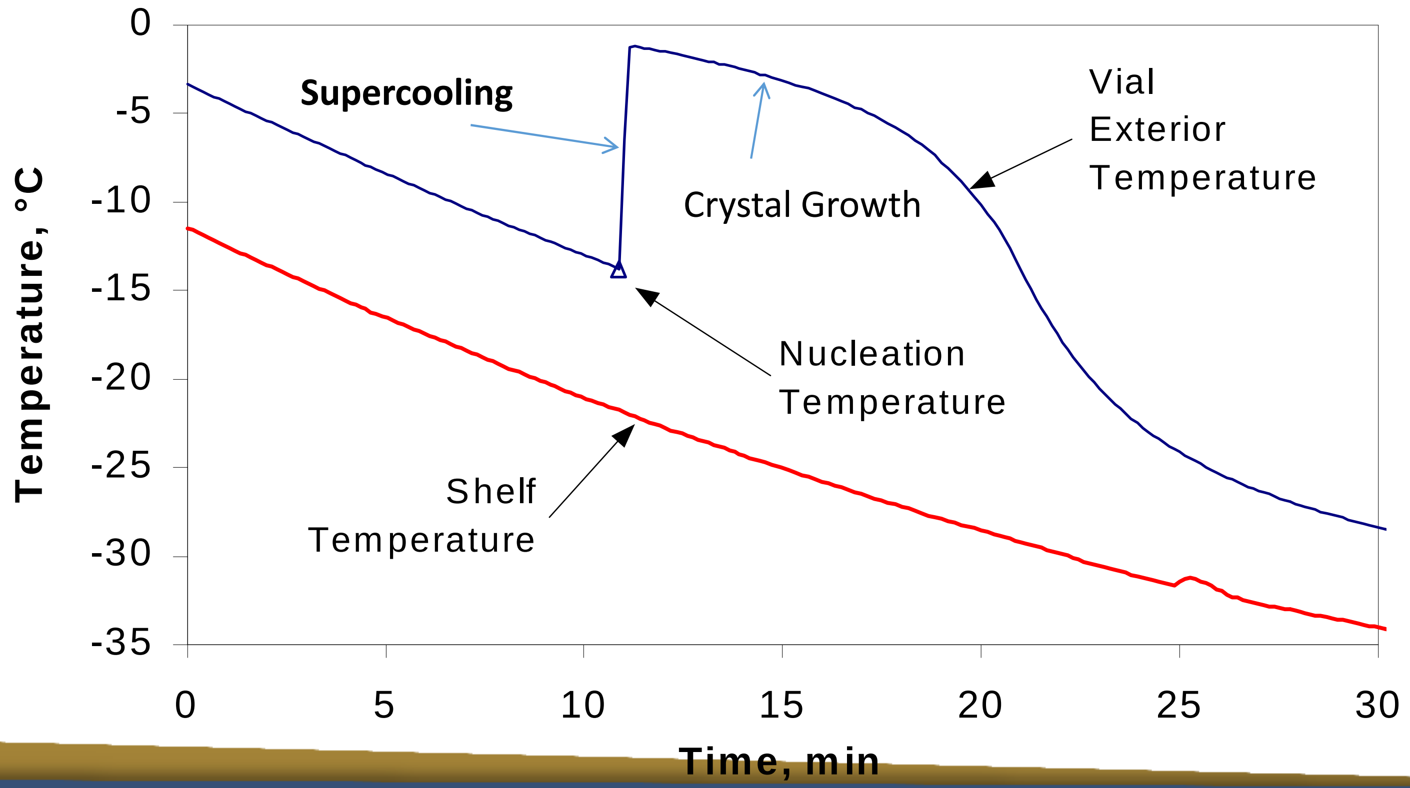
Fundamentals of Freeze Drying

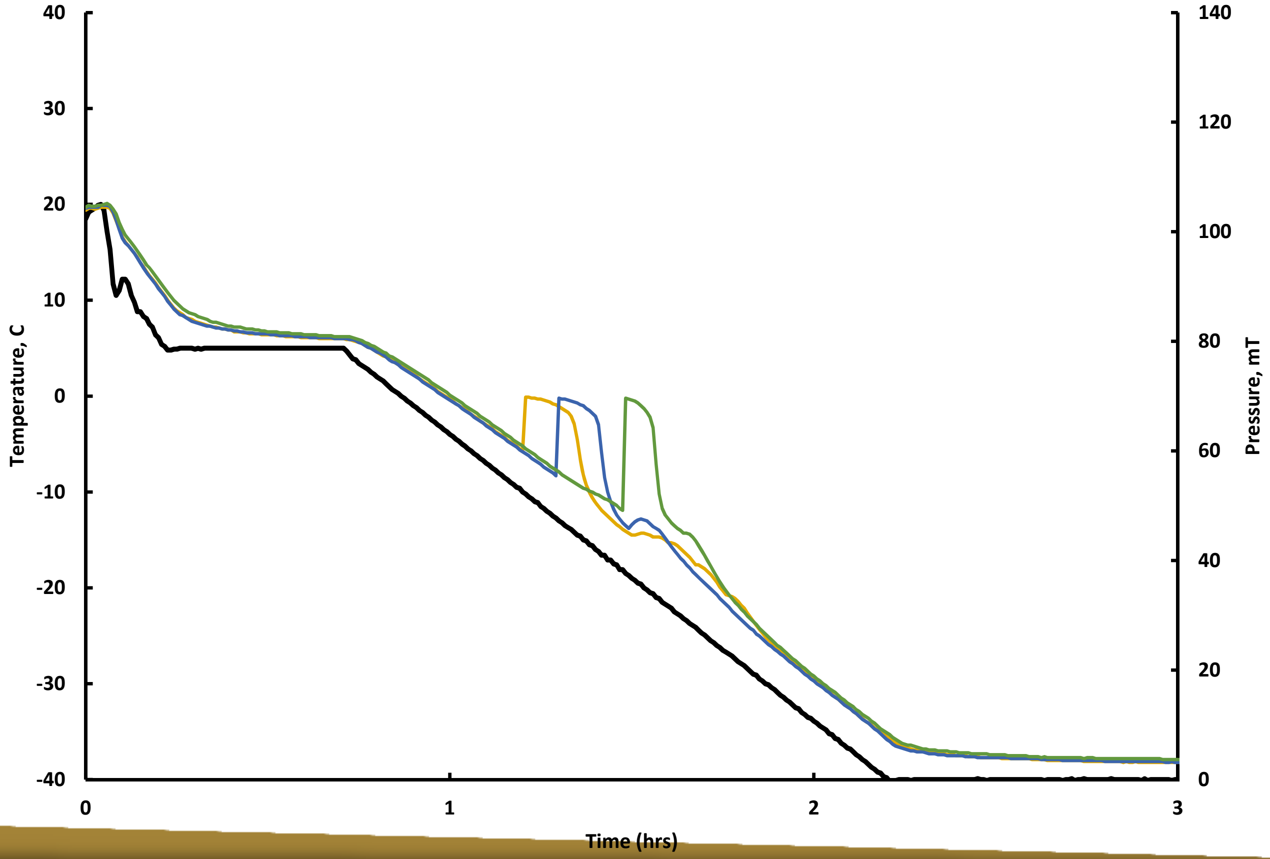
Lyo-Hub Summer School

