

9

MECHANISMS OF CONTROLLED RELEASE

Although there are hundreds of commercial products based on the controlled-release technologies, there are only several distinct mechanisms for controlled drug release. Table 9.1 lists the types of controlled-release mechanisms commonly used in the currently available controlled-release dosage forms. The controlled-release mechanisms can be broadly classified into physical and chemical mechanisms.

All controlled-release dosage forms are made based on one or combination of a few mechanisms listed above. Each mechanism has its advantages and limitations and it is highly important that we understand each mechanism. Thus, we will discuss each mechanism in detail with appropriate examples.

I. DISSOLUTION-CONTROLLED DRUG RELEASE

In dissolution-controlled drug-release devices, the drug release is controlled by dissolution of either polymeric membranes surrounding the drug core or polymeric matrix containing the drug. Since the dissolution of polymeric materials is the key to this mechanism, all the polymers used

Table 9.1 Mechanisms of Controlled Drug Release

Physical Mechanisms
Dissolution
Encapsulated dissolution system (Reservoir system)
Matrix dissolution system
Diffusion
Reservoir device
Nonporous membrane reservoir device
Microporous membrane reservoir device
Monolithic device
Nonporous matrix
Monolithic solution
Monolithic dispersion
Microporous matrix
Monolithic solution
Monolithic dispersion
Osmosis
Ion-exchange
Chemical Mechanisms
Chemical degradation
Enzymatic degradation

Table 9.2 Some Polymers used in Dissolution-Controlled Formulations

Natural Polymers	Synthetic Polymers
Proteins	Water-Soluble Polymers
Albumin	Poly(acrylic acid)
Gelatin	Poly(ethylene glycol)
	Poly(vinyl alcohol)
Polysaccharides	Polyvinylpyrrolidone
Alginate, sodium	Pluronic
Chitosan	Poloxamers
Carboxymethylcellulose, sodium salt	
Hydroxyethylcellulose	Biodegradable Polymers
Hydroxypropylcellulose	Poly(ϵ -caprolactone)
Hydroxypropylmethylcellulose	Poly(glycolic acid)
Methylcellulose	Poly(β -hydroxybutylate)
Starch (thermally modified)	Poly(lactic acid)
Xanthan gum	

are water soluble or degradable in water. Table 9.2 lists some of the water-soluble polymers. The choice of a particular polymer for a particular controlled-release dosage form depends on the nature of the dosage form (*i.e.*, dissolution mechanism, delivery period, delivery route, delivered drug, etc.).

Biodegradable polymers are hydrophobic and thus water insoluble. They, however, undergo hydrolysis and break down into smaller units. Even though they are not water soluble they are degradable in the body. Since the degradation products are biocompatible they are widely used in controlled drug delivery.

The dissolution-controlled drug-delivery systems can be divided into two different subgroups: encapsulated dissolution systems (or reservoir system) and matrix dissolution systems.

A. ENCAPSULATED DISSOLUTION SYSTEM (RESERVOIR SYSTEM)

In this system, the drug release is controlled by the thickness and the dissolution rate of the polymer membrane surrounding the drug core. Once the coating polymer membrane dissolves, the entire drug is immediately available for dissolution and absorption.

As shown in Figure 9.1, if the polymer membranes are of varying thickness that dissolve immediately, 3 h, 6 h, and 9 h after the administration, the dosage form containing all four different spheres can effectively release drug for up to 12 h. In the above example, only three different polymer membrane thicknesses were used, so the dosage form is a repeat action dosage form that may not produce zero-order release. If, however, a spectrum of different polymer membrane thicknesses is used, zero-order release is possible. The coated drug particles can be directly compressed into tablets or placed in capsules.

SmithKline & French Laboratories began its research on the development of sustained drug delivery systems in 1945 and introduced the Spansule[®] system in 1952. In the Spansule[®] system, each capsule contains hundreds of tiny beads. The drug-containing core of each bead is sur

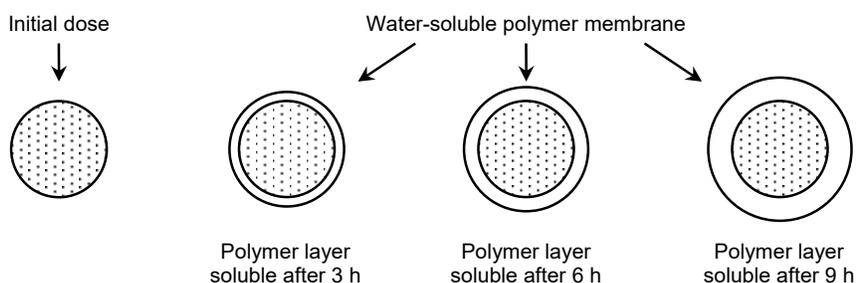


Figure 9.1 Drug reservoirs coated with a layer of different thickness. The drug without any layer is used for immediate release.

rounded by a layer of natural wax, such as beeswax or glyceryl monostearate. The drug-release kinetics from each bead is controlled by the thickness of the wax layer. Since the wax layers vary in thickness, the drug delivery from the beads is sustained, and the Spansule[®] system was designed to sustain drug release for about 12 h. The first drug used in the system was dextroamphetamine sulfate (Dexedrine[®]), which is used to treat narcolepsy (an uncontrollable need for short periods of sleep), obesity, and certain behavioral disturbances in children. Despite the technological success of the Spansule[®] system for the sustained drug delivery in 1952, the commercial success was not made until 1961 when SmithKline & French's Menley & James Laboratories division introduced Contac[®] capsules for the relief of the common cold and hay fever. The TV commercials at that time featured a magnified view of tiny beads falling from the capsule and bouncing just like hundreds of tennis balls bouncing on a tennis court. The Contac[®] capsules familiarized the public with the concept of sustained drug release. Since then numerous drugs have been introduced in the Spansule[®] form. Each bead can be coated with a variety of water-soluble polymers. Examples of dosage forms using this technology are listed in Table 9.3.

Table 9.3 Examples of Commercial Encapsulated Dissolution System

Product	Active ingredient(s)	Manufacturer
Spansule capsules		SmithKline Beecham
Compazine	prochlorperazine	
Dexedrine	dextroamphetamine sulfate	
Ornade	phenylpropanolamine HCl	
Feosol	ferrous sulfate	
Thorazine	chlorpromazine HCl	
Dexatrim	phenylpropranolamine	
Contac	phenylpropanolamine HCl chlorpheniramine maleate	
Sequel capsules		Lederle
Diamox	acetazolamide	
Ferro-sequels	ferrous fumarate docusae sodium	
SODAS* capsules		
Cardizem SR	diltiazem	Hoechst Marion Ruossel
Verelan	verapamil	Lederle Laboratories

*SODAS: Spheroidal Oral Drug Absorption System developed by Elan Corp. in Monksland, Athlone, Ireland.

The SODAS consists of multiple 1-mm spherical particles stored in a hard gelatin capsule. The spheres result in a wide distribution within the GI tract and are surrounded by rate-controlling polymers that allow dissolution and release to be independent of pH and food. A proportion of the beads are made to release drug immediately. Cardizem SR[®] (diltiazem HCl sustained-release capsules) is a multiparticulate formulation intended to for twice-daily administration. Cardizem SR[®] contains a blend of two types of sustained-release beads with different thicknesses of membrane coating (of povidone). The coating dissolves in the GI tract, and this results in sustained-release characteristic. Examples of large encapsulated dissolution systems are shown below.

1. Plendil[®]: felodipine extended-release tablets by Astra Merck, Inc.

Felodipine (calcium channel blocker) tablets are surrounded by a second layer of gel-forming substance (HPMC) that is activated upon contact with GI fluid. The gel-forming layer also contains felodipine. Felodipine is released over 12 h at a controlled rate by diffusion and through gradual attrition of the gel layer (Figure 9.2). The type and amount of gel-forming substance determines the drug-release rate. Dose dumping may occur if the tablet is divided or crushed. The time to maximum concentration of 10 mg of the immediate release formulation was 1 h compared with 2.9 h for the ER formulation.

2. Procanbid[®] (procainamide HCl) extended-release tablets

The release of procainamide HCl is controlled by two mechanisms using T-Kote[™] technology. The core of the tablet consists of a wax matrix that is then coated with a polymeric, controlled-release layer. Procanbid[®] contains black iron oxide, candelilla wax, carnauba wax, colloidal silicon dioxide, hydroxypropylcellulose, HPMC, magnesium stearate, polyacrylate dispersion, PEG 3350, PEG 8000, propylene glycol, semethicone emulsion, talc, and titanium dioxide. The Procanbid[®] T-Kote[™] delivery system is designed to control the release rate such that absorption is sustained throughout the 12-h dosing interval.

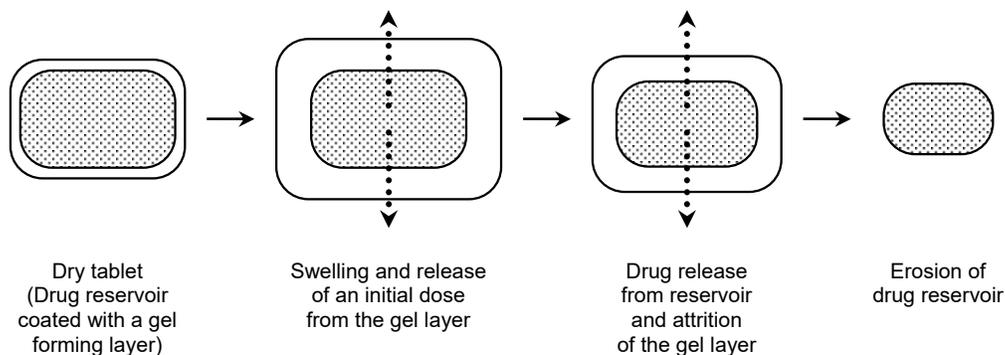


Figure 9.2 Schematic description of the Plendil[®] system.

B. MATRIX DISSOLUTION SYSTEM

In this type of devices, the drug is homogeneously distributed throughout the polymer matrix. Drug molecules are released as the polymer matrix dissolves. Since the size of the matrix decreases as more drug is released, the amount of drug released is also decreased. Thus, the drug release rate decreases and it results in nonzero-order release.

1. Micromatrix[®] systems

Small, spherical matrix systems can be prepared by some of the processes described in Chapter 7, Section IV. The granules obtained are either filled into hard gelatin capsules or compressed into tablets. Tempule[®] capsule is an example of the capsule dosage form. Examples of tablet dosage forms are Extentab[®], Timespan[®], Repetab[®], Dospan[®], and Chronotab[®].

2. Macromatrix systems

a. Adalat CC[®]

Adalat CC[®] is an extended-release formulation for nifedipine from Bayer. It is a tablet consisting of three parts: exterior film coat for light protection; outer coat for slow release of nifedipine; and inner core for fast release of nifedipine (Figure 9.3). The film coat is made of hydroxypropylmethylcellulose, polyethylene glycol, ferric oxide, and titanium dioxide. The outer coat and inner core are made of hydroxylpropylcellulose, lactose, corn starch, crospovidone, microcrystalline cellulose, silicon dioxide, and magnesium stearate.

The outer coat, slow-release formulation, contains nifedipine distributed in a matrix of a hydrophilic gel-forming polymer. On contact with gastric fluid, an erosion process begins at the tablet surface. The nifedipine contained in the matrix is dissolved and absorbed as the tablet passes through the GI tract. With advancing erosion of the outer coat, the fast-release inner core of nifedipine is exposed and begins to dissolve. The decreasing rate of nifedipine released from the tablet's outer coat is compensated by the increasing nifedipine release rate from its inner core.

C. DISSOLUTION RATE OF HOMOGENOUS MATRIX SYSTEMS

The rate of drug release from dissolution-controlled drug-delivery systems

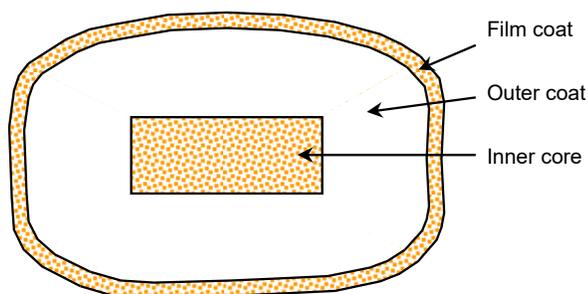
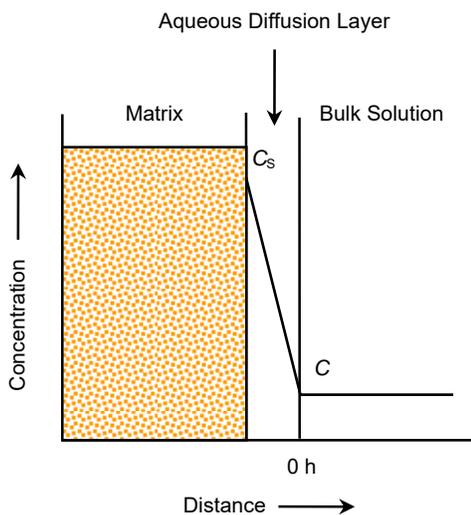


Figure 9.3 Schematic drawing of Adalat[®] CC.

depends on the rate of dissolution of the matrix. The rate at which a matrix dissolves can be described by the equation similar to the one used to describe Fick's law in Chapter 6.

As the polymeric matrix dissolves from the surface, the drug molecules have to move from the surface of the matrix to the bulk solution. Right at the surface of the matrix, a layer of water is stagnant regardless of the stirring in the bulk solution. This layer is called the aqueous diffusion layer or the stagnant aqueous layer. The thickness of the stagnant layer, h , is reduced as the bulk solution is stirred more vigorously. This aqueous diffusion layer essentially functions as a membrane through which drug molecules have to diffuse. For this reason, the same equation used to describe Fick's law can be used here.

Let's consider the release of drug molecules through the aqueous diffusion layer that is h -cm thick. The concentrations of drug at the surface of the matrix and in the bulk are C_s and C , respectively. Of course, C_s is larger than C . The difference between C_s and C is ΔC .



Let's define M , S , and D as follows: M is the total amount of drug (g or mol) dissolved from the surface S (cm^2) at time t ; S is the surface area of the exposed matrix; and D is the diffusion coefficient of the drug in aqueous solution. Then, we can write:

$$M = \frac{D \cdot S}{h} (C_s - C) t$$

and the rate of dissolution, dM/dt is

$$\frac{dM}{dt} = \frac{D \cdot S}{h} (C_s - C)$$

This equation is known as Noyes–Whitney equation.

For a small matrices consisting of uniformly sized particulates, it is much more convenient to deal with the total weight. So, by slight rearrangement of the Noyes–Whitney equation using the density (vol-

ume/weight) term, we obtain the well-known Hixon–Crowell Cube-Root Law.

$$M_0^{1/3} - M^{1/3} = kt$$

in which M_0 is the original mass of the particles and k is the cube-root dissolution rate constant.

D. BIODEGRADABLE POLYMERS

If the dosage form is administered orally, the polymers do not have to be degraded completely to their monomer states since we do not have removal problems. In many cases, however, drug-delivery systems may have to be implanted into the body by minor surgery. To avoid another surgery to remove the device after all of the drug is released, it would be desirable if polymers are truly biodegradable (*i.e.*, breaks down into monomers that are nontoxic). For this reason, extensive efforts have been made to synthesize biodegradable polymers. Biodegradable polymers are different from water-soluble polymers. They may be water soluble or may be not. Biodegradable polymers are those that undergo breakdown of the polymer chain into monomer units in the body. The degradation of proteins by enzymes or by chemical hydrolysis into smaller units, preferably into amino acid, is happening all the time in our body. There are many synthetic polymers which undergo similar degradation.

1. PLGA Protein Delivery Microparticles

Most protein drugs have to be injected daily to be effective. To avoid such daily injections, microparticle technologies (see Figure 9.4) have been used to prepare long-term protein delivery systems, ranging from weeks to months. The most widely used biodegradable polymers are poly(lactic acid), poly(glycolic acid), and poly(lactic-co-glycolic acid).

