Pre-formulation Studies

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Course Outcome	After successful completion of course students will be able to
CO205.1	Know the various pharmaceutical dosage forms and their manufacturing techniques.
CO205.2	Know various considerations in development of pharmaceutical dosage forms.
CO205.3	Compare the properties of various excipients and selection of suitable excipient to develop stable and effective dosage form
CO205.4	Design the dosage form based on Pre-formulation parameters
CO205.5	Formulate solid, liquid and semisolid dosage forms and evaluate them for their quality

Learning objectives

- To understand the concept and objective of pre-formulation studies
- To explain various physicochemical characteristics of drug substances and their importance in formulation of dosage form
- To interpret BCS classification of drugs & its significance
- To illustrate application of pre-formulation in the development of solid, liquid oral and Parenteral dosage forms and its impact on stability of dosage forms

Pre-formulation

- It is defined as the phase of research and development in which pre-formulation studies characterize physical and chemical properties of a drug molecule in order to develop safe, effective and stable dosage form.

- In pre-formulation studies, physicochemical properties of drug molecules are characterized either alone or in combination with excipients.

Pre-formulation

- The meaning of pre-formulation refers to the steps to be undertaken before formulation.
- Pre-formulation includes determination of physical chemical properties of drug substance with the goal of developing a new drug which is safe stable and efficacious.
- Each drug has intrinsic chemical and physical properties that were considered prior to the development of pharmaceutical formulation the purpose of pre-formulation study is to generate useful information for the formulator in the development of stable and bioavailable dosage form.
- Inappropriate pre-formulation study results in poor stability of active ingredients increase the overall cost of development and increased development time.
- After compiling all data it is transferred to the development pharmacist and for the day work on formulation of dosage form.

OBJECTIVES

- To establish the Physico-chemical parameters of a new drug entity
- To determine its kinetics and stability
- To establish its compatibility with common excipients
- It provides insights into how drug products should be processed and stored to ensure their quality
- To estimate problem may arise during formulation that is stability problem poor in Vivo dissolution and poor bioavailability
- To develop optimal drug delivery system.

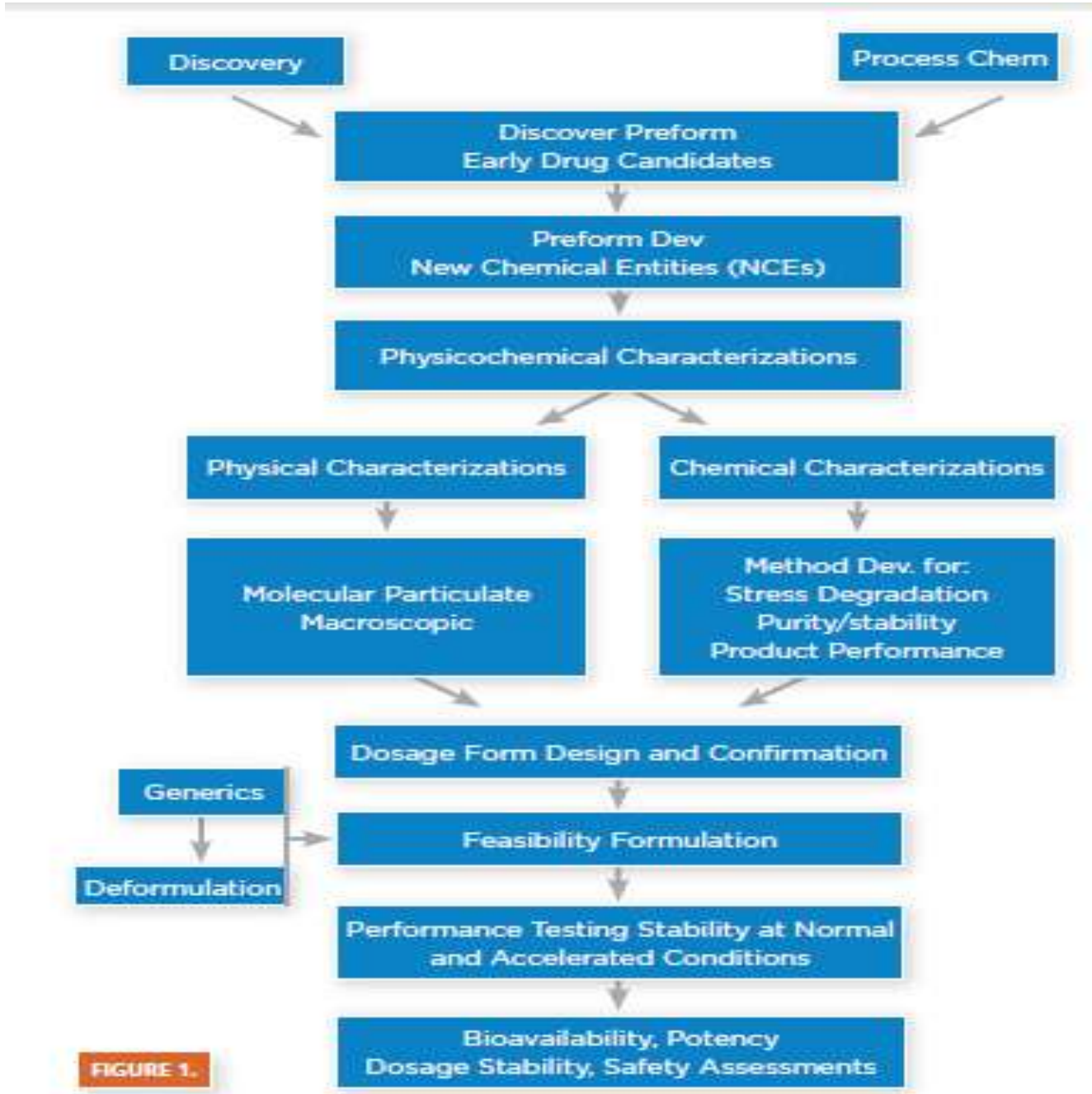

Discovery
Process Chem
Discover Preform
Early Drug Candidates
Preform Dev
New Chemical Entities (NCEs)
Physicochemical Characterizations
Physical Characterizations
Chemical Characterizations
Molecular Particulate
Macroscopic
Method Dev. for:
Stress Degradation
Purity/stability
Product Performance
Dosage Form Design and Confirmation
Generics
Deformulation
Feasibility Formulation
Performance Testing Stability at Normal
and Accelerated Conditions
Bioavailability, Potency
Dosage Stability, Safety Assessments

FIGURE 1.

GOALS

- To establish physico-chemical parameter of candidate drug molecule.
- To determine the Kinetic rate profile of drug substance.
- To establish the compatibility of candidate drug molecule with common excipients
- To choose the correct form of drug substance

Organoleptic Characters

- Colour, odour, taste of the new drug must be recorded.

Colour	Odour	Taste
❑Off-white	❑Pungent	❑Acidic
❑Cream Yellow	❑Sulphurous	❑Bitter
❑Tan	❑Fruity	❑Bland
❑Shiny	❑Aromatic	❑Intense
	❑Odourless	❑Sweet
		❑Tasteless

Physical Properties

1. Physical form (crystal & amorphous)
2. Particle size, shape,
3. Polymorphism
4. Flow properties,
5. Solubility profile (pka, pH, Partition Coefficient),

Physical Properties

1. Physical form (crystal & amorphous)

- Solid form are preferred for the formulation because they can be easily converted into tablet and capsule.
- A compound can be crystalline or amorphous depend upon internal structure.
- The habit and internal structure of the drug effects flow properties as well as chemical stability.
- In crystalline state atoms or molecules are arranged in highly ordered form and its associated with three dimensional array.
- While in amorphous forms are atoms or molecules are randomly placed as in a liquid they do not have any fixed internal structure.
- Solubility & dissolution rate are greater for amorphous form than crystalline, as amorphous form has higher thermodynamic energy.
    - Eg. Amorphous form of Novobiocin is well absorbed whereas crystalline form results in poor absorption

Physical Properties

- Crystal habit & internal structure of drug can affect bulk & physicochemical property of molecule.
- Crystal habit is description of outer appearance of crystal.
- Internal structure is molecular arrangement within the solid.
- Change with internal structure usually alters crystal habit.
- Eg. Conversion of sodium salt to its free acid form produce both change in internal structure & crystal habit
- Internal packing of molecules may have no long-range order (amorphous), different repeating packing arrangements (polymorphic crystals), solvent included (solvates and hydrates).
- These changes in internal packing of a solid will give rise to changes in properties.
- However, it is also possible to change the external shape of a crystal.

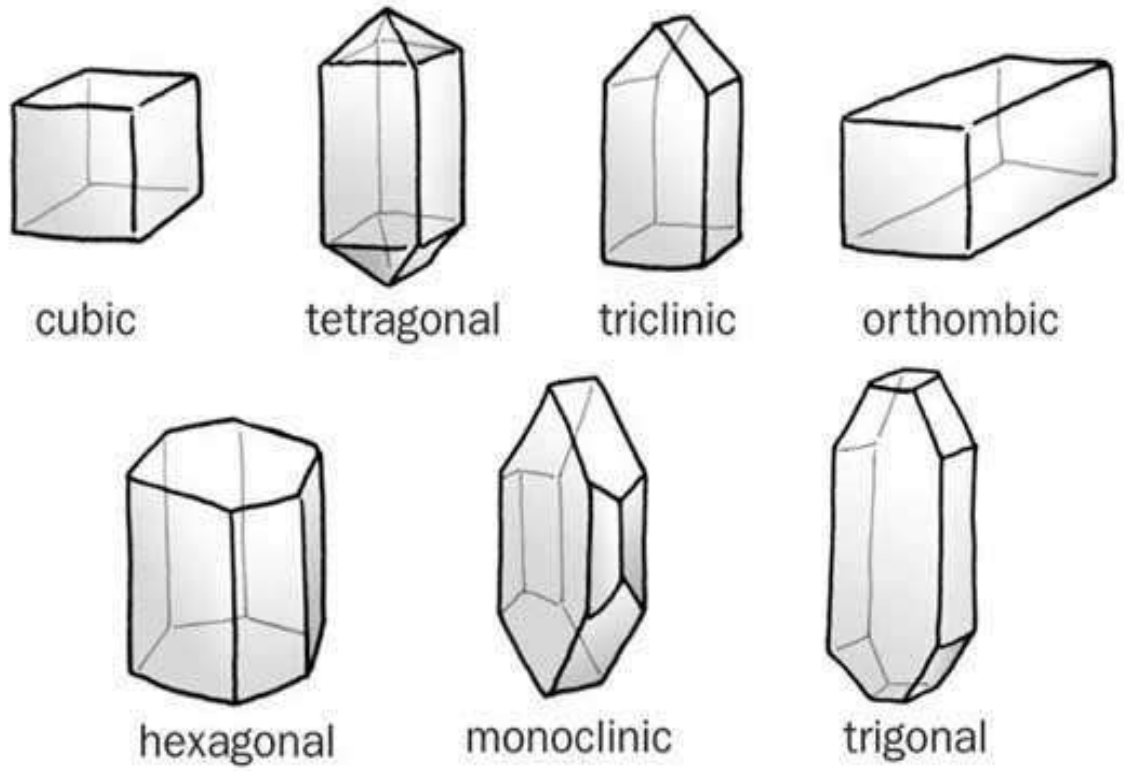
Crystalline	Amorphous
Crystalline form have fixed internal structure.	Amorphous forms do not have any fixed internal structure
Crystalline form has lesser thermodynamic energy as compared to its amorphous form.	Amorphous form has higher thermodynamics energy than its crystalline form
Crystalline forms are more stable than its amorphous forms.	Amorphous forms are less stable than its crystalline forms
Crystalline forms has lesser solubility than its amorphous form	Amorphous forms have a greater solubility than its crystalline forms
Crystalline forms has less tendancy to change its form during storage	Amorphous tends to the word to more stable form during storage

Melting point: Stable > metastable form > unstable form > amorphous form of the same drug

Dissolution rate: Stable < metastable form < unstable form < amorphous form of the same drug

Different shapes of crystals

- **Crystal habit-** The external shape is called the crystal habit and this is a consequence of the rate at which different faces grow.
- Changes in internal packing usually (but not always) give an easily distinguishable change in habit.
- However, for the same crystal packing it is possible to change the external appearance by changing the crystallization conditions.



