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CONTROLLED RELEASE TECHNOLOGY AND DESIGN OF ORAL CONTROLLED RELEASE DOSAGE FORMS

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37.1 INTRODUCTION

An oral controlled release drug delivery system is designed to deliver a drug in a controlled and predictable manner over a period of time or at a predetermined position in the gastrointestinal tract. There are several other terms used interchangeably to describe controlled release dosage forms. The U.S. Food and Drug Administration defines modified release dosage forms as those whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form [1]. Modified release oral dosage forms include extended release, that is, dosage forms designed to make the drug available over an extended period of time after ingestion, and delayed release, that is, dosage forms designed to provide a delay before drug release. Additionally, terms such as sustained release, prolonged release, pulsatile release, and targeted release have also been used in the literature. Orally disintegrating tablets that are designed to disintegrate more rapidly than an immediate release tablet can also considered being controlled release dosage forms. They disintegrate on contact with saliva, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids [2].

Over the past five decades, oral drug delivery systems have matured and currently are a dominant segment of the pharmaceutical market. Oral dosage forms are preferred because of their convenience and cost-effectiveness. Although they were once considered quite exotic, oral controlled release systems have now become commonplace and their advantages accepted both in the development of new molecular entities and in the product enhancement. The controlled release market was estimated to be worth over U.S. $17 billion globally in 2007 with a +2% year-on-year growth [3]. Some top-selling controlled release products in the U.S. market are listed in Table 37.1.

There are several reasons for pursuing the development of controlled release dosage forms. Controlled release formulations can reduce the dosing frequency and minimize side effects. Drugs with short biological half-lives (i.e., those where the drug is metabolized or rapidly eliminated from the blood stream) have to be dosed frequently in order to maintain efficacious levels in the blood. By slowing the rate at which the drug is released, a controlled release dosage form can increase the apparent half-life and maintain efficacious levels for a longer duration, thereby reducing the need for frequent dosing. Reducing the dosing frequency to once daily assures patient convenience and compliance and a reduction in the peak to trough blood concentrations of the drug results in a more uniform therapeutic effect and can potentially lead to a lower total dose. Controlled release dosage forms can reduce undesirable side effects that are related to high and rapidly rising drug peak blood levels. In some cases, the undesirable side effects are related to a local irritation of the upper part of the gastrointestinal tract by the

TABLE 37.1   Some Top-Selling Oral Controlled Release Products in the United States

Name	Drug	Indication	Company	Type of Controlled Release Formulation	US Sales in 2008[a] (in million dollars)
Effexor XR	Venlafaxine HCl	Antidepressant	Wyeth Pharmaceuticals (Pfizer, Inc.)	Diffusion through a coating membrane on spheroids	2.87
Oxycontin	Oxycodone	Opioid agonist for pain management	Purdue Pharma	Diffusion through a matrix tablet	2.16
Adderall XR	Amphetamine and Dextroamphetamine	Attention deficit hyperactivity disorder (ADHD)	Shire Pharmaceuticals	Capsule containing two types of drug-containing beads designed to give a double-pulsed delivery	1.34
Concerta	Methylphenidate	ADHD	Ortho-McNeil-Janssen Pharmaceuticals	Trilayer capsule shaped tablet with two distinct drug layers and a push layer (osmotic technology) and a drug overcoat layer	1.00
Niaspan	Niacin (nicotinic acid)	Antihyperlipidemic agent	Abbott Laboratories	Diffusion through the gel that forms by hydration of the matrix tablet	0.81
Stilnox	Zolpidem tartrate	Hypnotic for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance	Sanofi-aventis	Coated two-layer tablet with an immediate release and extended release layer	0.88
Detrusitol/ Detrol LA	Tolterodine L-tartrate	Treatment of overactive bladder	Pfizer, Inc.	Coated drug layer beads filled in a gelatin capsule	0.84

[a]Data from IMS Health.

drug. In such cases, a delayed release dosage form can help bypass the upper part of the gastrointestinal tract and reduce the frequency and intensity of these side effects.

Orally disintegrating tablets have the advantage that they can be taken without water. This can be very important to pediatric and geriatric patients, and to patients who have difficulty swallowing tablets or capsules. A controlled release dosage form intended to avoid degradation of acid-labile drugs is typically an enteric-coated dosage form (delayed release). The enteric coat prevents drug release in the acidic environment of the stomach, and, at a higher intestinal pH, the coating dissolves to enable drug release.

The rapid advance in the field of controlled release occurred because of two main reasons: (1) Interdisciplinary teams worked together on novel concepts and designs for drug delivery devices and (2) advances in many fields that could be related to controlled release. Chemical engineers and the science of chemical engineering played a major role by introducing concepts of mass transfer and drug diffusion through matrices and membranes, material properties of excipients, thermodynamics, and kinetics of drug release. The science of biopharmaceutics provided the understanding of gastrointestinal physiology and its relationship to controlled release dosage forms, with respect to both the transit of dosage forms and the absorption of drug as a function of position in the gastrointestinal tract. It also provided preclinical *in vivo* models such as beagle dogs that led to an increased understanding of the *in vivo* performance of controlled release dosage forms and their *in vitro–in vivo* relationships. Polymer science and engineering provided novel materials with a range of properties, which could be tailored to suit a particular application, for example, polymers that eroded with time, thereby releasing the drug. Advances in the understanding of the pharmacokinetics and pharmacodynamics of drugs allowed controlled release dosage forms to be designed in a rationale manner. Finally, advances in manufacturing science and engineering were important, for example, advances in the ability to manufacture precise laser drilled orifice in osmotic tablets at rates suitable for commercial production.

This chapter focuses on the design of oral controlled drug release dosage forms. However, the field of controlled release is much broader. It spans other pharmaceutical dosage forms such as long-acting injections and implants, transdermal patches, ocular devices, and targeted drug delivery systems. Furthermore, controlled release is also used in veterinary applications [4] and diverse fields such as the sustained release of fertilizers, insecticides, herbicides, fragrances, and the food industry [5].

37.2 DEVELOPMENT OF CONTROLLED RELEASE FORMULATIONS IN AN INDUSTRIAL SETTING

The rational development of controlled release formulations in the setting of a large multinational pharmaceutical company with discovery and development operations typically starts with establishing the rationale for modifying the release rate and the desired product profile, that is, defining the medical need. The next steps involve selection of the dose, delivery duration, and release kinetics based on the known or the assumed target blood levels. It is highly recommended that prior to initiating a development program, an assessment of the feasibility of developing a controlled release formulation based on the physicochemical and biopharmaceutical properties of the drug candidate be conducted and the most appropriate technology be selected based on the attributes of the technology and manufacturing considerations such as availability of commercial scale equipment, operator expertise, and prior experience with the technology [6].

Many compounds fail to become drugs because of their poor physicochemical and/or poor biopharmaceutical properties [7]. The physicochemical properties that have an impact on the feasibility of a controlled release formulation include molecular weight, partition coefficient, solubility, pH-solubility profile, potential for solubilization, salt forms, polymorphs, particle size distribution, and stability. The biopharmaceutical and pharmacokinetic properties that have an impact on the feasibility of a controlled release formulation include gastrointestinal transit of the dosage form, fed/fasted state, permeability, efflux, and extent of gut wall/first-pass metabolism. Good absorption throughout the length of the gastrointestinal tract is important in the successful development of controlled release formulations [8].

37.3 CONTROLLED RELEASE PROFILES AND MECHANISMS

37.3.1 Types of Controlled Release Profiles

Different drug release profiles and release rates may be required based on the pharmacokinetic and pharmacodynamic need of the medication. Commonly used drug release profiles are illustrated in Figure 37.1. The first four release profiles are based on the time dependence of their release rates, while the last one is based on the onset of drug release. In the case of zero-order release, the release rate
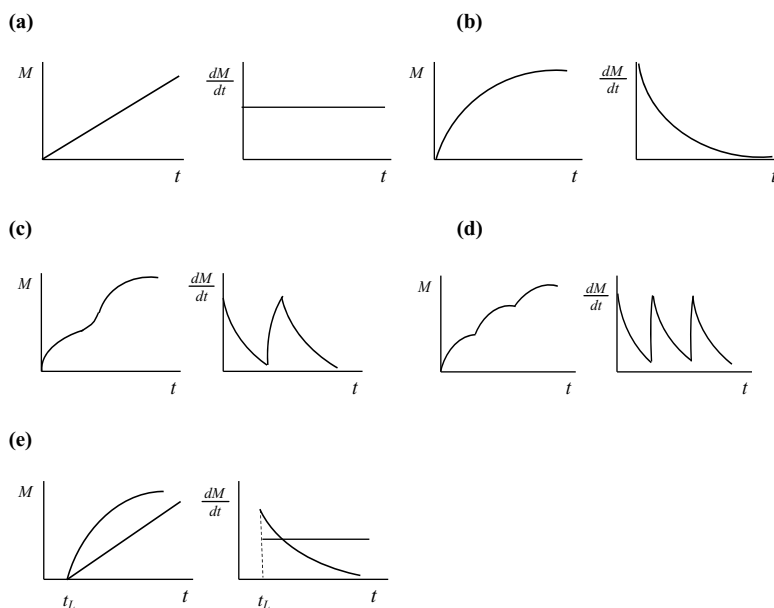

FIGURE 37.1 Schematic illustration of various types of release profiles commonly seen in oral controlled release dosage forms. (a) Zero-order release, (b) first-order release, (c) biphasic release, (d) pulsatile release, and (e) delayed or timed release.

remains constant, reflected by a linear relation between the amount of drug released and time. In the case of first-order release, the release rate decreases exponentially with time. Biphasic, multiphasic, and pulsatile release are typified by two or more modes of release. When there is no drug released until a lag time, t_L, the release profile is called delayed (or timed) release. After t_L, the release profile can be in any shape, such as zero-order or first-order release. It should be noted that there may be differences between the *in vitro* and the *in vivo* controlled release profiles because conditions of pH, hydrodynamics, fluid volume, and presence of enzymes and bacteria vary in the gastrointestinal tract.

37.3.2   Controlled Release Mechanisms and Structure of Controlled Release Systems

Various drug release profiles can be obtained by utilizing different drug release mechanisms, device geometry and structure, and materials. The following five major release mechanisms have been utilized alone or in combinations to design oral controlled release dosage forms: diffusion, erosion/degradation, ion exchange, swelling, and osmotic pressure.

The drug delivery systems are frequently referred to by the mechanism that dominates the drug release rate. Corresponding mathematical models are then derived based on the dominating drug release mechanism, the geometry of the delivery system, and the boundary conditions which the delivery systems are exposed to. The following sections describe the major drug release mechanisms, delivery systems, and their associated release profiles, and present essential mathematical equations of analytical or semianalytical solutions derived from mechanistic models. Interested readers are referred to specialized books [9–14] and original papers for the derivation of the equations.

37.3.3   Controlled Release Via Diffusion

Drug release from a device is considered diffusion-controlled when diffusion of drug molecules through the device is the rate-determining step. Depending on the structure of the delivery system, diffusion-controlled systems can be classified as membrane–reservoir (Figure 37.2a) or monolithic (matrix) systems (Figure 37.2b).

37.3.3.1   Membrane–Reservoir Systems   In membrane–reservoir systems, there is a drug-rich core (drug reservoir) enclosed by a membrane, which may or may not contain drug initially. Drug diffusion from the reservoir through the membrane is the rate-limiting step. Each delivery system can be made into various geometries. Figure 37.3 shows membrane–reservoir systems of four basic geometries—slab, cylinder, sphere and disk, which are commonly used for drug delivery. Irrespective of the geometry, membrane–reservoir systems should result in a zero-order release profile as long as the drug core provides a constant drug supply. This is true when an excess amount of solid drug is loaded in the core and drug dissolution is much faster than drug diffusion through the membrane. In this case, drug solution at the inner side of the membrane is maintained at a constant concentration that normally equals the drug saturation solubility. Once the excess drug is dissolved, the drug core can no long provide a constant supply, resulting in a decrease in the release rate.

