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Bioabsorbable Polymers for Implantable Therapeutic Systems

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ABSTRACT

For a long time, subcutaneous implantable drug pellets using nondegradable polymers have been used for long-term, continuous drug administration. The procedure requires surgical implantation and removal of the drug-containing devices or polymeric matrices, which has a significant negative impact on the acceptability of the product candidate. In addition, the release profile from such devices is neither constant nor readily controlled in terms of precision of rate of release and duration of action. These facts have led to the research and development of novel, controllable, nonirritating, noncarcinogenic, biocompatible, and bioabsorbable drug delivery systems for overcoming the drawbacks of nondegradable implantable pellets for prolonged continuous release. Biodegradable implantable systems release the drug over a long period of time with simultaneous or subsequent degradation in the tissue of the polymer to harmless constituents, thus avoiding removal once the therapy is complete. This approach has considerably improved patient acceptability and patient compliance. Various bioabsorbable polymers have been evaluated for controlled implantable drug delivery, including hydrogels, copolymers of polylactic and polyglycolic acids, polylactic acid, poly(orthoesters), polyanhydrides, poly(E-caprolactone), and polyurethanes. Their characteristics have been studied using a variety of drugs, like anticancer agents, hormone agonists and antagonists, nonsteroidal anti-inflammatory agents, neuroleptics, contraceptives, and others. The present paper describes the current research on implantable therapeutic systems, the bioabsorbable polymers, and the biologically active agents being used in this approach.

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INTRODUCTION

Subcutaneous tissue is essentially a sheet of areolar tissue lying directly underneath the skin. It is rich in fat, but poor in nerve network and hemoperfusion. Therefore, the subcutaneous tissue is an ideal location for implantation and prolonged drug administration because of its ready access to implantation, slow drug absorption, and low reactivity to the insertion of foreign materials. Insertion of artificial materials inside the body for a long term may evoke potentially undesirable body responses to the implanted materials. Serious adverse responses have been reported with silicon-gel filled implants (1), Teflon-coated temporomandibular joint implants (2), and Norplant® contraceptive implants (3). On insertion in a tissue, implants should elicit a desirable host response without any side effects, like carcinogenicity, toxicity, immunogenicity, or inflammation (4).

An implant made from a biodegradable polymer provides sustained drug release accompanied by concurrent or ensuing polymer degradation in the tissue, thus avoiding removal. The major advantage, therefore, is that these polymers are absorbable or degradable and form degradation products that are similar to either products that naturally occur in the body or that are nontoxic.

While it is possible to implant and remove drug-containing devices or polymeric matrices surgically, the requirement for such intervention could diminish the patient acceptability of the product candidate. This has led to the development of much interest in the biodegradable/bioabsorbable implantable therapeutic systems.

It is considered that the future application of these drug delivery systems will embrace two broad areas of therapeutic utility. The first is the delivery of the new class of biological mediators, most notably peptides and proteins produced by increasingly powerful synthetic methods and by recombinant DNA technology. One particularly intriguing application concerns the potential utility of polymeric systems in engineering novel controlled-release profiles to augment the immunogenicity of molecules in the new vaccination strategies. This contrasts with the historical emphasis on polymeric systems, which have focused on the ability to achieve long-term, zero-order profiles. As an additional property, biodegradable polymers also offer important opportunities for the protection of labile macromolecules, coupled with the advantages of controlled release. The second major area of future application of biodegradable polymeric implantable systems is in improved patient compliance. This approach has been exploited to therapeutic advantage for chronic diseases that affect populations for which socioeconomic and cultural factors often impose significant obstacles to sustained therapy with conventional dosage forms (5).

This article reviews the background of bioabsorbable implantable systems, the rationale behind the use of bioabsorbable polymers in implantable drug delivery systems and the type of such systems currently under investigation. It is expected that this information may be useful as a close representation of the past credentials and as a counsel for future research in this area of drug delivery systems.

