

# SOLID STATE PROPERTIES



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- **Crystal Properties**
  - **Polymorphic techniques**
  - **Solid State Stability**
  - **Flow Properties**
  - **Segregation**
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# CRYSTALLISATION & CRYSTAL PROPERTIES

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- Introduction
- Factors influencing Crystallization
- Nucleation
- Crystal growth
- Mechanism of Crystallization
- Crystal morphology & its role in Pharmacy

□ The process of formation of crystals from the supersaturated sol through the process of nucleation and crystal growth in order to produce a stable product under specified condition is termed as **CRYSTALLISATION**

□ Outer appearance~**HABIT** of crystal

□ Molecular structure ~ **INTRNAL STRUCTURE** of crystal

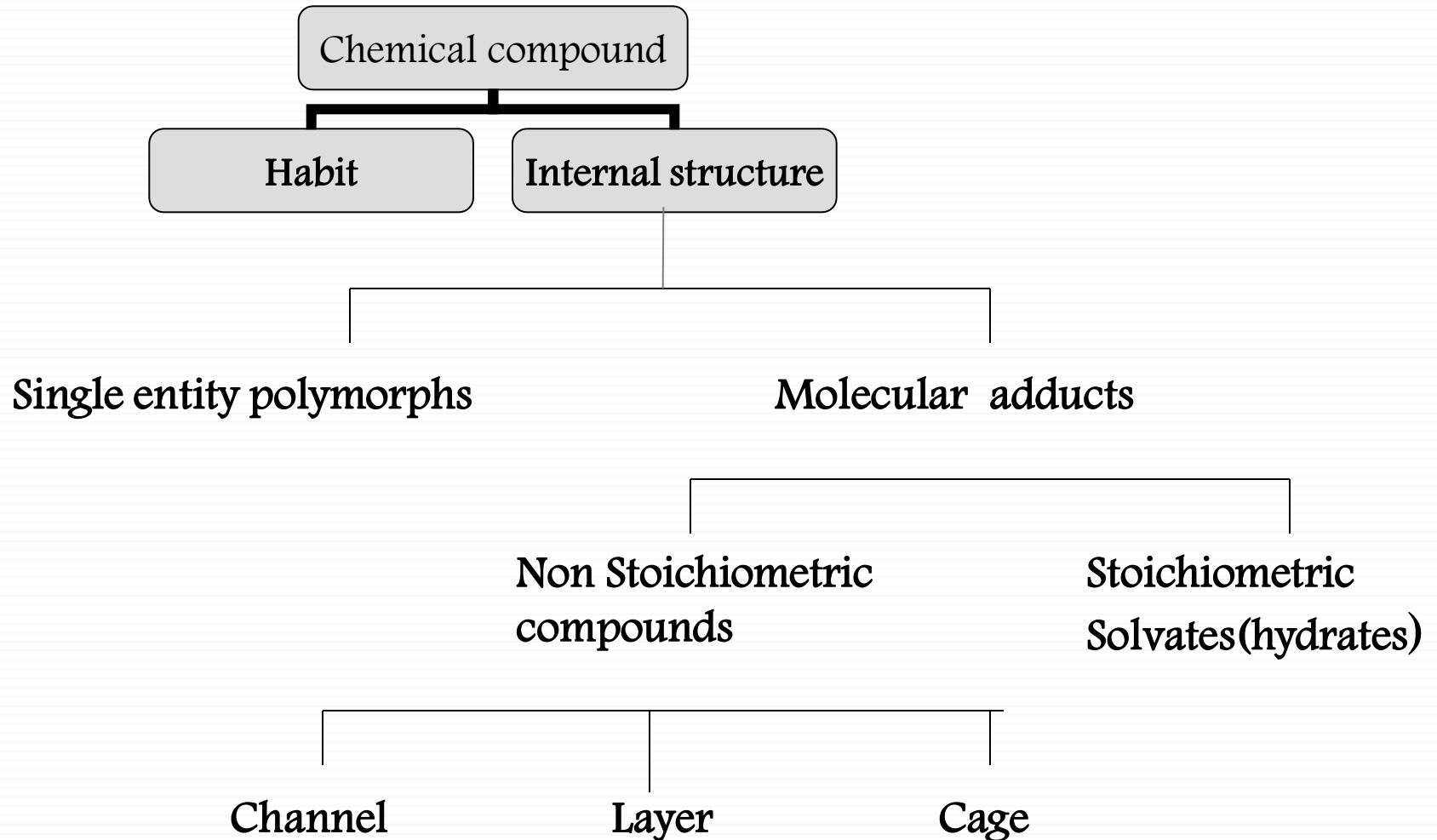
□ Crystallization

~describes production of solid single component from multicomponent fluid phase

~important for rational formulation, process development and stability of products

