES) is the fundamental factor underlying the glass-transition processes, regardless of the frequency that experimental methods probe. Whilst this has been proposed previously, we demonstrate, using *ab initio* molecular-dynamics (AIMD) simulations, that it is of critical importance to carefully consider

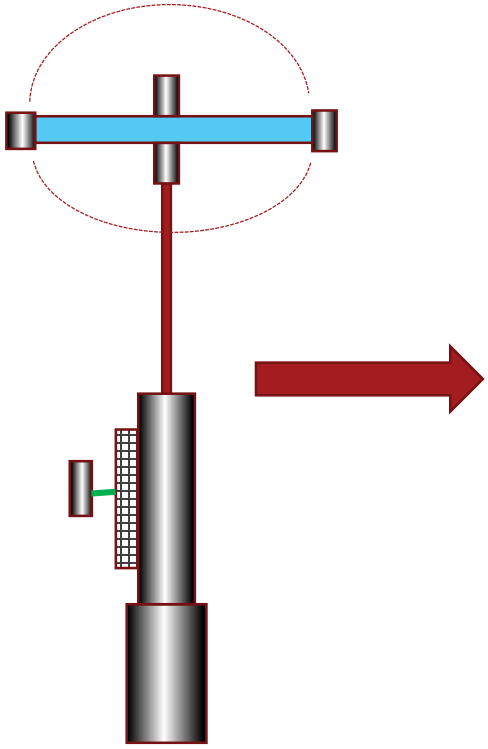


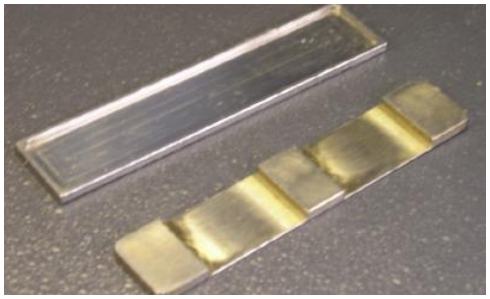
Ruggiero et. al. Phys. Chem. Chem. Phys. 19 (2017) and Kissi et. al. Phys. Chem B 122, (2018)

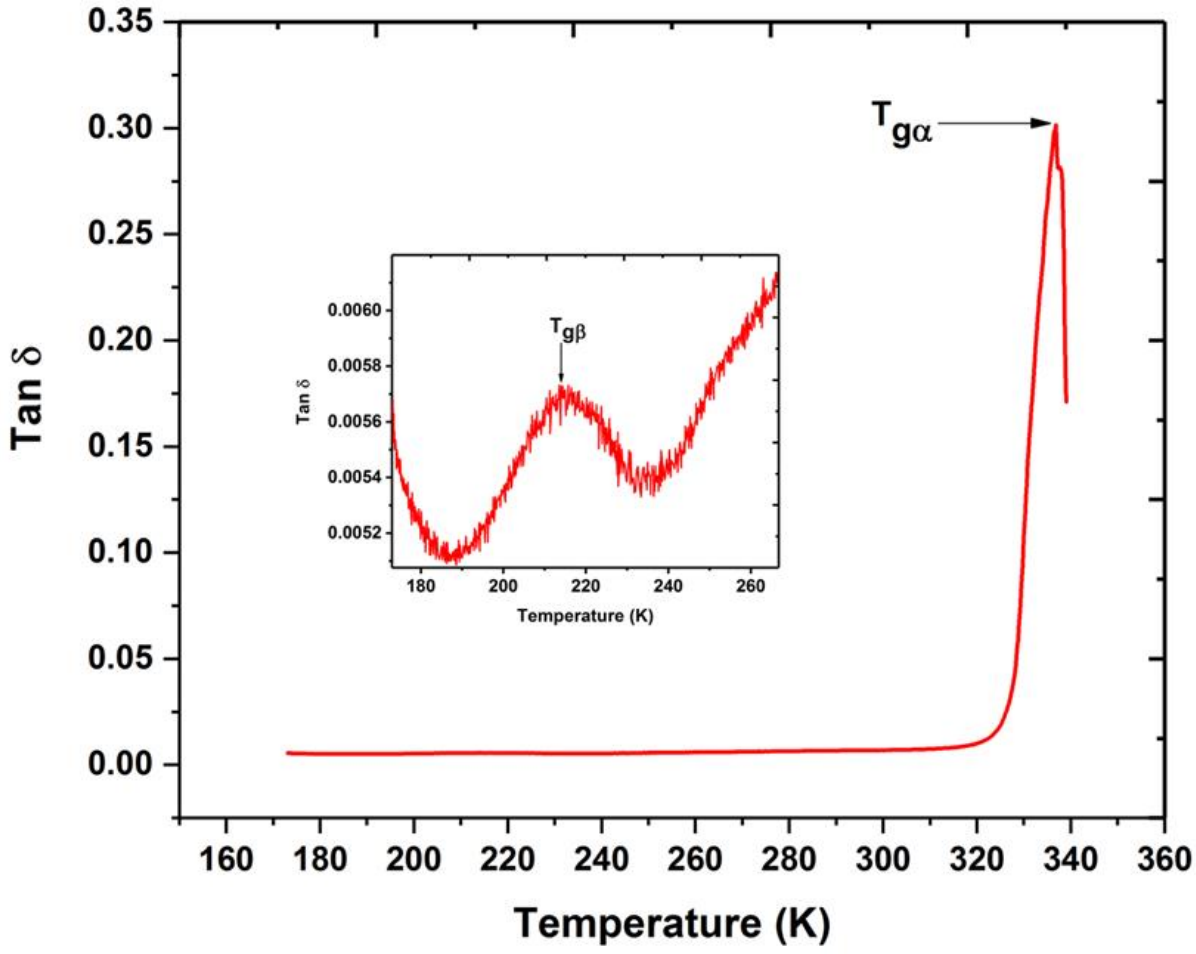
Dynamic Mechanical Analysis



Detecting Tgα and Tgβ with dynamic mechanical analysis (DMA)







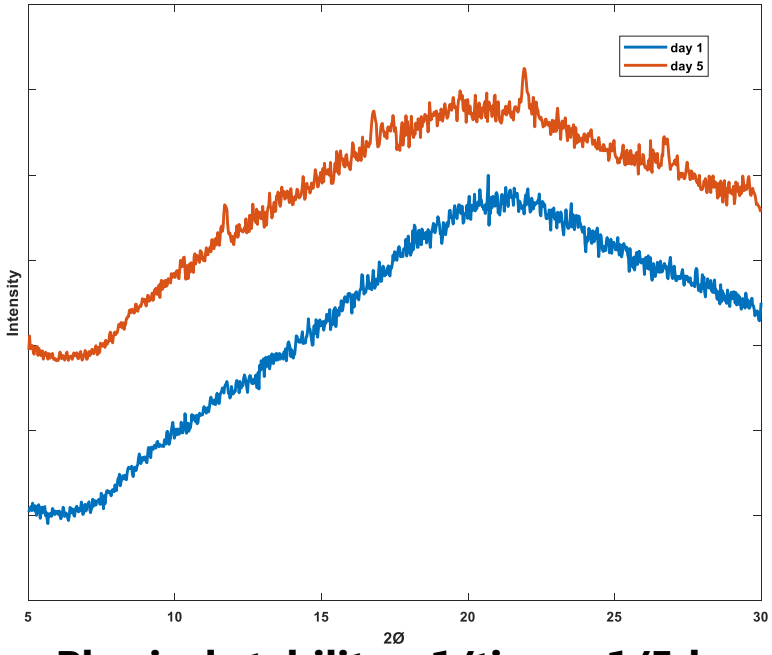
Which of these sets of molecular motion is responsible for the physical stability of amorphous drugs?

Determining the onset of crystallization of amorphous drugs

Sample Set 1: Quench cooled	Sample Set 2: Amorphous
Indomethacin	Zafirlukast
Nifedipine	Na-Taurocholate
Cimetidine	Zent X
Carvedilol	Zent V
Celecoxib	