Bioerodible Systems

In bioerodible systems (6), the drug is dispersed in a polymer that is slowly eroded biologically at a controlled rate. The bioerodible systems release the drug according to the rate of polymer erosion. In actual use, however, some diffusion of the drug from the polymer matrix might also occur. The major advantage of these bioerodible systems is that the polymer is eventually absorbed by the body, hence alleviating the need for surgical removal on completion of therapy. A big drawback, however, of these systems is that, as the implant is eroded, the surface area of the implant decreases. Thus, a geometry that does not change its surface area as a function of time is required to attain more-uniform and zero-order release (7).

Mechanism of Polymer Degradation

Polymer degradation can be defined as the conversion of an initially water-insoluble material to a water-soluble material. Any of the following mechanisms may be involved in polymer degradation.

A cross-linked network of water-soluble macromolecules remains insoluble as long as the cross-links are intact, but swells when placed in an aqueous environment. Degradation of these systems can occur either by cleavage of cross-links or by cleavage of the water-soluble polymer backbone. The matrix swells as the bonds are cleaved and eventually dissolves.

Sometimes hydrolysis, ionization, or protonation of a pendant group can also convert a water-insoluble macromolecule into a water-soluble one.

Hydrolytic cleavage of labile bonds in the polymer backbone can also cause polymer degradation. These systems are mainly used for the systemic administration of therapeutic agents from subcutaneous, intramuscular, or intraperitoneal implantation sites.

Mechanism of Drug Release

Drug release from bioerodible polymers can occur by any of the three mechanisms described below:

1. The active agent that is covalently attached to the polymer backbone may be released by the hydrolysis of the bond that attaches it to the backbone.
2. The active agent that is contained in a core surrounded by a bioerodible rate-controlling membrane is released as erosion of the polymeric membrane proceeds. At the same time, some diffusion of the drug out of the device might also take place.
3. The active agent, which is homogeneously dispersed in a polymer, is released by a mechanism of diffusion, by a combination of diffusion and erosion, or by erosion alone.

Hydrophilic Bioerodible Polymers

The hydrophilic bioerodible polymers undergo bioerosion by cleavage of the cross-links that hold the drug molecules to the polymer backbone. As these polymers are completely permeated by water, they undergo a bulk erosion process. The polymers with degradation products that are high molecular weight water-soluble molecules are generally used for topical, ocular, rectal, and intrauterine applications. For use in these applications, degradation to small products is not necessary. If, however, these polymers are to be used as implants, then they must degrade further so that the ultimate degradation products are small and water soluble. On the other hand, there are examples of polymers that have degradation products of relatively low molecular weight that are therefore used for systemic routes of drug delivery.

Thus, provided all the degradation products are toxicologically harmless, these polymers can be used for implantation applications. These polymers are unable to immobilize small molecules having good water solubility. Thus, they are useful only for small molecules with low water solubility or for large macromolecules, which although they are water soluble, do not leach out of the polymer matrix as they become physically entangled in the matrix. Release of such molecules is possible only when a large number of polymer chains have cleaved, and the degree of entanglement has substantially decreased.

Hydrophobic Bioerodible Polymers

Erosion of hydrophobic polymers proceeds by two distinct mechanisms namely bulk erosion and surface erosion. In bulk erosion, hydrolysis occurs throughout the bulk of the polymer and the mechanism of drug release involved is a combination of diffusion and erosion. As the process changes the characteristics of the matrix, the permeability of the polymer to the drug increases with time, but since this increase in permeability is not predictable, the increasing drug release rate also remains unpredictable. Furthermore the matrix can disintegrate before drug depletion and a large burst in the rate of drug delivery can take place.

In surface erosion, hydrolysis of the polymer is confined to the outer surface only, and the interior of the polymer matrix remains essentially unchanged. The drug release is constant, provided the devices maintain a constant surface geometry, unlike bulk erosion, for which release rates of incorporated drugs are neither constant nor predictable. The surface-eroding systems provide some additional advantages, too. First, the rate of drug release is directly proportional to drug loading. Second, as erosion is controlled by the area of the eroding front, the life of the device is directly proportional to the device thickness. Last, as the drug release mechanism does not involve diffusion, these devices release the drug at a constant and predictable rate.

