DRUG DELIVERY SYSTEMS

1. Introduction

For many decades, pharmaceuticals have primarily consisted of simple, fast-acting chemical compounds that are dispensed orally for the treatment of an acute disease or a chronic illness and have been mostly facilitated by drugs in various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injections. Even today these conventional dosage forms are the primary mode of drug administration for

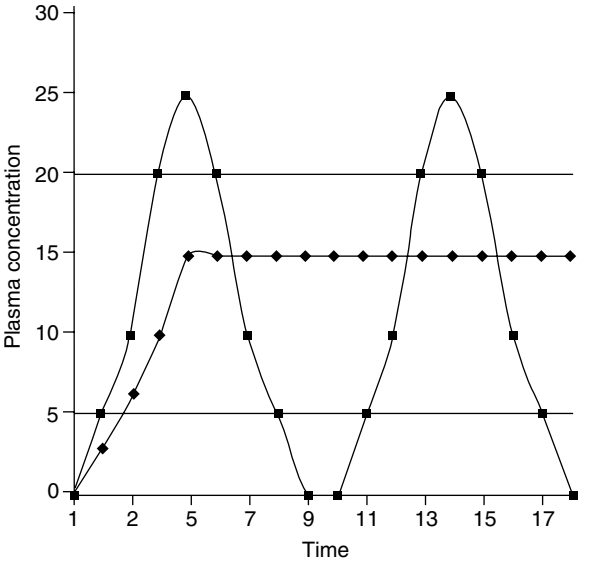


Fig. 1. Comparison of typical pharmacokinetic profiles seen for conventional vs. controled release formulations. ◆ CDR; ■ conventional; — toxic level; and — minimum therapeutic level.

prescription and over-the-counter drug products. Conventional drug formulations typically provide a prompt release of drug in a bolus form. For drugs which get cleared rapidly from the body, achieving and maintaining the drug concentration within the therapeutically effective range requires a multiple dosing regimen, often more than once a day. Such an inconvenient dosing regimen leads to lack of patient compliance as well as a significant fluctuation in drug levels in the plasma (Fig. 1). The premise of administration methods that allow the patients to safely treat themselves is as significant as any other health care development, particularly in developing countries where doctors, clean syringes, sterile needles, and sophisticated treatments are few and far between (1).

Recently, several technical advancements have resulted in the development of new technologies capable of controlling the administration of a drug at a targeted site in the body in an optimal concentration-versus-time profile (2–4). The term "drug delivery" covers a very broad range of techniques used to get therapeutic agents into human body. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/or targeting the delivery of drug to a tissue as described in various articles (5–7).

The rapid advancement of biomedical research has led to many creative applications for biocompatible polymers. As modern medicine discerns more mechanisms of both physiology and pathophysiology, the approach to healing is to mimic, or if possible, to recreate the physiology of healthy functioning. Thus, the area of responsive drug delivery has evolved. Also called "smart" polymers, for drug delivery, the developments fall in two categories: externally regulated or pulsatile systems (also known as "open-loop" systems) and self-regulated systems (also called "closed-loop").

2. Physiological Routes for Drug Delivery

Design of a drug delivery device is dictated by the properties of the physiological barrier, the effective plasma levels, and the total dosage.

2.1. Oral. The oral route for drug delivery includes the gastrointestinal (GI) tract and the oral cavity including the buccal mucosa. The buccal mucosa is considered separately because of differences in the approach to drug delivery via this route.

The primary function of the GI tract is the digestion and absorption of food. Thus, drugs entering the GI tract are exposed to a wide range of pH values, from 1–2 in the stomach to 5.0–6.5 in the small intestine, as well as high levels of various enzymes involved in the digestion of proteins, fats, and carbohydrates. The absorptive surface area of the small intestine is greatly increased over that of a simple tube by the presence of mucosal folds, villi (finger-like infoldings of the intestinal wall), and microvilli (found on the luminal surface of the enterocyte), resulting in a total surface area estimated to be between 250 and 1000 m^2. The colon has a large predominantly anaerobic bacterial population, 10^{11} to 10^{12} per gram on a dry wt basis (8,9), that constitute 40 to 55% of fecal solids in subjects consuming an average Western diet (10,11). Bacteria may contribute to the metabolism of xenobiotics, including drugs, and have a wide variety of enzymatic activities.

The transit of a dosage form through the GI tract can have a profound influence on its performance. Total GI transit time is between 24 and 48 h on average. Recovery of oral osmotic dosage forms gave a median transit time of 27.4 h with a wide range of 5.1 to 58.3 hours (12). Gastric emptying time is affected by the physical state of the drug (liquid vs solid), the size of the dosage form, the presence of food, the emotional state of the patient, the presence of disease, and certain medications. Gastric emptying time in the fasted state in humans varies between 0.5 and 2 h, and drugs given as small pellets or single units appear to leave the stomach en masse (13). After feeding, drugs that are dispersed or given as small pellets (2 to 5 mm) tend to empty from the stomach with the meal, whereas larger dosage forms are retained by the stomach until the meal has emptied (14,15). The delay in gastric emptying appears to be a function of the caloric content of the meal (16). Gastric emptying is delayed during pregnancy, severe exercise (moderate exercise accelerates it), stress, and in the elderly. Gastric stasis is associated with certain diseases, including diabetes and migraine. Emptying is accelerated in duodenal ulcer disease and slowed in gastric ulcer disease. Several drugs and other agents also affect gastric emptying. Anticholinergics, antihistamines, cyclic antidepressants, phenothiazines, and narcotic analgesics cause delay. Metoclopramide, domperidone, cisapride, anticholinesterase, sodium bicarbonate, and cigarette smoking accelerate emptying.

The transit time in the small intestine is 3–4 h, and is the least variable part of total transit (17). It is independent of the size and physical state of the drug dosage form or the presence of food, and is unaffected by certain disease states such as constipation, diarrhea, and ulcerative colitis that might reasonably be expected to influence transit (13,18). Pooling at the ileo-cecal junction for 4 to 12 h has been observed (19), as well as pooling at the hepatic flexure despite the absence of a sphincter. Colonic residence time is about 80% of total

GI transit time, and on average is 10 to 20 h, although it is extremely variable. In humans, the colon is 1 to 1.5 m long and has a surface area of about 1300 cm^2. It lacks the villi present in the small intestine, but the decrease in surface area may be compensated for by an increase in residence time. The main physiological function of the colon is the reabsorption of water and ions, reducing the volume of ileal effluent entering the colon (1 to 1.5 L) to an average stool output of 100 to 150 g per day. Colonic transit is characterized by periods of quiescence interspersed with bursts of activity. Solutions and small particles pass through the colon more slowly than large capsules (20).

Absorption of drugs across the wall of the GI tract is primarily the result of passive diffusion. Absorption is believed to take place by partitioning of the drug from the aqueous GI environment into the lipoidal membrane, diffusion through the membrane, and partitioning into the blood and body fluids. Most drugs are weak acids or weak bases that exist in an equilibrium between the ionized and unionized forms. The neutral species exhibit greater oil solubility than the ionic forms, and thus absorption of the unionized form of the drug predominates. Drug absorption depends on the pH at the absorptive site, the pK_a of the drug, and its oil/water partition coefficient. Although the pH partition hypothesis (21) may provide a useful approximation for drug absorption, some drugs are extremely well absorbed even though they are ionized throughout the GI tract. Active transport systems exist for the absorption of hexoses, amino acids (qv), and di- and tripeptides (22,23); a few drugs are taken up by these systems, eg, baclofen [1134-47-0], some β-lactam antibiotics, and angiotensin converting enzyme (ACE) inhibitors. After passage across the enterocyte, drugs enter the mesenteric circulation and are transported to the liver via the portal vein.

Drugs, such as opiates, may undergo metabolism both in the intestinal wall and in the liver (first-pass metabolism). The metabolism may be extensive and considerably reduce the amount of drug reaching the systemic circulation. Alternatively, the metabolite may be metabolically active and contribute significantly to the action of the parent drug. Some compounds undergo enterohepatic circulation in which they are secreted into the GI tract in the bile and are subsequently reabsorbed. Enterohepatic circulation prolongs the half-life of a drug.

For those compounds absorbed from a small part of the intestine, the amount of drug absorbed can be increased by extending the residence time of the dosage form in the GI tract. The two basic approaches used are gastric flotation or retention devices, and bioadhesive delivery systems. Flotation devices may be designed that float on the surface of the stomach contents in a way similar to that of lipids in the meal. These devices are sufficiently large to be retained by the stomach for prolonged periods. After deflation, the device is small enough to pass safely through the pylorus. Bioadhesive polymers have thus far shown little success in humans, although some increase in transit time has been shown in animal studies (24).

Drug absorption from the colon has become the subject of much attention. The development of dosage forms that release drug for 16 to 24 h depends on the drug being absorbed from the colon, because the bulk of the delivery period may be spent there. Only those compounds that exhibit good colonic absorption are suitable for extended delivery dosage forms, eg, metoprolol (25,26). Protein and peptide drugs are more readily available since the advent of recombinant DNA

technology, and the oral delivery of these compounds has become the holy grail of drug delivery. However, proteins (qv) present several challenges because of size, hydrophilicity, and susceptibility to hydrolysis and degradation by proteases. Compared to the upper GI tract, proteolytic activity is lower in the colon (27) and the residence time is longer, which has led to interest in the development of dosage forms targeted to the colon. However, it appears unlikely that significant absorption of proteins occurs from the colon in the absence of either protease inhibitors, absorption enhancers, or both.

Targeting drugs to the colon has followed two basic approaches, ie, delayed release and exploitation of the colonic flora. Delayed release generally relies upon enteric coating to ensure safe passage through the stomach, and a delay of 4 to 6 h before drug release. Enteric coating is a special polymeric coating, such as cellulose acetate phthalate, that is resistant to gastric fluids at low (1 to 3) pH but dissolves upon exposure to the higher pH of the intestinal contents (pH 5 to 7). The delay capitalizes on the fairly reproducible small intestinal transit time to release drug in the desired region of the GI tract. The time delay may be modified to release the drug in different regions of the GI tract. The possible disadvantage of this approach is that some patients have transit times outside the normal range.

Exploitation of the colonic flora relies on bacterial enzymes to cleave specific bonds. These enzymes include azoreductases, which cleave sulfasalazine to 5-acetylsalicylic acid and sulfapyridine (28); glycosidases, for the cleavage of dexamethasone glucoside (29); and glucuronidases, which cleave narcotic antagonist glucuronides (30). In all these examples, the active drugs are administered as prodrugs, which are then cleaved to yield the active moiety. Another approach has been to design polymeric drug delivery systems which contain diazo linkages (31,32) that are cleaved in the colon. The drug may be loaded into the polymer or the polymer may be used to coat a more conventional dosage form. There are concerns that must be addressed with regard to this approach, ie, treatment with antibiotics may decrease both the total number of bacteria and the balance between them; some patient groups, particularly the elderly, may have bacterial overgrowth in the ileum and also in the stomach, the latter being related to achlorhydria (33); and the toxicology of polymeric dosage forms containing azo bonds must be evaluated very carefully.

2.2. Rectal. The rectal route for drug delivery is an extremely unpopular one in the United States, but may present advantages in certain situations. Enemas containing either steroids or 5-acetylsalicylic acid for the treatment of proctitis, ie, inflammation of the rectum, offer good therapy in inflammatory bowel disease. The rectal route may be used when gastric stasis or vomiting is present, making the oral route of drug delivery untenable, eg, ergotamine for the treatment of migraine. The vascular drainage of the rectum may partially avoid first-pass metabolism which offers definite advantages for those drugs undergoing extensive metabolism.

2.3. Transdermal. The skin offers a formidable barrier to the entry of foreign compounds, including drugs, into the body, both in terms of a physical barrier and an immunological one. The principal barrier to drug diffusion lies in the outer few layers of the epidermis, the stratum corneum, which is 10–20 μm thick in humans and consists of sheets of keratinized epithelial cells joined

by tight junctions. The remainder of the epidermis, which is about 100 μm thick in humans, consists of living cells that are metabolically active. A drug applied to the skin must therefore diffuse through the epidermis to reach the blood capillaries in the dermis for distribution to the systemic circulation. Blood supply to the skin can vary tremendously from 200 to 4000 mL/(m^2· min) (34) as a result of its role in the control of body temperature. A fall in body temperature results in vasoconstriction and a rise in temperature in vasodilation. Drug delivery by the transdermal route avoids presystemic metabolism in the gastrointestinal tract or first-pass metabolism in the liver. The permeability of skin is low, which limits the usefulness of this route to highly permeable, potent compounds. Permeability varies somewhat with regions of the body. The greatest permeability is in the scrotum (35).

Generally, permeation is higher for low (<400) mol wt compounds that have adequate oil and water solubility. Highly lipophilic compounds penetrate easily through the stratum corneum, but a degree of hydrophilicity is necessary for penetration through more aqueous regions. Lipid–water partition coefficients have been correlated with permeation of compounds through skin. The use of absorption enhancers for transdermal delivery may be necessary as a result of the low permeability of a drug through skin. Ethanol has been the only enhancer in use in a commercially available system, and the flux of estradiol and nitroglycerin is linearly correlated with the flux of ethanol (36,37). Other absorption enhancers such as 1-dodecylazacycloheptan-2-one [59227-89-3] (Laurocapram) (38,39), terpenes (40), oleic acid [112-80-1] (41), pyrrolidones (42), *n*-alkanols (43,44), and alkyl esters (45) are candidates.

Dermal irritation and sensitization are issues specific to the transdermal route of drug delivery and can result in the cessation of therapy. Irritation may be defined as a local, reversible inflammatory response of the skin to the application of an agent without the involvement of an immunological mechanism. Acute, primary irritation occurs in response to a single application of an agent; cumulative irritation occurs following repeated applications of an agent that does not induce primary irritation. Irritation is manifested as erythema and edema, and is assessed using a standardized scoring system (46). The degree of irritation has been correlated with pK_a for a series of acids and bases (47,48). Sensitization results from an immune response to an antigen, which may lead to an exaggerated response upon repeated exposure to the antigen. A well-known example of contact sensitization is the response to poison ivy. Irritation or sensitization may occur in response to either the drug or a component of the transdermal system. Careful testing of both active and placebo patches is needed.

Transdermal drug delivery is associated with a relatively long time lag before the onset of efficacy, and removal of the system is followed by a correspondingly extended fall in plasma concentration, which probably results from formation of a drug depot in the skin that dissipates slowly. The time lag is approximately 3 to 5 h for many drugs that have low binding in the skin (49–51), but may be considerably longer. In contrast, plasma drug levels may be obtained between 2 and 5 min by the oral, buccal, or nasal routes.

Despite the limitations imposed by the physiology of the skin, several marketed controlled release transdermal drug delivery systems are available in the United States; for example, nitroglycerin for angina, estradiol for the relief of

postmenopausal symptoms and osteoporosis, clonidine for the treatment of hypertension, fentanyl as an analgesic, and nicotine as an aid to smoking cessation. These systems are designed to deliver drug for periods of one to seven days.

