Kirk-Othmer Encyclopedia of Chemical Technology.

CONTROLLED RELEASE TECHNOLOGY, PHARMACEUTICAL

Controlled-release dosage forms enhance the safety, efficacy, and reliability of drug therapy. They regulate the drug release rate to control drug action and reduce the frequency of drug administration to encourage patients to comply with dosing instructions. Conventional dosage forms often lead to wide swings in serum–drug concentrations. Most of the drug content is released soon after administration, causing drug levels in the body to rise rapidly, peak, and then decline sharply. For drugs whose actions correlate with their serum-drug concentration, these sharp fluctuations often cause unacceptable side effects at the peaks, followed by inadequate therapy at the troughs (Fig. 1). Administering smaller doses at more frequent intervals can damp concentration fluctuations, preventing over- and underdosing, but the inconvenience may cause patients to skip or delay doses, degrading efficacy. Compliance, measured as the percentage of patients taking 95% to 105% of prescribed oral medications, decreased from 67% with once-a-day regimens to 22% with four-times-a-day regimens (1). These difficulties are especially pronounced with drugs that have short half-lives and a narrow range of safe and effective concentrations. Precisely controlled release is particularly valuable for such agents (see Drug delivery systems).

The term controlled release technology generally refers to a variety of methods used to exert various degrees of control over drug release. The U.S. Food and Drug Administration (FDA) defines controlled release dosage forms as those formulations designed to release active ingredient(s) at rates that differ significantly from their corresponding immediate release forms (2). The indexing system of *Index Medicus* supports this broad definition by classifying these dosage forms as delayed-action preparations, and *Excerpta Medica* uses the index term sustained release preparations. The pharmaceutical literature contains a profusion of terms, including delayed-action, extended action, gradual release, prolonged release, protracted release, slow release, sustained release, depot, retard, and timed-release dosage forms, all emphasizing an increased duration of action (3).

To avoid confusion, several researchers have incorporated therapeutic intention into the definition of controlled release (4–7). Thus, controlled-release pharmaceuticals release drugs *in vivo* according to a predictable, therapeutically rational, programmed rate to achieve the optimal drug concentration in the minimal time (4). Specification by release rate complements specification by quantity; jointly considered, they fix the duration of drug release. Therefore, the drug's duration of action can become a design property of a controlled release dosage form rather than an inherent pharmacokinetic property of the drug molecule.

Under this more precise definition, controlled release drug delivery not only provides a predictable, patterned action, but controls the rate of drug release for a predetermined period. Controlled release systems deliver drugs at a constant rate (zero-order release), a predictably constant declining rate (first-order release), or some other specified rate or pattern of rates to achieve the optimal serum-drug concentrations. In many clinical situations, a constant serum–drug level is desirable and zero-order drug delivery systems are appropriate. However, the body responds to certain conditions, eg, heart rhythm disorders and hormone deficiencies, and to certain substances according to strong circadian or other nonconstant patterns (8, 9); in these cases, patterned or self-regulated delivery can enhance therapeutic efficacy. For a review of the pharmacokinetic and pharmacodynamic basis of controlled drug delivery, see Reference 10.

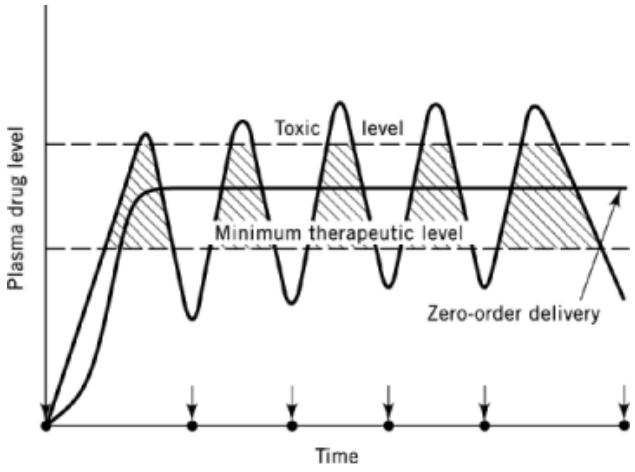

Fig. 1. Zero-order (controlled) delivery versus first-order (immediate-release) delivery (repeated administration). In zero-order delivery, the drug is released at a constant rate within the therapeutic range. In first-order delivery, each administration of the drug (represented by ↓) causes serum-drug concentrations to rise to a peak and then decline sharply, resulting in over- and underdosing.Courtesy of ALZA Corp., Palo Alto, Calif.

Most controlled release dosage forms administer drug according to their design, whether conceptually simple, eg, a fixed release rate for a fixed amount of time, or complex, eg, several different rates for different amounts of time. Alternatively, closed-loop systems contain a sensor to monitor drug concentration or to administer drug according to a biological need (11).

Although the field of controlled release technology is only a few decades old, the late 1980s and early 1990s have seen an explosion in research aimed at creating new drug delivery systems (12) as well as numerous publications that discuss controlled release. In addition, journals and societies have been established that are devoted to the advancement of drug delivery systems.

A principal focus of research and development in controlled release technology is the delivery of proteins and peptides (13, 14), owing in part to biotechnological advances that allow the large-scale production of therapeutically important natural proteins, such as insulin [9004-10-8], and analogues. Because these substances tend to be broken down and inactivated in the gastrointestinal tract before they can be absorbed in therapeutic amounts, researchers are looking into enhancing oral delivery, eg, using permeation enhancers to increase absorption, as well as using less conventional delivery sites and routes of administration including the rectum, skin, oral cavity, nose, eyes, lungs, uterus, and vagina.

1. Delivery Sites, Portals, and Systems

Controlled release pharmaceuticals provide local or systemic treatment and differ in design depending on their use and route of administration. The potential sites for controlled delivery of therapeutic agents and some of the systems designed for those sites merit discussion.

1.1. Gastrointestinal Tract

The gastrointestinal (GI) tract is the most familiar and widely used portal for drug delivery, largely because of the ease with which medications can be administered.

1.1.1. Stomach, Small Intestine, and Colon

These organs provide accessible portals for local delivery of therapeutic agents, including laxatives, antidiarrheal medications, gastroprotective agents such as sucralfate [54182-58-0], and anthelmintics.

They also are important portals for systemic therapy. However, many variables can influence drug dissolution and absorption in these areas, including rate of gastric emptying, intestinal motility, mass and pH of intestinal contents, and condition of the absorbing surfaces (15–17). These variables, in turn, can be affected by the patient's disease, posture, and eating habits, and even by such aspects of the treatment as the timing of doses (11).

Dosage forms have been designed to optimize the localized actions or systemic absorption of drugs by targeting specific GI tract areas for drug release. Many dosage forms have pH-sensitive enteric coatings that prevent digestion in the stomach, reducing local irritation and ensuring that the drug core does not dissolve until it reaches the small intestine or colon. Numerous pH-sensitive, polymer-coated oral preparations deliver 5-aminosalicylic acid [89-57-6] to the colon to treat chronic inflammatory bowel disease. Marketed controlled-release preparations of 5-aminosalicylic acid include Asacol (available in the United Kingdom and Sweden) and Claversal (available in Denmark), coated with Eudragit S [117385-53-2] and Eudragit L [76688-80-7], respectively, and Pentasa (available in Denmark), which is coated with ethylcellulose [9004-57-3] (18, 19). A different approach to colon-targeted delivery is the use of Eudragit RS [121381-94-0] microspheres loaded with 5-aminosalicylic acid and incorporated within a colon-targeted device (20). Another colon-targeted system in research is a miniature osmotic pump, the Osmet (ALZA Corp.) delivery system, coated with a substance insoluble in low pH gastric fluids but soluble in the higher pH of the colon. The system delivers the drug approximately 2 to 4 h after passing through the stomach (21). A colon-targeted dosage form with multiple small osmotic systems loaded in a gelatin capsule delivers beclomethasone dipropionate [5534-09-8]. *In vitro*, the system incorporates a 12-h delay before delivering the drug for 3 h at an increasing rate and then for 20 h at a constant rate (22).

Permeation enhancers are used to improve absorption through the gastric mucosa. For example, oral delivery of insulin (mol wt = 6000) has been reported from a water-in-oil- emulsion containing lecithin, nonesterified fatty acids, cholesterol [57-88-5], and the protease inhibitor aprotinin [9087-70-1] (23).

The design and fabrication of numerous commercially available controlled-release oral dosage forms have been widely reviewed (17, 24–27).

