Note: Large images and tables on this page may necessitate printing in landscape mode.

PHYSIOLOGIC FACTORS RELATED TO DRUG ABSORPTION: INTRODUCTION

The systemic absorption of a drug is dependent on (1) the physicochemical properties of the drug, (2) the nature of the drug product, and (3) the anatomy and physiology of the drug absorption site. All of these considerations are important in the manufacture and biopharmaceutic evaluation of drug products (). Proper drug product selection requires a thorough understanding of the physiologic and pathologic factors affecting drug absorption to assure therapeutic efficacy and to avoid potential drug–drug and drug–nutrient interactions. This chapter will focus on the anatomic and physiologic considerations for the systemic absorption of a drug.

ROUTE OF DRUG ADMINISTRATION

Drugs may be given by parenteral, enteral, inhalation, transdermal (percutaneous), or intranasal route for systemic absorption. Each route of drug administration has certain advantages and disadvantages. Some characteristics of the more common routes of drug administration are listed in . The systemic availability and onset of drug action are affected by blood flow to the administration site, the physicochemical characteristics of the drug and the drug product, and by any pathophysiologic condition at the absorption site.

Table 13.1 Common Routes of Drug Administration

Route	Bioavailability	Advantages	Disadvantages
Parenteral Routes			
Intravenous bolus (IV)	Complete (100%) systemic drug absorption.	Drug is given for immediate effect.	Increased chance for adverse reaction.
	Rate of bioavailability considered instantaneous.		Possible anaphylaxis.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption.	Plasma drug levels more precisely controlled.	Requires skill in insertion of infusion set.
	Rate of drug absorption controlled by infusion rate.	May inject large fluid volumes.	Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
		May use drugs with poor lipid solubility and/or irritating drugs.	
Intramuscular injection (IM)	Rapid from aqueous solution.	Easier to inject than intravenous injection.	Irritating drugs may be very painful.
	Slow absorption from nonaqueous (oil) solutions.	Larger volumes may be used compared to subcutaneous solutions.	Different rates of absorption depending on muscle group injected and blood flow.
Subcutaneous injection (SC)	Prompt from aqueous solution.	Generally, used for insulin injection.	Rate of drug absorption depends on blood flow and injection volume.
	Slow absorption from repository formulations.		
Enteral Routes			
Buccal or sublingual (SL)	Rapid absorption from lipid-soluble drugs.	No "first-pass" effects.	Some drugs may be swallowed.
			Not for most drugs or drugs with high doses.
Oral (PO)	Absorption may vary.	Safest and easiest route of drug administration.	Some drugs may have erratic absorption, be unstable in the gastointestinal tract, or be metabolized by liver prior to systemic absorption.
	Generally, slower absorption rate compared to IV bolus or IM injection.	May use immediate-release and modified-release drug products.	
Rectal (PR)	Absorption may vary from suppository.	Useful when patient cannot swallow	Absorption may be erratic.

		medication.	
	More reliable absorption from enema (solution).	Used for local and systemic effects.	Suppository may migrate to different position.
Other Routes			Some patient discomfort.
Transdermal	Slow absorption, rate may vary.	Transdermal delivery system (patch) is easy to use.	Some irritation by patch or drug.
	Increased absorption with occlusive dressing.	Used for lipid-soluble drugs with low dose and low MW.	Permeability of skin variable with condition, anatomic site, age, and gender.
			Type of cream or ointment base affects drug release and absorption.
Inhalation and intranasal	Rapid absorption.	May be used for local or systemic effects.	Particle size of drug determines anatomic placement in respiratory tract.
	Total dose absorbed is variable.		May stimulate cough reflex.
			Some drug may be swallowed.

Many drugs are not administered orally because of drug instability in the gastrointestinal tract or drug degradation by the digestive enzymes in the intestine. For example, erythropoietin and human growth hormone (somatrophin) are administered intramuscularly, and insulin is administered subcutaneously or intramuscularly, because of the potential for degradation of these drugs in the stomach or intestine. Biotechnology products () are often too labile to be administered orally and therefore are usually given parenterally. Drug absorption after subcutaneous injection is slower than intravenous injection. Pathophysiologic conditions such as burns will increase the permeability of drugs across the skin compared with normal intact skin.

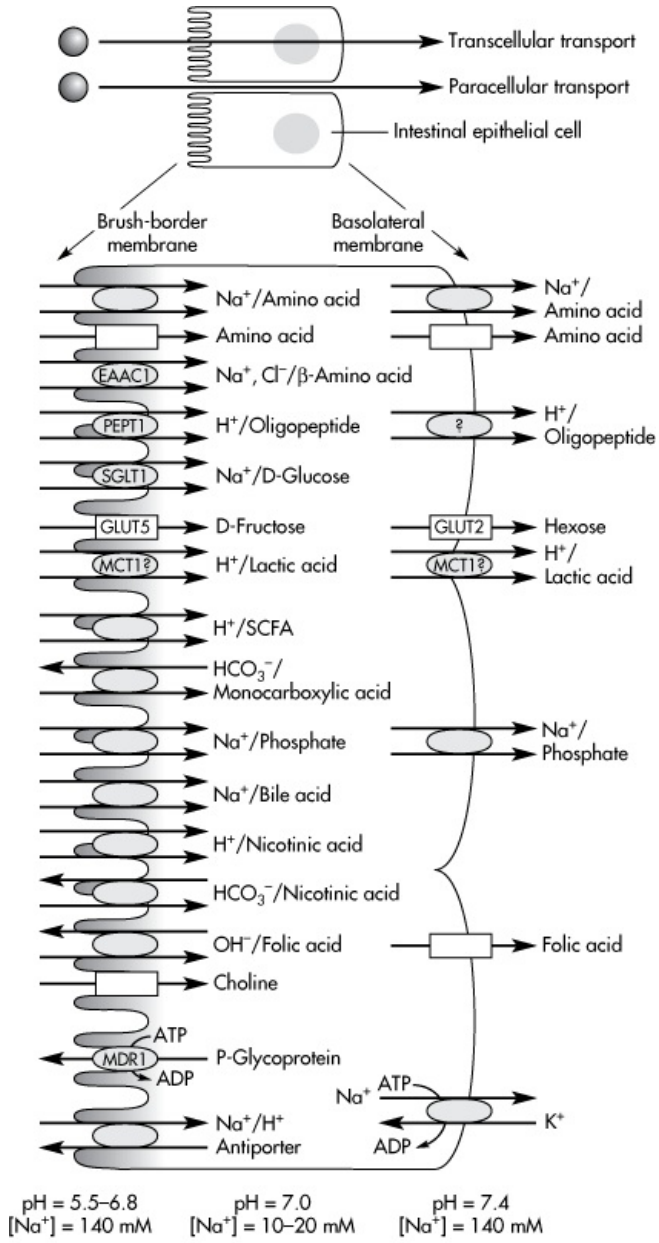
When a drug is administered by an extravascular route of administration (eg, oral, topical, intranasal, inhalation, rectal), the drug must first be absorbed into the systemic circulation and then diffuse or be transported to the site of action before eliciting biological and therapeutic activity. The general principles and kinetics of absorption from these extravascular sites follow the same principles as oral dosing, although the physiology of the site of administration differs.

NATURE OF CELL MEMBRANES

Many drugs administered by extravascular routes are intended for local effect. Other drugs are designed to be absorbed from the site of administration into the systemic circulation. For systemic drug absorption, the drug must cross cellular membranes. After oral administration, drug molecules must cross the intestinal epithelium by going either through or between the epithelial cells to reach the systemic circulation. The permeability of a drug at the absorption site into the systemic circulation is intimately related to the molecular structure of the drug and to the physical and biochemical properties of the cell membranes. Once in the plasma, the drug may have to cross biological membranes to reach the site of action. Therefore, biological membranes potentially pose a significant barrier to drug delivery.

Transcellular absorption is the process of drug movement across a cell. Some polar molecules may not be able to traverse the cell membrane but, instead, go through gaps or *tight junctions* between cells, a process known as *paracellular drug absorption*. shows the difference between the two processes. Some drugs are probably absorbed by a mixed mechanism involving one or more processes.

Figure 13-1.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Summary of intestinal epithelial transporters. Transporters shown by square and oval shapes demonstrate active and facilitated transporters, respectively. Names of cloned transporters are shown with square or oval shapes. In the case of active transporter, arrows in the same direction represent symport of substance and the driving force. Arrows going in the reverse direction mean the antiport.

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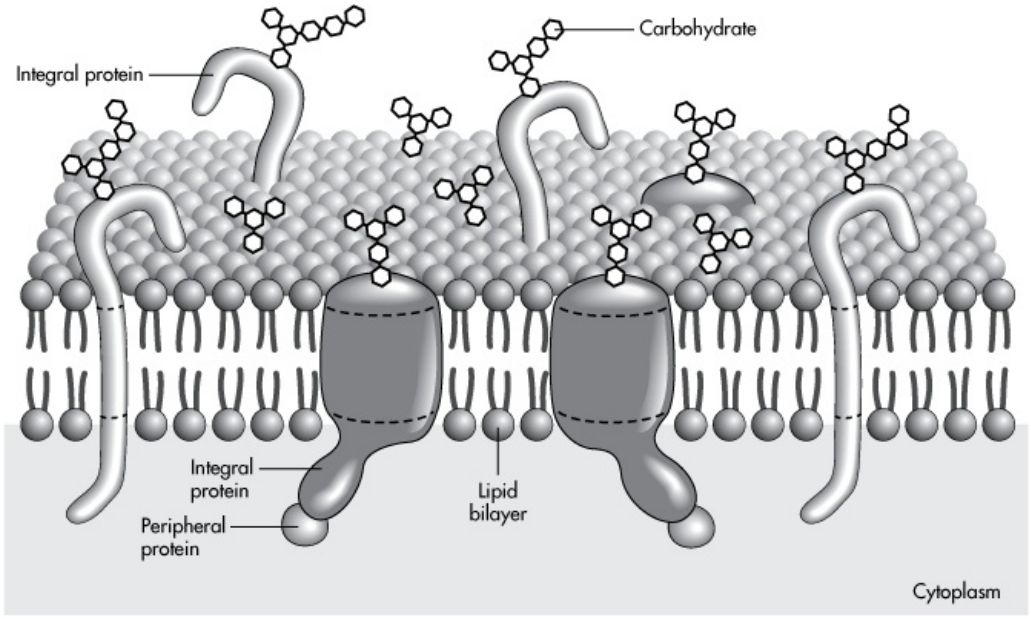
Membranes are major structures in cells, surrounding the entire cell (plasma membrane) and acting as a boundary between the cell and the interstitial fluid. In addition, membranes enclose most of the cell organelles (eg, the mitochondrion membrane). Functionally, cell membranes are semipermeable partitions that act as selective barriers to the passage of molecules. Water, some selected small molecules, and lipid-soluble molecules pass through such membranes, whereas highly charged molecules and large molecules, such as proteins and protein-bound drugs, do not.

The transmembrane movement of drugs is influenced by the composition and structure of the plasma membranes. Cell membranes are generally thin, approximately 70 to 100 Å in thickness. Cell membranes are composed primarily of phospholipids in the form of a bilayer interdispersed with carbohydrates and protein groups. There are several theories as to the structure of the cell membrane. The *lipid bilayer* or *unit membrane theory,* originally proposed by , considers the plasma membrane to be composed of two layers of phospholipid between two surface layers of proteins, with the hydrophilic "head" groups of the phospholipids facing the protein layers and the hydrophobic "tail" groups of the phospholipids aligned in the interior. The lipid bilayer theory explains the observation that lipid-soluble drugs tend to penetrate cell membranes more easily than polar molecules. However, the bilayer cell membrane structure does not account for the diffusion of water, small-molecular-weight molecules such as urea, and certain charged ions.

The *fluid mosaic model*, proposed by , explains the transcellular diffusion of polar molecules. According to this model, the cell membrane consists of globular proteins embedded in a dynamic fluid, lipid bilayer matrix (). These proteins provide a pathway for the selective transfer of certain polar molecules and charged ions through the lipid barrier. As shown in , transmembrane proteins are interdispersed throughout the membrane. Two types of pores of about 10 nm and 50 to 70 nm were inferred to be present in membranes based on capillary membrane transport studies (). These small pores provide a channel through which water, ions, and dissolved solutes such as urea may move across the membrane.