As discussed in Chapter 7, current technologies of making microparti-

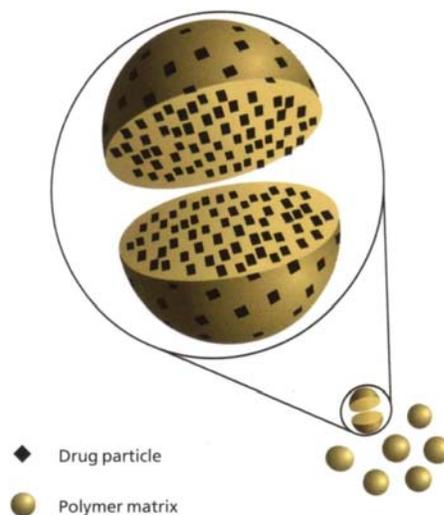


Figure 9.4 Example of a microparticle.

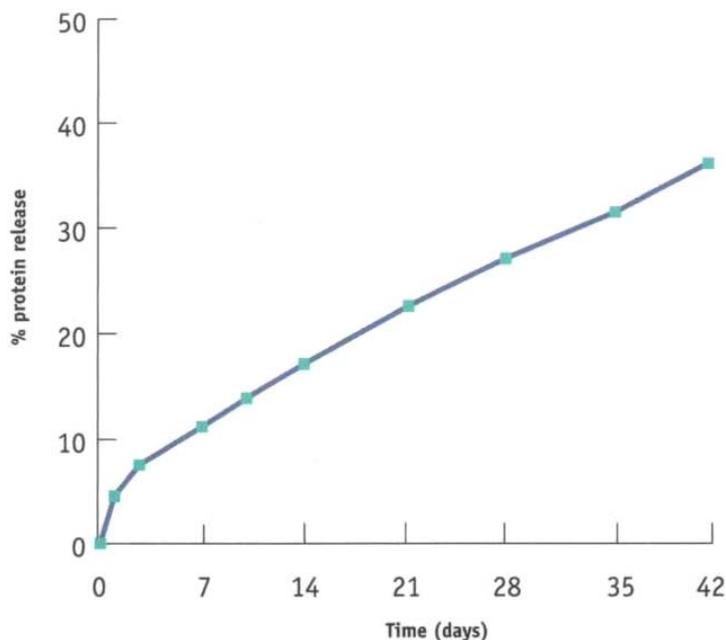


Figure 9.5 *In-vivo* dissolution performance of hGH-containing Hi-Load microparticles (West Pharmaceutical Services, Inc.).

cles usually result in matrix dissolution systems that show significant initial burst release (see Figure 9.5). New technologies need to be developed to prepare reservoir system microcapsules for protein delivery.

2. GLIADEL[®] Wafer

GLIADEL[®] wafer is a biodegradable, implantable polymer matrix made of poly[bis(*p*-carboxyphenoxy)propane-co-sebacic acid]. The polymer is synthesized by melt-condensation process. GLIADEL[®] wafers containing the chemotherapeutic agent carmustine are implanted into the brain to treat brain cancers. They are implanted in the surgical cavity created with a brain tumor is removed. As the wafer slowly erode in the brain, the drug is slowly released directly to the tumor site in high concentrations over an extended period of time.

3. Biodegradable Gel Systems

The SABER[™] system (Southern Biosystems, Inc.) is a biodegradable gel with an array of controlled release and other biomedical applications. SABER[™] begins as a low viscosity liquid and increase rapidly in viscosity after application owing to diffusional removal of solvent. The final high-viscosity form is adhesive, biocompatible, and biodegradable. The release of active ingredient can be varied from hours to months. The SABER[™] system uses a small amount of pharmaceutically acceptable organic solvent to create a low viscosity solution before application. The base component of SABER[™] is sucrose acetate isobutyrate. Sucrose acetate isobutyrate is a fully esterified sucrose molecule. Although it is a low molecular weight material, it has many properties associated with polymeric materials. Because of the nonpolymeric nature, only a small

amount of solvent, such as 15% ethanol and 30% propylene carbonate, needs to be used to dissolve the SABER™ system.

II. DIFFUSION-CONTROLLED DRUG RELEASE

The research on diffusion-controlled drug delivery began with the observation by Judah Folkman that silicone rubber absorbed certain dyes (*e.g.*, rhodamine B) from solution and subsequently released the dyes. In 1963 Folkman and Long performed systematic study to confirm the slow release of drugs such as digitoxin from the inside of the silicone rubber tubing for several days. In 1966, other researchers showed that when the progesterone-loaded silicone rubber tubing was implanted in cattle, it was able to prevent the animal from becoming fertile for more than a year. Since then, numerous polymers have been used in the diffusion-controlled drug-delivery systems. Table 9.5 lists some of the polymers used in diffusion-controlled dosage forms. All these polymers are hydrophobic and do not dissolve in aqueous solution.

In diffusion-controlled dosage forms, drug molecules have to diffuse through a polymer membrane or a polymer matrix to be released. Diffusion-controlled devices can be divided into reservoir and monolithic devices. The only difference between the two types is whether a drug is surrounded by a polymer membrane or distributed throughout the polymer matrix. As shown in Figure 9.6a, the reservoir devices are classified based on porosity of a polymer membrane. In nonporous reservoir systems, drug molecules have to diffuse through the polymer membrane. On the other hand, in microporous reservoir systems, drug molecules are released by diffusion through micropores that are usually filled with either water or oil. Microporous membranes can be prepared by making hydrophobic polymer membranes in the presence of water-soluble materials such as poly(ethylene glycol), which can be removed from the polymer matrix by dissolving in aqueous solution. Alternatively, microporous membranes can be prepared by stretching the formed membranes. Porous polyethylene or polypropylene membranes used in transdermal patches are usually prepared by stretching thin polymer membranes. In addition to nonporous and microporous devices, monolithic devices can be further classified based on the concentration of a loaded drug (Figure 9.6b). If a drug is loaded by soaking a polymer matrix in a drug solution, the drug concentration inside the matrix can not be higher than the drug solubility (*i.e.*, the concentration of a drug in a saturated solution at a certain temperature), if

Table 9.5 Diffusion-Controlled Drug-Release Formulation Polymers

Cellulose (Ethylcellulose)	Poly(hydroxypropylethyl methacrylate)
Chitin	Poly(methyl methacrylate)
Collagen	Poly(vinyl alcohol-co-methacrylate)
Nylon	Poly(vinyl chloride)
Poly(alkylcyanoacrylate)	Polyisobutene
Polyethylene	Polyurethane
Poly(ethylene-co-vinyl acetate)	Silicone rubber
Poly(hydroxyethyl methacrylate)	

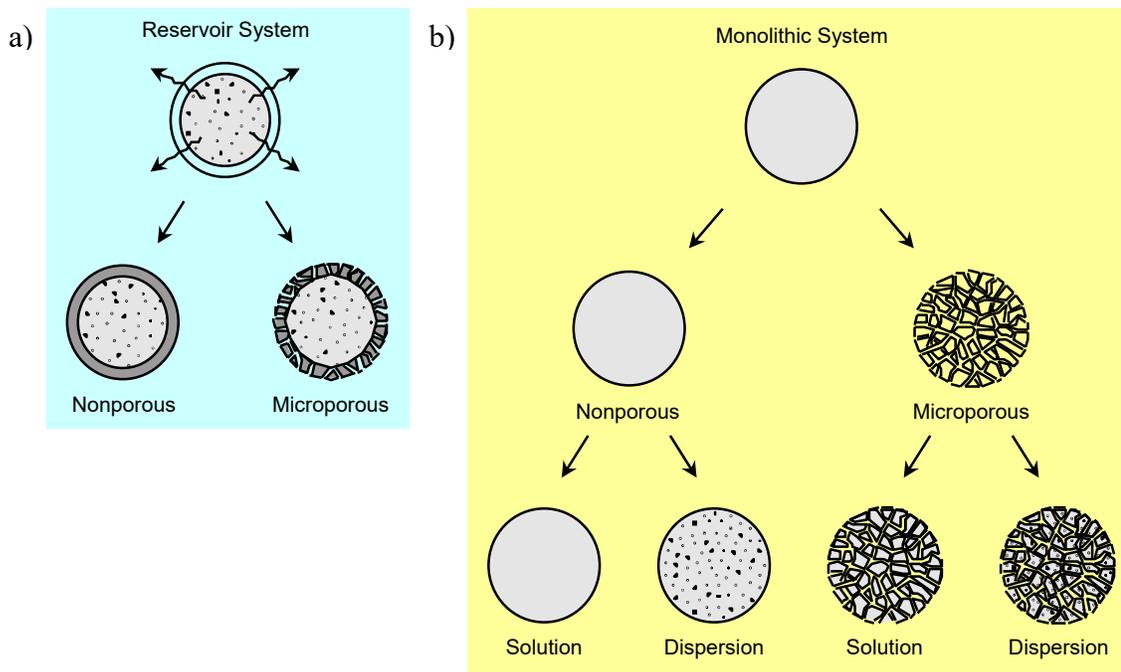


Figure 9.6 Reservoir and monolithic diffusion-controlled drug release systems. Both systems can be made of either nonporous or microporous polymeric membranes or matrices. Monolithic devices can be further classified into monolithic solution and monolithic dispersion systems. The dots inside the reservoir and monolithic dispersion systems represents excess drug particles.

the partition coefficient of a drug is 1. In this case, the monolithic device is called a monolithic solution. If a drug is added in such a way that the drug concentration inside a polymer matrix is larger than the drug solubility, the device is called a monolithic dispersion. In this case, extra drug exists as particles as indicated by black dots in Figure 9.6.

In diffusion-controlled dosage forms, drug molecules have to diffuse through the polymer membrane or polymer matrix to be released. Drug diffusion through polymer membrane or polymer matrix depends on the size of drug molecules and space available between polymer chains. Even though the space between polymer chains may be smaller than the size of drug molecules, drug can still diffuse through the polymer chains owing to the continuous movement of polymer chains by Brownian motion.

A. SOLUTE DIFFUSION THROUGH POLYMERIC MEMBRANES

Drug molecules can diffuse through the polymer chains even though the space between polymer chains may be smaller than the size of the drug molecules. The local freedom of movement of the polymer chains may provide the local microscopic viscosity which could be quite low. Thus, the local movement of the polymer chains is an important factor determining the diffusion coefficient of drugs.

In a rubbery polymer, such as silicone rubber, the polymer chains can move rather freely, while they have only limited movement in the glassy polymers such as polystyrene. Figure 9.7 shows the relationship between diffusion coefficient of drug molecules and their molecular weights.

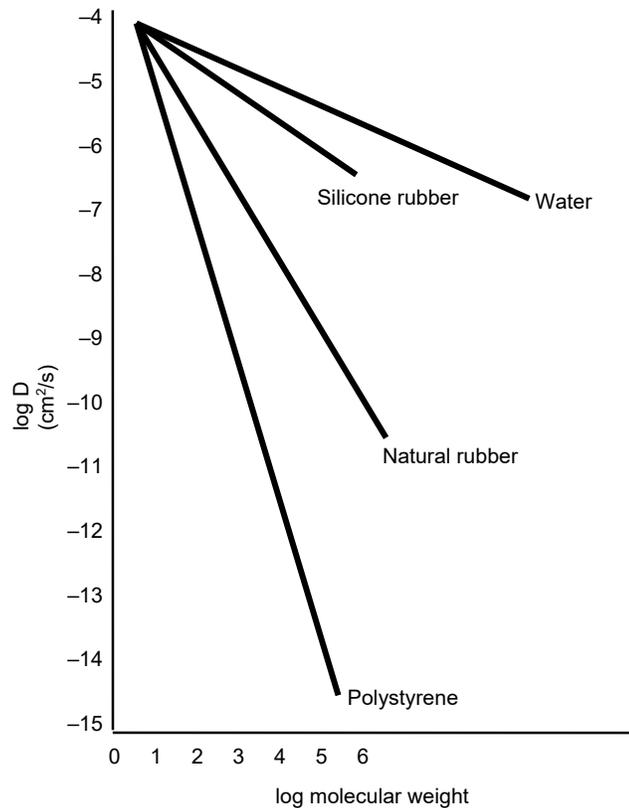


Figure 9.7 Diffusion coefficient of drug molecules as a function of their molecular weights.

We can make the following observations from the figure:

1. Diffusion in polymers is much more sensitive to molecular weight than is diffusion in water. The diffusion coefficients of drugs in polymers are small and decrease sharply with molecular size.
2. The diffusion coefficient is determined primarily by the size of the drug molecule. The dependence of the diffusion coefficient on molecular weight (MW) can be expressed as the following equation:

$$D = k (MW)^n$$

where k is the diffusion coefficient of a permeant of unit molecular weight (approximately 1×10^{-4} cm²/s in the Figure 9.7), and the exponent n varies from approximately 0.5 for water, 0.7 for silicone rubber, 2 for natural rubber to almost 5 for polystyrene.

B. RESERVOIR DEVICES

1. Reservoir devices with nonporous membranes

Figure 9.8 shows the drug release through polymer membranes in three different shapes. Let's ignore drug release through edges in the figures.

The differences in the equations for the three different types of devices are due to the different way of calculating the surface area, and otherwise

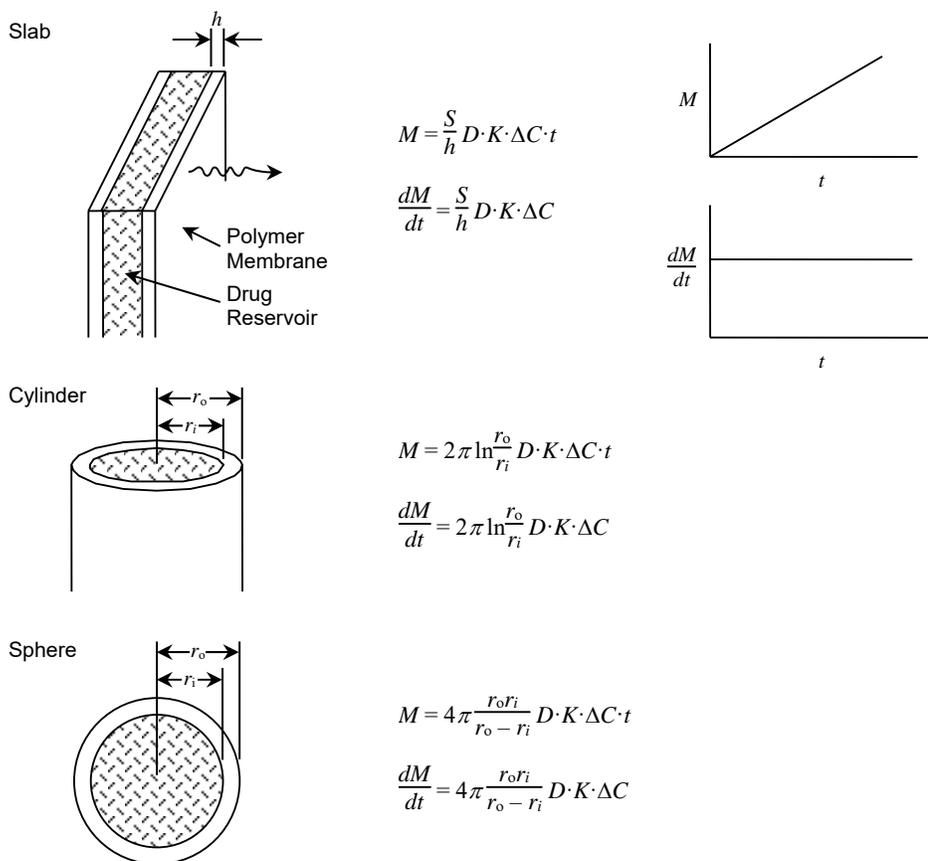


Figure 9.8 Reservoir devices in various shapes and their drug release rates.

they are the same equations. It is noted that for all three types of devices, the drug release rate is zero order.