37.3.3.2   Monolithic (Matrix) Systems   In the monolithic (or matrix) systems, uniformly distributed drug is released
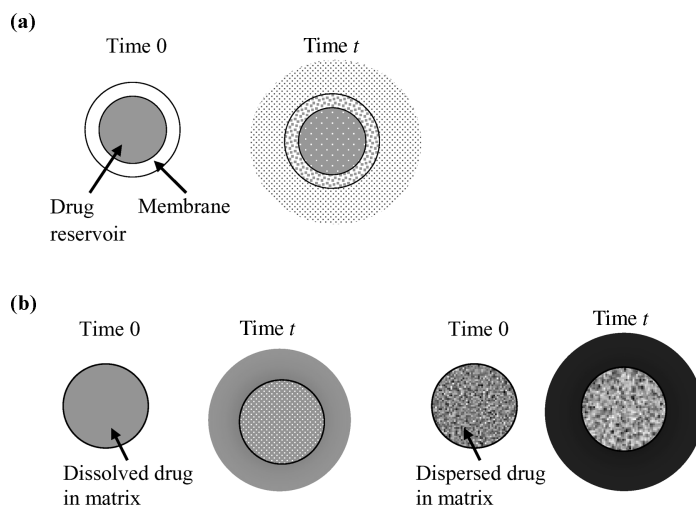

FIGURE 37.2 Schematic illustration of diffusion-controlled systems. (a) Membrane–reservoir system and (b) matrix system.
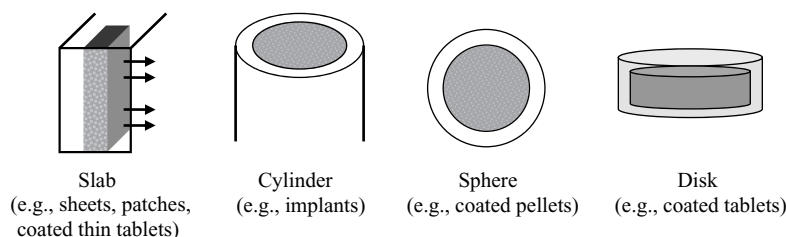
FIGURE 37.3   Membrane–reservoir systems of various geometries.

by diffusion through the matrix. Depending on the loading level and drug solubility in the matrix, the drug may exist as a molecular solution (dissolved drug) or a particle dispersion (dispersed drug). The drug loading level (C_0) relative to the drug solubility (C_s) and initial drug distribution in the matrix can influence the release profiles, as do the volume of release medium and stirring conditions.

A monolithic system usually provides first-order release profiles because the drug concentration within the matrix decreases with time and the diffusional distance increases with time. The nonlinearity of the release curve increases as the device is changed from slab to cylinder and from cylinder to sphere. Figure 37.4 compares release profiles of fractional drug release from one-dimensional slab, cylinder, and sphere with the same characteristic dimension ($a = 0.2$ cm) into a perfect sink, computed using AP-CAD® software.

37.3.4   Controlled Release Via Erosion or Degradation

Erosion- or degradation-controlled systems are special cases of matrix systems, in which matrix erosion or degradation is the rate-limiting step of drug release. Thus, while the rate of drug release for d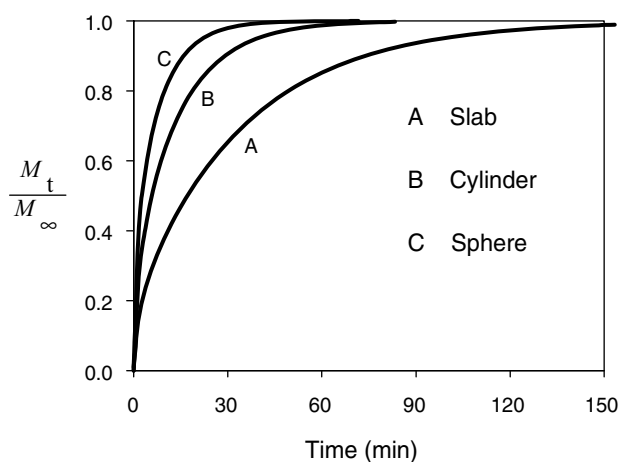issolution-based systems depends mostly on the drug solubility, erosion-based systems limit drug release by dissolution (erosion) or degradation of the materials that form the matrix. Pure erosion/degradation-controlled release is hard to find in oral controlled release dosage forms. Matrix erosion and degradation are often concurrent with other release mechanisms such as drug diffusion and dissolution. Biodegradable polymers typically used in erosion-controlled systems have been reviewed elsewhere [15].

37.3.4.1 Heterogeneous Erosion   When the matrix is rigid and hydrophobic with minimal hydration in the release medium, entrapped drug is released mainly by matrix surface erosion, that is, heterogeneous erosion (Figure 37.5a). If drug solubility in the medium is very low, drug release rate may still be dictated by matrix erosion (solution) even if the matrix is hydrophilic. The released drug particles may dissolve following release from the matrix. An ideal heterogeneous erosion-controlled system should give a zero-order release if it is a planar shape, or nonlinear release if it is a cylinder or a sphere. Again, the nonlinearity is higher for sphere than cylinder due to more dramatic reduction in the area toward the center of the device.
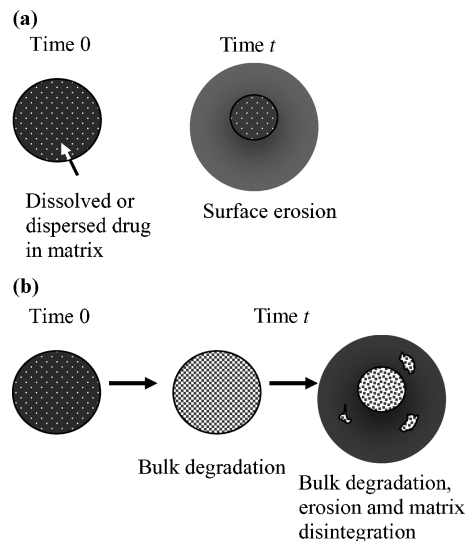

FIGURE 37.4   Comparison of release profiles of fractional drug release from one-dimensional slab, cylinder, and sphere with the same characteristic dimension ($a = 0.2$ cm) into a perfect sink, computed using AP-CAD software.

FIGURE 37.5   Schematic illustrations of erosion and degradation-controlled release. (a) Heterogeneous (surface) erosion and (b) homogeneous (bulk) degradation and erosion.
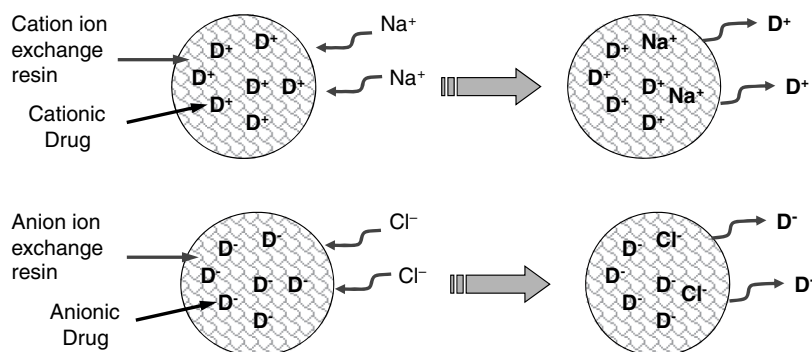
FIGURE 37.6   Schematic of ionic drug release from ion-exchange resin that involves steps of counterion diffusion into the resin, exchange with bound drug, and diffusion of dissociated drug out of the resin.

37.3.4.2 Homogeneous Degradation and Erosion

When the matrix undergoes bulk degradation, the molecular weight of the matrix polymer decreases gradually, resulting in a higher drug diffusion coefficient in the matrix with time. Eventually the matrix may disintegrate and dissolve, releasing the remaining drug. This process is named homogeneous degradation and erosion (Figure 37.5b). Usually a first-order release curve is seen for a period of time, followed by an accelerated release when disintegration of the device occurs. The rate of degradation of conventional biodegradable polymers, such as polylactides, is too slow to be suitable for oral controlled release dosage forms that are retained in the gastrointestinal tract for a maximum of about 24 h. Instead, microbially degradable polymers, especially azo cross-linked polymers, which are degraded specifically by colonic bacteria, have been investigated for colonic drug delivery. The release profile of such delivery system is rather complex and can vary from near zero-order to first-order release.

37.3.5   Controlled Release Via Ion Exchange

Ion-exchange resins, initially developed for water treatment, have been used in pharmaceutical dosage forms. Their applications include taste masking, sustained release, and gastric retention. They are designated either cationic or anionic based on the counterions. Cationic ion-exchange resins are comprised of anionic groups such as $-COO^-$ and $-SO_3^-$ groups, while anionic exchange resins contain $-NR_2^+$ or $-NR_3^+$ groups.

When an ionic drug is loaded into a matrix, for example, an ion-exchange resin or a polyeletrolyte with charges of opposite sign, its release from the matrix is normally controlled both by ion-exchange and by diffusion because the release process involves several essential steps: (1) Diffusion of counterions from release medium into the matrix; (2) exchange of counterions with bound drug molecules in the matrix; and (3) diffusion of free drug molecules out from the matrix into the medium.

These steps are depicted in Figure 37.6. In case of hydrophobic polyeletrolytes, matrix swelling may also play a role in the release kinetics. In general, a first-order release profile is seen in ion exchange-controlled delivery systems.

37.3.6   Controlled Release Via Swelling

When a swellable glassy polymer matrix is placed in a thermodynamically compatible solvent, it undergoes an abrupt transition from the glassy state to the rubbery state. Because the polymer chains at the glassy state are rigid, drug diffusion in the glassy region is negligible as compared to that in the rubbery region. Pharmaceutical dosage forms are usually made from swellable hydrophilic polymers such as hydroypropylmethylcellulose and polyethylene oxide. When a matrix tablet made from such polymer and loaded with drug is introduced into an aqueous medium, water penetrates into the matrix, wets the polymer and drug particles therein and fills the pores. In the hydrated layer, drug particles start to dissolve and drug molecules diffuse out from the wetted zone that has a boundary named the diffusion front (see Figure 37.7). The hydrated polymer chains gradually relax and disentangle forming a gel layer. Drug diffusion in the gel layer is much faster than in the dry glassy core and in the slightly hydrated layer as well. In contrast to pure diffusion-controlled hydrophobic matrix drug systems with little volume change during release, hydrophilic polymers undergo the glassy–rubbery transition and absorb large amount of water due to osmotic pressure. As a result, the volume of the device increases, so does the drug diffusion coefficient in the rubbery zone and matrix porosity if high quantities of water-soluble additives are added, or in the case of high initial drug loadings. A matrix drug device is classified as being swelling controlled if the change in polymer morphology by interaction with the external release medium controls or alters the drug release rate. Note that noncross-linked hydrophilic polymers may dissolve before all payload is released, which is often seen in pharmaceutical hydrophilic matrices.
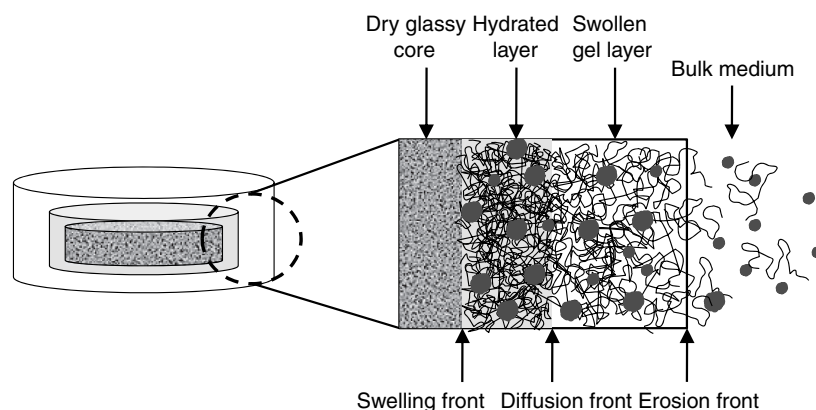
FIGURE 37.7   Illustration of drug release from a hydrophilic matrix tablet by swelling mechanism.

37.3.7   Controlled Release Via Osmotic Pressure

Osmotic-controlled release of drug molecules involves the regulation of osmotic permeation of water through the use of a semipermeable membrane. The diffusion of water across the semipermeable membrane induced by an existing chemical potential gradient between the dissolution medium and the tablet core creates a hydrostatic pressure. The hydrostatic pressure generated by the influx of water forces the release of a saturated solution of the drug through delivery ports in the device. In addition to the mechanism of osmotic pumping, drug release can also take place through the membrane as a result of the solution–diffusion mechanism. Since the device volume is constant, the volume of drug solution delivered will be equal to the volume of osmotic water uptake within a given time interval. Therefore, the rate of drug delivery will be constant as long as a constant osmotic pressure gradient is maintained across the membrane. Prolonged zero-order release can then be achieved with this system. However, as the reservoir concentration falls below saturation, the rate declines asymptotically. It is also conceivable for osmotic systems to achieve release rates much higher than systems that solely involve solution–diffusion mechanism.

