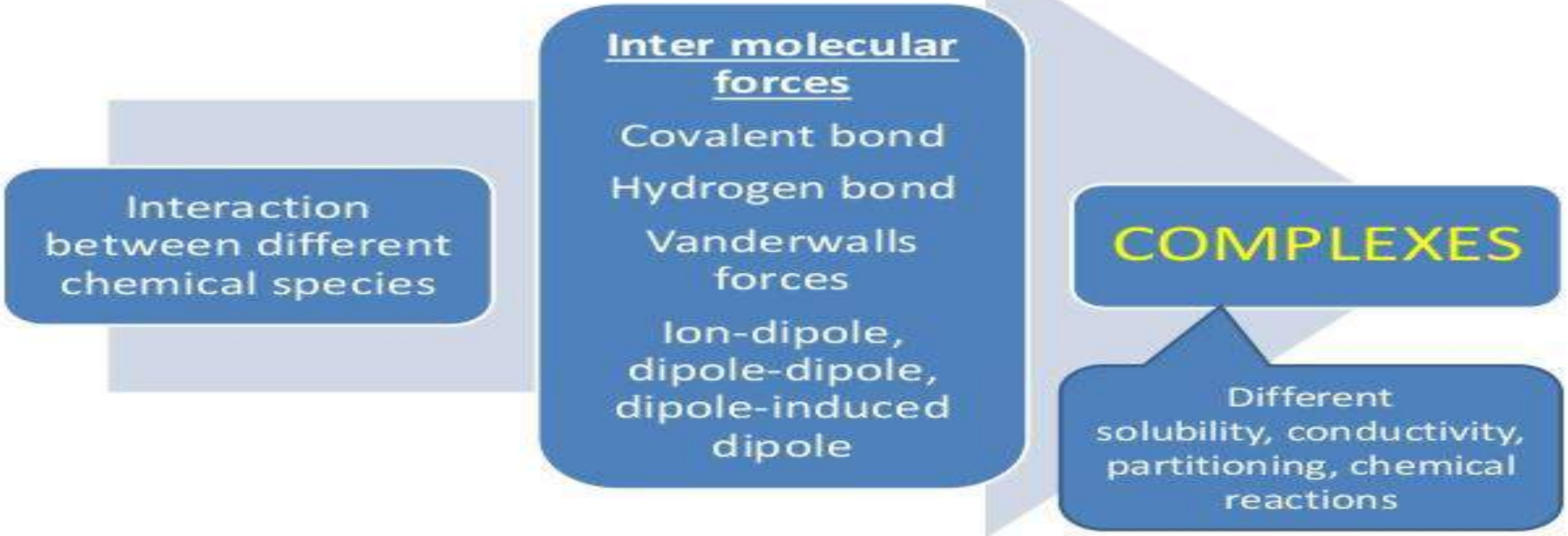
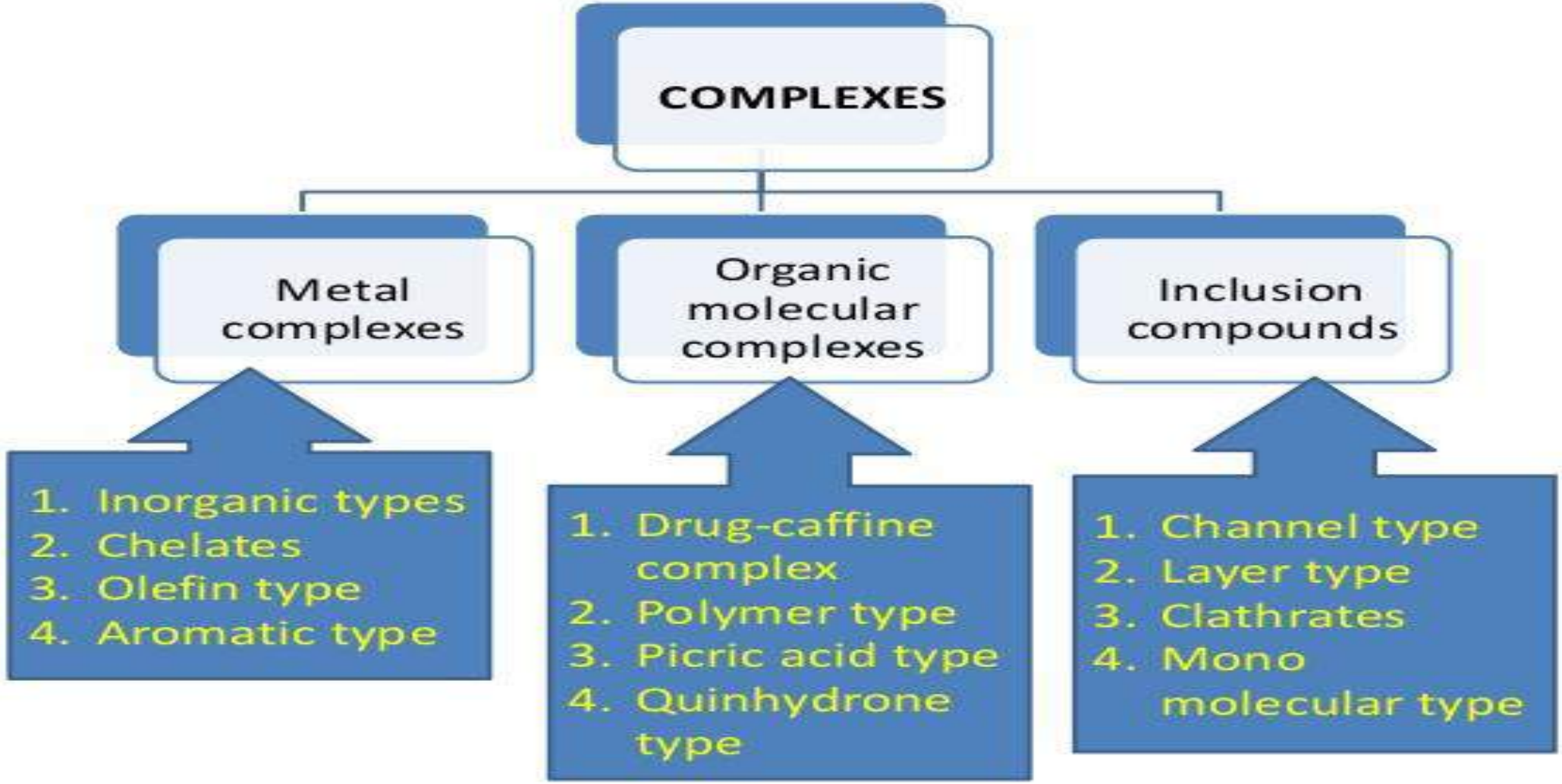
COMPLEXATION

