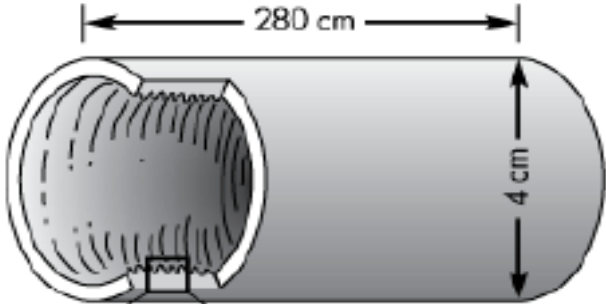

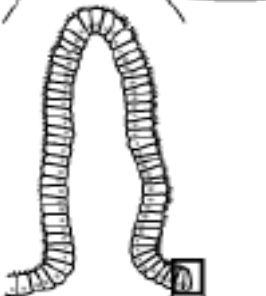



Drug Absorption in the Gastrointestinal Tract

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.

STRUCTURE	INCREASE IN SURFACE AREA (relative to cylinder)	SURFACE AREA (sq cm)
Area of simple cylinder 	1	3300
Folds of Kerckring (valvulae conniventes) 	3	10,000
Villi 	30	100,000
Microvilli 	600	2,000,000

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.

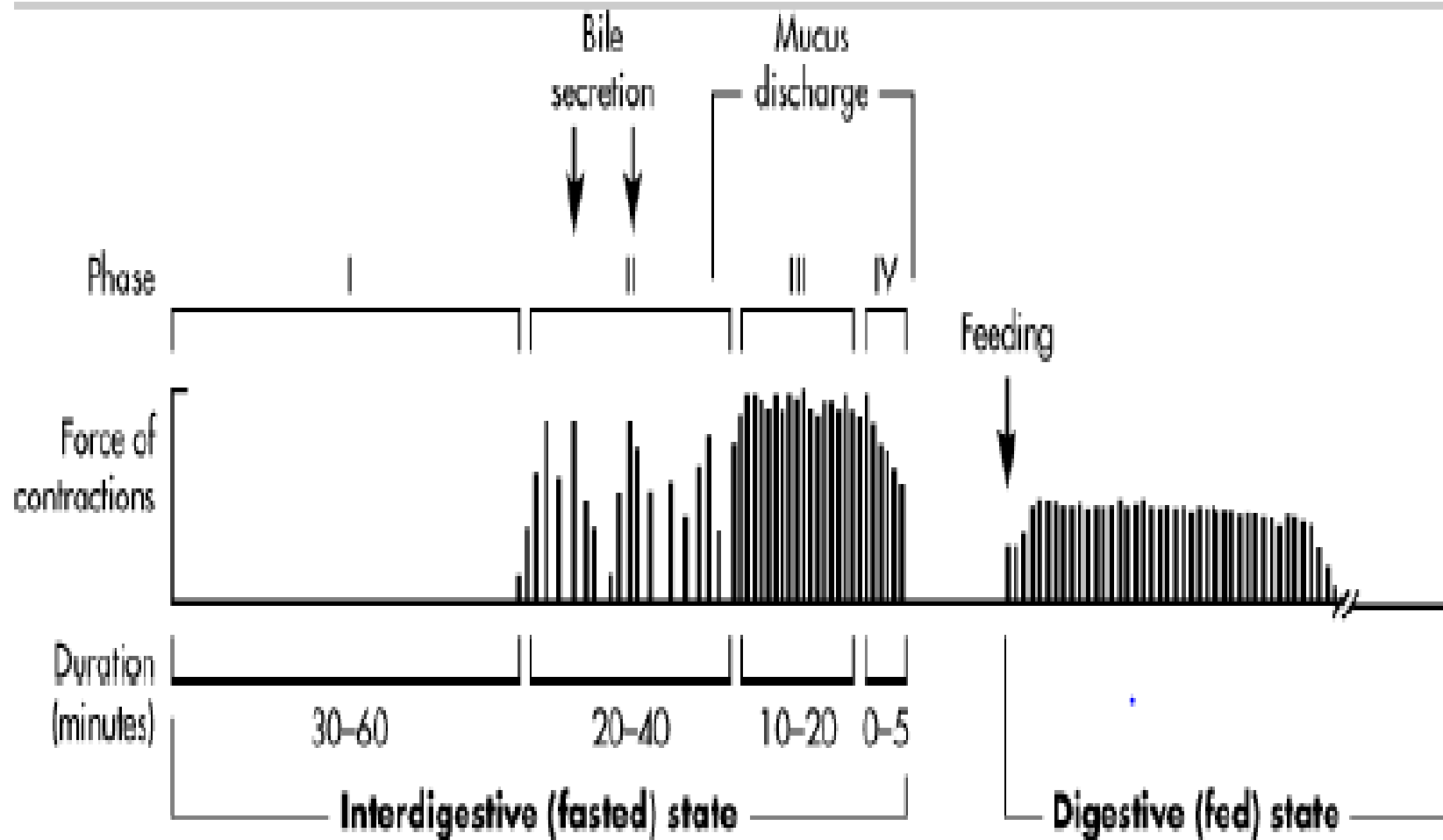


TABLE 13.4 Characteristics of the Motility Patterns in the Fasted Dog

PHASE	DURATION	CHARACTERISTICS
Fasted State		
I	30–60 min	Quiescence.
II	20–40 min	<ul style="list-style-type: none"> ▪ 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	<ul style="list-style-type: none"> ▪ Regular contractions (4–5 contractions/min) with high amplitude. ▪ Mucus discharge continues.
IV	0–5 min	<ul style="list-style-type: none"> ▪ Particle discharge continues. ▪ Irregular contractions. ▪ Medium descending amplitude. ▪ Sometimes absent.
Fed State		
One phase only	As long as food is present in the stomach	<ul style="list-style-type: none"> ▪ Regular, frequent contractions. ▪ Amplitude is lower than phase III. ▪ 4–5 Contractions/min.

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

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 (NaHCO₃)

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.

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 , 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 firstpass 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