Osmotic devices can be manually activated or self-activated. Manually activated devices have to be stored empty and loaded with water prior to use. Other versions have an impermeable seal between the semipermeable membrane and the water chamber, allowing the devices to be stored fully loaded with water. The osmotic pump then becomes activated when the seal is broken. Self-activated devices are activated by water imbibed from the gastrointestinal tract or the dissolution vessel medium driven by the device itself.

37.3.7.1 Rose–Nelson Pump   The Rose–Nelson pump [16] shown in Figure 37.8 consists of a drug chamber, a salt chamber containing excess solid salt, and a water chamber. The drug and the water chambers are separated by a rigid semipermeable membrane. Water moves from the water
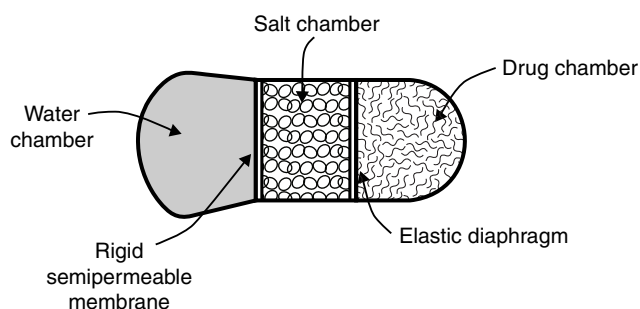

FIGURE 37.8   The three-chamber Rose–Nelson osmotic pump. Reprinted from Ref. 16, Copyright (1995), with permission from Elsevier.

chamber into the salt chamber as a result of the difference in osmotic pressure across the membrane. The increase in volume of the salt chamber as a result of water uptake moves the piston and causes drug to be pumped out of the device.

37.3.7.2 Higuchi–Leeper Pump   The Higuchi–Leeper pump differs from the Rose–Nelson pump in that the water chamber is absent (Figure 37.9). The Higuchi–Leeper pump usually consists of a salt chamber that contains a fluid solution with excess solid, and a rigid housing with the semipermeable membrane supported on a perforated frame.

37.3.7.3 Higuchi–Theeuwes Pump   The semipermeable membrane in the Higuchi–Theeuwes pump acts as the outer casing of the pump. As shown in Figure 37.10, the pump is comprised of a rigid rate-controlling outer semipermeable membrane surrounding a solid layer of salt coated on the inside by an elastic diaphragm and on the outside by the membrane. During its operation, water is osmotically drawn by the salt through the semipermeable membrane. This water increases the volume of the salt chamber, forcing the drug release from the chamber.
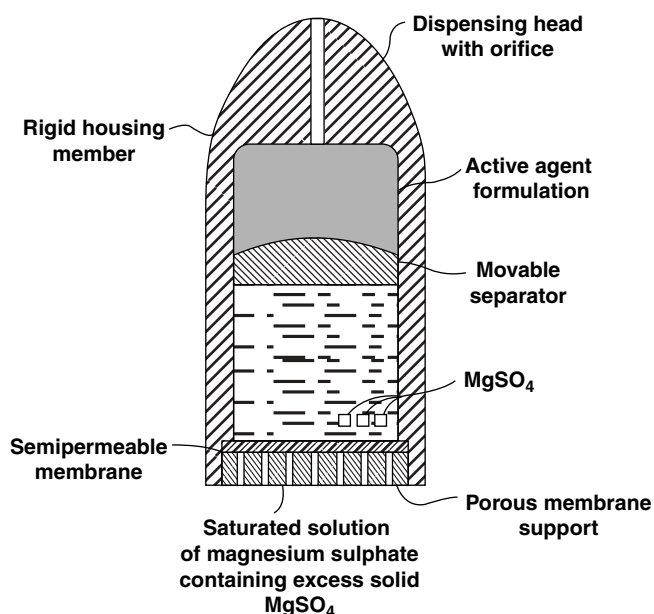
FIGURE 37.9 The Higuchi–Leeper pump. Reprinted from Ref. 16, with permission from Elsevier.
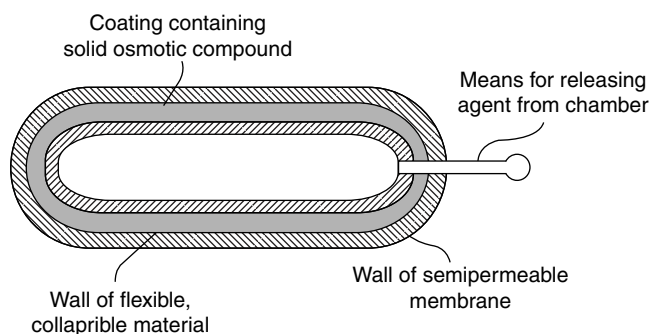

FIGURE 37.10 The Higuchi–Theuwes Pump. Reprinted from Ref. 16, with permission from Elsevier.

37.3.7.4 Elementary Osmotic Pump In these systems, a semipermeable membrane with a delivery orifice surrounds an osmotic core that contains the drug. The delivery rate from these devices is regulated by the osmotic pressure of the osmotic agent of the core formulation and by the water permeability of the semipermeable membrane (Figure 37.11). For example, the OROS® system developed by ALZA Corporation is used to deliver Acutrim, an over-the-counter appetite suppressant, at a controlled rate [17]. Similarly, Elan Corporation of Ireland has developed MODAS (multidirectional oral absorption system). This system differs from OROS in that it has a multitude of small pores through which the drug can exit.

37.3.7.5 Push–Pull Osmotic Pump The OROS system described in the previous section is somewhat limited
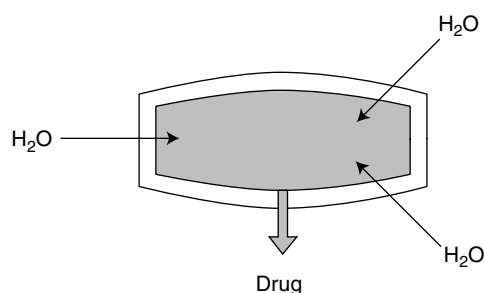

FIGURE 37.11 The elementary osmotic pump. Reprinted from Ref. 29, Copyright (2000), with permission from Marcel Dekker, Inc.

because it can only deliver drugs with good aqueous solubility. The push–pull osmotic pump, which delivers a suspension of drug, was an advancement over the elementary osmotic pump because it could be used for the delivery of low solubility drugs and it could be manufactured using conventional pharmaceutical equipment [18]. For this system, the core consisted of a bilayer tablet with one layer containing a swelling agent and other layer containing the drug formulation. The swelling agent functioned to push a suspension of drug from the orifice (Figure 37.12). ALZA Corporation, which was acquired by Johnson & Johnson in 2001, developed the gastrointestinal therapeutic system (GITS), using this dosage form to deliver Nifedipine to provide once-a-day dosing for hypertension [19].

37.3.7.6 Semipermeable Membranes Containing Micropores Innovations in the osmotic drug delivery field continued in the 1990s by the development of the controlled porosity osmotic pump tablet (CP-OPT) by Zentner and others [20–22]. The main advancement of the CP-OPT compared to the OROS system was the new design of the semipermeable membrane to contain pores sufficient in size to eliminate the need for laser drilling an orifice. The CP-OPT membrane also contains a pore former and plasticizer. This osmotic dosage form is designed to deliver a drug solution by an osmotic mechanism; therefore, limited in application
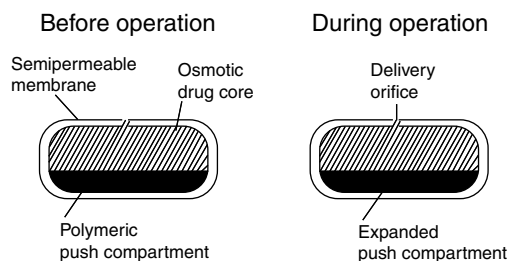

FIGURE 37.12 Illustration of the push–pull osmotic pump known as the gastrointestinal therapeutic systems. Reprinted from Ref. 19, Copyright (1987), with permission from Elsevier.

to soluble compounds. In the late 1990s, Okimoto and Stella [23–27] advanced the CP-OPT technology to encompass poorly water soluble compounds that could be solubilized by Captisol™ (sulfobutyl ether-β-cyclodextrin or (SBE)$_{7m}$-β-CD) that serves as both a solubility enhancing agent and an osmotic agent. The use of (SBE)$_{7m}$-β-CD enabled the osmotic release from CP-OPT of low solubility drugs such as prednisolone, chlorpromazine, and testosterone.

The asymmetric membrane (AM) film-coated tablet is a unique embodiment within the field of osmotic drug delivery. The membrane is formed by a phase inversion process and is composed of a several layers of polymer with a network of interconnecting pores [28]. The polymer acts as a semipermeable barrier while the interconnected pores provide a path for dissolved core components to exit. A laser-drilled orifice is not necessary in the AM system as required for the OROS technology, and similar to the CP-OPT. In fact, the entire AM film coating acts as hundreds of preformed delivery orifices. Therefore, the drug release can be adjusted by varying the type and concentration of the pore former present in the semipermeable membrane as well as the membrane thickness [29]. Unlike the CP-OPT, in the AM tablet design the porous, semipermeable membrane contains polyethylene glycol in a dual role, serving as plasticizer and pore former. The holes through which drug is released are pores created in the tablet coating as a result of the method of coating and polymer solution used or occur when the water-soluble component of the tablet coating is leached out after the tablet is swallowed [16]. As with Theeuwes's elementary osmotic pump, a porous membrane surrounds an osmotic core containing the drug. It has been demonstrated that the mechanism of drug release from spherical beads consisting mainly of phenylpropanolamine hydrochloride and sucrose that were coated with a porous ethylcellulose film is predominantly osmotic, irrespective of film porosity [30]. It has been shown that high water fluxes can be achieved with asymmetric membrane tablets [28, 29]. The asymmetric coating consists of a porous substrate with a thin outer skin. The high water fluxes from these asymmetric coatings permits the osmotic delivery of drugs with lower solubilities [29] (Figure 37.13).

37.3.7.7 Polymer Drug Matrix Systems   Polymer drug matrix systems are comprised of polymer-encapsulated drug particles dispersed within a polymer matrix (Figure 37.14). Several researchers have postulated different phenomena accounting for drug release. For example, Wright et al. [31] have postulated that drug release occurs as soon as water drawn osmotically in through the encapsulating polymer causes the coating to rupture. An osmotic pressure gradient is then believed to pump the dissolved drug to the surface through fractures created via interconnected pores. In other words, after rupturing, osmotic pressure driven convection is believed to be responsible for the release of the remaining
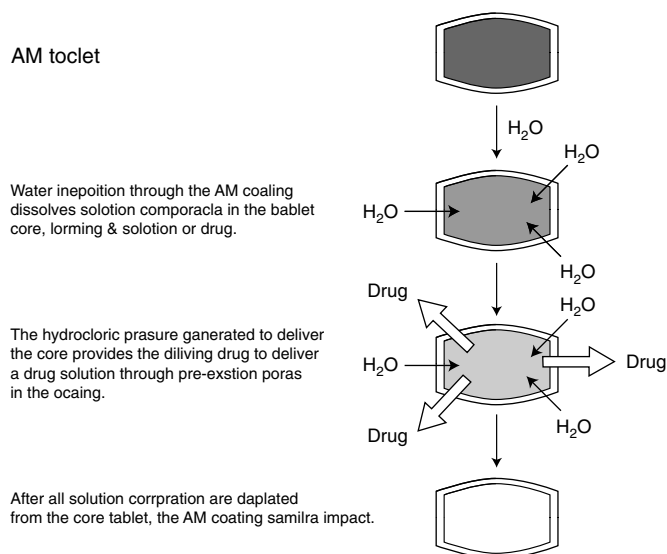
FIGURE 37.13   Semipermeable membrane containing micropores. Reprinted from Ref. 29, Copyright (2000), with permission from Marcel Dekker, Inc.
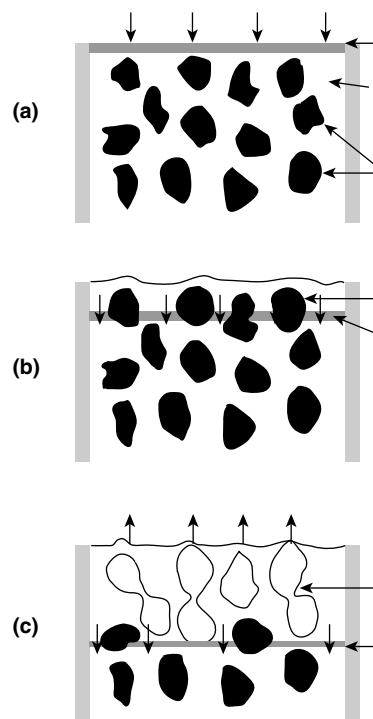

FIGURE 37.14   Polymer matrix system. (a) The diffusion of water to first layer of encapsulated particles. (b) Water imbibition into encapsulated particles. (c) Zone of interconnected capsules, imbibing capsules, and intact capsules. Reprinted from Ref. 32, Copyright (1994), with permission from Elsevier.

solid material in the capsule. According to Amsden et al. [32], release by diffusion is the most likely phenomena responsible for the release after the capsules rupture.

