

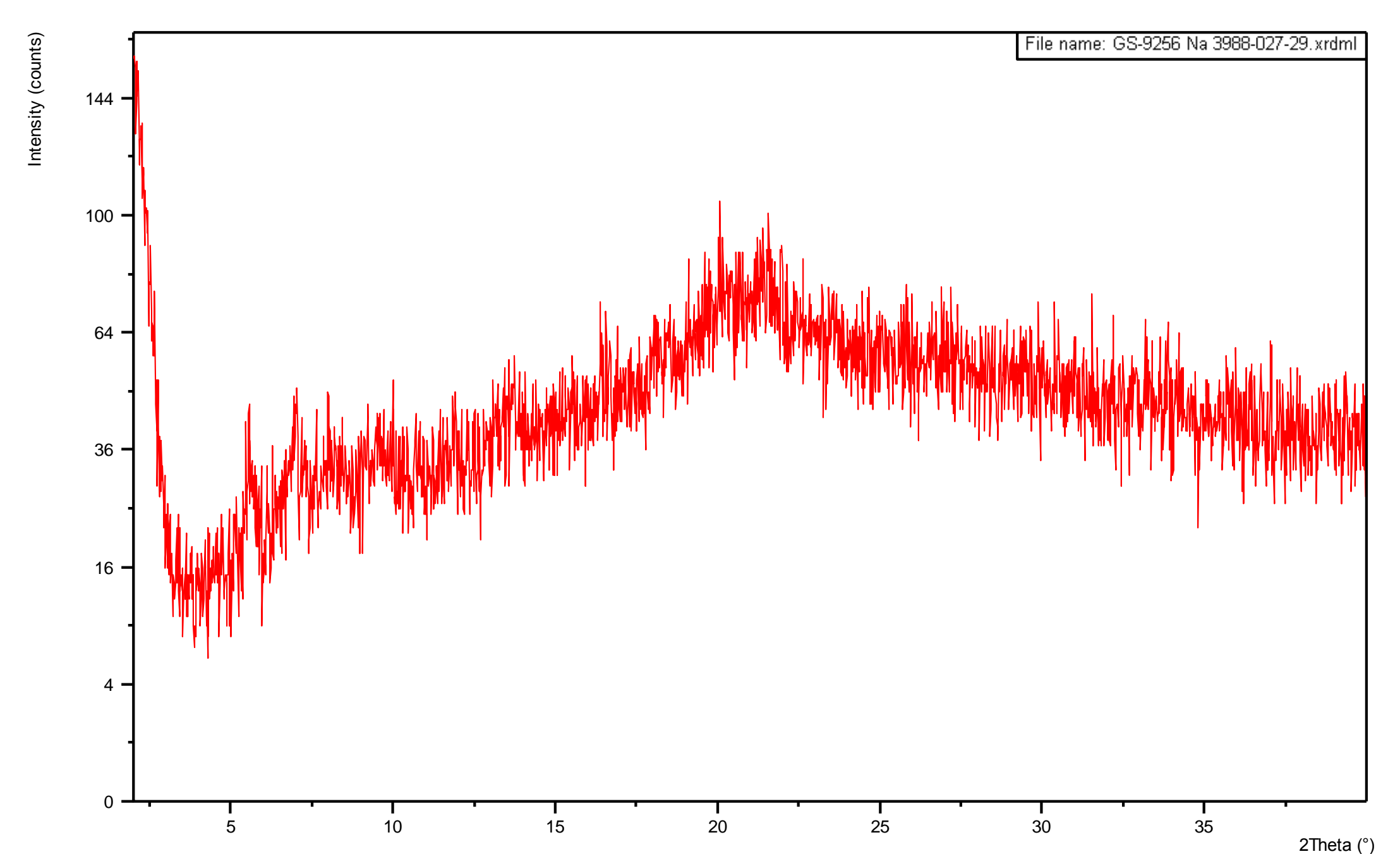
# Estimation of the Glass Transition Temperature (Tg) of an Amorphous Drug Substance from Dispersions in Polymeric Carriers

