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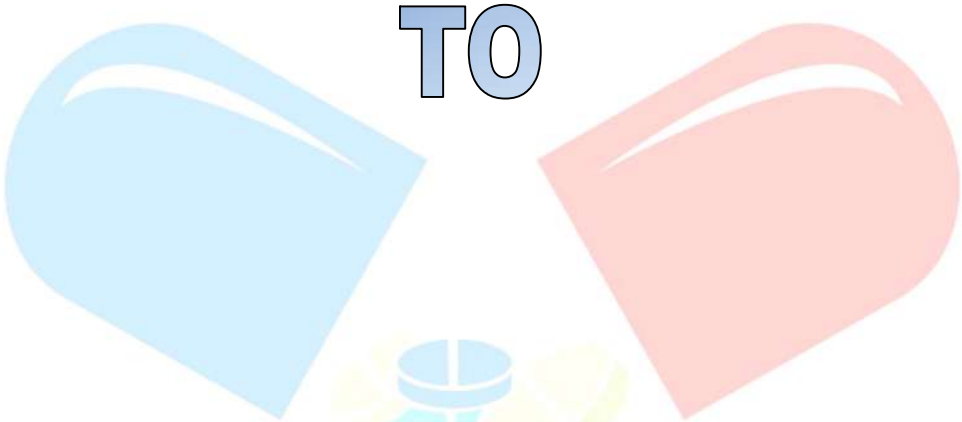

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PHYSICAL PHARMACEUTICS - I

UNIT 4

TOPIC :

- **Complexation and protein binding :** Introduction, Classification of Complexation, Applications, methods of analysis, protein binding, Complexation and drug action, crystalline structures of complexes and thermodynamic treatment of stability constants.

Complexation and Protein Binding

- Complexation is the association of two or more molecules or ions to form a new compound, known as a complex.
- These interactions often involve donor-acceptor mechanisms, where one species donates an electron pair (ligand), and the other accepts (metal or other acceptor).
- Forces involved: Van der Waals forces, dipole interactions, induced dipole interactions.
- Widely used in pharmaceuticals to:
  - Improve solubility and bioavailability.
  - Mask unpleasant taste or odor.
  - Alter drug pharmacokinetics.

Steps Involved in Complex Formation

1. Ligand orbital overlaps with the empty orbital of the metal ion.
2. Ligand donates an electron pair.
3. Metal ion accepts the electron pair.
4. **A** coordinate covalent bond is formed, resulting in a stable complex.

Classification of Complexation

Complexation can be broadly classified into three major types**:**

1. **Metal Ion Complexes**
2. **Organic Molecular Complexes**
3. **Inclusion / Occlusion Complexes**

1. Metal Ion Complexes

- These complexes involve a metal ion (usually a transition metal) as the central atom that binds to one or more ligands via coordinate covalent bonds.

Mechanism: Based on donor–acceptor interaction**.**

A. ***Inorganic Type***

- Ligands are inorganic molecules or ions.
- Form complexes with metal ions.
- Example: $Co(NH3)6Co(NH_3)_6Co(NH3)6^{3+}$ – a complex of cobalt with ammonia.

B. ***Chelates***

- Ligands offer two or more donor atoms to form ring-like structures with the metal ion.
- Ligands are bidentate or multidentate.
- Examples:
  - EDTA (Ethylenediaminetetraacetic acid)
  - Ethylenediamine

C. ***Olefin Type Complexes***

- Formed by the interaction of metal ions (e.g., Fe^{2+}, Hg^{2+}) with olefins (alkenes).
- Often used as catalysts in polymerization and other organic reactions.

D. ***Aromatic Complexes***

- Formed between metal ions and aromatic compounds (e.g., benzene).
- Types include:
  - Sigma (σ) Complexes
  - Pi (π) Complexes

- Sandwich Compounds (e.g., Ferrocene)

2. Organic Molecular Complexes

- These complexes are formed between two organic molecules through non-covalent interactions, such as:
  - Hydrogen bonding
  - Van der Waals forces
- These are also known as addition complexes or charge-transfer complexes.

*A. **Charge Transfer Complexes***

- Example: Benzene and Trinitrobenzene form a charge-transfer complex.