~reduces the free energy of the system

- A single internal structure for a compound can have several differences depending upon the environment for growing crystal
- Internal structure of a compound.....



- The physicochemical properties of these crystal forms are influenced by intermolecular forces present .
- Crystal formation is a special characteristic of a solid in which the molecules self organise into regular , repeating molecular patterns

## CRYSTAL FORMATION REQUIREMENTS

- Solvents should have good solubilising capacity so that concentrated sol's are formed
  - They should promote nucleation process
  - Suitable temp and cooling rate has to be followed and it can impact the crystal packing pattern
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# FACTORS INFLUENCING CRYSTALLISATION

- Solubility/solubility product
- Supersaturation
- Diffusivity/viscosity
- Temperature
- pH
- Solvent
- Soluble additives and impurities
- Reactivity of surface towards nucleation
- Volume of solution
- Rate at which supersaturation is created  
(Cooling rate, freezing rate, rate of pH change)

# SUPERSATURATION

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- A solution in which the chemical potential of solute is same/equilibrium to solid phase under specified conditions

~~~~ SATURATED SOLUTION

- The excess conc of solid phase present in sol that of saturated

---- SUPERSATURATED SOLUTION



✓ Saturated states is created by.....

Methods that regulate the solute activity or the conc  
Include,

- ♠ solvent removal either by evaporation /freezing
- ♠ addition of indifferent salts with ions participating in precipitation
- ♠ dissolution of metastable solid phase

Methods that regulate the solute solubility include.....

- ♠ temperature change
- ♠ pH change
- ♠ addition of solvent/additive that lower solubility of solute

- The no of molecules required to achieve effect is inversely prop to super saturation ,hence as super saturation increases probability of nucleation increases
- The driving force for nucleation and growth is diff in chemical super saturation potential of solute in a supersaturated sol and in a saturated sol

