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

MODIFIED-RELEASE DRUG PRODUCTS: INTRODUCTION

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such *immediate-release products* result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release.

The term *modified-release drug product* is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized" (). Several types of modified-release drug products are recognized:

1. *Extended-release drug products*. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

2. *Delayed-release drug products*. A dosage form that releases a discrete portion or portions of drug at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

3. *Targeted-release drug products*. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

The term *controlled-release drug product* was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery. Other terms, such as ER, SR, XL, XR, and CD, are also used to indicate an extended-release drug product. Many of these terms for modified-release drug products were introduced by drug companies to reflect either a special design for an extended-release drug product or for use as a marketing term.

Modified-release drug products are designed for different routes of administration based on the physicochemical, pharmacologic, and pharmacokinetic properties of the drug and on the properties of the materials used in the dosage form (). Several different terms are now defined to describe the available types of modified-release drug products based on the drug release characteristics of the products.

Table 17.1 Modified Drug Delivery

Route of Administration	Drug Product	Examples	Comments
Oral drug products	Extended release	Diltiazem HCl extended release	Once-a-day dosing.
	Delayed release	Diclofenac sodium delayed-release	Enteric-coated tablet for drug delivery into small intestine.
		Mesalamine delayed-release	Coated for drug release in terminal ileum.
	Oral mucosal drug delivery	Oral transmucosal fentanyl citrate	Fentanyl citrate is in the form of a flavored sugar lozenge that dissolves slowly in the mouth.
Transdermal drug delivery systems	Transdermal therapeutic system (TTS)	Clonidine transdermal therapeutic system	Clonidine TTS is applied every 7 days to intact skin on the upper arm or chest.
	Iontophoretic drug delivery		Small electric current moves charged molecules across the skin.
Ophthalmic drug delivery	Insert	Controlled-release pilocarpine	Elliptically shaped insert designed for continuous release of pilocarpine following placement in the cul-de-sac of the eye.
Intravaginal drug	Insert	Dinoprostone vaginal insert	Hydrogel pouch containing prostaglandin within a polyester

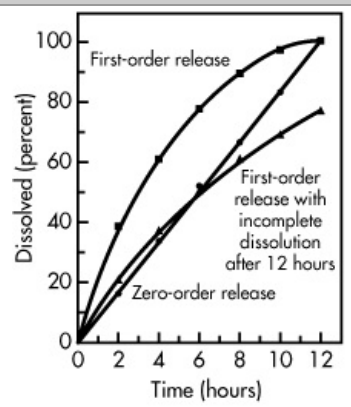
delivery			retrieval system.
Parenteral drug delivery	Intramuscular drug products	Depot injections	Lyophylized microspheres containing leuprolide acetate for depot suspension.
		Water-immiscible injections (eg, oil)	Medroxyprogesterone acetate (Depo-Provera®)
	Subcutaneous drug products	Controlled-release insulin	Basulin is a controlled-release, recombinant human insulin delivered by nanoparticulate technology.
Targeted delivery systems	IV injection	Daunorubicin citrate liposome injection	Liposomal preparation to maximize the selectivity of daunorubicin for solid tumors *in situ*.
Implants	Brain tumor	Polifeprosan 20 with carmustine implant (Gliadel wafer)	Implant designed to deliver carmustine directly into the surgical cavity when a brain tumor is resected.

EXAMPLES OF MODIFIED-RELEASE ORAL DOSAGE FORMS

An enteric-coated tablet is an example of a delayed-release type of modified-release dosage form designed to release drug in the small intestine. For example, aspirin irritates the gastric mucosal cells of the stomach. An enteric coating on the aspirin tablet prevents the tablet from dissolving and releasing its contents at the low pH in the stomach. The coating and the tablet later dissolve and release the drug in the higher pH of the duodenum, where the drug is rapidly absorbed with less irritation to the mucosal cells. Mesalamine (5-aminosalicylic acid) tablets (Asacol, Proctor & Gamble) is a delayed-release tablet coated with an acrylic-based resin that delays the release of mesalamine until it reaches the terminal ileum and colon. Mesalamine tablets could also be considered a targeted-release dosage form.

Various other unofficial terms are used to describe modified-release drug products. A *repeat-action tablet* is a type of modified-release drug product that is designed to release one dose of drug initially, followed by a second dose of drug at a later time. A *prolonged-action drug product* is designed to release the drug slowly and to provide a continuous supply of drug over an extended period. The prolonged-action drug product prevents very rapid absorption of the drug, which could result in extremely high peak plasma drug concentration. Most prolonged-release products extend the duration of action but do not release drug at a constant rate. A *sustained-release drug product* can be designed to deliver an initial therapeutic dose of the drug (loading dose), followed by a slower and constant release of drug. The rate of release of the maintenance dose is designed so that the amount of drug loss from the body by elimination is constantly replaced. With the sustained-release product, a constant plasma drug concentration is maintained with minimal fluctuations. shows the dissolution rate of three sustained-release products without loading dose. The plasma concentrations resulting from the sustained-release products are shown in .

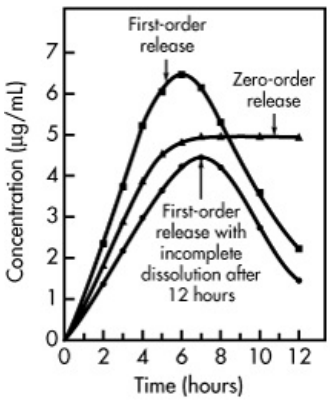
Figure 17-1.



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

Drug dissolution rates of three different extended-release products *in vitro*.

Figure 17-2.



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

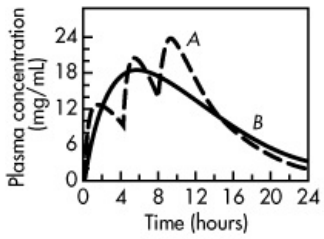
Simulated plasma–drug concentrations resulting from three different sustained-release products in

A prolonged-action tablet is similar to a first-order-release product except that the peak is delayed differently. A prolonged-action tablet typically results in peak and trough drug levels in the body. The product releases drug without matching the rate of drug elimination, resulting in uneven plasma drug levels in the body.

The use of these various terms for extended-release drug products does not mean that the drug is released at a constant or zero-order drug release rate. Many of these drug products release the drug at a first-order rate. Some modified-release drug products are formulated with materials that are more soluble at a specific pH, and the product may release the drug depending on the pH of a particular region of the gastrointestinal (GI) tract. Ideally, an extended-release drug product should release the drug at a constant rate, independent of both the pH and the ionic content within the entire segment of the gastrointestinal tract.

An extended-release dosage form with zero- or first-order drug absorption is compared to drug absorption from a conventional dosage form given in multiple doses in and , respectively. Drug absorption from conventional (immediate-release) dosage forms generally follows first-order drug absorption.

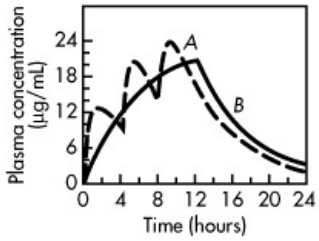
Figure 17-3.



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

Plasma level of a drug from a conventional tablet containing 50 mg of drug given at 0, 4, and 8 hours (A) compared to a single 150-mg drug dose given in an extended-release dosage form (B). The drug absorption rate constant from each drug product is first order. The drug is 100% bioavailable and the elimination half-life is constant.

Figure 17-4.



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

Bioavailability of a drug from an immediate-release tablet containing 50 mg of drug given at 0, 4, and 8 hours compared to a single 150-mg

drug dose given in an extended-release dosage form. The drug absorption rate constant from the immediate-release drug product is first order, whereas the drug absorption rate constant from the extended-release drug product is zero order. The drug is 100% bioavailable and the elimination half-life is constant.

BIOPHARMACEUTIC FACTORS

The major objective of an extended-release drug product is to achieve a prolonged therapeutic effect while minimizing unwanted side effects due to fluctuating plasma drug levels. Ideally, the extended-release drug product should release the drug at a constant, or zero-order, rate. After release from the drug product, the drug is rapidly absorbed, and the drug absorption rate should follow zero-order kinetics similar to an intravenous drug infusion. In all cases, the drug product is designed so that the rate of systemic drug absorption is limited by the rate of drug release via the drug delivery system. Unfortunately, most extended-release drug products that release a drug by zero-order kinetics *in vitro* do not demonstrate zero-order drug absorption when given *in vivo*. The lack of zero-order drug absorption from these extended-release drug products after oral administration may be due to a number of unpredictable events happening in the gastrointestinal tract during absorption.

Extended-release oral drug products remain in the GI tract longer than conventional, immediate-release drug products intended for rapid absorption. Thus, drug release from an extended-release drug product is more affected by the anatomy and physiology of the gastrointestinal tract and its contents compared to an immediate-release oral drug product. The physiologic characteristics of the GI tract, such as variations in pH, blood flow, GI motility, presence of food, enzymes, bacteria, etc, affects the position of the extended-release drug product within the GI tract and may affect the drug release rate from the product. In some cases, there may be a specific absorption site or location within the GI tract in which the extended-release drug product should release the drug.

Stomach

The stomach is a "mixing and secreting" organ, where food is mixed with digestive juices and emptied periodically into the small intestine. However, the movement of food or drug product in the stomach and small intestine is very different depending on the physiologic state. In the presence of food, the stomach is in the *digestive phase*; in the absence of food, the stomach is in the *interdigestive phase* (). During the digestive phase, the food particles or solids larger than 2 mm are retained in the stomach, whereas smaller particles are emptied through the pyloric sphincter at a first-order rate depending on the content and size of the meals. During the interdigestive phase, the stomach rests for a period of up to 30 to 40 minutes, coordinated with an equal resting period in the small intestine. Peristaltic contractions then occur, which ends with strong *housekeeper contractions* that move everything in the stomach through to the small intestine. Similarly, large particles in the small intestine are moved along only in the housekeeper contraction period.

A drug may remain for several hours in the stomach if it is administered during the digestive phase. Fatty material, nutrients, and osmolality may further extend the time the drug stays in the stomach. When the drug is administered during the interdigestive phase, the drug may be swept along rapidly into the small intestine. Dissolution of drugs in the stomach may also be affected by the presence or absence of food. When food is present, HCl is secreted and the pH is about 1–2. Although some food and nutrients can neutralize the acid and raise stomach pH, the fasting pH of the stomach is about 3–5. The release rates of some drugs are affected by food. For example, the extended-release drug product Theo-24 was shown to release drug at a higher rate in the presence of food (). Whether this more rapid drug release rate is related to a change in pH, the stomach-emptying rate, or a food–drug interaction is not known. A longer time of retention in the stomach may expose the drug to stronger agitation in the acid environment. The stomach has been described as having "jet mixing" action, which sends mixture at up to 50 mm Hg pressure toward the pyloric sphincter, causing it to open and periodically release chyme to the small intestine.