Physical Properties

- The degree of crystallinity of drug substance has marked effect on its hardness, density, transparency and diffusion.
- This influences both the choices of delivery system and activity as determined by the rate of delivery.
- As crystalline compound contain stoichiometric or non stoichiometric crystallization solvent.
- Non stoichiometric adducts are called inclusion or clathrates.
- While stoichiometric adducts are called solvates.
- The crystalline form of penicillin G as a potassium or sodium salt is considerable more stable and result in excellent therapeutic response than amorphous forms.
- If the compound contain water as a solvent then it is known as hydrate.

Molecular Adducts

- During the process of crystallization, some compounds have a tendency to trap the solvent molecules.

Non-Stoichiometric inclusion compounds (or adducts)

- In these crystals solvent molecules are entrapped within the crystal lattice and the number of solvent molecules are not included in stoichiometric number. Depending on the shape they are of three types :-
  - **Channel** When the crystal contains continuous channels in which the solvent molecule can be included. e.g . Urea forms channel.
  - **Layers:-** Here solvent molecules are entrapped in between layers of crystals.
  - **Clathrates(Cage):-** Solvent molecules are entrapped within the cavity of the crystal from all sides.

Molecular Adducts

Stoichiometric inclusion compounds (or stoichiometric adducts)

- This molecular complex has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice and has stoichiometric number of solvent molecules complexed.
- When the incorporated solvent is water, the complex is called hydrates and when the solvent is other than water, the complex is called solvates. Depending on the ratio of water molecules within a complex the following nomenclature is followed.
- Anhydrous : 1 mole compound + 0 mole water
- Hemihydrate: 1 mole compound + ½ mole water
- Monohydrate: 1 mole compound + 1 mole water
- Dihydrate : 1 mole compound + 2 moles water

Physical Properties

- If the compound have no water molecule within its crystal structure then it is called unhydrous.
- The dissolution rates of hydrates are less than corresponding unhydrous crystalline form.
- example glutethimide theophylline, caffeine, succinyl sulphathiazol, phenobarbitol.
- The dissolution rates of organic solvates are higher than corresponding pure crystalline form.
- Example 1, 4 dioxane solvate of nifedipine shows better solubility than dihydrate form.

Properties of solvates / hydrates

- Generally, the anhydrous form of a drug has greater aqueous solubility than its hydrates. This is because the hydrates are already in equilibrium with water and therefore have less demand for water. e.g. anhydrous forms of theophyline and ampicillin have higher aqueous solubility than the hydrates.
- Non aqueous solvates have greater aqueous solubility than the non-solvates. e.g. chloroform solvates of griseofulvin are more water soluble than their nonsolvate forms.

2. Particle size

- Particle size represents the dimensions of solid powders, liquid particles, and gases bubbles.
- Particle size mainly influence dissolution rate.
- Absorption rate of poorly soluble drug can be improved by reducing the particle size and thus enhances the bioavailability of drugs.
- Particle size is also considered during development of new chemical entities (NCEs) as it affect physical properties of active pharmaceutical ingredients and excipients.
- Particle size and shape significantly affect various manufacturing step, such as mixing, granulation, drying, milling, blending, coating, encapsulation, and compression.

Particle size

- As per ICH Guidelines, particle size is critical parameter which affects safety, efficacy, and stability of solid dosage form and certain liquid dosage forms like suspension and emulsion.

- During manufacturing of solid dosage forms like tablet and capsule, particle size influences a large number of parameters in processing, including capsule filling, porosity, and flowability.

- Similarly in suspension, physical properties and particle size of dispersed particles, both affect the stability of formulation.

Solubility and particle size

The particle size and surface area of drug exposed to a medium can affect solubility.

$$\log \frac{S}{So} = \frac{2\gamma V}{2.303RTr}$$

S –solubility of the small particles

S_o- solubility of the large particles

γ- surface tension

V – molar volume

R- gas constant

T- absolute temperature

r- radius of small particles

Particle size determination (PSD) - Methods

1. Optical Microscopy (Counting)
2. Sieving Method (Separation)
3. Sedimentation Method
4. Conductivity Method

TABLE 1 List of all Equivalent Spherical Diameters With Their Respective Definition and Formulas

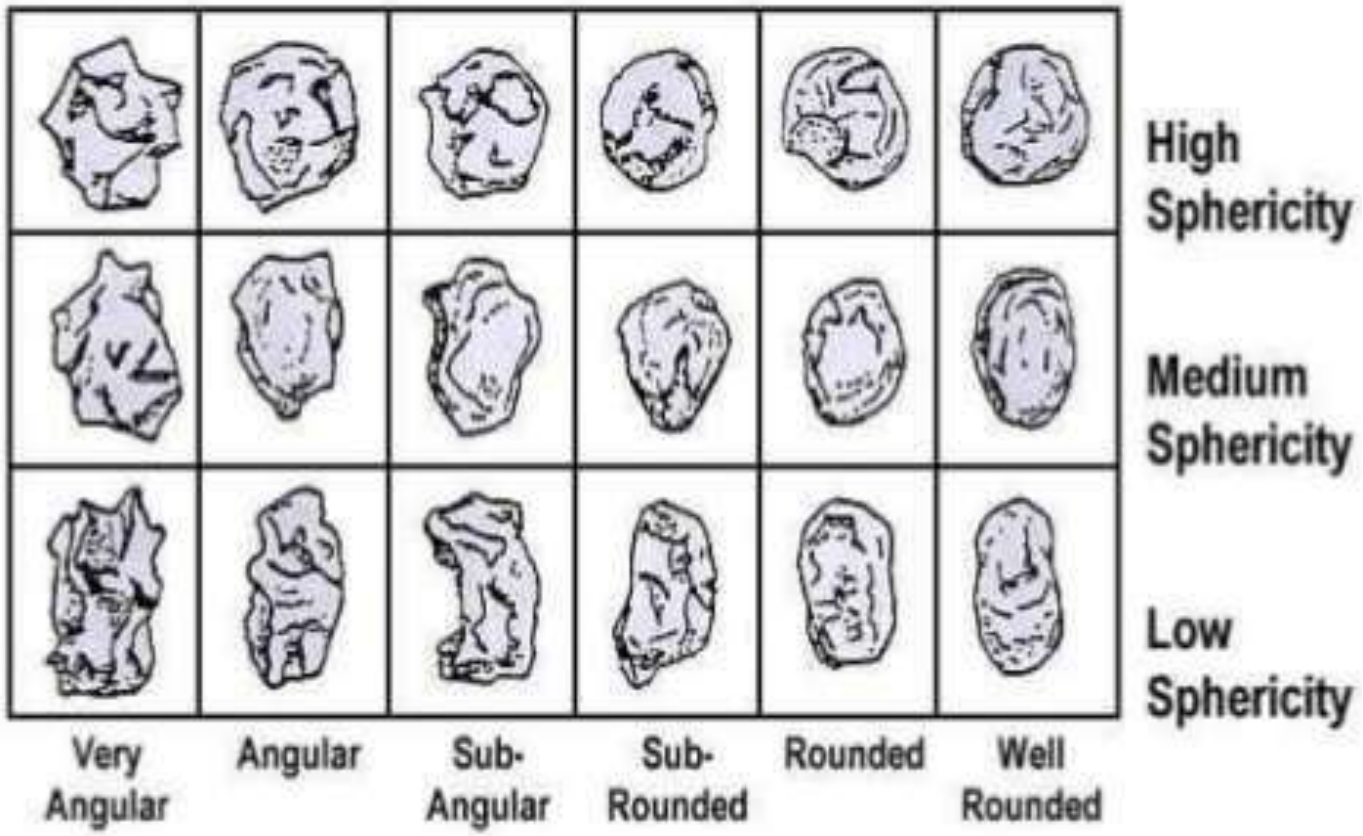
Name of Diameter	Symbol	Definition	Method	Formula
Surface diameter	Ds	Diameter of a sphere having the same surface area as that of particle	Adsorption	$D_{surface} = \left(\frac{6}{\pi} s_{particle}\right)^{1/2}$
Volume diameter	d_v	Diameter of a sphere having the same volume as that of particle	Laser diffraction	$D_{Volume} = \left(\frac{6}{\pi} v_{particle}\right)^{1/3}$
Projected area diameter	d_p	Diameter of a sphere having the same area as that of particle	Microscopy	$D_A = \left(\frac{4A}{\prod}\right)^{1/2}$
Stokes' diameter	d_{st}	Diameter of an equivalent sphere sediments at the same rate as that of particle	Sedimentation Elutriation	$D_S = \sqrt{\frac{18\eta V}{(P_S - P_L)g}}$
Sieve diameter	d_{sieve}	Diameter of a sphere that passes from same sieve aperture as that of particle	Sieving	D_{SIEVE}
Volume-surface diameter	d_{vs}	Diameter of a sphere having same volume to surface ration as that of particle	Adsorption	$D_{SV} = \frac{D_V{}^3}{D_S{}^2}$
Maximum length	d_{max}	Sphere of same maximum length as that of particle being measured	Microscopy	D_{max}
Hydrodynamic diameter	D_H	Sphere of same translational diffusion coefficient as that of particle being measured	Dynamic light scattering	$D_H = \frac{kT}{3\pi\eta D_{translation}}$
Aerodynamic diameter		Diameter of a sphere with similar density as that settles with the same speed	Cascade impactor	

Particle Shape

According to their shape particle divided are into two groups.

1) Symmetrical Particle

2) Asymmetrical Particle



Symmetrical Particle

- The particle having specific crystal shape and can be expressed in term of their diameter known as symmetrical particle.
- For example Spherical Shape
- Symmetrical particle are mainly found in spherical shape.
- So if we know the diameter of spherical particle we can easily determine its surface area and volume.

Asymmetrical particle

- The particle which have no specific crystal shape known as asymmetrical particles.
- As the asymmetry of particle increases then the surface area and volume of the particle also become complex to be determined.
- In order to determined their surface area and volume four different types of equivalent diameter are used i.e. Surface diameter, Volume diameter, Projected diameter, Stokes diameter.

Particle Shape Determination

- Particle shape also has influence on surface area, flow properties, packing and compaction of the particles.
- Spherical particles have minimum surface area and better flow properties.
- Shape can also have influence on rate of dissolution of drugs.

