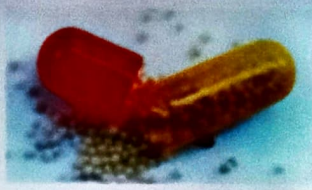
UNIT - I



PART - 1 PREFORMULATION STUDIES

Points to be covered in this topic

1. INTRODUCTION
2. GOALS & OBJECTIVES
3. STEPS OF PRODUCT DEVELOPMENT
4. PHYSIOCHEMICAL CHARACTERISTICS

❑ INTRODUCTION

- Preformulation is an **investigation of physical and chemical properties** of a drug substance **alone and when combined with excipients**, to **check its potential to be developed** as an **efficacious dosage form.**

PREFORMULATION

Study of physical properties of drugs

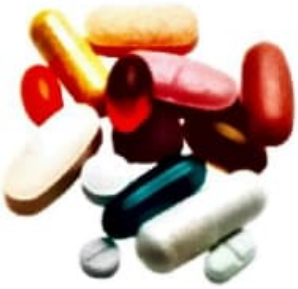
- Particle size & shape
- Density, Solubility
- Wetting property
- Dielectric constant
- Dissolution
- Formulation stability
- Bioavailability

Study of chemical properties of drugs

- Hydrolysis
- Oxidation
- Reduction
- Racemisation
- Polymerization
- Drug excipient
- Compatibility

❑ GOALS OF PREFORMULATION

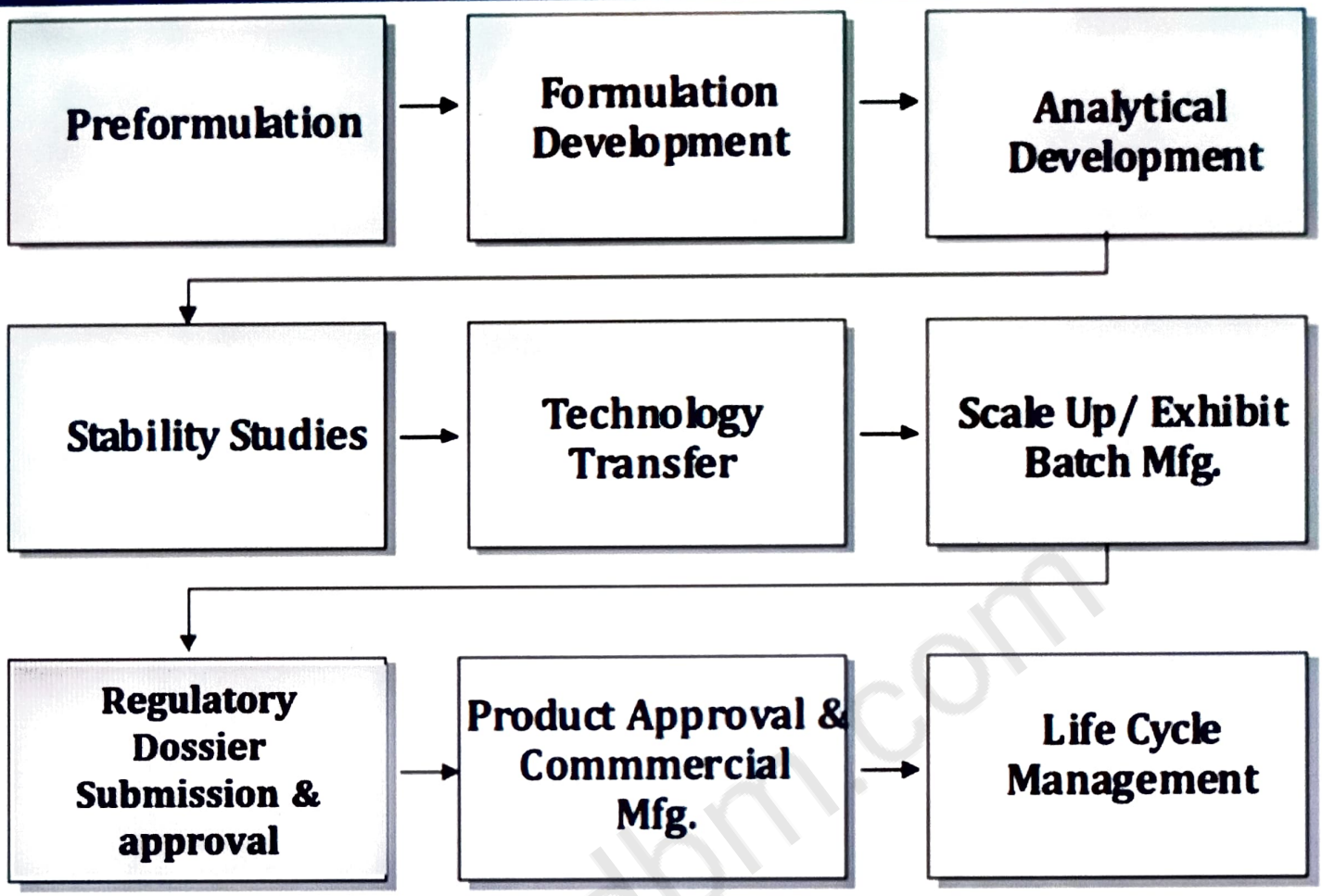
- To make elegant, safe, efficacious dosage form with good bioavailability.
- To formulate new dosage form of an already existing dosage form.
- Determination of all the properties of drug and the best suitable dosage form for the drug molecule.
- Predict stability of formulation during manufacture.
- Determine the shelf life of the marketed product.



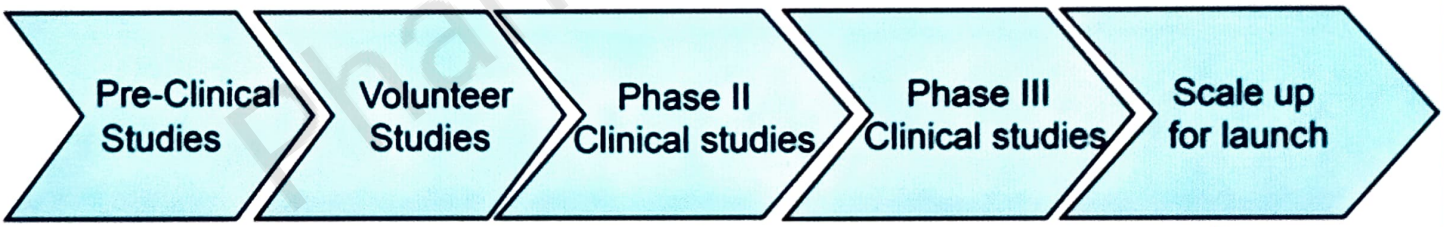
❑ OBJECTIVES OF PREFORMULATION

- To develop the most stable, safe and efficacious dosage form with maximum bioavailability.
- To select the most suitable excipient.
- To help in adjustment of pharmacokinetic properties.
- To elucidate possible chemical and/or physical reactions leading to drug degradation and give the solution to overcome this problem.
- To produce necessary & useful data for development of analytical method.
- To determine most stable polymorph and salt forms that give maximum bioavailability.
- To minimize time & money required for formulations.
- To confirm absence of barriers for development of a compound into a safe, marketable drug.

