Pre-formulation Studies

Chemical Properties of Drug Substances

a)Oxidation & Reduction

b)Hydrolysis

c)Photolysis

d)Racemisation

e)Polymerization

f)Isomerisation

Oxidation:

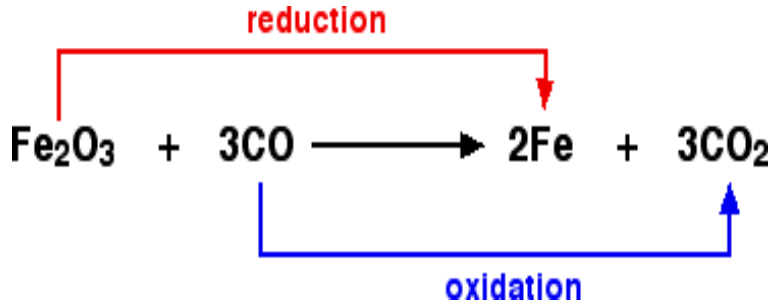
It is very common pathway for drug degradation in both liquid and solid formulation.

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.

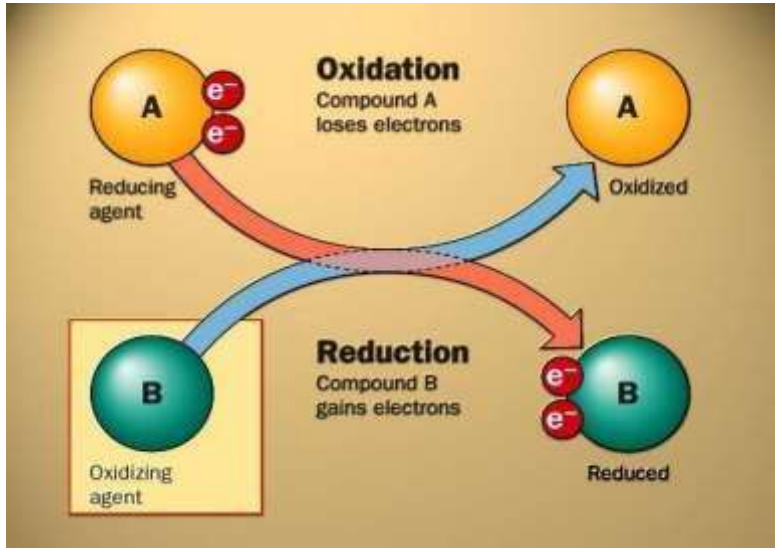
Oxidation occurs in two ways

- **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

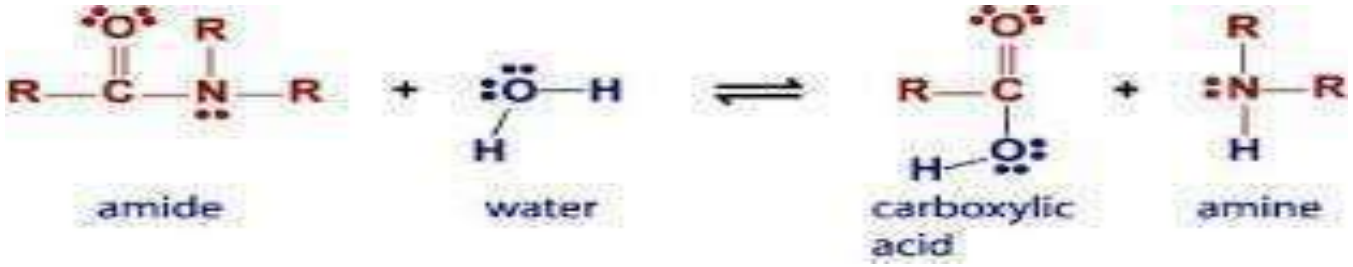
How to prevent oxidation?

