

# Solubility of Drugs



**V M Waghulkar ( M.Pharma.,D.B.M )  
Asst.Prof., Dept. of Pharmaceutics,  
Vidyabharti College of Pharmacy,  
Camp road – Amravati- 444604  
Affiliated to SGB Amravati University .  
Email- vijaywaghulkar@gmail.com**

# INDEX

---

- ❑ DEFINITION
- ❑ APPROACHES
- ❑ SOLUBILITY CONCEPTS
- ❑ SOLUBILISERS
- ❑ DISSOLUTION
- ❑ FDA Notes

# Definition

---

- ▣ **Solubility** may be defined as the maximum concentration of a substance that may be completely dissolved in a given solvent at a given temperature and pressure.

# Definition

---

- ▣ The USP/NF generally expresses the solubility in terms of the volume of solvent required to dissolve 1 gram of the drug at a specified temperature (eg. 1 g ASA in 300 ml H<sub>2</sub>O, 5 ml ethanol at 25°C).

# Solubility Importance

---

- ❑ Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response.
- ❑ More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity.

# Solubility characteristics

---

## ▣ *Descriptive term*

*Very Soluble*

*Freely Soluble*

*Soluble*

*Sparingly soluble*

*Slightly soluble*

*Very Slightly Soluble*

*Practically insoluble or insoluble*

## ▣ *Parts of solvent needed for 1 part of solute*

▣ *< 1*

▣ *1 to 10*

▣ *10 to 30*

▣ *30 to 100*

▣ *100 to 1000*

▣ *1000 to 10,000*

▣ *> 10,000*

# Saturation solubility

---

- ❑ **SATURATION SOLUBILITY** is understood as a maximum amount of solute that dissolves in a solvent at equilibrium.
- ❑ Equilibrium is a state where reactants and products reach a balance - no more solute can be dissolved in the solvent in the set conditions (temperature, pressure).
- ❑ Such a solution is called a **saturated solution**.

# MISCIBILITY

---

- ❑ The capacity of two or more liquids to form a **uniform blend**, that is, to dissolve in each other;
- ❑ Capable of being and remaining mixed in all proportions.
- ❑ Alcohol and water are miscible
- ❑ Oil and water are not miscible



## K<sub>sp</sub> - Solubility product constant definition

---

- ❑ Solubility product constant is simplified equilibrium constant (K<sub>sp</sub>)
- ❑ Defined for equilibrium between a solids and its respective ions in a solution.
- ❑ Its value indicates the degree to which a compound dissociates in water.
- ❑ The higher the solubility product constant, the more soluble the compound.
- ❑ The K<sub>sp</sub> expression for a salt is the product of the concentrations of the ions,
- ❑ with each concentration raised to a power equal to the coefficient of that ion in the balanced equation for the solubility equilibrium.

# Osmolarity

---

- ❑ Osmolarity - measure of the osmotic pressure exerted by a solution across a perfect semi-permeable membrane compared to pure water.
- ❑ Osmolarity is dependent on the number of particles in solution but independent of the nature of the particles.
- ❑ The osmotic pressure- usually relative to that of blood.

# Tonicity

is the relative concentration of solutes dissolved in solution which determine the direction and extent of diffusion-

---

- ❑ **Isotonic solutions**

- ❑ Isotonic solutions are two solutions that have the same concentration of a solute.

- ❑ **Hypertonic solution**

- ❑ Hypertonic solution is one of two solutions that has a higher concentration of a solute.

- ❑ **Hypotonic solution**

- ❑ Hypotonic solution is one of two solutions that has a lower concentration of a solute.

- ❑ Is a measure of the effective osmotic pressure gradient; the water potential of two solutions separated by a semi permeable membrane cell membrane.

# Osmolarity and tonicity

---

- ❑ Osmolality is a property of a particular solution and is independent of any membrane.
- ❑ Tonicity is a property of a solution in reference to a particular membrane.
- ❑ Tonicity is a measure of the osmotic pressure that a substance can exert across a cell membrane, compared to blood plasma.

---

## ❑ Drug absorption

is the movement of a drug into the bloodstream after administration.

Absorption affects bioavailability—how quickly and how much of a drug reaches its intended target (site) of action.

Factors that affect absorption (and therefore bioavailability) include.

The way a drug product is designed and manufactured

Its physical and chemical properties

Other ingredients it contains

The physiologic characteristics of the person taking the drug

How the drug is stored

# Drug absorption

---

- ❑ **is the movement of a drug into the bloodstream after administration.**
- ❑ **Absorption affects bioavailability—how quickly and how much of a drug reaches its intended target (site) of action.**