1.1.2. Rectum

Local treatment of conditions and diseases of the rectum, including hemorrhoids and local inflammation, usually involves drug-containing suppositories or enemas.

As a portal for systemic delivery, the rectum has advantages over other sites in the GI tract; for example, bypassing the upper gastrointestinal tract and the liver avoids enzymatic degradation and first-pass metabolism, in which some of the drug is lost during its first pass through the GI tract and the liver. Drugs delivered rectally include steroids, sedatives, antihistamines, tranquilizers, antiemetics, and headache medications. Poly(vinyl alcohol) hydrogels for rectal administration have been designed to increase the bioavailability of propranolol [525-66-6] (28). Numerous drugs, including antipyrine [60-80-0], theophylline [58-55-9], propranolol, and nifedipine [21829-25-4], have been administered via the rectum with the Osmet module (29). An oral controlled-release morphine [57-27-2] tablet (MSContin) has been enclosed in a gelatin capsule and given as a rectal suppository to terminally ill patients who cannot tolerate oral medications (30). Controlled-release morphine in a hydrogel has been tested in normal volunteers (31), and slow-release indomethacin [53-86-1] suppositories have been given to relieve postoperative pain after orthopedic surgery (32).

1.2. Skin

The skin's unique molecular transport and barrier properties pose a challenge for transdermal drug delivery. Diffusion of drugs through the stratum corneum, the outer layer primarily responsible for the skin's limited permeability, varies by drug, by skin site, and among individuals. Until recently, virtually all drugs applied to skin were topical treatments.

Now, however, dosage forms that use the skin as a reliable portal for systemic drug delivery are available. Despite skin's limited permeability, the transdermal route is appealing because it avoids first-pass metabolism and minimizes the dose necessary to achieve therapeutic serum-drug levels. To be suitable for systemic therapy from a transdermal delivery system, a drug must be nonirritating and potent and have a short half-life, low molecular weight, and low melting point (33). Creams and ointments that provide systemic drug delivery, such as estradiol [50-28-2] and progesterone [57-83-0] (Oestrogel and Progestogel) for menopausal symptoms, are messy and difficult to administer in consistent amounts, and have unpredictable absorption rates.

Passive transdermal delivery systems on the market tend to be either matrix or membrane controlled. In matrix devices, the structural and molecular characteristics of the drug-polymer matrix determine drug release. Examples of polymer matrix-controlled diffusional systems for angina prophylaxis include Nitro-Dur and Nitrodisc, which provide transdermal delivery of nitroglycerin [55-63-0], and Frandol, a tape that releases isosorbide dinitrate [87-33-2]. Matrix diffusional systems have been used for delivering drugs with a wide therapeutic index.

Membrane-controlled diffusional systems enhance transdermal delivery by increasing control over serum–drug concentrations. They are particularly suitable for delivering compounds with a narrow therapeutic index. Because it is predominantly the membrane rather than the skin that governs drug release, the system reduces the problem of differing skin absorption rates. Commercially available membrane-controlled systems are typically administered from once a day to once a week and include Transderm-Nitro (nitroglycerin) for angina, Catapres-TTS (clonidine [4205-90-7]) for hypertension, Estraderm (estradiol) for menopausal symptoms, Transderm Scōp (scopolamine [51-34-3]) for motion sickness, and Duragesic (fentanyl [437-38-7]) for severe chronic pain requiring narcotics. These were introduced by ALZA Corp.

Various strategies are available to overcome the barrier properties of skin. Permeation enhancers can facilitate transdermal transport of drugs with low percutaneous flux. Estraderm, for example, delivers 0.3 mL of the permeation enhancer ethanol [64-17-5] for every 4 mg estradiol. Other permeation enhancers, including Azone [59227-89-3] and esters of saturated and unsaturated fatty acids, are in experimental use (34). Numerous potential permeation enhancers have been reported in the literature, including various alcohols, propylene glycol [57-55-6], and sodium lauryl sulfate [151-21-3] (33). Ultrasound (phonophoresis), electrical charge (electrotransport), and bioconvertible drug precursors, or pro-drugs, also are being investigated as ways to enhance drug transport through the skin (28).

1.3. Oral Cavity

The oral mucous membranes are subject to many diseases and chronic lesions, for which a variety of local treatments are available. Rinses and swabbed liquids are effective but must be applied frequently. Slow-dissolving lozenges, eg, Mycostatin, which delivers the antifungal antibiotic nystatin [1400-61-9], and chewing gum that delivers the antifungal miconazole [22916-47-8] (35), can sustain drug release in the oral cavity, reducing the need for frequent reapplication (36). Incorporation of drugs in inert polymerized acrylics prolongs drug delivery for several days. The Actisite (ALZA Corp.) periodontal fiber, with an ethylene–vinyl acetate copolymer, is designed for placement in the periodontal pocket, where it releases tetracycline hydrochloride [64-75-5] at a controlled rate for 10 days for treatment of periodontal disease. This system is awaiting market approval from the U.S. Food and Drug Administration. Intrapocket devices in development include cellulose-based hollow fibers, poly(ethyl methacrylate) [9003-42-3] strips, and ethylcellulose [9004-57-3] slabs that release

chlorhexidine gluconate [18472-51-0], metronidazole [443-48-1], minocycline [10118-90-8], and tetracycline [60-54-8]. Biodegradable intrapocket devices are also being tested clinically, eg, a cross-linked protein matrix delivers chlorhexidine [55-56-1] for up to 90 h (37), and poly(hydroxybutyric acid) [52352-27-9] strips deliver tetracycline or metronidazole for approximately 4 days (38). Other degradable delivery devices are being developed, but no clinical data are available yet (30).

Oral mucosal membranes provide a port for systemic therapy as well. Nitroglycerin sublingual tablets (Nitrostat) abort acute angina attacks; methyl-testosterone [58-18-4] buccal tablets (Android 5) are indicated for testosterone [58-22-0] replacement therapy (39); and nicotine [54-11-5] gum (Nicorette) aids in smoking cessation.

1.4. Nose

Intranasal delivery of drugs, such as antihistamines and decongestants, to alleviate local symptoms is common. There is now increasing interest in using the nose as a portal for systemic drug delivery, particularly for the delivery of proteins and peptides (40). Several classes of nasal permeation enhancers have been investigated, including surfactants, such as polyoxyethylene-9-lauryl ether [977007-24-1], bile salts and bile salt derivatives, such as sodium taurodihydrofusidate [42907-93-7], and mucoadhesive systems (41). Controlled delivery from bioadhesive microspheres has been proposed to avoid the rapid clearance of therapeutic agents by nasal cilia. Such microspheres would have to be larger than 10 to 15 μm in order to remain in the nasal cavity and not travel to the lungs (42).

1.5. Eye

The eye is an easily accessible but problematic portal for local therapy, that is, for eye diseases or trauma, because constant tear flow and lacrimal–nasal drainage result in extensive drug loss. The most familiar local treatments (eye drops, suspensions, and ointments) require frequent application to achieve steady-state drug levels (43). Numerous approaches enhance local treatment by improving corneal permeation with ionophores, ion pairs, liposomes, or pro-drugs, or by reducing loss from drainage with viscosity-enhancing agents, suspensions, emulsions, ointments, or erodible or nonerodible matrices (44–48). The Ocusert (ALZA Corp.) ocular therapeutic system for the release of pilocarpine [92-13-7] to treat glaucoma was the first diffusion-controlled ocular system marketed (1975) (49). The Ocusert system is a small, flexible oval unit composed of a drug reservoir surrounded by a biocompatible ethylene–vinyl acetate [24937-78-8] membrane (Fig. 2). The patient inserts the system under the eyelid, where it releases the drug for seven days. The Lacrisert system, a rod-shaped insert that the patient places under the eyelid once or twice daily, slowly delivers hydroxypropylcellulose [9004-64-2] to treat dry-eye syndrome. The Bio-Cor collagen shield is a therapeutic film composed of porcine scleral tissue (high in collagen) for treatment of eye infections. A physician uses forceps to place the film on the anesthetized eye, where it conforms to the corneal surface and slowly dissolves within 12, 24, or 78 h (44, 50). The collagen shield has been used experimentally to deliver amphotericin B [1397-89-3] (51). Additional research activity includes development of an ocular polymeric drug delivery system for local therapy. The system utilizes the prepolymer α, ω-bis-(4-methacryloxybutyl)-poly(dimethylsiloxane) (M_2D_x) copolymerized with acrylate-based monomers for local therapy (52).

