5. Secondary Factors Influence Drug Absorption

- Biological factors of gastric intestinal (GI) tract
  - Gastric emptying
  - Gastric and intestinal pH
  - GI content
  - Food effect
  - GI transit time and motility
  - GI surface area
  - Drug stability in GI tract
  - Blood flow
  - Age

- Dosage form factors
  - Excipients
  - Diluents
  - Surfactants
  - Dosage forms

5.1. Gastric Emptying

- Anything slowing down gastric emptying is likely to slow down the rate (not extent) of drug absorption, and thus affecting onset of the therapeutic response.

Gastrointestinal (GI) track

Gastric Emptying Rate at Fasted State

- Fasted emptying of low volume of non-caloric liquids (50 ml)
  - 0-2 hrs
- Fasted emptying of high volume non-caloric liquids (200 ml)
  - $V = V_0 \exp(-k_gt)$, first order kinetics, rate is proportional to the volume remaining in the stomach.
  - $T_{1/2} = 10 – 20$ min
  - Increase absorption rate
Gastric Emptying Rate at Fed State

- Fed state emptying liquid
  - proportional caloric density (cal/ml)
  - Zero order, e.g. glucose, 2-3 kcal /min
  - Slow down drug absorption rate

- Fed state emptying solid
  - Proportional to caloric density
  - Size
    - < 7-10 mm particle can be emptied to intestine
    - > 7-10 mm (Phase III contraction) takes long time for gastric emptying
  - Slow down drug absorption rate

Gastric emptying controlled absorption (con’t)

Example:

- Acetaminophen
  - mw: 151
  - Solubility: 100 mM
  - Log Kp = 0.2
  - It is very permeable

Gastric emptying change absorption rate of acetaminophen

5.2. Surface area of different regions of GI influences drug absorption

- Stomach
  - Surface area with folds: 1 m²
  - Blood flow: 150 ml/min
  - No villi and microvilli, small surface area for drug absorption
5.2. Surface area of different regions of GI influences drug absorption (Con’t)

- Small intestine
  - duodenum, jejunum, ileum
  - has largest effective surface area for absorption due to the presence of
    - Folds of mucosa; Villi; Microvilli
  - is the most important region for carrier-mediated drug absorption
    - Most transporters are expressed in small intestine
  - Surface areas: 200 m²
  - Blood flow: 1000 ml/min

5.2. Surface area of different regions of GI influences drug absorption (Con’t)

- Large Intestine
  - No villi and microvilli, small surface area for drug absorption
  - Less transporter expression for carrier-mediated drug absorption
  - Receives 500-1500 ml per day

Example 1: Regional dependent absorption
Bidisomide

Bidisomide Plasma Levels from Oral, Duodenal and Jejunal Administration in Dogs (n=4)

Oral
Duodenum
Jejunum
5.3. pH of Gastrointestinal Tract

- GI pH change may:
  - Change drug solubility
  - Change drug dissolution
  - Change absorption
    - Ionization
    - Then, dissolution controls absorption

GI pH and Drug Absorption

- Human
  - Gastric pH 1-3.5
    - Gastric pH 4-6 after meal
    - H-2 blocker (famotidine) increase gastric pH to 5
  - Intestinal pH
    - Duodenum (pH 5-6.5)
    - Jejunum (pH 6-7)
    - Ileum (pH 7-7.5)
    - Colon (pH 6.5-8)
- Dog
  - Gastric pH 1.2 - 8
  - Less fluctuation after meal
  - H2 blocker increase gastric pH 7-8

GI pH Changes Dissolution

- The rate of dissolution from a dosage form, particularly tablets and capsules, is dependent on pH
  - Acidic drugs dissolve most readily in alkaline media and will have a greater dissolution in the intestinal fluids than in gastric fluids
  - Basic drugs will dissolve most readily in acidic solutions, and thus the dissolution will be greater in gastric fluids than in intestinal fluids
Effect of Gastric pH on drug absorption:
Example (dog model)

(A) Water
(B) Placebo capsule
(C) Pentagastrin
(D) Ranitidine

Effects of Gastric pH on absorption and bioavailability (con't)
Example: Dipyridamole

- Dipyridamole
  - Anti-platelet, anti-thrombosis
  - Weak base, pKa 6.4
  - Solubility:
    - < 1.5 ug/ml at pH 6-8;
    - > 1-10 mg/ml at pH 1.2

Gastric pH on absorption and bioavailability (Con't)
Example: Dipyridamole tablet dissolution at different pH

% Release vs Time (min)

Gastric pH on absorption and bioavailability (Con't)
Example: Dipyridamole in combination use of H2-antagonists

Plasma Conc. (ng/ml ± SEM) vs Time (h)
Clinical implication of pH dependent absorption

- Combination use of antacid with other drugs, especially weak basic drugs with pH-dependent solubility
  - Decrease bioavailability (more than 50-80%),
  - Many take antacid (H-2 blocker or other antacids)
  - Antacid is prescribed after surgery
    - e.g. some weak basic anti-thrombosis drugs should be avoided with combination use.

5.4. Food Effects on drug absorption

- Food (high fat) increase drug solubility and dissolution, increase bioavailability (BA) for certain drugs with low solubility
- Food (high fat) may stimulate bile salt secretion and increase drug solubility and dissolution, and increase BA for certain drugs with low solubility
- Food (high calories) decrease gastric emptying rate, delay the rate of absorption, and delay the onset of therapeutic drugs

5.4. Food Effects on drug absorption (Con’t)

- Food (high protein) may increase gastric pH---- decrease dissolution of weak base, decrease BA
- Food component may compete for drug absorption that mediated by transporter system
  - Grapefruit juice inhibit efflux pump (P-gp) and increase BA of P-gp substrates
- Food component form complex with drugs (complexation) and decrease drug absorption and bioavailability
  - Tetracycline with calcium (milk)

Food Effect Example:
Grapefruit Juice Inhibit P-gp and Increase Bioavailability

![Grapefruit Juice Inhibit P-gp and Increase Bioavailability](image)
5.6. Dosage Form Factors Influence Drug Absorption

- Drug has to be in solution for absorption
- Factors, which influence dissolution, may affect drug absorption
- Controlled drug releases formulation
  - Completely change absorption profiles, which is different from immediate release dosage forms.
  - The rate of drug release will control the rate of drug absorption

Summary

Factors Control Drug Absorption

- Permeability controlled drug absorption
  - If a drug has high water solubility and low membrane permeability (hydrophilic drugs), permeability usually limits (controls) absorption, unless it is carrier-mediated or paracellular absorption.
- Solubility (and dissolution) controlled drug absorption
  - If a drug has low solubility and high permeability (lipophilic drugs), solubility (and dissolution) usually limits (controls) absorption. Permeability does not limit absorption.
- Gastric emptying controlled drug absorption
  - If neither above two properties limits the absorption (for drugs with high solubility and high permeability), then gastric emptying rate limits (controls) the drug absorption

Summary

- Physiological factors influence drug absorption
  - Gastric emptying: change absorption rate
  - Surface: regional dependent absorption
  - pH effect: combination use of antacid may change bioavailability
  - Food effect: decrease or increase bioavailability

- Dosage form factor influence drug absorption
  - Changes in dissolution may change drug absorption
  - Controlled release formulations change absorption profiles compared to immediate release formulations