**Factors that affect absorption (and therefore bioavailability) include.**

**The way a drug product is designed and manufactured**

**Its physical and chemical properties**

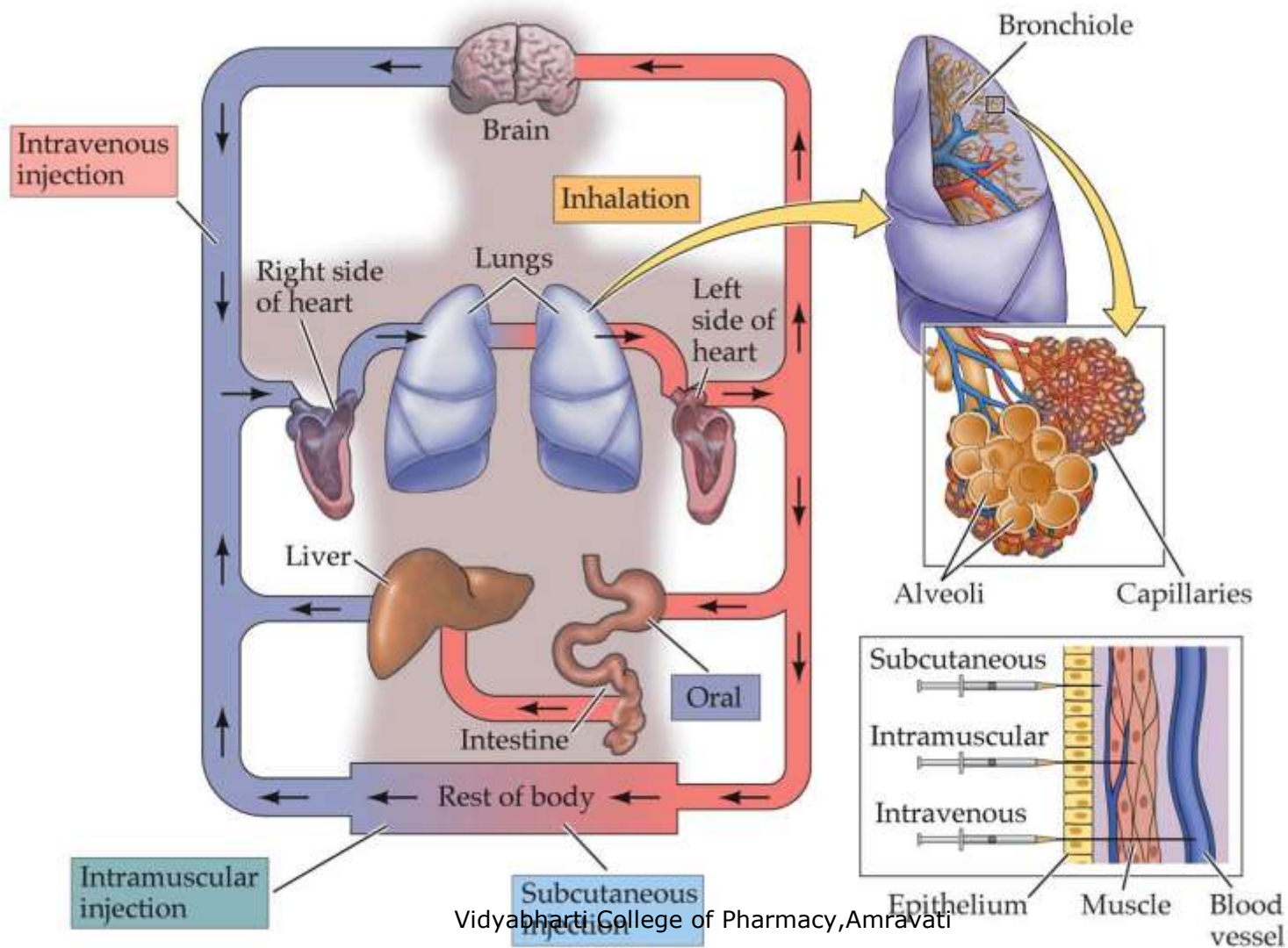
**Other ingredients it contains**

**The physiologic characteristics of the person taking the drug**

**How the drug is stored.**

- 
- ❑ Plasma has an osmolarity of about 0.3 osm/l
  - ❑ Absorption of drugs across membranes
  - ❑ Therapeutic efficacy- determined by quantum that reaches circulation- site of action

# Routes of Administration



Vidyabharti College of Pharmacy, Amravati



# Permeability

---

The rate at which a compound will pass through a membrane

- Expressed in units of cm/second
- Permeability value depends on the nature of the phases, and the compound itself
- ▣ If we could measure the permeability of a molecule in vitro, it would indicate whether the molecule might be absorbed in the body

# Types of Membranes:

---

- ❑ **Cell Membranes:** This barrier is permeable to many drug molecules but not to others, depending on their lipid solubility. Small pores, 8 angstroms, permit small molecules such as alcohol and water to pass through.
- ❑ **Walls of Capillaries:** Pores between the cells are larger than most drug molecules, allowing them to pass freely, without lipid solubility being a factor.

# Types of Membranes:

---

- ❑ **Blood/Brain Barrier:** This barrier provides a protective environment for the brain. Speed of transport across this barrier is limited by the lipid solubility of the psychoactive molecule.
- ❑ **Placental Barrier:** This barrier separates two distinct human beings but is very permeable to lipid soluble drugs.

# Lipophilicity of a drug provides a rough guide to its pharmacokinetic behavior

---

- | <b>□ <i>Log D at pH 7.4</i></b> | <b><i>Implications for drug development</i></b>   |
|---------------------------------|---|
| □ <i>Below 0</i>                | □ Intestinal and CNS permeability problems. Susceptible to renal clearance  |
| □ <i>0 to 1</i>                 | □ May show a good balance between permeability and solubility . At lower values, CNS permeability may suffer                      |
| □ <i>1 to 3</i>                 | □ Optimum range for CNS and non-CNS orally active drugs. Low metabolic liabilities, generally good CNS penetration                |
| □ <i>3 to 5</i>                 | □ Solubility tends to become lower. Metabolic liabilities increase  |
| □ <i>Above 5</i>                | □ Low solubility and poor oral bioavailability. Erratic absorption. High metabolic liability, although potency may still be high. |

# Bio-pharmaceutics

---

- ❑ determination of drug solubility, wrt its anticipated dose, is most important.
- ❑ Solubility - the ratio of the anticipated dose of a given drug to its solubility, together with the dissolution rate, determine the *fraction of the dose available for absorption.*

# Bio-pharmaceutics

---

- ❑ Gastric and intestinal fluids are a complex mixture of natural surfactants, salts, and buffers- important to determine the effect of pH, salts, and surfactants on a drug's solubility.