No ocular products for systemic therapy are commercially available, but research is under way on ocular systems for the systemic delivery of therapeutic agents such as insulin (53).

1.6. Lungs

The lungs are easily accessible for both local and systemic treatment. Local treatment of various lung and bronchial diseases typically involves the inhalation of drugs such as sodium cromoglycate [15826-37-6],

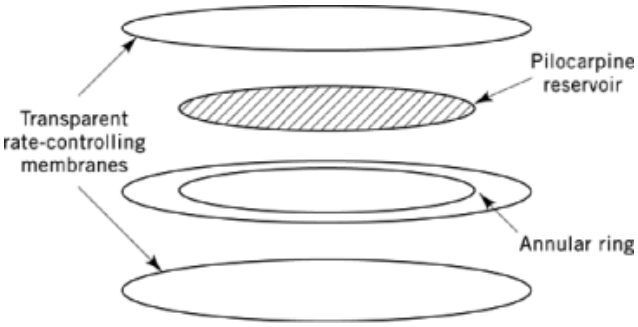

Fig. 2. Ocusert ocular therapeutic system. The Ocusert system releases pilocarpine at a controlled rate to treat glaucoma. In this schematic representation, the three disks and the ring are shown two-dimensionally. The patient inserts the Ocusert system under the eyelid, where it releases pilocarpine for seven days.Courtesy of ALZA Corp.

corticosteroids, pentamidine [100-33-4], and beta adrenoceptor agonists such as salbutamol [18559-94-9] and terbutaline [23031-25-6]. Solutions of these drugs are converted into aerosols and delivered with nebulizers or metered dose inhalers (54). Strategies to lengthen the duration of drug release into the respiratory tract include modifying a drug's molecular design, eg, salbutamol is modified to form salmeterol [89365-50-4]; changing the form of a drug, eg, from a salt suspension to a parent-free base; or incorporating drugs into liposomes (55, 56).

The lungs' large, permeable surface makes systemic delivery possible. For example, an inhaler delivers 360 μg per dose of aerosolized ergotamine tartrate [379-79-3] for migraine (54), and inhalant systems deliver anesthetic gases. Research is under way on the systemic delivery of proteins and peptides through the lungs (57, 58).

1.7. Uterus

As a portal for drug delivery, the uterus has had fairly limited use. The only local treatment is through intrauterine devices (IUDs) of contraceptive metals or steroid hormones, which provide long-term contraception. The two IUDs available in the United States are a copper-containing IUD (Paragard T 380A) that can be used for six years, and an ethylene–vinyl acetate copolymer IUD from ALZA Corp. (Progestasert) that releases progesterone at a nearly constant rate of approximately 65 μg per day for 1 year (see Contraceptives). Two IUDs that release the progestin levonorgestrel [797-64-8], one for 5 years and one for eight years, are available outside the United States (59, 60). No uterine dosage forms are available to deliver drugs for systemic therapy.

1.8. Vagina

The vagina is an accessible but little used route of drug administration. All commercially available vaginal delivery systems are for local therapy. Vaginal douches, suppositories, creams, foams, and ointments effectively deliver drugs for vaginal infections, contraception (spermicides), and vaginal dryness (estrogens). Controlled release prostaglandin E_2 [363-24-6] (Propress) for labor induction (cervical ripening) is available in the United Kingdom (61).

The permeability of the vaginal mucosa makes the vagina a route for systemic delivery as well. Vaginal rings that deliver contraceptive steroids for up to 21 days are being tested clinically (59, 62), as are rings delivering estradiol for postmenopausal estrogen replacement (63).

1.9. Intramuscular, Intravenous, and Subcutaneous Portals

These routes require injections, infusion systems, or implants. Injections for local treatment are limited to a few common drugs, including procaine [59-46-1] or cortisone [53-06-5] to ease pain and stiffness in joints and bursas. For systemic therapy, a wide variety of drugs are available in intramuscular or subcutaneous injections for intermittent dosing. Sustained systemic treatment can, of course, be achieved by intra-arterial or intravenous infusions with catheters attached to containers or pumps. Several miniaturized infusion pumps that attach to the patient, allowing prolonged ambulatory care, are now available, including the Baxter Infusor, the Mill Hill Infuser, and the Auto-Syringe (64). Sustained systemic treatment is also available through implants such as the Norplant system, a 5-yr contraceptive recently approved for marketing in the United States. The Norplant system is a set of six flexible, closed capsules made of Silastic (dimethylsiloxane–methyl-vinylsiloxane copolymer), each 34 mm long and 2.4 mm in diameter and containing 36 mg of levonorgestrel. The capsules are inserted beneath the skin of the upper arm (59). For agents such as insulin, a vapor-pressure-powered implantable system about the size and shape of a hockey puck provides long-term continuous infusion (65, 66).

2. Energy Sources for Controlled-Release

The design of a therapeutic system varies with its energy source as well as with its route of administration. For controlled drug delivery, energy sources are typically processes or properties, such as osmosis or elasticity, although some infusion pumps and transdermal diffusional systems also use electricity. The following section discusses primary energy sources for controlled-release technology and presents representative systems. Some overlap clearly exists; biodegradable devices, for example, often employ both biodegradation and diffusion processes for drug release.

2.1. Biodegradation

Since the 1970s, biodegradation, ie, the *in vivo* degradation of polymers to form biocompatible by-products (monomeric subunits or soluble polymer fragments) that are metabolized or excreted, has been investigated as an energy source for controlled drug delivery (67–72). Since the mid-1980s this field of research has expanded greatly, with researchers studying the release of numerous pharmaceutical agents from biodegradable polymers.

Three mechanisms for the biodegradation of polymers have been discussed (Fig. 3) (71). Mechanism I involves water-soluble polymers that are cross-linked by covalent bonds to make them insoluble. Hydrolytic cleavage of either the cross-links (type IA) or the backbone (type IB) yields water-soluble polymers or polymer fragments whose size depends on the density of the bonds being hydrolyzed. Mechanism II involves water-insoluble polymers that become soluble when pendent groups are hydrolyzed, ionized, or protonated. In Mechanism III, cleavage of the hydrolyzable bonds in the polymer backbone produces low molecular weight, water-soluble fragments. Actual biodegradation may be a combination of these mechanisms.

Biodegradable polymers have several advantages as drug carriers. They allow controlled release over a designated period of time, can target a specific body site, cause little or no tissue reaction, and cause less discomfort and inconvenience than multiple injections. Implants of biodegradable polymers need not be removed. Finally they enable the use of drugs with short *in vivo* half-lives and may improve the bioavailability of drugs having low aqueous solubility.

In order to become useful drug delivery devices, biodegradable polymers must be formable into desired shapes of appropriate size, have adequate dimensional stability and appropriate strength-loss characteristics, be completely biodegradable, and be sterilizable (70). The polymers most often studied for biodegradable drug delivery applications are carboxylic acid derivatives such as polyamides; poly(α-hydroxy acids) such as

