Lecture Notes: Session 3 - Physicochemical Properties: Partition Coefficient and Hydrogen Bonding

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Introduction

This lecture focuses on the physicochemical properties of partition coefficient and hydrogen bonding, which are critical for understanding drug absorption, distribution, and receptor interactions. The partition coefficient (Log P) quantifies lipophilicity, influencing a drug's ability to cross biological membranes. Hydrogen bonding governs drug-receptor interactions, affecting binding affinity and specificity. Using propranolol as an example, this session explores these properties and their impact on medicinal chemistry.

1 Partition Coefficient

The partition coefficient measures a drug's distribution between a lipophilic (non-polar) and hydrophilic (polar) phase, typically octanol and water, reflecting its lipophilicity.

1.1 Log P

Definition: Log P is the logarithm of the partition coefficient (P), defined as:

$$P = \frac{[\text{drug}]_{\text{octanol}}}{[\text{drug}]_{\text{water}}}$$

where $[\text{drug}]_{\text{octanol}}$ and $[\text{drug}]_{\text{water}}$ are the concentrations of the non-ionized drug in octanol and water, respectively. Log P = $\log_{10}(P)$.
Pharmacological Relevance:

- **Low Log P (<1):** Indicates high hydrophilicity, favoring solubility in aqueous environments but poor membrane penetration (e.g., poor CNS entry).
- **High Log P (>3):** Indicates high lipophilicity, enhancing membrane crossing (e.g., BBB penetration) but reducing aqueous solubility.
- **Optimal Log P (1–3):** Balances solubility and permeability for oral bioavailability.

Measurement:

- Experimentally determined via shake-flask method or HPLC.
- Computational tools (e.g., cLogP) predict Log P based on molecular structure.

Example - Propranolol:

- Chemical Structure: c1cc2c — C — cccCH$_2$ — NH — CH$_3$
- Log P: 3.0 (lipophilic, suitable for CNS penetration).
- Clinical Relevance: As a beta-blocker, propranolol's lipophilicity allows it to cross the blood-brain barrier, contributing to its use in treating anxiety and migraines, in addition to hypertension.

SAR Notes: The naphthalene ring and isopropylamine group in propranolol increase lipophilicity, enhancing membrane permeability but requiring formulation strategies to maintain solubility.

2 Hydrogen Bonding

Hydrogen bonding involves an electrostatic interaction between a hydrogen atom bonded to an electronegative atom (donor, e.g., O-H, N-H) and another electronegative atom with a lone pair (acceptor, e.g., O, N).

2.1 Donor/Acceptor Roles in Drug-Receptor Interactions

Definition: Hydrogen bonds stabilize drug-receptor complexes, enhancing binding affinity and specificity.
Key Features:

- **Donors:** Groups like hydroxyl (-OH), amine (-NH), or amide (-CONH-) donate a hydrogen atom.
- **Acceptors:** Groups like carbonyl (C=O), ether (-O-), or nitrogen lone pairs accept hydrogen bonds.
- Strength: Typically 2–10 kcal/mol, weaker than covalent bonds but critical for reversible binding.

Pharmacological Relevance:

- Enhances receptor specificity by forming precise interactions with complementary groups.
- Influences solubility and membrane permeability (more hydrogen bonds increase hydrophilicity).
- Excessive hydrogen bonding can reduce bioavailability by hindering membrane crossing.

Example - Propranolol:

- Structure: Contains a hydroxyl group (donor) and an ether oxygen (acceptor).
- Interaction: The hydroxyl group forms hydrogen bonds with serine or threonine residues in beta-adrenergic receptors, enhancing binding affinity.
- Clinical Relevance: These interactions contribute to propranolol's high potency as a non-selective beta-blocker.

SAR Notes:

- The hydroxyl group on the propanol side chain is critical for receptor binding.
- The ether oxygen can act as a hydrogen bond acceptor, stabilizing interactions with receptor sites.
- Modifying hydrogen bonding groups (e.g., replacing -OH with -CH_3) reduces receptor affinity but may enhance lipophilicity.

3 Clinical Implications

- **Partition Coefficient:** Log P guides drug design for specific targets. Propranolol's Log P (3.0) enables CNS penetration for neurological effects but requires careful formulation to ensure solubility. Drugs with high Log P (e.g., >5) may accumulate in fatty tissues, prolonging action but risking toxicity.
- **Hydrogen Bonding:** Critical for receptor binding but must be balanced. Propranolol's hydrogen bonding enhances beta-blocker activity, but excessive hydrogen bonds in a drug can reduce bioavailability by increasing hydrophilicity.
- **Formulation Strategies:** For drugs like propranolol, salt forms (e.g., propranolol hydrochloride) improve solubility, while lipophilicity ensures effective delivery to target tissues.

4 Key Learning Points

- Log P quantifies lipophilicity, with optimal values (1–3) balancing solubility and membrane permeability.
- Hydrogen bonding (donor/acceptor roles) enhances drug-receptor affinity and specificity, as seen in propranolol's interactions with beta-adrenergic receptors.
- Propranolol exemplifies how Log P (3.0) and hydrogen bonding groups (hydroxyl, ether) optimize CNS penetration and receptor binding.
- Understanding these properties enables the design of drugs with improved pharmacokinetic and pharmacodynamic profiles.