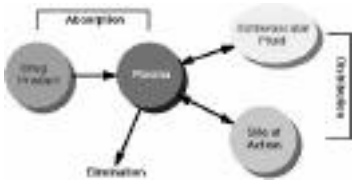
Physiological Factors Affecting Oral Administration

Objectives

- Describe how membrane permeability affects oral absorption
- Describe how GI physiology affects oral absorption
- Discuss how parameters of Fick's first law equation affect transport across membranes

ADME Processes



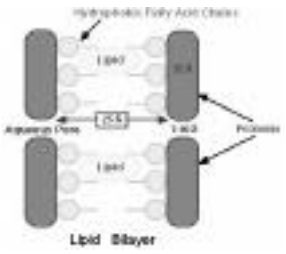
Factors Affecting Oral Absorption

- Membrane Physiology
  - Structure of the membrane
  - Transport processes
- Gastrointestinal Physiology
  - Characteristics
  - Gastric motility and emptying
  - Influence of food
  - Other factors

Membrane Physiology

- Membrane Structure
  - 1900 Overton - Frog muscle experiments
    - Lipid molecules cross readily
    - Larger lipid insoluble drugs are restricted
    - Small polar molecules cross
  - Membrane mostly lipid with small pores
  - Protein layer on the surface

Davson-Danielli Model



Another Model

Membrane in the Body

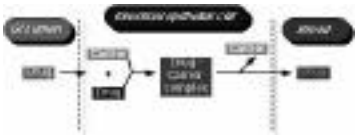
- Blood-brain barrier
  - None or very few pores - no polar materials can transfer but lipid material can transfer
- Renal tubules
  - Drugs reabsorbed if lipid in nature (pH - pKa dependent)
- Blood capillaries and Renal Glomerular membrane
  - Quite porous, molecules up to 69,000 Dalton
  - Allows removal of many polar compounds into urine

Transport across the Membrane

- Carrier mediated
  - Active
  - Facilitated
  - P-glycoprotein (reverse pump)
- Passive
- Pinocytosis
- Ion pair

Carrier Mediated

- Active or Facilitated



Active Transport

- Specialized mechanism (glucose, amino acids, 5-fluorouracil)
- Requires a carrier and form of energy
- Can be saturated
- Can proceed against a concentration gradient
- Competitive inhibition possible

Facilitated Transport

- Carrier required (e.g. vitamin B_{12})
- Saturable
- Can't go against a concentration gradient, just faster down-hill

Passive Transport

- Common process for many drugs
- Diffusion occurs from high concentration to low concentration
- Attempt to equalize concentrations on each side of the membrane
- After drug partitions into the (lipid) membrane a concentration gradient can be established

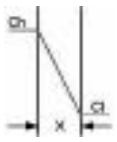
Fick's First Law

- Transport across the membrane is diffusion controlled

$$\text{Rate of Diffusion} = \frac{dM}{dt} = -\frac{D \cdot A \cdot (Ch - Cl)}{x}$$

Fick's First Law

- Parameters
  - D: Diffusion coefficient
  - A: Surface area
  - x: Membrane thickness
  - (Ch-Cl): Concentration difference



Diffusion Coefficient

- Related to
  - Size and lipid solubility of the drug
  - Viscosity of the diffusion medium
- Lipid solubility ↑ D ↑ dM/dt ↑
- Molecular size ↑ D ↓ dM/dt ↓

Surface Area

- As surface area ↑ diffusion ↑
- For example, intestinal lining surface area (villae and microvillae) are much larger than that of stomach. Faster absorption from intestine

Membrane Thickness

- Thinner membranes lead to faster diffusion
- e.g. membrane in the lung is quite thin.

Concentration Gradient

- Since V is at least 4 L (plasma volume) and often much larger concentrations in plasma (Cl) are often much lower than in the GI tract (Ch)
- Normally Cl << Ch

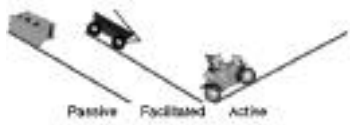
$$\frac{dM}{dt} = -D \cdot A \cdot Ch = -\frac{D \cdot A \cdot Xg}{X \cdot Vg} \cdot ka$$

Absorption often appears first order

Other Mechanisms

- Pinocytosis
  - e.g. Vitamin A, D, E and K, peptides in newborn
- Ion Pair transport
  - e.g. quaternary ammonium compounds

Transport across the Membrane



Gastrointestinal Physiology

Characteristics of GI Tract

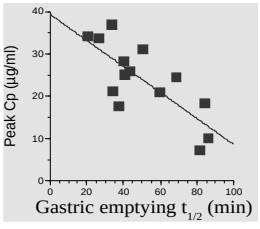
	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Buccal	≈ 6	thin	good fast absorption	small	short	yes
Esophagus	6	very thick	-	small	short	-
Stomach	1 - 3 decompos-ition HA	normal	good	small	30 - 40 min	no
Duodenum	5 - 7 Bile duct	normal	good	very large	very short window effect	no
Small Intestine	6 - 7	normal	good	very large 10-14 ft 80 cm2/cm	≈ 3 hr	no
Large Intestine	6.8 - 7	normal	good	not large 4 - 5 ft	long up to 24 hr	some

Gastric Emptying - Motility

- Often better absorption from small intestine
- Thus slowed stomach emptying often delays absorption
- Slowed emptying - greater degradation e.g. l-dopa

Gastric Emptying and Motility

Paracetamol Absorption



Heading, R.C. et al. 1973 "The dependence of paracetamol absorption on the rate of gastric emptying" Brit J Pcol **47**, 415

Factors Affecting Gastric Emptying

- Volume ingested - increase at first then slows
  - – - bulky slower
- Meal type
  - – Fatty food - decrease
  - – Carbohydrate - decrease
  - – Increased temperature - increase

Factors Affecting Gastric Emptying…

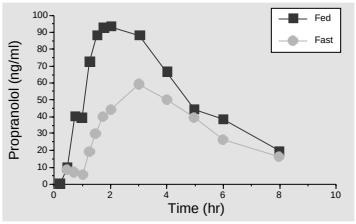
- Body position - lying on left - decrease
- Drugs
  - – Anticholinergic (e.g. atropine) - decrease
  - – Narcotic (e.g. morphine) - decrease
  - – Analgesics (e.g. aspirin) - decrease

Effect of Food

- Food can affect stomach emptying
- Generally extent not affected
- Occasionally fatty food results in increase
  - – Griseofulvin - dissolved in fatty food
  - – Propranolol - interaction with food

Effect of Food

Propranolol Absorption



Melander, A. et al. 1977 "Enhancement of the bioavailability of propranolol and metaprolol by food" Clin Pcol Ther, **22**, 108

Other Factors

- Intestinal motility and transit time
- Food retards transit

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