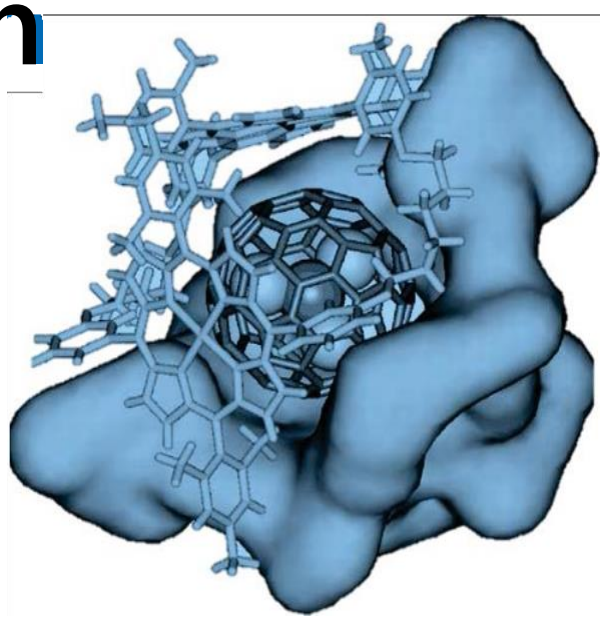
FACULTY OF PHARMACEUTICAL SCIENCES, RAMAUNIVERSITY, KANPUR

B.PHARM 3rd SEM
PHYSICAL PHARMACEUTICS-I
BP302T

MR. PEEYUSH
Assistant professor
Rama university, kanpur

Complexation



Overview

Classification

Introduction
Metal ion complexes Organic Complexes
Inclusion Complexes

Methods of Analysis

Method of Continuous Variation PH Titration
Distribution Method Solubility Method
Spectroscopy

Learning Objectives

1. Define the three classes of complexes with pharmaceutically relevant examples.
2. Describe chelates, their physically properties, and what differentiates them from organic molecular complexes.
3. Describe the types of forces that hold together organic molecular complexes with examples.
4. Describe the forces in polymer–drug complexes used for drug delivery.
5. Discuss the pharmaceutical applications of cyclodextrins.
6. Describe the methods of analysis of complexes and determine their stoichiometric ratios and stability constants.

Classification

Introduction
Metal ion complexes Organic
Complexes Inclusion Complexes

INTRODUCTION

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

Complexes can be divided broadly into three classes depending the type of the acceptor substance:

1. Metal ion complexes
2. Organic molecular complexes
3. Inclusion complexes

Intermolecular forces involved in the formation of complexes:

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

Introduction

Types of Complexes

Metal Ion Complexes

A. Inorganic type
B. Chelates
C. Olefin type
D. Aromatic type

II. Organic Molecular Complexes

A. Quinhydrone type
B. Picric acid type
C. Caffeine and other drug complexes
D. Polymer type

III. Inclusion Compounds

A. Channel lattice type
B. Layer type
C. Clathrates
D. Monomolecular type
E. Macromolecular type

Metal ion complex (coordination complex) consists of a transition-metal ion (e.g. cobalt, iron, copper, nickel and zinc) linked or coordinated with one or more counter ions or molecules to form a complex.

The ions or molecules (e.g. Cl^-, NH_3, H_2O, Br^-, I^-, CN^-, etc.) directly bound with the metal are called ligands.

The interaction between the metal and the ligand represents a Lewis acid-base reaction in which the metal ion (Lewis acid) combines with a ligand (Lewis base) by accepting a pair of electrons from the ligand to form the coordinate covalent or electrostatic forces:

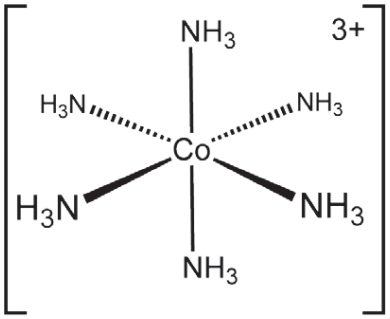
$$Co^{3+} + 6\,(:NH_3) \;<\; [Co(NH_3)_6]^{3+}$$

Metal ion Complexes

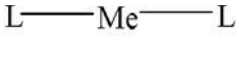
Inorganic Complexes

The number of ligands bound to the metal ion is defined as coordination number.

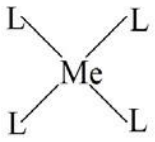
The coordination number of cobalt is six, since it complexed with six NH_3 groups.



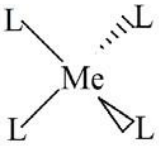
Coordination number usually determine the geometry of the complex.



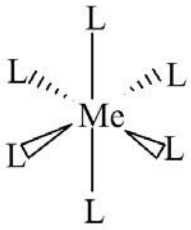
CN = 2 (linear)



CN = 4 (square planar)

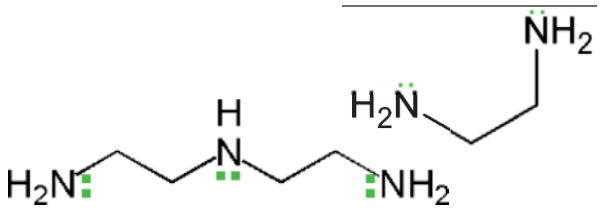


CN = 4 (tetrahedral)



CN = 6 (octahedral)

