PHYSICAL PHARMACEUTICS-I

UNIT 4 NOTES

COMPLEXATION

- INTRODUCTION
- CLASSIFICATION OF COMPLEXATION
- APPLICATION
- METHOD OF ANALYSIS
- PROTEIN BINDING
- COMPLEXATION AND DRUG ACTION
- CRYSTALLINE STRUCTURE

IMPERFECT PHARMACY

CONNECT WITH US ON :

IMPERFECT PHARMACY APP

@IMPERFECTPHARMACY

COMPLEXATION

- Complexation is simply defined as process of complex Formation by the association of two or more compounds through covalent or Non- covalent interactions.
- Complexes are the compounds that mainly involves two components, i.e, Ligands & Metal Ions.
- They are formed by Donor Acceptor Mechanism.
- They intermolecular forces involved in process of complex formation are Covalent bonds, Vanderwall forces, Dipole - Dipole Interaction & Hydrogen Bonds etc.

STEPS INVOLVED IN COMPLEXATION

- The ligand orbital overlaps the empty metal ion.
- Ligands donates the electric pair.
- Metal ions accepts it.
- Forms complex by Co-ordinate covalent bond.

L: ⟶ M

CLASSIFICATION OF COMPLEXATION

Complexation can be mainly classified into 3 types:

- Metal Ion Complexes
- Organic Molecular Complexes
- Inclusion / Occlusion Complexes

Metal Ion Complexes

- Inorganic types
- Chelates
- Olefin Type
- Aromatic Type

Organic Molecular Complexes

- Quinhydrone Type
- Picric Acid Type
- Caffine Complexes
- Polymer Type

Inclusion / Occlusion Complexes

- Channel Latice Type
- Layer Type
- Elatharates
- Monomoleclar Type
- Macromolecular Type

① METAL ION COMPLEXES

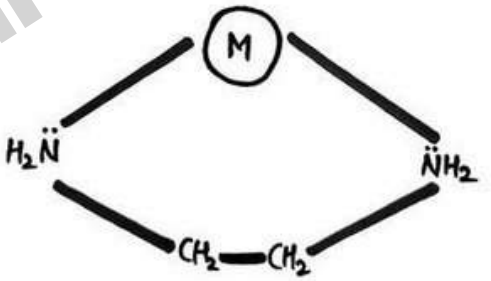
- These complexes include Metals as a central atom that is bonded to one or more ligands.
- They basically includes coordinate covalent bonds.
- Complexation is based on Donor Acceptor Mechanism.

Inorganic Type

- In this ligands are inorganic in nature.
- Metal ions forms complexes with inorganic ligands.
- Example : $[Co(NH_3)_6]$

Chelates

- Chelates are the complexes in which ligand provides two or more
- donor atom.
- Ligands are generally Bidentate or Mithdentate. i.e EDTA, Ethylenediamene.
- Complexes are mostly cyclic structure / closed rings.

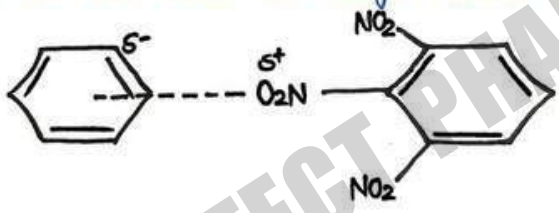


Olefin Types

- Interaction of aqueous solution of metal ions (iron, mercury etc) with Olefin (Alkenes) leads to the formation of Olefin Complexes,
- They are mainly used as catalyst.

② ORGANIC MOLECULAR COMPLEX

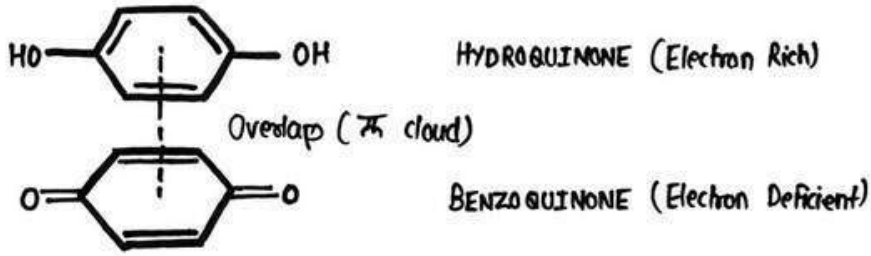
- These type of complexes formed by non-covalent interactions b/w two organic molecules held together by weaker forces or hydrogen bonding.
- They are also known as Addition Complex, because they are formed by addition of two organic molecules.
- They are also known as Charge Transfer Complex.