- 0%RH, 298 K

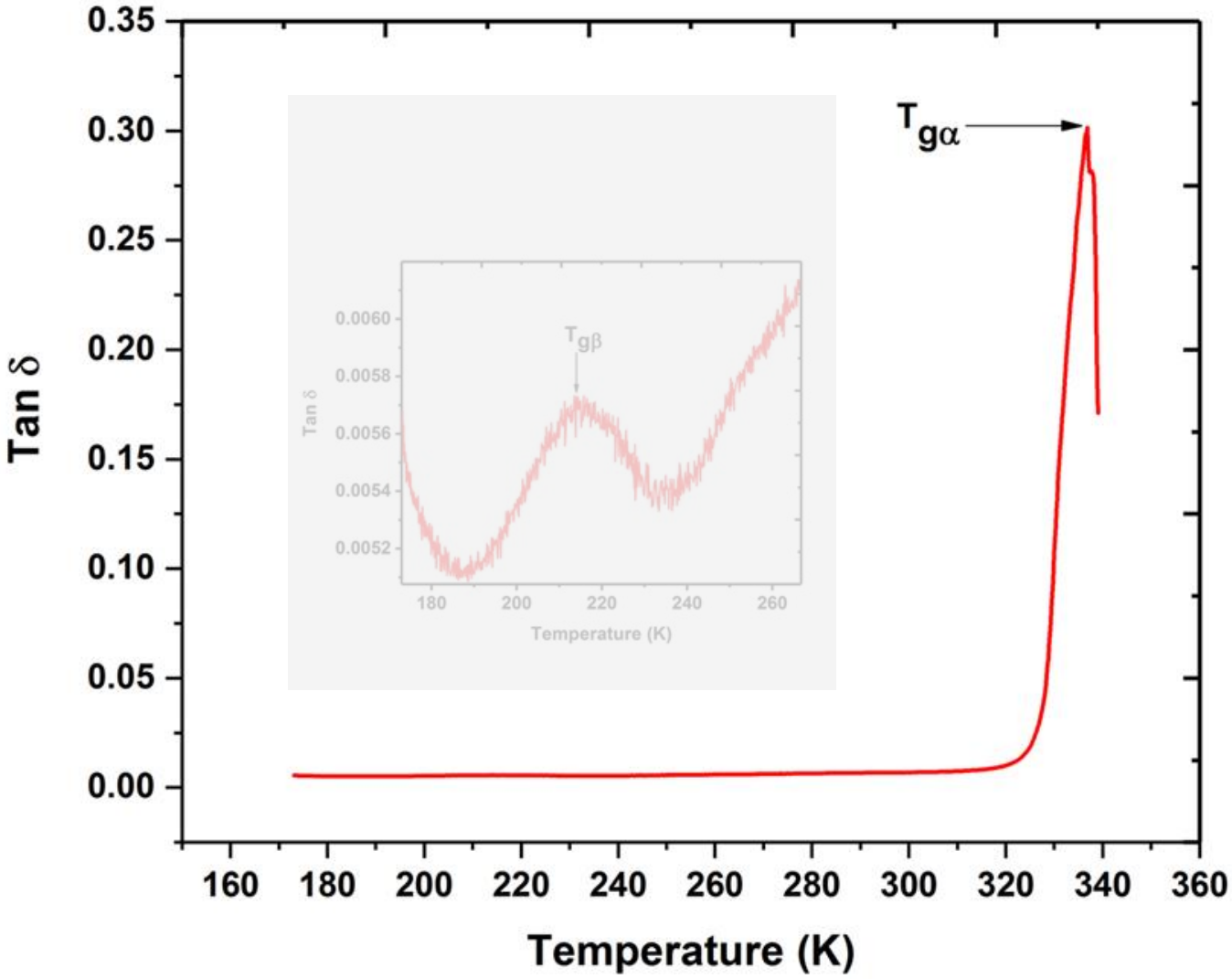
X-Ray Powder Diffractometer



Physical stability= 1/time =1/5days

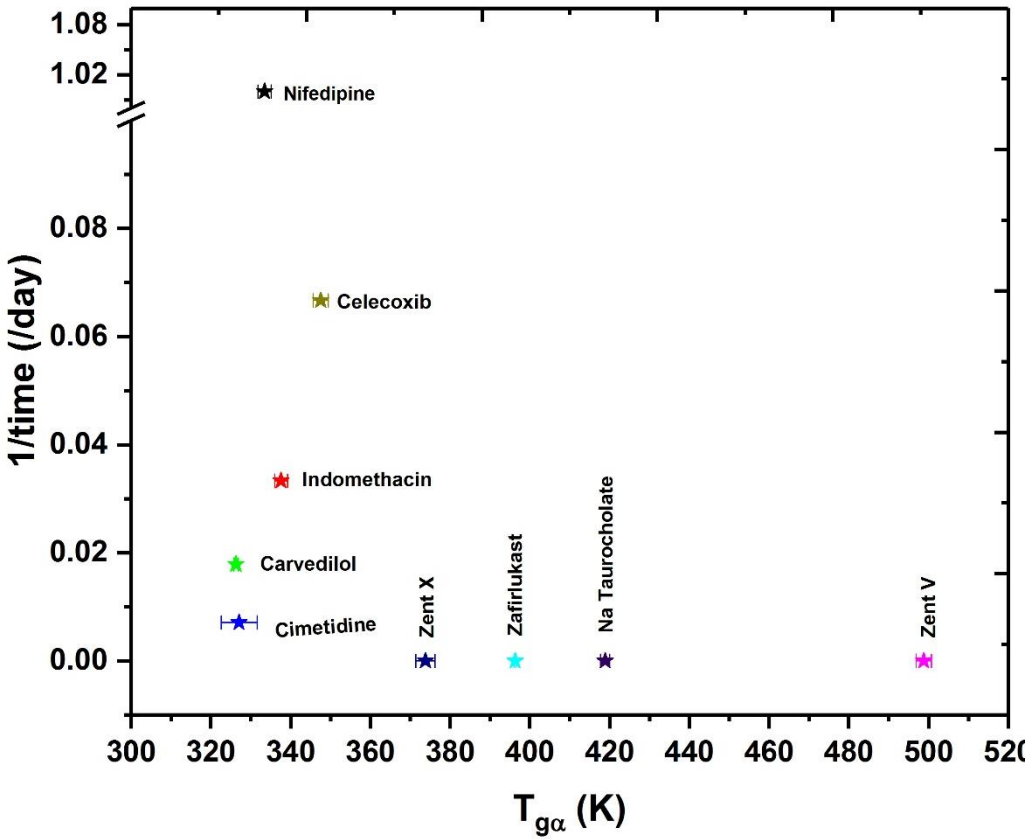
Correlating the transition temperatures to physical stability

The $T_{g\alpha}$



Correlating the transition temperatures to physical stability

The $T_{g\alpha}$

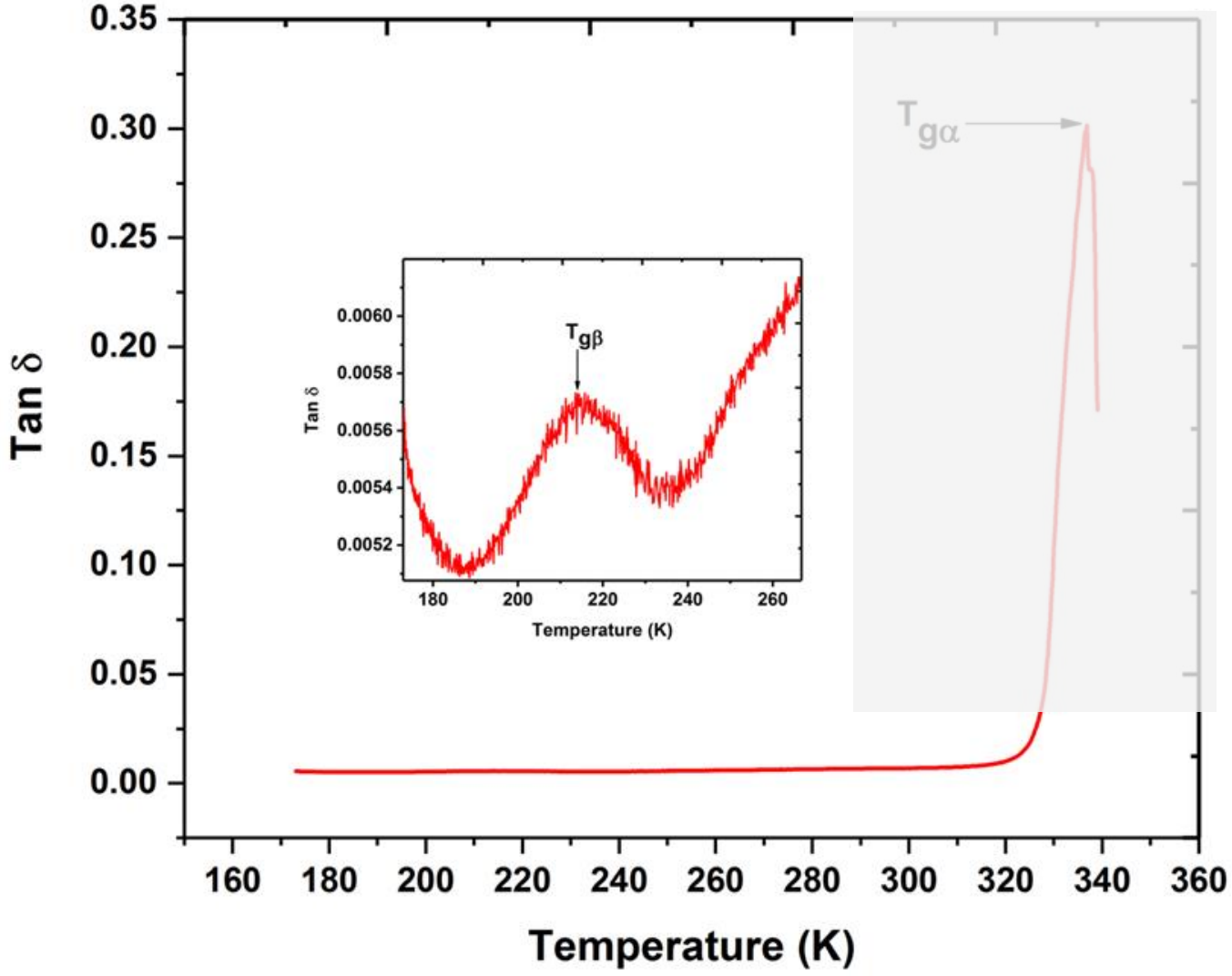


- **At the current storage condition (0% RH, 296 K), the $T_{g\alpha}$ does not provide adequate information on the physical stability**

The lack of correlation as observed for the $T_{g\alpha}$ and the onset of recrystallization (1/time (/day))