37.4 MATHEMATICAL EQUATIONS FOR DRUG RELEASE FROM CONTROLLED RELEASE DOSAGE FORMS

37.4.1 Diffusion-Controlled Systems

Diffusion-controlled systems can be described by Fick's second law. The general governing equation of release kinetics for one-dimensional (1D) release is

$$\frac{\partial C}{\partial t} = \frac{1}{x^\alpha}\left[\frac{\partial}{\partial x}\left(x^\alpha D \frac{\partial C}{\partial x}\right)\right] \tag{37.1}$$

where $\alpha = 0$ for slab, $\alpha = 1$ for cylinder, and $\alpha = 2$ for sphere; D is the drug diffusion coefficient in the device; c is the drug concentration as a function of time t and distance x. The 1D release model is applicable to infinite large slab or infinite long cylinder, where drug release from the edge of the slab or the ends of the cylinder is negligible.

For general multidimensional problems, the governing equation is

$$\frac{\partial C}{\partial t} = D\left[\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} + \frac{\partial^2 C}{\partial z^2}\right] \tag{37.2}$$

With appropriate initial and boundary conditions, the partial differential equations can be solved analytically or numerically. Up to date, only handful explicit exact solutions and approximate analytical solutions for simple geometries have been obtained. The final expressions are presented below without detailed derivation. Interested readers can find procedures of derivation in the cited references. For complex delivery systems with two- or three-dimensional (2D or 3D) release, numerical methods, such as finite element method [33–35], finite difference method [36, 37], and Monte Carlo method can be employed, which will not be elaborated here.

37.4.2 Membrane–Reservoir Systems

37.4.2.1 Exact Solution for 1D Slab with Constant Reservoir in a Sink [10, 38]

$$M = \frac{DKC_r t}{\delta} + \frac{2KC_r \delta}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\left[1 - \exp\left(\frac{-Dn^2\pi^2 t}{\delta^2}\right)\right]$$

$$+ \frac{4C_m\delta}{\pi^2}\sum_{m=0}^{\infty}\frac{1 - \exp\left(\frac{-D(2m+1)^2}{\delta^2}\pi^2 t\right)}{(2m+1)^2} \tag{37.3}$$

where M is the cumulative amount of drug released from unit area; δ is the membrane thickness; C_r is the drug concentration in the reservoir, which is normally taken as the drug solubility in the presence of excess dispersed drug; C_m is the initial drug concentration in the membrane; K is the partition coefficient of drug between the membrane and the reservoir; and D is the drug diffusion coefficient in the membrane. This equation predicts drug released from unit area until all dispersed drug is exhausted. By letting $C_m = 0$ and $t \to \infty$ in equation 37.3, drug released at steady state and time lag, t_l, can be obtained as

$$M = \frac{DKC_r}{\delta}(t - t_l) \tag{37.4}$$

Similarly by letting $C_m = C_r$ and $t \to \infty$, the initial burst time t_b is found from

$$M = \frac{DKC_r}{\delta}(t + t_b) \tag{37.5}$$

where $t_l = \delta^2/(6D)$ and $t_b = \delta^2/(3D)$

37.4.2.2 Analytical Solution for 1D Slab with Nonconstant Reservoir in a Sink [38]
After all solid drug is dissolved, the drug concentration in the reservoir decreases with time. The amount of drug released from unit area is then described by

$$M = C_s V\left[1 - \exp\left(-\frac{DK}{\delta V}t\right)\right] \tag{37.6}$$

where V is the volume of the reservoir with unit area. This equation is based on pseudosteady state assumption and mass balance.

Using equation 37.3 for time up to t^*, the time at which all dispersed drug is depleted, and equation 37.6 after t^* one can obtain a release profile covering the entire release course from constant reservoir to nonconstant reservoir. To find t^*, let $M = (C_r - C_s) \times V$; substitute it into the left-hand side of equation 37.3, and then solve for t^*.

37.4.2.3 Exact Solution for 1D Cylinder with Constant Reservoir in a Sink [38]

$$M = \frac{2\pi KC_r Dt}{\ln\left(\frac{b}{a}\right)} + 4\pi\sum_{n=1}^{\infty}\left(\frac{KC_r J_0(b\alpha_n)}{J_0(a\alpha_n) - J_0(b\alpha_n)} + C_m\right)$$

$$\times \frac{J_0(a\alpha_n)[1 - \exp(-D\alpha_n^2 t)]}{\alpha_n^2[J_0(a\alpha_n) + J_0(b\alpha_n)]} \tag{37.7}$$

where M is the cumulative amount of drug released from a cylinder of constant reservoir through a membrane of unit length; a and b, respectively, are the internal and the external radius of the cylindrical membrane, which defines the

membrane thickness $\delta = b - a$. α_n values are the positive roots of $J_0(a\alpha_n)Y_0(b\alpha_n) - J_0(b\alpha_n)Y_0(a\alpha_n)$, J_0 and Y_0 are Bessel function of the first and the second kind of order zero.

Similar to slab case, the corresponding steady-state drug released with lag time or initial burst are

$$M = \frac{2\pi DKC_r}{\ln\left(\frac{b}{a}\right)}(t - t_1) \tag{37.8}$$

$$t_1 = \frac{2\ln\left(\frac{b}{a}\right)}{D} \sum_{n=1}^{\infty} \frac{J_0(a\alpha_n)J_0(b\alpha_n)}{\alpha_n^2[J_0^2(b\alpha_n) - J_0^2(a\alpha_n)]} \tag{37.9}$$

$$M = \frac{2\pi DKC_r}{\ln\left(\frac{b}{a}\right)}(t + t_b) \tag{37.10}$$

$$t_b = \frac{2\ln\left(\frac{b}{a}\right)}{D} \sum_{n=1}^{\infty} \frac{J_0^2(a\alpha_n)}{\alpha_n^2[J_0^2(b\alpha_n) - J_0^2(a\alpha_n)]} \tag{37.11}$$

37.4.2.4 Analytical Solution for 1D Cylinder with Nonconstant Reservoir in a Sink [38]

$$M = C_s V \left[1 - \exp\left(-\frac{2DK}{a^2 \ln\left(\frac{b}{a}\right)} t \right) \right] \tag{37.12}$$

where V is the volume of the cylindrical reservoir with unit length.

37.4.2.5 Exact Solution for Sphere with Constant Reservoir in a Sink [38]

$$M = \frac{4\pi ab DKC_r t}{\delta} + \frac{8ab\delta(KC_r - C_m)}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2}$$

$$\times \left[1 - \exp\left(\frac{-Dn^2\pi^2 t}{\delta^2} \right) \right]$$

$$+ \frac{8b^2\delta C_m}{\pi} \sum_{n=0}^{\infty} \frac{1}{n^2} \left[1 - \exp\left(\frac{-Dn^2\pi^2 t}{\delta^2} \right) \right] \tag{37.13}$$

where a and b, respectively, are the internal and external radius of the spherical membrane, which defines the membrane thickness $\delta = b - a$. This equation describes the drug release from constant reservoir through a spherical membrane. Similar to slab case, the corresponding steady-state drug released with lag time or initial burst are

$$M = \frac{4\pi ab DKC_r}{\delta}(t - t_1) \tag{37.14}$$

$$M = \frac{4\pi ab DKC_r}{\delta}(t + t_b) \tag{37.15}$$

where $t_1 = \delta^2/(6D)$ and $t_b = b\delta^2/(3aD)$.

37.4.2.6 Analytical Solution for Sphere with Nonconstant Reservoir in a Sink [38]

$$M = C_s V \left[1 - \exp\left(-\frac{3bDK}{\delta a^2} t \right) \right] \tag{37.16}$$

where V is the volume of the spherical reservoir.

37.4.2.7 Analytical Solution for 2D Tablet with Constant Reservoir in a Sink [39]

$$M = 2[\pi a^2 M_a + (H - \delta_a)M_r + M_c] \tag{37.17}$$

where M is the cumulative amount released from the axial direction and radial direction, M_a and M_r, are given in equations 37.3 and 37.7, respectively, and M_c is expressed below

$$M_c = \frac{\pi KC_r t}{\ln\left(\frac{a}{b}\right)} \left\{ \frac{D_a}{\delta_a} \left[\frac{a^2 - b^2}{2} - a^2 \ln\left(\frac{a}{b}\right) \right] - D_r\delta_a \right\} \tag{37.18}$$

where a and b are internal and external radius of the tablet, δ_a is axial membrane thickness, and the radial membrane thickness $\delta_r = b - a$. H is the half-thickness of the tablet. D_a and D_r are the drug diffusion coefficients in the axial and the radial directions, respectively. The parameters for radial and axial directions can be identical for symmetric coating, or different for asymmetric coating. The amount of drug released at the steady state with time lag or initial burst are

$$M = 2\pi KC_r \left(\frac{a^2 D_a}{\delta_a} + \frac{2(H - \delta_a)D_r}{\ln\left(\frac{b}{a}\right)} \right)(t - t_1) \tag{37.19}$$

$$t_1 = \frac{\frac{a^2 h}{6} + 4(H - \delta_a)\sum_{n=1}^{\infty} \frac{J_0(a\alpha_n)J_0(b\alpha_n)}{\alpha_n^2[J_0^2(b\alpha_n) - J_0^2(a\alpha_n)]}}{\frac{a^2 D_a}{\delta_a} + \frac{2(H - \delta_a)D_r}{\ln\left(\frac{b}{a}\right)}} \tag{37.20}$$

$$M = 2\pi KC_r \left(\frac{a^2 D_a}{\delta_a} + \frac{2(H - \delta_a)D_r}{\ln\left(\frac{b}{a}\right)} \right)(t + t_b) \tag{37.21}$$

$$t_b = \frac{\frac{a^2 h}{3} + 4(H - \delta_a)\sum_{n=1}^{\infty} \frac{J_0^2(a\alpha_n)}{a_n^2[J_0^2(a\alpha_n) - J_0^2(b\alpha_n)]}}{\frac{a^2 D_a}{\delta_a} + \frac{2(H - \delta_a)D_r}{\ln\left(\frac{b}{a}\right)}} \tag{37.22}$$

37.4.2.8 Analytical Solution for 2D Tablet with Nonconstant Reservoir in a Sink [39]

$$M = C_s V \left\{ 1 - \exp\left[\frac{-2KD_r}{a^2 \ln\frac{b}{a}} - \frac{KD_a}{h(H - \delta_a)} \right.\right.$$
$$\left.\left. - \frac{\pi K}{V} \left(\frac{D_a}{\delta_a} \left(\frac{a^2 - b^2}{2\ln(\frac{a}{b})} - a^2 \right) - \frac{D_r \delta_a}{\ln(\frac{a}{b})} \right) \right] t \right\}$$

$$(37.23)$$

where V is the volume of the tablet reservoir.

Although the equations for describing drug release kinetics for membrane–reservoir systems are presented above separately for constant and nonconstant reservoir, the total amount of drug released during the entire course can be combined seamlessly based on mass balance as outlined by Zhou et al. [39].