$$\Delta\mu = \Delta\mu_1 - \Delta\mu_{eq}$$

□ Supersaturation is represented by,

$$\sigma = \Delta\mu / RT = \ln(a / a_{eq}) = \ln(\gamma_1 c_1 / \gamma_{eq} c_{eq})$$

$$\Delta\mu = RT \ln (a / a_{eq}) = RT \ln(\gamma_1 c_1 / \gamma_{eq} c_{eq})$$

$$\sigma = \ln (c/s)$$

where c~ conc of crystallizing substance in s.s sol  
s~ solubility

# NUCLEATION

- ♪ The process by which crystal forms-nucleation and growth
- ♪ Nucleation –small mass, crystal can grow
- ♪ Growth –addition of more solute molecules to nucleation site.
- ♪ To achieve nucleation and growth, s.s sol is needed (amount of solute dissolved in liquid > true solubility)
- ♪ s.s sol's are thermodynamically unstable.....move back to true solubility, here excess sol ppt's
- ♪ Some s.s sol's not crystallised—scratching., rough surface/glass spicule..as nucleation site
- ♪ Solvent promotes nucleation....if solvent binds to molecular organizing Functionalities of solat,crs'n impeded..
- ♪ Finding appropriate solvent is imp

- **Pharmaceutical process in which s.s states achieved include**

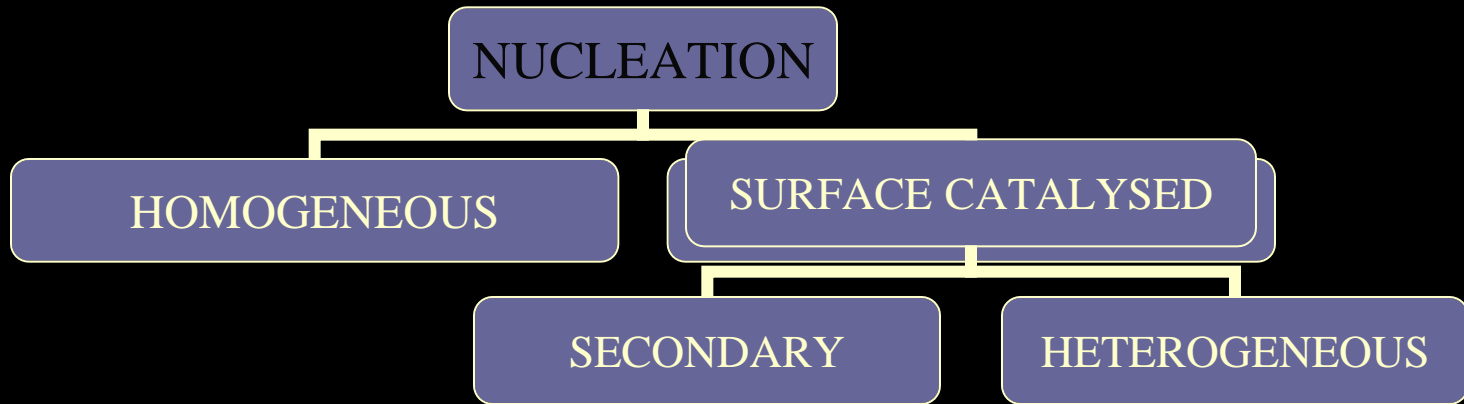
- **freezing**
- **freeze drying**
- **spray drying**
- **drying of wet granules**

- **Other processes by.....**

- **changing solubility**
- **during isolation of solid state forms**
- **during dissolution of weak bases (where pH changes-GIT)**



- **Nucleation phenomena –imp in control of micromeritic properties in crystallization of polymorph**
- **Spontaneous nucleation-mol's of low K.E, so that attraction between them is sufficient**



Catalysed by the surfaces of crystallising solutes

Catalysed by the interfaces/surfaces other than the crystallising solutes (from seed crystal)

## HOMOGENEOUS NUCLEATION

- OCCURS IN LARGE VOL'S (> 100ul)

Because sol contains random impurities that induce nucleation

- In thermodynamic consideration for nucleation, free energy change for aggregate undergoing phase transition is...

$$\Delta G = \Delta G_v + \Delta G_s$$

where,

$\Delta G_s$  – surface free energy associated with formation of aggregate

$\Delta G_v$  – volume free energy change associated with phase transition

$$\Delta G V = \sim \alpha L^3 V K_B \ln (c/s)$$

