



UNIT-IV

COMPLEXATION AND PROTEIN BINDING:

INTRODUCTION:

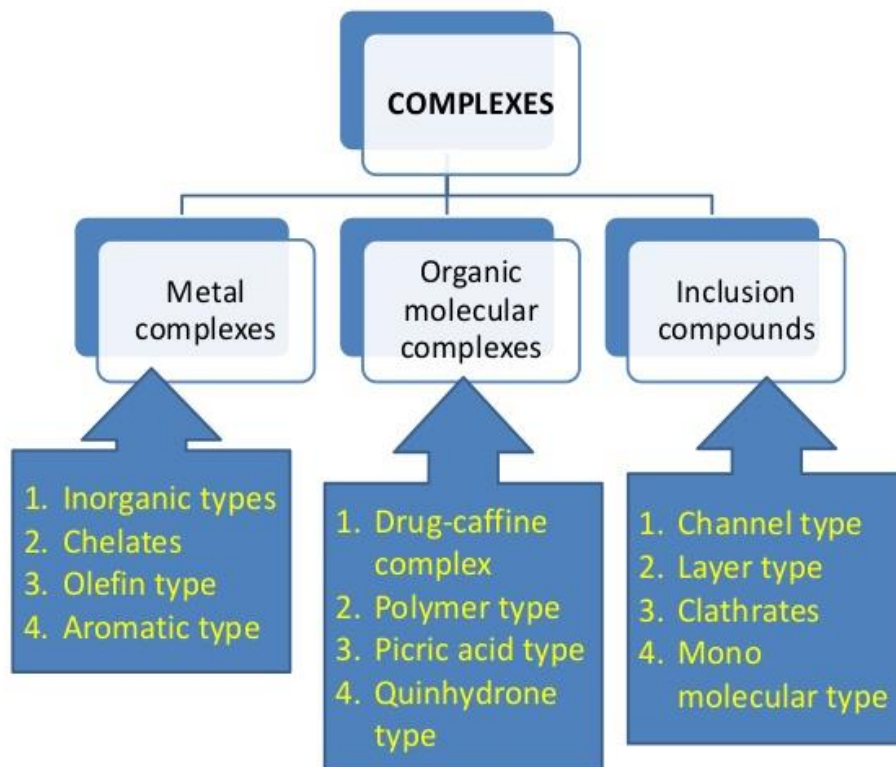
- Complexation is the process of complex formation that is the process of characterization the covalent or non-covalent interactions between two or more compounds.
- The ligand is a molecule that interacts with another molecule, the Drug, to form a complex. Drug molecules can form complexes with other 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.
- *Once complexation occurs, the physical and chemical properties of the complexing species altered are;*
 - ✓ Chemical (pH), instrumental (UV/IR spectra, conductance)
 - ✓ Formulation (solubility, partitioning, stability, drug delivery by ion-exchange resins. Example: Delsym, Tussionex, Kayexalate, Renagel, Cholestyramine)
 - ✓ Pharmacokinetic – permeability (bioavailability), protein binding (distribution)
- *Forces involved in complex formation:*
 - Covalent bond.
 - Co-ordinate covalent bond.
 - Van der Waals force of dispersion.

- Dipole-Dipole interaction.
- Hydrogen bond.

➤ **Beneficial effects of complexation:**

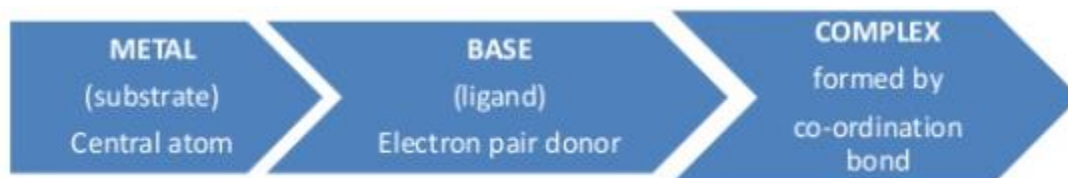
- Drug complexation, therefore, can lead to beneficial properties such as enhanced aqueous solubility (e.g., theophylline complexation with ethylenediamine to form aminophylline) and stability (e.g., inclusion complexes of labile drugs with cyclodextrins).
- Complexation also can aid in the optimization of delivery systems (e.g., ion-exchange resins) and affect the distribution in the body after systemic administration as a result of protein binding.
- In some instances, complexation also can lead to poor solubility or decreased absorption of drugs in the body.
- For some drugs, complexation with certain hydrophilic compounds can enhance excretion.

