Distribution of Drugs

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Definition

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitial (extracellular) and/or intracellular compartments of tissues.

It determines which tissues the drug reaches, how long it stays there, and thus influences both therapeutic and toxic effects.

Major Compartments

Compartment	Description
Plasma (Intravascular)	Drug initially enters after absorption or injection
Interstitial Fluid	Bathes tissue cells; exchange site between blood and cells
Intracellular Fluid	Within cells where drug may act or be stored
Transcellular Fluids	CSF, synovial, ocular, pleural, peritoneal fluids, etc.

Processes Involved

- Physicochemical properties of the drug (lipid solubility, molecular weight, ionization)
- Transport mechanisms (passive or active)
- Plasma protein binding
- Tissue binding
- Body barriers (e.g., BBB, placenta)

🧠 Mechanisms of Distribution

Distribution Pathway

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Blood → Interstitial Fluid → Intracellular Fluid / Body Reservoirs

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Movement through:

→ Passive diffusion (major route)
→ Active transport (for selective uptake)

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Modified by:

→ Blood flow / vascularity
→ Body barriers (BBB, Placenta)
→ Redistribution between organs

Drug Reservoirs

Certain body components can accumulate drugs and act as reservoirs, releasing them slowly over time — influencing duration and intensity of action.

Reservoir Site	Mechanism / Example	Significance
Plasma Proteins	Drugs bind reversibly to albumin (acidic drugs) or α_1-acid glycoprotein (basic drugs)	Acts as temporary store, regulates free drug concentration
Liver	Binds drugs like chloroquine	May contribute to prolonged action
Adipose Tissue	Lipid-soluble drugs (thiopental, DDT)	Acts as storage depot
Bones	Binds tetracycline, heavy metals	May cause toxicity or prolonged action

Transcellular fluids	CSF, synovial fluid, aqueous humor	Important for local therapeutic effects
Placenta / Breast Milk	Passive diffusion of unionized drugs	May cause fetal or neonatal toxicity

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💧 Factors Affecting Drug Distribution

🧍 I. Factors Related to the Body

1. 🧬 Transport Mechanism

- Passive diffusion: For lipid-soluble drugs, along concentration gradient.
- Active transport: Selective, carrier-mediated, energy-dependent.

2. ♡ Vascularity / Blood Flow

- Organs with high perfusion (liver, kidney, heart, brain) receive drugs rapidly.
- Poorly perfused tissues (fat, muscle) take longer.

- Redistribution: Movement of drug from highly perfused → less perfused tissues (e.g., thiopental).

3. 📦 Body Barriers

a. Blood-Brain Barrier (BBB)

- Structure: Tight junctions between capillary endothelial cells + astrocytic foot processes.
- Permits: Lipid-soluble, non-ionized drugs (e.g., barbiturates).
- Blocks: Polar, ionized drugs.
- Transporters: Uptake (OATs, OCTs) & Efflux (P-glycoprotein).
- Disruption: In meningitis, inflammation, or trauma → increased permeability.

b. Placental Barrier

- Allows lipid-soluble, non-ionized drugs to cross via passive diffusion.

- Contains transporters (e.g., P-gp, BCRP) that can limit fetal exposure.

💊 II. Factors Related to the Drug

1. 💧 Lipid Solubility

- Higher lipid solubility → easier CNS penetration (e.g., thiopental).
- Determines extent of crossing lipid barriers.

2. ⚛ Molecular Size

- Small molecules diffuse easily; large ones require carriers or remain in plasma.

3. ⚡ Degree of Ionization

- Only unionized forms cross membranes.
- Leads to ion trapping in compartments of differing pH.

4. 🧫 Cellular and Tissue Binding

- Drugs may bind to intracellular components (e.g., proteins, organelles).

- Creates reservoirs affecting:
    - ⏳ Duration of action
    - 💉 Therapeutic & toxic effects

🧬 Plasma Protein Binding (PPB)

⚙️ Concept

Drugs reversibly bind to plasma proteins such as:

- Albumin: binds acidic drugs (e.g., warfarin, phenytoin)
- α_1-acid glycoprotein: binds basic drugs (e.g., propranolol)
- Globulins / Lipoproteins: bind steroidal and lipid-soluble drugs

🧮 Free vs. Bound Drug

Property	Free Drug	Bound Drug (PPB)

Pharmacological Activity	Active	Inactive
Diffusion Across Membranes	Possible	Not possible
Metabolism / Excretion	Possible	Retarded
Acts as	Effector	Reservoir

📈 Clinical Significance of PPB

- Acts as a reservoir maintaining equilibrium between bound and free drug
- Determines loading dose requirements
- Affects drug interactions — one drug can displace another, increasing free fraction → toxicity
- Alters volume of distribution (Vd) and half-life (t½)
- Disease states (hepatic/renal) ↓ protein → ↑ free drug fraction → requires dose adjustment

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📦 Volume of Distribution (Vd)

🧭 Definition

The apparent (hypothetical) volume in which a drug would need to be uniformly distributed to produce the observed plasma concentration.

$$Vd = \text{Amount of drug in body (D)} / \text{Plasma concentration (C)}$$

🧠 Interpretation

Type	Value of Vd	Implication
Low Vd (<10 L)	Drug confined to plasma	Highly protein-bound
Moderate Vd (10–40 L)	Drug in extracellular fluids	Water-soluble
High Vd (>40 L)	Drug distributed into tissues	Lipid-soluble, tissue-bound

🧮 Clinical Significance

Helps determine loading dose:

- Loading dose = Vd × Target concentration (TC)

- Correlates with half-life (t½) and duration of action
- Large Vd → longer duration → may require higher loading dose

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 Loading Dose

⚙ Definition

A single large dose given to rapidly achieve the desired plasma concentration (therapeutic level).

💡 Formula:

$$\text{Loading Dose} = Vd \times \text{Target Concentration (TC)}$$

📝 Example:

If Vd = 40 L and desired plasma concentration = 2 mg/L
→
Loading dose = 40 × 2 = 80 mg

🧩 Clinical Significance

- Used when rapid onset is required (e.g., digoxin,

lidocaine)

- Must consider protein binding and toxicity risk
- Especially important in drugs with large Vd

🔁 Maintenance Dose

⚙️ Definition

The repeated dose required per unit time to maintain a steady-state concentration of drug in plasma.

- Balances rate of administration = rate of elimination
- Ensures sustained therapeutic effect without toxicity

💊 Each maintenance dose replaces the amount eliminated since the previous dose.

🧮 Formula

$$\text{Maintenance Dose} = \text{Clearance (CL)} \times \text{Target Concentration (TC)}$$

🧭 Flowchart: Overview of Distribution Concepts

Drug in Bloodstream

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Distribution to Tissues

→ Free form ↔ Bound to plasma proteins

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Free drug → Pharmacological effect → Metabolism / Excretion

Bound drug → Reservoir → Slow release

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Volume of Distribution (Vd) determines dose

→ Loading Dose (achieve target level rapidly)
→ Maintenance Dose (sustain level over time)

Summary Table

Concept	Definition	Clinical Significance
Distribution	Reversible transfer of drug between blood and tissues	Determines onset, duration, site of action
Drug Reservoirs	Sites where drugs accumulate reversibly	Prolongs or delays action
PPB	Binding of drug to plasma proteins	Affects free fraction, half-life, interactions
Vd	Apparent volume for uniform drug distribution	Used to calculate loading dose
Loading Dose	Initial large dose	Rapid achievement of therapeutic level
Maintenance Dose	Repeated doses to maintain steady state	Sustains therapeutic action