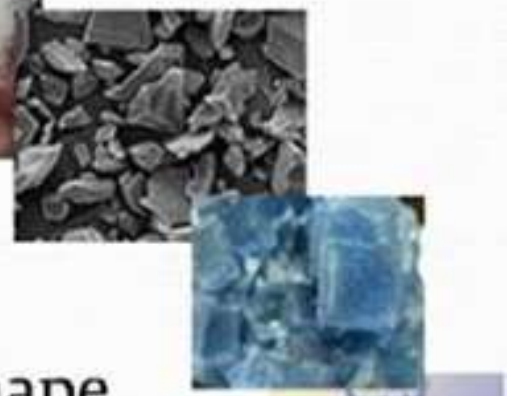
Techniques of determination are:

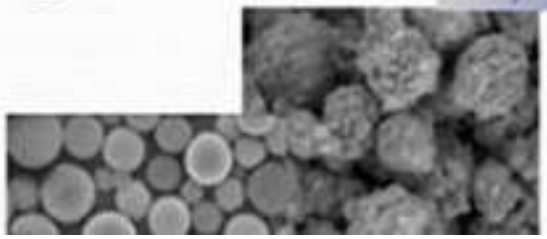
- Microscopy
- Light scattering

Different types of Particle Shape

Particle Shape

- Acicular – needle-shaped
- Angular – sharp-edged
- Crystalline – geometric shape
- Dendritic – branched crystalline shape
- Granular equidimensional irregular shape
- Spherical – global shape





Surface area= $\alpha_s d^2{}_p = \pi d_s{}^2$

Where α_s is $surface\ area\ factor$ and d_s is the equivalent surface diameter

Volume= $\alpha_v d^3{}_p = \frac{\pi d_v{}^2}{6}$

α_v is the volume factor and dv is the equivalent volume diameter.

Surface area and volume

For a sphere $\alpha_s = \pi d_s{}^2/d^2{}_p$ = 3.142 and $\alpha_v = \frac{\pi d_v{}^3}{6 d^3{}_p}$ = 0.524

The ratio $\alpha_s/\ \alpha_v$ is used to characterize particle shape.

If $\alpha_s/\ \alpha_v$=6, particle is spherical in shape.

When $\alpha_s/\ \alpha_v$ >6, particle becomes asymmetric.

3. Need to study polymorphism????

- Depending upon their relative stability, one of the several polymorphic form will be **physically more stable than others.**
- **Stable polymorph** represents the **lowest energy** state, has **highest melting point and least aqueous solubility.**
- **Metastable form** represent the **higher energy state**, have **lower melting point and high aqueous solubility .**
- Metastable form converted to the stable form due to their higher energy state.
- Metastable form shows better bioavailability and therefore **preferred in formulations.**
- Only 10% of the pharmaceuticals are present in their metastable form.

- Solubility (particularly important in suspensions and biopharmaceutically), melting point, density, crystal shape, optical and electrical properties and vapour pressure are often very different for each polymorph.
- Polymorphism is remarkably common, particularly within certain structural groups: 63% of barbiturates, 67% of steroids and 40% of sulphonamides exhibit polymorphism.
- The steroid progesterone has five polymorphs, whereas the sulphonamide sulphabenzamide has four polymorphs and three solvates.

Polymorphism

It is the ability of the compound to crystallize as more than one distinct crystalline species with different internal lattice.

Different crystalline forms are called polymorphs but their chemical composition remain same.

Polymorphs are of 2 types

- Enatiotropic
- Monotropic

The polymorph which can be changed from one form into another by varying temp or pressure is called as Enantiotropic polymorph.

- Eg. Sulphur.

One polymorph which is unstable at all temp. & pressure is called as Monotropic polymorph.

- Eg. Glyceryl stearate.

Polymorphism

Polymorphs differ from each other with respect to their physical property such as

- Solubility
- Melting point
- Density
- Hardness
- Compression characteristic

Characteristics of polymorphs

Characteristics	Stable polymorph	Metastable polymorph	Unstable polymorph
Packing of molecules in crystal lattice	Tightly packed	Less tightly packed	Loosely packed
Melting point	Highest	Moderate	Lowest
Rate of dissolution	Lowest	Moderate	Highest

Polymorphism and bioavailability

- Many drugs are hydrophobic and have very limited solubility in water. If the drug remains in several polymorphic forms then the stable one will produce the slowest rate of dissolution and it may show minimum bioavailability.
- For highly water soluble drugs polymorphism does not show any problem in dissolution rate
- Example: Chloramphenicol palmitate has three polymorphs α(stable), β(metastable) and γ (unstable). When chloramphenicol palmitate suspension is prepared from α or β polymorph it is found that bioavailabilty is higher with the metastable form.
- Example: Two polymorphs of aspirin can be obtained by recrystallization of aspirin from 95% ethanol or n-hexane. The polymorph obtained from n-hexane is found to have greater solubility in water than the polymorph obtained from ethanol.

Polymorphism and melting point of cocoa butter suppositories

- Theobroma oil or cocoa butter suppositories are meant to be melted at body temperature 37°C but should remain as solid at room temperature during storage period.
- Cocoa butter is available in three polymorphs–α (m.p. 20°C),β (m.p.36°C) and γ (m.p. 15°C). a-form is the metastable form, b-form is the stable form and g-form is the unstable form. During melting of cocoa butter by fusion method the following phenomena are found:

Procedure	Observation	Explanation
The cocoa butter is melted applying high temperature (60°C) and then quickly chilled.	The suppositories melts below 30°C i.e. at room temperature it will melt. So it will be difficult to handle at room temperature.	If melted at high temperature and cooled very quickly then the molecules form the a-crystals in more amount so the suppositories melt below 30°C. The metastable a-form will revert to stable b-form, but it will take several days for this procedure.
The cocoa butter is melted at low temperature (40 to 50°C) and then cooled slowly.	The suppositories do not melt at room temperature. The melting point will be above 36°C .	The use of low temperature and slow cooling rate allows direct formation of b-crystals having a melting point of 36°C.

- So during preparation of cocoa butter suppositories 2/3rd portion of cocoa-butter base is melted and then the container is removed from the heat source. The rest of the base is melted by stirring only without application of heat.

Polymorphism and caking of suspension

- In case of a suspension the particles will sediment below and the particles will come closer to each other.
- During a long storage life the suspension may experience several cycles of temperature change.
- During the hot period the metastable form will get dissolved in the stagnant layer and during the cool period the particles will grow and crystal bridges may form with the stable crystals.
- These crystal-bridges will give rise to irreversible caking of suspension.

Methods of characterization of polymorphs

1. Hot stage microscopy,
2. Differential Thermal Analysis,
3. Differential Scanning Calorimetry
4. Thermogravimetric Analysis (TGA)
5. X-ray powder diffraction
6. IR-Spectroscopy

4. Flow Properties of Powders

- Powders may be free-flowing or cohesive (Sticky).
- Many common manufacturing problems are attributes to powder flow when powder transfer through large equipment such as hopper.
- Uneven powder flow -excess entrapped air within powders capping or lamination.
- Uneven powder flow increase particle's friction with die wall causing lubrication problems and increase dust contamination risks during powder transfer.
- Powder storage, which for example result in caking tendencies within a vial or bag after shipping or storage time.
- Separation of small quantity of the powder from the bulk-specifically just before the creation of individual doses such as during tableting, encapsulation and vial filling which affect the weight uniformity of the dose (under or over dosage).

Parameters to evaluate the flowability of a powder.

- **Carr's compressibility index.**
- **Hausner ratio.**
- **The angle of repose(ϴ).**

Carr's compressibility index

- A volume of powder is filled into a graduated glass cylinder and repeatedly tapped for a known duration. The volume of powder after tapping is measure.

- Carr's index (%) $= 100\ (\frac{Tapped\ density - Bulk\ density}{Tapped\ density})$

- Bulk density $= \frac{\text{Weight}}{\text{Bulk volume}}$

- Tapped density = $\frac{\text{Weight}}{\text{Tapped volume}}$

Carr's compressibility index

Relationship between powder flowability and % compressibility

Flow description	% Compressibility	Examples
Excellent flow	5 – 15	Free flowing granules
Good	12 – 16	Free flowing powdered granules
Fair to Passable	18 – 21	Powdered granules
Poor	23 – 35	Very fluid powders
Very Poor	33 -38	Fluid cohesive powders
Extremely poor	> 40	Fluid cohesive powders

Hausner Ratio

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Poured or bulk density}}$$

Hausner ratio was related to inter-particlefriction:

- Value less than 1.25 indicates good flow (=20%Carr).
- The powder with low inter-particle friction, such as coarsespheres.
- Valuegreater than1.5 indicates poor flow (= 33% Carr's or CompressibilityIndex)).
- More cohesive, less free-flowing powders such as flakes.
- Between 1.25 and 1.5 (added glidant normally improves flow).
- >1.5 (added glidant doesn't improve flow).

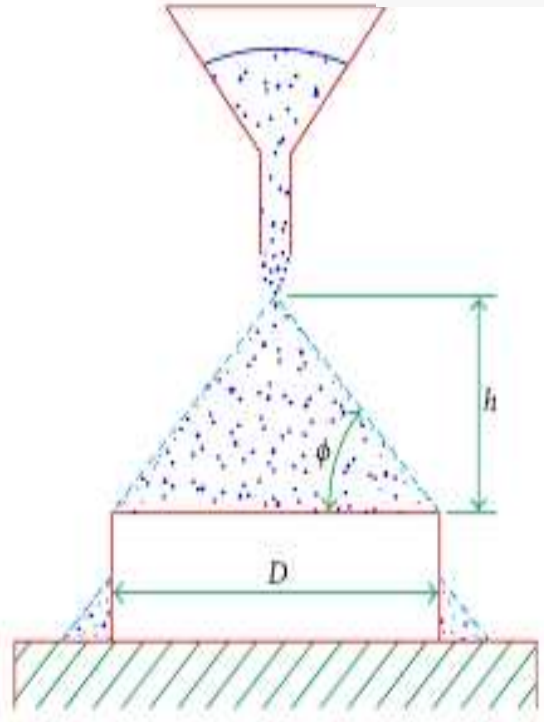
- Significance: It is related to interparticle friction. So it can be used to predict powder flow properties. For coarse, free flowing powders the Hausner ratio is approximately 1.2.
- For more cohesive, less ree-flowing powder (e.g. flakes) will have a Hausner ration greater than 1.5.
- Interpretation: Greater the Hausner ratio more cohesive will be the powder and flowability will be reduced.

Angle of repose

- Angle of repose of a powder sample is a parameter that shows interparticle cohesion.
- If cohesion between powder particles is less then powder flow-property is better. Due to cohesion, powder experiences a drag force against flow.
- Interparticle cohesive forces are due to non-specific van der Waals forces.
- It increases as particle size decreases and moisture content increases.
- Surface tension forces between adsorbed liquid layers at the particle surface and Electrostatic forces arising from contact or friction with the wall of the equipment.

Angle of Repose

- The sample is poured onto the horizontal surface and the angle of the resulting pyramid is measured.
- The user normally selects the funnel orifice through which the powder flows slowly and reasonably constantly.



Angle of repose=Tan ø=h/r

$Ø=\tan^{-1}(h/r)$

Angle of Repose

Flow Property	Angle of Repose
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very Poor	56-65
Very, Very Poor	>65

The rougher and more irregular the surface of the particles, the higher will be the angle of repose.

Factors affecting the flow properties of powder

1. Particle's size & Distribution
2. Particle shape & texture
3. Surface Forces

How flow properties can be improved

1. Alteration of Particle's size & Distribution
2. Alteration of Particle shape & texture
3. Alteration of Surface Forces
4. Formulation additives (Flow activators)

Alteration of Particle's size & Distribution

- There is certain particle size at which powder's flow ability is optimum.
- Coarse particles are more preferred than fine ones as they are less cohesive.
- The size distribution can also be altered to improve flow ability by removing a proportion of the fine particle fraction or by increasing the proportion of coarser particle's such as occurs in granulation.