PREPARED BY AYESHA

Def: **Complex compounds are defined as those molecules in which most of the bonding structures can be described by classical theories of valency between atoms, but one/more of these bonds are some what anomalous.**



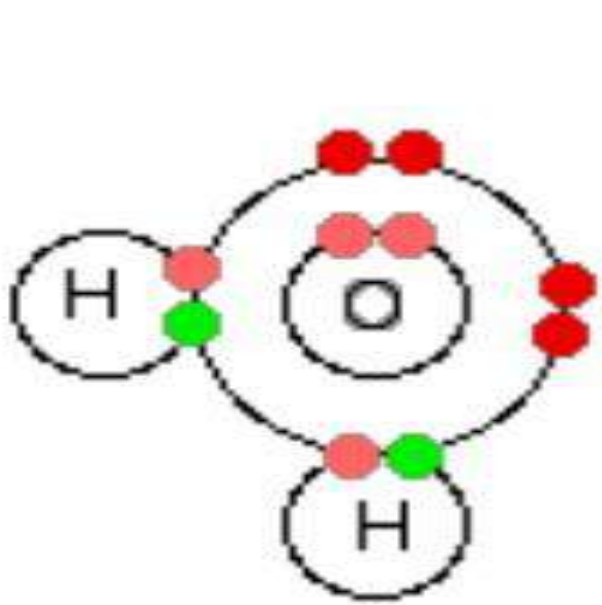

COMPLEXES
Metal complexes
Organic molecular complexes
Inclusion compounds
1. Inorganic types
2. Chelates
3. Olefin type
4. Aromatic type
1. Drug-caffine complex
2. Polymer type
3. Picric acid type
4. Quinhydrone type
1. Channel type
2. Layer type
3. Clathrates
4. Mono molecular type

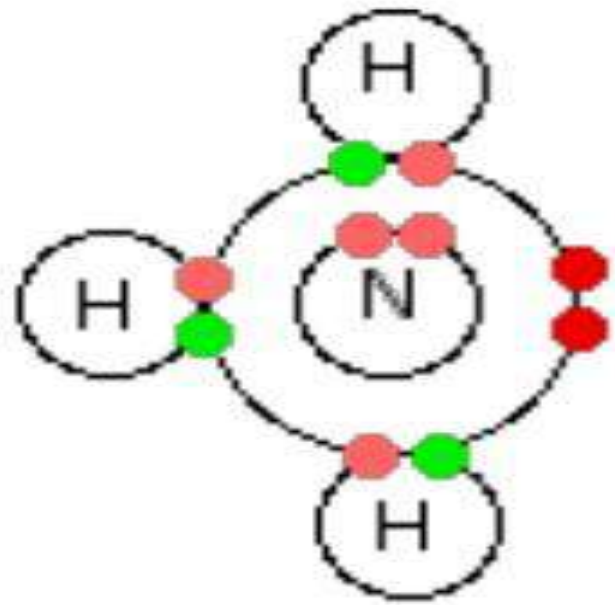
I) Metal complexes:

METAL
(substrate)
Central atom

BASE
(ligand)
Electron pair donor

COMPLEX
formed by
co-ordination
bond

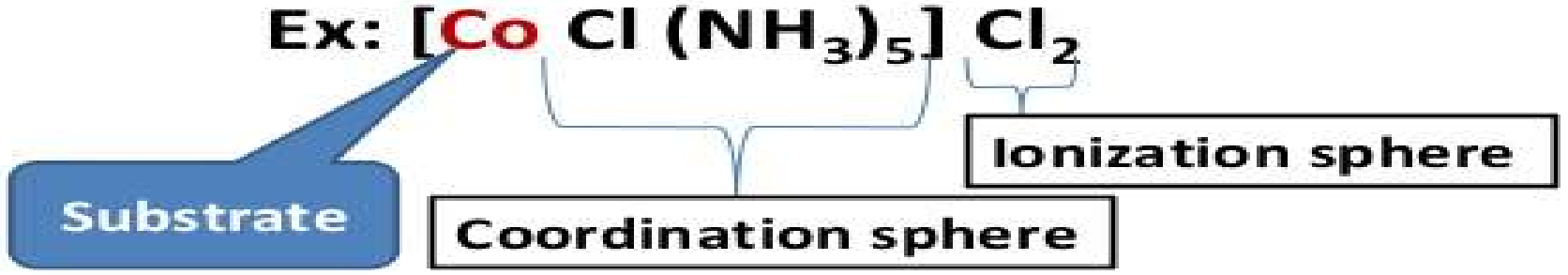




I-A) INORGANIC COMPLEXES:

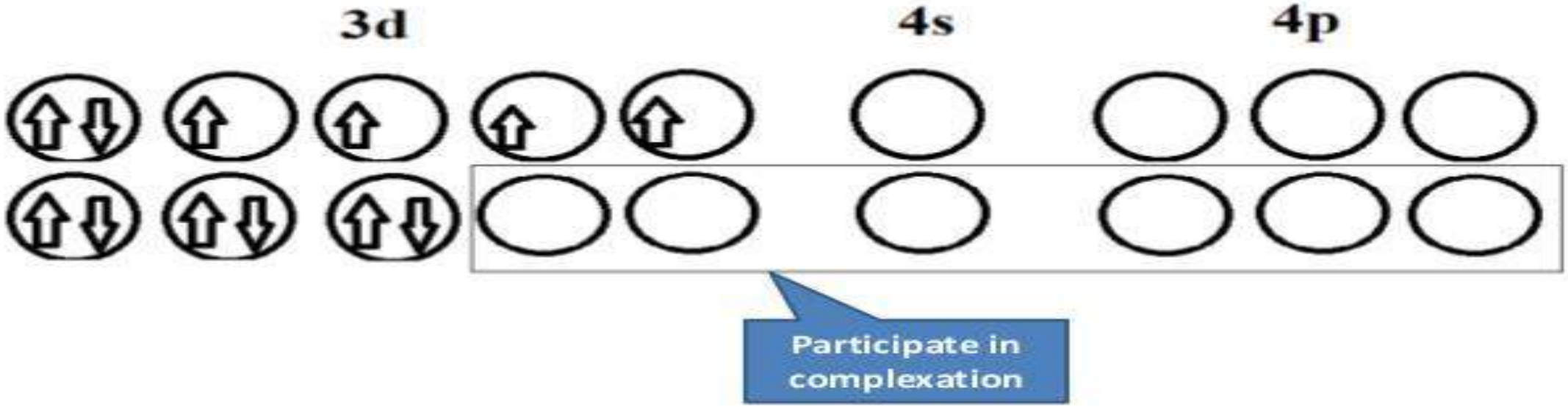
Werner postulates:

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: [Co Cl $(NH_3)_5$] Cl_2

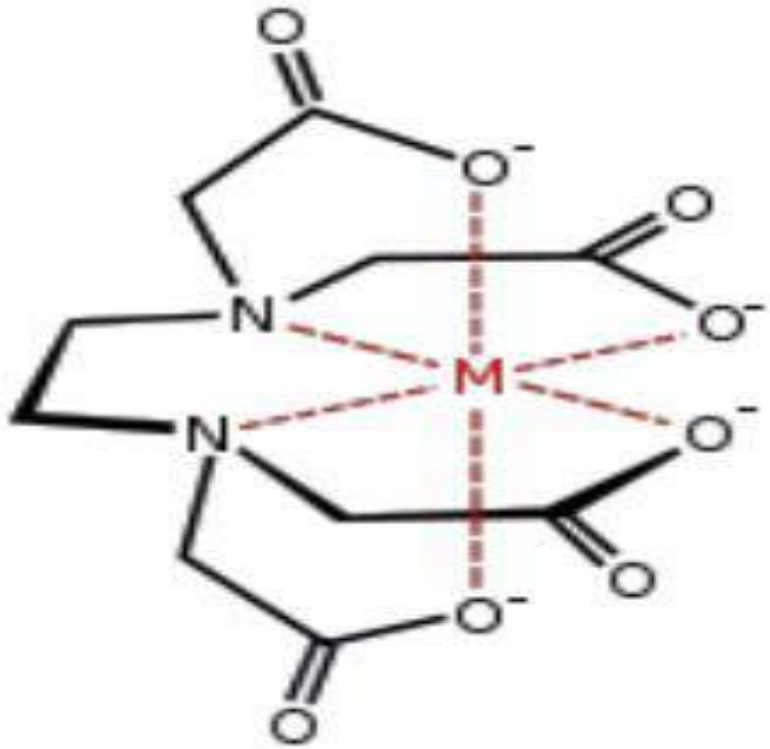
1. Compound ionize to form **[Co Cl $(NH_3)_5]^{+2}$ and $2Cl^-$** .
2. Central chlorine do not precipitate with silver nitrate.
3. Substrate and ligand are bonded with coordination bond.
4. Coordination number is maximum number of atoms and groups that combine with central atom in coordination sphere.
5. Co-ordination number for cobalt is **6.**



I-B) CHELATES:

These are group of metal ion complexes in which a substrate/ ligand provides 2/more donor groups to combine with a metal ion.

Ligands- didentate, tridentate, polydentate.



- **Hexadentate - ethylenediaminetetraacetic acid (EDTA)- Has a total of six points (4:0 and 2: N) for attachment of metal ions.**

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

Ex: 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 (Ca^{+2}) + EDTA → EDTA-Ca^{+2} (ppt) → filter → Pure water.

3. DURG ANALYSIS:

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

4. ANTI-COAGULANT:

Blood (Ca^{+2}) + EDTA/Citrates/Oxalates → prevent thrombin formation → no clotting.

1-C,D: OLEFIN AND AROMATIC TYPE:

a. These involves Lewis acid-base reactions

b. These type of complexes can be used as catalysts in the manufacturing of bulk drugs, intermediates and in drug analysis.

II. ORGANIC MOLECULAR COMPLEXES:

1. Interaction between 2 organic molecules ➔ Complex ➔ temperature change ➔ molecular compound.
2. These complexes have (H)bonds/ weak vander wall forces/ dipole-induced dipole interactions.
3. Energy of attraction is 3K.Cal/mole
4. Bond distance is $3A^0$

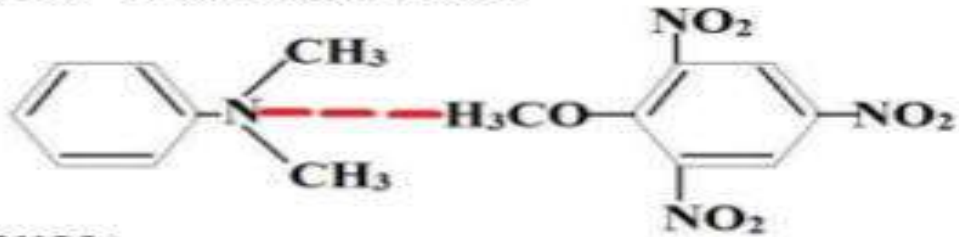
Complex	Molecular compound
Reaction in COLD TEMPERATURE	Reaction in HOT TEMPERATURE
Weak attraction forces	Strong electrostatic interactions
Complexes can not be separated from solutions	Compounds can be separated from solutions

PRINCIPLE/ MECHANISM:

1. Donar-Acceptor type:-

Bonds between uncharged species is formed and **stabilized by dipole-dipole interactions.**

EX: N-Dimethyl aniline + 2,4,6-Trinitro anisole.



2. Charge transfer complexes:-

•One molecule polarizes other resulting in electrostatic interactions for complex formation with high inter molecular bonding.

•Complex is **stabilized by resonance.**

Ex: Benzene + Trinitro benzene.

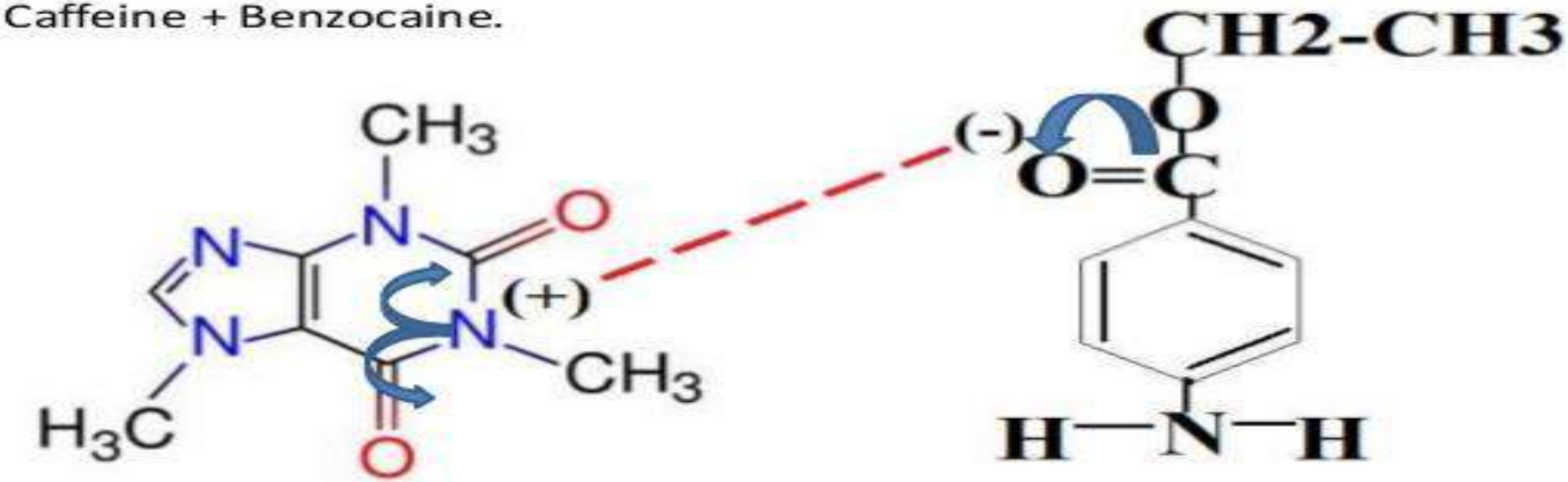
2-A) DRUG & CAFFINE COMPLEX:

Acidic drugs (benzocaine, procaine) + Caffeine ➔ Complexes

Mechanism:

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

Ex: Caffeine + Benzocaine.



DRUG & CAFFINE COMPLEX 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.

2-B) POLYMER COMPLEXES:

Polymers with nucleophilic oxygen (PEG/CMC)
+Drugs(tannic acid/salicylic acid/phenols) ➔ Complexes.

Disadvantages:

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

2-C) PICRIC ACID COMPLEXES:

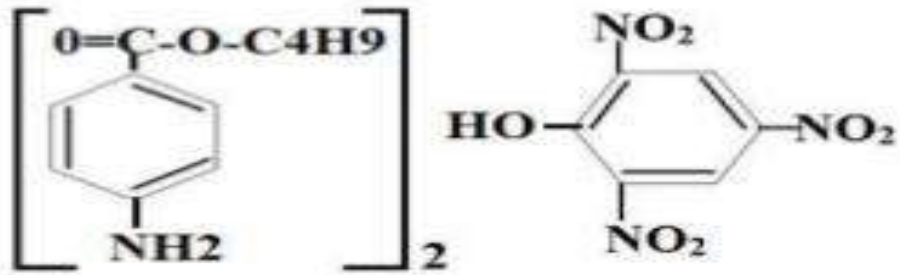
Picric acid (strong acid) + strong base ➔ Salt.

Picric acid (strong acid) + weak base ➔ Complexes.

Ex: BUTESIN PICRATE

Picric acid (antiseptic) + Butesin (anesthetic)

1% ointment used for burns and abrasions.



DISADVANTAGES:

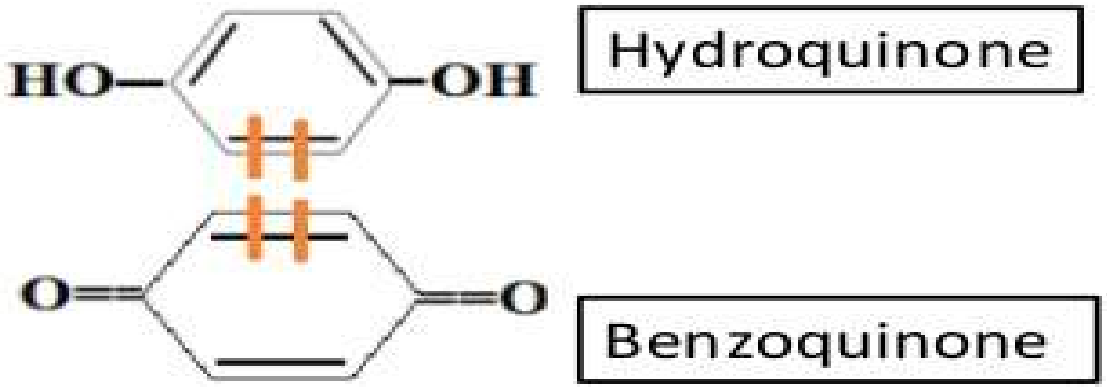
Picric acid + Carcinogenic Agents ➔ COMPLEX ➔ increase carcinogenic activity.

2-d) QUINHYDRONE COMPLEXES:

Alcoholic solutions of equimolar quantities of Hydroquinone and Benzoquinone form Quinhydrone complexes (green crystals)

Mechanism:

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



Applications:

Used as electrode in pH determination.

3.INCLUSION COMPLEXES/OCCLUSION COMPOUNDS:

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

3-A) CHANNEL LATTICE TYPE.

Host (tubular channel)- Deoxycholic acid, urea, thiourea, amylose

Guest (long unbranched straight chain compounds)- paraffin, esters, acids, ethanol.

Ex: Starch-iodine solution (starch-host)

Urea-methyl α-lipolate (urea-host)

Applications:

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

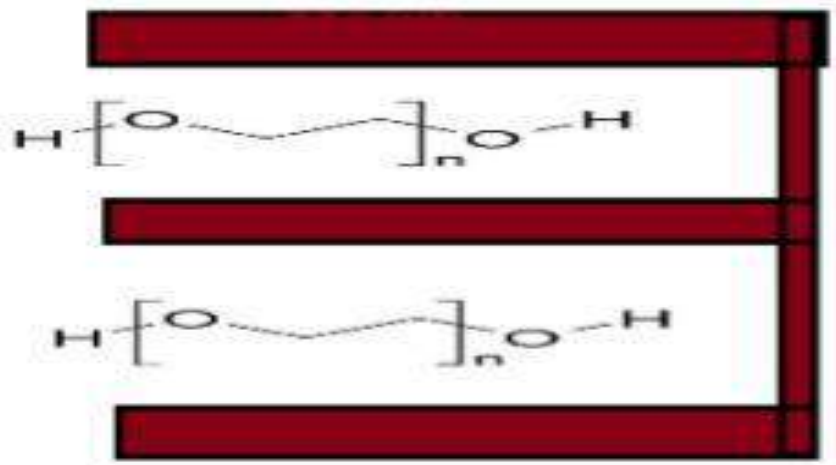
3-B) LAYER TYPES:

Host (Layers With Gaps)- clays, bentonite, montmorillite

Guest (entrapped in gaps)- hydrocarbons, alcohols, glycols.

Use:

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



3-C)CLATHRATES: (cage like structure)

During crystallization some compounds (host) form cage like structures in which coordinating compound (guest) is entrapped.