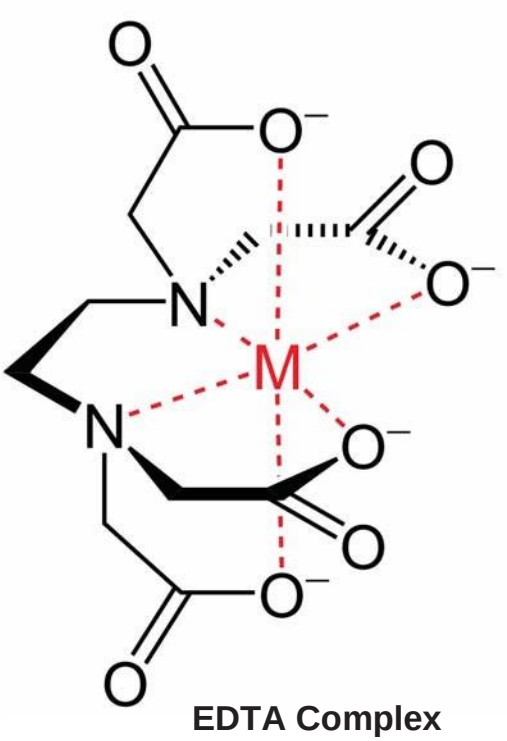
- Compound (e.g. NH_3) which has a single pair of electrons for bonding with the metal ion, is called unidentate ligand.
- Ligands with two or three groups are known as bidentate or tridentate respectively.
- Ethylenediaminetetraacetic acid (EDTA) has six points for attachment (two nitrogen and four oxygen donor groups) and is called hexadentate.



Metal ion Complexes

Chelates

- Chelation is the formation of two or more coordinate bonds between a multidentate ligand (organic compound called chelating agent) and a single central atom.
- The bonds in the chelate may be ionic, primary covalent, or coordinate type.



EDTA Complex

Organic Molecular Complexes

Organic molecular complexes are formed as a result of non-covalent interactions between a ligand and a substrate.

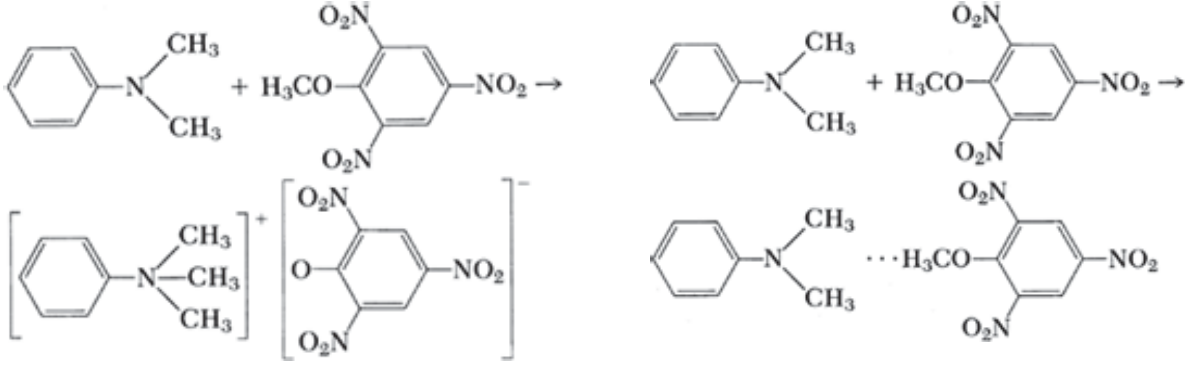
The interactions can occur through van der waals forces, charge transfer, hydrogen bonding or hydrophobic effects.

Many organic complexes are so weak that they cannot be separated from their solutions as definite compounds, and they are often difficult to detect by chemical and physical means.

Organic Molecular Complexes

Complexation differs from the formation of organic compounds in the forces between the constituents:

E.g. Dimethylaniline and 2,4,6-trinitroanisole react in the cold to give a molecular complex. However at elevated temperature, they react to yield a salt, in which the molecules are held together by primary valence bonds.



Salt **Complex**

Organic Molecular Complexes

Charge transfer complex is an association of two or more molecules in which a fraction of electronic charge is transferred between the molecular entities.

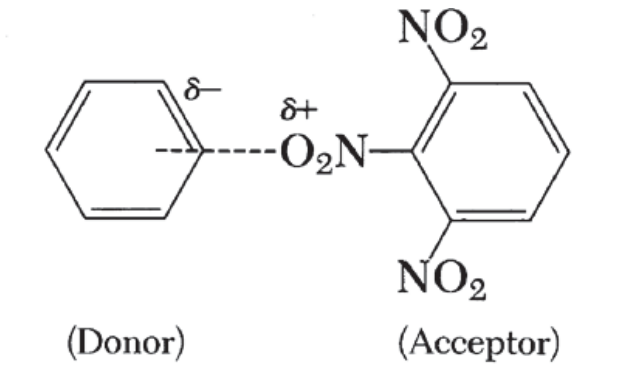
The molecules from which the charge is transferred is called the electron donor and the receiving species is called the electron acceptor

Attraction in charge-transfer complexes is weaker than in covalent forces.

Usually these complexes is formed by sharing of w-electrons

E.g. Complex between benzene and trinitro benzene (1:1 type). (polar nitro group of trinitro benzene induce a dipole in the readily polarizable benzene molecules, resulting in electrostatic attraction).

The difference between a *donor–acceptor* and a *charge transfer* complex is that in the latter type, resonance makes the main contribution to complexation, whereas in the former, London dispersion forces contribute more to the stability of the complex.

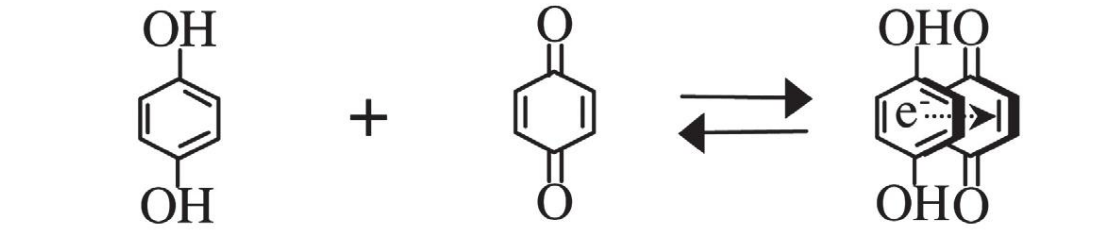


Organic Molecular Complexes

Quinhydrone Complex

This molecular complex is formed by mixing equimolar quantities of benzoquinone with hydroquinone.