2.4. Buccal. The oral mucosa consists of several different types of mucosa. In humans, the gingiva and hard palate are keratinized squamous epithelium; the buccal and sublingual mucosa are nonkeratinized. The total oral surface area is about 100 cm^2, about 30 cm^2 of which is made up of the buccal mucosa. Buccal mucosa has a high blood flow of 20–30 mL/min for each 100 g of tissue (52,53) and good lymphatic drainage. Vascular drainage is directly into the systemic circulation, and thus first-pass metabolism is avoided. Buccal epithelium has an average thickness of 0.58 mm (54) and is penetrated by connective tissue papillae that may reach to within 0.1 mm of the surface (55,56). The epithelial thickness varies from 20 cell rows over the papillae to 40 to 50 cell rows throughout the rest of the tissue. The buccal mucosa is readily accessible to the patient for self-administration of drugs, as well as rapid removal of the dosage form should it be necessary.

The use of a bioadhesive, polymeric dosage form for sustained delivery raises questions about swallowing or aspirating the device. The surface area is small, and patient comfort should be addressed by designing a small (less than 2 cm^2), thin (less than 0.1 mm (4 mil) thick) device that conforms to the mucosal surface. The buccal route may prove useful for peptide or protein delivery because of the absence of protease activity in the saliva. However, the epithelium is relatively tight, based on its electrophysiological properties. An average conductance in the dog is 1 mS/cm^2 (57) as compared to conductances of about 27 and 10 mS/cm^2 in the small intestine and nasal mucosa, respectively (58,59); these may be classified as leaky epithelia. Absorption of proteins and peptides, which has been reviewed (60), is generally low and somewhat erratic. The judicious use of absorption enhancers may be necessary and can be accomplished in a very controlled manner in this area. The mouth is routinely exposed to a wide variety of agents of different pH and osmolarity and appears to be more robust than many other epithelia. Exposure to a wide range of pH values produced damage only at the extremes of pH 1, 2, and 14 (61).

Commercially available buccal or sublingual dosage forms include nitroglycerin for angina, buprenorphine [52485-79-7] for pain relief, ergotamine for the treatment of migraine, methyltestosterone [58-18-4] for hypogonadism, captopril for hypertensive emergencies, and nifedipine [21829-25-4] for hypertensive emergencies and acute angina. Nicotine gum is available as a smoking cessation aid. Absorption is predominantly from the oral cavity, with a minor contribution from intestinal absorption of swallowed drug (62). These dosage forms are essentially tablets that dissolve rapidly over a few minutes. An alternative approach is the use of a bioadhesive, polymeric system that would provide sustained drug delivery over an extended period of time. The use of a backing material that is impermeable to the drug and saliva directs the drug toward the mucosa and prevents drug loss because of swallowing. The feasibility of this approach has been demonstrated in clinical trials (63,64).

2.5. Nasal. The nasal passages serve several physiological functions, eg, filtration of particulates from inspired air, warming and humidification of air, and olfaction. The surface area of about 180 cm^2 in the adult (65) is lined with

pseudostratified columnar epithelium, which forms the primary barrier to drug absorption. The nose has good vascular drainage and an estimated blood supply of 40 mL/min for each 100 g of tissue (66). The nasal cavity is obviously accessible, absorption is very rapid, and first-pass metabolism in the liver is avoided. A potential disadvantage is the rapid mucociliary clearance rate for removal of trapped particles from the nose. The estimated turnover rate is 15 minutes (67). Both the common cold and conditions such as allergic rhinitis can affect clearance as well as the extent of absorption (68,69). The nasal route is used primarily for topical delivery of drugs, generally in aerosol form, for the treatment of allergic rhinitis and cold/flu symptoms. This route may have utility for rapid delivery of proteins or peptides, ie, compounds which may require pulsatile rather than sustained delivery.

The permeability of the nasal mucosa is similar to that of the ileum, and it is therefore a leaky epithelium. The structural requirements for drug absorption from the nasal cavity have been analyzed (70). Examination of data for 24 compounds has shown that the nasal route is suitable for the efficient, rapid delivery of many drugs having mol wts <1000. Mean bioavailability is 70%, without the use of adjuvants. This limit may be extendable to compounds of at least 6000 mol wt using adjuvants. Many adjuvants, however, enhance absorption by disruption of the cells, eg, the degree of enhancement of nasal insulin absorption was positively correlated with the membrane lytic activity of a series of nonionic surfactants (71). Another approach is to prolong the residence time using bioadhesive agents such as methylcellulose, carboxymethylcellulose, hydroxypropyl cellulose [9005-18-9], and polyacrylic acid (72–74), or bioadhesive microspheres that also protect proteins from degradation (75).

The effects of drugs and adjuvants must be assessed, both in short-term administration and during chronic treatment. Local effects include changes in mucociliary clearance, cell damage, and irritation. Chronic erosion of the mucous membrane may lead to inflammation, hyperplasia, metaplasia, and deterioration of normal nasal function (76).

2.6. Pulmonary. The trachea and bronchi are lined with pseudostratified ciliated columnar epithelium, similar to that found in the nasal passages. The bronchi divide to give rise to bronchioles, the larger ones being lined with simple columnar ciliated epithelium and the smaller ones with simple cuboidal nonciliated epithelium. The goblet cell population also decreases, and clearance of mucus by the cilia of the respiratory tract is of lesser importance in the deep lung. The barrier to drug absorption in the alveolae is the thin alveolar–capillary barrier that consists of squamous epithelial cells. Drug delivery to the lung is primarily for local therapy, but pulmonary delivery may offer opportunities for systemic delivery of compounds, including vaccines (see VACCINE TECHNOLOGY) (77).

Two primary factors involved in pulmonary drug delivery are delivery of the drug to the desired region of the respiratory tract, and permeation through the epithelial barrier. Delivery of the drug is highly dependent on the particle size; larger (5–10 μm) particles are lost by impaction in the upper airways and small (<0.5 μm) particles are expired. The ideal particle size for reaching the lung appears to be 1–2 μm (77,78). The barrier properties of the epithelium are not well-defined and, as in many other epithelia, are not solely dependent on the mol wt of the compound. Difficulties may be encountered in calculating

bioavailability by the pulmonary route as a result of failure to deliver drug to the appropriate region of the respiratory tract.

2.7. Ocular. Drug delivery to the eye presents several challenges based on anatomy and physiology. The eye is isolated from the rest of the body by blood–eye barriers that include the retinal pigment layer, the ciliary epithelium which provides a barrier to proteins and antibiotics, and the thick walls of the blood vessels in the iris. The sclera and cornea provide physical protection to the eye. The cornea has an outer epithelial layer about five cells thick, an aqueous layer, and an inner endothelium. Drugs therefore have to cross two lipid layers and an aqueous layer to enter the eye, and compounds such as acetazolamide [59-66-5] that are readily absorbed elsewhere cannot effectively cross the corneal barrier. The epithelium is rate-limiting for most drugs; the aqueous region, ie, the stroma, is rate-limiting for very lipophilic drugs.

The eye is highly innervated, and patient comfort is of paramount importance in order to achieve good compliance. The eye is designed to keep the surface free of foreign bodies by blinking, tear production, and rapid drainage into the nasolacrimal duct. The average volume of tears is 7 μL, which is replaced at the rate of 16%/min except when sleeping or under anesthesia. The total precorneal volume is 20 μL, and excess solution applied to the eye is lost by spillage. Two approaches used to increase the residence time of drugs in the eye, and consequently the amount of drug absorbed, are increasing the viscosity of the solution and the use of an implant, such as Ocusert, or hydrogel contact lenses loaded with drug. Polymers that undergo a phase change from a liquid to a gel in response to temperature, pH, or ionic strength also show promise in this field.

2.8. Vaginal. The vaginal mucosa consists of stratified squamous epithelium, thrown into numerous transverse folds or rugae. The area is well supplied with both blood and lymphatic drainage. Changes in the human vaginal epithelium are considerably less pronounced during the estrous cycle than those observed in subhuman primates and many other animals. This route may offer opportunities for systemic delivery for the treatment of diseases, such as osteoporosis, in which the patient population is predominantly female. In a study in the rat, the ovulation-inducing activity of leuprolide [53714-56-0] was compared after intravenous, subcutaneous, oral, rectal, nasal, and vaginal administration (79). Vaginal administration exhibited the greatest potency of all the nonparenteral routes studied.

3. Need of Controlled Drug Release Systems

The ways in which drugs or new biological products are administered have gained increasing attention in the past few decades. Controlled release systems provide numerous benefits over the conventional dosage forms. Conventional dosage forms, which are still predominant for the pharmaceutical products, are not able to control either the rate of drug delivery or the target area of drug administration and provide an immediate or rapid drug release. This necessitates frequent administration in order to maintain a therapeutic level. As a result, drug concentrations in the blood and tissues fluctuate widely (Fig. 1). The concentration of drug is initially high, that can cause toxic and/or side

effects, then quickly fall down below the minimum therapeutic level with time elapse (1,6). The duration of therapeutic efficacy is dependent upon the frequency of administration, the half-life of the drug, and release rate from the dosage form. In contrast, controlled release dosage forms are not only able to maintain therapeutic levels of drug with narrow fluctuations but they also make it possible to reduce the frequency of drug administration (80). Drug concentration profile in serum depends on the preparation technology, which may generate different release kinetics resulting in different pharmacological and pharmacokinetic responses in the blood or tissues (81).

Controlled drug release formulations offer several advantages over conventional dosage forms. Some of the salient features of controlled release formulations are as follows. (*1*) The drug is released in a controlled fashion that is most suitable for the application. The control could be in terms of onset of release (delayed vs. immediate), duration of release, and release profile itself. (*2*) The frequency of doses could be reduced thereby enhancing patient compliance. (*3*) The drug could be released in a targeted region. This could be achieved either by tailoring the formulation to release the drug in that particular environment or by timed release of the drug. By targeting drug release, drug efficacy could be maximized. (*4*) By targeting the drug to the desired site, systemic exposure of the drug could be reduced, thereby decreasing systemic side effects (especially for toxic drugs). (*5*) The drug could be protected from the physiological environment for a longer duration of time. Thus the effective residence time of the drug could be extended.

However, controlled release products do not always provide positive effects for every type of formulation design. Negative effects outweigh benefits in the following circumstances (82,83): (*1*) Dose dumping; (*2*) less accurate dose adjustment; (*3*) increased potential for first-pass metabolism; (*4*) dependence on residence time in gastrointestinal (GI) tract; and (*5*) delayed onset.

The limitations of controlled drug release formulations (CDRFs) technology making some drugs unsuitable for formulations are as follows (84,85): (*1*) There is a risk of drug accumulation in the body if the administered drug has a long half-life, causing the drug to be eliminated at a slower rate than it is absorbed. (*2*) Some drugs have a narrow therapeutic index, and thus, need to administer repeatedly to maintain the serum drug level within a narrow range. Such drugs may not be feasible for CDRF. (*3*) If the GI tract limits the absorption rate of the drug, the effectiveness of the CDRF is limited (for oral controlled release). (*4*) If a drug undergoes extensive first-pass clearance, its controlled release formulation may suffer from lower bioavailability. (*5*) The cost of CDRF may be substantially higher than the conventional form.

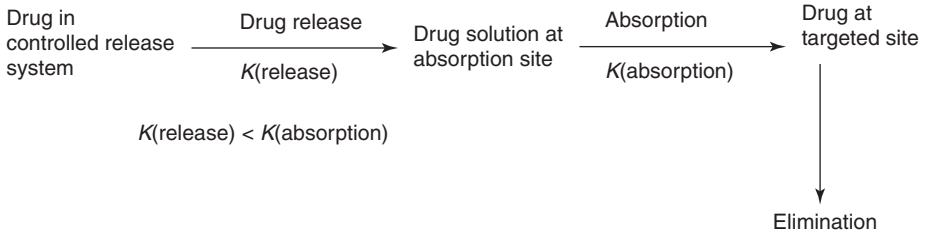
Especially from the point of view of cost, improvement of safety and efficacy of the new products alone has not been enough to justify introducing new CDRF products. Evaluation of economic benefits, costs, and quality of life impact need to be assessed.

4. Design of Controlled Release Systems

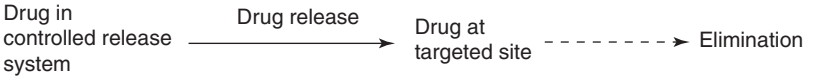
A controlled release system comprises a drug and the material in which the drug is loaded. This system must be biocompatible and friendly with the body.

Because of this reason, selection of the drug and the polymer along with desired properties is a prime factor in designing a controlled release system to deliver the drug at the desired site of action in the body (86).

Before designing a controlled drug release system, one has to select the route of drug delivery with several considerations which include physical and chemical properties of the drug, doses of the drug, route of administrations, type of drug delivery system desired, desired therapeutic effect, physiologic release of the drug from delivery system, bioavailability of the drug at the absorption site, and pharmacodynamics of the drugs (82,87). These properties of the drug can be discussed in two ways, viz. behavior of the drug in its delivery system and behavior of the drug and its delivery system in the body. In the former part, drug properties can influence release characteristics from its delivery systems, for example, in any controlled release system, drug availability is controlled by the drug release kinetics rather than absorption, and the associated rate constant for drug release are smaller than the absorption rate constant. To control drug release, one can employ a variety of approaches, such as, dissolution (88,89), diffusion (90,91), swelling (92,93), osmotic pressure (94,95), complexation (96), ion-exchange (97,98), and magnetic field (99,100).



In the second part, behavior of the drug and its delivery system is extremely complex, involving the fate of drug during transit to the target area as well as its fate in the biophase. The effectiveness of the drug at its target area depends on the pharmacokinetics of the drug and its carrier in the body (101).



4.1. Physicochemical Properties of Drugs. Physicochemical properties of the drug affect the drug release performance of a controlled drug release system in the body (102). These properties, which include aqueous solubility, drug stability, molecular size, partition coefficient, and protein binding, may prohibit/restrict placement of drug in controlled release, restrict the route of drug administration, and significantly restrict the drug release performance for one reason or the other. Physicochemical properties can be determined from *in vitro* experiment, while biological properties are those that result from typical pharmacokinetic studies on the absorption, distribution, metabolism, and excretion characteristics of the drug and those resulting from pharmacological studies (101). Compounds with very low aqueous solubility usually suffer oral bioavailability problems because of limited GI transit time of the undisclosed particles and limited solubility at absorption site. Unfortunately, for many drugs, the

site of maximum absorption is the area in which the drug is least soluble. Thus, choice of oral controlled/sustained release formulations is limited by aqueous solubility of the drug. This property may be useful for matrix-type devises where these limitations can be utilized to achieve sustained/controlled drug release; however, dissolution-limited bioavailability may occur. Partition coefficient (103) and molecular size of the drug influence not only the permeation of a drug across biological membrane but also the diffusion across or through a rate-controlling membrane or matrix (104). Drugs with extremely high partition coefficient (ie, drugs having high oil solubility) readily penetrate the membranes but are unable to proceed further, while the drug with excessive aqueous solubility, for example, low oil–water partition coefficient, cannot penetrate the membranes. Hence, a balance in the partition coefficient is needed to give an optimum flux for permeation through the biological and rate-controlling membranes.