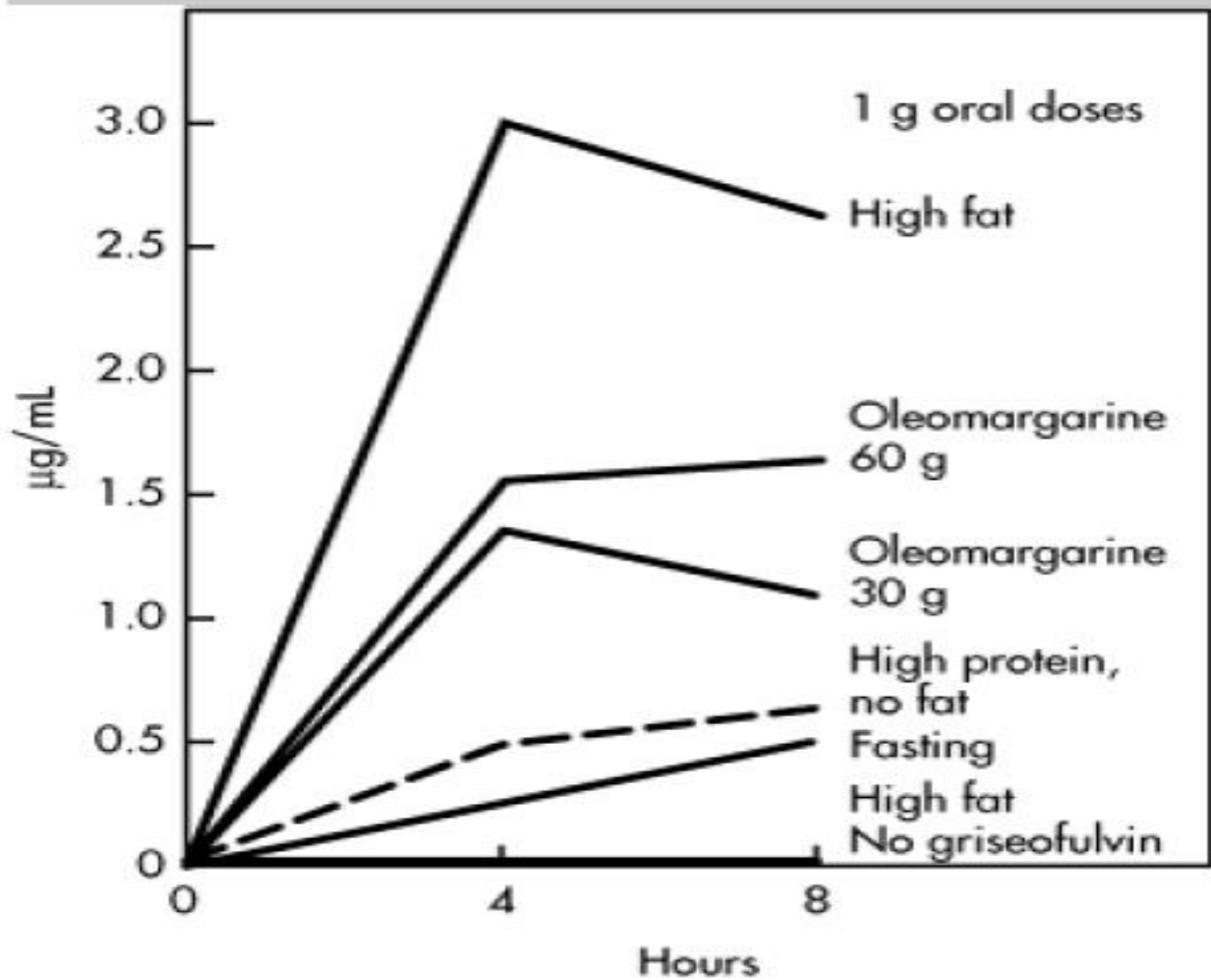
An increase in splanchnic blood flow

A change luminal metabolism of the drug substance

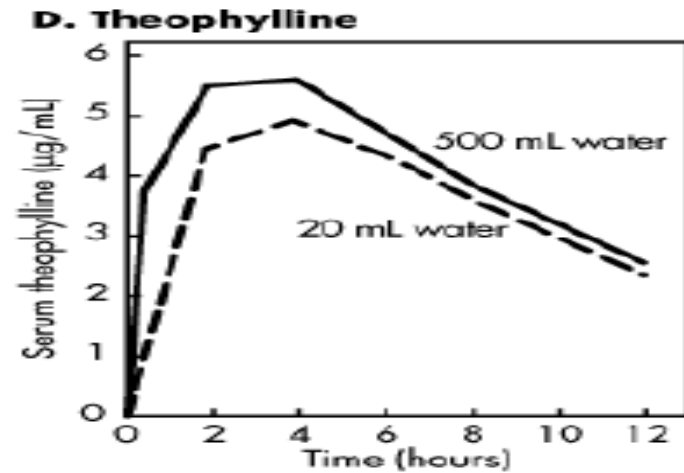
