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Biopharmaceutic Considerations in Drug Product Design: Introduction

Drugs are not generally given as pure chemical drug substances but are formulated into finished dosage forms (drug products), such as tablets, capsules, ointments, etc, before being administered to patients for therapy. Formulated drug products usually include the active drug substance and selected ingredients (*excipients*) that make up the dosage form. Drug products are designed to deliver drug for local or systemic effects. Common drug products include liquids, tablets, capsules, injectables, suppositories, transdermal systems, and topical products such as creams and ointments. The design and formulation of drug products requires a thorough understanding of the biopharmaceutic principles of drug delivery.

Biopharmaceutics is the study of the *in-vitro* impact of the physicochemical properties of drugs and drug products on drug delivery to the body under normal or pathologic conditions. A primary concern in biopharmaceutics is the bioavailability of drugs. *Bioavailability* refers to the measurement of the rate and extent of active drug that becomes available at the site of action. Because the systemic blood circulation delivers therapeutically active drug to the tissues and to the site of action of the drug, changes in bioavailability affect changes in the pharmacodynamics and toxicity of a drug. The aim of biopharmaceutics is to adjust the delivery of drug from the drug product in such a manner as to provide optimal therapeutic activity and safety for the patient.

Biopharmaceutic studies allow for the rational design of drug products based on (1) the physical and chemical properties of the drug substance; (2) the route of drug administration, including the anatomic and physiologic nature of the application site (eg, oral, topical, injectable, implant, transdermal patch, etc); and (4) desired pharmacodynamic effect (eg, immediate or prolonged activity); (5) toxicologic properties of the drug; (6) safety of excipients; and (7) effect of excipients and dosage form on drug delivery. For example, some drugs are intended for topical or local therapeutic action at the site of administration. For these drugs, systemic absorption is undesirable. Drugs intended for local activity are designed to have a direct pharmacodynamic action without affecting other body organs. These drugs may be applied topically to the skin, nose, eye, mucous membranes, buccal cavity, throat, or rectum. A drug intended for local activity may be given intravaginally, into the urethral tract, intranasally, into the ear, on the eye, or orally. Examples of drugs used for local action include anti-infectives, antifungals, local anesthetics, antacids, astringents, vasoconstrictors, antihistamines, and corticosteroids. However, some systemic drug absorption may occur with drugs used for local activity.

Each route of drug application presents special biopharmaceutic considerations in drug product design. For example, the design of a vaginal tablet formulation for the treatment of a fungal infection must use ingredients compatible with vaginal anatomy and physiology. An eye medication may require special biopharmaceutic considerations, including appropriate pH, isotonicity, sterility, local irritation to the cornea, draining by tears, and concern for systemic drug absorption.

For a drug administered by an extravascular route (eg, intramuscular injection), local irritation, drug dissolution, and drug absorption from the intramuscular site are some of the factors that must be considered. The systemic absorption of a drug from an extravascular site is influenced by the anatomic and physiologic properties of the site and the physicochemical properties of the drug and the drug product. If the drug is given by an intravascular route (eg, IV administration), systemic drug absorption is considered complete or 100% bioavailable, because the drug is placed directly into the general circulation.

In some cases, a drug product is designed so that it may be used in conjunction with a specialized medical device or packaging component. For example, a drug solution or suspension may be formulated to work with a nebulizer or metered-dose inhaler for administration into the lungs. Both the physical characteristics of the nebulizer and the formulation of the drug product can influence the droplet particles and the spray pattern that the patient receives upon inhalation of the drug product.

By choosing the route of drug administration carefully and properly designing the drug product, the bioavailability of the active drug can be varied from rapid and complete absorption to a slow, sustained rate of absorption or even virtually no absorption, depending on the therapeutic objective. Once the drug is systemically absorbed, normal physiologic processes for distribution and elimination occur, which usually are not influenced by the specific formulation of the drug. The rate of drug release from the product and the rate and extent of drug absorption are important in determining the distribution, onset, intensity, and duration of drug action.

Biopharmaceutic considerations often determine the ultimate dose and dosage form of a drug product. For example, the dosage for a drug intended for local activity, such as a topical drug product (eg, ointment), is often expressed in concentration or as percentage of the active drug in the formulation (eg, 0.5% hydrocortisone ointment). The amount of drug applied is not specified because the concentration of the drug at the active site relates to the pharmacodynamic action. However, biopharmaceutic studies must be performed to ensure that the drug product does not irritate, cause an allergic response, or allow significant systemic drug absorption. In contrast, the dosage of a drug intended for systemic absorption is given on the basis of mass, such as milligrams or grams. In this case, dosage is based on the amount of drug that is absorbed systemically and dissolved in an apparent volume of distribution to produce a desired drug concentration at the target site. The therapeutic dose may be based on the weight or surface area of the patient, to account for the differences in the apparent volume of distribution. Thus, doses are expressed as mass per unit of body weight (mg/kg) or mass per unit of body surface area (mg/m^2). For many commercial drug products, the dose is determined on average body weights and may be available in several dose strengths, such as 10-mg, 5-mg, and 2.5-mg tablets, to accommodate differences in body weight and possibly to titrate the dose in the patient.

Rate-Limiting Steps in Drug Absorption

Systemic drug absorption from a drug product consists of a succession of rate processes (). For solid oral, immediate-release drug products (eg, tablets, capsules), the rate processes include (1) disintegration of the drug product and subsequent release of the drug, (2) dissolution of the drug in an aqueous environment, and (3) absorption across cell membranes into the systemic circulation. 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.

Figure 14-1.

Rate processes of drug bioavailability.

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 (eg, 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.

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, the *United StatesPharmacopeia* (USP) has established an official disintegration test. Solid drug products exempted from disintegration tests include troches, tablets that are intended to be chewed, and drug products intended for sustained release or prolonged or repeat action.

The process of disintegration does not imply complete dissolution of the tablet and/or the drug. Complete disintegration is defined by the USP () as "that state in which any residue of the tablet, except fragments of insoluble coating, remaining on the screen of the test apparatus in the soft mass have no palpably firm core." The official apparatus for the disintegration test and procedure is described in the USP. Separate specifications are given for drug products that are designed not to disintegrate. These products include troches, chewable tablets, and modified-release drug products.

Although disintegration tests allow for precise measurement of the formation of fragments, granules, or aggregates from solid dosage forms, no information is obtained from these tests 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 Biopharmaceutical Classification System (BCS) for highly soluble and highly permeable drugs (). In general, the disintegration test serves as a component in the overall quality control of tablet manufacture.

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 dissolves in a specific mass or volume of solvent at a given temperature (eg, 1 g of NaCl dissolves in 2.786 mL of water at 25°C). Solubility is a static property; wheareas dissolution is a dynamic property. In biologic systems, drug dissolution in an aqueous medium is an important prior condition for systemic absorption. The rate at which drugs with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the gastrointestinal 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. The dissolution test is required for all U.S. Food and Drug Administration (FDA)-approved solid oral drug products. *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 ().

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

The overall rate of drug dissolution may be described by the *Noyes–Whitney equation* (Eq. 14.1),

where dC/dt = rate of drug dissolution at time t, D = diffusion rate constant, A = surface area of the particle, C_s = 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.

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 movements 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 specified 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 oral 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.

Physicochemical Nature of the Drug

In addition to their effect on dissolution kinetics, the physical and chemical properties of the drug substance as well as the excipients are important considerations in the design of a drug product (). For example, intravenous solutions are difficult to prepare with drugs that have poor aqueous solubility. Drugs that are physically or chemically unstable may require special excipients, coatings, or manufacturing processes to protect the drug from degradation. The potent pharmacodynamic activity of drugs such as estrogens and other hormones, penicillin antibiotics, cancer chemotherapeutic agents, and others, may cause adverse reactions to personnel who are exposed to these drugs during manufacture and also presents a problem.

Table 14.1 Physicochemical Properties for Consideration in Drug Product Design	
pK_a and pH profile	Necessary for optimum stability and solubility of the final product.
Particle size	May affect the solubility of the drug and therefore the dissolution rate of the product.
Polymorphism	The ability of a drug to exist in various crystal forms may change the solubility of the drug. Also, the stability of each form is important, because polymorphs may convert from one form to another.
Hygroscopicity	Moisture absorption may affect the physical structure as well as stability of the product.
Partition coefficient	May give some indication of the relative affinity of the drug for oil and water. A drug that has high affinity for oil may have poor release and dissolution from the drug product.
Excipient interaction	The compatibility of the excipients with the drug and sometimes trace elements in excipients may affect the stability of the product. It is important to have specifications of all raw materials.

pH stability profile	The stability of solutions is often affected by the pH of the vehicle; furthermore, because the pH in the stomach and gut is different, knowledge of the stability profile would help to avoid or prevent degradation of the product during storage or after administration.

Solubility, pH, and Drug Absorption

The *solubility–pH profile* is a plot of the solubility of the drug at various physiologic pH values. In designing oral dosage forms, the formulator must consider that the natural pH environment of the gastrointestinal tract varies from acidic in the stomach to slightly alkaline in the small intestine. 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. The solubility–pH profile gives a rough estimation of the completeness of dissolution for a dose of a drug in the stomach or in the small intestine. Solubility may be improved with the addition of an 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 a fast-dissolving drug. To be effective, however, the controlled-release drug product must be a nondisintegrating dosage form. The buffering agent is released slowly rather than rapidly, so that the drug does not dissolve immediately in the surrounding gastrointestinal fluid.

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 (active pharmaceutical ingredient) 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 problems 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.