37.4.3 Monolithic (Matrix) Systems Containing Dissolved Drug ($C_0 \leq C_s$)

37.4.3.1 Exact Solution for 1D Slab with Dissolved Drug ($C_0 \leq C_s$) in a Sink [10]

$$\frac{M_t}{M_0} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left[\frac{-D(2n+1)^2 \pi^2 t}{4l^2} \right]$$

$$(37.24)$$

where l is the half thickness of the slab, $M_0 = 2C_0 l$, C_0 is the initial drug loading, and D is the drug diffusion coefficient. If l is defined as the thickness of the slab, the equation is

$$\frac{M_t}{M_0} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left[\frac{-D(2n+1)^2 \pi^2 t}{l^2} \right]$$

$$(37.25)$$

37.4.3.2 Exact Solution for 1D Slab with Dissolved Drug ($C_0 \leq C_s$) in a Well-Stirred Finite Volume [10]

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_n^2} \exp\left(\frac{-Dq_n^2 t}{l^2} \right) \qquad (37.26)$$

where the q_n values are the nonzero positive roots of $\tan q_n = -\alpha q_n$ and effective volume ratio, $\alpha = L/Kl$. K is the partition factor between solute in the slab in equilibrium and that in the solution. L is the thickness of the external volume, on one side of the slab, excluding the space occupied by the half thickness of the slab. Note that in a finite volume, the amount of drug released at equilibrium, M_∞, may be smaller than the initial payload, M_0, because the external medium may be saturated by the released drug before all payload is released. Should the saturation occur, the time for $\frac{M_t}{M_\infty}$ to reach unity is shorter than $\frac{M_t}{M_0}$ and the difference

between these two increases as the effective volume ratio decreases. This phenomenon is seen in all geometries [33–35].

37.4.3.3 Exact Solution for 1D Cylinder with Dissolved Drug ($C_0 \leq C_s$) in a Sink [10]

$$\frac{M_t}{M_0} = 1 - \sum_{n=1}^{\infty} \frac{4}{R^2 q_n^2} \exp(-Dq_n^2 t) \qquad (37.27)$$

where the q_n values are the roots of $J_0(Rq_n) = 0$ and $J_0(x)$ is the Bessel function of the first kind of order zero, R is the radius of the cylinder, and $M_0 = C_0 \pi R^2$.

37.4.3.4 Exact Solution for 1D Cylinder with Dissolved Drug ($C_0 \leq C_s$) in a Well-Stirred Finite Volume [10]

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{4\alpha(1+\alpha)}{4 + 4\alpha + \alpha^2 q_n^2} \exp\left(\frac{-Dq_n^2 t}{R^2} \right) \qquad (37.28)$$

where the q_n values are the nonzero positive roots of $\alpha q_n J_0(q_n) + 2J_1(q_n) = 0$, $J_1(x)$ is the Bessel function of the first order, $\alpha = V/(\pi R^2 K)$, K is the partition factor between solute in the cylinder and that in the medium at equilibrium, and V is the external volume excluding the space occupied by the cylinder.

37.4.3.5 Exact Solution for Sphere with Dissolved Drug ($C_0 \leq C_s$) in a Sink [10]

$$\frac{M_t}{M_0} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(\frac{-Dn^2 \pi^2 t}{R^2} \right) \qquad (37.29)$$

where R is the radius of the sphere and $M_0 = 4\pi R^3 C_0/3$.

37.4.3.6 Exact Solution for Sphere with Dissolved Drug ($C_0 \leq C_s$) in a Well-Stirred Finite Volume [10]

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{6\alpha(1+\alpha)}{9 + 9\alpha + \alpha^2 q_n^2} \exp\left(\frac{-Dq_n^2 t}{R^2} \right) \qquad (37.30)$$

where q_n values are the nonzero positive roots of $\tan q_n = 3q_n/(3 + \alpha q_n^2)$ and $\alpha = 3V/(4\pi R^3 K)$. K is the partition factor between solute in the sphere in equilibrium and that in the solution. V is the external volume excluding the space occupied by the sphere.

37.4.3.7 Exact Solution for 2D Tablet with Dissolved Drug ($C_0 \leq C_s$) in a Sink [40]
Considering drug release from all surfaces of a matrix tablet with symmetric properties, Fu et al. derived an exact solution:

$$\frac{M_t}{M_0} = 1 - \frac{8}{H^2 R^2} \sum_{m=1}^{\infty} \exp(-D\alpha_m^2 t)(\alpha_m^{-2}) \sum_{n=1}^{\infty} \exp(-D\beta_n^2 t)(\beta_n^{-2})$$

$$(37.31)$$

where α_m values are the roots of $J_0(R\alpha) = 0$, $\beta_n = (2n+1)\pi/2H$, R is the radius, and H is the half-thickness of a tablet.

37.4.4 Monolithic (Matrix) Systems Containing Dispersed Drug ($C_0 > C_s$)

37.4.4.1 Exact Solution for 1D Slab with Dispersed Solute ($C_0 > C_s$) in a Sink [41]

$$M_t = \frac{2C_s}{\text{erf}(\beta^*)}\sqrt{\frac{Dt}{\pi}} \tag{37.32}$$

β^* can be found from the following equation

$$\sqrt{\pi}\beta^*\exp(\beta^*)\text{erf}(\beta^*) = \frac{C_s}{C_0 - C_s} \tag{37.33}$$

where C_0 is the initial drug concentration and C_s is drug solubility in the matrix. This equation predicts a linear plot of M_t versus $\sqrt{t}$, that is, a square root relationship. It is only applicable when the excess dispersed drug is present.

37.4.4.2 Analytical Solution for 1D Slab with Dispersed Solute ($C_0 > C_s$) in a Sink [42]

$$M_t = \sqrt{DC_s(2C_0 - C_s)t} \tag{37.34}$$

This solution calculates drug released from unit area based on pseudosteady state assumption and is generally applicable for $C_0 > 3C_s$.

37.4.4.3 Analytical Solution for 1D Cylinder with Dispersed Solute ($C_0 > C_s$) in a Sink [43]

$$M_t = \pi C_0(R_0^2 - r^2) \tag{37.35}$$

$$\frac{r^2}{2}\ln\left(\frac{r}{R_0}\right) + \frac{R_0^2 - r^2}{4} = \frac{C_s Dt}{C_0} \tag{37.36}$$

where R_0 is the radius of the cylinder and r is the moving front of dispersed drug. For a given series of r such as $r_1, r_2, \ldots, r_n$, solve for $M_{t1}, M_{t2}, \ldots M_{tn}$ from equation 37.35 and $t_1, t_2, \ldots, t_n$ from equation 37.36, and then correlate M_t and t to get a release profile This solution is based on pseudosteady state assumption and is generally applicable for $C_0 > 3C_s$.

37.4.4.4 Analytical Solution for a Sphere with Dispersed Solute ($C_0 > C_s$) in a Sink [42]

$$M_t = \frac{4}{3}\pi R_0^3 C_0 - 4\pi\left[\frac{r^3 C_0}{3} + \frac{C_s r}{6}(R_0^2 + rR_0 - 2r^2)\right] \tag{37.37}$$

$$t = \frac{1}{6DC_sR_0}\left[C_0(R_0^3 + 2r^3 - 3R_0r^2)\right.$$
$$\left. + C_s\left(4r^2R_0 + R_0^3\ln\frac{R_0}{r} - R_0^3 - R_0^2r - 2r^3\right)\right] \tag{37.38}$$

where R_0 is the radius of the sphere, r is dispersed drug moving front. Using the same approach given in the case of 1D cylinder a correlation between M_t and t is obtained. This solution is based on pseudosteady state assumption and is generally applicable for $C_0 > 3C_s$.

37.4.4.5 Analytical Solution for a 2D Tablet with Dispersed Solute ($C_0 > C_s$) in a Sink [44]

$$M_t = 2C_0\pi[H(R^2 - r^2) + zr^2] \tag{37.39}$$

where R is radius and H is half thickness, C_0 is initial drug loading, and r and z are the moving front of dispersed drug in the radial and the axial directions, respectively. They are given as follows

$$z = \sqrt{\frac{2D_a}{D_r}\left[\frac{r^2}{2}\ln\frac{r}{R} + \frac{R^2 - r^2}{4}\right]} \tag{37.40}$$

$$t(r) = \frac{C_0}{C_sD_r}\left[\frac{r^2}{2}\ln\frac{r}{R} + \frac{R^2 - r^2}{4}\right] \tag{37.41}$$

For a given series of r such as $r = 0, r_1, \ldots, R$, solve for corresponding t and z from equations 37.40 and 37.41, and then substitute r and z into equation 37.39 to calculate M_t and correlate M_t with t. This solution is based on pseudosteady state assumption and is generally applicable for $C_0 \gg C_s$.

37.4.4.6 Assumptions, Applications, and Implementations of Models for Diffusion-Controlled Systems
Certain important assumptions were used in the derivation of the models presented above for membrane reservoir and matrix systems such as dissolution much faster than diffusion, constant material properties and no dimensional change during the complete release process. If these assumptions can be justified for a given delivery system and release process, the mechanistic models for diffusion-controlled release can be applied for prediction of release kinetics, sensitivity tests of formulation variables, parameter identification of dosage forms, and *in vitro–in vivo* correlation. Compared with regression models such as $M_t = kt^n$, mechanistic models can reveal more information about effects of important formulation variables on drug release kinetics, such as dimension (R, l, δ), geometry, material properties (D, C_s, K), and initial loading (C_0, C_m). It is noticed that transcendental expression and nonlinear equations are involved in the mechanistic models, which is cumbersome for daily usage. However several computer software packages for dosage form design such as AP-CAD and Simulation Plus have been developed to implement the computation tasks.

Mathematical models aforementioned for diffusion-controlled systems describe the general trends of the drug release process. However, one major assumption made is that drug dissolution is much faster than drug diffusion, which

means all or part of the drug, depending on the drug solubility, has dissolved in the beginning of the release process. As a phenomenological approximation, it is acceptable for quick dissolving drugs. While it may not be suitable for poorly water-soluble drugs and thus the drug dissolution process needs to be taken into account. Improved models have been proposed to embrace both drug diffusion and dissolution processes [45–49]. The governing equations describe diffusion- and dissolution-controlled drug release processes are presented as follows for a one-dimensional slab problem. The second term on the right-hand side of equation 37.42 depicts the change rate of concentration of dispersed drug due to drug dissolution that is described by equation 37.43 as an example.

$$\frac{\partial C_d}{\partial t} = D\frac{\partial^2 C_d}{\partial x^2} - \frac{\partial C_{sd}}{\partial t} \tag{37.42}$$

$$\frac{\partial C_{sd}}{\partial t} = -K_d(C_s - C_d) \tag{37.43}$$

where C_d is the concentration of dissolved drug, C_{sd} is the concentration of dispersed drug, and K_d is the dissolution rate coefficient of drug.

For the coupled partial differential equations of diffusion and dissolution, explicit exact or analytical solutions, such as those for diffusion-controlled systems, have not been found yet. Hence, numerical approaches such as finite element [47, 48] and finite difference [49] methods have been used to solve this mathematical problem.

37.4.5 Erosion-Controlled Systems

37.4.5.1 Surface (Heterogeneous) Erosion

Analytical Solutions for a 1D Slab, Cylinder, and Sphere [50]

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{aC_0}\right)^n \tag{37.44}$$

where k_0 is surface erosion constant (mg/(hr-cm^2)), a is the radius of a sphere or a cylinder or the half thickness of a slab, and $n = 1, 2$, and 3 for slab, cylinder, and sphere, respectively.

Analytical Solutions for a 2D Tablet [14]

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{r_0 C_0}\right)^2 \left(1 - \frac{2k_0 t}{l_0 C_0}\right) \tag{37.45}$$

where r_0 and l_0, respectively, are the initial radius and initial thickness of the tablet.

37.4.5.2 Bulk (Homogeneous) Erosion
There are few explicit analytical solutions available for bulk erosion problems. Lee developed a model for drug release from an erodible slab with consideration of simultaneous diffusion and erosion processes [51]. A more comprehensive model including erosion, diffusion, and chemical reaction was developed by Thombre and Himmelstein [52–54] for a slab in a sink. The model considered water, drug, acid generator, and acid with partial differential equations as follows:

$$\frac{\partial C_i}{\partial t} = \frac{\partial}{\partial x}\left(D_i(x,t)\frac{\partial C_i}{\partial x}\right) + v_i \quad i = A, B, C, E \tag{37.46}$$

where C_i and D_i, respectively, are the concentration and diffusion coefficient of the diffusing species and v_i is the net sum of synthesis and degradation rate of species. A, B, C, and E are water, acid generator, acid, and drug respectively. Concentration-dependent diffusion coefficient is expressed as

$$D_i = D_i^0 \exp\left[\frac{\mu(C_D^0 - C_D)}{C_D^0}\right], \quad i = A, B, C, E \tag{37.47}$$

Finite difference method was used to solve the equations with various initial and boundary conditions.