Poorly soluble compounds represent an estimated 60% of compounds in development and many major marketed drugs

# Bio-pharmaceutics

---

- ❑ Dissolution of poorly, water soluble drugs can be problematic for drugs that otherwise have good permeability characteristics in the gastrointestinal tract.
- ❑ Poor dissolution can reduce bioavailability of these drugs in formulations developed for oral delivery.
- ❑ Different strategies for enhancing dissolution exist.

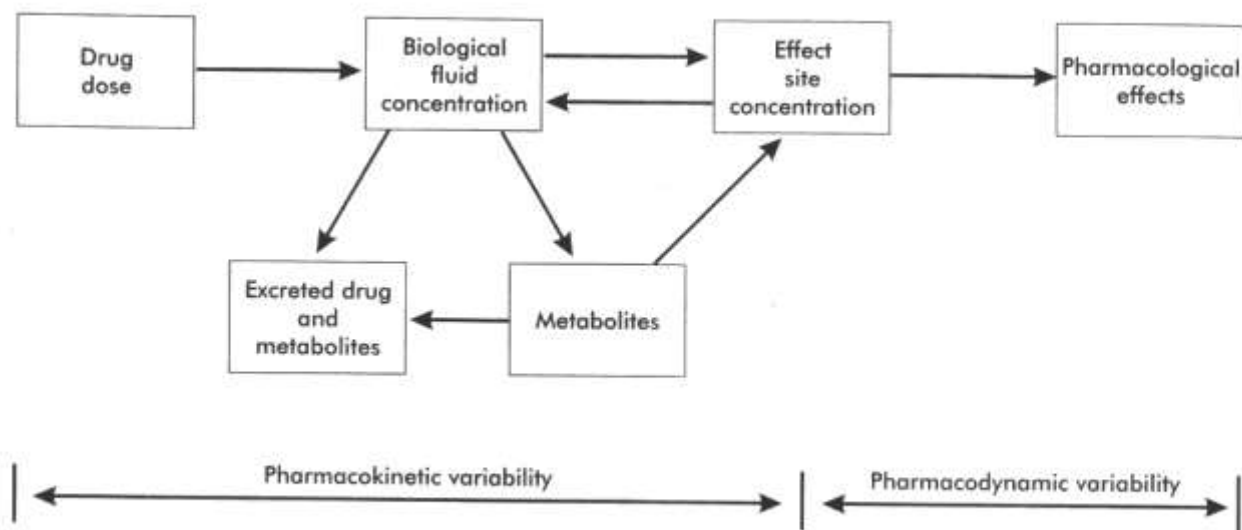
# Bio-pharmaceutics

---

- ❑ Theoretically, micronisation should be able to achieve large surface areas;
- ❑ however, micronised drug powders are extremely cohesive due to high energy milling processes causing significant dislocation of crystal structure on the particle surface.
- ❑ These particles tend to agglomerate during the solid state processing and unless properly formulated can lead to poor dissolution performance.

