

SOLID STATE:

- Formed by cooling liquid
- It consist ions, atoms & molecules
- Stronger inter particle attraction than liquid.

Characteristics of solid:

- Definite shape, Stiffness and Rigidity
- Definite volume
- Definite M.P.
- Practically incompressible (Bcz molecules are close)
- Slow diffusion

Application of solids:

- Drug and excipient generally in solid form
- For prepare some dosage form like tablet, capsule, powder etc.
- Fine powder by dispersion by injection
- Easy to handle, transport and storage
- More stability
- Good mechanical strength

Classification of solid:**Based on Nature of Bond:**

1. Metallic bonding: Mg, Cu, Indium
2. Ionic Bonding: Electrostatic force of attraction, Eg; NaCl
3. Valence (atomic bonding):
 - a. Covalent Bonding: Diamond
 - b. Vander Walls forces: Graphite
4. Molecular bonding: Where weak vander walls forces, Eg: Naphthalene

Based on Structure:

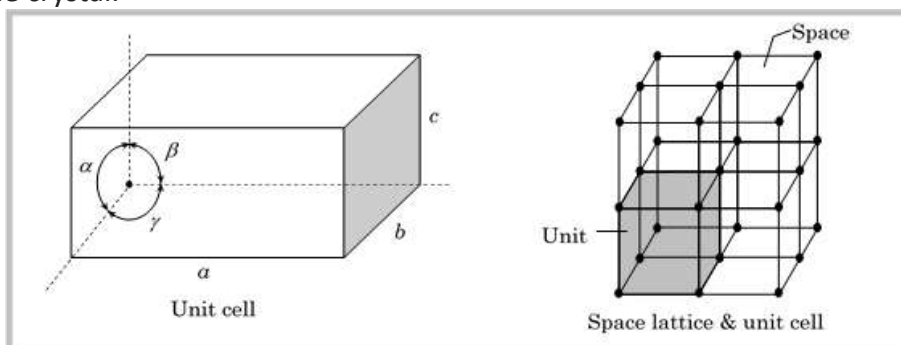
1. Crystalline: Arrangement of regularly repeated atom, E.g.: Metal, Alloy, Minerals
2. Non-Crystalline (Amorphous): E.g.: Glass, Wood, Plastics, ceramics

Based on Physical properties:

1. Anisotropic: Different physical properties in different direction
2. Isotropic: Same Physical properties in all direction

CRYSTAL:

- **Crystal/Crystallinity:** Defined as a coordination of matter resulting from an orderly cohesive three dimensional arrangement of its component particle in shape.
- This three dimensional arrangement is called as **Crystal lattice**.
- **Faces:** Crystal lattice bound by specific surface, this surface known as faces.
- **Interfacial angle:** Angle between two faces
- **Unit cell:** Smallest geometrical shape/Portion of the crystal, which is repetitive unit to build up the whole crystal.



Crystal System (Bravais Lattice system):

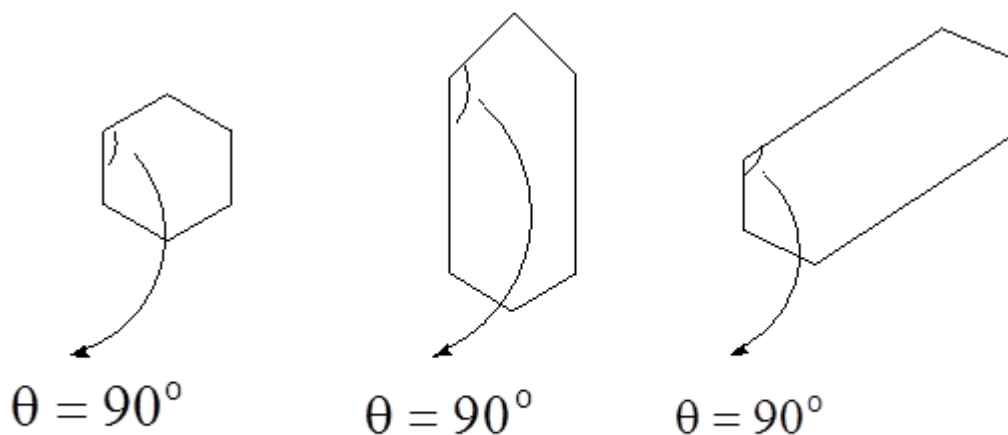
- The three dimensional system may be represented by X, Y and Z axes
- Where Length of unit size edge $\rightarrow a, b, c$
- Angle between the unit cell edge $\rightarrow \alpha, \beta, \gamma$

