

# PHAR 7632 Chapter 11

## Physiological Factors Affecting Oral Absorption

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### Physiological factors affecting oral absorption

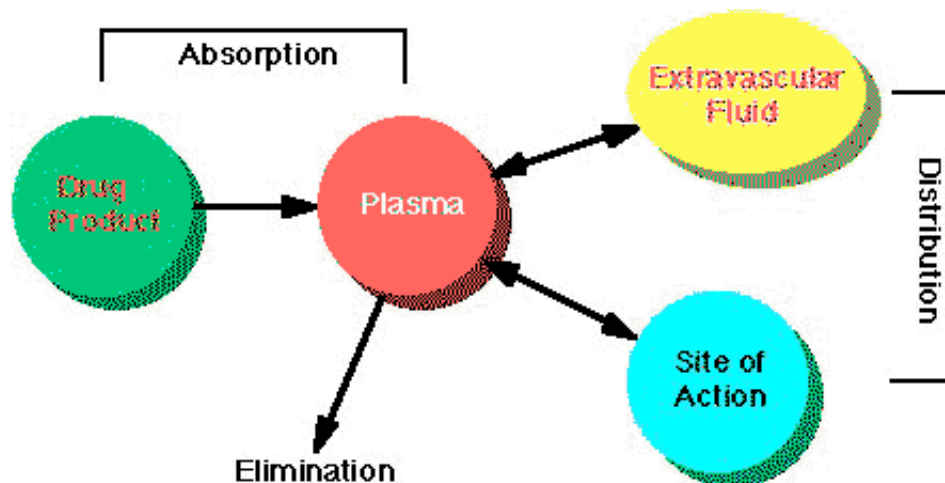
#### Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- be able to describe membrane structure and how it might effect drug transport
- be able to describe the differences between passive, facilitated and active transport
- be able to describe the effect of parameters of Fick's first law on passive drug transport across membranes
- be able to describe the relationship between GI physiology and drug absorption including changes in stomach emptying time and the presence of food

In the next few Chapters physiological, physical-chemical, and formulation factors which can influence the observed rate and extent of oral absorption will be discussed.

Looking briefly at the overall picture of drug absorption, distribution, and elimination.



**Figure 11.1.1 Diagram Representing Absorption, Distribution, Metabolism and Excretion**

The ultimate goal is to have the drug reach the site of action in a concentration which produces a pharmacological effect. No matter how the drug is given (other than IV) it must pass through a number of biological membranes before it reaches the site of action.

We can start by looking at:

- Membrane Physiology
  - Considering the structure of membranes
  - Transport processes
- Gastrointestinal physiology
  - Characteristics of gastrointestinal physiology
  - Gastric motility and emptying
  - Influence of food

- Other factors
- 

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# PHAR 7632 Chapter 11

## Physiological Factors Affecting Oral Absorption

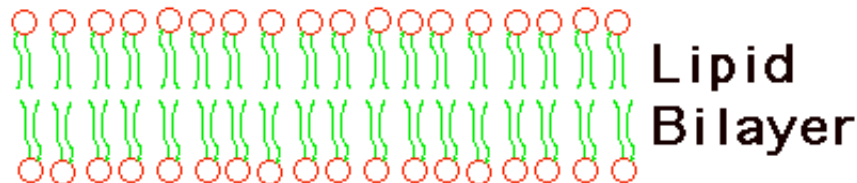
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### Membrane physiology

