19/11/2022

DATE 19 11 2022

UNIT-IV

Complexation and Protein Binding :-

Complex :-

Complex compounds are defined as those molecules in which most of the bonding structure can be describe by classical theories of valency b/w atoms.

* Intermolecular forces involve in the formation of complex are :-
  - → Co-ordinate bond
  - → Covalent bond
  - → Ion-dipole bond
  - → Dipole-dipole
  - → Vander-walls force
  - → Hydrogen Bonding
  - → Dipole-Induce dipole bond

** Complexation may be defined as an association of two or more species capable of independent existence.

⇒ Ligand :-

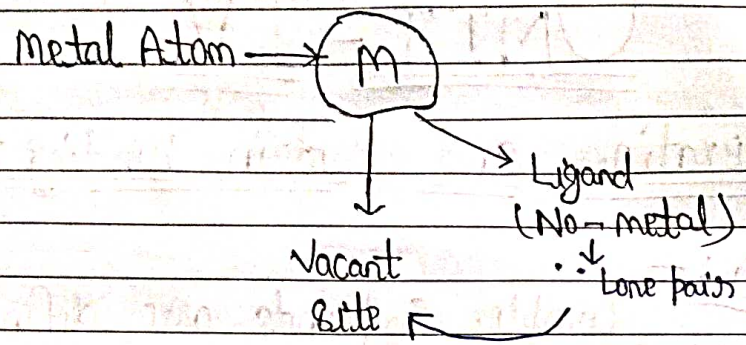
They consist of lone pair.
It is a molecule that interact with another (metal atom) molecule and form a complex by donating its lone pair.

Eg:-

NH_3 , H_2O.

⇒ Metal Atom :- It consist of vacant orbital & interact with ligand to form a complex.

Eg:- Nickle (Ni)



It gets attach on vacant site Metal atom, Non-metal atom complex.

⇒ Application of Complex in Pharmacy & Medicine:-

(I) Reduced Toxicity:- Cyclodextrin are effected in reducing the Ulcerogenic effect of Indomethacin.

(II) Chemical Stability:- Complex formation will effect chemical reactivity. Either inhibitory or catalytic effect may be observe.

Eg:- The rate of hydrolysis of Benzocaine can be reduced by Complexing with Caffine.

(III) Physical State:- Complexation process improves processing characteristics by converting liquid to solid complex.

Eg:-
β-cyclodextrin complex with nitroglycerin.

(IV) Solid-State Stability:- Complexation process inhance solid state stability of drug.

Eg:-
β-cyclodextrin complex with Vitamin A & D are chemically stabilized.

DATE

(V.) Solubility :- Many examples of solubility enhancement by complexation have been reported.

E.g:- At low conc. caffine inhances the solubility of p-amino benzoic acid (PABA).

(Vi.) Dissolution :- If solubility is enhanced the dissolution rate also increase and ~~compas~~ Complexation is one possible method to accomplish this objective.

E.g:-

The dissolution rate of Pinoorbital is enchanced by using cyclodextrin complex.

(Vii.) Partition Coefficient :-

E.g:-

Per magnet ions can be transferred into benzene phase from water by complexation with a Crown ether through Ion pair mechanism.

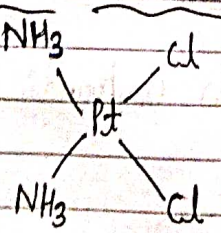
(Viii.) ~~Reduce~~ Anti-dote for metal poisoning :-

Toxic metal ions such as Arsenic, mercury & Antimony bind to Thio (SH) group of various enzymes and interfere with their normal function.

E.g:- EDTA ⟶ Lead poisoning.

⇒ Examples of Drug Complex :-

(a) Cis-platin (Cancer) :-



* This is a Co-ordination complex that has broad application in Human cancer chemotherapy.
* It has di-valent platinum bound to two potentially living group the Chlorides.