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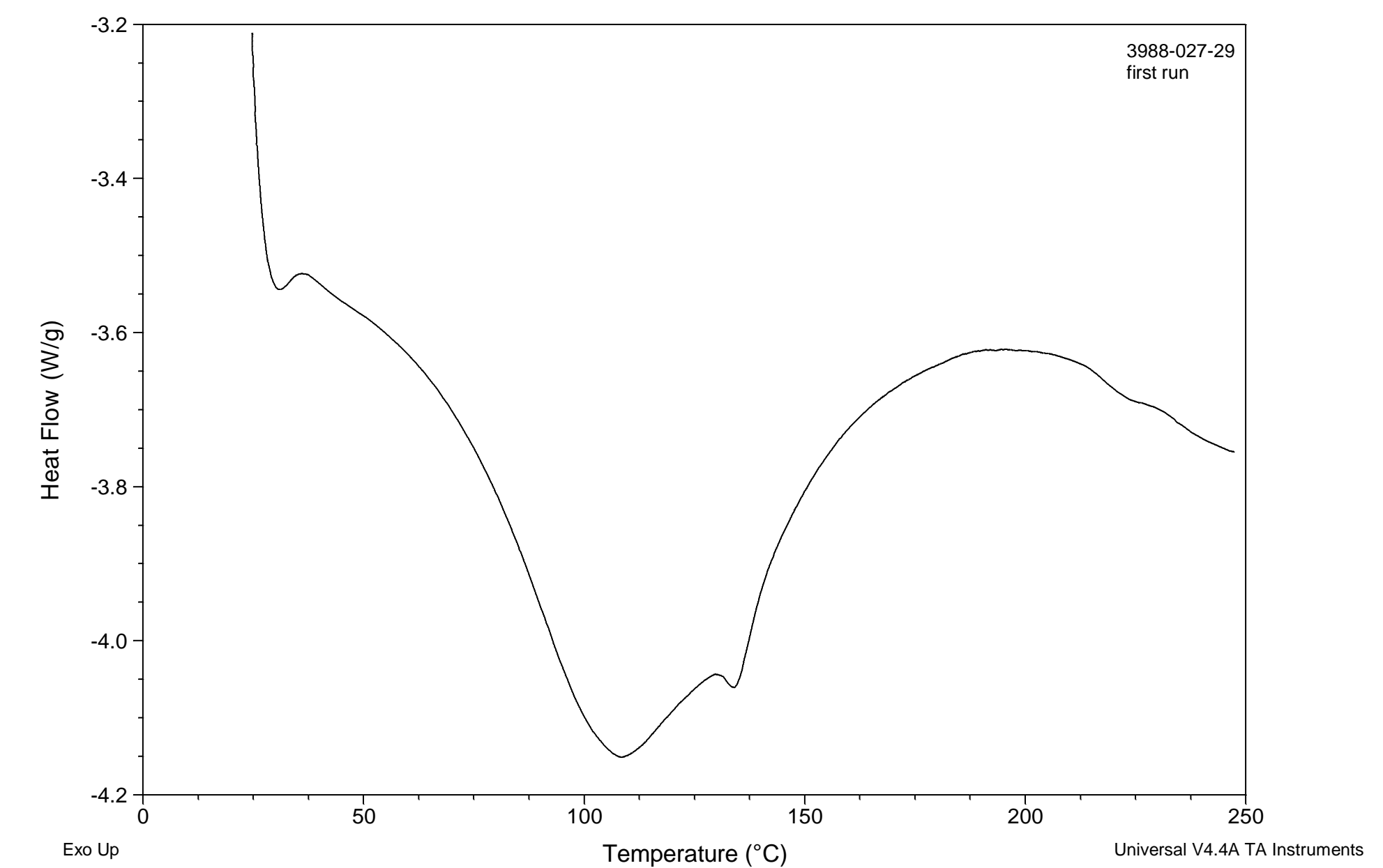
## Introduction

- A poorly soluble BCS Class IV drug is proposed for dosing from the amorphous state
- Determining the Tg of the drug is essential for assessing the physical stability of the amorphous form
- The amorphous state is a high energy state that may spontaneously convert to a lower energy crystalline form
  - Exposure from the crystalline form is poorer due to insolubility
- The amorphous state is characterized by a glass transition temperature (Tg), above which molecular mobility increases and the amorphous compound can crystallize
  - As a “rule of thumb”, it is suggested to have a Tg ≥ 50 °C above the intended storage temperature<sup>1</sup>
- Typically the Tg can be directly identified and measured in a DSC thermogram as a change in the heat capacity

