Physical Pharmacy

Complexation

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Complexation

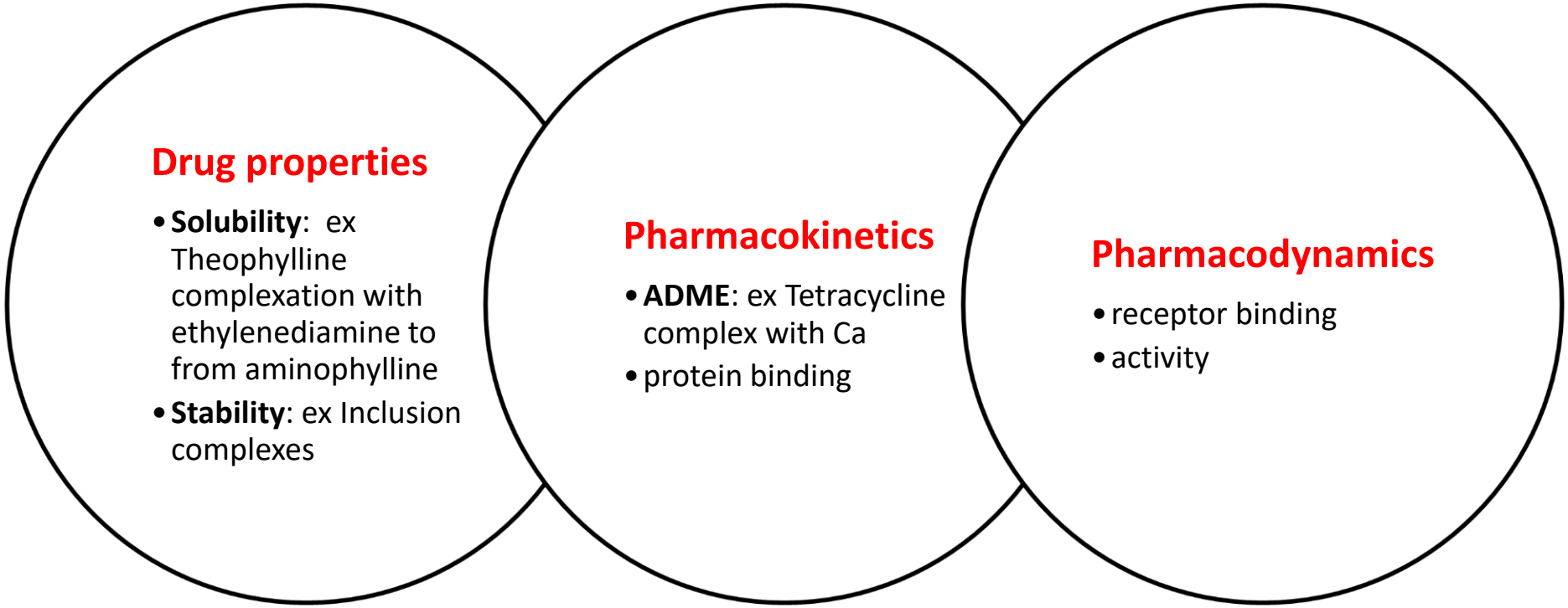
- Complexes are compounds that result from donor–acceptor mechanisms between two or more chemical species.

- Intermolecular forces involved in the formation of complexes:

1. Coordinate covalence (important in metal complexes).
2. Hydrogen bonds (important in molecular complexes).
3. Van der Waals forces.
4. Charge transfer.
5. Hydrophobic interaction.

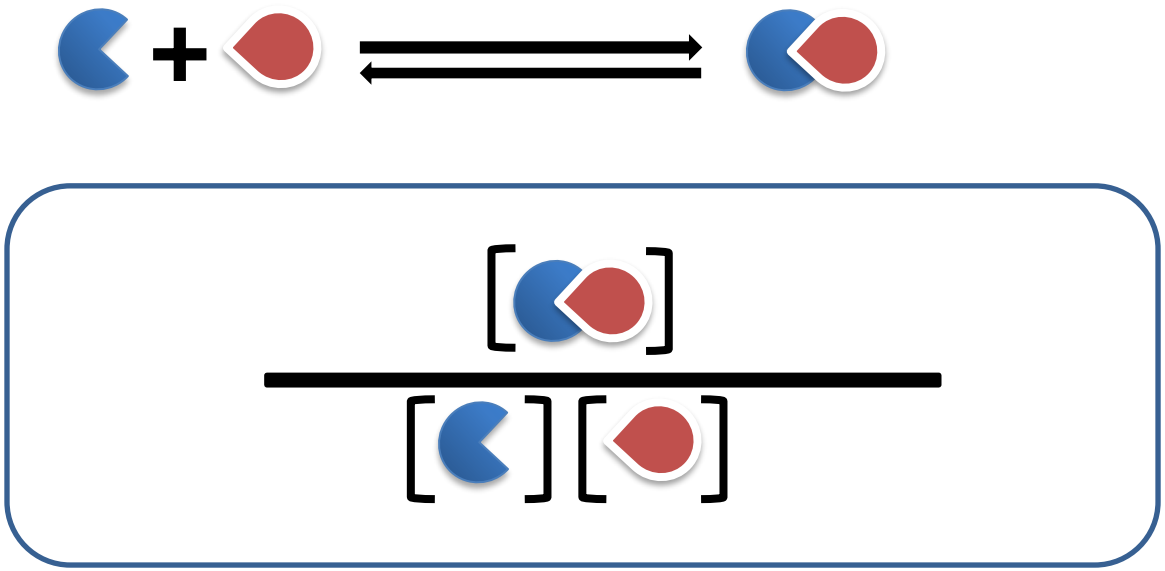
Complexation

- Once complexation occurs, the physical and chemical properties of the complexing species are altered. In pharmacy these alterations have to be considered or employed.