Particle size and particle size distribution studies are important for drugs that have low water solubility. Many drugs are very active intravenously but are not very effective when given orally, because of poor oral absorption. Griseofulvin, nitrofurantoin, and many steroids are drugs with low aqueous solubility; reduction of the particle size by milling to a micronized form has improved the oral absorption of these drugs. Smaller particle size results in an increase in the total surface area of the particles, enhances water penetration into the particles, and increases the dissolution rate. 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 a 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   -polymorph in the suspension. The   form is more soluble and better absorbed (see). 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. Re-formulation of a product may be necessary if a new crystal form of a drug is used. 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.

Figure 14-3.
Comparison of mean blood serum levels obtained with chloramphenicol palmitate suspensions containing varying ratios of   and   polymorphs, following single oral dose equivalent to 1.5 g chloramphenicol. Percentage polymorph   in the suspension. ()

Figure 14-4.
Dissolution behavior of erythromycin dihydrate, monohydrate, and anhydrate in phosphate buffer (pH 7.5) at 37°C. ()

Formulation Factors Affecting Drug Dissolution

Excipients 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. Some of the excipients used in the manufacture of solid and liquid drug products are listed in and .

Table 14.2 Common Excipients Used in Solid Drug Products	
Excipient	**Property in Dosage Form**
Lactose	Diluent
Dibasic calcium phosphate	Diluent
Starch	Disintegrant, diluent
Microcrystalline cellulose	Disintegrant, diluent
Magnesium stearate	Lubricant
Stearic acid	Lubricant
Hydrogenated vegetable oil	Lubricant
Talc	Lubricant
Sucrose (solution)	Granulating agent
Polyvinyl pyrrolidone (solution)	Granulating agent
Hydroxypropylmethylcellulose	Tablet-coating agent
Titinium dioxide	Combined with dye as colored coating
Methylcellulose	Coating or granulating agent
Cellulose acetate phthalate	Enteric coating agent

Table 14.3 Common Excipients Used in Oral Liquid Drug Products	
Excipient	**Property in Dosage Form**
Sodium carboxymethylcellulose	Suspending agent
Tragacanth	Suspending agent
Sodium alginate	Suspending agent
Xanthan gum	Thixotropic suspending agent

Veegum	Thixotropic suspending agent
Sorbitol	Sweetener
Alcohol	Solubilizing agent, preservative
Propylene glycol	Solubilizing agent
Methyl, propylparaben	Preservative
Sucrose	Sweetener
Polysorbates	Surfactant
Sesame oil	For emulsion vehicle
Corn Oil	For emulsion vehicle

Excipients in the drug product may also affect the dissolution kinetics of the drug, either by altering the medium in which the drug is dissolving or by reacting with the drug itself. Some of the more common manufacturing problems that affect dissolution are listed in . 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. 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 with the drug and thus decrease the dissolution rate. Large drug particles 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*. The solid drug dissolves rapidly in the reactive solvent surrounding the solid particle. However, as the dissolved drug molecules diffuse outward into the bulk solvent, the drug may precipitate out of solution with a very fine particle size. These small particles have enormous collective surface area, dispersing and redissolving readily for more rapid absorption upon contact with the mucosal surface.

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 be added intentionally to the formulation to enhance the rate and extent of drug absorption or to delay or slow the rate of drug absorption (). For example, excipients that increase the aqueous solubility of the drug generally increase the rate of dissolution and drug 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 carriers to increase drug diffusion across the intestinal wall. In contrast, many excipients may retard drug dissolution and thus reduce drug absorption.

Table 14.4 Effect of Excipients on the Pharmacokinetic Parameters of Oral Drug Products[a]				
Excipients	**Example**	k_a	T_{MAX}	**AUC**
Disintegrants	Avicel, Explotab			/—
Lubricants	Talc, hydrogenated vegetable oil			/—
Coating agent	Hydroxypropylmethyl cellulose	—	—	—
Enteric coat	Cellulose acetate phthalate			/—
Sustained-release agents	Methylcellulose, ethylcellulose			/—
Sustained-release agents (waxy agents)	Castorwax, Carbowax			/—
Sustained-release agents (gum/viscous)	Veegum, Keltrol			/—

ᵃThis may be concentration and drug dependent. ↑ = Increase, ↓ = decrease, — = no effect, k_a = absorption rate constant, t_{max} = time for peak drug concentration in plasma, AUC = area under the plasma drug concentration–time curve.

Common excipients found in oral drug products are listed in and . Excipients should be pharmacodynamically inert. However, excipients may change the functionality of the drug substance and the bioavailability of the drug from the dosage form. For solid oral dosage forms such as compressed tablets, excipients may include (1) a diluent (eg, lactose), (2) a disintegrant (eg, starch), (3) a lubricant (eg, magnesium stearate), and (4) other components such as binding and stabilizing agents. If used improperly in a formulation, the rate and extent of drug absorption may be affected. For example, shows that an excessive quantity of magnesium stearate (a hydrophobic lubricant) in the formulation may retard drug dissolution and slow the rate of drug absorption. The total amount of drug absorbed may also be reduced (). To prevent this problem, the lubricant level should be decreased or a different lubricant selected. Sometimes, increasing the amount of disintegrant may overcome the retarding effect of lubricants on dissolution. However, with some poorly soluble drugs an increase in disintegrant level has little or no effect on drug dissolution because the fine drug particles are not wetted. The influence of some common ingredients on drug absorption parameters is summarized in . These are general trends for typical preparations.

Figure 14-5.

Effect of lubricant on drug dissolution. Percentage of magnesium stearate in formulation.

Figure 14-6.

Effect of lubricant on drug absorption. Percentage of magnesium stearate in formulation. Incomplete drug absorption occurs for formulation with 5% magnesium stearate.

Dissolution and Drug Release Testing

Dissolution and drug release tests are *in-vitro* tests that measure the rate and extent of dissolution or release of the drug substance from a drug product, usually in an aqueous medium under specified conditions. The dissolution test is an important quality control procedure for the drug product and is often linked to product performance *in vivo*. *In-vitro* drug dissolution studies are most often used for monitoring drug product stability and manufacturing process control. The USP-NF (United States Pharmacopeia) sets standards for dissolution and drug release tests of most drug products. Ideally, the dissolution method used for a particular drug product *in vitro* relates to the bioavailability of the drug *in vivo* (see *in-vitro–in-vivo* correlation, below). In addition, the dissolution method should be able to discriminate changes in formulation of the drug product. Furthermore, dissolution and drug release tests are important quality control components for the manufacture of the drug product. As a quality control test, dissolution and drug release testing may be used for:

Batch-to-batch drug release uniformity

Stability

Scale-up and postapproval changes (SUPAC)

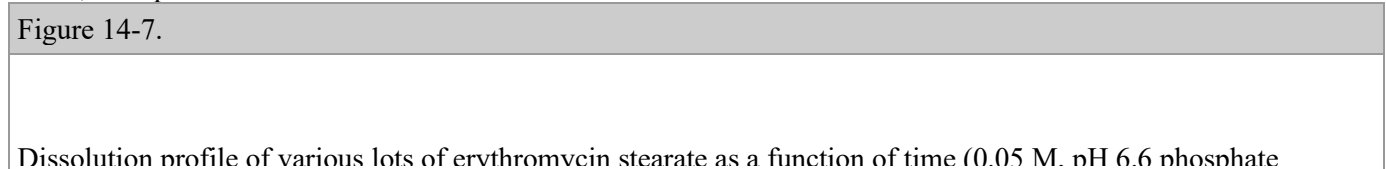Predicting *in-vivo* performance

Often, the dissolution test is a valuable tool in formulation development. A suitable dissolution method may uncover a formulation problem with the drug product that could result in a bioavailability problem. Each dissolution method is specific for the drug product and its formulation. The dissolution test should be able to distinguish between acceptable and unacceptable drug formulations as observed by different drug dissolution rates under the same experimental conditions. A suitable dissolution test should be able to reflect changes in the formulation, manufacturing process, and physical and chemical characteristics of the drug, such as particle size, polymorphs, and surface area (). The dissolution test is a major requirement for scale-up and postapproval changes, SUPAC (see). After a change is made in a formulation, the manufacturer should assess the potential effect of the change on bioequivalence, which usually includes multipoint and/or multimedia dissolution profiling and, if necessary, an *in-vivo* bioequivalence study.

Dissolution Conditions

The development of an appropriate dissolution test requires the investigator to try different agitation rates, different media (including volume and pH of medium), and different kinds of dissolution apparatus (). The current USP-NF (United States Pharmacopeia) lists officially recognized dissolution apparatus. Once a suitable dissolution test is obtained, acceptable dissolution criteria are developed for the drug product and its formulation. These criteria or dissolution specifications (eg, percent of drug dissolved in 30 minutes) are used to investigate formulation problems. For example, devised a method using pH 6.6 phosphate buffer as the dissolution medium instead of 0.1 N HCL to avoid instability of the antibiotic drug erythromycin. Using the USP paddle method at 50 rpm and a temperature of 22°C, the dissolution of the various erythromycin tablets was shown to vary with the source of the bulk active drug (as shown in and).

Table 14.5 Conditions that May Affect Drug Dissolution and Release
Drug substance
Particle size
Polymorph
Surface area
Chemical stability in dissolution media
Formulation of drug product
Excipients (lubricants, suspending agents, etc)
Medium
Volume
pH
Molarity
Co-solvents, added enzymes/surfactants
Temperature of medium
Apparatus
Hydrodynamics
Agitation rate
Shape of dissolution vessel
Placement of tablet in vessel
Sinkers (for floating products and products that stick to side of vessel)

Table 14.6 Dissolution of Erythromycin Stearate Bulk Drug and Corresponding Tablets

	Percent Dissolution After 1.0 hr		
Curve No.	Bulk Drug	500-mg Tablet	250-mg Tablet
4	49	44	
6	72	70	
7	75	70	
—	78	—	80
8	82	75	
9	92	85	

From , with permission.