The following nonporous membranes have been used in the development of commercial controlled release products.

a. Poly(ethylene-co-vinyl acetate) (or EVA Copolymer)

One of the advantages of using EVA copolymers is that the permeability properties can be controlled rather easily by changing the content of the vinyl acetate. Thus, it is possible to tailor a release rate to a desired value by small change in the membrane composition. The changes in permeability are related to changes in the glass-transition temperature and crystallinity of the polymer. Polyethylene has a crystallinity of 70%. The crystallinity becomes 0 at 60% of vinyl acetate content.

i. Ocusert® system

Ocusert® system is an ocular insert that releases pilocarpine either 20 or 40 $\mu\text{g/hr}$ for the management of glaucoma for up to 7 d. A thin disk of pilocarpine alginate complex is sandwiched between two transparent sheets of nonporous EVA copolymer. The membranes permit the tear fluid to penetrate into the drug reservoir compartment to dissolve pilocarpine from the complex.

ii. Progestasert[®] IUD

A suspension of progesterone crystals in silicone medical fluid is wrapped with nonporous EVA copolymer. Its daily release rate is at least 65 $\mu\text{g}/\text{d}$ for 1 y.

b. Silicone rubber

Silicone rubber has a very high permeability to steroids that have a low water solubility. Owing to the low water solubility, the boundary-layer effect is significant in this delivery system. Since a typical diffusion coefficient of steroids through silicone rubber is $5 \times 10^{-7} \text{ cm}^2/\text{s}$, the maximum flux of 200 $\mu\text{g}/\text{cm}^2 \cdot \text{h}$ is possible.

i. Norplant[®] subdermal implant

The Norplant[®] birth control system (Generation I) is an implant containing the progestin levonogestrel in the nonporous silicone medical grade tubing, both ends sealed with silicone medical grade adhesive. Norplant is composed of six dimethylsiloxane/methylvinylsiloxane copolymer capsules, 2.4 mm in diameter and 34 mm in length, each containing 36 mg of levonogestrel. The system releases 85 $\mu\text{g}/\text{d}$ of drug initially, which declines to as low as 30 $\mu\text{g}/\text{d}$ during its useful life (up to 7 y). Blood-plasma concentration of 0.30 ng/mL over five years were observed in clinical trials (John *et al.*, 1985). The typical failure rate in the first year is 0.2% compared to 3% with oral contraceptives.

In Generation II Norplant[®], levonorgestrel is loaded as a solid dispersion in silicone elastomer matrix, and only two units are used instead of six units for Generation I.

c. Ethylcellulose**i. Micro-K[®] 10 potassium chloride controlled release Extencaps[®] (Robins)**

Micro-K Extencaps[®] are hard gelatin capsules, each containing 750 mg of dispersible, small crystalline particles of KCl. Each particle of KCl is microencapsulated with a polymeric (ethylcellulose) coating that allows for the controlled release of K and Cl ions over an 8- to 10-h period.

ii. K-Dur[®] Microburst Release System[®] (KCl extended release system)

K-DUR[®] Microburst Release System[®] from Key Pharmaceuticals, Inc. K-DUR is a tablet formulation (not enteric coated or wax matrix) containing individually microencapsulated KCl crystals which disperse upon tablet disintegration. Inactive ingredients are crospovidone, ethylcellulose, hydroxypropyl cellulose, magnesium stearate, and microcrystalline cellulose. K-Dur[®] begins disintegrating into microencapsulated crystals within seconds in simulated gastric fluid at 37 °C, and completely disintegrate in one minute in the absence of outside agitation.

iii. Theo-24[®]

Theo-24[®] was the first commercial product for 24-h theophylline therapy on the market. It was developed by Searle but is now sold by UCB Phar-

ma, Inc. Theo-24[®] uses a chemical timing complex to produce very small theophylline-coated beads that provide dependable zero-order controlled drug release. A tiny sphere of sugar and starch forms the core of the bead. The core is first coated with theophylline and then with a timing complex. The resulting beads are put into capsules for oral administration. When the capsule dissolves in the GI tract, the timing coating (ethylcellulose) on the bead, which is insoluble, slowly erodes. The drug, which is highly soluble, moves through the coating into the GI tract. In the core, the starch swells and pushes the drug out while the dissolving sugar also helps carry the drug through the chemical timing complex. This results in a constant release (Ranade & Hollinger, 1996).

2. Reservoir devices with microporous membranes

Diffusion of drug molecules through nonporous, homogeneous, dense polymer membranes (*i.e.*, solution-diffusion membranes) occurs through the free space between polymer chains (left figure in Figure 9.9). On the other hand, drug diffusion through microporous membranes occurs through liquid-filled pores within the membrane (right figure in Figure 9.9). For water-soluble drugs, the diffusion through water-filled pores will be much faster than diffusion through nonporous hydrophobic membranes. For hydrophobic drugs, the pores can be filled with hydrophobic liquids such as oils.

Micropores are usually not straight and have geometrically longer average path than the thickness of the membrane. Thus, drug molecules actually have to diffuse longer distance than the thickness of the membrane to be released. This factor has to be considered in the diffusion of drug molecules. Such a factor is known as the tortuosity (τ); the higher the tortuosity, the longer the path. If drug molecules are released only through the micropores, then the surface area of the membrane for drug release is much smaller than the actual surface area. Thus, the fractional volume of the membrane pores has to be considered using a parameter known as porosity (ϵ).

We have the following equation for the drug release through nonporous membranes.

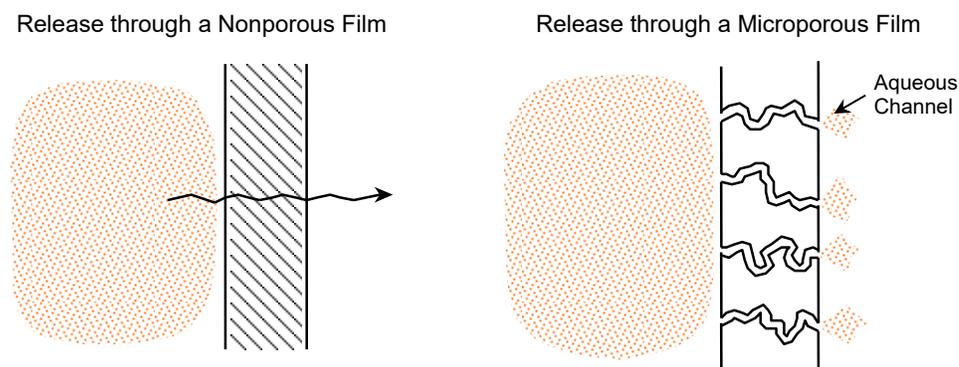


Figure 9.9 Drug diffusion through nonporous (left) and porous (right) membranes.

$$M = \left(\frac{S \cdot D \cdot K \cdot \Delta C}{h} \right) \cdot t$$

For microporous membranes, we have to consider both porosity (ε) and tortuosity (τ). Porosity and tortuosity are related to the surface area and the membrane thickness, respectively. Thus, the equation becomes

$$M = \left(\frac{\varepsilon \cdot S \cdot D \cdot K \cdot \Delta C}{h \cdot \tau} \right) \cdot t$$

Since the diffusion through the microporous membranes occurs through the liquid in the micropores, the diffusion coefficient (D) and the partition coefficient (K) have to be changed to those for the liquid. If we define the diffusion coefficient and the partition coefficient of drug molecules in the liquid as D_0 and K_0 , we obtain

$$M = \left(\frac{\varepsilon}{\tau} \right) \cdot \left(\frac{S \cdot D_0 \cdot K_0 \cdot \Delta C}{h} \right) \cdot t$$

For water-soluble drugs through the aqueous channels, K_0 should be 1.

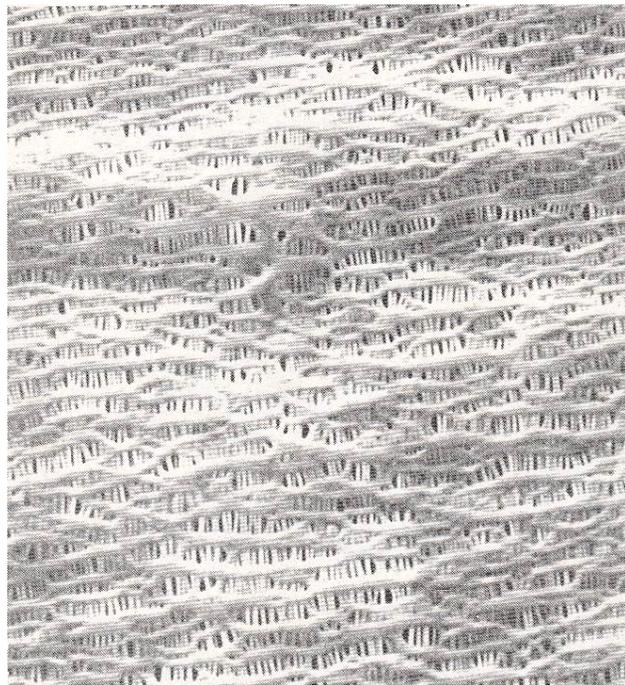


Figure 9.10 Celgard[®], a microporous membrane made by repeatedly stretching polypropylene film at high and low temperatures. The process creates minute, parallel rips in the film, spanned by microfibers that define an average pore size of several hundred Ångstroms. Because polypropylene repels water, such a membrane normally is watertight but is permeable to gases and other substances—qualities that suit it for use in blood-oxygenation devices and drug-delivery systems. If the membrane is treated chemically to make it wettable, it can also serve as a microfilter capable of separating microorganisms such as bacteria from water (Celanese Separation Products).

Microporous membranes can be prepared by making hydrophobic polymer membranes in the presence of water-soluble materials such as poly(ethylene glycol). After membrane is formed, the water-soluble materials can be removed by dissolving them in aqueous solution.

Alternatively, microporous membranes can be prepared by stretching the formed membranes (see Figure 9.10). Many of the membranes used in the transdermal patches are made this way (*e.g.*, Cellanese polypropylene membrane). The same approach can be used to make microporous hollow fibers.

a. Polypropylene film

***i.* Transderm-Scop® (Alza/Ciba-Geigy)**

Transderm-Scop®, developed by Alza, is the first transdermal product approved by FDA. Scopolamine is released at the rate of 10 $\mu\text{g}/\text{h}$ for 72 h for the prevention of motion-induced nausea. Scopolamine in a mineral oil reservoir has to diffuse through the oil-impregnated polypropylene film. The drug is also dispersed in the adhesive polymer (*e.g.*, polyisobutylene adhesive) to form a solid drug reservoir. Thus, Transderm-Scop® is a multilaminate dosage form.

***ii.* Catapres-TTS® (transdermal therapeutic system).**

This was also developed by Alza in 1984. It delivers clonidine at the rate of 0.1–0.3 mg/day for 7 d in the treatment of hypertension. Its reservoir system is made of mineral oil-polyisobutylene colloidal silica. Oil-impregnated polypropylene film is used for controlling drug release.

***iii.* Pest control products**

Microporous polypropylene film (Celgard) is used to control insects such as the Japanese beetle, whitefly, house fly, and apple maggots. The active ingredients (*e.g.*, hormones) can be released at a constant, predictable rate using microporous polypropylene membrane.

***iv.* Disposable butane lighter**

Microporous polypropylene film (Celgard) is also used in a disposable butane lighters. The microporous membrane replaces a complex, mechanical valve assembly used to maintain a constant flow of butane for a constant flame height, regardless of ambient pressure and fuel level.

b. EVA copolymer film

***i.* Transderm-Nitro® (Transdermal Therapeutic system by Alza/Ciba-Geigy)**

The drug reservoir is a dispersion of nitroglycerin-lactose triturate (*i.e.*, suspension) in the silicone medical fluid (*i.e.*, oil). The drug release of from the reservoir is controlled by the rate-controlling microporous membrane of EVA copolymer. It delivers nitroglycerin at dosage rate of 0.5 mg/cm²/d for relief of anginal attacks.

Advanced Membrane Applications

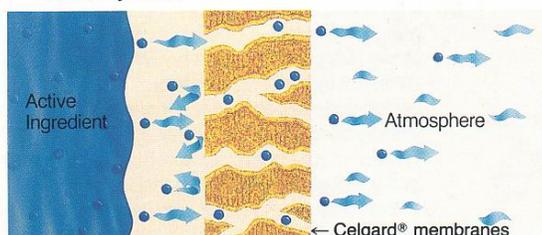
CELGARD®

Hoechst Separations Technologies

Celgard® Membranes for Controlled Release Applications

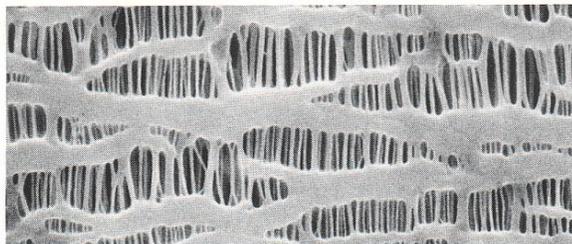
Celgard microporous membranes, manufactured and marketed by the Separations Products Division of Hoechst Celanese Corporation (HCSPD), offer exceptional performance in controlled release applications.

The transport of gases, vapors and liquids through Celgard membranes is by convective mass transfer. Materials move through the membrane pores in response to differences in concentration or pressure that exist across the membrane. As a result, controlled release products using Celgard membranes are classified by "zero order" release. This means Celgard membranes provide a constant rate of release independent of time or the amount of active ingredient that remains in the system.



Uniform Pore Structure

The surface structure of Celgard membranes is composed of small parallel slits, or pores, aligned in a series of rows. The pores are formed on the molecular level without the use of extractants and solvents, resulting in an extremely uniform porosity. Ranging in size from .05 to .1 microns, these pores create tortuous, interconnecting channels leading from one membrane surface to the other—and cover 40% to 60% of the membrane surface, depending on the product type. Substances normally used in controlled release applications, such as pheromones, insecticides, and fragrances, flow readily through these complex channels. In addition, Celgard membranes form a bacterial barrier, are chemically resistant and water repellent.



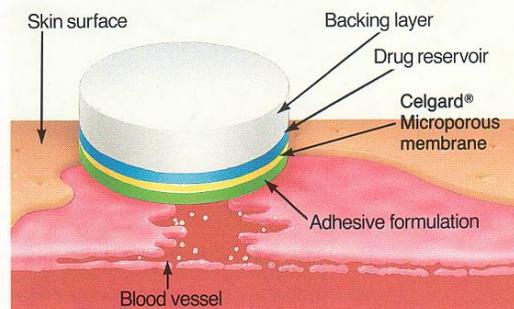
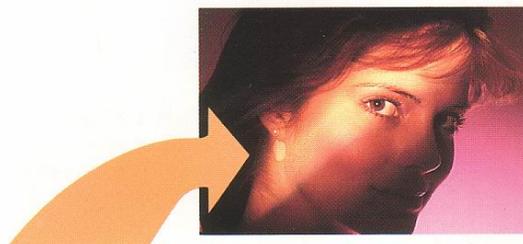
An SEM photo of Celgard® 2500 polypropylene microporous membrane, at 20,000 magnification, demonstrates the superior uniformity of pore structure.

Diverse Applications

Celgard microporous membranes combine the selectivity of membrane separations processes with chemical stability, ease of fabrication and durability of specially engineered polymeric materials.

With their uniform pore structure and thinness, Celgard membranes perform well in a wide range of rate controlled applications. For example:

- Transdermal drug delivery systems are possible through the use of Celgard membrane technology. Celgard membranes are used to contain and then, through a combination of pore size, permeability, and surface tension, regulate the flow of medications for absorption by the skin.



Thanks to Celgard® membranes, transdermal drug delivery (shown just behind the ear) may be the way to improved treatment and a better life for thousands of patients. The Celgard membranes allow constant lower dosages, and reduce the risk of side effects.

