Biopharmaceutics

Lecture-5

Anatomic and physiologic considerations

1. Gastric Emptying Time

   Anatomically, a swallowed drug rapidly reaches the stomach. Eventually, the stomach empties its content in 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.

Factors influencing gastric emptying

- A number of factors affect gastric emptying time (Table 13.5). Some factors that tend to delay gastric emptying include consumption of meals high in fat, cold beverages, and anticholinergic drugs.
- Liquid and small particles less than 1mm 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.

2. Intestinal motility

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

3. Perfusion of the gastrointestinal tract

- The blood flow to the GI tract is important in carrying absorbed drug to the systemic circulation.
- 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.

4. 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 (Table13.6).
- Digested foods contain amino acids, fatty acids, and many nutrients that may affect intestinal pH and solubility of drugs.
- Some effects of food on the bioavailability of a drug from a drug product include:

1. Delay in gastric emptying
2. Stimulation of bile flow
3. A change in the pH of the GI tract
4. An increase in splanchnic blood flow
5. A change luminal metabolism of the drug substance
6. Physical or chemical interaction of the meal with the drug product or drug substance

- 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 increase the solubility of fat-soluble drugs through micelle formation.
- for some basic drugs (e.g., cinnarizine) with limit aqueous solubility, the presence of food in the stomach stimulate 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 of water to ensure that drugs will wash the esophagus.
- Generally, the bioavailability of drugs is better in patients in the fasted state and with a large volume of water (Fig. 13-14).
- The solubility of many drugs is limited, and sufficient fluid is necessary for dissolution of the drug.
- 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.

5. Double-peak phenomenon

- Some drugs, such as ranitidine, cimetidine, and dipyridamole, after oral administration produce a blood concentration curve consisting of two peaks.
- 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 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)
- Tablets 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 disintegrate may have delayed gastric emptying, resulting in a second absorption peak.

Biopharmaceutic considerations in drug product design

- Rate-limiting steps in drug absorption
- In the process of drug disintegration, dissolution, and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence.
- The slowest step in a series of kinetic processes is called the rate-limiting step.

- Except for controlled-release products, disintegration of a solid oral drug product is usually more rapid than drug dissolution and drug absorption.
- For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exerts a rate-limiting effect on drug bioavailability.
- In contrast, for a drug that has a high aqueous solubility, the dissolution rate is rapid, and the rate at which the drug crosses or permeates cell membranes is the slowest or rate-limiting step.

Pharmaceutic factors affecting drug bioavailability

- Considerations in the design of a drug product that will deliver active drug with the desired bioavailability characteristics include

1. The type of drug product (e.g., solution, suspension, suppository)'
2. The nature of the excipients in the drug product,
3. The physicochemical properties of the drug molecule, and
4. The route of drug administration.

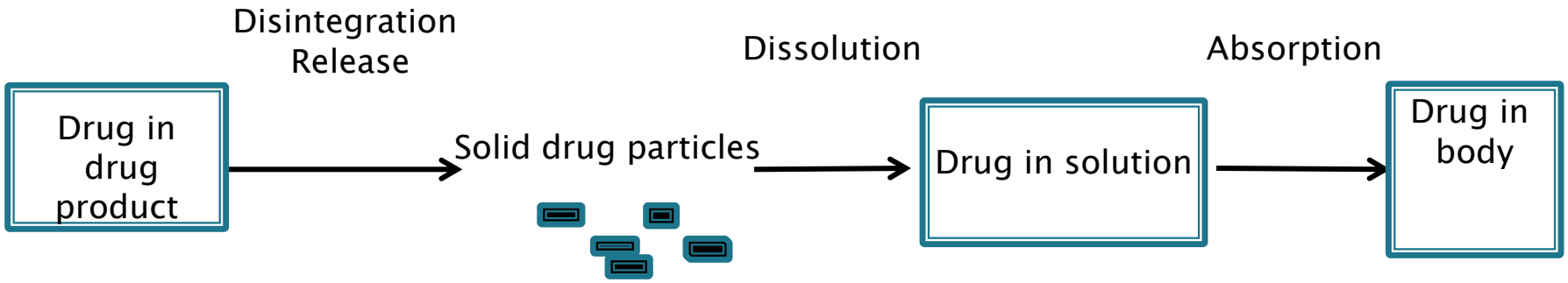


Figure 14-1. rates processes of drug bioavailability

Disintegration

- For immediate-release, solid oral dosage forms, the drug product must disintegrate into small particles and release the drug.
- To monitor uniform tablet disintegration, USP has established an official disintegration test.
- Solid drug products exempted from disintegration test include troches, tablets that are intended to be chewed, and drug products intended for sustained release or prolonged or repeat action.
- Disintegration tests give no information on the rate of dissolution of the active drug.
- However, there has been some interest in using only the disintegration test and no dissolution test for drug products that meet the BCS for highly soluble and highly permeable drug.