Complex formation is due to overlapping of the w-framework of the electron-defficient benzoquinone with the w-framework of the electron-rich hydroquinone (charge transfer).

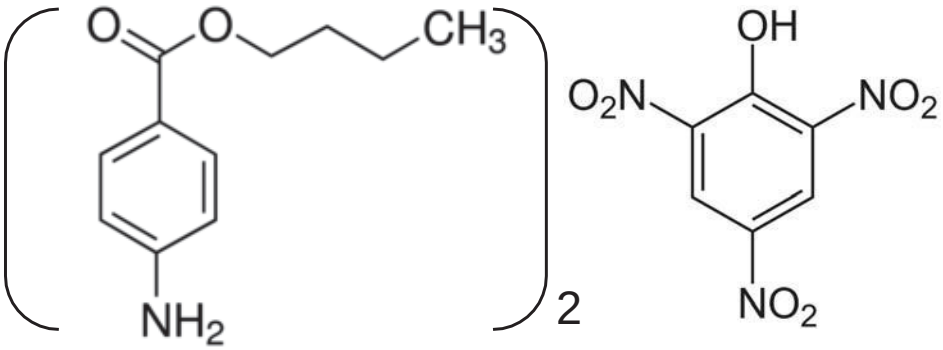


Hydroquinone (colorless) Benzoquinone (yellow) Quinhydrone (purple)

Picric Acid Complexes

Picric acid (2,4,6-trinitrophenol), is a strong acid that forms complexes with many weak bases such as poly-nuclear aromatic compounds.

An example is Butesin picrate (local anaesthetic) which is a complex formed between two molecules of butyl p-aminobenzoate with one molecule of picric acid.



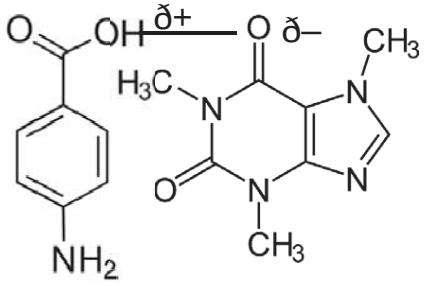
Organic Molecular Complexes

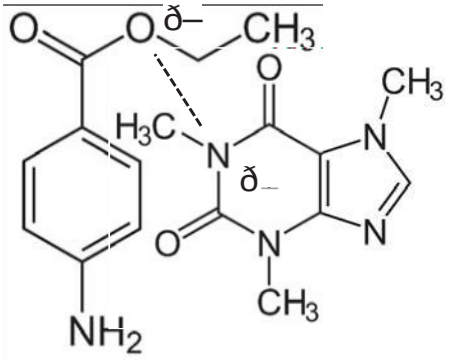
Caffeine Complexes

Caffeine forms complexes with a number of drugs owing to the following factors:

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





Organic Molecular Complexes

Caffeine Complexes

Caffeine forms water soluble complexes (more soluble than caffeine itself) with organic acid *anions*, but the complexes formed with organic acids, such as gentisic acid, are less soluble than caffeine alone.

Such insoluble complexes provide caffeine in a form that masks its normally bitter taste in chewable tablets.

Organic Molecular Complexes

Polymer Complexes

Polymeric materials such as eudragit, chitosan, polyethylene glycols (PEG), polyvinylpyrrolidone (PVP) and sodium carboxymethyl cellulose (CMC), which are usually present in liquid, semisolid and solid dosage forms, can form complexes with a large number of drugs.

Such interactions can result in precipitation, flocculation, solubilization, alteration in bioavailability or other unwanted physical, chemical, and pharmacological effects.

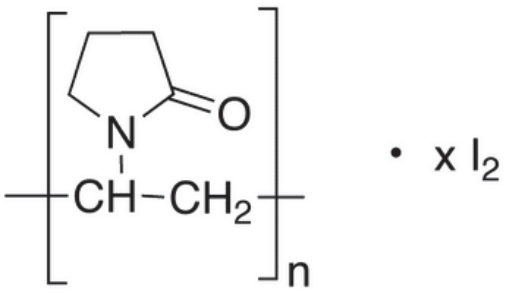
Organic Molecular Complexes

Polymer Complexes

Polymer–drug complexes however can also be used to modify biopharmaceutical parameters of drugs.

Polymeric complex between naltrexone and eudragit improves the dissolution rate of naltrexone.

Povidine-iodine is a stable complex of PVP and iodine, which possess superior antibacterial activity.



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.

These complexes generally do not have any adhesive forces working between their molecules and are therefore also known as no-bond complexes.

Inclusion Complexes

Channel Lattice Type

In this complex, the host component crystallizes to form channel-like structure into which the guest molecule can fit.

The guest molecule must possess a geometry that can be easily fit into the channel-like structure