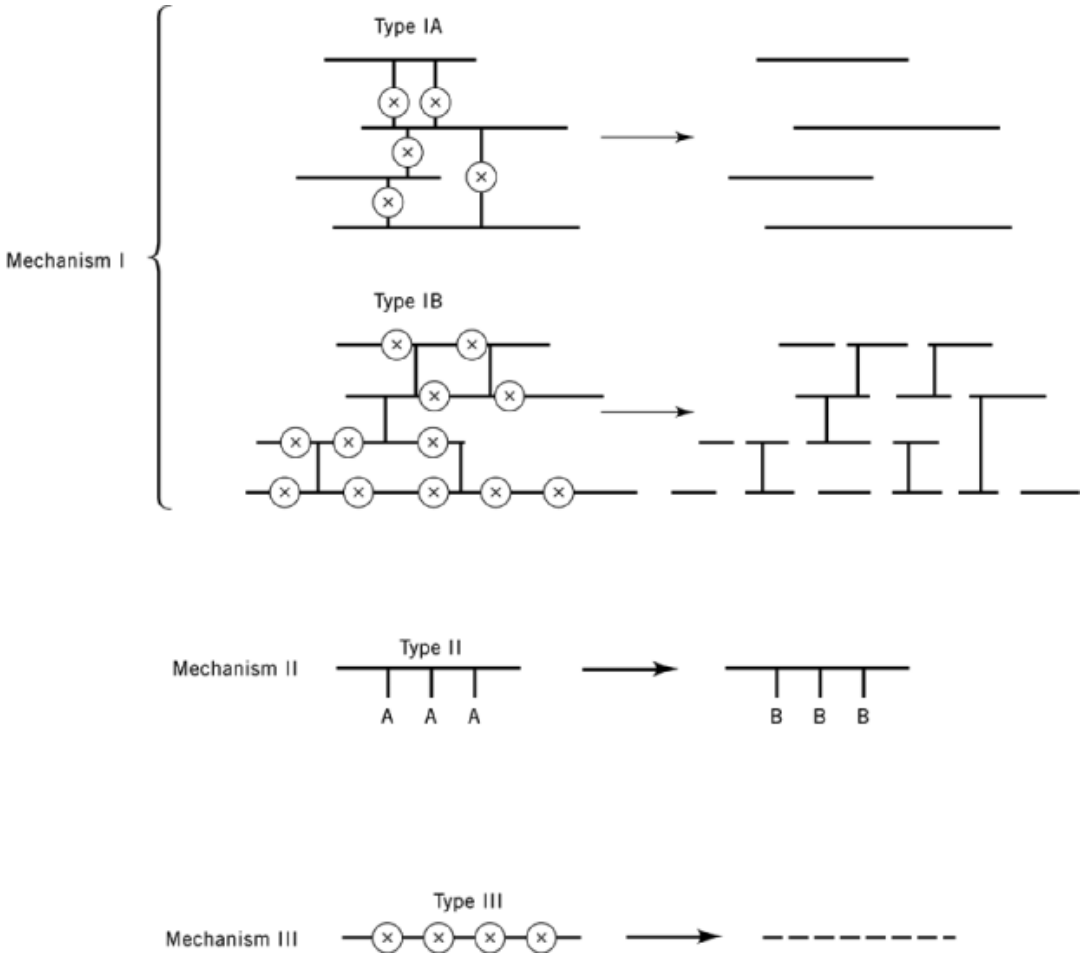

Fig. 3. Mechanisms for polymer degradation. The illustration is a schematic representation of three degradation mechanisms: I, cleavage of cross-links; II, hydrolysis, ionization, or protonation of pendent groups; III, backbone cleavage. Actual biodegradation may be a combination of these mechanisms.Courtesy of CRC Press, Inc., Boca Raton, Fla.

poly(lactic acid) [26100-51-6] and poly(glycolic acid) [26124-68-5]; cross-linked polyesters; poly(orthoesters); polyanhydrides; and poly(alkyl 2-cyanoacrylates). The relative stability of hydrolytically labile linkages in these polymers (70) is as follows: C—C > amide > esterorthoester > anhydride

Homopolymers and copolymers of lactic acid [598-82-3] and glycolic acid [79-14-1], originally developed for use in absorbable sutures (qv) (for example, Dexon and Vicryl), are particularly appealing for controlled drug delivery because of their demonstrated safety. Many types of pharmaceutical agents, including narcotic antagonists, contraceptive steroids, antiinflammatory steroids, anticancer agents, antimalarials, antibiotics, peptides, and local anesthetics, have been incorporated into these polymers. Systems based on the polymers have been prepared in several forms, including cylinders and rods, particles and powders, microcapsules and microspheres, beads, films, fibers, and needles.

Drug release from biodegradable devices occurs by degradation of the polymer, by diffusion, or by a combination of these two processes. In bulk or homogeneous degradation, hydrolysis occurs throughout the polymer. In surface or heterogeneous degradation, hydrolysis is confined to the surface of the device. The

mechanism and duration of drug release are in part determined by the method used to combine the active agents with the polymer. The manufacture of reservoir-type devices involves surrounding a core of the drug with a biodegradable membrane. Monolithic or matrix devices are fabricated by dispersing the drug homogeneously throughout the polymer. The release rate of a drug from a biodegradable matrix is affected by the amount of the drug present; its diffusibility and solubility in the polymer; the composition, molecular weight, and porosity of the polymer; the device geometry; and the presence of additives.

Biodegradable dosage forms are in various stages of clinical testing, and some are approved for marketing. Two products based on lactic and glycolic acid are available in the United States. Lupron Depot, marketed by TAP Pharmaceuticals, contains leuprolide acetate [74381-53-6], an analogue of LHRH (leuteinizing hormone releasing hormone [9034-40-6] (73); Zoladex, introduced by ICI Pharma in 1987 and now available in 27 countries (74), contains goserelin acetate, also an LHRH analogue (75). Both systems are injected once a month for the palliative treatment of prostate cancer. Another biodegradable system uses injectable microspheres or implants to deliver nafarelin [76932-56-4], a third LHRH analogue, formulated with erodible lactic acid–glycolic acid copolymers [34346-01-5] for approximately 1 month for the treatment of endometriosis or prostate cancer (76, 77). Atrix Labs is developing a product containing a biodegradable polymer in liquid form that contains an antimicrobial or antibiotic agent combined with a solution of poly(glycolic acid) or a copolymer of lactic or poly(glycolic acid) (78). The liquid is injected into the periodontal pocket, where it solidifies, releasing agents such as tetracycline hydrochloride [64-75-5] or chlorhexidine diacetate [56-95-1] that aid in controlling the microorganisms that cause periodontitis. InSite Vision is developing a biodegradable system for treating ophthalmological conditions such as glaucoma or dry-eye syndrome. The liquid solidifies when introduced into the conjunctival sac underneath the lower eyelid (79).

2.2. Diffusion

Diffusional drug delivery systems utilize the physicochemical energy resulting from concentration differentials. Drug molecules diffuse through a polymer matrix or through a polymer membrane film from a region of high concentration to one of low concentration.

2.2.1. Matrix Diffusional Systems

In matrix diffusional systems, the drug is dispersed in an appropriate vehicle, usually a high viscosity lipophilic or hydrophilic polymer. The drug is generally in solid form, although it can be liquid. Such systems are inexpensive and easy to formulate, typically, by blending the drug into the polymer using conventional polymer mixing procedures and then shaping the adduct by extrusion or molding.

Release of drugs from the outer surface of matrix devices into the appropriate body site begins when dissolved drug molecules leave the surface of the system and move into the receptor. The developing concentration gradient causes more molecules to dissolve and diffuse into the system's surface. The undissolved drug particles replenish the concentration of dissolved drug molecules. In this process of dissolution–diffusion–release, the distance from the surface of the system to the undissolved drug continually grows, forcing the dissolving drug molecules to traverse an ever-increasing expanse.

Release kinetics of the matrix system have been derived (80) and refined (81):

$$\frac{dM_t}{dt} \frac{A}{2} \frac{(2DC_sC_o)^{1/2}}{t^{1/2}} \qquad (1)$$

where $dM_{t/dt}$ is the rate of release of the drug from the surface of the system, A is the surface area of the system, D is the diffusion coefficient of drug molecules through the polymer, C_s is the solubility of the drug in the polymer, C_o is the total concentration (dissolved and dispersed) of the drug in the matrix, and t is time.

Matrix diffusional devices generally have C_o very much greater than C_s, so that at the end of the system's scheduled operating life some undissolved drug remains in the system. The release rate from such systems

declines as a function of the inverse square root of time during most of the release interval; the plot of cumulative release versus $t^{1/2}$ is a straight line. Although this declining release rate is a limitation when constant drug delivery is required, it can be an advantage when the resultant plasma drug profile coincides with the body's natural rhythm for substances such as hormones (33). For example, after daily morning application of Testoderm (ALZA Corp.), a matrix transdermal system for treatment of hypogonadism awaiting FDA approval, resulting serum-drug levels mimic the circadian pattern of testosterone observed in normal young men (82).

Another matrix diffusional implant consists of an outer layer of micronized, crystalline 17β-estradiol dispersed in silicone rubber over a nonmedicated, cylindrical silicone rubber core. The system, implanted subcutaneously in the ears of cattle, releases estradiol for up to 400 days with $t^{1/2}$ kinetics to improve growth rate and feed efficiency (83).

Although current matrix diffusional systems are most suitable for small-molecule compounds, it has been demonstrated (84) that solid hydrophobic polymers allow dispersed powdered macromolecules of nearly any size, for example, ethylene–vinyl acetate copolymers containing dispersed polypeptides, to be released for periods exceeding 100 days.