IUPAC :-

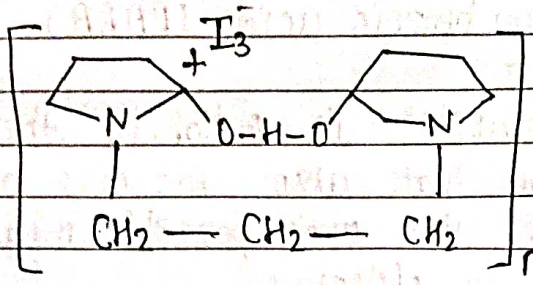
* Cis-di chloro-di amine platinum-2.
* Trade Name ~~Platinol~~ Platinol

PAGE

DATE

(6.) Povidone Iodine :- In this case (PVP) Polyvinyl Pyrrolidone it's a water soluble polymer & forms a water soluble complex with Iodine.

Structure:-



Povidone Complex

Classification Of Complexes :-

1. Metal Ion Complexes :-

A. Inorganic type
B. Chelates
C. Olefin type
D. Aromatic type
   (i) Pi bond Complexes
   (ii) Sigma bond Complexes
   (iii) Sandwich Compounds.

2. Organic Molecular Complexes :-

A. Quinhydrone type
B. Picric acid type
C. Caffeine and other drug Complexes (Hydrogen bonded Complexes)
D. Polymer type

3. No-Bond Complexes or Inclusion Compounds
A. Clathrate
B. Channel lattice type
C. Layer type
D. Monomolecular type
E. Macromolecular type

DATE

1. Metal Ion Complexes :

A. Inorganic Type :- In this type of complex the Central atom or Acceptor in the Complex is a metal or metal-ion which accept electron from the donar.

* The donar Compound is also known as Ligand and is set to be Co-ordinated with the acceptor molecule.

* The type of bonding b/w the metal & the ligand may be electrostatic or Co-valent.

Example:-

Hexamine, Cobalt III Chloride $[CO(NH_3)_6]^{3+}Cl^-$ formed by reaction b/w Ammonia and Cobalt chloride.

B. Chelates :- A substance containing two or more donor groups may combine with the metal Ion to form a complex known as Chelates.

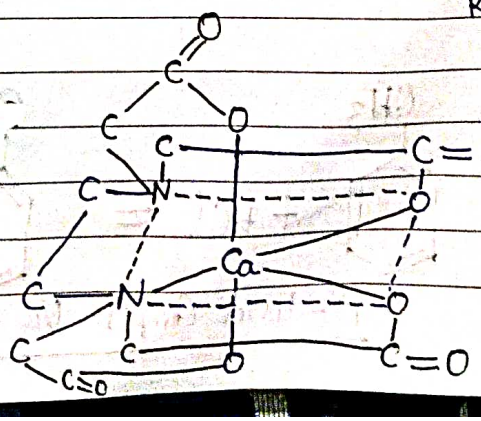
* The bond in the chelate may be Ionic or Primary Covalent type or Co-ordinate Covalent type.

* Ligands may have more than one group capable of bonding with the metal Ion. when the ligand provide two Centre for attachment to the central metal ion then, the chelate is known as Bi-dentate.

→ A molecule with 3 donor groups is tridentate. known as.

Example:-

Ethylenediamine tetraacetic acid sequestering Calcium ions.



PAGE

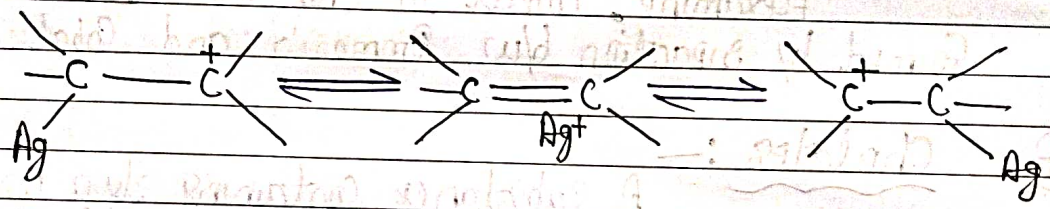
DATE

C. Olefin Type :-

Aqueous solution of certain metal ion such as platinum, Iron, Palladium, mercury & Silver can absorb olefin such as ethylene to yield water soluble complex.

* Although metal olefin complex have found little application in pharmaceutical field these have been employed as catalyst in the polymerization of unsaturated hydrocarbon such as ethylene & propylene to form polyethylene & polypropylene.