CHARGE TRANSFER COMPLEX B/W BENZENE & TRI NITRO BENZENE

QUINHYDRONE COMPLEX

- These complex are formed by alcoholic solution of Benzoquinone and Hydroquinone, when mixed in equimolar concentration.



QUINHYDRONE

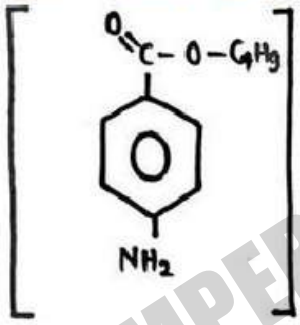
AROMATIC COMPLEXES

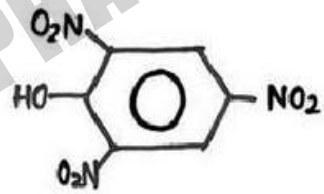
- Interaction of metal ions with Aromatic molecules (such as Benzene) form Aromatic complex.
- They are mainly 3 types:

① Sigma (σ) complexes
② Pi (π) complexes
③ Sandwitch compounds

PICRIC ACID COMPLEX

- Picric Acid is a strong acid & when it forms complexes with weak bases when the complex is known as Picric Acid complex





Caffiene Complexes

- When caffiene forms complexes with acidic drugs then it is known as caffiene complexes.
- Drugs such as Benzocaine, Procaince & Tetracaine form complexes with caffiene.

Polymer Complexes

- Many polymeric materials such as Polyethylene, Glycols, Carbowaxes Forms complexes with various drugs that is known as Polymer Complexes.
- These complexes helps in increasing stability & sustained release of drugs.

③ Inclusion / Occlusion Complex

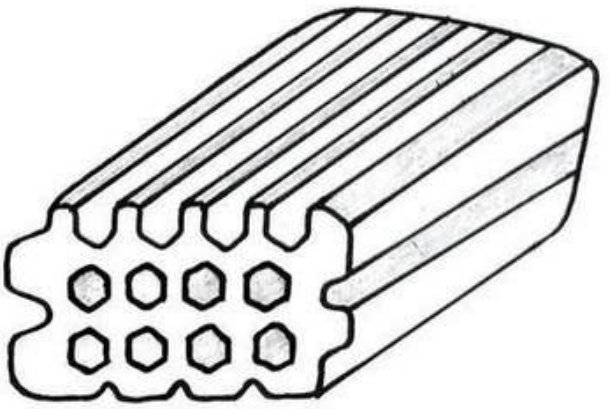
- They are also known as Entrapment Complex.
- They contains two molecules system.