Where,

$l$  – characteristic length

$V$  – molecular vol of crystalline solute

$K_B$  – Boltzmann const

$T$  – temperature

$\alpha$  – volume shape factor

for homogeneous nucleation ,

$$\Delta G S = \beta l^2 \gamma_{12}$$

Where,

$\beta$  – area shape factor

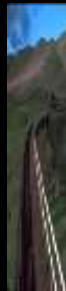
$\gamma$  – interfacial energy/unit area

- Overall free energy for nucleation is decreased by a large Supersaturation ratio(  $c/s$ ) and by a low interfacial energy
- Nucleation rate is controlled by following parameters.....
  - $\tau$  molecular / ionic transport
  - $\tau$  viscosity
  - $\tau$  supersaturation
  - $\tau$  solubility
  - $\tau$  solid-liquid interfacial tension
  - $\tau$  temperatue
- Nucleation rate will increase by increase in supersaturation
- At const supersaturation the rate will increase with increase in Solubility
- The dependence of nucleation on solubility...leaving an unstable A system do not seek out most stable zone rather than nearest Metastable zonetime reached with loss of free energy



# HETEROGENEOUS NUCLEATION

- In this unintentionally / intentionally added surfaces / interfaces may promote nucleation
- The reactivity of crystal surfaces has significant effect in isolation of desired solid state modifications and in control of conversions between these modifications....because the formation of 2-d nuclei is lowered by presence of appropriate substrate.....
- This is given by.....



$$\Delta G_s = \gamma_{12}A_{12} + (\gamma_{23} - \gamma_{13})A_{23}$$

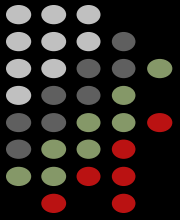
where,

$\gamma$  – interaction energy per area

A – surface area of interfaces

- Increase in surface area of substrate will enhance heterogeneous nucleation
- This nucleation effect dissolves metastable solid phases, since this nucleation can occur at low driving forces

# CRYSTAL GROWTH

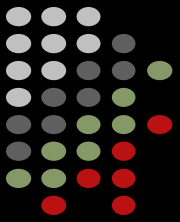


- As stable nuclei form, crystal grow into macroscopic crystals, this Portion of crystallization is termed as crystal growth.
- Several stages through which growth inits(tacked onto space lattice to form crystals) pass .....