Figure 13-2.



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Model of the plasma membrane including proteins and carbohydrates as well as lipids. Integral proteins are embedded in the lipid bilayer; peripheral proteins are merely associated with the membrane surface. The carbohydrate consists of monosaccharides, or simple sugars, strung together in chains attached to proteins (forming glycoproteins) or to lipids (forming glycolipids). The asymmetry of the membrane is manifested in several ways. Carbohydrates are always on the exterior surface and peripheral proteins are almost always on the cytoplasmic, or inner, surface. The two lipid monolayers include different proportions of the various kinds of lipid molecule. Most important, each species of integral protein has a definite orientation, which is the same for every molecule of that species.

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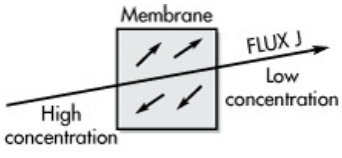
PASSAGE OF DRUGS ACROSS CELL MEMBRANES

Passive Diffusion

Theoretically, a lipophilic drug may pass through the cell or go around it. If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption. *Passive diffusion* is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration. This process is *passive* because no external energy is expended. In , drug molecules move forward and back across a membrane. If the two sides have the same drug concentration, forward-moving drug molecules are balanced by molecules moving back, resulting in no net transfer of drug. When one side is higher in drug concentration, at any given time, the number of forward-moving drug molecules will be higher than the number of backward-moving molecules; the net result will be a transfer of molecules to the alternate side, as indicated in the figure by the big arrow. The rate of transfer is called *flux*, and is represented by a vector to show its direction in space. The tendency of molecules to move in all directions is natural, because molecules possess kinetic energy and constantly collide with one another in space. Only left and right molecule movements are shown in , because movement of molecules in other directions will not result in concentration changes because of the limitation of the container wall.

Figure 13-3.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Passive diffusion of molecules. Molecules in solution diffuse randomly in all directions. As molecules diffuse from left to right and vice versa (small arrows), a net diffusion from the high-concentration side to the low-concentration side results. This results in a net flux (*J*) to the right side. Flux is measured in mass per unit area (eg, mg/cm^2).

Passive diffusion is the major absorption process for most drugs. The driving force for passive diffusion is higher drug concentrations on the mucosal side compared to the blood. According to *Fick's law of diffusion*, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.

$$\frac{dQ}{dt} = \frac{DAK}{h}(C_{GI} - C_p) \qquad (13.1)$$

where dQ/dt = rate of diffusion, D = diffusion coefficient, K = lipid water partition coefficient of drug in the biologic membrane that controls drug permeation, A = surface area of membrane; h = membrane thickness, and $C_{GI} - C_p$ = difference between the concentrations of drug in the gastrointestinal tract and in the plasma.

Because the drug distributes rapidly into a large volume after entering the blood, the concentration of drug in the blood initially will be quite low with respect to the concentration at the site of drug absorption. For example, a drug is usually given in milligram doses, whereas plasma concentrations are often in the microgram-per-milliliter or nanogram-per-milliliter range. If the drug is given orally, then $C_{GI} \gg C_p$ and a large concentration gradient is maintained, thus driving drug molecules into the plasma from the gastrointestinal tract.

Given Fick's law of diffusion, several other factors can be seen to influence the rate of passive diffusion of drugs. For example, the degree of lipid solubility of the drug influences the rate of drug absorption. The partition coefficient, *K*, represents the lipid–water partitioning of a drug across the hypothetical membrane in the mucosa. Drugs that are more lipid soluble have a larger value of *K*. The surface area, *A*, of the membrane also influences the rate of absorption. Drugs may be absorbed from most areas of the gastrointestinal tract. However, the duodenal area of the small intestine shows the most rapid drug absorption, due to such anatomic features as villi and microvilli, which provide a large surface area. These villi are less abundant in other areas of the gastrointestinal tract.

The thickness of the hypothetical model membrane, *h*, is a constant for any particular absorption site. Drugs usually diffuse very rapidly through capillary plasma membranes in the vascular compartments, in contrast to diffusion through plasma membranes of capillaries in the brain. In the brain, the capillaries are densely lined with glial cells, so a drug diffuses slowly into the brain as if a thick lipid membrane existed. The term *blood–brain barrier* is used to describe the poor diffusion of water-soluble molecules across capillary plasma membranes into the brain. However, in certain disease states such as meningitis these membranes may be disrupted or become more permeable to drug diffusion.

The diffusion coefficient, *D*, is a constant for each drug and is defined as the amount of a drug that diffuses across a membrane of a given unit area per unit time when the concentration gradient is unity. The dimensions of *D* are area per unit time—for example, cm^2/sec.

Because *D*, *A*, *K*, and *h* are constants under usual conditions for absorption, a combined constant *P* or permeability coefficient may be defined.

$$P = \frac{DAK}{h} \qquad (13.2)$$

Furthermore, in Equation 13.1 the drug concentration in the plasma, C_p, is extremely small compared to the drug concentration in the gastrointestinal tract, C_{GI}. If C_p is negligible and *P* is substituted into Equation 13.1, the following relationship for Fick's law is obtained:

$$\frac{dQ}{dt} = P(C_{GI}) \qquad (13.3)$$

Equation 13.3 is an expression for a first-order process. In practice, the extravascular absorption of most drugs tends to be a first-order absorption process. Moreover, because of the large concentration gradient between C_{GI} and C_p, the rate of drug absorption is usually more rapid than the rate of drug elimination.

Many drugs have both lipophilic and hydrophilic chemical substituents. Those drugs that are more lipid soluble tend to traverse cell membranes more easily than less lipid-soluble or more water-soluble molecules. For drugs that act as weak electrolytes, such as weak acids and bases, the extent of ionization influences the rate of drug transport. The ionized species of the drug contains a charge and is more water soluble than the nonionized species of the drug, which is more lipid soluble. The extent of ionization of a weak electrolyte will depend on both the pK_a of the drug and the pH of the medium in which the drug is dissolved. *Henderson and Hasselbalch* used the following expressions pertaining to weak acids and weak bases to describe the relationship between pK_a and pH:

For weak acids,

$$\text{Ratio} = \frac{[\text{salt}]}{[\text{acid}]} = \frac{[A^-]}{[HA]} = 10^{(pH - pK_a)} \qquad (13.4)$$

For weak bases,

$$\text{Ratio} = \frac{[\text{base}]}{[\text{salt}]} = \frac{[RNH_2]}{[RNH_3^+]} = 10^{(pH-pK_a)} \qquad (13.5)$$

With Equations 13.4 and 13.5, the proportion of free acid or free base existing as the nonionized species may be determined at any given pH, assuming the pK_a for the drug is known. For example, at a plasma pH of 7.4, salicylic acid (pK_a = 3.0) exists mostly in its ionized or water-soluble form, as shown below:

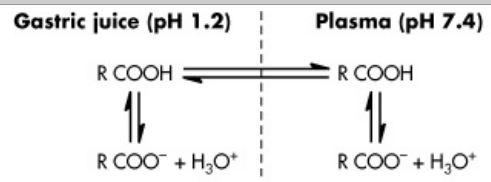
$$\text{Ratio} = \frac{[\text{salt}]}{[\text{acid}]} = 10^{(7.4-3.0)}$$

$$\log \frac{[\text{salt}]}{[\text{acid}]} = 7.4 - 3.0 = 4.4$$

$$\frac{[\text{salt}]}{[\text{acid}]} = 2.51 \times 10^4$$

In a simple system, the total drug concentration on either side of a membrane should be the same at equilibrium, assuming Fick's law of diffusion is the only distribution factor involved. For diffusible drugs, such as nonelectrolyte drugs or drugs that do not ionize, the drug concentrations on either side of the membrane are the same at equilibrium. However, for electrolyte drugs or drugs that ionize, the total drug concentrations on either side of the membrane are not equal at equilibrium if the pH of the medium differs on respective sides of the membrane. For example, consider the concentration of salicylic acid (pK_a = 3.0) in the stomach (pH 1.2) as opposed to its concentration in the plasma (pH 7.4) (). According to the Henderson–Hasselbalch equation (Eq. 13.4) for weak acids, at pH 7.4 and at pH 1.2, salicylic acid exists in the ratios that follow.

Figure 13-4.



Model for the distribution of an orally administered weak electrolyte drug such as salicylic acid.

In the plasma, at pH 7.4:

$$\text{Ratio} = \frac{(RCOO^-)}{(RCOOH)} = 2.51 \times 10^4$$

In gastric juice, at pH 1.2:

$$\text{Ratio} = \frac{(RCOO^-)}{(RCOOH)} = 10^{(1.2-3.0)} = 1.58 \times 10^{-2}$$

The total drug concentration on either side of the membrane is determined as shown in .

Table 13.2 Relative Concentrations of Salicylic Acid as Affected by pH

Drug	Gastric Juice (pH 1.2)	Plasma (pH 7.4)
RCOOH	1.0000	1
$RCOO^-$	0.0158	25100
Total drug concentration	1.0158	25101

Thus, the pH affects distribution of salicylic acid (RCOOH) and its salt ($RCOO^-$) across cell membranes. It is assumed that the acid, RCOOH, is freely permeable and the salt, $RCOO^-$, is not permeable across the cell membrane. In this example the total concentration of salicylic acid at equilibrium is approximately 25,000 times greater in the plasma than in the stomach (). These calculations can also be applied to weak bases, using Equation 13.5.

According to the *pH–partition hypothesis*, if the pH on one side of a cell membrane differs from the pH on the other side of the membrane, then (1) the drug (weak acid or base) will ionize to different degrees on respective sides of the membrane; (2) the total drug concentrations (ionized plus nonionized drug) on either side of the membrane will be unequal; and (3) the compartment in which the drug is more highly ionized will contain the greater total drug concentration. For these reasons, a

weak acid (such as salicylic acid) will be rapidly absorbed from the stomach (pH 1.2), whereas a weak base (such as quinidine) will be poorly absorbed from the stomach.

Another factor that can influence drug concentrations on either side of a membrane is a particular *affinity* of the drug for a tissue component, which prevents the drug from moving freely back across the cell membrane. For example, a drug such as dicumarol binds to plasma protein, and digoxin binds to tissue protein. In each case, the protein-bound drug does not move freely across the cell membrane. Drugs such as chlordane are very lipid soluble and will partition into adipose (fat) tissue. In addition, a drug such as tetracycline might form a complex with calcium in the bones and teeth. Finally, a drug may concentrate in a tissue due to a specific uptake or active transport process. Such processes have been demonstrated for iodide in thyroid tissue, potassium in the intracellular water, and certain catecholamines into adrenergic storage sites. Such drugs may have a higher total drug concentration on the side where binding occurs, yet the free drug concentration that diffuses across cell membranes will be the same on both sides of the membrane.

Instead of diffusing into the cell, drugs can also diffuse into the spaces around the cell as an absorption mechanism. In *paracellulardrug absorption,* drug molecules smaller than 500 MW diffuse into the tight junctions, or spaces between intestinal epithelial cells.

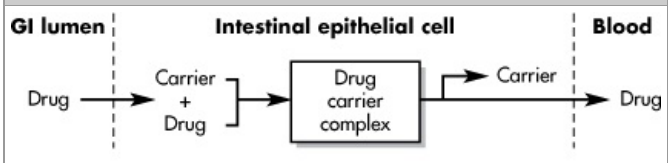
Carrier-Mediated Transport

Theoretically, a lipophilic drug may pass through the cell or go around it. If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption. In the intestine, drugs and other molecules can go through the intestinal epithelial cells by either diffusion or a carrier-mediated mechanism. Numerous specialized carrier-mediated transport systems are present in the body, especially in the intestine for the absorption of ions and nutrients required by the body.