❑ STEPS OF PRODUCT DEVELOPMENT



Drug Development



Preformulation studies To determine best formulation for **animal** studies

Preformulation studies to determine best formulation for **volunteer** study

Preformulation studies to determine best **clinical trial** formulation

Preformulation studies for **final formulation and manufacture**

❑ PHYSIOCHEMICAL CHARACTERISTICS

PREFORMULATION PARAMETERS

PHYSICAL CHARACTERISTICS

- **Bulk characteristics**
- **Solubility analysis**
- **Stability analysis**

CHEMICAL CHARACTERISTICS

- Oxidation
- Photolysis
- Polymerization
- Decarboxylation
- Hydrolysis
- Racemization
- Isomerization
- Enzyme decomposition

ORGANOLEPTIC PROPERTRIES

- Colour
- Odour
- Particle size
- Particle shape
- Crystal habit
- Polymorphism
- Hygroscopy

PART - 2 PREFORMULATION STUDIES

PHYSICAL PROPERTIES

Points to be covered in this topic

1. BULK CHARACTERISTICS
2. SOLUBILITY ANALYSIS
3. STABILITY ANALYSIS

PHYSICAL CHARACTERISTICS / PROPERTIES

Bulk characteristics

- Particle size
- Surface area
- Crystallinity
- Flow properties
- Polymorphism
- Hygroscopicity
- Compressibility

Solubility analysis

- Aqueous solubility
- Intrinsic solubility
- Dissociation constant
- Partition coefficient
- Common ion effect
- Solubilization
- Dissolution

Stability analysis

- Solid state stability
- Solution state stability

❑ BULK CHARACTERISTICS

1. Particle size

- Particle size is characterized using these terms :-

  Very coarse, Coarse, Moderately coarse, Fine ,Very fine.

- Particle size can influence variety of important factors :-

  Dissolution rate, Suspendability, Uniform distribution, Penetrability, Lack of grittiness

✓ Determination of Particle size

S. N	METHOD	SIZE RANGE	INSTRUMENT	FEATURES
1.	Microscopy	0.2-100 µm	Optical microscope	Feret, Martin and projected diameter is measured
		0.001 - 0.1 µm	Transmission Electron Microscope	
		0.01-1000 µm	Scanning Electron Microscope	✓It can detect presence of agglomerates & particles of more than one component ✓Diameter is 2 dimension :- Length and breadth, thickness is not estimated
		01-1000 µm	Light microscope	
2.	Sieving	50-1500 µm	Mechanical shaker	Standard sieves are used calibrated by National Bureau of Standards.
3.	Sedimentation	1-200 µm	Anderson pipette	Stoke's diameter is measured
4.	Conductivity	0.5-500 µm	Coulter counter	Equivalent volume diameter is measured

2. Surface area

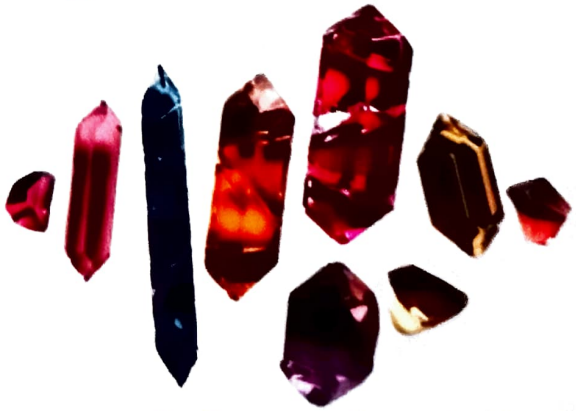
- The specific **surface area increases** with **decreasing particle size.**
- The specific **surface area is also increased** if the **particle has pores.**
- The **specific surface area is important** for the **industrial process and for chemical reactions.**

✓ Determination of surface area

S. N	CHARACTERISTICS	ADSORPTION METHOD	AIR PERMEABILITY METHOD
1.	Surface area measurement	Volume of nitrogen absorbed to form a monolayer	Rate at which gas or liquid permeates a bed of powder
2.	Equation used	BET equation	Poiseulli's equation, Kozency-Carman eq.
3.	Instrument	Quantasorb	Fisher subsieve sizer
4.	Detector	Thermal conductivity	Water monometer

3. Crystallinity

- It refers to degree of structural order in a solid.
- The **degree of crystallinity has a big influence** on **hardness, transparency, density and diffusion.**



✓ **Considerable factors**

- **Flow properties**
- **Compaction**
- **Stability**

✓ **Crystal habit** : **It is the characteristic external shape** of an individual crystal or **crystal group.** A single crystal's **habit is a description of its** general shape and its crystallographic forms, **plus how well developed each form.**

✓ Difference between crystalline and amorphous form

CRYSTALLINE	AMORPHOUS
Orderly molecular arrangement of an identifiable shape	Less order with no identifiable shape
Long range order	Short-range order
Arranged in a fix molecular order	Randomly arranged molecules
Low aqueous solubility	High aqueous solubility
Low chemical reactivity	High chemical reactivity
Low water sorption	High water sorption
Low molecular mobility	High molecular mobility
Poor compressibility	Good compressibility

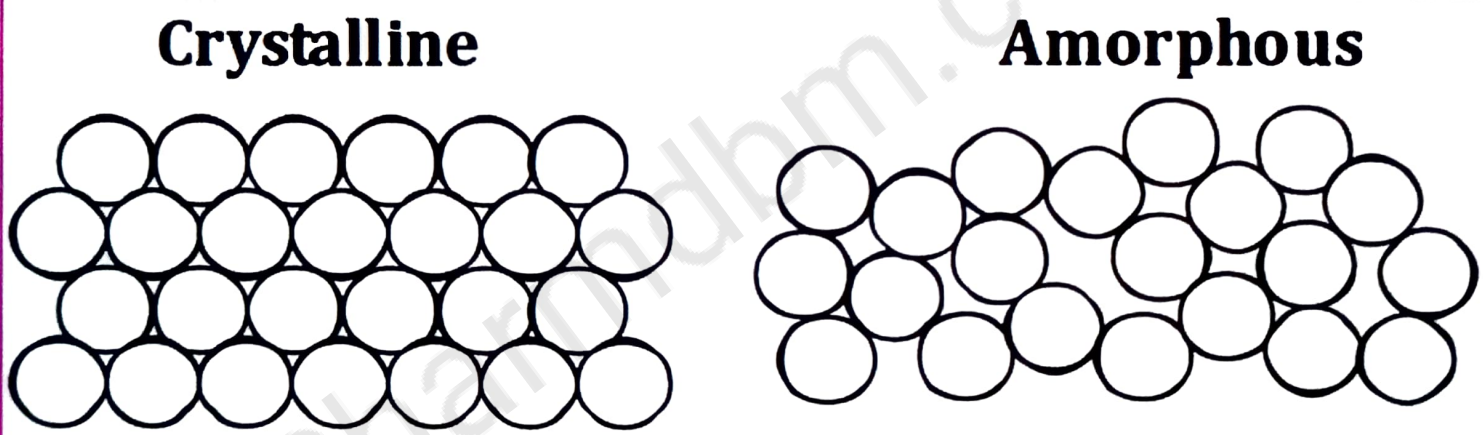


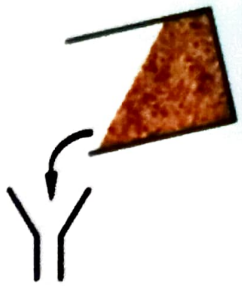
Fig. Structure of Crystalline and Amorphous form