Dissolution and solubility

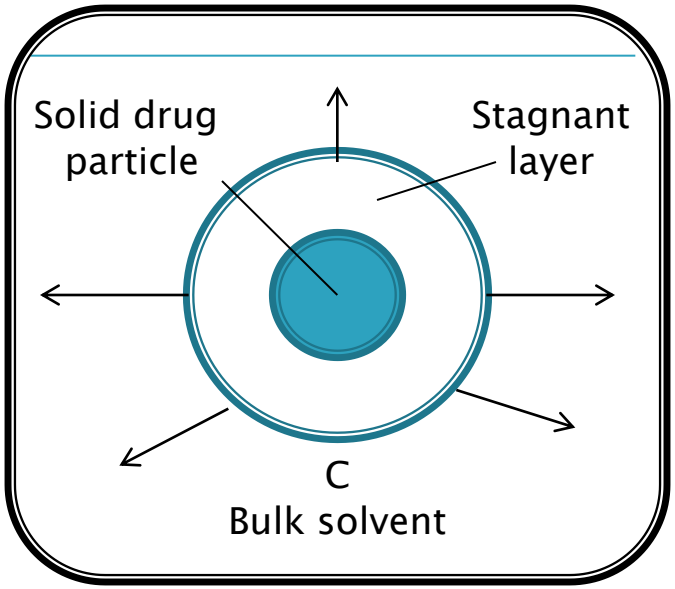
- Dissolution is the process by which a solid drug substance becomes dissolved in a solvent.
- Solubility is the mass of solute that dissolve in specific mass or volume of solvent at a given temperature.
- Solubility is a static property; whereas dissolution is a dynamic property.
- The rate at which drugs with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the GI tract often controls the rate of systemic absorption of the drug.
- Thus, dissolution tests may be used to predict bioavailability and may be used to discriminate formulation factors that affect drug bioavailability.

- Noyes and Whitney (1897) and other investigators studied the rate of dissolution of solid drugs.
- According to their observations, the steps in dissolution include the process of drug dissolution at the surface of the solid particle, thus forming a saturated solution around the particle.
- The dissolved drug in the saturated solution, known as the stagnant layer, diffuses to the bulk of the solvent from regions of high drug concentration to regions of low drug concentration (Fig. 14-2).
- The overall rate of drug dissolution may be described by the Noyes-Whitney equation (Eq. 14.1).

$$\frac{dc}{dt} = \frac{DA}{h}(c_s - c)$$

- Where dc/dt = rate of drug dissolution at time t, D = diffusion rate constant, A = surface area of the particle, Cs = concentration of drug (equal to solubility of drug) in the stagnant layer, C = concentration of drug in the bulk solvent, and h = thickness of the stagnant layer, the rate of dissolution, dc/dt, is the rate of drug dissolved per time expressed as concentration change in the dissolution fluid.

Figure 14-2. dissolution of a solid drug particle in a solvent. (Cs = concentration of drug in the stagnant layer, C = concentration of drug in the bulk solvent.)



- The Noyes-Whitney equation shows that dissolution in a flask may be influenced by the physicochemical characteristics of the drug, the formulation, and the solvent. Drug in the body, particularly in the gastrointestinal tract, is considered to be dissolving in an aqueous environment.
- Permeation of drug across the gut wall (a model lipid membrane) is affected by the ability of the drug to diffuse (D) and to partition between the lipid membrane. A favorable partition coefficient ($K_{oil/water}$) will facilitate drug absorption.