Drug stability in biological media provides the bioavailability; for example, drugs that are unstable in the stomach can be placed in a slowly soluble form or have their release delayed until they reach the small intestine. Drug and plasma protein interaction influences the duration of drug action. It is well known that blood proteins are mostly recirculated and not eliminated; thus, drug protein binding can serve as a depot for drug producing a prolong release profile if a high degree of drug binding occurs.

4.2. Biological Properties of Drugs. At the time of designing a system, a comprehensive picture of drug deposition must be very clear and this should be based on a complete examination of pharmacological action of the drug in the *in vivo* experiments, which include adsorption, distribution, metabolism, and excretion (ADME) (Fig. 2). The pharmacological action of a drug can be correlated better with the concentration–time course of the drug (or its active metabolite) in the blood or some other biophase than with the absolute dose administered, and it involves pharmacokinetics and pharmacodynamics of a drug in the body. Pharmacokinetics facilitates predictions of time course of drug concentrations and drug action in the body (101,105), while pharmcodynamics offer a quantitative assessment of the time course of drug effect on the body after administration by any route (101,106). From a pharmacokinetics standpoint, there are two fundamental approaches to design the formulations that allow for the attainment of the desired therapeutic concentration of the drug and are maintained throughout a dosing interval (83). The first approach involves selection of the drugs that have long enough elimination half-lives to be administered infrequently. This approach can be successful if an analog from a class of biologically active drug has a long elimination half-life or can be adopted in the early stage of a new developing drug candidate to avoid a time-consuming and cost-extensive research and development program in animal/human. In the second approach, drug formulations are modified in such a way that the fluctuation in drug concentrations during a dosing interval is reduced. Thus, with a prior knowledge of a drug's elimination and distribution pharmacokinetics and the use of correct approach to the estimation of mean resident time (MRT) (the time a drug molecule takes to traverse through the body and that can be used to compare dosage forms), it is possible to design formulation having particular release characteristics with predictive impacts on the MRT of a drug in the body.

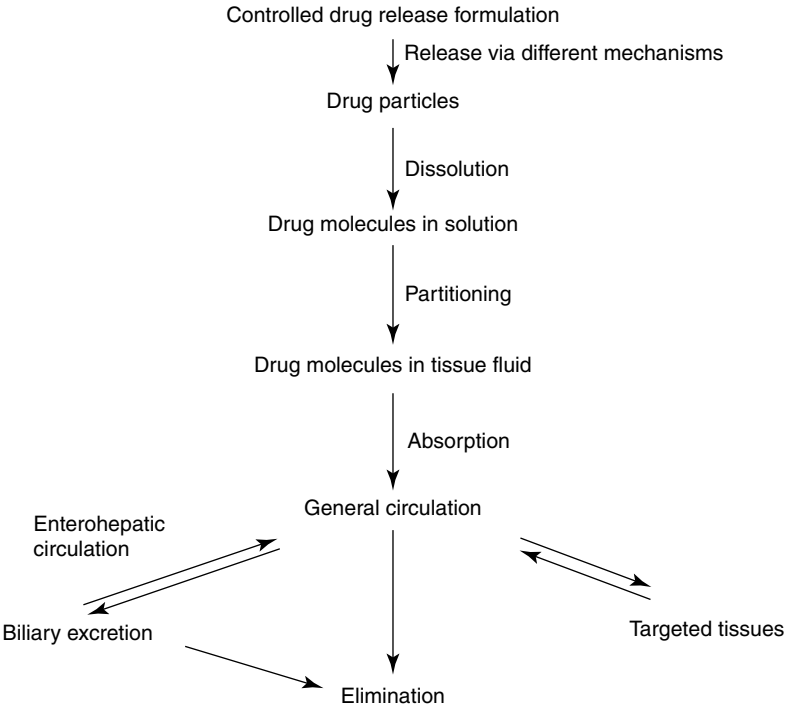


Fig. 2. Fate of drug in controllled release formulation.

Pharmacodynamics of a drug has a significant impact on the design and development of sustained release products, which can also be approached by two fundamental routes. First, if pharmacokinetics of a drug is known then this can be linked to available pharmacodynamic data, resulting in a unified concept relating the kinetics of the drug (or an active metabolite) to the time course of drug effect (82,107). In the second case where pharmacokinetics of the drug cannot be defined accurately [ie, AUCs (area under the curve) cannot be accurately measured because of assay sensivity limitation] or where drug effect is apparently unrelated to concentrations, alternative approaches can be utilized. In this case, one can study the relationship of drug effect and steady-state drug concentration at various drug-dosing levels in the same individual. By using sustained release dosage forms resulting in varying release rate constants, one can derive valuable information regarding a drug product.

Each drug is characterized by its own pharmacokinetic–pharmacodynamic (PK-PD) profile (as a part of the drug-approval process) on the basis of the physicochemical properties, conformation, and other structural attributes that govern the transport within the body and across various barriers. The number and type of biological hurdles a drug has to overcome governs the design of delivery systems as well as the route of administration. Compared to the general "sigmoid" PK-PD profile for conventional molecules, the PK-PD relationship of biopharmaceuticals is complicated by short biological half-life, instability, multiple biological actions and operation of compensatory regulatory events in the body.

Once the PK-PD relations have been established, plasma levels can be substituted for therapeutic effects that can aid in setting PK bioequivalence standards. In near future, one of the major objectives of CDRF technology should be to match medication delivery in time with biological rhythm (108,109). One such CDRF is Covera-HS (Pharmacia Corp; verapamil HCl) tablets, which attempts to match the body circadian rhythm for treatment of blood pressure rate (108). Covera-HS is taken at bedtime and the drug release is retarded during the sleep period (4–5 h) to achieve optimal blood levels between early morning and noon.

4.3. Factors That May Make a Drug Unsuitable for CDRF. Some drugs are not fit for controlled release because of the nature of drug action, physical limitations (large dose, duration of drug release), and alternative administration, ie, oral daily doses vs. monthly implant, etc. Drugs that are given at acute situations are usually not useful for controlled extended release, for example, tissue plasminogen activator (TPA) that is given during a heart attack to dissolve blood clotting and allow blood flow. Any delay in medication may result in death. In another example, when someone is suffering from a headache and needs immediate relief, these controlled release systems are not useful. Drugs that have a beneficial effect in the body at specific times during the day should be given only at that time, and not be delivered in large doses of controlled release formulations, which may otherwise result in unnecessary dose dumping.

Thus, the following drug properties and therapeutic requirement should be taken into account in designing a controlled release system: (*1*) Drug elimination half-life; (*2*) doses to be administered; (*3*) therapeutic index; (*4*) low solubility; (*5*) route of administration; (*6*) poor absorption; (*7*) extensive first-pass clearance; (*8*) difference in time course of circulating drug level with its pharmacological effects; and (*9*) PD vs. PK of the drugs.

5. Development Basics

5.1. Control of Drug Concentration Levels Over Time. The overall goal in developing controlled release devices is maintaining the drug in the therapeutic range (zero-order release kinetics) and targeting delivery to specific tissues (lowering systemic exposure and side effects). Polymers have been used in developing all four types of devices, classified by release mechanism: (*1*) diffusion controlled, both reservoir and monolithic; (*2*) chemically controlled release, that is, bioerodible carriers; (*3*) solvent controlled release, where swelling of the matrix is the mechanism that enables the entrapped drug to come out; and (*4*) externally controlled release (110).

Although newer and more powerful drugs continue to be developed, increasing attention is being given to the methods of administering these active substances. In conventional drug delivery, the drug concentration in the blood rises when the drug is taken, then peaks, and declines. Maintaining drug in the desired therapeutic range by using just a single dose or targeting the drug at a specific area (lowering the systemic drug level) are goals that have been successfully attained by using commercially available controlled release devices (111). However, there are many clinical situations where the approach of a

constant drug delivery rate is insufficient, such as the delivery of insulin for patients who have diabetes mellitus, antiarrhythmics for patients who have heart rhythm disorders, gastric acid inhibitors for ulcer control, nitrates for patients who have angina pectoris, as well as selective β-blockade, birth control, general hormone replacement, immunization, and cancer chemotherapy. Furthermore, studies in the field of chronopharmacology indicate that the onsets of certain diseases exhibit strong circadian temporal dependence. Thus, treatment of these diseases could be optimized by using responsive delivery systems (112), which are, in essence, man-made imitations of healthy function.

5.2. Biocompatibility. When designing a controlled delivery device, the effects of the drug must be taken into account and also the potential effects of the device itself on the biological system (113). In other words, both the effects of the implant on the host tissues and the effects of the host on the implant must be considered. These are some of the important potential effects: inflammation and the "foreign body reaction," immunologic responses, systemic toxicity, blood–surface interactions, thrombosis, device-related infection, and tumorigenesis (113). Many of these effects actually comprise the body's defense mechanism against injury; placement of a drug delivery device in the body causes injury and therefore, elicits these reactions. However, the degree of perturbation is strongly impacted by the biomaterial that comprises the device.

The first response to be triggered is inflammation. The cellular and molecular mechanisms have been well described, but avoiding them has not yet been achieved. Many of the inflammatory responses are local to the site of implantation and dissipate relatively quickly. Some of the most potent chemical mediators, such as lysosomal proteases and oxygen-derived free radicals also play an important role in the degradation and wear of biomaterials (110).

The products of degradation and wear can cause immune responses and/or nonimmune systemic toxicity. Thus, when testing a delivery device, both the intact device and its degradation products must be thoroughly examined *in vitro* before implantation *in vivo*. An additional phenomenon that can hamper the device's function is fibrous encapsulation of the biomaterial. These reactions can be very specific to the host, and *in vivo* experiments are not always indicative of the human response.

5.3. Classification of "Smart" Polymers. "Intelligent" controlled release devices can be classified as open- or closed-loop systems, as shown in Fig. 3. Open-loop control systems (Fig. 3**a**) are those where information about the controlled variable is not automatically used to adjust the system inputs to compensate for the change in process variables. In the controlled drug delivery field, open-loop systems are known as pulsatile or externally regulated. Externally controlled devices apply external triggers such as magnetic, ultrasonic, thermal, or electric irradiation for pulsatile delivery.

Closed-loop control systems, on the other hand, are defined as systems where the controlled variable is detected, and as a result the system output is adjusted accordingly. Closed-loop systems are known in the controlled drug delivery field as self-regulated. The release rate in self-regulated devices is controlled by feedback information without any external intervention, as shown in Fig. 3**b**. Self-regulated systems use several approaches for rate control mechanisms (114,115) such as pH-sensitive polymers, enzyme–substrate reactions,

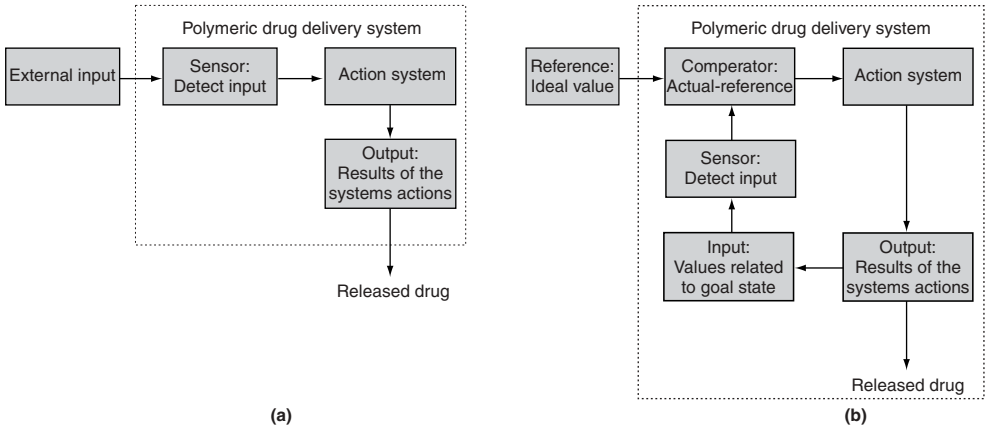


Fig. 3. Schematic representation of drug delivery systems and their control mechanisms: (**a**) open-loop system; (**b**) closed-loop system.

pH-sensitive drug solubility, competitive binding, antibody interactions, and metal concentration-dependent hydrolysis.

6. Pulsatile Systems

6.1. Magnetically Stimulated Systems. *Feasibility.* Drug molecules and magnetic beads are uniformly distributed within a solid polymeric matrix in magnetically triggered systems. Although drug is released by diffusion when the device is exposed to fluids, a much higher release rate is obtained in the presence of an external oscillating magnetic field. The magnetic system was characterized *in vitro* (116–118). Subsequent *in vivo* (119) studies showed that when polymeric matrices made of ethylene–vinyl acetate copolymer (EVAc) that contain insulin and magnetic beads are placed subcutaneously in diabetic rats for two months, glucose levels can be repeatedly and reproducibly decreased on demand by applying an oscillating magnetic field.

Mechanisms. The two principal parameters that control the release rates in these systems are the magnetic field characteristics and the mechanical properties of the polymer matrix. It was found that when the frequency of the applied field was increased from 5 to 11 Hz, the release rate of bovine serum albumin (BSA) from EVAc copolymer matrices rose linearly (116). Investigation into the effect of magnetic field frequency and repeated field application on insulin release from alginate matrices and found that using repeated applications, inverse effects can occur: high frequencies gave a significant release enhancement for the second magnetic field application (120). Subsequent stimulation resulted in decreased enhancement due to faster depletion at high frequencies.

The mechanical properties of the polymeric matrix also affect the extent of magnetic enhancement (116). For example, the modulus of elasticity of the EVAc copolymer can easily be altered by changing the vinyl acetate content of the copolymer. The release rate enhancement induced by the magnetic field increases as

the modulus of elasticity of EVAc decreases. A similar phenomenon was observed for cross-linked alginate matrices: higher release rate enhancement for less rigid matrices (120). Edelman also enhanced release rates observed in response to an electromagnetic field (50 G, 60 Hz) applied for 4 minutes were independent of the duration of the interval between repeated pulses (121).

6.2. Ultrasonically Stimulated Systems. *Feasibility.* Release rates of substances can be repeatedly modulated at will from a position external to the delivery system by ultrasonic irradiation (122). Both bioerodible and nonerodible polymers were used as drug carrier matrices.

The bioerodible polymers evaluated were polyglycolide, polylactide, poly (bis(*p*-carboxyphenoxy)) alkane anhydrides and their copolymers with sebacic acid. Both the polymer erosion and drug release rates were enhanced when the bioerodible samples were exposed to ultrasound. The system's response to ultrasonic triggering was rapid (within 2 minutes) and reversible. The releasing agents, *p*-nitroaniline, *p*-aminohippurate, bovine serum albumin, and insulin, were tested for integrity following exposure to ultrasonic energy and were found intact.

The enhanced release was also observed in nonerodible systems exposed to ultrasound where the release is diffusion-dependent. Release rates of zinc bovine insulin from EVAc copolymer matrices were 15 times higher when exposed to ultrasound compared to the unexposed periods.