ACTIVE TRANSPORT

Active transport is a carrier-mediated transmembrane process that plays an important role in the gastrointestinal absorption and in renal and biliary secretion of many drugs and metabolites. A few lipid-insoluble drugs that resemble natural physiologic metabolites (such as 5-fluorouracil) are absorbed from the gastrointestinal tract by this process. Active transport is characterized by the transport of drug against a concentration gradient—that is, from regions of low drug concentrations to regions of high concentrations. Therefore, this is an energy-consuming system. In addition, active transport is a specialized process requiring a carrier that binds the drug to form a carrier–drug complex that shuttles the drug across the membrane and then dissociates the drug on the other side of the membrane ().

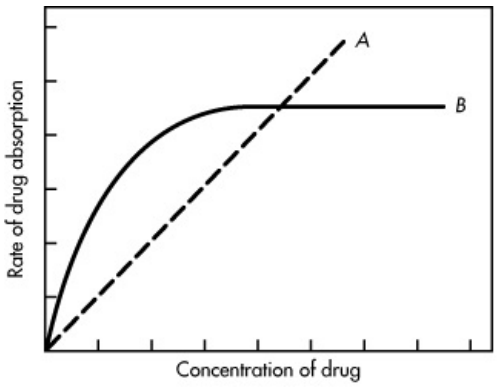
Figure 13-5.



Hypothetical carrier-mediated transport process.

The carrier molecule may be highly selective for the drug molecule. If the drug structurally resembles a natural substrate that is actively transported, then it is likely to be actively transported by the same carrier mechanism. Therefore, drugs of similar structure may compete for sites of adsorption on the carrier. Furthermore, because only a fixed number of carrier molecules are available, all the binding sites on the carrier may become saturated if the drug concentration gets very high. A comparison between the rate of drug absorption and the concentration of drug at the absorption site is shown in . Notice that for a drug absorbed by passive diffusion, the rate of absorption increases in a linear relationship to drug concentration. In contrast, when a drug is absorbed by a carrier-mediated process, the rate of drug absorption increases with drug concentration until the carrier molecules are completely saturated. At higher drug concentrations, the rate of drug absorption remains constant, or zero order.

Figure 13-6.



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Comparison of the rates of drug absorption of a drug absorbed by passive diffusion (line *A*) and a drug absorbed by a carrier-mediated system (line *B*).

FACILITATED DIFFUSION

Facilitated diffusion is also a carrier-mediated transport system, differing from active transport in that the drug moves along a concentration gradient (ie, moves from a region of high drug concentration to a region of low drug concentration). Therefore, this system does not require energy input. However, because this system is carrier mediated, it is saturable and structurally selective for the drug and shows competition kinetics for drugs of similar structure. In terms of drug absorption, facilitated diffusion seems to play a very minor role.

CARRIER-MEDIATED INTESTINAL TRANSPORT

Various carrier-mediated systems (transporters) are present at the intestinal brush border and basolateral membrane for the absorption of specific ions and nutrients essential for the body (). Many drugs are absorbed by these carriers because of the structural similarity to natural substrates (). A transmembrane protein, P-glycoprotein (Pgp), has been identified in the intestine. Pgp appears to reduce apparent intestinal epithelial cell permeability from lumen to blood for various lipophilic or cytotoxic drugs and is discussed in more detail below. Other transporters are also present in the intestines (). For example, many oral cephalosporins are absorbed through the amino acid transporter. Cefazolin, a parenteral-only cephalosporin, is not available orally because it cannot be absorbed to a significant degree through this mechanism.

Table 13.3 Intestine Transporters and Examples of Drugs Transported

Transporter	Examples	
Amino acid transporter	Gabapentin	D-Cycloserine
	Methyldopa	Baclofen
Oligopeptide transporter	L-dopa Cefadroxil	 Cephradine
	Cefixime	Ceftibuten
	Cephalexin	Captopril
	Lisinopril	Thrombin inhibitor
Phosphate transporter	Fostomycin	Foscarnet
Bile acid transporter	S3744	
Glucose transporter	*p*-Nitrophenyl-β-D-glucopyranoside	
P-glycoprotein efflux	Etoposide	Vinblastine
Monocarboxylic acid transporter	Cyclosporin A Salicylic acid	 Benzoic acid
	Pravastatin	

Adapted from .

Vesicular Transport

Vesicular transport is the process of engulfing particles or dissolved materials by the cell. Pinocytosis and phagocytosis are forms of vesicular transport that differ by the type of material ingested. *Pinocytosis* refers to the engulfment of small solutes or fluid, whereas *phagocytosis* refers to the engulfment of larger particles or macromolecules, generally by macrophages. *Endocytosis* and *exocytosis* are the processes of moving specific macromolecules into and out of a cell, respectively.

During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material and then engulfs the material, incorporating it into the cell (). Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell.

Vesicular transport is the proposed process for the absorption of orally administered Sabin polio vaccine and various large proteins.

Figure 13-7.

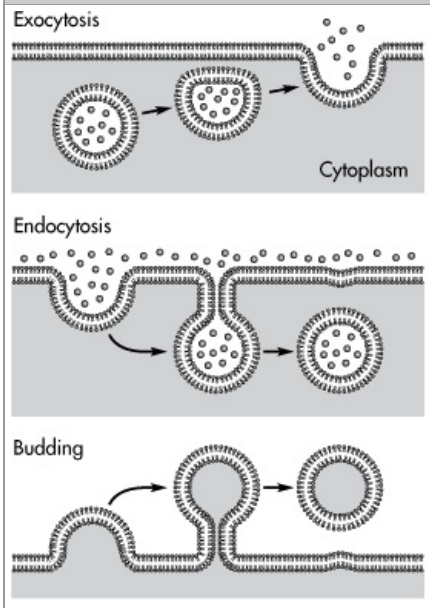

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Diagram showing exocytosis and endo-cytosis.

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An example of exocytosis is the transport of a protein such as insulin from insulin-producing cells of the pancreas into the extracellular space. The insulin molecules are first packaged into intracellular vesicles, which then fuse with the plasma membrane to release the insulin outside the cell.

Pore (Convective) Transport

Very small molecules (such as urea, water, and sugars) are able to cross cell membranes rapidly, as if the membrane contained channels or pores. Although such pores have never been directly observed by microscopy, the model of drug permeation through aqueous pores is used to explain renal excretion of drugs and the uptake of drugs into the liver.

A certain type of protein called a *transport protein* may form an open channel across the lipid membrane of the cell (). Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of the membrane.

Ion-Pair Formation

Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds with extreme pK_a values. Strong electrolyte drugs maintain their charge at all physiologic pH values and penetrate membranes poorly. When the ionized drug is linked up with an oppositely charged ion, an *ion pair* is formed in which the overall charge of the pair is neutral. This neutral drug complex diffuses more easily across the membrane. For example, the formation of ion pairs to facilitate drug absorption has been demonstrated for propranolol, a basic drug that forms an ion pair with oleic acid, and quinine, which forms ion pair with hexylsalicylate ().

An interesting application of ion pairs is the complexation of amphotericin B and DSPG (disteroylphosphatidylglycerol) in some amphotericin B/liposome products. Ion pairing may transiently alter distribution, reduce high plasma free drug concentration, and reduce renal toxicity.

ORAL DRUG ABSORPTION

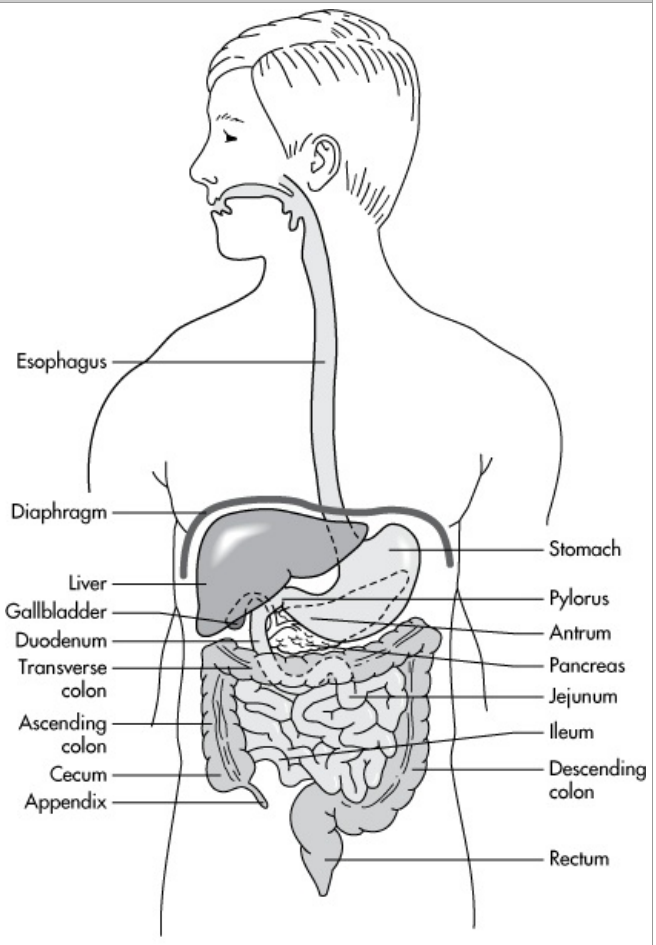
The oral route of administration is the most common and popular route of drug dosing. The oral dosage form must be designed to account for extreme pH ranges, the presence or absence of food, degradative enzymes, varying drug permeability in the different regions of the intestine, and motility of the gastrointestinal tract. In this chapter we will discuss intestinal variables that affect absorption; dosage-form considerations will be discussed in , , , and .

Anatomic and Physiologic Considerations

The normal physiologic processes of the alimentary canal may be affected by diet, contents of the gastrointestinal (GI) tract, hormones, the visceral nervous system, disease, and drugs. Thus, drugs given by the enteral route for systemic absorption may be affected by the anatomy, physiologic functions, and contents of the alimentary tract. Moreover, the physical, chemical, and pharmacologic properties of the drug itself will also affect its own absorption from the alimentary canal.

The *enteralsystem* consists of the alimentary canal from the mouth to the anus (). The major physiologic processes that occur in the GI system are secretion, digestion, and absorption. Secretion includes the transport of fluid, electrolytes, peptides, and proteins into the lumen of the alimentary canal. Enzymes in saliva and pancreatic secretions are also involved in the digestion of carbohydrates and proteins. Other secretions, such as mucus, protect the linings of the lumen of the GI tract. Digestion is the breakdown of food constituents into smaller structures in preparation for absorption. Food constituents are mostly absorbed in the proximal area (duodenum) of the small intestine. The process of absorption is the entry of constituents from the lumen of the gut into the body. Absorption may be considered as the net result of both lumen-to-blood and blood-to-lumen transport movements.

Figure 13-8.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Gastrointestinal tract.

Drugs administered orally pass through various parts of the enteral canal, including the oral cavity, esophagus, and various parts of the gastrointestinal tract. Residues eventually exit the body through the anus. The total transit time, including gastric emptying, small intestinal transit, and colonic transit, ranges from 0.4 to 5 days (). The most important site for drug absorption is the small intestine. Small intestine transit time (SITT) ranges from 3 to 4 hours for most healthy subjects. If absorption is not completed by the time a drug leaves the small intestine, absorption may be erratic or incomplete. The small intestine is normally filled with digestive juices and liquids, keeping the lumen contents fluid. In contrast, the fluid in the colon is reabsorbed, and the lumenal content in the colon is either semisolid or solid, making further drug dissolution erratic and difficult. The lack of the solubilizing effect of the chyme and digestive fluid contributes to a less favorable environment for drug absorption.

ORAL CAVITY

Saliva is the main secretion of the oral cavity, and it has a pH of about 7. Saliva contains ptyalin (salivary amylase), which digests starches. Mucin, a glycoprotein that lubricates food, is also secreted and may interact with drugs. About 1500 mL of saliva is secreted per day.

ESOPHAGUS

The esophagus connects the pharynx and the cardiac orifice of the stomach. The pH of the fluids in the esophagus is between 5 and 6. The lower part of the esophagus ends with the esophageal sphincter, which prevents acid reflux from the stomach. Tablets or capsules may lodge in this area, causing local irritation. Very little drug dissolution occurs in the esophagus.