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

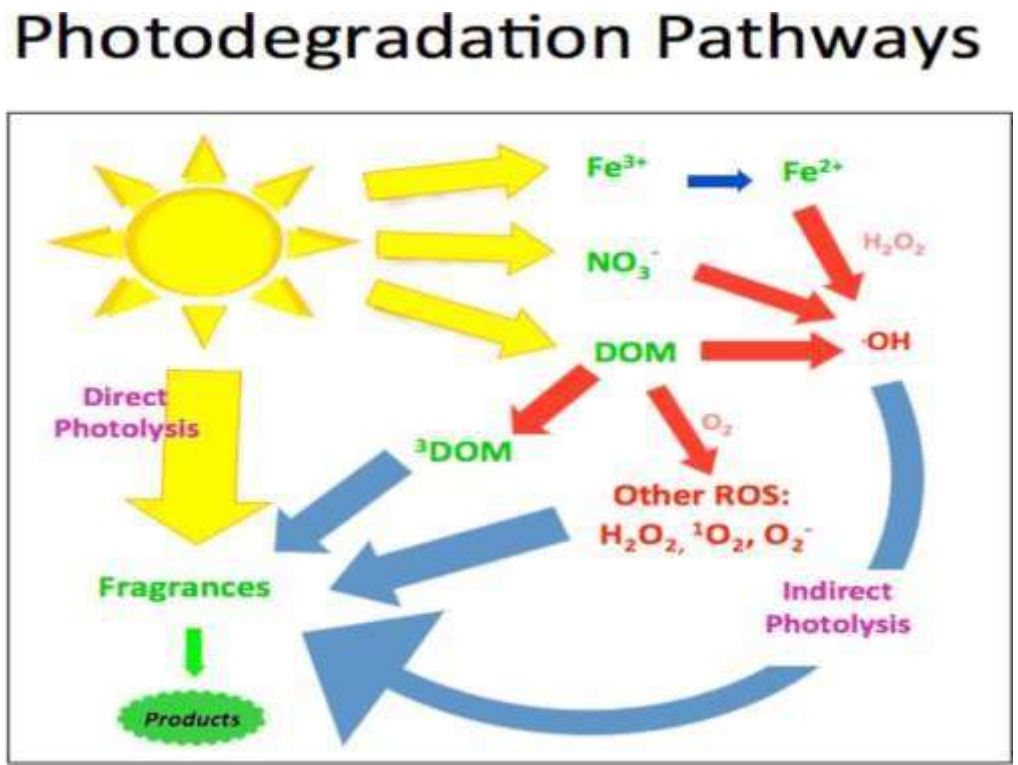
- **Suitable packing.**

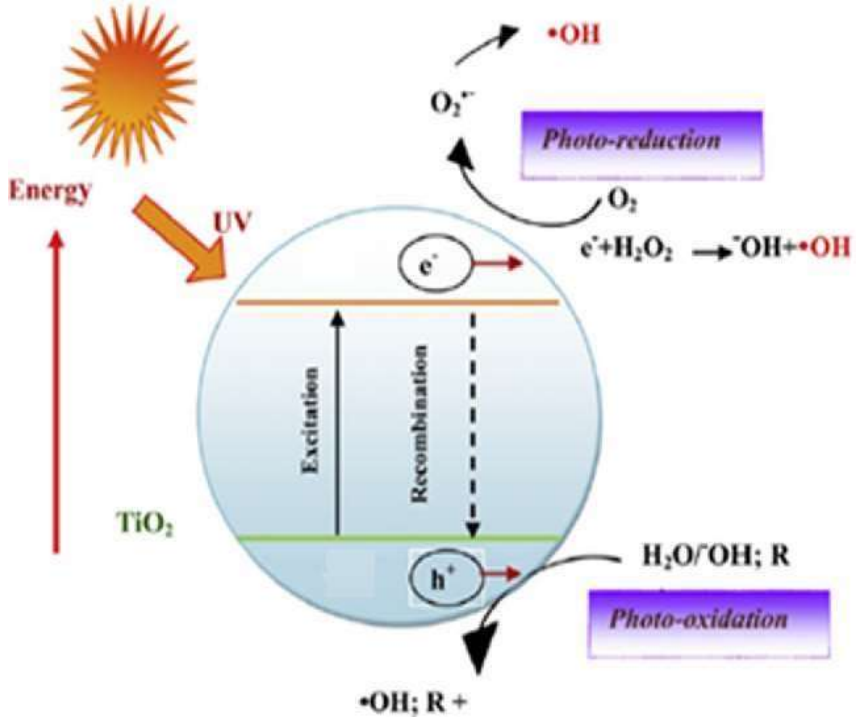
  Yellow-green glass gives the best protection in U.V. region while Amber gives considerable protection against U.V. radiation but little from I.R.

- **Protection of drug from light**

  Nifedipine is manufactured under Na light.