Figure 14-7.

Dissolution profile of various lots of erythromycin stearate as a function of time (0.05 M, pH 6.6 phosphate

buffer).
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Visual observations of the dissolution and disintegration behavior of the drug product are important and should be recorded. Dissolution and disintegration patterns can indicate manufacturing variables. These observations are particularly useful during method development and formulation optimization.

The size and shape of the dissolution vessel may affect the rate and extent of dissolution. For example, dissolution vessels range in size from several milliliters to several liters. The shape may be round-bottomed or flat, so the tablet might lie in a different position in different experiments. The usual volume of the medium is 500–1000 mL. Drugs that are poorly water soluble may require use of a very-large-capacity vessel (up to 2000 mL) to observe significant dissolution. In some cases, 1% sodium lauryl sulfate (SLS) may be used as the dissolution medium for water-insoluble drugs. *Sink conditions* is a term referring to an excess volume of medium that allows the solid drug to dissolve continuously. If the drug solution becomes saturated, no further net drug dissolution will take place. According to the USP-NF, "the quantity of medium used should be not less than 3 times that required to form a saturated solution of the drug substance."

The amount of agitation and the nature of the stirrer affect hydrodynamics of the system, thereby affecting the dissolution rate. Stirring rates must be controlled, and specifications differ between drug products. Low stirring rates (50–75 rpm) are more discriminating of formulation factors affecting dissolution than higher stirring rates. However, higher dissolution rate may be needed for some special formulations in order to obtain reproducible dissolution rates. Suspensions that contain viscous or thickening agents may settle into a diffusion-controlled "cone-shape" region in the flask when stirring rate is too slow. The temperature of the dissolution medium must be controlled, and variations in temperature must be avoided. Most dissolution tests are performed at 37°C. However, for transdermal drug products, the recommended temperature is 32°C.

The nature of the dissolution medium will also affect the dissolution test. The solubility of the drug must be considered, as well as the total amount of drug in the dosage form. The dissolution medium should not be saturated by the drug (ie, sink conditions are maintained). Usually, a volume of medium larger than the amount of solvent needed to completely dissolve the drug is used in the dissolution test. Which medium is best is a matter of considerable controversy. The dissolution medium in many USP dissolution tests is deaerated water or, if substantiated by the solubility characteristics of the drug or formulation, a buffered aqueous solution (typically pH 4–8) or dilute HCl may be used. The significance of deaeration of the medium should be determined. Various investigators have used 0.1 N HCl, phosphate buffer, simulated gastric juice, water, and simulated intestinal juice, depending on the nature of the drug product and the location in the gastrointestinal tract where the drug is expected to dissolve.

The design of the dissolution apparatus, along with the factors described above, has a marked effect on the outcome of the dissolution test. No single apparatus and test can be used for all drug products. Each drug product must be tested individually with the dissolution test that best correlates to *in-vivo* bioavailability.

Usually, the report on the dissolution test will state that a certain percentage of the labeled amount of drug product must dissolve within a specified period of time. In practice, the absolute amount of drug in the drug product may vary from tablet to tablet. Therefore, a number of tablets from each lot are usually tested to get a representative dissolution rate for the product.

Compendial Methods of Dissolution

The USP-NF provides several official methods for carrying out dissolution tests of tablets, capsules and other special products such as transdermal preparations. Tablets are grouped into uncoated, plain-coated, and enteric-coated tablets. The selection of a particular method for a drug is usually specified in the monograph for a particular drug product. Buccal and sublingual tablets are tested applying the uncoated tablet procedure. lists various types of dissolution apparatus and the type of drug products that is often used with the apparatus. For Apparatus 1 and 2, low rotational speeds affect the reproducibility of the hydrodynamics; whereas at high rotational speeds, turbulence may occur. Dissolution profiles that show the drug dissolving too slowly or too rapidly may justify increasing or decreasing the rotational speed ().

Table 14.7 Dissolution Apparatus		
Apparatus[a]	**Name**	**Drug Product**
Apparatus 1	Rotating basket	Tablets
Apparatus 2	Paddle	Tablets, capsules, modified drug products, suspensions
Apparatus 3	Reciprocating cylinder	Extended-release drug products
Apparatus 4	Flow cell	Drug products containing low-water-soluble drugs
Apparatus 5	Paddle over disk	Transdermal drug products

Apparatus 6	Cylinder	Transdermal drug products
Apparatus 7	Reciprocating disk	Extended-release drug products
Rotating bottle	(Non-USP-NF)	Extended-release drug products (beads)
Diffusion cell (Franz)	(Non-USP-NF)	Ointments, creams, transdermal drug products

[a]Apparatus 1–7 refer to compendial dissolution apparatus in USP-NF.

Rotating Basket Method (Apparatus 1)

The rotating basket apparatus (Apparatus 1) consists of a cylindrical basket held by a motor shaft. The basket holds the sample and rotates in a round flask containing the dissolution medium. The entire flask is immersed in a constant-temperature bath set at 37°C. The rotating speed and the position of the basket must meet specific requirements set forth in the current USP. The most common rotating speed for the basket method is 100 rpm. Dissolution calibration standards are available to make sure that these mechanical and operating requirements are met. Calibration tablets containing prednisone are made specially for dissolution tests requiring disintegrating tablets, whereas salicylic acid calibration tablets are used as a standard for nondisintegrating tablets. Apparatus 1 is generally preferred for capsules and for dosage forms that tend to float or disintegrate slowly.

Paddle Method (Apparatus 2)

The paddle apparatus (Apparatus 2) consists of a special, coated paddle that minimizes turbulence due to stirring (). The paddle is attached vertically to a variable-speed motor that rotates at a controlled speed. The tablet or capsule is placed into the round-bottom dissolution flask, which minimizes turbulence of the dissolution medium. The apparatus is housed in a constant-temperature water bath maintained at 37°C, similar to the rotating-basket method. The position and alignment of the paddle are specified in the USP. The paddle method is very sensitive to tilting. Improper alignment may drastically affect the dissolution results with some drug products. The same set of dissolution calibration standards is used to check the equipment before tests are run. The most common operating speeds for Apparatus 2 are 50 rpm for solid oral dosage forms and 25 rpm for suspensions. Apparatus 2 is generally preferred for tablets. A *sinker*, such as a few turns of platinum wire, may be used to prevent a capsule or tablet from floating. A sinker may also be used for film-coated tablets that stick to the vessel walls or to help position the tablet or capsule under the paddle (). The sinker should not alter the dissolution characteristics of the dosage form.

Figure 14-8.

Typical setup for performing the USP dissolution test with the Distek 2000. The system is equipped with a height adjustment ring for easy adjustment of paddle height.
(Drawing courtesy of Distek inc, Somerset, NJ.)

Reciprocating Cylinder Method (Apparatus 3)

The reciprocating cylinder apparatus (Apparatus 3) consists of a set of cylindrical, flat-bottomed glass vessels equipped with reciprocating cylinders for dissolution testing of extended-release products, particularly bead-type modified-release dosage forms. Six units are tested, and the dissolution medium is maintained at 37°C.

Flow-Through-Cell Method (Apparatus 4)

The flow-through-cell apparatus (Apparatus 4) consists of a reservoir for the dissolution medium and a pump that forces dissolution medium through the cell holding the test sample. Flow rate ranges from 4 to 16 mL/min. Six samples are tested during the dissolution testing, and the medium is maintained at 37°C. Apparatus 4 may be used for modified-release dosage forms that contain active ingredients having very limited solubility.

There are many variations of this method. Essentially, the sample is held in a fixed position while the dissolution medium is pumped through the sample holder, thus dissolving the drug. Laminar flow of the medium is achieved by using a pulseless pump. Peristaltic or centrifugal pumps are not recommended. The flow rate is usually maintained between 10 and 100 mL/min. The dissolution medium may be fresh or recirculated. In the case of fresh medium, the dissolution rate at any moment may be obtained, whereas in the official paddle or basket method, cumulative dissolution rates are monitored. A major advantage of the flow-through method is the easy maintenance of a sink condition for dissolution. A large volume of dissolution medium may also be used, and the mode of operation is easily adapted to automated equipment.

Paddle-over-Disk Method (Apparatus 5)

The USP-NF also lists a paddle-over-disk method for testing the release of drugs from transdermal products. The apparatus (Apparatus 5) consists of a sample holder or disk assembly that holds the product. The entire preparation is placed in a dissolution flask filled with specified medium maintained at 32°C. The paddle is placed directly over the disk assembly. Samples are drawn midway between the surface of the dissolution medium and the top of the paddle blade at specified times. Similar to dissolution testing with capsules and tablets, six units are tested during each run.

Acceptance criteria are stated in the individual drug monographs.

Cylinder Method (Apparatus 6)

The cylinder method (Apparatus 6) for testing transdermal preparation is modified from the basket method (Apparatus 1). In place of the basket, a stainless steel cylinder is used to hold the sample. The sample is mounted onto cuprophan (an inert porous cellulosic material) and the entire system adheres to the cylinder. Testing is maintained at 32°C. Samples are drawn midway between the surface of the dissolution medium and the top of the rotating cylinder for analysis.

Reciprocating Disk Method (Apparatus 7)

In the reciprocating disk method for testing transdermal products, a motor drive assembly (Apparatus 7) is used to reciprocate the system vertically, and the samples are placed on disk-shaped holders using cuprophan supports. The test is also carried out at 32°C, and reciprocating frequency is about 30 cycles per minute. The acceptance criteria are listed in the individual drug monographs.

Methods for Testing Enteric-Coated Products

USP-NF lists two methods (Method A and Method B) for testing enteric-coated products. The latest revision of the USP-NF should be consulted for complete details of the methods.