(i) Host molecule

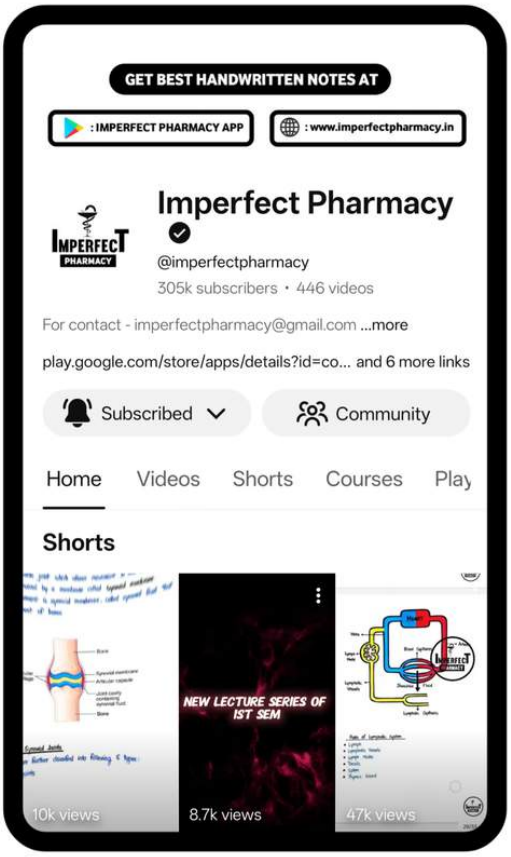
(ii) Guest molecule

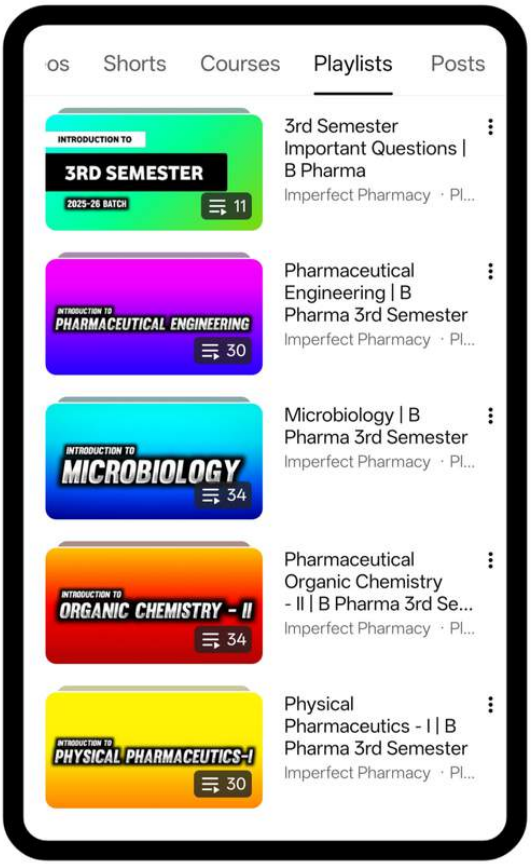
Channel Type

- In this host molecules formed channels through crystallization.
- Guest molecules gets entraped in these channels & form complex.

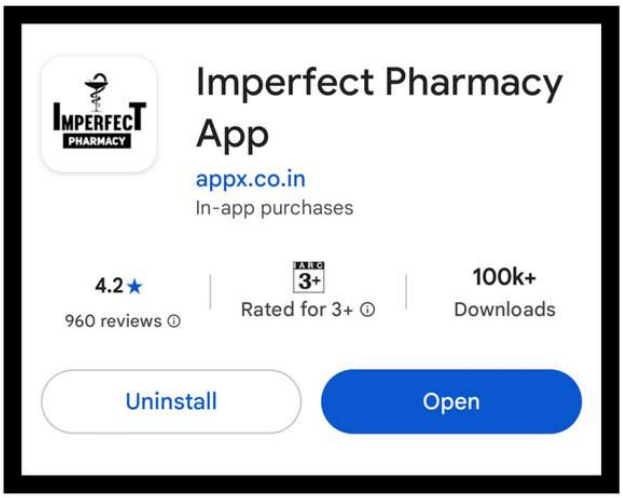


FOR LECTURE VIDEOS VISIT OUR CHANNEL



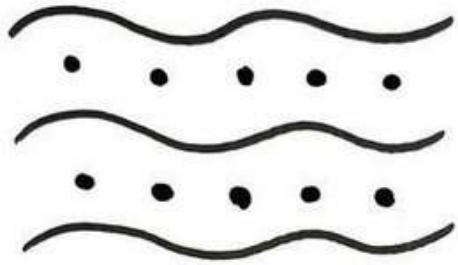


FOR MORE CONTENT : VISIT OUR APP



Layer Type

- In these host & guest are arranged in a layer type structure & form complex.
- They form alternate layer of Guest & Host molecules.

