The Four Cornerstones of Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Elimination

Absorption and distribution are influenced by the formulation:

Medicinal Agent --> Formulation --> Medication

Galenic = Science of pharmaceutical formulation

(Galenos of Pergamon, 129-199 AD)
Drug Administration and Absorption

Routes of Drug Administration:

- Oral
- Topical (Percutaneous)
- Rectal or Vaginal
- Pulmonary
- Parenteral
Oral Drug Administration

• Pills
  – Antiquated single-dose unit; round, produced by mixing drug powder with syrup and rolling into shape

• Tablets
  – Oblong or disk-like shape, produced through mechanical pressure; filler material provides mass; starch or carbonates facilitate disintegration
Oral Drug Administration

• Coated Tablets
  – Tablet covered by a “shell” (wax, highly specialized polymers = Eudragit®) to facilitate swallowing, cover bad taste or protect active ingredient from stomach acid
Oral Drug Administration

- **Matrix Tablets**
  - Drug is embedded in inert “carrier” meshwork --> extended or targeted (intestinal) release

- **Capsules**
  - Oblong casing (Gelatin); contains drug in liquid, powder or granulated form

- **Troches or Lozenges; Sublingual Tablets**
  - Intended to be held in the mouth until dissolved
Oral Drug Administration

- Capsule
- Coated tablet
- Capsule with coated drug pellets
- Matrix tablet

Drug release vs. Time
Oral Drug Administration

- **Aequous Solutions (with Sugar=Syrup)**
  - Mostly for pediatric use
  - 20 drops=1g

- **Alcoholic Solutions (=Tinctures)**
  - Often plant extracts
  - 40 drops=1g

- **Suspensions**
  - Insoluble drug particles in aequous or lipophilic media
Percutaneous Drug Administration

Specific formulation determined by physician/dermatologist:

- based on skin type:
  - Dry vs. Oily
  - Young vs. Old
  - Intact vs. Injured

- based on drug properties:
  - Hydrophilic vs. Lipophilic
  - Soluble vs. Insoluble
Percutaneous Drug Administration
Percutaneous Drug Administration

- **Ointment and Lipophilic Cream**
  - Either pure lipophilic base (lanolin=wool fat; paraffin oil; petroleum jelly) or “water-in-oil” emulsions

- **Paste**
  - Ointment with >10% pulverized solids (e.g. Zinc- or Titanium-Oxide)

- **Lotion and Hydrophilic Cream**
  - “oil-in-water” emulsions

- **Gels**
  - Either alcohol or aequous solution based (Ethanol gels --> Cooling effect)
  - Increased consistency due to gel-forming agents
Percutaneous Drug Administration

• Transdermal Drug Delivery Systems = “Patches” (Nicotin, Isosorbid-Nitrate)

  – **Single Layer**
    • Inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation.

  – **Multi-Layer**
    • Similar to Single-layer, however, the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.

  – **Reservoir**
    • Inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive.
Other Topical Drug Administration

• Eye Drops
  • Sterile; Isotonic; pH-neutral

• Nose Drops/Nasal Sprays
  • Viscous Solutions

• Pulmonary Formulations
  • Inhalation anesthetics (Hospital use only)
  • Nebulizers (mostly propellant operated)
    • dispense defined amount of Aerosol
      (= dispersion of liquid or or solid particles in a gas)
    • Size of aerosol particles determines depth of penetration into the respiratory tract:
      >100 µm: Nasopharynx
      10-100 µm: Trachea, bronchii
      <10 µm: Bronchioli, alveoli
Other Topical Drug Administration

• Suppositories
  • Drug incorporated into a fat with a melting point ~35°C
    • Rectal: Absorption mostly intended into systemic circulation (e.g. analgesics)
    • Vaginal: Effects intended to be confined to site of application (e.g. candidiasis)
Parenteral Drug Administration

Sterile; iso-osmolar; pyrogen-free; pH=7.4

- Ampules
  - Single use (mostly with fracture ring)

- Single and Multi-dose Vials
  - 10-100 ml; contain preservatives

- Cartridge ampules

- Infusions
  - Solution administered over an extended period of time
Parenteral Drug Administration

• Advantages:
  – 100% “Absorption”
  – Drug enters general circulation without hepatic passage -->
    No first-pass hepatic elimination
  – Better bioavailability of hydrophilic drugs

• Bioavailability/Speed of Absorption
  – **Intravenous** (i.v.): Fastest (infusions; cardio-vascular drugs)
  – **Intramuscular** (i.m.): Medium (anti-inflammatory; antibiotics)
  – **Subcutaneous** (s.c.): Slowest (vaccines; insulin; depot contraceptives)
Drug Distribution
Drug Distribution

• To be absorbed and distributed, drugs must cross barriers (membranes) to enter and leave the blood stream.
• Body contains two type of barriers which are made up of epithelial or endothelial cells:
  – External (Absorption Barriers): Keratinized epithelium (skin), ciliated epithelium (lung), epithelium with microvilli (intestine), etc.
  These epithelial cells are connected via *zonulae occludens* (tight junctions) to create an unbroken phospholipid bilayer. Therefore, drugs MUST cross the lipophilic membrane to enter the body (except parenteral).
Drug Distribution

- **Internal (Blood-Tissue Barriers):** Drug permeation occurs mostly in the capillary bed, which is made up of endothelial cells joined via *zonulae occludens*.