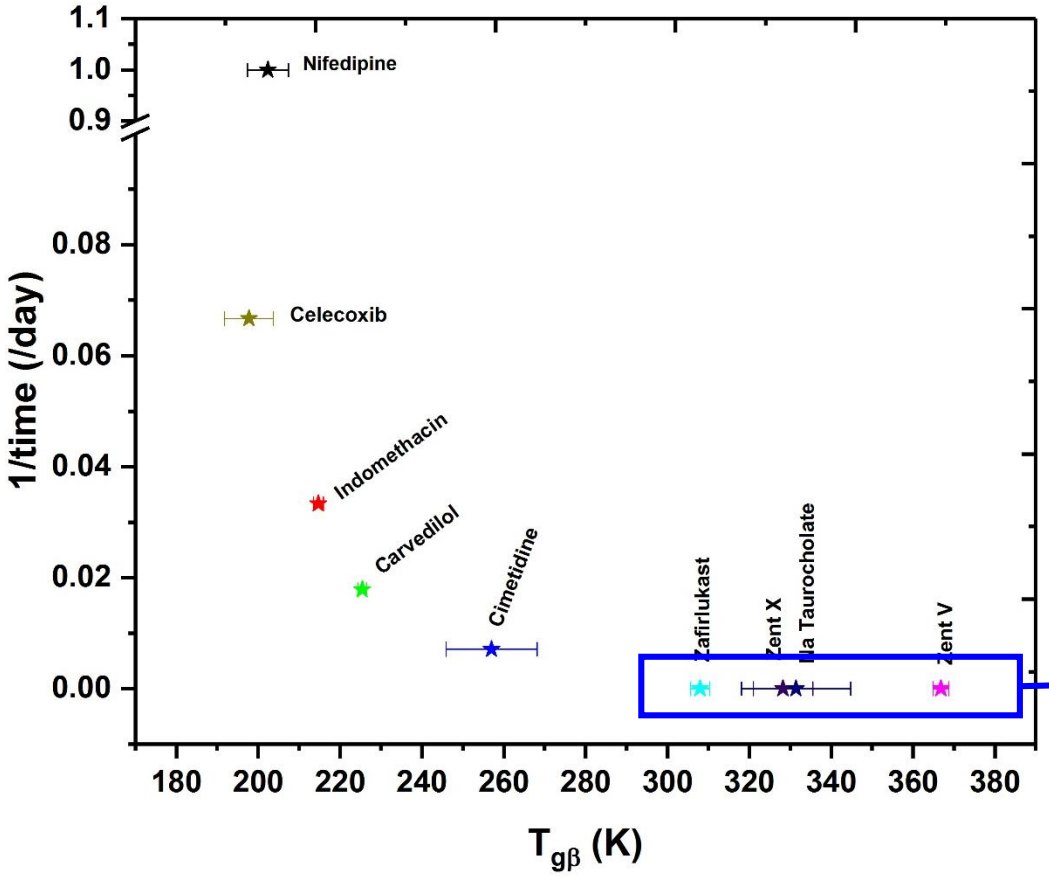
Correlating the transition temperatures to physical stability

The $T_{g\beta}$



Correlating the transition temperatures to physical stability

The Tgβ

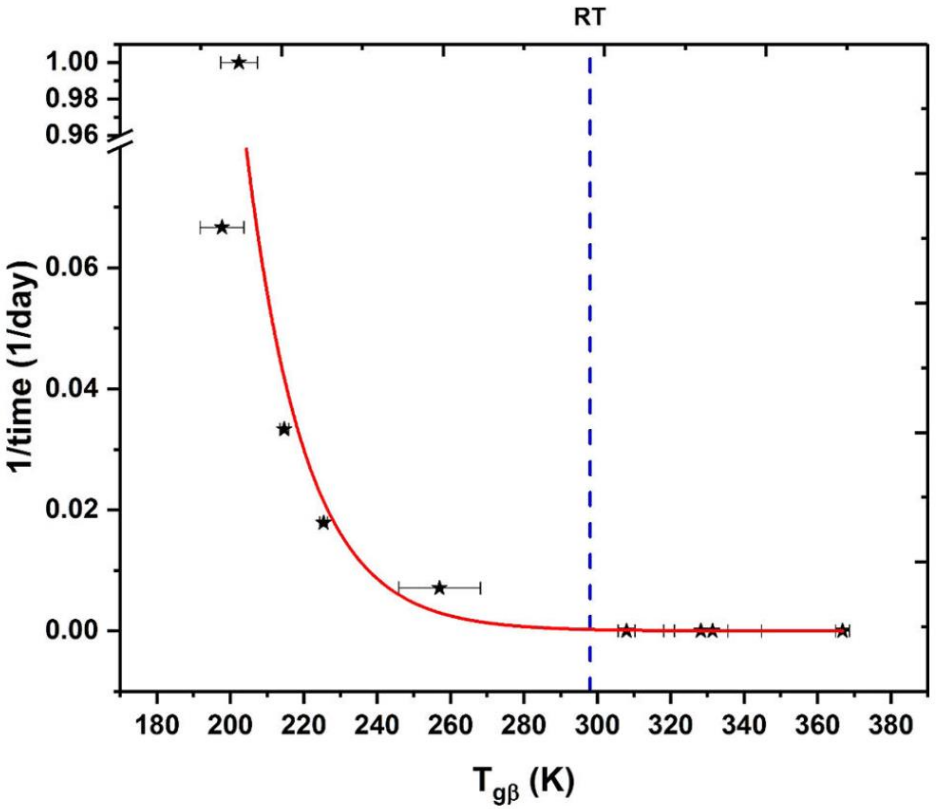


- **At the experimental storage condition (0% RH, 296K), there is a correlation between T_β and physical stability**

These drugs are stable, they have less energy at RT and will NOT crystallize

The correlation between T_β and onset of recrystallization (1/time (/day)).

An empirical correlation for predicting onset of crystallization



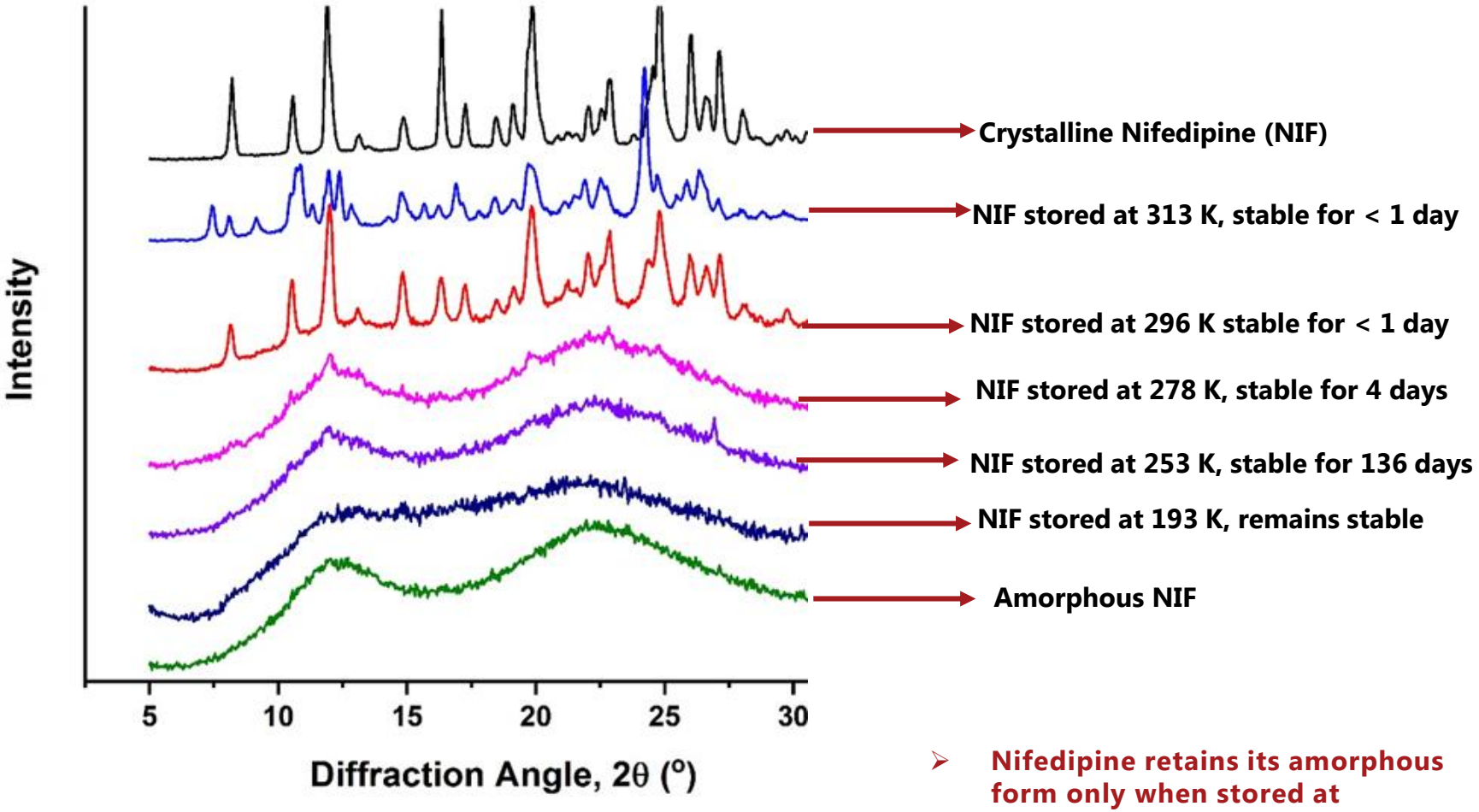
- **Based on the observed correlation, an empirical correlation for predicting the onset of crystallization is proposed and drugs that have a $T_{g\beta}$ at or above ambient temperature (blue dashed line) are physically stable**

TAKE HOME MESSAGE

- **Amorphous drug stability is controlled by their β-relaxation.**

At what temperature is amorphous nifedipine stable? Is it Tg-50?