4. Flow properties

- Powder flow, also known as flowability, is defined as **the relative movement of a bulk of particles among neighboring particles or along the container wall surface.**
- **Flowability** – Capacity of any **substance to flow is called as flowability.**
- **Bulk density-** It is defined as the **mass of many particles** of the material **divided by the total volume they occupy.**
- **Flow property of powders** can be measured by – **Fixed cone method.**

Formula for measurement of flow property

$$\theta = tan^{-1} + \frac{H}{R}$$



✓ Where,

θ = Angle of repose

H = Powder bed height

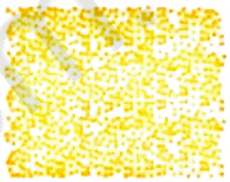
R = Radius of powder bed

Fine sand

Dry sand

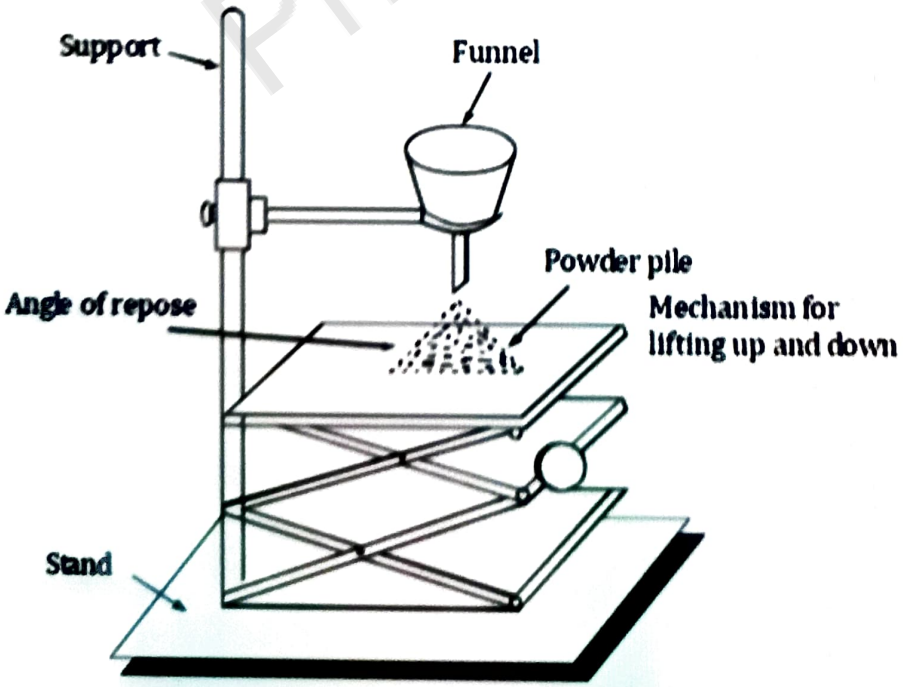
Moist sand

Coarse sand



Angular pebbles

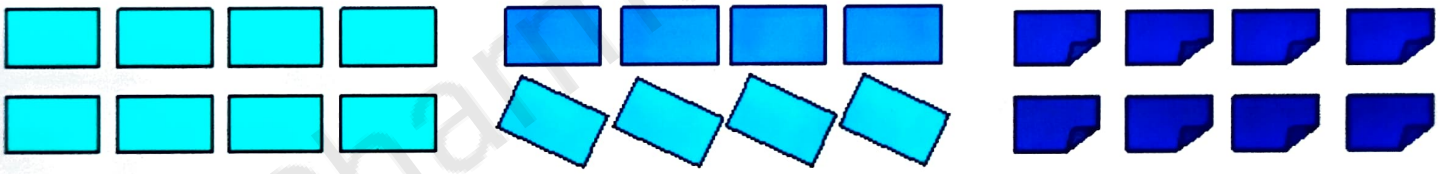
Water-saturated sand



FLOW PROPERTIES	REPOSE ANGLE (°)	HAUSNER RATIO
Excellent	25-30	01 – 1.11
Good	31-35	1.12 – 1.18
Fair	36-40	1.19 – 1.25
Passable	41-45	1.26 – 1.34
Poor	46-55	1.35 – 1.45
Very poor	56-65	1.46 – 1.59
Very very poor	> 66	1.6

5. Polymorphism

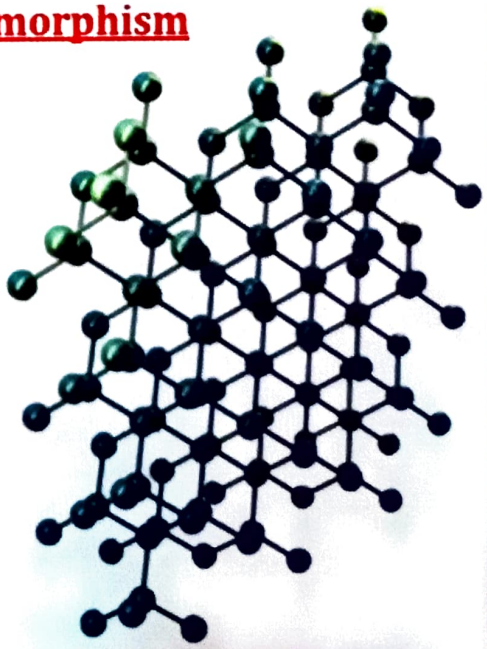
- Polymorphism is the **ability of a substance to crystallize** into **different crystalline forms.**
- These **crystalline forms are called polymorphs** or crystalline modifications.
- **Polymorphs have the same liquid or gaseous** state but they **behave differently in the solid state.**



Polymorphs - 1 | **Polymorphs - 1** | **Polymorphs - 1**

✓ **Important techniques used to determine polymorphism**

- DSC (Differential Scanning Calorimetry)
- XRD (X-Ray Diffraction)
- Polarizing microscope
- Dissolution study
- Infrared analysis
- DTA (Differential Thermal Analysis)
- Hot stage microscopy
- Polarized light microscopy