Bioabsorbable Polymers for Implants

Hydrogels

Swellable polymers, which are water insoluble, are commonly called *hydrogels* and are used as controlled-release systems that have good swelling characteristics in aqueous media.

These hydrogels have the following advantages:

1. They are biocompatible.
2. As these are soft and rubbery, they cause minimal mechanical irritation on in vivo implantation.
3. Hydrogels have low water/hydrogel tension, which decreases protein adsorption and cell adhesion.
4. Drug release from the hydrogels can be regulated by controlling the water swelling and cross-linking density.
5. These polymers can be used for both hydrophilic and hydrophobic drugs and for charged solutes (8).

An account of the various hydrogels is given next.

Polyhydroxyalkyl Methacrylates

Poly(2-hydroxyethylmethacrylate) matrices containing methotrexate have been investigated as controlled-

release implants. Radiation-induced polymerization of hydrophilic monomers (hydroxyethylmethacrylate and related compounds) at a low temperature (−78°C) was performed to immobilize methotrexate in the polymer matrix. The effect of drug loading and different amounts of cross-linking agents on the in vitro drug release was studied. The diffusion of methotrexate from the hydrogel matrices was proportional to the square root of time according to an equation proposed by Higuchi (9).

Firsov, Nazarov, and Fomina (10) prepared implants containing gentamicin using the following polymers: (a) polymethylmethacrylate, (b) copolymers of 2-hydroxyethylmethacrylate, *N*-vinylpyrrolidone and allylic alcohol, (c) monocarboxycellulose, (d) cross-linked collagen, and (e) alginic acid and its mixed sodium-calcium salts. The drug-release characteristics of all were compared in vitro, and it was reported that the implants made from (a) and (c)–(e) had pronounced prolongation effects. The antibiotic levels in the implantation zones followed a three-phase character. The drug concentration reached its maximum in phase 1, was practically constant in phase 2, and slowly decreased in phase 3. The drug concentration and the areas under the curves (AUCs) were compared, and it was observed that the sustained-release and other pharmacokinetic characteristics of implants made from (c)–(e) were similar to those prepared from (a).

Apart from the matrix systems (mentioned above), subcutaneous hydrogel reservoir systems for implantable use were also prepared. The hydrogel used for the preparation of implants was a non-erodible Hydron-type copolymer of 2-hydroxyethylmethacrylate. The implant was a small-diameter, thin-walled cylindrical capsule capable of long-term delivery of predetermined doses of various active compounds (11).

Ethylenevinyl Alcohol

The feasibility of using cross-linked copolymers of ethylene oxide and propylene oxide, called poloxamers, as monolithic implants for administration of various drugs was studied by Gander (12).

An external control system for drug release was investigated by Miyazaki et al. (13). A polymeric system composed of ethylenevinyl alcohol copolymer (nondegradable) containing insulin was implanted subcutaneously in diabetic rats. The effects of external ultrasound on the release kinetics of insulin from the polymeric system, which is capable of in vivo delivery, at increased rates on demand were studied.

Polyethylene Oxide

Monolithic devices composed of varying ratios of polyethylene oxide and hydrophobic polydimethyl siloxane were studied for progesterone release after subdermal implantation (14).

Polyacrylic Acid

Hydrogels based on copolymers of poly(acrylamide-*co*-monomethyl itaconate) were investigated for the release of 5-fluorouracil (15).

Polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP) hydrogels cross-linked with *N,N'*-methylenebisacrylamide undergo biodegradation if the cross-link density is less than 1%. This delivery system was demonstrated by incorporation of chymotrypsin into the gel by mechanical entrapment during emulsion polymerization of *N*-vinylpyrrolidone. The amounts of chymotrypsin released during a 50-hr period at 25°C from a gel with 0.3%, 0.6%, and 1.0% cross-linking agent were 100%, 81%, and 64%, respectively. The times required for the dissolution of the same gels were listed as 2–3 days, more than 10 days, and insoluble respectively. The cross-link density controlled the rates of both the hydrogel dissolution and the diffusional release of chymotrypsin.