Nifedipine Tg 322 K, Tgβ 202 K



- Nifedipine retains its amorphous form only when stored at temperatures below its Tgβ. An indication that below that temp molecular mobility is frozen out

Take home message

- **Various techniques can determine the glass transition temperatures due to the potential energy surrounding the amorphous molecules**
- **Amorphous drug stability is controlled by their β-relaxation.**
- **Their physical stability is predictable with the Tgβ**

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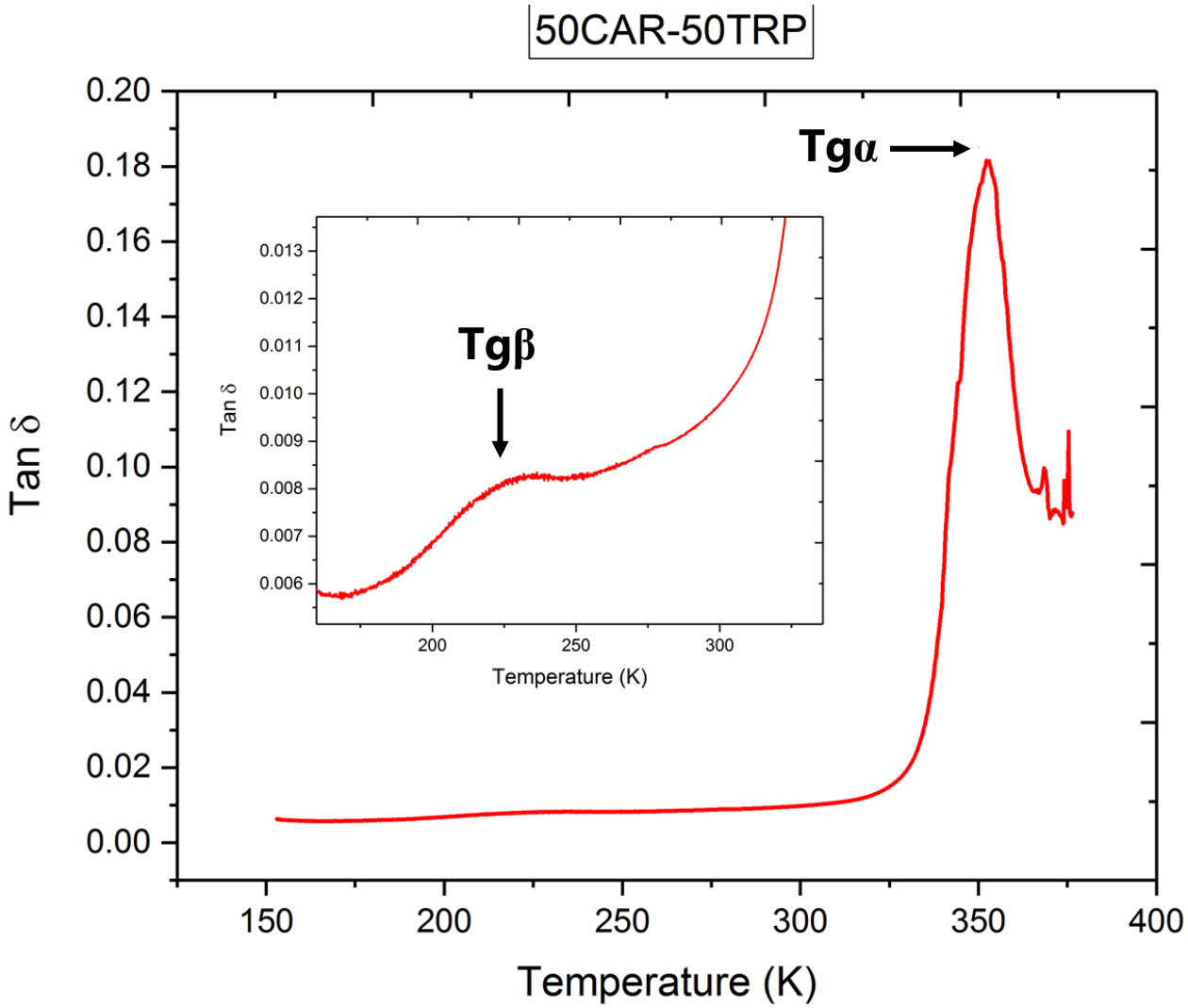
- Introduction to amorphous drugs
- Linking transition temperatures in physical stability of neat amorphous drugs
- **Linking transition temperatures to drug loading in co-amorphous systems**
  - **Transition temperatures**
  - **Predicting drug loading**

Transition temperatures in co-amorphous systems

- Co-amorphous systems : A one phase amorphous system (single Tgα) as a result of amorphizing two crystalline materials.

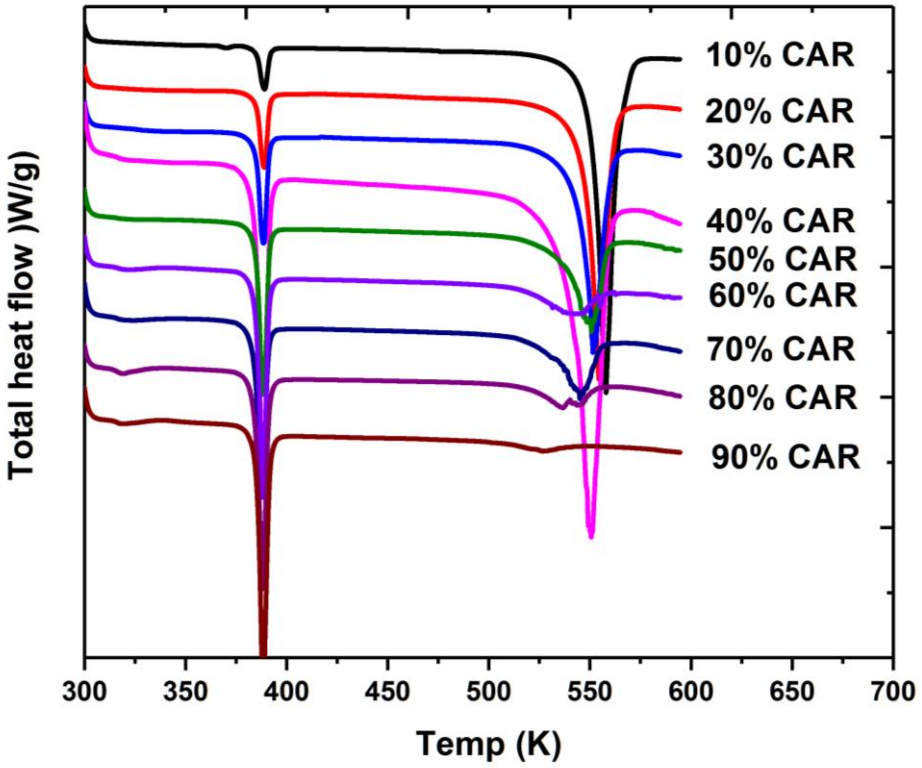
- Co-amorphous system used: **Carvedilol + Tryptophan**
- Characterised the transition temperatures using DMA and DSC

Transition temperatures in co-amorphous CAR-TRP

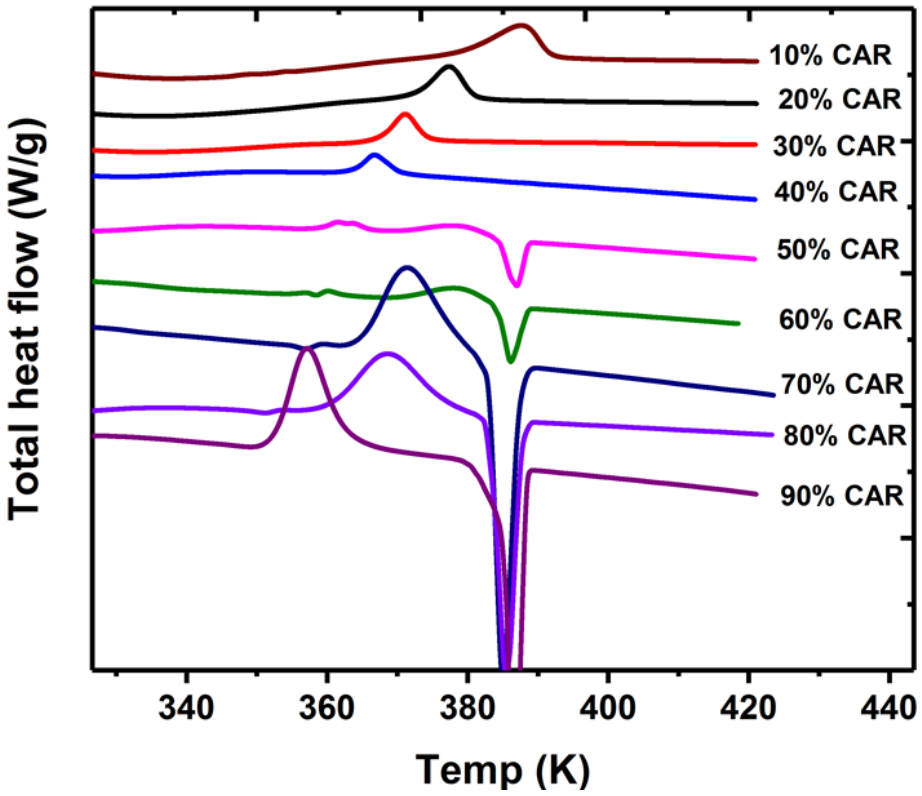


Why even study the transition temperatures of co-amorphous systems?