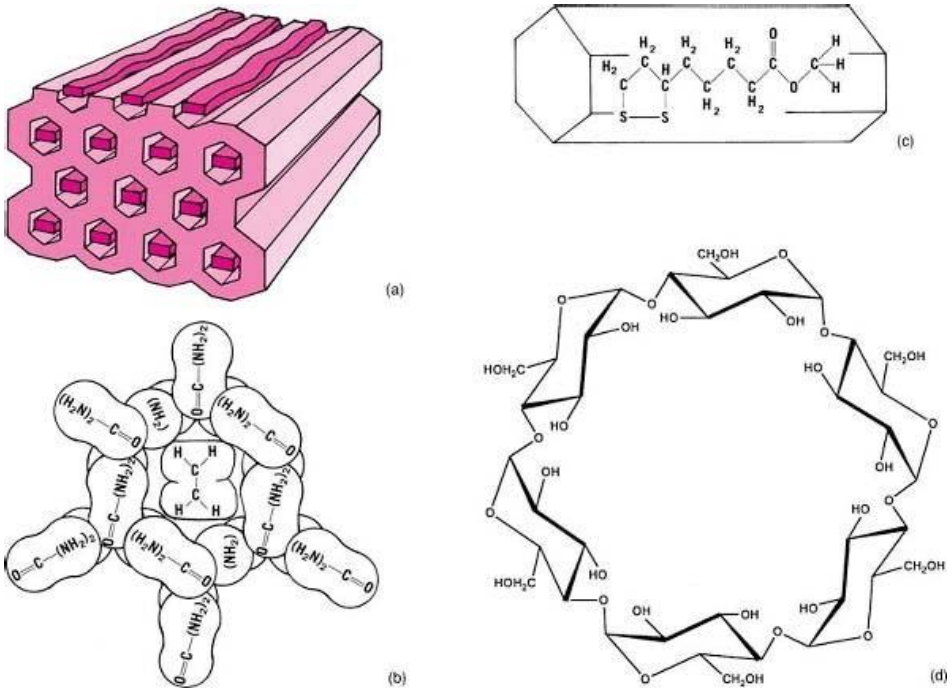
Channel lattice complexes provides a mean of separation of optical isomers.

The cholic acids (bile salt) is an example of this complex type. The crystals of deoxycholic acid are arranged to form a channel into which the complexing molecule can fit.

The well-known starch–iodine complex is a channel-type complex consisting of iodine molecules entrapped within spirals of the glucose residues

Inclusion Complexes

Channel Lattice Type



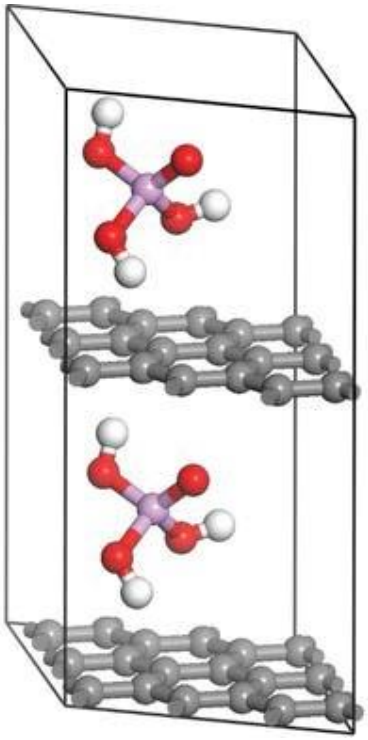
Inclusion Complexes

Layer Type

Layer type complex (or intercalation compound) is a type of inclusion compound in which the guest molecule is diffused between the layers of carbon atom, to form alternate layers of guest and host molecules.

Montmorillonite, the principal constituent of bentonite, can trap hydrocarbons, alcohols, and glycols between the layers of their lattices.

Graphite can also intercalate compounds between its layers.



Inclusion Complexes

Clathrates

The clathrates are compounds that crystallize in the form of a cage-like lattice in which the coordinating compound is entrapped.

One official drug, warfarin sodium, is in the form of crystalline clathrate containing water and isopropyl alcohol.

Clathrates can be used to separate optical isomers.

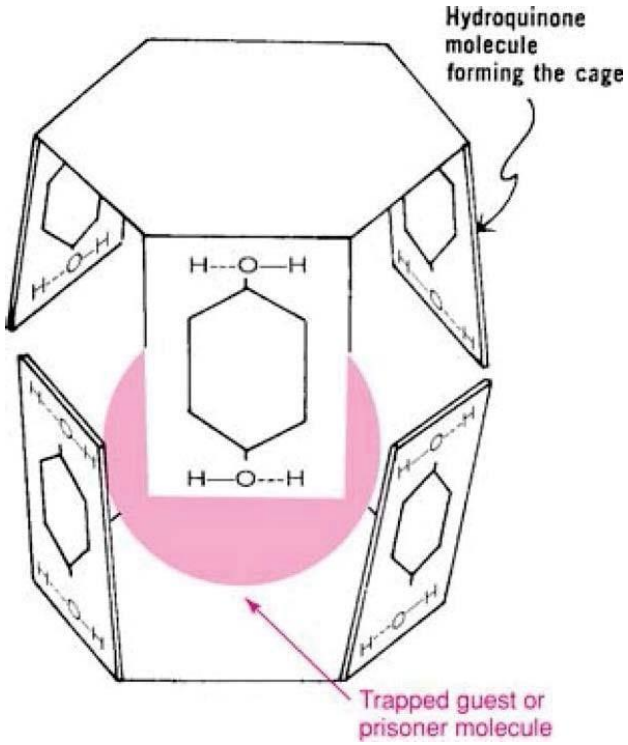
Inclusion Complexes

Clathrates

Hydroquinone crystallizes in a cage-like hydrogen-bonded structure, in which small molecules such as methyl alcohol, CO_2, and HCl may be trapped in these cages.

Size of the guest molecule is important for complex formation.

If the size is too small, the guest molecule will escape from the cage of the host and if the size is too big, it will not be fit inside the cage.



Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

Monomolecular inclusion complex involves the entrapment of guest molecules into the cage-like structure formed from a single host molecule.