Hoechst Separations Technologies

- Utilizing Celgard® microporous membrane technology, a line of high performance pest control products for insects such as the Japanese beetle, whitefly, house fly and apple maggots are now available. In lab and field studies, insect traps containing Celgard membranes were shown to release active ingredients at a constant, predictable rate.



Pest control traps using Celgard® microporous membrane technology offer a safe and effective alternative to conventional forms of pest protection such as pesticide sprays. They are non-toxic and do not contaminate groundwater.

- In disposable lighters, Celgard membranes replace a complex, mechanical valve assembly used to maintain a consistent flow of butane for a constant flame height, regardless of ambient pressure and fuel level.



The end user of membrane technology is becoming increasingly sophisticated. Here, Celgard® membranes are utilized in a disposable butane lighter. The membrane regulates the flow of butane to maintain constant flame height.

Fabrication and Design Flexibility

Available in both polypropylene and polyethylene variants, Celgard membranes are strong, tough and flexible — offering fabrication and processing versatility. Celgard membranes can be adhesive-bonded to woven and non-woven materials and other substrates, as well as thermally bonded to non-woven materials. Heat sealing or ultrasonic welding is also possible. Custom membrane widths are available by special order.

Proven Performance

Because of unique characteristics and reliable performance, Celgard microporous membranes can be used in such diverse applications as electrochemical systems, composites manufacturing, sterile packaging, batteries and medical devices, as well as a variety of other industrial and life science applications.

Our ongoing development programs generate product variants designed to serve targeted market segments and specific customers. We work in partnership with our customers — often in non-traditional ways — as we strive to develop a broad range of products for a variety of industries. This is an inherent part of our corporate-wide Value System that emphasizes the highest standards for our Performance, People, and Process. The result has been technological advancement in every industry we have touched.

We invite you to challenge us with your controlled release requirements, and together, we can translate your application requirements into product form.

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*Membrane Technologies
and Systems Tailored to Your Needs*

To the best of our knowledge the information contained herein is accurate. However, neither Hoechst Celanese Corporation nor any of its affiliates assumes any liability whatsoever for the accuracy or completeness of the information contained herein. Final determination of the suitability of any product for any use contemplated, the manner of such use, and whether there is infringement of patents is the sole responsibility of the user.

Users of any products should satisfy themselves by independent investigation that the product can be used safely. We may have described certain hazards, but we cannot guarantee that these are the only hazards that exist.

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Hoechst Celanese



ii. Estraderm® (Ciba-Geigy)

This is the first product which used a skin absorption enhancer. Estradiol is dissolved in ethanol and HPMC reservoir and is released over 3–4 d for the relief of postmenopausal syndrome.

iii. Fluoride releasing device

Hydrophilic polymer matrix containing NaF or Na₂PO₃F is coated with EVA copolymer by dip coating in the EVA copolymer in chloroform. A thin button can be glued to one of the back molars for the prevention of tooth decay. Controlled release of fluoride for 6 mo to 1 y is possible.

c. Ethylcellulose**i. Inderal® LA propranolol HCl long-acting capsules (Wyeth-Ayerst Laboratories)**

Inderal® LA uses polymer coated controlled diffusion technology to achieve 12-h release of therapeutic levels of propranolol for the treatment of hypertension. Inderal® LA consists of small spheroids contained in a gelatin capsule. Each spheroid which contains propranolol and a microcrystalline cellulose mixture is coated with a porous membrane made of a mixture of ethylcellulose, hydroxypropyl methylcellulose, and plasticizer. Polymer coating used gives the drug higher than normal density of 1. Higher density formulation helps keep the drug in the upper alimentary canal for a substantially longer time (Ranade & Hollinger, 1996).

ii. Cardizem CD®

Cardizem CD® is a once-a-day formulation based on the spheroidal oral drug absorption system (SODAS) technology developed by Elan Corp. in Monksland, Athlone, Ireland. It consists of two populations of sustained release beads that differ only by the thickness of the polymer (ethylcellulose) surrounding them. The ethylcellulose membrane also contains water-soluble polymers which dissolve to create pores in the membrane. The thin polymer beads release 40% of the total diltiazem in the first 12 h.

C. MONOLITHIC DEVICES

In monolithic devices, drug molecules are dispersed uniformly throughout the polymer matrix which is nonporous and water-insoluble. As shown in the following figure (left in Figure 9.11) monolithic devices do not have any polymer membrane as in the reservoir devices (right).

Since there is no polymer membrane surrounding the drug reservoir, the monolithic devices have no danger of drug dumping due to minor defects. In addition, they are easier to make than the reservoir devices and cost less to manufacture.

1. Preparation of monolithic devices

Monolithic devices are much easier to fabricate than the reservoir devices. The monolithic devices can be made by a variety of methods, and a few methods are described below.

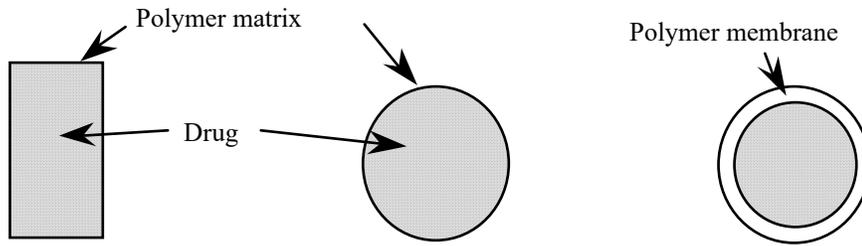


Figure 9.11 Comparison of monolithic device (left and center) and reservoir device (right).

a. Crosslinking of polymers

Drug particles are blended with a liquid polymer or a viscous base polymer, and then the polymer chains are crosslinked to form a monolithic device.

b. Molding

Drug particles are mixed with a rubbery polymer at an elevated temperature. The resultant drug-polymer dispersion is then molded or extruded to form a drug delivery device of various shapes and sizes.

c. Solvent casting

Drug and polymer are dissolved in a common solvent. This is followed by solvent evaporation at an elevated temperature and/or under a vacuum.

The above mentioned methods are much simpler than the methods used to make encapsulated microparticles. The drug release rate from the monolithic devices, however, is not zero-order. Initially, drug molecules residing near the surface of the monolithic device are released. At later times, drug molecules from the device interior are released. Since those drug molecules have to migrate longer distance than those near the surface, the path length for release becomes larger. In addition, the surface area of drug release may become smaller and smaller in time. This means that the release from a monolithic matrix decreases with time. As a result, we observe nonzero-order release. The less desirable feature of nonzero-order release is overcome by the advantages described above.

Monolithic devices can be divided into monolithic solution and monolithic dispersion devices. The main difference between the two is that the monolithic dispersion has excess drugs so that the drug concentration is maintained above the solubility (saturated concentration) for a long period of time.

2. Monolithic solution

Monolithic solution can be easily prepared by placing the polymer matrix into the drug solution and let it equilibrate. The maximum drug concentration that can be obtained is the solubility of the drug in the polymer matrix.

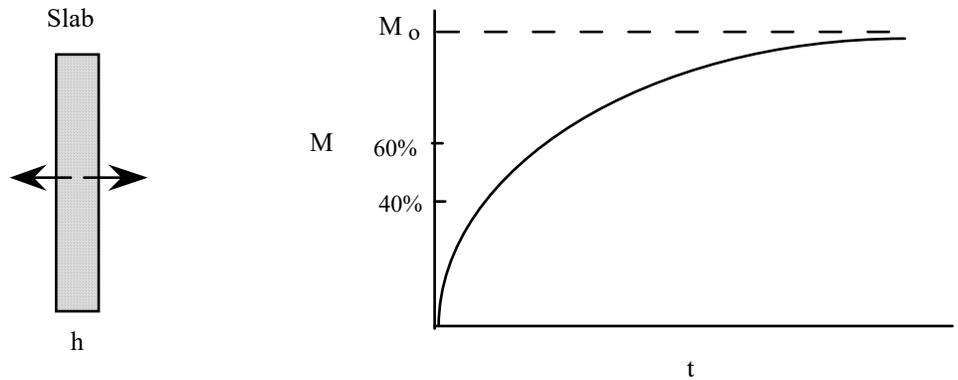


Figure 9.12 Drug release from a monolithic device in a slab geometry.

The drug release from a slab geometry under the sink condition can be described by the following equation.

$$M = M_o \left[1 - \left(\frac{8\sigma}{(2n+1)^2\pi^2} \right) \exp\left(\frac{-D(2n+1)^2\pi^2 t}{h^2} \right) \right]$$

where M is the cumulative amount of drug released per $S \text{ cm}^2$ in time t and M_o is the total amount of drug dissolved in the matrix. The plot of M as a function of time is shown in Figure 9.12.

The above equation is too complex and too clumsy for practical applications. So, two simple equations are used to approximate the drug release for the first 40–60% of drug release and the last 40–60% of drug release.

The early-time approximation is:

$$M = M_o \left(\frac{16Dt}{\pi h^2} \right)^{1/2} \quad \text{for } 0 \leq \frac{M}{M_o} \leq 0.6$$

and the late-time approximation is:

$$M = M_o \left[1 - \left(\frac{8}{\pi^2} \right) \exp\left(\frac{-\pi^2 Dt}{h^2} \right) \right] \quad \text{for } 0.4 \leq \frac{M}{M_o} \leq 1.0$$

The drug-release rate at any time can be obtained by differentiating the above equations. Thus, we have:

$$\frac{dM}{dt} = M_o \left(\frac{2D}{\pi h^2 t} \right)^{1/2} \quad \text{for } 0 \leq \frac{M}{M_o} \leq 0.6$$

and

$$\frac{dM}{dt} = M_o \left[\left(\frac{8D}{h^2} \right) \exp\left(\frac{-\pi^2 Dt}{h^2} \right) \right] \quad \text{for } 0.4 \leq \frac{M}{M_o} \leq 1.0$$

One example of monolithic solution devices is Sergeants[®] flea collars for your dogs and cats.

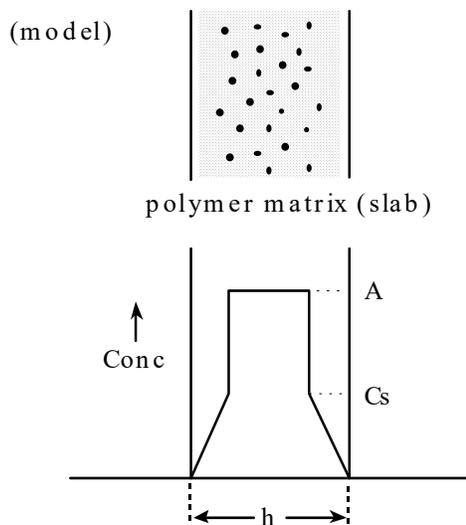


Figure 9.13 Model for the drug release from a monolithic dispersion. The top figure shows the presence of dispersed drugs as well as dissolved drugs and the bottom figure shows the concentration profile in the monolithic dispersion.

3. Monolithic dispersions

The drug concentration in the polymer matrix is much higher than the solubility (C_s) of the drug in the polymer matrix. Thus, there are dissolved drugs and dispersed drugs (*i.e.*, undissolved solid drugs). Monolithic dispersion can be prepared by synthesizing polymer matrix in the presence of solid drug particles.

In the following model (see Figure 9.13), dissolved drug molecules are shown as dots while the dispersed drug particles are shown as block circles. C_s is the saturation concentration of drug in the matrix and A is the total drug concentration (*i.e.*, dissolved drug + dispersed drug). When the dissolved drug is released from the surface layer of the device, dispersed drug is dissolved to maintain the saturated concentration (C_s). When the surface layer releases all of the drug, the next layer begins to release the drug.

According to this model, known as the Higuchi model, the cumulative amount of drug released (M) can be described by the following Higuchi equation.

$$M = S [D C_s (2A - C_s) t]^{1/2}$$

Thus,

$$dM/dt = (S/2) [D C_s (2A - C_s)]^{1/2} (1/t)^{1/2}$$

Please note that the terms in $S [D C_s (2A - C_s)]$ are all constants, and the plot of M as a function of $t^{1/2}$ should result in a linear line, if the drug release follows the Higuchi model (Figure 9.14). As the above equation for dM/dt indicates, the drug release rate is not constant. The reason that the drug release rate decreases in time is that drug molecules have to migrate longer distances to be released as time goes on.

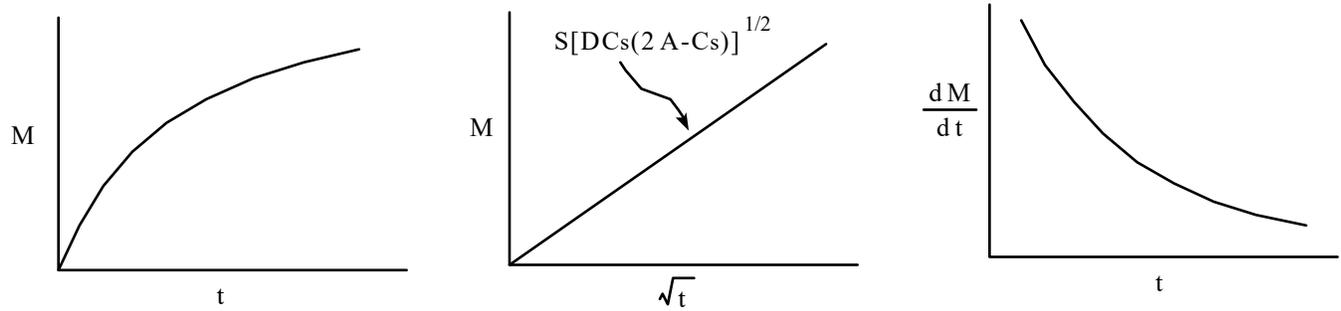


Figure 9.14 Drug release following the Higuchi model. The amount of drug release becomes linear if plotted as a function of $t^{1/2}$ (center). The drug release rate decreases in time.

Sample calculation

The release of ethynodiol diacetate through a silicone rubber dosage form (diffusion-controlled monolithic dispersion) is calculated using the following Higuchi equation.

$$Q = M/S = [D C_s (2A - C_s) t]^{1/2}$$

The amount of drug per unit volume of the silicone matrix (A) is 100 mg/mL, the solubility of the drug in the silicone polymer (C_s) is 1.5 mg/mL, and the diffusivity of the drug in the silicone matrix (D) is 3.4×10^{-2} cm²/d. The rate of drug release from the silicone dosage form at day 1 is?

$$\begin{aligned} dQ/dt &= (1/2) [D C_s (2A - C_s)]^{1/2} (1/t)^{1/2} \\ &= (1/2)[(3.4 \times 10^{-2} \text{ cm}^2/\text{d})(1.5 \text{ mg/mL})((2 \cdot 100 - 1.5) \text{ mg/mL})]^{1/2} (1/1 \text{ d})^{1/2} \\ &= 1.59 \text{ mg}/(\text{cm}^2 \cdot \text{d}) \end{aligned}$$

Note: the release rate is dQ/dt , and NOT $dQ/dt^{1/2}$.

4. Effect of nonzero-order release on pharmacological effect.

Since the diffusion-controlled monolithic devices have nonzero-order drug release (*i.e.*, the drug release rate decreases as time goes on), a question arises as to whether the diffusion-controlled monolithic devices are not as good as the diffusion-controlled reservoir devices. What do you think?