- **Avoiding sunbath**



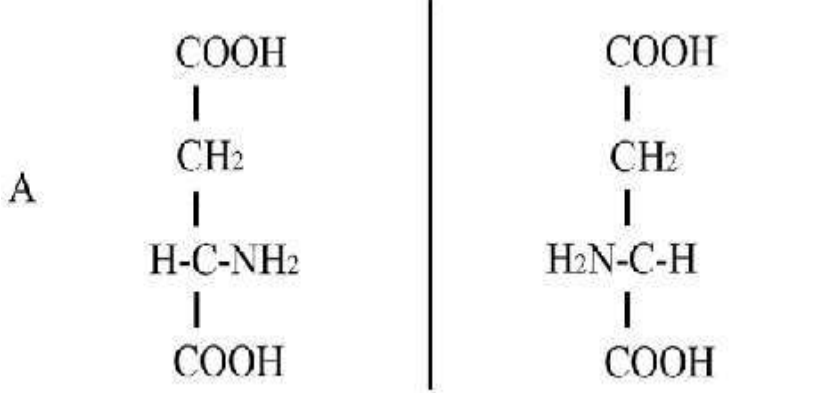


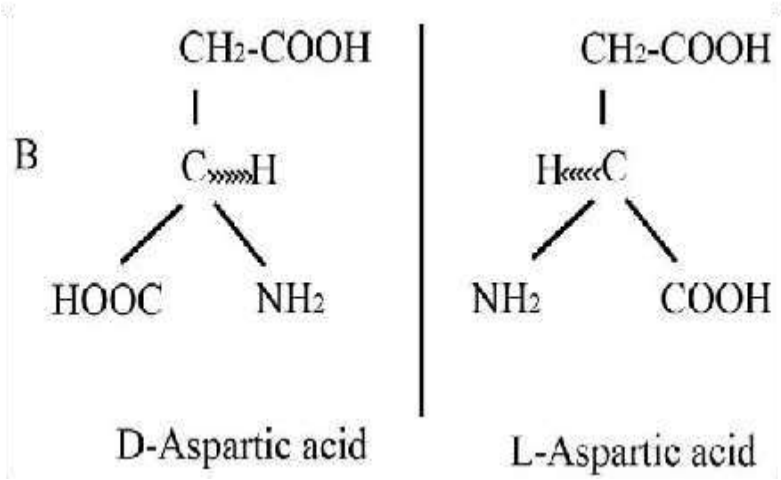
Racemization

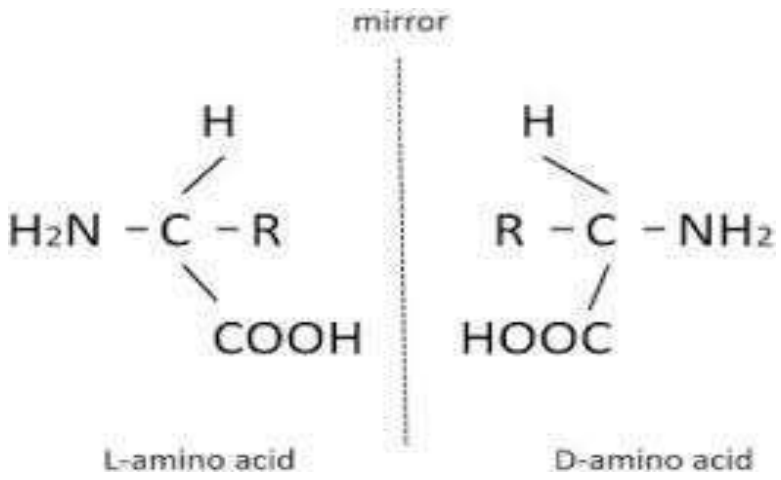
- It is the process in which one enantiomer of a compound, such as an L-amino acid, converts to the other enantiomer.

- 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.