## The Drug is Amorphous by X-ray Powder Diffraction

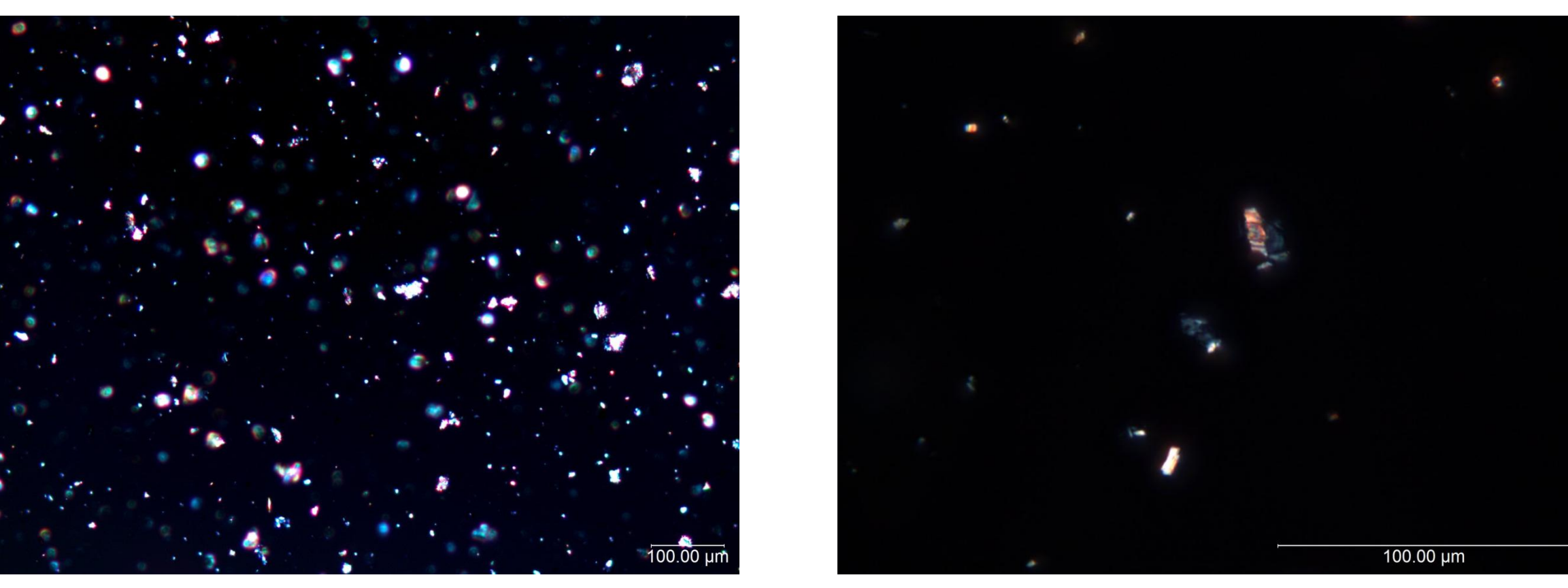


## The DSC Thermogram Shows No Indicative Events

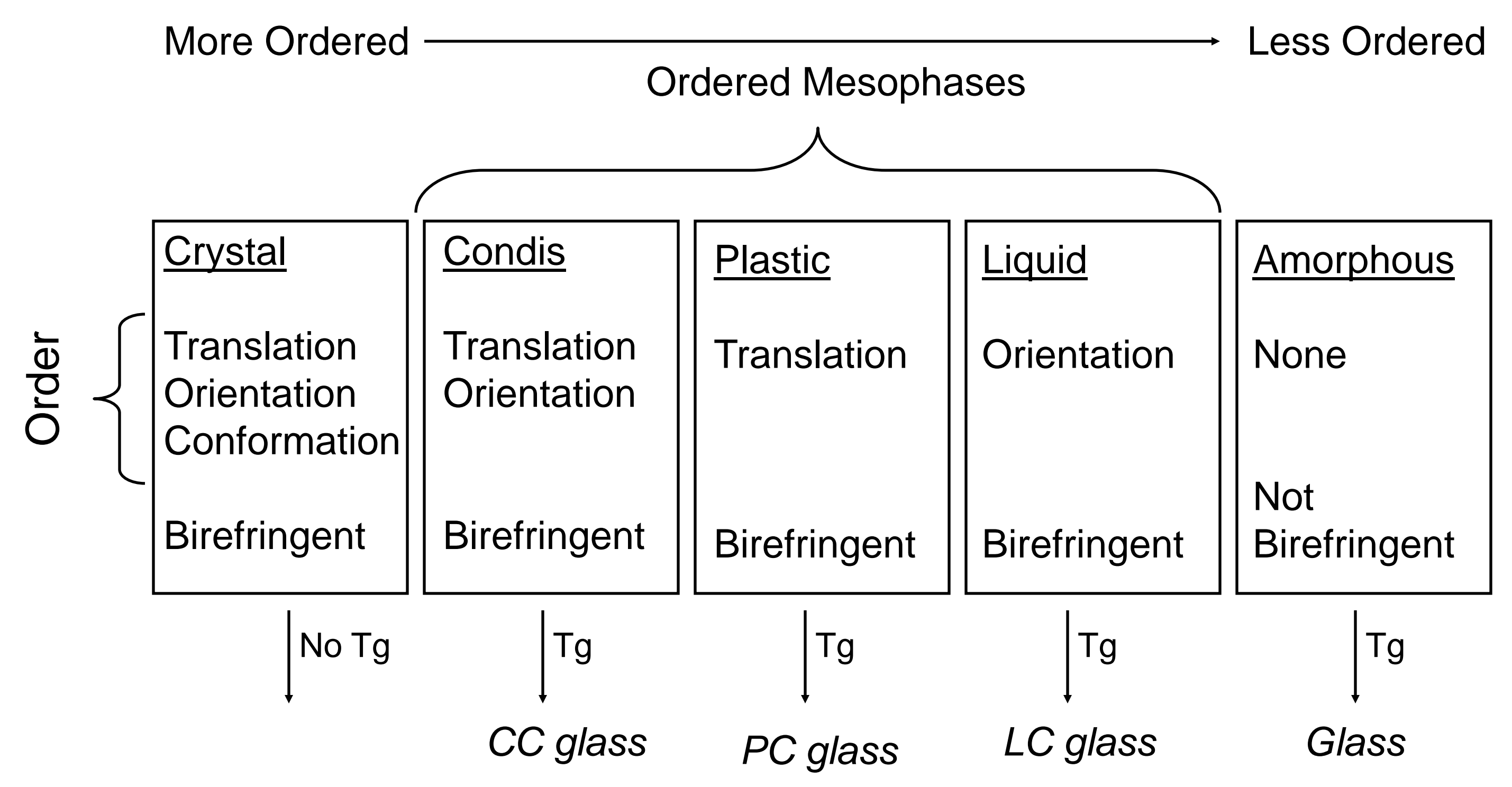


• modulated DSC (mDSC) was also attempted and no apparent Tg was observed.

## Polarized Light Microscopy Indicates the Material is Ordered



## Phases of Material<sup>2</sup>



*It was postulated that this is a semi-ordered material with a Tg that could be greater than the decomposition temperature onset of ~175 °C.*

## Calculating the Tg

The Tg of an unknown can be estimated by measuring the impact of the unknown on the Tg of a known glassy compound, for example, the polymers PVP or Plasdane S630.

The rearranged **Fox Equation<sup>3</sup>** assumes equal densities and calculating the Tg of the unknown (e.g., Tg<sub>unk</sub>) from the observed Tg<sub>mix</sub>, Tg<sub>polymer</sub>, w<sub>polymer</sub>, and w<sub>unk</sub>

$$1/Tg_{unk} = w_{unk}/(1/Tg_{mix} - w_{polymer}/Tg_{polymer})$$

The rearranged **Gordon-Taylor<sup>4</sup>** equation employs the density of the two components in the calculation. For this evaluation, a range of K values were used.

$$Tg_{unk} = \{Tg_{mix}[w_{unk} + K*w_{polymer}] - (K*w_{polymer}*Tg_{polymer})\}/w_{unk}$$