Alteration of Particle shape & texture

- Generally, more spherical particles have better flow properties than more irregu particles.
- Spherical particles are obtained by spray drying,or by temperature cycling crystallization.

Alteration of Particle shape & texture

- Particles with very rough surfaces will be more cohesive and have a greater tendency to interlock than smooth surfaced particles.

Alteration of Surface Forces

- Reduction of electrostatic charges can improve powder flowability.
- Electrostatic charges can be reduced by altering process conditions to reduce frictional contacts.
- Moisture content of particle greatly affects powder's flowability.
- Adsorbed surface moisture films tend to increase bulk density and reduce porosity.
- Drying the particles will reduce the cohesiveness and improve the flow.
- Hygroscopic powder's stored and processed under low humidity conditions.

Addition of Formulation additives (Flow activators)

- Flow activators are commonly referred as a glidants.
- Flow activators improve the flowability of powders by reducing adhesion and cohesion.

e. g. Talc, maize starch and magnesium stearate.

Application of free flowing powders in pharmacy

- Powders are required to produce tablets or capsules. Free flowing powders flow uniformly into the die cavity of tablet punching machine and inside the empty gelatin shells. A free flowing powder produces uniform content of drug in the tablets and capsules.
- Free flowing powders show reproducible filling of tablet dies and capsules dosators, which improve weight uniformity and physicomechanical properties (e.g. hardness).
- Poor powder flow can result in excess entrapped air within powders which in some high-speed tabletting conditions may promote capping or laminations.

Application of free flowing powders in pharmacy

- Poor powder flow can result from excess fine particles in a powder, which increase friction in between particle and die wall. It may cause lubrication problem.
- In industry powders are required to flow from one location to another and this is achieved by different methods, such as gravity feeding, fluidization in gases and liquids and hydraulic transefer. In each of these examples powders are required to flow.
- In capsule filling machine, especially Lily type capsule filling machine the powder must be free flowing to uniformly fill the base of the capsule shells. In case of Zanasi-type filling machine cohesive powders are required.

5. solubility profile

Solubility and pH

- Another technique, if the drug is to be formulated into a liquid product, is adjustment of the pH of the solvent to enhance solubility.

- However, for many drug substances pH adjustment is not an effective means of improving solubility. Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or that may cause stability problems with formulation ingredients.

- Adjustment of pH usually has little effect on the solubility of substances other than electrolytes.

- In many cases, it is desirable to use co-solvents or other techniques such as complexation, micronization, or solid dispersion to improve solubility.

Ionization constant

- Ionization constant: the equilibrium constant for the ionization of a weak acid or base. Strong acids, e.g., HCl, are ionized at all pH values, whereas the ionization of weak acids is dependent on pH.
- Weak acid: an acid that gives a 10% or less yield of hydronium ions when dissolved in water.
- Weak base: a base that gives a 10% or less yield of hydroxide ions when dissolved in water.
- A constant that depends upon the equilibrium between the ions and the molecules that are not ionized in a solution or liquid—symbol K; also called dissociation constant
- It is necessary to know the extent to which the molecule is ionized at a certain pH, since properties such as solubility, stability, drug absorption and activity are affected by this parameter.
- The degree of a drug's ionization depends both on the pH of the solution in which it is presented to the biologic membrane and on the pKa , or dissociation constant, of the drug (whether an acid or base). The concept of pKa is derived from the Henderson–Hasselbalch equation.

Ionization constant:

- Acid dissociation constants are sometimes expressed by

$$pKa = -\log_{10} Ka$$

- The Henderson–Hassel Balch equation provides an estimate of the ionized and unionized drug concentration at a particular pH.

$$HA = H^{+} + A^{-}$$

- For acidic compounds

$$pH = pKa + log \frac{(\text{ionized drug})}{(\text{un ionized drug})} = pKa + log \frac{(A^{-})}{(HA)}$$

- For basic compounds

$$pH = pKa + log \frac{(\text{unionized drug})}{(\text{ionized drug})} = pKa + log \frac{(HA)}{(A^{-})}$$

Determination of pKa

- pKa of a drug molecule can be determined by various methods:
  - Potentiometric (pH) method
  - Spectrophotometric method
  - Partition-coefficient method
  - Conductometric method
  - Solubility method
- Among all the methods potentiometric and spectrophotometric methods are most popular and accurate methods by which the pKa are determined

Significance of pKa

- From the pKa of a weak acid or weak base the unionized fraction of a drug can be determined at a certain pH.
- The unionized fraction has greater absorption rate through any biological membrane. So while designing a dosage form how a weak acid or weak base will behave in any biological fluid and its rate of absorption and the site of absorption can be guessed from the pKa.
- Ibuprofen, a weak acid is absorbed maximum from stomach and Nitrazepam, a weak base will be absorbed preferrentially from duodenum.
- The solubility of a weakly acidic and weakly basic drug can be increased if the drug remains in ionized state. So the solubility vs. pH is plotted to get pH-solubility profile of a drug. While designing a dosage form (oral, ophthalmic or parenteral) the pH the solution is buffered to that pH where the solubility is maximum and the drug is reasonably stable.

SOLUBILITY

- Definition
- The maximum amount of solute that is soluble in one part of solution to make a saturated solution at a certain temperature is called the *solubility* of the drug.
-
- Significance of solubility
- Increased bioavailability:
  - In dealing with a new drug substance, it is extremely important to know something about its solubility characteristics, especially in aqueous solution, in order to elicit a therapeutic response. Any drug having solubility less than 10mg/mL in physiologic pH range (pH 1 to 7) will produce bioabsorption problem. A solubility less than 1mg/mL require salt formation of the drug for better bioavailability.
  - When the solubility of a drug cannot be increased by salt formation (e.g. in neutral molecules, glycosides, alcohols, steroids or where the pKa of a basic drug is less than 3 and the pKa of an acidic drug is more than10) then the drug is dissolved with a cosolvent and filled in a soft gelatin capsule.
  - Griseofulvin, an antifungal drug, when given orally the absorption is very less. So it is given with fat meal. The rate of dissolution rate of griseofulvin is increased by micronization (in a fluid energy mill) or by solid dispersion technique to increase its oral bioavailability.

SOLUBILITY

- Taste masking: Chloramphenicol is very bitter in taste so it is very difficult to make a paediatric liquid dosage form with chloramphenicol base. Chloramphenicol palmitate is taken, the solubility of which is very low compared to chloramphenicol base. When a suspension is prepared due to its low solubility it does not produce any bitter taste.

- Reducing degradation in the GIT: Drugs like erythromycin will degrade while passing through the acid environment of stomach, so erythromycin is delivered as erythromycin proprionate or estolate while preparing paediatric suspension. This solubility of these esters are very less in acidic pH. Thus they are saved from gastric pH.
-

Determination of solubility of the drug

Step-1:

- **Method A:** Some excess amount of drug is dissolved in 10ml of solvent. The suspension is shaken overnight (24hrs) in a fixed temperature water bath.
- **Method B:** Some excess amount of drug is dissolved in 10ml of solvent by heating, then the suspension is put in a fixed temperature water bath.

Step-2: The solids are separated from saturated solution either by filtration through membrane or by centrifugation.

Step-3: The filtrate (or supernatant liquid after centrifugation) is assayed to determine the solubility of the drug. The assay method may be gravimetric, UV-spectrophotometric, HPLC etc.

Intrinsic solubility of a drug (S_o)

- This is the fundamental solubility of a drug when it is completely unionized.
  - For a weak acid the intrinsic solubility is the solubility of the drug determined in a strongly acidic solution.
  - For a weak base the intrinsic solubility is the solubility of the drug determined in a strongly alkaline solution.
  - For a non-ionic molecule there will be no measurable change in the solubility in either acidic or alkaline solution.
-
- In case of weak acid and weak base the solubility can be manipulated by changing the pH of the solution.
- In case of non-ionizable molecules the solubility can be manipulated either by changing the solvent, or by addition of cosolvent or by complexation.
-

Approaches of increasing the solubility of drugs

1. By changing the pH of the solution

- For a weak acid the relationship between the pH of the solution and the solubility of the drug is:
-

$$pH = pKa + \log \frac{S - S_0}{S_0}$$

where S = overall solubility of the drug = Concentration of ionized fraction + Concentration of unionized fraction (S_u) For a weak base (BH^+) the relationship between the pH of the solution and the solubility of the drug is:

$$pH = pKa + \log \frac{S_0}{S - S_0}$$

-
  So in case of a weakly acidic drug the solubility can be increased by increasing the pH and for a weakly basic drug the solubility can be increased by decreasing the pH.

2. By changing the solvent

- The first preference of solvent is water. If the solubility is very less in water then water may be replaced, either partially or completely, with one or more water-soluble solvents like ethanol, glycerol, sorbitol, propylene glycol etc.
- The solvents are called cosolvents, and the phenomenon as cosolvency. These types of non-toxic cosolvents are used in designing oral liquid dosage forms

3.By changing the polymorphs

- Whenever a drug is crystallized from some solvent, depending on the conditions of crystallization, the polymorphic shape is changed.
- For example, if cooled very quickly then metastable polymorphs will be formed and if cooled very slowly then stable crystalls will form. The metastable form has higher solubility that the stable polymorph.
- While crystallization solvent molecules may be entrapped within the crystal lattice in stochiometric ratio – these types of crystals are called solvates. If the solvent molecule entrapped are water (H_2O) molecules then the crystals will be called hydrates.
- The solubility of these pseudopolymorphs may be arranged in ascending order:

Hydrates < Anhydrous < Solvates

4.By adding a suitable surfactant

- A sufractant when dissolved in water in a concentration over the critical micelle concentration (CMC) will produce micelles. The drug, both ionized and unionized forms, will partition between water and micelle. If the concentration of surfactant is increased over CMC the partition of the drug into the micelle will increase which will show an apparent increase of solubility of the drug.
- Sodium lauryl sulfate, a surfactant, increases the solubility of benzoic acid.
- In case of oral liquid dosage forms generally non-ionized surfactants are used (e.g polysorbate 80 i.e. Tween80) to increase the solubility of a drug.

5.By complexation

- Caffeine increase the solubility of benzoic acid by forming a water-soluble complex. Solubility of para aminobenzoic acid (PABA) can be increased by complexing with caffeine.

Approaches of decreasing the solubility of drugs

By esterification:

- The soubility of chloramphenicol can be decrease by forming its ester with palmitic acid.

By coating with polymers

- Drug particles may be coated with ethylcellulose to retard its water solubility. Cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HPMCP) etc. polymers reduce the solubility of drug particles in the acid medium of stomach.

By changing the polymorph

- Stable polymorphs have lower aqueous solubility than the metastable forms. So by changing the condition of crystallization stable polymorphs may be produced.

By selecting the hydrated forms

- Anhydrous ampicillin has greater water solubility than ampicillin-trihydrate. In anhydrous forms the drug powder has an inherent demand for water, hence its solubility is higher than the hydrates where the demand for water is satisfied.

Partition coefficient

The lipophilicity of an organic compound is usually described in terms of a partition coefficient, log P, which can be defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases:

$$\mathbf{logP} = \frac{(\mathbf{Unionised\ compound})_{\mathbf{org}}}{(\mathbf{Unionised\ compound})_{\mathbf{aq}}}$$

Partition coefficient

- The octanol–water partition coefficient is commonly used in formulation development.

$$P = \frac{(\text{Conc. of drug in octanol})}{(\text{Conc. of drug in water})}$$

- P depends on the drug concentration only if the drug molecules have a tendency to associate in solution. For an ionizable drug, the following equation is applicable:

$$P = \frac{(\text{Conc. of drug in octanol})}{[1-\alpha](\text{Conc. of drug in water})}$$

where α equals the degree of ionization.