Crystalline physical mixture of CAR-TRP

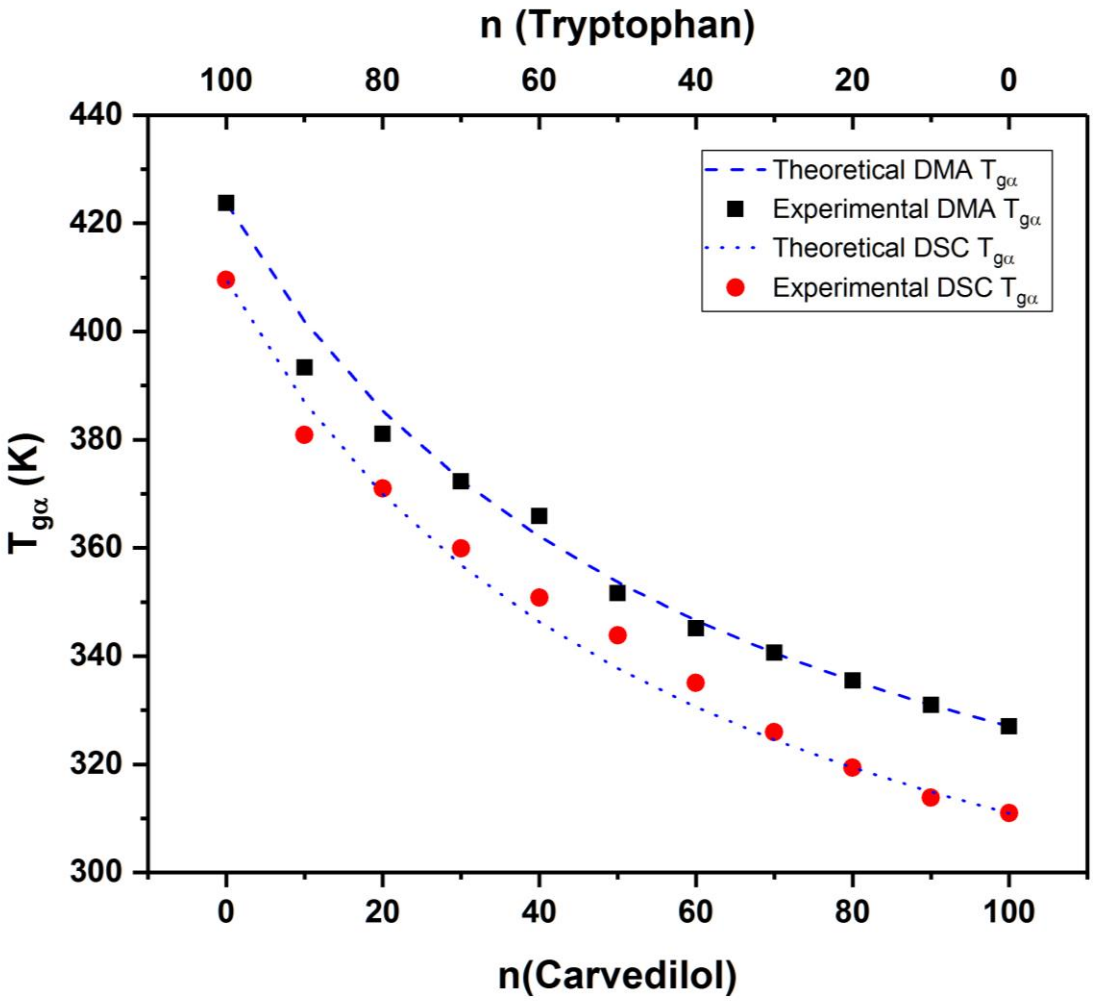


Co-amorphous CAR-TRP

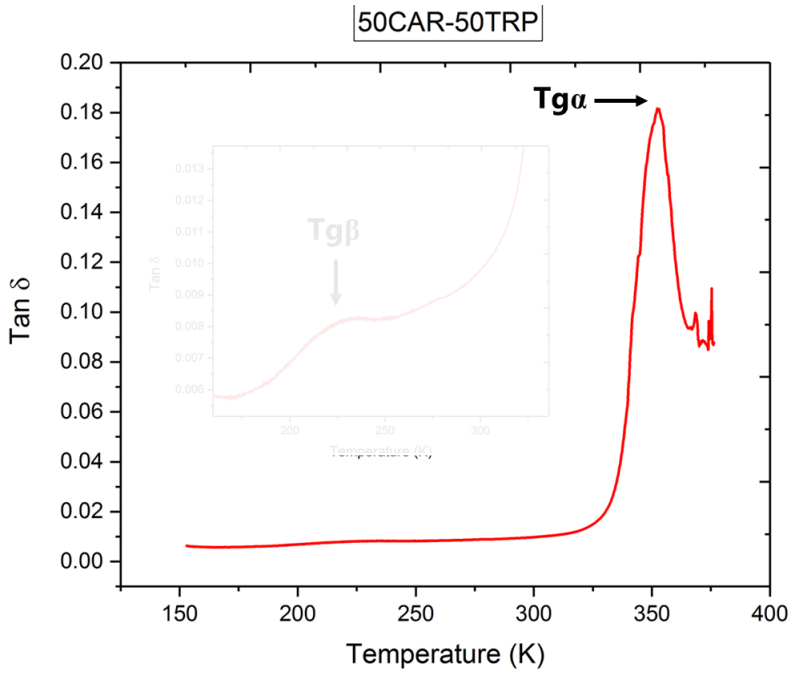


All %s are molar ratios

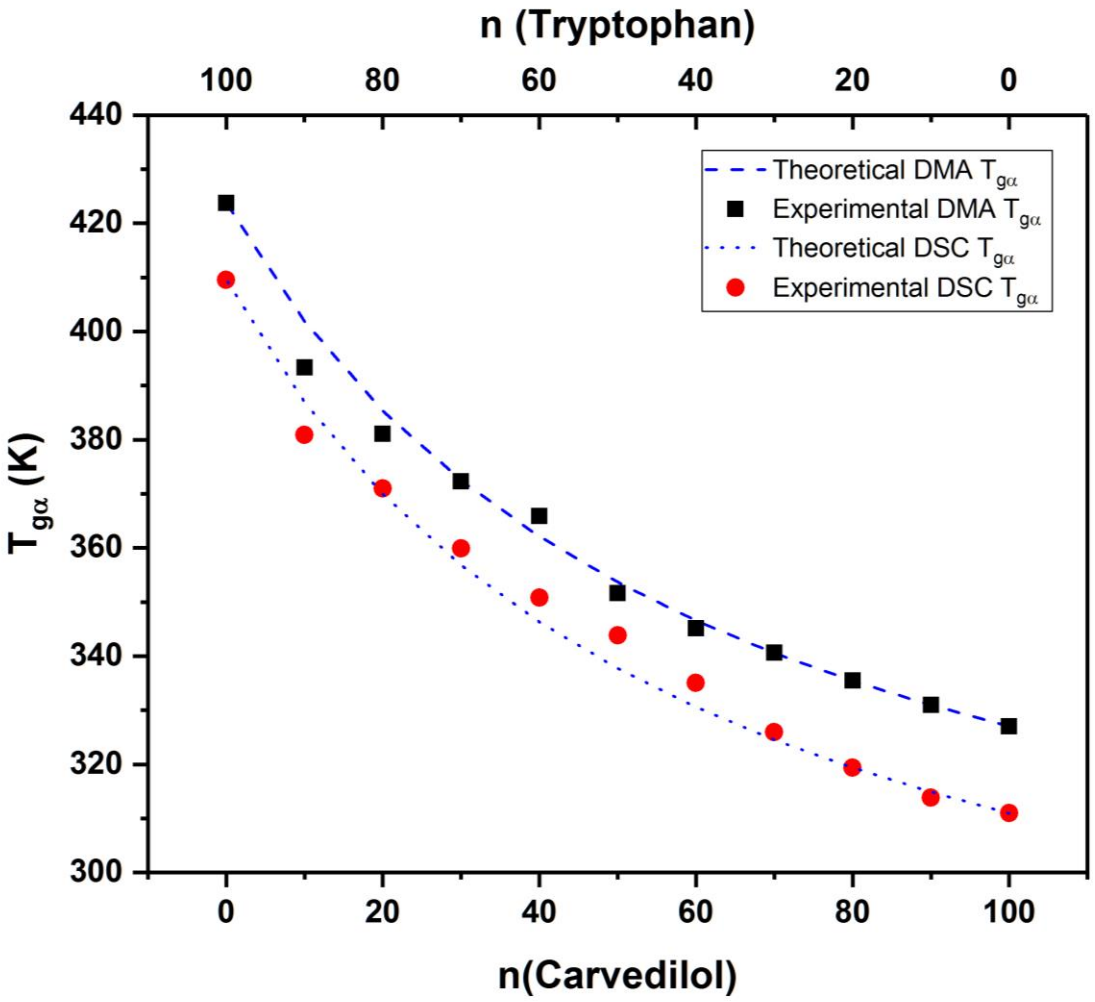
Evolution of DSC and DMA $T_{g\alpha}$ CAR-TRP



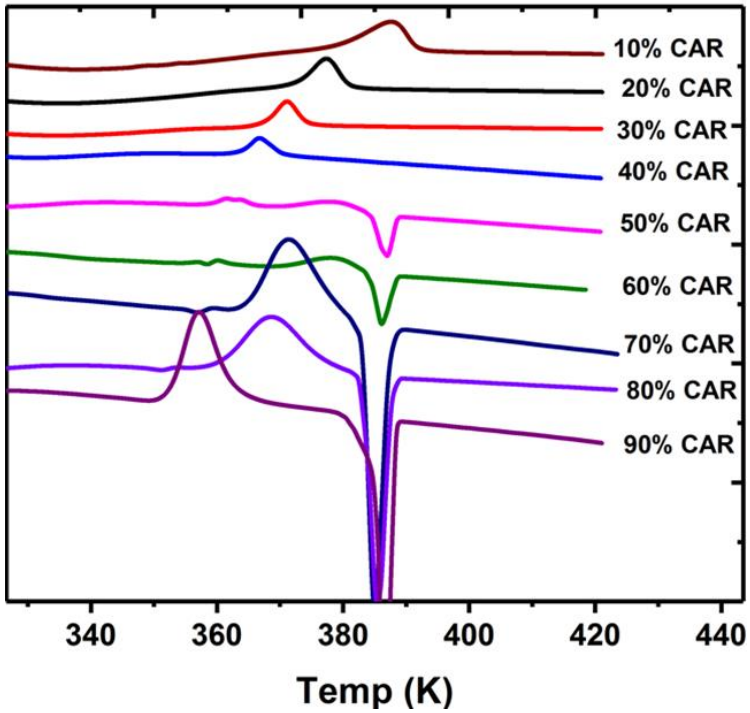
- **Both DMA and DSC give the same information on the evolution of $T_{g\alpha}$**
- **Temperature difference is from the different relaxation time Average τ(DSC) = 100s, τ (DMA) = 0.159s**