LAWS OF CRYSTALLOGRAPHY:

- Generally three laws are used to explain
- Law of constancy of interfacial angles, law of rational indices, law of symmetry

1. Law of constancy of interfacial angles:

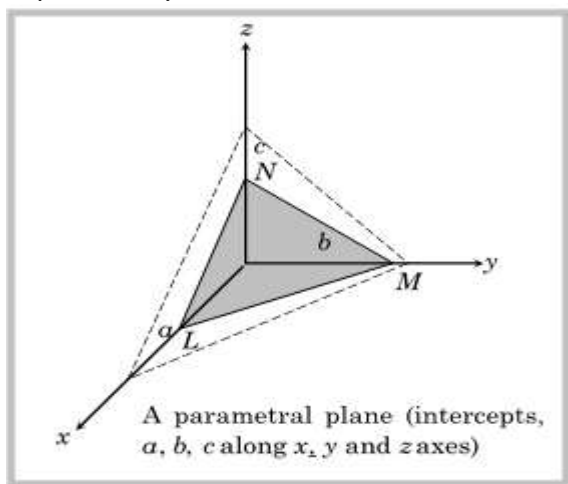
- "The angle between the corresponding faces (plane) remain constant in a crystal"
- The angle of intersection of any two corresponding faces would be the same.



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2. Laws of Rational Indices (hauy's Law):

- "The ratio between intercepts in the axes for the different faces of a crystal can always be expressed by Rational indices."



- - Here,
 - ABC = Unit cell
 - LMN = any faces of crystal
- So, intercept for unit cell as,
 - OA = a, OB = b, OC = c
 - Value of **a, b, c** are called as **weiss indices** of the plane
 - a, b, c may be
 - Whole number (1,2,3,4.....)
 - Infinity factor with whole number (∞)
 - Fraction of whole number with infinity factor and whole number (1/4, 1/3)
- Due to infinity and fraction they are unusual to use, so we convert them to miller indices.

- **Miller Indices** of a plane are obtained by taking reciprocal of Weiss coefficient & multiplying throughout by smallest number (LCM) that will express all the reciprocals.
- So, Let consider LMN faces of crystal,
 - Intercept for LMN,
 - $OL = la, OM = mb, ON = nc$
 - Where l,m,n are either whole number including fraction of whole number or infinity.
 - If, there is Weiss indices given as $a : \infty b : 2c$
- So, miller indices

○ a	b	c
○ 1	∞	2 (Weiss indices)
○ $1/1$	$1/\infty$	$\frac{1}{2}$ (Reciprocal of Weiss indices)
○ $1/1*2$	$1/\infty*2$	$\frac{1}{2}*2$ (LSM of weiss indices gives)
○ 2	0	1 (\leftarrow This is Miller indices)
- So, miller indices for above is also given as
 - 2a, 0b, 1c
- By this we easily express dimension of crystal on various axis.

3. Law of Symmetry:

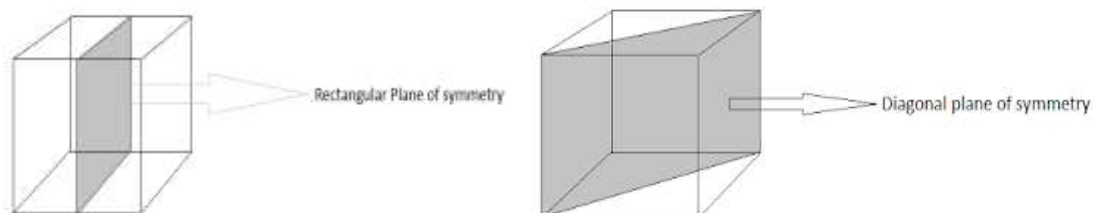
- "All crystals of the same substance possess the same elements of symmetry (similarity)"
- Symmetry associated with crystal are generally three types
 - Plane symmetry
 - Axis/Line symmetry
 - Centre of Symmetry