Partition coefficient

- The most common method for determining partition and distribution coefficients is the shake flask method.
- In this technique, the candidate drug is shaken between octanol (previously shaken together to presaturate each phase with the other) and water layers, from which an aliquot is taken and analyzed using UV absorption, HPLC or titration.
- In terms of experimental conditions, the value of the partition coefficient obtained from this type of experiment is affected by such factors as temperature, insufficient mutual phase saturation, pH and buffer ions and their concentration, as well as the nature of the solvents used and solute examine.

Partition coefficient

- Compounds with log P values between 1 and 3 show good absorption,
- log P greater than 6 or less than 3 often have poor transport characteristics.
- Highly non-polar molecules have a preference to reside in the lipophilic regions of membranes, and very polar compounds show poor bioavailability because of their inability to penetrate membrane barriers.
- Thus, there is a parabolic relationship between log P and transport, i.e., candidate drugs that exhibit a balance between these two properties will probably show the best oral bioavailability.

Methods to determine P

- Shake flask method
- Chromatographic method (TLC, HPTLC)
- Counter current and filter probe method

Applications of P:-

1. Extraction of crude drugs
2. Recovery of antibiotics from fermentation broth
3. Recovery of biotechnology-derived drugs from bacterial cultures
4. Extraction of drugs from biologic fluids for therapeutic drug monitoring
5. Absorption of drugs from dosage forms (ointments, suppositories, transdermal patches)
6. Study of the distribution of flavouring oil between oil and water phases of emulsions

Chemical Properties of Drug Substances

a)Oxidation & Reduction

b)Hydrolysis

c)Photolysis

d)Racemisation

e)Polymerization

f)Isomerisation

Oxidation:

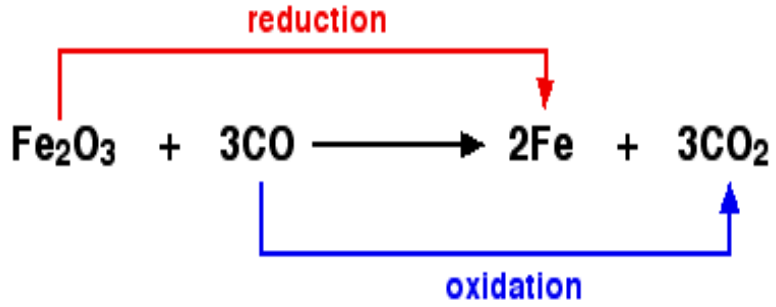
It is very common pathway for drug degradation in both liquid and solid formulation.

Oxidation is the gain of oxygen, loss of hydrogen and/or loss of electrons.

When iron reacts with oxygen it forms a chemical called rust. The iron is oxidized and the oxygen is reduced.

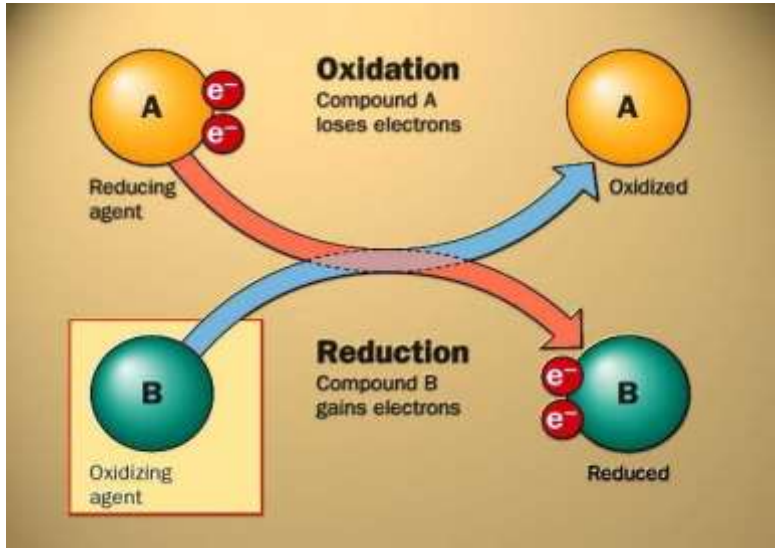
Oxidation occurs in two ways

- Auto oxidation
- Free radical oxidation



Functional group having high susceptibility towards oxidation:-

- Substituted aromatic group (Toluene, Phenols, Anisole).
- Alkenes
- Ethers
- Thioethers
- Amines



Factors affecting oxidation process

1) Oxygen concentration
2) Light
3) Heavy metals particularly those having two or more valence state
4) Hydrogen & Hydroxyl Ion
5) Temperature

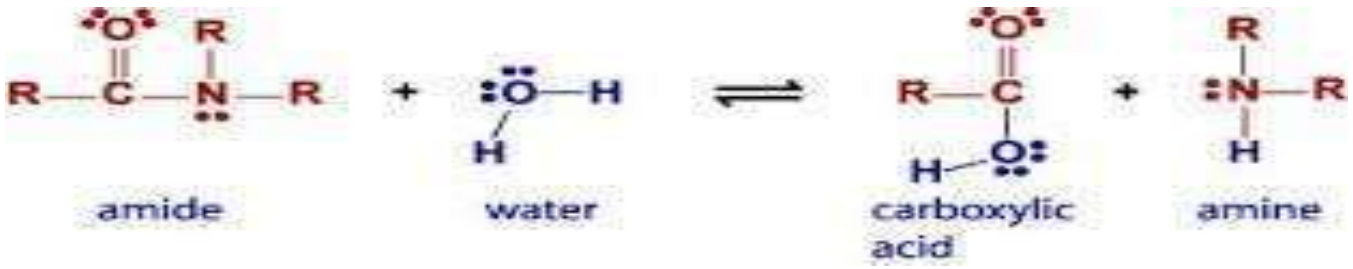
How to prevent oxidation?

1. Reducing oxygen content
2. Storage in a dark and cool condition
3. Addition of chelating agent (Eg. EDTA, Citric acid, Tartaric acid)
4. Adjustment of pH
5. Changing solvent (Eg. Aldehydes, ethers, Ketones, may influence free radical reaction)
6. Addition of an antioxidant or reducing agent (e.g. H_2, CO, Zn etc)

Hydrolysis

- **It is the cleavage of chemical bonds by the addition of water.**
- The reaction of water with another chemical compound to form two or more products, involving ionization of the water molecule usually splitting the other compound.

- **Examples** include :
  - the catalytic conversion of starch to glucose,
  - saponification, and
  - the formation of acids or bases from dissolved ions.
- When this attack is by a solvent other than water then it is known as **solvolysis.**



Conditions that catalysis the breakdown are:

1. Presence of hydroxyl ion
2. Presence of hydride ion
3. Presence of divalent ion
4. Heat
5. Light
6. Ionic hydrolysis
7. Solution polarity and ionic strength
8. High drug concentration

Prevention of hydrolysis:

❖pH Adjustment

- Formulate the drug solution close to its pH of optimum stability.
- Addition of water miscible solvent in formulation.
- Optimum buffer concentration.

❖Addition of surfactant

- Nonionic, cationic, and anionic surfactant stabilizes the drug against base catalysis.

❖Salts and Esters Eg. Phosphate esters of clindamycine

- The solubility of pharmaceuticals undergoing ester hydrolysis can be reduced by forming less soluble salts.
- By use of complexing agent.

Photolysis:

- **Photo dissociation**, **photolysis**, or **photodecomposition** is a chemical reaction in which a chemical compound is broken down by photons.

- Since a photon's energy is inversely proportional to its wavelength, electromagnetic waves with the energy of visible light or higher, such as ultra violet , X-rays and gamma rays are usually involved in such reactions.

Photodecomposition pathway

- **N-Dealkylation**

  Di-phenylhydramine, Chloroquine, Methotrexate

- **Dehalogination**

  Chlorpropamide, Furosemide

- **Dehydrogenation of Ca++channel blocker**

  Solution of Nifedipine

- **Oxidation**

  Chlorpromazine & other Phenothiazines give N- & S-oxides in the presence of sunlight

Prevention of photodecomposition

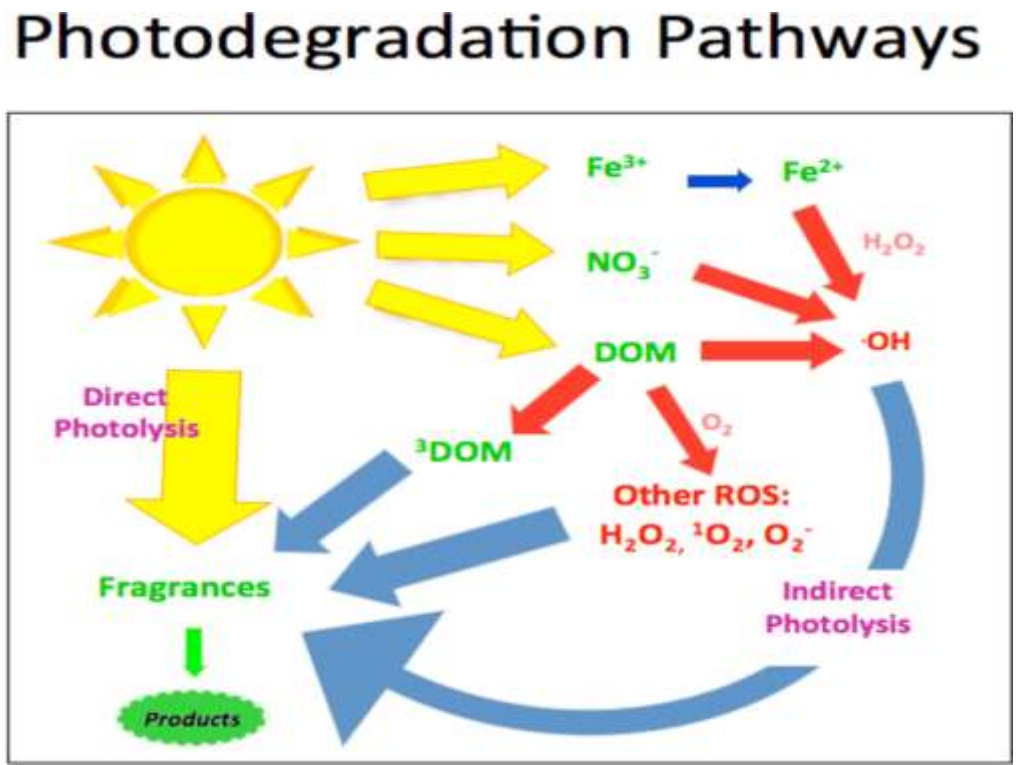
- **Suitable packing.**

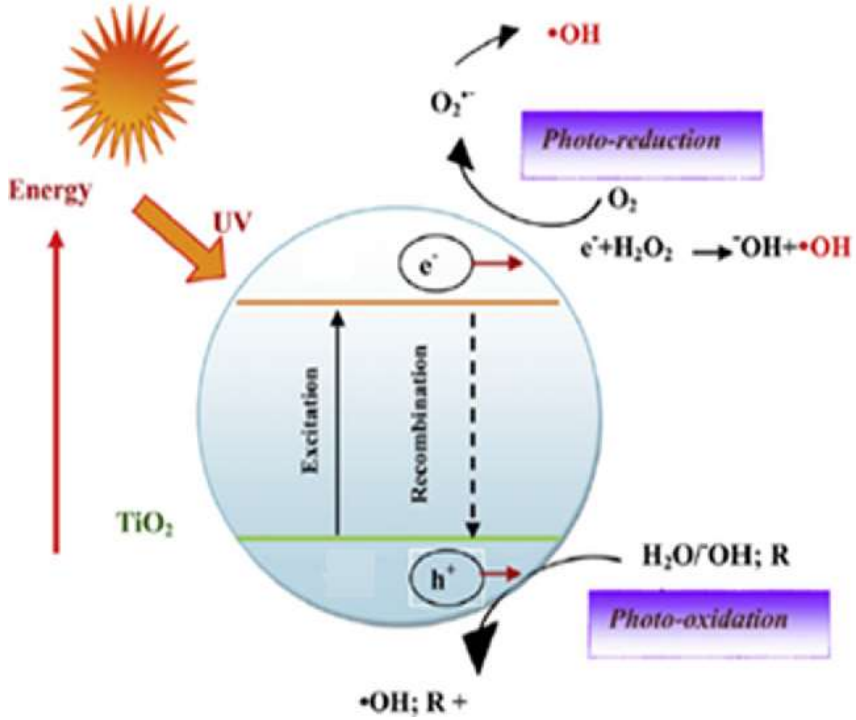
  Yellow-green glass gives the best protection in U.V. region while Amber gives considerable protection against U.V. radiation but little from I.R.