In vivo studies (122) have suggested the feasibility of ultrasound-mediated drug release enhancement. Implants composed of polyanhydride polymers loaded with 10% *p*-aminohippuric acid (PAH) were implanted subcutaneously in the backs of catheterized rats. When exposed to ultrasound, a significant increase in the PAH concentration in urine was detected (400%). Rat's skin histopathology of the ultrasound-treated area after an exposure of 1 hour at 5 W/cm^2 did not reveal any differences between treated and untreated skin.

Similar phenomena were observed responding the evaluation of the effect of ultrasound (1 MHz) on the release rates of insulin from ethylene vinyl alcohol copolymer matrices and reservoir type drug delivery systems (123). When diabetic rats that received implants containing insulin were exposed to ultrasound (1 W/cm^2 for 30 min), a sharp drop in blood glucose levels was observed after the irradiation, indicating a rapid rate of release of insulin at the implanted site.

During the past 40 years, numerous clinical reports have been published concerning phonophoresis (124), the technique of using ultrasonic irradiation to enhance transdermal drug delivery. Ultrasound nearly completely eliminated the usual lag time for transdermal delivery of drugs. Ultrasound irradiation (1.5 W/cm^2 continuous wave or 3 W/cm^2 pulsed wave) for 3–5 minutes increased the transdermal permeation of insulin and mannitol in rats by 5–20-fold within 1–2 hours after ultrasound application.

Similar studies were performed that evaluated the effect of ultrasound (1 MHz) on indomethacin permeation in rats. Pronounced effects of ultrasound on transdermal absorption for all three ranges of intensities (0.25, 0.5, and 0.75 W/cm^2) were observed (125). The effects of ultrasound on the transdermal permeation of the electron-dense tracer, lanthanum nitrate were examined (126), and it was demonstrated that exposure of the skin to ultrasound can induce considerable and rapid tracer transport through an intercellular route. Prolonged

exposure of the skin to high-frequency ultrasound (20 min, 16 MHz), however, resulted in structural alterations of epidermal morphology. Tachibana and coworkers (127–129) reported using low-frequency ultrasound (48 KHz) to enhance transdermal transport of lidocaine and insulin through hairless mice skin. Low-frequency ultrasound was also used by (130,131) to enhance transport of various low molecular weight drugs, including salicylic acid and corticosterone, as well as high molecular weight proteins, including insulin, γ-interferon, and erythropoeitin, through human skin *in vitro* and *in vivo*.

Mechanisms. It was proposed (122) that cavitation and acoustic streaming are responsible for the augmented degradation and release of bioerodible polymers. In experiments conducted in a degassed buffer where cavitation was minimized, the observed enhancement in degradation and release rates was much smaller. It was also considered that several other parameters (temperature and mixing effects) might be responsible for the augmented release due to ultrasound. However, experiments were conducted which suggested that these parameters were not significant. It has also been demonstrated that the extent of release rate enhancement can be regulated by the intensity, frequency, or duty cycle of the ultrasound.

Speculation that the ultrasound caused increased temperatures in their delivery system, which may facilitate diffusion in discussed in Ref. 123. The increased temperature caused by ultrasound or other forms of irradiation can be used as a trigger to cause collapsing of a hybrid hydrogel that has protein domains (132).

The role played by various ultrasound-related phenomena, including cavitation, thermal effects, generation of convective velocities, and mechanical effects during phonophoresis is evidulated in Ref. 133. The authors' experimental findings suggest that among all the ultrasound-related phenomena evaluated, cavitation plays the dominant role in sonophoresis using therapeutic ultrasound (frequency: 1–3 MHz; intensity; 0–2 W/cm^2). Confocal microscopy results indicate that cavitation occurs in the keratinocytes of the stratum corneum upon ultrasound exposure. The authors hypothesized that oscillations of the cavitation bubbles induce disorder in the stratum corneum lipid bilayers, thereby enhancing transdermal transport. The theoretical model developed to describe the effect of ultrasound on transdermal transport predicts that sonophoretic enhancement depends most directly on the passive permeant diffusion coefficient in water, not on the permeant diffusion coefficient through the skin.

6.3. Electrically Stimulated Systems. *Feasibility.* Electrically controlled systems provide drug release by the action of an applied electric field on a rate-limiting membrane and/or directly on the solute and thus control its transport across the membrane. The electrophoretic migration of a charged macrosolute within a hydrated membrane results from the combined response to the electrical forces on the solute and its associated counterions in the adjacent electrolyte solution (134).

Electrically controlled membrane permeability has also been of interest in the field of electrically controlled or enhanced transdermal drug delivery (eg, iontophoresis, electroporation) (135,136).

Anionic gels as vehicles for electrically modulated drug delivery were studied (137). Agarose and combinations of agarose and anionic polymers

(polyacrylic acid, xanthan gum) were evaluated. The authors conclude that the use of carbomer (polyacrylic acid) in conjunction with agarose enables the formulator to achieve zero-order release by electrical field application. Increased anisotropicity of a gel system due to the application of electrical current could alter the effectiveness of the drug delivery system.

D'Emanuele and Staniforth (138) proposed a drug delivery device that consists of a polymer reservoir that has a pair of electrodes placed across the rate-limiting membrane. By altering the magnitude of the electric field between the electrodes, the authors proposed to modulate the drug release rates in a controlled and predictable manner. A linear relationship was found between current and propanolol HCL permeability through poly(2-hydroxyethyl methacrylate) (PHEMA) membranes cross-linked with ethylene glycol dimethacrylate (1%v/v). It was found that buffer ionic strength, drug reservoir concentration, and electrode polarity have significant effects on drug permeability (139).

Labhassetwar and co-workers (140) propose a similar approach for modulating cardiac drug delivery. The authors studied a cardiac drug implant in dogs that can modulate electric current. A cation-exchange membrane was used as an electrically sensitive rate-limiting barrier on the cardiac-contacting surface of the implant. The cardiac implant demonstrated *in vitro* drug release rates that were responsive to current modulation. *in vivo* results in dogs confirmed that electrical modulation resulted in regional coronary enhancement of drug levels and a current-responsive increase in drug concentration.

A different approach for electrochemical controlled release is based on polymers that bind and release bioactive compounds in response to an electric signal (141). The polymer has two redox states, only one of which is suitable for ion binding. Drug ions are bound in one redox state and released from the other. The attached electrodes switch the redox states, and the amount of current passed can control the amount of ions released. A proposal to use this method of electrochemical pulse stimulation on a novel composite polpyrrole film for delivering cationic drugs directly to the central nervous system (CNS) is discussed in Ref. 142.

By encapsulating drugs in multicomponent hydrogel microspheres, a synthetic mimic of the secretory granule that can be triggered to release the bioactive agent by various forms of external stimulation (143). The external protective lipid membrane was porated by electrical stimulation. Following electroporation, the hydrogel microsphere quickly swells to dissipate the pH gradient. The swelling leads to a burst of drug release. Thus, an off/on irreversible mechanism is described that can be triggered in a controlled fashion (143).

Mechanisms. Four different mechanisms for the transport of proteins and neutral solutes across hydrogel membranes have been reported (144): (*1*) electrically and chemically induced swelling of a membrane to alter the effective pore size and permeability, (*2*) electrophoretic augmentation of solute flux within a membrane, (*3*) electrosmotic augmentation of solute flux within a membrane, and (*4*) electrostatic partitioning of charged solutes into charged membranes.

The effect of electric current on solute release from cross-linked poly(2-acrylamido-2-methylpropane sulfonic acid-*co*-*n*-butylmethacrylate) has been studied (145). Edrophonium chloride, a positively charged solute, was released in an on-off pattern from a matrix (monolithic) device by an electric field. The

mechanism was explained as an ion exchange between a positive solute and the hydroxonium ion, followed by fast release of the charged solute from the hydrogel. The fast release was attributed to electrostatic force, a squeezing effect, and electro-osmosis of the gel. However, the release of neutral solute was controlled by diffusion effected by swelling and deswelling of the gel.

6.4. Photostimulated Systems. *Feasibility.* Photoinduced phase transition of gels was reported (146). Copolymer gels of *N*-isopropylacrylamide and the photosensitive molecule bis(4-dimethylamino)phenyl-(4-vinylphenyl)-methyl leucocyanide showed a discontinuous volume phase transition upon ultraviolet irradiation that was caused by osmotic pressure of cyanide ions created by the ultraviolet irradiation.

Photoresponsive degradation of heterogeneous hydrogels comprised of cross-linked hyaluronic acid and lipid microspheres for temporal drug delivery has been proposed (147). Visible light induced degradation of cross-linked hyaluronic acid gels by photochemical oxidation using methylene blue as the photosensitizer. Hyaluronic acid gels are inflammation-responsive (148).

By combining technologies developed for targeted drug delivery and external photostimulation of the active agent released, polymeric micelles to deliver water-insoluble, photosensitizing anticancer drugs can be used (149).

Mechanisms. Photoresponsive gels reversibly change their physical or chemical properties upon photoradiation. A photoresponsive polymer consists of a photoreceptor, usually a photochromic chromophore, and a functional part. The optical signal is captured by the photochromic molecules, and then isomerization of the chromophores in the photoreceptor converts it to a chemical signal.

A phase transition in polymer gels induced by visible light, where the transition mechanism is due only to the direct heating of the network polymer by light has been reported (150).

7. Self-Regulated Systems

7.1. Environmentally Responsive Systems. Polymers that alter their characteristics in response to changes in their environment have been of great recent interest. Several research groups have been developing drug delivery systems based on these responsive polymers that more closely resemble the normal physiological process. Drug delivery in these devices is regulated by an interaction with the surrounding environment (feedback information) without any external intervention. The most commonly studied polymers that have environmental sensitivity are either pH- or temperature-sensitive. There are also inflammation-sensitive systems and systems that use specific binding interactions.

Temperature-Sensitive Systems. Temperature-sensitive polymers can be classified into two groups based on the origin of the thermosensitivity in aqueous media. The first is based on polymer–water interactions, especially, specific hydrophobic/hydrophilic balancing effects and the configuration of side groups. The other is based on polymer–polymer interactions in addition to polymer–water interactions. When polymer networks swell in a solvent, there is usually a negligible or small positive enthalpy of mixing or dilution. Although a positive

enthalpy change opposes the process, the large gain in entropy drives it. The opposite is often observed in aqueous polymer solutions. This unusual behavior is associated with a phenomenon of polymer phase separation as the temperature is raised to a critical value that is known as the lower critical solution temperature (LCST). *N*-Alkyl acrylamide homopolymers and their copolymers, including acidic or basic comonomers, show this LCST (151,152). Polymers characterized by LCST usually shrink as the temperature is increased through the LCST. Lowering the temperature below the LCST results in swelling of the polymer. Bioactive agents such as drugs, enzymes, and antibodies may be immobilized on or within temperature-sensitive polymers; examples of such uses are discussed below. Responsive drug release patterns regulated by external temperature changes have been recently demonstrated by several groups (151,153–166).

pH-Sensitive Systems. The pH range of fluids in various segments of the gastrointestinal tract may provide environmental stimuli for responsive drug release. Several research groups (167–181) studied polymers that contain weakly acidic or basic groups in the polymeric backbone. The charge density of the polymers depends on the pH and ionic composition of the outer solution (the solution to which the polymer is exposed). Altering the pH of the solution causes swelling or deswelling of the polymer. Thus, drug release from devices made from these polymers display release rates that are pH-dependent. Polyacidic polymers are unswollen at low pH because the acidic groups are protonated and hence un-ionized. Polyacid polymers swell as the pH increases. The opposite holds for polybasic polymers because ionization of the basic groups increases as the pH decreases. The swelling properties of polybasic gels are also influenced by buffer composition (concentration and p*K*a) (182). A practical consequence proposed is that these gels may not reliably mediate pH-sensitive, swelling-controlled release in oral applications because the levels of buffer acids in the stomach (where swelling and release are expected) generally cannot be controlled. However, the gels may be useful as mediators of pH-triggered release when precise rate control is of secondary importance.

More than two phases (swollen and collapsed) are found in gels that consist of copolymers of randomly distributed positively and negatively charged groups (168). Polymer segments in these gels interact with each other through attractive or repulsive electrostatic interactions and through hydrogen bonding. The combination of these forces seems to result in the existence of several phases, each characterized by a distinct degree of swelling, and abrupt jumps occur between them. The existence of these phases presumably reflects the ability of macromolecular systems to adopt different stable conformations in response to changes in environmental conditions. The largest number of phases was seven in copolymer gels prepared from acrylic acid (the anionic constituent) and methacryl-amidopropyl-trimethyl ammonium chloride (460 mmol/240 mmol). A similar approach was proposed (178); membranes made from grafted poly (methacrylic acid-*g*-ethylene glycol) copolymer showed pH sensitivity due to complex formation and dissociation. Uncomplexed equilibrium swelling ratios were 40 to 90 times higher than those of complexed states and varied according to copolymer composition and polyethylene glycol graft length.

Temporally controlled drug delivery systems that couple pH oscillators and membrane diffusion properties have been proposed (183). By changing the pH of a solution relative to the p*K*a, a drug may be rendered charged or uncharged. Because only the uncharged form of a drug can permeate across lipophilic membranes, a temporally modulated delivery profile may be obtained by using a pH oscillator in the donor solution.

Using pH-sensitive bioerodible polymers an enzyme–substrate reaction produces a pH change that is used to modulate the erosion of a pH-sensitive polymer containing a dispersed therapeutic agent (184).

Bioerodible hydrogels that contain azoaromatic moieties have been synthesized (185). Hydrogels that have lower cross-linking density underwent a surface erosion process and degraded at a faster rate. Hydrogels that have higher cross-linking densities degraded at a slower rate by a process in which the degradation front moved inward to the center of the polymer.

Recently, recombinant DNA methods were used to create artificial proteins that undergo reversible gelation in response to changes in pH or temperature (186). The proteins consist of terminal leucine zipper domains that flank a central, flexible, water-soluble polyelectrolyte segment. Formation of coiled-coil aggregates of the terminal domains in near-neutral aqueous solutions triggers formation of a three-dimensional polymer network, where the polyelectrolyte segment retains solvent and prevents precipitation of the chain. Dissociation of the coiled-coil aggregates by elevating pH or temperature causes dissolution of the gel and a return to the viscous behavior that is characteristic of polymer solutions. The authors suggest that these hydrogels have potential in bioengineering applications that require encapsulation or controlled release of molecules and cellular species.

Inflammation-Responsive Systems. An inflammation-responsive drug delivery system based on biodegradable hydrogels of cross-linked hyaluronic acid is discussed in Ref. 148. Hyaluronic acid is specifically degraded by hydroxyl radicals that are produced locally at inflammatory sites by phagocytic cells such as leukocytes and macrophages. In their approach, drug-loaded lipid microspheres were dispersed into degradable matrices of cross-linked hyaluronic acid.

A biodegradable, biocompatible, inflammation-responsive microsphere system has been developed (187). The gelatin microspheres were synthesized by complex coacervation, a low temperature method that does not denature the encapsulated active agent. Gelatinase and stromelysin are activated in the synovial fluid of an inflamed joint. These enzymes degrade the gelatin microspheres and thus cause release of the bioactive protein, making this delivery system potentially useful for treating osteoarthritis.