5. Examples of monolithic dispersions

a. Silicone rubber

i. Nitrodisc[®] (Searle) (known as Microseal Drug Delivery System)

A suspension of nitroglycerin and lactose triturate in an aqueous solution of 40% PEG 400 is prepared by dispersing it homogeneously with isopropyl palmitate, as dispersing agent, in a mixture of viscous silicone elastomer, which is then crosslinked by catalyst. The resultant drug-polymer dispersion is then molded to form a solid medicated disk *in situ* on a drug-

impermeable metallic plastic laminate, with surrounding adhesive rim, by injection molding under instantaneous heating. Nitrodisc[®] transdermal system releases nitroglycerin at the rate of 0.5 mg/cm²/d. (See also 6.c.).

ii. Compudose[®] subdermal implant

Micronized estradiol crystals are dispersed in a viscous silicone elastomer. Then, the estradiol-dispersing polymer is coated around a rigid (drug-free) silicone rod by extrusion to form a cylindrical implant. Compudose[®] subdermal implant is used for subcutaneous implantation in steers for growth promotion. It releases estradiol for 200–400 d.

b. PVP-PVA matrix

i. Nitro-Dur I[®] (Key Pharm) (known as Transdermal Infusion System)

Nitro-Dur I[®] is a transdermal patch delivering 0.5 mg/cm²/d of nitroglycerin for the treatment of angina pectoris. An aqueous solution of glycerol, poly(vinyl alcohol), and PVP (*i.e.*, plasticized PVP–PVA system) is heated. The temperature of the solution is gradually lowered and nitroglycerin and lactose triturate are dispersed just above the congealing temperature of the solution. The mixture is solidified in a mold at or below room temperature. Then, it is sliced to form a medicated polymer disk. An adhesive rim is surrounding the medicated disk.

c. Pressure-sensitive adhesive polymer

i. Nitro-Dur II[®] (Key Pharm — Shering-Plough)

The drug is directly dispersed in a pressure-sensitive adhesive polymer (*e.g.*, polyisobutylene, polyacrylate based adhesive polymer). Then, the medicated adhesive polymers are spread by solvent casting onto a flat sheet of drug-impermeable backing support to form a single layer of drug reservoir.

d. Plasticized PVC-poly(vinyl acetate) copolymer

i. Nitroglycerin patch from Health Chem Bolar

PVC–PVA copolymers were plasticized by di-(2-ethylhexyl)phthalate and isopropyl palmitate.

e. Poly(HEMA) crosslinked with ethylene glycol dimethacrylate

i. Synchro-Mate-B[®] (GD Searle/Ceva)

Synchro-Mate-B[®] is used for estrus-synchronization treatment for cattle. It slowly releases the hormone norgestomet from a poly(HEMA) matrix which is implanted beneath the skin of an animal's ear for 9 d and is then removed. This ensures that all of the females are fertile at the same time, so that they all can be conveniently inseminated, either naturally or artificially. In this way, an entire herd of cattle can be managed on essentially the same schedule.

f. Methyl acrylate and methyl methacrylate copolymer**i. Gradumet[®] (Abbott Laboratories)**

The Gradumet[®] is an inert, porous, plastic matrix that is impregnated with a drug. The drug is slowly leached from the Gradumet as it passes through the GI tract. The expended matrix is not absorbed and is excreted in the stool.

Examples are Desoxyn[®] (methamphetamine HCl) Gradumet[®] tablets and Fero-Gradumet[®] Filmtab[®] tablets for iron deficiency.

g. Wax**i. Slow-K[®] (Ciba-Geigy)**

Ciba-Geigy's Slow-K[®] (potassium chloride) tablet uses a wax matrix. It is intended to provide an extended release of potassium from the matrix to minimize the likelihood of producing high, localized concentrations of potassium within the GI tract. The wax-matrix delivery system employs a tablet made up of a honeycomb type of wax matrix. As the tablet passes through the GI tract, the active ingredient is slowly released from the matrix and is absorbed in the body.

ii. Slow-Fe[®]

Ciba-Geigy has also introduced a slow iron tablet in a wax matrix called Slow-Fe[®].

iii. Drug release from the matrix. Drugs are loaded as granules.

K-tab[®]: potassium chloride extended-release tablets. Inactive ingredients: castor oil, cellulosic polymers, colloidal silicon dioxide, magnesium stearate, paraffin, polyvinyl acetate, titanium dioxide, vanillin, and vitamin E.

Slow-K[®]: potassium chloride extended-release tablets. Wax matrix preparation. Inactive ingredients: cetostearyl alcohol (for wax matrix), (for granulation) acacia, gelatin, iron oxide, magnesium stearate, PVP, parabens (preservative), sodium benzoate, starch, sucrose, and titanium dioxide, vanillin, and vitamin E.

h. Alginate**i. Isoptin SR[®]: Verapamil HCl sustained-release oral caplets from Knoll Laboratories.**

Verapamil HCl is a calcium ion influx inhibitor (calcium ion antagonist) and used for hypertension. The effect of immediate release verapamil is prolonged by incorporating verapamil into a matrix of the natural polysaccharide sodium alginate, which swells when it comes in contact with GI fluid. Verapamil diffuses through a gel-like matrix and is totally released over approximately 7 h.

Pharmacokinetic studies comparing the maximum concentration of one 240 mg tablet of Isoptin SR[®] versus two half 240 mg tablets show a non-significantly higher concentration with the two half tablets without any

difference in the area under the curve or time to maximum concentration (McEwen *et al.*, 1989). No difference was observed between two 120 mg tablets of Isoptim SR and one 240 mg tablet of Isoptim SR.

ii. Calan SR[®]: Verapamil HCl sustained-release oral caplets from Searle

The inactive ingredients of Calan SR[®] include alginate, carnauba wax, HPMC, magnesium stearate, microcrystalline cellulose, PEG, PVP, talc, titanium dioxide, and coloring agents.

Sustained characteristics are not altered when the caplet is divided in half. Apparently, the exposure of new surfaces does not make a big difference in the total amount of drug released in a given time period.

i. Blend of cellulose and noncellulose material

i. Synchron[®] System

The Synchron[®] system is a patented procedure developed by Forest Laboratories. The Synchron[®] system based on the blending of cellulose and noncellulose material with a drug. These materials are combined into a homogeneous mixture from which tablets are made. When the Synchron[®] system tablet comes in contact with water, the outer layer of the matrix softens to a gel-like consistency that allows the trapped drug to release at a controlled rate. The simplicity of this system allows the completion of a desired drug formulation within a matter of months.

Theochron[®], a controlled-release theophylline product (Teva Pharmaceuticals USA), is based on the Synchron[®] system.

j. Ethylcellulose

i. Dilacor XR[®]: a one-per-day oral formulation of diltiazem HCl, based on Jago's (currently Genta Inc.'s) Geomatrix[™] technology. 120, 180, 240 mg capsule (Rhône-Poulenc Rorer Pharmaceutical Inc.)

Dilacor XR[®] capsules contain degradable, controlled-release tablets designed to release diltiazem over a 24-h period. Geomatrix[™], a registered trademark of Jago Research AG, Zollikon, Switzerland, is a patented controlled release system incorporated in the tablets. Each Dilacor XR[®] capsule contains multiple 60-mg extended-release diltiazem HCl tablets. The 60-mg tablets consist of two inactive surfaces sandwiched around the core containing the active drug (diltiazem HCl) in hydrophilic and hydrophobic materials (HPMC, and hydrogenated castor oil) swellable in an aqueous medium. The inactive surfaces are composed on a methylcellulose and ethylcellulose combination that eventually disintegrates. The drug is released as a result of swelling of the core, which acts as a long-acting drug release reservoir. Controlled release of diltiazem begins within 1 h, with maximum plasma concentrations being achieved 4–6 h after administration. The inactive surfaces hydrate at a rate much slower than the core, thereby regulating the release of the drug and assuring constant 24 h drug delivery.

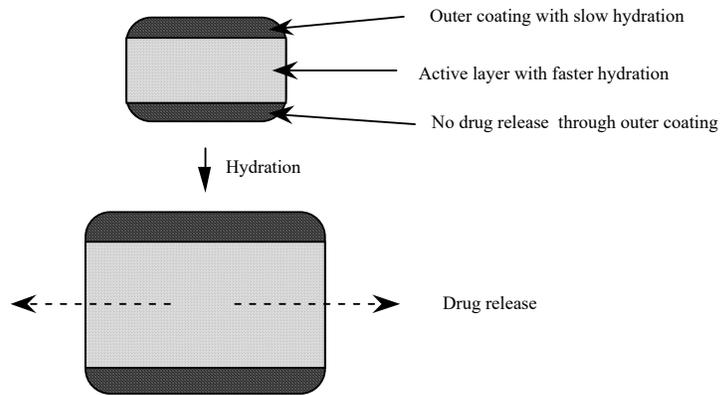


Figure 9.15 Schematic description of drug release from a Geometrix™ dosage form.

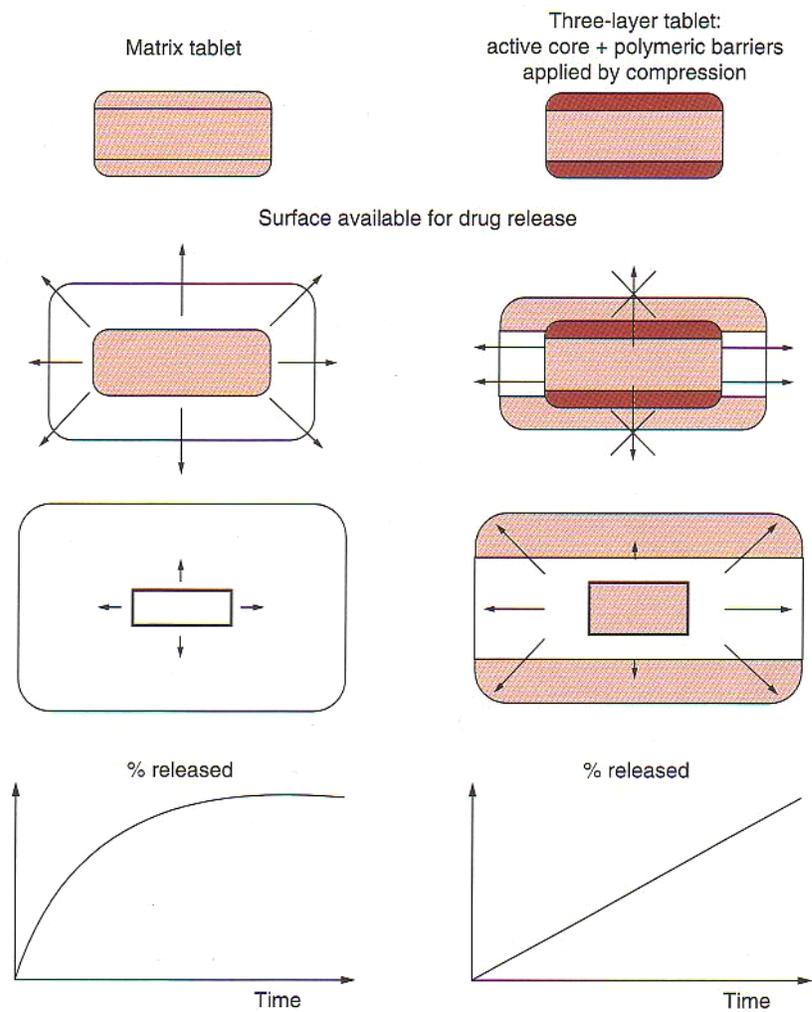


Figure 9.16 Effect of the application of polymeric layers (barriers) on the release of drug from a matrix core.

Figure 9.15 shows a schematic of the release mechanism of Dilacor XR® after oral administration of the dry tablet. At the first stage of initial

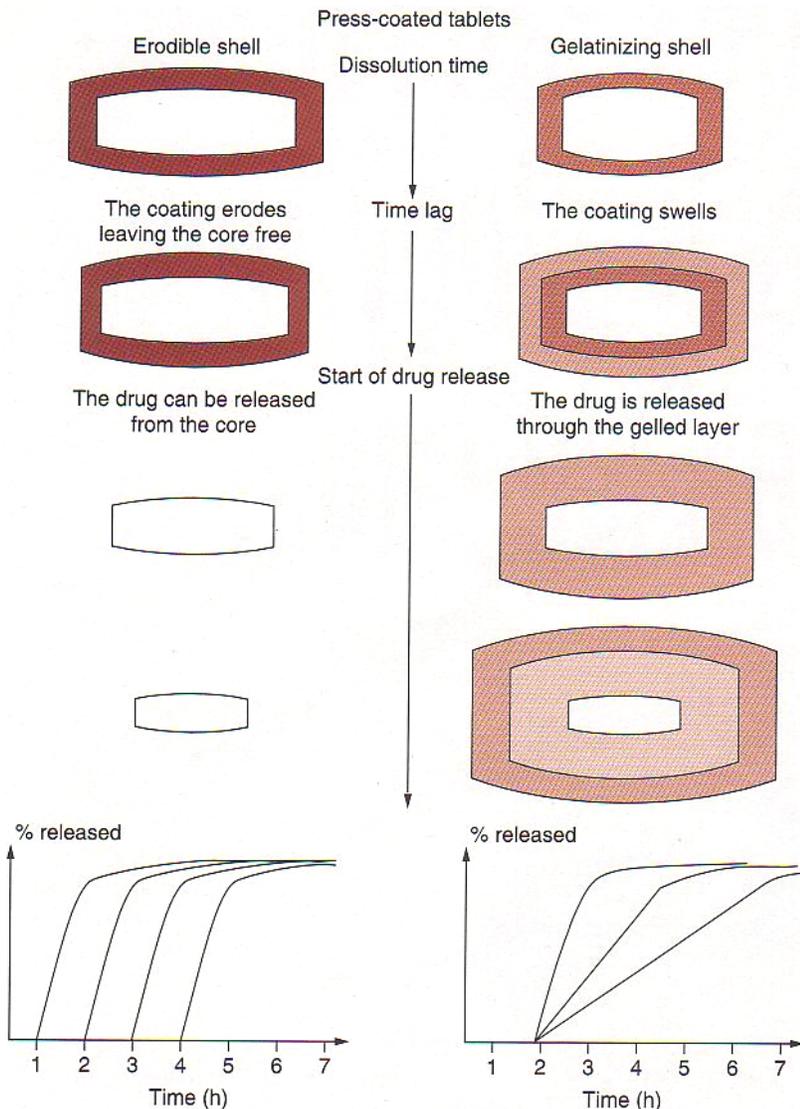


Figure 9.17 Dissolution behavior of press-coated delivery devices (Colombo, 1993; Conte & Maggi, 1998).

wetting, when exposed to the aqueous environment of the abdominal tract, the core layer begins to hydrate. Drug is released during this initial hydration phase, which results in rapid onset of action. As the tablet hydrates, the drug release occurs predominantly through the sidewall. This model resembles diffusion through a constrained, tortuous matrix (Frishman, 1993).

More examples of multilayer tablets are shown in Figure 9.16–9.20.

k. Microsponge system

Baby Fresh with UltraGuard® is a baby wipe marketed over the counter by Scott Paper Company. It incorporates the microsponge system that contains an active ingredient to help prevent diaper rash. The microsponge system developed by Advanced Polymer Systems, Inc., is a drug delivery

system in which an active ingredient is entrapped in the pores of the microscopic sponge.

The microsponge system is also used in EveryStep[®], an odor-fighting foot powder with five microsponge entrapments (sold over the counter by Advanced Polymer Systems, Inc.) and Exact[®] acne treatment in a cream formulation for the controlled release of benzoyl peroxide.