- In addition to these factors, the temperature of the medium and the agitation rate also affect the rate of drug dissolution.
- *In vivo,* the temperature is maintained at a constant 37°C, and the agitation (primarily peristaltic movement in the gastrointestinal tract) is reasonably constant.
- In contrast, *in-vitro* studies of dissolution kinetics require maintenance of constant temperature and agitation. Temperature is generally kept at 37°C, and the agitation or stirring rate is held to a specific rpm (revolutions per minute).
- An increase in temperature will increase the kinetic energy of the molecules and increase the diffusion constant ,D .
- Moreover, an increase in agitation of the solvent medium will reduce the thickness, h, of the stagnant layer, allowing for more rapid drug dissolution.

- Factors that affect drug dissolution of a solid dosage form include

1. The physical and chemical nature of the active drug substance,
2. The nature of the excipients, and
3. The method of manufacture.

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Lecture-6

Physicochemical nature of the drug

- Solubility, pH, and drug absorption
- the solubility–pH profile is a plot of the solubility of the drug at various physiologic pH values.
- a basic drug is more soluble in an acidic medium, forming a soluble salt. Conversely, an acid drug is more soluble in the intestine, forming a soluble salt at the more alkaline pH.
- Solubility may be improved with the addition of acidic or basic excipient. Solubilization of aspirin, for example, may be increased by the addition of an alkaline buffer.
- In the formulation of controlled-release drugs, buffering agents may be added to slow or modify the release rate of fast-dissolving drug.

- Stability, pH, and drug absorption
- the stability–pH profile is a plot of the reaction rate constant for drug degradation versus pH. If drug decomposition occurs by acid or base catalysis, some prediction of degradation of the drug in the gastrointestinal tract may be made.
- For example, erythromycin has a pH-dependent stability profile. In acidic medium, as in the stomach, erythromycin decomposition occurs rapidly, whereas in neutral or alkaline pH, the drug is relatively stable.
- Consequently, erythromycin tablets are enteric coated to protect against acid degradation in the stomach.

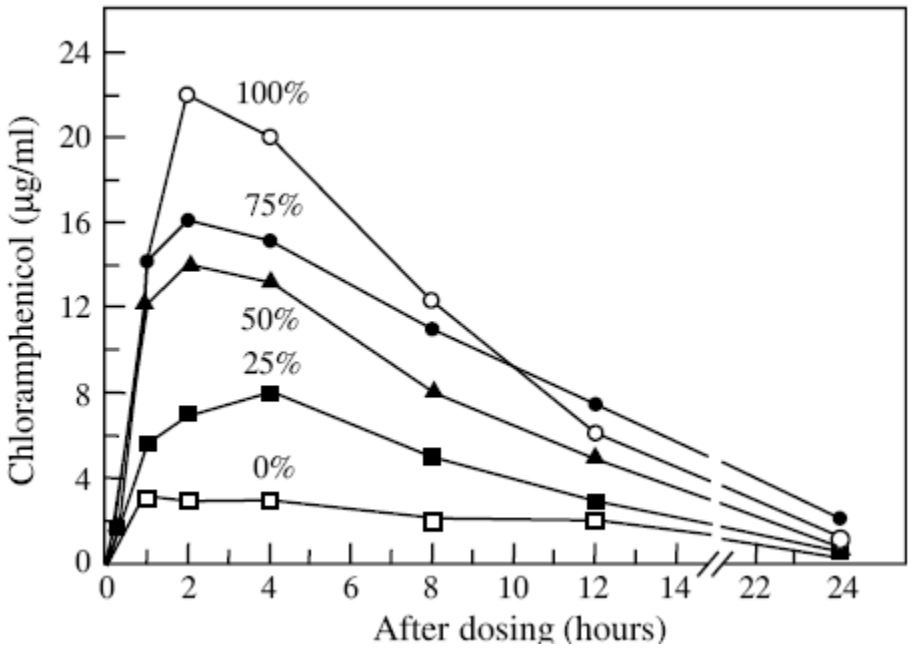
- this information also led subsequently to the preparation of a less water-soluble erythromycin salt that is more stable in the stomach.
- The dissolution rate of erythromycin powder varied from 100% dissolved in 1 hour to less than 40% dissolved in 1 hour.
- The slow-dissolving raw drug material also resulted in slow-dissolving drug products. Therefore, the dissolution of powdered raw drug material is a very useful in-vitro method for predicting bioavailability of the erythromycin product in the body.