Small Intestine and Transit Time

The small intestine is about 10 to 14 feet in length. The duodenum is sterile, while the terminal part of the small intestine that connects the cecum contains some bacteria. The proximal part of the small intestine has a pH of about 6, because of neutralization of acid by bicarbonates secreted by the duodenal mucosa and the pancreas. The small intestine provides an enormous surface area for drug absorption because of the presence of microvilli. The small-intestine transit time of a solid preparation has been concluded to be about 3 hours or less in 95% of the population (). Transit time for meals from mouth to cecum (beginning of large intestine) has been reviewed by . Various investigators have used the lactulose hydrogen test, which measures the appearance of hydrogen in a patient's breath, to estimate transit time. Lactulose is metabolized rapidly by bacteria in the large intestine, yielding hydrogen that is exhaled. Hydrogen is normally absent in a person's breath. These results and the use of gamma-scintigraphy studies confirm a relatively short GI transit time from mouth to cecum of 4 to 6 hours.

This transit time interval was concluded to be too short for extended-release dosage forms that last up to 12 hours, unless the drug is to be absorbed in the colon. The colon has little fluid and the abundance of bacteria may make drug absorption erratic and incomplete. The transit time for pellets has been studied in both disintegrating and nondisintegrating forms using both insoluble and soluble radiopaques. Most of the insoluble pellets were released from the capsule within 15 minutes. Scattering of pellets were seen in the stomach and along the entire length of the small intestine at 3 hours. At 12 hours most of the pellets were in the ascending colon, and at 24 hours the pellets were all in the descending colon, ready to enter the rectum. With the disintegrating pellets, there was more scattering of the pellets along the GI tract. The pellets also varied widely in their rate of disintegration *in vivo* ().

Large Intestine

The large intestine is about 4 to 5 feet long. It consists of the cecum, the ascending and descending colons, and eventually ends at the rectum. Little fluid is in the colon, and drug transit is slow. Not much is known about drug absorption in this area, although unabsorbed drug that reaches this region may be metabolized by bacteria. Incompletely absorbed antibiotics may affect the normal flora of the bacteria. The rectum has a pH of about 6.8–7.0 and contains more fluid compared to the colon. Drugs are

absorbed rapidly when administered as rectal preparations. However, the transit rate through the rectum is affected by the rate of defecation. Presumably, drugs formulated for 24 hours' duration must remain in this region to be absorbed.

Several extended-release and delayed-release drug products, such as mesalamine delayed-release tablets (Asacol), are formulated to take advantage of the physiologic conditions of the GI tract (). Enteric-coated beads have been found to release drug over 8 hours when taken with food, because of the gradual emptying of the beads into the small intestine. Specially formulated "floating tablets" that remain in the top of the stomach have been used to extend the residence time of the product in the stomach. None of these methods, however, is consistent enough to perform reliably for potent medications. More experimental research is needed in this area.

DOSAGE FORM SELECTION

The properties of the drug and required dosage are important in formulating an extended-release product. For example, a drug with low aqueous solubility generally should not be formulated into a nondisintegrating tablet, because the risk of incomplete drug dissolution is high. Instead, a drug with low solubility at neutral pH should be formulated, so that most of the drug is released before it reaches the colon, since the lack of fluid in the colon may make complete dissolution difficult. Erosion tablets are more reliable for these drugs because the entire tablet eventually dissolves.

A drug that is highly water soluble in the acid pH in the stomach but very insoluble at intestinal pH may be very difficult to formulate into an extended-release product. Too much coating protection may result in low bioavailability, while too little protection may result in dose dumping in the stomach. A moderate extension of duration with enteric-coated beads may be possible. However, the risk of erratic performance is higher than with a conventional dosage form. The osmotic type of controlled system may be more suitable for this type of drug.

In addition, with most single-unit dosage forms, there is a risk of erratic performance due to variable stomach emptying and GI transit time. Selection of a pellet or bead dosage form may minimize the risk of erratic stomach emptying, because pellets are usually scattered soon after ingestion. Disintegrating tablets have the same advantages because they break up into small particles soon after ingestion.

ADVANTAGES AND DISADVANTAGES OF EXTENDED-RELEASE PRODUCTS

Extended-release drug products offer several important advantages over immediate-release dosage forms of the same drug. Extended release allows for sustained therapeutic blood levels of the drug; sustained blood levels provide for a prolonged and consistent clinical response in the patient. Moreover, if the drug input rate is constant, the blood levels should not fluctuate between a maximum and minimum, as in a multiple-dose regimen with an immediate-release drug product (). Highly fluctuating blood concentrations of drug may produce unwanted side effects in the patient if the drug level is too high, or may fail to exert the proper therapeutic effect if the drug level is too low. Another advantage of extended release is patient convenience, which leads to better patient compliance. For example, if the patient needs to take the medication only once daily, he or she will not have to remember to take additional doses at specified times during the day. Furthermore, because the dosage interval is longer, the patient's sleep may not be interrupted to take another drug dose. With the longer-available dose, the patient awakes without having subtherapeutic drug levels. The patient may also derive an economic benefit in using a extended-release drug product. A single dose of an extended-release product may cost less than an equivalent drug dose given several times a day in rapid-release tablets. For patients under nursing care, the cost of nursing time required to administer medication is decreased if only one drug dose is given to the patient each day.

For some drugs which have long elimination half-lives, such as chlorpheniramine, the inherent duration of pharmacologic activity is long. Moreover, minimal fluctuations in blood concentrations of these drugs are observed after multiple doses are administered. Therefore, there is no rationale for extended-release formulations of these drugs. However, such drug products are marketed with the justification that extended-release products minimize toxicity, decrease adverse reactions, and provide patients with more convenience and, thus, better compliance. In contrast, drugs with very short half-lives need to be given at frequent dosing intervals to maintain therapeutic efficacy. For drugs with very short elimination half-lives, an extended-release drug product maintains the efficacy over a longer duration.

There are also a number of disadvantages in using extended-release medication. If the patient suffers from an adverse drug reaction or accidentally becomes intoxicated, the removal of drug from the system is more difficult with an extended-release drug product. Orally administered extended-release drug products may yield erratic or variable drug absorption as a result of various drug interactions with the contents of the GI tract and changes in GI motility. The formulation of extended-release drug products may not be practical for drugs that are usually given in large doses (e.g., 500 mg) in conventional dosage forms. Because the extended-release drug product may contain two or more times the dose given at more frequent intervals, the size of the extended-release drug product may have to be quite large, too large for the patient to swallow easily.

The extended-release dosage form contains the equivalent of two or more drug doses given in a conventional dosage form. Therefore, failure of the extended-release dosage form may lead to dose dumping. *Dose dumping* can be defined either as the release of more than the usual fraction of drug or as the release of drug at a greater rate than the customary amount of drug per dosage interval, such that potentially adverse plasma levels may be reached (;). With delayed release or enteric drug products, two possible problems may occur if the enteric coating is poorly formulated. First, the enteric coating may become degraded in the stomach, allowing for early release of the drug, possibly causing irritation to the gastric mucosal lining. Second, the enteric coating may fail to dissolve at the proper site, and therefore the tablet may be lost prior to drug release, resulting in incomplete absorption.

In recent years, pharmaceutical manufacturers have made new extended-release drug products of branded drugs that are losing patent protection. Although these extended-release drug products may have some of the advantages stated above, the cost of the medication may be much higher than that of the generic drug in a conventional drug product given several times a day.

KINETICS OF EXTENDED-RELEASE DOSAGE FORMS

The amount of drug required in an extended-release dosage form to provide a sustained drug level in the body is determined by the pharmacokinetics of the drug, the desired therapeutic level of the drug, and the intended duration of action. In general, the total dose required (D_{tot}) is the sum of the maintenance dose (D_m) and the initial dose (D_I) released immediately to provide a therapeutic blood level.

$$D_{tot} = D_I + D_m \qquad (17.1)$$

In practice, D_m (mg) is released over a period of time and is equal to the product of t_d (the duration of drug release) and the zero-order rate k_r^0 (mg/hr). Therefore, Equation 17.1 can be expressed as

$$D_{tot} = D_I + k_r^0 t_d \qquad (17.2)$$

Ideally, the maintenance dose (D_m) is released after D_I has produced a blood level equal to the therapeutic drug level (C_p). However, due to the limits of formulations, D_m actually starts to release at $t = 0$. Therefore, D_I may be reduced from the calculated amount to avoid "topping." ()

$$D_{tot} = D_I - k_r^0 t_p + k_r^0 t_d \qquad (17.3)$$

Equation 17.3 describes the total dose of drug needed, with t_p representing the time needed to reach peak drug concentration after the initial dose.

For a drug that follows a one-compartment open model, the rate of elimination (R) needed to maintain the drug at a therapeutic level (C_p) is

$$R = kV_D C_p \qquad (17.4)$$

where k_r^0 must be equal to R in order to provide a stable blood level of the drug. Equation 17.4 provides an estimation of the release rate (k_r^0) required in the formulation. Equation 17.4 may also be written as

$$R = C_p Cl_T \qquad (17.5)$$

where Cl_T is the clearance of the drug. In designing an extended-release product, D_I would be the loading dose that would raise the drug concentration in the body to C_p, and the total dose needed to maintain therapeutic concentration in the body would be simply

$$D_{tot} = D_I + C_p Cl_T \tau \qquad (17.6)$$

For many sustained-release drug products, there is no built-in loading dose (ie, $D_I = 0$). The dose needed to maintain a therapeutic concentration for τ hours is

$$D_0 = C_p \tau Cl_T \qquad (17.7)$$

where τ is the dosing interval.

Example

What dose is needed to maintain a therapeutic concentration of 10 µg/mL for 12 hours in a sustained-release product? (**a**) Assume that $t_{1/2}$ for the drug is 3.46 hours and V_D is 10 L. (**b**) Assume that $t_{1/2}$ of the drug is 1.73 hours and V_D is 5 L.

a. $$k = \frac{0.693}{3.46} = 0.2/\text{hr}$$

$$Cl_T = kV_D = 0.2 \times 10 = 2\ \text{L/hr}$$

From Equation 17.7,

$$D_0 = (10\ \mu\text{g/mL})(1000\ \text{mL/L})(12\ \text{hr})(2\ \text{L/hr})$$
$$= 240{,}000\ \mu\text{g} \quad \text{or} \quad 240\ \text{mg}$$

b. $$k = \frac{0.693}{1.73} = 0.4\ \text{hr}$$

$$Cl_T = 0.4 \times 5 = 2\ \text{L/hr}$$

From Equation 17.8,

$$D_0 = 10 \times 2 \times 1000 \times 12 = 240{,}000\,\mu\text{g} \quad \text{or} \quad 240\ \text{mg}$$

In this example, the amount of drug needed in a sustained-release product to maintain therapeutic drug concentration is dependent on both V_D and the elimination half-life. In part **b** of the example, although the elimination half-life is shorter, the

volume of distribution is also smaller. If the volume of distribution is constant, then the amount of drug needed to maintain C_p is dependent simply on the elimination half-life.

shows the influence of $t_{1/2}$ on the amount of drug needed for an extended-release drug product. was constructed by assuming that the drug has a desired serum concentration of 5 µg/mL and an apparent volume of distribution of 20,000 mL. The release rate *R* decreases as the elimination half-life increases. Because elimination is slower for a drug with a long half-life, the input rate should be slower. The total amount of drug needed in the extended-release drug product is dependent on both the release rate *R* and the desired duration of activity for the drug. For a drug with an elimination half-life of 4 hours and a release rate of 17.3 mg/hr, the extended-release product must contain 207.6 mg to provide a duration of activity of 12 hours. The bulk weight of the extended-release product will be greater than this amount, due to the presence of excipients needed in the formulation. The values in show that, in order to achieve a long duration of activity (≥12 hours) for a drug with a very short half-life (1–2 hours), the extended-release drug product becomes quite large and impractical for most patients to swallow.