STOMACH

The stomach is innervated by the vagus nerve. However, local nerve plexus, hormones, mechanoreceptors sensitive to the stretch of the GI wall, and chemoreceptors control the regulation of gastric secretions, including acid and stomach emptying. The fasting pH of the stomach is about 2 to 6. In the presence of food, the stomach pH is about 1.5 to 2, due to hydrochloric acid secreted by parietal cells. Stomach acid secretion is stimulated by gastrin and histamine. Gastrin is released from G cells, mainly in the antral mucosa and also in the duodenum. Gastrin release is regulated by stomach distention (swelling) and the presence of peptides and amino acids. A substance called intrinsic factor for vitamin B-12 absorption and various gastric enzymes, such as pepsin, which initiates protein digestion, are secreted into the gastric lumen to initiate digestion.

Basic drugs are solubilized rapidly in the presence of stomach acid. Mixing is intense and pressurized in the antral part of the stomach, a process of breaking down large food particles described as *antral milling*. Food and liquid are emptied by opening the pyloric sphincter into the duodenum. Stomach emptying is influenced by the food content and osmolality. Fatty acids and mono- and diglycerides delay gastric emptying (). High-density foods generally are emptied from the stomach more slowly. The relation of gastric emptying time to drug absorption is discussed more fully in the next section.

DUODENUM

A common duct from the pancreas and the gallbladder enters into the duodenum. The duodenal pH is about 6 to 6.5, because of the presence of bicarbonate that neutralizes the acidic chyme emptied from the stomach. The pH is optimum for enzymatic digestion of protein and peptide food. Pancreatic juice containing enzymes is secreted into the duodenum from the bile duct. Trypsin, chymotrypsin, and carboxypeptidase are involved in the hydrolysis of proteins into amino acids. Amylase is involved in the digestion of carbohydrates. Pancreatic lipase secretion hydrolyzes fats into fatty acid. The complex fluid medium in the duodenum helps to dissolve many drugs with limited aqueous solubility.

The duodenum is a site where many ester prodrugs are hydrolyzed during absorption. The presence of proteolytic enzymes also makes many protein drugs unstable in the duodenum, preventing adequate absorption.

JEJUNUM

The jejunum is the middle portion of the small intestine, between the duodenum and the ileum. Digestion of protein and carbohydrates continues after addition of pancreatic juice and bile in the duodenum. This portion of the small intestine generally has fewer contractions than the duodenum and is preferred for *in-vivo* drug absorption studies.

ILEUM

The ileum is the terminal part of the small intestine. This site has fewer contractions than the duodenum and may be blocked off by catheters with an inflatable balloon and perfused for drug absorption studies. The pH is about 7, with the distal part as high as 8. Due to the presence of bicarbonate secretion, acid drugs will dissolve. Bile secretion helps to dissolve fats and hydrophobic drugs. The ileocecal valve separates the small intestine from the colon.

COLON

The colon lacks villi and has limited drug absorption also, because of the more viscous and semisolid nature of the lumen contents. The colon is lined with mucin that functions as lubricant and protectant. The pH in this region is 5.5 to 7 (). A few drugs, such as theophylline and metoprolol, are absorbed in this region. Drugs that are absorbed well in this region are good candidates for an oral sustained-release dosage form. The colon contains both aerobic and anaerobic microorganisms that may metabolize some drugs. For example, L-dopa and lactulose are metabolized by enteric bacteria. Crohn's disease affects the colon and thickens the bowel wall. The microflora also become more anaerobic. Absorption of clindamycin and propranolol are increased, whereas other drugs have reduced absorption with this disease ().

RECTUM

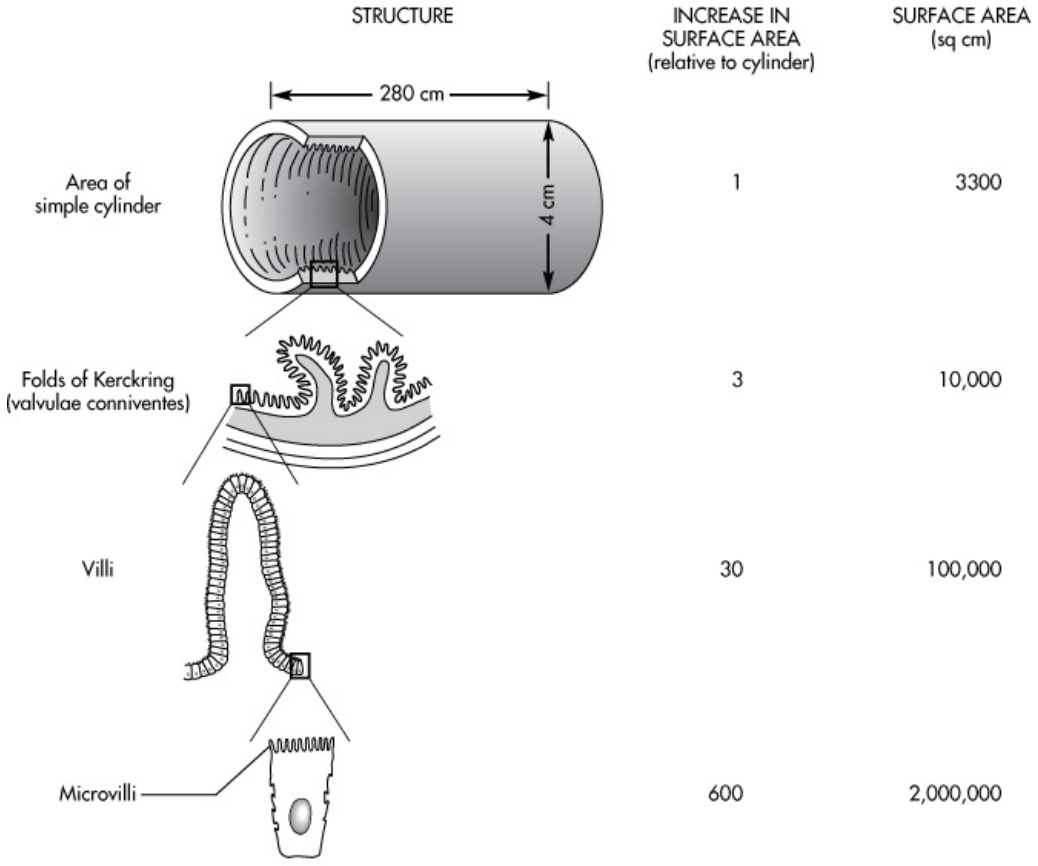
The rectum is about 15 cm long, ending at the anus. In the absence of fecal material, the rectum has a small amount of fluid (approximately 2 mL) with a pH about 7. The rectum is perfused by the superior, middle, and inferior hemorrhoidal veins. The inferior hemorrhoidal vein (closest to the anal sphincter) and the middle hemorrhoidal vein feed into the vena cava and back to the heart. The superior hemorrhoidal vein joins the mesenteric circulation, which feeds into the hepatic portal vein and then to the liver.

Drug absorption after rectal administration may be variable, depending on the placement of the suppository or drug solution within the rectum. A portion of the drug dose may be absorbed via the lower hemorrhoidal veins, from which the drug feeds directly into the systemic circulation; some drugs may be absorbed via the superior hemorrhoidal vein, which feeds into the mesenteric veins to the hepatic portal vein to the liver, and be metabolized before systemic absorption.

Drug Absorption in the Gastrointestinal Tract

Drugs may be absorbed by passive diffusion from all parts of the alimentary canal including sublingual, buccal, GI, and rectal absorption. For most drugs, the optimum site for drug absorption after oral administration is the upper portion of the small intestine or duodenum region. The unique anatomy of the duodenum provides an immense surface area for the drug to diffuse passively (). The large surface area of the duodenum is due to the presence of valvelike folds in the mucous membrane on which are small projections known as *villi*. These villi contain even smaller projections known as *microvilli,* forming a brush border. In addition, the duodenal region is highly perfused with a network of capillaries, which helps to maintain a concentration gradient from the intestinal lumen and plasma circulation.

Figure 13-9.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Three mechanisms for increasing surface area of the small intestine. The increase in surface area is due to folds of Kerkring, villi, and microvilli.

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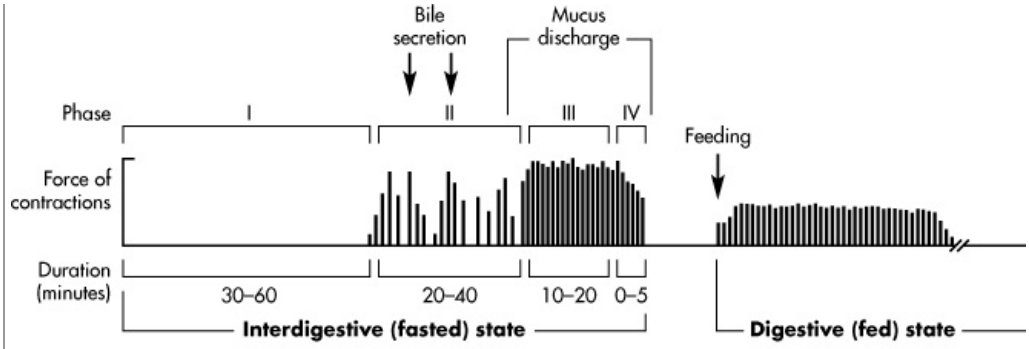
GASTROINTESTINAL MOTILITY

Once a drug is given orally, the exact location and/or environment of the drug product within the GI tract is difficult to discern. GI motility tends to move the drug through the alimentary canal, so the drug may not stay at the absorption site. For drugs given orally, an anatomic absorption window may exist within the GI tract in which the drug is efficiently absorbed. Drugs contained in a nonbiodegradable controlled-release dosage form must be completely released into this absorption window to be absorbed before the movement of the dosage form into the large bowel.

The transit time of the drug in the GI tract depends on the physiochemical and pharmacologic properties of the drug, the type of dosage form, and various physiologic factors. Physiologic movement of the drug within the GI tract depends on whether the alimentary canal contains recently ingested food (digestive or fed state) or is in the fasted or interdigestive state (). During the fasted or interdigestive state, alternating cycles of activity known as the *migrating motor complex* (MMC) act as a propulsive movement that empties the upper GI tract to the cecum. Initially, the alimentary canal is quiescent. Then, irregular contractions followed by regular contractions with high amplitude (housekeeper waves) push any residual contents distally or farther down the alimentary canal. In the fed state, the migrating motor complex is replaced by irregular contractions, which have the effect of mixing intestinal contents and advancing the intestinal stream toward the colon in short segments (). The pylorus and ileocecal valves prevent regurgitation or movement of food from the distal to the proximal direction.

Figure 13-10.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

A pictorial representation of the typical motility patterns in the interdigestive (fasted) and digestive (fed) state.

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Table 13.4 Characteristics of the Motility Patterns in the Fasted Dog

Phase	Duration	Characteristics
Fasted State		
I	30–60 min	Quiescence.
II	20–40 min	• Irregular contractions.
		• Medium amplitude but can be as high as phase III.
		• Bile secretion begins.
		• Onset of gastric discharge of administered fluid of small volume usually occurs before that of particle discharge.
		• Onset of particle and mucus discharge may occur during the latter part of phase II.
III	5–15 min	• Regular contractions (4–5 contractions/min) with high amplitude. • Mucus discharge continues.
		• Particle discharge continues.
IV	0–5 min	• Irregular contractions.
		• Medium descending amplitude.
		• Sometimes absent.
Fed State One phase only	As long as food is present in the stomach	• Regular, frequent contractions.
		• Amplitude is lower than phase III.
		• 4–5 Contractions/min.

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GASTRIC EMPTYING TIME

Anatomically, a swallowed drug rapidly reaches the stomach. Eventually, the stomach empties its contents into the small intestine. Because the duodenum has the greatest capacity for the absorption of drugs from the GI tract, a delay in the gastric emptying time for the drug to reach the duodenum will slow the rate and possibly the extent of drug absorption, thereby prolonging the onset time for the drug. Some drugs, such as penicillin, are unstable in acid and decompose if stomach emptying is delayed. Other drugs, such as aspirin, may irritate the gastric mucosa during prolonged contact.