CLASSIFICATION OF COMPLEXATION:



Metal ion complexes:

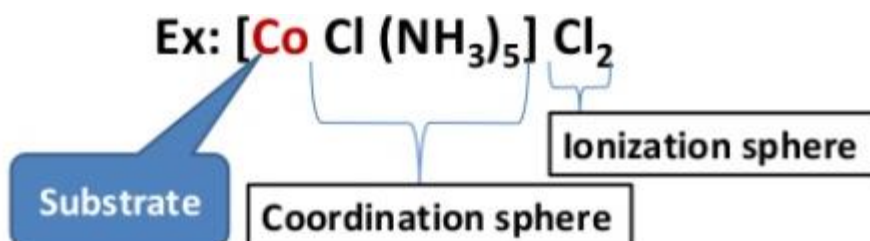
- Metal ion includes the central atom as Drug and it interacts with a base (Electron-pair donor, ligand), forming co-ordination bonds between the species.



Inorganic complexes:

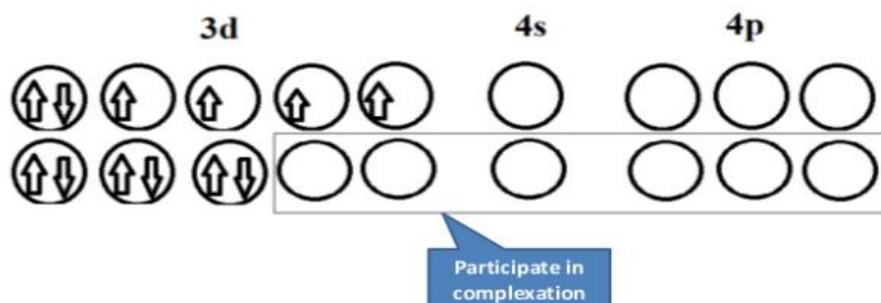
Werner postulates:

1. There are 2 types of valences.
 - primary (ionic),
 - secondary (coordinate).
2. Same type of anion/ radical/ molecule may be held by any one / both type of valence.
3. Every central atom has fixed number of non-ionic valences (co- ordination number)
4. The co-ordination atoms occupy the first sphere/coordination sphere, other atoms occupy second/ ionization sphere.
5. Neutral molecules/ions may satisfy non-ionic valences.
6. The non-ionic valences are directed to specific positions in space.



- Ex: $[\text{Co Cl} (\text{NH}_3)_5] \text{Cl}_2$
 1. Compound ionize to form $[\text{Co Cl} (\text{NH}_3)_5]^{+2}$ and 2Cl^- .
 2. Central chlorine do not precipitate with silver nitrate.

3. Substrate and ligand are bonded with coordination bond.
4. Coordination number is maximum number of atoms and groups that combine with central atom in coordination sphere.
5. Co-ordination number for cobalt is 6.



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.
- Hexadentate - ethylenediaminetetraacetic acid (EDTA)- Has a total of six points (4:O and 2:N) for attachment of metal ions.

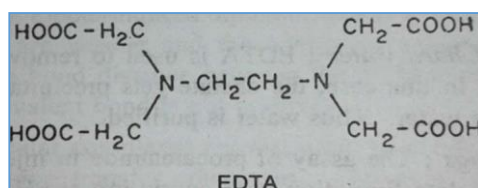


Figure: Structure of EDTA.

Sequestering:

This is a process in which the property of metal is suppressed without removing it from the solution.

Sequestering Agent:

This is a ligand which forms a stable water soluble metal chelate.

Example: chlorophyll, hemoglobin.