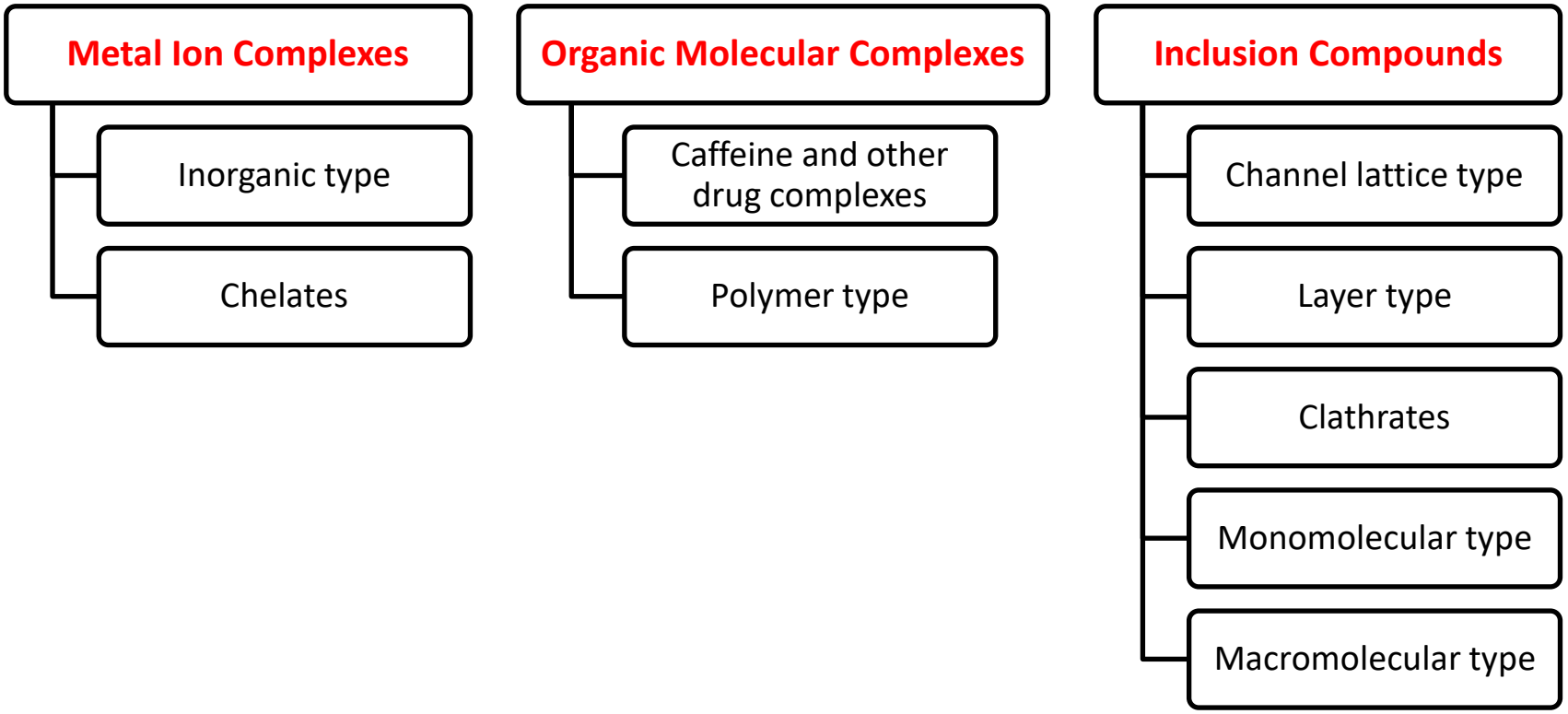
Complex stability constant

- A measure of the tendency of a the substrate and the ligand (ligands) to form a particular complex is given by the stability constant K_s
- Also called formation constant, K_f, which is the equilibrium constant for the complex ion formation. **The larger K_s is, means?**



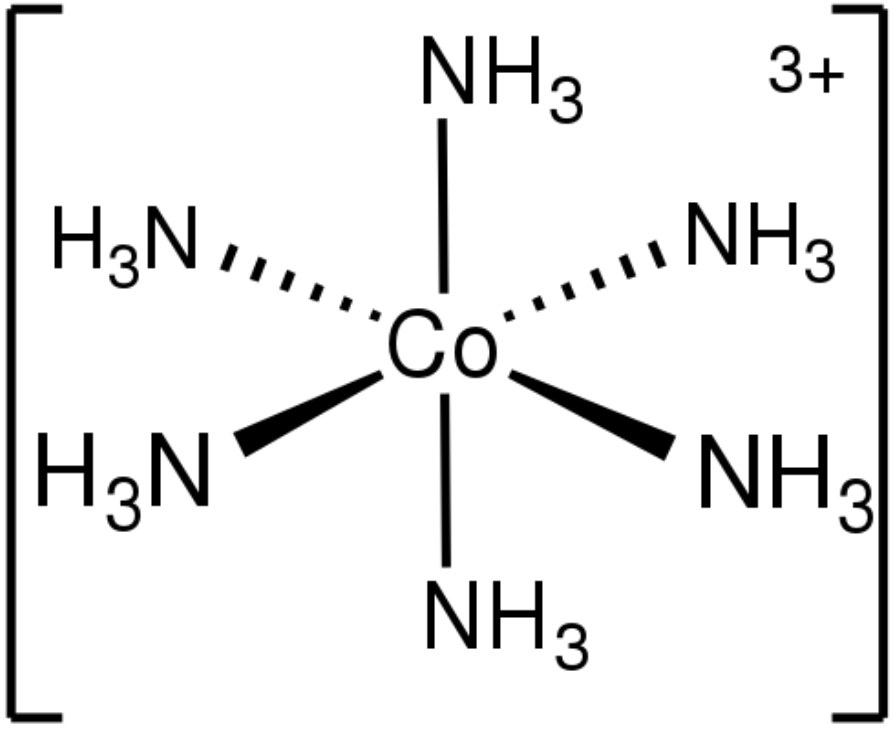
Complexation

- Complexation, is the covalent or non-covalent interactions between two or more compounds that are capable of independent existence.
- The ligand (donor) is a molecule that interacts with another molecule, the substrate (acceptor), to form a complex.



Metal ion complexes

- Also known as coordination complex: **Lewis acid-base** reaction between donor and acceptor molecules **(coordinate covalent bond).**
- Central atom or ion (metallic) (substrate) joined or surrounded by array of bound neutral molecules or anions (called ligands).



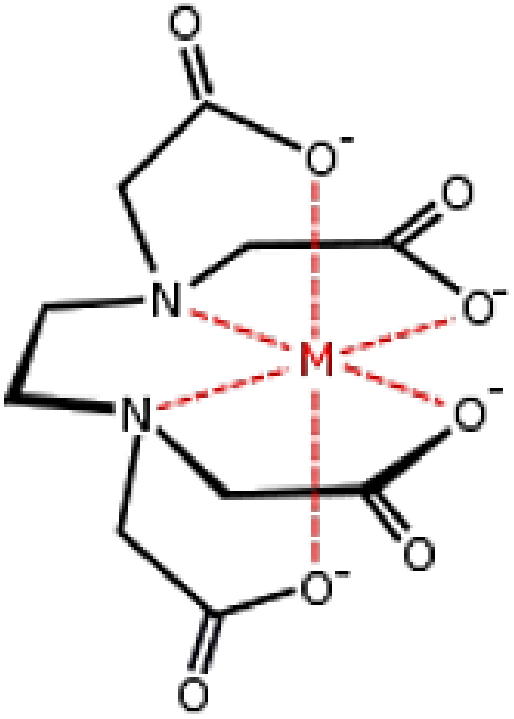
- The number of ligands bound to the metal ion is defined as **coordination number**. For cobalt it is six.
- Coordination number usually determine the geometry of the complex.

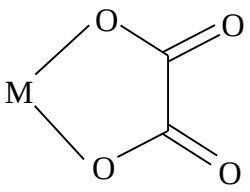
- Metals can make complexes with inorganic or organic ligands
- all inorganic ligands are **unidentate** which mean one binding site with the substrate

Metal ion complexes (Chelates)

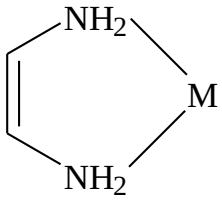
- Ligands with two or three groups are known as bidentate or tridentate respectively (**multidentate**).
- Ethylenediaminetetraacetic acid (EDTA) has six points for attachment (two nitrogen and four oxygen donor groups) an is called hexadentate.
- Multidentate ligands should have specific steric orientation.

WHY?

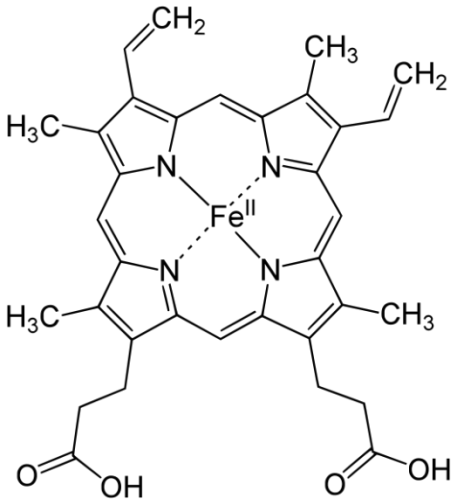




Oxalate (bidentate)



Ethylendiamine (bidentate)