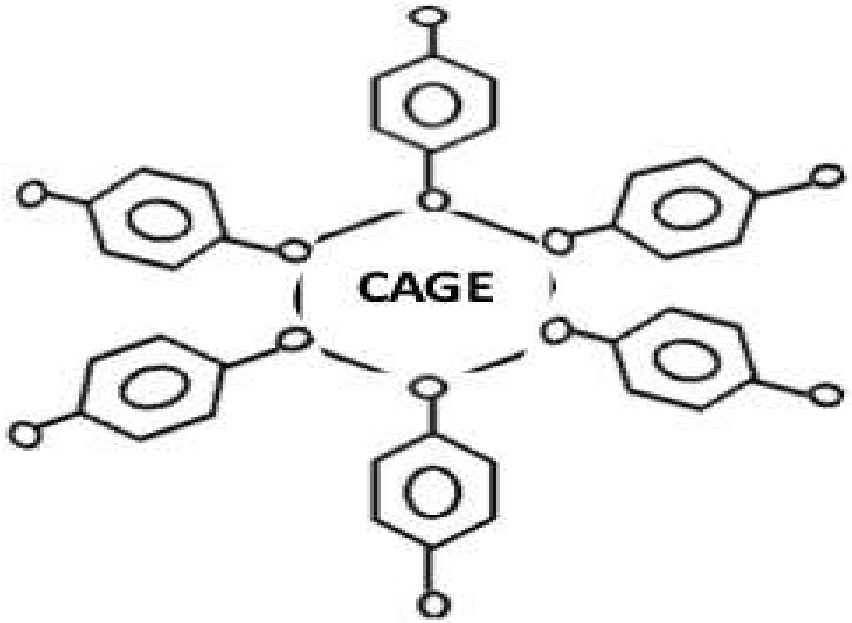
Ex: **warfarin sodium** (water + isopropyl alcohol)

Hydroquinone form cage with hydrogen bonds and hole have diameter of $4.2A^{O}$.

This can entrap methanol, carbon dioxide, hydrochloric acid.

APPLICATIONS:

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



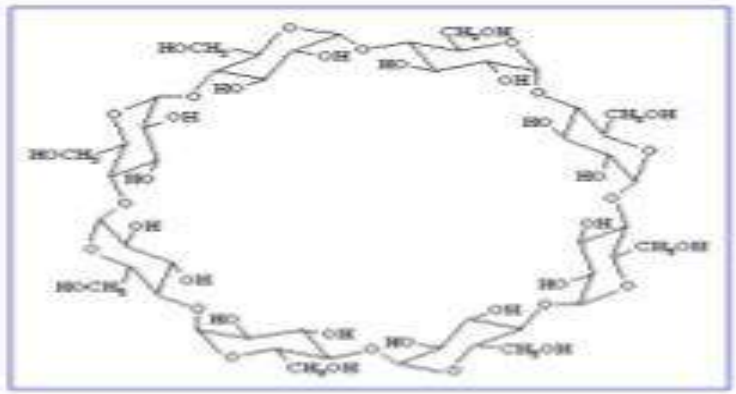
3-D) MONO MOLECULAR INCLUSION COMPLEX:

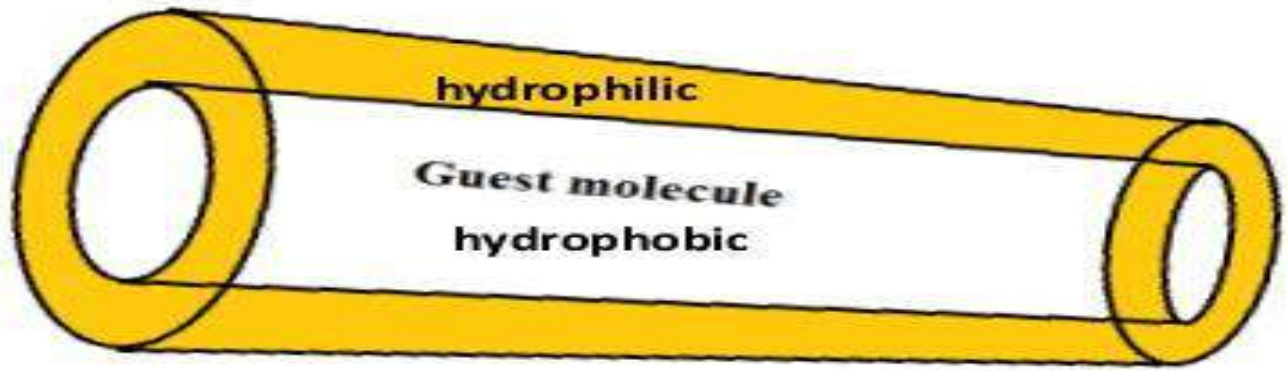
Single guest molecule entrapped by single host molecule.

HOST- Cyclodextrins.

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

Cyclodextrins	Cavity diameter (A°)	Glucopyranose units
α	5	6
β	6	7
γ	8	8





MONO MOLECULAR INCLUSION COMPLEX 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

COMPLEXATION –Applications in pharmacy

- Physical state
- Volatility
- Solid state Stability
- Chemical stability
- Solubility
- Dissolution

- Partition coefficient
- Absorption & bioavailability
- Reduced toxicity
- Antidote in metal poisoning
- Drug action through metal poisoning
- Antibacterial activity

1. Physical state:

Liquid substance → Solid complex → improve process characteristics.

Ex: Nitroglycerine (Explosive) + β-CD → Explosion proof Complex

2. Volatility:

Substances (volatile / unpleasant odour) → Complex → Reduce volatility & Mask odour

3. Solid state stability

Vitamin-A,D + β-CD → Chemically stable solid complex.

4. Chemical stability

Complexation ➔ Reduce Reactivity, Improve stability.

Ex: Caffeine + Benzocaine Complex ➔ Prevent benzocaine hydrolysis.

5. Solubility:

PABA (insoluble) + Caffine ➔ Complex improves solubility of PABA

6. Dissolution:

Phenobarbitol (insoluble) + β-CD ➔ Complex improves Solubility & Dissolution.

7. Partition Coefficient:

(Water + Benzene) + Permanganate ions ➔ Partition in to WATER.

(Water + Benzene) + Permanganate ions + Crown ether ➔ Partition in to Benzene.

8. Absorption & bioavailability

β-CD + Barbiturates ➔ Complex ➔ Improves Bioavailability

Tetracyclines + Ca+2 / Mg+2 ➔ Insoluble metal Complex ➔ Reduced Absorption & Bioavailability

9. Reduced Toxicity:

β-CD + Indomethacin ➔ Reduce ulcerogenic effect

β-CD + Chlorpramazine ➔ Reduce local tissue toxicity.