6. Hygroscopicity

- Hygroscopicity is the **tendency of a solid substance to absorb moisture from the surrounding atmosphere,** which is occurs usually at **normal room temperature** and these type of substances are **known as hygroscopic substances.**
- **Hygroscopy is the phenomenon** of **attracting and holding water molecules** via either absorption or adsorption from the **surrounding environment,** which is usually **at normal or room temperature.**
  - **E.G. Sodium hydroxide, Glycerin, Honey, Methanol, Sulfuric acid.**

✓ Methods used for determination of hygroscopicity

- **TGA (Thermo Gravimetric Analysis)**
- **Karl Fischer Titration- composition**
- **Gas chromatography**
- **Gravimetry**

7. Compressibility

- Compressibility is a **measure of the relative volume** change of powders, that is, its **ability to decrease in volume or deform under pressure.**
- This property is **useful in selecting appropriate** formulation ingredients.
- It is the ability of something to be **reduced in volume or size under pressure** and is **determined by carr's index.**

✓ Carr's index is calculated by

$$C = \frac{\rho_T - \rho_B}{\rho_T}$$

Where,

C = Carr's index

ρ_T = Tapped density

ρ_B = Bulk density

COMPRESSIBILITY	INDEX FLOW PROPERTY
15%	Excellent
18%	Good
25%	Poor
100%	Very Poor

❑ SOLUBILITY ANALYSIS

1. Aqueous solubility

Aqueous solubility is a key physicochemical attribute required for the **characterization of an active pharmaceutical ingredient (API)** during **drug discovery.**

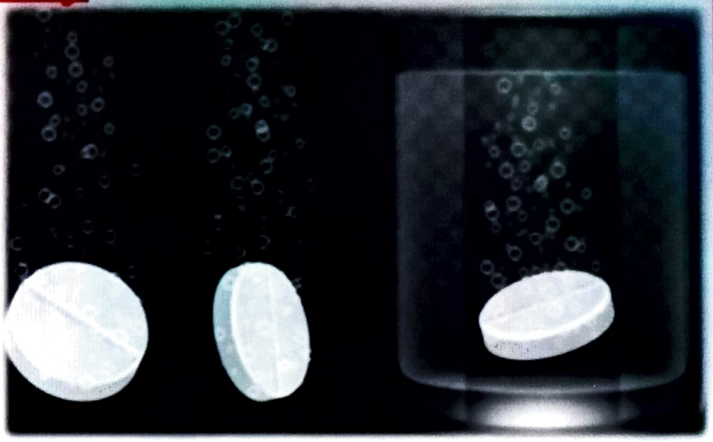
- **Ideally be measured at 2 temperatures 4°C and 37°C**
- **4°C - To ensure physical stability**
- **37°C - To support biopharmaceutical evaluation.**
- **If solubility is less than 1mg/ml, the absorption will poor.**

✓ Solubility based classification of drugs :

S. NO.	DESCRIPTIVE PHASE	APPROXIMATE QUANTITIES OF SOLVENT IN PER GRAM OF SOLUTE
1.	Very Soluble	Less than 1 part
2.	Freely Soluble	1-10 parts
3.	Soluble	10-30 parts
4.	Sparingly Soluble	30- 100 parts
5.	Slightly Soluble	100- 1000 parts
6.	Very Slightly Soluble	1000- 10,000 parts
7.	Practically Insoluble	More than 10,000 parts

✓ Methods to determine solubility

- Equilibrium solubility method
- Turbidometric solubility method
- Ultrafiltration on LC/MS method
- Direct solubility method



2. Intrinsic solubility

Intrinsic solubility is the equilibrium solubility of free acid and free base form of an ionisable compound at a pH where it is fully un-ionised

- Measured at a pH where the substance is uncharged
- For acid, measured at a pH 2 below the acids pKa
- For base measured at a pH units above its pKa

✓ The solubility of weakly acidic and weekly basic drug as a function of pH, can be predicted with the help of following equation :-

- $S = C_o \{1 + (K_1 / [H^+])\}$ ---------- for weak acids
- $S = C_o \{1 + ([H^+] / K_2)\}$ ---------- for weak bases

3. Dissociation constant

The **pKa value is the method used to indicate** the **strength of an acid.** It is the **negative log of the acid dissociation constant** or Ka value. **Lower the pKa, stronger the acid.**

✓ **Significance**

- Tells the ionized and unionized form of drug.
- When pH = pKa, that means 50% of drug is ionized form and 50% of drug is in ionized form.

✓ **For Acidic drug**

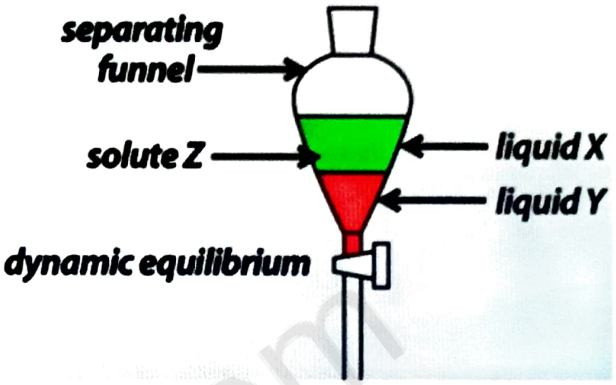
$$pH = pKa + \log \frac{[Ionized]}{[Unionized]}$$

✓ **For Basic drug**

$$pH = pKa + \log \frac{[Unionized]}{[Ionized]}$$

4. Partition coefficient

- **The partition coefficient (P)** is defined as the **ratio of the equilibrium concentrations** of a dissolved substance in a **two-phase** system consisting of **two largely immiscible solvents.**
- Ratio of unionized drug distributed between organic (n-octanol) and aqueous (water).
- **It has no unit**
- **High log Po/w → Hydrophobic drug.**
- **Low log Po/w → Hydrophilic drug.**



✓ **Formula for determining (P)**

$$\text{Partition coefficient (p)} = \frac{\text{Conc. of drug in organic phase}}{\text{Conc. of drug in aqueous phase}}$$

✓ **Methods to determine (P)-**

- **Shake flask methods**
- **Chromatographic method (TLC, HPLC)**
- **Counter current and filter probe method**

5. Common ion effect

- The **common-ion effect refers** to the decrease in solubility of an ionic precipitate by the addition to the **solution of a soluble compound** with an ion in **common with the precipitate**.
- This behavior is a consequence of Le Chatelier's principle for the equilibrium reaction of the ionic **association/dissociation**.