- **Protection of drug from light**

  Nifedipine is manufactured under Na light.

- **Avoiding sunbath**



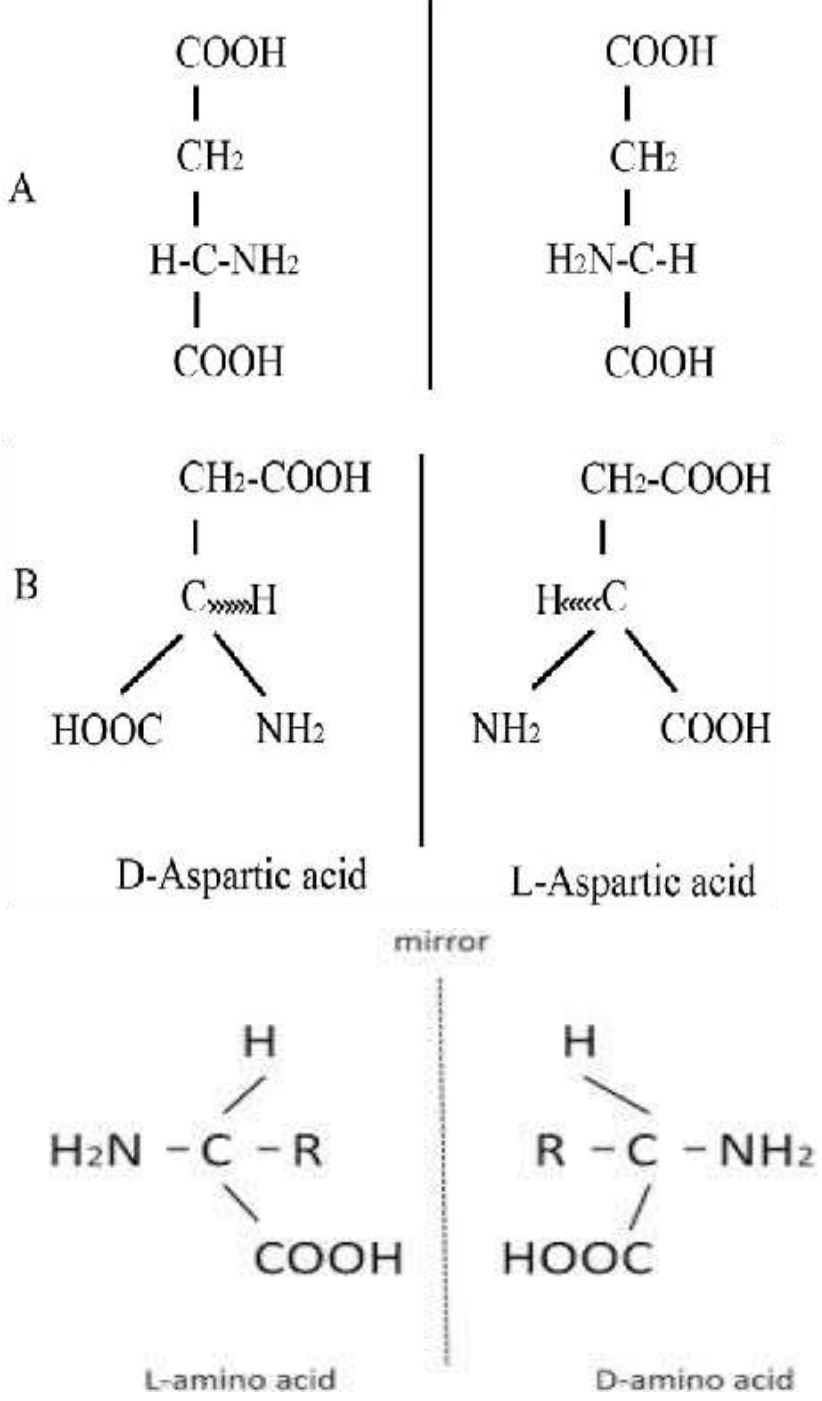


Racemization

- It is the process in which one enantiomer of a compound, such as an L-amino acid, converts to the other enantiomer.

- The compound then alternates between each form while the ratio between the (+) and (–) groups approaches 1:1, at which point it becomes optically inactive.

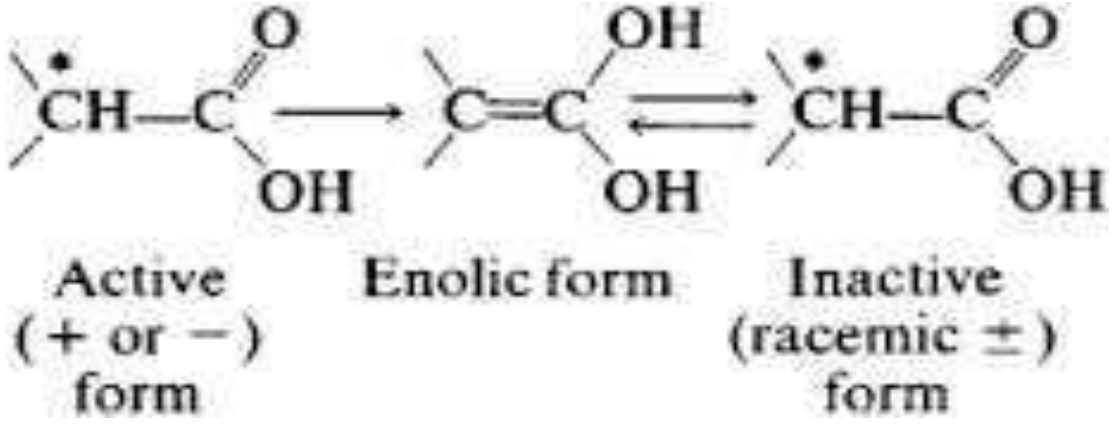
- If the racemization results in a mixture where the enantiomers are present in equal quantities, the resulting sample is described as racemeric or a racemate.

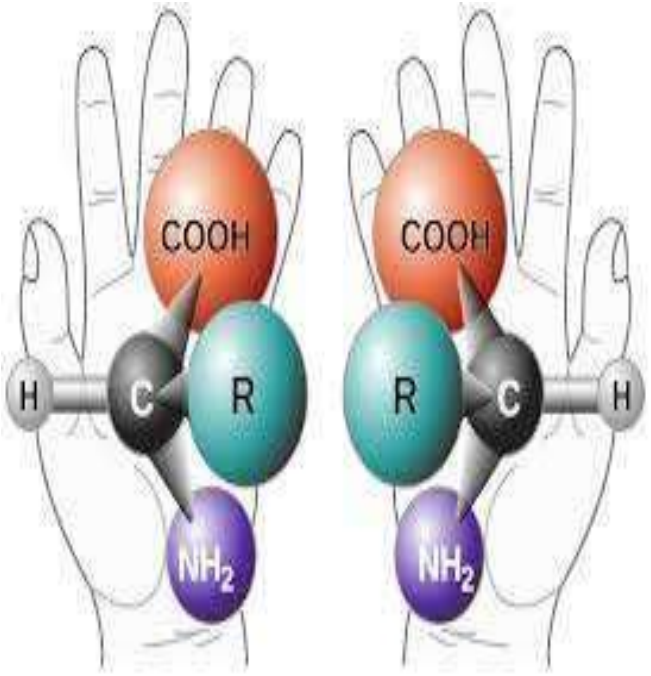


- The inter-conversion from one isomer to another can lead to different pharmacokinetic properties (ADME) as well as different pharmacological & toxicological effect.

- Example: L-epinephrine is 15 to 20 times more active than D-form, while activity of racemic mixture is just one half of the L-form.

- It depends on
  - Temperature,
  - Solvent,
  - Catalyst &
  - Presence or absence of light





- **Biological significance:**
- Many psychotropic drugs show differing activity or efficacy between isomers, e.g. Amphetamine is often dispensed as racemic salts while the more active dextro-amphetamine is reserved for severe indications;
- Another example is Methadone, of which one isomer has activity as an opioid agonist and the other as an NMDA antagonist.

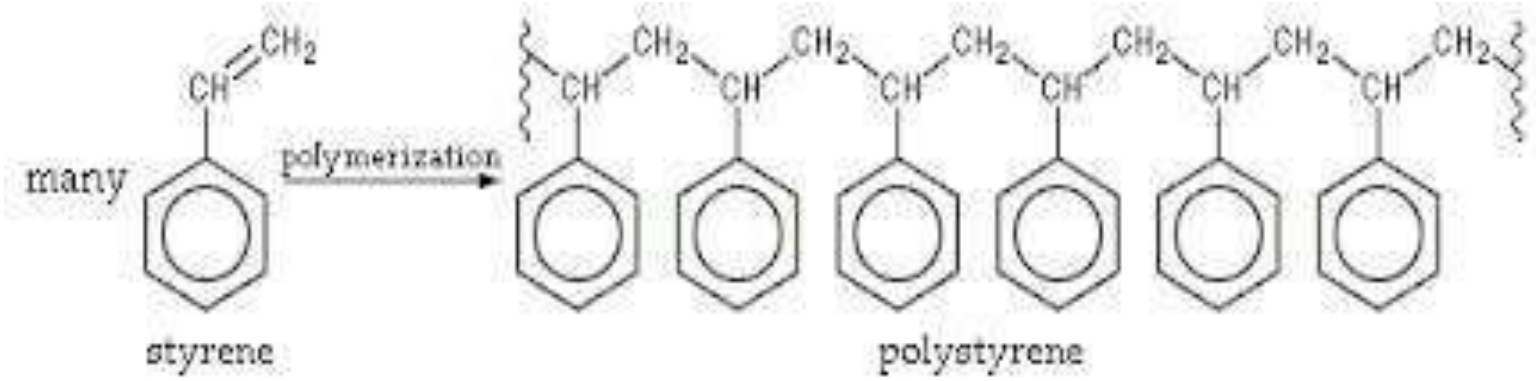
Polymerization

- Polymerization is a process of reacting monomer molecules together in a chemical reaction to form polymer chains or three-dimensional networks.

- It is a continuous reaction between molecules.

- More than one monomer reacts to form a polymer.

- Darkening of glucose solution is due to polymerization of breakdown product [5- (hydroxyl methyl) furfural. (a colorless liquid used in synthetic resin manufacture).
- Eg. Shellac on aging undergoes polymerization & hence prolongs disintegration time & dissolution time.



