Lecture Notes: Session 2 - Physicochemical Properties: Ionization and Solubility

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Introduction

This lecture focuses on the physicochemical properties of ionization and solubility, critical for understanding drug absorption, distribution, and bioavailability. Ionization, governed by pKa and the Henderson-Hasselbalch equation, determines a drug's charge state in physiological environments. Solubility influences dissolution rate and drug delivery. Using aspirin as an example, this session explores these concepts and their impact on medicinal chemistry.

1 Ionization

Ionization refers to a drug's ability to gain or lose protons, affecting its charge and influencing absorption, distribution, and receptor interactions. The degree of ionization depends on the drug's pKa and the pH of the environment.

1.1 pKa

Definition: pKa is the negative logarithm of the acid dissociation constant (Ka), indicating the strength of an acid or base. A lower pKa signifies a stronger acid, while a higher pKa indicates a stronger base.
Pharmacological Relevance:

- Ionized forms (charged) are more water-soluble but less lipid-soluble, affecting membrane permeability.
- Non-ionized forms (neutral) are more lipid-soluble, facilitating absorption across cell membranes.

Example - Aspirin (Acetylsalicylic Acid):

- Chemical Structure: c1cc2c(cc1)C(=O)OC(=O)C2
- pKa: 3.5 (carboxylic acid group).
- At gastric pH (1.5), aspirin is mostly non-ionized, enhancing absorption. At blood pH (7.4), it is predominantly ionized, increasing solubility but reducing membrane crossing.

1.2 Henderson-Hasselbalch Equation

Equation: For a weak acid, the Henderson-Hasselbalch equation relates pH, pKa, and the ratio of ionized to non-ionized forms:

$$\text{pH} = \text{pKa} + \log_{10}\left(\frac{[\text{A}^-]}{[\text{HA}]}\right)$$

where $[\text{A}^-]$ is the ionized form and [HA] is the non-ionized form.
Application:

- Predicts ionization state in different physiological compartments (e.g., stomach, blood, intestine).
- Helps design drugs with optimal absorption profiles.

Example Calculation - Aspirin at pH 7.4:

- pKa = 3.5, pH = 7.4.
- $$7.4 = 3.5 + \log_{10}\left(\frac{[\text{A}^-]}{[\text{HA}]}\right)$$
- $$\log_{10}\left(\frac{[\text{A}^-]}{[\text{HA}]}\right) = 7.4 - 3.5 = 3.9$$
- $$\frac{[\text{A}^-]}{[\text{HA}]} = 10^{3.9} \approx 7943$$
- Percentage ionized:

$$\frac{[\text{A}^-]}{[\text{A}^-] + [\text{HA}]} \times 100 \approx \frac{7943}{7943 + 1} \times 100 \approx 99.99\%$$

- Conclusion: At pH 7.4, aspirin is almost fully ionized, enhancing solubility in blood but limiting membrane permeability.

2 Solubility

Solubility is the ability of a drug to dissolve in a solvent (e.g., water, physiological fluids), directly impacting dissolution rate and bioavailability. Poor solubility can limit a drug's therapeutic efficacy.

2.1 Factors Influencing Dissolution Rate

The dissolution rate is governed by the Noyes-Whitney equation:

$$\frac{dC}{dt} = \frac{DA(C_s - C)}{h}$$

where dC/dt is the dissolution rate, D is the diffusion coefficient, A is the surface area, C_s is the saturation solubility, C is the concentration in the bulk solution, and h is the diffusion layer thickness.
Key Factors:

- **Chemical Structure:**
  - Polar groups (e.g., hydroxyl, amine) increase water solubility.
  - Non-polar groups (e.g., alkyl chains) decrease solubility.
- **Crystal Form:**
  - Amorphous forms dissolve faster than crystalline forms due to higher energy states.
  - Polymorphism affects solubility (e.g., different crystal packing).
- **Particle Size:**
  - Smaller particles increase surface area, enhancing dissolution rate.
- **pH and Ionization:**
  - Ionized forms are more soluble in aqueous environments.
  - pH adjustment (e.g., salt formation) can enhance solubility.
- **Solvent Properties:**
  - Cosolvents (e.g., ethanol) or surfactants improve solubility of hydrophobic drugs.
- **Temperature:**
  - Higher temperatures generally increase solubility for solids.

Example - Aspirin:

- Structure: Contains a carboxylic acid (polar) and an acetyl group (less polar).
- Solubility: Poorly soluble in water (3 mg/mL at 25°C) but increases in alkaline pH due to ionization.
- Strategies to Improve:
  - Form sodium salicylate (salt form) to enhance solubility.
  - Micronization to reduce particle size.
  - Use of cosolvents like polyethylene glycol.
- Clinical Relevance: Enhanced solubility ensures adequate dissolution in the intestine for systemic absorption.

3 Clinical Implications

- **Ionization:** Determines absorption site (e.g., non-ionized aspirin absorbs in the stomach, ionized form in the intestine). Affects formulation (e.g., enteric-coated tablets to protect stomach).
- **Solubility:** Critical for oral bioavailability. Poor solubility (e.g., BCS Class II drugs like aspirin) requires formulation strategies like salt formation or nanoparticle delivery.
- **Example - Aspirin:** Its pKa and solubility profile make it effective for rapid pain relief when formulated appropriately, but GI irritation is a concern due to ionization in the stomach.

4 Key Learning Points

- Ionization, governed by pKa and the Henderson-Hasselbalch equation, determines a drug's charge state, impacting absorption and distribution.
- Solubility, influenced by chemical structure, crystal form, particle size, pH, and solvent properties, is critical for dissolution and bioavailability.
- Aspirin exemplifies how ionization (pKa 3.5) and solubility (poor in water) guide formulation and clinical use.
- Understanding these properties enables the design of drugs with optimized pharmacokinetic profiles.