✓ **Salting out -**

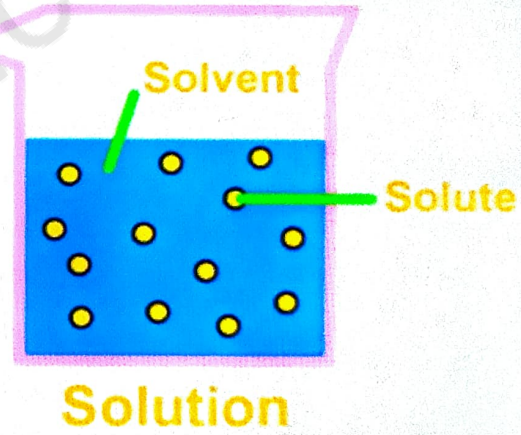
- Removal of water **molecules as solvent due to completing** hydration of other ions.
- **E.G :- Chlortetracycline, Papaverine, Bromhexine, Triamterene**

✓ **Salting in -**

- Reverse of salting out. **Arises with larger anions.**
- These hydrotropes **increase the solubility** of **poorly water soluble compounds.**
- The process by which a **solid solute enters into a solution** i.e. mass **transfer from solid surface to liquid phase.**
- **E.G :- Benzoate, Salicylate - which can open the water structure**

6. Solubilization

- It is the **process incorporating the solubilizate (Compound that undergoes Solubilization)** into micelles.
- It may occur in a system consisting of a solvent, association colloid and at **least one other solubilizate.**

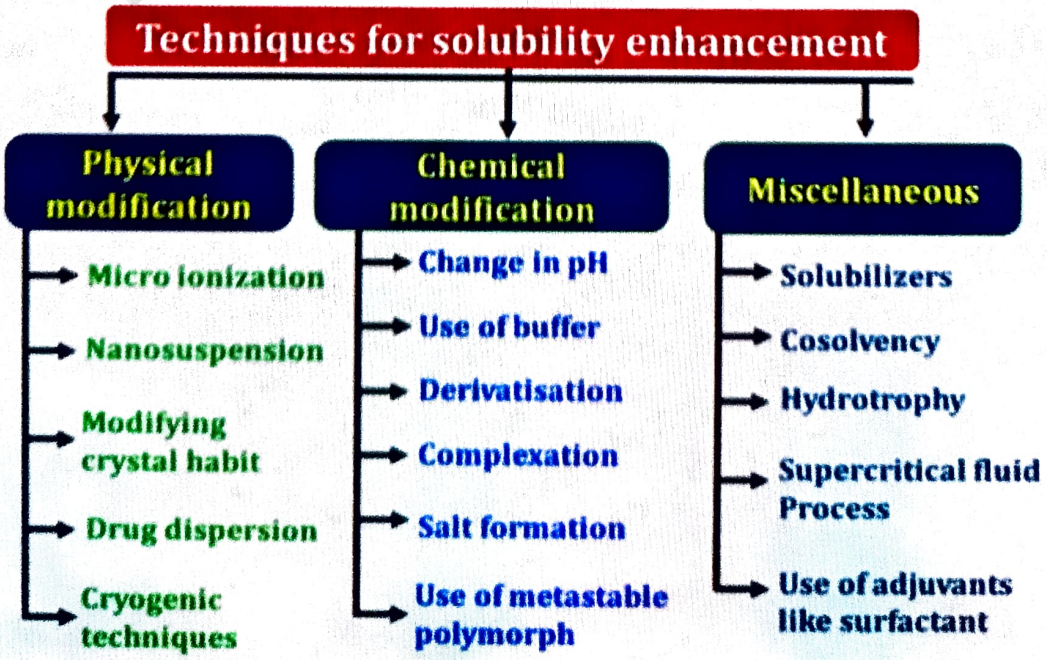


✓ **Approaches to increase solubility -**

- **Micronization**
- **Change in pH**
- **Cosolvency**

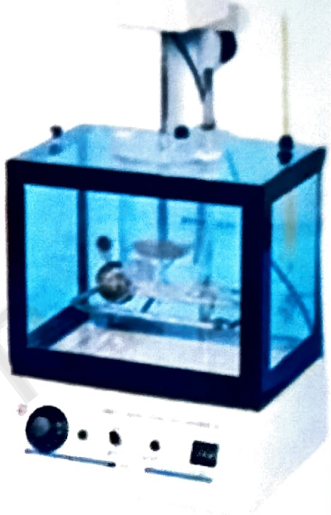
✓ **Commonly used cosolvents**

Ethanol, Sorbitol, Glycerin, Propylene glycol, Dimethyl acetamide, DMSO



7. Dissolution

- Dissolution is the process **where a solute in gaseous, liquid,** or **solid phase dissolves** in **a solvent to form a solution.**
- **Solubility is the maximum concentration** of a solute that can [illegible]lve in a **solvent at a given temperature.**

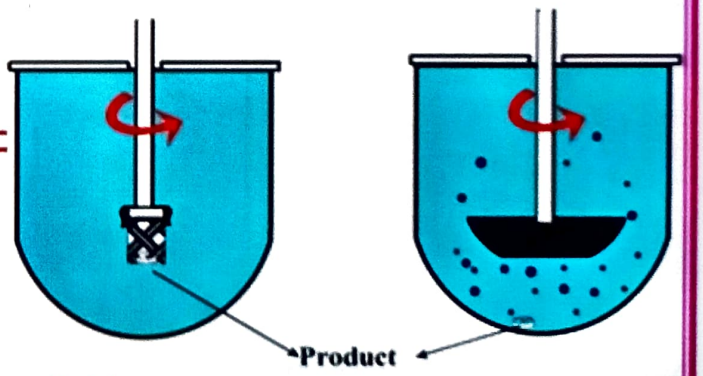


❖ Dissolution can affect :-

- **Onset of action**
- **Intensity of action**
- **Duration of response**
- **Control the overall bioavailability of drug form**

❖ Types of dissolution :-

- **Intrinsic dissolution** :- The **rate of dissolution** of a pure pharmaceutical active ingredient **when condition speed, pH, ionic strength** kept constant **is known as intrinsic dissolution.**
- **Particulate dissolution** :- This methods determines the dissolution of **solids at different surface area.**

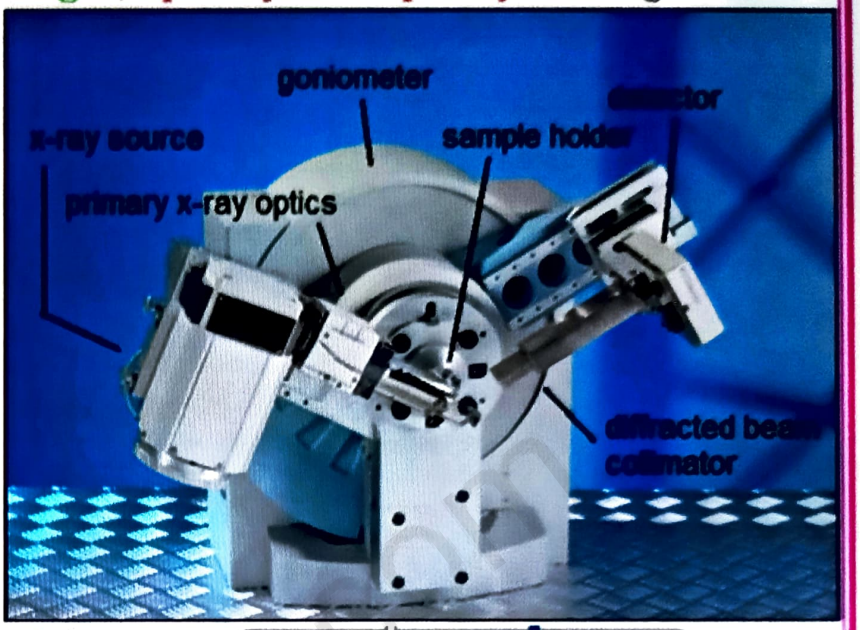


❖ Factors affecting dissolution :-

- **Factors related to Physicochemical Properties of Drug**
- **Factors related to Drug Product Formulation**
- **Processing Factor**
- **Factors Relating Dissolution Apparatus**
- **Factors Relating Dissolution Test Parameters Dissolution**