37.4.6 Ion Exchange-Controlled Systems

37.4.6.1 Drug Loading Onto Ion-Exchange Spheres [55]

$$F = \frac{3}{\lambda\theta_0}B_1\left[\sqrt{\tau}\exp\left(-\frac{1}{4\tau}\right) + \sqrt{\pi}\tau\,\mathrm{erf}\left(\frac{1}{2\sqrt{\tau}}\right) - 2\sqrt{\tau}\right] \tag{37.48}$$

where F is the fraction of drug loaded onto the sphere, $\lambda = 3V/(4\pi R^3)$, $\theta_0 = C_0/C_{\max}$, V is the external fluid volume, R is the radius of sphere, C_0 is the initial solute concentration in the external solution, and $C_{\max}$ is the maximum solute binding capacity of the ion-exchange spheres, $\tau = Dt/R^2$, D is diffusion coefficient of polymer, and B_1 is obtained by solving equation 37.49.

$$\frac{B_1}{\sqrt{\tau}} = (1-\alpha)B_1\gamma - \beta[1 + B_1\gamma] \\ \left\{\theta_0 - \frac{3B_1}{\lambda}\left[\sqrt{\tau}\exp\left(-\frac{1}{4\tau}\right) + \tau\gamma - 2\sqrt{\tau}\right]\right\} \tag{37.49}$$

where $\alpha = VRK_{des}/(DA)$, $\beta = VRK_{ads}C_{\max}/(DA)$, and $\gamma = \sqrt{\pi}\,\mathrm{erf}[1/(2\sqrt{\tau})]$, A is the surface area of sphere, K_{des} is the dissociation rate constant, and K_{ads} is the association rate constant.

37.4.6.2 Drug Release from Ion-Exchange Spheres [56]

$$\frac{M_\tau}{M_0} = 1 - \frac{3}{\theta_{RS}^0}\int_0^1\left(\theta_{s^+} + \frac{K\theta_{s^+}}{\theta_{Na^+} + K\theta_{s^+}}\right)x^2 dx \tag{37.50}$$

$$\frac{M_\tau}{M_0} = 1 - \frac{3}{\theta_{RS}^0}\int_0^1\left(\theta_{s^+} + \frac{\sqrt{K^2\theta_{s^+}^4 + 8K\theta_{s^+}^2\theta_{Ca^{2+}}} - K\theta_{s^+}^2}{4\theta_{Ca^{2+}}}\right)x^2 dx \tag{37.51}$$

where $M_0 = 4\pi R^3 C_{RS}^0/3$, C_{RS}^0 is the initial concentration of the drug in the sphere which is bound with binding sites of the ion-exchange polymer, K is Langmuir isotherm constant, $x = r/R$, C_m is maximum solute binding capacity of the ion-exchange sphere. $\theta_{s^+} = C_{s^+}/C_m$, $\theta_{Na^+} = C_{Na^+}/C_m$, and $\theta_{Ca^{2+}} = C_{Ca^{2+}}/C_m$, detailed numerical procedure can be found from the original reference [56].

37.4.7   Swelling-Controlled Systems

Swelling-controlled release involving solvent penetration into and drug release out from a polymeric matrix system, such as 1D planar and cylindrical devices, beads or 2D tablets, have been modeled and solved numerically [57–59]. The following presents governing equations for a 2D tablet in a perfect sink. Equations 37.52–37.54 describe the rates of solvent penetration, drug diffusion and dissolution, respectively. Dimensional change due to swelling and matrix erosion is expressed by equation 37.55, where the first term on the right-hand side represents the dimensional increase from swelling and the second term for polymer dissolution. Water concentration-dependent diffusion coefficients are expressed by equations 37.56 and 37.57.

$$\frac{\partial C_w}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(rD_w\frac{\partial C_w}{\partial r}\right) + \frac{\partial}{\partial z}\left(Dw\frac{\partial C_w}{\partial z}\right) \qquad (37.52)$$

$$\frac{\partial C_d}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(rD_d\frac{\partial C_d}{\partial r}\right) + \frac{\partial}{\partial z}\left(D_d\frac{\partial C_d}{\partial z}\right) - \frac{\partial C_{sd}}{\partial t} \quad (37.53)$$

$$\frac{\partial C_{sd}}{\partial t} = -K(C_s - C_d) \qquad (37.54)$$

$$z_t r_t^2 = 2\int_0^{z_t}\int_0^{r_t}\left[\frac{C_w(r,z,t)}{\rho_w} + \frac{C_d(r,z,t)}{\rho_d}\right]r\,dr\,dz$$
$$+ \frac{1}{2\pi\rho_p}\left(m_{p,0} - \int_0^t K_p A_s dt\right) \qquad (37.55)$$

$$D_w = D_w^{eq}\exp\left[-\beta_w\left(1 - \frac{C_w}{C_w^{eq}}\right)\right] \qquad (37.56)$$

$$D_d = D_d^{eq}\exp\left[-\beta_d\left(1 - \frac{C_w}{C_w^{eq}}\right)\right] \qquad (37.57)$$

where C_d is the concentration of dissolved drug, C_{sd} is the concentration of dispersed drug, C_s is the drug solubility, K is the dissolution rate coefficient of drug, C_w is the solvent concentration, D_d and D_w are the diffusion coefficients of drug and solvent, respectively, D_d^{eq} and D_d^{eq} are equivalent coefficients of drug and solvent at saturated solvent state, β_d and β_w are characteristic constants for drug and solvent, respectively. For initial drug loading below the drug solubility, the dissolution term in equation 37.53 can be omitted.

37.4.8   Osmotic Pressure-Controlled Systems

The basic equations for the osmotic component of drug release versus time from osmotic pressure-controlled systems are obtained by expressing the mass delivery rate (dm/dt) from the dosage form as a product of the total volumetric flow rate (dV/dt) of water into the interior of the device and the concentration of drug, C, in the solution or suspension being released. For several osmotic dosage forms, the expression for the volumetric flow rate is derived from irreversible thermodynamics.

37.4.8.1   Miniosmotic Pump   The pumping rate is given by the following equation:

$$\frac{dm_t}{dt} = \frac{A\theta\Delta\pi C}{h} \qquad (37.58)$$

where $\frac{dm_t}{dt}$ is the drug release rate, C is the concentration of the drug in the chamber, A is the surface area of the membrane, θ is the osmotic permeability, h is the membrane thickness, and $\Delta\pi$ is the osmotic pressure difference between the two solutions on either side of the membrane.

37.4.8.2   Elementary Osmotic Pump   The release of drug from this system is controlled by the solvent influx (water) across the semipermeable membrane whereby this influx of water carries the drug to the outside via the orifice. According to Theeuwes [60], the general expression for the solute delivery rate, $\frac{dm}{dt}$, obtained by pumping through the orifice can be described by

$$\frac{dm}{dt} = \frac{dV}{dt}C \qquad (37.59)$$

where C is the concentration of the compound in the dispensed fluid expressed per unit volume of the solution, and $\frac{dV}{dt}$ is the volume flux across the semipermeable membrane. The volume flux is described as follows:

$$\frac{dV}{dt} = \frac{A}{h}L_p(\sigma\Delta\pi - \Delta P) \qquad (37.60)$$

where $\Delta\pi$ and ΔP are the osmotic and hydrostatic pressure differences, respectively, between the inside and the outside of the device; L_p is the hydraulic permeability; σ is the reflection coefficient; A is the membrane area; and h is the membrane thickness. Since $\Delta\pi \gg \Delta P$ and the hydrostatic pressure inside the device is minimized as the delivery orifice increases, ΔP can be omitted from equation 37.60. Furthermore, when the osmotic pressure of the core, π, is significantly larger than the osmotic pressure of the dissolution fluid, equation 37.58 can be written as

$$\frac{dm}{dt} = \frac{A}{h}\theta\pi C \qquad (37.61)$$

where θ equals $L_p\sigma$.

Theeuwes [60] characterized the mode of release mathematically, namely, zero-order delivery rate and nonzero-order release, over the entire life of the system.

$$\left(\frac{dm}{dt}\right)_z = \frac{A}{h}\theta\pi_s S \qquad (37.62)$$

Equation 37.62 defines the zero-order release rate from $t = 0$ until a time t_z, where S is the solubility, and π_s is the osmotic pressure at saturation. The solubility in equation 37.62 replaces the concentration term, C, from time $t = 0$ to $t = t_z$ by assuming the rate of dissolution of a single compound within the system is much larger than the rate of pumping.

The nonzero-order release rate, as defined by Theeuwes [60], as a function of time, indicates a parabolic decline:

$$\frac{dm}{dt} = \frac{F_s S}{\left[1 + \frac{F_s}{V}(t - t_z)\right]^2} \qquad (37.63)$$

where F_s is the flux during the zero-order time and is related to the volume flux, F, into the device during nonzero release by

$$\frac{F_s}{F} = \frac{\pi_s}{\pi} = \frac{S}{C} \qquad (37.64)$$

Moreover, the nonzero release rate can be further written as a fraction of the zero-order rate:

$$\frac{dm}{dt} = \frac{\left(\frac{dm}{dt}\right)_z}{\left[1 + \frac{1}{SV}\left(\frac{dm}{dt}\right)_z(t - t_z)\right]^2} \qquad (37.65)$$

In order for the aforementioned equations defining the mode of drug release from an elementary osmotic device to be applicable, osmotic pumping has to be the sole mechanism of release. Therefore, the size of the orifice must be such that it is smaller than a maximum size to minimize the solute diffusion through the orifice. It is also imperative to have the orifice larger than a minimum size to reduce hydrostatic pressure inside the system. Hydrostatic pressure within the system will decrease the osmotic influx as well as it may cause an increase in the volume of the system.

The equations for the elementary osmotic pump represent the mass delivered per unit time due to the mechanism of osmotic pumping. In fact, the total mass delivered per unit time from such systems results from osmotic pumping, diffusion through the orifice, and diffusion through the membrane itself [60]. If diffusion through the orifice is negligible, we have

$$\left(\frac{dm}{dt}\right)_t = \left(\frac{dm}{dt}\right)_o + \left(\frac{dm}{dt}\right)_d \qquad (37.66)$$

where $\left(\frac{dm}{dt}\right)_0$ is the rate of release due to osmotic pumping, and $\left(\frac{dm}{dt}\right)_d$ is the release rate resulting from diffusion, as demonstrated by Zentner et al., for KCl release rates from controlled porosity osmotic tablet [61].

The total zero-order release rate during the steady state portion can then be expressed by

$$\left(\frac{dm}{dt}\right)_{t,z} = \frac{A}{h}(\theta\pi_s S + PS) \qquad (37.67)$$

where P is the permeability coefficient of the drug in the polymer. In a similar fashion, the total nonzero-order rate can be given as

$$\frac{dm}{dt} = \frac{F_s}{S}C^2 + \frac{A}{h}PC \qquad (37.68)$$

However, to express $\frac{dm}{dt}$ as a function of time, the concentration, C, inside the system must be expressed as a function of time.