Table 17.2 Release Rates for Extended-Release Drug Products as a Function of Elimination Half-Life[a]

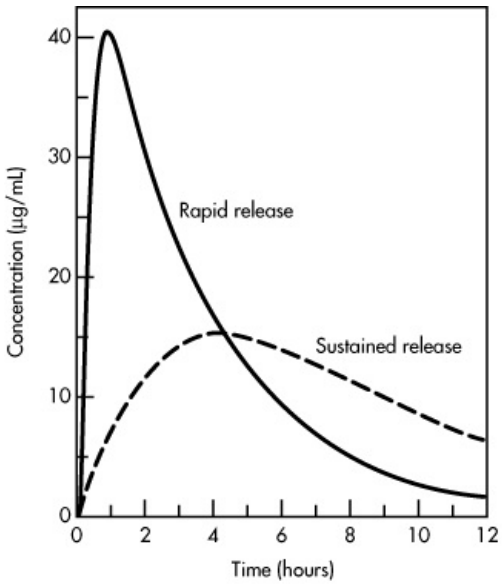
			Total (mg) to Achieve Duration			
$t_{1/2}$ (hr)	k (hr^{-1})	R (mg/hr)	6 hr	8 hr	12 hr	24 hr
1	0.693	69.3	415.8	554.4	831.6	1663
2	0.347	34.7	208.2	277.6	416.4	832.8
4	0.173	17.3	103.8	138.4	207.6	415.2
6	0.116	11.6	69.6	92.8	139.2	278.4
8	0.0866	8.66	52.0	69.3	103.9	207.8
10	0.0693	6.93	41.6	55.4	83.2	166.3
12	0.0577	5.77	34.6	46.2	69.2	138.5

[a] Assume $C_{desired}$ is 5 µg/mL and the V_D is 20,000 mL; $R = kV_DC_p$: no immediate-release dose.

PHARMACOKINETIC SIMULATION OF EXTENDED-RELEASE PRODUCTS

The plasma drug concentration profiles of many extended-release products fit an oral one-compartment model assuming first-order absorption and elimination. Compared to an immediate-release product, the extended-release product typically shows a smaller absorption rate constant, because of the slower absorption of the extended-release product. The time for peak concentration (t_{max}) is usually longer (), and the peak drug concentration (C_{max}) is reduced. If the drug is properly formulated, the area under the plasma drug concentration curve should be the same. Parameters such as C_{max}, t_{max}, and area under the curve (AUC) conveniently show how successfully the extended-release product performs *in vivo*. For example, a product with a t_{max} of 3 hours would not be very satisfactory if the product is intended to last 12 hours. Similarly, an excessively high C_{max} is a sign of dose dumping due to inadequate formulation. The pharmacokinetic analysis of single- and multiple-dose plasma data has been used by regulatory agencies to evaluate many sustained-release products. The analysis is practical because many products can be fitted to this model even though the drug is not released in a first-order manner. The limitation of this type of analysis is that the absorption rate constant may not relate to the rate of drug dissolution *in vivo*. If the drug strictly follows zero-order release and absorption, the model may not fit the data.

Figure 17-5.



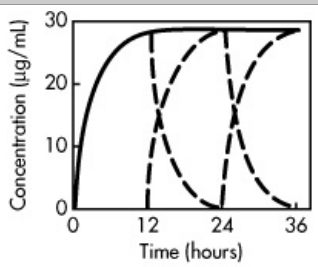
Plasma drug concentration of a sustained-release and a regular-release product. Note the difference of peak time and peak concentration of the two products.

Various other models have been used to simulate plasma drug levels of extended-release products (). The plasma drug levels from a zero-order, extended-release drug product may be simulated with Equation 17.8.

$$C_p = \frac{D_s}{V_D k}(1 - e^{-kt}) \qquad (17.8)$$

where D_s = maintenance dose or rate of drug release (mg/min), C_p = plasma drug concentration, k = overall elimination constant, and V_D = volume of distribution. In the absence of a loading dose, the drug level in the body rises slowly to a plateau with minimum fluctuations (). This simulation assumes that (1) rapid drug release occurs without delay, (2) perfect zero-order release and absorption of the drug takes place, and (3) the drug is given exactly every 12 hours. In practice, the above assumptions are not precise, and fluctuations in drug level do occur.

Figure 17-6.



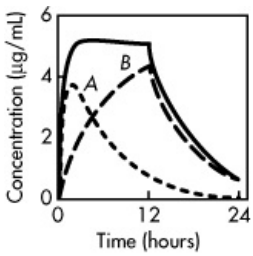
Simulated plasma drug level of a extended-release product administered every 12 hours. The plasma level shows a smooth rise to steady-state level with no fluctuations.

When a sustained-release drug product with a loading dose (rapid release) and a zero-order maintenance dose is given, the resulting plasma drug concentrations are described by

$$C_p = \frac{D_i k_a}{V_D(k_a - k)}(e^{-kt} - e^{-k_a t}) + \frac{D_s}{V_D k}(1 - e^{-kt}) \qquad (17.9)$$

where D_i = immediate-release (loading dose) dose and D_s = maintenance dose (zero-order). This expression is the sum of the oral absorption equation (first part) and the intravenous infusion equation (second part). An example of a zero-order release product with loading dose is shown in . The contribution due to the loading and maintenance dose is shown by the dashed lines. The inclusion of a built-in loading dose in the extended-release product has only limited use.

Figure 17-7.



Simulated plasma drug level of a extended-release product with a fast-release component (A), and a maintenance component (B). The solid line represents total plasma drug level due to the two components.

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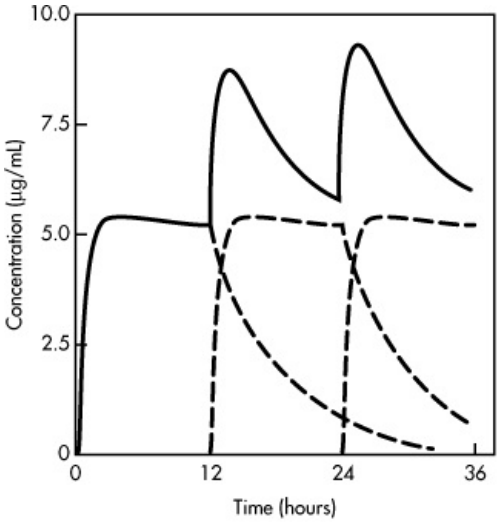
With most extended-release products, the patient is given more than one dose, and there is no need for a built-in loading dose with subsequent doses. Putting a loading dose in the subsequent dosing would introduce more drug into the body than necessary, because of the "topping" effect (). In situations where a loading dose is necessary, the rapid-release product is used to titrate a loading dose that will bring the plasma drug level to therapeutic level.

Figure 17-8.



Simulated plasma level for a extended-release product given every 12 hours. The product has a built-in loading dose of 160 mg and a maintenance rate of 27.2 mg/hr. The plateau level was achieved rapidly after the first dose. Note the spiking peak following each dose due to the topping of the loading dose.

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A pharmacokinetic model that assumes first-order absorption of the loading and maintenance dose has also been proposed. This model predicts spiking peaks due to loading dose when the drug is administered continuously () in multiple doses.

TYPES OF EXTENDED-RELEASE PRODUCTS

General approaches to manufacturing an extended-release drug product include the use of a matrix structure in which the drug is suspended or dissolved, the use of a rate-controlling membrane through which the drug diffuses, or a combination of both. Among the many types of commercial preparations available, none works by a single drug-release mechanism. Most extended-release products release drug by a combination of processes involving dissolution, permeation, and diffusion. The single most important factor is water permeation, without which none of the product release mechanisms would operate. Controlling the rate of water influx into the product generally dictates the rate at which the drug dissolves. Once the drug is dissolved, the rate of drug diffusion may be further controlled to a desirable rate. shows some common extended-release product examples and the mechanisms for controlling drug release, and lists the compositions for some drugs.

Table 17.3 Examples of Oral Extended-Release Products

Type	Trade Name	Rationale
Erosion tablet	Constant-T	Theophylline
	Tenuate Dospan	Diethylpropion HCI dispersed in hydrophilic matrix
	Tedral SA	Combination product with a slow-erosion component (theophylline, ephedrine HCI) and an initial-release component theophylline, ephedrine HCI, phenobarbital)
Waxy matrix tablet	Kaon *CI*	Slow release of potassium chloride to reduce GI irritation
Coated pellets in capsule	Ornade spansule	Combination phenylpropanolamine HCI and chlorpheniramine with initial- and extended-release component
Pellets in tablet	Theo-Dur	Theophylline
Leaching	Ferro-Gradumet (Abbott)	Ferrous sulfate in a porous plastic matrix that is excreted in the stool; slow release of iron decreases GI irritation
	Desoxyn gradumet tablet (Abbott)	Methamphetamine methylacrylate methylmethacrylate copolymer, povidone, magnesium stearate; the plastic matrix is porous
Coated ion exchange	Tussionex	Cation ion-exchange resin complex of hydrocodone and phenyltoloxamine
Flotation–diffusion	Valrelease	Diazapam
Osmotic delivery	Acutrim	Phenylpropanolamine HCI (Oros delivery system)
	Procardia-XL	GITS—gastrointestinal therapeutic system with NaCI-driven (osmotic pressure) delivery system for nifedipine
Microencapsulation	Bayer timed-release	Aspirin
	Nitrospan	Microencapsulated nitroglycerin
	Micro-K Extencaps	Potassium chloride microencapsulated particles

Table 17.4 Composition and Examples of Some Modified-Release Products

K-Tab (Abbott)	750 mg or 10 mEq of potassium chloride in a film-coated matrix tablet. The matrix may be excreted intact, but the active ingredient is released slowly without upsetting the GI tract.
	Inert ingredients: Cellulosic polymers, castor oil, colloidal silicon dioxide, polyvinyl acetate, paraffin. The product is listed as a waxy/polymer matrix tablet for release over 8–10 hr.
Toprol-XL tablets (Astra)	Contains metoprolol succinate for sustained release in pellets, providing stable beta-blockade over 24 hr with one daily dose. Exercise tachycardia was less pronounced compared to immediate-release preparation. Each pellet separately releases the intended amount of medication.
	Inert ingredients: Paraffin, PEG, povidone, acetyltributyl citrate, starch, silicon dioxide, and magnesium stearate.
Quinglute Dura tablets (Berlex)	Contains 320 mg quinidine gluconate in a prolonged-action matrix tablet lasting 8–12 hr and provides PVC protection.
	Inert ingredients: Starch, confection's sugar, and magnesium stearate.
Brontil Slow-Release capsules (Carnrick)	Phendimetrazine tartrate 105 mg sustained pellet in capsule.
Slow Fe tablets (Ciba)	Slow-release iron preparation (OTC medication) with 160 mg ferrous sulfate for iron deficiency.
	Inert ingredients: HPMC, PEG shellac, and cetostearyl alcohol.
Tegretol-XR tablets (Ciba Geneva)	Carbamazepine extended-release tablet.
	Inert ingredients: Zein, cetostearyl alcohol, PEG, starch, talc, gum tragacanth, and mineral oil.
Sinemed CR tablets (Dupont pharma)	Contains a combination of carbidopa and levodopa for sustained release delivery. This is a special erosion polymeric tablet for Parkinson's disease treatment.
Pentasa capsules (Hoechst Marion/Roussel)	Contains mesalamine for ulcerative colitis in a sustained-release mesalamine coated with ethylcellulose. For local effect mostly, about 20% absorbed versus 80% otherwise.
Isoptin SR (Knoll)	Verapamil HCI sustained-release tablet.
	Inert ingredients: PEG, starch, PVP, alginate, talc, HPMC, methylcellulose, and microcrystalline cellulose.
Pancrease capsules (McNeil)	Enteric-coated microspheres of pancrelipase. Protects the amylase, lipase, and protease from the action of acid in the stomach.
	Inert ingredients: CAP, diethyl phthalate, sodium starch glycolate, starch, sugar, gelatin and talc.
Cotazym-S (Organon)	Enteric-coated microspheres of pancrelipase.
Eryc (erythromycin	Erythromycin enteric-coated tablet that protects the drug from instability and irritation.