Part 2 – The Freezing Process

A Closer Look at the Freezing Process



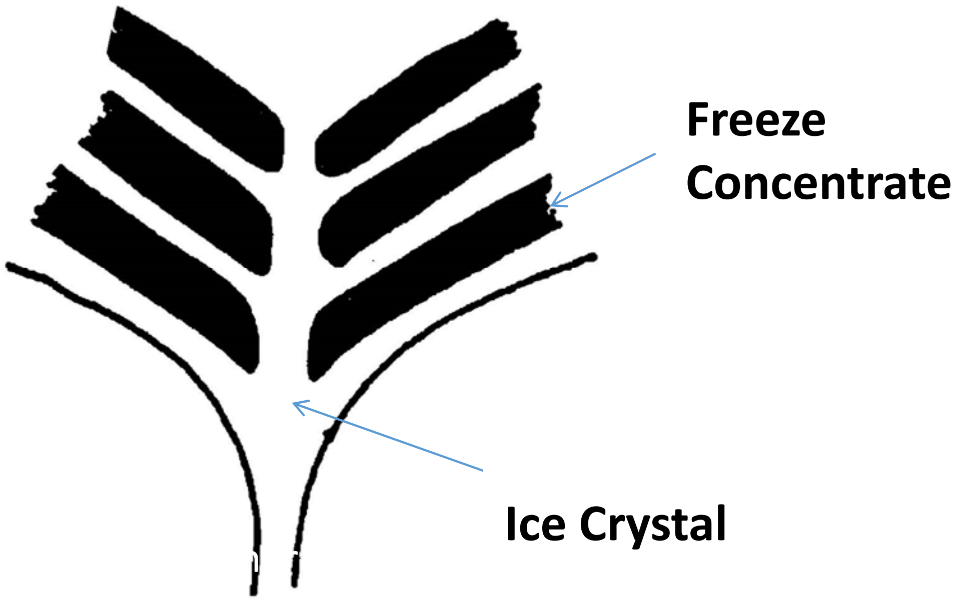
Freezing Process Data – A Stochastic Process