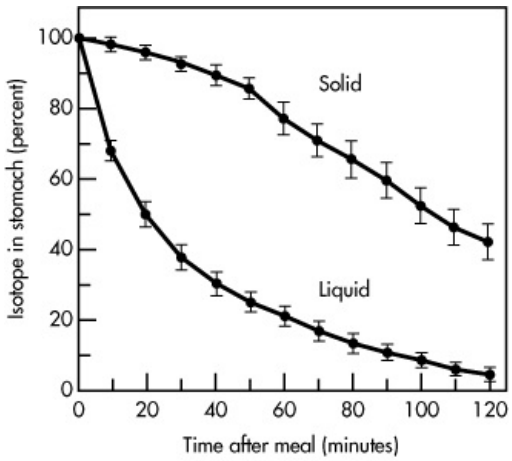
A number of factors affect gastric emptying time (). Some factors that tend to delay gastric emptying include consumption of meals high in fat, cold beverages, and anticholinergic drugs (;). Liquids and small particles less than 1 mm are generally not retained in the stomach. These small particles are believed to be emptied due to a slightly higher basal pressure in the stomach over the duodenum. Different constituents of a meal empty from the stomach at different rates. Feldman and associates (1984) observed that 10 oz of liquid soft drink, scrambled egg (digestible solid), and a radio-opaque marker (undigestible solid) were 50% emptied from the stomach in 30 minutes, 154 minutes, and 3 to 4 hours, respectively. Thus, liquids are generally emptied faster than digested solids from the stomach ().

Table 13.5 Factors Influencing Gastric Emptying

	Factor	Influence on Gastric Emptying
1.	Volume	The larger the starting volume, the greater the initial rate of emptying, after this initial period, the larger the original volume, the slower the rate of emptying.
2.	Type of meal	
	Fatty acids	Reduction in rate of emptying is in direct proportion to their concentration and carbon chain length; little difference is detected from acetic to octanoic acids; major inhibitory influence is seen in chain lengths greater than 10 carbons (decanoic to stearic acids).
	Triglycerides	Reduction in rate of emptying; unsaturated triglycerides are more effective than saturated ones; the most effective in reducing emptying rate were linseed and olive oils.
	Carbohydrates	Reduction in rate emptying, primarily as a result of osmotic pressure; inhibition of emptying increases as concentration increases.
	Amino acids	Reduction in rate of emptying to an extent directly dependent upon concentration, probably as a result of osmotic pressure.
3.	Osmotic pressure	Reduction in rate of emptying to an extent dependent upon concentration for salts and nonelectrolytes: rate of emptying may increase at lower concentrations and then decrease at higher concentrations.
4.	Physical state of gastric contents	Solutions or suspensions of small particles empty more rapidly than do chunks of material that must be reduced in size prior to emptying.
5.	Chemicals	
	Acids	Reduction in rate of emptying dependent upon concentration and molecular weight of the acid; lower molecular weight acids are more effective than those of higher molecular weight (in order of decreasing effectiveness: HCl, acetic, lactic, tartaric, citric acids).
	Alkali ($NaHCO_3$)	Increased rate of emptying at low concentrations (1%), and decreased rate at higher concentrations (5%).
6.	Drugs	
	Anticholinergics	Reduction in rate of emptying.
	Narcotic analgesics	Reduction in rate of emptying.
	Metoclopramide	Increase in rate of emptying.
	Ethanol	Reduction in rate of emptying.
7.	Miscellaneous	
	Body position	Rate of emptying is reduced in a patient lying on left side.
	Viscosity	Rate of emptying is greater for less viscous solutions.
	Emotional states	Aggressive or stressful emotional states increase stomach contractions and emptying rate; depression reduces stomach contraction and emptying.
	Bile salts	Rate of emptying is reduced.
	Disease states	Rate of emptying is reduced in some diabetics and in patients with local pyloric lesions (duodenal or pyloric ulcers; pyloric stenosis) and hypothyroidism; gastric emptying rate is increased in hyperthyroidism.
	Exercise	Vigorous exercise reduces emptying rate.
	Gastric surgery	Gastric emptying difficulties can be a serious problem after surgery.

From , with permission.

Figure 13-11.



Gastric emptying of a group of normal subjects using the dual-isotope method. The mean and 1 SE of the fraction of isotope remaining in the stomach are depicted at various time intervals after ingestion of the meal. Note the exponential nature of liquid emptying and the linear process of solid emptying.

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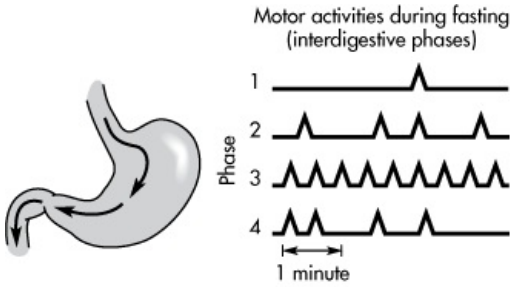
Large particles, including tablets and capsules, are delayed from emptying for 3 to 6 hours by the presence of food in the stomach. Indigestible solids empty very slowly, probably during the interdigestive phase, a phase in which food is not present and the stomach is less motile but periodically empties its content due to housekeeper wave contraction ().

Figure 13-12.



Motor activity responsible for gastric emptying of indigestible solids. Migrating myoelectric complex (MMC), usually initiated at proximal stomach or lower esophageal sphincter, and contractions during phase 3 sweep indigestible solids through open pylorus.

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INTESTINAL MOTILITY

Normal peristaltic movements mix the contents of the duodenum, bringing the drug particles into intimate contact with the intestinal mucosal cells. The drug must have a sufficient time (*residence time*) at the absorption site for optimum absorption. In the case of high motility in the intestinal tract, as in diarrhea, the drug has a very brief residence time and less opportunity for adequate absorption.

The average normal small intestine transit time (SITT) was about 7 hours in early studies using indirect methods based on the detection of hydrogen after an oral dose of lactulose (fermentation of lactulose by colon bacteria yields hydrogen in the breath). Newer studies using gamma scintigraphy have shown SITT to be about 3 to 4 hours. Thus a drug may take about 4 to 8 hours to pass through the stomach and small intestine during the fasting state. During the fed state, SITT may take 8 to 12 hours. For modified-release or controlled-dosage forms, which slowly release the drug over an extended period of time, the dosage form must stay within a certain segment of the intestinal tract so that the drug contents are released and absorbed before loss of the dosage form in the feces. Intestinal transit is discussed further in relation to the design of sustained-release products in .

In one study reported by , utilizing a radioopaque marker, mean mouth-to-anus transit time was 53.3 hours. The mean colon transit time was 35 hours, with 11.3 hours for the right (ascending transverse portion), 11.4 hours for the left (descending and portion of the transverse), and 12.4 hours for the rectosigmoid colon. Dietary fiber has the greatest effect on colonic transit. Dietary fiber increases fecal weight, partly by retaining water and partly by increasing bacterial mass ().

PERFUSION OF THE GASTROINTESTINAL TRACT

The blood flow to the GI tract is important in carrying absorbed drug to the systemic circulation. A large network of capillaries and lymphatic vessels perfuse the duodenal region and peritoneum. The splanchnic circulation receives about 28% of the cardiac output and is increased after meals. Once the drug is absorbed from the small intestine, it enters via the mesenteric vessels to the hepatic-portal vein and the liver prior to reaching the systemic circulation. Any decrease in mesenteric blood flow, as in the case of congestive heart failure, will decrease the rate of drug removal from the intestinal tract, thereby reducing the rate of drug bioavailability ().

The role of the lymphatic circulation in drug absorption is well established. Drugs are absorbed through the lacteal or lymphatic vessels under the microvilli. Absorption of drugs through the lymphatic system bypasses the first-pass effect due to liver metabolism, because drug absorption through the hepatic-portal vein is avoided. The lymphatics are important in the absorption of dietary lipids and may be partially responsible for the absorption for some lipophilic drugs. Many poorly water-soluble drugs are soluble in oil and lipids, which may dissolve in chylomicrons and be absorbed systemically via the lymphatic system. Bleomycin or aclarubicin were prepared in chylomicrons to improve oral absorption through the lymphatic system (,).

EFFECT OF FOOD ON GASTROINTESTINAL DRUG ABSORPTION

The presence of food in the GI tract can affect the bioavailability of the drug from an oral drug product (). Digested foods contain amino acids, fatty acids, and many nutrients that may affect intestinal pH and solubility of drugs. The effects of food are not always predictable and can have clinically significant consequences. Some effects of food on the bioavailability of a drug from a drug product include ():

- Delay in gastric emptying
- Stimulation of bile flow
- A change in the pH of the GI tract
- An increase in splanchnic blood flow
- A change luminal metabolism of the drug substance
- Physical or chemical interaction of the meal with the drug product or drug substance

Table 13.6 Drugs with Absorption Reduced, Delayed, Increased, or Not Affected by the Presence of Food

Reduced	Delayed	Increased	Not Affected
Amoxicillin	Acetaminophen	Canrenone	Cephradine
Ampicillin	Amoxicillin	Dicoumarol	Chlorpropamide
Aspirin	Aspirin	Griseofulvin	Digoxin (elixir)
Demethylchlortetracycline	Cefaclor	Hydralazine	Glibenclamide
Ethanol	Cephalexin	Hydrochlorothiazide	Glipizide
Isoniazid	Cephradine	Metoprolol	Melperone
Levodopa	Digoxin (solid)	Oxazepam	Metronidazole
Furosemide	Nitrofurantoin	Phenytoin	Penicillin V (acid)
Methacycline	Potassium ion	Propoxyphene	Prednisone
Oxytetracycline	Sulfadiazine	Propranolol	Propylthiouracil
Penicillin G	Sulfadimethoxine	Metaxalone	Theophylline
Penicillin V (K)	Sulfanilamide	**Slightly Increased**	
Penicillin V (Ca)	Sulfisoxazole	Hetacillin	
Penicillin V (acid)			
Phenacetin			
Phenethicillin			
Phenylmercaptomethyl-penicillin			
Pivampicillin			
Propantheline			
Rifampin			
Tetracycline			
Slightly Reduced			
Doxycycline			

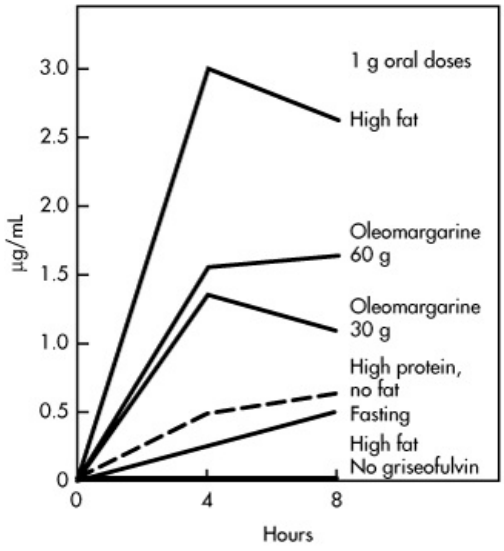
From , with permission.

Food effects on bioavailability are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiologic changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general,

meals that are high in total calories and fat content are more likely to affect GI physiology and thereby result in a larger effect on the bioavailability of a drug substance or drug product. The FDA recommends the use of high-calorie and high-fat meals to study the effect of food on the bioavailability and bioequivalence of drug products. ()

The absorption of some antibiotics, such as penicillin and tetracycline, is decreased with food; whereas other drugs, particularly lipid-soluble drugs such as griseofulvin and metazalone, are better absorbed when given with food containing a high fat content (). The presence of food in the GI lumen stimulates the flow of bile. Bile contains bile acids, which are surfactants involved in the digestion and solubilization of fats, and also increases the solubility of fat-soluble drugs through micelle formation. For some basic drugs (eg, cinnarizine) with limited aqueous solubility, the presence of food in the stomach stimulates hydrochloric acid secretion, which lowers the pH, causing more rapid dissolution of the drug and better absorption. Absorption of this basic drug is reduced when gastric acid secretion is reduced ().

Figure 13-13.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

A comparison of the effects of different types of food intake on the serum griseofulvin levels following a 1.0-g oral dose.

