Unit-4

Physical Pharmaceutics

Complexation and protein binding:

Introduction, Classification of Complexation, Applications, methods of analysis, protein binding, Complexation and drug action, crystalline structures of complexes and thermodynamic treatment of stability constants.

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Complexation:

Introduction:

- Complexation is the process of complex formation that is the process of characterization the covalent or non-covalent interactions between two or more compounds.
- The ligand is a molecule that interacts with another molecule, the Drug, to form a complex.
- Drug molecules can form complexes with other small molecules or with macromolecules such as proteins.
- A coordination complex is the product of a Lewis acid-base reaction in which neutral molecules or anions (called ligands) bond to a central metal atom (or ion) by coordinate covalent bonds
- Simple ligands include water, ammonia and chloride ions.

Classification of Complexation

A. Metal ion complexes:

- Inorganic type
- Chelates
- Olefin type
- Aromatic type

B. Organic molecular complexes

- Quinhydrone type
- Picric acid type
- Caffeine and other drug complexes
- Polymer type

C. Non-Bonded or Inclusion/ occlusion compounds

- Channel lattice type
- Layer type
- Clathrates
- Monomolecular type
- Macromoleular type

Metal ion complexes:

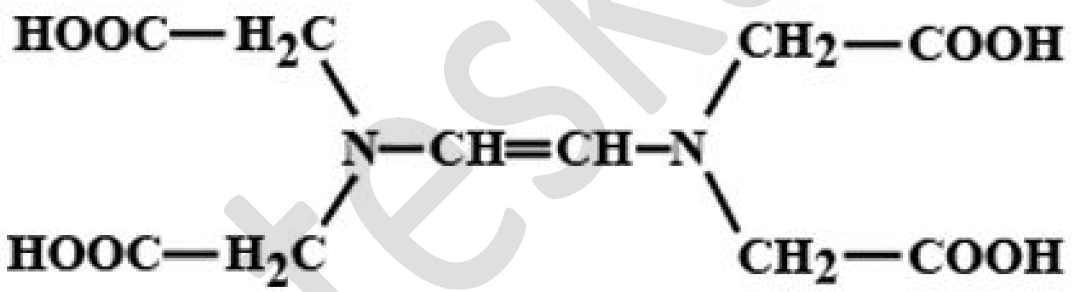
- Metal ion includes the central atom as Drug and it interacts with a base (Electron-pair donor, ligand), forming co-ordination bonds between the species.

Inorganic type:

In this Complex ligand are inorganic in nature which attached with metal atom.

Chelates –

- The chelates are a group of metal ion complexes in which a substance (Ligands) provides two or more donor groups to combine with a metal ion.
- Some of the bonds in a chelate may be ionic or of the primary covalent type, whereas others are coordinate covalent links.
- When the ligand provides one group for attachment to the central ion, the chelate is called monodentate.
- Pilocarpine behaves as a monodentate ligand toward Co(II), Ni(II), and Zn(II) to form chelates of pseudotetrahedral geometry.



Olefin type –

- The aqueous solution of certain metal ions like Pt, Fe, Pd, Hg and Ag can absorb olefins such as ethylene to yield water soluble complexes.
- These are uses as catalyst in the manufacture of bulk drugs and analysis of drugs.

Aromatic type –

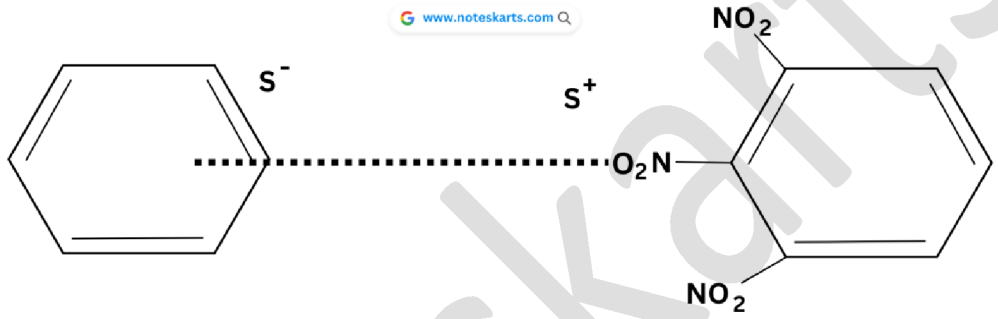
- **Pi (π) complexes –** Aromatic bases (Benzene, toluene and Xylene) form pi-bond complexes with metal ions like Ag by Lewis acid-base reactions.
- **Sigma (σ) complexes –** sigma bond complexes involve in the formation of a sigma-bond between ion and a carbon of aromatic ring.
- **"Sandwich" compounds –** The are relatively stable complexes involving in the delocalized covalent bond between the d-orbital of transition metal and a molecular orbit of the aromatic ring.

Organic molecular complexes:

- They also known as addition complexes are formed by the union of two organic molecules held together by electrostatic forces, ionic, covalent and also by hydrogen bonded complexes.