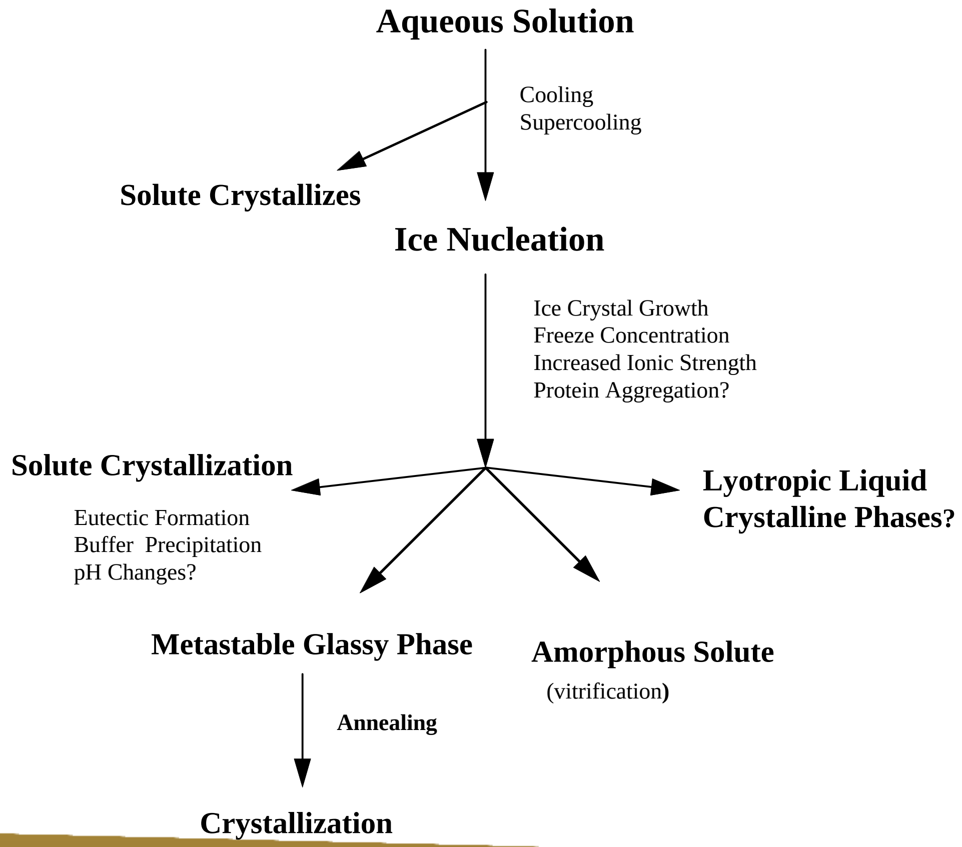
Supercooling in Freeze-Drying

- Since we fill our product into clean, sterilized vials, and we sterile filter the formulation, there is relatively little “foreign” material to help nucleate the ice crystals, so we tend to get a **lot** of supercooling.
- Why do we care?
  - Because, the more the system supercools, the faster it freezes once we do get nucleation of ice crystals. Fast freezing generates small ice crystals, and slow freezing causes relatively large ice crystals. Small ice crystals leave behind small pores in the dried layer, and the small pores have a higher resistance to flow of water vapor than large pores. Thus variability in supercooling causes variability in the drying rate.
  - It’s a misperception that controlling the ramp rate of the shelf during freezing controls the freezing rate. Supercooling effects are more important

Freeze Drying Behavior is Largely Determined by What Happens to the Freeze Concentrated Solute(s)



What Happens to the Freeze Concentrate?