2.2.2. Membrane Diffusional Systems

Membrane diffusional systems are not as simple to formulate as matrix systems, but they offer much more precisely controlled and uniform drug release. In membrane-controlled drug delivery, the drug reservoir is intimately surrounded by a polymeric membrane that controls the drug release rate. Drug release is governed by the thermodynamic energy derived from the concentration gradient between the saturated drug solution in the system's reservoir and the lower concentration in the receptor. The drug moves toward the lower concentration at a nearly constant rate determined by the concentration gradient and diffusivity in the membrane (33).

The drug can be in dry powder form, dispersed in liquid, or in a solid polymer matrix. The membrane can be a solid, single-component polymeric film, a polymer blend, a microporous or macroporous film, or a film of hydrophilic polymer particles dispersed in a hydrophobic polymer matrix. The rate-controlling membrane and the active core may be combined by many different techniques, such as laminating the drug element and solid membrane as films, coating a shaped drug element with a volatile solution of the membrane polymer, form-fill-and-seal processing (used in producing single-serve condiment packages), microencapsulating the drug, filling a tubular membrane with a dissolved or suspended drug, or loading the drug into membrane capsules.

If the drug is enclosed within a polymer membrane, the release rate is represented by the equation

$$\frac{dM_t}{dt} = DK\frac{C_s}{l} \qquad (2)$$

where K is the coefficient of the drug partition between the reservoir and the membrane, C_s is the solubility of the drug in the reservoir, l is the thickness of the membrane, and D is the diffusivity of the drug in the membrane.

A variety of membrane-controlled systems are available. Transdermal membrane-controlled systems, composed of a drug-impermeable backing, a drug reservoir, a rate-controlling polymeric membrane, an adhesive layer, and a protective peel strip, deliver numerous drugs, including scopolamine, nitroglycerin, estradiol, and fentanyl. Figure 4 shows a schematic illustration of a membrane-controlled transdermal system in place on the skin. Nicoderm (ALZA Corp.), the transdermal therapeutic system delivers controlled amounts of nicotine for 24 h as an aid in smoking cessation. Other systems include the Ocusert ocular system and the Progestasert intrauterine device.

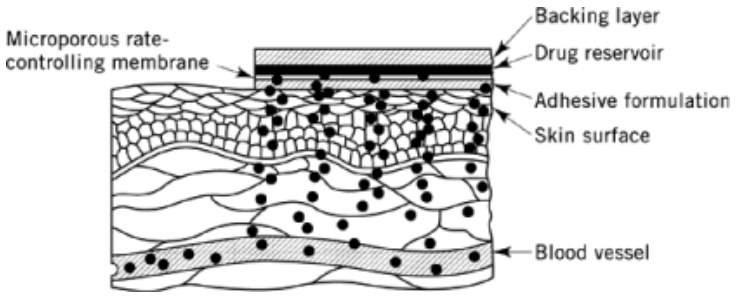

Fig. 4. Schematic of transdermal therapeutic system in operation. The drug diffuses through the intact skin into capillaries and is then carried into the general circulation.Courtesy of ALZA Corp.

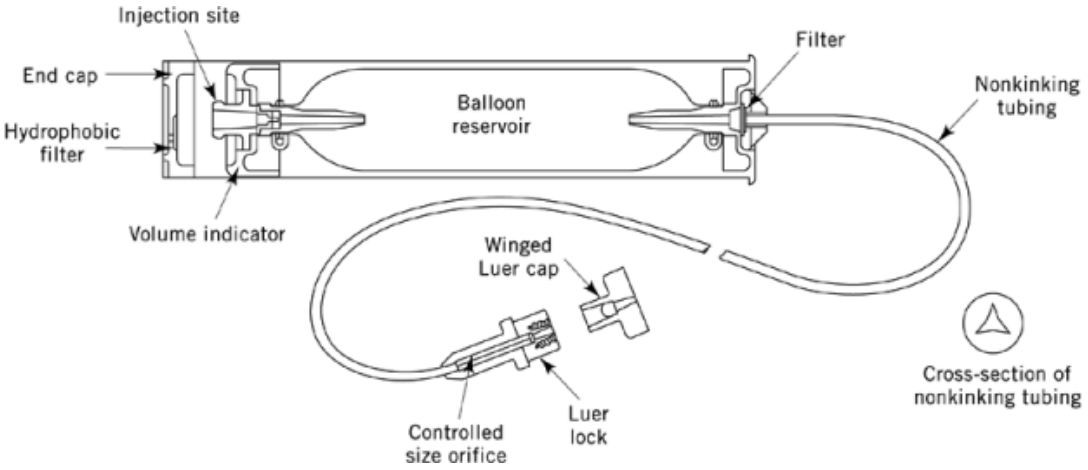

Fig. 5. Baxter Infusor Portable Infusion System. This portable, lightweight infusion system provides continuous, controlled drug delivery. The tubular rubber reservoir is shown fully inflated and ready to deliver the drug in liquid form.Courtesy of Baxter Healthcare Corp., Round Lake, Ill.

2.3. Elasticity

A portable infusion controlled-release device, the Baxter Infusor, utilizes energy stored in a distended, elastomeric rubber tube to deliver drug solutions at constant rates of flow through fixed resistances (85). The pharmacist inflates the drug reservoir with a loaded syringe inserted through a septum at the filling port, and the liquid drug is metered through a glass capillary. Figure 5 shows the tubular rubber reservoir fully inflated and ready to deliver a drug in liquid form. A description of the physicochemical properties of the elastomeric component and the design of the elastomeric reservoir is available (85–87). The system provides continuous delivery of cancer chemotherapeutic agents, for example 5-FU [51-21-8], interleukin-2 [85898-30-2], interferon [82115-62-6], methotrexate [59-05-2], cytosine arabinoside [147-94-4], doxorubicin [23214-92-8], bleomycin [11056-06-7], or cisplatin [15663-27-1] (see Chemotherapeutics, anticancer). An alternative design allows patient-controlled delivery of analgesics such as meperidine [57-42-1] or morphine sulfate [64-31-3] (88) (see Analgesics, antipyretics, and antiinflammatory agents).

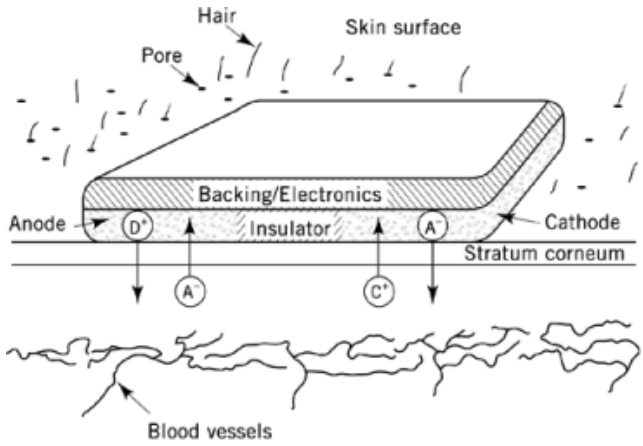

Fig. 6. Electrically assisted transdermal therapeutic system. Electrotransport facilitates passage of drugs (D^+) through the skin and into adjacent tissue and the systemic circulation.Courtesy of ALZA Corp.

2.4. Electrokinetics

Electrokinetics, the motion produced by an electrical field, is expected to play an increasingly important role in enhancing transdermal drug delivery. Commercial transdermal therapeutic systems, which typically rely solely on passive diffusion, cannot effectively deliver substances such as proteins and peptides that diffuse through the skin too slowly to achieve the desired dosing rate. In an electrical field, transdermal transport of ionized compounds occurs primarily through the sweat glands and hair follicles, the so-called shunt pathways through the stratum corneum, significantly increasing transport rates (89, 90).

Electrically assisted transdermal drug delivery, ie, electrotransport or iontophoresis, involves the three key transport processes of passive diffusion, electromigration, and electroosmosis. In passive diffusion, which plays a relatively small role in the transport of ionic compounds, the permeation rate of a compound is determined by its diffusion coefficient and the concentration gradient. Electromigration is the transport of electrically charged ions in an electrical field, that is, the movement of anions and cations toward the anode and cathode, respectively. Electroosmosis is the volume flow of solvent through an electrically charged membrane or tissue in the presence of an applied electrical field. As the solvent moves, it carries dissolved solutes.