10. Antidote in metal poisoning:

Arsenic, Mercury (Toxic metal ions) + (-SH) groups of enzymes → Effect normal functioning.

Dimercaprol + Arsenic, → Complex → Easily eliminated
Mercury from body.

11. Drug action through metal poisoning:

8-Hydroxy Quinoline + Iron → Complex → Enter malarial parasite → Accumulation of metal → Anti-Malarial action.

12. Antibacterial activity:

PAS + Cupric ions → Cupric Complex + Chelates.
(anti-Tubercular drug)

Chelates → 30 times more fat soluble → Penetrate in to cells → High anti-Tubercular action.

Method of analysis:

Estimation of 2 parameters

1. Stoichiometric ratio of Ligand: Metal / Donar : Acceptor
2. Stability Constant of complex.

Methods:

1. Method of continuous variation.
2. Distribution method
3. Solubility method
4. pH titration method.

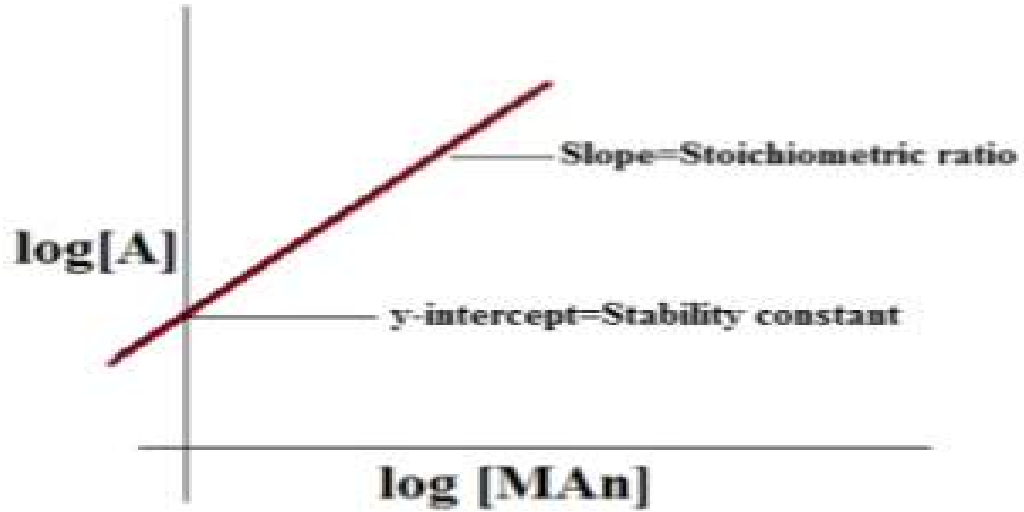
General procedure:

Equation for complexation

M + n A ➔ MAn

Stability constant

$$K = \frac{[MAn]}{[M][A]n}$$



Applying Log on both sides

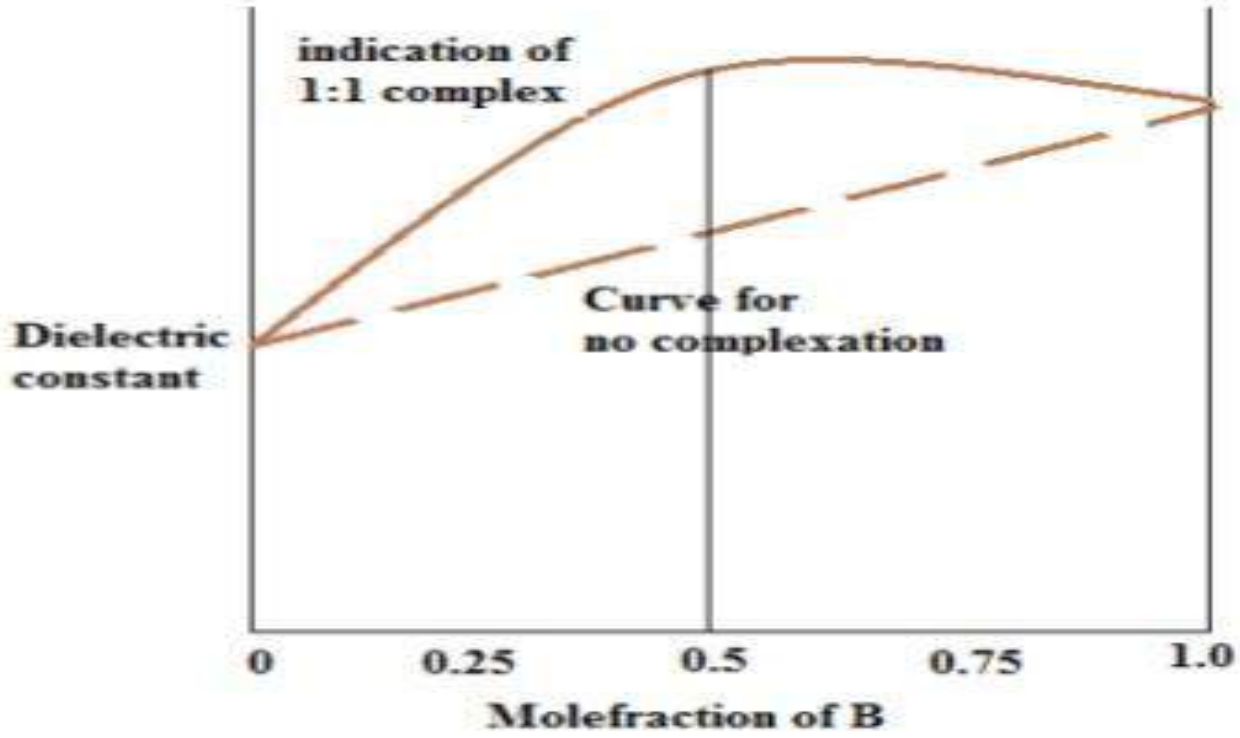
Log [MAn] = log K + log [M] + n log [A]