*B. **Quinhydrone Complex***

- Formed by hydroquinone (electron donor) and benzoquinone (electron acceptor) in alcohol solution.
- A classic example of an organic redox pair forming a complex.

*C. **Picric Acid Complex***

- Formed by strong acidic picric acid and weak bases.
- The interaction leads to a colored complex.

*D. **Caffeine Complexes***

- Caffeine interacts with acidic drugs (e.g., benzocaine, procaine, tetracaine) to form stable complexes.

*E. **Polymer Complexes***

- Formed between drug molecules and polymeric substances such as:
  - Polyethylene glycol

- Carbomers
- Polyvinylpyrrolidone

- Use: Enhance stability and promote sustained release of drugs.

3. Inclusion / Occlusion Complexes

➢ Also known as entrapment complexes, where one molecule (guest) is physically trapped inside the cavity of another molecule (host).

A. ***Channel Lattice Type***

- The host forms channels upon crystallization.
- The guest molecule gets trapped in these channels.

B. ***Layer Type***

- Host and guest molecules are arranged in alternate layers forming a layered complex structure.

C. ***Clathrates***

- Host molecules form a cage-like crystalline lattice that traps guest molecules inside.

D. ***Monomolecular Complex***

- A single guest molecule is entrapped in the cavity of one host molecule.
- Common in cyclodextrin complexes.

E. ***Macromolecular Complex***

- Involves multiple guest molecules being entrapped in the large cavity of a host (e.g., polymeric hosts).

Applications of Complexation

Complexation is widely used in pharmaceutical sciences due to its ability to alter and enhance the physicochemical and biological properties of drugs.

1. Conversion of Physical State
   - Complexation can change a substance from solid to liquid, liquid to gas, etc.
   - Helps in modifying drug formulation and improving processing.

2. Reduction of Volatility
   - Complex formation can reduce the volatility of certain compounds.
   - Useful in stabilizing volatile drugs and minimizing evaporation losses.

3. Increase in Physical Stability
   - Complexes, especially with polymers or metals, enhance the stability of solid drugs during storage and handling.

4. Increase in Chemical Stability
   - Complexation can protect drugs from oxidation, hydrolysis, or photodegradation, thereby improving shelf life.

5. Enhancement of Solubility
   - Poorly soluble drugs form water-soluble complexes (e.g., with cyclodextrins), thereby increasing solubility in aqueous systems.

6. Improvement in Dissolution Rate
   - Complexes can enhance the rate at which a drug dissolves in biological fluids, improving its therapeutic effectiveness.

7. Increase in Bioavailability
   - By improving solubility and dissolution, complexation enhances the amount of drug absorbed into systemic circulation.

Methods of Analysis of Complexation

1. Method of Continuous Variation (Job's Method):

Principle:

This method is based on the measurement of a physical property (such as absorbance, pH, conductivity) of a series of mixtures containing varying molar ratios of two components while keeping the total molar concentration constant.

Procedure:

- Prepare several solutions with different molar ratios of the two components (e.g., metal ion and ligand) but with a constant total molar concentration.
- Measure a property (absorbance, etc.) for each solution.
- Plot the measured property against the mole fraction of one component.
- The maximum or minimum in the plot indicates the stoichiometric ratio of complex formation.

Application:

- To determine the stoichiometry of a complex.
- Commonly used in spectrophotometric analysis.

2. pH Titration Method:

Principle:

Complexation can influence the pH of a solution. By titrating a ligand with a metal ion (or vice versa), changes in pH reflect the formation of the complex.

Procedure:

- Titrate a ligand solution with a standard metal ion solution.
- Monitor the pH using a pH meter.
- A sudden change in pH indicates **the** formation of a complex**.**

Application:

- Used for complexes involving acid-base reactions**.**
- Useful for chelating agents**.**

3. Distribution Method:

Principle:

This method is based on the change in partitioning of a solute between two immiscible solvents due to complex formation.

Procedure:

- A ligand is allowed to partition between two phases (like water and chloroform).
- In presence of a metal ion, complex formation alters its distribution.
- Measure the concentration in both phases**.**
- Change in distribution ratio confirms complexation.