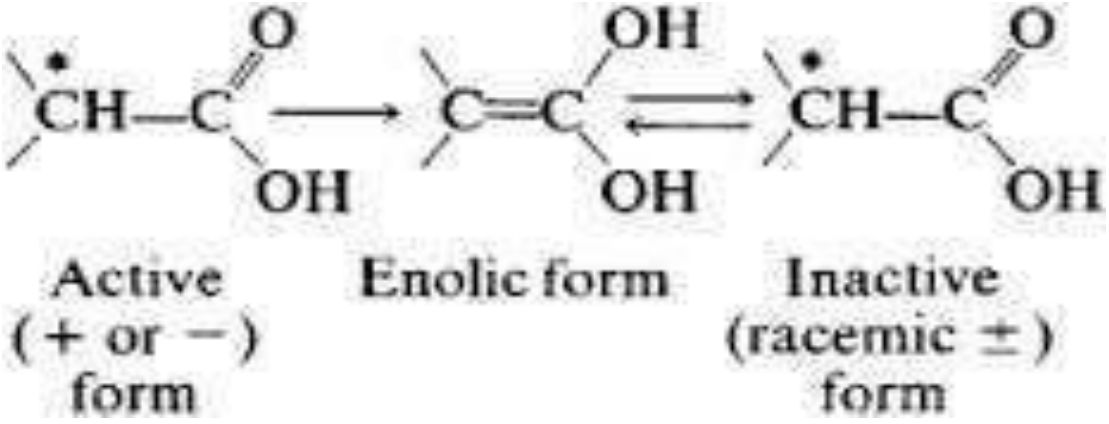


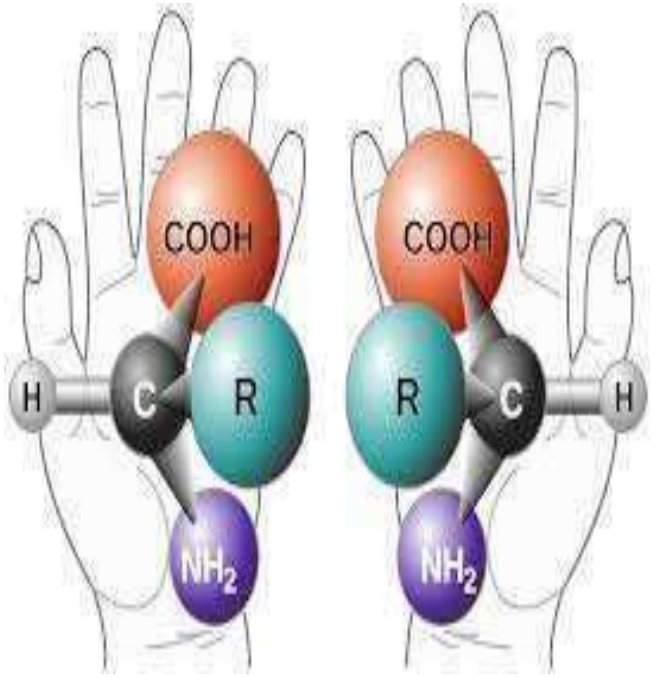


- The inter-conversion from one isomer to another can lead to different pharmacokinetic properties (ADME) as well as different pharmacological & toxicological effect.

- Example: L-epinephrine is 15to 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

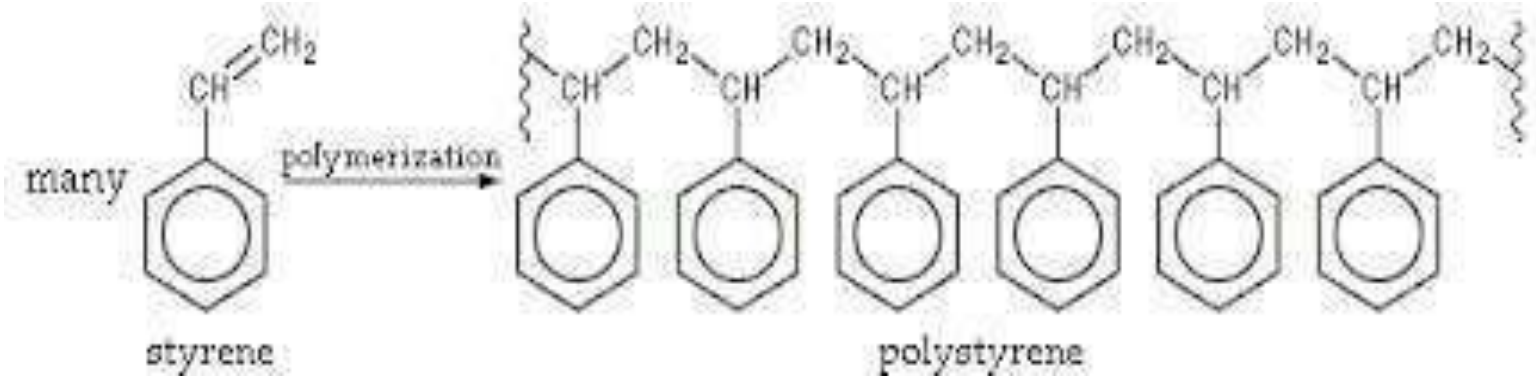




- **Biological significance:**
- Many psychotropic drugs show differing activity or efficacy between isomers, e.g. Amphetamine is often dispensed as racemic salts while the more active dextro-amphetamine is reserved for severe indications;
- Another example is Methadone, of which one isomer has activity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