Both methods require that the dissolution test be performed in the apparatus specified in the drug monograph (usually Apparatus 2 or Apparatus 1). The product is first tested with 0.1 N HCl for 2 hours and then changed to pH 6.8 buffer medium. The buffer stage generally runs for 45 minutes or for the time specified in the monograph. The objective is that no significant dissolution occurs in the acid phase (less than 10% for any sample unit), and a specified percentage of drug must be released in the buffer phase. Specifications are set in the individual drug monographs.

Meeting Dissolution Requirements

Dissolution test times and specifications are usually established on the basis of an evaluation of dissolution profile data. The dissolution test time points should be selected to characterize adequately the ascending and plateau phases of the dissolution curve. USP-NF sets dissolution requirements for many products (). The requirements apply to both the basket and the paddle methods. The amount of drug dissolved within a given time period (Q) is expressed as a percentage of label content. The Q is generally specified in the monograph for a drug product to pass the dissolution test. Three stages (S_1, S_2, and S_3) of testing are allowed by USP-NF. Initially, six tablets or capsules are tested for the dissolution test. If the dissolution test fails to meet the criteria for S_1, then six more units are tested. Dissolution testing continues until the dissolution criteria are met or until the three stages are exhausted ().

Table 14.8 Dissolution Acceptance		
Stage	**Number Tested**	**Acceptance Criteria**
S_1	6	Each unit is not less than $Q + 5\%$
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$

Adapted with permission from *United States Pharmacopeia* .

For many products the passing value for Q is set at 75% in 45 minutes. Some products require a Q of 85% in 30 minutes, others 75% in 60 minutes. For a new drug product, setting the dissolution specification requires a thorough consideration of the physical and chemical properties of the drug. In addition to the consideration that the dissolution test must ensure consistent bioavailability of the product, the test must provide for variation in manufacturing and testing variables so that a product may not be improperly rejected ().

Alternative Methods of Dissolution Testing

Rotating Bottle Method

The rotating bottle method was suggested in NF-XIII (National Formulary) but has become less popular since. The rotating bottle method was used mainly for controlled-release beads. For this purpose the dissolution medium may be easily changed, such as from artificial gastric juice to artificial intestinal juice. The equipment consists of a rotating rack that holds the sample drug products in bottles. The bottles are capped tightly and rotated in a 37°C temperature bath. At various times, the samples are removed from the bottle, decanted through a 40-mesh screen, and the residues are assayed. To the remaining drug residues within the bottles are added an equal volume of fresh medium and the dissolution test is continued. A dissolution test with pH 1.2 medium for 1 hour, pH 2.5 medium for the next 1 hour, followed by pH 4.5 medium for 1.5 hours, pH 7.0 medium for 1.5 hours, and pH 7.5 medium for 2

hours was recommended to simulate condition of the gastrointestinal tract. The main disadvantage is that this procedure is manual and tedious. Moreover, it is not known if the rotating bottle procedure results in a better *in-vitro–in-vivo* correlation (see below) for drugs.

Intrinsic Dissolution Method

Most methods for dissolution deal with a finished drug product. Sometimes a new drug or substance may be tested for dissolution without the effect of excipients or the fabrication effect of processing. The dissolution of a drug powder by maintaining a constant surface area is called *intrinsic dissolution*. Intrinsic dissolution is usually expressed as mg/cm^2/min. In one method, the basket method is adapted to test dissolution of powder by placing the powder in a disk attached with a clipper to the bottom of the basket.

Peristalsis Method

The peristalsis method attempts to simulate the hydrodynamic conditions of the gastrointestinal tract in an *in-vitro* dissolution device. The apparatus consists of a rigid plastic cylindrical tubing fitted with a septum and rubber stoppers at both ends. The dissolution chamber consists of a space between the septum and the lower stopper. The apparatus is placed in a beaker containing the dissolution medium. The dissolution medium is pumped with peristaltic action through the dosage form.

Diffusion Cells

Static and flow-through diffusion cells are commercially available to characterize *in-vitro* drug release and drug permeation kinetics from a topical drug product (eg, ointment, cream) or transdermal drug product. The *Franz diffusion cell* is a static diffusion system that is used for characterizing drug permeation through a skin model (). The source of skin may be human cadaver skin or animal skin (eg, hairless mouse skin). Anatomically, each skin site (eg, abdomen, arm) has different drug permeation qualities. The skin is mounted on the Franz diffusion cell system. The drug product (eg, ointment) is placed on the skin surface and the drug permeates across the skin into a receptor fluid compartment that may be sampled at various times. The Franz diffusion cell system is useful for comparing *in-vitro* drug release profiles and skin permeation characteristics to aid in selecting an appropriate formulation that has optimum drug delivery.

Figure 14-9.

The Franz diffusion cell.
(Courtesy of Hanson Research Corporation [http://www.hansonresearch.com/vert-diffusion-cell.htm], with permission.)

Problems of Variable Control in Dissolution Testing

Various equipment and operating variables are associated with dissolution testing. Depending on the particular dosage form involved, the variables may or may not exert a pronounced effect on the rate of dissolution of the drug or drug product. Variations of 25% or more may occur with the same type of equipment and procedure. The centering and alignment of the paddle is critical in the paddle method. Turbulence can create increased agitation, resulting in a higher dissolution rate. Wobbling and tilting due to worn equipment should be avoided. The basket method is less sensitive to the tilting effect. However, the basket method is more sensitive to clogging due to gummy materials. Pieces of small particles can also clog up the basket screen and create a local non-sink condition for dissolution. Furthermore, dissolved gas in the medium may form air bubbles on the surface of the dosage form unit and can affect dissolution in both the basket and paddle methods.

The interpretation of dissolution data is probably the most difficult job for the pharmacist. In the absence of *in-vivo* data, it is generally impossible to make valid conclusions about bioavailability from the dissolution data alone. The use of various testing methods makes it even more difficult to interpret dissolution results, because there is no simple correlation among dissolution results obtained with various methods. For many drug products, the dissolution rates are higher with the paddle method. Dissolution results at 50 rpm with the paddle method may be equivalent to dissolution at 100 rpm with the basket method. In a study of sustained-release theophylline tablets compressed at various degrees of hardness, found that, at 50 rpm, dissolution with the paddle method was faster than that of the basket method for tablets of 4.0-kg hardness. However, with tablets of 6.8-kg hardness, similar dissolution profiles were obtained at 125 rpm for the basket and paddle methods over a period of 6 hours. With both methods, increased dissolution rates were observed as the rates were increased. Apparently, the composition of the formulation as well as the process variables in manufacturing may both be important. No simple correlation can be made for dissolution results obtained with different methods.

In a comparison of the paddle and basket methods in evaluating a sustained-release pseudoephedrine–guaifenesin preparation, found that the paddle method was more discriminating in demonstrating dissolution differences among drug products. At 100 rpm, the basket method failed to pick up formulation differences detected by the paddle method.

In the absence of *in-vivo* data, the selection of the dissolution method is based on the type of drug product to be

tested. For example, a low-density preparation may be poorly wetted in the basket method. A gummy preparation may clog up the basket screen; therefore the paddle method is preferred. A floating dosage form (eg, suppository) may be placed in a stainless steel coil (sinker) so that the dosage form remains at the bottom of the dissolution flask. For many drugs, a satisfactory dissolution test may be obtained with more than one method by optimizing the testing conditions.

In-Vitro–In-Vivo Correlation

In-vitro–in-vivo correlation (IVIVC) establishes a relationship between a biological property of the drug (such as pharmacodynamic effect or plasma drug concentration) and a physicochemical property of the drug product containing the drug substance, such as dissolution rate (). In order to have an IVIVC, some property of the drug release from the drug product *in vitro*, under specified conditions, must relate to *in-vivo* drug performance. Dissolution tests should discriminate formulation factors that may affect bioavailability of the drug (see). In some cases, dissolution tests for immediate-release solid oral drug products may be overdiscriminating and a clinically acceptable product might perform poorly in the dissolution test. When a proper dissolution method is chosen, the rate of dissolution of the product may be correlated to the rate of absorption of the drug into the body. Well-defined *in-vitro–in-vivo* correlations have been reported for modified-release drug products () but have been more difficult to predict for immediate-release drug products. An IVIVC should be evaluated to demonstrate that predictability of *in-vivo* performance of a drug product from its *in-vitro* dissolution characteristics is maintained over a range of *in-vitro* dissolution release rates and manufacturing changes. The *in-vitro* dissolution characteristics are dependent on the physical properties of the active pharmaceutical ingredient (API), the drug formulation, the hydrodynamics of the dissolution apparatus, and the dissolution medium. IVIVC may be useful for establishing upper and lower dissolution specifications for a solid oral dosage form.

For multisource drug products such as brand-name drug products and marketed generic drug products containing the same active drug, USP-NF may list multiple dissolution tests, one for each product. For example, USP-NF includes 10 separate dissolution tests for theophylline extended-release capsules that are labeled for dosing every 12 hours. USP-NF has separate and distinct dissolution test requirements for two different phenytoin sodium capsules. For extended-release phenytoin sodium capsules, USP-NF states that "not more than 35%, between 30% and 70% and not less than 85% of the labeled amount of $C_{15}H_{11}N_2NaO_2$ in the Extended Capsules dissolves in 30 minutes, 60 minutes, and 120 minutes, respectively, under the specified dissolution conditions." In contrast, about tolerances for "Prompt Phenytoin Sodium Capsules," USP states "not less than 85% of the labeled amount of $C_{15}H_{11}N_2NaO_2$ in the Prompt Capsules dissolves in 30 minutes.*"*

It is important to note that multisource, pharmaceutically equivalent drug products may not be bioequivalent even if these drug products meet the same USP-NF monograph specifications. In the United States, only FDA-approved generic, bioequivalent drug products that meet the requirements for therapeutic equivalence may be interchanged. These generic drug products are listed in the FDA publication, Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book (www.fda.gov/cder/orange/default.htm). Bioequivalent drug products are discussed in .