Application:

- Used in the determination of stability constants**.**

- Helpful in studying lipophilic drug-metal complexes.

4. Solubility Method:

Principle:

Complexation affects the solubility of a compound. The formation of a soluble complex may increase the solubility of a poorly soluble drug.

Procedure:

- Measure the solubility of a drug in the absence and presence of a complexing agent.
- An increase or decrease in solubility indicates complex formation.

Application:

- Commonly used to improve drug solubility in formulations.
- Example: Cyclodextrin inclusion complexes.

5. Spectrophotometric Method:

Principle:

Complex formation can cause a change in the absorption spectrum (UV or visible) of one or both components.

Procedure:

- Measure the absorbance of solutions with different molar ratios of ligand and metal ion.
- Analyze absorbance data to confirm the formation and stability of complexes.

Application:

- Widely used for quantitative analysis of complexes.
- Determines stoichiometry and stability constants.

Protein Binding

- Protein binding is the reversible or irreversible interaction between a drug and plasma proteins. Only the unbound (free) drug is pharmacologically active. The protein-bound drug is inactive and not available for metabolism or excretion.

$$\text{Drug} + \text{Protein} \leftrightarrow \text{Drug-Protein Complex}$$

Types of Drug-Protein Binding:

1. **Reversible Binding**
   - Non-covalent interactions (hydrogen bonds, van der Waals, ionic)
   - Most common and pharmacologically significant
2. **Irreversible Binding**
   - Rare; involves covalent bonding
   - May lead to toxicity or long-lasting effects

Plasma Proteins Involved In Drug Binding

1. Albumin

- Most abundant plasma protein (~60% of plasma proteins).
- Synthesized in the liver.
- Major binding protein for acidic and neutral drugs.
- Has multiple binding sites, including:
  - Site I: Binds Warfarin
  - Site II: Binds Diazepam
  - Site III: Binds Digoxin
  - Site IV: Binds Tamoxifen

2. Globulins

- A group of proteins that include α, β, and γ-globulins.
- Involved in immune function and transport.
- Binds hormones, metal ions, and some basic drugs.

3. α-Acid Glycoprotein (AAG)

- Binds mainly to basic drugs (e.g., propranolol, lidocaine).
- Levels increase in inflammatory conditions, affecting drug binding.

4. Lipoproteins

- Responsible for binding lipophilic (fat-soluble) drugs.
- Important when albumin or AAG is saturated or deficient.

Significance of Protein Binding

Effect	Explanation
Reduces free drug concentration	Only unbound drug can cross membranes, exert effects, or be metabolized.
Decreases distribution	Bound drug cannot move freely across biological membranes.
Reduces metabolism & excretion	Bound drug is not filtered by the kidneys or metabolized by the liver.
Increases half-life	The drug remains in the system longer due to slower clearance.
Helps in sustained release	Acts as a reservoir for prolonged drug action.
Useful in diagnosis	Protein-binding profiles help in understanding drug behavior and dosage design.

Factors Affecting Protein Binding

Factor	Explanation
Molecular Size	Larger drugs may bind differently compared to smaller ones.
Molecular Shape	Better fit between ligand and binding site increases affinity.
Competition	Other drugs or endogenous substances can displace the drug.
pH	Alters the ionization of both drug and protein, affecting binding.
Drug Concentration	Higher concentrations may saturate protein binding sites.
Temperature	Affects protein structure and drug-binding affinity.

Complexation and Drug Action

- Drug molecules have the ability to form complexes with other small molecules or with macromolecules such as proteins. Upon complexation, the physical and chemical properties of the involved species are significantly altered, which can influence the drug's pharmacokinetics and pharmacodynamics.
- For some drugs, complexation with hydrophilic compounds improves water solubility and thereby enhances excretion, especially through the kidneys. This property is often exploited in drug design to reduce drug toxicity or to shorten the duration of action when necessary.
- In many cases, drugs that bind to plasma proteins become inactive temporarily, as the bound form is not available to interact with receptors. This binding reduces the free drug concentration in plasma, which is essential for therapeutic action. An example of such a case is naphthoquinones, where strong protein binding limits their pharmacological effect.
- However, not all drugs lose activity upon protein binding. Some retain their pharmacological activity despite being bound to plasma proteins. This is possible when the binding is reversible and a sufficient amount of free (unbound) drug remains available to reach the target site. Penicillins and sulfadiazine are examples of such drugs that, although they bind to proteins, still exhibit therapeutic effects.