37.4.8.3 Semipermeable Membrane containing Micropores

Many researchers have shown that besides simple diffusion, osmotic pumping mechanism contributes significantly to the release of drugs from film-coated preparations [30, 62]. The zero-order steady state release for such systems under the influence of zero hydrostatic pressure can be expressed by equation 37.67. According to Lindstedt et al. [63], the equations presented by Theeuwes cannot describe osmotic pumping as contributing to the mechanism of drug release. They argue that since during zero-order release a steady state is maintained with no volume expansion of the tablets, the net bulk volume flux through the membrane must be zero. It therefore follows that release of drugs would be independent of osmotic pressure and be exclusively diffusive. Therefore, they presented the solute flux, F_s, as follows:

$$F_s = CF_v(1 - \sigma) + \frac{A}{h}P_s\Delta C \qquad (37.69)$$

where

$$F_v = \frac{A}{h}L_p(\Delta P - \Delta\pi) \qquad (37.70)$$

In order to remove the limitation of zero net bulk volume flux through the membrane, the membrane was considered to consist of two areas with different reflectivity. The release rate, Q, is the sum of the solute fluxes in areas 1 and 2:

$$Q = F_{s1} + F_{s2} = (1 - \sigma_1)F_{v1}C_1 + (1 - \sigma_2)F_{v2}C_2 + D_s \qquad (37.71)$$

where $F_{v1} + F_{v2} = 0$ at steady state, since they are equal and in opposite direction, and

$$D_s = \left(\frac{A_1}{h_1}P_{s1} + \frac{A_2}{h_2}P_{s2}\right)\Delta C \qquad (37.72)$$

is the diffusional release through areas 1 and 2. Equation 37.70 reduces to

$$Q = (1-\sigma_2)(-F_{v1})C_s + D_s \qquad (37.73)$$

The assumptions were that the bulk volume flux in area 1 is directed into the tablet and C_1 is zero and C_2 is equal to the concentration in the core, C_s, and $-F_{v1} = F_{v2}$. Therefore,

$$Q = (1-\sigma_2)\frac{A_1}{h_1}L_{p1}(\sigma_1\Delta\pi - \Delta P)C_s + D_s \qquad (37.74)$$

It was further inferred that the low-reflective area is very small compared to the total area. From this inference, it was concluded that the release rate is calculated from

$$Q = (1-\sigma_2)\frac{A}{h}L_{p1}(\sigma_1\Delta\pi - \Delta P)C_s + D_s \qquad (37.75)$$

If ΔP is assumed negligible and $\sigma_2 < \frac{\Delta P}{\Delta\pi}$ since the volume flux is directed out of the tablet and $F_{v2} > 0$, equation 37.74 is reduced to

$$Q = \frac{A}{h}L_{p1}\sigma_1\Delta\pi C_s + D_s \qquad (37.76)$$

37.4.8.4 Push–Pull Osmotic Pump

Drug release from this system is controlled by the solvent influx (water) across the semipermeable membrane into the tablet core and resulting simultaneous push action from the swelling layer. According to Swanson et al. [19], the general expression for the solute delivery rate, $\frac{dm}{dt}$, obtained by pumping through the orifice can be simply modified from equation 37.59, is given as

$$\frac{dm}{dt} = \frac{dV}{dt}C_s \qquad (37.77)$$

where C_s is the concentration of the drug in suspension in the dispensed fluid expressed per unit volume of the solution.

The osmotic volume flow into the osmotic compartment is described as

$$(dV/dt)_o = k/h A_p(H) \pi_p(H) \qquad (37.78)$$

where k is the osmotic membrane permeability coefficient, h is the membrane thickness, A_p is the area of the push compartment, and π_p is the imbibition pressure of the push compartment. An additional consideration for the push–pull system is the osmotic volume imbibition flow into the drug compartment is described as

$$(dV/dt)_D = k/h(A - A_p(H))\pi_D(H) \qquad (37.79)$$

where A is the total area of the dosage form and π_D is the imbibition pressure in the drug compartment.

The total volume flow from the dosage form is the summation of the osmotic flow into the osmotic compartment and the osmotic imbibition flow into the drug compartment, as described below:

$$dV/dt = (dV/dt)_o + (dV/dt)_D \qquad (37.80)$$

The concentration of dispensed drug from the dosage form can be expressed as

$$C_s = F_D C_o \qquad (37.81)$$

where F_D is the fraction of drug in the drug compartment and C_o is the concentration of solids dispensed from the dosage form.

Substituting equations 37.78 and 37.79 into equation 37.80, and substituting equations 37.80 and 37.81 into equations 37.77, the total drug release is given as

$$dm/dt = [k/h A_p(H)\pi_p(H)] + [k/h(A - A_p(H))\pi_D(H)]F_D C_o \qquad (37.82)$$

37.4.8.5 Polymer Drug Matrix Systems

The osmotic release mechanism from the polymer matrix-type of device is expressed by the model developed by Wright et al. [31]:

$$\frac{dm}{dt} = \frac{3\alpha\rho\phi\Delta\Pi S_o L_p}{d(\lambda_b^3 - 1)\left[1 - \left(\frac{6\phi}{\pi}\right)^{1/3}\right]} \qquad (37.83)$$

where $\frac{dm}{dt}$ is the zero-order release rate, α is a constant of proportionality, ρ is the solid density of the drug, ϕ is the volumetric loading of the drug, $\Delta\Pi$ is the osmotic pressure difference between the capsule solution and the external medium, S_o is the surface area of the device, L_p is the polymer hydraulic permeability, d is the particle size, and λ_b is the polymer extension ratio at rupture. In deriving this model, it was assumed that the drug particles were spherical and were released by osmotic rupturing. Also, the matrix was considered to consist of two zones, a ruptured capsule zone separated from a zone of water imbibing capsules by a moving water front.

Schirrer et al. [64] developed the following model by assuming that the water flow into a capsule per unit time per unit area at the capsule–polymer interface is constant for a given osmotic agent and is directly proportional to the volumetric loading:

$$\frac{1}{Q_o}\frac{dQ}{dt} = \frac{S_o\Phi}{V_o\phi^{1/3}3(\lambda_b - 1)} \qquad (37.84)$$

where Φ is the water flow into a capsule per unit time per unit area at the capsule–polymer interface, Q is the volume of salt released, Q_o is the initial volume of salt in the matrix, and V_o is the initial volume of the device. The rate of mass drug release is defined as

$$\frac{dm}{dt} = \rho \frac{dQ}{dt} \qquad (37.85)$$

According to Amsden et al. [65], these models are limited because of their dependence on drug density and undefined constant of proportionality. Further, it is believed that at low drug loading a portion of the drug will be released by dissolution and diffusion. Based on these premises, a model was developed. Paramount to this model is the assumption that the solutes that remain in a capsule after it ruptures were released by diffusion and not convection. Also, the model accounts for capsule swelling and that not all capsules in the monolith were ruptured. The model is expressed as follows:

$$\frac{dm}{dt} = \frac{8\pi\{f(1-F_D)\phi\}^{2/3} S_o L_p E\omega C_{sat}(\lambda_b^3 - 1)}{3dt_b^*} \qquad (37.86)$$

where f is the mass fraction of material remaining after the initial burst that is released by osmotic pressure induced polymer rupturing, $f(1-F_D)$ is the mass fraction of particles in the monolith released by rupturing, F_D represents the mass fraction of particles released by dissolution and diffusion, S_o is as defined previously, and E is the Young's modulus of elasticity.

$$f = 1 - \exp\left(-\frac{\pi}{4}\left(\frac{h_c}{h}\right)^2\right) \qquad (37.87)$$

where h_c and h are the critical wall thickness for rupturing to occur and the average wall thickness, respectively.

$$C_s\omega = C_s \exp\left[\frac{-DA_o(t_b)}{V_f h}\right] \qquad (37.88)$$

where D is the drug diffusivity, A_o is the cross-sectional area of the channel, C_s is the agent saturation concentration, V_f is the capsule volume after rupture, t_b is the time require for sufficient water to flow into a capsule to induce rupture, and

$$t_b^* = \frac{4L_p E t}{r_o^2} \qquad (37.89)$$

where r_o is the initial particle radius.

37.5 CASE STUDY

37.5.1 Background for Example 37.1

A controlled release formulation was required for a drug to reduce the high dosing frequency related to its short half-life (2.5–3.8 h) and to reduce C_{max}-related side effects. The projected dose strengths were 2 and 10 mg. The drug

solubility was greater than 100 mg/mL at pH 4. The dose–solubility map indicated that an osmotic dosage form based on asymmetric membrane technology would be suitable for this drug [8].

EXAMPLE 37.1

An asymmetric membrane tablet core is composed of 10 mg of a highly soluble drug and mannitol ($\pi = 38$ atm) as osmogen. This core tablet is coated with a 15% w/w semipermeable coating composed of cellulose acetate, polyethylene glycol, acetone, and water. The drug release into various media (distilled water, sucrose solutions, and saturated drug solutions) is listed in Tables 37.2 and 37.3.
(a) What are the osmotic pressures of the sucrose solutions in Table 37.2?
(b) What osmotic pressure will shut down the osmotic release mechanism for this AM tablet?
(c) What percentage of the release mechanism is due to diffusion?

Solution
(a) The osmotic pressures for sucrose solutions can be located in the *Handbook of Chemistry and*

TABLE 37.2 Drug Release from Asymmetric Membrane Tablet into Media Containing Varying Sucrose Concentrations

	% Drug Dissolved				
Time (h)	Distilled Water	216.2 g/L Sucrose	363.7 g/L Sucrose	470.6 g/L Sucrose	601 g/L Sucrose
0	0	0	0	0	0
2	10.5	7.1	5.0	2.1	0.95
6	32.1	21.5	14.8	6.2	3.7
12	60.8	45.2	30.0	12.4	5.4
18	81.7	63.7	44.9	18.4	7.1
24	99.9	88.3	59.6	24.7	6.4

TABLE 37.3 Drug Release from Asymmetric Membrane Tablet into Saturated Drug Solution Media

Time (h)	Π Release Shut-Off	Diffusional Release Shut-Off (D)	Cumulative Release (Π + D)	Actual Drug Release
0	0	0	0	0
2	5.1	13.1	18.2	12.8
6	3.7	40.9	44.6	—
8	—	—	—	52.2
16	—	—	—	84.5
18	7.1	86.1	93.2	—
24	6.4	91.8	98.2	93.9

% Drug dissolved = milligram released/total milligram in tablet * 100%.
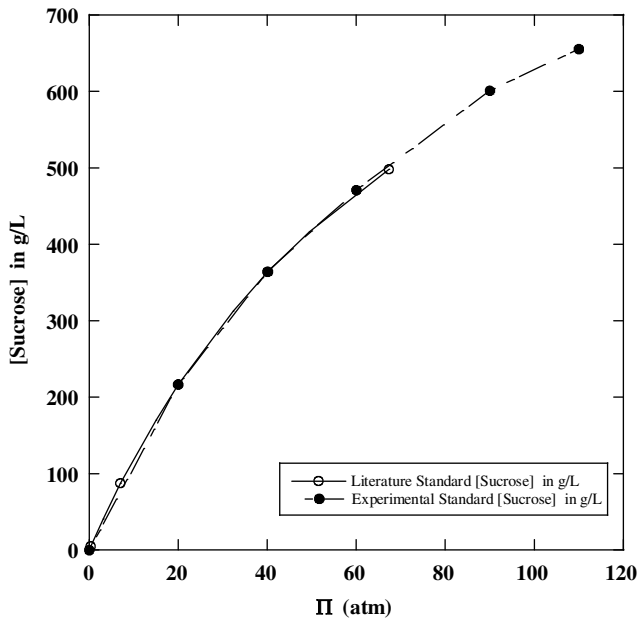
FIGURE 37.15 Calibration curve for sucrose solutions prepared to produce osmotic pressures ranging from 0 to 100 atm.

Physics [66]. These literature standard values are plotted in Figure 37.15, which are similar to experimental results reported by am Ende and Miller [67], and demonstrate consistency with accepted standards. The sucrose solution concentrations of 0, 216, 364, 471, and 601 g/L have osmotic pressures of 0, 20, 40, 60, and 90 atm, respectively.

(b) The drug release profiles from Table 37.2 are plotted in Figure 37.16, and slopes for the initial 0–60% release are
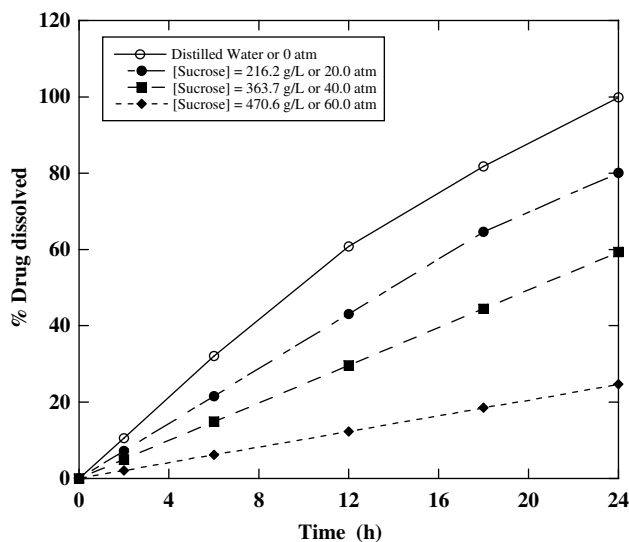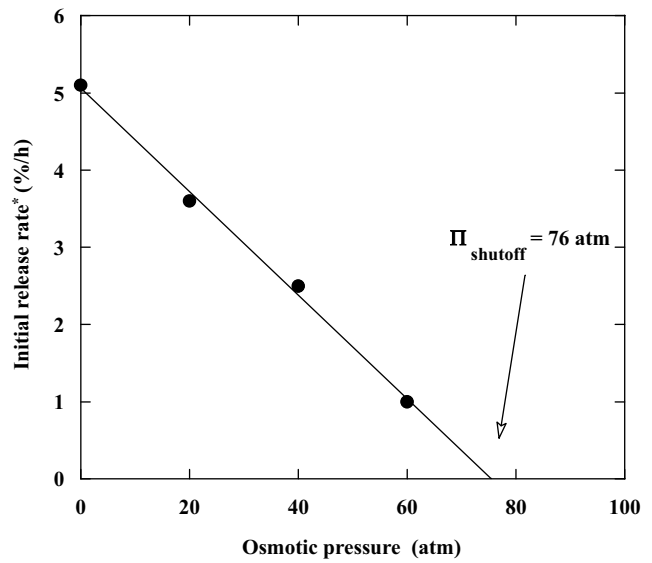

FIGURE 37.16 Drug release from AM tablets into varying concentrations of sucrose solutions, and associated osmotic pressures determined in list item (a).