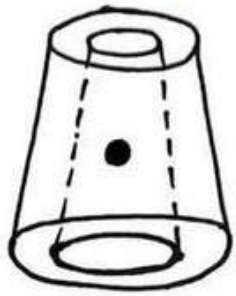


Clathrates

In catharates Host molecules formed cage like structure in which guest molecules gets entraped.

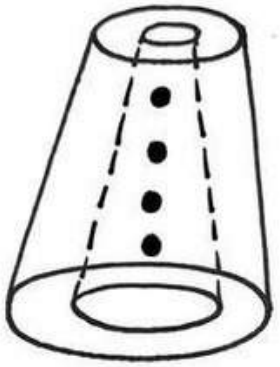
Monomolecular Complex

Monomolecular inclusion compounds involves entrapment of single guest molecules in the cavity of host molecule.



Macromolecular Complex

- They involves entrapment of multiple guest molecules in the cavity of host molecule.



LIGANDS

- Ligands are ions or molecules that contain one or more part of electron that can be shared with metal ions to form complex.
- It can be anion, cation or neutral atom.

Types

Ligands are mainly 3 types :

① Monodentate Ligands
② Bidentate Ligands
③ Multidentate Ligands

Mondentate Ligands

- These ligands only have single lone pair of electron for bonding with central atom.
- Example : NH_3, H_2O etc.

Bidentate Ligands

- They contains two donor atom
- Example : Ethylenediamene

Multidentate Ligands

- They are also known as polydentate Ligands.
- They contains more than two donor atoms.
- Example : EDTA (Ethylene Diamene Tetraacetic Acid)

APPLICATION OF COMPLEXATION

- Conversion From one physical state to other physical state.
- Reduction of volatility.
- Increasing stability of solid drug.
- Increasing chemical stability of drug.
- Increasing Solubility.
- Increasing Dissolution.
- Increasing Bioavailability.
- Reducing Toxicity.
- Treatment of metal poisoning.
- Masking Unpleasant Odour , Taste.

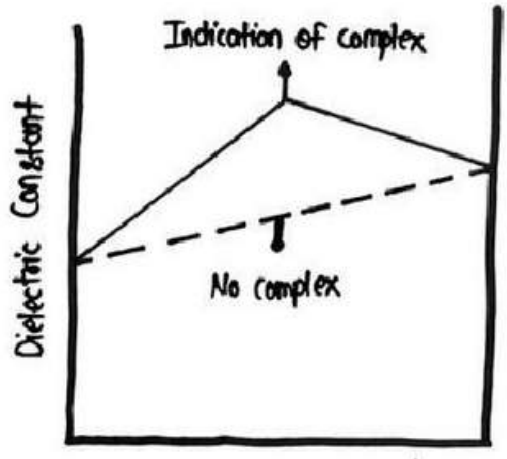
METHOD OF ANALYSIS

In method of analysis, we basically find out that whether the process of complexation occurs or not through various methods:

1. Method of continuous Variation
2. pH Titration Method
3. Distribution Method
4. Solubility method

Method of Continuous Variation

- This method is based on the fact that after the formation of complexation the physiochemical properties of species gets changed.
- According to this process, when two components are mixed & no interaction occurs, then value of the property is additive & graph is straight line.
- If complex formed then value of the property go from maximum that indicates the complex is formed.

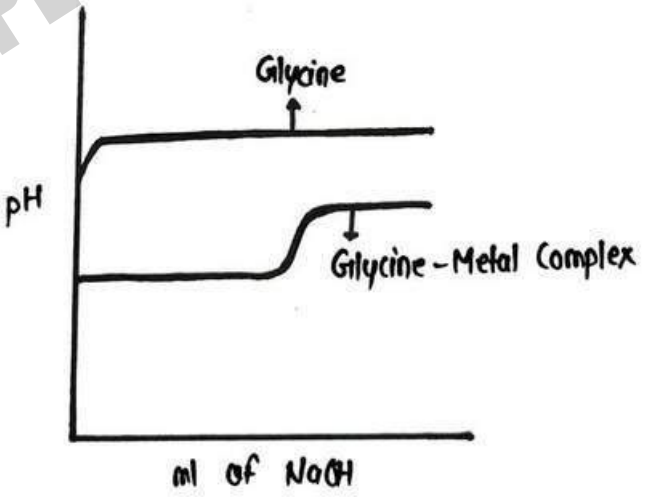


pH Titration Method

- This method is used for when complexation is achieved by change in pH.
- This method is considered as most reliable method.
- e.g. Chelation of cupric ion by glycone.