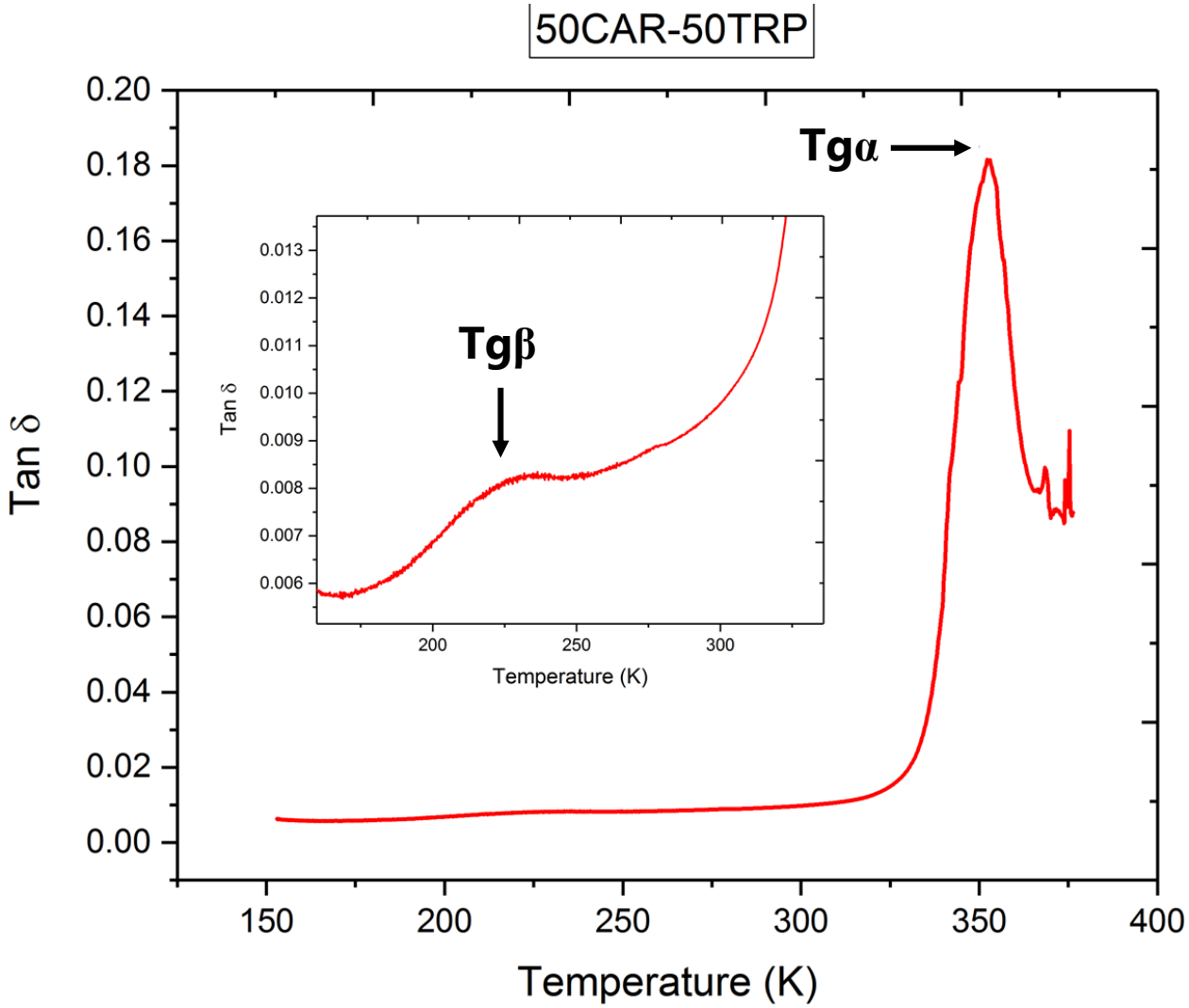
Evolution of DSC and DMA $T_{g\alpha}$ CAR-TRP



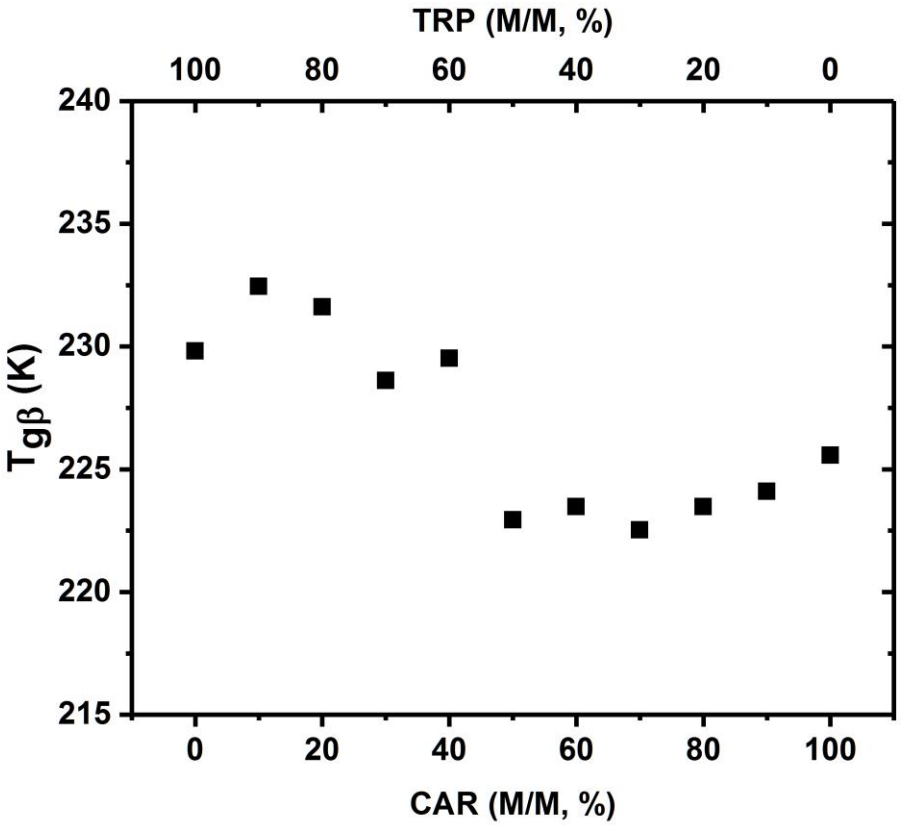
- **Both DMA and DSC give the same information on the evolution of $T_{g\alpha}$**
- **Temperature difference is from the different relaxation time Average τ(DSC) = 75.5s, τ (DMA) = 0.15s**



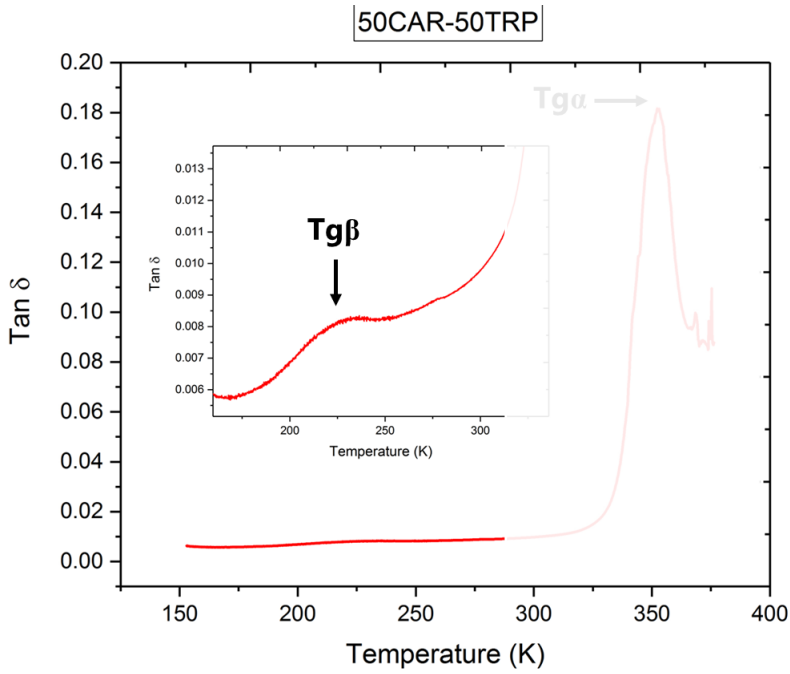
Transition temperatures in co-amorphous CAR-TRP