Blood-Tissue Barrier is developed differently in various capillary beds:

- **Cardiac muscle:** high endo- and transcytotic activity-> drug transport via vesicles
- **Endocrine glands, gut:** *Fenestrations* of endothelial cells (= pores closed by diaphragms) allow for the passage of small molecules.
- **Liver:** Large *fenestration* (100 nm) without diaphragms-> drugs exchange freely between blood and interstitium
- **CNS, placenta:** Endothelia lack pores and possess only little trans-cytotic activity-> drugs must diffuse transcellularly, which requires specific physicochemical properties -> Barriers are very restrictive, permeable only to certain types of drugs.

![EC fenestrae](image)
Drug Distribution

• **Membrane Permeation:**
  - **Passive Diffusion:**
    • Requires some degree of lipid solubility, which is in part determined by the charge of the molecule
    • For weak acids or bases (which account for the vast majority of drugs), the charge of the molecule in dependence of the pH of the medium is determined by the Henderson-Hasselbalch Equation:
      \[ \log \left( \frac{[H^+\text{Drug}]}{[\text{Drug}]} \right) = pK_a - pH \]
  - **Active Transport:** Drugs “highjack” cellular transporter (e.g. L-DOPA uptake via L-amino acid carrier)
  - **Receptor-mediated Endocytosis:** Clathrin-coated pits form endosomal vesicles; receptor gets “recycled” to the cell surface
Drug distribution

Drug concentration is a function of absorption AND elimination:

Typical plasma drug concentration as function of time after a single oral dose

\[ AUC = \text{Area Under Curve} \]
Bioavailability (F): the AUC of the (orally) administered drug divided by the AUC of the intravenously administered drug.
Drug Distribution

Bioavailability:

- Intravenous: 100% by definition
- Intramuscular: 75 to ≤100%
- Subcutaneous: 75 to ≤100%
- Oral: 5 to ≤100%
- Rectal: 30 to ≤100%
- Inhalation: 5 to ≤100%
- Transdermal: 80 to ≤100%
Drug Distribution

Volume of Distribution ($V_d$) [ml or l]:

\[ V_d = \frac{\text{Amount of drug in the body [mg]}}{\text{drug concentration}_{\text{plasma}} [\text{mg/ml}]} \]

- $V_d$ is an apparent volume (volume that the drug must be distributed in to produce measured plasma concentration).
- Drug with near complete restriction to plasma compartment would have $V_d = \text{plasma volume (0.04 L/kg)} = 2.8 \text{ L/70 kg patient}$
- But: Many drugs are highly tissue bound => large $V_d$
  
e.g. Chloroquine: $V_d = 13,000 \text{ L}$
Drug Distribution

Rate of Elimination:

Drug elimination via kidney occurs by filtration => with falling blood concentration the amount of drug filtered per time unit diminishes.

Drug elimination via liver occurs by metabolism, where most enzymes operate in the quasi-linear range of their concentration-activity curve => with falling blood concentration the amount of drug metabolized per time unit diminishes.

==> Vast majority of drugs follows **first-order kinetics** (= rate is proportional to drug concentration).

Only three drugs follow **linear, zero-order** (= concentration-independent) elimination characteristic: Ethanol, Aspirin and Phenytoin.
Drug Distribution

Clearance (CL) [ml/min]:

\[
CL = \frac{\text{Rate of Elimination [mg/min]}}{\text{Drug concentration}}_{\text{plasma (C}_P\text{) [mg/ml]}}
\]

where

\[
\text{Rate of Elimination [mg/min]} = k [1/\text{min}] \times C_P [\text{mg/ml}] \times V_d [\text{ml}]
\]

and

\[
\text{Elimination rate constant (k) [1/min]} = \frac{\ln 2}{t_{1/2} (=\text{half-life})}
\]

\[
\ln 2 = 0.693
\]

\[
CL [\text{ml/min}] = \text{Elimination rate constant (k) [1/min]} \times V_d [\text{ml}] = \ln 2 \times V_d / t_{1/2}
\]

- It is the sum of all separate organ clearances:
  \[CL = CL_{\text{renal}} + CL_{\text{liver}} + CL_{\text{other}}\]