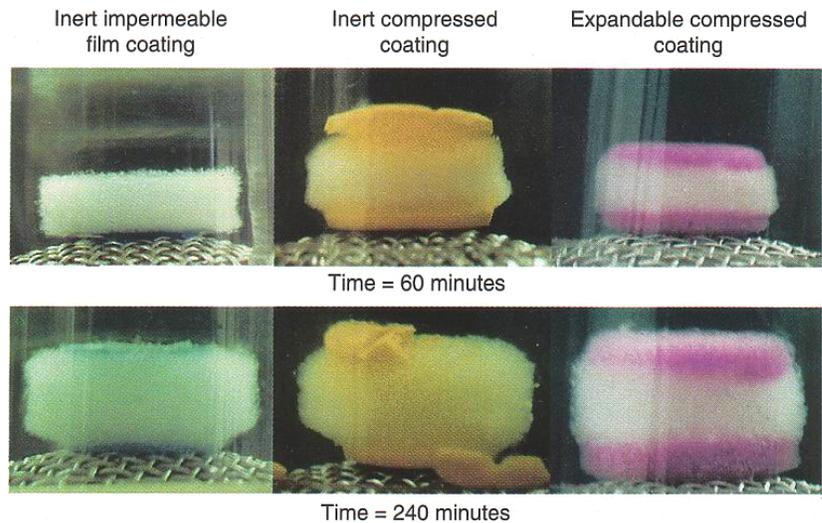


Figure 9.18 Comparison of the morphological behavior in dissolution of three different types of barrier coatings

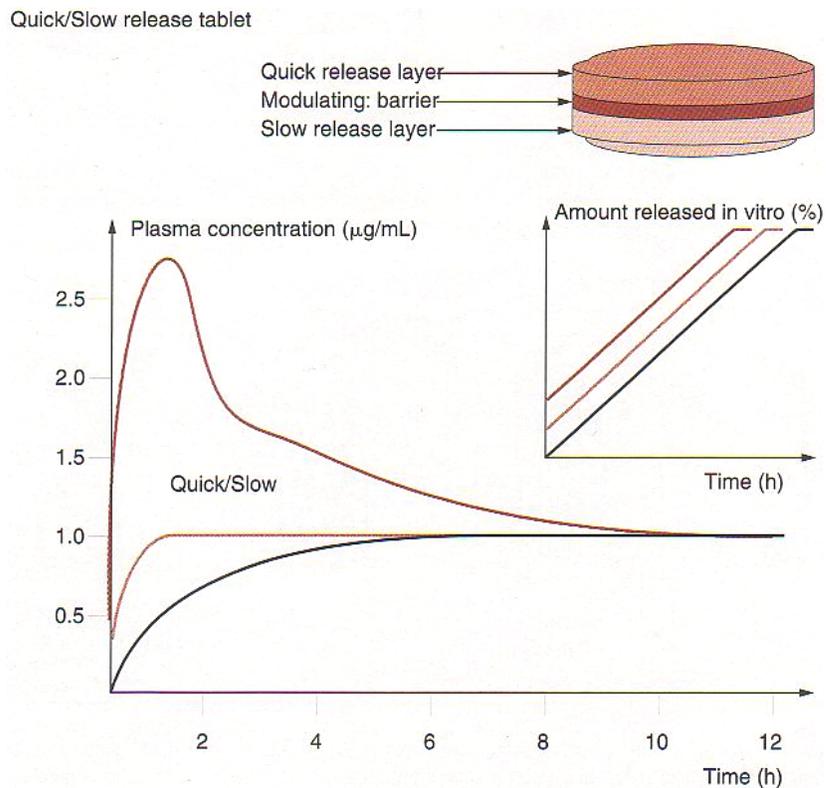


Figure 9.19 Simulated plasma levels for different formulations of a model drug.

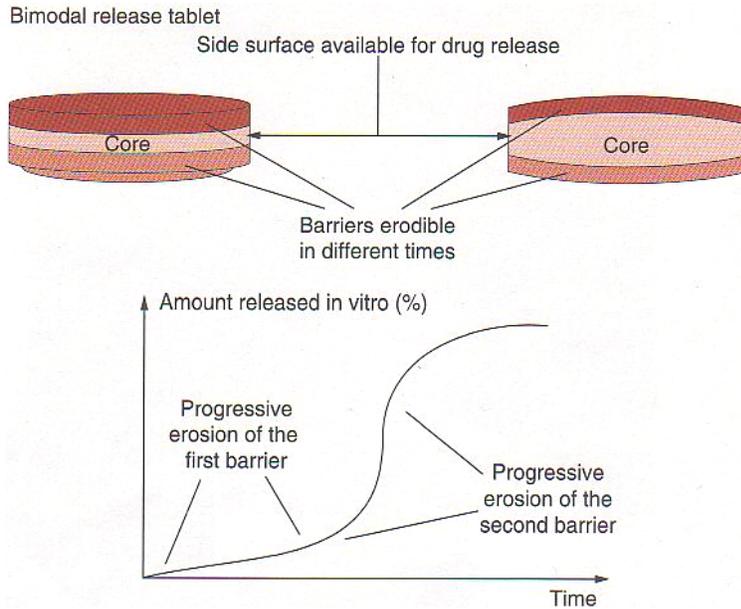


Figure 9.20 Performance of a bimodal-release tablet (Colombo, 1993; Conte & Maggi, 1998).

I. Gel or cotton pad system

Pro-Step[®] (Lederle, Division of American Cyanamid Co.) and Nicolan[®] (Elan) deliver nicotine for 24 h at the rate of 24 mg/d. Methacrylic acid copolymer solution of nicotine is dispersed in a pad of nonwoven viscose and cotton. Nicotinnel TTS[®], or Habitrol[®] (Basel Pharmaceutical, Division of Ciba-Geigy), delivers nicotine for 24 h at the rates of 7, 14, and 21 mg/d.

6. Examples of complex monolithic devices

To obtain the desirable drug release profiles from the monolithic devices, variations of monolithic devices can be prepared.

a. Multiple layer monolithic devices

i. Deponit[®] system (Pharma-Schwarz/Lohmann, Wyeth-Ayerst)

This transdermal nitroglycerin delivery system is made of layered isobutylene adhesive and drug mixture.

The drug release rate from the diffusion-controlled monolithic devices is time-dependent. To make the release rate less time-dependent, the monolithic devices was modified to have the drug loading level varied in an incremental manner to form a gradient of drug reservoir to compensate for the increase in diffusional path. In this way, (near) zero-order release can be obtained.

b. Mixture of monolithic dispersion and diffusion-controlled reservoir systems**i. Syncro-Mate-B[®] implant**

The Syncro-Mate-B[®] implant is fabricated by dissolving norgestomet, a potent progestin, in the alcoholic solution of a linear ethylene glycomethacrylate polymer (Hydron S[®]). The polymer chain is then cross-linked with ethylene dimethacrylate, a cross-linking agent, to form a solid cylindrical drug-dispersed Hydron implant. This tiny subdermal implant is engineered to release norgestomet upon hydration in the subcutaneous tissue for up to 16 d for the control and synchronization of estrus in livestock.

ii. Synchro-Mate-C[®] implant (Searle/Ceva)

A suspension of norgestomet is made in an aqueous solution of PEG 400, in a viscous mixture of silicone elastomers. After the addition of catalyst the suspension is delivered into silicone medical-grade tubing, which serves as the mold as well as the coating membrane. Polymerization is done *in situ*. The polymerized drug-polymer composition is then cut into a cylindrical drug delivery device with open ends.

This tiny cylindrical implant is designed to be inserted into the subcutaneous tissue of the livestock's ear flap and to release norgestomet at zero-order for up to 20 d for the control and synchronization of estrus and ovulation as well as for up to 160 d for growth promotion.

iii. PRODAS[®] (Programmable Oral Drug Absorption System) (Elan)

The PRODAS[®] formulation contains three different types of beads in the size range 1.5 to 4 mm in diameter. A portion of beads are made by direct compression of the drug for immediate release. Another portion of beads can be made as monolithic matrix minitables. This is simply the polymer matrix in which the drug is dispersed homogeneously. The last portion of the beads is the monolithic matrix beads coated with rate-controlling polymer membrane. The combination of the three different types of beads (minitables) may maintain rather constant drug concentration in blood.

c. Combination of microreservoir-matrix system

This is a hybridization of the reservoir and matrix dispersion type systems.

i. Nitro Disc[®] (G.D. Searle Pharmaceuticals)

The drug compartment of Nitro Disc[®] is formed by first suspending the drug solids in an aqueous solution of a water-miscible drug solubilizer (*e.g.*, PEG) and then homogeneously dispersing the drug suspension with controlled aqueous solubility, in a lipophilic polymer, by high shear mechanical force, to form thousands of unleachable microscopic drug reservoirs. This system is immediately crosslinked by the addition of polymeric crosslinking agents to form a matrix.

The drug release from the microreservoir-type device can follow either a partition-control or matrix diffusion-control process depending on the relative magnitude of solubilities of drug in the liquid compartment and in

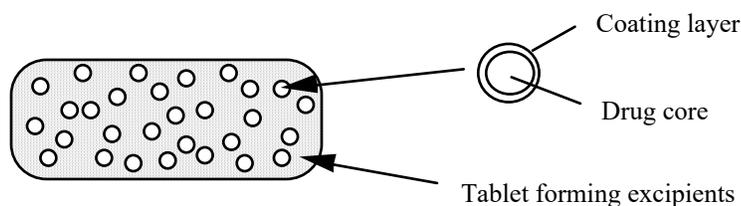


Figure 9.21 Schematic description of a Toprol-XL[®] tablet.

the polymer matrix. Thus, the release profile may be zero-order or $t^{1/2}$ -order.

ii. Toprol-XL[®] tablets

Toprol-XL[®] tablets are metoprolol succinate extended release tablets manufactured by Astra-Merck. Each tablet consists of an inert substance compressed with polymer-coated pellets of solid metoprolol succinate, cardioselective adrenoceptor blocking agent. In the GI tract, the tablet disintegrates to release the pellets. Each pellet acts as a separate drug delivery unit (see Figure 9.21) designed to deliver the drug at zero-order over a 20-h period. Inactive ingredients are silicone dioxide, cellulose compounds, sodium stearyl fumarate, PEG, titanium dioxide, and paraffin.

III. OSMOSIS-CONTROLLED DRUG RELEASE

Osmosis is a phenomenon that can be found in our daily lives. When flowers are thirsty, we water them, and water is absorbed into their roots. When we soak our hands in water for a while, our fingers wrinkle. The two phenomena may appear totally irrelevant, but in fact, both occur as a result of osmosis. The salt concentration inside the root of flowers is much higher than that in the surrounding soil, and the salt and protein concentrations in the outer layer of the epidermis (*i.e.*, stratum corneum) are much higher than that in the bath water. Water naturally flows into the area with higher salt concentration as if water molecules are pushed with high pressure through the root or skin membranes. Osmosis has been successfully used in the development of controlled-release drug-delivery systems, and in fact, the osmosis-based dosage forms have been the biggest success story in the controlled-release drug-delivery area.

A. OSMOSIS AND OSMOTIC PRESSURE

The phenomenon known as osmosis has been used in the development of zero-order drug-delivery systems. Osmosis is the natural movement of water into a solution through a semi-permeable membrane. Only water molecules can move through the semi-permeable membranes. Solutes can not diffuse through it. The examples of semi-permeable membrane and their water vapor transmission values are listed in Table 9.6. The water vapor transmission value of the semi-permeable membranes differs widely, and selection of a semi-permeable membrane depends on the nature of the applications. In the development of controlled release dosage forms, cellulose acetate has been used most frequently.

Film	WVTR ^a
Poly(vinyl alcohol)	100
Polyurethane	30-1-50
Cellulose acetate	40-75
Ethylcellulose	75
Cellulose acetate butyrate	50
Poly(vinyl chloride), cast	10-20
Poly(vinyl chloride), extruded	6-15
Polycarbonate	8
Ethylene vinyl acetate	1-3
Polyesters	2
Cellophane, polyethylene coated	>1.2
Polyethylene	0.5-1.2
Polypropylene	0.7
Poly(vinyl chloride), rigid	0.7

^a Water vapor transmission value expressed in g/100 in²/24 hr/1 mm thick film.

Understanding osmotic pressure is important since it is used as the energy source in the osmosis-controlled devices. Osmotic pressure is the excess pressure that must be applied to the solution to prevent osmosis. In Figure 9.22, osmotic pressure (π_s) occurs owing to the presence of solute in the left chamber. Water molecules migrate from the right chamber to the left to dilute the solution. This leads to increase in the water level in the left chamber. If the pressure equivalent to π_s is applied to the left chamber, the movement of water will be inhibited and the water level will remain the same for both chambers.

Osmotic pressure can be calculated using the following equation:

$$\pi = nRT/V$$

where π is in atm, n is in mol, R is in L·atm/mol·K, T is in K, and V is in liters.

Example

What is the osmotic pressure of the sucrose solution (1 g of sucrose in 100 mL water) at 25 °C?

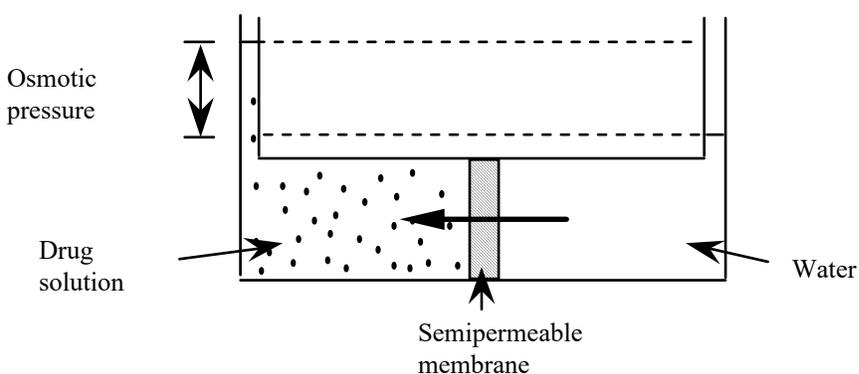


Figure 9.22 Movement of water from the right chamber to the left due to the presence of solute in the left chamber.

$$\pi = (1 \text{ g}/342 \text{ g/mol}) (0.082 \text{ L}\cdot\text{atm/mol}\cdot\text{K}) (298 \text{ K}) / 0.1 \text{ L} = 0.71 \text{ atm}$$

B. OSMOSIS-CONTROLLED DEVICES

The simplest form of controlled-release devices based on osmotic pressure is shown in Figure 9.23. The presence of drug (and other solute that can act as an osmotic agent) is wrapped with a semi-permeable membrane. The diffusion of water through the semi-permeable membrane causes building up of a pressure inside the device. This results in release of drug molecules through a fine orifice on the membrane.

The drug release from the osmosis-controlled devices is described by:

$$M = (S/h) k' \pi_s C_s t$$

Thus, the release rate is

$$dM/dt = (S/h) k' \pi_s C_s$$

From the equation we can derive a few conclusion regarding the release rate.

- 1) The drug-delivery rate is determined by area (S), thickness (h) of the semipermeable membrane, and permeability (k') of the semipermeable membrane.
- 2) π_s remains constant as long as the concentration (C_s) of drug (or other solute) in the osmotic core is maintained constant. This can be easily achieved by having drug suspension. In this situation, the drug-delivery rate will be constant until the drug concentration inside the device falls below saturation. This means that the drug-release rate will be zero-order.
- 3) The osmotic-controlled systems require only osmotic pressure to be effective, and this makes the systems essentially independent of the environment. Thus, the changes in pH or the ionic strength in the environment will not affect the drug-release rate. The pH-independent zero-order release means that the osmotic-controlled oral-dosage form releases drug at the same rate whether it is in the stomach or in the intestine.

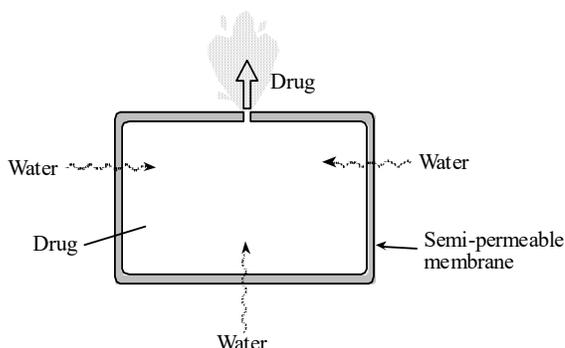


Figure 9.23 Diffusion of water through a semi-permeable membrane and the release of drug through the orifice.

C. COMPARISON BETWEEN DIFFUSION-CONTROLLED RESERVOIR DEVICE AND OSMOTIC DEVICE

Drug release from diffusion-controlled reservoir device

$$M = (S/h) D K \Delta C t$$

Drug release from the osmosis-controlled devices

$$M = (S/h) k' \pi_s C_s t$$

The two equations are basically the same. This is because drug release from the osmotic device is controlled by the rate of water diffusion through the semi-permeable membrane.