Mass transport of species (i) under an electrical field is governed by

$$J_i = -D_i\left(\frac{dC_i}{dx}\right) - \left(\frac{z_i D_i F C_i}{RT}\right)\left(\frac{d\phi}{dx}\right) + uC_i \qquad (3)$$

where J_i is the flux of i, D_i is the diffusion coefficient, C_i is the concentration, dC_i/dx is the concentration gradient, z_i is the ionic charge, F is the Faraday constant, $d\varphi/dx$ is the electrical field, R is the gas constant, T is the temperature, and u is the velocity of the convective flow via electroosmosis (91). Detailed discussions of electrotransport theory are available (92–95).

A simple electrotransport therapeutic system is composed of an electrical power source, an anode, and a cathode (Fig. 6). The anode and cathode are typically composed of multiple layers. For example, the anode can incorporate an electrode in conjunction with a skin-contacting hydrogel containing the salt of a cationic drug (D^+). As the anode is discharged, the drug moves through the skin, carrying a fraction of the current. Simultaneously, anions move from the skin into the anode hydrogel. At the cathode the situation is reversed: anions move from the cathode hydrogel into the skin while cations move in the opposite direction.

Electrotransport technology offers a number of benefits for therapeutic applications, including systemic or local administration of a wide variety of therapeutic agents with the potential administration of peptides and proteins; long-term noninvasive administration, improving convenience and compliance; controlled release, providing a desired delivery profile over an extended period with rapid onset of efficacious plasma drug levels and in some cases reduced side effects; and a transport rate relatively independent of skin type or site. Additional benefits include easy inception and discontinuation of treatment, patterned and feedback-controlled delivery, and avoidance of first-pass hepatic metabolism.

Electrotransport of some 46 different compounds has been investigated (96). Perhaps most promising is the potential for transdermal delivery of peptides and proteins. Several researchers have reported preliminary results showing successful delivery of peptides and proteins including leuprolide [53714-56-0] (97), insulin (98, 99), growth hormone releasing factor (100), and calcitonin [9007-12-9] (101).

Commercially available electrotransport systems are bulky and limited to acute applications (96). One example, the Drionic system used for the treatment of hyperhidrosis (excessive perspiration), is presoaked in water for 30 min before each 20- to 30-min treatment. Another system, the Phoresor, approved for the delivery of lidocaine [137-58-6] for local anesthesia, and of dexamethasone [50-02-2] for treatment of local inflammation such as bursitis or tendinitis, is powered by a 9 V replaceable battery and features a disposable, fillable drug electrode.

Future electrotransport therapeutic systems will differ substantially from those just described. They will draw on advances in microelectronics and transdermal system technology to provide transdermal therapy for compounds with low passive permeation rates, patterned or pulsed drug delivery, on-demand drug administration such as patient-controlled analgesia, or closed-loop drug delivery using a biosensor. Electrotransport systems may be completely integrated and will likely be the size of a conventional transdermal system, that is, smaller than 50 cm^2, and easy to wear for extended periods.

2.5. Osmosis

Osmosis, a natural process in which molecules of a solvent move through a semipermeable membrane from a region of low to high solute concentrations, is the energy source for several commercially available therapeutic systems. Osmotic systems for human therapy have a solid core, usually shaped like a standard tablet, that contains the drug and often the osmotic agents. This core is coated with a semipermeable, rate-controlling membrane containing one or more laser-drilled orifices. In an aqueous environment such as the gastrointestinal tract, the osmotic activity of the core components establishes an osmotic activity gradient across the membrane, drawing water into the system at a rate controlled by the membrane's composition, thickness, and area. Drug delivery begins when the water enters the system to dissolve or suspend the drug; the drug solution or suspension flows out of the delivery orifice or orifices at a rate equal to the rate of water inflow through the membrane.

The simplest osmotic dosage form, ALZA Corporation's OROS elementary osmotic pump (Fig. 7), combines the drug and sometimes an osmotic agent in a monolithic core and delivers the drug in solution (102). The mass delivery rate with time (dm/dt) of the drug solution is described by equation 4, where L_p is the hydraulic permeability of the membrane, α is the membrane reflection coefficient, $\Delta\pi$ is the osmotic pressure gradient, ΔP is the hydrostatic back pressure, A is the area of the membrane, C is the dissolved concentration of the drug, and h is the membrane thickness.

$$\frac{dm}{dt} = \frac{L_p\,(\alpha\Delta\pi - \Delta P)AC}{h} \qquad (4)$$

The delivery port can be sized sufficiently large that the back pressure is negligibly small. Equation 4 then reduces to equation 5, where k represents the osmotic water permeability of the membrane and S represents

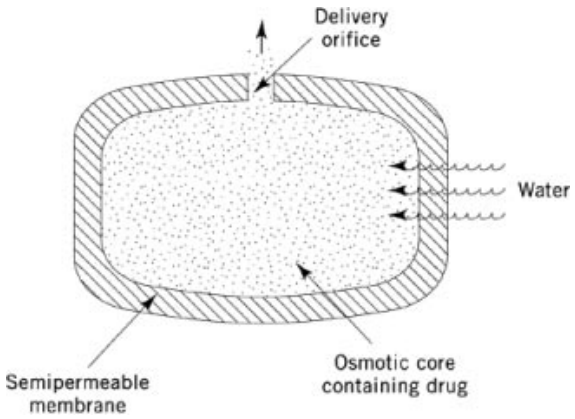

Fig. 7. A basic elementary osmotic pump.Courtesy of ALZA Corp.

the solubility of the drug at saturated concentration.

$$\frac{dm}{dt} = \frac{k\Delta\pi AS}{h} \qquad (5)$$

This equation describes the steady-state, or zero-order, release of the drug. When the drug completely dissolves, its concentration within the system begins to dilute, and the release rate follows a parabolic decline with time (102). Acutrim (ALZA Corp.), delivering phenylpropanolamine hydrochloride [154-41-6] for appetite suppression, is an example of an elementary osmotic pump.

Another type of osmotic device has the osmotic agent and the drug in separate layers (Fig. 8). Incoming water causes the osmotic layer to hydrate and expand and the drug layer gradually to go into solution or suspension. The dissolved or suspended drug is released from the system orifice(s). The net effect is to release the drug at a zero-order rate. This Push–Pull system can release a variety of compounds, ranging from highly soluble drugs to insoluble drugs suspended in osmotic hydrogel carriers or in carriers that solvate at body temperature. Procardia XL, delivering nifedipine for angina and hypertension, is a Push–Pull osmotic system.

Two osmotic systems have been developed primarily for research. The Osmet delivery module is used for clinical studies, and the Alzet mini-osmotic pump (Fig. 9) is used for nonclinical studies. Both systems are fabricated without drugs and can be filled by the researcher with various drugs in solution or suspension. The drug reservoir is a deformable, elastomeric chamber coated with an osmotic layer that is overcoated with a semipermeable membrane. As the systems imbibe water, a hydrostatic pressure is generated between the membrane and the wall of the drug chamber, deforming the chamber and slowly releasing the drug. The Osmet module has been used to explore the effects on drug actions of rate-controlled oral, vaginal, or rectal drug delivery and is designed to deliver a drug over an 8-, 12-, or 24-h period. The Alzet system is a miniaturized, implantable osmotic pump that can deliver a drug to a body cavity, blood vessel, or local tissue site. The reservoir volume of commercially available Alzet systems ranges from 100 to 2000 μL, and delivery durations range from days to weeks (103).