An infection-responsive delivery system was developed and discussed in Ref. 188. As in an inflammatory response, inflection responses are characterized by the secretion of specific proteins. By responding to thrombin-like activity in infected wound fluid, the novel system released gentimycin as needed, thus avoiding problematic overexposure to antibiotics.

7.2. Systems Using Specific Binding Interactions. All of the following drug delivery systems use a specific binding interaction to manipulate the microenvironment of the device and thus modulate the rate of drug release

from the polymer. The basic principles of binding and competitive binding are the underlying mechanism of the function of these systems.

Systems Using Antibody Interactions. The use of hapten–antibody interactions to suppress the enzymatic degradation and permeability of polymeric reservoirs or matrix drug delivery systems has been discussed (189). The delivery device consists of naltrexone contained in a polymeric reservoir or dispersed in a polymeric matrix configuration. The device is coated by covalently grafting morphine to the surface. Exposure of the grafted surface to antibodies to morphine results in coating of the surface by the antibodies, a process that can be reversed by exposure to exogenous morphine. Antibodies on the surface or in the pores of the delivery device block or impede the permeability of naltrexone in a reservoir configuration or enzyme-catalyzed surface degradation and the concomitant release of the drug from a matrix device. A similar approach was proposed for responsive release of a contraceptive agent. The β subunit of human chorionic gonadotropin (HCG) is grafted to the surface of a polymer, which is then exposed to antibodies to β-HCG. The appearance of HCG in the circulatory system (indication of pregnancy) causes release of a contraceptive drug. (HCG competes for the polymer-bound antibodies to HCG and initiates release of the contraceptive drug.)

A hypothetical reversible antibody system for controlled release of ethinyl estradiol (EE) has been proposed (189,190). EE stimulates biosynthesis of sex-hormone-binding globulin (SHBG). High serum levels of EE stimulate the production of SHBG, which increases the concentration of SHBG bound to the polymer surface and reduces the EE release rate. When the EE serum level falls, the SHBG level falls, as does binding of the SHBG to the polymer surface, which produces an automatic increase in the EE release rate.

The reversible binding of antigen to antibody that is the basis for swelling of a hydrogel that could lead to release of a bioactive agent was recently reported (191) and the grafting of both antigen and antibody in the polymer network that causes the formation of reversible cross-linking is described. In the presence of free antigen that competes with the immobilized antigen, swelling ensues (191) and creates an antigen-responsive hydrogel.

Systems Using Chelation. Self-regulated delivery of drugs that function by chelation was also suggested (192). These include certain antibiotics and drugs for treating arthritis, as well as chelators used for treating metal poisoning. The concept is based on the ability of metals to accelerate the hydrolysis of carboxylate or phosphate esters and amides by several orders of magnitude. Attachment of the chelator to a polymer chain by a covalent ester or amide link prevents premature loss by excretion and reduces its toxicity. In the presence of the specific ion, a complex with the bound chelating agent forms, followed by metal-accelerated hydrolysis and subsequent elimination of the chelated metal. Measurement of the rates of hydrolysis of poly(vinyl alcohol) coupled with quinaldic acid chelator (PVA-QA) in the presence of Co(II), Zn(II), Cu(II), and Ni(II) confirmed that it is possible to retain the susceptibility of the esters to metal-promoted hydrolysis in a polymer environment.

Recently, reported (193) was the development of a calcium-responsive drug delivery system. Calcium in external media reactivates α-amylase that was immobilized after being reversibly inactivated in a starch matrix. The activated

enzyme causes degradation of the matrix, thus releasing an entrapped active agent. These investigators also developed a compartmental mathematical model that describes the release and degradation mechanisms involved (194).

7.3. Systems Using Enzymes. In this approach, the mechanism is based on an enzymatic reaction. One possible approach studied is an enzymatic reaction that results in a pH change and a polymer system that can respond to that change.

Urea-Responsive Delivery. Heller and co-workers (184) were the first to attempt using immobilized enzymes to alter local pH and thus cause changes in polymer erosion rates. The proposed system is based on converting urea to NH_4HCO_3 and NH_4OH by the action of urease. Because this reaction causes a pH increase, a polymer that is subjected to increased erosion at high pH is required.

The authors suggested a partially esterified copolymer of methyl vinyl ether and maleic anhydride. This polymer displays release rates that are pH-dependent. The polymer dissolves by ionizing the carboxylic acid group. The pH-sensitive polymer that contains dispersed hydrocortisone is surrounded by urease immobilized in a hydrogel that is prepared by cross-linking a mixture of urease and BSA with glutaraldehyde. When urea diffuses into the hydrogel, its interaction with the enzyme leads to a pH increase, therefore, resulting in enhanced erosion of the pH-sensitive polymer and concomitant increases in the release rate of hydrocortisone.

Refs. 195,196 give information on a nonerodible system based on a similar idea. The system is comprised of a pH-sensitive membrane, produced by copolymerizing 4-carboxy acrylanilide with methacrylate, sandwiched within a membrane that contains urease immobilized in free radically cross-linked *N*,*N*-methylenebisacrylamide. The permeation of a model substance, (1,4-bis-2-hydroxyethoxy) benzene, varied with the urea concentration in the external solution.

Morphine Triggered Naltrexone Delivery System. A naltrexone drug delivery system that would be passive until drug release is initiated by the appearance of morphine external to the device has been developed (197–204). Naltrexone is a long acting opiate antagonist that blocks opiate-induced euphoria, and thus the intended use of this device is to treat heroin addiction. Activation is based on the reversible inactivation of enzymes achieved by the covalent attachment of hapten close to the active site of the enzyme–hapten conjugate with the hapten antibody. Because the antibodies are large molecules, access of the substrate to the enzyme's active site is sterically inhibited and thus effectively renders the enzyme inactive. Triggering of drug release is initiated by the appearance of morphine (hapten) in the tissue and dissociation of the enzyme–heptan–antibody complex that renders the enzyme active. This approach is being developed by incorporating the naltrexone in a bioerodible polymer. The polymer matrix is then covered by a lipid layer that prevents water entry, and this prevents its degradation and therefore also the release of naltroxane. The system is placed in a dialysis bag. The bag contains lipase (enzyme) that is covalently attached to morphine and reversibly inactivated by antimorphine complexation. Thus, when morphine is present in the tissues that surround the device, morphine diffuses into the dialysis bag, displaces the

lipase-morphine conjugate from the antibody, and allows the now activated enzyme to degrade the protective lipid layer. This in turn permits degradation of the polymeric core and subsequent release into the body of the narcotic antagonist, naltrexone.

A key component of this morphine-responsive device is the ability to inactivate an enzyme reversibly and completely and to disassociate the complex rapidly using concentrations as low as 10^{-8} to 10^{-9} M. To achieve this sensitivity, lipase was conjugated with several morphine analogs and complexed with polyclonal antimorphine antibodies purified by affinity chromatography. *in vivo* studies (200) suggest that the concentration of morphine in a device implanted in a typical heroin-addicted patient is estimated at about 10^{-7} to 10^{-8} M. Recent studies have shown that reaching such sensitivity is possible (198).

7.4. Glucose-Responsive Insulin Delivery. The development of glucose-sensitive insulin-delivery systems has used several approaches, including immobilized glucose oxidase in pH-sensitive polymers, competitive binding, and a polymer–complex system. None of the present modes of treatment, including insulin pumps, fully mimics the physiology of insulin secretion. Therefore the development of a "smart" insulin-delivery system could significantly help patients who have diabetes to control their blood glucose level and thus avoid the various severe complications including eye disease, gangrene of the extremities, cardiovascular disease, and renal failure (205).

Polymer–Complex System. A glucose-sensitive insulin release system based on a sol–gel transition is proposed in Ref. 206. A phenylboronic acid (PBA) moiety was incorporated in poly(*N*-vinyl-2-pyrrolidone) by the radical copolymerization of *N*-vinyl-2-pyrrolidone with *m*-acrylamidophenylboronic acid [poly(NVP-*co*-PBA)]. Insulin was incorporated into a polymer gel formed by a complex of poly(vinyl alcohol) with poly(NVP-*co*-PBA). PBA can form reversible covalent complexes with molecules that have diol units, such as glucose or PVA. By adding glucose, PVA in the PVA–boronate complex is replaced by glucose. This leads to a transformation of the system from the gel to the sol state that facilitates the release of insulin from the polymeric complex. The same group of researchers (207) modified the approach and suggested glucose-responsive gels based on complexation between polymers that have phenylboronic acid groups and PVA. The introduction of an amino group into phenylborate polymers was effective in increasing the complexation ability and the glucose responsivity at physiological pH.

The modified insulin that contains two gluconic acid units per insulin (G-Ins) was bound into a PBA gel column, and the G-Ins release profile in response to varying concentrations of glucose was studied (208). Concentration of released G-Ins from PBA gel responded to concentration changes of the eluting glucose. These polymeric complexes have been applied as interpenetrating polymer networks to achieve pulsatile insulin release in response to changes in glucose concentration.

Competitive Binding. The basic principle of competitive binding and its application to controlled drug delivery was first presented by Brownlee and Cerami (209) who suggested the preparation of glycosylated insulins that are complementary to the major combining site of carbohydrate binding proteins such as Concavalin A (Con A). Con A is immobilized on Sepharose™ beads.

The glycosylated insulin, which is biologically active, is displaced from the Con A by glucose in response to, and proportional to, the amount of glucose present that competes for the same binding sites. Also it was form found that the release rate of insulin also depends on the binding affinity of an insulin derivative to Con A and can be influenced by the choice of the saccharide group in glycosylated insulin (210–217). By encapsulating the glycosylated insulin-bound Con A by using a suitable polymer that is permeable to both glucose and insulin, the glucose influx and insulin efflux would be controlled by the encapsulation membrane.

It was found (211) that glycosylated insulins are more stable to aggregation than commercial insulin and are also biologically active. The functionality of the intraperitoneally implanted device was tested in pancreatectomized dogs by an intravenous glucose tolerance test (IVGTT). The effect of an administered 500 mg/kg dextrose bolus on blood glucose level was compared with normal and pancreatectomized dogs without an implant. The results of this study indicated that the diabetic dogs that had the implant had normal glucose levels (216). In addition, the blood glucose profile for a period of 2 days demonstrated that a diabetic dog, implanted with the self-regulating insulin delivery system, could maintain acceptable glucose levels (50–180 mg/dL) for the majority of the experiment (40 hours) (213–215). A proposed modification based on hydrophilic nylon microcapsules that contained Con A and succinil-amidophenyl-glucopyranoside insulin is discussed in Ref. 210. The thin wall of these microcapsules and large surface area resulted in rapid diffusion of glucose and glycosalated insulin and therefore, a much shorter lag time.

To limit the leakage of Con A (which is toxic) and allow preparation of porous microspheres, the Con A was cross-linked by first blocking the sugar binding sites and then reacted it with glutaraldehyde. The porous microspheres demonstrated rapid exchange between succinil-amidophenyl-glucopyranoside insulin and glucose, and had a short response time.

Ref. 218 reports was cross-linked a gel system that swells and shrinks in response to specific saccharides. The gel consists of a covalently cross-linked polymer network of *N*-isopropylacrylamide in which the lectin, Con A, is immobilized. Con A displays selective binding affinities for certain saccharides. For example, when the saccharide dextran sulfate is added to the gel, it swells to a volume up to fivefold the original volume. Replacing dextran sulfate with nonionic saccharide α-methyl-D-mannopyranoside brings about collapse of the gel, almost to its native volume. The process is reversible and repeatable.

A similar approach for delivering insulin is discussed in Ref. 220. It was shown that a self-regulating delivery device, responsive to glucose, operates *in vitro*. The device comprises a reservoir of insulin and a gel membrane that determines the delivery rates of insulin. The gel consists of a synthetic polysucrose and the lec, Con A. The mechanism is one of displacing the branched polysaccharide from the lec receptors by incoming glucose. The gel loses its high viscosity as a result but reforms upon removal of glucose and thus provides the rate-controlling barrier to the diffusion of insulin or any other antihyperglycemic drugs.

A similar approach is the synthesis of glucose-sensitive membranes based on the interaction between polymer-bound glucose and Con A (221–223).

Immobilized Glucose Oxidase in pH-Sensitive Polymers. Responsive drug delivery systems based on pH-sensitive polymers have been developed along three different approaches: pH-dependent swelling, degradation, and solubility.

pH-Dependent. Glucose-dependent insulin release was proposed (224–226) based on the fact that insulin solubility is pH-dependent. Insulin was incorporated into ethylene vinyl acetate (EVAc) copolymer matrices in solid form. Thus, the release was governed by its dissolution and diffusion rates. Glucose oxidase was immobilized to Sepharose™ beads which were incorporated along with insulin into EVAc matrices. When glucose entered the matrix, the gluconic acid produced caused a rise in insulin solubility and consequently enhanced release. To establish this mechanism at the physiological pH of 7.4, the insulin was modified by three additional lysine groups so that the resultant isoelectric point was 7.4. *in vitro* and *in vivo* studies demonstrated the response of the system to changes in glucose concentration. In the *in vivo* experiments, a catheter was inserted into the left jugular vein, and polymer matrices that contained insulin and immobilized enzyme were implanted sabcutaneously in the lower back of diabetic rats. Serum insulin concentrations were measured for different insulin matrix implants. A 2 *M* glucose solution was infused, 15 minutes into the experiments, through the catheter. Rats that received trilysine insulin/glucose oxidase matrices showed a 180% rise in serum insulin concentration which peaked at 45 minutes into the experiment. Control rats that received matrices that contained no insulin, or insulin but no glucose oxidase, or diabetic rats without implants showed no change in serum insulin.

pH-Dependent Degradation. Heller and co-workers (197,198,227) suggested a system in which insulin is immobilized in a pH-sensitive bioerodible polymer prepared from 3,9-bis-(ethylidene 2,4,8,10-tetraoxaspirol(5,5)undecane and *N*-methyldiethanolamine), which is surrounded by a hydrogel that contains immobilized glucose oxidase. When glucose diffuses into the hydrogel and is oxidized to gluconic acid, the resultant lowered pH triggers enhanced polymer degradation and release of insulin from the polymer in proportion to the concentration of glucose. The response of the pH-sensitive polymers that contained insulin to pH pulses was rapid. Insulin was rapidly released when the pH decreased from 7.4 to 5.0. Insulin release was shut off when the pH increased. The amount of insulin released showed dependence on pH change. However, when the *in vitro* studies were repeated in a physiological buffer, the response of the device was only minimal, even at very low pH pulses. The authors found that the synthesized amine-containing polymer undergoes general acid catalysis and the catalyzing species is not the hydronium ion but rather the specific buffer molecules used. Therefore, further development of this system will require developing a bioerodible polymer that has adequate pH sensitivity and also undergoes specific ion catalysis.

pH-Dependent Swelling. Systems based on pH-sensitive polymers consist of immobilized glucose oxidase in a pH-responsive hydrogel that encloses a saturated insulin solution or is incorporated with insulin (228–238). As glucose diffuses into the hydrogel, glucose oxidase catalyzes its conversion to gluconic acid, thereby lowers the pH in the microenvironment of the hydrogel, and causes swelling. Because insulin should permeate the swelled hydrogel more rapidly,

faster delivery of insulin in the presence of glucose is anticipated. As the glucose concentration decreases in response to the released insulin, the hydrogel should contract and decrease the rate of insulin delivery.