#### Membrane structure

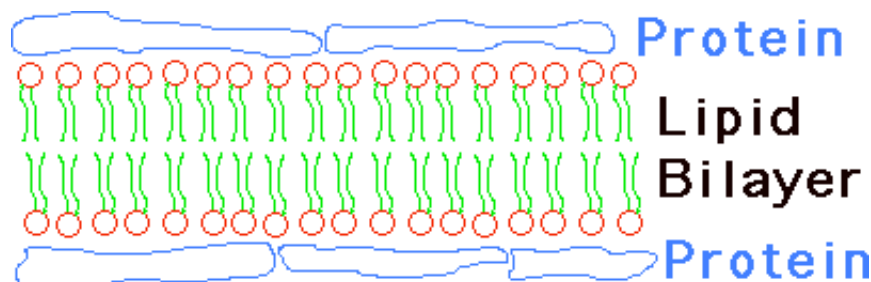
In 1900 Overton performed some simple but classic experiments related to cell membrane structure. By measuring the permeability of various types of compounds across the membranes of a frog muscle he found that lipid molecules could readily cross this membrane, larger lipid insoluble molecules couldn't and small polar compounds could slowly cross the membrane. He suggested that membranes were similar to lipids and that certain molecules (lipids) moved across membranes by dissolving in the membrane.

These results suggest that the biologic membrane is mainly lipid in nature but contains small aqueous channels or pores.



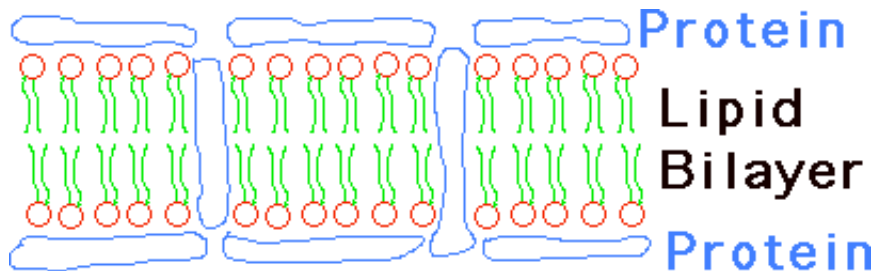
**Figure 11.2.1 Lipid Bilayer**

Other experiments involving surface tension measurements have suggested that there is also a layer of protein on the membrane. These results and others have been incorporated into a general model for the biological membrane. This is the Davson-Danielli model (1935).



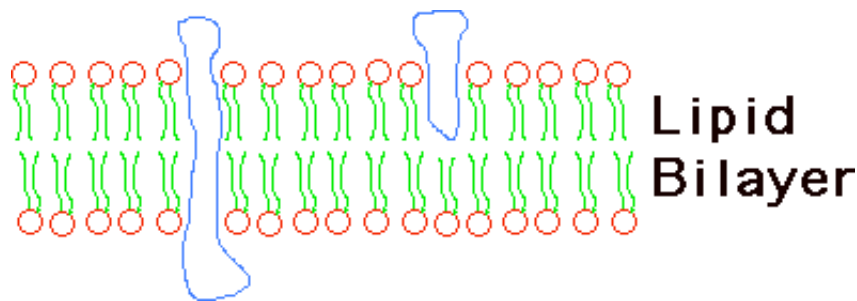
**Figure 11.2.2 The Davson-Danielli Model**

Later work (Danielli, 1975) suggested the presence of "active patches" and protein lining to pores in the membrane.



**Figure 11.2.3 Modified Davson-Danielli Model**

Work during the 1970s and 1980s suggested the model proposed by Singer and Nicolson 1972 called the fluid mosaic model. With this model the lipid bilayer is retained but the protein drifts between the lipid rather than forming another layer on either side of the lipid bilayer.



**Figure 11.2.4 The Fluid Mosaic Model**

The membrane then acts as a lipid barrier with protein formed pores. The protein within the membrane can act transport enhancers in either direction depending on the protein. [An animation from BBC Education.](#)

The barriers between various organs, tissues and fluids areas will consist of cells of different structure and membranes characteristics. In some cases the cells are loosely attached with extracellular fluid freely moving between the cells. Drugs and other compounds, lipid or not, may freely move across this barrier. In other cases there may be tight junctions between the cells which will prevent non lipid movement.



**Figure 11.2.5 Loosely Attached Cell Barrier**



**Figure 11.2.6 Cell Barrier with Tight Junctions**

These are general structures of the cellular layer. Layers in different parts of the body have somewhat different characteristics which influence drug action and distribution. In particular, membrane protein form and function, intracellular pore size and distribution is not uniform between different parts of the body.