- Particle size and drug absorption
- The effective surface area of a drug is increased enormously by a reduction in the particle size. Because dissolution takes place at the surface of the solute (drug), the greater the surface area, the more rapid is the rate of drug dissolution.
- The geometric shape of the particle also affects the surface area, and, during dissolution, the surface is constantly changing. In dissolution calculations, the solute particle is usually assumed to have retained its geometric shape.
- For poorly soluble drugs, a disintegrant may be added to the formulation to ensure rapid disintegration of the tablet and release of the particles.
- The addition of surface-active agents may increase wetting as well as solubility of these drugs.

- Polymorphism, solvates, and drug absorption
- Polymorphism refers to the arrangement of drug substance in various crystal forms or polymorphs. In recent years the term polymorph has been used frequently to describe polymorphs, solvates, amorphous forms, and desolvated solvates.
- Amorphous forms are noncrystalline forms, solvates are forms that contain a solvent (solvate) or water (hydrate), and desolvated solvates are forms that are made by removing the solvent from the solvate.

- Polymorphs have the same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics, some polymorphic crystals have much lower aqueous solubility than the amorphous forms, causing a product to be incompletely absorbed.
- Chloramphenicol, for example, has several crystal forms, and when given orally as a suspension, the drug concentration in the body was found to be dependent on the percent of β-polymorph in the suspension. The β form is more soluble and better absorbed.

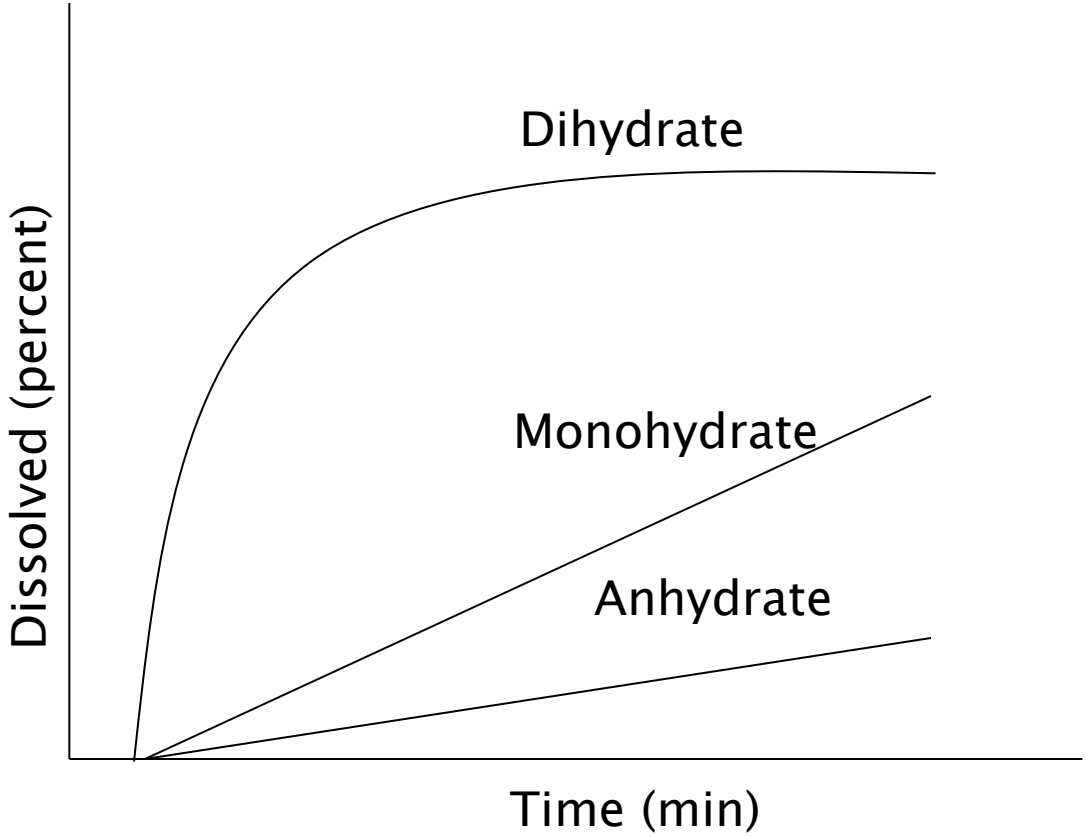
Comparison of mean blood serum levels obtained with chloramphenicol palmitate suspensions containing varying ratio of α and β polymorphs, following single oral dose equivalent to 1.5 g chloramphenicol. Percentage polymorph β in the suspension.