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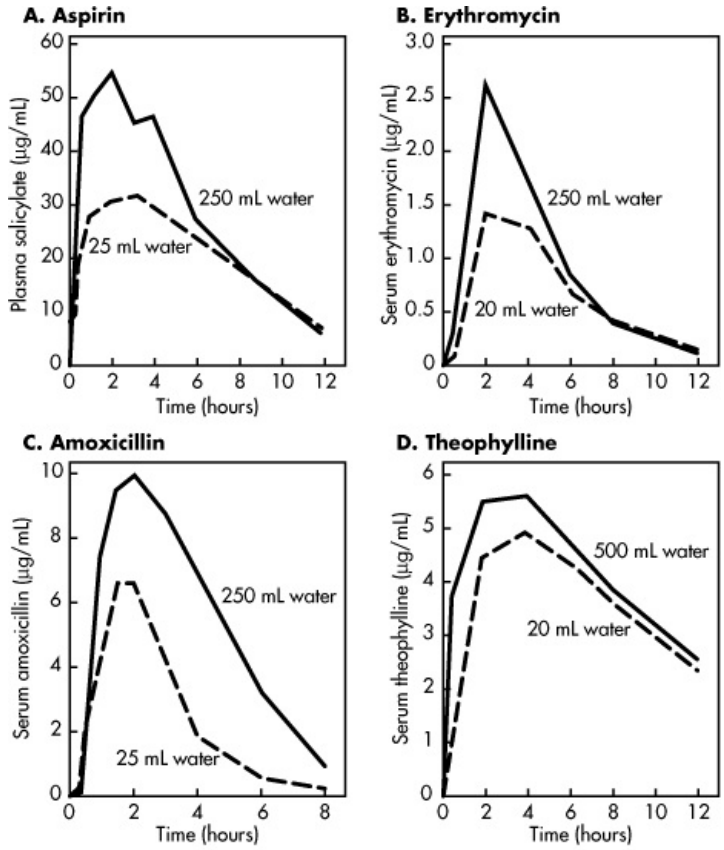
Most drugs should be taken with a full glass (approximately 8 fluid ounces) of water to ensure that drugs will wash down the esophagus. Generally, the bioavailability of drugs is better in patients in the fasted state and with a large volume of water (). The solubility of many drugs is limited, and sufficient fluid is necessary for dissolution of the drug. Some patients may be on several drugs that are dosed frequently for months. These patients are often nauseous and are reluctant to take a lot of fluid. For example, HIV patients with active viral counts may be on an AZT or DDI combination with one or more of the protease inhibitors, Invirase (Hoffmann-La Roche), Crixivan (Merck), or Norvir (Abbott). These HIV treatments appear to be better than any previous treatments but depend on patient compliance in taking up to 12 to 15 pills daily for weeks. Any complications affecting drug absorption can influence the outcome of these therapies. With antibiotics, unabsorbed drug may influence the GI flora. For drugs that cause GI disturbances, residual drug dose in the GI tract can potentially aggravate the incidence of diarrhea.

Figure 13-14.



Mean plasma or serum drug levels in healthy, fasting human volunteers (n = 6 in each case) who received single oral doses of aspirin (650-mg) tablets, erythromycin stearate (500-mg) tablets, amoxicillin (500-mg) capsules, and theophylline (260-mg) tablets, together with large and small accompanying volumes of water.

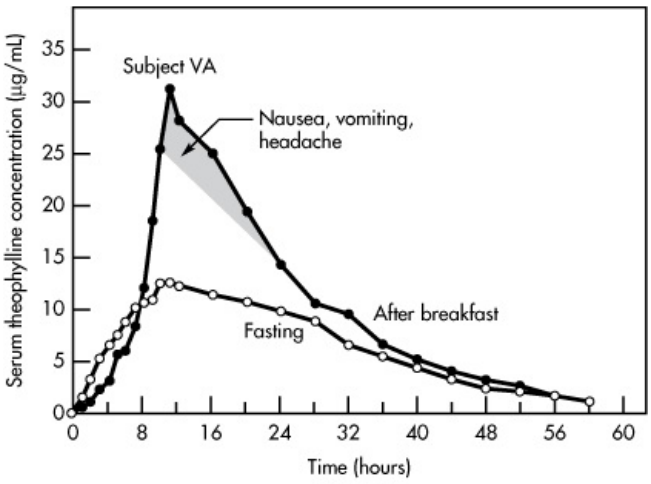
()

Some drugs, such as erythromycin, iron salts, aspirin, and nonsteroidal anti-inflammatory agents (NSAIDs), are irritating to the GI mucosa and are given with food to reduce this irritation. For these drugs, the rate of absorption may be reduced in the presence of food, but the extent of absorption may be the same and the efficacy of the drug is retained.

The GI transit time for enteric-coated and nondisintegrating drug products may also be affected by the presence of food. Enteric-coated tablets may stay in the stomach for a longer period of time because food delays stomach emptying. Thus, the enteric-coated tablet does not reach the duodenum rapidly, delaying drug release and systemic drug absorption. In contrast, since enteric-coated beads or microparticles disperse in the stomach, stomach emptying of the particles is less affected by food, and these preparations demonstrate more consistent drug absorption from the duodenum. The presence of food may delay stomach emptying of enteric-coated tablets or nondisintegrating dosage forms for several hours. Fine granules (smaller than 1 to 2 mm in size) and tablets that disintegrate are not significantly delayed from emptying from the stomach in the presence of food.

Food can also affect the integrity of the dosage form, causing an alteration in the release rate of the drug. For example, theophylline bioavailability from Theo-24 controlled-release tablets is much more rapid when given to a subject in the fed rather than fasted state because of dosage form failures, known as dose-dumping. (.)

Figure 13-15.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Theophylline serum concentrations in an individual subject after a single 1500-mg dose of Theo-24 taken during fasting and after breakfast. The shaded area indicates the period during which this patient experienced nausea, repeated vomiting, or severe throbbing headache. The pattern of drug release during the food regimen is consistent with "dose dumping."

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Food may enhance the absorption of a drug beyond 2 hours after meals. For example, the timing of a fatty meal on the absorption of cefpodoxime proxetil was studied in 20 healthy adults (). The area under the plasma concentration–time curve and peak drug concentration were significantly higher after administration of cefpodoxime proxetil tablets with a meal and 2 hours after a meal relative to dosing under fasted conditions or 1 hour before a meal. The time to peak concentration was not affected by food, which suggests that food increased the extent but not the rate of drug absorption. These results indicate that absorption of cefpodoxime proxetil is enhanced with food or if the drug is taken closely after a heavy meal.

Timing of drug administration in relation to meals is often important. Pharmacists regularly advise patients to take a medication either 1 hour before or 2 hours after meals to avoid any delay in drug absorption. Since fatty foods may delay stomach emptying time beyond 2 hours, patients who have just eaten a heavy, fatty meal should take these drugs 3 hours or more after the meal, whenever possible. Products that are used to curb stomach acid secretion are usually taken before meals, in anticipation of acid secretion stimulated by food. Famotidine (Pepcid), and cimetidine (Tagamet) are taken before meals to curb excessive acid production.

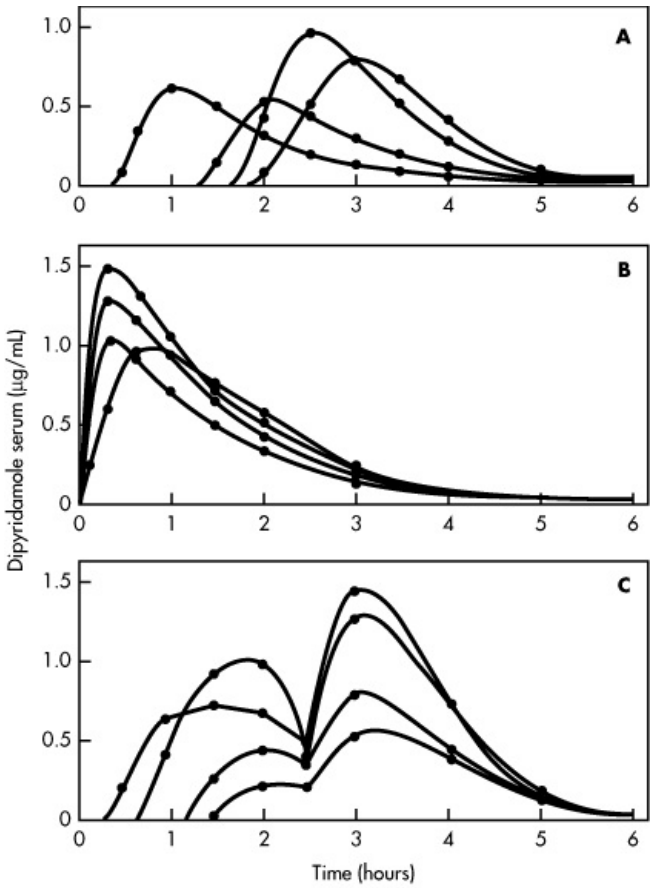
Fluid volume tends to distend the stomach and speed up stomach emptying; however, large volume of nutrients with high caloric content supersedes that faster rate and delays stomach emptying time. Reduction in drug absorption may be caused by several factors. For example, tetracycline hydrochloride absorption is reduced by milk and food that contains calcium, due to tetracycline chelation. However, significant reduction in absorption may simply be the result of reduced dissolution due to increased pH. Co-administration of sodium bicarbonate raises the stomach pH and reduces tetracycline dissolution and absorption ().

Ticlopidine (Ticlid) is an antiplatelet agent that is commonly used to prevent thromboembolic disorders. Ticlopidine has enhanced absorption after a meal. The absorption of ticlopidine was compared in subjects who received either an antacid or food or were in a control group (fasting). Subjects who received ticlopidine 30 minutes after a fatty meal had an average of 20% increase in plasma concentration over fasting subjects, whereas antacid reduced ticlopidine plasma concentration by approximately the same amount. There was a higher gastrointestinal complaint in the fasting group. Many other drugs have reduced gastrointestinal side effects when taken with food. The decreased gastrointestinal side effects associated with food consumption may greatly improve tolerance and compliance in patients.

DOUBLE-PEAK PHENOMENON

Some drugs, such as ranitidine, cimetidine, and dipyridamole, after oral administration produce a blood concentration curve consisting of two peaks (). This double-peak phenomenon is generally observed after the administration of a single dose to fasted patients. The rationale for the double-peak phenomenon has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic recycling, or failure of a tablet dosage form.

Figure 13-16.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Serum concentrations of dipyridamole in three groups of four volunteers each. **A.** After taking 25 mg as tablet intact. **B.** As crushed tablet. **C.** As tablet intact 2 hours before lunch.

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The double-peak phenomenon observed for cimetidine () may be due to variability in stomach emptying and intestinal flow rates during the entire absorption process after a single dose. For many drugs, very little absorption occurs in the stomach. For a drug with high water solubility, dissolution of the drug occurs in the stomach, and partial emptying of the drug into the duodenum will result in the first absorption peak. A delay in stomach emptying results in a second absorption peak as the remainder of the dose is emptied into the duodenum.

In contrast, ranitidine () produces a double peak after both oral or parenteral (IV bolus) administration. Ranitidine is apparently concentrated in the bile within the gallbladder from the general circulation after IV administration. When stimulated by food, the gallbladder contracts and bile containing drug is released into the small intestine. The drug is then reabsorbed and recycled (enterohepatic recycling).

Tablet integrity may also be a factor in the production of a double-peak phenomenon. compared a whole tablet or a crushed tablet of dipyridamole in volunteers and showed that a tablet that does not disintegrate or incompletely disintegrates may have delayed gastric emptying, resulting in a second absorption peak.

METHODS FOR STUDYING FACTORS THAT AFFECT DRUG ABSORPTION

Gamma Scintigraphy to Study Site of Drug Release

Gamma scintigraphy is a technique commonly used to track drug dosage form movement from one region to another within the GI tract after oral administration. Gamma scintigraphy also has many research applications and is widely used for formulation studies, such as the mechanism of drug release from a hydrophilic matrix tablet (). Generally a nonabsorbable radionuclide that emits gamma rays is included as marker in the formulation. In some studies, two radiolabels may be used for simultaneous detection of liquid and solid phases. One approach is to use labeled technesium (Tc^{99m}) in a capsule matrix to study how a drug is absorbed. The image of the capsule breaking up in the stomach or the GI tract is monitored using a gamma camera. Simultaneously, blood levels or urinary excretion of the drug may be measured. This study can be used to correlate residence time of the drug in a given region after capsule breakup to drug absorption. The same technique is used to study drug absorption mechanisms in different regions of the GI tract before a drug is formulated for extended release.