Aqueous Solution

Cooling
Supercooling

Solute Crystallizes

Ice Nucleation

Ice Crystal Growth
Freeze Concentration
Increased Ionic Strength
Protein Aggregation?

Solute Crystallization

Eutectic Formation
Buffer Precipitation
pH Changes?

Lyotropic Liquid Crystalline Phases?

Metastable Glassy Phase

Annealing

Crystallization

Amorphous Solute

(vitrification)

What is a Eutectic Mixture, and Why Do We Care?

- A eutectic mixture is an intimate physical mixture of two or more crystalline solids, where this mixture melts at a precise temperature, as if it were a single, pure compound.
- We care about eutectic mixtures because the eutectic melting temperature represents the "failure point" if this temperature is reached during primary drying. This is sometimes called "meltback."
- Some examples of eutectic melting temperatures:
  - Sodium chloride/ice (melts at about -22° C)
  - Glycine/ice (about -4° C)
  - Mannitol/ice (about -2° C)
  - Polyethylene glycol/ice (about -16° C)
  - Calcium chloride/ice (about -51° C)

Things to Keep in Mind About Eutectic Crystallization

- Just because, for example, sodium chloride is present in the formulation does not necessarily mean that it crystallizes and forms a eutectic mixture. It may, or it may not, depending on
  - The relative concentration of sodium chloride in the formulation (other formulation components tend to "get in the way."
  - The effective freezing rate. Fast freezing may not allow enough mobility of the sodium chloride for it to crystallize. It may "get stuck" in the amorphous state because the system gets too viscous, too fast.

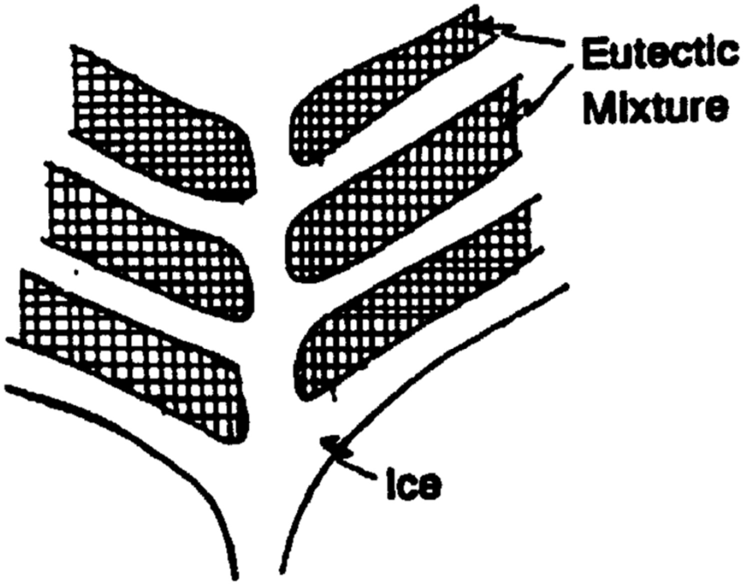
What if Nothing Happens to the Freeze-Concentrated Solute; That is, No Component Crystallizes?

- In this case, the freeze-drying behavior is determined by the *viscoelastic properties* of the freeze concentrate, and the product is characterized by the *glass transition temperature* of the freeze concentrate.
- This glass transition temperature in the frozen system is called Tg’, and it is the basis for what we call collapse in freeze drying. Collapse generally ruins the pharmaceutical acceptability of the product.
- Amorphous freeze-dried solids have a glass transition temperature as well. This is important in determining the physical stability of the drug product. For example, freeze-dried sucrose at a residual moisture level of about 0.5% has a Tg of about 65^{o}C.