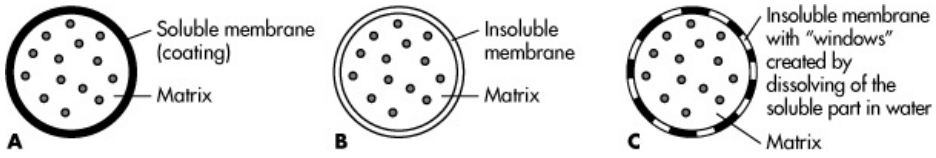
delayed-release capsules) (Warner-Chilcott)	
Dilantin Kapseals (Parke-Davis)	Extended-release phenytoin capsule which contains beads of sodium phenytoin, gelatin, sodium lauryl sulfate, glyceryl monooleate, PEG 200, silicon dioxide, and talc.
Micro-K Extencaps (Robbins)	Ethylcellulose forms semipermeable film surrounding granules by microencapsulation for release over 8–10 hr without local irritation.
	Inert ingredients: Gelatin, and sodium lauryl sulfate.
Quinidex Extentabs (Robbins)	300 mg dose, 100 mg release immediately in the stomach and is absorbed in the small intestine. The rest is absorbed later over 10–12 hr in a slow-dissolving core as it moves down the GI tract.
	Inert ingredients: White wax, carnauba wax, acacia, acetylated monoglyceride, guar gum, edible ink, calcium sulfate, corn derivative, and shellac.
Compazine Spansules (GSK)	Initial dose of prochlorperazine release first, then release slowly over several hours.
	Inert ingredients: Glycerylmonostearate, wax, gelatin, sodium lauryl sulfate.
Slo-bid Gyrocaps (Rhone-Poulenc Rorer)	A controlled-release 12–24-hr theophylline product.
Theo-24 capsules (UCB Pharma)	A 24-hr sustained-release theophylline product. Inert ingredients: Ethylcellulose, edible ink, talc, starch, sucrose, gelatin, silicon dioxide, and dyes.
Sorbitrate SA (Zeneca)	The tablet contains isosorbide dinitrate 10 mg in the outer coat and 30 mg in the inner coat.
	Inert ingredients: Carbomer 934P, ethylcellulose, lactose magnesium stearate, and Yellow No. 10.

Drug Release from Matrix

A *matrix* is an inert solid vehicle in which a drug is uniformly suspended. A matrix may be formed by compressing or fusing the drug and the matrix material together. Generally, the drug is present in a small percentage, so that the matrix protects the drug from rapid dissolution and the drug diffuses out slowly over time. Most matrix materials are water insoluble, although some matrix materials may swell slowly in water. Drug release using a matrix dosage form may be achieved using tablets or small beads, depending on the formulation composition and therapeutic objective. shows three common approaches by which matrix mechanisms are employed. In , the drug is coated with a soluble coating, so drug release relies solely on the regulation of drug release by the matrix material. If the matrix is porous, water penetration will be rapid and the drug will diffuse out rapidly. A less porous matrix may give a longer duration of release. Unfortunately, drug release from a simple matrix tablet is not zero order. The *Higuchi equation* describes the release rate of a matrix tablet:

$$Q = DS\left(\frac{P}{\lambda}\right)(A - 0.5SP)^{1/2}\sqrt{t} \qquad (17.10)$$

Figure 17-9.



Examples of three different types of modified matrix-release mechanisms.

where Q = amount of drug release per cm^2 of surface at time t, S = solubility of drug in g/cm^3 in the dissolution medium, A = content of drug in insoluble matrix, P = porosity of matrix, D = diffusion coefficient of drug, and λ = tortuosity factor.

represents a matrix enclosed by an insoluble membrane, so the drug release rate is regulated by the permeability of the membrane as well as the matrix. represents a matrix tablet enclosed with a combined film. The film becomes porous after dissolution of the soluble part of the film. An example of this is the combined film formed by ethylcellulose and methylcellulose. Close to zero-order release has been obtained with this type of release mechanism.

Gum-Type Matrix Tablets

Some excipients have a remarkable ability to swell in the presence of water and form a substance with a gel-like consistency. When this happens, the gel provides a natural barrier to drug diffusion from the tablet. Because the gel-like material is quite viscous and may not disperse for hours, this provides a means for sustaining the drug for hours until all the drug has been completely dissolved and has diffused into the intestinal fluid. A common gelling material is gelatin. However, gelatin dissolves rapidly after the gel is formed. Drug excipients such as methylcellulose, gum tragacanth, Veegum, and alginic acid form a viscous

mass and provide a useful matrix for controlling drug dissolution. Drug formulation with these excipients provides sustained drug release for hours. The drug diazepam, for example, has been formulated using methylcellulose to provide sustained release. In the case of sustained-release diazepam, claims were made that the hydrocolloid (gel) floated in the stomach to give sustained release. In other studies, however, materials of various densities were emptied from the stomach without any difference as to whether the drug product was floating on top or sitting at the bottom of the stomach.

The most important consideration in this type of formulation appears to be the gelling strength of the gum material and the concentration of gummy material. Modification of the release rates of the product may further be achieved with various amounts of talc or other lipophilic lubricant.

Polymeric Matrix Tablets

The use of polymeric material in prolonging the release rate of drug has received increased attention. The most important characteristic of this type of preparation is that the prolonged release may last for days or weeks rather than for a shorter duration (as with other techniques). The first example of an oral polymeric matrix tablet was Gradumet (Abbott Laboratories), which is marketed as an iron preparation. The plastic matrix provides a rigid geometric surface for drug diffusion, so that a relatively constant rate of drug release is obtained. In the case of the iron preparation, the matrix reduces the exposure of the irritating drug to the GI mucosal tissues. The matrix is usually expelled unchanged in the feces after all the drug has leached out.

Polymeric matrix tablets for oral use are generally quite safe. However, for certain patients with reduced GI motility caused by disease, polymeric matrix tablets should be avoided, because accumulation or obstruction of the GI tract by matrix tablets has been reported. As an oral sustained-release product, the matrix tablet has not been popular. In contrast, the use of the matrix tablet in implantation has been more popular.

The use of biodegradable polymeric material for extended release has been the focus of intensive research. One such example is the use of polylactic acid copolymer, which degrades to natural lactic acid and eliminates the problem of retrieval after implantation.

The number of polymers available for drug formulations is increasing and includes polyacrylate, methacrylate, polyester, ethylene–vinyl acetate copolymer (EVA), polyglycolide, polylactide, and silicone. Of these, the hydrophilic polymers, such as polylactic acid and polyglycolic acid, erode in water and release the drug gradually over time. A hydrophobic polymer such as EVA releases the drug over a longer duration time of weeks or months. The rate of release may be controlled by blending two polymers and increasing the proportion of the more hydrophilic polymer, thus increasing the rate of drug release. The addition of a low-molecular-weight polylactide to a polylactide polymer formulation increased the release rate of the drug and enabled the preparation of an extended-release system (). The type of plasticizer and the degree of cross-linking provide additional means for modifying the release rate of the drug. Many drugs are incorporated into the polymer as the polymer is formed chemically from its monomer. Light, heat, and other agents may affect the polymer chain length, degree of cross-linking, and other properties. This may provide a way to modify the release rate of the polymer matrices prepared. Drugs incorporated into polymers may have release rates that last over days, weeks, or even months. These vehicles have been often recommended for protein and peptide drug administration. For example, EVA is biocompatible and was shown to prolong insulin release in rats.

Hydrophobic polymers with water-labile linkages are prepared so that partial breakdown of the polymers allows for desired drug release without deforming the matrix during erosion. For oral drug delivery, the problem of incomplete drug release from the matrix is a major hurdle that must be overcome with the polymeric matrix dosage form. Another problem is that drug release rates may be affected by the amount of drug loaded. For implantation and other uses, the environment is more stable compared to oral routes, so a stable drug release from the polymer matrix may be attained for days or weeks.

Pellet-Type Sustained-Release Products

The pellet type of sustained-release drug product is also often referred to as a bead-type dosage form. In general, the beads are prepared by coating drug powder onto preformed cores called *nonpareil seeds*. The nonpareil seeds are made from slurry of starch, sucrose, and lactose. Preparation of the cores is tedious. The rough core granules are rounded for hours on a coating pan and then classified according to size. The drug-coated beads generally provide a rapid-release carrier for the drug depending on the coating solution used. Coatings may be aqueous or nonaqueous. Aqueous coatings are preferred. Nonaqueous coatings may leave residual solvents in the product, and removal of solvents during manufacture presents danger to workers and the environment. Cores are coated by either sprayed pan coating or by air-suspension coating. Once the drug beads are prepared, they may be further coated with a protective coating to allow a sustained or prolonged release of the drug.

The use of various amounts of coating solution can provide beads with various coating protection. A careful blending of beads may achieve any release profile desired. Alternatively, a blend of beads coated with materials of different solubility may also provide a means of controlling dissolution of the drug.

Some products take advantage of bead blending to provide two doses of drug in one formulation. For example, a blend of rapid-release beads with some pH-sensitive enteric-coated material may provide a second dose of drug release when the drug reaches the intestine.

The pellet dosage form can be prepared as a capsule or tablet. When pellets are prepared as tablets, the beads must be compressed lightly so that they do not break. Usually, a disintegrant is included in the tablet, causing the beads to be released rapidly after administration. Formulation of a drug into pellet form may reduce gastric irritation, because the drug is released slowly over a period of time, therefore avoiding high drug concentration in the stomach. Dextroamphetamine sulfate timed-release pellets (Dexedrine Spansule) is an early example of a beaded dosage form. Another older product is a pellet-type extended-release product of theophylline (Gyrocap). shows the frequency of adverse reactions after theophylline is administered as solution versus pellets. If theophylline is administered as a solution, a high drug concentration may be reached in the body

due to rapid drug absorption. Some side effects may be attributed to the high concentration of theophylline. Pellet dosage form allows drug to be absorbed gradually, therefore reducing the incidence of side effects by preventing a high C_{max}.