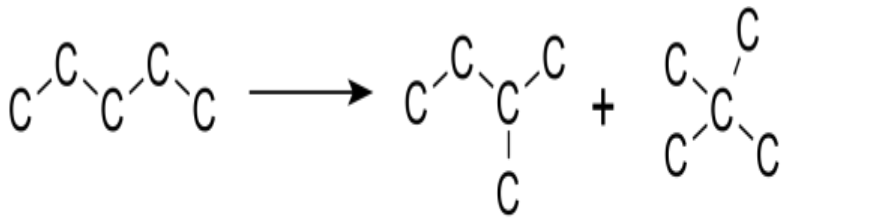


Isomerizaton

- ✓ 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.

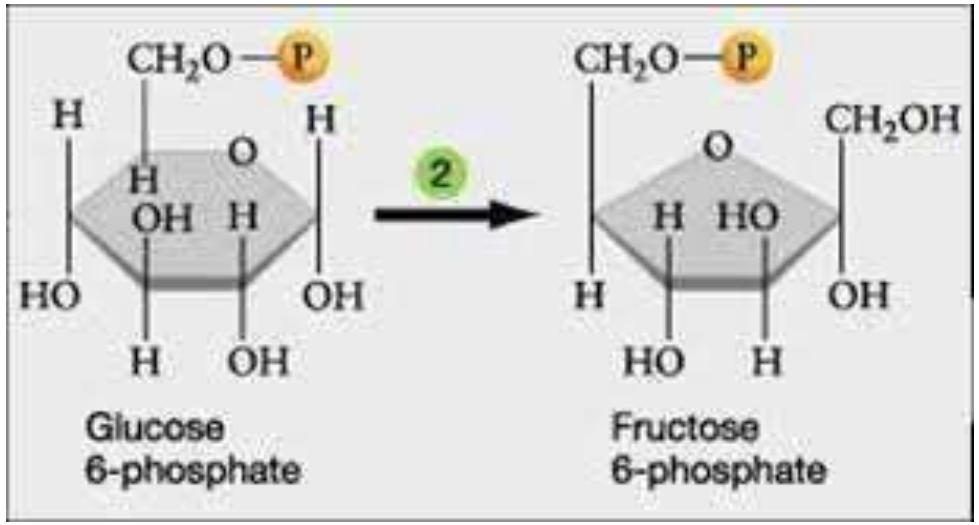


pentane 2-methylbutane 2,2-dimethylpropane

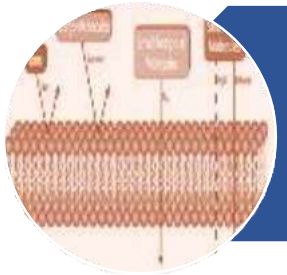
Significance:

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

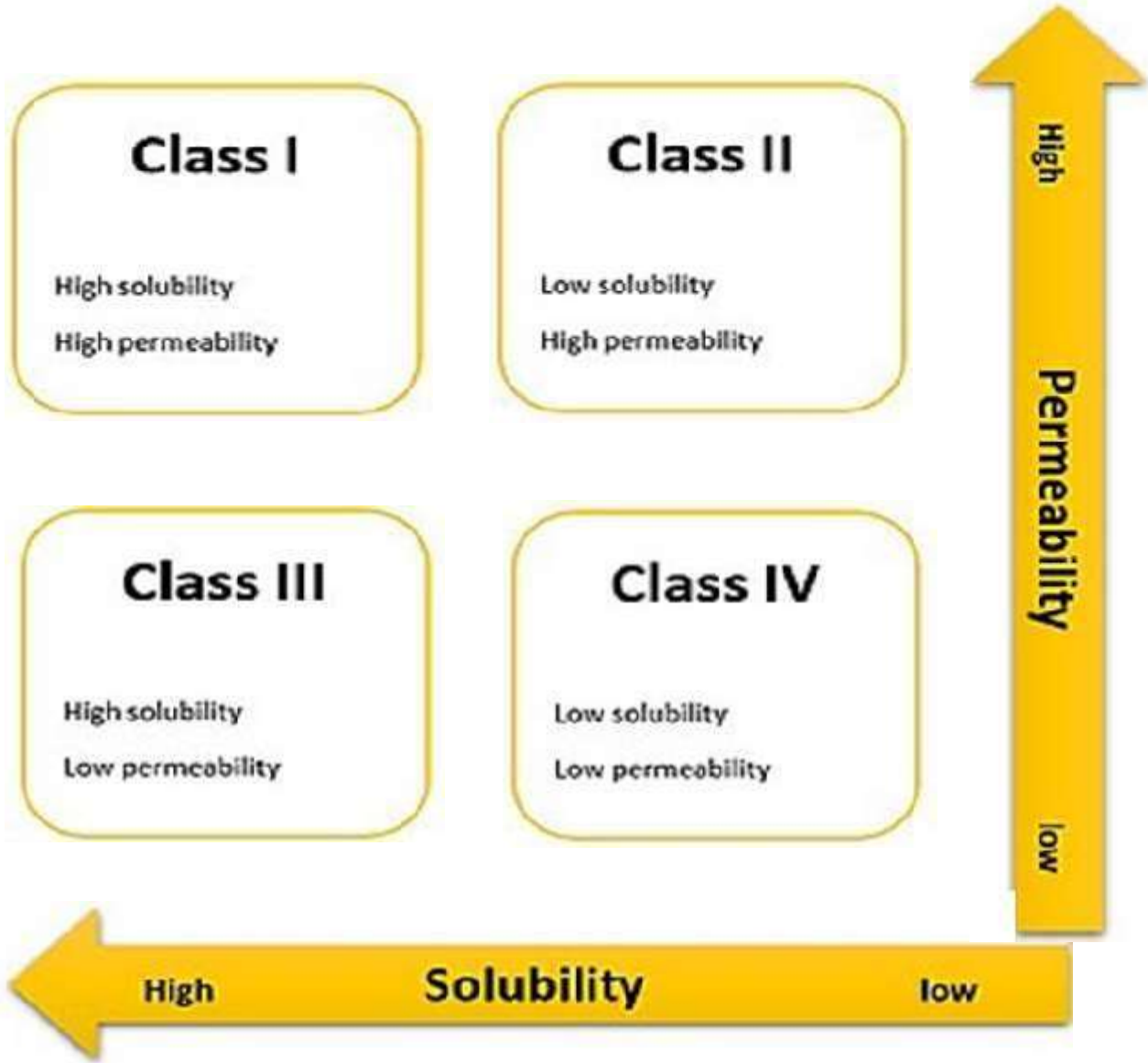


A scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability

Established by Gordon Amidon et al.