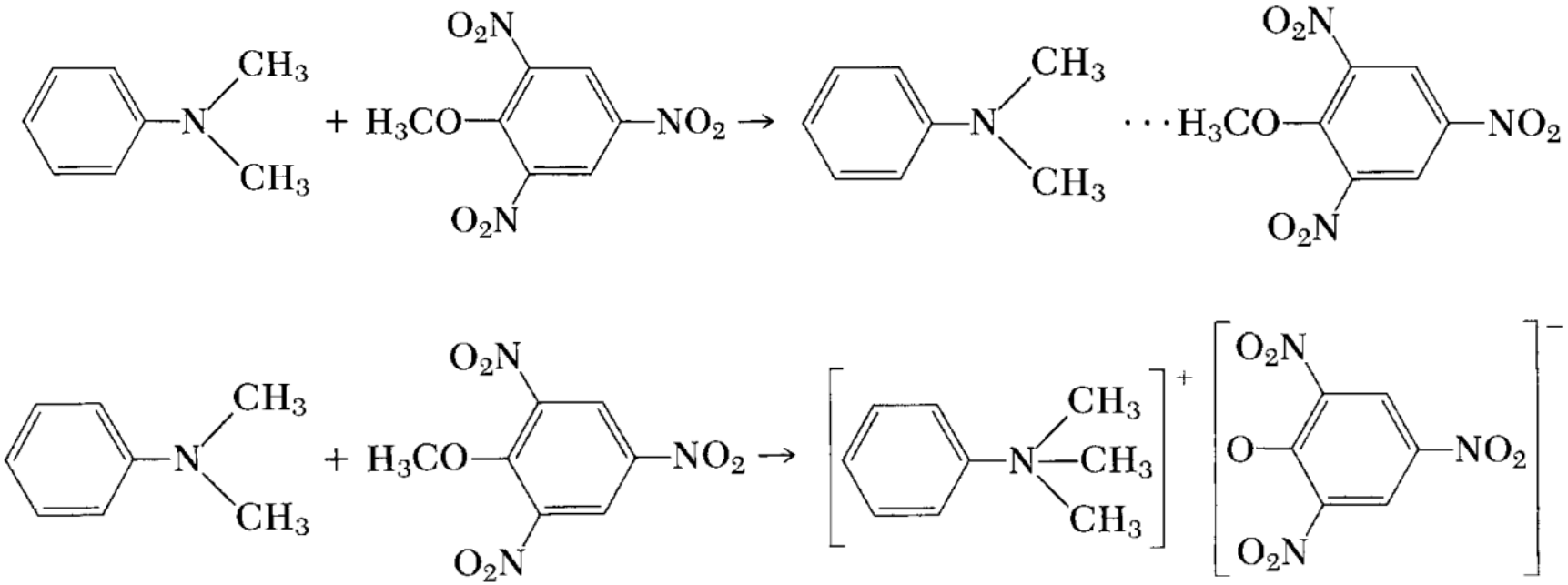


- B12
- hemoglobin
- alcohol dehydrogenase
- chlorophyll
- albumin

If the same metal ion binds with two or more sites on a multidentate ligand, the complex is called chelate.

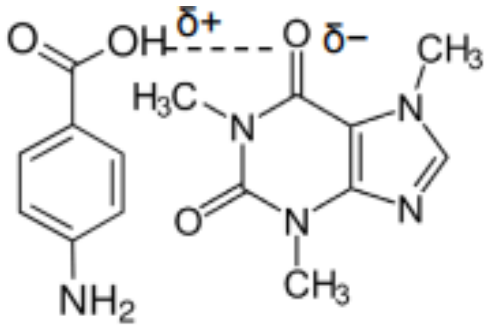
Organic molecular complexes

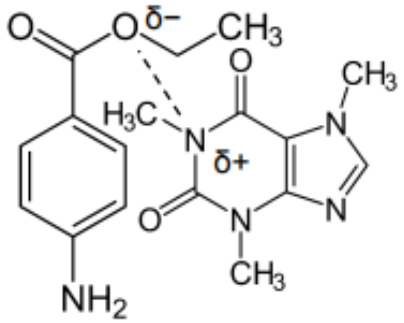
- **No metal** substrate
- Molecules held by weak forces
- E.g. dimethylaniline complexation with 2,4,6 trinitroanisole in cold water VS salt formation at elevated temp.



Organic molecular complexes – Caffeine

- Caffeine forms complexes with several drugs:
- **Hydrogen bonding** between the polarizable carbonyl group of caffeine and the hydrogen atom of the acidic drugs such as p-amino benzoic acid and gentisic acid.
- **Dipole-dipole** interaction between the electrophilic nitrogen of caffeine and the carboxy oxygen of esters such as benzocaine or procaine



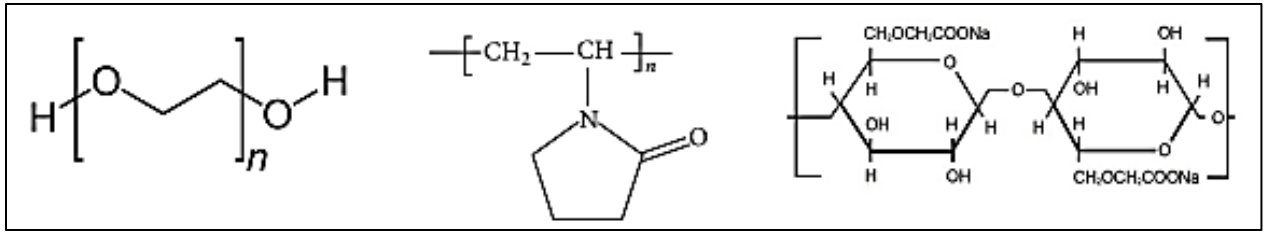


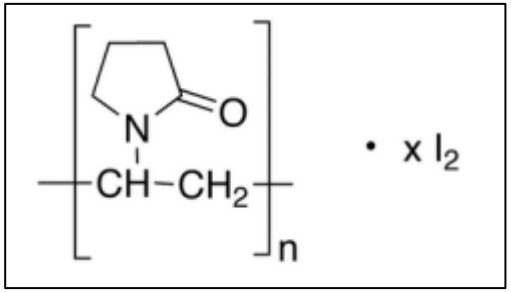
- **Water soluble** complexes with organic acid anions.
- **Less soluble** complexes with organic acids, such as gentisic acid. **why good for chewable tablets?**

Organic molecular complexes - Polymer complexes

- Polymeric materials such as Eudragit, chitosan, polyethylene glycols (PEG), polyvinylpyrrolidone (PVP) and sodium carboxymethyl cellulose (CMC), can form complexes with a large number of drugs.

1. Incompatibility and stability problems
2. Interaction with plastic containers.
3. Precipitation and solubility problems.
4. Changing dissolution rate, absorption, and bioavailability.





- Polymeric complex between naltrexone and Eudragit improves the dissolution rate of naltrexone.

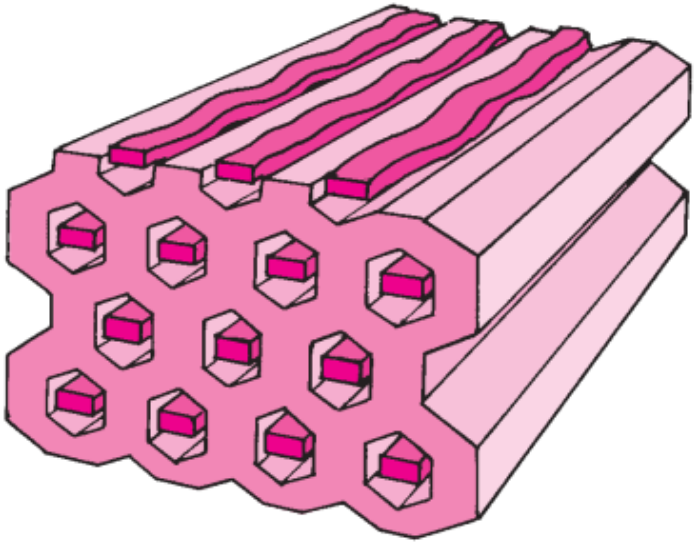
Inclusion Complexes

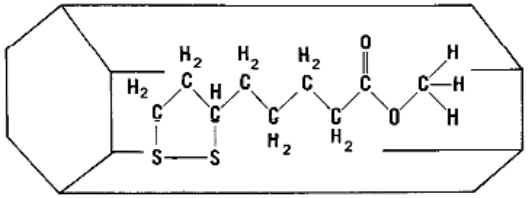
- An inclusion compound is a complex in which one chemical compound (the ‘host’) forms a cavity in which molecules of a second compound (‘guest’) are entrapped.
  Also known as no-bond complexes.