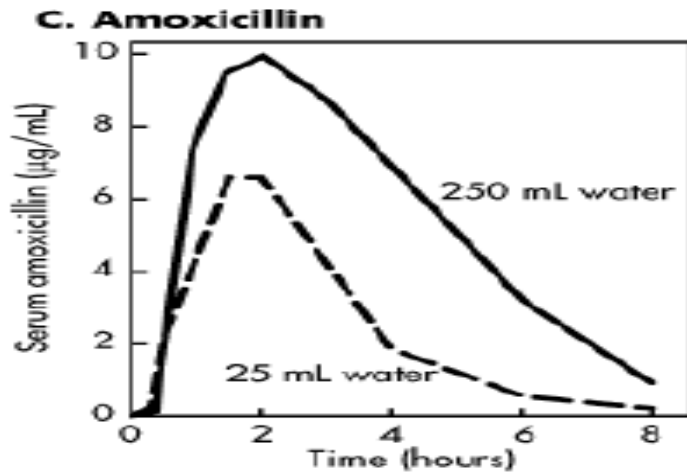
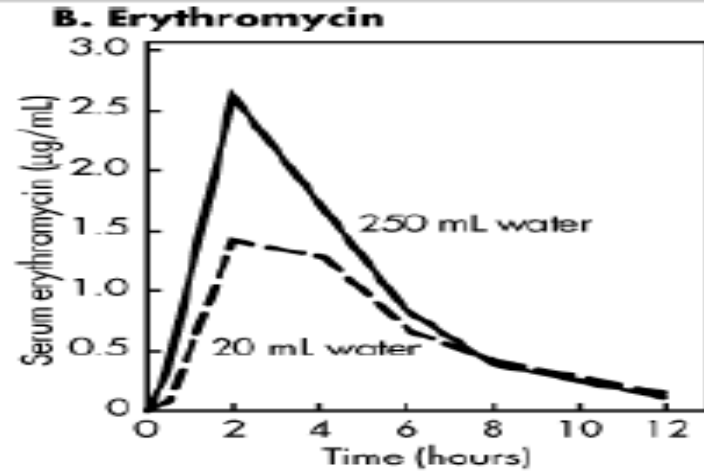
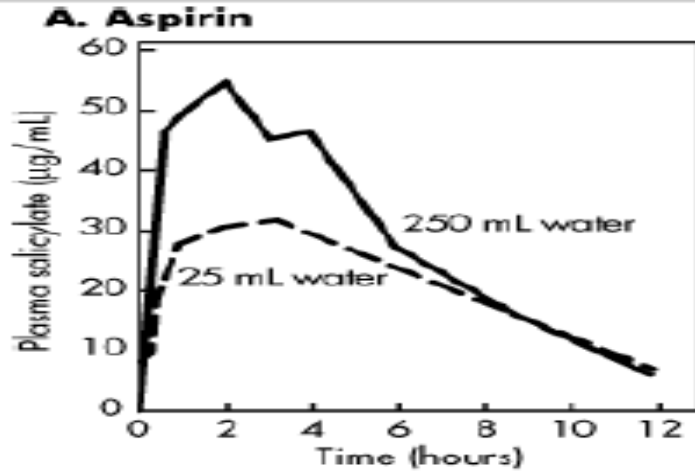
Physical or chemical interaction of the meal with the drug product or drug substance