  - transport of growth unit from the bulk sol to impingement site
  - adsorption of growth unit to impingement site
  - diffusion of growth units for impingement site to growth site
  - incorporation into lattice

- All these steps are rate limiting and are dependent on supersaturation temperature, additives and the hydrodynamics of the system.
- The rate of crystal growth is influenced by rate of heat transfer and changes taking place at the surface

# MECHANISM



## CRYSTAL GROWTH

VOLUME DIFFUSION  
CONTROLLED

SURFACE INTEGRATION  
CONTROLLED

LAYER  
GROWTH

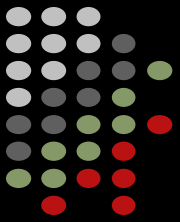
CONTINUOUS  
GROWTH

2-D Nucleation

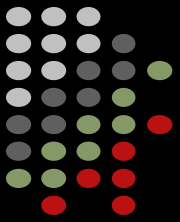
Screw Dislocation



- Crystal growth is **Volume Diffusion Controlled** when the diffusion of molecules from the bulk to the crystal surface is the rate limiting step
- Crystal growth is considered **Surface Integration Controlled** if the incorporation of a growth unit into lattice is the slowest process
- Roughness of crystal surface determines whether growth occurs by the continuous ( relatively rough surfaces ) or the layer ( relatively smooth surfaces ) mechanism.

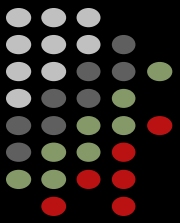


- ⊕ Crystal growth by layer growth mechanism describes the formation of steps ( layers ) by two different mechanisms...
  - ⊕ **2 – D Nucleation, when nuclei at crystal surfaces act as sources of steps that allow for the further incorporation of growth units**
  - ⊕ **Screw Dislocation, accounts for growth at lower super saturations.**
  
- ⊕ When the supersaturation is below the threshold for formation of 2~ D nuclei, the presence of screw dislocations provides a source of steps for addition of growth units in infinite sequence of equidistant and parallel steps.



## EXPERIMENTAL STRATEGIES

- ✓ The growth rate is expressed as.....
  - Overall linear growth rate, which is the rate of change of volume equivalent diameter with time
  - Linear growth rate, which is the rate of displacement of a crystal face in a direction perpendicular to the face
  - Velocity, height and spacing of growth steps spreading across a crystal surface