Biopharmaceutic Drug Classification System

The Biopharmaceutic Drug Classification system, BCS, discussed more fully in , is a predictive approach to relate certain physicochemical characteristics of a drug substance and drug product to *in-vivo* bioavailability. The BCS is not a direct *in-vitro–in-vivo* correlation. For example, the drug substance from an immediate-release oral drug product would tend to be rapidly and mostly absorbed if the drug substance and drug product meet the criteria for BCS Class I drugs. A BCS Class I drug product contains a highly soluble drug substance that is highly permeable and from which the drug rapidly dissolves from the drug product (). Since predictability is a major function of IVIVC, any system that predicts *in-vivo* performance from *in-vitro* data may be considered an IVIVC ().

Dissolution Rate versus Absorption Rate

If dissolution of the drug is rate limiting, a faster dissolution rate may result in a faster rate of appearance of the drug in the plasma. It may be possible to establish a correlation between rate of dissolution and rate of absorption of the drug.

The absorption rate is usually more difficult to determine than peak absorption time. Therefore, the absorption time may be used in correlating dissolution data to absorption data. In the analysis of *in-vitro–in-vivo* drug correlation, rapid drug dissolution may be distinguished from the slower drug absorption by observation of the absorption time for the preparation. The absorption time refers to the time for a constant amount of drug to be absorbed. In one study involving three sustained-release aspirin products (), the dissolution time for the preparations were linearly correlated to the absorption times (). The results from this study demonstrated that aspirin was rapidly absorbed and was very much dependent on the dissolution rate for absorption.

Figure 14-10.

An example of correlation between time required for a given amount of drug to be absorbed and time required for the same amount of drug to be dissolved *in vitro* for three sustained-release aspirin products.
()

Percent of Drug Dissolved versus Percent of Drug Absorbed

If a drug is absorbed completely after dissolution, a linear correlation may be obtained by comparing the percentage of drug absorbed to the percentage of drug dissolved. In choosing the dissolution method, one must consider the appropriate dissolution medium and use a slow dissolution stirring rate so that *in-vivo* dissolution is approximated. Aspirin is absorbed rapidly, and a slight change in formulation may be reflected in a change in the amount and rate of drug absorption during the period of observation (and). If the drug is absorbed slowly, which occurs when absorption is the rate-limiting step, a difference in dissolution rate of the product may not be observed. In this case, the drug would be absorbed very slowly independent of the dissolution rate.

Figure 14-11.

An example of continuous *in-vivo–in-vitro* correlation of aspirin.
()

Maximum Plasma Concentrations versus Percent of Drug Dissolved *In-Vitro*

When different drug formulations are tested for dissolution, a poorly formulated drug may not be completely dissolved and released, resulting in lower plasma drug concentrations. The percentage of drug released at any time interval will be greater for the more bioavailable drug product. When such drug products are tested *in-vivo*, the peak drug serum concentration will be higher for the drug product that shows the highest percent of drug dissolved. An example of *in-vitro–in-vivo* correlation for 100-mg phenytoin sodium capsules is shown in . Several products were tested (). A linear correlation was observed between the maximum drug concentration in the body and the percent of drug dissolved *in-vitro*.

Figure 14-12.

In-vitro–in-vivo correlation between C_{max} and percent drug dissolved. Top, 30 min (slope = 0.06, $r = 0.902$, $p < 0.001$). Bottom, 60 min (slope = 0.10, $r = 0.940$, $p < 0.001$.) (Letters on graph indicate different products.)
()

The dissolution study on the phenytoin sodium products () showed that the fastest dissolution rate was product C, for which about 100% of the labeled contents dissolved in the test (). Interestingly, these products also show the shortest time to reach peak concentration (t_{max}). The t_{max} is dependent on the absorption rate constant. In this case, the fastest absorption would also result in the shortest t_{max} (see).

Figure 14-13.

In-vitro–in-vivo correlation between t_{max} and percent drug dissolved in 30 minutes by basket method. Letters on graph indicate different products.
()

Serum Drug Concentration versus Percent of Drug Dissolved

In a study on aspirin absorption, the serum concentration of aspirin was correlated to the percent of drug dissolved using an *in-vitro* dissolution method (). The dissolution medium was simulated gastric juice. Because aspirin is rapidly absorbed from the stomach, the dissolution of the drug is the rate-limiting step, and various formulations with different dissolution rates will cause differences in the serum concentration of aspirin by minutes ().

Figure 14-14.

Example of *in-vivo–in-vitro* two-point correlation between 10-minute serum level and percent dissolved at 1.2

minutes (O) and the 20-minute serum level and percent dissolved 4.2 minutes (   ).
()

Failure of Correlation of *In-Vitro* Dissolution to *In-Vivo* Absorption

Although there are many published examples of drugs with dissolution data that correlate well with drug absorption in the body, there are also many examples indicating poor correlation of dissolution to drug absorption. There are also instances where a drug has failed the dissolution test and yet is well absorbed. The problem of no correlation between bioavailability and dissolution may be due to the complexity of drug absorption and the weakness of the dissolution design. For example, a product that involves fatty components may be subjected to longer retention in the gastrointestinal tract. The effect of digestive enzymes may also play an important role in the dissolution of the drug *in vivo*. These factors may not be adequately simulated with a simple dissolution medium. An excellent example showing the importance of dissolution design is shown in . Dissolution tests using four different dissolution media were performed for two quinidine gluconate sustained-release tablets (). Brand BE was known to be bioavailable, whereas product BO-1 was known to be incompletely absorbed. It is interesting to see that using acid medium as well as acid followed by pH 7.4 buffer did not distinguish the two products well, whereas using water or pH 5.4 buffer as dissolution medium clearly distinguished the "good" product from the one that was not completely available. In this case, the use of an acid medium is consistent with the physiologic condition in the stomach, but this procedure would be misleading as a quality control tool. It is important that any new dissolution test be carefully researched before being adopted as a method for predicting drug absorption.

Figure 14-15.
Dissolution profile of two quinidine gluconate sustained release products in different dissolution media. Each data point is the mean of 12 tablets. (= product BE, O = product BO-1.) ()

Biopharmaceutic Considerations

Some of the major biopharmaceutic considerations in the design of a drug product are given in . The prime considerations in the design of a drug product are safety and efficacy. The drug product must effectively deliver the active drug at an appropriate rate and amount to the target receptor site so that the intended therapeutic effect is achieved. The finished dosage form should not produce any additional side effects or discomfort due to the drug and/or excipients. Ideally, all excipients in the drug product should be inactive ingredients alone or in combination in the final dosage form.

Table 14.9 Biopharmaceutic Considerations in Drug Product Design	
Pharmacodynamic considerations	Patient considerations
Therapeutic objective	Compliance and acceptability of drug product
Toxic effects	Cost
Adverse reactions	Manufacturing considerations
Drug considerations	Cost
Chemical and physical properties of drug	Availability of raw materials
Drug product considerations	Stability
Pharmacokinetics of drug	Quality control
Bioavailability of drug	Method of manufacturing
Route of drug administration	
Desired drug dosage form	
Deslred dose of drug	

The finished drug product is a compromise of various factors, including therapeutic objectives, pharmacokinetics, physical and chemical properties, manufacturing, cost, and patient acceptance. Most important, the finished drug product should meet the therapeutic objective by delivering the drug with maximum bioavailability and minimum adverse effects.

Pharmacodynamic Considerations

Therapeutic considerations concern the pharmacodynamic and pharmacologic properties of the drug, including the desired therapeutic response as well as the type and frequency of toxic and/or adverse reactions of the drug. The therapeutic objective will influence the type of drug product to be manufactured. A drug used to treat an acute illness should be formulated to release the drug rapidly, allowing for quick absorption and rapid onset. For example,

nitroglycerin is formulated in a sublingual tablet for the treatment of angina pectoris. For prophylactic use in the treatment of certain chronic diseases such as asthma, an extended- or controlled-release dosage form is preferred. The extended-release dosage form releases the drug slowly, thereby controlling the rate of drug absorption and allowing for more constant plasma drug concentrations. In some cases, an immediate-drug-release component is included in the extended-release dosage form, to allow for both rapid onset followed by a slower sustained release of the drug. Controlled release and modified release dosage forms are discussed in .

Drug Considerations

As discussed earlier, the physicochemical properties of the drug () are major factors that are controlled or modified by the formulator. These physicochemical properties influence the type of dosage form and the process for the manufacture of the dosage form. Physical properties of the drug—such as dissolution, particle size, and crystalline form—are influenced by methods of processing and manufacturing. If the drug has low aqueous solubility and an intravenous injection is desired, a soluble salt of the drug may be prepared. Chemical instability or chemical interactions with certain excipients will also affect the type of drug product and its method of fabrication. There are many creative approaches to improve the product; only a few are discussed in this chapter.

Drug Product Considerations

Pharmacokinetics of the Drug

Knowledge of the pharmacokinetic profile of the drug is important to estimate the appropriate amount (dose) of drug in the drug product and a release rate that will maintain a desired drug level in the body. The therapeutic window determines the desired or target plasma drug concentration that will be effective with minimal adverse effects. Drug concentrations higher than the therapeutic window (eg, minimum toxic concentration) may cause more intense pharmacodynamic and/or toxic response; drug concentrations below the therapeutic window (eg, minimum effective concentration) may be subtherapeutic. For drugs with a narrow therapeutic window, knowledge of the pharmacokinetic profile enhances drug therapy for many products through the development of an appropriate dosage regimen, including the size of the dose and the dosing frequency, to achieve and maintain the target drug concentration.