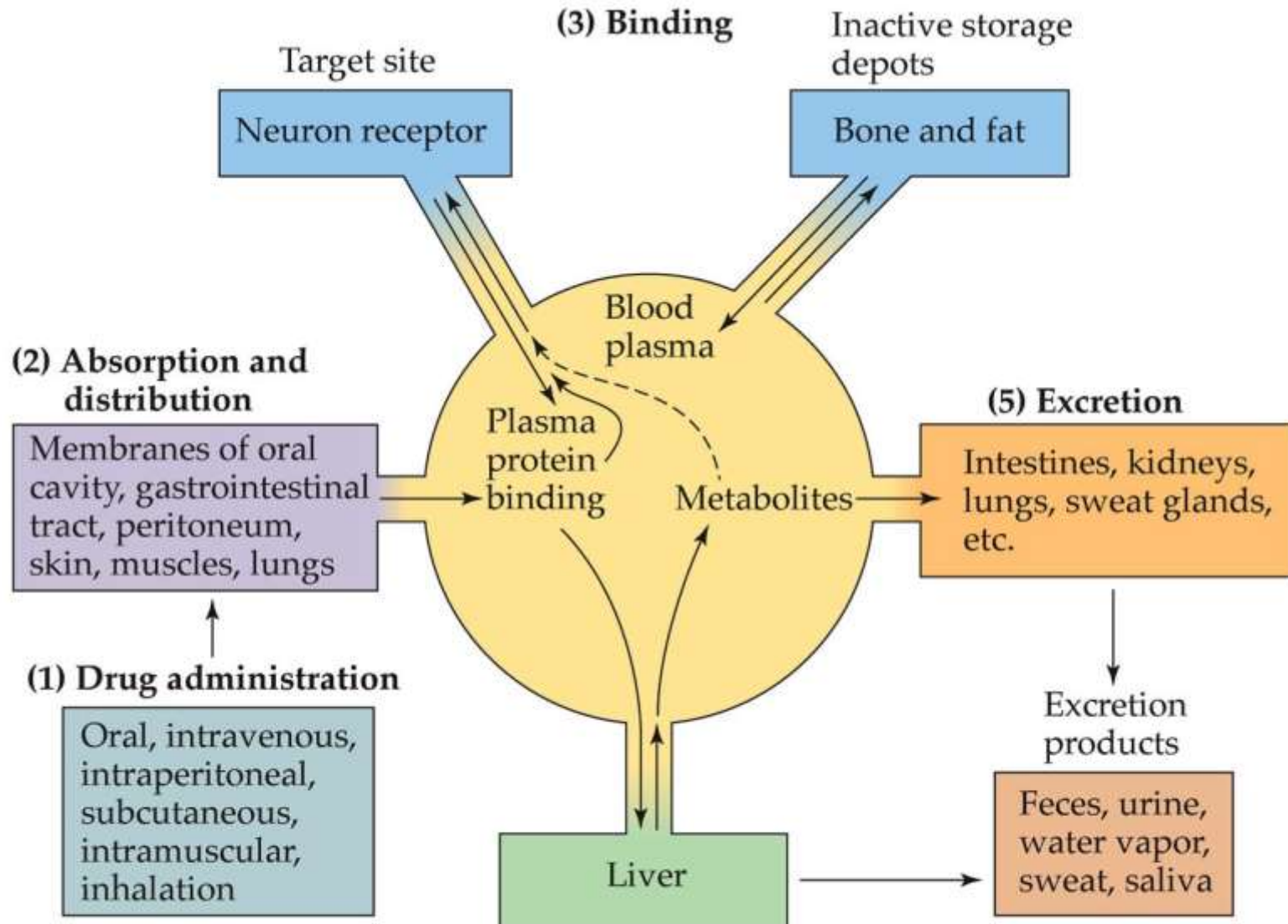


# Overview



**Figure 8-1.** Pharmacokinetic and pharmacodynamic variability as determinants of the dose-effect relationship.

# Pharmacokinetics



Vidyabharti College of Pharmacy, Amravati

# Poorly soluble drugs

---

- ❑ **Poor bioavailability leading to high dose and/or multiple dosage units per dose**
- ❑ **Highly variable pharmacokinetics leading to inadequate therapy and/or safety concerns**
- ❑ **Significant food effects on bioavailability leading to dosing restrictions in labeling and consequent patient compliance problems**

# Approaches

---

- ❖ Buffers
- ❖ Co-solvents (GRAS approved)
- ❖ Additives/complexes -surfactants, polymers, cyclodextrins)
- ❖ Lipid-based systems (solutions, emulsions)
- ❖ Solid-state modification (particle size reduction, salt formation, solid-state stabilisation of the amorphous state)

# Approaches

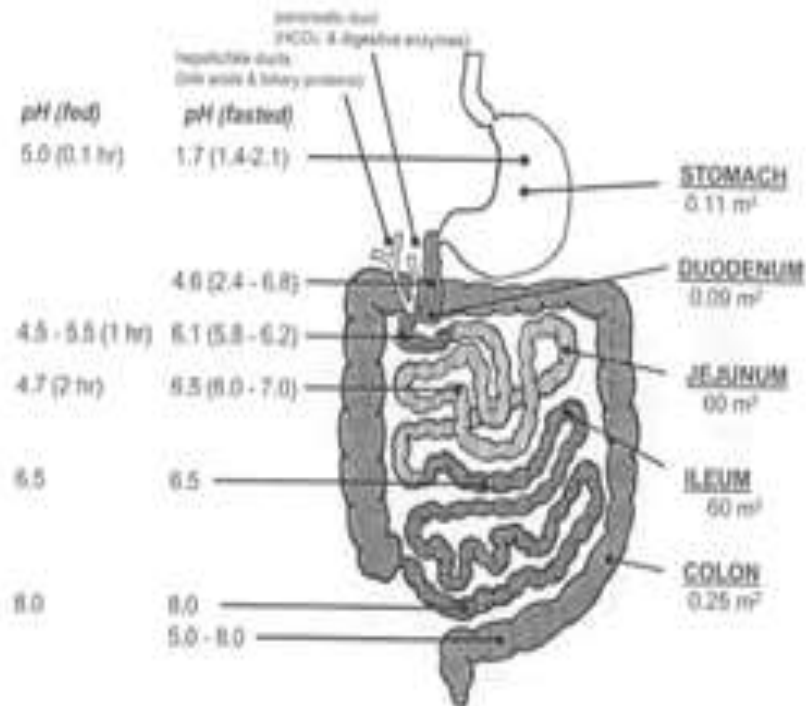
---

- ❑ Buffering Agents
- ❑ minimize changes in hydrogen ion concentration- maintain pH even on dilution or addition of strong acids or bases
- ❑ pH-effective concentration of hydrogen ions in solution. Range 0-14
- ❑ Multi media dissolution

# Buffers

380 Current Topics in Multidisciplinary Chemistry (2015) Vol. 3, No. 4

Chen Sheng



# Co-solvent

---

## Propylene glycol

- ❑ Solvent in elixirs and pharmaceutical preparations
- ❑ Solvent and coupling agent in the formulation of sun screen, lotion, shampoos, shaving creams and other similar products
- ❑ Emulsifier in cosmetic and pharmaceutical creams

# Propylene glycol

---

- Propylene Glycol USP/EP (PG USP/EP) is tested against the specifications of the United States, European and Japanese Pharmacopoeia, plus the Food Chemicals Codex (FCC) and complies with requirements for pharmaceutical applications worldwide



# Propylene Glycol

---

- ❑ Propylene Glycol (PG), known also by the systematic name propane-1,2-diol, is an
- ❑ organic compound (a diol alcohol) that is usually a tasteless, odorless and colorless
- ❑ clear oily liquid. It is hygroscopic and miscible with water, acetone and chloroform.