Horbett and co-workers (228–235) immobilized glucose oxidase in a cross-linked hydrogel made from *N*, *N*-dimethylaminoethyl methacrylate (DMA), hydroxyethyl methacrylate (HEMA), and tetraethylene glycol dimethacrylate (TEGDMA). It was previously shown that membranes prepared at −70°C by radiation polymerization retain enzymatic activity (239). To obtain sufficient insulin permeability through the gels, porous HEMA/DMA gels were prepared by polymerization under conditions which induce a separation into two phases during polymerization: one phase is rich in polymer, and the other is rich in solvent plus unreacted monomer. When gelation occurs after phase separation, the areas where the solvent/monomer phase existed become fixed in place as pores in the polymer matrix. The authors used a dilute monomer solution to obtain a porous gel, whose pores were typically 1–10 μm in diameter (215).

The rate of insulin permeation through the membranes was measured in the absence of glucose in a standard transport cell; then glucose was added to one side of the cell to a concentration of 400 mg/dL, and the permeation measurement was continued. The results indicated that the insulin transport rate is enhanced significantly by the addition of glucose. The average permeability after addition of 400 mg/dL glucose was 2.4 to 5.5 times higher than before glucose was added. When insulin permeabilities through the porous gels were measured in a flowing system, where permeabilities were measured as fluid flowed continuously past one side of the membrane, no effect of glucose concentration on insulin permeabilities could be detected. The authors propose that inappropriate design of the membranes used in the experiments is the explanation for their lack of response to glucose concentration (214).

A mathematical model that describes these glucose-responsive hydrogels demonstrates two important points (228,229): (*1*) Progressive response to glucose concentration over a range of glucose concentrations can be achieved only by using a sufficiently low glucose oxidase loading; otherwise, depletion of oxygen makes the system insensitive to glucose. (*2*) A significant pH decrease in the membrane and resultant swelling can be achieved only if the amine concentration is sufficiently low that pH changes are not prevented by the buffering of the amines.

The great advantage of reservoir systems is the ease by which they can be designed to produce constant release rate kinetics, but their main disadvantage is leaks that are dangerous because all of the incorporated drug could be released rapidly. To overcome this problem, incorporating the drug (insulin) and the enzyme (glucose oxidase) into the pH-responsive polymeric matrices has been prepared (236,237). Furthermore, a compartmental math model that describes the pH-responsive swelling of the matrix and can be used to optimize the system further has been developed (238).

Two approaches to glucose-responsive insulin delivery systems have been investigated (195,196,240–243): One approach is similar to that reported in Ref. 234. The polymers were prepared from 2-hydroxyethyl acrylate (HEA)-*N*,*N*-dimethylaminoethyl methacrylate (DMA), 4-trimethylsilystyrene (TMS),

by radical polymerization of the corresponding monomers in dimethylformamide (DMF). The mole fractions of HEA, DMA, and TMS in the copolymer were 0.6, 0.2, and 0.2, respectively. Membranes were prepared by solvent casting. Capsules that contained insulin and glucose oxidase were prepared by interfacial precipitation using gelatin as an emulsion stabilizer. The average diameter of the polymer capsules obtained was 1.5 mm (240,243). The water content of HEA–DMA–TMS copolymer membranes increased as the pH of the medium decreased. An especially drastic change was observed in the pH range of 6.15 to 6.3. The permeation of insulin through the copolymer membrane increases in response to pH decreases. The permeation rate of insulin at pH 6.1 was greater than that at pH 6.4 by about 42 times. The permeation of insulin through the copolymer membranes was very low in buffer solution without glucose. Adding 0.2 M glucose to the upstream compartment induced an increase in the permeation rate of insulin. When glucose was removed, the permeation rates of insulin gradually returned to their original levels (240).

Podual and co-workers recently reported a glucose-sensitive system that works on the same principle but utilizes a different polymer (244). The authors found that poly(diethyl aminoethyl methacrylate-*g*-ethylene glycol) that contained glucose oxidase and catalase resulted in matrices that were reproducibly and reversibly glucose-sensitive.

Another approach (242) is based on a glucose oxidase immobilized membrane and a redox polymer that has a nicotinamide moiety. The device consists of two membranes. One membrane that contains the immobilized glucose oxidase acts as a sensor for glucose and forms hydrogen peroxide by an enzymatic reaction; the other membrane is a redox polymer that has a nicotinamide moiety that controls the permeation of insulin by an oxidation reaction with the hydrogen peroxide formed. The oxidation of the nicotinamide group increases hydrophilicity and therefore should enhance the permeability to water-soluble molecules such as insulin. The results showed relatively small increases in insulin permeability.

Porous poly(vinylidene fluoride) membranes (average pore size of 0.22 μm) pretreated by air plasma, and subsequently, acrylamide graft polymerized on the treated surface is reported in Refs. 245,246. The polyacrylamide was then hydrolyzed to poly(acrylic acid). In the pH range of 5–7, grafted poly(acrylic acid) chains are solvated and dissolved but cannot diffuse into the solution phase because they are grafted to the porous membrane. Thus, they effectively close the membrane pores. In the pH range of 1 to 5, the chains collapse, and the permeability increases. To achieve sensitivity of the system to glucose, glucose oxidase was immobilized onto a poly(2-hydroxyethyl methacrylate) gel.

Ito and co-workers (247) adopted the approach proposed in Ref. 246 using a porous cellulose membrane that had surface-grafted poly(acrylic acid) as a pH-sensitive membrane. By immobilizing glucose oxidase onto the poly(acrylic acid)-grafted cellulose membrane, it became responsive to glucose concentrations. The permeation coefficient after glucose addition was about 1.7 times that before the addition of glucose. The authors suggest improving the proposed system (sensitivity of insulin permeability to glucose concentrations) by modifying the graft chain density, length, and size, or density of pores.

An implantable "mechanochemical" pump that functions by converting changes in blood glucose activity into a mechanical force, generated by the swelling polymer that pumps insulin out of the device has been described (248,249).

More recently, a self-regulating oscillatory drug delivery based on a polymeric membrane whose permeability to the substrate of an enzyme-catalyzed reaction is inhibited by the product of that reaction has been proposed (250). This negative feedback system can, under certain conditions, lead to oscillations in membrane permeability and in the levels of substrate and product in the device. Any one of these oscillating variables can then be used to drive a cyclic delivery process. The product concentration in the chamber inhibitorily affects the permeability of the membrane to the substrate. That is, increasing product concentration causes decreasing flux of substrate into the device. Siegel proposed several means of controlled drug delivery based on this idea. Drug solubility could be affected by substrate or product concentration, which oscillates. Alternatively, the drug permeability of the membrane can oscillate with time along with the substrate permeability.

8. Polymers in Controlled Drug Release Formulations

Polymers have been widely used to encapsulate drugs in the form of reservoir or matrix to release the drug at the proximity of the desired site (Table 1). Thus, there must be clarity about the biocompatibility, toxicity, and elimination of these polymers (251,252). Novel concepts for polymer-based controlled release systems that have emerged over the years include new polymers, new methods for drug linkages, and new processes for drug encapsulation (253). The active ingredient could be either physically entrapped into the polymer matrix by an emulsification-, atomization-, or agitation-based process or could be linked to the polymer backbone via physical or chemical bonds. The drug release is typically observed to be diffusion-controlled, polymer erosion controlled, or a combination of the two. Hence, drug release properties strongly depend on the physical and chemical properties of the polymer. Even a minor variation in the polymer structure, such as an endgroup modification, may be sufficient to modify its degradation characteristics and subsequently the drug release properties. Furthermore, different polymer properties are desired for different drugs and different applications. This has led to an intensive effort in developing novel polymeric systems for controlled release applications. Development of such novel formulations is further fueled by the growing demand for patient-friendly medicines in the pharmaceutical and biotechnology industries.

Various natural, semisynthetic, and synthetic polymers are in use as the structural backbone for both controlled release and conventional drug delivery systems (Table 1). Polymers selected in the preparation of the dosage form must comply with the following requirements:

Safety. Harmful/toxic impurities must be removed from polymers before their usage in CDRFs. The residual monomers, initiators, and other chemicals used in the polymer synthesis/modification must be removed after the

Table 1. **Polymers in Controlled Release Technology**

Polymer	Controlled release mechanism	Special notes
	Natural or semisynthetic	
albumin	dissolution	
cellulose	dissolution and diffusion	binder, diluent, disintegrant
chitin	diffusion	
chitosan	dissolution	
cellulose acetate	osmosis	
ethylcellulose	osmosis	
cellulose acetate butyrate	osmosis	
carboxymethylcellulose, sodium salt cross-linked	dissolution	
gelatin	dissolution	
hydroxypropylmethyl cellulose	dissolution	binder
starch thermally modified	dissolution	
xanthan gum	dissolution	
collagen	diffusion	
guar gum		
karana gum		binder
dextrin		
sodium starch glycolate		
methyl cellulose		binder
tragacanth gum		
aliginic acid		binder
cellulose acetate phthalate		entric coating material
cellulose acetate trimelliate		entric coating material
poloxamer	diffusion	
	Synthetic	
nylon		
poly(ethylene glycol)	dissolution	
poly(glycolic acid)	dissolution	
poly(lactic acid)	dissolution	
poly(vinyl alcohol)	dissolution and osmosis	
poly(vinylpyrrolidinone), cross-linked	dissolution	binder
poly(urethane)	osmosis	
poly(vinyl chloride), cast	osmosis	
poly(vinyl chloride), extruded	osmosis	
poly(carbonates)	osmosis	
poly(vinyl fluoride)	osmosis	
ethylene vinyl acetate	osmosis	
cellophane, polyethylene-coated	osmosis	
poly(ethylene)	osmosis	
ethylene–propylene copolymer	osmosis	
polypropylene	osmosis	
poly(vinyl chloride) rigid	osmosis	
poly(alkylcyanoacrylate)	diffusion	
poly(ethylene-*co*-vinyl acetate)	diffusion	
poly(hydroxyethyl methacrylate)	diffusion	
poly(hydroxypropylethyl methacrylate)	diffusion	
poly(methyl methacrylate)	diffusion	
poly(vinyl alcohol-*co*-methacrylate)	diffusion	
polyisobutene	diffusion	
silicone rubber	diffusion	
	diffusion	

polymerization/modification. The chemicals employed in the polymer fabrication processes (ie, additives, stabilizers, plasticizers, and catalyst residues) are carefully selected to meet regulatory requirements.

Physical and mechanical properties. The polymers must possess the necessary mechanical properties required for the dosage form design, such as elasticity, compactability, resistance to tensile, swelling and shear stresses, and resistance to tear and fatigue.

Biocompatibility. The polymer should not cause significant local irritation to the surrounding tissues. If biodegradable, then the polymer degradation by-products must be nontoxic, nonimmunogenic, and noncarcinogenic.

There are many ways to synthesize new polymers and modify existing polymers. Different monomers (for addition polymerization or condensation polymerization) may be used or existing polymers may be modified. However, only a handful of polymers are used in pharmaceutical drug delivery systems because of their commercial availability, established biocompatibility, and government registration. Table 1 is listed with the polymers used or evaluated for controlled release. Most polymers used in pharmaceutical dosage forms were not originally designed for this purpose. However, the production of new, life-saving, genetically engineered drugs (peptides and proteins), which have characteristically short half-lives, presents an opportunity for significant research in the area of polymer development in order to prolong their therapeutic effects in human body.

9. Polymer Fabrication and Drug Encapsulation

Encapsulation of the therapeutic agent into a polymer matrix can be brought about by a variety of methods. These methods depend on the desired fabrication of the polymer matrix. Some of the common techniques used for drug encapsulation for different polymer forms are described here.

9.1. Polymer Films and Rods. Polymer films can be cast by various techniques including dip coating, spin coating, hot-melt casting, and solvent casting. Typical applications for polymer films are in the medical device industry as coatings for controlled release from devices and implants such as stents. These applications require the polymer to be elastomeric to allow flexible films at micron-size thickness. The films can be casted with the drug encapsulated by homogenization/solubilization in the polymer melt/solution. The polymer film could also be extruded using a single or double screw extruder. Screw extrusion is also used to fabricate another form of polymer, ie, drug encapsulated rods/cylinders. Such extruded rods could be implanted subcutaneously to provide sustained drug delivery.

9.2. Polymer Microspheres. For applications in drug delivery, it is desired that the polymer formulation should be present as an injectable form. From this perspective, the polymer–drug combination could be fabricated as microspheres that can be suspended in an injection vehicle prior to injection. Subcutaneous or intramuscular injections are used for microspheres whereas smaller particles (in the nano range) could be injected intravenously.

Microspheres can be fabricated using a variety of techniques, some of which are described below.

Spray Drying. In spray drying the polymer and drug are dissolved in a common solvent and spray-atomized to create microspheres. This technique is useful to create particles in the size range of up to 50 μm, wherein the polymer has a sufficiently high glass-transition temperature to allow formation of discrete microparticles during atomization. The size and morphology of microparticles created using the spray drying technique depends on the nature of the polymer as well as the spray dryer operating parameters including chamber volume, flow rate, and nozzle design (254).

Solvent Evaporation. In this technique the drug is emulsified/dispersed in the polymer solution. This emulsion/dispersion is further emulsified in a surfactant bath to allow for the formation of solid microparticles consisting of the drug encapsulated within the polymer matrix. Variations of this technique include single emulsion and double emulsion microencapsulation. Since microparticles are created during the slow evaporation of the solvent, this technique is also termed as solvent evaporation technique. Solvent evaporation/emulsification techniques are useful when the desired particle size is higher and/or when the drug is not soluble in the organic solvent (Fig. 4).

Freeze Spray Atomization. In this process a suspension of drug in an organic polymer solution is atomized into a liquid nitrogen bath. Absolute ethanol is added to extract the organic solvent. This process is particularly feasible for proteins since the protein is in a solid, less reactive form, making it less susceptible to damage during processing. Furthermore, the low temperature maintained throughout the process prevents thermal denaturation of the protein (255). This process has been utilized in the production of the first commercially

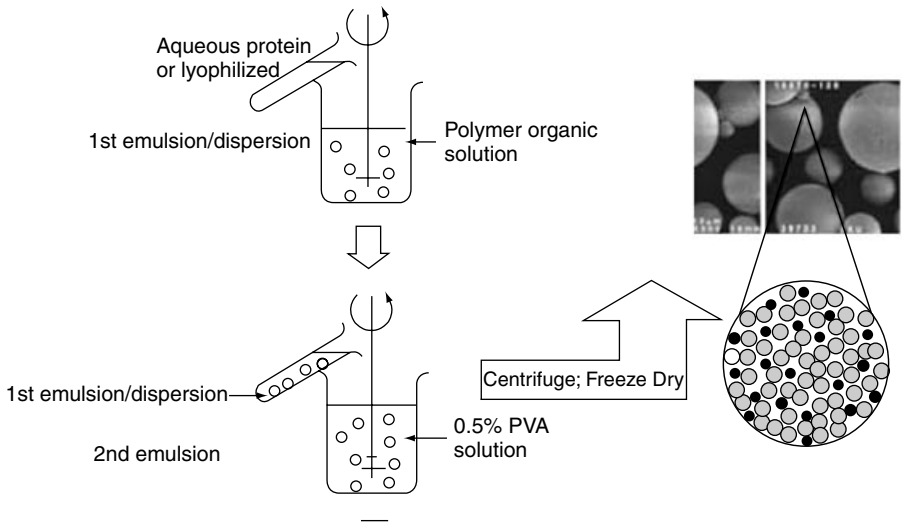


Fig. 4. Schematic representation of the emulsion-based microencapsulation processes; the single emulsion process utilizes lyophilized drug in the first step whereas the double emulsion process utilizes an aqueous solution of the drug in the first step.

available polymer-based sustained release protein formulation, Nutropin Depot, marketed by Genentech.