The Push-Melt osmotic system (Fig. 10) (104), developed primarily for zero-order delivery of drugs to the rumina of cattle, consists of a surrounding semipermeable membrane, typically cellulose ester polymers plus plasticizers (105); an osmotic tablet, such as sodium chloride [7647-14-5] dispensed in sodium polyacrylate [9003-04-7]; a separating layer; a drug dispersed in a thermoresponsive carrier; and an iron weight that also contains the delivery orifice. The iron weight increases the density of the system so that it is retained in the

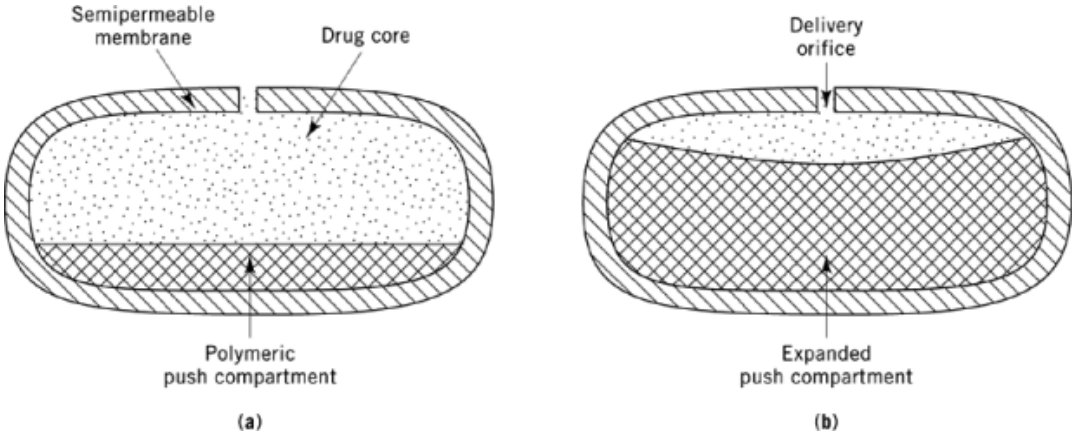

Fig. 8. Example of a Push–Pull osmotic pump where (**a**) represents the pump before operation, and (**b**), during operation.Courtesy of ALZA Corp.

rumen for more than 120 days. The thermoresponsive carrier melts at body temperature, allowing the drug to be released from the system as the osmotic tablet imbibes water. This dosage form has been developed to deliver the anthelmintic drug ivermectin [70288-86-7] (IVOMEC SR bolus) and the nutritional supplement sodium selenite [10102-18-8] (Dura Se bolus), both from ALZA Corp.

A drug-dedicated osmotic implant for human and veterinary use has been developed to deliver hormones, peptides, and proteins that are digested or rendered inactive after oral administration (106).

2.6. pH Sensitivity

Dosage forms that employ pH sensitivity to trigger the release of active agents have been designed with both physical and chemical mechanisms. Systems with physical mechanisms are discussed here; a description of chemical mechanisms, such as pH-sensitive hydrogels, is available (107).

Delivery systems that respond to changes in pH have been known to the pharmaceutical industry for more than a century. The pH-sensitive enteric coating is probably the oldest controlled-release technology. Unna introduced an enteric tablet coating based on keratin in 1884 (108). Enteric coatings are used primarily to protect the gastric mucosa from local irritation or to ensure that tablets do not dissolve until they reach the intestine.

Enteric coatings are generally formulated from anionic polymers with pendent carboxyl groups and typically have a pK_a of 4 to 6. In the low pH gastric fluids (about two units below the pK_a), only 1% of the carboxyl groups ionize; 99% of the carboxyl groups are protonated, and the carboxyl groups can form hydrogen bonds with each other or with other portions of the polymer. The insoluble polymer film thus retains its integrity and provides a barrier to moisture. When the dosage form reaches the higher pH intestinal fluids, ionization of the pendent groups increases and the enteric material dissolves (109). The extent of this ionization as a function of media pH can be described by the Henderson-Hasselbach equation (110):

$$\mathrm{pH} = \mathrm{pK}_a + \log\frac{\text{ionized}}{\text{nonionized}} \qquad (6)$$

The most commonly used polymers are cellulose acetate phthalate [9004-38-0] (CAP), poly(vinyl acetate phthalate) [34481-48-6] (PVAP), hydroxypropylmethyl-cellulose phthalate [71138-97-1] (HPMCP), and polymethacrylates (111) (see Cellulose esters). Acrylate copolymers are also available (112). Figure 11 shows the

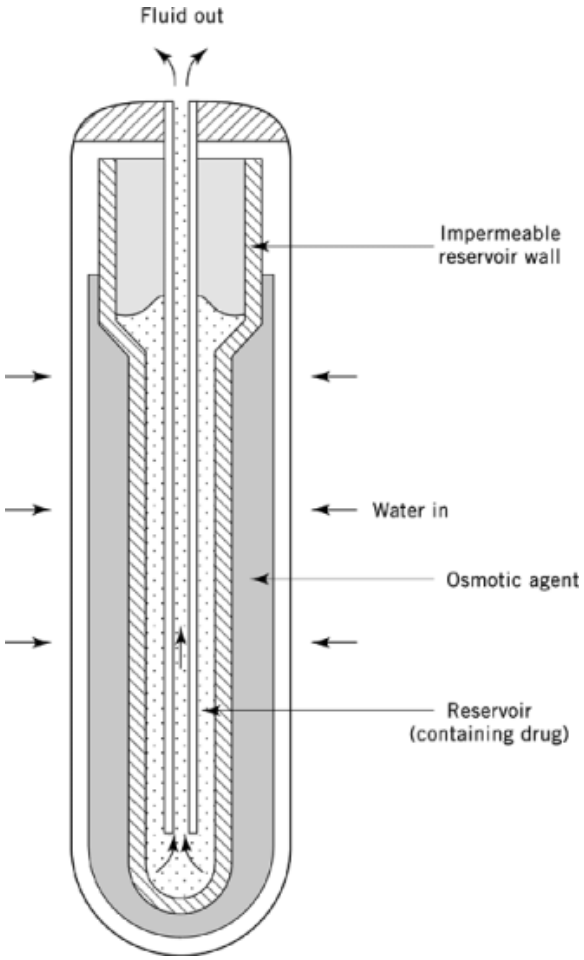

Fig. 9. Mini-osmotic pump.Courtesy of ALZA Corp.

dissolution behavior of some commercially available enteric materials. Some manufacturers supply grades designed to dissolve at specific pH values with increments as small as 0.5 pH unit (113).

Other dosage forms can be designed to use pH sensitivity. Examples include microcapsules or liposomes that release drugs by changes in pH (114) and may be used to treat tumor cells, which reportedly have a pH substantially lower than that of healthy tissues; and a dosage form incorporating pH-sensitive electrodes in a feedback system with mechanical pumps (115) that continuously monitors gastric pH values with a nasogastric electrode and intravenously infuses appropriate levels of antiulcer medication in response to changes in intragastric pH.

2.7. Vapor Pressure

The Shiley Infusaid implantable infusion pump utilizes energy stored in a two-phase fluorinated hydrocarbon fluid. The pump consists of a refillable chamber that holds the drug and a chamber that holds the fluid. The equilibrium vapor pressure of the fluid, a constant 60 kPa (450 mm Hg), compresses the bellows, pumping the

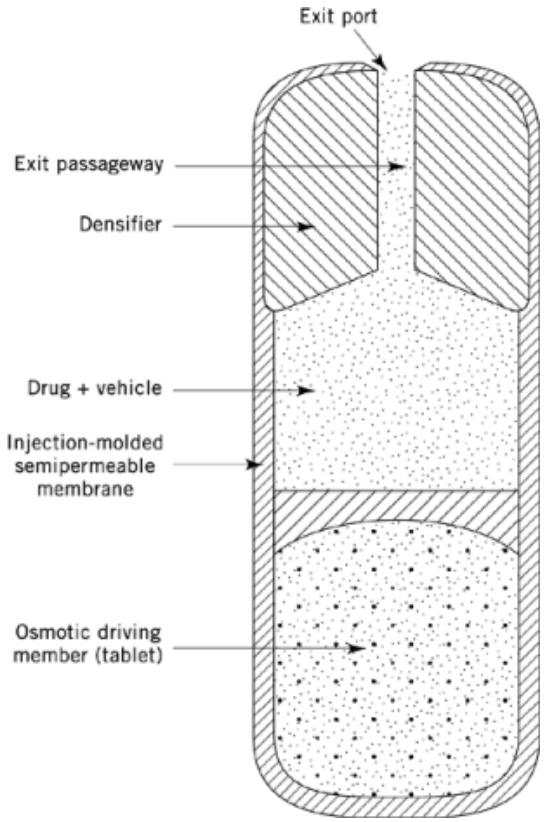

Fig. 10. Structure of Push-Melt osmotic pump, developed primarily for veterinary therapeutic applications.Courtesy of ALZA Corp.

drug through a bacterial filter, a capillary flow restrictor, and an infusion cannula to the target body site (56, 116).

3. Emerging Applications of Controlled-Release Technology

Several application areas of controlled-release technology will be increasingly important. Systems being investigated or developed employ many of the mechanisms discussed earlier.