FIGURE 37.17 Initial drug release rates from AM tablets as a function of media osmotic pressure.

*Initial release rate determined by linear regression over 0 – 60% release profile.

calculated using linear fits. The initial release rates as a function of sucrose media osmotic pressure are 5.1, 3.6, 2.5, 1.0 %/h for 0, 20, 40, and 60 atm, respectively. These resulting initial release rates are then plotted as a function of media osmotic pressure, as shown in Figure 37.17. The
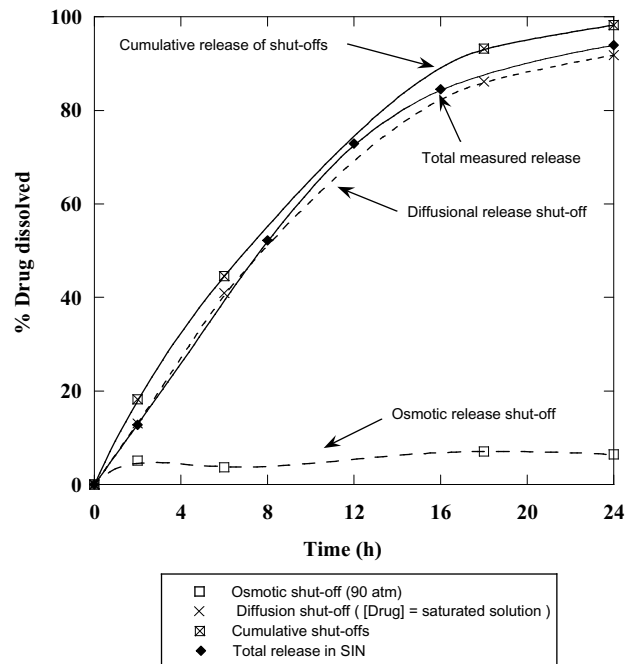

FIGURE 37.18 Drug release from AM tablets into media with osmotic pressure in excess of the determined shut-off, for example, 90 atm, and into media saturated with drug to determine diffusional shut-off. [54] Reprinted from Ref. 67, Copyright (2007), with permission from Springer.
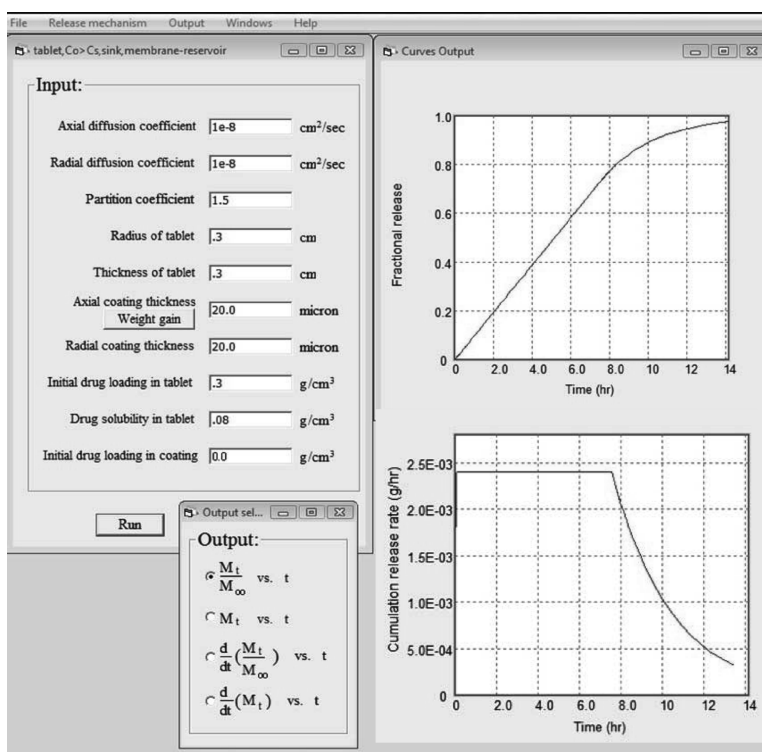
FIGURE 37.19   Fractional drug release profile (top right) and release rate (bottom right) of a 2D membrane-coated tablet predicted by equations 37.17 and 37.23 and computed by AP-CAD software package. In this example, identical axial and radial coating thickness and diffusion coefficients were used (see the input parameter values on the left panel).

media osmotic pressure that would shut down drug release is determined by extrapolation to be 76 atm.

(c) The drug release profiles listed in Table 37.3 are plotted in Figure 37.18. The diffusional contribution is approximately 5% of the total drug release, as demonstrated when all osmotic release is shut-off by saturating the media with drug.

EXAMPLE 37.2

Compressed tablets of a model drug were coated with ethylcellulose and 20% diethyl phthalate, a plasticizer. The tablet that is 0.6 cm in diameter and 0.3 cm in thickness contains 30% drug. The drug solubility in the tablet was estimated to be 0.1 g/cm^3. The drug diffusion coefficient in the coating was evaluated previously to be 1×10^{-8} cm^2/s by fitting experimental release curves using a two-dimensional tablet model of membrane–reservoir system.

(a) Calculate fractional release and release rate of a tablet, and 20 μm coating thickness;

(b) If a zero-order release up to 12 h is desirable, what should be the coating thickness?

(c) What is the release rate at this coating thickness?

Solution

(a) The fractional release and release rate were computed based on equations (37.17), (37.18), and (37.23) and plotted in Figure 37.19.

(b) By implementing computer simulation using various coating thickness, an optimal thickness of 31.5 μm was found to give zero-order release up to 12 h.

(c) With this coating thickness, the tablet provides a release rate of 1.5 mg/h.

EXAMPLE 37.3

Inert matrix tablets of two model drugs of different solubilities were made by compression of drug-excipient matrix granules. The granules were prepared by using acrylic polymer dispersion (Eudragit® FS 30D) as the granulating agent. The tablet has a diameter of 0.6 cm and a thickness of 0.3 cm and contains 30% drug. The solubility of drug A in the tablet was estimated to be 0.1 g/cm^3 and drug B 0.01 g/cm^3. The drug diffusion coefficient in the coating was evaluated previously to be 8×10^{-7} cm^2/s by fitting experimental release curves of tablets containing a low initial drug loading ($C_0 < C_s$) using the two-dimensional tablet model
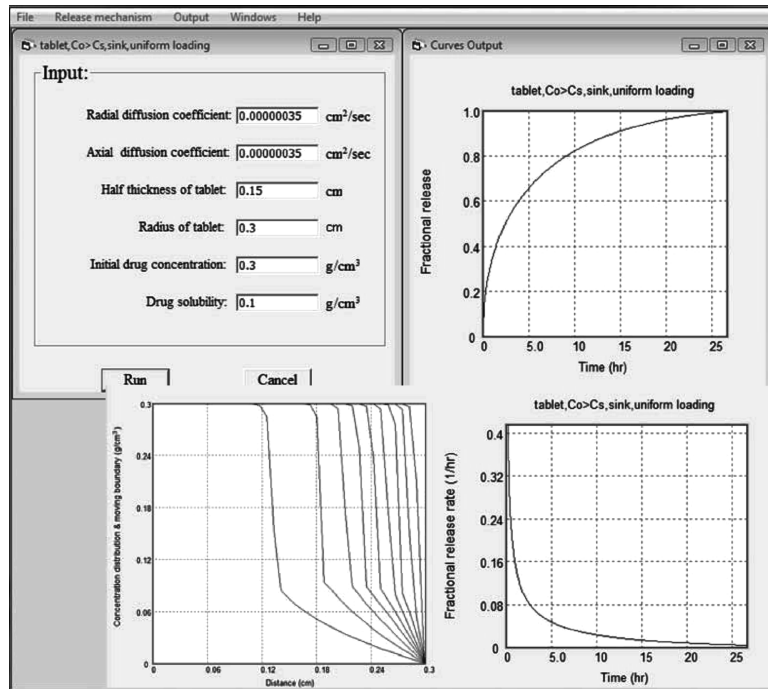
FIGURE 37.20   Fractional release (top right), release rate (bottom right), and concentration profiles at various times (bottom left) of a matrix tablet containing a water-soluble drug with the dimension, initial drug loading, and diffusion coefficient indicated in the left panel.
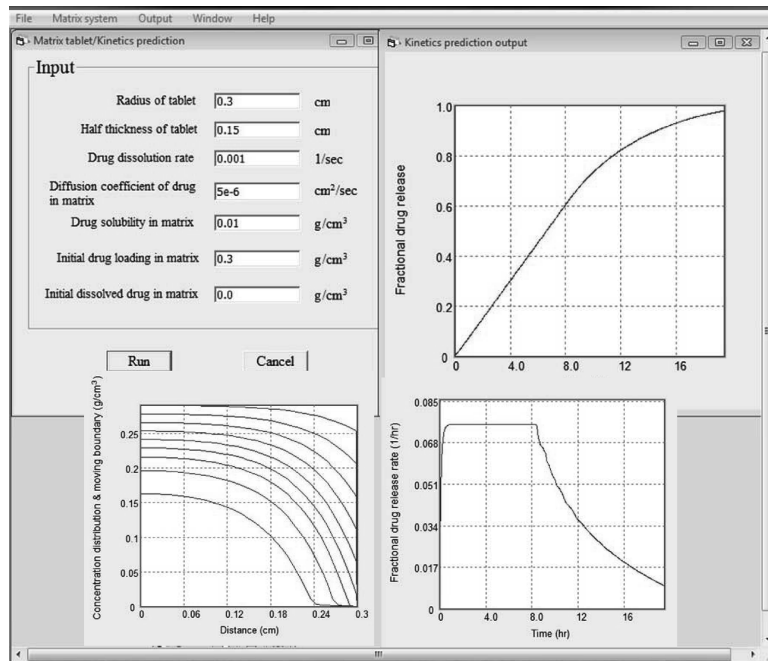

FIGURE 37.21   Fractional release (top right), release rate (bottom right), and concentration profiles at various times (bottom left) of a matrix tablet containing a poorly water-soluble drug with the dimension, initial drug loading, diffusion coefficient, and drug dissolution rate constant indicated in the left panel.

(equation 37.31). How would drug solubility and dissolution influence the rate and release profiles?

Solution

Because the tablets contained initial drug loading greater than drug solubility, analytical solutions for 2D matrix tablets with $C_0 > C_s$ (equations 37.39–37.41) were used to compute drug release profiles of drug A. It is reasonable to assume the dissolution of drug A is much faster than diffusion. The results are presented in Figure 37.20. For drug B, its solubility is one-tenth of that of drug A, the model with a drug dissolution term (equation 37.53) was applied and solved numerically using AP-CAD software package. The results are shown in Figure 37.21. Comparing the results in Figure 37.20 with those in Figure 37.21, it is seen that the release profile becomes more linear when drug dissolution becomes more significant.

37.6 CONCLUSIONS

Controlled release technology and the design of controlled release dosage forms were discussed in this chapter. The equations governing the rate of drug release have been derived based on the dominant mechanism of drug release, for example, Fick's second law of diffusion for nonerodible monolithic and reservoir devices and irreversible thermodynamics for certain osmotic systems. In addition to physicochemical factors, biopharmaceutical factors such as mechanism of drug absorption and gastrointestinal transit of the dosage form must be considered in the design of oral controlled release dosage forms.

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