6. Polymorphism

6.1 Introduction

Mitscherlich (1821) first defining the polymorphism

Arsenate, phosphate, sulfur

Wohler and Liebig (1832) first discovering the polymorphism of organic compounds.

Bezamide

Ostwald (1899) suggesting the *Rule of Stages* that the a crystallization system progresses from the supersaturated state to equilibrium state in stages, each stage representing the smallest possible change in free energy.

- In the chemical and pharmaceutical industries the demand for high yield and high production rates has forced to operate process far from equilibrium, so exacerbating the tendency to from polymorphic structure that for given temperature, pressure and composition are not most stable.

Ex)

Chemical product	Number of polymorphs	Applications
Ammonium nitrate	5	Explosive, fertilizer
Aspirin	4	Pharmaceuticals
Calcium carbonate	3	Filler for plastics
Copper phthalocyanine	4	Pigment
Indigo	2	Disperse dye
Lead azide	2	Explosive
Lead chromate	2	Pigment
Pentaerythritol tetranitrate	2	Explosive
Phenobarbitone	13	Pharmaceuticals
Sorbitol	2	Sweetener
Sulphathiazole	4	Pharmaceuticals
Tetraethyl lead	6	Fuel additive
Titanium oxide	3	Pigment
Titanium trichloride	4	Catalyst
Tirglycerides	4	Fats and oils

- Solvate

The solute and solvent are part of crystal structure.

Ex) calcium oxalate monohydrate

- Compounds

The crystal composed of multicomponents.

Ex) $KCl.MgCl_26H_2O$

- Amorphous solid

Solid materials without long-range order.

Ex) glass

- Mesophase

Liquid-like droplet

Ex) liquid crystalline

6.2 Thermodynamics

- Transition temperature

Temperature at which two or more polymorphs are in equilibrium.

$$\frac{dT}{dP} = \frac{T_t \Delta V}{\Delta H_t}$$ - Clapeyron equation

- Chemical potentials between two polymorphs

IF μ_{solid} *(II)* < μ_{solid}*(I), phase II* is more stable than *phase I* and

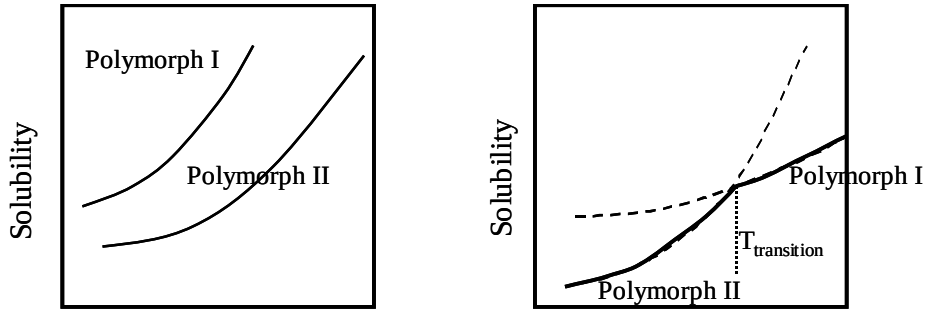
x_{eq}*(II)* < x_{eq}*(I)*

- Monotropic ; *(irreversible transformation)*

the relative solubility of polymorphs independent of temperature.

- Enantiotropic ; *(reversible transformation)*

the relative solubility of polymorphs dependent on temperature.



- Monotropic -

- Enantiotropic -

6.3 Structure

6.4 Phase transition

- Transformation;

Appropriate positional changes of molecules in solid state to yield a new lower free energy.

1) Reconstructive transformations

Crystals of metastable structure is disintegrated to re-construct new crystals of stable structure in saturated medium.

2) Displacive transfromations

Transformation in solid state.

$$\Delta G = \Delta H - T\Delta S$$

If endothermic ($\Delta H>0$), $\Delta S>0$ ***(order-disorder transformation).***

- *n*th-order phase transition

one for which the *n*th derivative of the free energy with temperature is discontinuous.

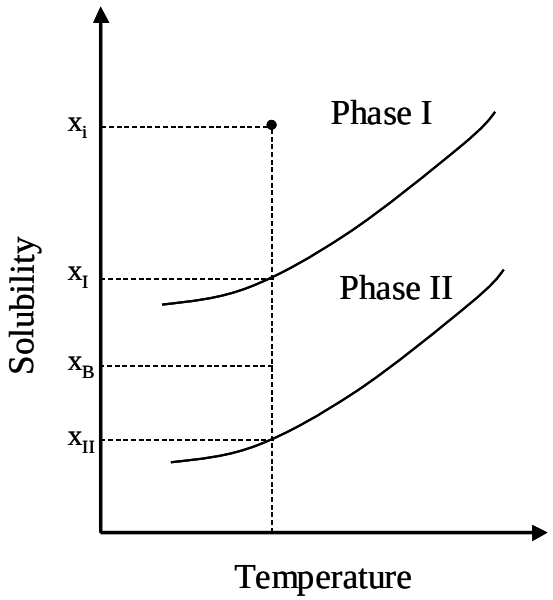
A transition in which the molar Gibbs energy (or chemical potential) and its (n-1)th-order derivatives are continuous, whereas the nth-order derivatives with respect to temperature and pressure are discontinuous at transition point.