Chelates applications:

1. INCREASING SOLUBILITY:

Fruit juices and drugs (ascorbic acid) + Fe/Cu → oxidative degradation.

Add EDTA + Fe/Cu → stable Chelate

2. PURIFICATION OF HARD WATER:

Hard water (Ca²⁺) + EDTA → EDTA-Ca²⁺ (ppt) → filter → Pure water.

3. DRUG ANALYSIS:

Procainamide + cupric ions (1:1) at pH 4-4.5 → Coloured complex → detect by Colourimetry.

4. ANTI-COAGULANT:

Blood (Ca²⁺) + EDTA/Citrates/Oxalates → prevent thrombin formation → no clotting.

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 used 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** – These 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.

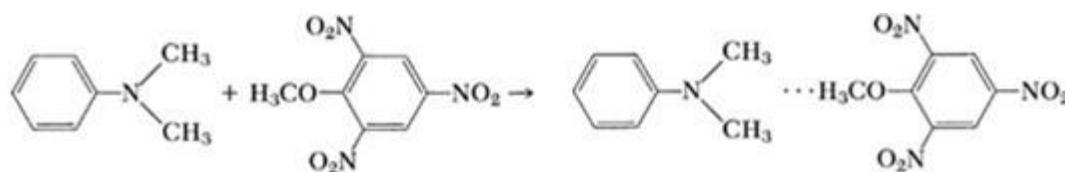
Organic molecular complexes:

- Many organic complexes are so weak that they cannot be separated from their solutions as definite compounds.

- The energy of attraction between the constituents is probably less than 5 kcal/mole for most organic complexes.
- Because the bond distance between the components of the complex is usually greater than 3 Å, a covalent link is not involved.

Complex	Molecular compound
Reaction in cold temperature	Reaction in hot temperature
Weak attraction forces	Strong electrostatic interactions
Complexes cannot be separated from solutions	Compounds can be separated from solutions

- An organic coordination compound or molecular complex consists of constituents held together by weak forces of the donor-acceptor type or by hydrogen bonds.
- **Donor Acceptor type** – In this the bond is between uncharged species but lacks charge transfer. The dipole-dipole interaction and London dispersion forces (Dotted lines) make the complex stable. Example - The compounds dimethylaniline and 2,4,6-trinitroanisole react in the cold to give a molecular complex.



- **The charge transfer Complexes** - In this one molecule polarizes the other, resulting in a type of ionic interaction or charge transfer, and these molecular complexes are often referred to as charge transfer complexes. The resonance makes the complex more stable. The intermolecular bonding is quite higher compared to donor-acceptor type complexes. For example, the polar nitro groups of trinitrobenzene induce a dipole in the readily.

Caffeine and other drug complexes -

- Drugs such as benzocaine, procaine and tetracaine form complexes with caffeine.
- A number of acidic drugs are known to form complexes with caffeine.
- Acidic drugs (benzocaine, procaine) + Caffeine \longrightarrow Complexes

Mechanism:

1. Dipole-dipole forces/ hydrogen bonding between acid (H) atom and caffeine carboxyl group.
2. Interaction of non-polar parts.

Example: Caffeine + Benzocaine.

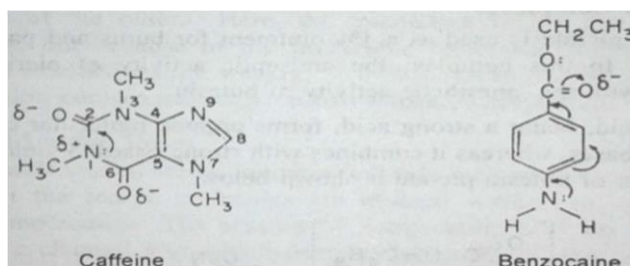


Figure: Structure of caffeine and Benzocaine.

Applications:

1. These complexes can improve / extend absorption and bioavailability of drug.
2. These complexes can enhance/ inhibit solubility and dissolution rate of drug.
3. Caffeine+ gentisic acid complexes mask bitter taste of caffeine.