Plane Symmetry:

- If crystal can be divided by an imaginary plane into two equal parts, each of which is a mirror image of the other.
- E.g. Cubic crystal have generally nine planes of symmetry; 3- rectangular & 6- Diagonal

Rectangular planes of symmetry:

- These are the planes situated midway and parallel to the two opposite faces. Since a cubic crystal has six faces, i.e. three pairs of opposite faces, it has three rectangular plane of symmetry as shown in following figure,

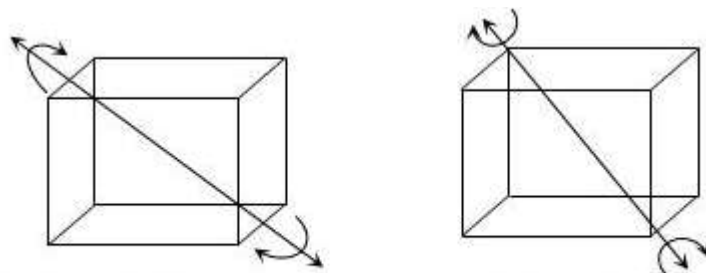


Diagonal plane of Symmetry:

- These are the plane touching the opposite edges. Since there are 12 edges or six pairs of edges. So there are 6 diagonal plane of symmetry. As they lie like the diagonal that is why these are called as diagonal plane of symmetry.

Line/Axis Symmetry:

- On rotation about an imaginary line, crystal gives the same appearance more than once during one complete rotation (360°)
- If original appearance repeated after rotation of
 - $180^\circ \rightarrow$ 2 fold axis symmetry (Diad axis symmetry)
 - $120^\circ \rightarrow$ 3 fold axis symmetry (Triad axis symmetry)
 - $90^\circ \rightarrow$ 4 fold axis symmetry (Tetraad axis symmetry)
 - $60^\circ \rightarrow$ 6 fold axis symmetry (Hexaad axis symmetry)



Axis of two fold symmetry

Axis of three fold symmetry

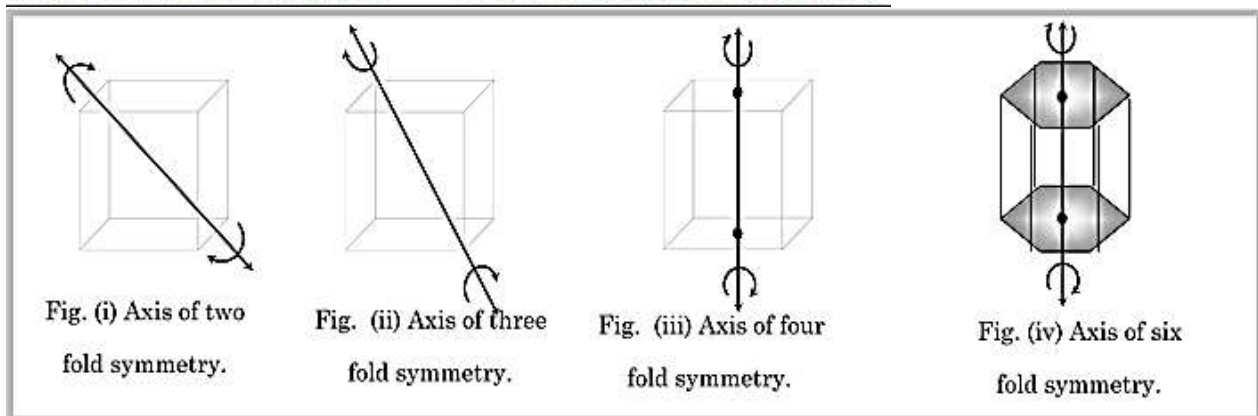


Fig. (i) Axis of two
fold symmetry.

Fig. (ii) Axis of three
fold symmetry.

Fig. (iii) Axis of four
fold symmetry.

Fig. (iv) Axis of six
fold symmetry.

Crystal Habit:

- It is the description of the outer appearance of a crystal,
- Where changes in crystal size, development of faces number of faces & kind/type of faces of substances crystal that termed as **crystal habit**.