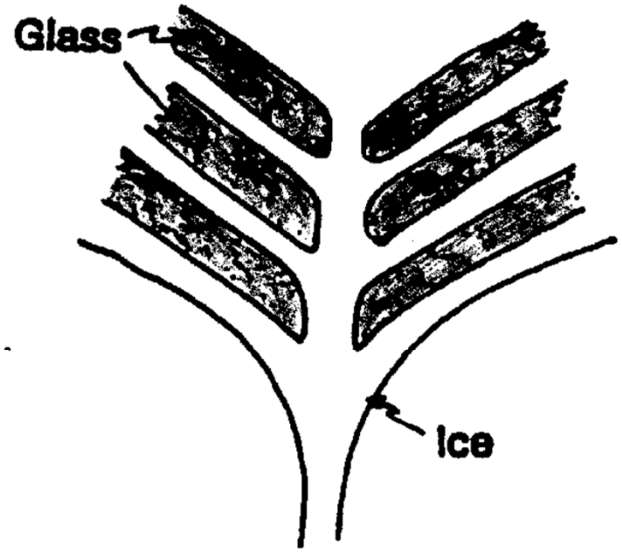
Glass Transition Temperatures

The glass transition temperature of the freeze-concentrated solute determines the ***collapse temperature*** during freeze-drying. Below Tg’, the freeze-concentrated material is rigid enough to support its own weight after the ice has sublimed away. Above Tg’, the freeze concentrated material undergoes viscous flow after the supporting ice structure is gone, resulting in collapse.