- In general, the crystal form that has the lowest free energy is the most stable polymorph.
- A drug that exists as an amorphous form (noncrystalline form) generally dissolves more rapidly than the same drug in a more structurally rigid crystalline form.
- Some polymorphs are metastable and may convert to a more stable form over time. A change in crystal form may cause problems in manufacturing the product.
- For example, a change in the crystal structure of the drug may cause cracking in a tablet or even prevent a granulation from being compressed into a tablet.

- Some drugs interact with solvent during preparation to form a crystal called a solvate.
- Water may form special crystals with drugs called hydrates; for example, erythromycin hydrates have quite different solubility compared to the anhydrous form of the drug.
- Ampicillin trihydrate, on the other hand, was reported to be less absorbed than the anhydrous form of ampicillin because of faster dissolution of the latter.

Dissolution behavior of erythromycin dihydrate, monohydrate, and anhydrate in phosphate buffer (pH 7.5) at 37°C



Formulation factors affecting drug dissolution

- Excipents are added to a formulation to provide certain functional properties to the drug and dosage form.
- Some of these functional properties of the excipients are used to improve the compressibility of the active drug, stabilize the drug against degradation, decrease gastric irritation, control the rate of drug absorption from the absorption site, increase drug bioavailability, etc.

- Excipients in the drug product may also affect the dissolution kinetics of the drug, either by altering the medium in which the drug is dissolved or by reacting with the drug itself.
- Some of the more common manufacturing problems that affect dissolution are listed in Table 14.4. effect of excipients on the pharmacokinetic parameters of oral drug products .
- excipients (Disintegrants, lubricants, coating agent, enteric coat, sustained-release agents: waxy agents and gum/viscous).
- Parameters Ka = absorption rate constant, T_{max} = time for peak drug concentration in plasma, AUC = area under the plasma drug concentration-time curve.

- Other excipients include suspending agents that increase the viscosity of the drug vehicle and thereby diminish the rate of drug dissolution from suspensions.
- Tablet lubricants, such as magnesium stearate, may repel water and reduce dissolution when used in large quantities (Figure14-5) and consequently affecting drug absorption (Figure14-6)
- Coatings, particularly shellac, will crosslink upon aging and decrease the dissolution rate.
- However, surfactants may affect drug dissolution in an unpredictable fashion. Low concentrations of surfactants decrease the surface tension and increase the rate of drug dissolution, whereas higher surfactants concentrations tend to form micelles within the drug and thus decrease the dissolution rate.

Figure 14-5.