Table 17.5 Incidence of Adverse Effects of Sustained-Release Theophylline Pellet versus Theophylline Solution[a]

	Volunteers Showing Side Effects	
Side Effects	**Using Solution**	**Using Sustained-Release Pellets**
Nausea	10	0
Headache	4	0
Diarrhea	3	0
Gastritis	2	0
Vertigo	5	0
Nervousness	3	1

[a]After 5-day dosing at 600 mg theophylline/24 hr, adverse reaction points on fifth day: solution, 135; pellets, 18.

From , with permission.

A second example involves the drug bitolterol mesylate (Tornalate). A study in dogs indicated that the incidence of tachycardia was reduced using an extended-release bead preparation, whereas the bronchodilation effect was not reduced. Administering the drug as extended-release pellets apparently reduced excessively high drug concentration in the body and avoided stimulated increase in heart rate. Studies also reported reduced gastrointestinal side effects of the drug potassium chloride in pellet or microparticulate form. Potassium chloride is irritating to the GI tract. Formulation in pellet form reduces the chance of exposing high concentrations of potassium chloride to the mucosal cells in the GI tract.

Many extended-release cold products also employ the bead concept. A major advantage of the pellet dosage form is that the pellets are less affected by the effect of stomach emptying. Because numerous pellets are within a capsule, some pellets will gradually reach the small intestine each time the stomach empties, whereas a single extended-release tablet may be delayed in the stomach for a long time as a result of erratic stomach emptying. Stomach emptying is particularly important in the formulation and *in-vivo* behavior of enteric-coated products. Enteric-coated tablets may be delayed for hours by the presence of food in the stomach, whereas enteric-coated pellets are relatively unaffected by the presence of food.

Prolonged-Action Tablets

An approach to prolong the action of a drug is to reduce the aqueous solubility of the drug, so that the drug dissolves slowly over a period of several hours. The solubility of a drug is dependent on the salt form used, and an examination of the solubility of the various salt forms of the drug should be the first step in drug development. In general, the base or acid form of the drug is usually much less soluble than the corresponding salt. For example, sodium phenobarbital is more water soluble than phenobarbital, the acid form of the drug. Diphenhydramine hydrochloride is more soluble than the base form, diphenhydramine.

In cases where it is inconvenient to prepare a less soluble form of the drug, the drug may be granulated with an excipient to slow dissolution of the drug. Often, fatty or waxy lipophilic materials are employed in formulations. Stearic acid, castor wax, high-molecular-weight polyethylene glycol (Carbowax), glyceryl monosterate, white wax, and spermaceti oil are useful ingredients in providing an oily barrier to slow water penetration and the dissolution of the tablet. Many of the lubricants used in tableting may also be used as lipophilic agents to slow dissolution. For example, magnesium stearate and hydrogenated vegetable oil (Sterotex) are actually used in high percentages to cause sustained drug release in a preparation. The major disadvantage of this type of preparation is the difficulty in maintaining a reproducible drug release from patient to patient, because oily materials may be subjected to digestion, temperature, and mechanical stress, which may affect the release rate of the drug.

Ion-Exchange Products

Ion-exchange preparations usually involve an insoluble resin capable of reacting with either an anionic or cationic drug. An anionic resin is negatively charged so that a positively charged cationic drug may react with the resin to form an insoluble nonabsorbable resin–drug complex. Upon exposure in the GI tract, cations in the gut, such as potassium and sodium, may displace the drug from the resin, releasing the drug, which is absorbed freely. The main disadvantage of ion-exchange preparations is that the amount of cation–anion in the GI tract is not easily controllable and varies among individuals, making it difficult to provide a consistent mechanism or rate of drug release. A further disadvantage is that resins may provide a potential means of interaction with nutrients and other drugs.

Ion exchange may be used in extended-release liquid preparations. An added advantage is that the technique provides some protection for very bitter or irritating drugs. Ion exchange has been combined with a coating to obtain a more effective sustained-release product. For example, the drug dextromethorphan (Tussionex) was formulated using the ion-exchange principle to mask the bitter taste and to prolong the duration of action of the drug. In the past, amphetamine was formulated with ion-exchange resins to provide prolonged release as an appetite suppressant in weight reduction.

A general mechanism for the formulation of cationic drugs is

$$H^+ + \text{resin}{-}SO_3^-\text{drug}^+ \rightleftharpoons \text{resin}{-}SO_3^-H^+ + \text{drug}^+$$

Insoluble drug complex — Soluble drug

For anionic drugs, the corresponding mechanism is

$$Cl^- + \text{resin}{-}N^+(CH_3)_3\text{drug}^- \rightleftharpoons \text{resin}{-}N^+(CH_3)_3Cl^- + \text{drug}^-$$

Insoluble drug complex — Soluble drug

The insoluble drug complex containing the resin and drug dissociates in the GI tract in the presence of the appropriate counter ions. The released drug dissolves in the fluids of the GI tract and is rapidly absorbed.

Core Tablets

A core tablet is a tablet within a tablet. The core is usually used for the slow-drug-release component, and the outside shell contains a rapid-release dose of drug. Formulation of a core tablet requires two granulations. The core granulation is usually compressed lightly to form a loose core and then transferred to a second die cavity, where a second granulation containing additional ingredients is compressed further to form the final tablet.

The core material may be surrounded by hydrophobic excipients so that the drug leaches out over a prolonged period of time. This type of preparation is sometimes called a *slow-erosion core tablet*, because the core generally contains either no disintegrant or insufficient disintegrant to fragment the tablet. The composition of the core may range from wax to gum or polymeric material. Numerous slow-erosion tablets have been patented and are sold commercially under various trade names.

The success of core tablets depends very much on the nature of the drug and the excipients used. As a general rule, this preparation is very much hardness dependent in its release rate. Critical control of hardness and processing variables are important in producing a tablet with a consistent release rate.

Core tablets are occasionally used to avoid incompatibility in preparations containing two physically incompatible ingredients. For example, buffered aspirin has been formulated into a core and shell to avoid a yellowing discoloration of the two ingredients upon aging.

Microencapsulation

Microencapsulation is a process of encapsulating microscopic drug particles with a special coating material, therefore making the drug particles more desirable in terms of physical and chemical characteristics. A common drug that has been encapsulated is aspirin. Aspirin has been microencapsulated with ethylcellulose, making the drug superior in its flow characteristics; when compressed into a tablet, the drug releases more gradually compared to a simple compressed tablet.

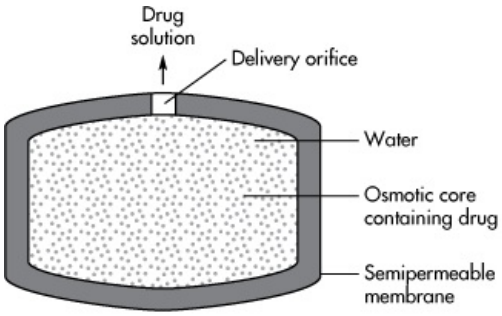
Many techniques are used in microencapsulating a drug. One process used in microencapsulating acetaminophen involves suspending the drug in an aqueous solution while stirring. The coating material, ethylcellulose, is dissolved in cyclohexane, and the two liquids are added together with stirring and heating. As the cyclohexane is evaporated by heat, the ethylcellulose coats the microparticles of the acetaminophen. The microencapsulated particles have a slower dissolution rate because the ethylcellulose is not water soluble and provides a barrier for diffusion of drug. The amount of coating material deposited on the acetaminophen determines the rate of drug dissolution. The coating also serves as a means of reducing the bitter taste of the drug. In practice, microencapsulation is not consistent enough to produce a reproducible batch of product, and it may be necessary to blend the microencapsulated material in order to obtain a desired release rate.

Osmotic Extended-Release Products

The osmotic pump represents a newer concept in extended-release preparations. Drug delivery is controlled by the use of an osmotically controlled device that promotes a constant amount of water into the system, either by dissolving and releasing a constant amount of drug per unit time or by the use of a "push–pull" system that pushes the drug out at a constant rate as water flows into an expandable osmotic compartment. Drug is released via a single laser-drilled hole in the tablet.

One preparation consists of an outside layer of semipermeable membrane filled with a mixture of drug and osmotic agent (). When the device is placed in water, osmotic pressure generated by the osmotic agent within the core causes water to move into the device, which forces the dissolved drug to move out of the drug delivery orifice. The rate of drug delivery is relatively constant and unaffected by the pH of the environment. A similar osmotic product available for implantation is the osmotic *minipump*. Another osmotic oral drug product is the "push–pull" system called Gastrointestinal Therapeutic System (GITS), developed by Alza Corporation for nifedipine (Procardia XL) and other drugs. The system consists of a semipermeable membrane and a two-layer core of osmotic ingredient and active drug. As water enters the system, the osmotic pressure builds up from the inner layer, pushing the drug out through a laser-drilled orifice in the drug layer. An example of GITS uses acetazolamide for the treatment of ocular hypertension in glaucoma. The drug was delivered from the system at zero-order rate for 12 hours at 15 mg/hr, as shown in .

Figure 17-10.



Cross-sectional diagram of simple osmotic delivery system (gastrointestinal therapeutic system).

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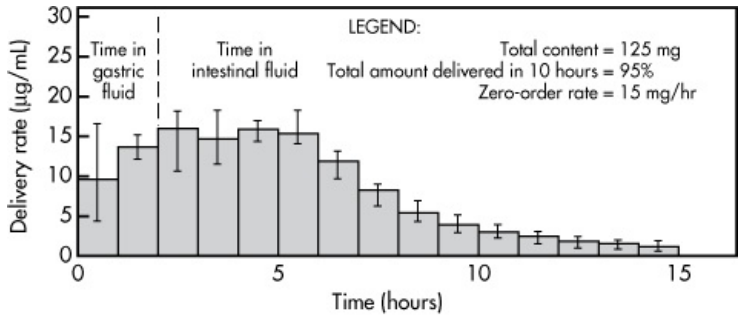
Figure 17-11.



Pattern of delivery of acetazolamide from elementary osmotic pump therapeutic system delivering 70% of the total content (125 mg) at specified rate of 15 mg/hr in 6 hours and 80% in 8 hours.

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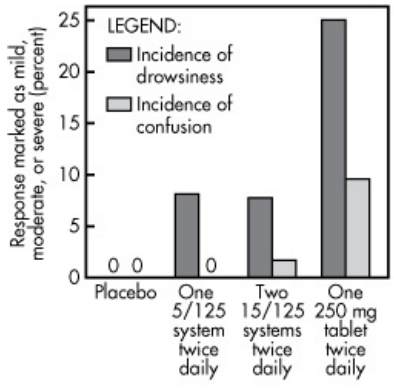
The frequency of side effects experienced by patients using GITS was considerably less than that with conventional tablets (). When the therapeutic system was compared to the regular 250-mg tablet given twice daily, ocular pressure was effectively controlled by the osmotic system. The blood level of acetazolanine using GITS, however, was considerably below that from the tablet. In fact, the therapeutic index of the drug was measurably increased by using the therapeutic system. The use of extended-release drug products, which release drug consistently, may provide promise for administering many drugs that previously had frequent adverse side effects because of the drug's narrow therapeutic index. The osmotic drug delivery system has become a popular drug vehicle for many products that require extended period of drug delivery for 12 to 24 hours ().

Figure 17-12.



Incidence of drowsiness and confusion on acetazolamide given in three regimens. More frequent incidence of side effects were seen with the tablet over the osmotic system.

