Dermal absorption (percutaneous/skin): transport of chemicals from outer surface of skin into systemic circulation

- Penetration: entry into particular layer or structure
- Permeation: penetration through one layer into a second
- Resorption: uptake of substance into skin lymph & vascular system → systemic absorption

Determinants of absorption

- Drug molecule characteristics: physical state; molecular size (<500); lipid/water partition coefficient (K_{ow}10-1000); less ionization; local skin effects (more hydration)
- Skin characteristics: anatomical site; temperature; hydration of stratum corneum (SC); damage to SC ; metabolism; diseased skin; desquamation; blood & lymph flow
- Vehicle characteristics: solubility; volatility; distribution in SC; excipients; effect on SC; pH
- Application dose: concentration; skin area dose (film thickness, concentration); total skin area in contact with vehicle; duration of exposure

Features of patch delivery systems

- Occlusive barrier
- Drug reservoir
- Vehicle (drug dissolved in)
- Semi-permeable membrane against skin

Constant rate of delivery achieved in patches

- Excess non-vehicle dissolved in drug
  - Dissolved drug in vehicle absorbed into body
  - Non-dissolved drug can become dissolved in vehicle and available

Improving portioning of drug into skin (absorption)

- Hydration of skin due to occlusion: expands reservoir volume available to drugs within SC (increases absorption 5-10 x)
- Excipients (ethanol): alters skin barrier structure, good solvent properties, and positively affects Cv & Km
  - Propylene glycol ADRs: burning, stinging, contact dermatitis
  - DMSO: superb solvent, expands SC
    - ADRs: skin irritation, toxicity

Criteria for drug selection

- High potency
  - Typically 5 mg
  - Patch can't exceed 50 cm^2
  - Effective when slow over long period
- Clinical need
  - Narrow therapeutic window
  - Extensive first-pass effect orally
  - Multiple dosing
  - Unpleasant SEs from short half-life
  - Highly fluctuating plasma levels

Skin absorption mechanisms

- Transcellular: through keratin-packed corneocytes by partitioning in & out of cell membrane
- Intercellular: around corneocytes in lipid-rich extracellular regions
- Appendageal: bypasses corneocytes; enters shunts by hair follicles, sweat glands & sebaceous glands
  - RARE

Steps for drug absorption into systemic circulation

1. Release from formulation
2. Penetration into stratum corneum
3. Permeation/diffusion through SC
4. Partitioning from SC into epidermis
5. Reaches capillaries located in dermis

Drug concentrations accumulate

Topical: Ka > Kel = local tissue concentration accumulation (NOT systemic)

Patch: Ka >>> Kel = systemic accumulation

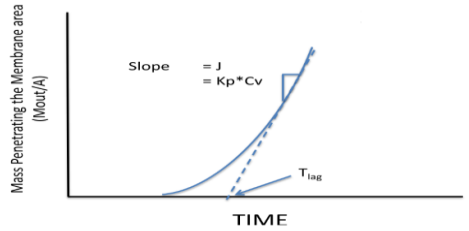
Permeability across body

Nail << palm/sole < trunk/extremities < face/scalp < < scrotum

[most patches placed on trunk or extremities]

Absorption kinetics

- $J = -D \frac{\partial C}{\partial X}$ g cm^2h^{-1} = cm^2h^{-1} * g cm^{-3}/cm
  Flux = diffusion coefficient * concentration gradient / linear distance travelled
- Jss = Kp * Co
  = permeability coefficient for given solute in given vehicle (cm/h) * concentration in donor compartment
- C_o = Km * Cv
  = partition/distribution coefficient between skin & vehicle * concentration of drug in vehicle



- Zero-order
- Over time, flux approaches Jss & cumulative amount of skin penetrating skin increases linearly

Advantages of TDDS

- Improved patient compliance
- Improved efficacy (continuous release)
- Reduced toxicity (no peaks/troughs, lower total absorbed dose)
- Bypass hepatic first-pass metabolism
- Avoid local GI SEs or metabolism
- Decrease dosing frequency
- Avoid painful injections
- Decreased cost to pt

Limitations of TDDS

- Difficulty of permeation
- Skin irritation (contact dermatitis)
- Technical development problems
  - Batch-batch variations
  - Storage & settling
  - Migration of active drug
  - Crystallization

Physical enhancement methods for transdermal absorption

- Stripping: remove SC (adhesive type or cyanoacrylate glue)
- Iontophoresis: slight electrical current applied from external electrode → molecules driven across SC (electrophoresis) = programmable drug delivery
- Electroporation: short high voltage (100 V) electrical pulses induce structural rearrangement of SC lipids → pore formation
- Ultrasound: low frequency (<1 MHz) ultrasound generate cavitation bubbles which oscillate & implode → shockwaves that increase skin permeability to water-soluble molecules & some macromolecules