Example :- Silver - Olefin Complex.

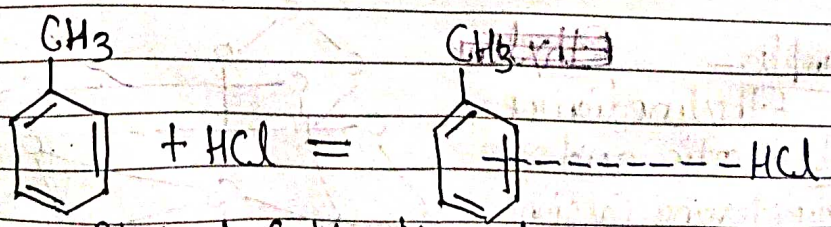


D. Aromatic Complex :-

(i) Pi (π) bond Complex :- Aromatic bases such as Benzene, Toluene, Xylene to form pi bond complex with metal ion such as Silver (Ag) (Ag^+) by Lewis acid-base reaction.

* The stability of the complex depend on the basic strength of the aromatic hydrocarbon. Thus, the greater the basic strength of the aromatic hydrocarbon the more stable is the complex.

Example :-



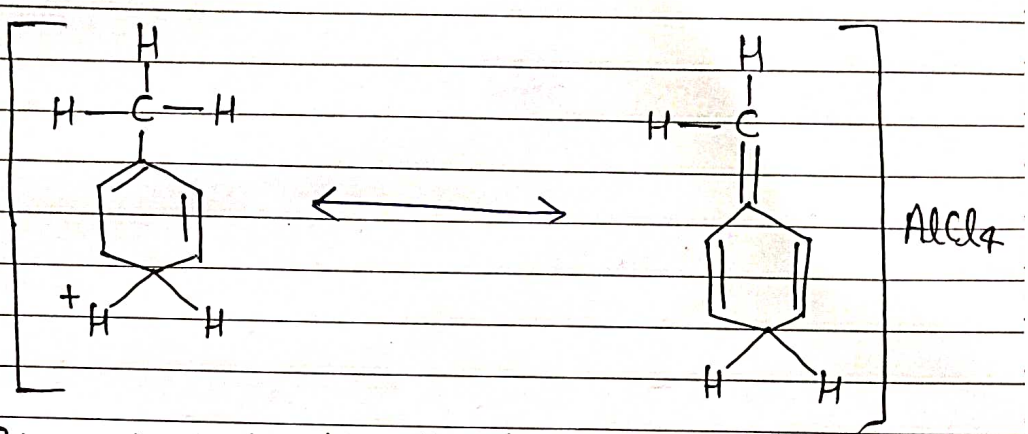
Pi - bond Complex b/w Toluene & HCl

(o)

(ii.) Sigma bond Complex :- It involves the formation of σ bond b/w and. Ion and the Carbon of the aromatic ring.

* These complex are very reactive & difficult to isolate.

Example :-

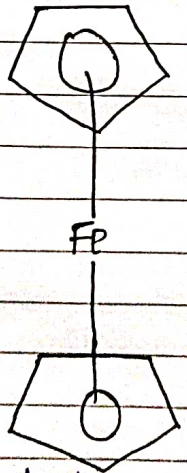


Sigma-bond Complex of toluene with HCl. $AlCl_3$.

(iii) Sandwich Compounds :-

These are relatively stable Complex involving a delocalised Co-valent bond b/w the d- orbital of a transition metal and a molecular orbital of the aromatic ring.

Example :-



Ferrocene

In this one π electron of each ring is used in binding the metal atom & it exhibits an aromatic character. Such Compounds are known as Sandwich Compounds because of the layer structure of ring-metal Complexes.

13/12/2022

DATE

2. Organic Molecules Complex :-

Organic molecular Complex also known as addition Complexes are formed by the union or addition of two organic molecules held together by electrostatic forces or Hydrogen bond.