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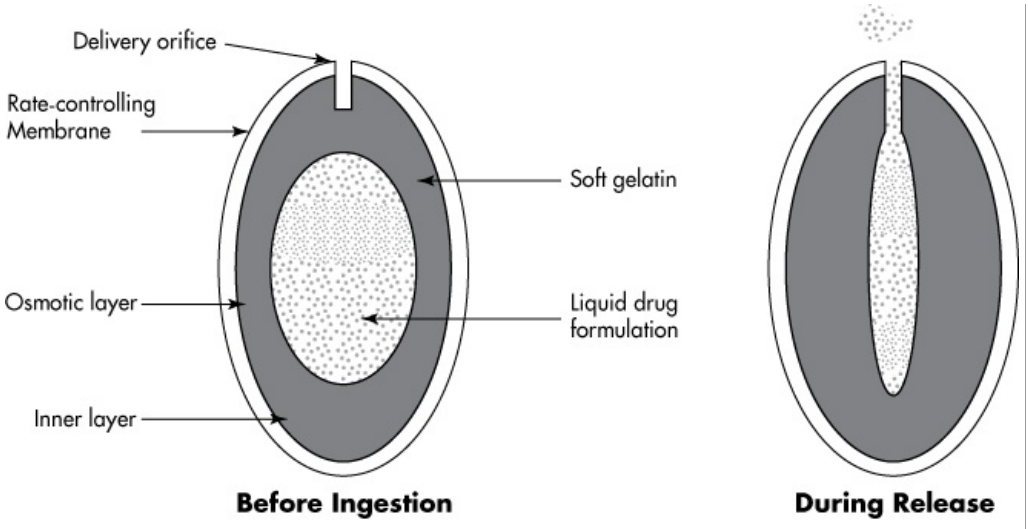
Table 17.6 OROS Osmotic Therapeutic Systems[a]

Trade Name	Manufacturer	Generic Name	Description
Acutrim	Ciba	Phenylpropanolamine	Once-daily, over-the-counter appetite suppressant
Covera-HS	Searle	Verapamil	Controlled-Onset Extended-Release (COER-24) system for hypertension and angina pectoris
DynaCirc CR	Sandoz Pharmaceuticals	Isradipine	Treatment of hypertension
Efidac 24	Ciba Self-Medication		Over-the-counter, 24-hour extended-release tablets providing relief of allergy and cold symptoms, containing either chlorpheniramine maleate, pseudoephedrine hydrochloride, or a combination of pseudoephedrine hydrochloride/brompheniramine maleate
Glucotrol XL	Pfizer	Glipizide	Extended-release tablets indicated as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes
Minipress XL	Pfizer	Prazosin	Extended-release tablets for treatment of hypertension
Procardia XL	Pfizer	Nifedipine	Extended-release tablets for treatment of angina and hypertension
Adalat CR	Bayer AG	Nifedipine	An Alza-based OROS system of nifedipine introduced internationally
Volmax	Glaxo-Wellcome	Albuterol	Extended-release tablets for the relief of bronchospasm in patients with reversible obstructive airway disease

[a]Alza's OROS Osmotic Therapeutic Systems use osmosis to deliver drug continuously at controlled rates for up to 24 hr.

A newer osmotic delivery system is the L-Oros Softcap (Alza), which claims to enhance bioavailability of poorly soluble drug by formulating the drug in a soft gelatin core and then providing extended drug delivery through an orifice drilled into an osmotic driven shell (). The soft gelatin capsule is surrounded by the barrier layer, the expanding osmotic layer, and the release-rate-controlling membrane. A delivery orifice is formed through the three outer layers but not through the gelatin shell. When the system is administered, water permeates through the rate-controlling membrane and activates the osmotic engine. As the engine expands, hydrostatic pressure inside the system builds up, thereby forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice and be pumped out of the system. At the end of the operation, liquid drug fill is squeezed out, and the gelatin capsule shell becomes flattened. The osmotic layer, located between the inner layer and the rate-controlling membrane, is the driving force for pumping the liquid formulation out of the system. This layer can gel when it hydrates. In addition, the high osmotic pressure can be sustained to achieve a constant release. This layer should comprise, therefore, of a high-molecular-weight hydrophilic polymer and an osmotic agent. It is a challenge to develop a coating solution for a high-molecular-weight hydrophilic polymer. A mixed solvent of water and ethanol was used for this coating composition.

Figure 17-13.



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

Configuration of L-OROS SOFTCAP.

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Transdermal Drug Delivery Systems

A transdermal drug delivery system (or patch) is a drug-dosage form intended for delivering a dose of medication across the skin for systemic drug absorption. The transdermal delivery system is popular with patients because it delivers the drug dose through the skin in a controlled rate over an extended period of time. Transdermal products allow a unique route of administration for drugs (,). More examples are listed in and . Transdermal products vary in patch design, but many units consist of drugs impregnated on a reservoir layer supported by a backing. Drug diffusion is controlled by a semipermeable membrane next to the reservoir layer. 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 before application.

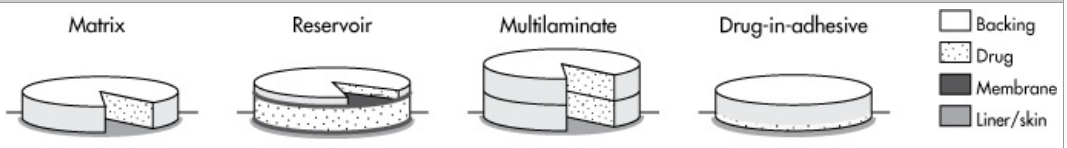
Table 17.7 Examples of Transdermal Delivery Systems

Type	Trade Name	Rationale
Membrane-controlled system	Transderm-Nitro (Novartis)	Drug in reservoir, drug release through a rate-controlling polymeric membrane
Adhesive diffusion-controlled system	Deponit system (PharmaSchwartz)	Drug dispersed in an adhesive polymer and in a reservoir
Matrix dispersion system	Nitro-Dur (Key)	Drug dispersed into a rate-controlling hydrophilic or hydrophobic matrix molded into a transdermal system
Microreservoir system	Nitro-Disc (Searle)	Combination reservoir and matrix-dispersion system

Table 17.8 Transdermal Delivery Systems

Trade Name	Manufacturer	Generic Name	Description
Catapres-TTS	Boehringer Ingelheim	Clonidine	Once-weekly product for the treatment of hypertension
Duragesic	Janssen Pharmaceutical	Fentanyl	Management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means
Estraderm	Ciba Geigy	Estradiol	Twice-weekly product for treating certain postmenopausal symptoms and preventing osteoporosis
Nicoderm CQ	Hoechst Marion	Nicotine	An aid to smoking cessation for the relief of nicotine-withdrawal symptoms
Testoderm	Alza	Testosterone	Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Transderm-Nitro	Novartis	Nitroglycerin	Once-daily product for the prevention of angina pectoris due to coronary artery disease; contains nitroglycerin in a proprietary, transdermal therapeutic system
Transderm Scop		Scopolamine	Prevention of nausea and vomiting associated with motion sickness

Figure 17-14.



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

The four basic configurations for transdermal drug delivery systems.

Nitroglycerin is commonly administered by transdermal delivery. Transdermal delivery systems of nitroglycerin may provide hours of protection against angina, whereas the duration of nitroglycerin given in a sublingual tablet may be only a few minutes. Several commercial transdermal preparations are available, including Nitro-Disc (Searle), Transderm-Nitro (Novartis), and Nitro-Dur (Key Pharmaceuticals). These preparations are placed over the chest area and provide up to 12 hours of angina protection. In a study comparing these three dosage forms in patients, no substantial difference was observed among the three preparations. In all cases, the skin was found to be the rate-limiting step in nitroglycerin absorption. There were fewer variations among products than of the same product among different patients.

The skin is a natural barrier to prevent the influx of foreign chemicals (including water) into the body and the loss of water from the body (). To be a suitable candidate for transdermal drug delivery, the drug must possess the right combination of physicochemical and pharmacodynamic properties. The drug must be highly potent so that only a small systemic drug dose is needed and the size of the patch (dose is also related to surface area) need not be exceptionally large, not greater than 50 cm^2 (). Physicochemical properties of the drug include a small molecular weight (<500 Da), and high lipid solubility. The elimination half-life should not be too short, to avoid having to apply the patch more frequently than once a day.

After the application of a transdermal patch, there is generally a lag time before the onset of the drug action, because of the drug's slow diffusion into the dermal layers of the skin. When the patch is removed, diffusion of the drug from the dermal layer to the systemic circulation may continue for some time until the drug is depleted from the site of application. The solubility of drug in the skin rather than the concentration of drug in the patch layer is the most important factor controlling the rate of drug absorption through the skin. Humidity, temperature, and other factors have been shown to affect the rate of drug absorption through the skin. With most drugs, transdermal delivery provides a more stable blood level of the drug than oral dosing. However, with nitroglycerin, the sustained blood level of the drug provided by transdermal delivery is not desirable, due to induced tolerance to the drug not seen with sublingual tablets.

Transdermal Therapeutic Systems (TTS, Alza) consist of a thin, flexible composite of membranes, resembling a small adhesive bandage, which is applied to the skin and delivers drug through intact skin into the bloodstream. Other examples of products delivered using this system are shown in . Transderm Nitro consists of several layers: (1) an aluminized plastic backing that protects nitroglycerin from loss through vaporization; (2) a drug reservoir containing nitroglycerin adsorbed onto lactose, colloidal silicon dioxide, and silicone medical fluid; (3) a diffusion-controlling membrane consisting of ethylene–vinyl acetate copolymer; (4) a layer of silicone adhesive; and (5) a protective strip.

Other transdermal delivery manufacturers have made transdermal systems in which the adhesive functions both as a pressure-sensitive adhesive and as a controlling matrix. Dermaflex (Elan) is a uniquely passive transdermal patch system that employs a hydrogel matrix into which the drug is incorporated. Dermaflex regulates both the availability and absorption of the drug in a manner that allows for controlled and efficient systemic delivery of many drugs.

An important limitation of transdermal preparation is the amount of drug that is needed in the transdermal patch to be absorbed systemically to provide the optimum therapeutic response. The amount of drug absorbed transdermally is related to the amount of drug in the patch, the size of the patch, and the method of manufacture. A dose–response relationship is obtained by applying a proportionally larger transdermal patch that differs only in surface area. For example, a 5-cm^2 transdermal patch will generally provide twice as much drug absorbed systemically as a 2.5-cm^2 transdermal patch.

In general, drugs given at a dose of over 100 mg would require too large a patch to be used practically. However, new advances in pharmaceutic solvents may provide a mechanism for an increased amount of drug to be absorbed transdermally. Azone, a *permeation enhancer*, is a solvent that increases the absorption of many drugs through the skin. This solvent is relatively nontoxic.

For ionic drugs, absorption may be enhanced transdermally by *iontophoresis*, a method in which an electric field is maintained across the epidermal layer with special miniature electrodes. Some drugs, such as lidocaine, verapamil, insulin, and peptides, have been absorbed through the skin by iontophoresis. A process in which transdermal drug delivery is aided by high-frequency sound is called *sonophoresis*. Sonophoresis has been used with hydrocortisone cream applied to the skin to enhance penetration for treating "tennis elbow" and other mild inflammatory muscular problems. Many such novel systems are being developed by drug delivery companies.