Bioavailability of the Drug

The stability of the drug in the gastrointestinal tract, including the stomach and intestine, is another consideration. Some drugs, such as penicillin G, are unstable in the acidic medium of the stomach. The addition of buffering in the formulation or the use of an enteric coating on the dosage form will protect the drug from degradation at a low pH. Some drugs have poor bioavailability because of first-pass effects (presystemic elimination). If oral drug bioavailability is poor due to metabolism by enzymes in the gastrointestinal tract or in the liver, then a higher dose may be needed, as in the case of propranolol, or an alternative route of drug administration, as in the case of insulin. Drugs that are only partially absorbed after oral administration usually leave residual drug in the gastrointestinal tract, which may cause local bowel irritation or alter the normal gastrointestinal flora. Designing dosage forms to contain unabsorbed drug contains risk that under unusual conditions (eg, change in diet or disease condition), complete drug absorption can occur leading to excessive drug bioavailability and toxicity. If the drug is not absorbed after the oral route or a higher dose causes toxicity, then the drug must be given by an alternative route of administration, and a different dosage form such as a parenteral drug product might be needed.

Dose Considerations

The size of the dose in the drug product is based on the inherent potency of the drug and its apparent volume of distribution, which determines the target plasma drug concentration needed for the desired therapeutic effect. For some drugs, wide variation in the size of the dose is needed for different patients because of large intersubject differences in the pharmacokinetics and bioavailability of the drug. Therefore, the drug product must be available in several dose strengths to allow for individualized dosing. Some tablets are also scored for breaking, to allow the administration of fractional doses.

The size and shape of a solid oral drug product are designed for easy swallowing. The total size of a drug product is determined by the dose of the drug and any additional excipients needed to manufacture the desired dosage form. For oral dosage forms, if the required dose is large (1 g or more), then the patient may have difficulty in swallowing the drug product. For example, many patients may find a capsule-shaped tablet (caplet) easier to swallow than a large round tablet. Large or oddly shaped tablets, which may become lodged in the esophageal sphincter during swallowing, are generally not manufactured. Some esophageal injuries due to irritating drug lodged in the esophagus have been reported with potassium chloride tablets and other drugs. Older patients may have more difficulties in swallowing large tablets and capsules. Most of these swallowing difficulties may be overcome by taking the product with a large amount of fluid.

Dosing Frequency

The dosing frequency is related to the clearance of the drug and the target plasma drug concentration. If the pharmacokinetics show that the drug has a short duration of action due to a short elimination half-life or rapid clearance from the body, the drug must be given more frequently. To minimize fluctuating plasma drug concentrations and improve patient compliance, an extended-release drug product may be preferred. An extended-

release product contains two or more doses of the drug that are released over a prolonged period ().

Patient Considerations

The drug product must be acceptable to the patient. Poor patient compliance may result from poor product attributes, such as difficulty in swallowing, disagreeable odor, bitter medicine taste, or two frequent and/or unusual dosage requirements. In recent years, creative packaging has allowed the patient to remove one tablet each day from a specially designed package so that the daily doses are not missed. This innovation improves compliance. Of course, pharmacodynamic factors, such as side effects of the drug or an allergic reaction, also influence patient compliance.

Route of Drug Administration

The route of drug administration () affects the bioavailability of the drug, thereby affecting the onset and duration of the pharmacologic effect. In the design of a drug dosage form, the pharmaceutical manufacturer must consider (1) the intended route of administration; (2) the size of the dose; (3) the anatomic and physiologic characteristics of the administration site, such as membrane permeability and blood flow; (4) the physicochemical properties of the site, such as pH, osmotic pressure, and presence of physiologic fluids; and (5) the interaction of the drug and dosage form at the administration site, including alteration of the administration site due to the drug and/or dosage form. Although drug responses are quite similar with different routes of administration, there are examples in which severe differences in response may occur. For example, with the drug isoproterenol, a difference in activity of a thousandfold has been found, attributed to different routes of administration. shows the change in heart rate due to isoproterenol with different routes of administration. Studies have shown that isoproterenol is metabolized in the gut and during passage through the liver. The rate and types of metabolite formed are found to be different depending on the routes of administration.

Figure 14-16.
Dose–response curve to isoproterenol by various routes in dogs. ()

Oral Drug Products

The major advantages of oral drug products are the convenience of administration, safety, and the elimination of discomforts involved with injections. The hazard of rapid intravenous administration causing toxic high concentration of drug in the blood is avoided. The main disadvantages of oral drug products are the potential problems of reduced, erratic, or incomplete bioavailability. Unabsorbed drug may also alter the contents and microbiologic flora of the gastrointestinal tract. In addition, nausea or gastrointestinal discomfort may occur with drugs that cause local irritation. Bioavailability may be altered by drug and food interactions (see).

Highly ionized drug molecules are not absorbed easily. The ganglion-blocking drugs hexamethonium, pentolinium, and bretylium are ionized at intestinal pH. Therefore, they are not sufficiently absorbed orally to be effective. Neomycin, gentamicin, and cefamandole are not well absorbed orally. In the case of neomycin, after oral administration the drug will concentrate in the gastrointestinal tract to exert its local antibacterial effect. Drugs with large molecular weights may not be well absorbed when given orally. There is some evidence that large drug molecules may be absorbed through the lymphatic system when formulated with a "carrier." The mechanism is not known. Some large molecules are absorbed when administered in solution with a surface-active agent. For example, cyclosporine has been given orally with good absorption when formulated with a surfactant in oil. A possible role of the oil is to stimulate the flow of lymph as well as to delay retention of the drug. Oily vehicles have been used to lengthen the gastrointestinal transit time of oral preparations.

Absorption of Lipid-Soluble Drugs

Most hydrophobic drugs are poorly soluble in water and generally are not well absorbed orally because of failure of the drug to dissolve in the fluids of the gastrointestinal tract. These lipophilic drugs are more soluble in lipids or oily vehicles. Lipid-soluble drugs given with fatty excipients mix with digested fatty acids, which are emulsified by bile in the small intestine. The emulsified drug is then absorbed through the GI mucosa or through the lymphatic system. A normal digestive function of the small intestine is the digestion and absorption of fats such as triglycerides. These fats are first hydrolyzed into monoglycerides and fatty acids by pancreatic lipase. The fatty acids then react with carrier lipoproteins to form chylomicrons, which are absorbed through the lymph. The chylomicrons eventually release the fatty acids, and any lipophilic drugs incorporated in the oil phase. Fat substances trigger receptors in the stomach to delay stomach emptying and reduce GI transit rates. Prolonged transit time allows more contact time for increased drug absorption.

When griseofulvin or phenytoin was given orally in corn oil suspensions, an increase in drug absorption was demonstrated (). The increase in absorption was attributed to the formation of mixed micelles with bile secretions, which aid drug dissolution.

The bioavailability of metaxalone (Skelaxin), a hydrophobic drug, is greatly increased when it is given with a high-fat meal. In addition, stomach emptying may be delayed depending on the volume and nature of the oil. Long-chain

fatty acids (above C-10) are more effective than short-chain acids in delaying stomach emptying. Unsaturated fatty acids are more effective than saturated straight-chain fatty acids; triglycerides are not as effective as fatty acids. Oleic acid, arachis oil, and myristic acid also delay stomach emptying. For example, the bioavailability of a water-insoluble antimalarial drug was increased in dogs when oleic acid was incorporated as part of a vehicle into a soft gelatin capsule ().

Calcium carbonate, a source of calcium for the body, was only about 30% available in a solid dosage form, but was almost 60% bioavailable when dispersed in a special vehicle as a soft gelatin capsule (). Bleomycin, an anticancer drug (MW 1500), is poorly absorbed orally and therefore was formulated for absorption through the lymphatic system. The lymphotropic carrier was dextran sulfate. Bleomycin was linked ionically to the carrier to form a complex. The carrier dextran (MW 500,000) was too large to be absorbed through the membrane and pass into the lymphatic vessels ().

Gastrointestinal Side Effects

Many orally administered drugs are irritating to the stomach. These drugs may cause nausea or stomach pain when taken on an empty stomach. In some cases, food or antacids may be given together with the drug to reduce stomach irritation. Alternatively, the drug may be enteric coated to reduce gastric irritation. A common drug that causes irritation is aspirin. Buffered aspirin tablets, enteric-coated tablets, and granules are available. However, enteric coating may sometimes delay or reduce the amount of drug absorbed. Furthermore, enteric coating may not abolish gastric irritation completely, because the drug may occasionally be regurgitated back to the stomach after the coating dissolves in the intestine. Enteric-coated tablets may be greatly affected by the presence of food in the stomach. The drug may not be released from the stomach for several hours when stomach emptying is delayed by food. Buffering material or antacid ingredients have also been used with aspirin to reduce stomach irritation. When a large amount of antacid or buffering material is included in the formulation, dissolution of aspirin may occur quickly, leading to reduced irritation to the stomach. However, many buffered aspirin formulations do not contain sufficient buffering material to make a difference in dissolution in the stomach.

Certain drugs have been formulated into soft gelatin capsules to improve drug bioavailability and reduce gastrointestinal side effects. If the drug is formulated in the soft gelatin capsule as a solution, the drug may disperse and dissolve more rapidly, leaving less residual drug in the gut and causing less irritation. This approach may be useful for a drug that causes local irritation but will be ineffective if the drug is inherently ulcerogenic. Indomethacin, for example, may cause ulceration in animals even when administered parenterally.

There are many options available to the formulator to improve the tolerance of the drug and minimize gastric irritation. The nature of excipients and the physical state of the drugs are important and must be carefully assessed before a drug product is formulated. Some excipients may improve the solubility of the drug and facilitate absorption, whereas others may physically adsorb the drug to reduce irritation. Often, a great number of formulations must be tested before an acceptable one is chosen.