1. Method of continuous variation.

Physical properties

1. Dielectric constant
2. Refractive index
3. Spectrophotometric extinction coefficient

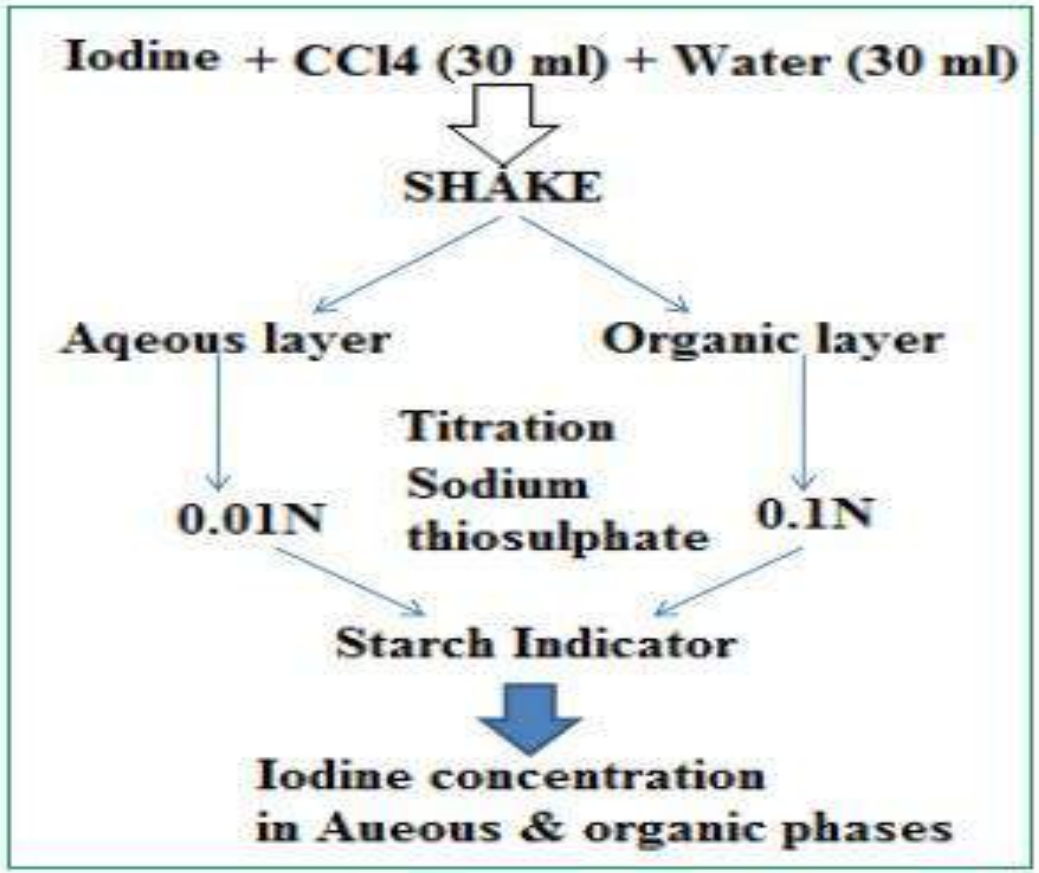
→ Characteristics of species.



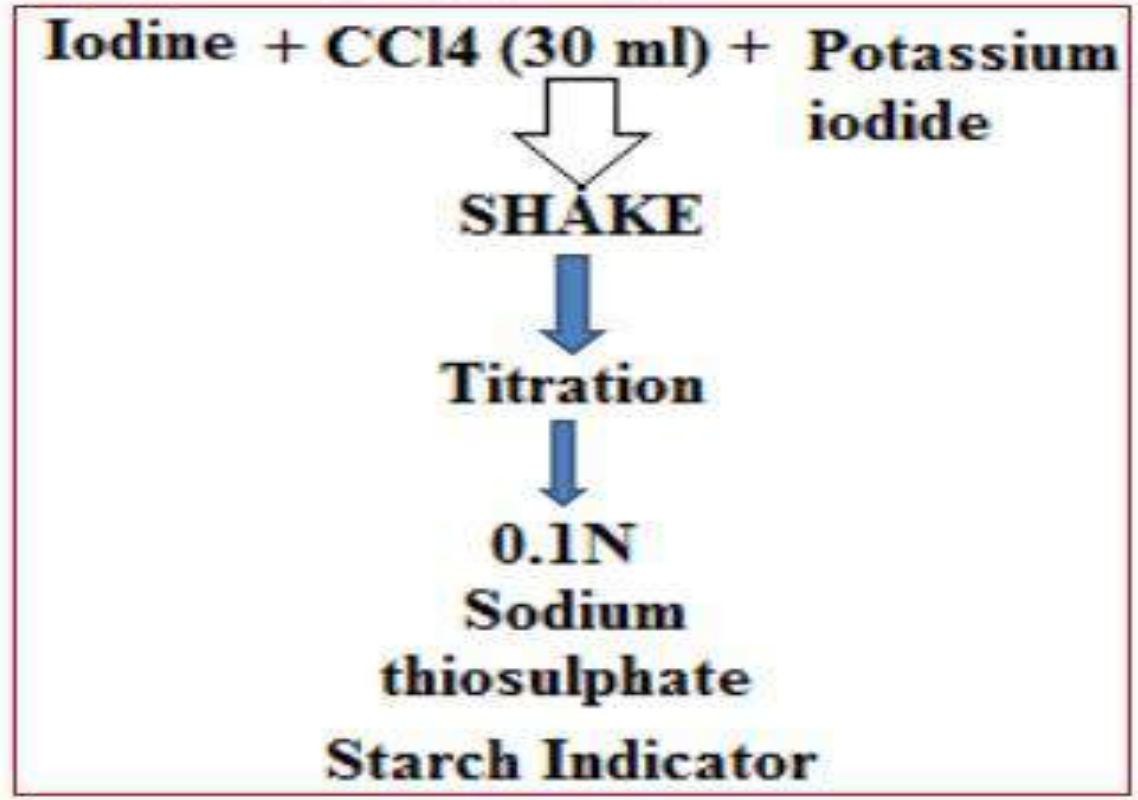
1. Due to complexation physical properties result may be maximum or minimum.
2. At maximum/ minimum point note concentration of individual species.
3. Calculate stoichiometric ratio of species.