Cyclodextrins are a family of compounds made up of sugar molecules bound together in a ring (cyclic oligosaccharides)

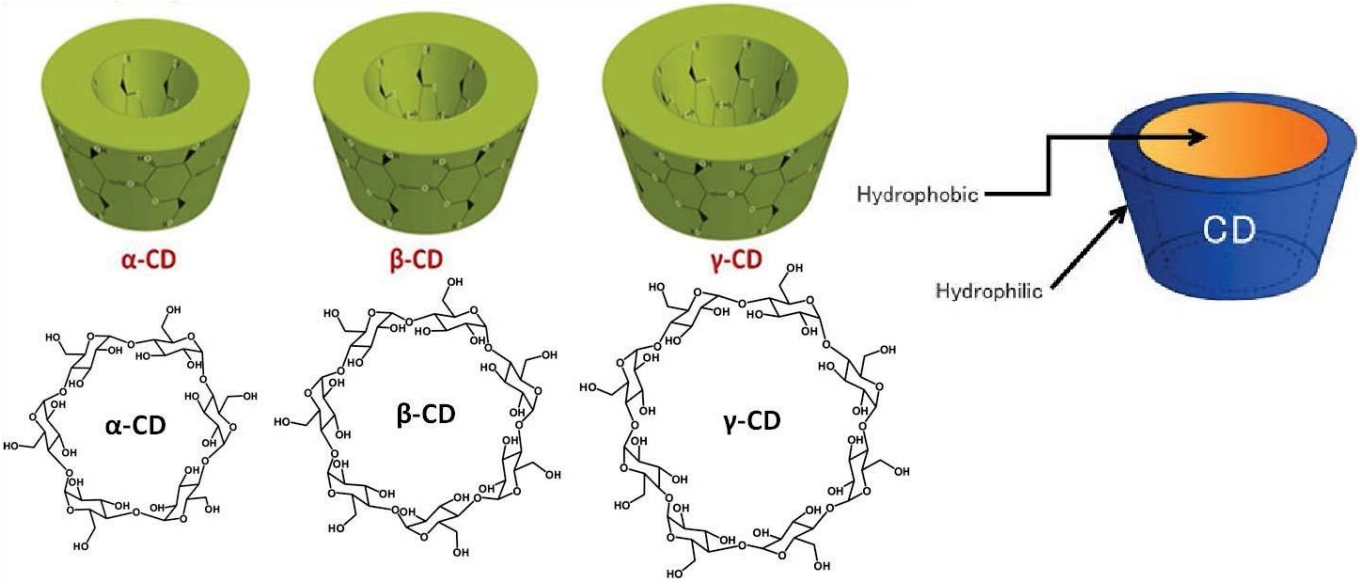
They consist of 6, 7, and 8 units of glucose referred to as a, þ, and ç cyclodextrins, respectively.

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

Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

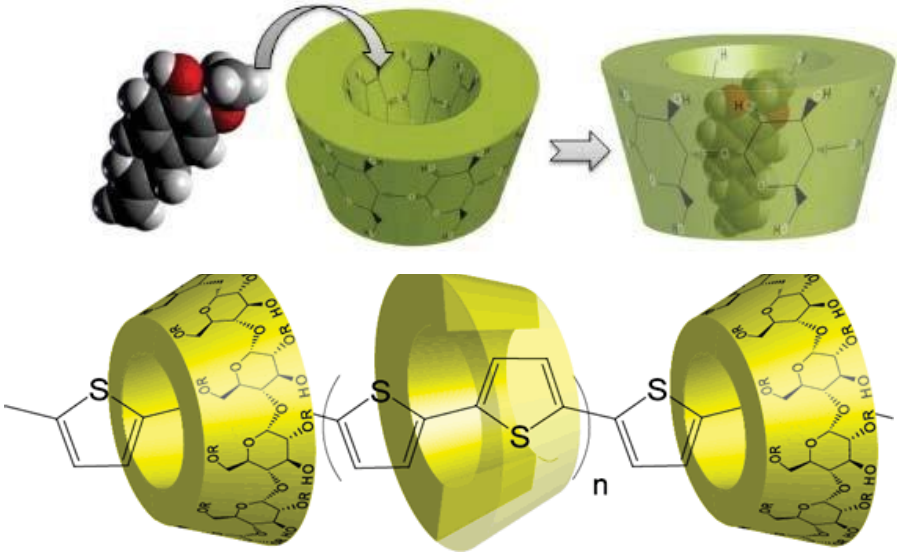
Cyclodextrons have truncated cone structure with a hydrophobic interior cavity because of the CH_2 groups, and a hydrophilic exterior due to the presence of hydroxyl group.



Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

Molecules of appropriate size and stereochemistry get entrapped in the cyclodextrin cavity by hydrophobic interaction by squeezing out water from the cavity.



Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

Cyclodextrins can enhance the solubility and bioavailability of hydrophobic compounds due to the large number of hydroxyl groups on the CDs.

Cavity size is the major determinant as to which cyclodextrin is used in complexation.

a-Cyclodextrins have small cavities that are not capable of accepting many molecules. ç-Cyclodextrins have much larger cavities than many molecules to be incorporated.

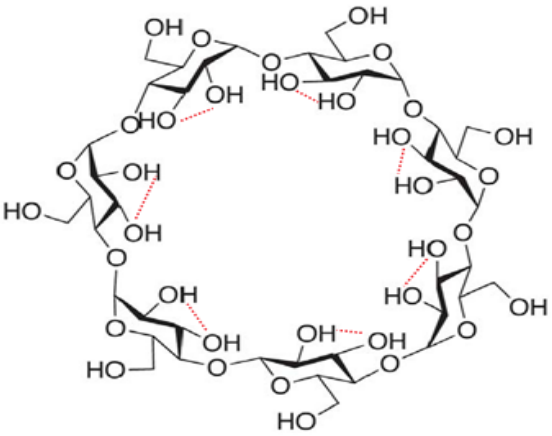
The cavity diameter of þ-cyclodextrins has been found to be the most appropriate size for most drugs. For this reason, þ-cyclodextrin is most commonly used as a complexing agent

Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

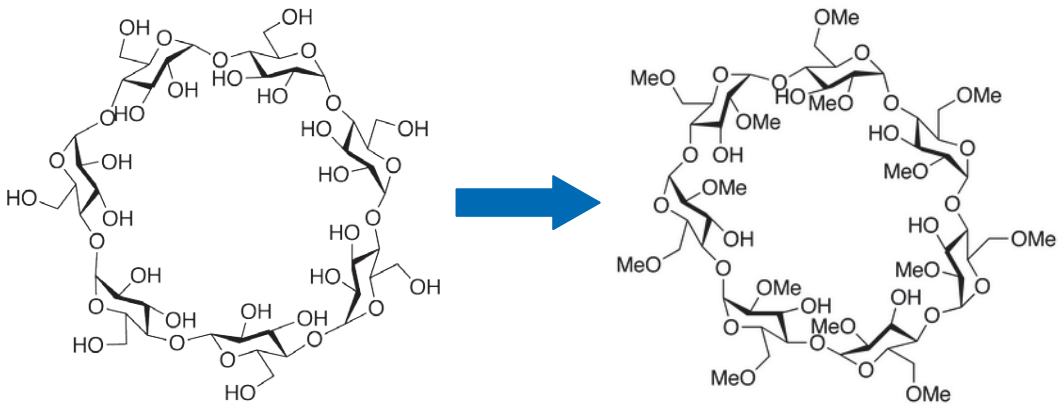
Although þ-CD contains a high number of hydroxyl groups, þ-CD solubility is the lowest compared to the a-CD or ç-CD.

This is due to the formation of an internal hydrogen bond network between the secondary hydroxyl groups.



Monomolecular Inclusion Compounds: Cyclodextrins

Partial alkylation of some of the OH groups in CD reduces the intermolecular hydrogen bonding, leaving some OH groups free to interact with water, thus increasing the aqueous solubility of CD.



Inclusion Complexes

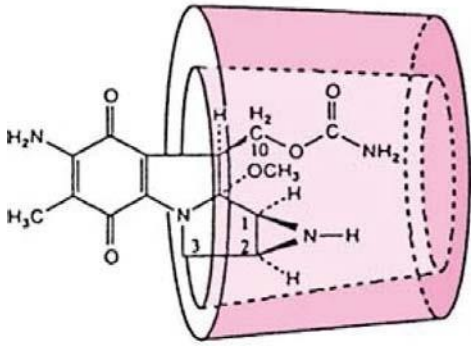
Monomolecular Inclusion Compounds: Cyclodextrins

In addition to hydrophilic derivatives, hydrophobic forms of þ-CD have been used as sustained release drug carriers.

Inclusion Complexes

Monomolecular Inclusion Compounds: Cyclodextrins

In addition to improving the solubility of compounds, complexation with cyclodextrin has been used to improve the stability of many drugs by inclusion of the compound and protecting certain functional groups from degradation.



Complexation with cyclodextrins has also been used to mask the bitter taste of certain drugs such as femoxetine.

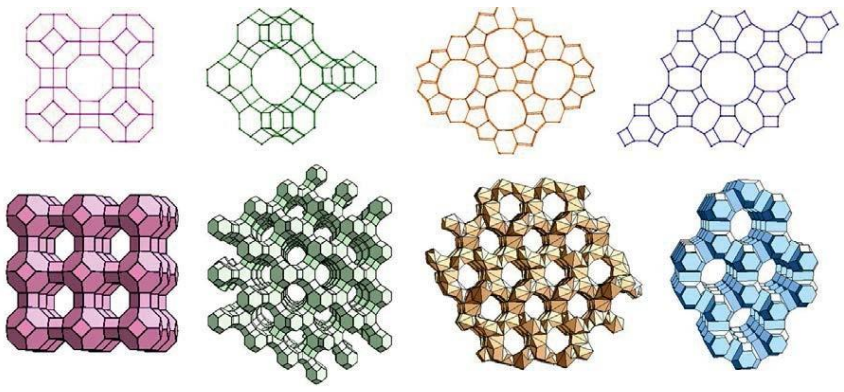
Inclusion Complexes

Macromolecular Inclusion Compounds

Macromolecular inclusion compounds, (*molecular sieves*) include substances such as zeolites, dextrins, and silica gel.

The atoms are arranged in three dimensions to produce cages and channels in which the guest molecules are entrapped.

Synthetic zeolites can be made to a definite pore size to separate molecules of different dimensions.



Methods of Analysis

Method of Continuous Variation PH
Titration
Distribution Method Solubility
Method Spectroscopy

Methods of Analysis

A determination of the **(1) *stoichiometric ratio*** of ligand to metal (or donor to acceptor) and the **(2) *stability constant*** for complex formation are important in the study and application of complexes.

Several methods for estimation of these parameters have been developed:

1. **Method of continuous variation**
2. **pH Titration method**
3. **Distribution Method**
4. **Solubility Method**
5. **Spectroscopy**

The stoichiometry of a metal–ligand complexation reaction can be determined by three methods:

(A) Job's method (B) Mole ratio method (C) Slope ratio method

Job's Method

In **Job's method**, a series of solution are prepared with variable ratios of metal and ligand but with fixed total concentrations (the total ligand + metal concentration are the same for all solutions).

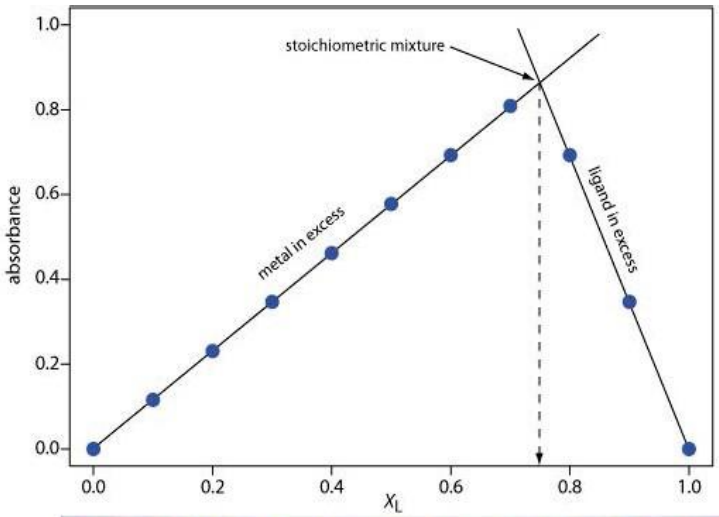
An additive property that is proportional to the concentration of the formed complex (e.g. absorbance) is measured and plotted against the mole fraction from 0 to 1 for one of the components of a mixture (e.g. Ligand).