Charge transfer complexes:

- These complexes are generally formed by sharing of **π-electrons.** In these types of complexation one of the constituent molecules of the complex polarizes the other resulting in a type of ionic interaction or charge transfer.



(Change Transfer complex between benzene and tri-nitro benzene)

Polymers Type –

- Many pharmaceutical additives such as polyethylene glycols (PEGs), carboxymethyl cellulose (CMC) contain nucleophilic oxygen. These can form complexes with various drugs.
- E.g. Polymers: carbowaxes, pluronics etc. Drugs: tannic acid, salicylic acid, phenols etc.

Carboxy methyl cellulose + Amphetamine – Poorly absorbed drugs.

Picric acid types –

- Picric acid, being a strong acid, forms organic molecular complexes with weak bases, whereas it combines with strong bases (anesthetic activity of butesin) to yield salts.

Inclusion Complexes:

- These complexes are also called occlusion compounds in which one of the components is trapped in the open lattice or cage like crystal structure of the other.

Channel types –

- Channels are formed by crystallization of the host molecules, the guest component is usually limited to long, unbranched straight chain compounds.

Layer types –

- Compounds such as clays, montomorillorite (constituent of bentonite), can entrap hydrocarbons, alcohols and glycols.
- They form alternate monomolecular (monoatomic) layers of guest and host.
- Their uses are currently quite limited; however these may be useful for catalysis on account of a larger surface area.

Clathrates –

- It is available as white crystalline powder, during crystallization, certain substances form a cage-like lattice in which the coordinating compound is entrapped.

Monomolecular types –

- Monomolecular inclusion compounds involve the entrapment of a single guest molecule in the cavity of one host molecule.
- Most of the host molecules are cyclodextrins.
- The interior of the cavity is relatively hydrophobic, whereas the entrance of the cavity is hydrophilic in nature

Applications of Complexation:

Physical state:

- Complexation process improves processing characteristics by converting liquid to soild complex. β-cyclodextrine complexes with nitroglyerine.

Volatility:

- Complexation process reduces Drug volatility for following benefits;

Stabilise system.

- Overcome unpleasant odour (I2 complexes with Poly Vinyl Pyrollidone, PVP).

Solid state stability:

- Complexation process enhances solid state stability of drugs.
- β-cyclodextrine complexes with Vitamin A and D.

Chemical stability:

- Complex formation inhibit chemical reactivity (Mostly inhibit).
- The hydrolysis of Benzocaine is decreased by complexing with Caffeine.

Solubility:

- Complexation process enhances solubility of drug.
- Caffeine enhances solubility of PABA (Para Amino Benzoic Acid) by complex formation.

Dissolution:

- Complexation process enhances dissolution of drug.
- β-cyclodextrine increases the dissolution of Phenobarbitone by inclusion complex.

Methods of analysis Complexation:

- After Complexation process we have to know whether the complex is made or not.

For this we use following methods:

A. Method of Continuous Variation
B. pH Titration Method
C. Distribution Method
D. Solubility Method

A. Method of Continuous Variation:

- We know than when two or more species associated they formed a complex and due to formation of complex their physical properties would have changed such as Dielectric Constant, Refractive index etc.
- When there is no complexation between the species, the value of property is additive. On complexation these properties changes but additive rule do not hold good.
- The change in the characteristics proves that the complexation has been taken place.
- Let's take two species A and B whose individual dielectric constant in solid form and Absorbance in solution form were measured.

Then two species in both forms were mixed.

- The dielectric constant and absorbance were determined.
- The individual values are subtracted with mixed additive values and result was found out.
- If result is zero then no complexation and if result is not zero then there is complexation.

B. pH Titration Method

- This method is applicable for that complex that produces the changes in pH on interaction. The significant change in pH will determine that complexation has been taken place.
- Let us take 75 ml of glycine solution and it is titrated with strong alkali NaOH solution.
- The pH was recorded. A graph was drawn between pH and volume of NaOH added.
- In another test, complex solution of glycine and copper salt is titrated. The change in pH with increments of NaOH solution also recorded. A graph was drawn between pH and volume of NaOH added.
- The two plots are compared and it is seen that the plot of glycine with copper is well below that of the pure glycine, which indicated that complexation is obtained throughout the titration range.

C. Distribution Method:

- The method of distributing a solute between two immiscible solvents can be used to determine the stability constant for certain complexes.
- The distribution behavior of a solute between two immiscible liquids is expressed by distribution or partition co-efficient.
- Principle - When a solute complexes with an added substance, the solute distribution pattern changes depending on the nature of the complex.
- The complexation of iodine by potassium iodide.