#### **Examples of some barrier types.**

**Blood-brain barrier.** The cellular barrier between the blood and brain have very tight junctions effectively eliminating transfer between the cells. Additionally there are specific transport mechanisms, such as P-glycoproteins which actively causes the removal of drugs and other compounds from the brain. This will prevent many polar (often toxic materials) materials from entering the brain. However, smaller lipid materials or lipid soluble materials, such as diethyl ether, halothane, can easily enter the brain across the cellular membrane. These compounds are used as general anesthetics.

**Renal tubules.** In the kidney there are a number of regions important for drug elimination. In the tubules drugs may be reabsorbed. However, because the membranes are relatively non-porous, only lipid compounds or non-ionized species (dependent of pH and pKa) are reabsorbed.

**Hepatic blood vessels.** The capillaries are lined with a basement membrane broken in part by sinusoids and fenestrations interspersed with cells held together with tight junctions. The result is a barrier that allows considerable transfer between the blood and hepatocytes.

**Blood capillaries and renal glomerular membranes.** These membranes are quite porous allowing non-polar and polar molecules

(up to a fairly large size, just below that of albumin, M.Wt 69,000) to pass through. This is especially useful in the kidney since it allows excretion of polar (drug and waste compounds) substances.

## Transport across the membranes

### Carrier mediated

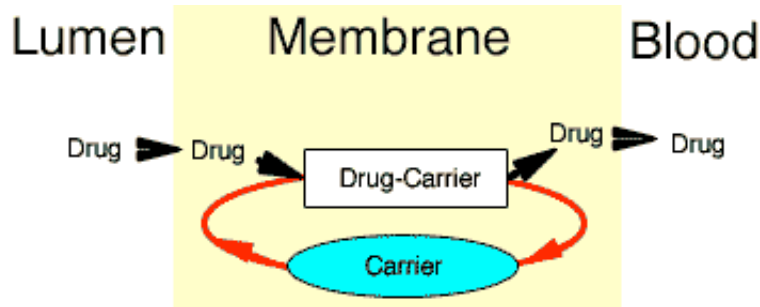


Figure 11.2.7 Carrier-Mediated Transport Process

Redrawn from Shargel, L. and Yu, A.B.C. 1985  
**Applied Biopharmaceutics and Pharmacokinetics**,  
 2nd ed., Appleton-Century-Crofts, Norwalk, CT

### Active

The body has a number of specialized mechanisms for transporting particular compounds; for example, glucose and amino acids. Sometimes drugs can participate in this process; e.g. 5-fluorouracil. Active transport requires a carrier molecule and a form of energy.

- the process can be saturated
- transport can proceed against a concentration gradient
- competitive inhibition is possible

[An animation from BBC Education.](#)

### Facilitated

A drug carrier is required but no energy is necessary. e.g. vitamin B12 transport.

- saturable if not enough carrier
- no transport against a concentration gradient only downhill but faster

[An animation from BBC Education.](#)

### P-glycoprotein

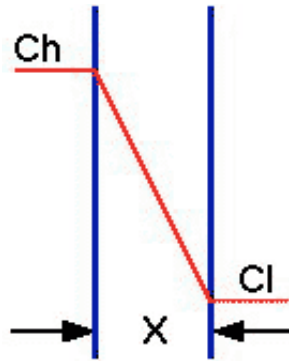
P-glycoprotein transporters (PGP, MDR-1) are present throughout the body including liver, brain, kidney and the intestinal tract epithelia. They appear to be an important component of drug absorption acting as reverse pumps generally inhibiting absorption. This is an active, ATP-dependent process which can have a significant effect on drug bioavailability. P-glycoprotein works against a range of drugs (250 - 1850 Dalton) such as cyclosporin A, digoxin,  $\beta$ -blockers, antibiotics and others. This process has been described as multi-drug resistance (MDR). Additionally P-glycoprotein has many substrates in common with cytochrome P450 3A4 (CYP 3A4) thus it appears that this system not only transports drug into the lumen but causes the metabolism of substantial amounts of the drug as well (e.g. cyclosporin).