Quinhydrone type –

- The molecular complex of this type is obtained by mixing alcoholic solutions of equimolar quantities of hydroquinone and benzoquinone (green crystals).

Mechanism:

1. Overlapping of π electrons of molecules
2. (H) bonding for stabilizing complex.

Applications: Used as electrode in pH determination.

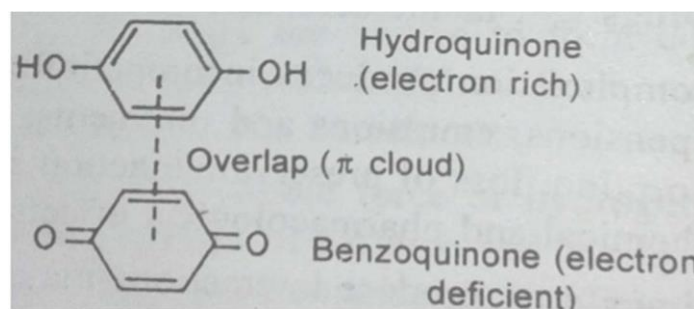


Figure: The complexes of hydroquinone and benzoquinone.

Polymers Type –

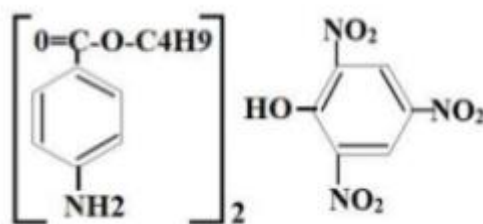
- Many pharmaceutical additives such as polyethylene glycols (PEGs), carboxymethyl cellulose (CMC) contain nucleophilic oxygen. These can form complexes with various drugs.
- Examples are:
 - Polymers: carbowaxes, pluronics etc.
 - Drugs: tannic acid, salicylic acid, phenols etc.
- Carboxy methyl cellulose + Amphetamine – Poorly absorbed drugs.

Disadvantages:

1. Incompatibilities in suspension, emulsion, ointments.
2. Complexes + Container ➡ drug loss
3. Complexes + preservatives ➡ decrease preservative action.

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.
- Picric acid (strong acid) + strong base ➡ Salt.
- Picric acid (strong acid) + weak base ➡ Complexes.
- Example: BUTESIN PICRATE
- Picric acid (antiseptic) + Butesin (anesthetic) - 1% ointment used for burns and abrasions.



Disadvantages:

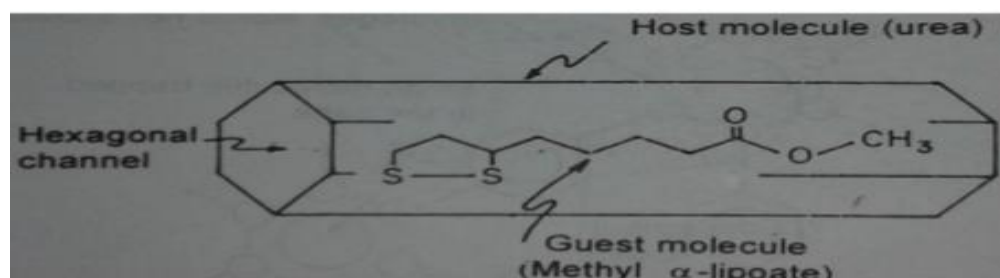
- ✓ Picric acid + Carcinogenic Agents \longrightarrow complex \longrightarrow increase carcinogenic activity.

Inclusion Complexes:

- One compound is trapped in lattice/cage like structure of other compound.
- Interaction are due to suitable molecular structure.
- Prediction of complex formation is difficult.