$$Cu^{2+} + 2NH_2 + CH_2COO^- \longleftrightarrow Cu(NH_2CH_2COO)_2 + 2H^+$$

- As the two portion are formed in the reaction of the equation the addition of glycine to a solution containing cupric ion should result in decrease in pH.
- Titration curve is obtained by adding a strong base to solution of glycine & to another solution containing Glycine & Cupric ion. When we plot the graph of pH vs volume of NaOH, the curve for Glycine Metal Complex is well below that for the Glycine alone.
- The decreased in pH show that complexation occurs.



Distribution Method

- This method is based on the basis of partition coefficient.
- Example : Potassium Iodide Complex

$$I_2 + KI \longrightarrow KI_3$$

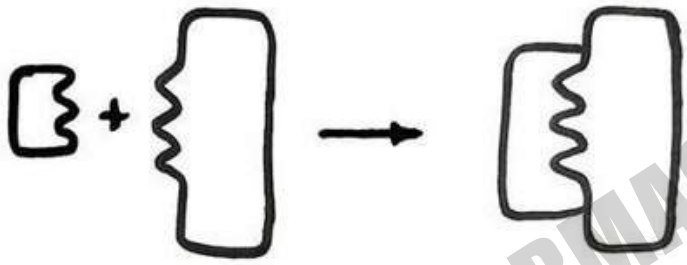
- The distribution coefficient of iodine b/w disulfide & water is 625.
- The K value of Potassium Iodide complex is 954.
- The change is value of K proves that complexation occurs.

Solubility Method

- This method is based on the basis of solubility of Individual components & Complex compound.
- This can be observed by comparing the solubility of the compound before & after the complexing agent.
- The precipatation or charge in turbidity may indicate the complex formation.

PROTEIN BINDING

- The phenomenon of complex formation of drugs with protein is called as Protien Binding.
- A protein bound drug is neither metabolized nor excreted, hence it is pharmcologically Inactive.



Drug + Protien → Protein Drug Complex

Types

Protein binding is of two types:

1. Reversible Protein Binding
2. Irreversible Protein Binding

- **Reversible Binding** It involves weak bonds such as H. Bonds, Hydrophobic bonds, Vander wall Forces etc.

- **Irreversible Binding** Irreversible bonding arises as a result of covalent binding & often a reason for the carcinogenic or tissue toxicity of the drug.

Protein Involves In Protein Binding

Generally these 4 proteins are involved in protein binding:

1. Albumin
2. Globumin
3. α- acid Glycoprotein
4. Lipoprotein

Albumin

- It is the major protein for binding of drugs.
- It is synthesized in liver.
- It is the major component in Plasma Proteine.
- It has 4 binding site:
    1. Site I : Warfarin
    2. Site II : Diazepam
    3. Site III : Digoxine
    4. Site IV : Tamoxifen

Globulin

Globulins are group of proteins in blood that play an important role in liver function & fighting infection.

α- Acid Glycoprotein

Mostly basic drugs binds with α- acid glycoprotein.

Lipoprotein

Liphophilic or lipid soluble drugs binds with Lipoprotein.

SIGNIFICANCE

- Protein binding disturbs absorbtion equilibirium.
- It decreases distribution of drugs.
- It decreases metabolism of drugs & enhanced half life.
- Protein binding helps in sustained release of drugs.
- It also helps in various diagnosis.

Factors Affecting

- **Moleculer Size:** Large molecules may have different binding interactions compare to smaller ones.
- **Shapes:** Complementary shapes b/w ligand & protein binding site influences binding affinity.
- **Competition:** Presence of other substances that can compete for same binding site affect protein binding.
- **pH:** pH changes can alter protein charge that affects binding.
- **Concentration:** Higher concentration of ligands may increase the likelihood of binding.
- **Temperature:** Temperature influences protein confirmation, affecting binding characteristics.