# Others

---

- ❑ Polysorbate 80
- ❑ SLS
- ❑ DOSS
- ❑ PEG
- ❑ Ethanol/ IPA

# Polyethylene glycols

---

## Polyethylene glycols

- parenteral,
- topical,
- ophthalmic,
- oral
- rectal preparations

# Polyethylene glycols

---

- ❑ stable, hydrophilic substances
- ❑ water soluble
- ❑ viscosity adjustment
- ❑ emulsion stabilizers
- ❑ 30% v/v, PEG 300 and PEG 400 - vehicle for parenteral dosage forms
- ❑ solid dispersions –for poorly soluble drugs

# Surfactants

---

- ❑ **Anionic** -Sodium lauryl sulphate SDS  
Sodium caprate
- ❑ **Cationic** -Tetradecyl trimethyl ammonium bromide (for steroids)'Hexadecyl trimethyl ammonium bromide
- ❑ **Nonionic** -Polysorbate (Tween), Span, Brij, Triton series, PEG-stearate, PEG-lauryl ether

# HLB

---

The Hydrophilic-lipophilic balance of a surfactant is a measure of the degree to which it is hydrophilic or lipophilic

Value close to 0- hydrophobic

Value close to 20 - hydrophilic

# HLB Values

---

The HLB value can be used to predict the surfactant properties of a molecule:

- ❑ A value from 3 to 6 indicates a W/O emulsifier
- ❑ A value from 7 to 9 indicates a wetting agent
- ❑ A value from 8 to 12 indicates an O/W emulsifier
- ❑ A value from 12 to 15 is typical of detergents
- ❑ A value of 15 to 20 indicates a solubiliser or hydrotrope.

# Non ionic surfactants

---

- ▣ Each surfactant has a hydrophilic group and a lipophilic group
- # must have both or it would not be surface active
  - the hydrophilic group is usually a polyhydric [polyhydric-an alcohol with OH's attached] alcohol or ethylene oxide
- # the lipophilic group is usually a fatty acid or a fatty alcohol



# Solubility enhancer's

---

- ❑ polysorbate 20, 60, 80
- ❑ lecithins
- ❑ Pluronic F-68R
- ❑ PEG-400 Castor Oil
- ❑ Cyclodextrins

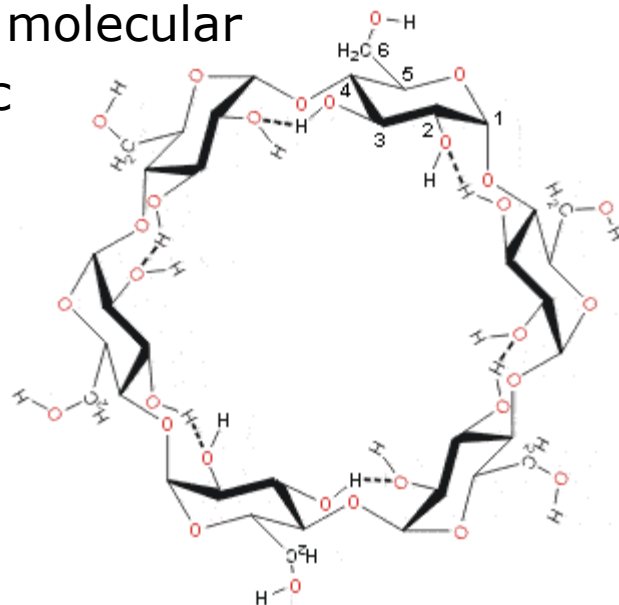
# Cyclodextrins

---

- ❑ To increase aqueous solubility of drugs.
- ❑ To increase chemical stability of drugs.
- ❑ To enhance drug delivery to and through biological membranes.
- ❑ To increase physical stability of drugs.
- ❑ To convert liquid drugs to microcrystalline powders.
- ❑ To prevent drug-drug and drug-excipient interactions.
- ❑ To reduce local irritation after topical or oral administration.
- ❑ To prevent drug absorption into skin or after oral administration.

# Cyclodextrins

- non-reducing cyclic glucose oligosaccharides
- 6, 7 or 8 D-glucopyranonsyl residues ( $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrin respectively)
- cavities have different diameters
- hydrophilic groups - outside of the molecular cavity & inner surface is hydrophobic



# SEDDS

---

- ❑ Self emulsifying drug delivery systems
  - ❑ Uses oil as internal phase
  - ❑ Provides high drug solubility
  - ❑ Uses surfactant and co surfactant
  - ❑ Large oil/water interfacial energy results in
    - Self emulsification upon aqueous dilution
- Emulsion stability

# SEDDS

---

- ❑ Emulsification without high shear mixing
- ❑ Non aqueous concentrate protects drug unstable in water
- ❑ Droplet size < 100 microns
- ❑ Enhanced bio-availability
- ❑ Elimination of solid dissolution process
- ❑ Distribution of micelle-solubilized drug in gut wall

# SEDDS

---

SE system composed of:

- Polyoxyl 40 hydrogenated castor oil (Cremophor® RH 40),
- Sorbitan monooleate (Montane® 80)
- Diethylene glycol monoethyl ether (Transcutol® HP)

Ketoprofen aqueous solubility in dilution was measured in pH 1.2 buffer for a filled SE system capsule compared to a marketed powder capsule.

The solubility of ketoprofen was 15 times higher for the SE system.



# Salt formation

---

- ❑ drug substances can be classified as being either acids or bases
- ❑ Can also exist as ionic species
- ❑ state of ionization of a substance affects its degree of aqueous solubility
- ❑ E.g. high solubility of sodium benzoate as opposed to the low solubility of benzoic acid.