# TECHNIQUES FOR MEASUREMENT OF CRYSTAL GROWTH RATES

- Crystal population by methods that measure particle size and number
- Growth rates of individual crystal faces by optical microscopy with use of flow cell system
- Development of surface topography at molecular level by atomic force microscopy





# MIER'S SUPERSATURATION THEORY



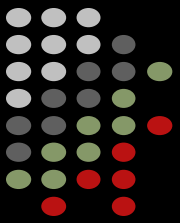
- A solution must be saturated before any solid matter can crystallize out. If the temperature of a saturated solution is allowed or solvent is allowed to evaporate from such a solution, the excess of solid material separates out.

On lowering the temperature of saturated solution very carefully, it is often possible to cool it considerably without the separation of crystals, such a condition is said to be as SUPERSATURATED.

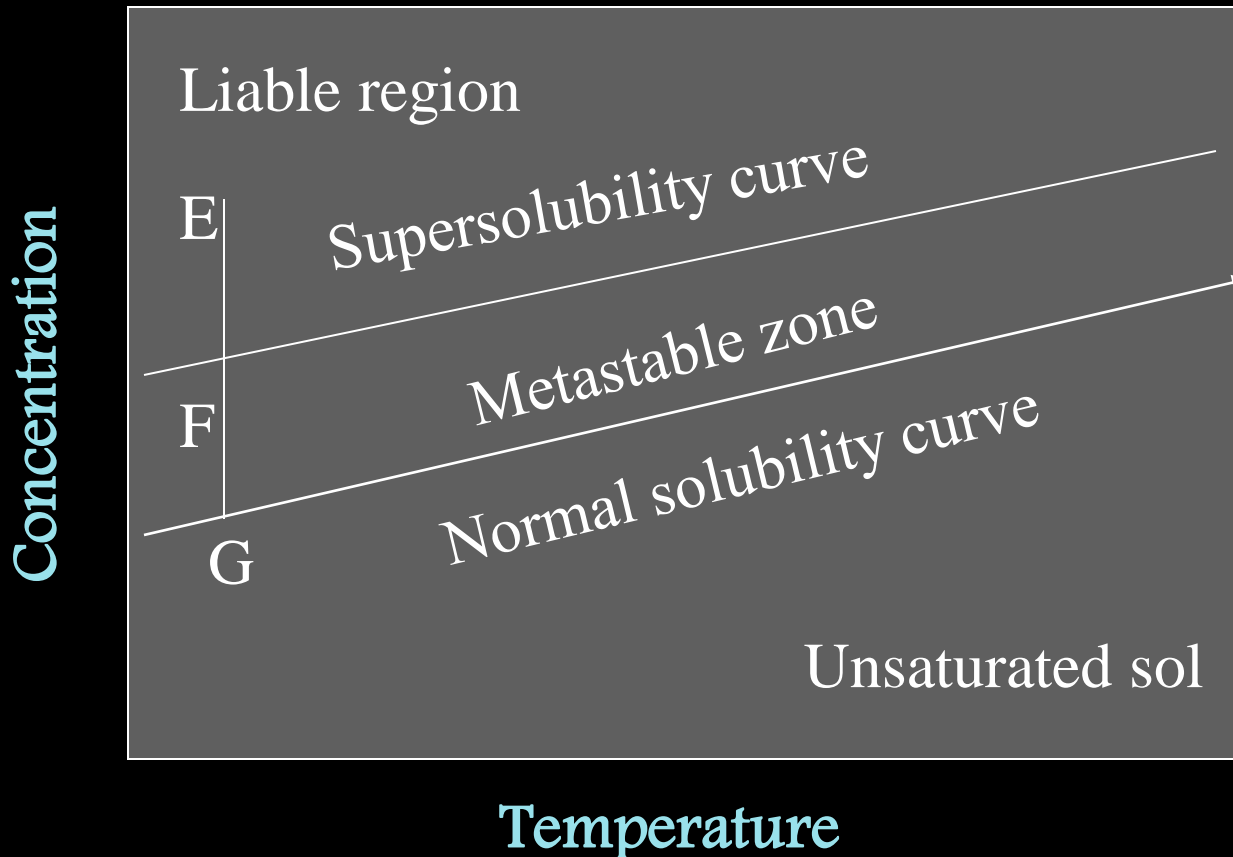
- The formation of crystals from solution involves
  - Creation of crystalline nuclei
  - Growth of these nuclei into crystals



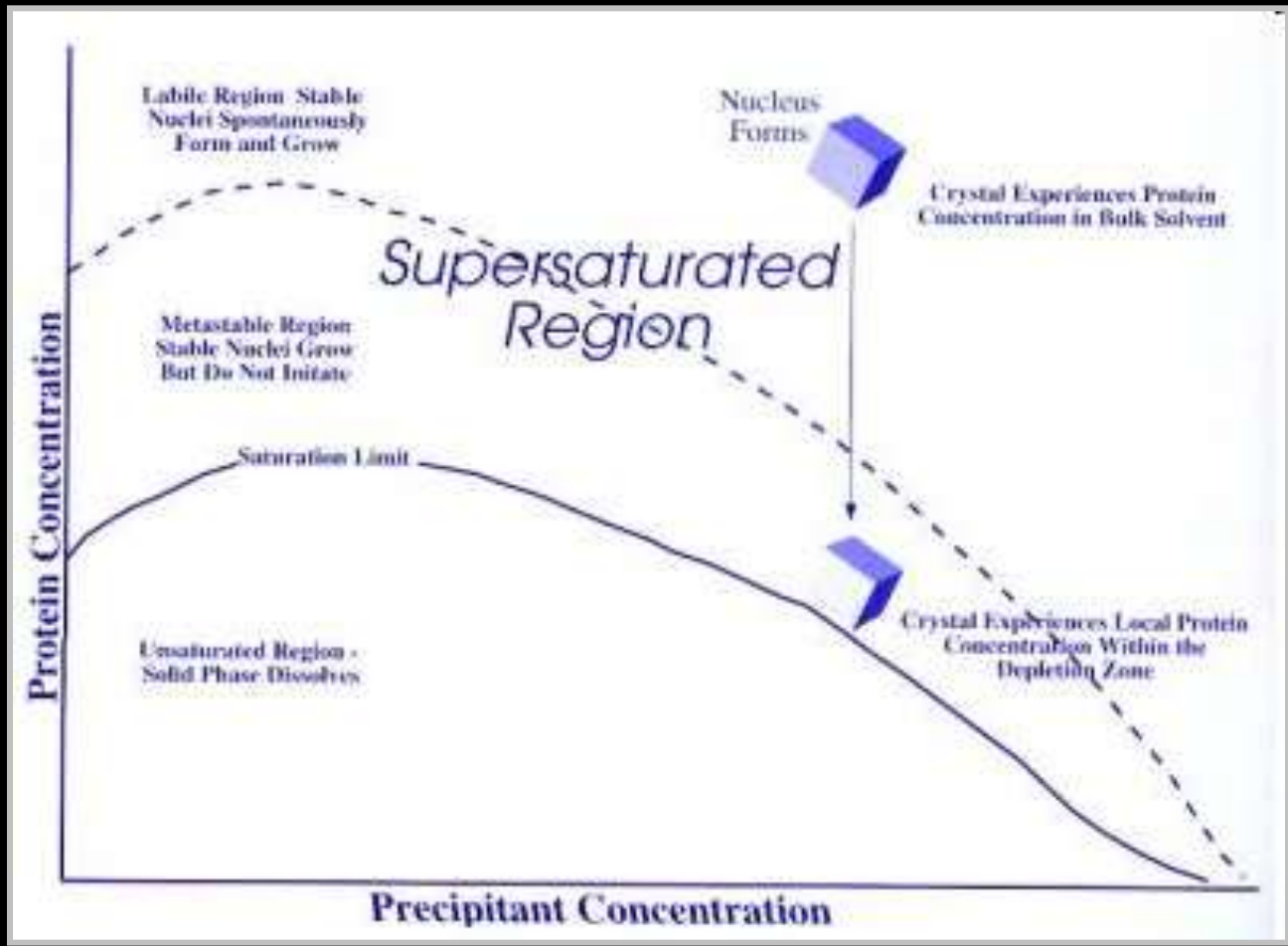
- Nuclei may arise spontaneously. Although it is rare by the introduction of minute crystals of the dissolved substance .....**SEEDING.**
- The driving force for the nucleation and subsequent growth of the crystals is the supersaturation of the solution
- In crystallization process the nuclei formation should be under control since the number of nuclei will control the size of the crystal



# MECHANISM OF CRYSTALLISATION



- Creation of crystalline nuclei and growth of nuclei into crystals





- Large crystals may be obtained as a result of slow cooling of solutions just above saturation point, due to reduction in number of spontaneous nuclei and will then grow to the desired size before new nuclei appear.
- Conversely, rapid cooling increases the degree of supersaturation resulting in a large number of nuclei and a crop of small crystals





- Nuclei may originate in the following ways.....
  - Spontaneously due to cooling an unseeded solution into the liable region
  - Deliberate seeding by crystals left from previous batch
  - Fortuitous seeding by crystals left from previous batch
  - Attrition of existing crystals giving rise to fragments that acts as seeds