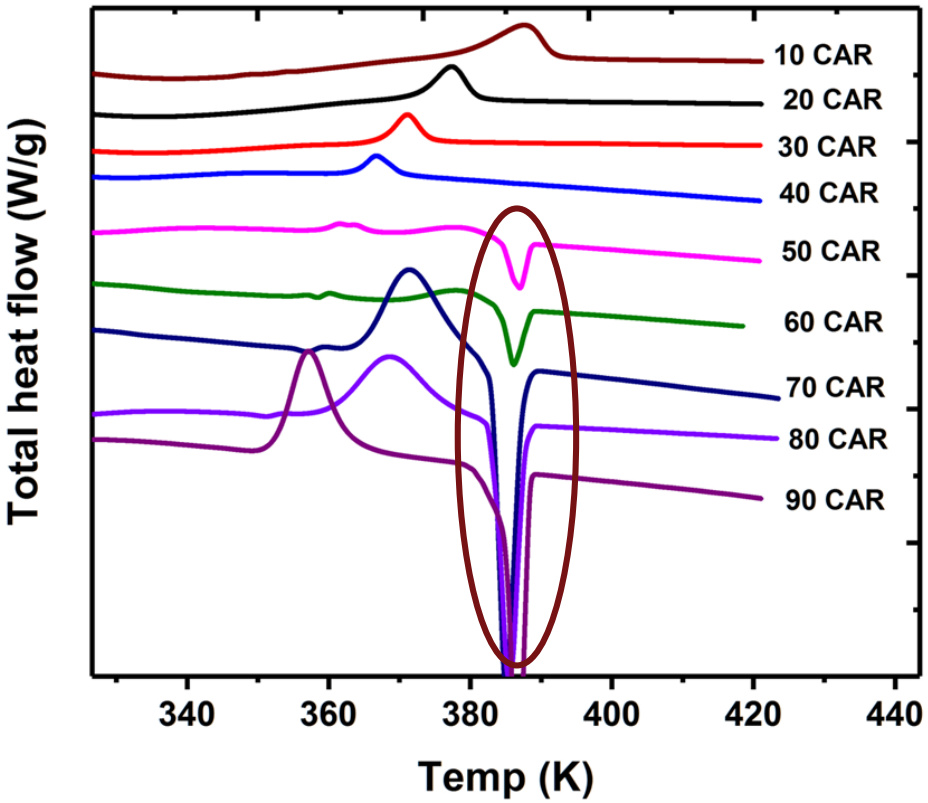
Evolution of Tgβ in CAR-TRP

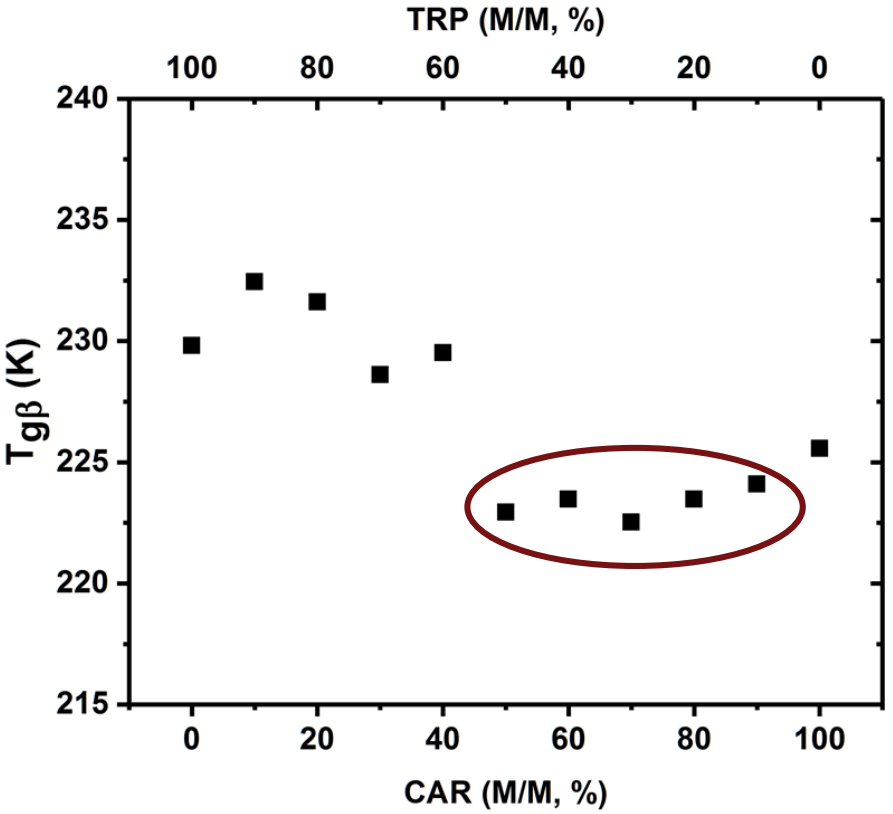


- **Similar Tgβ values irrespective of Concentration of the drug**
- **Indication of excess component**

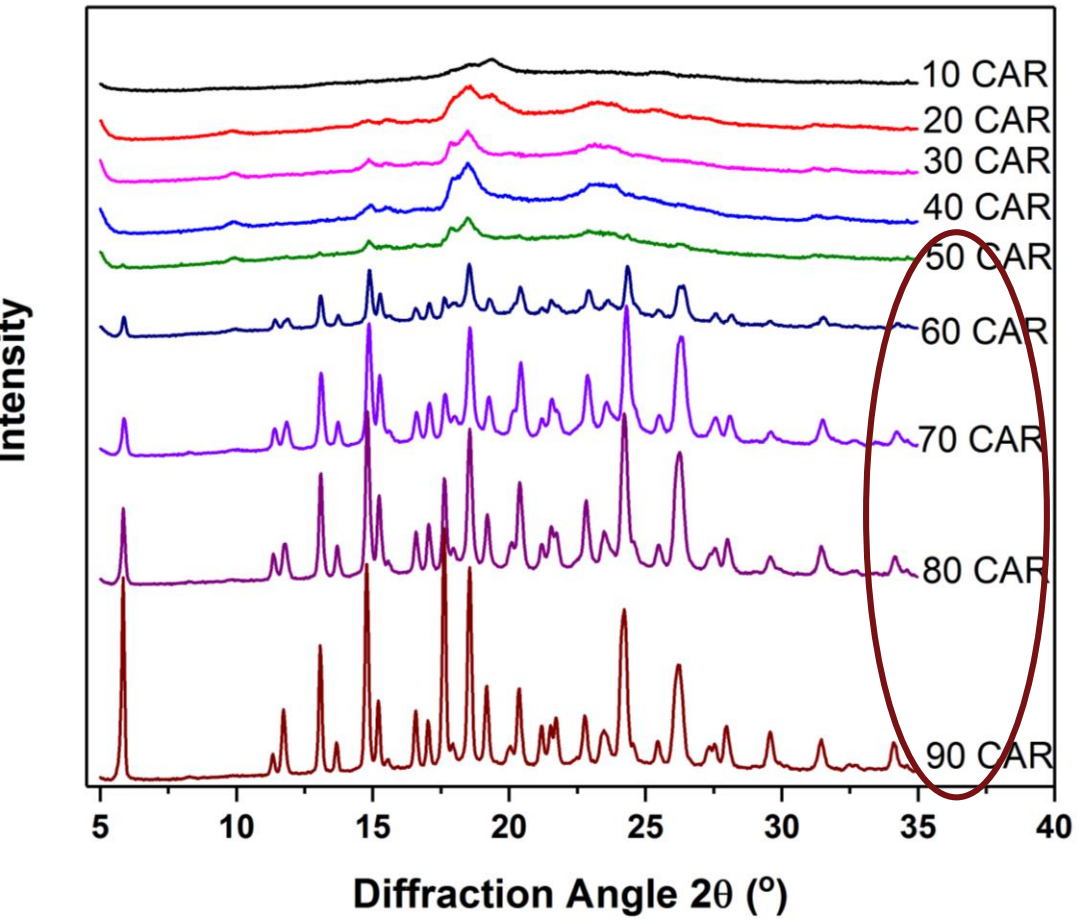


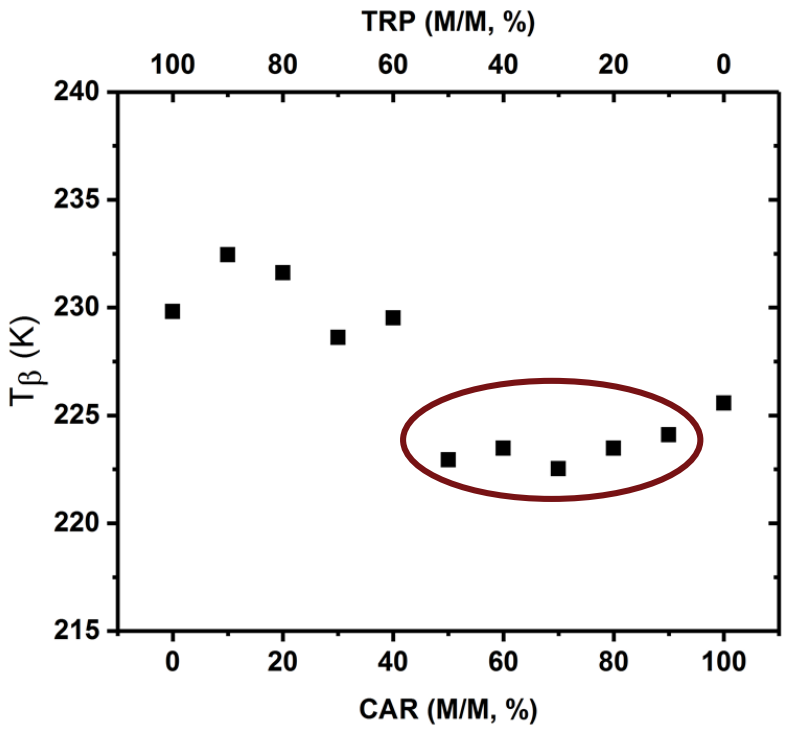
Thermal behaviour of co-amorphous CAR-TRP