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.



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.



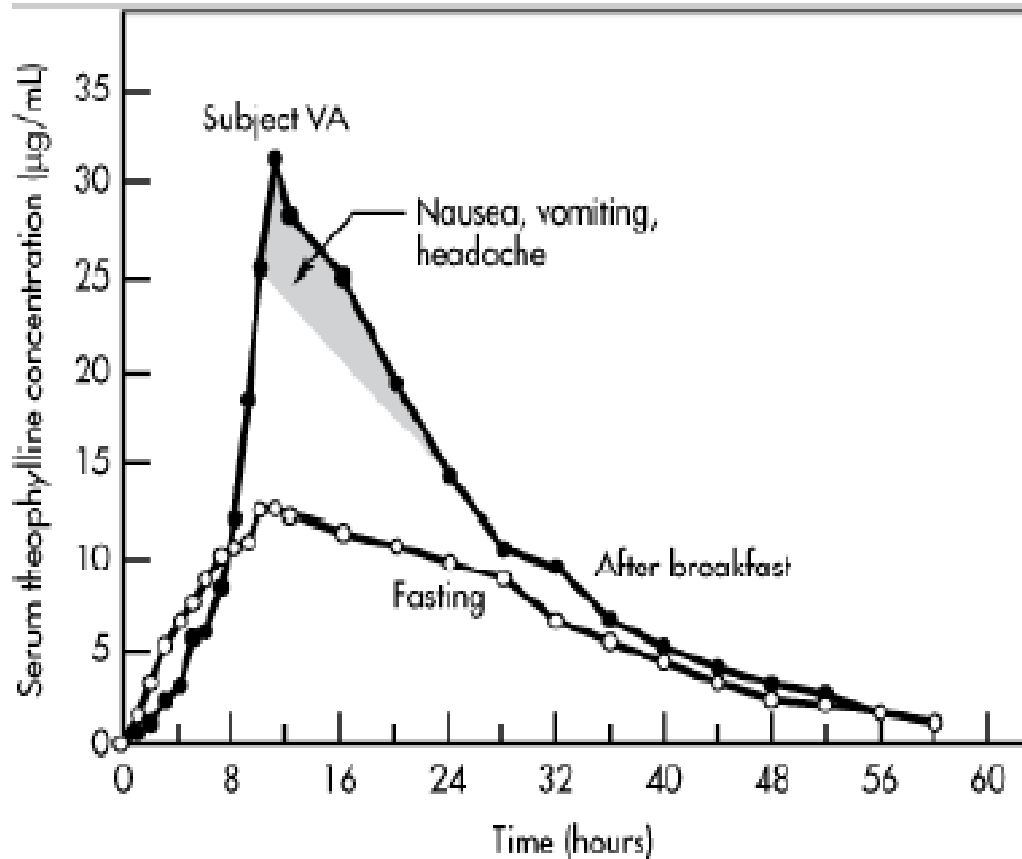
The solubility of many drugs is limited, and **sufficient fluid is necessary for dissolution of the drug**. Some patients may be on several drugs that are dosed frequently for months. These patients are often nauseous and are reluctant to take a lot of fluid. For example, HIV patients with active viral 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.

