Lecture Notes: Session 4 - Physicochemical Properties: Protein Binding and Chelation

SNS College of Pharmacy and Health Sciences

August 2025

Introduction

This lecture explores the physicochemical properties of protein binding and chelation, which significantly influence drug pharmacokinetics and pharmacodynamics. Protein binding, particularly to plasma proteins like albumin, affects drug distribution and duration of action. Chelation, the formation of metal ion complexes, enhances the activity of certain drugs, such as tetracyclines. Using warfarin and tetracycline as examples, this session examines these properties and their implications in medicinal chemistry.

1 Protein Binding

Protein binding refers to the reversible interaction of drugs with plasma or tissue proteins, primarily albumin, which impacts drug distribution, bioavailability, and duration of action. The extent of binding influences the free (unbound) drug concentration, which is pharmacologically active.

1.1 Albumin Interactions

Overview:

- *Primary Protein:* Human serum albumin (HSA) is the most abundant plasma protein (35–50 g/L), with multiple binding sites for drugs.
- *Binding Sites:*
  - Site I (warfarin site): Binds acidic drugs (e.g., warfarin, NSAIDs).
  - Site II (diazepam site): Binds benzodiazepines and some NSAIDs.
- *Mechanism:* Binding occurs via hydrophobic interactions, hydrogen bonding, and van der Waals forces. Acidic drugs with high lipophilicity bind strongly to albumin.

Pharmacological Implications:

- *Distribution:* Bound drugs are restricted to the plasma compartment, reducing tissue distribution.

- *Duration:* High protein binding prolongs half-life by acting as a reservoir, releasing free drug slowly.
- *Efficacy:* Only the free fraction exerts pharmacological effects, as bound drugs are inactive.

Example - Warfarin:

- *Chemical Structure:* c1cc2c
- *Properties:* Anticoagulant, highly bound to albumin (99
- *Pharmacokinetics:* Half-life of 36–42 hours due to extensive binding, low free fraction (1
- *Clinical Relevance:* High protein binding minimizes rapid clearance but increases risk of drug interactions.

1.2 Displacement

Overview:

- *Definition:* Displacement occurs when one drug displaces another from albumin binding sites, increasing the free fraction of the displaced drug.
- *Mechanism:* Competitive binding at Site I or II, often involving drugs with similar physicochemical properties (e.g., acidic, lipophilic).

Pharmacological Implications:

- *Increased Free Drug:* Displacement can enhance efficacy but also toxicity (e.g., increased bleeding risk with warfarin).
- *Clinical Concerns:* Significant for drugs with narrow therapeutic indices.

Example - Warfarin Displacement:

- *Scenario:* Co-administration with ibuprofen (also binds Site I) displaces warfarin, increasing free warfarin concentration.
- *Impact:* Elevated free warfarin enhances anticoagulant effects, risking hemorrhage.
- *Management:* Monitor INR (International Normalized Ratio) and adjust doses.

Structural Factors:

- Lipophilicity and acidic groups (e.g., carboxylic acid in warfarin) enhance albumin binding.
- Structural modifications (e.g., reducing lipophilicity) can decrease binding to minimize interactions.

2 Chelation

Chelation involves the formation of coordinate bonds between a drug and a metal ion, creating stable complexes that enhance pharmacological activity or stability. Chelation is critical for certain drugs, particularly antibiotics like tetracyclines.

2.1 Metal Ion Complexes in Drug Activity

Overview:

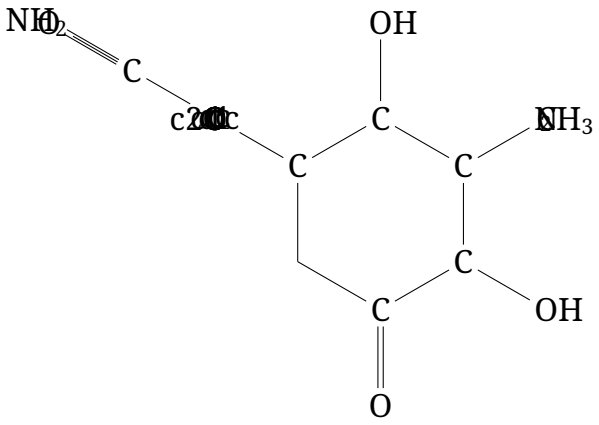
- *Definition:* Chelation occurs when a drug (ligand) forms multiple coordinate bonds with a metal ion (e.g., Ca^{2+}, Mg^{2+}, Fe^{2+}), creating a stable ring structure.
- *Mechanism:* Chelating groups (e.g., hydroxyl, carbonyl) donate electron pairs to the metal, forming 5- or 6-membered rings.

Pharmacological Implications:

- *Enhanced Activity:* Chelation can improve target binding (e.g., bacterial enzymes in tetracyclines).
- *Stability:* Complexes protect drugs from degradation.
- *Interactions:* Chelation with dietary metals (e.g., calcium in milk) can reduce bioavailability.

Example - Tetracycline:

- *Chemical Structure:*



- *Chelation Sites:* Enol and keto groups at positions 10–12 form complexes with divalent cations (e.g., Ca^{2+}, Mg^{2+}).
- *Mechanism:* Tetracycline binds to bacterial 30S ribosomal subunit, inhibiting protein synthesis. Chelation with Mg^{2+} enhances ribosomal binding.
- *Pharmacokinetics:* Half-life of 6–12 hours, reduced absorption if taken with dairy due to calcium chelation.
- *Clinical Use:* Broad-spectrum antibiotic for acne, respiratory infections.

Structural Factors:

- *Chelating Groups:* Hydroxyl, carbonyl, or amine groups are critical for metal coordination.
- *Ring Size:* 5- or 6-membered chelate rings are most stable.
- *Example Issue:* Tetracycline's chelation with calcium reduces oral bioavailability, requiring administration away from meals.

3 Clinical Implications

- **Protein Binding:**
  - High binding (e.g., warfarin) prolongs action but risks interactions. Low binding may lead to rapid clearance.
  - Displacement (e.g., warfarin with NSAIDs) requires careful monitoring in polypharmacy.
- **Chelation:**
  - Enhances activity (e.g., tetracycline's antibacterial effect) but can limit bioavailability if chelation occurs in the gut.
  - Patient counseling needed (e.g., avoid dairy with tetracyclines).
- **Design Considerations:** Modifying lipophilicity or chelating groups can optimize pharmacokinetics and minimize adverse interactions.

4 Key Learning Points

- Protein binding to albumin (e.g., warfarin) affects drug distribution and duration, with displacement causing potential toxicity.
- Chelation (e.g., tetracycline with Mg^{2+}) enhances drug activity but may reduce bioavailability if mismanaged.
- Structural features like lipophilicity (protein binding) and chelating groups (e.g., hydroxyl, carbonyl) drive these properties.
- Understanding protein binding and chelation informs drug design for improved efficacy and safety.