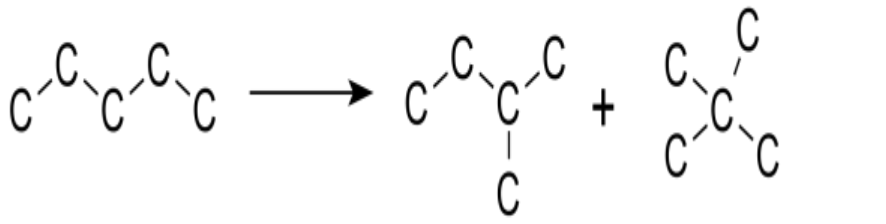
Isomerizaton

- ✓ Is the process by which one molecule is transformed into another molecule which has exactly the same atoms, but the atoms have a different arrangement.
  e.g. A-B-C → B-A-C (these related molecules are known as isomers).

Examples:-

- ○ Tetracycline & its derivatives can undergo reversible Isomerization at pH range 2-6.

- ○ Trans-cis Isomerization of Amphotericin B.

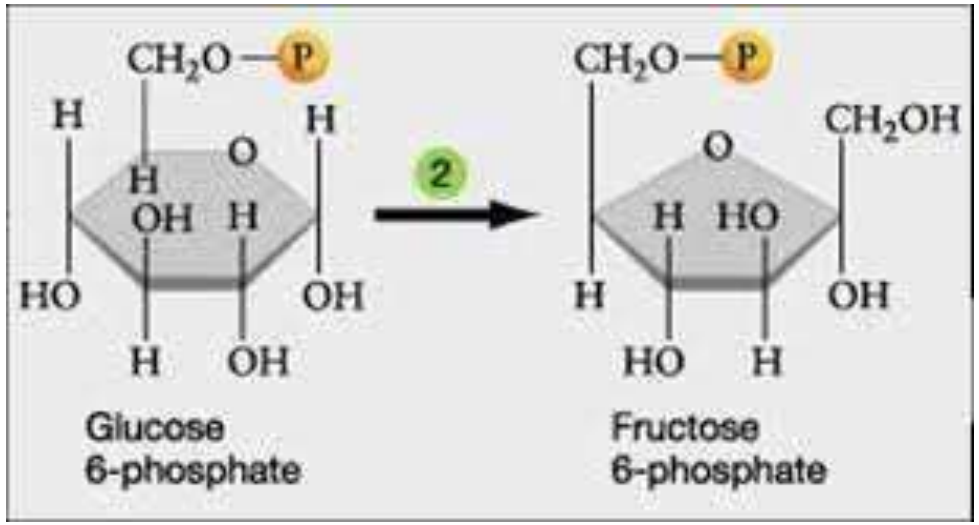


pentane 2-methylbutane 2,2-dimethylpropane

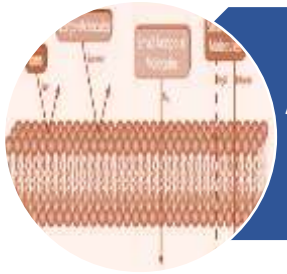
Significance:

Isomerism finds its importance in the field of clinical pharmacology and pharmacotherapeutics, as isomers differ in their pharmacokinetic and pharmacodyanmic properties.

- Cetrizine to levocetrizine is one of such examples, where effective and safer drug has been made available.
- Levocetrizine has smaller volume of distribution than its dextroisomer.
- Esomeprazole is more bioavailable than racemic omeprazole;



Biopharmaceutical Classification System

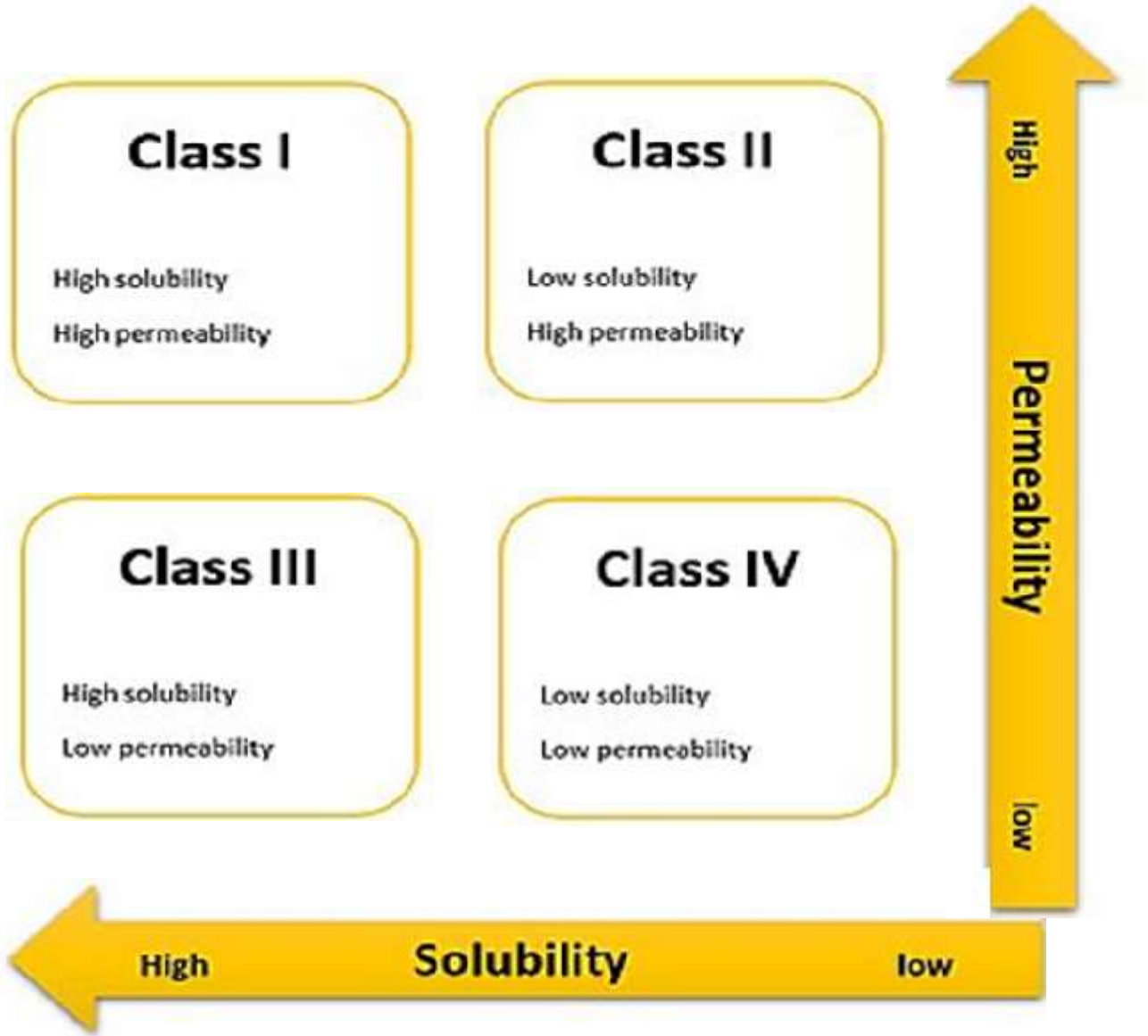


A scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability

Established by Gordon Amidon et al.

BCS has gained importance worldwide as a drug product regulation tool for scale-up and post-approval changes

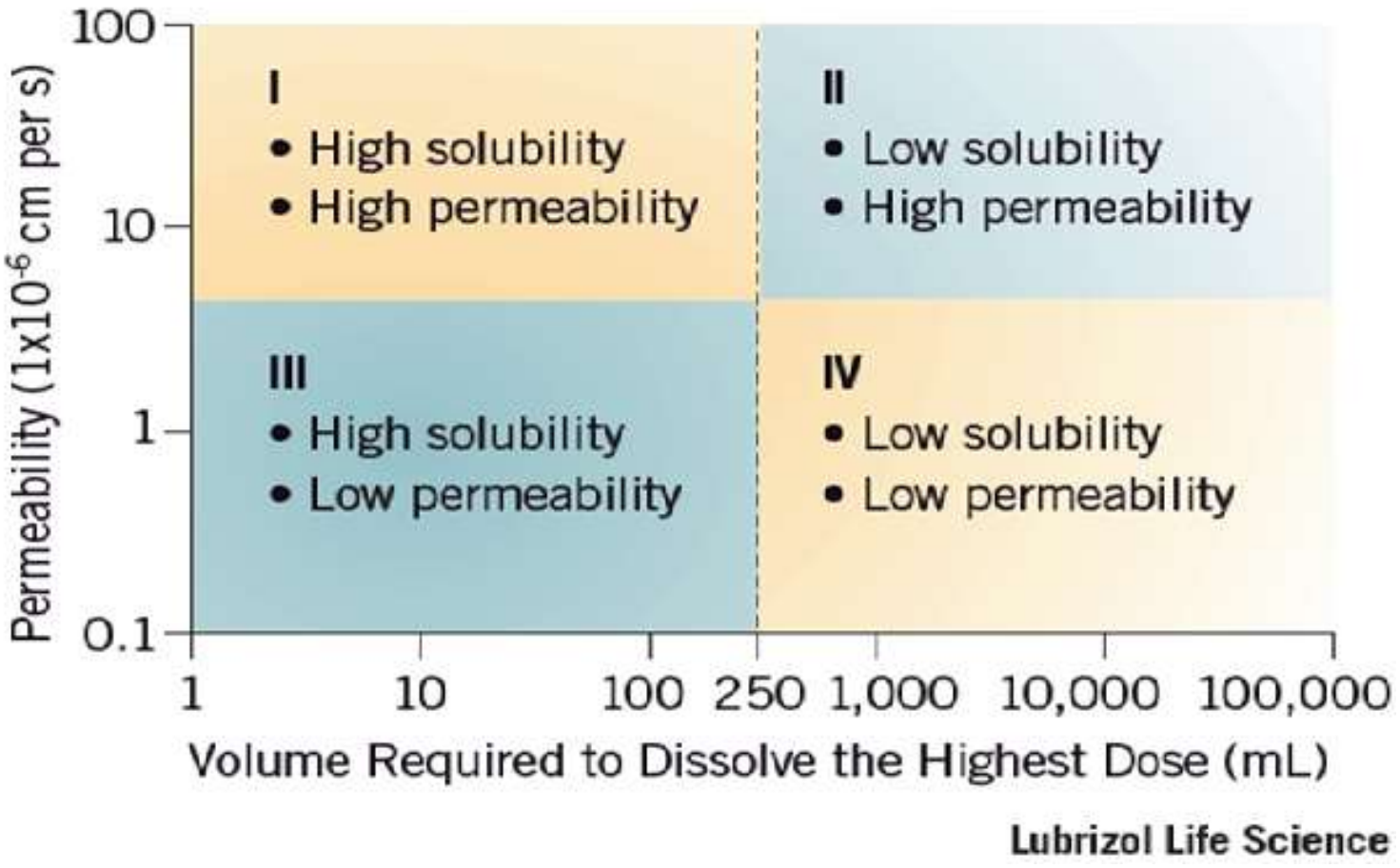
The aim of the BCS is to provide a regulatory tool for the replacement of certain BE studies by conducting accurate *in vitro* dissolution tests.