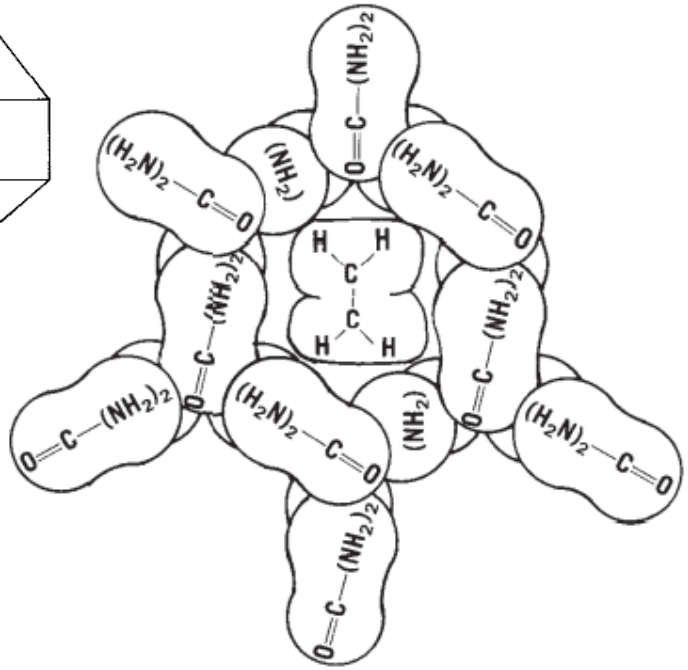
- Channel lattice type
- Layer type
- Clathrates
- Monomolecular type
- Macromolecular type

Inclusion Complexes - Channel Lattice Type

- The host crystallizes to form channel-like structure into which the guest molecule can fit.
- Geometry of the guest plays a very important role
- The cholic acids (bile salt) is an example of this complex type.
- The well-known starch–iodine complex is a channel-type complex consisting of iodine molecules entrapped within spirals of the glucose residues

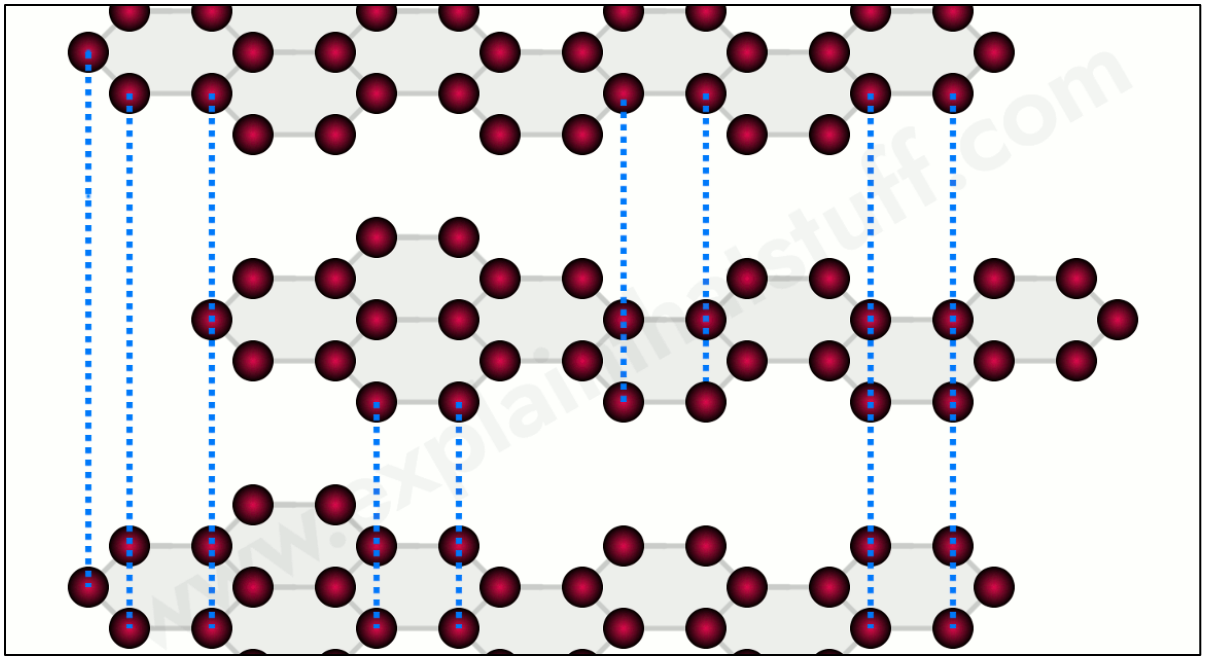






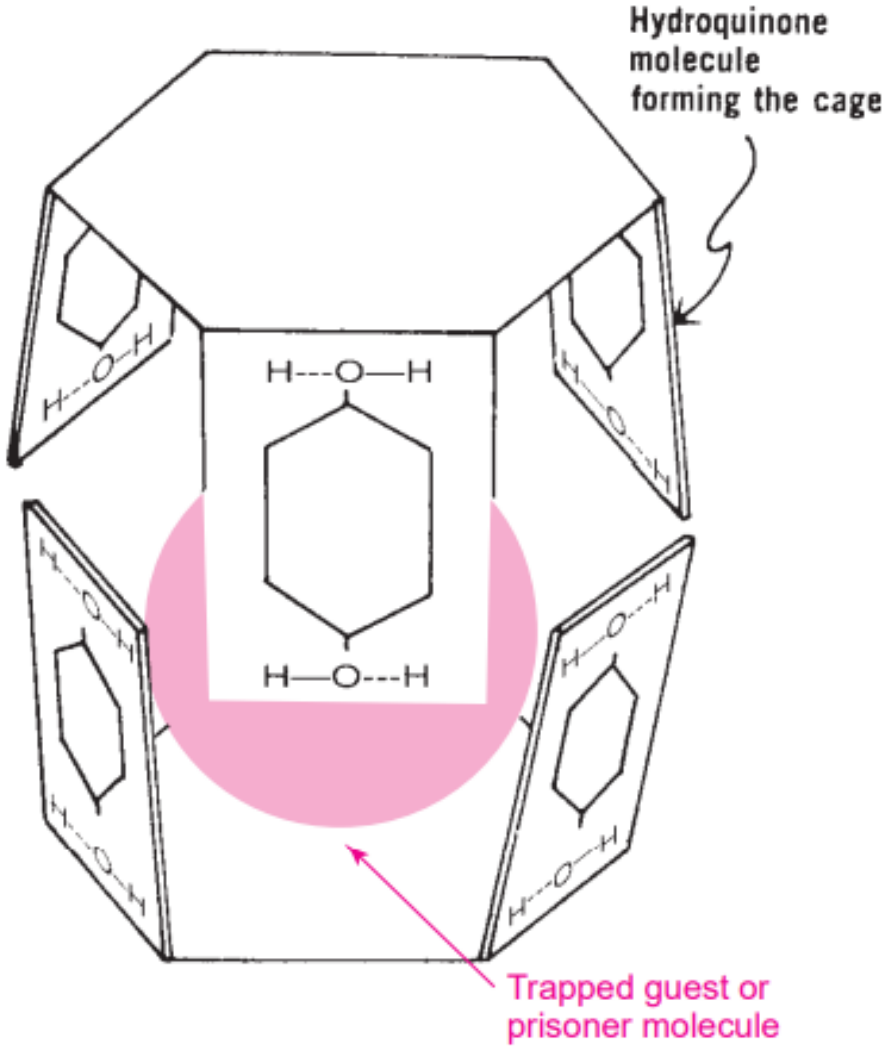
Inclusion Complexes - Layer Type

- The crystals arrange in layers that can trap small molecules such as alcohols and glycols
- Intercalate compounds between its layers. Example: bentonite and graphite