Why it matters



Crystalline Solute



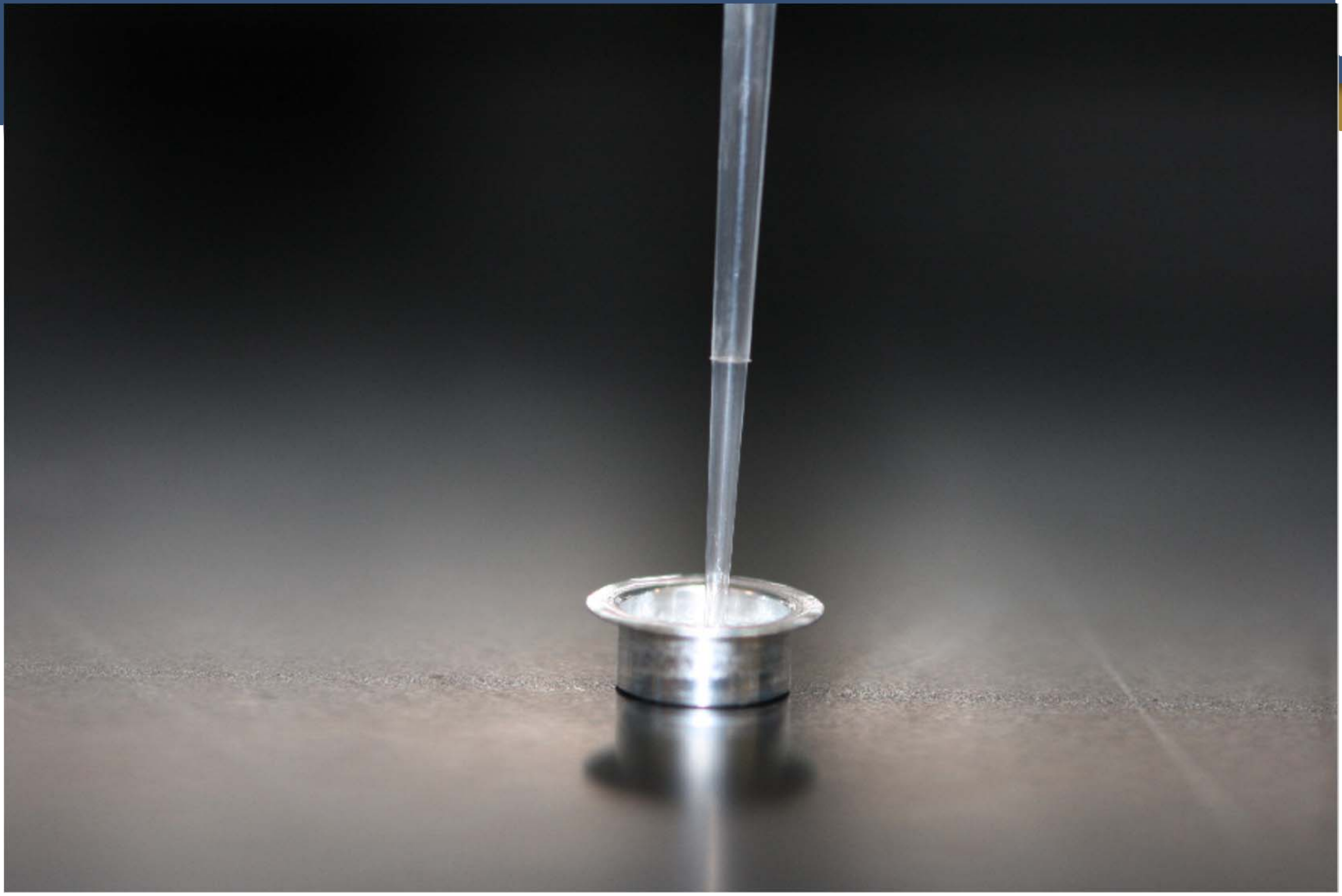
Amorphous Solute

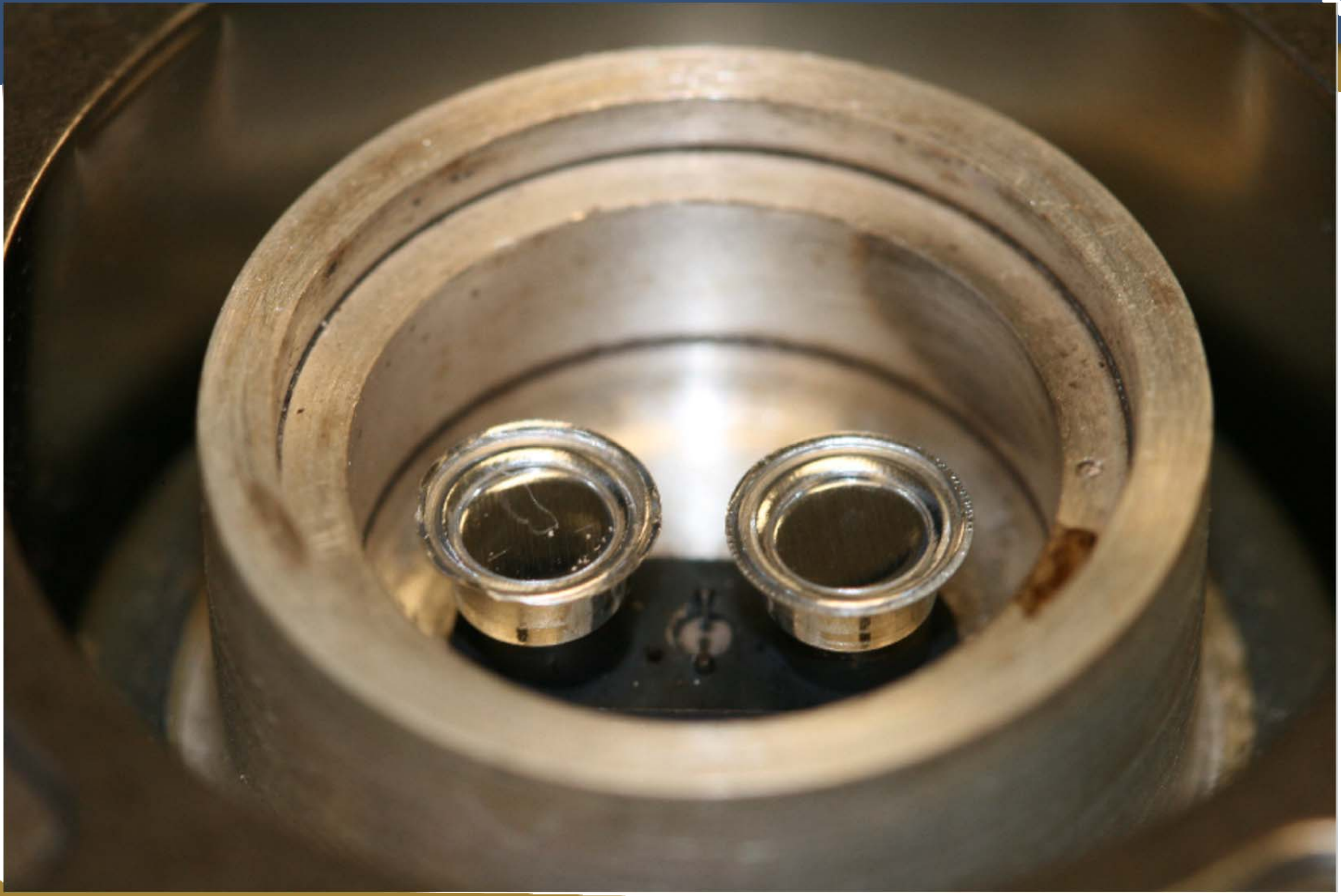
Effect of Physical State of Some Drugs on Stability – Three Months at 50ºC