Panoderm XL patch technology (Elan) is a new system that delivers a drug through a concealed miniature probe which penetrates the stratum corneum. Panoderm XL is fully disposable and may be programmed to deliver drugs as a preset bolus, in continuous or pulsed regimen. The complexity of the device is hidden from the patient and is simple to use. Panoderm (Elan) is

an electrotransdermal drug delivery system that overcomes the skin diffusion barriers through the use of low-level electric current to transport the drug through the skin. Several transdermal products, such as fentanyl, hydromorphone, calcitonin, and LHRH (luteinizing hormone–releasing hormone), are in clinical trials. More improvements in absorption enhancers and delivery systems will be available in the future for transdermal preparations.

Combination Products

Combination products consist of the drug in combination with a device and or biologic that is physically, chemically, or otherwise combined or mixed and produced as a single entity. Possible combinations include drug/device, biologic/device, drug/biologic, or drug/device/biologic. The device and/or biologic is intended for use with the approved drug and influences the route of administration and pharmacokinetics of the drug. For example, designs for metered-dose inhalers for inhalation therapy greatly influence the delivery of the drug into the lungs.

Implants and Inserts

Polymeric drug implants can deliver and sustain drug levels in the body for an extended period of time. Both biodegradable and nonbiodegradable polymers can be impregnated with drugs in a controlled drug delivery system. For example, levo-norgestrel implants (Norplant system, Wyeth-Ayerst) is a set of six flexible closed capsules made of silastic (dimethylsiloxane/methylvinylsiloxane copolymer), each containing 36 µg of the progestin levonorgestrel. The capsules are sealed with silastic adhesive and sterilized. The Norplant system is available in an insertion kit to facilitate subdermal insertion of all six capsules in the mid-portion of the upper arm. The dose of levonorgestrel is about 85 µg/day, followed by a decline to about 50 µg/day by 9 months and to about 35 µg/day by 18 months, declining further to about 30 µg/day (). The levonorgestrel implants are effective for up to 5 years for contraception and then must be replaced. An intrauterine progesterone contraceptive system (Progestasert, Alza) is a T-shaped unit that contains a reservoir of 38 µg of progesterone. Contraceptive effectiveness for Progestasert is enhanced by continuous release of progesterone into the uterine cavity at an average rate of 65 µg/day for 1 year.

A dental insert available for the treatment of peridontitis is the doxycycline hyclate delivery system (Atrigel). This is a subgingival controlled-release product consisting of two syringe mixing systems that, when combined, form a bioabsorbable, flowable polymeric formulation. After administration under the gum, the liquid solidifies and then allows for controlled release of doxycycline for a period of 7 days.

CONSIDERATIONS IN THE EVALUATION OF MODIFIED-RELEASE PRODUCTS

The two important requirements for preparing extended-release products are (1) demonstration of safety and efficacy and (2) demonstration of controlled drug release.

For many drugs, data are available demonstrating the safety and efficacy for those drugs given in a conventional dosage form. Bioavailability data demonstrating comparable blood levels to an approved extended-release product are acceptable. The bioavailability data requirements are specified in the Code of Federal Regulations, 21 CFR 320.25(f). The important points are as follows.

1. The product should demonstrate sustained release, as claimed, without dose dumping (abrupt release of a large amount of the drug in an uncontrolled manner).

2. The drug should show steady-state levels comparable to those reached using a conventional dosage form given in multiple doses, and which was demonstrated to be effective.

3. The drug product should show consistent pharmacokinetic performance between individual dosage units.

4. The product should allow for the maximum amount of drug to be absorbed while maintaining minimum patient-to-patient variation.

5. The demonstration of steady-state drug levels after the recommended doses are given should be within the effective plasma drug levels for the drug.

6. An *in-vitro* method and data that demonstrate the reproducible extended-release nature of the product should be developed. The *in-vitro* method usually consists of a suitable dissolution procedure that provides a meaningful *in-vitro–in-vivo* correlation.

7. *In-vivo* pharmacokinetic data consist of single and multiple dosing comparing the extended-release product to a reference standard (usually an approved nonsustained-release or a solution product).

The pharmacokinetic data usually consist of plasma drug data and/or drug excreted into the urine. Pharmacokinetic analyses are performed to determine such parameters as $t_{1/2}$, V_D, t_{max}, AUC, and k.

Pharmacodynamic and Safety Considerations

Pharmacokinetic and safety issues must be considered in the development and evaluation of a modified-release dosage form. The most critical issue is to consider whether the modified-release dosage form truly offers an advantage over the same drug in an immediate-release (conventional) form. This advantage may be related to better efficacy, reduced toxicity, or better patient compliance. However, because the cost of manufacture of a modified-release dosage form is generally higher than the cost for a conventional dosage form, economy or cost savings for patients also may be an important consideration.

Ideally, the extended-release dosage form should provide a more prolonged pharmacodynamic effect compared to the same drug given in the immediate-release form. However, an extended-release dosage form of a drug may have a different pharmacodynamic activity profile compared to the same drug given in an acute, intermittent, rapid-release dosage form. For example, transdermal patches of nitroglycerin, which produce prolonged delivery of the drug, may produce functional tolerance to

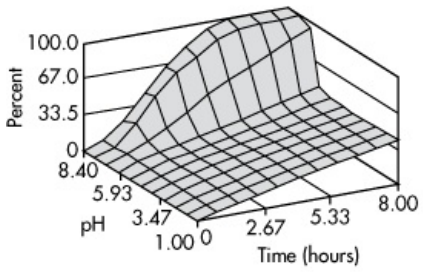
vasodilation that is not observed when nitroglycerin is given sublingually for acute angina attacks. Certain bactericidal antibiotics such as penicillin may be more effective when given in intermittent (pulsed) doses compared to continuous dosing. The continuous blood level of a hormone such as a corticosteroid might suppress adrenocorticotropic hormone (ACTH) release from the pituitary gland, resulting in atrophy of the adrenal gland. Furthermore, drugs that act indirectly or cause irreversible toxicity may be less efficacious when given in an extended-release rather than in conventional dosage form.

Because the modified-release dosage form may be in contact with the body for a prolonged period, the recurrence of sensitivity reactions or local tissue reactions due to the drug or constituents of the dosage form are possible. For oral modified-release dosage forms, prolonged residence time in the GI tract may lead to a variety of interactions with GI tract contents, and the efficiency of absorption may be compromised as the drug moves distally from the duodenum to the large intestine.

Moreover, dosage form failure due to either dose dumping or to the lack of drug release may have important clinical implications. Another possible unforeseen problem with modified-release dosage forms is an alteration in the metabolic fate of the drug, such as nonlinear biotransformation or site-specific disposition.

Design and selection of extended-release products are often aided by dissolution tests carried out at different pH units for various time periods to simulate the condition of the GI tract. Topographical plots of the dissolution data may be used to graph the percent of drug dissolved versus two variables (time, pH) that may affect dissolution simultaneously. For example, have shown that extended-release preparations of theophylline, such as Theo-24, have a more rapid dissolution rate at a higher pH of 8.4 (), whereas Theo-Dur is less affected by pH (). These dissolution tests *in vitro* may help to predict the *in-vivo* bioavailability performance of the dosage form.

Figure 17-15.



Topographical dissolution characterization of theophylline controlled release. Topographical dissolution characterization (as a function of time and pH) of Theo-24, a theophylline controlled-release preparation, which has been shown to have a greater rate and extent of bioavailability when dosed after a high-fat meal than when dosed under fasted conditions.

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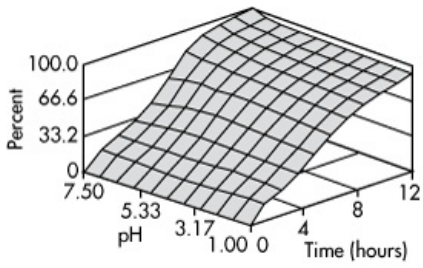
Figure 17-16.



Topographical dissolution characterization of theophylline extended release. Topographical dissolution characterization (as a function of time and pH) of Theo-Dur, a theophylline controlled-release preparation, the bioavailability of which was essentially the same whether administered with food or under fasted conditions.

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EVALUATION OF MODIFIED-RELEASE PRODUCTS

Dissolution Studies

Dissolution requirements for each of the three types of modified-release dosage form are published in the USP-NF. Some of the key elements for the *in-vitro* dissolution/drug release studies are listed in . Dissolution studies may be used together with bioavailability studies to predict *in-vitro–in-vivo* correlation of the drug release rate of the dosage forms.

Table 17.9 Suggested Dissolution/Drug Release Studies for Modified-Release Dosage Forms
Dissolution studies
1. Reproducibility of the method.
2. Proper choice of medium.
3. Maintenance of sink conditions. 4. Control of solution hydrodynamics.
5. Dissolution rate as a function of pH, ranging from pH 1 to pH 8 and including several intermediate values.
6. Selection of the most discriminating variables (medium, pH, rotation speed, etc) as the basis for the dissolution test and specification.
Dissolution procedures
1. Lack of dose dumping, as indicated by a narrow limit on the 1-hr dissolution specification.
2. Controlled-release characteristics obtained by employing additional sampling windows over time. Narrow limits with an appropriate *Q* value system will control the degree of first-order release.
3. Complete drug release of the drug from the dosage form. A minimum of 75–80% of the drug should be released from the dosage form at the last sampling interval.
4. The pH dependence/independence of the dosage form as indicated by percent dissolution in water, appropriate buffer, simulated gastric juice, or simulated intestinal fluid.

Adapted from , with permission.

In-Vitro–In-Vivo Correlations

A general discussion of correlating dissolution data to blood-level data for immediate-release oral drug products is presented in . Ideally, the *in-vitro* drug release of the extended-release product should relate to the bioavailability of the drug *in vivo*, so that changes in drug dissolution rates will be correlated directly to changes in drug bioavailability. Methods for establishing *in-vitro–in-vivo correlation* are discussed by and in the USP-NF. The following is a brief summary of the various categories of dissolution showing different degrees of correlation to *in-vivo* data.

CORRELATION LEVEL A

Level A is the highest level of correlation, in which a 1:1 relationship between *in-vitro* dissolution and *in-vivo* bioavailability is demonstrated. Included in Level A are extended-release dosage forms that demonstrate an *in-vitro* drug release essentially independent of the dissolution medium. In this case, the *in-vitro* dissolution curve is compared directly to the percentage of drug absorbed calculated from the plasma drug concentration–time curve using a pharmacokinetic model or a model-independent method.

Generally, the percentage of drug absorbed may be calculated by the Wagner–Nelson or Loo–Riegelman procedures or by direct mathematical deconvolution, a process of mathematical resolution of blood level into an input (absorption) and an output (disposition) component (). The main advantage of a Level A correlation is that the quality control procedure of the *in-vitro* dissolution/drug release test is predictive of drug product performance *in vivo*.

CORRELATION LEVEL B

Correlation Level B is based on the principle of statistical moment analysis (see). The mean residence time of the drug in the body and mean dissolution time *in vitro* are determined and correlated. This level of correlation is less than a Level A 1:1 correlation because the complete *in-vivo* plasma drug concentration–time curve is not fully described by the mean residence time.