2. Distribution method:

- Partition coefficient / Distribution changes due to complexation.
- By conducting 2 experiments stability constant is estimated.



$$K = \frac{[K^+I^-_3]}{[I_2]\ [K^+I^-]}$$

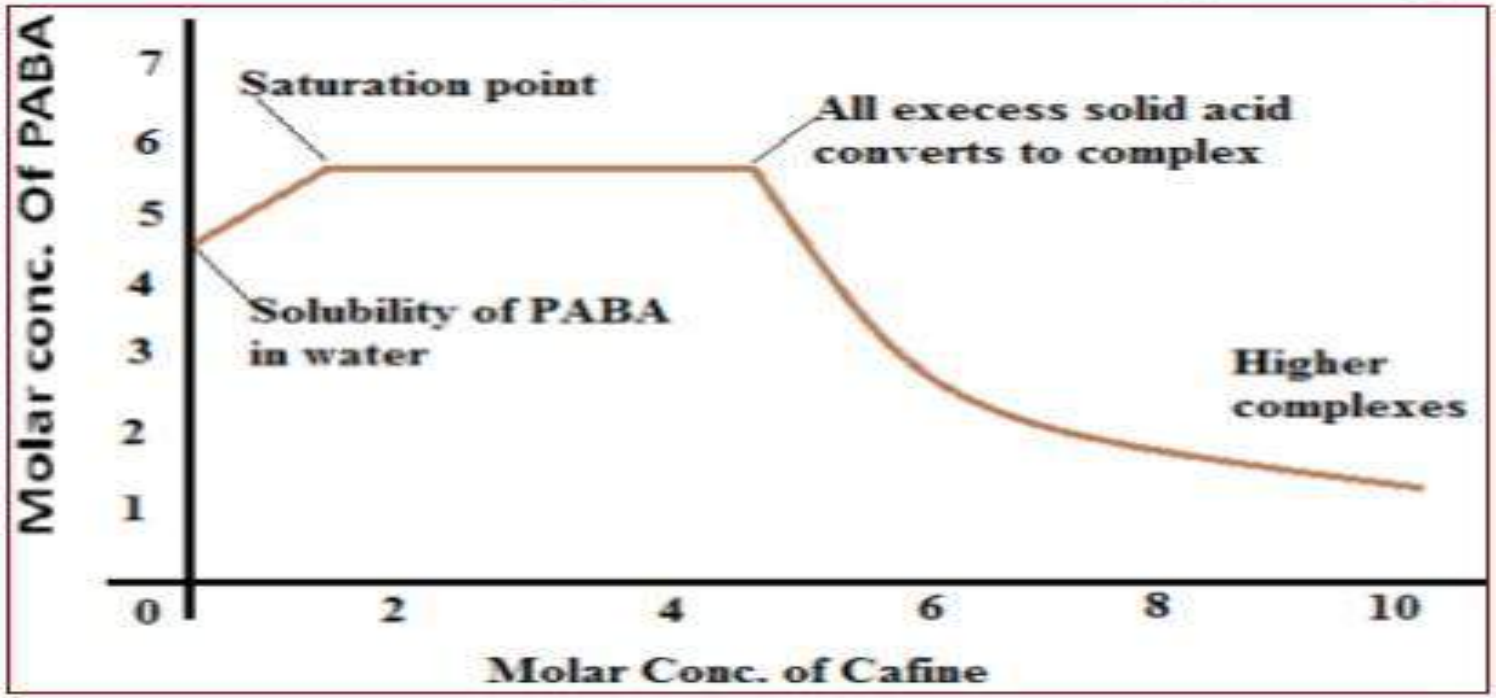


3. Solubility method:

- When mixture form complexes solubility may increase/ decrease.
- Experiments are conducted to estimate parameters

Experiment:

1. Caffeine (Complexing agent) taken in different concentrations
2. Add PABA, Agitate, Filter & analyze drug content.



$$K = \frac{[\text{PABA-Caffeine}]}{[\text{PABA}]\ [\text{Caffeine}]}$$

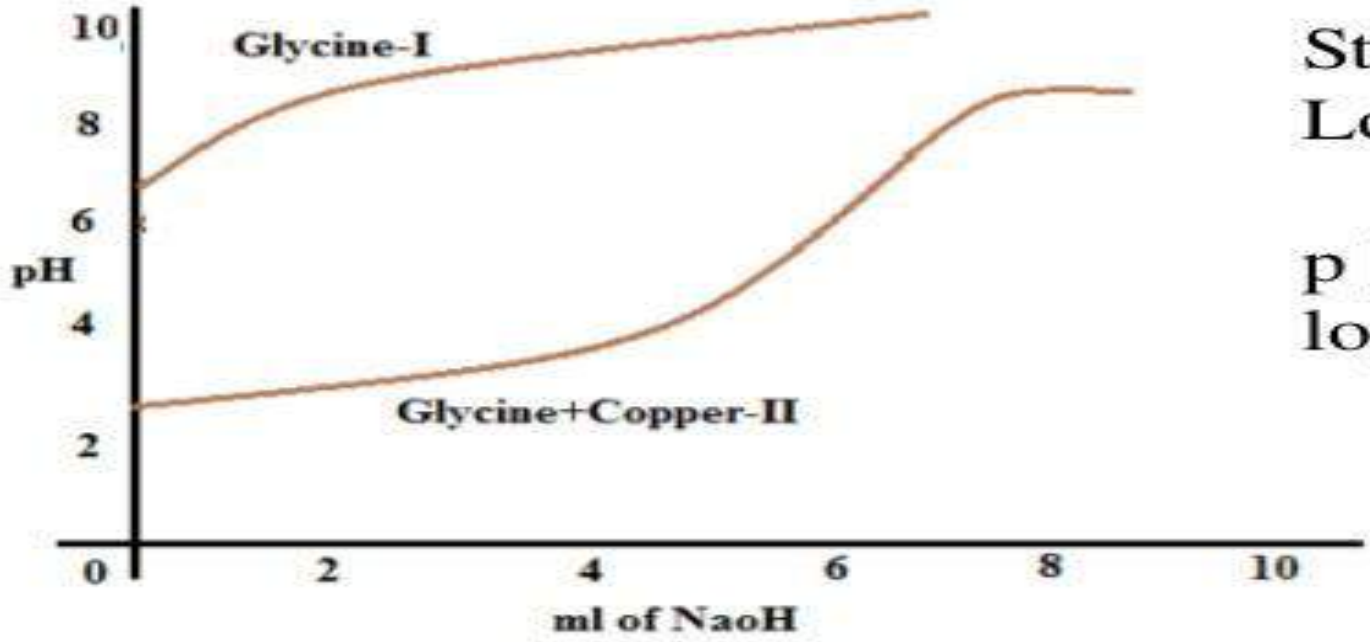
4. pH titration method.

This method is suitable if complexation produces change in pH.

Experiment:

1. Glycine solution (75 ml) titrated with NaoH, pH is recorded.
2. Glycine solution (75 ml) + Cu^{+2} Complex titrated with NaoH, pH is recorded. (Complexation releases Protons and pH decreases)

➢ Quantity of alkali = Concentration of ligand bound.



Stability constant

$\text{Log } \beta = 2 \text{ X p [A]}$

$\text{p [A]} = \text{pKa-pH-log([HA]initial-[NaoH])}$

THANK YOU.....