⇒ There are two types of Organic Molecules Complex:-

(i) Charge Transfer Complex
(ii) Hydrogen Bonded Complex

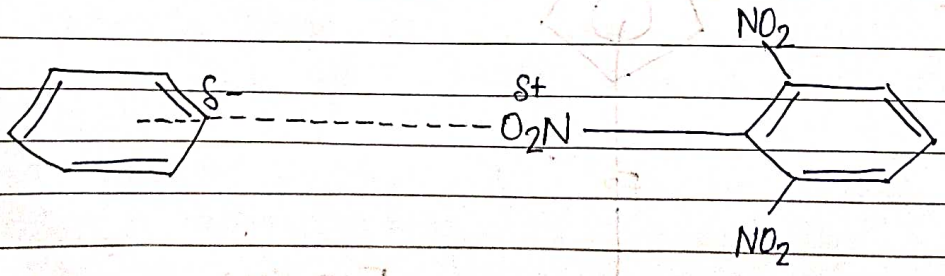
(i) Charge Transfer Complex:-

These Complex are formed by sharing of Pi (π) electrons.

* In this types of Complexes one of the Constituent molecules of the Complex polarizes the other which result in a type of Ionic interaction or Charge transfer.

E.g:-

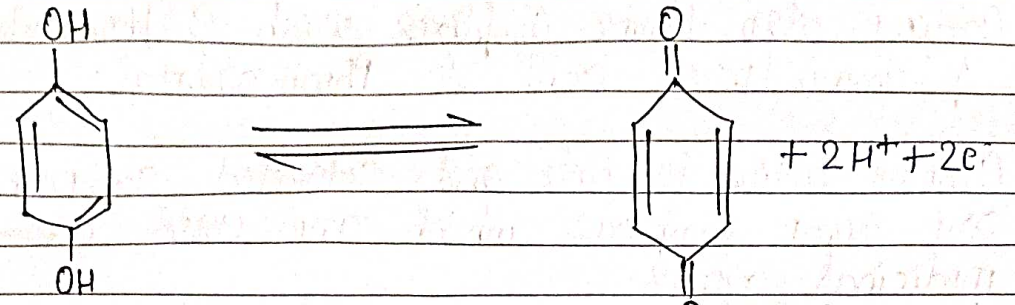
1:1 Complex formed between Benzene & Trinitrobenzene.



A. Quinhydrone Complex:-

It is an example of molecular Complex formed by mixing alcoholic solution of equimolar quantities of Benzoquinone and Hydroquinone when Green Crystal of Quinhydrone Complex settles down.

DATE



Hydroquinone Benzoquinone

B. Picric Acid Complex :-
(2,4,6 Trinitro phenol)

2,4,6 Trinitro phenol form complex with many aromatic Compounds.

* The stability of these complexes depend on the number of electron attracting groups on the nitro group and the ring complexity & presence of electron releasing group on the second compound.

Eg:-
Butesin Picrate.

(ii) Hydrogen Bonded Complex :-

* The hydrogen bonding is considered an example of dipole - dipole interaction.
* A large no. of Compounds containing the -OH or -NH bond exhibit hydrogen bonding.
* The most extensively used example of Hydrogen bonding is Caffeine Complexes.

C. Caffeine & other drug Complexes :-

* Caffeine forms Complexes with a number of drugs such as - Benzocaine, Tetracaine & Procaine which enhances the stability & appearance of pharmaceutical preparation of these drugs.

DATE

* Caffeine also forms complexes with Sulphonamide, p-amino benzoic acid & Phenobarbital.

* Caffeine Sodium benzoate and Citrated Caffeine are some complexes which are used as medicinal agents.

* Complexation between drug & complexing agents has been found to improve or impair the absorption & bioavailability of certain drugs.

E.g:- Sodium Salicylate was found to significantly influence the release of benzocaine from topical vehicle due to formation of molecular complexes.

D: Polymer Complexes :-

* Polymeric material such as -
  → SCMC (Sodium Carboxy methyl Cellulose)
  → PEG (Polyethylene Glycol)
  → PVP (Polyvinyl Pyrrolidone)
  → Poly stearate
  which are usually present in suspension, Emulsion, suppositories & some solid dosage form can form complexes with large no. of drugs.

* PVP has been shown to form molecular complexes with many substances.