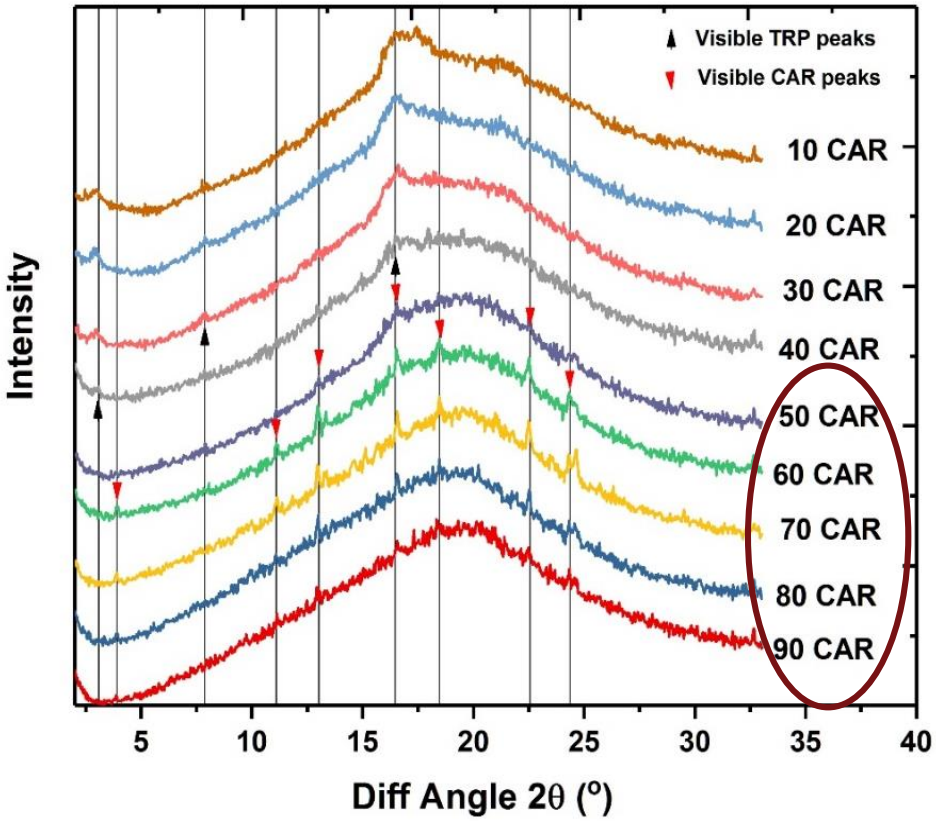


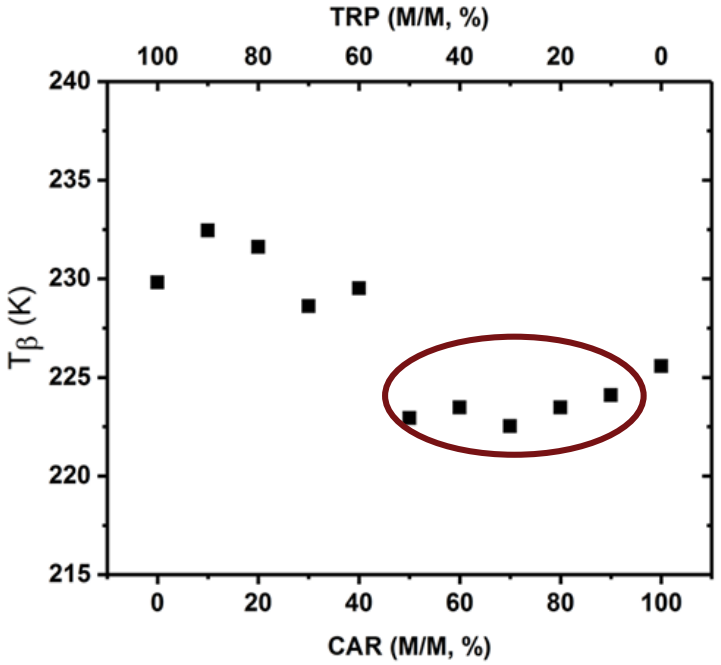
Physical stability at 373 K for 20mins



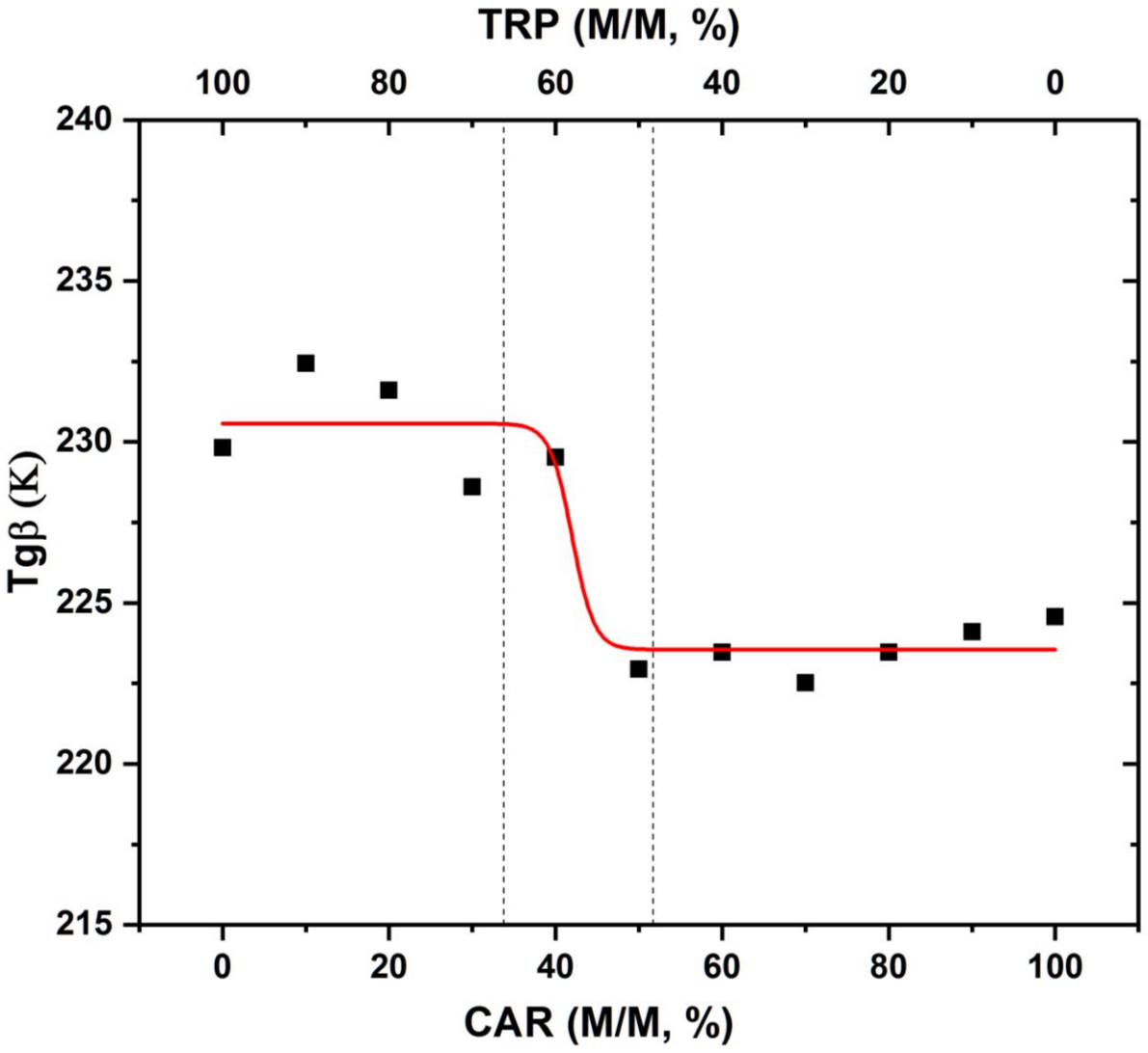


Physical stability at 313K for 62weeks





Predicting stable drug loading ratios

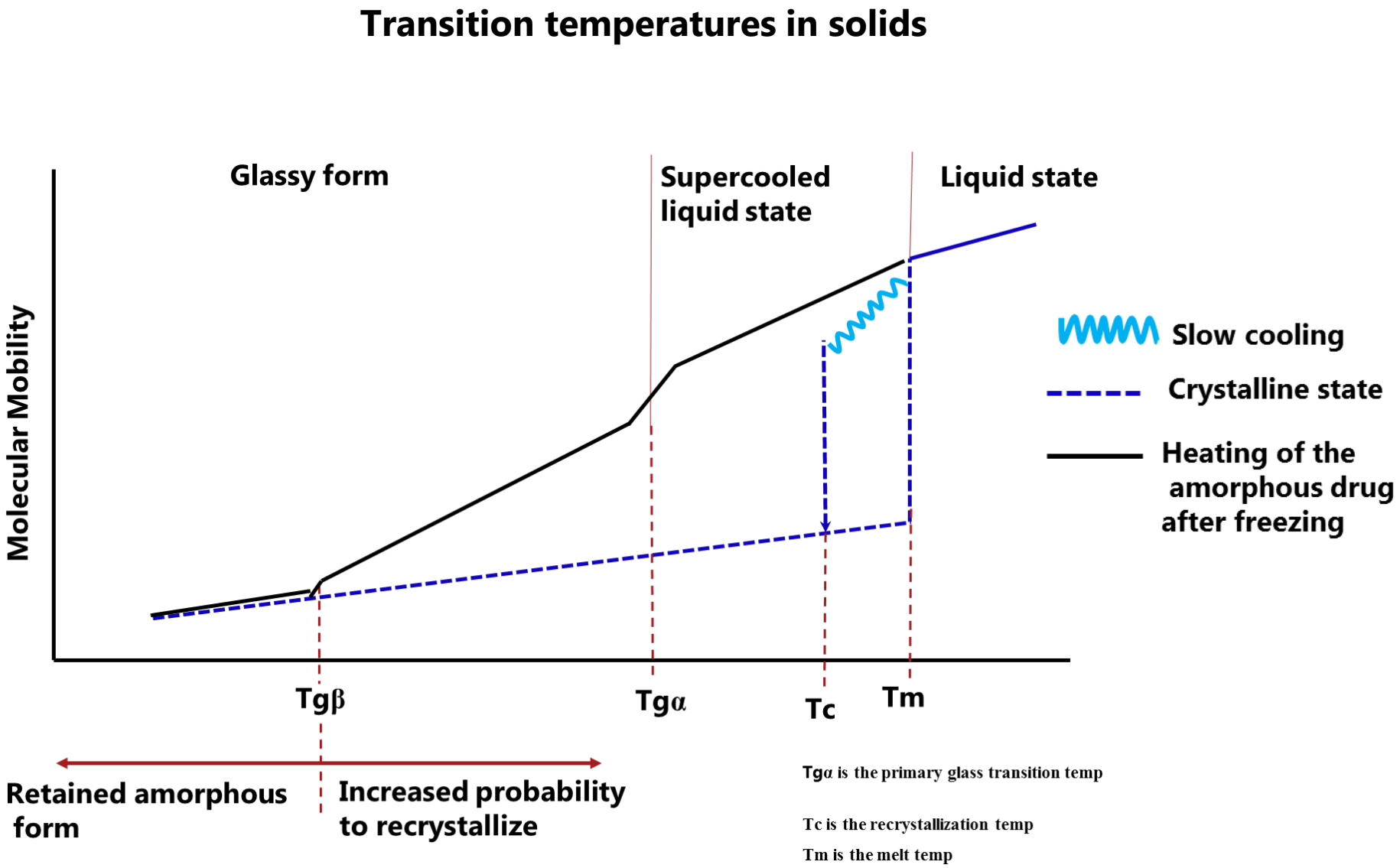


In CAR-TRP co-amorphous systems, ratios between 32 and 53% drug may contain the stable ratios

Take home message

- **The Tgα does not provide adequate info on stability or excess**
- **The Tgβ is a qualitative measure of excess parameter**
- **The excess parameter will determine the physical stability of co-amorphous drug amino acid systems**

Summary 1


Transition temperatures in solids
Glassy form
Supercooled liquid state
Liquid state
Molecular Mobility
Slow cooling
Crystalline state
Heating of the amorphous drug after freezing
Tgβ
Tgα
Tc
Tm
Retained amorphous form
Increased probability to recrystallize
Tgα is the primary glass transition temp
Tc is the recrystallization temp
Tm is the melt temp

Summary 2

- **In neat amorphous drugs, Tgβ is the best predictor of physical stability.**

- **In co-amorphous systems the Tgβ can serve as a measure of the excess parameter and hence a predictor of optimal drug loading ratios.**

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