Cellulose Derivatives

For the incorporation of the nonsteroidal, postcoital antifertility drug centchroman, hydroxypropylmethylcellulose/ethylcellulose (HPMC/EC) was used as matrices. These polymers can accommodate large amounts of drug and provide controlled drug release over a period of time. The films showed an initial burst effect, followed by steady release. Incorporation of carbopol in the HPMC/EC films did not improve the release profile (16).

Other hydrogels that offer the potential of being used in implantable systems are the following:

- Polyvinyl alcohol (PVA): PVA cross-linked with glutaraldehyde forms a water-swellable micromatrix that was used for sustaining the release of proxyphylline and theophylline (17). PVA is especially used for the controlled delivery of peptides and proteins. Its permeability can be tailored to meet a wide range of uses (8,18).
- Poly(*N*-acrylolylpyrrolidine): Permeation of drugs through this polymer is mainly affected by degree of hydration regardless of chemical composition and temperature (19).
- Cross-linked gelatin: This biopolymer is nontoxic and inexpensive and has potential for use with a wide variety of agents, like chlorpromazine (20).

Few reports are available on bioabsorbable hydrogel implants. Several biodegradable carriers, like copolymers of 2-hydroxyethylmethacrylate, *N*-vinylpyrrolidone and allylic alcohol, monocarboxyl cellulose, collagen, alginic acid and its salts (10), HPMC, PVP, and PVA, can be exploited for use in implantable systems.

Polylactic Acid/Glycolic Acid Copolymers

The copolymers of lactic acid (LA) and glycolic acid (GA) have been extensively studied over their entire compositional ranges for sustained-release effects. The major copolymer series are those of (*l*) lactic acid/glycolic acid and (*dl*) lactic acid/glycolic acid. Most of the copolymer composition range is taken up by amorphous polymers. For the (*l*) LA/GA system, 25–75% GA compositions are amorphous, while for the (*dl*) LA/GA system, compositions of 0–70% GA copolymers are amorphous (21).

Materials are released from the poly(lactide-*co*-glycolide) (PLGA) composed matrices via a combination of diffusion and erosion. As the drug particles, which are solvated, diffuse out of the matrix, the exposed polymer is hydrolyzed and released as monomers. New drug/matrix surface is thus exposed, and the process of diffusion and erosion continues (5).

The physical advantages of PLGA copolymers include strength, hydrophobicity, and pliability. The polymer is water insoluble, but is miscible with a wide variety of biologically active compounds. Systems have been devised successfully for the delivery of a range of chemical classes of biologically active compounds and to achieve delivery periods that range from days to years (5).

PLGA polymers can be prepared in any molar ratio of lactic to glycolic acids. The proportion chosen is important in determining the in vivo degradation rates (22). Polymers prepared in a 50:50 ratio are hydrolyzed much faster than those that have a higher proportion of either of the monomer. For use in drug delivery systems, LA is usually selected as the predominant species because it is more hydrophobic than GA (5). PLGA copolymers can also be rendered hydrophobic by reaction of the terminal OH and/or COOH groups with long-chain fatty acids and/or fatty alcohols or their derivatives. These hydrophobic polyesters are useful as matrix or coating materials for implants (23).

Degradation and release properties of pellets fabricated from PLGA polymers provided by three commercial units were studied by Schmitt, Douglas, and Robert (24). The studies were conducted in phosphate buffer saline of pH 7.2 at 37°C. The molecular weight of the polymers decreased (with two distinct regions of decrease) continuously after exposure to the buffer. The mass loss experiments gave sigmoidal curves that indicated bulk erosion. For the release studies, amaranth was incorporated into the polymers. There was an initial burst release, followed by a lag period of 15–25 days, during which little or no dye was released. This was followed by a second period of release lasting approximately 10 days, until all the dye was released.