Method of Continuous Variation

Job's Method

For a constant total concentration of *A* and *B*, the complex is at its greatest concentration at a point where the species *A* and *B* are combined in the ratio in which they occur in the complex.

The line therefore shows a break or a change in slope at the mole fraction corresponding to the complex.



Job's Method

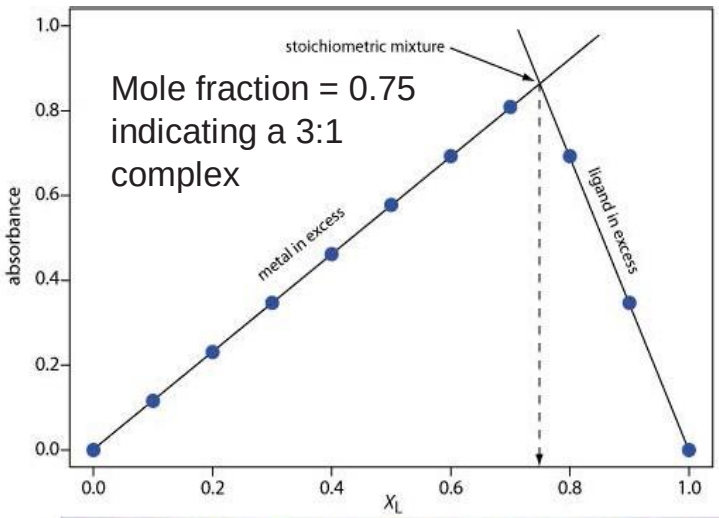
E.g. the change in slope occurs at a mole fraction of 0.75:

$$\frac{X_L}{X_M} = \frac{0.75}{1 - 0.75} = 3$$

This indicate a complex formation of the 3:1 type (ligand : metal).

The calibration curve flattens out when there is no longer enough ligand to react with all of the metal ions.

Job's method is restricted to the formation of a single complex



Method of Continuous Variation

Mole Ratio Method

In the **mole ratio method**, a series of solutions are prepared with a fixed amount of the metal and a variable amount of the ligand (or vice versa).

An additive property that is proportional to the concentration of the formed complex (e.g. absorbance) is measured and plotted against the mole ratio of the component with the variable amounts (e.g. Ligand).

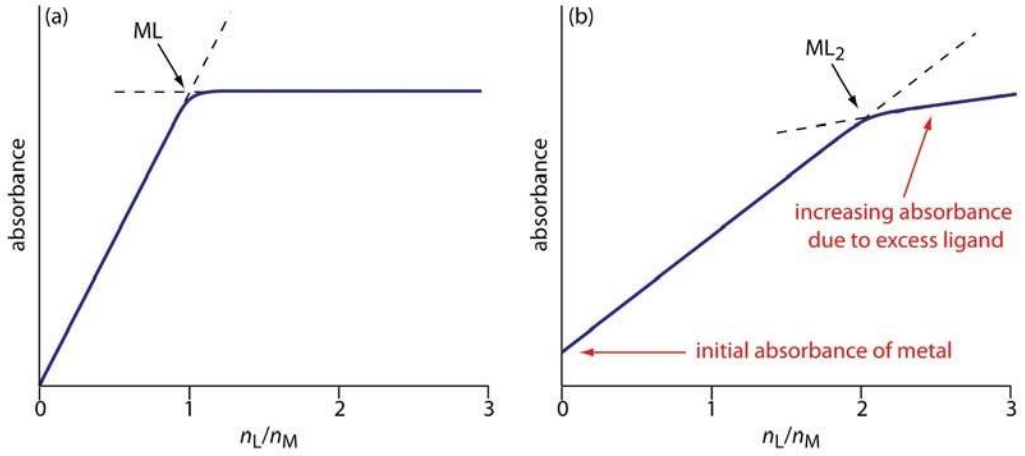
The formed complex is at its greatest concentration at a point where the species *A* and *M* are combined in the ratio in which they occur in the complex (indicated by a change in the slope at the mole ratio that forms the complex).

Method of Continuous Variation

Mole Ratio Method

The change in slope (a) occurs at a mole ratio of 1 indicating a complex of the 1:1 type, while the change in slope (b) occurs at a ratio of 2 indicating a complex of the 2:1 type.

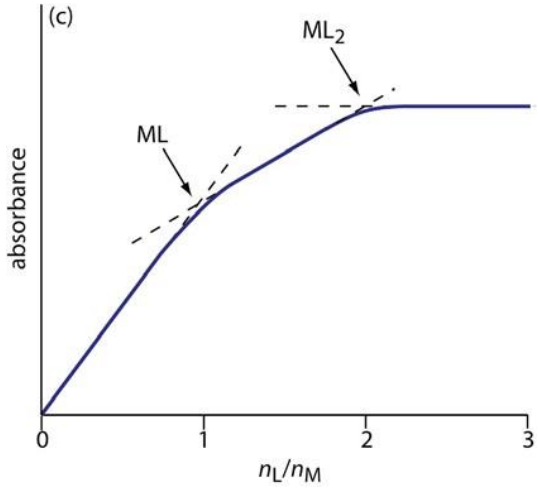
The calibration curve flattens out when there is no longer enough ligand to react with all of the metal ions.



Method of Continuous Variation

Mole Ratio Method

Unlike Job's method, the mole-ratio method can be used to investigate the formation of higher complexes in solution.



Slope Ratio Method

In the **slope-ratio method** two sets of solutions are prepared:

The first set of solutions contains a large excess of metal and a variable concentrations of ligand (all the ligand reacts in forming the metal–ligand complex).

The absorbance of the formed complex is plotted against the ligand concentration and the slope of the line is determined.

A second set of solutions is prepared with a large excess of ligand and a variable concentration of metal (all the metal reacts in forming the metal–ligand complex). .