1) First-order transition is characterized by discontinuous entropy, enthalpy and heat capacity curves.

2) Second-order transition is characterized by continuous entropy and enthalpy but discontinuous heat capacity curves.

6.5 Kinetics : *solvent-mediated and solid state transformations*

- Solvent-mediated transformation (reconstructive transformation)



X_i is supersaturated to both crystals of phase I and II.

X_B is supersaturated to crystal of phase II but undersaturated to crystal of phase I.

The supersaturation for growth of polymorph II

$$\sigma = \frac{(x - x_{II})}{x_{II}}$$

The supersaturation at transformation process

$$\sigma_{I,II} = \frac{(x_I - x_{II})}{x_{II}}$$

(i) dissolution of polymorph I

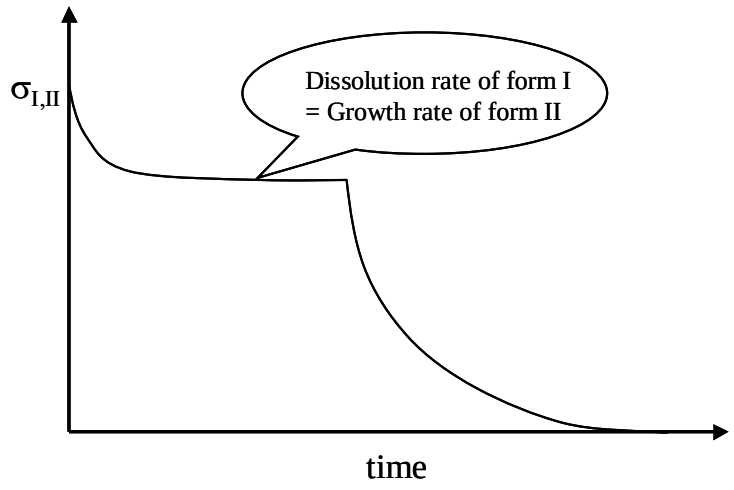
$$\frac{dr_I}{dt} = -k_D(\sigma_{I,II} - \sigma)$$

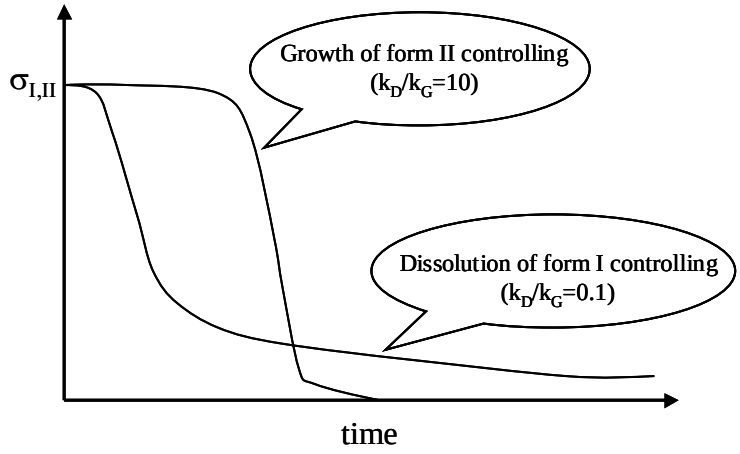
(ii) growth of polymorph II

$$\frac{dr_{II}}{dt} = -k_G\sigma$$

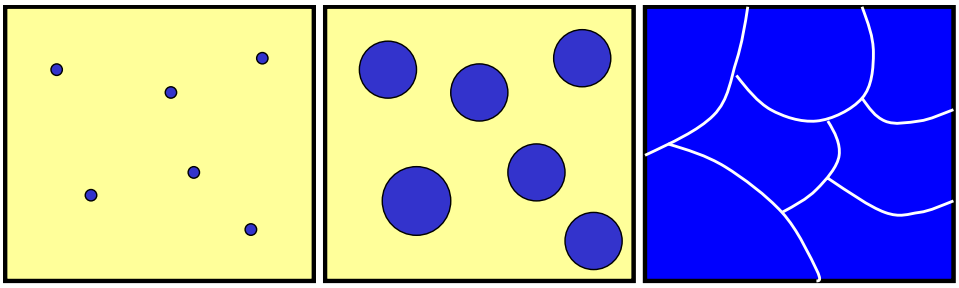
(iii) mass balance

$$\sigma = \sigma_i - (\sigma_i - \sigma_{I,II})(\frac{r_I}{r_{I,i}})^3 - \sigma_i(\frac{r_{II}}{r_{II,f}})^3$$





- Solid state transformation (displacive transformation)



The relationship between the transformed volume and time is given as,

$$\frac{V(t)}{V(total)} = 1 - \exp(-kt^n)$$

where n is determined by the dimensionality of growth (1, 2, or 3).

6.6 Conclusion

- Polymorphism will impact on process operation as well as physical properties of product!!!