❑ STABILITY ANALYSIS

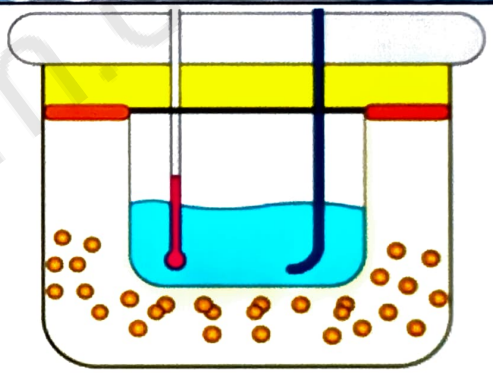
Stability of a drug is defined as the **extent to which a product remains** within **specified limits to identify strength, quality and purity** throughout the **period of storage and use.**



1. Solid state stability

✓ Techniques used :-

- Solid state NMR
- Powdered XRD
- Raman spectroscopy
- Dynamic vapor sorption.
- Differential Scanning Calorimetry
- Thermo gravimetric analysis
- Fourier Transform IR Spectroscopy

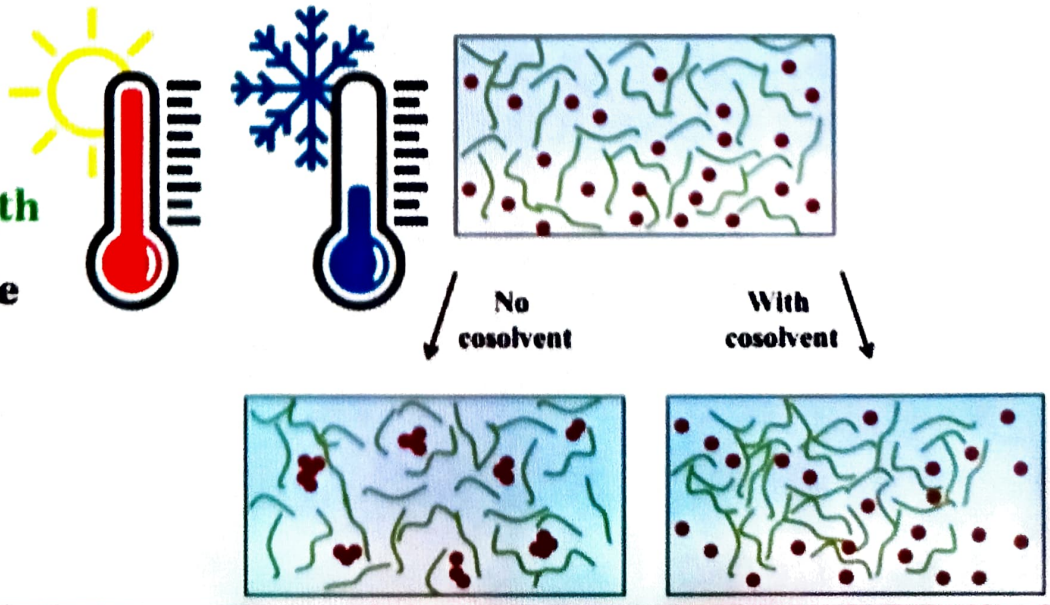


2. Solution state stability

Solution state stability is a **critical part of the drug development process** along the **path to producing robust clinical supplies.**

✓ Solution state stability involves study of :-

- pH
- Cosolvent
- Ionic strength
- Temperature
- Oxygen

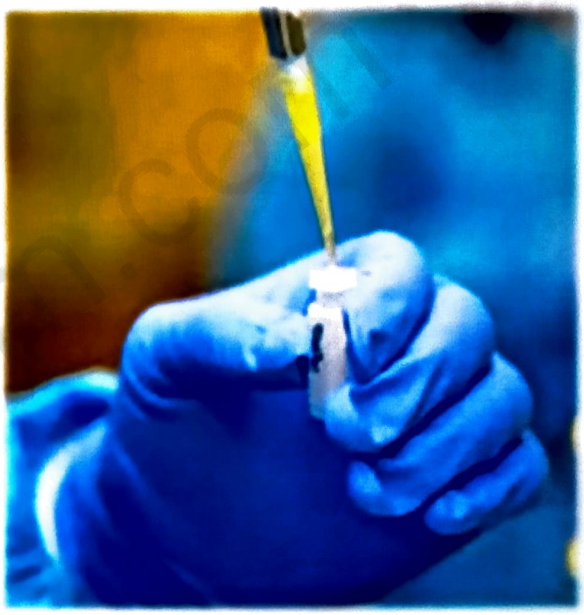


UNIT - I PREFORMULATION STUDIES

PART – 3 CHEMICAL PROPERTIES

Points to be covered in this topic

1. OXIDATION
2. HYDROLYSIS
3. REDUCTION
4. ISOMERIZATION
5. RACEMIZATION
6. POLYMERIZATION
7. BCS CLASSIFICATION
8. PHOTOLYSIS
9. DECARBOXYLATION
10. APPLICATION OF PREFORMULATION



❑ OXIDATION

- **Oxidation is the loss of electrons** or an **increase in the oxidation state** of a **chemical or atoms within it.**
- Oxidation occurs when the **oxidation state of a molecule, atom or ion is increased.**

✓ Antioxidants

- **Oil soluble** - Free radical acceptor and inhibit free radical chain process.

  E.G. Hydroquinone, Propyl gallate, BHA, BHT Lecithin, Tocopherol.
- **Water soluble** - Oxidized itself and prevent oxidation of drug.