* Insoluble complexes are formed to when aqueous solution of added to Tannic acid and Polyethylene acid.
  → On the other hand soluble complexes are formed with Iodine ~~the~~ whose solubility increases ~~from~~ form ~~0.5~~ 0.034% in water at 25°C to

DATE

0.58 % by 1 % PVP.

* Certain Polymer Complexes which alter the solubility & release characteristics of drug used in ~~and~~ sustained release technology.

3. No-Bonded or Inclusion Complex :-

* These Complex are form due to the ability of one of the Compound or Constituent of the Complex to get interact in the open lattice or Cage like crystal structure of the other Constituents.

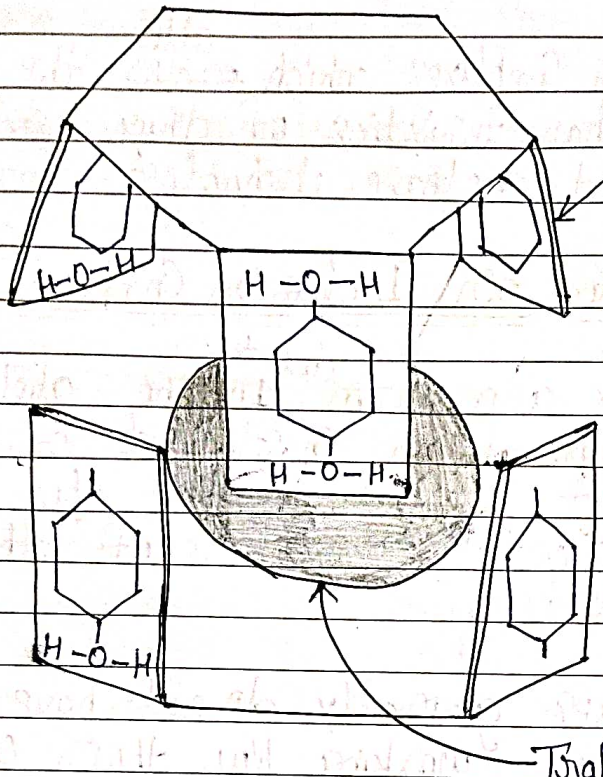
* These Complexes generally do not have any adhesive forces working b/w their Constituent molecules & therefore also known as No-bond Complexes.

A. Clathrates :-

* Clathrates are inclusion compounds in which a molecules a 'guest Compound' gets intrapped with in the Cage like structure formed by the association of several molecule of host Compound

* The guest Compound may be Solid, liquid or Gas & may be released from the Complex by dissolving, heating or grinding the clathrate.

* In such Complexes the size of the guest molecule is important for Complex formation. If the size is too small it will fit in the Cage or Host. and will escape from the Cage like structure or Host & if the size is too big it will not accumodate in size the Cage.

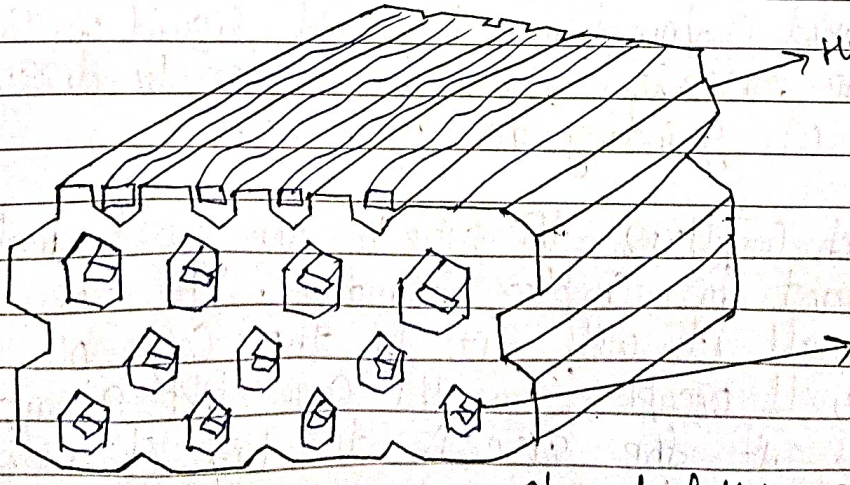


Clathrate Complex

B: Channel Lattice Complexes:-

* These are inclusion compounds in which the host component crystallizes forming channel like structure into which the guest molecule fit.