# Polymorphism

---

- ❑ API's can exist as polymorphs
- ❑ Polymorphs are crystalline materials that have the same chemical composition but a different arrangement of atoms at the molecular level.
- ❑ pseudopolymorphic forms, referred to as hydrates (water incorporation) or solvates (solvent incorporation)



# Polymorphism

---

- ❑ different forms
- ❑ similar in chemical structure
- ❑ different physical properties
- ❑ Different chemical properties
- ❑ Different solubility, stability and bioavailability

# Particle size

---

## Micronization and Nanoparticle technology

- Primarily increase surface area for dissolution
- Addresses only the dissolution rate aspect of the problem with delivery of poorly soluble drugs
- Introduces manufacturing complexity

# Solid dispersion technology

---

## **Solid dispersion technology**

- ❑ **Stabilizes a more rapidly dissolving “amorphous state” of the drug in a solid matrix**
- ❑ **Addresses only the dissolution rate aspect of the problem with delivery of poorly soluble drugs**
- ❑ **Introduces significant physical stability concerns and manufacturing complexity**
- ❑ **HPMC, PVP, PEG**

# Dissolution

---

## Environmental factors

- ❑ Intensity of agitation and rate of flow of fluid
- ❑ Concentration gradient
- ❑ Temperature of dissolution medium
- ❑ Composition of the medium- pH, ionic strength, tonicity

# Classification

---

	Parts of Solvent per	Parts of Drug Solubility
Very Soluble	<1 part	>1 gm/mL
Freely Soluble	1 to 10 parts	100 mg/mL to 1 gm/ml
Soluble	10 to 30 parts	30 to 100 mg/mL

## **The Poorly Soluble Drugs Fall in Categories Below**

Sparingly Soluble	30 to 100 parts	10 to 30 mg/mL
Slightly Soluble	100 to 1,000 parts	1 to 10 mg/mL
Very Slightly Soluble	1,000 to 10,000 parts	0.1 to 1 mg/ml
Insoluble	>10,000 parts	< 0.1 mg/ml = 100 µg/mL

***Poorly Soluble Drugs***

***<100 µg/mL to 30 mg/mL***

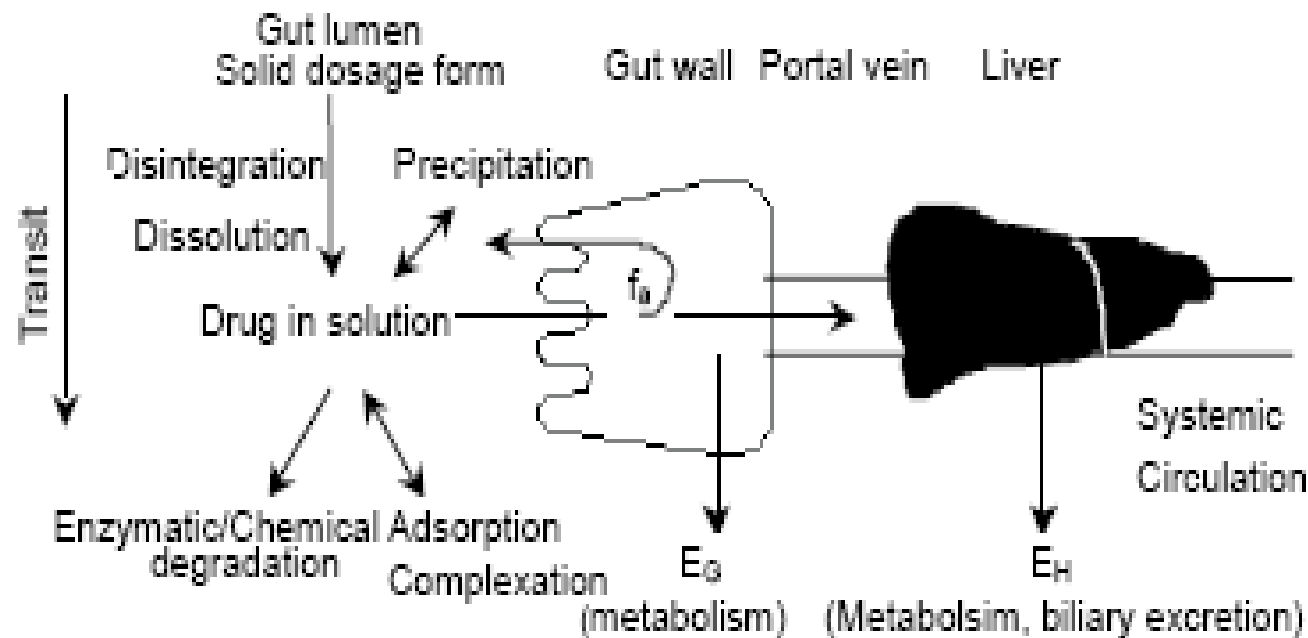
# Dissolution

---

## Drug properties

- ❑ Polymorphism
- ❑ Amorphous state and solvation
- ❑ Free acid/ base/ salt form
- ❑ Particle size
- ❑ surfactants

# Dissolution-Absorption



# Dissolution-Absorption

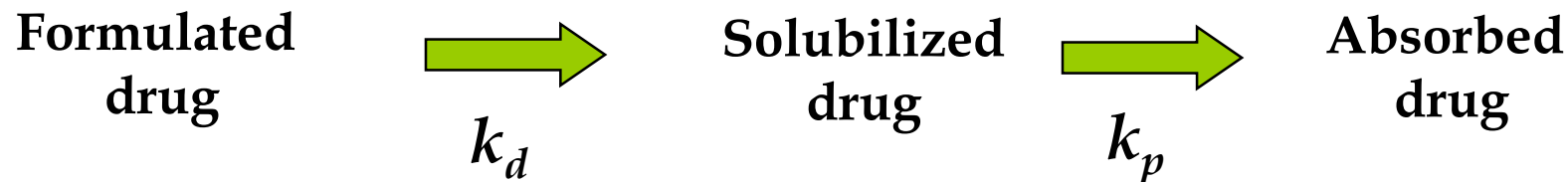
---

- ❑ **Attributes that can affect the dissolution and permeability rates include those**
  - **Related to API solubilization**
    - ❑ API salt form, polymorph, particle size, surface area or wetting
  - **Related to cohesive properties of the drug product that influence disintegration**
    - ❑ Porosity, hardness, wetting, swelling/water penetration