Habit of crystal depends on:

- Condition of crystallization such as,
 - Solvent used: affect on habit by absorbing on faces surface
 - E.g. Resorcinol if, crystallise with solvent
 - **Benzene** → Needle shape crystal
 - **Butyl acetate** → Prism shape crystal
 - **Temperature:**
 - Concentration:
 - Pressure:
 - Impurities:
 - Super saturation: generally formed prism / needle shape crystal
 - Cooling rate:
 - E.g. Naphthalene form different crystal by cooling rate
 - Naphthalene → recrystallized in cold ethanol/methanol → thin plate crystal
 - Naphthalene → Slow evaporation → prism shape crystal
 - Co-solvent:
 - E.g. NaCl, If we used cosolvent as below
 - **Urea** as a cosolvent → octahedral shape crystal
 - **No cosolvent** → Cubic shape crystal

Polymorphism:**Definition:**

- **Polymorphism:**
 - Ability of compound or element to crystallize as more than one distinct crystalline species with different internal lattice.
 - Example:
 - Chloramphenicol Palmitate: Form A, B, C
 - Phenobarbitone: Form I, II, III
 - Spironolactone: Form I (needle shape, 205⁰C MP), Form II (Prism, 210⁰C MP)
- **Allotropy** : polymorphism in **elements**
 - Example: O₂ and O₃.
 - Carbon
 - Cubic shape: diamond
 - Hexagonal shape: graphite
 - Sulphur:
 - Rhombic Form & Monoclinic Form
- **Transition temperature:**
 - At specific pressure, usually 1 atm. Pressure the temperature at which two Polymorphs have identical free energy and at that temp. Both forms co-exist and have identical solubility in any solvent and identical vapor pressure.
- Polymorphs are different in their Melting Point,
 - High melting point species is most stable form of polymorphs.
- No. are given to polymer in Roman numerical in order of stability at room temperature.
 - Form – I most stable → Higher melting point → lowest energy
- Many drug substances can exist in more than one crystalline form with different space lattice arrangements. This property is known as polymorphism.
- The different crystal forms are called polymorphs.
- When polymorphism occurs, the molecules arrange themselves in two or more different ways in the crystal
 - They may be packed differently in the crystal lattice or
 - There may be differences in the orientation or conformation of the molecules at the lattice sites.
- At specific temperature and pressure one form has the strongest intermolecular force and is most thermodynamically stable. Polymorphism is not a concern if the drug is inherently well absorbed or if energy differences among them are small.
- Polymorphism is quite common for the same material to crystallize in different (more than one) arrangement of molecules in crystal.
- Polymorphism can be classified in to two types according to their stability with respect to the different range of temperature and pressure.
 - Monotropic system
 - Enantiotropic system

Monotropic System:

- For monotropic system, sometimes only one polymorph is stable, which had lower free energy content and solubility at all temperatures and pressure below melting point and
- All other polymorph being unstable, such types of polymorphs are called as monotropes.
- Eg. Glycerin stearate

Enantiotropic System:

- For enantiotropic system, if one of the polymorphs is stable at certain temperature and pressure, while the other polymorph is stable at various temperatures and pressure, then the two polymorphs are called as enantitropes.eg. Sulphur

PSEUDOPOLYMORPHISM:

- Phenomenon in which solvent molecule are incorporated in the crystal lattice of solid are known as solvates. The solvates can exist in different crystal form (compare to real crystal form) called pseudo-polymorphism.
- In case the solvent is water they are known as hydrates.
- Solubility and bioavailability:
 - Anhydrous form < hydrous form
 - Reason:
 - Hydrates are already in interaction with water and therefore have less energy for crystal break up for further interaction with water.
- Test:
 - Differentiated from true form by melting behavior in silicon oil using hot stage microscopy
 - Pseudo-polymorphs: evolve gas (solvent vapors) causes bubbling
 - True polymorphs: merely melt forming a second globular phase
- Note :- aqueous solubility of organic solvate is greater than that of non solvate
 - E.g. Chloroform solvate of Griseofulvin

Properties of polymorphs:

- Polymorph shows same property in liquid and gaseous state but differs only in solid state.
- Polymorph differs from each other with respect to physical properties like,
 - Solubility
 - Melting point
 - Density and hardness
 - Compression characteristics and etc.
- Dissolution characteristic:
 - Amorphous > meta-stable > stable