Clinically significant substrates of PGP include digoxin, cyclosporine, fexofenadine, paclitaxel, tacrolimus, nortriptyline and phenytoin (Humma 2003). A number of compounds can act as PGP inhibitors including atorvastatin (digoxin AUC increased), cyclosporine (increased paclitaxel absorption), grapefruit juice (increased paclitaxel absorption) and verapamil. Rifampin and St.

John's wort have been reported to induce PGP expression (Ritschel and Kearns, 2004).

The distribution of PGP polymorphism varies by race. The 'normal' 3435C allele is found in 61% African American and 26% in European American. The clinically important 3435T polymorph is found in 13% of African American and 62% of European American. The 3435T allele has been associated with reduced PGP expression (concentration) and consequently higher absorption. Digoxin levels were higher in healthy subjects with the 3435T allele compared with results in subjects with the 3435C allele (Humma, 2003).

## Passive



**Figure 11.2.8 Diagram of Passive Transport with a Concentration Gradient**

Most (many) drugs cross biologic membranes by passive diffusion. Diffusion occurs when the drug concentration on one side of the membrane is higher than that on the other side. Drug diffuses across the membrane in an attempt to equalize the drug concentration on both sides of the membrane.

If the drug partitions into the lipid membrane a concentration gradient can be established.

The rate of transport of drug across the membrane can be described by Fick's first law of diffusion:-

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

**Equation 11.2.1 Fick's First Law, Rate of Diffusion**

The parameters of this equation are:-

**D:** diffusion coefficient. This parameter is related to the size and lipid solubility of the drug and the viscosity of the diffusion medium, the membrane. As lipid solubility increases or molecular size decreases then D increases and thus dM/dt also increases.

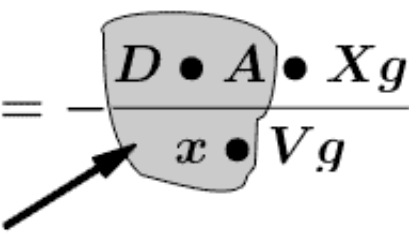
**A:** surface area. As the surface area increases the rate of diffusion also increase. The surface of the intestinal lining (with villae and microvillae) is much larger than the stomach. This is one reason absorption is generally faster from the intestine compared with absorption from the stomach.

**x:** membrane thickness. The smaller the membrane thickness the quicker the diffusion process. As one example, the membrane in the lung is quite thin thus inhalation absorption can be quite rapid.

**(Ch - Cl):** concentration difference. Since V, the apparent volume of distribution, is at least four liters and often much higher the drug concentration in blood or plasma will be quite low compared with the concentration in the GI tract. It is this concentration gradient which allows the rapid complete absorption of many drug substances.

Normally  $Cl \ll Ch$  then:-

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

constant,  $k_a$  

Thus the absorption of many drugs from the G-I tract can often appear to be first-order. [Simple diffusion animation by BBC Education.](#)

## Pinocytosis

Larger particles are not able to move through membranes or interstitial spaces so other processes must be available. These processes involve the entrapment of larger particles by the cell membrane and incorporation into the cell, cytosol. A spontaneous incorporation of a small amount of extracellular fluid with solutes is called pinocytosis. Phagocytosis is a similar process involving the incorporation of larger particles. Examples include Vitamin A, D, E, and K, peptides in newborn.