Drug	Physical State	% Potency Loss
Cefamandole Nafate	Crystalline	0.9
	Amorphous	15
Cefalothin Sodium	Crystalline	< 1
	Amorphous	30
Cefachlor H_2O	Crystalline	6
	Amorphous	36

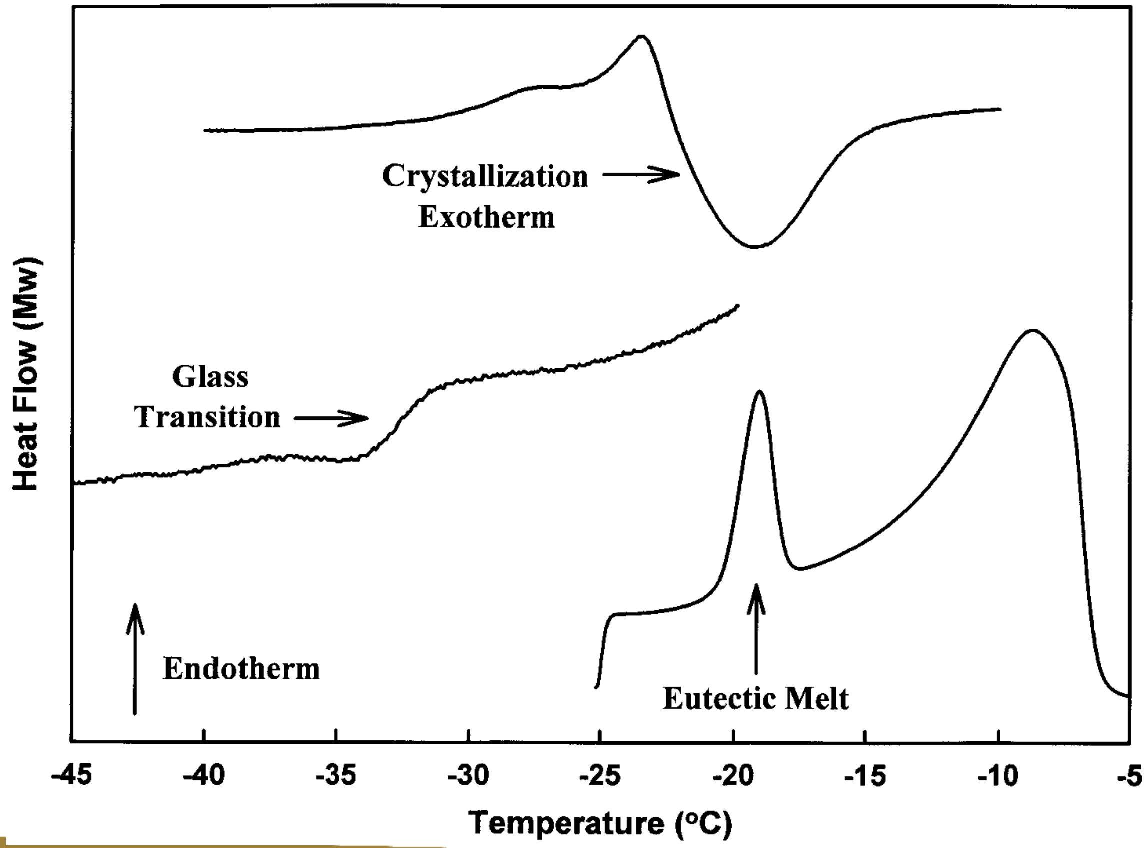
The Most Common Characterization Tools

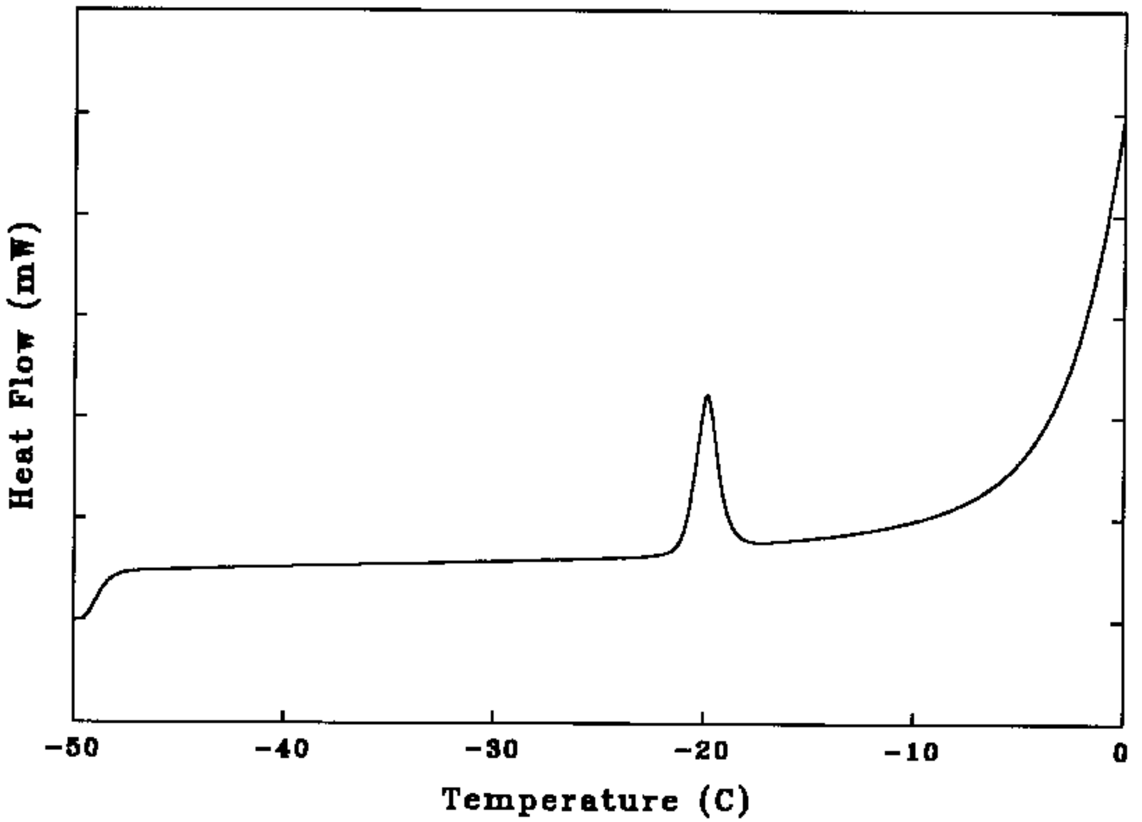
- Thermal Analysis
