Understanding the Gastrointestinal, Drug and Dosage Form Processes
Controlling Absorption I. GI Physiology

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Understanding the Gastrointestinal, Drug and Dosage Form Processes Controlling Absorption

I. GI Physiology

II. Biopharmaceutics of oral drug absorption.

III. Preclinical Models and Simulation Tools: Successful Integration and Optimized Clinical Outcome.
Acknowledgements

CONTROLED RELEASE IN ORAL DRUG DELIVERY
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Animal Model Systems Suitable for Controlled Release Modeling
Steven C. Sutton and Philip L. Smith


Chapter 4
Animal Model Systems Suitable for Controlled Release Modeling
Learning Objectives

• Describe the anatomy & physiology of the stomach, duodenum, jejunum, ileum, ileal-cecal junction, and the ascending, transverse and descending large intestine.

• Describe what when & where the gall bladder and pancreas secrete in the small intestine.

• Describe what conditions lead to a high stomach pH, and what problems could then arise.
Esophageal transit

- Normal esophageal transit time: 5-15 seconds.
- Elderly:
  - Lack of coordinated tongue, oropharynx, esophagus movements
  - Capsule separates from bolus of water
  - Dry swallow
  - Capsule sticks;

The Gastro-intestinal tract
Stomach-anatomy

resting volume: 30 ml
Motility of the stomach

0-2 hrs: Pylorus is initially completely shut.

2-4 hrs: Pylorus allows 2mm particles to empty

Stomach-function

- Acidic pH, enzymes
- Mixing, grinding
- Reservoir (controlled emptying).

Effect of stomach contractions on tablet erosion

- grinding forces can disintegrate the formulations and cause dose dumping
- min tablet strength: 10-15 kp

<table>
<thead>
<tr>
<th>Specie</th>
<th>Fasted</th>
<th>Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Dog</td>
<td>3.2</td>
<td>3.2</td>
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Low stomach pH - normal

• Stomach acid results in degradation of some drugs

• Susceptable API are formulated with enteric coat
  – Normally dissolves at higher pH (eg 6 -7)

• Or are administered with:
  – Antacids
  – H2 antagonists
  – Proton pump inhibitors
High stomach pH - achlorhydria

• Achlorhydria (pH >5.1 in men, > 6.8 in women¹), or the administration of antacids, H2 antagonists, or proton pump inhibitors raises gastric pH.

– Result: less/no dissolution of weak bases


How can food increase exposure?

- Buffering stomach contents resulting in a transient rise in gastric pH (weak bases)
- Solubilizing effects from bile acid & lecithin secretion
- Increase in small intestine water volume
- Delay in gastric emptying*

How long is pH elevated?

1-2 hours

Gastric emptying

- Impact of the pyloris and dosage form size
- Effect of food
  - Calories
  - Volume
  - Consistency
  - Fat
  - Protein
  - Carbohydrates
The pyloris and dosage form size

INTESTINAL TRACT

Gall bladder & pancreatic secretions enter the duodenum

Transit through the duodenum is faster than through the jejunum.

Transit through the ileum is slower than through the jejunum.

Gastric emptying and Duodenal passage of a non-disintegrating capsule

Fasted volunteer
Supine position
Real time

Small intestine
Intestinal Folds

Intestinal Villi.
Intestinal microvilli

Glycocalyx & mucous

Tight junctions

Paracellular space


Tight Junctions

• Negatively charged
• 4-8 angstrom pore diameter
• Paracellular transport (eg atenolol, propranolol)

pH and bile acids in upper jejunum

Small intestine total water volume: 100 ml
Range: 50-150ml

Functions of the Small Intestine.

- Mixing
- Peristalsis
- Propagation
- Absorption

- Bile acids
  - Secretion into duodenum
  - Reabsorption from ileum

Housekeeper wave (MMC)

Small intestine transit time (SITT)

Shortened SITT when fed

MMC and small intestine transit

Ileal-cecal junction


http://ar.photos1.fotosearch.com/bthumb/LIF/LIF145/PED06020.jpg
Small intestine transit of pellets & a tablet in the same subject.