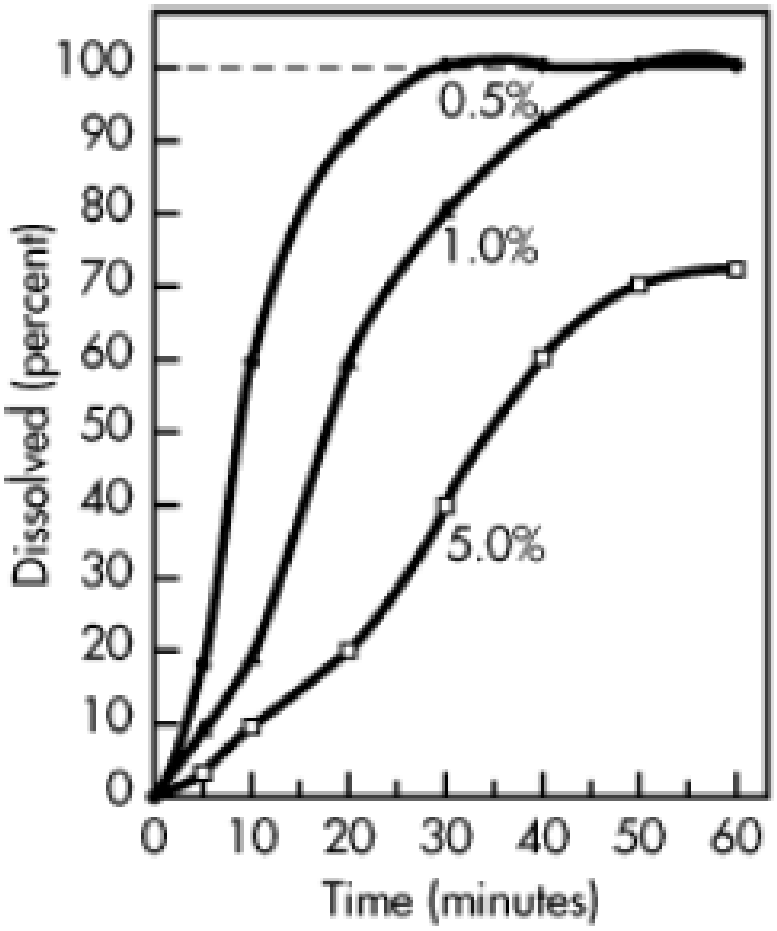
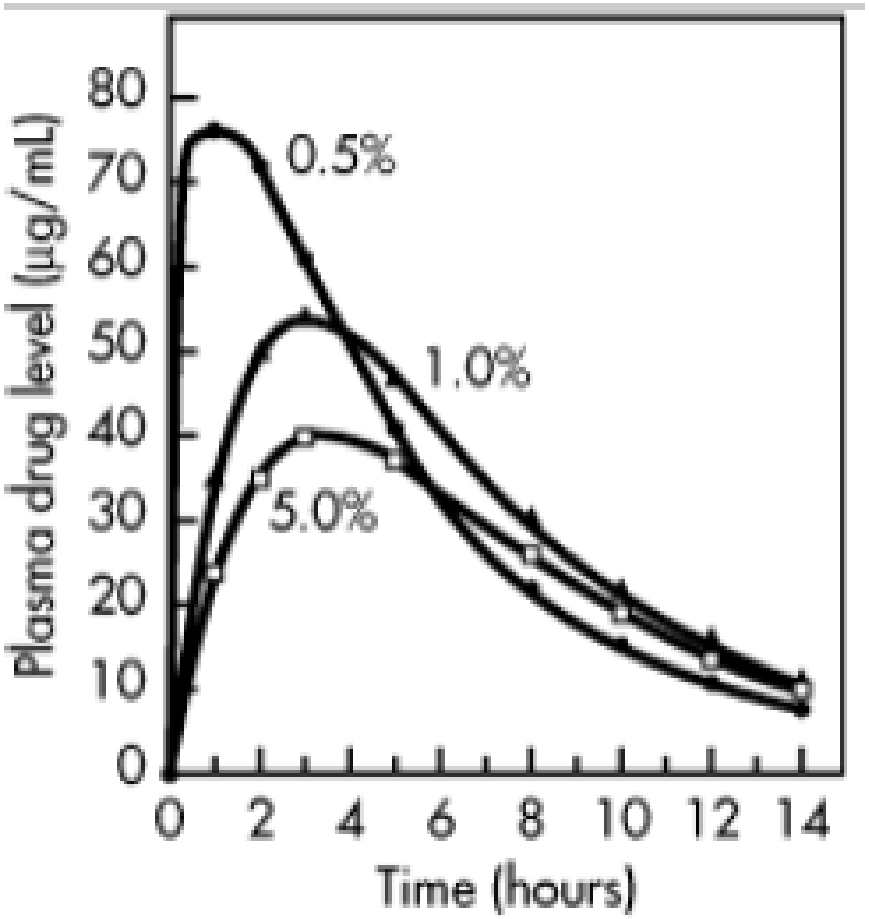


Figure 14-6.



- Large drug particle have a smaller surface area and dissolve more slowly than smaller particles.
- High compression of tablets without sufficient disintegrant may cause poor disintegration of a compressed tablet.
- Some excipients, such as sodium bicarbonate, may change the pH of the medium surrounding the active drug substance. Aspirin, a weak acid when formulated with sodium bicarbonate, will form a water-soluble salt in an alkaline medium, in which the drug rapidly dissolves. The term for this process is dissolution in a reactive medium.

- Excipients in a formulation may interact directly with the drug to form a water-soluble or water-insoluble complex. For example, if tetracycline is formulated with calcium carbonate, an insoluble complex of calcium tetracycline is formed that has a slow rate of dissolution and poor absorption.
- Excipients may increase the retention time of the drug in the gastrointestinal tract and therefore increase the total amount of drug absorbed.
- Excipients may act as carrier to increase drug diffusion across the intestinal wall. In contrast, many excipients may retard drug dissolution and thus reduce drug absorption.