* The guest molecule must be of a geometry that can easily fit channel like structure.



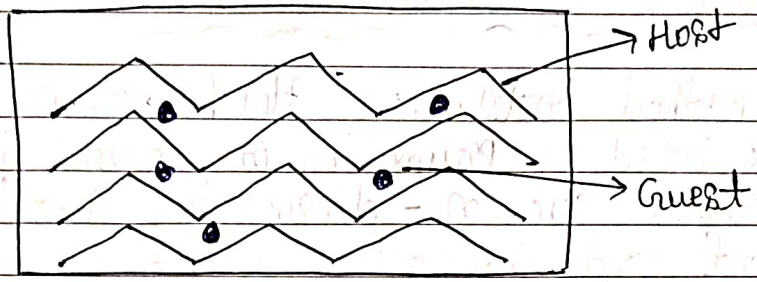
Channel lattice Complex of urea

DATE

C. Layer Type:-

* These are inclusion compounds in which guest molecule is diffuse b/w the layer of Carbon atom to form alternate layers of host & guest molecule.

E.g.:-
Montmorillonite.

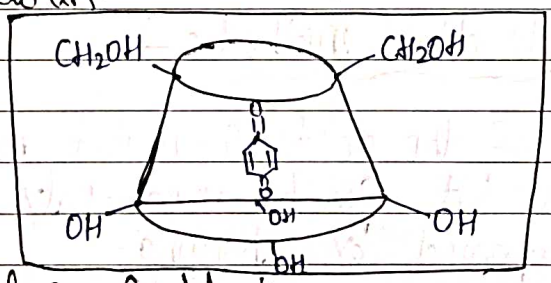


Bentonite-Hydrocarbon

D. Monomolecular Complex:-

These inclusion complex involves intrapment of one guest molecule into the cage like structure form a single host molecule.

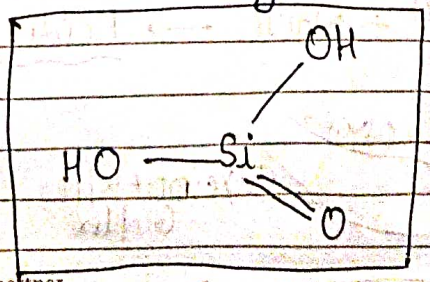
Eg:- Cyclodextrin.



Cyclodextrin

E. Macromolecular Complex:-

* Macromolecular inclusion Compound molecular seives as they are commonly known as, include synthetic Zealites, dextrins, Silica gel, and related substances.
* The atoms in these are arranged in 3 dimensions to provide cages & channels and the guest molecule are intrapped with in.



Silica gel

DATE

Method of Analysis of Complexation :-

(i) Continuous Variation
(ii) pH titration method
(iii) Distribution method
(iv) Solubility Method

(i) Method of Continuous Variation :-

This method determines Stoichiometric ratio of Complex based on estimation of certain properties of Complex such as - dissociation constant, dielectric constant and refractive index.

A + B → When Complexation does not occurs → Physical properties are same as A & B.
→ When Complexation does occurs.
↳ Physical properties differ from A&B.

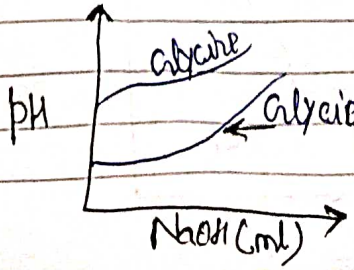
(ii) pH Titration method :-

* This is one of the most convenient method for studying Complexation but can be used only when Complexation is accompanied by changing.

* The Complexation of Cupric ion (Cu^{2+}) and Glycine give a Complex of Copper glycine is one such example that is accompanied by changing pH.

Glycine + NaOH → Base pH

Glycine + Cu^{2+} + NaOH → Acidic pH



DATE

(iii) Distribution method :-

* This method describes the distribution of a solute b/w two immiscible solvent.

* The complexation b/w Iodine & Potassium Iodide can be used as an example of to explain this method.

Let.