The absorbance of the formed complex is plotted against the metal concentration and the slope of the line is determined.

Method of Continuous Variation

Slope Ratio Method

The stoichiometric ratio of metal to ligand is inversely proportional to the ratio of the slopes:

$$Stoichiometric\ ratio\ (\text{L:M}) = \frac{\text{Slope}_\text{M}}{\text{Slope}_\text{L}}$$

E.g. The slope of the first line (variable metal) is 1.56×10^{-3} and the slope of the other line (variable ligand) is 5.3×10^{-4}. What is the stoichiometric ratio of this complex?

$$Stoichiometric\ ratio\ (\text{L:M}) = \frac{\text{Slope}_\text{M}}{\text{Slope}_\text{L}} = \frac{1.56 \times 10^{-3}}{5.3 \times 10^{-4}} = 3$$

$$Stoichiometric\ ratio\ (\text{L:M}) = 3{:}1\ (\text{L:M})$$

The slope-ratio method also is limited to systems in which only a single complex is formed.

pH Titration Method

pH titration method can be used whenever the complexation is accompanied by a change in pH.

E.g. The chelation of the cupric ion by glycine:

$$Cu^{2+} + 2NH^{+}_{3}CH_2COO^{-} = Cu(NH_2CH_2COO)_2 + 2H^{+}$$

Because 2 protons are formed in the reaction, the addition of glycine to Cu^{2+} solution should result in a decrease in pH.

Titration curves can be obtained by adding a strong base to a solution of glycine alone and to another solution containing (glycine + copper salt) and plotting the pH against the volume of base added.

pH Titration Method

The curve for the metal-glycine mixture is well below that for the glycine alone.

The difference in pH for a given quantity of base added indicates the occurrence of a complex.

Distribution Method

The method of distributing a solute between two immiscible solvents can be used to determine the stability constant for certain complexes.

The complexation of by potassium iodide is an example to illustrate this Method.

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

The distribution method iodine has been used to study caffeine and polymer complexes with a number of acidic drugs such as benzoic acid, salicylic acid, and acetylsalicylic acid.

Note: This method is described in details in "lab. 2 Complexation".

Solubility Method

Solubility method is the most widely used method is the study the inclusion complexation.

According to the solubility method, excess quantities of the drug are placed in well-stoppered containers, with a solution of the complexing agent in various concentrations.

The bottles are agitated in a constant temp. bath until equilibrium is reached. Then, the supernatant liquid are removed and analyzed to obtain the total drug concentration.

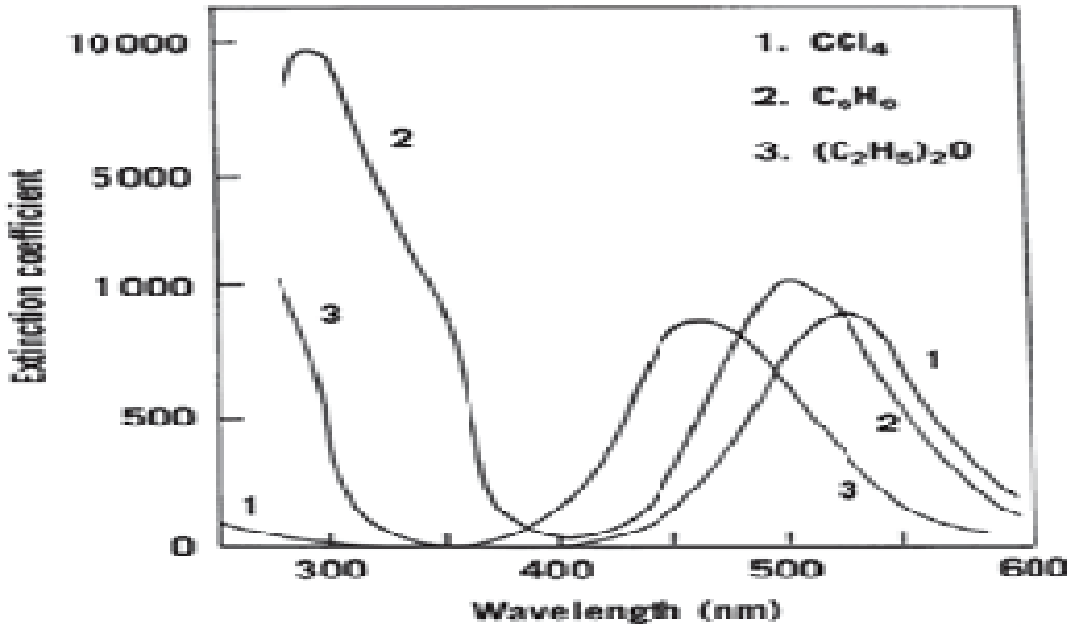
The concentration of the drug is plotted against the concentration of caffeine to obtain a curve that can be used to calculate the stability constant.

This method is used for charge transfer complexes.

When Iodine is analyzed with non-complexing solvent (e.g. CCl_4) a curve is obtain with a single peak at about 520 nm.

A solution of iodine in benzene exhibits a maximum shift to 475 nm, and a new peak with higher intensity at 300 nm.

A solution of iodine in diethyl ether shows a still greater shift to lower wavelength and the appearance of a new maximum.



SPECTROSCOPY

In benzene and ether, iodine is electron acceptor and the organic solvent is donor, while in CCl_4, no complex is formed.

The shift towards the UV region becomes greater as the electron donor solvent becomes a stronger electron-releasing agent.

References

Jain, G., Khar, R. K. & Ahmad, F. J. 2013. *Theory and Practice of Physical Pharmacy*, Elsevier Health Sciences APAC.

Sinko, P. J. M. a. N. 2006. *Martin's physical pharmacy and pharmaceutical sciences: physical chemical and biopharmaceutical principles in the pharmaceutical sciences,* Philadelphia, Lippincott Williams & Wilkins.