Class I
High solubility
High permeability
Class II
Low solubility
High permeability
Class III
High solubility
Low permeability
Class IV
Low solubility
Low permeability
High
Permeability
low
High
Solubility
low

Biopharmaceutical Classification System (BCS) of drug substances

Class I **High Permeability** **High Solubility**	• Example: metoprolol, paracetamol • Those compounds are well absorbed and their absorption rate is usually higher than excretion.
Class II **High permeability** **Low solubility**	• Example: glibenclamide, bicalutamide, • ezetimibe, aceclofenac • The bioavailability of those products is limited by their solvation rate. A correlation between the *in vivo* bioavailability and the *in vitro* solvation can be found.
Class III **Low permeability** **High solubility**	• Example: cimetidine • The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.
Class IV **Low permeability,** **Low solubility**	• Example: Bifonazole • Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

Biopharmaceutical Classification System (BCS) (as defined by the FDA after Amidon et al.)



	High Solubility	Low Solubility
High Permeability	**Class 1** Abacavir Acetaminophen *Acyclovir*[b] *Amiloride*[S,I] Amitryptyline [S,I] Antipyrine *Atropine* **Buspirone**[c] Caffeine *Captopril* Chloroquine [S,I] **Chlorpheniramine** Cyclophosphamide Desipramine **Diazepam** **Diltiazem** [S,I] **Diphenhydramine** Disopyramide **Doxepin** Doxycycline Enalapril Ephedrine Ergonovine Ethambutol Ethinyl Estradiol Fluoxetine[I] Glucose Imipramine[I] **Ketorolac** Ketoprofen Labetolol Levodopa [S] Levofloxacin [S] **Lidocaine**[I] Lomefloxacin **Meperidine** Metoprolol Metronidazole **Midazolam** [S,I] **Minocycline** Misoprostol **Nifedipine** [S] Phenobarbital Phenylalanine Prednisolone **Primaquine** [S] Promazine Propranolol [I] **Quinidine**[S,I] Rosiglitazone Salicylic acid Theophylline Valproic acid **Verapamil** [I] Zidovudine	**Class 2** **Amiodarone** [I] **Atorvastatin**[S, I] **Azithromycin**[S ,I] **Carbamazepine** [S,I] **Carvedilol** Chlorpromazine [I] **Cisapride**[S] *Ciprofloxacin* [S] **Cyclosporine** [S, I] **Danazol** **Dapsone** Diclofenac Diflunisal Digoxin [S] *Erythromycin* [S,I] Flurbiprofen **Glipizide** **Glyburide**[S,I] Griseofulvin Ibuprofen **Indinavir** [S] Indomethacin **Itraconazole** [S,I] **Ketoconazole** [I] **Lansoprazole**[I] **Lovastatin** [S,I] *Mebendazole* Naproxen Nelfinavir [S,I] Ofloxacin Oxaprozin Phenazopyridine Phenytoin[S] Piroxicam Raloxifene [S] **Ritonavir** [S,I] **Saquinavir** [S,I] **Sirolimus** [S] Spironolactone [I] **Tacrolimus** [S,I] Talinolol[S] **Tamoxifen** [I] **Terfenadine** [I] Warfarin

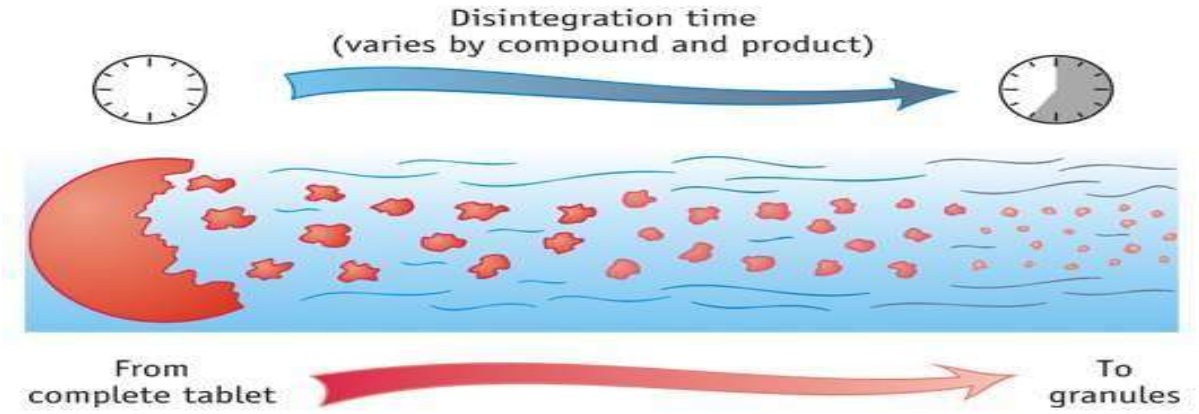
	High Solubility	Low Solubility
Low Permeability	**Class 3** Acyclovir Amiloride Amoxicillin Atenolol Atropine Bisphosphonates Bidisomide Captopril Cefazolin Cetirizine Cimetidine Ciprofloxacin Cloxacillin Dicloxacillin Erythromycin Famotidine Fexofenadine Folinic acid Furosemide Ganciclovir Hydrochlorothiazide Lisinopril Metformin Methotrexate Nadolol Pravastatin S Penicillins Ranitidine Tetracycline Trimethoprim Valsartan Zalcitabine	**Class 4** Amphotericin B Chlorthalidone Chlorothiazide Colistin Ciprofloxacin Furosemide Hydrochlorothiazide Mebendazole Methotrexate Neomycin

Class–I High Solubility High Permeability

- Drugs dissolved rapidly
- Drugs absorbed rapidly
- Rapid therapeutic action
- Excellent property
- Ideal for oral route
- e.g. Metoprolol, Diltiazem, Verapamil, Propranolol,

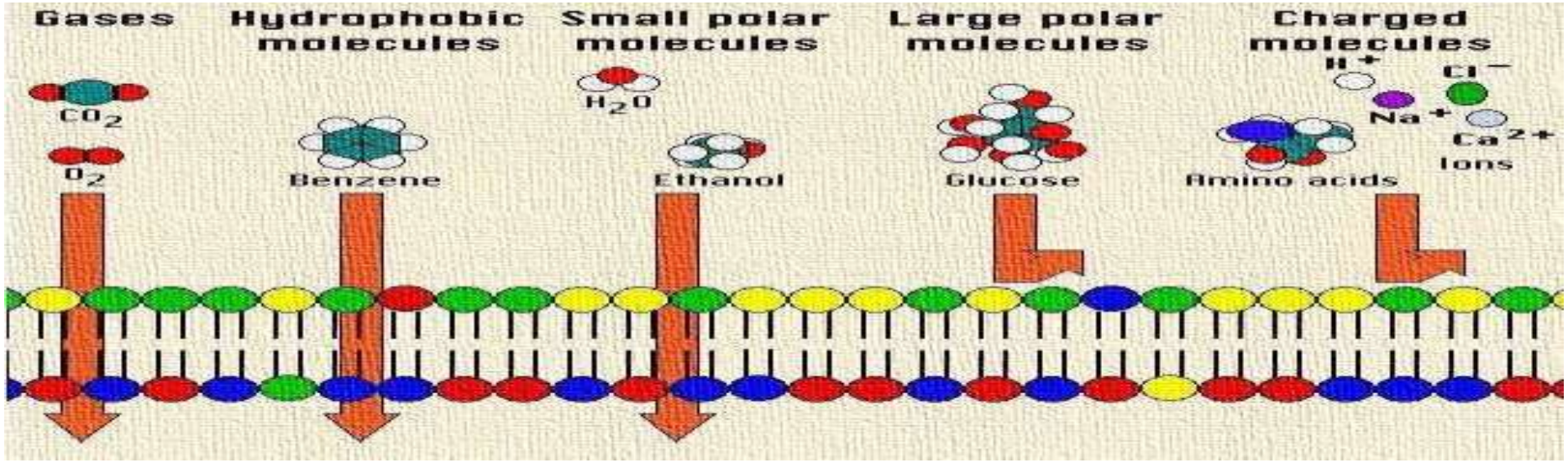
Class – II Low Solubility High Permeability

- Drugs dissolve slowly
- Drugs absorbed rapidly
- Controlled released drugs
- Oral / IV route for administration
- E.g. Glibenclamide, Ezetimibe, Phenytoin, Nifedipine

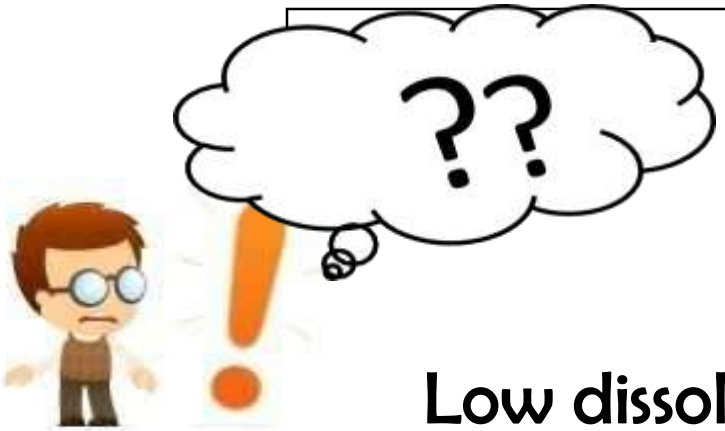


Class – III High Solubility Low Permeability

- Dissolved rapidly
- Absorbance is limited
- Incomplete bioavailability
- Oral / IV route for administration
- Ex. Cimetidine, Acyclovir, Captopril

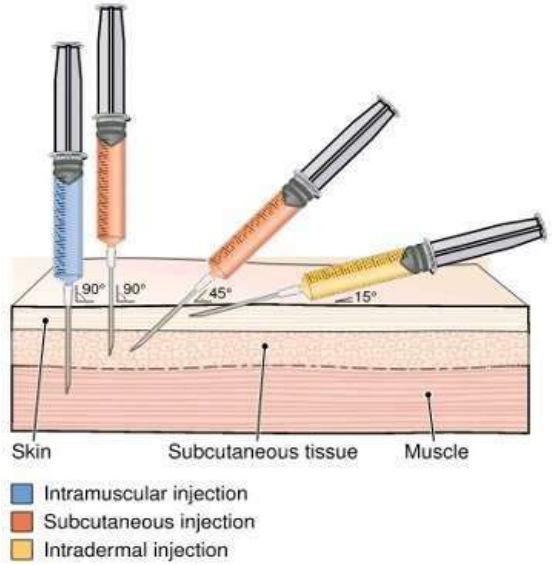


Class – IV-Low Solubility Low Permeability



Low dissolution rate

- Low permeability property
- Slow or low therapeutic action
- IV or other routes are required
- Ex. Hydrochlorothiazide



BCS can be used as a key component to guide drug delivery system design for any route of administration

BCS Class	Solubility	Permeability	Oral Dosage Form Approach	Chances of Non-oral Dosage Form being Required
1	High	High	Simple solid oral dosage form	
2	Low	High	• Techniques to increase surface area like particle size reduction, solid solution, solid dispersion • Solutions using solvents and/ or surfactants	
3	High	Low	Incorporate permeability enhancers, maximize local lumenal concentration	
4	Low	Low	Combine 2 and 3	

Significance of BCS

- Regulatory tool for replacement of certain BE studies.
- It can save both time and money—if the immediate -release, orally administered drug meets specific criteria, the FDA will grant a waiver for expensive and time-consuming bio-equivalence studies.
- Valuable tool for formulation scientist for selection of design of formulated drug substance.
- When integrated with other information provide a tremendous tool for efficient drug development.
- Reduces cost and time of approving Scale- up and post approval challenges.
- Applicable in both pre-clinical and clinical drug development process.
- Works as a guiding tool in development of various oral drug delivery systems.

THANK YOU