→ Iodine in 50 ml CCl_4 & 50 ml water for this assume value of partition coefficient be x.

In this condition, complex is not formed.

→ Iodine in 50 ml CCl_4 & KI for this value of partition coefficient be y.

In this condition complex is formed.

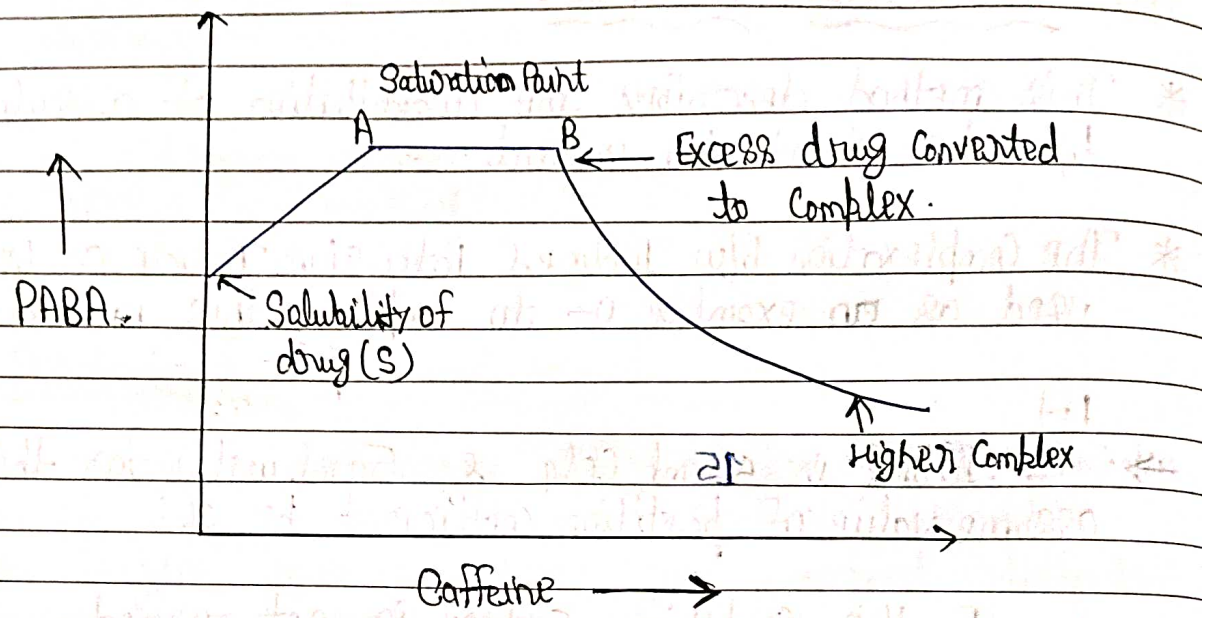
- If complex is formed in IInd condition then the value of x & y will be different.
- If complex is not formed in Ist condition then the value of x & y will be same.

(iv) Solubility method :-

In this method complex formation is based on the solubility of component in presence of complexing agent.

Eg:-

Complexation of PABA & Caffeine.



Protein Binding :-

Plasma proteins such as albumin, globulin and α-acid glycoprotein or lipoproteins present in the body have been known to bind with a large number of drug molecules.

(i) Facilitate the distribution of drugs throughout the body.

(ii) Retard the excretion of a drug which may accumulate in the body.

(iii) Alter the duration of action of a drug.

(iv) Displace body hormones or a co-administered agent.

(v) Alter the therapeutic effect by forming a drug-protein complex which is itself biologically active.

DATE

Mechanism of Protein Binding :-

After the administration of drug.

↓

Drug reaches stomach & dissolute.

↓

After the dissolution of a drug absorption of drug takes place.

↓

Drug transport from stomach to blood capillary.

↓

In blood capillary plasma protein such as albumin, Globulin, Lipoprotein, α-acid glycoprotein drug binds with

↓

Drug molecule binds with protein which form drug protein Complex.

↓

Then, the drug protein complex reaches the size of action where the complex (drug protein Complex) dissociate & drug molecules attach to the injured cell.

↓

The unbounded plasma protein separate.