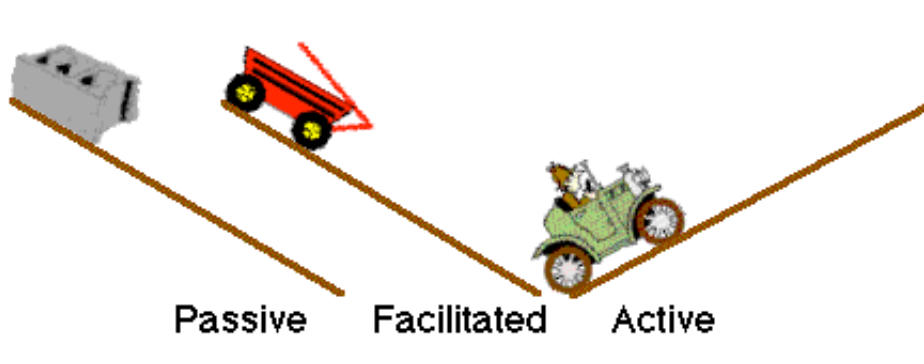


Figure 11.2.9 Illustration of Different Transport Mechanisms

## References

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- [From the Lipid Bilayer to the Fluid Mosaic: A Brief History of Membrane Models](#)
- Ritschel, W.A. and Kearns, G.L. 2004 **Handbook of Basic Pharmacokinetics ... including Clinical Applications**, 6th ed., American Pharmaceutical Association, Washington, DC ISBN 1-58212-054-4
- Humma, L.M., Ellingrod, V.L. and Kolesar, J.M. 2003 **Lexi-Comp's Pharmacogenomics Handbook**, Lexi-Comp, Hudson, OH ISBN 1-59195-060-0
- [One hundred years of membrane permeability: does Overton still rule?](#) Qais Al-Awqati 1999 **Nature Cell Biology**, 1(8) pp E201 - E202
- [Biology 1010, Donaldson, L.](#) York University, Toronto, CA - especially Chapter 8 <http://dryden.biol.yorku.ca/biol1010.html>
- [P450, UGT and P-gp Drug Interactions](#)

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# PHAR 7632 Chapter 11

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### Gastrointestinal (GI) Physiology

### Characteristics of GI physiology

**Table 11.3.1 GI Physiology and Drug Absorption** Washington et al., 2001

	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
BUCCAL	approx 6	thin	Good, fast absorption with low dose	small	Short unless controlled	yes
ESOPHAGUS	6-7	Very thick, no absorption	-	small	short, typically a few seconds, except for some coated tablets	-
STOMACH	1.7-4.5 decomposition, weak acid unionized	normal	good	small	30 min (liquid) - 120 min (solid food), delayed stomach emptying can reduce intestinal absorption	no
DUODENUM	5 - 7 bile duct, surfactant properties	normal	good	very large	very short (6" long), window effect	no
SMALL INTESTINE	6 - 7	normal	good	very large 10 - 14 ft, 80 cm <sup>2</sup> /cm	about 3 hours	no
LARGE INTESTINE	6.8 - 7	-	good	not very large 4 - 5 ft	long, up to 24 hr	lower colon, rectum yes

## Gastric emptying and motility

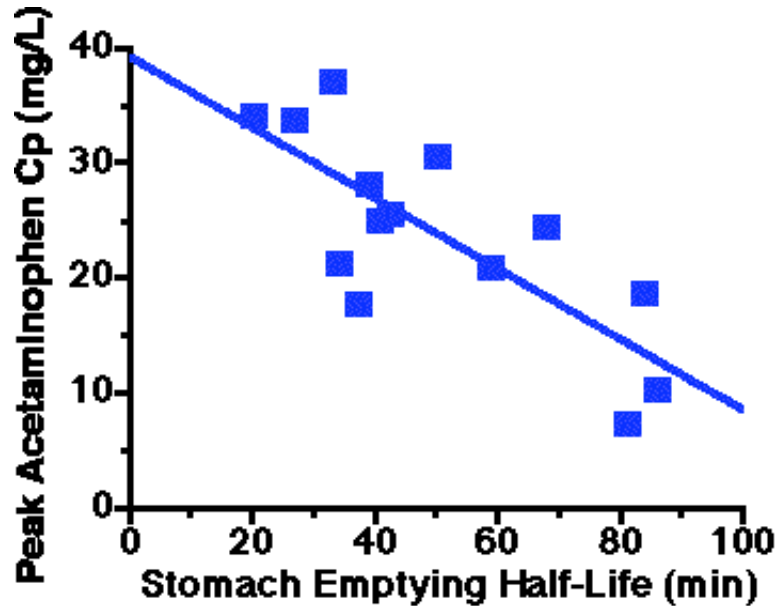


Figure 11.3.1 Dependence of Peak Acetaminophen Plasma Concentration as a Function of Stomach Emptying Half-life