$$K = (\rho_{unk}*Tg_{unk})/(\rho_{polymer}*Tg_{polymer})$$

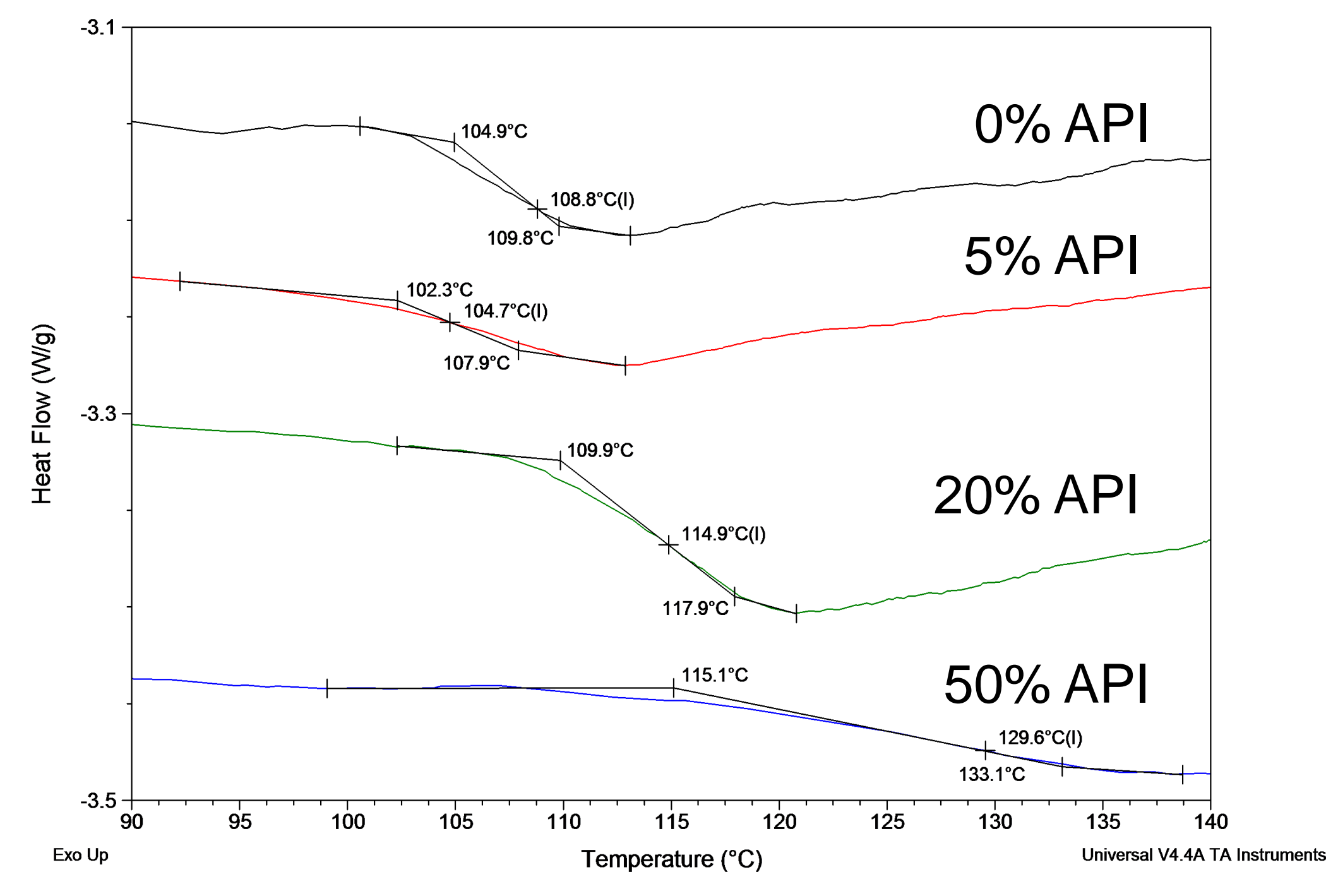
References: 1. Hancock and Zografi, *J. Pharm. Sci.* **1997**, 86, 1  
 2. Wunderlich, *J. Appl. Polym. Sci.* **2007**, 105, 49  
 3. Fox, T.G. *J. Appl. Phys.* **1950**, 21, 581  
 4. Gordon, M.; Taylor, J.S. *J. Appl. Chem.* **1952**, 2, 493

## Evaluating PVP and Plasdane S630

PVP (Tg ~ 177 °C) and Plasdane S630 (Tg ~ 106 °C) were evaluated. It was found that the API is an “antiplasticizer” with the mixtures having a higher Tg than the pure polymer. The apparent Tg for mixtures with PVP was greater than the decomposition temperature, rendering the PVP data suspect.

## Estimating the Tg from Plasdane S630 Dispersions

Data from the dispersions behaved non-linearly, indicating a non-ideal dispersion. Therefore, the calculated Tg depends on the amount of polymer present in the mixture.



The estimated values for the Tg, using a discrete range of K values, from the 20% and 50% loading conditions are below.

Equation Used	K Value	Temp Est from 20% (°C)	Temp Est from 50% (°C)
Fox	n/a	148	155
Gordon-Taylor	0.6	129	139
	0.8	134	143
	1.2	144	151
	1.4	149	155

## Conclusions

- It was necessary to determine the Tg of a x-ray amorphous drug to be delivered in the amorphous form.
- PLM analysis indicated the material was ordered, suggesting a mesophasic material
- The Tg was estimated from mixtures of the test article with polymers of a known Tg
- It was estimated that the Tg is > 50 °C above any expected storage temperature that would be encountered by the amorphous drug