Identification of Polymorphism:

Techniques available are:

- Optical crystallography
- Hot and cold stage microscopy help to know:
 - Stability of various forms.
 - Transition temperature
 - M.P.
- X-ray diffraction
 - Use Bragg's equation: $n\lambda = 2d\sin\theta$
 - Where,
 - d = distance for different planes of crystal.
 - λ = wavelength of x-ray.
 - θ = angle of incidence.
- DSC-X ray diffraction:
 - To study transitions during cooling and heating.
- IR spectroscopy
- FTIR
- Thermal method
 - DSC (differential scanning calorimetry)
 - DTA (differential thermal analysis)
 - TGA (thermal gravimetric analysis)
 - Here heat loss or gain from physical or chemical changes occurring in sample is recorded as function of temperature as substance is heated at uniform sale.
- Dilatometry
 - Measure change in volume caused by thermal or chemical effect.
- Proton NMR

- Tetra hertz pulse spectroscopy.
- Time resolved X-ray scattering.
- LASER-RAMAN spectroscopy.

Effect of Polymorphism on Formulation:

- Bioavailability:
 - Lower is thermodynamic activity of polymorph lower will be its apparent solubility and consequently its absorption. Therefore utilization of polymorph having significantly greater thermodynamic activity (i.e. solubility) than a stable modification may provide therapeutic blood level from otherwise inactive drugs.
 - E.g.:- Novobiocin,
 - Its Sodium salt - active orally and unstable in solution.
 - Crystalline - poorly absorbed (↓BA), stable chemically.
 - E.g.:- Chloramphenicol palmitate suspension
 - Where B.A. depend on amount of form B present in suspension , since it is greater bio-available form.
- Manufacturing dosage form:
- Suspension:
 - Crystal growth: ↓Syringability this affect its B.A.
 - Caking
 - E.g. :- Cortisone acetate suspension exist in five forms
 - Form II $\xrightarrow{\text{Convert to}}$ Form V (stable form)
 - RESULT:-Caking
 - Remedy: Conversion should first be allowed and then final suspension should be prepared.
- Suppository:
 - Theobroma oil: - 4 form (MP)
 - Alpha Form (metastable) - 18⁰ C
 - Gamma Form (metastable) - 22⁰ C
 - Beta' (Beta prime) - 28⁰ C
 - Beta form(Stable) - 34.5⁰ C
 - When theobroma base is heated (melted to 50-60⁰ C nuclei of stable beta form are destroyed and mass doesn't crystallize until it is super cooled to about 15⁰ C and suppository will melt at R.T.
 - REMIDY: - Melt base not above 35-36⁰ C so that stable Beta form will not lost.

Stability characteristic:

- Polymorphs varies in their stability characteristics,
 - Stable form
 - low energy state
 - high melting point
 - low aqueous solubility
 - Meta-stable form
 - High energy state
 - Low melting point
 - High aqueous solubility
- (Note: meta-stable form cannot be called unstable if it is kept dry it will remain stable for years.)

Problem caused due to ageing of dosage form containing meta stable form:

- meta-stable form $\xrightarrow{\text{Convert to}}$ stable
- Example:
 - Cortisone acetate aqueous suspension

- Form II $\xrightarrow{\text{Convert to}}$ Form V (less soluble)
- Result: leads to cackling
- REMIDY:
 - Dehydrating the molecule environment
 - By adding viscosity builder like PVP, CMC, gelatin
- Difference in melting point between polymorphs is a measurement of the meta-stable polymorph stability.

Melting point Difference between polymorphs	Stability of polymorphs
Less than 1 ⁰ C	Significantly more stable.
Less than 25 ⁰ C	Unstable form can be obtained easily before solid-solid transition.
Between 25 ⁰ – 50 ⁰ C	Lower melting species will be difficult to crystallize and will revert rapidly.

ISOMORPHOUS:

- It is the ability of forming crystals of similar shape by different chemical substance, such substances are said to be isomorphs (same shape)
- Isomorphism due to same chemical constitution.
- E.g. $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ & $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ have same crystal shape.
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