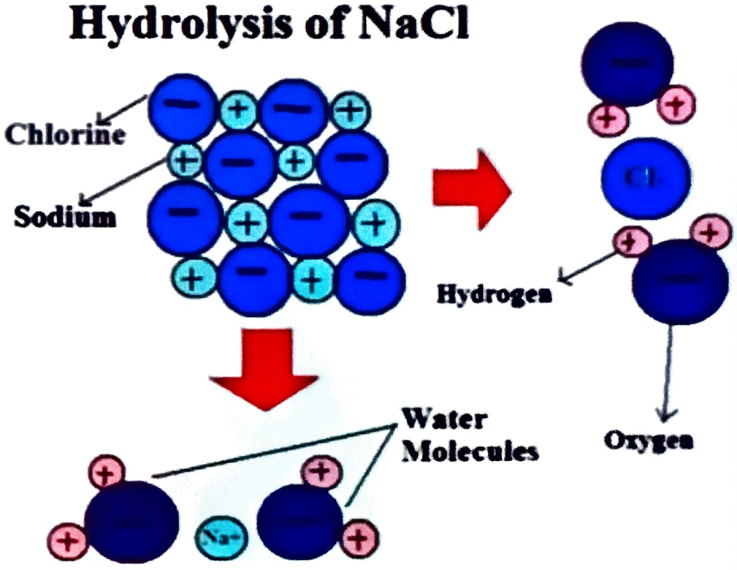
  E.G. Sodium metabisulphate, sodium bisulphite, Acetyl cysteine, Ascorbic acid, Sodium thiosulfate, sulfur dioxide, Thioglycolic acid, Thioglycerol.

❑ HYDROLYSIS

- Hydrolysis is a common form of a chemical reaction where **water is mostly used to break down** the **chemical bonds** that **exists between a particular substance.**
- Hydrolysis is derived from a Greek word **hydro meaning water** and **lysis which translates to the word break** or to unbind.

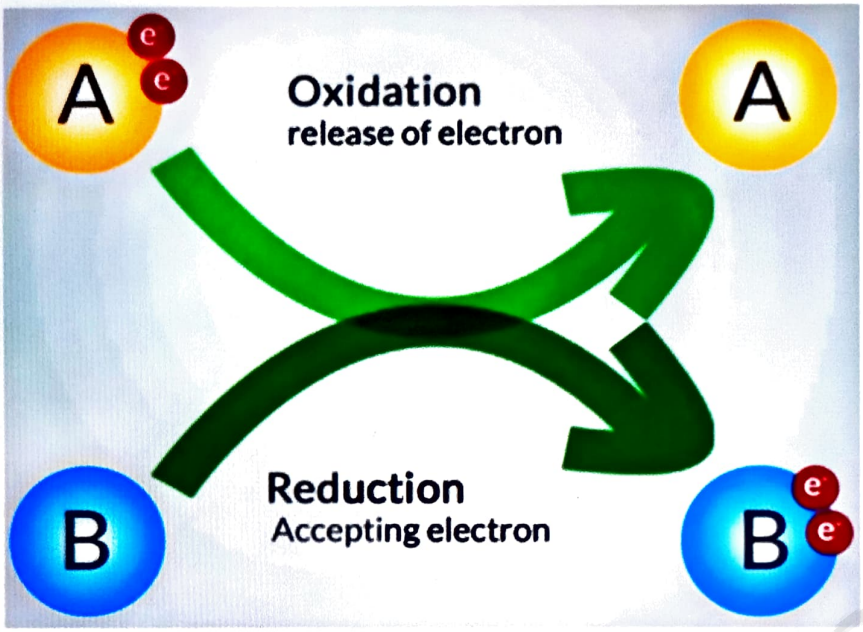
✓ Order of hydrolysis

Lactam
↓
Ester
↓
Amide
↓
Imide



❑ REDUCTION

- **Reduction is the gain of electrons** or a decrease in the oxidation **state of a chemical or atoms within it.**



O – Oxidation
I – is
L – Loss of electrons

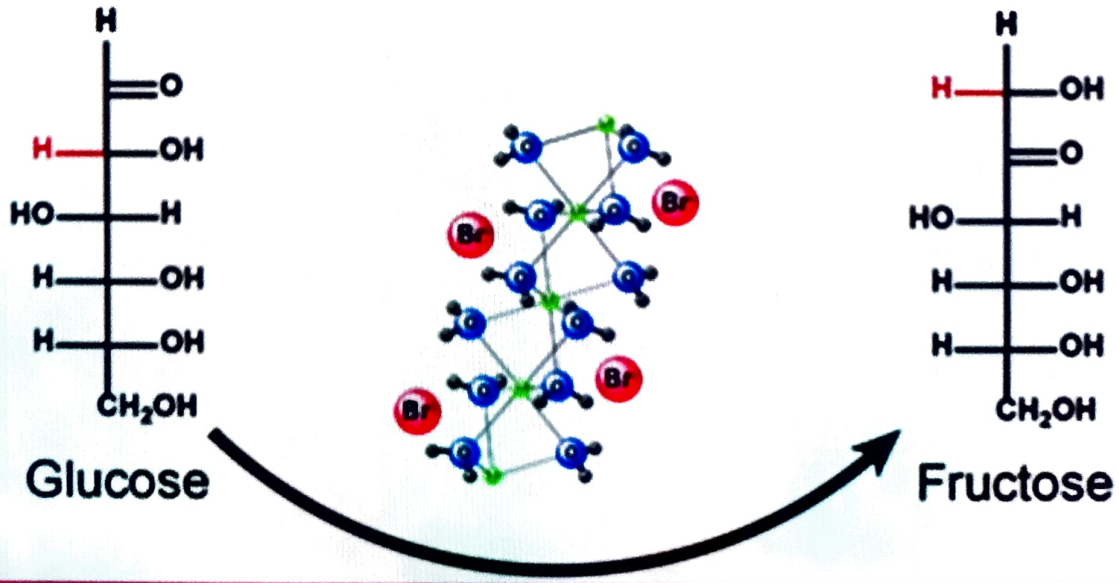
R – Reduction
I – is
G – Gain of electrons

❑ ISOMERIZATION

- Isomerization is the process in which a molecule, **ion or molecular fragment** is **transformed into an isomer with a different chemical structure. Fructose is isomerized form of Glucose.**
- **Enolization is an example of isomerization, as is tautomerization.**