1. Osmotic devices

a. OROS[®] Osmotic Therapeutic Systems

Alza Corp. developed two different types of osmotic devices, known as OROS[®] Osmotic Therapeutic Systems. They are also called gastrointestinal therapeutic systems or elementary osmotic pumps. OROS[®] refers to “oral osmotic.” Alza’s OROS[®] systems use osmosis to make oral drug administration more precise, reliable, and convenient. OROS[®] systems can deliver drug compounds at continuously controlled rates for up to 24 h. The first generation of OROS[®] product was the elementary osmotic pump. A delivery portal is drilled on a semipermeable membrane surrounding the core of drug which may act as its own osmotic agent (see Figure 9.23).

b. The Push-Pull[™] OROS[®]

Alza Corp. subsequently developed an advanced OROS[®] system known as the Push-Pull[™] OROS[®]. The inside of OROS[®] is divided by a flexible impermeable membrane into two compartments: a drug compartment where the delivery portal is present and an osmotic agent compartment (see Figure 9.24). It works as follows. A semipermeable membrane surrounds an osmotically active drug core. The core is composed of two layers: an “active” layer containing the drug, and a pharmacologically inert but osmotically active “push” layer. After ingestion, the tablet overcoating (HPMC) is quickly dissipated in the gastrointestinal tract, allowing water to enter the tablet through the semipermeable membrane. The poly(ethylene oxide) polymer swells in the osmotic (“push”) layer and exerts pressure against the “active” drug layer, releasing the drug (*e.g.*, nifedipine or isradipine as a fine suspension) through the laser-drilled tablet orifice which has been positioned on the “active” drug layer side. Drug delivery is essentially constant as long as the osmotic gradient remains constant and, after predetermined amount (*e.g.*, 20, 60, or 90 mg of nifedipine, and 5 or 10 mg of isradipine) is released, gradually falls to a negligible amount. The controlled rate of drug delivery into the gastrointestinal lumen is independent of pH or gastrointestinal motility. The delivery of a

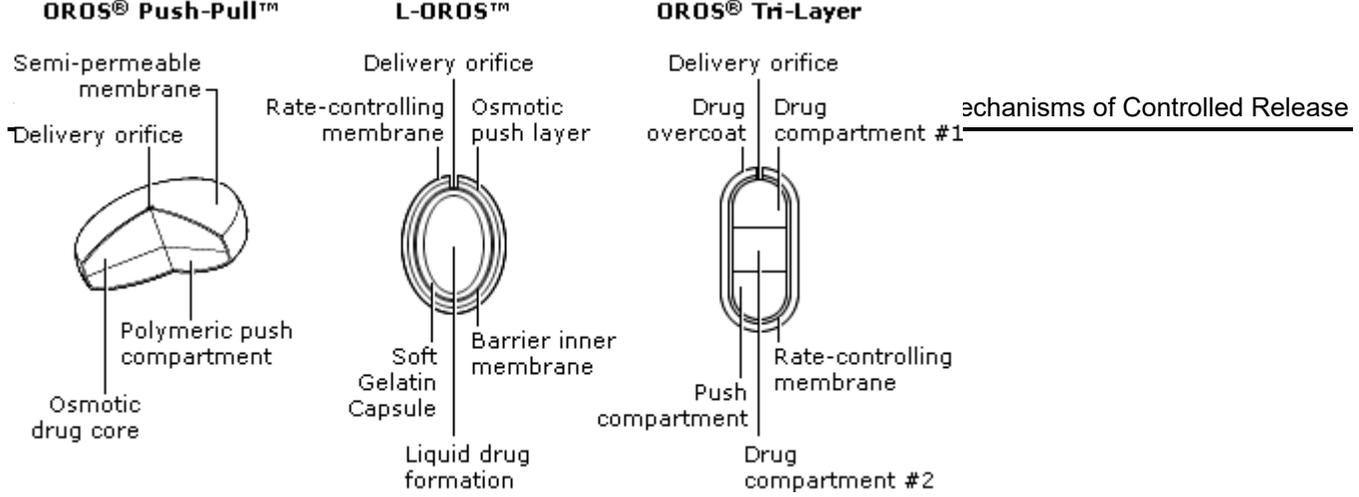


Figure 9.24 Alza's Push-Pull™ OROS® technology.

drug depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the GI tract. The biologically inert core of the tablet remains intact and, unless it becomes trapped, is eliminated in the feces.

c. Multi-directional oral absorption systems

Elan Corp. of Ireland has developed its own osmotic pressure system that is called multi-directional oral-absorption system (MODAS®). MODAS® consists of a tablet core surrounded by a semipermeable membrane with a multitude of small pores through that the drug solution can exit. The rate of drug solution release can be controlled by the composition of the membrane. Since the drug release is multi-directional, drug is not concentrated in any one area of the GI tract (Ranade & Hollinger, 1996).

Sample calculation of drug release from osmotic devices

(a) The drug release from OROS® tablets can be described by:

$$\frac{dM}{dt} = \left(\frac{S}{h}\right) k' \cdot \pi_s \cdot C_s$$

In the delivery of indomethacin, the following values were identified: $S = 2.2 \text{ cm}^2$; $h = 250 \text{ }\mu\text{m}$; $k' = 2.8 \times 10^{-6} \text{ cm}^2 \cdot \text{atm}^{-1} \cdot \text{h}^{-1}$; $\pi_s = 245 \text{ atm}$; and $C_s = 330 \text{ mg} \cdot \text{mL}^{-1}$. Calculate dM/dt .

$$\begin{aligned} \frac{dM}{dt} &= \left(\frac{2.2 \text{ cm}^2}{0.025 \text{ cm}}\right) (2.8 \times 10^{-6} \text{ cm}^2 \cdot \text{atm}^{-1} \cdot \text{h}^{-1})(245 \text{ atm})(330 \text{ mg} \cdot \text{mL}^{-1}) \\ &= 19.9 \text{ mg} \cdot \text{h}^{-1} \end{aligned}$$

If we also consider the drug release from the device by simple diffusion through the membrane, the above equation has to be modified as follows:

$$\frac{dM}{dt} = \left(\frac{S}{h}\right) k' \cdot \pi_s \cdot C_s + \left(\frac{S}{h}\right) DK \cdot C_s = \left(\frac{S}{h}\right) (k' \cdot \pi_s + DK) C_s$$

If the value of DK is $1.22 \times 10^{-4} \text{ cm}^2/\text{h}$, then what is dM/dt ?

$$\begin{aligned}\frac{dM}{dt} &= \left(\frac{2.2 \text{ cm}^2}{0.025 \text{ cm}} \right) (6.86 \times 10^{-4} \text{ cm}^2 \cdot \text{h}^{-1} + 1.22 \times 10^{-4} \text{ cm}^2 \cdot \text{h}^{-1}) (330 \text{ mg} \cdot \text{mL}^{-1}) \\ &= 23.5 \text{ mg} \cdot \text{h}^{-1}\end{aligned}$$

From the above calculation we can see that _____% of the drug is released by osmosis and _____% of the drug is released by diffusion through the membrane. (Answers: 85%, 15%)

(b) The approximate osmotic pressure π_s produced by a saturated phenobarbital sodium solution in an osmotic pump-like device is given by the following equation:

$$\pi_s = \nu(n/V) RT = \nu(C_s/M) RT$$

where ν is the number of species resulting from ionization of phenobarbital sodium (*i.e.*, 2), $C_s = 100 \text{ g/L}$, the molecular weight of the drug $M = 254.2 \text{ g/mol}$, $R = 0.082 \text{ L} \cdot \text{atm} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$, and $T = 310 \text{ K}$. Calculate the osmotic pressure produced by the drug.

$$\begin{aligned}\pi_s &= 2 \left(\frac{100 \text{ g}}{1 \text{ L}} \cdot \frac{1 \text{ mol}}{254.2 \text{ g}} \right) (0.082 \text{ L} \cdot \text{atm} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}) (310 \text{ K}) \\ &= 20 \text{ atm}\end{aligned}$$

3. Commercial products

a. Acutrim[®]

The first OROS[®] product (elementary osmotic pump) introduced in the U.S. was Acutrim[®], an appetite suppressant, launched by Ciba Geigy in 1983. In this system, phenylpropanolamine is released at zero order over a period of 16 h. It initially delivers a 20-mg bolus dose and then delivers 3.5 mg/h of phenylpropanolamine. The bolus dose is coated on the semi-permeable membrane for immediate release (Barnhart, 1991). The plasma concentration of phenylpropanolamine remains at around 60 ng/mL for 16 h. This concentration is equivalent to the trough plasma levels achieved by the conventional dosage form.

b. Osmosin[®]

In early 1983, Merck Sharp & Dohme introduced indomethacin on an OROS[®] delivery system in the U.K. and a few European countries under the name Osmosin[®]. Soon after its debut, it was reported that Osmosin[®] caused severe GI problems in some patients as well as possibly several death. While allegations of an increased incidence of these problems with Osmosin[®] were never conclusively confirmed, the product was off the market since September 1983.

c. Minipress XL[®]

Minipress XL[®] (prazosin) extended-release tablets for treatment of hypertension. Introduced in France by Pfizer Inc. in April 1989 under the name

Alpress LP[®]. It was approved in January 1992 and marketed by Pfizer, Inc.

d. Procardia XL[®]

Procardia XL[®] (nifedipine) extended-release tablets for the treatment of angina and hypertension. It was introduced in the U.S. by Pfizer in October 1989. It was also introduced outside the U.S. by Bayer AG in May 1991 as Adalat CR[®] and now available in more than 35 countries.

Compared to control conventional nifedipine formulation, Procardia XL[®] had fewer side effect (32% versus 58%), higher compliance rates (93% versus 76%), and lower cost of therapy (\$45.71 versus \$60.60) (Hilleman *et al.*, 1993).

e. Volmax[®]

Volmax[®] (albuterol) extended-release tablets are for the relief of bronchospasm in patients with reversible obstructive airway disease. It delivers Ventolin[®] (antiasthmatic drug, albuterol) for 12 h. It was introduced outside the U.S. by Glaxo in August 1987, and now marketed in more than 35 foreign countries. Muro Pharmaceutical, under license from Glaxo, introduced the product in the U.S. in the fall of 1993; co-promoted in the U.S. by Forest Labs.

f. Glucotrol XL[®]

Glucotrol XL[®] (glipizide) extended-release tablet is used for the treatment of non-insulin dependent diabetes. It is indicated as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes. Introduced in the U.S. by Pfizer Inc. in May 1994 and co-promoted by Alza.

g. Efidac 24[®]

i. Efidac 24[®] Pseudoephedrine

Efidac 24[®] Pseudoephedrine (pseudoephedrine hydrochloride) is the first over-the-counter 24-h extended-release tablets providing relief of nasal congestion and cold symptoms. It was introduced in the U.S. by Ciba Self-Medication Inc. in September 1993.

ii. Efidac 24[®] Chlorpheniramine

Efidac 24[®] Chlorpheniramine (chlorpheniramine maleate) is the first over-the-counter 24-h extended-release tablets providing relief of allergy symptoms. Introduced in the U.S. by Ciba Self-Medication Inc. in March 1995.

iii. Efidac 24[®] Pseudoephedrine/Brompheniramine

Efidac 24[®] Pseudoephedrine/Brompheniramine (pseudoephedrine hydrochloride/brompheniramine maleate) is the first over-the-counter 24-h extended-release tables providing temporary relief of nasal congestion from the common cold, hay fever, or other upper respiratory allergies associated with sinusitis, and temporary relief of runny nose, sneezing, itching of the

nose or throat, and itchy, watery eyes from hay fever or other upper respiratory allergies. The product was cleared for marketing by the U.S. Food and Drug Administration in April 1996.

h. DynaCirc CR[®]

DynaCirc CR[®] (isradipine) is used for the treatment of hypertension. Sandoz Pharmaceuticals Corp. received FDA marketing clearance in June 1994. Isradipine is delivered from the DynaCirc CR[®] (isradipine) controlled-release tablet by the Push-Pull[™] mechanism.

i. Covera-HS[™]

Covera-HS[™] formulation (also called controlled-onset, extended-release delivery system or COER-24[™]) is used for management of both hypertension and angina pectoris. It is designed for bedtime dosing for a maximum plasma concentration of verapamil in the morning hours. Thus, verapamil is released 4–5 h after ingestion. The delay is introduced by a layer (HEC, HPC, HPMC) between the active drug core and outer semipermeable membrane. As water from the gastrointestinal enters the tablet, this delay coating is solubilized and released. As tablet hydration continues, the osmotic layer expands and pushes against the drug layer, releasing drug through precision laser-drilled orifices in the outer membrane at a constant rate. Searle began marketing Covera-HS[™] in the U.S. in June 1996.

j. Adalat CR[®]

A once-a-day tablet for the treatment of hypertension based on oral osmotic controlled-release technology. The product is marketed by Bayer AG.

k. Calan SR[®]

This is a calcium ion antagonist in OROS[®] tablet. It allows once-a-day dosing for the management of essential hypertension. Marketed by GD Searle & Co.

l. Teczem[®]

Teczem[®] is an oral osmotic formulation is used as a second-line hypertension therapy. Merck & Co., Inc., and Hoechst Marion Roussel Inc. that developed Teczem[®] licensed the technology from Alza Corp.

m. Tiamate[®]

This is the oral osmotic version of diltiazem developed by Merck & Co., Inc., and marketed by Hoechst Marrion Roussel Inc. A second-line hypertension therapy.

n. Concerta[®]

Concerta[®] is designed to have a 12-h duration effect with a peak plasma methylphenidate concentration at around 6–8 h after administration for attention deficit hyperactivity disorder (see Figure 9.25). A gradual decrease in plasma concentrations results in a prolonged duration of action after once-daily morning dose.

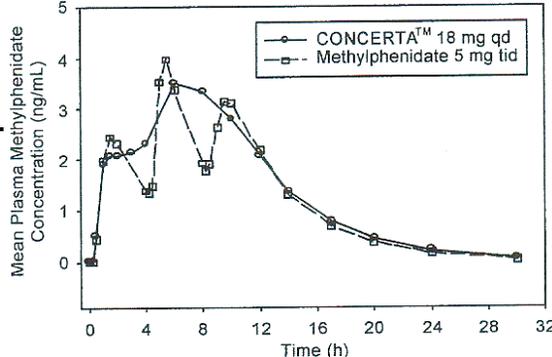


Figure 9.25 Mean plasma methylphenidate concentrations with Concerta[®] and immediate-release methylphenidate (mean plasma methylphenidate concentrations after a single 18-mg dose of Concerta[®] and three doses of immediate-release methylphenidate 5-mg every 4 h).

o. DUROS[®]

DUROS[®] is for the zero-order delivery of protein drugs. DUROS[®] is a small drug-delivery system specifically designed for the long-term parenteral delivery of potent therapeutic agents to humans. The system is implanted subcutaneously and is retrievable. It has a piston between drug reservoir and osmotic engine to drive the drug through an orifice (see Figure 9.26).

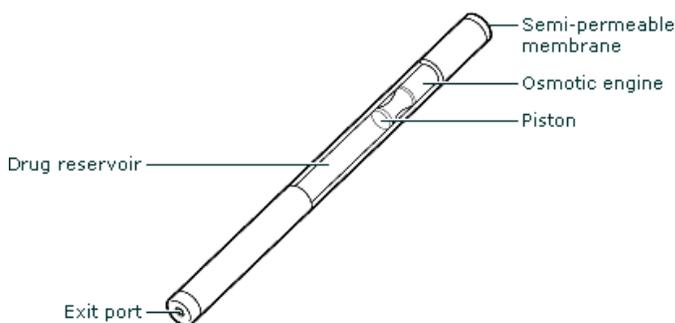


Figure 9.26 Schematic of the DUROS[®] implant.

