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 B₁₂)
• 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

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

- 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 $\uparrow$ $D$ $\uparrow$ $\frac{dM}{dt}$ $\uparrow$
- Molecular size $\uparrow$ $D$ $\downarrow$ $\frac{dM}{dt}$ $\downarrow$

Surface Area

- As surface area $\uparrow$ diffusion $\uparrow$
- For example, intestinal lining surface area (villi and microvilli) 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 (CI) are often much lower than in the GI tract (Ch)
- Normally CI << Ch

\[
\frac{dM}{dt} = -D \cdot A \cdot Ch = -D \cdot A \cdot Xg
\]

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
Characteristics of GI Tract

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>Membrane</th>
<th>Blood Supply</th>
<th>Surface Area</th>
<th>Transit Time</th>
<th>By-pass from</th>
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<tr>
<td>Buccal</td>
<td>&lt; 6</td>
<td>thin</td>
<td>good fast</td>
<td>small</td>
<td>short</td>
<td>yes</td>
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<tr>
<td>Esophagus</td>
<td>8</td>
<td>very thick</td>
<td>small</td>
<td>short</td>
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<tr>
<td>Stomach</td>
<td>1–3</td>
<td>decompos-</td>
<td>normal</td>
<td>normal</td>
<td>20–40 min</td>
<td>no</td>
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<tr>
<td></td>
<td>(ion H+)</td>
<td></td>
<td>good</td>
<td>small</td>
<td></td>
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<tr>
<td>Duodenum</td>
<td>5–7</td>
<td>bile duct</td>
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<td>very large</td>
<td>very short</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>good</td>
<td>window effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>6–7</td>
<td>normal</td>
<td>very large</td>
<td>very large</td>
<td>&lt; 3 hr</td>
<td>no</td>
</tr>
<tr>
<td>Large intestine</td>
<td>6.8–7</td>
<td>normal</td>
<td>not large</td>
<td>long up to 24 hr</td>
<td>some</td>
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</tbody>
</table>

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

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

![Graph showing the effect of food on propranolol absorption.]


Other Factors

- Intestinal motility and transit time
- Food retards transit

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