# Basic Concept of BCS

---



**$k_d$  = dissolution rate**

- **function of solubility (including food), drug product quality attributes**

**$k_p$  = permeability rate**

- **major function of API molecular structure**
- **minor dependence on salt form, food?, excipients, etc.**

# SUPAC-IR/BCS: For some 'Level 2' Changes

	<i>HS/HP</i>	<i>LS/HP</i>	<i>HS/LP</i>	<i>LS/LP</i>
Critical Process	Gastric Emptying	Dissolution	Permeability	D/P
IVIVC	Not likely	Likely	Not likely	(?)
Method	0.1 N HCl	pH 1 - 7.4	App/Comp	In Vivo BE
Acceptance Criteria	Single point 85% in 15 min	Multiple profiles (f2 > or = 50)	Single profile (f2 > or = 50)	AUC & Cmax 90% CI 80-125%

Note: NTI drugs excluded for some Level 2 Changes

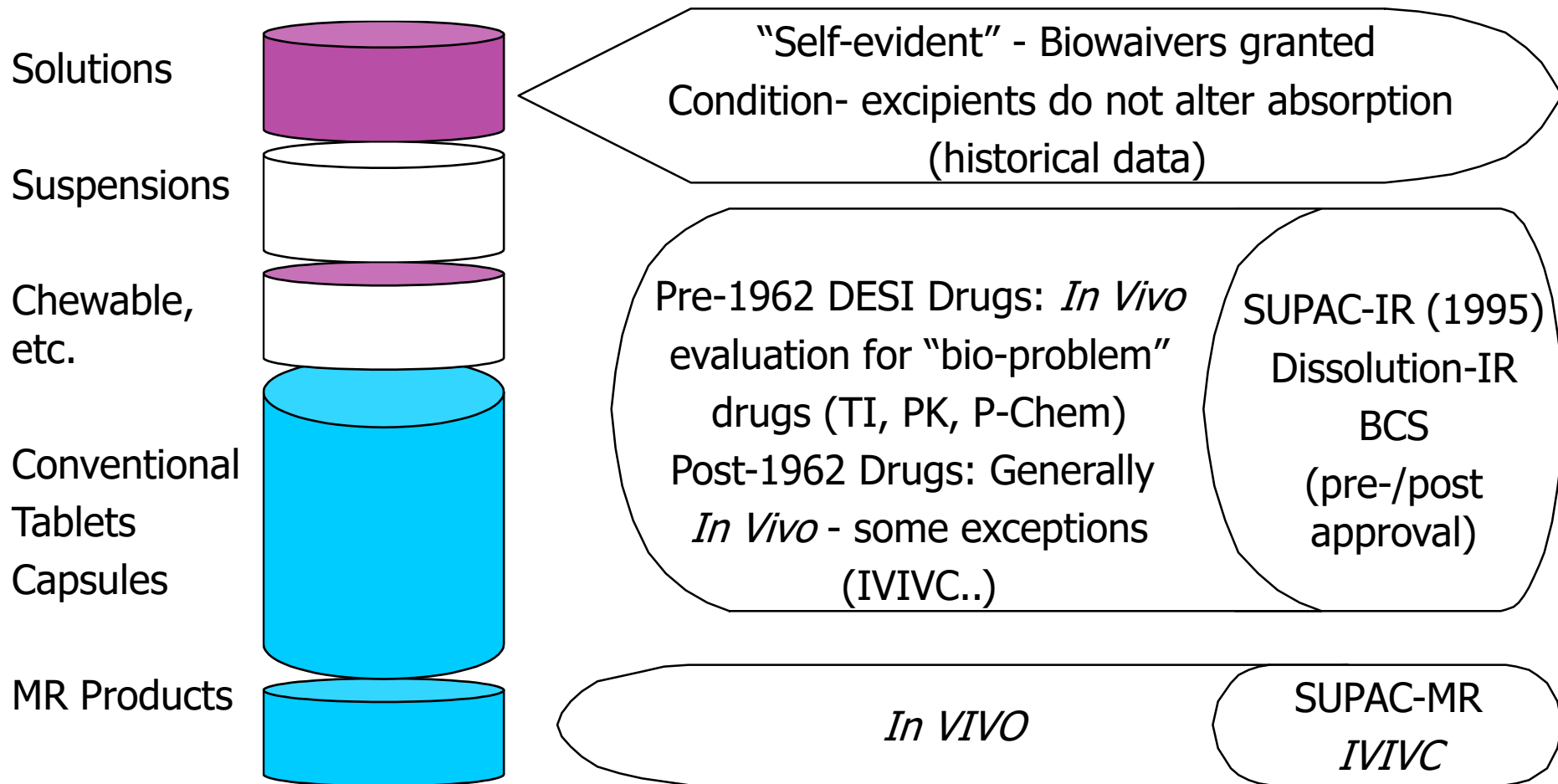
Vidyabharti College of Pharmacy, Amravati