Gamma scintigraphy has been used to study the effect of transit time on the absorption of theophylline (). *In-vitro* drug release characteristics were correlated with total gastrointestinal transit time. The results showed a significant correlation between the *in-vitro* release of theophylline and the percent of the total amount of theophylline absorbed *in-vivo*. This study illustrates the

importance of gamma scintigraphy for the development of specialized drug dosage forms.

Markers to Study Effect of Gastric and GI Transit Time on Absorption

Many useful agents are available that may be used as tools to study absorption and understand the mechanism of the absorptive process. For example, mannitol has a concentration-dependent effect on small intestinal transit. showed that small concentrations of mannitol included in a pharmaceutical formulation could lead to reduced uptake of any drug absorbed exclusively from the small intestine. No significant differences between the gastric emptying times of the four solutions of different concentrations tested were observed.

Similarly, demonstrated that codeine slowed GI transit, decreased stool water content, and diminished drug absorption when compared to controls. The results indicated that stool water content may be an important determinant in colonic drug absorption. In contrast, the sugar lactulose accelerated GI transit, increased stool water content, and enhanced drug absorption from the distal gut. Quinine absorption was greater when given with lactulose compared to no lactulose.

studied the effects of gastric emptying and GI transit on the absorption of several drug solutions (furosemide, atenolol, hydrochlorothiazide, and salicylic acid) in healthy subjects. These drugs may potentially be absorbed differently at various sites in the GI system. Subjects were given 20 mg oral metoclopramide or 60 mg oral codeine phosphate to slow gastric emptying. The study showed that gastric emptying affects the absorption of salicylic acid, but not that of furosemide, hydrochlorothiazide or atenolol. *In-vivo* experiments are needed to determine the effect of changing transit time on drug absorption.

Remote Drug Delivery Capsules (RDDCs)

Drug absorption *in-vivo* may be studied either directly by an intubation technique that directly takes samples from the GI tract, or remotely with a special device, such as the Heidelberg capsule. The *Heidelberg capsule* () is a device used to determine the pH of the stomach. The capsule contains a pH sensor and a miniature radio transmitter (invented by H. G. Noeller and used at Heidelberg University in Germany decades ago). The capsule is about 2 cm x 0.8 cm and can transmit data to the outside after the device is swallowed and tethered to the stomach. Other, newer telemetric methods may be used to take pictures of various regions of the GI tract.

An interesting *remote drug delivery capsule* (RDDC) with electronic controls for noninvasive regional drug absorption study was recently reported by . This device was used to study absorption of ranitidine hydrochloride solution in 12 healthy male volunteers. Mean gastric emptying of the RDDC was 1.50 hours, and total small intestine transit was 4.79 hours. The capsule was retrieved from the feces at 30.25 hours. The onset of ranitidine serum levels depended on the time of capsule activation and the site of drug release.

Osmotic Pump Systems

The osmotic pump system is a drug product that contains a small hole from which dissolved drug is released (pumped out) at a rate determined by the rate of entrance of water from the GI tract across a semipermeable membrane due to osmotic pressure (). The drug is either mixed with an osmotic agent or is located in a reservoir. Osmotic pump systems may be used to study drug absorption in different parts of the GI tract because the rate of drug release is constant (zero order) and generally not altered by the environment of the gastrointestinal tract. The constant rate of drug release provides relatively constant blood concentrations.

In-Vivo GI Perfusion Studies

In the past, segments of guinea pig or rat ileums were cut and used to study drug absorption; however, we now know that many of the isolated preparations were not viable shortly after removal, making the absorption data collected either invalid or difficult to evaluate. In addition, the differences among species make it difficult to extrapolate animal data to humans.

GI perfusion is an *in-vivo* method used to study absorption and permeability of a drug in various segments of the GI tract. A tube is inserted from the mouth or anus and placed in a specific section of the GI tract. A drug solution is infused from the tube at a fixed rate, resulting in drug perfusion of the desired GI region. The jejunal site is peristaltically less active than the duodenum, making it easier to intubate, and therefore it is often chosen for perfusion studies. Perfusion studies in other sites such as the duodenum, ileum, and even the colon have also been performed by gastroenterologists and pharmaceutical scientists.

have applied perfusion techniques in humans to study permeability in the small intestine and the rectum. These methods yield direct absorption information in various segments of the GI tract. The regional jejunal perfusion method was reported to have great potential for mechanistic evaluations of drug absorption.

Intestinal Permeability to Drugs

Drugs that are completely absorbed ($F > 90\%$) after oral administration generally demonstrate high permeability in models *in-vitro*. Previously, poor drug absorption was mostly attributed to poor dissolution, slow diffusion, degradation, or poor intestinal permeation. Modern technology has shown that poor or variable oral drug bioavailability among individuals is also the result of individual genetic differences in intestinal absorption (). Interindividual differences in membrane proteins, ion channels, transporters, and antiporters (such as P-glycoprotein, P-gp) that mediate directional transport of drugs and their metabolites across biological membranes can change the extent of drug absorption, or even transport to the site of action elsewhere in the body. It is now clear that the behavior of drugs in the body is the result of an intricate interplay between these nuclear hormone receptors, drug transporters, and the drug-metabolizing systems. This insight provides another explanation for erratic drug absorption beyond poor formulation and first-pass metabolism.

Alternative methods to study intestinal drug permeability include *in-vivo* or *in-situ* intestinal perfusion in a suitable animal model (eg, rats), and/or *in-vitro* permeability methods using excised intestinal tissues, or monolayers of suitable epithelial cells such as

Caco-2 cells. In addition, the physicochemical characterization of a drug substance (eg, oil/water partition coefficient) provides useful information to predict a drug's permeability.

CACO-2 CELLS FOR *IN-VITRO* PERMEABILITY STUDIES

Although *in-vivo* studies yield much definitive information about drug permeability in humans, they are tedious and costly to perform. The *Caco-2* cell line is a human colon adenocarcinoma cell line that differentiates in culture and resembles the epithelial lining of the human small intestine. The permeability of the cellular monolayer may vary with the stage of cell growth and the cultivation method used. However, under controlled condition, using monolayers of Caco-2 cells, the permeability of a drug may be determined. Caco-2 cells can also be used to study interactions of drugs with the transporter P-glycoprotein discussed below.

Drug permeability using the Caco-2 cell line has been suggested as an *in-vitro* method for passively transported drugs. In some cases, the drug permeability may appear to be low due to efflux of drugs via membrane transporters such as P-glycoprotein (P-gp). Permeability studies using the Caco-2 cell line have been suggested as a method for classifying the permeability of a drug according to the Biopharmaceutics Classification System, BCS (;). The main purpose of the BCS classification is to classify a drug as having high or low permeability as a predictor of systemic drug absorption from the GI tract (see).

DRUG TRANSPORTERS

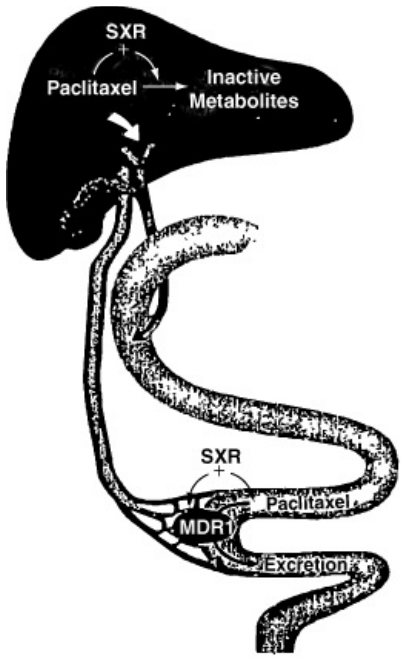
Several transport proteins are expressed in the intestinal epithelial cells. Although some transporters facilitate absorption, other transporters, such as P-glycoprotein may effectively inhibit drug absorption. P-gp, an energy-dependent, membrane-bound protein, is an *efflux transporter* that mediates the secretion of compounds from inside the cell back out into the intestinal lumen, thereby limiting overall absorption. Thus, drug absorption may be reduced or increased by the presence or absence of efflux proteins. The role of efflux proteins is generally believed to be a defense mechanism for the body to excrete and reduce drug accumulation.

P-glycoprotein is expressed also in other tissues such as the blood–brain barrier, liver, and kidney, where it limits drug penetration into the brain, mediates biliary drug secretion, and renal tubular drug secretion, respectively. Efflux pumps are present throughout the body and are involved in transport of a diverse group of hydrophobic drugs, natural products, and peptides. Many drugs and chemotherapeutic agents, such as cyclosporin A, verapamil, terfenadine, fexofenadine, and most HIV-1 protease inhibitors are substrates of P-gp (see). In addition, individual genetic differences in intestinal absorption may be the result of genetic differences in P-gp and other transporters.

Clinical Examples

Multidrug resistance (MDR) to cancer cells has been linked to efflux transporter proteins such as P-gp that either exclude or extrude chemotherapeutic agents from the cells (). Paclitaxel (Taxol) is an example of coordinated metabolism, efflux, and triggering of hormone nuclear receptor to induce efflux protein (). P-gp (see MDR1 in) is responsible for 85% of paclitaxel excretion back into the GI tract (). Paclitaxel induces the steroid xenobiotic receptor SXR (also known as PXR), which in turn activates MDR1 transcription and P-gp expression, resulting in even further excretion of paclitaxel into the intestinal fluid. Paclitaxel also induces CYP 3A4 and CYP2C8 transcription, resulting in increased paclitaxel metabolism. Thus, in response to a xenobiotic challenge, SXR can induce both a first line of defense (intestinal excretion) and a backup system (hepatic drug inactivation) that limits exposure to potentially toxic compounds. In contrast to paclitaxel, docetaxel is a closely related antineoplastic agent that does not activate SXR but has a much better absorption profile.

Figure 13.17



Mechanism of coordinated efflux and metabolism of paclitaxel by SXR.

()

Mutations of other transporters, particularly those involved in reuptake of serotonin, dopamine, and gamma-aminobutyric acid (GABA) are presently being studied with regard to clinically relevant changes in drug response. Pharmacogenetic variability in these transporters is an important consideration in patient dosing. When therapeutic failures occur, the following questions should be asked: (1) Is the drug a substrate for P-gp and/or CYP3A4? (2) Is the drug being co-administered with anything that inhibits either P-gp and/or CYP3A4? For example, grapefruit juice and many drugs can affect drug metabolism and oral absorption.

EFFECT OF DISEASE STATES ON DRUG ABSORPTION

Drug absorption may be affected by any disease that causes changes in (1) intestinal blood flow, (2) gastrointestinal motility, (3) changes in stomach emptying time, (4) gastric pH that affects drug solubility, (5) intestinal pH that affects the extent of ionization, (6) the permeability of the gut wall, (7) bile secretion, (8) digestive enzyme secretion, or (9) alteration of normal GI flora. Some factors may dominate, while other factors sometimes cancel the effects of each other. Pharmacokinetic studies comparing subjects with and without the disease are generally necessary to establish the effect of the disease on drug absorption. Several clinical examples are given below.

Patients in an advanced stage of *Parkinson's disease* may have difficulty swallowing and greatly diminished gastrointestinal motility. A case was reported in which the patient could not be controlled with regular oral levodopa medication because of poor absorption. Infusion of oral levodopa solution using a j-tube gave adequate control of his symptoms. The patient was subsequently placed on this mode of therapy.

Patients on tricyclic antidepressants (imiprimine, amitriptyline, and nortriptyline) and antipsychotic drugs (phenothiazines) with anticholinergic side effects may have reduced gastrointestinal motility or even intestinal obstructions. Delays in drug absorption, especially with slow-release products, have occurred.

Achlorhydricpatients may not have adequate production of acids in the stomach; stomach HCl is essential for solubilizing insoluble free bases. Many weak-base drugs that cannot form soluble salts will remain undissolved in the stomach when there is no hydrochloric acid present and are therefore unabsorbed. Salt forms of these drugs cannot be prepared because the free base readily precipitates out due to the weak basicity.