Small intestinal transporter proteins

• Uptake transporters
  – Solute Carrier superfamily (SLC)
    • OATP
    • PEPT1
    • MRP3

• Efflux transporters
  – ATP-binding Cassette superfamily (ABC)
    • MDR1 (more prevalent in jejunum & colon)
    • BCRP
    • MRP3
## Differences between Uptake & Efflux transporters

### Uptake transporters
- Transport along the concentration gradient
- Do not require energy
- Located on the apical membrane
- Enable absorption

### Efflux transporters
- Transport against the concentration gradient
- Require energy
- Located on the apical and basolateral membranes
- Impede absorption (if located only on the apical membrane)
Small intestinal transporter proteins

• There are regional differences in the distribution of both SLC and ABC transporters along the length of the intestine and across different species

Intestinal metabolism & extraction

• The absorptive cells lining the intestine are the first barrier to substances that may do us harm.
• These cells contain numerous enzymes that metabolize substances before they can pass on to the liver.
• These cells also contain efflux transporters that excrete substances out of the body.
Intestinal metabolism & extraction

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Intestinal enzymes

• Cytochrome p450 isozymes
  – CYP3A4
  – CYP2C9
• Glucorono-syl-transferases
• Alcohol dehydrogenase
Cytochrome p-450 isozymes

• CYP3A4
  – 80% of the total intestine CYP
• CYP2C9
  – 15% of the total intestine CYP
CYP3A4

- Most important intestinal extraction process: Many drugs are substrates
- Levels are highest in upper small intestine (duodenum)
- Levels decrease progressively to the distal ileum
- Wide interindividual variability in expression
  - Results in wide variability in drug bioavailability
CYP3A4

• Low concentration relative to liver (1%)
• Regardless, can be responsible for metabolizing a substantial amount of oral dose
• The intestinal enzymes remove ≥50% of the oral dose of:
  – Tacrolimus, buspirone, atorvastatin, cyclosporine
Synergy with P-gp

• Many drugs that are substrates for CYP3A4 are also substrates of P-gp
• Efflux by P-gp and subsequent reabsorption
  – Prolongs the API contact with the cells’ enzymes
Small intestinal metabolism

• Species differences in gut metabolism may confuse the interpretation of PK results with CR formulations
Colon: the large intestine

• Shorter than the small intestine
• Much larger diameter
• Water content
  – Ascending: ~10 mls (fasted) 180 mls (fed) as viscous mush
  – Transverse: none (mostly gas)
  – Descending: none (storage)
• Functions:
  – water absorption
  – some nutrient absorption (fatty acids)
  – storage

http://www.loveyourcolon.org/sites/default/files/digestivetract.jpg
Transit of a nondisintegrating capsule through the transverse colon.

male volunteer supine position, 6 h after ingestion real time

Summary

- **Esophagus**
  - Transports food and medication from the oral cavity to the stomach

- **Stomach**
  - Controls delivery of its contents to the small intestine
  - Grinds contents
  - pH may be elevated due to disease, medication

- **Small intestine**
  - Digestion & absorption
  - Mixing with bile acids, lecithin forms micelles
  - Housekeeper wave or MMC
    - Every 2 hours unless fed
  - ~100 mls water
  - Duodenum
    - Rapid transit
    - Bile acids & enzymes enter
    - Most active uptake transport/absorption and metabolism
Summary (continued)

- **Jejunum**
  - Most nutrient absorption occurs here
  - Most passive absorption

- **Ileum**
  - Small intestine contents are often delayed at the ileal-cecal junction before entering the colon
  - Bile acids absorbed

- **Colon – water absorption**
  - Neutral pH
  - Ascending may have water
  - Transverse contains gas
  - Descending is primarily storage
  - Some reducing bacteria may degrade susceptible API
  - Diffusion of API from dosage forms drops considerably as water is absorbed
  - Higher levels of efflux transporters
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Pharmaceutical Sciences. Yes. It's good here.

Thank you!

Questions?