✓ **Drugs showing isomerization**

Noradrenaline, Doxepin

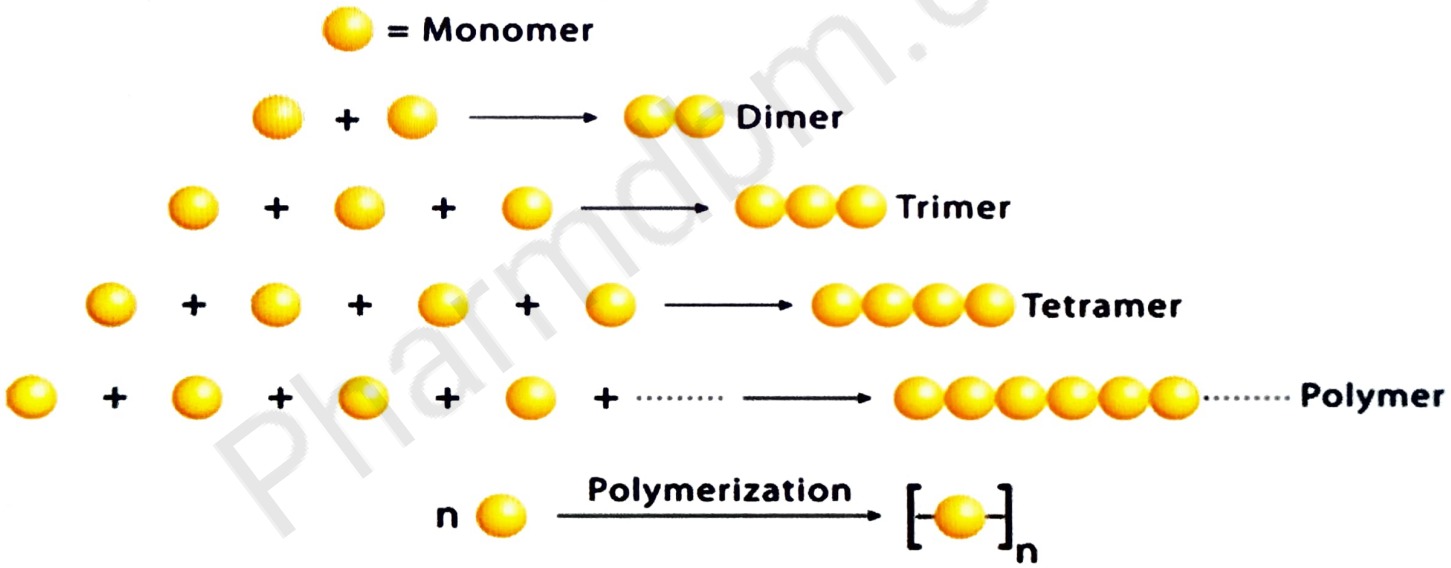


❑ RACEMIZATION

- **Racemization is a conversion**, by heat or **by chemical reaction,** of an **optically active compound** into a **racemic form.**
- Half of the **optically active substance** becomes its mirror **image referred as racemic mixtures.**

❑ POLYMERIZATION

- Any process in which relatively **small molecules, called monomers,** combine chemically to **produce a very large chainlike** or **network molecule, called a polymer.**
- The **monomer molecules may be all alike**, or they may represent two, three, or more different compounds.



❑ BCS CLASSIFICATION

The Biopharmaceutics Classification System (BCS) is a system classifying a **drug substance (API)** based on its **minimum aqueous solubility** in the pH **range of 1–7.5,** dose and human fraction absorbed or intestinal membrane permeability. The **drugs are classified in BCS** on the **basis of solubility, permeability, and dissolution.**

Biopharmaceutical Classification System

CLASS	SOLUBILITY	PERMEABILITY	ABSORPTION	EXAMPLE
I	High	High	Well absorbed	Diltiazem Propranolol Metoprolol
II	Low	High	Variable	Nifedipine Carbamazepin Naproxen
III	High	Low	Variable	Insulin Metformin Cimetidine
IV	Low	Low	Poor absorption	Taxol Chlorothiazide Furosemide

✓ Significance of Biopharmaceutical Classification System

- **Class I drugs :-** Are best suited for controlled release formulation because they have **high solubility and high absorption rate.**

- **Class II drugs :-** Are required for some dosage modifications through drug **size reduction (Micronization),** use of surfactants, development of **microemulsion technique etc.**

- **Class III drugs :-** Dosage forms are developed through **high frequency capsules,** by manipulating gastric retention time, **permeability enhancers** etc, **because they have low permeability.**

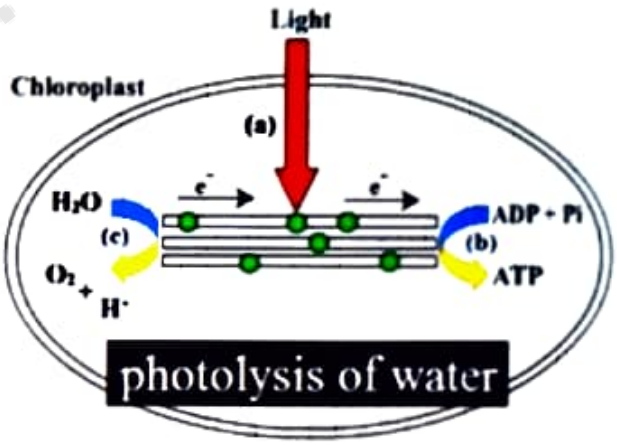
- **Class IV drugs :-** Are modified through all above mentioned techniques **because they are less soluble and less permeable.**

❑ PHOTOLYSIS

- **Photodissociation, Photolysis, or Photofragmentation** is a chemical reaction in **which molecules of a chemical compound** are **broken down by photons.**
- It is defined as the **interaction of one or more photons** with **one target molecule.**
- **Photodissociation is not limited to visible light.**

✓ **Important photostabilizers**

- **Colorants - Curcumine, Azorubine**
- **Pigments - Iron oxide, TiO_2**
- **Coating – Titanium dioxide and zinc oxide.**



❑ DECARBOXYLATION

- **Decarboxylation is a chemical reaction** that removes a **carboxyl group and releases carbon dioxide.**
- Usually, decarboxylation refers to a **reaction of carboxylic acids,** removing a **carbon atom from a carbon chain.**

✓ **Drug showing decarboxylation reaction :**

- **Naproxen**
- **Flurbiprofen**
- **Benzoxaprofen**

❑ APPLICATION OF PREFORMULATION

IN SOLID DOSAGE FORM DEVELOPMENT

- Solid dosage form acquires **most of the pharmaceutical market.**
- Most of the companies would like to introduce their new molecule in **market as tablet or capsule dosage form** for manufacturing, safety.
- The **typical parameter studies for solid dosage forms** relate to the ability of a powder mix to flow **well in manufacturing machines.**
- Preformulation **influences on type of dosage form, container closure system, selection of excipients.**
- **Solid state characterization is important step** which determines the **next step in the formulation work of studied API.**

IN LIQUID DOSAGE FORM DEVELOPMENT

- After solid dosage form **second largest market is of liquid dosage form.**
- Liquid dosage form has certain advantages like easy **administration, fast absorption** & variety of dosage form like **syrup, emulsion, suspension.**
- **Characterization of drug in solid form** for **particle size and surface area** during formulation of **liquid dosage form is also important.**

IN PARENTERAL DOSAGE FORM DEVELOPMENT

- **Parenteral word means outside of intestine.**
- **The drugs which are injected into body come under parenteral.**

✓ **Preformulation studies of parenteral dosage form include bulk characterization like**

- **Particle size, Powder flow properties**
- **Crystallinity and Polymorphism**

✓ **Solubility study** - pka determination, Partition coefficient

- Stability, Spectroscopic study
- **Microscopic, Chromatographic studies**