Channel types –

- Channels are formed by crystallization of the host molecules, the guest component is usually limited to long, unbranched straight chain compounds.
- **Host** (tubular channel)- Deoxycholic acid, urea, thiourea, amylose
- **Guest** (long unbranched straight chain compounds)- paraffin, esters, acids, ethanol.
- Example: Starch-iodine solution (starch-host) Urea-methyl α -lipolate (urea-host)

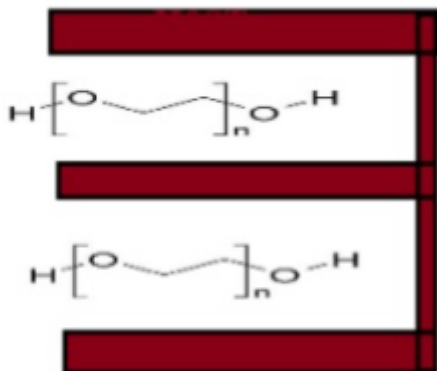


Applications:

- ✓ Separation of isomers: Dextro, levo-terpineol are separated using Digitoxin.
- ✓ In analysis of dermatological creams, long chain compounds interfere and removed by complexation with urea.

Layer types –

- Compounds such as clays, montmorillonite (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.

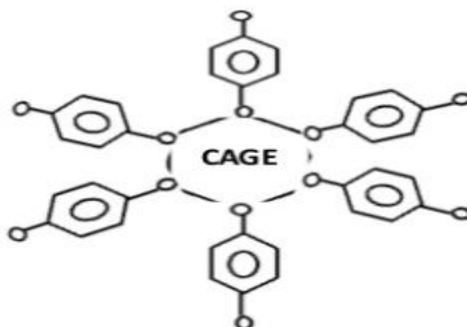


Use:

- ✓ Due to their large surface area they are used as catalysts.

Clathrates -

- It is available as white crystalline powder, during crystallization, certain substances form a cage-like lattice in which the coordinating compound is entrapped.
- Example: warfarin sodium (water + isopropyl alcohol)
- Hydroquinone form cage with hydrogen bonds and hole have diameter of 4.2\AA .
- This can entrap methanol, carbon dioxide, hydrochloric acid.

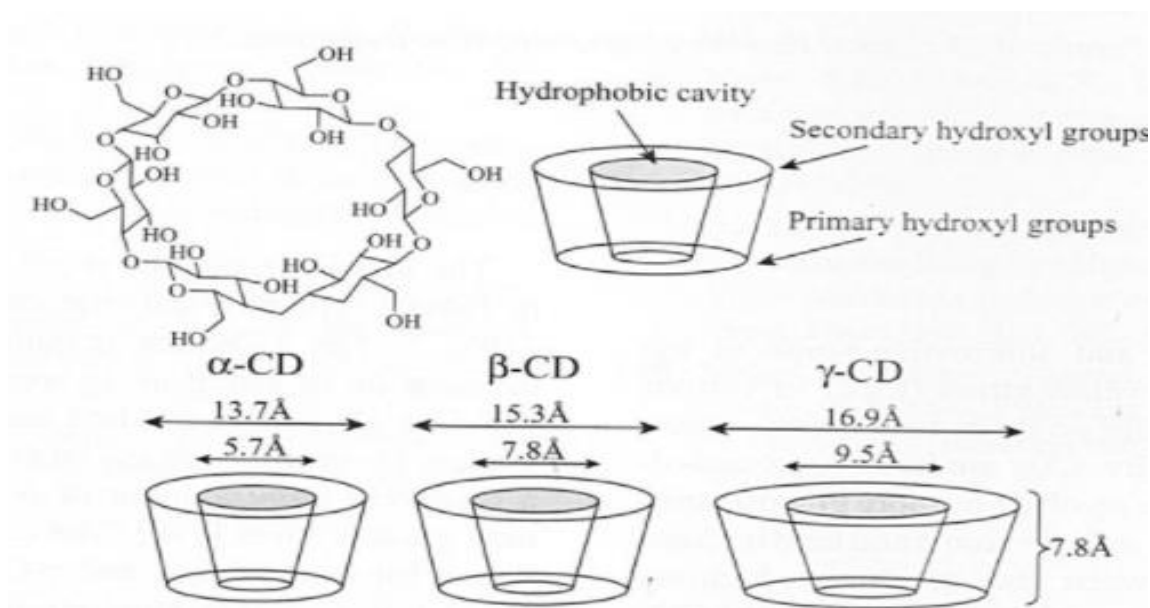
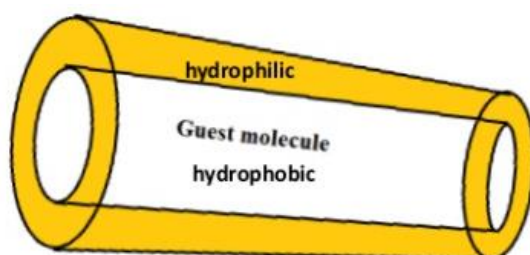