Redrawn from Heading, R.C., Nimmo, J., Prescott, L.F. and Tothill, P. 1973.  
The dependence of paracetamol absorption on the rate of gastric emptying,  
*Br. J. Pharmacol.*, **47**, 415-421

Generally drugs are better absorbed in the small intestine (because of the larger surface area) than in the stomach, therefore quicker stomach emptying will increase drug absorption. For example, a good correlation has been found between stomach emptying time and peak plasma concentration for acetaminophen. The quicker the stomach emptying (shorter stomach emptying time) the higher the plasma concentration, Figure 11.3.1.

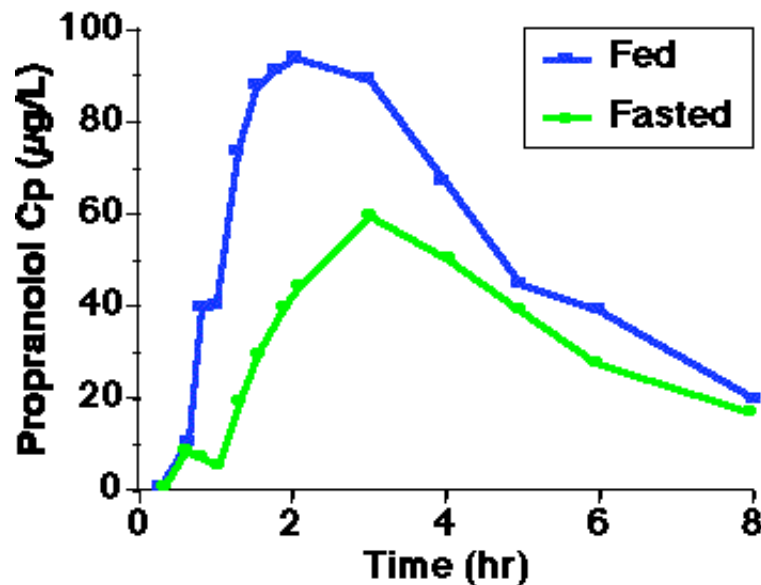
Also slower stomach emptying can cause increased degradation of drugs in the stomach's lower pH; e.g. l-dopa.

**Table 11.3.2 Factors Affecting Gastric Emptying**

<b>Volume of Ingested Material</b>	As volume increases initially an increase then a decrease. Bulky material tends to empty more slowly than liquids
<b>Type of Meal</b>	
Fatty food	Decrease
Carbohydrate	Decrease
Temperature of Food	Increase in temperature, increase in emptying rate
<b>Body Position</b>	Lying on the left side decreases emptying rate. Standing <i>versus</i> lying (delayed)
<b>Drugs</b>	
Anticholinergics (e.g. atropine)	Decrease
Narcotic (e.g. morphine)	Decrease
Analgesic (e.g. aspirin)	Decrease

From Mayersohn, M. 1971.  
**Physiological Factors Influencing Drug Absorption,**  
*Can. Pharm. J.*, 164-169

## Effect of Food



**Figure 11.3.2 Effect of Fasting *versus* Fed on Propranolol Concentrations**

Melander, A., Danielson, K., Schersten, B. and Wahlin, E. 1977.  
**Enhancement of the bioavailability of propranolol and metoprolol by food,**  
*Clin. Pharmacol. Ther.*, **22**, 108-112

Food can effect the rate of gastric emptying. For example fatty food can slow gastric emptying and retard drug absorption. Generally the extent of absorption is not greatly reduced. Occasionally absorption may be improved. Griseofulvin absorption is improved by the presence of fatty food. Apparently the poorly soluble griseofulvin is dissolved in the fat and then more readily absorbed.