Inclusion Complexes - Clathrates

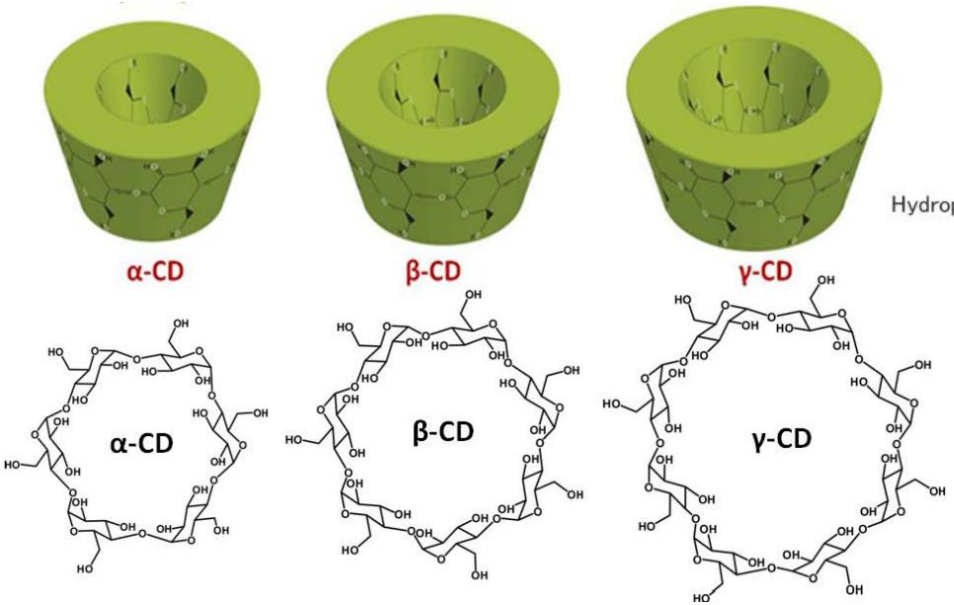
- Compounds that crystallize in the form of a cage-like lattice in which the coordinating compound is entrapped.
- Hydroquinone crystals that traps methanol, CO_2 and HCl but not smaller and larger molecules.
- One official drug, warfarin sodium, is in the form of crystalline clathrate containing water and isopropyl alcohol.

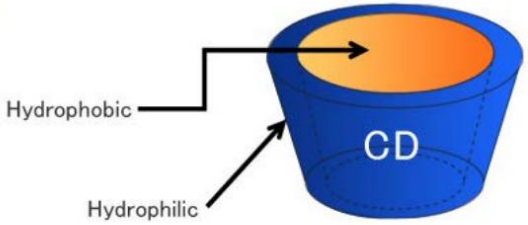


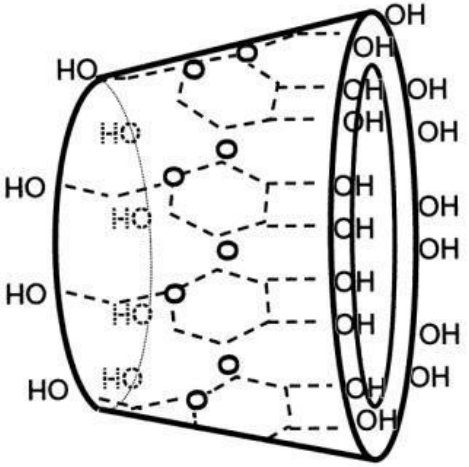
Inclusion Complexes - Monomolecular

- Involve entrapment of a single guest molecule in the cavity of one host molecule.
- Cyclodextrins: One of the most important molecular complexations is the interaction between molecules and cyclodextrin to form reversible inclusion complexes.
- Types:

Cyclodextrin type	Glucose units	Internal diameter	Aqueous solubility	USP name
α-cyclodextrins	6	4.7-5.3 Å	14.5 g/100 mL	Alfadex
β-cyclodextrins	7	6.0-6.5 Å	1.85 g/100 mL	Betadex
γ-cyclodextrins	8	7.5-8.3 Å	23.2 g/100 mL	Gammadex

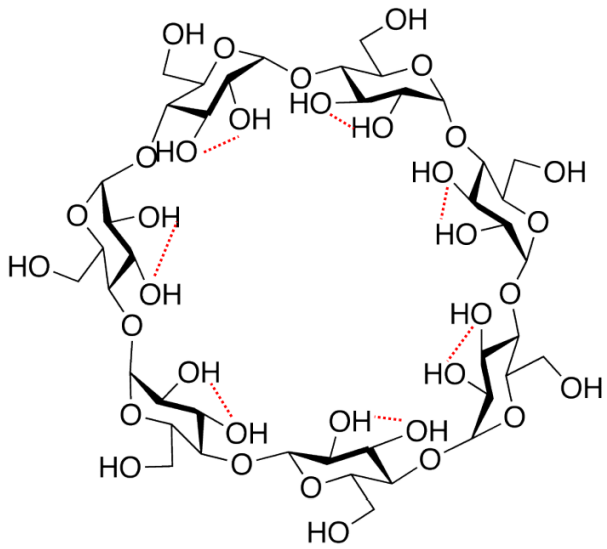






Inclusion Complexes - Monomolecular

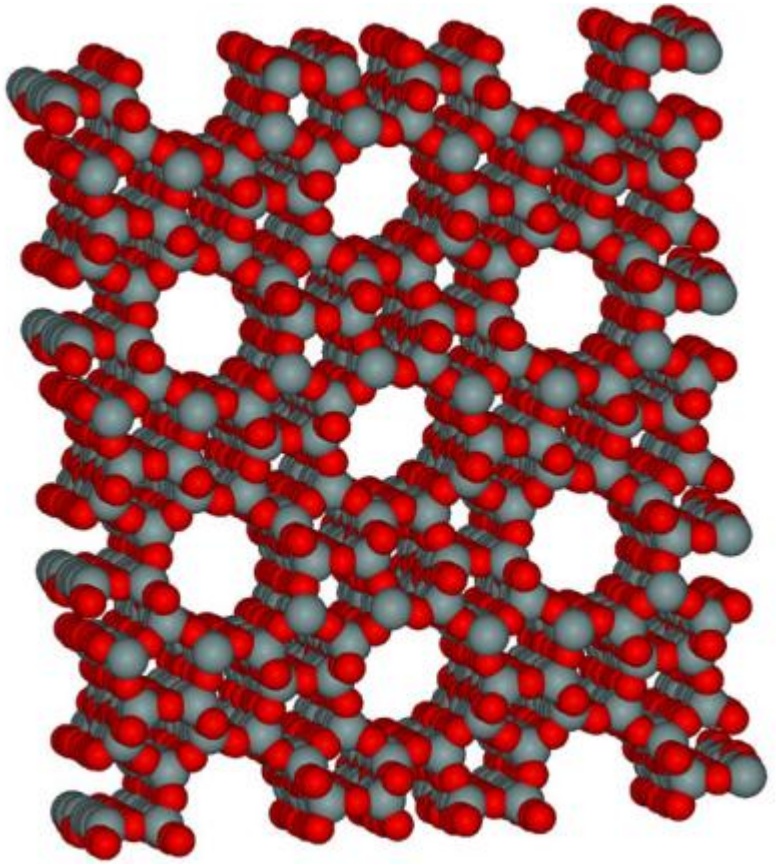
- Molecules of appropriate size and stereochemistry get entrapped in the cyclodextrin cavity by hydrophobic interaction by squeezing out water from the cavity.
- **Why ß-Cyclodextrins are most commonly used as a complexing agents?**
- **How to fix the issues of the ß-Cyclodextrins**



Property changed by employment of CDs	Examples
↑ Aqueous Solubility	Prostaglandins; NSAIDs
↑ Stability	Aspirin, atropine, digoxin
↑ Absorption & Bioavailability	Phenytoin, digoxin
↓ Taste and Odor	Prostaglandins, NSAIDs, famoxetine
↔ Change from Liquid to Solid	Nitroglycerin, methyl salicylate
↓ Volatility	Menthol, salicylic acid
↓ Stomach Irritation	NSAIDs
↓ Incompatibilities	Vitamins

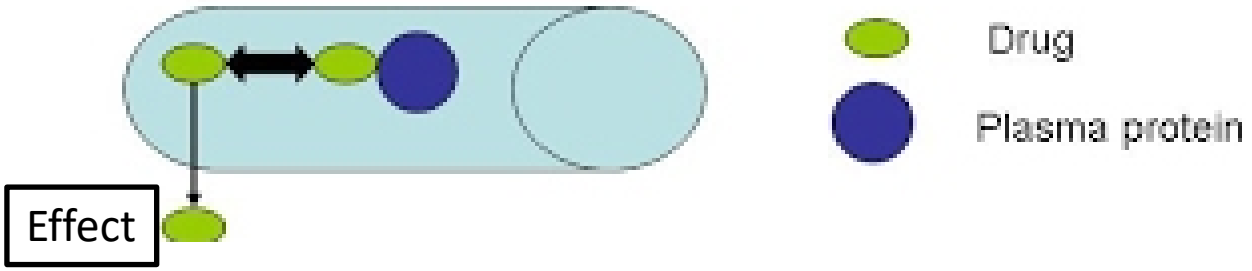
Inclusion Complexes - Macromolecular Inclusion Compounds

- Also called molecular sieves. Molecules arranged in 3-D to form cages and channels with different pore size.
- Used to separate molecules with different dimensions.
- Example: zeolites, dextrins and silica gels.