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

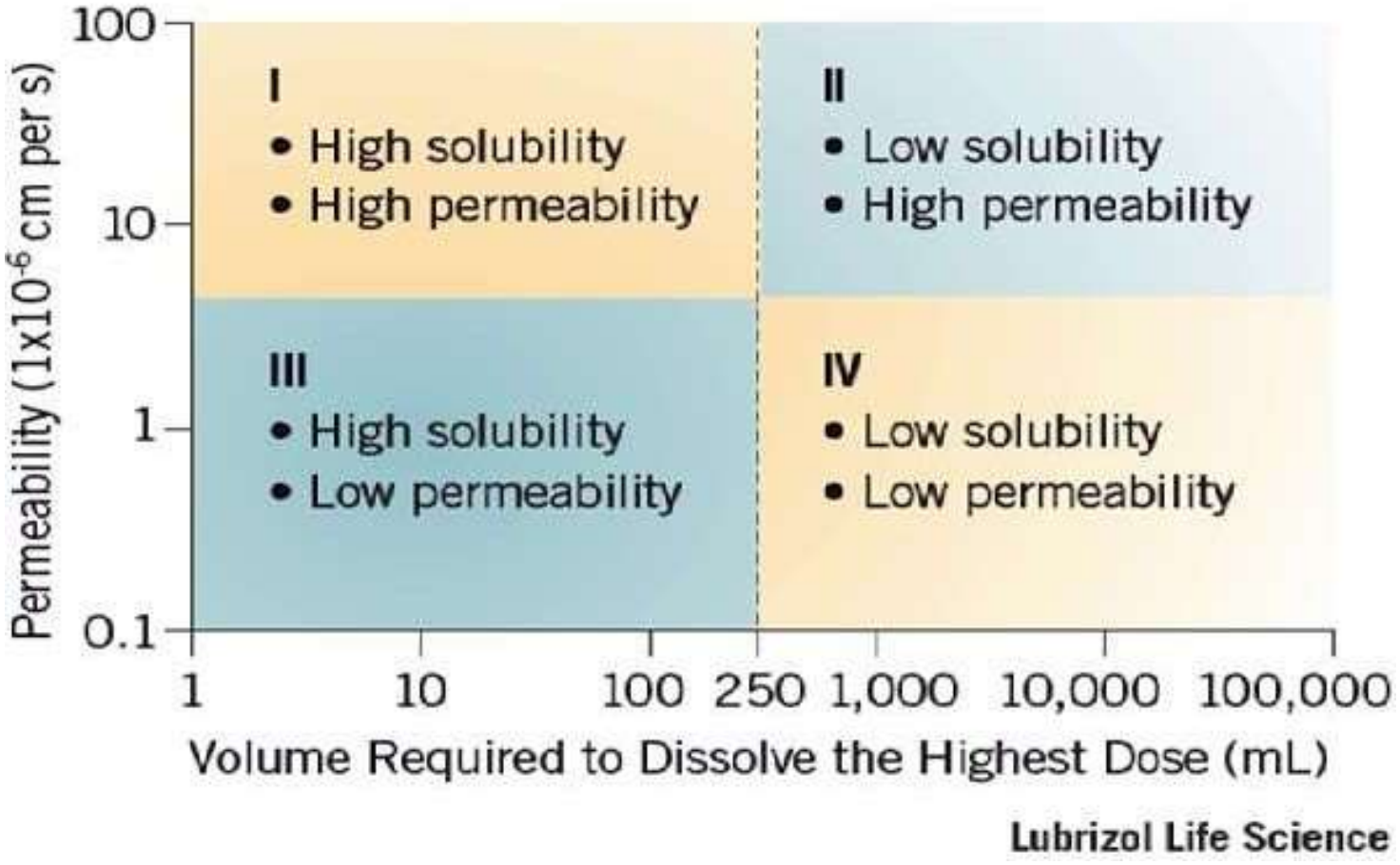
The aim of the BCS is to provide a regulatory tool for the replacement of certain BE studies by conducting accurate *in vitro* dissolution tests.


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

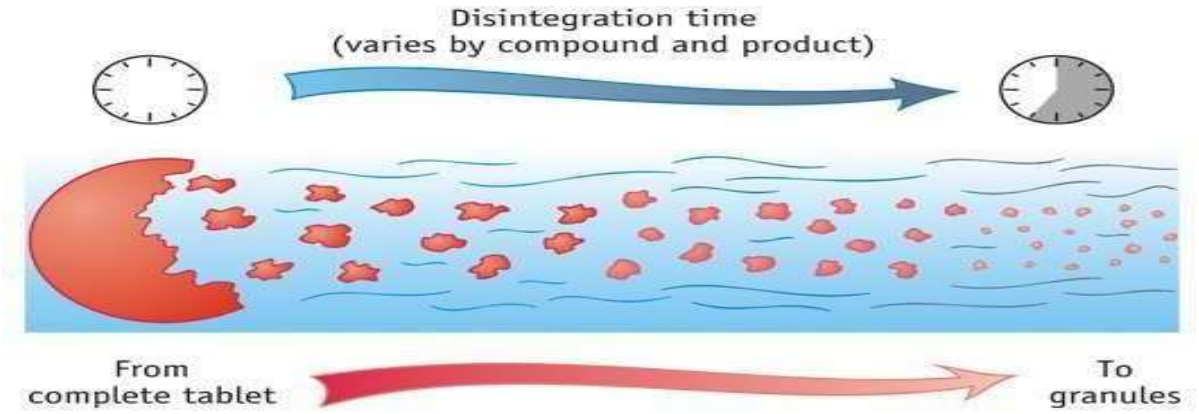
	High Solubility	Low Solubility
Low Permeability	**Class 3** Acyclovir Amiloride Amoxicillin Atenolol Atropine Bisphosphonates Bidisomide Captopril Cefazolin Cetirizine Cimetidine Ciprofloxacin Cloxacillin Dicloxacillin Erythromycin Famotidine Fexofenadine Folinic acid Furosemide Ganciclovir Hydrochlorothiazide 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,