Buccal and Sublingual Tablets

A drug that diffuses and penetrates rapidly across mucosal membranes may be placed under the tongue and be rapidly absorbed. A tablet designed for release under the tongue is called a *sublingual tablet*. Nitroglycerin, isoproterenol, erythrityl tetranitrate, and isosorbide dinitrate are common examples. Sublingual tablets usually dissolve rapidly.

A tablet designed for release and absorption of the drug in the buccal (cheek) pouch is called a *buccal tablet*. The buccal cavity is the space between the mandibular arch and the oral mucosa, an area well supplied with blood vessels for efficient drug absorption. A buccal tablet may release drug rapidly or may be designed to release drug slowly for a prolonged effect. For example, Sorbitrate sublingual tablet, Sorbitrate chewable tablet, and Sorbitrate oral tablet (Zeneca) are three different dosage forms of isosorbide dinitrate for the relief and prevention of angina pectoris. The sublingual tablet is a lactose formulation that dissolves rapidly under the tongue and is then absorbed. The chewable tablet is chewed, and some drug is absorbed in the buccal cavity; the oral tablet is simply a conventional product for GI absorption. The chewable tablet contains flavor, confectioner's sugar, and mannitol, which are absent in both the oral and sublingual tablets. The sublingual tablet contains lactose and starch for rapid dissolution. The onset of sublingual nitroglycerin is rapid, much faster than when nitroglycerin is taken orally or absorbed through the skin. The duration of action, however, is shorter than with the other two routes. Drug absorbed through the buccal mucosa will not pass through the liver before general distribution. Consequently, for a drug with significant first-pass effect, buccal absorption may provide better bioavailability than oral administration. Some peptide drugs have been reported to be absorbed by the buccal route, which provides a route of administration without the drug being destroyed by enzymes in the GI tract.

A newer approach to drug absorption from the oral cavity has been the development of a translingual nitroglycerin spray (Nitrolinqual Pumpspray). The spray, containing 0.4 mg per metered dose, is given by spraying one or two metered doses onto the oral mucosa at the onset of an acute angina attack.

Fentanyl citrate is a potent, lipid-soluble opioid agonist that crosses mucosal membranes rapidly. Fentanyl has been formulated as a transdermal drug product (Durapress) and as an oral lozenge on a handle (Actiq) containing fentanyl

citrate for oral transmucosal delivery. According to the manufacturer, fentanyl bioavailability from Actiq is about 50%, representing a combination of rapid absorption across the oral mucosa and slower absorption through swallowing and transport across the gastrointestinal mucosa.

Nasal Drug Products

Nasal products provide a simple means of local and/or systemic drug delivery. The nasal mucosa are highly vascularized and easily accessible. The vehicle used for nasal administration must be nonirritating and well tolerated. The most common drug products for local activity are the nasal vasoconstrictors phenylephrine and naphazoline. An example of a new nasal delivery for both local and systemic effect is ipratropium bromide, a drug used for rhinitis and the common cold. In patients with perennial rhinitis, about 10% of the drug was absorbed intranasally (). Nasacort AQ nasal spray (Rhone-Poulenc-Rorer) is triamcinolone acetonide delivered to the nasal area by spray.

Each puff delivers about 50   g of the drug. It is useful for allergic rhinitis. The action is partially systemic and local. Another example is levocabastine, a histamine H1-receptor antagonist developed as levocabastine nasal spray. Peak plasma concentrations (C_{max}) occur within 1 to 2 hours, with systemic availability ranging from 60% to 80% (). Benefits of levocabastine are predominantly mediated through local antihistaminic effects, with some systemic contribution. Butorphanol tartrate nasal spray (Stadol NS) is an opioid analgesic available as a nasal spray for the treatment of pain as a preoperative or preanesthetic medication, as well as for pain relief during labor and for migraine headache. The nasal route offers an alternative to injection. Some biological products such as peptides and proteins have been suggested for nasal delivery, because they are then not digested by enzymes as they are in the GI tract. The luteinizing hormone-releasing hormone agonist buserelin acetate (Suprefact[R] nasal spray—Aventis Pharma) has been formulated with oleic acid for systemic nasal delivery in an experimental formulation. Therapeutic proteins, such as recombinant interferon-alpha/D, have also been investigated for nasal delivery. Detectable levels of

interferon-alpha   /D in serum were achieved via the nasal route and in the lung. Drug bioavailability was 6.8% from the lung in the rat, and 2.9% from the nasal cavity in the rabbit (). Other examples of nasal delivery drug products for systemic drug absorption are Nicotrol for the delivery of nicotine to aid smokers in quitting smoking, and Miacalcin for the delivery of calcitonin salmon, a parathyroid agent for the treatment of postmenopausal osteoporosis.

An *in-vitro* human nasal model was developed as a tool to study the local tolerability of nasal powder forms using excised nasal mucosa in a diffusion chamber (). The suitability of this model was tested using Sandostatin, an octapeptide analog of somatostatin. The drug is also used for ocular treatment of allergic rhinoconjunctivitis as eye drops; it was about 30–60% available systemically by that route.

Recently, a live influenza virus vaccine, FluMist[R] (influenza virus vaccine live, intranasal—Wyeth), has been marketed for intranasal delivery. FluMist is indicated for active immunization for the prevention of disease caused by influenza A and B viruses.

Colonic Drug Delivery

There has been considerable research into the delivery of drugs specifically to the colon after oral administration (). Crohn's disease or chronic inflammatory colitis may be more effectively treated by direct drug delivery to the colon. One such drug, mesalamine (5-aminosalicylic acid, Asacol) is available in a delayed-release tablet coated with an acrylic-based resin that delays the release of the drug until it reaches the distal ileum and beyond. Protein drugs are generally unstable in the acidic environment of the stomach and are also degraded by proteolytic enzymes present in the stomach and small intestine. Researchers are investigating the oral delivery of protein and peptide drugs by protecting them against enzymatic degradation for later release in the colon.

Over 500 different bacterial species inhabit the colon, although five frequent species dominate the microflora. Within the cecum and colon, anaerobic species dominate and bacterial counts of 10^{12}/mL have been reported. Drugs

such as the   -blockers, oxprenolol and metoprolol, and isosorbide-5-mononitrate are well absorbed in the colon, similar to absorption in the small intestine. Thus, these drugs are suitable candidates for colonic delivery. The nonsteroidal anti-inflammatory drug naproxen has been formed into a prodrug naproxen-dextran that survives intestinal enzyme and intestinal absorption. The prodrug reaches the colon, where it is enzymatically decomposed into naproxen and dextran ().

Rectal and Vaginal Drug Delivery

Products for rectal or vaginal drug delivery may be administered in either solid or liquid dosage forms. Rectal drug administration can be used for either local or systemic drug delivery. Rectal drug delivery for systemic absorption is preferred for drugs that cannot be tolerated orally (eg, when a drug causes nausea) or in situations where the drug cannot be given orally. A sustained-release preparation may be prepared for rectal administration. The rate of release of the drug from this preparation is dependent on the nature of the base composition and on the solubility of the drug involved. Rectal drug absorption may partially bypass the first-pass effects due to enzymes in the liver. Drug absorbed in the lower rectal region does not pass through the liver, whereas drug absorbed in the upper rectal region

passes through the hepatic portal vein. Release of drug from a suppository depends on the composition of the suppository base. A water-soluble base, such as polyethylene glycol and glycerin, generally dissolves and releases the drug; on the other hand, an oleaginous base with a low melting point may melt at body temperature and release the drug. Some suppositories contain an emulsifying agent that keeps the fatty oil emulsified and the drug dissolved in it.

Vaginal drug delivery is generally for local drug delivery, but some systemic drug absorption can occur. Progesterone vaginal suppositories have been evaluated for the treatment of premenstrual symptoms of anxiety and irritability. Antifungal agents are often formulated into suppositories for treating vaginal infections. Fluconazole, a triazole antifungal agent, has been formulated to treat vulvovaginal candidiasis. The result of oral doses is comparable with that of a clotrimazole vaginal suppository. Many vaginal preparations are used for the delivery of antifungal agents.

Parenteral Drug Products

In general, intravenous (IV) bolus administration of a drug provides the most rapid onset of drug action. After IV bolus injection, the drug is distributed via the circulation to all parts of the body within a few minutes. After intramuscular (IM) injection, drug is absorbed from the injection site into the bloodstream (). Plasma drug input after oral and IM administration involves an absorption phase in which the drug concentration rises slowly to a peak and then declines according to the elimination half-life of the drug. (Note that the systemic elimination of all products is essentially similar; only the rate and extent of absorption may be modified by formulation.) The plasma drug level peaks instantaneously after an IV bolus injection, so a peak is usually not visible. After 3 hours, however, the plasma level of the drug after intravenous administration has declined to a lower level than after the oral and intramuscular administration. In this example (), the areas under the plasma curves are all approximately equal, indicating that the oral and intramuscular preparations are both well formulated and are 100% available. Frequently, because of incomplete absorption or metabolism, oral preparations may have a lower area under the curve.

Figure 14-17.

Plasma concentration of a drug after the same dose is administered by three different routes.

Drug absorption after an intramuscular injection may be faster or slower absorption than after oral drug administration. Intramuscular preparations are generally injected into a muscle mass such as in the buttocks (gluteus muscle) or in the deltoid muscle. Drug absorption occurs as the drug diffuses from the muscle into the surrounding tissue fluid and then into the blood. Different muscle tissues have different blood flow. For example, blood flow to the deltoid muscle is higher than blood flow to the gluteus muscle. Intramuscular injections may be formulated to have a faster or slower drug release by changing the vehicle of the injection preparation. Aqueous solutions release drug more rapidly, and the drug is more rapidly absorbed from the injection site, whereas a viscous, oily, or suspension vehicle may result in a slow drug release and consequently slow and sustained drug absorption. Viscous vehicles generally slow down drug diffusion and distribution. A drug in an oily vehicle must partition into an aqueous phase before systemic absorption. A drug that is very soluble in oil and relatively insoluble in water may have a relatively long and sustained release from the absorption site because of slow partitioning. Drugs, including peptides and proteins, have also been formulated as emulsions, suspensions, liposomes, and nanoparticles for parenteral injection. A change in a parenteral drug product from a solution to an emulsion, liposome, etc, will alter the drug's distribution and pharmacokinetic profile.