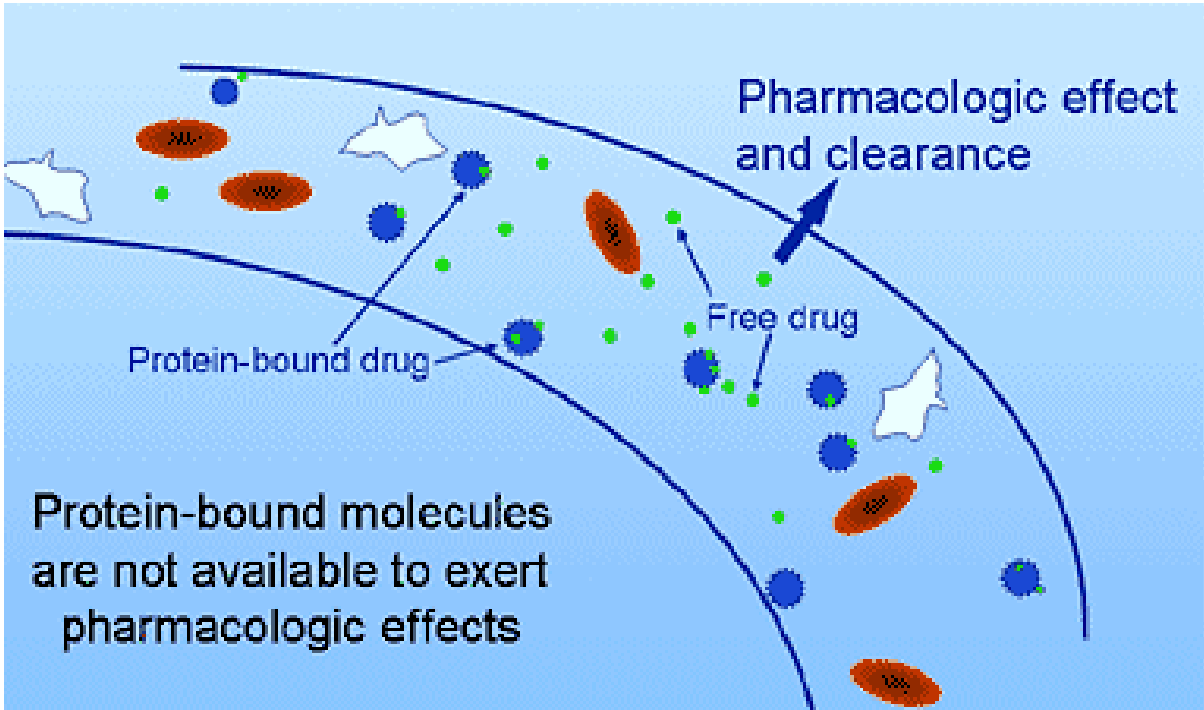
Drug-protein binding

- Once drug enter blood circulation complexes can form between the drug molecule and blood proteins.
- Among the plasma proteins, albumin is the most important owing to its high concentration relative to the other proteins.
- The binding of drugs to proteins contained in the body can influence their action in a number of ways:
  - Affect distribution of drugs throughout the body,
  - Inactivate the drug by not enabling a sufficient concentration of free drug to develop at the receptor site.
  - Retard the excretion of a drug.



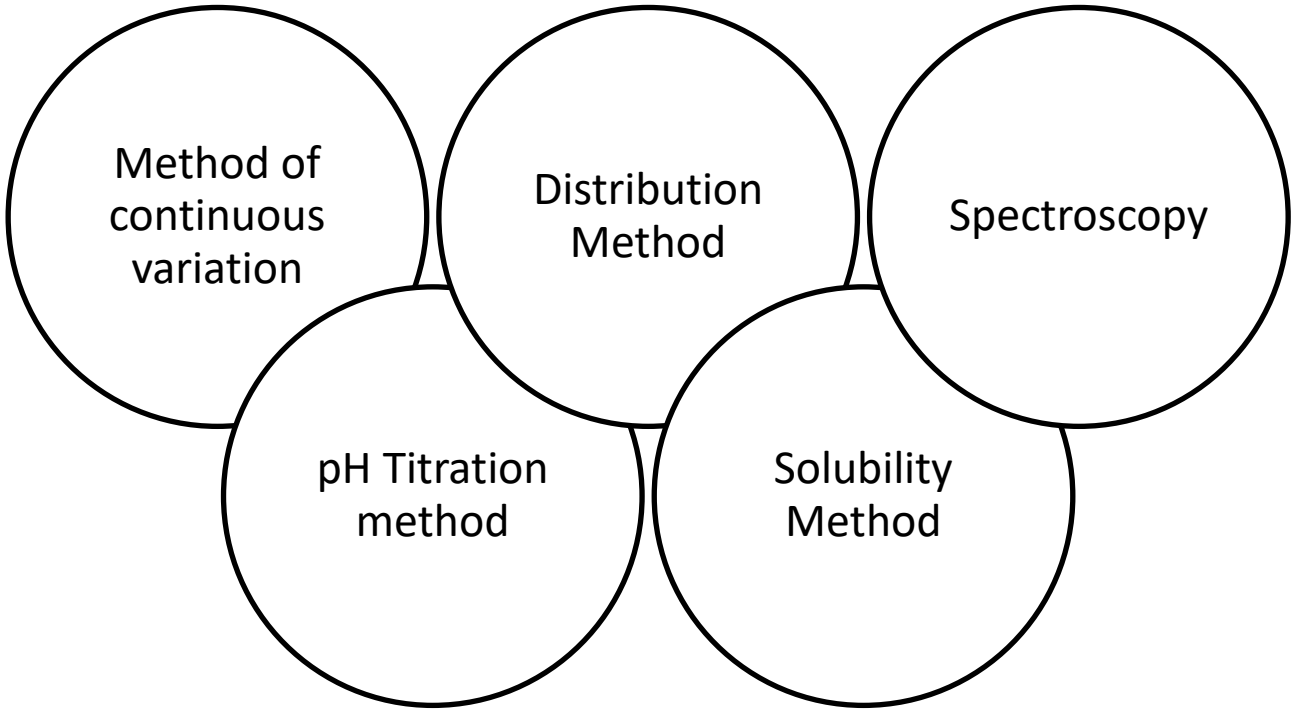
Drug-protein binding

- An example of a drug that extensively binds to plasma proteins is Warfarin **(so Ks is?)**. Administration of another drug that has higher affinity for plasma proteins (for example several NSAID) will displace warfarin from its binding sites and cause serious hemorrhage to the patient.
- Some diseases decrease available protein in blood (age, malnutrition and trauma).**how is this related to drug toxicity?**