$$I_2 + K^+ I^- \text{ ---------- } K^+ I_3^-$$

The Equilibrium stability constant,

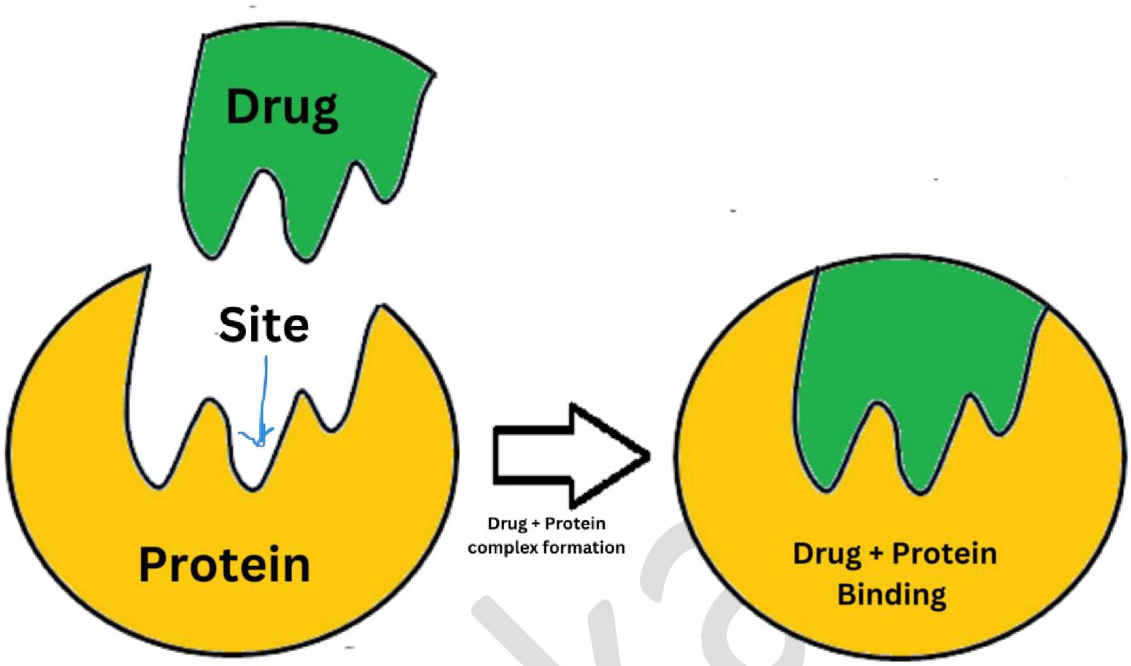
$$K = [K^+ I_3^-] / [I_2] [K^+ I^-]$$

- The distribution coefficient of iodine between disulfide and water is 625.
- The K value of Iodine-Potassium iodide complex is 954.
- This change in distribution coefficient proves that the complexation has taken place.

Protein Binding:

- The term protein binding normally refers to the reversible association of a drug with the proteins of the plasma compartment of blood, and this binding is due to electrostatic and hydrophobic forces between drug and protein.

Protein + drug ⇌ Protein-drug complex



Protein binding may be divided into –

1. Intracellular binding.
2. Extracellular binding.

Mechanisms of protein drug binding:

Reversible:

In this type of protein binding the drug is bind with the protein with very weak forces like hydrogen bonding, weak Vander waal's forces of attraction.
So they can easily release the drug and drug becomes free and it binds with the receptor.
It is responsible for the pharmacological action of the drug.

Irreversible:

In this type of protein binding the drug bind with the protein with strong bond like covalent bond.
Drug after binding with protein cannot release and drug do not become free so they not give any pharmacological action.

Complexation and Drug Action:

- Complexes can after the pharmacological activity of the agent by inhibiting interaction with receptor.
- Protein binding complex also affect absorption metabolism and drug action by interfering with receptor site of action.
- The action of drug to remove toxic metals ion from human bodies is through complexation reaction.
- In some cases, complexation also lead to poor staubility or decrease absorption of the drugs in the body.
- The irreversible protein binding also inhibit the drug of action by not release the drugs from protein.
- Ex: Complexation of drug is the GIT fluids may alter rate and extent of drug absorption.

Crystalline Structures of Complexes:

- Complex or co-ordination compounds cover the range from quite simple inorganic salts to elaborate metal-organic hybrid materials and intricate bioactive metalloproteinase.
- Their present uses and their potential applications are diverse due to their compositions, their molecular and crystal structures and their chemical and physical properties.
- Besides their use as chemical reactants, complex compounds are considered for extraction processes and as active agent in remedies and for drug delivery.

Thermodynamic Treatment Of Stability Constants.

- The stability constants of the metal complexes are related to thermodynamic properties such as free energy (ΔG), enthalpy (ΔH) and entropy charge (ΔS).

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

Where,

- ΔG = Gibbs free energy
- ΔH = Enthalpy
- T = Temperature
- ΔS = Enthalpy

If ΔG = -ve then Rate of Complexation increases and Rate of Complexation increase then stability consist increases.

ΔG = -ve × Rate of Complexation ↑ × Stability constant ↑

If ΔG = +ve then Rate of Complexation decrease then stability constant decrease.

ΔG = +ve × Rate of Complexation ↓ × Stability constant ↓

If

Temprature ↑ = ΔG = -ve

Temprature ↓ = ΔG = +ve

Stability Constant:

- It is an equilibrium constant for the formation of a complex in solution.
- It is the measure of the strength of the interaction between the reagent that come together to form the complex.