- Microscopic Observation



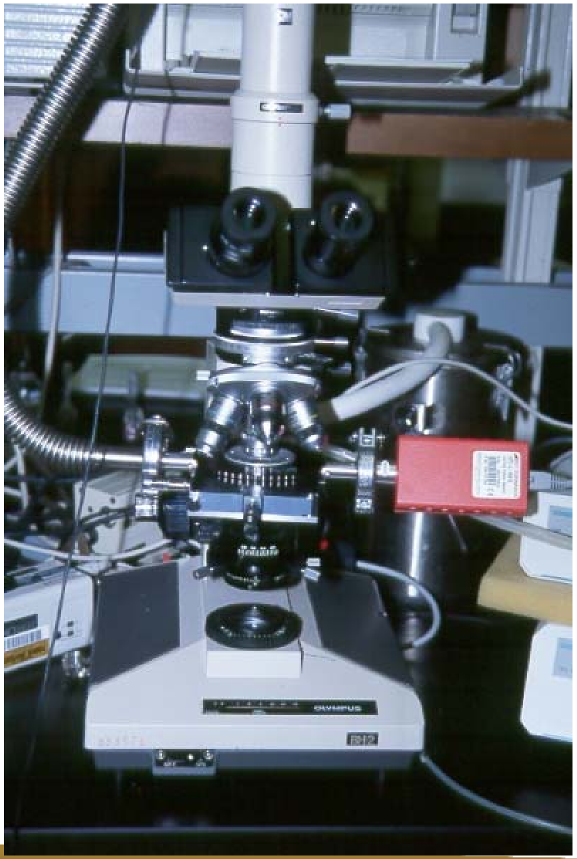


Thermal Transitions in Frozen Systems




Heat Flow (mW)
-50
-40
-30
-20
-10
0
Temperature (C)

Equipment



Controlled Nucleation in Freeze Drying

- Rapid Depressurization (Praxair method)
- Ice Fog (IMA Life)
- Millrock method (uses condenser to generate ice fog)