9.3. Polymer *In Situ* Gels. Drug encapsulation for injectable gels could be carried out by simple mixing of the drug into the polymer gel. To obtain sustained release, it is desirable that the polymer gel should acquire some viscosity upon injection into the body. Such *in situ* gelation characteristics could be achieved by various mechanisms such as those described below:

Temperature-Induced Gelation. Thermoreversible gelation could be obtained for ABA-type block copolymers wherein A denotes a hydrophilic segment while B denotes a hydrophobic segment. Because of the alternating block structure, such polymers undergo micellization driven by increasing temperature. The formation of micelles is thermodynamically favorable in ABA block structures, especially when the hydrophobic–hydrophilic balance is appropriately achieved. An example of such thermoreversible polymers includes PEG–PLGA–PEG (256) and Pluronics, which are ABA-type block copolymers of PEG and PPG. In each of the examples, the polymers could be engineered to be solutions at room temperature and converted into semisolid gels at body temperature.

pH-Induced Gelation. If the polymer is soluble at a certain pH and is insoluble at pH 7.4, then it would undergo pH-induced gelation on injection into the body. Examples of such polymers include synthetic polymers such as polyacrylic acid and natural polymers such as chitosan.

Solvent-Induced Gelation. Solvent-induced gelation could be obtained for a water-insoluble polymer, dissolved in a biocompatible solvent to create an injectable solution. When the solution is injected the solvent diffuses out and water from the physiological environment diffuses in. This diffusion process leads to a phase transition for the polymer as it goes from the solvent phase to a nonsolvent phase and forms a semisolid gel (257). Several factors such as polymer crystallinity, hydrophilicity, and water uptake govern the sol–gel transition and subsequently the drug release characteristics.

10. Classification of CDRFs

Drug delivery systems have been classified on the basis of route administration, for example, parenteral, eternal, respiratory, transdermal, and miscellaneous flow (Fig. 5). Controlled release systems are based on the release mechanisms that may be erosion, diffusion, or chemically controlled, and thus these are classified under the heading of various categories of drug delivery. For example, under eternal drug delivery systems, release of a drug can be controlled by various mechanisms like diffusion, osmosis, or chemically controlled mechanism. In the broad way, these devices are of two types, as reservoir devices and matrix devices. The former involve the encapsulation of a drug within the polymeric shell, while the latter describe a system in which a drug is well dispersed throughout within the polymer matrix. However, on the basis of drug release mechanism, these devices can be classified into three types, as shown in Figure 6. Some examples of controlled release systems are described briefly here.

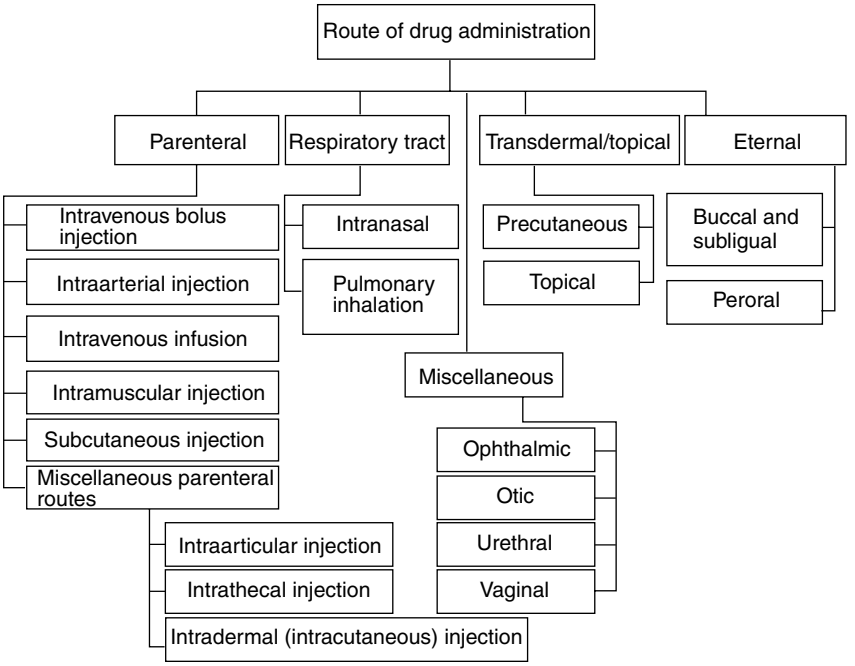


Fig. 5. Various routes of drug administration.

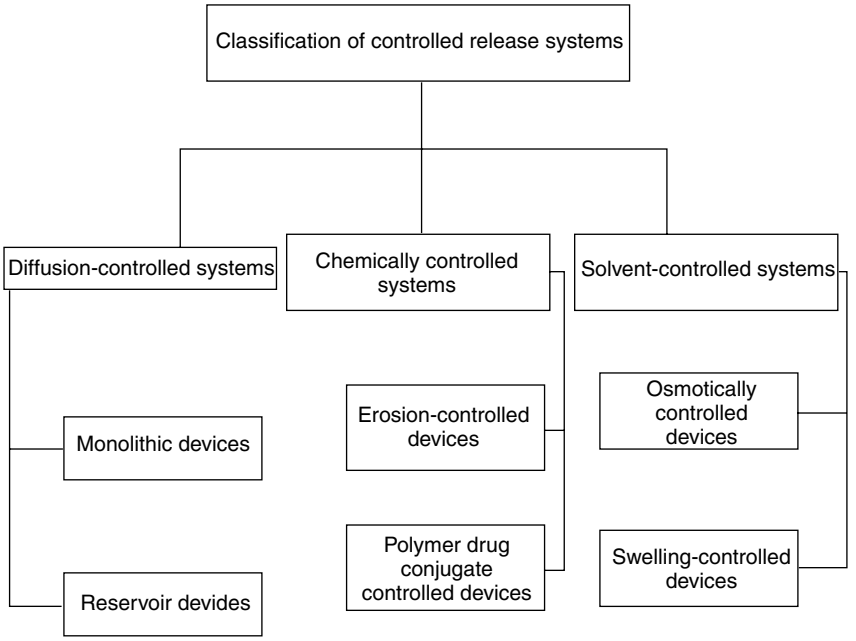


Fig. 6. Classification of controlled release systems.

10.1. Diffusion-Controlled. Two types of diffusion-controlled systems have been used including reservoir systems (drug coated by a polymer membrane) and matrix systems (drug dispersed in a polymer matrix). In the reservoir systems, the drug is encapsulated by a polymeric membrane through which the drug is released by diffusion. This polymeric membrane is known as solution diffusion membrane (implying the mechanism of drug transport) and can be microporous or nonporous. In nonporous membrane, drug release is governed by the diffusion through polymer and thus, release can be controlled by selecting a polymer showing desirable drug solubility and diffusivity in the polymer matrix (see Membrane Technology). In microporous membranes, pores with the size range 1.0 nm to several hundred millimeters are filled with drug permeable liquid or gel medium. Thus, diffusion of the drug through the medium in the pore will dominate the drug release process. These systems are very useful in the delivery of high molecular weight drugs such as protein and peptide drugs. Matharu and co-workers (91) reported the theoretical considerations, designing, and engineering of a "barrier coated-reservoir" type of a delivery system for theophylline using poly(vinyl alcohol) (PVA) as the coating material. After getting the desired theoretical *in vitro* release profile, *in vivo* studies were carried out on a dog model.

In monolithic systems, the drug is dissolved or dispersed homogeneously throughout the water-insoluble polymer matrix which may be microporous or nonporous (258). Monolithic systems are not suitable for zero-order release; however, it can be achieved by adjusting the physical shape of the device (259).

10.2. Dissolution-Controlled. Dissolution-controlled systems can also be classified as reservoir and matrix devices. Polymers used for these devices are generally water-soluble but water-insoluble polymers can also be used as long as they absorb water and disintegrate the drug. In reservoir devices, drug particles are coated with water-soluble polymeric membranes. The solubility kinetics of the membrane depends on the thickness of the membrane and type of the polymer used. Thus, drug release can be achieved and controlled by preparing devices with alternating layers of drug and polymeric coats or by preparing a mixture of particles which have different coating characteristics. Matrix dissolution devices are generally prepared by compressing powder mix of drug and a water-soluble or water-swellable polymer. They can also be made by casting and drying of a polymer solution containing a suitable amount of dissolved or dispersed drug. A variety of other excipient may optionally be included to aid formulation properties. The influence of excipients and formulation factors on the dissolution behavior of the methyl hydroxyethyl cellulose (MHEC) tablets has been investigated (260). The use of drugs with higher solubility leads to a slight acceleration of the release because of the contribution of diffusion to the release process (caused by channels formed as a result of drug solubilization). Furthermore, alterations of the composition of the dissolution medium affect drug release.

10.3. Degradation/Erosion-Based Systems. While early research on polymer-based controlled release systems involved both degradable and nondegradable polymers, degradable polymers are preferred for parenteral drug delivery applications. Degradation of the polymer eliminates the need for a surgery to recover the spent polymer after the entire drug is released. It also reduces issues

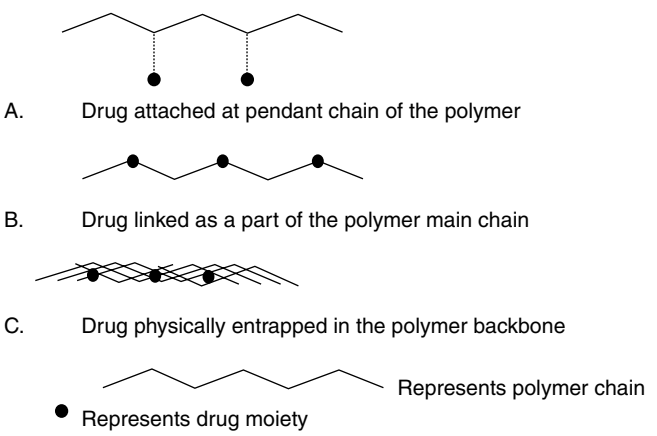


Fig. 7. Schematic representation of different embodiments of polymer-based controlled release formulations.

related to the long-term safety of the polymer. For biodegradable polymers, release of the drug is often intricately tied up with the polymer degradation profile. As can be seen in Figure 7, polymer degradation could be either enzymatic (facilitated by specific enzymes in the body), hydrolytic, or a combination of the two. The drug could be either physically entrapped in the polymer matrix wherein it would be released by diffusion and/or erosion of the polymer mass. Alternatively, the drug could also be chemically attached to the polymer backbone. In such a situation, the drug is released by the enzymatic/hydrolytic cleavage of the chemical bond between the polymer and the drug. A further classification of polymer degradation is established based on the polymer mass erosion patterns. If the polymer is hydrophobic then it restricts the diffusion of water into its matrix and hence polymer erosion may be restricted to the surface (as is the case for certain polyanhydrides). A more conventional case for majority of polymers including PLA and PLGA is when erosion occurs throughout the bulk of the polymer matrix (termed as *bulk erosion*). Bulk erosion is associated with a drop in pH within the interior of the matrix. While such a pH drop is detrimental to pH labile drugs, it could be utilized to stabilize certain type of basic drugs such as campothein (261).

Various diffusion models have been proposed for different scenarios and embodiments (262). Ritger and Peppas (263) proposed an empirical equation that has been successful in modeling the drug release for several formulation scenarios. This equation correlated the fraction of drug released to the time as

$$M_t/M_o = kt_n$$

M_t and M_o denote the drug release at time t and total amount of drug in the formulation respectively. The empirical coefficients k and n are related to the kinetics and diffusion mechanism respectively. When $n = 0.5$, this equation obeys Fick's law of diffusion. On the other hand, $n = 1$ denotes case II diffusion to play a prominent role. The key feature of this model is its simplicity as well as its ability to offer insights on the diffusion mechanisms based on the value of k.

Table 2. **Important Properties of the Polymer that Influence Its Degradation Characteristics**

Property	Effect on degradation kinetics
chemical linkages	the type of hydrolytic linkage determines rate of degradation. For example, anhydride bonds are known to degrade faster than ester bonds
molecular weight	higher the molecular weight, slower is the degradation rate
morphology	porous forms (higher surface area) may be more susceptible to hydrolysis because of enhanced access for water penetration
crystallinity	higher crystallinity leads to slower degradation
water uptake	water uptake leads to faster degradation because of a better access for water to attack the polymer chains.
polymerization conditions	use of catalysts, reaction temperature, etc may affect the degradation properties of the polymer
chain defects	chain defects are often associated with faster degradation. Lesser the uniformity in structure, higher is the rate of hydrolysis.

Mathematical models have also been proposed to incorporate polymer degradation kinetics as an integral part of the theoretical framework explaining drug release characteristics (264). Similarly, kinetic models have been used to explain degradation profiles of the polymer. As listed in Table 2, several polymer properties play an important role in their degradation behavior.

10.4. Osmotic Delivery Systems. Osmosis-controlled devices comprises a core reservoir of drugs, with or without osmotically active salt, coated with a semipermeable membrane. The presence of salt or drug molecules creates an osmotic pressure gradient across the membrane and the diffusion of water into the device gradually forces the drug molecules out through an orifice made in the device. For a durable device, the mechanical strength of semipermeable membrane should be strong enough to resist the stress building inside the device. The drug release rate from the osmotic devices, which is directly dependent on the rate of external water diffusion, can be controlled by the type, thickness, and area of the semipermeable membrane. Alza developed osmotic devices such as elementary osmotic pump system for oral administration and Alzet osmotic pump for implant. A recent review by Singh and co-workers discusses osmosis as a phenomenon for controlled drug delivery, along with the device concepts such as Rose Nelson pump, Higuchi osmotic pump, and Higuchi Theeuwes osmotic pump (265).