3.1. Patterned Delivery

Although steady serum–drug concentrations are the preferred mode of therapy for many drugs, patterned delivery of some compounds, including the peptides calcitonin [9007-12-9], growth hormone [9002-72-6], and corticotropin-releasing hormone [9015-71-8], mimics the body's own secretion patterns or responses to certain compounds or diseases. Osmotic pumps can be programmed to deliver drugs in a variety of patterns. In one patterned delivery system for nocturnal asthma, an elementary osmotic pump releases a delayed pulse of salbutamol [18559-94-9], superimposed over a steady delivery rate, approximately 7 h after dosing (Fig. 12). For cattle, the Synanthic Multidose system delivers five pulses of the anthelmintic oxfendazole [53716-50-0]

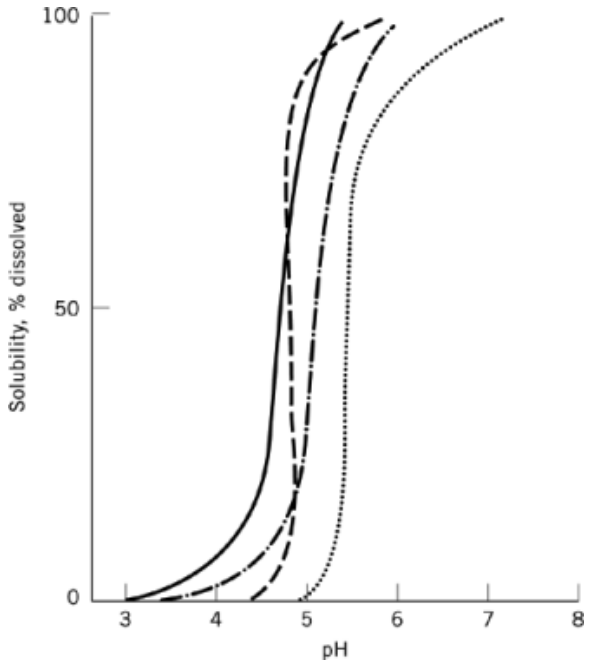

Fig. 11. Dissolution as a function of pH of various enteric polymers. (—) represents HPMCP (HP-50); (_ _ _), HPMCP (HP-55); (— — —), PVAP; (. . .), CAP.Courtesy of Colorcon, Inc., West Point, Pa.

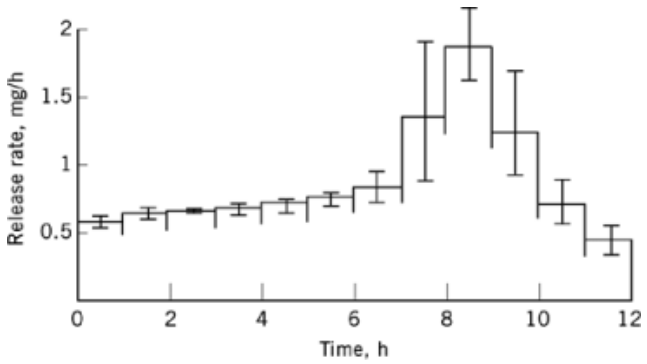

Fig. 12. Profile of patterned delivery of salbutamol, for nocturnal asthma, from an elementary osmotic pump. A delayed pulse of salbutamol, superimposed over a steady delivery rate, is released approximately 7 h after dosing (117).Courtesy of ALZA Corp.

over a 4-month period. The system consists of a central magnesium rod attached to a steel and weight. Plastic segments containing the drug are sequentially positioned on the rod. In the rumen, the rod erodes as a result of electrolytic action, and the plastic segments are delivered at 3-wk intervals (118, 119). Patterned delivery is also possible with electrically assisted transdermal systems that apply an intermittent, and sometimes varying, electrical charge to enhance drug permeation at programmed intervals.

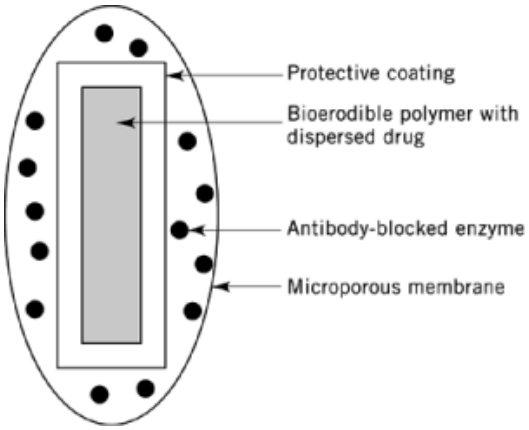

Fig. 13. Proposed triggered delivery system with the drug dispersed in a rate-controlled polymer. A protective coating surrounds the polymer, and a microporous membrane surrounds the entire device.Courtesy of Butterworth-Heinemann Ltd., Oxford, UK.

3.2. Targeted Delivery

By delivering drugs to the specific cells or organs where action is required, targeted dosage forms may enhance therapeutic outcome and avoid many toxic effects. Colon-targeted systems, for example, enable a drug to reach its destination without being digested in the stomach. One approach to targeted delivery is to couple a pharmacological agent to a macromolecular vector specifically taken up by target cells. Vectors include antibodies, nanoparticles, polysaccharides, synthetic polypeptides, liposomes, synthetic and natural cells, polymer-based microcapsules, albumin, and glycoprotein conjugates (120–122). Recently, companies have begun developing systems to circumvent the blood–brain barrier and target the brain. CytRx has patented a copolymer for treatment of tumors (123); Pharmatec US/Neurex claims to be able to deliver neuropeptides to the brain with a patented carrier system (124); and Gynex claims to deliver estradiol to the brain (125).

3.3. Triggered and Closed-Loop Delivery

Triggered delivery systems release a drug in response to a signal from the body, for example, the presence of a substance to be controlled, such as morphine, or from the patient. Triggered delivery of the morphine antagonist naltrexone [16590-41-3] has been explored by several groups. A device containing naltrexone dispersed in a biodegradable polymer core, eg, a partially esterified copolymer of methyl vinyl ether [107-25-5] and maleic anhydride [108-31-6] that is stable at low pH but erodes rapidly at pH 7.4 (a physiologic pH), has been described (126) (Fig. 13). A protective coating (an acidic hydrogel or a hydrophobic compound) surrounds the polymer, and a microporous membrane surrounds the entire device. An antibody-blocked enzyme between the protective coating and the membrane is freed by the entry of morphine from the body. The free enzyme degrades the protective coating around the core and exposes it to the body's higher pH, allowing the release of naltrexone (126–129).

The ultimate controlled-release device, a closed-loop system, delivers a metered amount of a drug each time it encounters a signal from the body, for example, the plasma concentration of a metabolite or a substance such as glucose [50-99-7], until the system is depleted (8, 128–130). Closed-loop insulin delivery has been the focus of much research. Rapidly changing blood glucose levels require system response times of 15 min or less (131, 132). One approach envisions a hydrogel polymer membrane containing pendent tertiary amine groups and entrapped glucose oxidase [9001-37-0]. Glucose oxidase catalyzes the reaction of glucose and oxygen to produce

gluconic acid and hydrogen peroxide [7722-84-1]. As the membrane pH decreases, the pendent amine groups are ionized, resulting in membrane swelling and increased membrane permeability to insulin. The principal hydrogel types investigated are based on 2-hydroxyethyl methacrylate [868-77-9], *N,N*-dimethylaminoethyl methacrylate [2867-47-2], and polyacrylamide [9003-05-8] (119).

Another approach utilizes the plant lectin concanavalin A (Con A) [11028-71-0], which has a high binding affinity for specific saccharides. Con A is immobilized on Sepharose [9012-36-6] beads or cross-linked to form a gel. Glycosylated insulin (*p*-succinyl aminophenyl glucopyranoside insulin) is bound to the sites on the Con A. Con A–glycosylated insulin is then placed in a microporous synthetic membrane pouch. When glucose diffuses through the membrane, it displaces the bound glycosylated insulin, which diffuses out through the membrane (133, 134).

A mechanochemical pump being developed incorporates a glucose-sensitive hydrogel. As glucose diffuses into the hydrogel in one chamber, it reacts with glucose oxidase, changing the pH of the hydrogel and causing it to swell. The swelling exerts pressure against a diaphragm, pressurizing two adjoining chambers and opening a valve to release insulin. The pH-sensitive hydrogels investigated to date have been linear copolymers of *N,N*-diethylaminoethyl methacrylate hydrochloride [2421-44-5]and nonionic methacrylates (135, 136) (see Methacrylic polymers).

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