Dapsone, itraconazole, and ketoconazole may also be less well absorbed in the presence of achlorhydria. In patients with acid reflux disorders, proton pump inhibitors, such as omeprazole, render the stomach achlorhydric, which may also affect drug absorption. Co-administering orange juice, colas, or other acidic beverages can facilitate the absorption of some medications requiring an acidic environment.

HIV-AIDSpatients are prone to a number of gastrointestinal (GI) disturbances, such as increased gastric transit time, diarrhea, and achlorhydria. Rapid gastric transit time and diarrhea can alter the absorption of orally administered drugs. Achlorhydria may or may not decrease absorption, depending on the acidity needed for absorption of a specific drug. Indinavir, for example, requires a normal acidic environment for absorption. The therapeutic window of indinavir is extremely narrow, so optimal serum concentrations are critical for this drug to be efficacious.

Congestive heart failure (CHF) *patients* with persistent edema have reduced splanchnic blood flow and develop edema in the

bowel wall. In addition, intestinal motility is slowed. The reduced blood flow to the intestine and reduced intestinal motility results in a decrease in drug absorption. For example, furosemide (Lasix), a commonly used loop diuretic, has erratic and reduced oral absorption in patients with CHF and a delay in the onset of action.

Crohn's disease is an inflammatory disease of the distal small intestine and colon. The disease is accompanied by regions of thickening of the bowel wall, overgrowth of anaerobic bacteria, and sometimes obstruction and deterioration of the bowel. The effect on drug absorption is unpredictable, although impaired absorption may potentially occur because of reduced surface area and thicker gut wall for diffusion. For example, higher plasma propranolol concentration has been observed in patients with Crohn's disease after oral administration of propranolol. Alpha-1-acid glycoprotein level is increased in Crohn's disease patients. Higher alpha-1-acid glycoprotein may affect the protein binding and distribution of propranolol in the body and result in higher plasma concentration.

Celiac disease is an inflammatory disease affecting mostly the proximal small intestine. Celiac disease is caused by sensitization to gluten, a viscous protein found in cereals. Patients with celiac disease generally have an increased rate of stomach emptying and increased permeability of the small intestine. Cephalexin absorption appears to be increased in celiac disease, although it is not possible to make general predictions about these patients. Other intestinal conditions that may potentially affect drug absorption include corrective surgery involving peptic ulcer, antrectomy with gastroduodenostomy, and selective vagotomy.

Drugs that Affect Absorption of Other Drugs

Anticholinergic drugs in general may reduce stomach acid secretion. Propantheline bromide is an anticholinergic drug that may slow stomach emptying and motility of the small intestine. Tricyclic antidepressants and phenothiazines also have anticholinergic side effects that may cause slower peristalsis in the GI tract. Slower stomach emptying may cause delay in drug absorption.

Metoclopramide is a drug that stimulates stomach contraction, relaxes the pyloric sphincter, and, in general, increases intestinal peristalsis, which may reduce the effective time for the absorption of some drugs and thereby reduce the peak drug concentration and the time to reach peak drug concentration. For example, digoxin absorption from a tablet is reduced by metoclopramide but increased by an anticholinergic drug, such as propantheline bromide. Allowing more time in the stomach for the tablet to dissolve generally helps with the dissolution and absorption of a poorly soluble drug, but would not be helpful for a drug that is not soluble in stomach acid.

Antacids should not be given with cimetidine, because antacids may reduce drug absorption. Antacids containing aluminum, calcium, or magnesium may complex with drugs such as tetracycline, ciprofloxacin, and indinavir, resulting in a decrease in drug absorption. To avoid this interaction, antacids should be taken 2 hours before or 6 hours after drug administration. As mentioned, proton pump inhibitors, such as omeprazole, render the stomach achlorhydric, which may also affect drug absorption.

Cholestyramine is a nonabsorbable ion-exchange resin for the treatment of hyperlipemia. Cholestyramine adsorbs warfarin, thyroxine, and loperamide, similar to activated charcoal, thereby reducing absorption of these drugs.

Absorption of calcium in the duodenum is an active process facilitated by vitamin D, with calcium absorption as much as four times more than that in vitamin D deficiency states. It is believed that a calcium-binding protein, which increases after vitamin D administration, binds calcium in the intestinal cell and transfers it out of the base of the cell to the blood circulation.

Nutrients that Interfere with Drug Absorption

Many nutrients substantially interfere with the absorption or metabolism of drugs in the body (;). The effect of food on bioavailability was discussed earlier. Oral drug–nutrient interactions are often drug specific and can result in either an increase or decrease in drug absorption.

Absorption of water-soluble vitamins, such as vitamin B-12 and folic acid, are aided by special absorption mechanisms. Vitamin B-12 absorption is facilitated by intrinsic factors in the stomach, where it forms a complex with the factor and is carried in the intestinal stream to the ileum, where it binds to a specific receptor. Vitamin B-12 then ultimately disassociates from the complex and is absorbed.

Grapefruit juice often increases bioavailability, as observed by an increase in plasma levels of many drugs that are substrates for cytochrome P450 (CYP) 3A4 (see). Grapefruit juice contains various flavonoids such as naringin that inhibits certain cytochrome P-450 enzymes involved in drug metabolism. In this case, the observed increase in the plasma drug blood levels is due to decreased presystemic elimination in the GI tract and/or liver. Indirectly, the amount of drug absorbed systemically from the drug product is increased. Grapefruit juice can also block drug efflux by inhibiting P-gp for some drugs.

MISCELLANEOUS ROUTES OF DRUG ADMINISTRATION

For systemic drug absorption, the oral route is the easiest, safest, and most popular route of drug administration. Increasingly popular nonparenteral alternatives to oral drug delivery for systemic drug absorption include nasal, inhalation, and transdermal drug delivery. Nasal, inhalation, and topical drug delivery may also be used for local drug action.

Nasal Drug Delivery

Nasal drug delivery may be used for either local or systemic effects. Because the nasal region is richly supplied with blood vessels, nasal administration is also useful for systemic drug delivery. However, the total surface area in the nasal cavity is relatively small, retention time in the nasal cavity is generally short, and some drug may be swallowed. These factors may limit the nose's capacity for systemic delivery of drugs requiring large doses. Surfactants are often used to increase systemic penetration, although the effect of chronic drug exposure on the integrity of nasal membranes must also be considered. In general, a drug must be sufficiently lipophilic to cross the membranes of the nasal epithelium in order to be absorbed. Small molecules with balanced lipophilic and hydrophilic properties tend to be absorbed more easily. This observation poses a

challenge for nasal delivery of larger molecules such as proteins and peptides, which would benefit from delivery routes that avoid the degradative environment of the intestine. Dosage forms intended for nasal drug delivery include nasal drops, nasal sprays, aerosols, and nebulizers ().

Depending on the metabolic, absorption, and chemical profile of the drug, some drugs are rapidly absorbed through the nasal membrane and can deliver rapid therapeutic effect. Various hormones and insulin have been tested for intranasal delivery. In some cases the objective is to improve availability, and in other cases it is to reduce side effects. Vasopressin and oxytocin are older examples of drugs marketed as intranasal products. In addition, many opioids are known to be rapidly absorbed from the nasal passages and can deliver systemic levels of the drug almost as rapidly as an intravenous injection (). A common problem with nasal drug delivery is the challenge of developing a formulation with nonirritating ingredients. Many surfactants that facilitate absorption tend to be moderately or very irritating to the nasal mucosa.

Intranasal corticosteroids for treatment of allergic and perennial rhinitis have become more popular since intranasal delivery is believed to reduce the total dose of corticosteroid required. A lower dose also leads to minimization of side effects such as growth suppression. This logic has led to many second-generation corticosteroids such as beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide that are being considered for intranasal delivery (). However, the potential for growth suppression in children varies. In one study, beclomethasone dipropionate reduced growth in children, but mometasone furoate nasal spray used for 1 year showed no signs of growth suppression. Overall, the second-generation corticosteroid by nasal delivery have been concluded to cause minimal systemic side effects ().

Inhalation Drug Delivery

Inhalation drug delivery may also be used for local or systemic drug effects. The lung has a potential absorption surface of some 70 m^2, a much larger surface than the small intestine or nasal passages. When a substance is inhaled, it is exposed to membranes of the mouth or nose, pharynx, trachea, bronchi, bronchioles, alveolar sacs, and alveoli. The lungs and their associated airways are designed to remove foreign matter from the highly absorptive peripheral lung surfaces via mucociliary clearance. However, if compounds such as aerosolized drug can reach the peripheral region of the lung, absorption can be very efficient.

Particle (droplet) size and velocity of application control the extent to which inhaled substances penetrate into airway spaces. Optimum size for deep airway penetration of drug particles is 3 to 5 µm. Large particles tend to deposit in upper airways, whereas very small molecules (<3 µm) are exhaled before absorption can occur. Most inhalation devices deliver approximately 10% of the administered dose to the lower respiratory tract. A number of devices such as spacers (to reduce turbulence and improve deep inhalation) have been developed to increase lung delivery. An *in-vitro* device useful to measure the particle size emitted from an aerosol or a mechanically produced fine mist is the cascade impacter.

Topical and Transdermal Drug Delivery

Topical drug delivery is generally used for local drug effects. Drug may be applied as an ointment or cream to the skin or various mucous membranes such as intravaginally. Even though the objective is to obtain a local drug effect, some of the drug may be absorbed systemically. For transdermal drug delivery the drug is incorporated into a transdermal therapeutic system or patch, but it may be incorporated into an ointment as well (). Transdermal drug delivery is generally for systemic drug absorption. The advantages of transdermal delivery include continuous release of drug over a period of time, low presystemic clearance, and good patient compliance.

Other routes of drug administration are discussed elsewhere and in .

FREQUENTLY ASKED QUESTIONS

1. What is an "absorption window"?

2. Why are some drugs absorbed better with food and others are retarded by food?

3. If a drug is administered orally as a solution, does it mean that all of the drug will be systemically absorbed?

4. What is the biggest biological factor that contributes to delay in drug absorption?

LEARNING QUESTIONS

1. A recent bioavailability study in adult human volunteers demonstrated that after the administration of a single enteric-coated aspirin granule product given with a meal, the plasma drug levels resembled the kinetics of a sustained-release drug product. In contrast, when the product was given to fasted subjects, the plasma drug levels resembled the kinetics of an immediate-release drug product. Give a plausible explanation for this observation.

2. The aqueous solubility of a weak-base drug is poor. In an intubation (intestinal perfusion) study, the drug was not absorbed beyond the jejunum. Which of the following would be the correct strategy to improve drug absorption from the intestinal tract?

a. Give the drug as a suspension and recommend that the suspension be taken on an empty stomach.

b. Give the drug as a hydrochloride salt.

c. Give the drug with milk.

d. Give the drug as a suppository.

3. What is the primary reason that protein drugs such as insulin are not given orally for systemic absorption?

4. Which of the following statements are true regarding an acidic drug with a pK_a of 4?

a. The drug is more soluble in the stomach when food is present.

b. The drug is more soluble in the duodenum than in the stomach.

c. The drug is more soluble when dissociated.

5. Which region of the gastrointestinal tract is most populated by bacteria? What types of drugs might affect the gastrointestinal flora?

6. Discuss methods by which the first-pass effect (presystemic absorption) may be circumvented.

7. Misoprostol (Cytotec, GD Searle) is a synthetic prostaglandin E1 analog. According to the manufacturer, the following information was obtained when misoprostol was taken with an antacid or high-fat breakfast:

Condition	C_{max} (pg/mL)	AUC_{0-24} hr (pg hr/mL)	t_{max} (min)
Fasting	811 ± 317[a]	417 ± 135	14 ± 8
With antacid	689 ± 315	349 ± 108[b]	20 ± 14
With high-fat breakfast	303 ± 176[b]	373 ± 111	64 ± 79[b]

[a]Results are expressed as the mean ± SD (standard deviation).

[b]Comparisons with fasting results statistically significant, $p < 0.05$.

What is the effect of antacid and high-fat breakfast on the bioavailability of misoprostol? Comment on how these factors affect the rate and extent of systemic drug absorption.

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