**Importance of Complexation & Drug Action:**

* · Once complexation occurs, the physical and chemical properties of the complexing species are altered.
* These properties include solubility, stability, partitioning, energy absorption and emission, and conductance of the drug .
* Drug complexation can lead to beneficial propertiessuch as enhanced aqueous solubility (e.g. theophylline complexation with ethylenediamine to from 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.
* Aqueous solubility of tetracycline decreases substantially when it complexes with calcium ions and coadministration of some drugs with antacids decreases absorption from the gastrointestinal tract.
* Drug complexation with hydrophilic compounds also can enhance excretion.
* · Complexes can alter the pharmacologic activity of the agent by inhibiting interactions with receptors.
* Complexation of a ligand with a substrate molecule can occur as a result of coordinate covalent bonding or one or more of the following noncovalent interactions:

Van der Waals forces

Dipolar forces

Electrostatic forces

Hydrogen bonding

Charge transfer

Hydrophobic interactions.

Protein binding: Binding of drugs into proteins may

* Facilitate the distribution of drugs into the body.
* Inactivating the drug
* Retarding the excretion of drug
* Interaction of a drug with proteins
* Displacement of body hormones or coadministered agent.

Formation of drug-protein complex that is biologically active.

Important proteins: albumin and alpha1-acid glycoprotein

Types of drug- protein binding:

* Reversible Covalent interaction
* Irreversible Covalent interaction

Irreversible: Covalent interaction:

Accounts for certain toxicities of drugs and carcinogens

E.g. high dose of acetaminophen causes hepatotoxicity

Protein Binding Affects

Distribution

Tissue penetration

Clearance

Interaction

**Effect of Protein Binding:**

* The pharmacokinetic/pharmacodynamic (PK/PD) profiles of a drug are largely affected by the reversible binding to plasma proteins
* The binding of small molecules to plasma proteins is a very important parameter in drug metabolism and pharmacokinetic studies.
* Generally, only free drugs are available for diffusion and transport across cell membranes to its target sites.
* Protein binding inactivates the drug, because sufficient concentration of drug cannot be built up at the receptor site for action.
* High degree of protein binding in the blood circulation prevents urinary excretion
* Drug/protein complexes may act as a “storage depot” in the blood circulation due to its prolonged circulation time
* Determining the level of protein binding is critical and directly correlates with the in vivo efficacy of a drug