Applications:

1. Synthetic metallo- aluminosilicates act as molecular sieves.
2. The pores store volatile gases and toxic substances.
3. The entrapped molecule can be removed by physical process.

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.
- Cyclodextrins are cyclic oligo saccharides containing minimum of 6 D- gluco pyranose units attached by α -1,4 linkages.



Applications:

1. Enhanced solubility: Retonic acid (solubility= 0.5mg/ml) Retonic acid + β -CD (solubility= 160 mg/ml)
2. Enhanced dissolution: Famotidine/ Tolbtamide + β -CD
3. Enhanced stability: Asprin/Ephedrine/Testosterone + β -CD (no reaction with other functional groups)
4. Sustained release: Ethylated β -CD + Diltiazem

Applications of Complexation:

➤ *Physical state:*

- Complexation process improves processing characteristics by converting liquid to solid complex.
- Example: β -cyclodextrine complexes with nitroglycerine and forms crystalline inclusion complex which is explosion proof.

➤ *Volatility:*

- Complexation process reduces Drug volatility for following benefits;
 - To stabilise system.
 - Overcome the unpleasant odour
 - Example: in the formulation, I2 complexes with Poly Vinyl Pyrollidone, PVP.

➤ *Solid state stability:*

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

➤ *Chemical stability:*

- Complex formation alter chemical reactivity (Mostly inhibit and sometimes catalytic).
- Example: The hydrolysis of Benzocaine is decreased by complexing with Caffeine.

➤ *Solubility:*

- Complexation process enhances solubility of drug.

- Example: At low concentrations, caffeine enhances solubility of PABA (Para Amino Benzoic Acid) by complex formation.
- ***Dissolution:***
 - Complexation process enhances dissolution of drug which is possible by enhanced solubility.
 - Example: β -cyclodextrine increases the dissolution of Phenobarbitone by inclusion complex.
- ***Partition co-efficient:***
 - Complexation process enhances the partition coefficient of certain drugs.
 - Example: Permanganate ion with benzene through ion pair mechanism.
- ***Absorption and Bioavailability:***
 - Complexation process reduces the absorption and bioavailability of Tetracycline by complexing with cations like Ca^{+2} , Mg^{+2} and Al^{+3} .
 - Complexation process enhances the bioavailability of Indomethacine and Barbiturates by complexing with β -cyclodextrine.
- ***Reduced toxicity:***
 - β -cyclodextrine reduces ulcerogenic effects of Indomethacine.
 - β -cyclodextrine reduces local tissue toxicity of Chlorpromazine.
- ***Antidote for metal poisoning:***
 - BAL (British Anti Lewisite) reduces toxicity of heavy metals by complexing with As, Hg and Sb.
- ***Drug actin through Metal Poisoning:***
 - 8-Hydroxy quinoline complexes with Fe that is normally present in the body.
 - The complex penetrate cell membranes of the malarial parasite and thereby exhibit greater antimalaria activity.
- ***Antitubercular activity:***
 - PAS (Para Amino Salysylic acid) complexes with Cupric ion exhibit greater Antitubercular activity.

➤ ***Development of Novel Drug delivery system:***

- The Complexation of drug with polymers used in the formulation of sustained drug delivery device.

➤ ***Assay of Drugs:***

- The complexometric titrations are used to assay of the drug containing the metal ion.

➤ ***As therapeutic Tools:***

- Both CITRATES and EDTA are used as preservation of blood as anti-coagulant.

➤ ***As Diagnostic agent:***

- Ta^{90} complexes with citrate are used for diagnosis of Kidney and measurement of Glomerular Filtration Rate.

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