- Clearance is the volume of plasma cleared of all drug per unit of time (a constant for any given drug [ml/min])

- The actual quantity of drug [mg] removed per time unit [min] depends on both the clearance [ml/min] and the concentration [mg/ml].
Drug Distribution

Half-life ($t_{1/2}$) [min]:

$$= \ln 2 \times V_d \,[\text{ml}] / \text{CL} \,[\text{ml/min}]$$  

or

$$= \ln 2 / \text{Elimination rate constant (k)} \,[1/\text{min}]$$  

- Half-life is the time required for the concentration of a drug to fall by 50%
- The half-life is constant and related to (k) for drugs that follow first-order kinetics
Drug Distribution

Dosage Regimens:
With multiple dosing or continuous infusion, a drug will accumulate until the amount administered per time unit equals the amount eliminated per time unit. The plasma concentration at this point is called the steady-state concentration ($C_{SS}$) [mg/ml]:

$$C_{SS} = \frac{\text{Infusion rate [mg/min]}}{\text{Clearance [ml/min]}}$$

Typically, 90% of the $C_{SS}$ is reached after 3.3 half-lifes; ~100% after 5 half-lifes.
Drug Distribution

**Loading Dose:**
For drugs with long $t_{1/2}$, 3-5 half-lifes is too long to wait for $C_{SS}$
$\Rightarrow$ loading dose is used.
Loading dose must ‘fill’ the $V_d$ to achieve the target $C_P$:

$\text{Loading dose [mg]} = V_d [\text{ml}] \times C_P [\text{mg/ml}]$

**Maintenance Dose:**
Must replace the drug that is being eliminated over time:

$C_{SS} [\text{mg/ml}] = \frac{\text{Infusion rate [mg/min]}}{\text{Clearance [ml/min]}} \Rightarrow$

$\text{Infusion rate [mg/min]} = \text{Clearance [ml/min]} \times C_{SS} [\text{mg/ml}] \Rightarrow$

$\text{Infusion rate [mg/min]} = \ln 2 \times V_d [\text{ml}] / t_{1/2} [\text{min}] \times C_{SS} [\text{mg/ml}]$
Drug Distribution

- **Drug Binding to Plasma Proteins:**
  - Primarily albumin (4.6g/100ml), also β-globulins and acidic glycoproteins
  - Other specialized plasma proteins (transcortin; thyroxin-binding globulin; etc.)

  Binding to plasma proteins is **instantaneous** and **reversible**.
  - Of great importance, as the **free (=effective)** drug concentration determines intensity of response

  Drug-protein binding also influences biotransformation and elimination =>
  **Binding to plasma proteins is equivalent to depot formulations**

  - **Possible site for drug interactions:**
    - If two drugs bind to the same site on e.g. the albumin molecule, then drug B has the potential of displacing drug A from its binding site --> **effective concentration of drug A is increased** --> Toxic concentration or increased elimination

  - **Impaired liver function:**
    - can lead to altered pharmacokinetics of drugs that bind to albumin at high rates due to decreased albumin concentrations in the blood
In this example the treatment would not be effective as a therapeutic concentration in the blood is not maintained.
In this example severe toxicity would occur as the therapeutic concentration in the blood is exceeded due to accumulation of the drug.
In this example the treatment would be effective as the therapeutic concentration in the blood is maintained without approaching toxic levels.
Therapeutic Range

- **Therapeutic Index:**
  \[ = \frac{\text{Maximum non-toxic dose}}{\text{Minimum effective dose}} \]
  
  **Problem:**
  Does not take into account variability between individuals

  \[ \Rightarrow \text{“Improved formula”}: \]

  \[ = \frac{\text{LD}_{50}}{\text{ED}_{50}} \]

  **Problems:**
  - \( \text{LD}_{50} \) reflects only death, but no other toxic side effects (e.g. Ototoxicity of aminoglycosides)
  - \( \text{ED}_{50} \) depends on condition treated (e.g. Aspirin: Headache vs. rheumatism)
  - \( \text{LD}_{50} \) depends on patients overall condition (e.g. Aspirin: dangerous to asthmatic patients)

  \[ \Rightarrow \]

  Therapeutic Index is not particularly useful to describe the clinical usefulness of a drug!
Drug Metabolism and Elimination

• **Elimination** of drugs occurs primarily through renal mechanism
  – Secretion into bile also possible, but allows for re-absorption in the intestine

• **Secretion** into the urine requires ionized or hydrophilic molecules, but:
  – Most drugs are not small molecules that are highly ionized at body pH
  – Most drugs are poorly ionized and lipophilic
    => This decreases renal excretion and facilitates renal tubular reabsorption
  – Many drugs are highly protein bound, and therefore not efficiently filtered in the kidney
  – Most drugs would have a long duration of action if termination of their effects depended only on renal excretion

**Solution: Drug Metabolism**