Propranolol plasma concentrations are larger after food than in fasted subjects. This may be an interaction with components of the food.

## Other factors

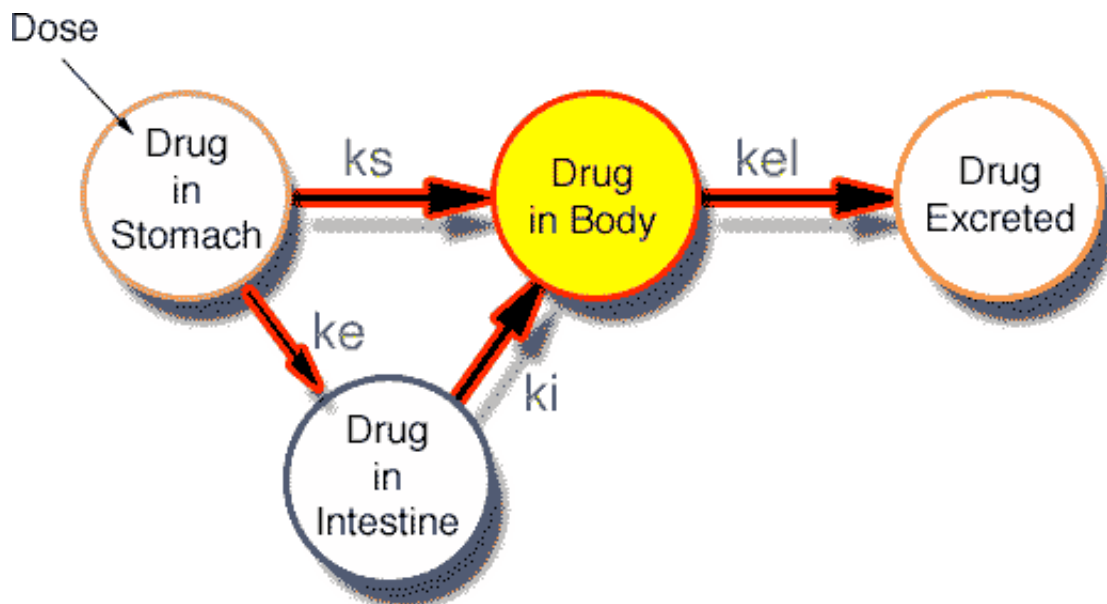
Intestinal Motility and Transit Time (Mayersohn, 1971)

Food Retards transit

## Some items to consider

**Item 1.** The larger surface area of the small intestine means that many drugs are much better absorbed from this region of the GI tract compared with from the stomach. For some drugs the rate of absorption from the stomach is so low that stomach emptying time or rate controls the rate of absorption of the drug. For acetaminophen (paracetamol) the rate of absorption from the stomach is so slow relative to the absorption from the intestine that time of peak absorption or peak concentration after oral administration can be used to determine stomach emptying rate. (Petrying and Blake, 1993)

First try simulating concentration *versus* time after an Oral Dose: Dose = 250 mg;  $k_{el} = 0.10 \text{ hr}^{-1}$ ;  $k_s = 0.12 \text{ hr}^{-1}$ ;  $k_e = 1.4 \text{ hr}^{-1}$ ;  $k_i = 2.1 \text{ hr}^{-1}$ ;  $V = 24 \text{ L}$ . This  $k_e$  value represents a stomach emptying time of 30 minutes (0.5 hr). Compare this line with lines generated with slower stomach emptying, that is, lower  $k_e$  values. Plot  $C_{pmax}$  (or  $t_{max}$ ) versus stomach emptying half-life. [Explore the problem as a Linear Plot - Java Applet](#)



**Figure 11.3.1 One Compartment Model with Absorption from Stomach and Intestine**

The equations for this model after [Oral Absorption](#) was developed using Laplace transforms.

## References

- Heading, R.C., Nimmo, J., Prescott, L.F. and Tothill, P. 1973. **The dependence of paracetamol absorption on the rate of gastric emptying**, *Br. J. Pharmacol.*, **47**, 415-421
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