Crystalline Structures of Complexes

→ When two or more chemical species form a complex, the resulting compound may exist in a crystalline or amorphous form. Crystalline complexes are solids that possess a regular, repeating arrangement of atoms, ions, or molecules. Their structure can be studied using X-ray diffraction techniques, which provide insights into the stoichiometry, geometry, and bonding in the complex.

Characteristics of Crystalline Complexes

1. **Highly Ordered Structure**
   - Molecules are arranged in a fixed, periodic lattice.
   - Leads to sharp melting points and well-defined crystal shapes.
2. **Definite Stoichiometry**
   - The ratio of metal to ligand or drug to complexing agent is fixed (e.g., 1:1, 1:2).
3. **Specific Geometry**
   - The geometry of the complex depends on the coordination number and bonding (e.g., tetrahedral, octahedral).
4. **Solid-State Stability**
   - Crystalline complexes are often more stable than their amorphous counterparts.

Methods to Determine Crystalline Structure

1. X-ray Crystallography
   - Gold standard for determining 3D arrangement of atoms.
   - Reveals bond lengths, angles, coordination geometry.
2. Infrared (IR) Spectroscopy
   - Detects changes in vibrational frequencies due to complex formation.
3. Differential Scanning Calorimetry (DSC)
   - Determines melting point and thermal behavior of complexes.
4. Powder X-ray Diffraction (PXRD)
   - Used when single crystals are not available.

- Gives fingerprint patterns to distinguish crystalline vs. amorphous forms.

Examples of Crystalline Complexes in Pharmaceuticals:

Complex	Structure Type	Use/Importance
Cisplatin ($PtCl_2(NH_3)_2$)	Square planar	Anticancer drug
Iron-Dextran Complex	Polymeric crystalline	Parenteral iron supplement
Cyclodextrin-Drug Complex	Cage-like inclusion structure	Solubility enhancement
Calcium-EDTA Complex	Octahedral	Heavy metal detoxification

Importance in Pharmaceutics

1. **Solubility and Bioavailability**
   - Crystalline inclusion complexes (e.g., drug–cyclodextrin) improve drug solubility.
2. **Stability and Shelf Life**
   - Crystalline forms are generally more stable than amorphous ones.
3. **Controlled Release**
   - Crystalline complexes may exhibit slow dissolution, aiding in sustained-release formulations.
4. **Identification and Quality Control**
   - Crystalline structures provide unique XRD patterns, useful for drug identification and purity testing.

Limitations

- Crystallization may be difficult for large, flexible molecules.
- Crystalline complexes may have poor solubility, requiring formulation techniques to improve bioavailability.

Thermodynamic Treatment of Stability Constants

- When a complex is formed between a ligand and a metal ion (or drug molecule), it is often reversible and governed by equilibrium thermodynamics. The stability constant (also called the formation constant) expresses the equilibrium position for the formation of a complex.
- Understanding the thermodynamics behind this helps predict:
  - How stable a complex is
  - How temperature affects stability
  - Whether the formation is spontaneous or not

General Complexation Reaction

Let's consider a simple 1:1 complex formation:

$$M + L \rightleftharpoons ML$$

Where:

- M = Metal ion or drug
- L = Ligand or complexing agent
- ML = Formed complex

The **stability constant (K)** is given by:

$$K - \frac{[ML]}{[M][L]}$$

This is known as the **stepwise stability constant (K_1)**.

If the complex forms in multiple steps (e.g., ML, ML_2, etc.), we can define:

$$K_1 - \frac{[ML]}{[M][L]}$$

$$K_2 - \frac{[ML_2]}{[ML][L]}$$

The **overall stability constant (β_2)** is:

$$\beta_2 - [ML_2]/[M][L]^2 - K_1 \times K_2$$