# FDA CDER

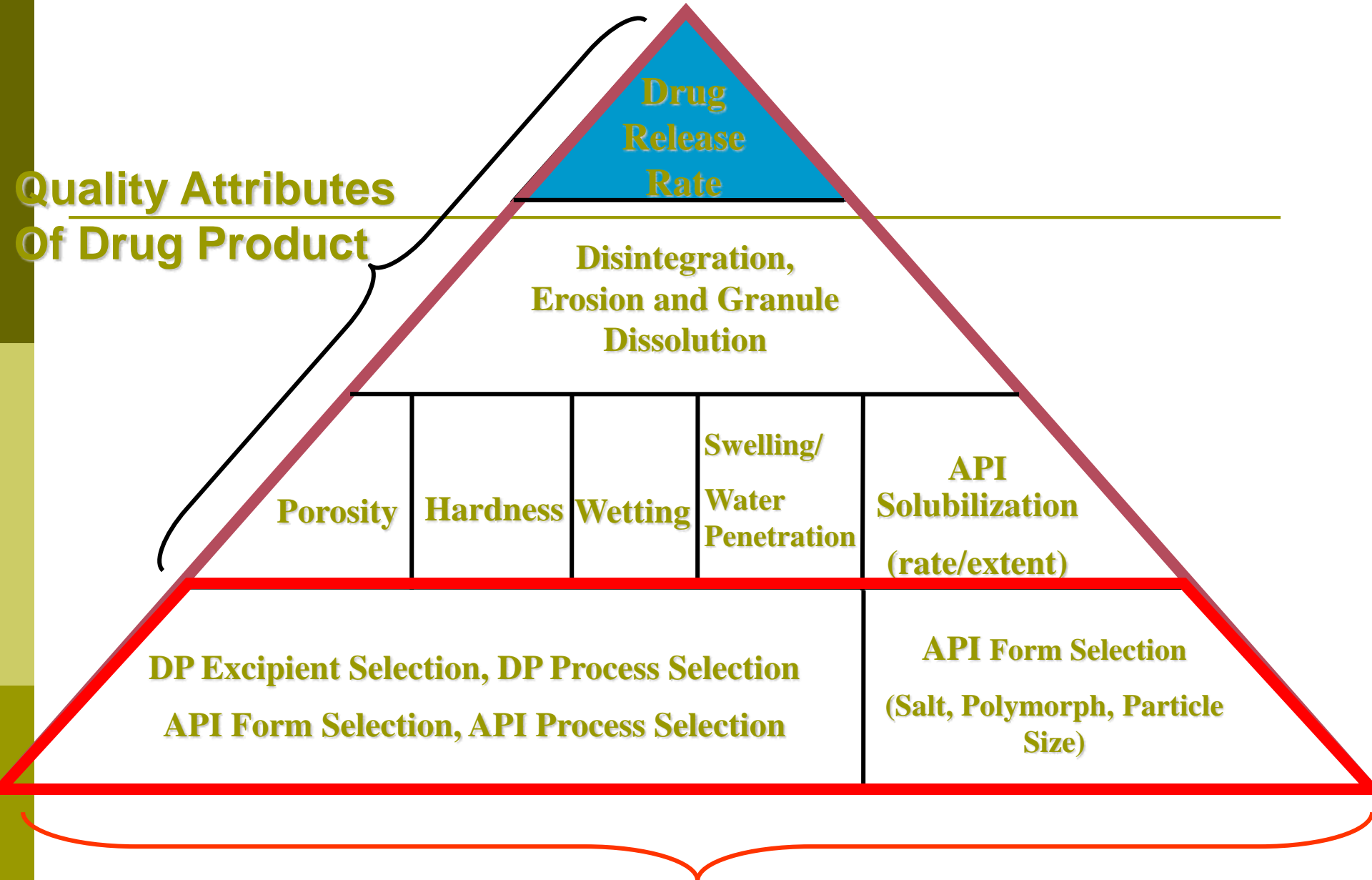
---

- ❑ Importance
- ❑ Classification
- ❑ Approaches to availability
- ❑ Approaches to equivalence
- ❑ Science behind the techniques

# Regulatory Bioequivalence: An Overview



## Quality Attributes Of Drug Product



Features of “Quality by Design”: doing things consciously\*

Vidyabharti College of Pharmacy, Amravati

\*A Quality by Design Approach to Dissolution Based on the Biopharmaceutical Classification System, R. Reed

# Connecting QbD to Quality Attributes

QBD Factors ↓	Porosity	Hardness	Wetting	Swelling/ Penetration	API Solubilization
DP Excipient Selection	PS of excipients (match to API) Hardness/ Brittleness of excipients Granule strength	Bonding Index Brittle Fracture Index Compression force profile via simulation Other mechanical properties	Contact angle measurements	Solubility of excipients Microscopic evaluation of swellability	Analysis described in porosity, wetting and swelling
DP Process Selection*	1 <sup>st</sup> choice: wet granulation 2 <sup>nd</sup> choice: dry granulation 3 <sup>rd</sup> : direct comp.	1 <sup>st</sup> choice: dry granulation 2 <sup>nd</sup> choice: wet granulation/direct compression	1 <sup>st</sup> choice: wet granulation 2 <sup>nd</sup> choice: direct comp. 3 <sup>rd</sup> : dry granulation	1 <sup>st</sup> choice: wet granulation 2 <sup>nd</sup> choice: direct comp. 3 <sup>rd</sup> : dry granulation	1 <sup>st</sup> choice: wet granulation 2 <sup>nd</sup> choice: direct comp. 3 <sup>rd</sup> : dry granulation
API Form Selection	PS of API (match to excipients) Hardness/ Brittleness of API	Bonding Index Brittle Fracture Index Compression force profile via simulation Other mechanical properties	Contact angle measurements	Counter ion selection Polymorph selection Solubility of API form Microscopic evaluation of swellability	Counter ion selection Polymorph selection Analysis described in porosity, wetting and swelling
API Process Selection	N/A	Crystallization/ Milling – mechanical property; shape/size	Milling	N/A	Crystallization/ Milling – shape/size

Vidyabharti College of Pharmacy, Amravati

\*use DP excipient selection measurements to facilitate DP process selection

*Thank you!*



# **ACKNOWLEDGEMENT**

---

- ❑ I would like to express my special thanks of gratitude to Slide share for such nice presentation ,also thanks to my students who have listen carefully.