IV. ION EXCHANGE-CONTROLLED DRUG RELEASE

Ion-exchange resins are water-insoluble polymeric materials containing ionic groups. Polymer chains with ionic groups are inherently water-soluble. So, to make water-insoluble resins the polymer chains have to be crosslinked. If the crosslinking density is low, then the system becomes a hydrogel. To prevent extensive swelling in water, the resins are extensively crosslinked. Thus, resins are simply highly crosslinked polyelectrolytes. Ion exchange resin is also used to make hard water soft (see Figure 9.27). The ion exchange in the water softener removes multi-valent ions

WORKING KNOWLEDGE

WATER FILTERS

by Louis A. Bloomfield
Department of Physics, University of Virginia
Author of How Things Work:
The Physics of Everyday Life

Despite the name, the most common type of water filter does not produce chemically pure water. If it did, the water would not taste right to us. Instead the filter's activated carbon and its ion exchange resin remove unwanted ions and molecules from water, leaving those that make it pleasant to drink. This selectivity has a practical aspect: it extends the life of the filter. The filter's capacity for chemicals is limited by the laws of thermodynamics. As the water becomes more pure and orderly, the filter becomes more impure and disorderly. This accumulating disorder and the associated consumption of the filter's potential energy lessen its effectiveness. By leaving innocuous and desirable chemicals, such as fluoride, in the water, the filter avoids an early demise.

ACTIVATED CARBON is a highly porous material that acts as a sponge for unwanted molecules like benzene (○) and some pesticides (◊) and oils (⌘). Such molecules bind chemically and physically to surfaces in the carbon's extensive network of large and small pores. A single gram (0.04 ounce) of activated carbon may have more than 1,000 square meters (about 11,000 square feet) of surface area inside it—nearly the size of a football or soccer field—so its pores can trap countless molecules before running out of room. The activated carbon also initiates a chemical reaction that converts free chlorine—HOCl (●) and OCl⁻ (●)—which utilities put in water to kill germs, into chloride (●-) and hydrogen (●+) ions, which are safe and taste all right.

ION EXCHANGE RESIN is a specially prepared plastic that replaces toxic metal ions such as lead (●⁺⁺), copper (●⁺⁺), mercury (●⁺⁺) and cadmium (●⁺⁺) with harmless hydrogen ions. It also removes enough calcium (●⁺⁺) and magnesium (●⁺⁺) ions to stop hard-water deposits from forming in kettles and teacups—but it leaves some of those ions in so that the taste of the water is not spoiled.



Figure 9.27 Diagram of an ion exchange resin cartridge in a water filter.

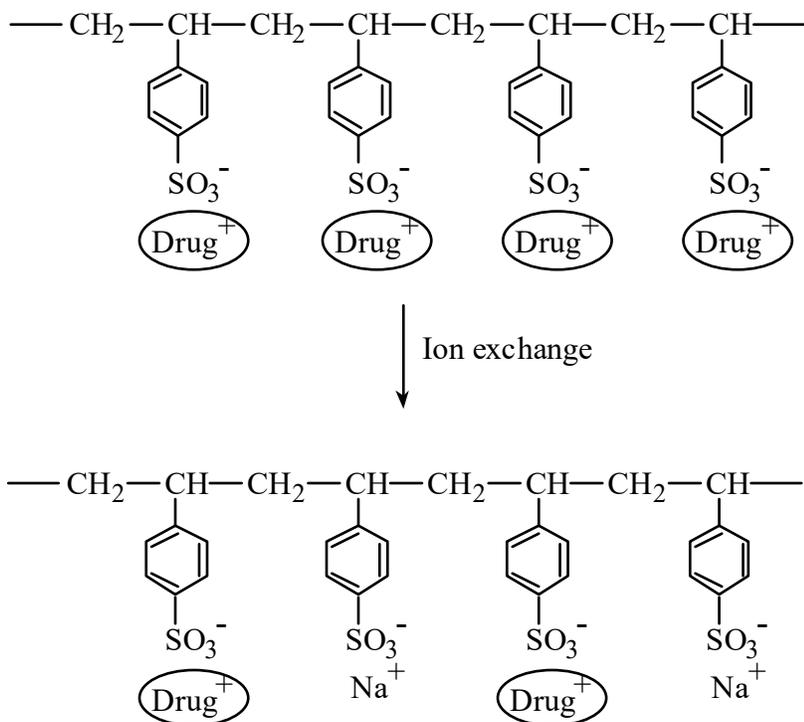


Figure 9.28 Drug release from ion-exchange resin by replacing ions. Cationic drug molecules attached to poly(styrene sulfonic acid) are released as a result of ion exchange with counter ions such as Na^+ .

such as calcium ions be exchange with sodium ions. The same phenomenon can be used for controlled drug delivery, as long as drug molecules have charges.

The charges in the resin can interact with drug molecules with opposite charge by electrostatic interaction. As shown in Figure 9.28, a cationic drug (*e.g.*, dextromethorphan) is attached to the sulfonate ion on the polymer chain by electrostatic interaction. Thus, the drug molecules can be replaced with other cations such as Na^+ and K^+ , and the detached drug is released from the ion-exchange resin.

The drug release from ion-exchange devices depends on replacement of the drug molecules by other electrolytes. Thus, the rate of drug release depends on:

1. area of diffusion (*i.e.*, surface area of resin particles)
2. crosslinking density
3. ionic strength (*i.e.*, concentration of replacing ions such as Na^+ or K^+ for cationic drugs and Cl^- for anionic drugs).
4. coating of the drug-resin complex

To have a further control over drug release, the ion-exchange resins can be coated with water-insoluble polymers such as ethylcellulose to provide diffusion-controlled drug release. In this way, more predictable drug release can be obtained. Usually, both non-coated and ethylcellulose-coated ion-exchange resins are used together. Ethylcellulose can be coated by the Wurster coating process.

There are a few advantages of the ion exchange-controlled dosage forms. Ion-exchange resins can be easily made into suspension dosage forms that allow tailoring of individual dose. This is an advantage for pediatrics and geriatrics where the adjustment of the dose is necessary. Since a drug is released slowly in small quantities, the GI irritation is substantially reduced. Since all drug molecules are initially bound to polymer chains, this dosage form can effectively provide taste abatement.

Suspension of ion-exchange resins were first developed by Pennwalt Pharmaceutical Company, and the system is called the Pennkinetic[®] system. It uses poly(styrene sulfonic acid) resins coated with ethylcellulose. Delsym[®] delivers dextromethorphan for 12 h, and Corsym[®] delivers codeine and chlorpheniramine.

Figure 9.29 shows the *in vitro* drug release profiles and *in vivo* pharmacokinetics of dextromethorphan delivered by the Pennkinetic[®] system.

V. CHEMICAL AND ENZYMATIC DEGRADATION

A. PRODRUG APPROACH

A prodrug is a compound resulting from chemical modification of a pharmacologically active compound with pro-moiety, which provides different physicochemical properties to overcome biological barriers. The concept of the prodrug approach was first suggested in 1958 by A. Albert, who visualized it as a way to temporarily change the physicochemical characteristics of a drug to optimize its biological utility. Prodrugs can liberate active compounds *in vivo* by enzymatic or hydrolytic cleavage.

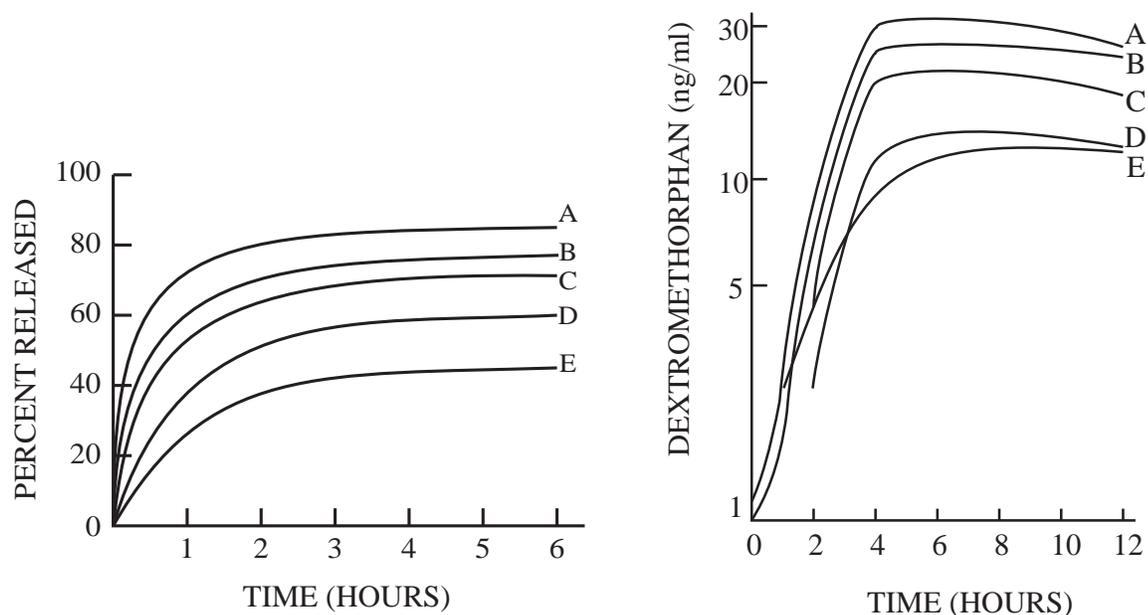


Figure 9.29 *In vitro* release profiles (left) and *in vivo* blood concentration profiles in human subjects (right) of dextromethorphan delivered by Pennkinetic[®] system. The ratios of immediate-release and sustained-release components were: 100:0 (A); 77.5:22.5 (B); 55:45 (C); 27.5: 72.5 (D); and 0:100 (E).

The prodrug approach has been used widely for improving bioavailability of many drugs after oral administration. A water-soluble derivative of a hydrophobic drug can be developed to be a substrate for enzymes in the surface coat of the brush border region of the microvillus membrane. The water-soluble derivative becomes insoluble with a high membrane-water partition coefficient just prior to reaching the membrane. Reversible modification of the physicochemical properties of a drug results in better intestinal transport properties and hence improved blood levels by orders of magnitude for water-insoluble drug. The prodrug approach is also used to reduce local side effects (*e.g.*, aspirin irritation).

Prodrugs, in a limited sense, can be sustaining in their own right. If a prodrug has much less water solubility, and hence a slower dissolution rate in aqueous fluid than the parent drug, appearance of the parent drug in the body is slowed, because the dissolution process would be rate limiting. In fact, the dissolution rate of 7,7'-succinyliditheophylline is 35 times slower than theophylline under the same conditions, and its dissolution rate is independent of pH within the physiological pH range. Many derivatives of aspirin have been made to reduce gastric irritation, rather than to increase its absorption.

Recently, a prodrug approach was used to develop compartment specific delivery vehicles for cytotoxic drugs. Immunogen, Inc., developed tumor-activated prodrugs (TAP) technology, which reduce hematological toxicity after intravenous injection into the blood stream. TAP therapy allows conversion of highly potent drugs into inactive prodrugs by linking them covalently to monoclonal antibodies. The prodrug is non-toxic in circulation and is claimed to be activated only upon specific delivery to the tumor site. Although the TAP approach has a potential for targeting only to the cancer cells, its efficacy still remains to be seen.

B. CHEMICAL DEGRADATION

Drug molecules can be attached to the polymer backbone by covalent bonding and the drug release can be controlled by the rate of cleavage of the bonds. In chemical degradation, the drug release is based on the hy-

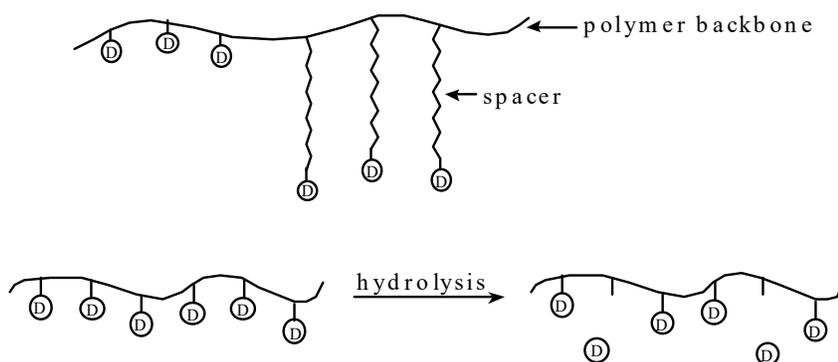


Figure 9.30 Release of drug molecules from a polymer chain by hydrolysis. Drug molecules can be attached to the polymer backbone through a variety of spacers.

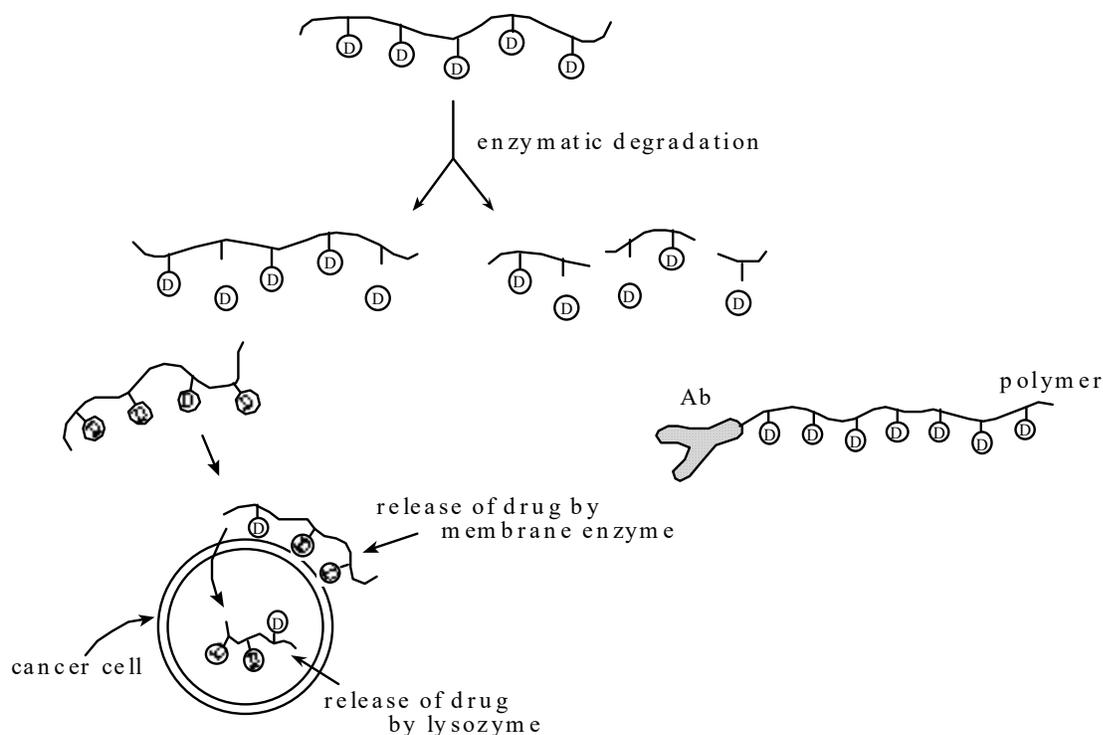


Figure 9.31 Release of drug molecules from a polymer chain by enzymatic degradation. Antibody against a target molecule can be attached to the polymer chain as a homing device. Drug can be released after the drug-polymer complex is taken up by the target cell.

drololysis of the drug-polymer bonds (Figure 9.30). Thus, the drug release in this case depends on the nature of the covalent bonds and pH of the environment. This is a rather slow process compared to drug release by other mechanisms. Since the drug-containing polymer molecule is a chemically modified compound that liberates drug *in vivo* as a result of hydrolytic degradation, it is, by definition, a prodrug.

C. ENZYMATIC DEGRADATION

In this case, the drug release from the polymer chain depends on the enzymatic degradation of the bonds (Figure 9.31).

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