10.5. Ion-Exchange Systems. Polyelectrolytes have been used as cross-linker to form water-insoluble ion-exchange resins. The drug is bound to the ionic groups by salt formation during absorption and released after being replaced by appropriately charged ions in the surrounding media. For cationic drug delivery, poly(styrene sulfonic acid) and poly(acrylic acid) can be used as anionic ion-exchange resin where sulfonic and carboxylic groups make the complexes with cationic drugs and hydrogen ions and/or other cation such as sodium or potassium ions activate the release of cationic drugs by replacing them from the drug–resin complex. On the other hand, cationic ion-exchange resins like poly(dimethylamino ethyl methacrylate) have been used for the delivery of

anionic drug, in which basic group namely amino or quaternary amino group makes a complex with anionic drugs. The interaction of a series of *O-n*-acyl propranolol prodrugs (I, R = C1–9 alkyl or CH_3C) with strong cation exchange resins has been reported and various variables that control loading and release profiles have been investigated (97). The effect of *O-n*-acyl chain-length on the loading and release profiles was detected by molecular size, for example, the loading was inhibited for the groups with increased size, and release rates were reduced. Again, this enables some control of release profiles but the approach was found to be most suitable for drugs that were active at low doses, which allow full use of these variations without the necessity for large amounts of resin in the delivery system. Sometimes, the ion-exchange resins are additionally coated with a polymer film, such as acrylic acid and methacrylate copolymer or ethylcellulose, to regulate the swelling of the resin and to further control the drug release. The Pennkinetic system is an example of the devices based on these mechanism to deliver dextromethorphan from the ethylcellulose-coated poly(styrene sulfonate).

10.6. Polymeric Prodrugs. Many water-soluble polymers possess functional groups to which drug molecules can be covalently attached and thus, these polymers that have no therapeutic effect serve as drug carriers. The drug molecules are gradually released from the polymer by hydrolytic or enzymatic cleavage. If the cleavage occurs by chemical hydrolysis, the drug release depends on the nature of the covalent bonds and pH of the environment; however, it is very slow in the body. If the drug molecule is released by enzymatic hydrolysis, the release is mainly dependent on the concentration of enzymes. Thus, the exact release profile depends on the *in vivo* condition and not on the delivery system itself. To be a useful carrier, a polymer should possess certain features: (*1*) The polymer should remain water-soluble even after drug loading; (*2*) molecular weight of the polymer should be large enough to permit glomerular filtration but small enough to reach all cell types; and (*3*) Drug-carrier linkages should be stable in body fluid and yet degradable after capturing in target cells.

This can be achieved by making the linkage degradable by lisosomal enzymes, in which the polymer is nontoxic, nonimmunogenic, biocompatible, and degradable by lysosomal enzymes to be eliminated from the body after releasing drugs. Starch derivatives, dextran (266), poly(aminoacids), PVP, and poly(hydroxypropyl methacrylamide) have been used as polymeric drug carriers.

10.7. Magnetically Stimulated Systems. The two principle parameters controlling the release rates in these systems are magnetic field characteristics and mechanical properties of the polymer matrix. It was found that when the frequency of the applied field was increased from 5 to 11 Hz, the release rate of the bovine serum albumin (BSA) from ethylene vinyl acetate (EVAc) copolymer matrices rose in linear fashion (267). The mechanical properties of the polymeric matrix also affect the extent of magnetic enhancement (267). For example, the modulus of elasticity of the EVAc copolymer can be easily altered by changing the vinyl acetate content of the copolymer. The release rate enhancement induced by the magnetic field increases as the modulus of elasticity of EVAc decreases. A similar phenomenon was observed for cross-linked alginate matrices: higher release rate enhancement for less rigid matrices (268). Edlemean and co-workers (269) also showed that enhanced release rates

observed in response to an electromagnetic field (50 G, 60 Hz) applied for 4 min were independent of duration of the interval between repeated pulses.

10.8. Photostimulated Systems. Photoresponsive gels reversibly change their physical or chemical properties upon photoradiation. A photoresponsive polymer consists of a photoreceptor, usually a photochromic chromophore, and a functional part. The optical signal is captured by the photochromic molecules and then the isomerization of the chromophores in the photoreceptor converts it to a chemical signal. A phase transition in polymer gels induced by visible light, where the transition mechanism is due to the direct heating of the network polymer by light has been reported (270).

10.9. Ultrasonically Stimulated Systems. Kost and co-workers (271) proposed that cavitation and acoustic streaming are responsible for the augmented degradation and release of biodegradable polymers. Miyazaki and co-workers (272) speculated that the ultrasound caused increased temperature in their delivery system, which may facilitate diffusion.

10.10. Electrically Stimulated Systems. In the late 1980s, Grimshaw (273) reported four different mechanisms for the transport of proteins and neutral solutes across hydrogel membranes: (*1*) Electrically and chemically induced swelling of a membrane to alter the effective pore size and permeability; (*2*) electrophoric augmentation of solute flux within a membrane; (*3*) electroosmotic augmentation of solute flux within a membrane; and (*4*) electrostatic partitioning of charged solutes into charged membranes.

Drug release from electric current sensitive polymers has been studied (274). Edrophonium chloride, a positively charged solute, was released in an on-off pattern from a matrix device by an electric field. The mechanism was explained as an ion exchange between positive solute and hydroxonium ion, followed by fast release of the charged solute from the hydrogel. The fast release was attributed to the electrostatic force, the squeezing effect, and the electroosmosis of the gel. However, the release of neutral solute was controlled by diffusion affected by swelling and deswelling of the gel.

11. Representative Applications

11.1. Controlled Release of Peptides and Proteins. Sustained release applications are especially useful for proteins/peptides because of their short half-lives (275). This concept was first utilized commercially in Lupron Depot, which was introduced as a sustained release formulation of a lutenizing hormone-releasing hormone (LHRH), leuprolide acetate, with poly(lactic acid) as the polymer (276). Following the success of Lupron Depot, other sustained release formulations of LHRH analogues have also been commercialized, including Zoladex wherein the LHRH peptide is encapsulated in PLA-extruded rods, and Trelstar depot wherein the peptide is encapsulated in PLGA polymer matrices.

Recently, a once-in-four-weeks formulation of a cyclic peptide Octreotide, encapsulated in biodegradable PLGA–glucose polymer matrix, has also been commercialized under the trade name Sandostatin LAR (Novartis Pharmaceuticals Corp.) (277). In 2000, a human growth hormone sustained release formulation (Nutropin Depot) became the first polymer-based sustained release

formulation of a therapeutic protein to receive marketing approval from the Food and Drug Administration. This commercialized formulation encapsulates a zinc-complexed form of recombinant human growth hormone in a PLGA matrix (254). Other therapeutic proteins that are being tested for encapsulation in polymer matrices include bone morphogenic protein (278), erythropoietin (279), and nerve growth factor (280).

11.2. Controlled Release of Antirestenotic Agents from Stent Coatings. Stents are tiny wire scaffold-like devices, which have become the most successful and widely used innovation in interventional cardiology of the last decade. These devices are inserted inside blocked sections of coronary arteries and expanded into place using a balloon catheter in a procedure called an angioplasty. In as many as 40% of patients receiving angioplasty, a new blockage develops at the site because of scar tissue growth and inflammation, a condition referred to as restenosis. More than 500,000 Americans are treated for restenosis annually. Stents coated with a biocompatible polymer, encapsulating an antirestenotic agent, have proven to be a successful therapy to reduce or eliminate restenosis. Several drugs including cytostatic agents (Rapamune), antiproferative agent (Paclitaxel), and antiinflamatory agents have been encapsulated in micron-thick films that coat the metallic stent (281). The polymers used for this application are required to be elastic, biocompatible, and hemocompatible. Lewis and co-workers (282) demonstrated the use of phosphorylcholine-based polymers for this application. Other polymers tested for this application include polylactide and polyurethane (283).

11.3. Polymeric Systems for the Treatment of Cancer. By providing sustained release at the desired site, high doses of toxic drugs can be delivered to the site without introducing the drug into systemic circulation. This results in a major advantage for the administration of chemotherapeutic drugs, wherein the drugs can be encapsulated into polymer matrices and administered directly into the tumor area. Gliadel (Guilford Pharmaceuticals) implant is a product based on the above concept, encapsulating a chemotherapeutic agent, carmustine, into a biodegradable polymer, fabricated as a dime-sized wafer. Several wafers are implanted by the surgeon into the brain cavity during a tumor resection surgery. By direct release of the drug in the tumor region in the brain, the problem of overcoming the blood-brain barrier is resolved. Also, high doses of the chemotherapeutic agent are delivered at the tumor site, thus making the therapy significantly more effective than systemic administration. Other chemotherapeutic agents that are also being developed as sustained release formulations include paclitaxel and cisplatin (284).

The biggest success of polymer controlled release systems in cancer therapy however has been in the area of prostate cancer treatment. This therapy is unique since it uses a hormone-suppressant rather than a chemotherapeutic agent to minimize cancer cell growth in the prostate. Several products include Lupron Depot (TAP Pharmaceuticals), Zoladex (Astra-Zeneca), and Trelstar Depot (Debio RP, Pharmacia). Lupron Depot involves PLA microspheres, Zoladex formulation is an extruded rod, whereas Trelstar depot consists of PLGA microspheres, all of which incorporate LHRH analogues.

11.4. Sustained Release of Drugs for CNS-Related Disorders. Another area of application for polymer-based controlled release technologies is for

the sustained delivery of drugs for the central nervous system (CNS) related disorders. CNS-related drugs include a wide range of therapeutics including pain management agents, drugs to prevent substance abuse, as well as drugs for conditions such as schizophrenia, Parkinson's and Alzheimer's disease. Drugs such as lidocaine and bupivicaine have been studied for sustained local anesthesia at the site of surgery (285). For this application, the anesthetic agent is encapsulated in a biodegradable polymer and injected in the proximity of the site of pain. The drug is released facilitating high concentrations at the local site, without reaching the threshold levels of systemic toxicity. In other cases such as schizophrenia, Parkinson's and Alzheimer's diseases, sustained release of the medication may reduce the chance of missed doses and aid in an effective dose regimen.

11.5. Gene Therapy. For more than two decades, researchers have been working to alleviate disease through gene therapy. In this type of treatment a gene is delivered to cells, allowing them to produce their own therapeutic proteins. Traditionally, DNA delivery systems have been classified as viral vector-mediated systems and nonviral vector-mediated systems (286). Currently, because of their highly evolved and specialized components, viral systems are by far the most effective means of DNA delivery, achieving high efficiencies (>90%) for both delivery and expression (287). The most promising nonviral gene delivery system thus far, other than the "gene gun," is the DNA vaccine application, which comprises of ionic complexes formed between DNA and polycationic liposomes (288,289).

Nonviral vectors can be divided into two broad categories—physical and chemical—according to Huang. Physical methods involve taking plasmids and forcing them into cells through such means as electroporation or particle bombardment. Chemical methods use lipids, polymers, or proteins that will complex with DNA, condensing it into particles and directing it to the cells. Nonviral systems for gene delivery have several potential advantages over viral vectors. Viruses can cause an immune response that can make repeat administrations ineffective. Nonviral vectors can also carry more DNA than viruses, allowing the delivery for larger genes. In addition, nonviral vectors are easier and less expensive to manufacture. The plasmids that are used in nonviral systems can be produced in bacteria such as *Escherichia coli*. The same production facilities can be used to manufacture a variety of plasmids incorporating different genes. Many recent reviews describe various aspects of nonviral vectors for gene therapy including different polymers and success and failure stories (290–292).

12. Controlled Release Systems in Market

Controlled release has gained a good impact among the various drug delivery technologies because of patient compliances, safety of drug, and minimum side effects. Various controlled release systems according to their drug availabilities, route of administration, and length of action in the body are presented in Figure 8. It had been estimated that the world pharmaceuticals sales was nearly $400 billion during the year 2000 and about 12.5% or $50 billion for drugs

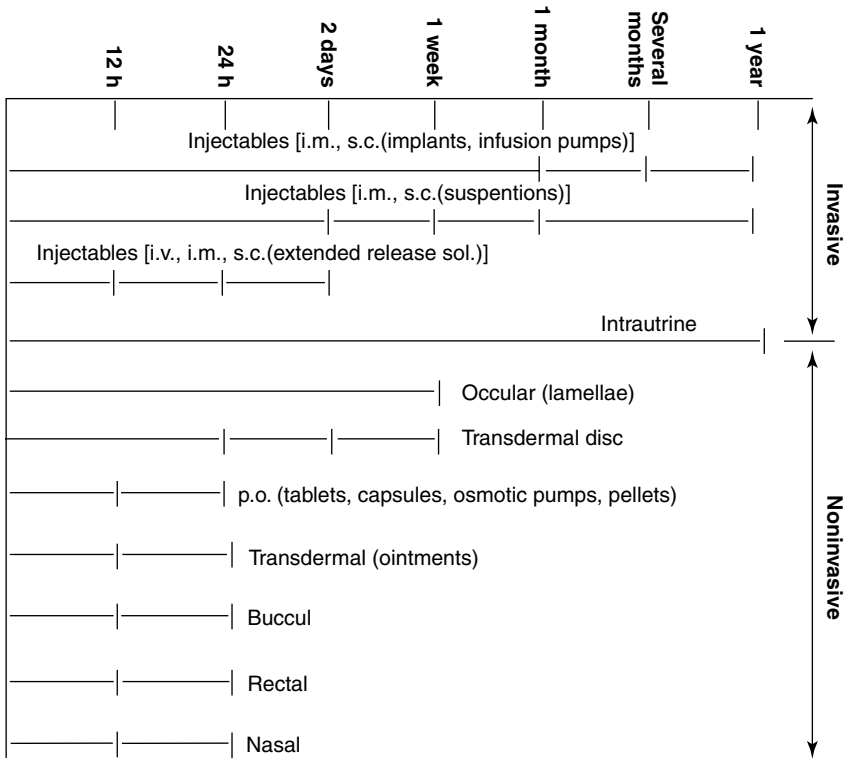


Fig. 8. Route of administration and length of action in the body.

Table 3. **Some Examples of Controlled Release Products in Market**

Technology	Technology name (drug)	Application	Company
liposome-based formulations	Evacet (Doxorubicin)	breast cancer and other cancers	Elan with acquisition of Liposome, Inc.
one-yearly drug implant	Viadur (Leuprolide)	prostate cancer	ALZA/J&J
biodegradable implants	Gliadel (BCNU[a])	treatment of brain cancer	Guilford Pharmaceuticals, Inc.
biodegradable microsphere for sustained-release for peptides/proteins	ProLease	delivery of peptides and small molecules	Alkermes, Inc.
time release oral drug release	Pulsincap	drug release at predetermined time or location in the GI-tract	RP Scherer Corp.
oral controlled release system to control the release of a specific drug	Geomatrix	predetermined therapeutic objective for a drug	SkyePharma

[a] *N*,*N*-bis(2-chloroethyl)-*N*-nitrosourea.

involving special drug delivery technology. Sales of drug delivery products are expected to more than double to $104 billion in 2005. Among them, more than 20% share goes to controlled drug release technologies. Examples of controlled release technologies available in the market place are given in Table 3.

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JOSEPH KOST
SMADAR A. LAPIDOT
Ben-Gurion University of the Negev

NEERAJ KUMAR
University of Tennessee Health Science Center

MAHESH CHAUBAL
Drugdel.com

A. J. DOMB
The Hebrew University of Jerusalem

RAVI KUMAR
N. V. MAJETI
University of Saarland