↓

→

DATE

[Drug Absorb]

⇓

[Free drug in Plasma]

⇓

[Protein bond drug in plasma
(No Pharmacological response
than for no therapeutic action)]

[Protein] [Drug] P'calogical & Therapeutic action shows.

⇒ Methods used for Determining Protein Binding :-

1. Equilibrium Dialysis method.
(agitation)
2. Ultrafiltration
(Centrifugation)
3. Dynamic Dialysis
(rate of disappearance ∝ Conc. of unbound.)

1. Equilibrium Dialysis Method :-

In this method a protein solution is enclosed with a semi-permeable membrane such as Cellophic or Cellulose molecule which is permeable to small drug molecule & not to macromolecule such as protein.

↓

DATE

↓

Then, the protein solution is immersed into drug solution.

↓

Than, the solution is agitated until the equilibrium reached.

↓

Samples from both side of the memb. are analysed.

↓

If the concentration of the drug within the membrane somethan the protein it indicates that no protein binding occur.

↓

If the Conc.^{n} within the membrane is more it indicates that the protein binding has occur.

2. Ultrafiltration :-

This method is similar to Equilibrium Dialysis method in that the protein & drug solution are separated by SPM (semi-permeable membrane).

↓

Hydraulic pressure or centrifugation is used in ultrafiltration to force the solvent & free drug across the membrane.

↓

This method is more convienent than other method for determination.

↓

Since, this method is less time consuming.

DATE

3. Dynamic Dialysis :-

This is a kinetic method for stirring the protein binding of drugs

↓

This method is based on the rate of disappearance of a drug from a dialysis membrane or dialysis cell.

↓

Therefore,

Rate of disappearance ∝ Conc^n of unbounded drug.

* The apparatus consist of a jacketed (temp. controlled) beaker into which a buffer solution is placed.

* A cellophin dialysis memb. containing the protein/drug solution is suspended into the buffer.

↓

Both the solution are stirred continuously or analysed by Spectrophotometrically.

↓

The dialysis process followed the rate law (first order reaction).

$$\frac{-d[Dt]}{dt} = K[Df]$$

Where, Dt = total drug Conc^n

Df = Conc^n of free drug/ unbound drug in the dialysis bag.

$\frac{-d[Dt]}{dt}$ = It is the rate of loss of drug from the drug.

K = first order rate constant.

DATE

Complexation and Drug Action :-

* Complexes can alter the pharmacological activity of drug by inhibiting interaction with receptor.

* Once Complexation occurs the physical & chemical properties of the Complexing species are changed. Such as - Solubility, Physical state, Stability and energy absorbtion & emmission etc.

* Drug Complexation leads to beneficial properties such as enhanced aqueous solubility -

→ ↑ Absorption → ↑ Bioability → ↑ Drug action.

* In some cases solubility decreases such as Solubility of tetracycline decreases when it complexes with Calcium Ion.

Thermodynamic Treatment of Stability Constant :-

* The thermodynamics of metal ion Complex formation provides much significant information.

* In particular it is useful in distinguishing b/w Enthalpic & Entropic effect.

* Enthalpic effect depend on bond strength.
* Entropic effect depend on change in odour of the Solution.

* Stability Constant of metal Complexes
↓
related to thermodynamic properties.

Free energy change (ΔG) | Enthalpy (ΔH) | Entropy change (ΔS)

PAGE

DATE

So, from equation $\Delta G_1 = -2.303\ RT \log K$.

Standard enthalpy change ΔH obtained from slop of plot $\log K$ vs $1/T$.

$$\log K = -\Delta H / 2.303\ RT + \text{Constant}$$

When value K at two temperature are known then equation can be written as —

$$\log\left(\frac{K_2}{K_1}\right) = -\frac{\Delta H}{2.303R}\ \frac{T_2 - T_1}{T_1 T_2}$$

* So standard entropy change can be obtained by
$\Delta G_1 = \Delta H - T\Delta S$

then if ΔH and ΔS become negative

↓

Stability Constant of Complexes increases.

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 metalloproteins.

* Their present uses & their potential applications are diverse due to their Compositions, their molecular and crystal structures and their chemical & 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.