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.



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

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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."

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 cefepodoxime 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 cefepodoxime 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 cefepodoxime 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.**

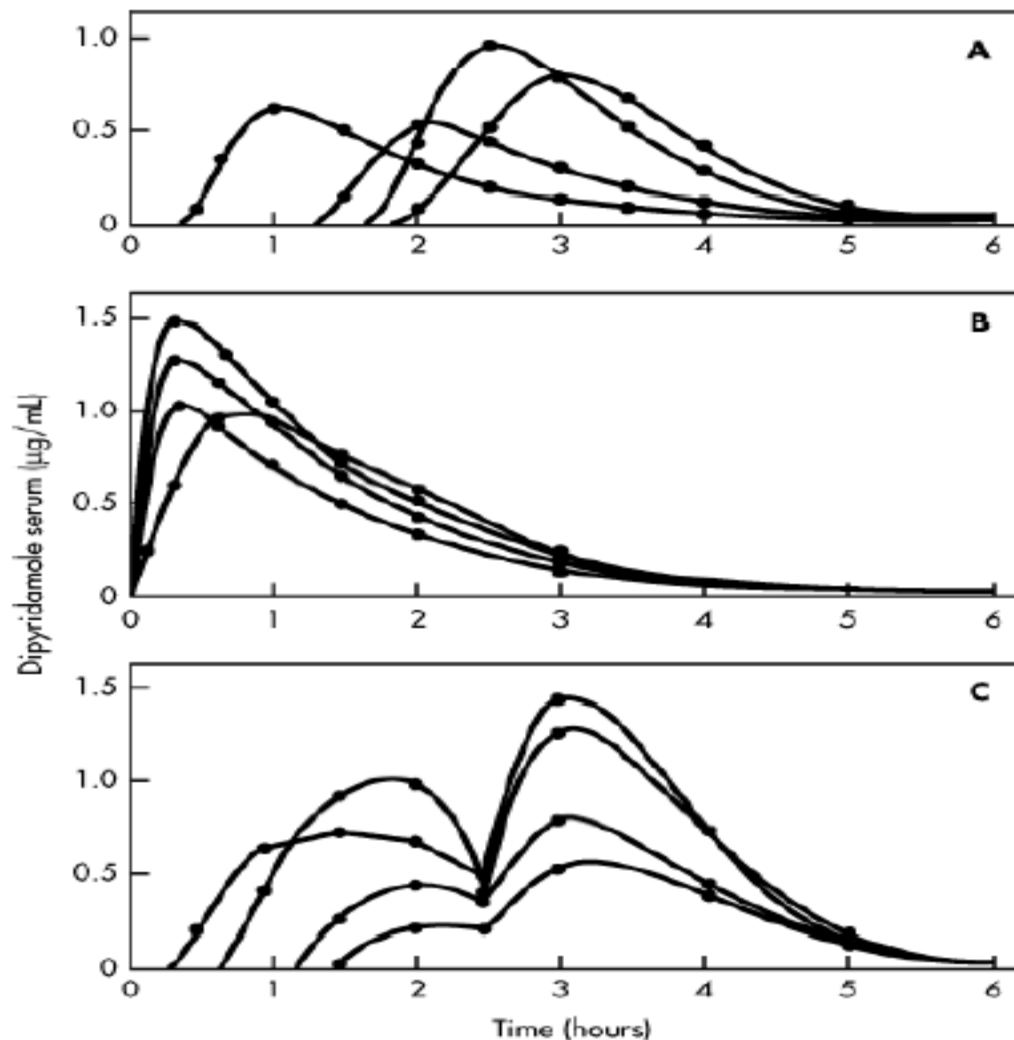
Fluid volume tends to distend the stomach and speed up stomach emptying; however, large volume of nutrients with high caloric content supersedes that faster rate and delays stomach emptying time. Reduction in drug absorption may be caused by several factors. For example, **tetracycline hydrochloride 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.

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.



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

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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.