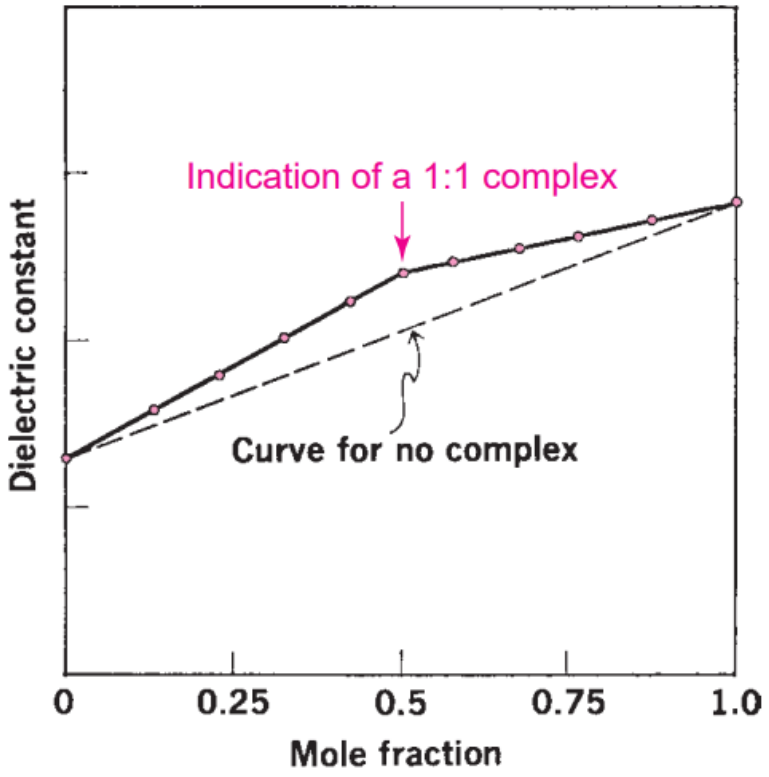
Methods of Analysis of complexes

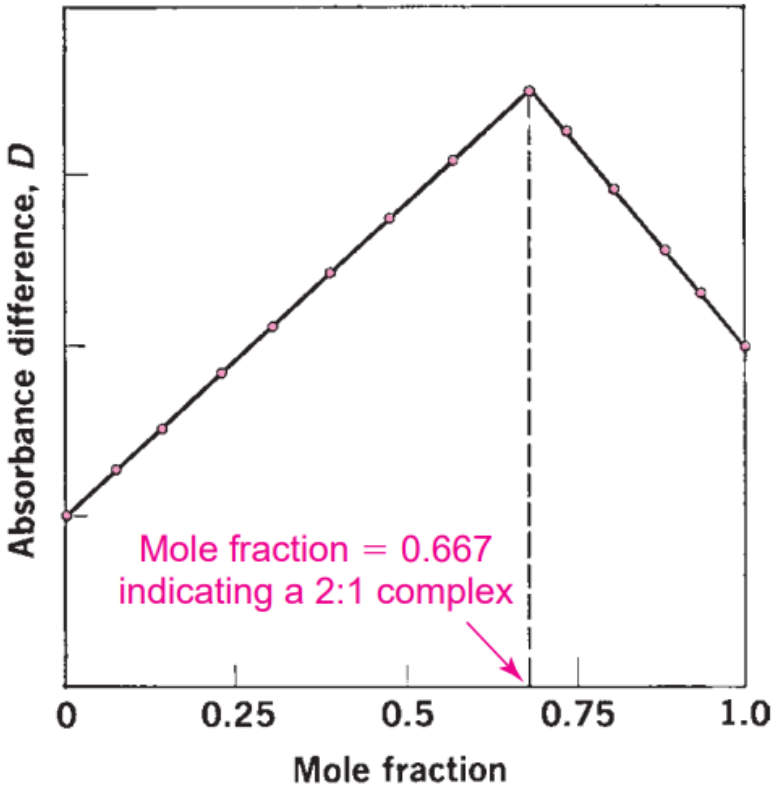
- stoichiometric ratio of ligand to metal (or donor to acceptor)
- stability constant for complex formation

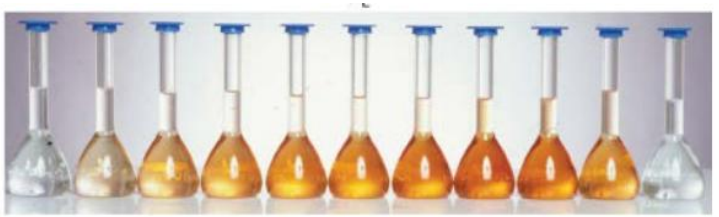


Method of Analysis - Continuous variation

- Use of an additive property
- If no interaction occurs when the components mixed, then the value of the property is the weighted mean of the values of the separate species in the mixture.



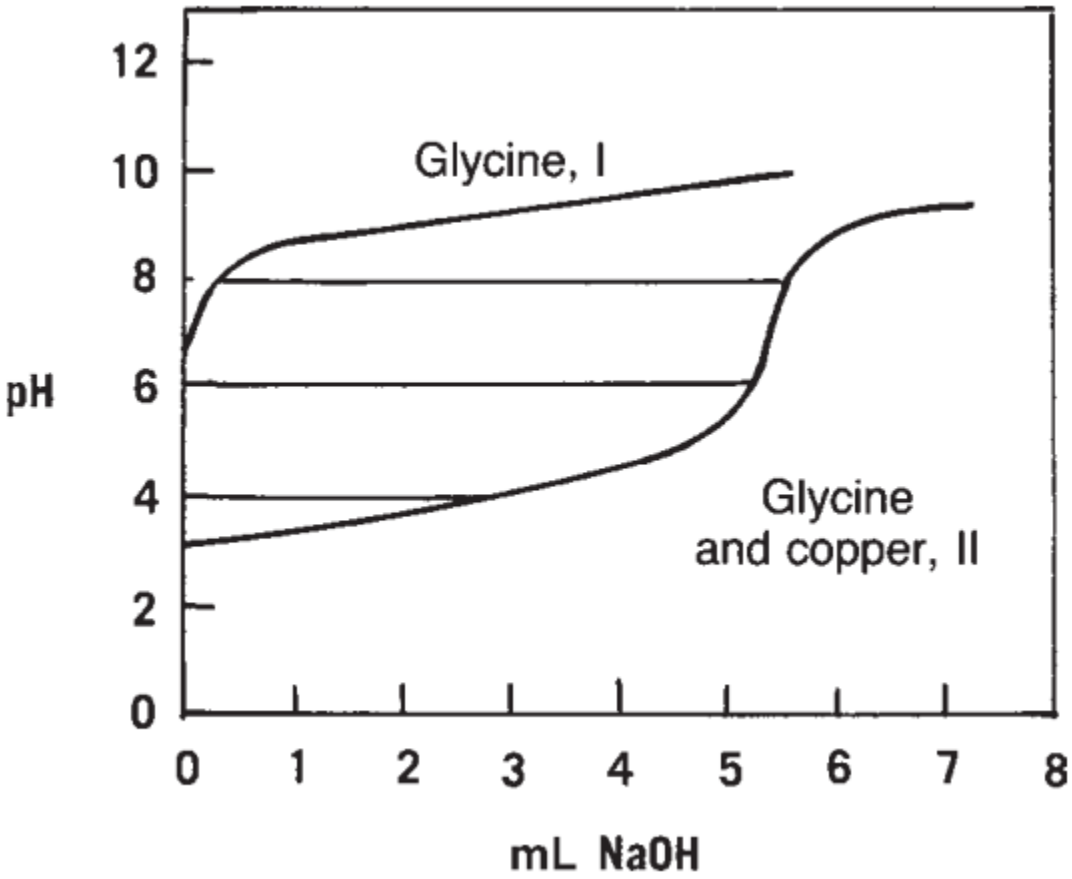




Method of Analysis - pH Titration

- Most reliable method
- Complexation should be affected by change in pH.
- E.g.: Glycine with Cupper