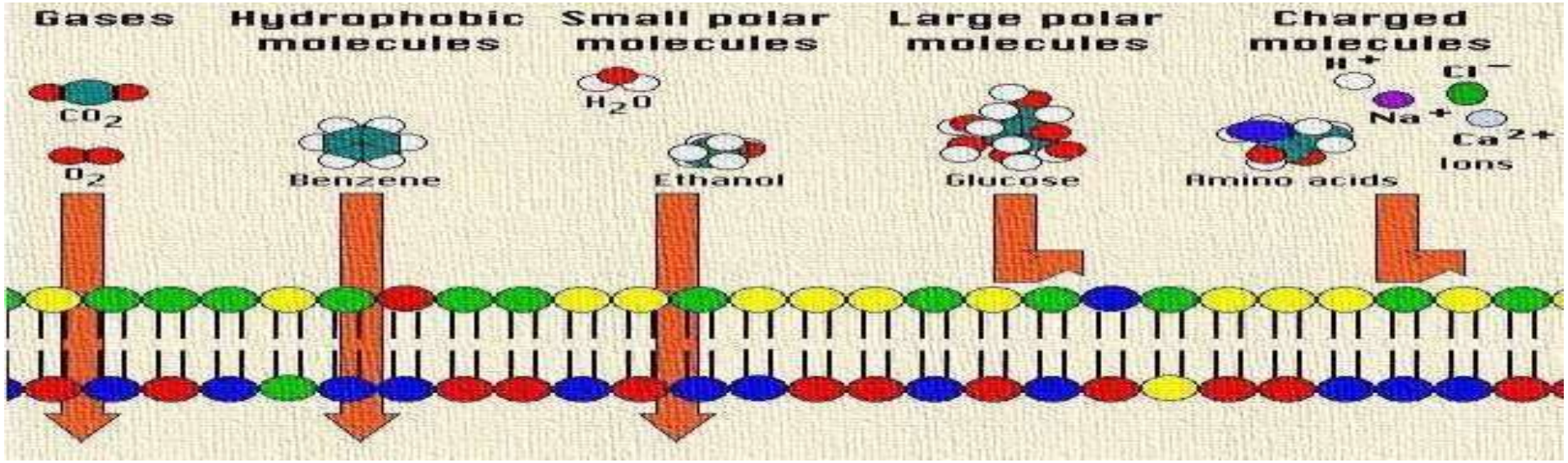
Class – II Low Solubility High Permeability

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

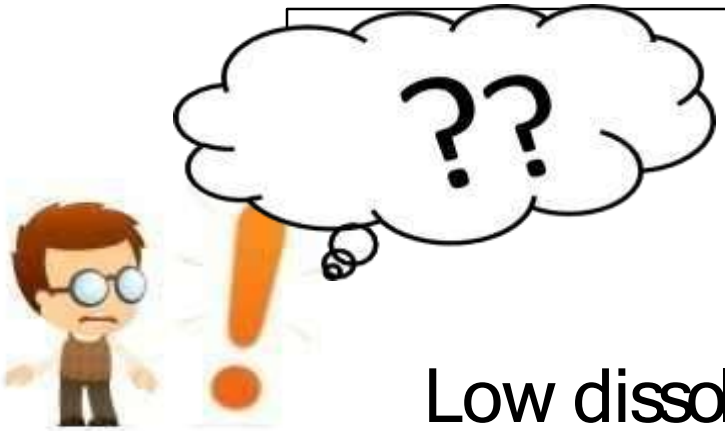


Class– III High Solubility Low Permeability

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

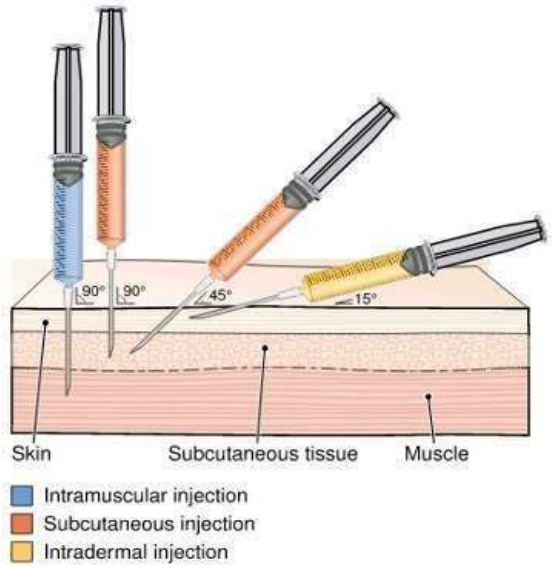


Class – IV-Low Solubility Low Permeability



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