CORRELATION LEVEL C

Correlation Level C uses a single point in the dissolution curve to correlate to plasma drug concentration–time data. For example, a single dissolution time at $t_{50\%}$, $t_{90\%}$, and so forth, may be selected and correlated to pharmacokinetic parameters, such as AUC, t_{max}, or C_{max}. This is the weakest level of correlation because only partial relationship between absorption and dissolution is evident. Some examples of this correlation are given in .

Pharmacokinetic Studies

Various types of pharmacokinetic studies may be required by the Food and Drug Administration (FDA) for marketing approval of the modified-release drug product, depending on knowledge of the drug, its clinical pharmacokinetics, and its biopharmaceutics (). Furthermore, the extended-release dosage form should be available in several dosage strengths to allow flexibility for the clinician to adjust the dose for the individual patient.

Both single- and multiple-dose steady-state crossover studies using the highest strength of the dosage form may be performed. The reference dosage form may be a solution of the drug or the full NDA-approved conventional, immediate-release dosage form given in an equal daily dose as the extended-release dosage form. If the dosage strengths differ from each other only in the amount of the drug– excipient blend, but the concentration of the drug–excipient blend is the same in each dosage form, then the FDA may approve the NDA or ANDA on the basis of single- and multiple-dose studies of the highest dosage strength, whereas the other lower-strength dosage forms may be approved on the basis of comparative *in-vitro* dissolution studies (). The latest FDA Guidance for Industry should be consulted for regulatory requirements (www.fda.gov/cder/guidance/index.htm). have described several types of such pharmacokinetic studies.

CASE ONE

The first case involves the extended-release oral dosage form of a modified immediate-release drug for which extensive pharmacodynamic or pharmacokinetic data exist. Both single- and multiple-dose steady-state crossover studies are required. In the case of the single-dose study, a well-controlled pharmacokinetic study must also be performed to define the effects of a concurrent high-fat meal on the extended-release dosage form. This food study, comparing fasting versus fed subjects, is to determine (1) whether there is any need for labeling specifications of special conditions for administration of the dosage form with respect to meals, and (2) whether the absorption pattern of the extended-release dosage compares to that for the immediate-release (conventional) form of the same drug.

CASE TWO

The second case concerns nonoral extended-release dosage forms. Pharmacokinetic studies for the evaluation of extended-release dosage forms designed for an alternate route of administration would require studies similar to case 1, but would not need a food-effect study. However, when the route of administration is changed from the oral route, other factors may require consideration. An alternative route of administration may alter the biotransformation pattern of active or inactive metabolites. For example, isoproterenol given orally forms a sulfate conjugation as a result of metabolism within the cells of the small intestine, whereas after IV administration, isoproterenol forms a 3-O-methylated metabolite via catechol O-methyltransferase (COMT). Clinical efficacy may be altered by an alternative route of administration when a drug is switched from the oral to the parenteral or transdermal route. In this case, possible risk factors, such as irritation or sensitivity at the site of application, must also be studied.

CASE THREE

In case 3, studies involve the generic equivalent of an NDA-approved, extended-release product. The same bioequivalence studies are required to establish the equivalence of the formulation used in efficacy studies if the formula is different from the one intended for marketing and generic approval. The establishment of bioequivalence is based on both pharmacokinetic and statistical analyses.

CASE FOUR

Finally, case 4 addresses an extended-release dosage form as an NDA. For an NDA, the studies required for new extended-release dosage forms are clinical and pharmacokinetic studies including dose linearity, bioavailability, food effects, fluctuation of the plasma drug concentrations, and characterizations of the plasma drug concentration–time profile.

The FDA's Center for Drug Evaluation and Research (CDER) maintains a website (www.fda.gov/cder) that lists regulatory guidances to provide the public with the FDA's latest submission requirements for NDAs and ANDAs.

EVALUATION OF *IN-VIVO* BIOAVAILABILITY DATA

A properly designed *in-vivo* bioavailability study is performed. The data are then evaluated using both pharmacokinetic and statistical analysis methods. The evaluation may include a pharmacokinetic profile, steady-state plasma drug concentrations, rate of drug absorption, occupancy time, and statistical evaluation of the computed pharmacokinetic parameters.

Pharmacokinetic Profile

The plasma drug concentration–time curve should adequately define the bioavailability of the drug from the dosage form. The bioavailability data should include a profile of the fraction of drug absorbed (Wagner–Nelson) and should rule out dose dumping or lack of a significant food effect. The bioavailability data should also demonstrate the extended-release characteristics of the dosage form compared to the reference or immediate-release drug product.

Steady-State Plasma Drug Concentration

The fluctuation between the C^{∞}_{max} (peak) and C^{∞}_{min} (trough) concentrations should be calculated:

$$\text{Fluctuation} = \frac{C^{\infty}_{max} - C^{\infty}_{min}}{C^{\infty}_{av}} \qquad (17.11)$$

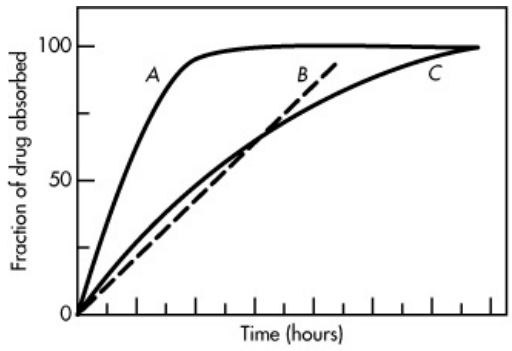
where C^{∞}_{av} is equal to [AUC]/τ

An ideal extended-release dosage form should have minimum fluctuation between C_{max} and C_{min}. A true zero-order release will have no fluctuation. In practice, the fluctuation in plasma drug levels after the extended-release dosage form should be less than the fluctuation after the same drug given in an immediate-release dosage form.

Rate of Drug Absorption

For the extended-release drug product to claim zero-order absorption, an appropriately calculated input function such as used in the Wagner–Nelson approach should substantiate this claim. The difference between first-order and zero-order absorption of a drug is shown in . The rate of drug absorption from the conventional or immediate-release dosage form is generally first order, as shown by . Drug absorption after an extended-release dosage form may be zero order (), first order (), or an indeterminate order (). For many extended-release dosage forms, the rate of drug absorption is first order, with an absorption rate constant k_a smaller than the elimination rate constant k. The pharmacokinetic model when $k_a > k$ is termed *flip-flop pharmacokinetics* and is discussed in .

Figure 17-17.



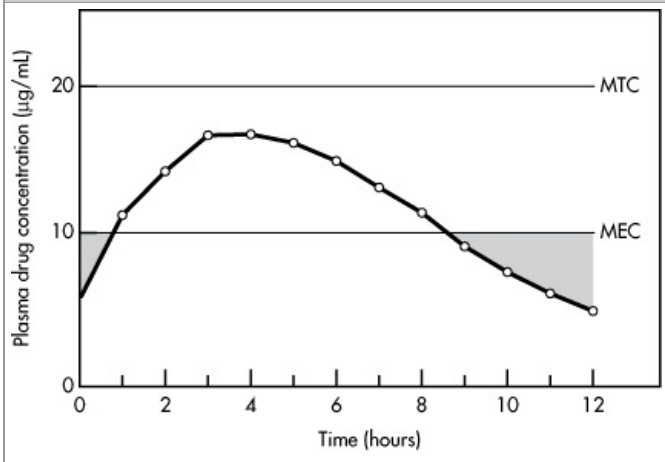
Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

The fraction of drug absorbed using the Wagner–Nelson method may be used to distinguish between the first-order drug absorption rate of a conventional (immediate-release) dosage form (A) and *an* extended-release dosage form (C). Curve B represents *an* extended-release dosage form with zero-order absorption rate.

Occupancy Time

For drugs for which the therapeutic window is known, the plasma drug concentrations should be maintained above the minimum effective drug concentration (MEC) and below the minimum toxic drug concentration (MTC). The time required to obtain plasma drug levels within the therapeutic window is known as *occupancy time* ().

Figure 17-18.



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

Occupancy time.

Bioequivalence Studies

Bioequivalence studies for extended-release drug products are discussed in detail in . Bioequivalence studies may include (1) a fasting study, (2) a food-intervention study, and (3) a multiple dose study. The FDA's Center for Drug Evaluation and Research (CDER) maintains a website (www.fda.gov/cder) that lists regulatory guidances to provide the public with the FDA's latest submission requirements for NDAs and ANDAs.

Statistical Evaluation

Variables subject to statistical analysis generally include plasma drug concentrations at each collection time, AUC (from zero to last sampling time), AUC (from zero to time infinity), C_{max}, t_{max}, and elimination half-life $t_{1/2}$. Statistical testing may include an analysis of variance (ANOVA), computation of 90% and 95% confidence intervals on the difference in formulation means, and the power of ANOVA to detect a 20% difference from the reference mean.

FREQUENTLY ASKED QUESTIONS

1. Are extended-release drug products always more efficacious than immediate-release drug products containing the same drug?

2. What are the advantages and disadvantages of a zero-order rate for drug absorption?

LEARNING QUESTIONS

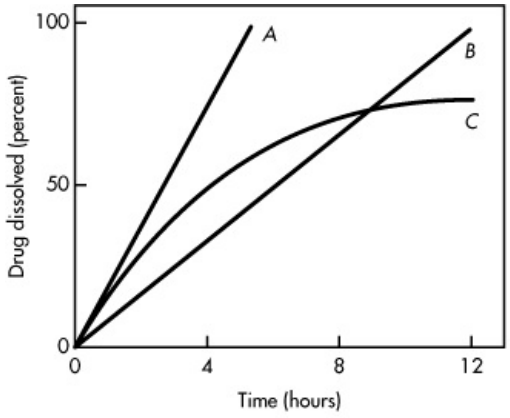
1. The design for most extended-release or sustained-release oral drug products allows for the slow release of the drug from the dosage form and subsequent slow absorption of the drug from the gastrointestinal tract.

a. Why does the slow release of a drug from an extended-release drug product produce a longer-acting pharmacodynamic response compared to the same drug prepared in a conventional, oral, immediate-release drug product?

b. Why do manufacturers of sustained-release drug products attempt to design this dosage form to have a zero-order rate of systemic drug absorption?

2. The dissolution profiles of three drug products are illustrated in .

Figure 17-19.



Dissolution profile of three different drug products. Drug dissolved (percent).

a. Which of the drug products in release drug at a zero-order rate of about 8.3% every hour?

b. Which of the drug products does not release drug at a zero-order rate?

c. Which of the drug products has an almost zero-rate of drug release during certain hours of the dissolution process?

d. Suggest a common cause of slowing drug dissolution rate of many rapid-release drug products toward the end of dissolution.

e. Suggest a common cause of slowing drug dissolution of a sustained-release product toward the end of a dissolution test.

3. A drug is normally given at 10 mg four times a day. Suggest an approach for designing a 12-hour zero-order release product.

a. Calculate the desired zero-order release rate.

b. Calculate the concentration of the drug in an osmotic pump type of oral dosage form that delivers 0.5 mL/hr of fluid.

4. An industrial pharmacist would like to design a sustained-release drug product to be given every 12 hours. The active drug ingredient has an apparent volume of distribution of 10 L, an elimination half-life of 3.5 hours, and a desired therapeutic plasma drug concentration of 20 µg/mL. Calculate the zero-order release rate of the sustained-release drug product and the total amount of drug needed, assuming no loading dose is required.

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