$$Cu^{2+} 2NH_3{}^{+} CH_2 COO^{-} = Cu(NH_2CH_2COO)_2 + 2H^{+}$$

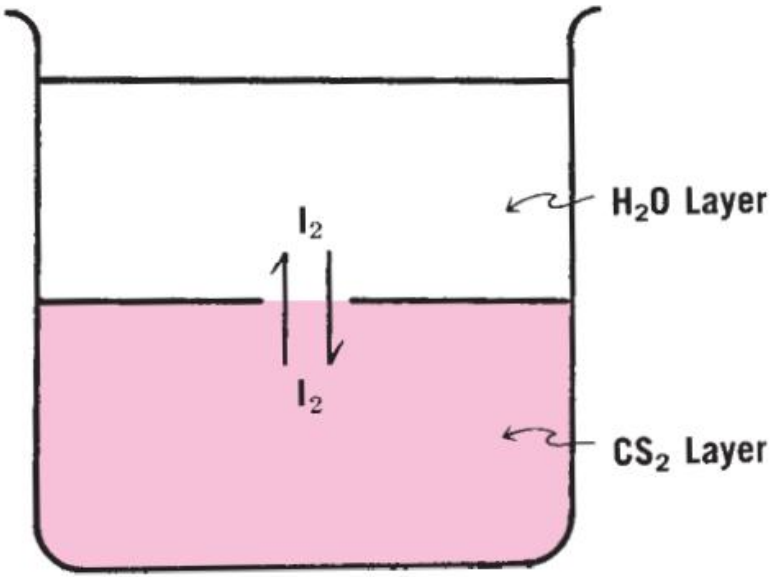


Method of Analysis - Distribution method

- Measure the stability constant by distribution of the complex bet two immiscible solvents.
- E.g.: Iodine and Potassium Iodide in water and CS_2
- The distribution method has been used to study caffeine and polymer complexes with a number of acidic drugs such as benzoic acid, salicylic acid, and acetylsalicylic acid.

$$I_2 + I^- \rightleftharpoons I_3^-$$

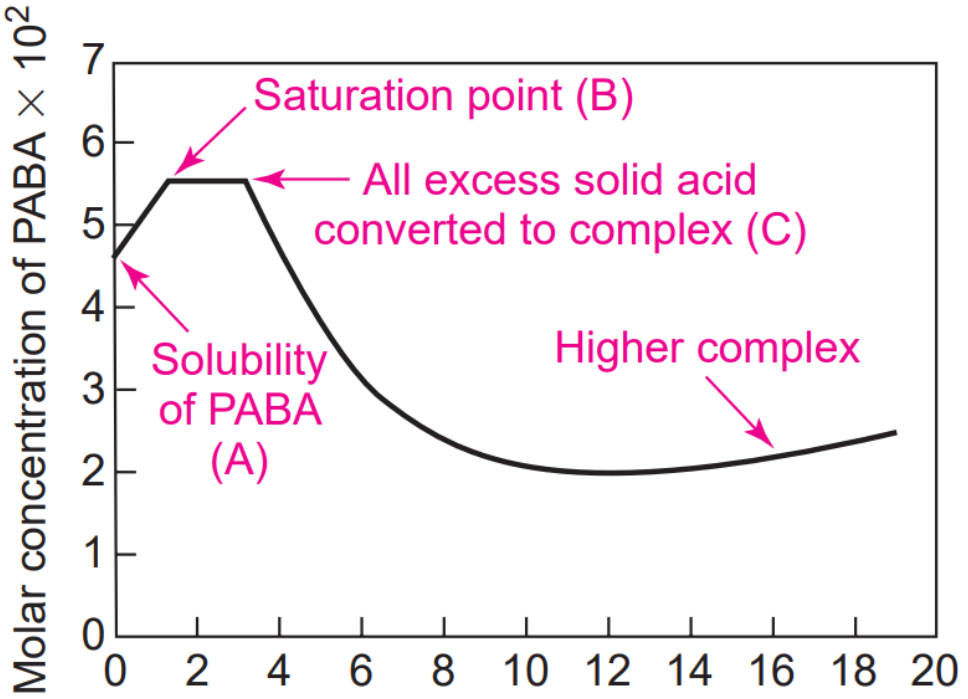
- Refer to Example 10-2 in the book



Method of Analysis – Solubility method

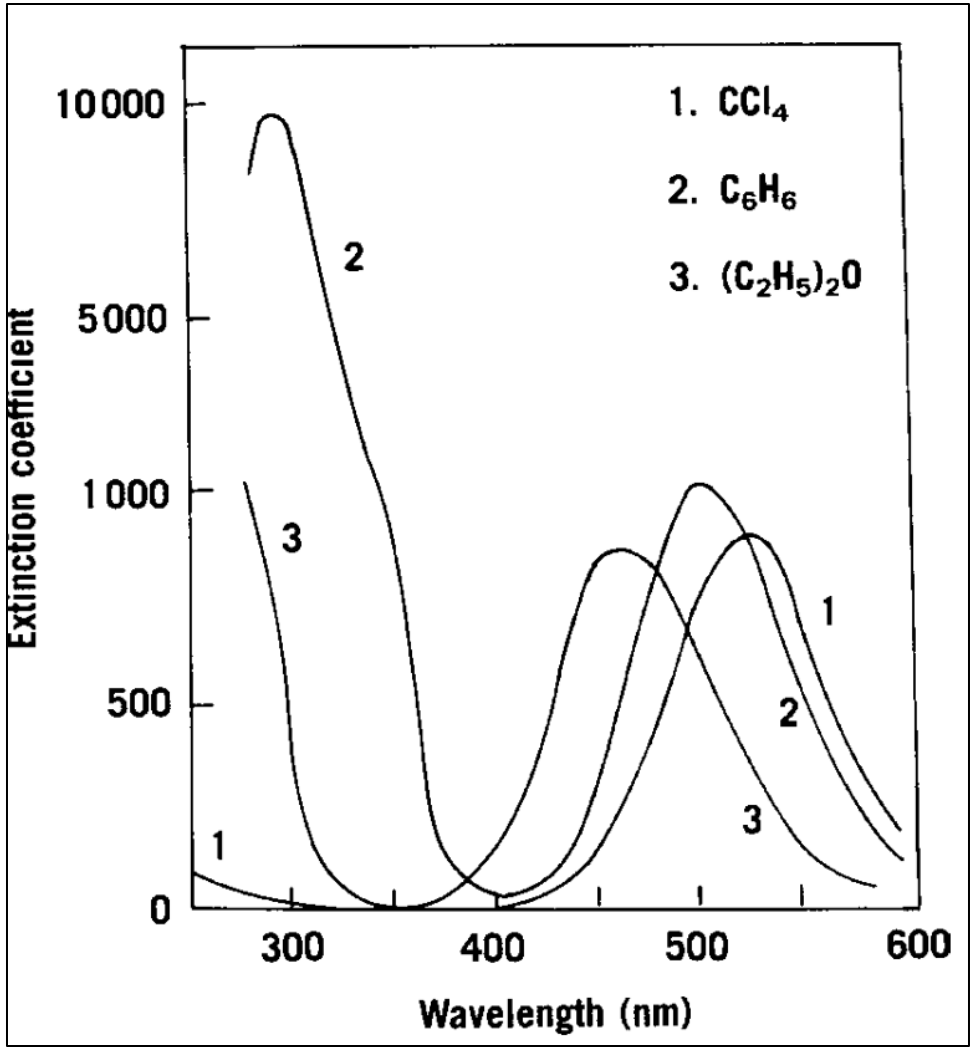
- Measure the solubility by shake flask method.
- E.g.: Para amino benzoic acid (PABA) + Caffeine.
- Most widely used in study of inclusion complexation.

1. Excess quantities of the drug added to the complexing agent in various concentrations.
2. The bottles are agitated in a constant temp. bath until equilibrium and then analyzed.



Method of Analysis - Spectroscopy

- Absorption spectroscopy in the visible and ultraviolet regions.
- E.g.: I_2 in CCl_4 = one peak 520nm (Violet)
- Benzene = 475nm & 300nm (Red)
- Diethyl ether =450nm & 300nm (Red)
- I_2 is electron acceptor; in CCl_4 no complex (not a donor). The other 2 solvents act as electron releasing agents and form charged transfer complex with I_2.



Questions?