Clinical Example

Haloperidol (Haldol) is a butyrophenone antipsychotic agent with pharmacologic effects similar to the piperazine phenothiazines. Haloperidol is available for oral and IM administration. Two IM preparations of haloperidol are available, including haloperidol lactate in an aqueous vehicle and haloperidol deconate in a nonaqueous sesame oil vehicle. shows the t_{max} and elimination half-life of haloperidol after the oral, IM, or IV administration.

Table 14.10 Pharmacokinetic Parameters for Haloperidol after Oral and Parenteral Administration			
Route	**Percent Absorption**	**Time for Peak Concentration, t_{max}**	**Elimination Half-Life**
Oral	60	3–5 hr	24 (12–38) hr
IM	75	0.33 hr	21 (13–36) hr
Deconate		6th day (4–11 days)	3 wk
IV	100	Immediate	14 (10–19) hr

Adapted from *Facts and Comparisons* (1997).

Haloperidol lactate is given in an aqueous solution and after intramuscular injection has a time for peak drug concentration of 20 minutes and an elimination half-life of 21 days. In contrast, haloperidol deconate, the deconate ester of the butyrophenone, is lipid soluble and is formulated in sesame oil. Due to the slow drug release from the oil after IM administration, the time for peak drug concentration is 4–11 days and the elimination half-life is about 3 weeks. Thus, the suggested dosage interval between intramuscular injections for haloperidol deconate is 4 weeks.

A major advantage of intramuscular injections compared to intravenous bolus injections is the flexibility of formulation. A drug that is not water soluble cannot be easily administered by the intravenous route. A nonaqueous injection for intravenous administration must be given very slowly to avoid any drug precipitation in the vein. Propylene glycol and PEG 400 in combination with other solvents have been used in intravenous preparations. Parenteral dosage forms for intravenous administration containing suspensions, liposomes, or nanoparticles have been developed for the administration of antineoplastic drugs. In this case, the dosage form may alter the distribution of the drug, because small particles are engulfed by macrophages of the reticuloendothelial system, resulting in drug concentration in the liver and spleen.

Inhalation Drug Products

Drugs administered into the respiratory system, such as bronchodilators and corticosteroids, may be formulated as aerosols or inhalation solutions. An aerosol preparation with suitable propellant can administer drug rapidly into the bronchial region. The advantages of drugs given by inhalation include (1) rapid absorption and rapid onset of activity (eg, bronchodilators), (2) avoidance of first-pass effects or metabolism prior to systemic absorption (eg, isoproterenol, bitolterol), and (3) localization of drug activity to the lung and minimum systemic toxicity (eg, dexamethasone).

The particle size of the suspension (or, in the case of a solution, the size of the mist particles) is important in determining the extent of penetration into the bronchioles. For coarse particles, inertia carries the drug for a short distance up the nasal cavity. Drugs with small particles move by sedimentation or brownian movement deeper into the bronchioles.

Many aerosol products are designed for drug therapy of chronic obstructive pulmonary disease (COPD), particularly asthma. For example, Intal (Rhone-Poulenc-Rorer) delivers sodium cromolyn to a patient through inhalation. The propellants for aerosols have been the chlorinated fluorocarbons (CFCs, such as Freons, DuPont). Freons commonly used include dichlorodifluoromethane (Freon-12) and dichlortetrafluoroethane (Freon-114). However, these compounds deplete the ozone layer of the stratosphere, and other propellants are now being investigated to replace CFCs. The new propellants include classes of hydrofluoroalkanes (HFAs), which do not contain chlorines. HFA-227 and HFA-134a show promise as new propellents for medical inhalers because they are nonflammable, not chemically reactive, and do not have ozone-depleting potential. Some examples of inhalation and intranasal products are shown in .

Table 14.11 Examples of Inhalation and Intranasal Drug Products			
	Drug Product	**Generic Name**	**Indication**
Inhalation	Proventil	Albuterol	Bronchodilator
	Beconase	Beclomethasone diproprionate	Anti-inflammatory steroid
	Foradil Aerolizer	Formoterol fumarate inhalation powder	Bronchodilator
	Pulmicort	Budesonide inhalation powder	Anti-inflammatory steroid
	Turbuhaler		
	Virazole	Ribavirin for inhalation solution	Antiviral nucleoside
	Mucomyst	Acetylcysteine	Mucolytic
Intranasal	Flonase	Fluticasone proprionate	Anti-inflammatory steroid
	FluMist	Influenza virus intranasal vaccine	Live (attenuated) influenza virus
	Nasalcrom	Cromolyn sodium	Mast cell stabilizer
	Nasalcort	Triamcinolone actonide	Anti-inflammatory steroid

Transdermal Drug Products

Transdermal administration delivers a drug into the patient's systemic circulation through the skin for systemic activity. For example, scopolamine has been delivered through the skin of the ear for relief of motion sickness. Transdermal administration may release the drug over an extended period of several hours or days without the discomforts of gastrointestinal side effects or first-pass effects. For example, Estraderm delivers estradiol for estrogen replacement therapy in postmenopausal women and is applied twice a week. Many transdermal products deliver drug at a constant rate to the body, similar to a zero-order infusion process. As a result, a stable, plateau level

of the drug may be maintained. Many therapeutic categories of drugs are now available as transdermal products ().

Table 14.12 Transdermal Products		
Drug	**Product**	**Drug Class**
Estradiol	Vivelle	Estrogen
Fentanyl	Duragesic	Opiate agonist
Nicotine	Habitrol Tran	Smoking control
	Nicoderm	Smoking control
	Nicotrol	Smoking control
	Prostep patch	Smoking control
Naftifine HCI	Naftin	Antifungal
Nifedipine	Adalat	Calcium channel blocker
Nitroglycerin	Nitrodisc	Antiangina
	Nitro-Dur	Antiangina
Clonidine	Catopress	Antihypertensive
Ethinylestradiol and norelgestromin	Evra	Contraception

Transdermal products vary in design. In general, the patch contains several parts: (1) a backing or support layer; (2) a drug layer (reservoir containing the dose); (3) a release-controlling layer (usually a semipermeable film), (4) a pressure-sensitive adhesive (PSA); and (5) a protective strip, which must be removed prior to application. (See ,). The release-controlling membrane may be a polymeric film such as ethylvinyl copolymer, which controls the release rate of the dose and its duration of action. The PSA layer is important for maintaining uninterrupted skin contact for drug diffusion through the skin. In some cases, the drug is blended directly into an adhesive, such as acrylate or silicone; performing the dual functions of release control and adhesion, this product is known as "drug in adhesive." In other products, the drug dose may be placed in a separate insoluble matrix layer, which helps control the release rate. This is generally known as a "matrix patch," and provides a little more control of the release rate as compared to the simple "reservoir" type of patch. Multilayers of drugs may be involved in other transdermal products using a "laminate" design. In many cases, drug permeation through the skin is the slowest step in the transdermal delivery of drug into the body. See for discussion of modified-release patches.

Scale-Up and Postapproval Changes (Supac)

Any changes in a drug product after it has been approved for marketing by the FDA is known as a *postapproval change*. Postapproval changes may include analytical, manufacturing, and packaging changes in a drug product after it has been approved for marketing by the FDA (). A major concern of industry and the FDA is that if a pharmaceutical manufacturer makes any change in the formulation, scales up the formulation to a larger batch size, changes the process, equipment, or manufacturing site, whether these changes will affect the identity, strength, purity, quality, safety, or efficacy of the approved drug product. In addition any changes in raw material (ie, material used for preparing active pharmaceutical ingredient), excipients, or packaging (including container closure system) should also be shown not to affect the quality of the drug product. SUPAC is discussed in more detail in .

Frequently Asked Questions

1. What physical or chemical properties of a drug substance are important in designing a drug for **(a)** oral administration or **(b)** parenteral administration?

2. For a lipid-soluble drug that has very poor aqueous solubility, what strategies could be used to make this drug more bioavailable after oral administration?

3. For a weak ester drug that is unstable in highly acid or alkaline solutions, what strategies could be used to make this drug more bioavailable after oral administration?

4. How do excipients in a drug product that are physically inert, chemically inert, and nontoxic change the bioavailability of the active drug substance?

Learning Questions

1. What are the two rate-limiting steps possible in the oral absorption of a solid drug product? Which one would apply to a soluble drug? Which one could be altered by the pharmacist? Give examples.

2. What is the physiologic transport mechanism for the absorption of most drugs from the gastrointestinal tract? What area of the gastrointestinal tract is most favorable for the absorption of drugs? Why?

3. Explain why the absorption rate of a soluble drug tends to be greater than the elimination rate of the drug.

4. What type of oral dosage form generally yields the greatest amount of systemically available drug in the least amount of time? (Assume that the drug can be prepared in any form.) Why?

5. What effect does the oral administration of an anticholinergic drug, such as atropine sulfate, have on the bioavailability of aspirin from an enteric-coated tablet? (*Hint:* Atropine sulfate decreases gastrointestinal absorption.)

6. Drug formulations of erythromycin, including its esters and salts, have significant differences in bioavailability. Erythromycin is unstable in an acidic medium. Suggest a method for preventing a potential bioavailability problem for this drug.

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