Complexation And Drug Action

- Complexation refers to the association b/w two or more molecules to form a non-covalent or coordinate complex.

Effect Of Complexation On Drug Action

- Complexation can significantly modify drug behaviour, influencing its physiochemical properties, pharmacokinetics, & pharmacodynamics.
- The following are the major effects :

① Effect On Solubility

- Complexation may increase or decrease the aqueous solubility of a drug depending on the type of complex formed.
- Soluble complexes are enhance the solubility of poorly water-soluble drugs.
- Example : Cyclodextrin complexes improve solubility of drugs like Nifedipine, Indomethacin & Ibuprofen.

② Effect On Stability

- Complexation often protect drugs from degradation by shielding them from environmental factors like light, oxygen or metal ions.
- Example : - EDTA (a chelating agent) complexes with trace metal ions such as Fe^{3+} or Cu^{2+}, preventing oxidative degradation of vitamins & antibiotics.
  - Caffiene form complexes with bezoic acid derivatives to reduce volatility & photodecomposition.

Prolonged Or Controlled Drug Action

- Formation of weak complexes can lead to slow release of active drug, producing sustained effect.
- Example : Caffiene - Salicylate complex

Reduction Of Toxicity Or Irritation

- Complexation can reduce local irritation or mask unpleasant taste or odor.
- Examples: Complexation of iodine with polyvinylpyrrolidine (PVP-iodine) reduces iodine irritation but retains antiseptic activity.

Targeted Drug Delivery

- Complexes with macromolecules (like albumin or cyclodextrins) can act as carriers, delivering drugs to specific tissues.

Crystalline Structure Of Complexes

- Complexes can exist in crystalline form, where the molecules or ions arranged in a definite, repeating pattern within a crystal lattice.
- The crystalline structure of a complex influences its stability, solubility, melting point & bioavailability.
- Crystalline complexes have a definite & regular arrangement of metal ions & ligands in a three-dimensional lattice.
- They may show specific geometrics such as octahedral, tetrahedal, or square planar depending on coordination number & bonding.
- The crystalline form provides greater stability, defined composition & reduced hygroscopicity compared to amorphous forms.
- In pharmaceuticals, crystal structure affects solubility & bioavailability of drug complexes.

Thermodynamic Treatment Of Stability Constant

- The stability constant (K) of a complex indicates the extent of association b/w a metal ion & a ligand to form a complex in solution.
- Thermodyamic treatment helps to understand & quantify how strongly a complex is formed & how stable it remains under different conditions

Definition Of Stability Constant

For a complex formation reaction:

$$M + L \rightleftharpoons ML$$

Where M = Metal ion
L = Ligand
ML = Complex

The stability constant (k) is given by:

$$K = \frac{[ML]}{[M][L]}$$

A higher K value indicates a more stable complex.

THERMODYNAMIC RELATIONSHIP

- The stability of a complex is governed by thermodynamic parameters
  - Free energy (ΔG)
  - Enthalpy (ΔH)
  - Entropy (ΔS)

$$\Delta G = \Delta H - T\Delta S$$

- Relationship law stability constant & change in Gibbs free energy (ΔG) can be explained by following equation

$$\Delta G = -2.303\, RT \log K$$

- Where,
  - ΔG = Change in Gibbs free energy
  - R = Gas constant
  - T = Absolute Temperature
  - K = Stability Constant

- Now if ΔG is negative, complex formation is spontaneous & complex is stable.
- If ΔG is positive, formation of complex is non spontaneous & complex will be unstable.

THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER

IMPERFECT PHARMACY

JOIN US ON :


IMPERFECT PHARMACY


IMPERFECT PHARMACY


@IMPERFECTPHARMA


IMPERFECT PHARMACY


@IMPERFECTPHARMACY


IMPERFECT PHARMACY


IMPERFECTPHARMACY@GMAIL.COM