An investigation was carried out to study the effect of manufacturing procedure on the in vitro degradation of two PLGA copolymers, 85:15 and 50:50 (lactic acid:glycolic acid) that were fabricated as implants. Implants were compressed from microcapsules prepared by the nonsolvent-induced phase separation using two solvent-nonsolvent systems: methylene chloride–hexane (nonpolar) and acetone–phosphate buffer (polar). Results showed that both PLGA 85:15 and 50:50 implants prepared by the nonpolar procedure degraded faster than the implants prepared by the polar procedure, and the decrease in number-average and weight-average molecular weights of the polymer followed pseudo-first-order kinetics (25).

Biodegradable implants based on PLGA copolymer have been employed for delivering micromolecules and macromolecules (26). Luteinizing hormone-releasing hormone (LHRH) analog, nafarelin (27), and LHRH agonist, des-gly-(leu)-gonadorelin ethylamide monoacetate (28) have been incorporated into PLGA copolymers and subcutaneously implanted into rats. The influence of composition and molecular weight of the polymer on the release characteristics of the drugs has been studied.

Another implantable system using three layers (the outer layer containing 25 g PLGA in 75g AcOEt, the middle layer containing 5 g methotrexate and 25 g PLGA in 75 g of AcOEt deposited on the first layer, followed by a third layer with the same composition) was prepared to release methotrexate at a constant rate of 63 μg/day in vitro and in vivo (29).

Other classes of drugs that have been successfully incorporated into PLGA copolymers are those that require a sustained-release effect, such as disulfiram (30), finasteride, an antiandrogen (31), and melanotan-1, an alpha-melanocyte-stimulating hormone analog (32). The in vitro release of melanotan-1 exhibited a triphasic profile, with an initial rapid release, followed by a secondary phase of slow release, then a tertiary phase of rapid release due to the erosion of the polymer. The initial rapid release was less than 5% of the drug load, and the tertiary phase commenced after about 3 weeks. The factors controlling the drug release are degradation and erosion of the polymer, which may in turn be controlled by the physical properties of the polymer, such as viscosity and molecular weight.

The rate of release can also be controlled by manipulating the percentage drug content in the drug-polymer composite. This is illustrated by the release of the narcotic antagonist naltrexone from PLGA matrix beads. Four different drug-loading percentages, ranging from 50% to 80%, were prepared in a 75:25 (lactic acid:glycolic acid) PLGA copolymer prepared as 1.6-mm rods. Analysis of drug release in vitro showed that the release rates increased as the drug loading increased. The time taken to achieve 80% release varied from 8 to 45 days (33).

An implantable controlled-release system for the antiarthritic drug diclofenac sodium was produced by entrapping the nonsteroidal anti-inflammatory drug (NSAID) in a biodegradable matrix of PLGA copolymer (34,35). A modification of the above is a gel-forming implantable system of diclofenac that can be easily administered in addition to obviating the need for surgical procedures and special injecting equipment (36).

Very-soluble macromolecules, such as proteins, are released relatively rapidly from PLGA systems. Long-term delivery of proteins such as antigens for single-dose immunization systems or of peptide hormones in various therapeutic settings thus requires PLGA matrix systems with very low drug contents. The gross physical features of the dosage form, such as the shape and the size, however, have a less-significant effect on the drug release rates (5). Schwendenman et al. (37) have described the role of controlled release in the delivery of therapeutic peptides and proteins. They have also emphasized the role of biodegradable injectables such as PLGA microspheres as vaccine adjuvants.

Implants of PLGA containing phosphorothioate oligodeoxynucleotide were studied for their release behavior. Psuedo-zero-order release lasted for more than 20 days, and it did not depend on the molecular weight of the copolymer (38).

Brain delivery of neurotrophic factors via the systemic route is limited by the blood brain barrier. Direct infusion into the intraventricular spaces is currently the mode of administration available clinically. Alternatively, controlled-release systems can be the delivery of choice using bioerodible polymers such as PLGA. The biocompatibility and the degradation profile of PLGA implants have been extensively studied by Kon et al. (39).

Apart from the PLGA copolymers, a new biodegradable copolymer of GA and lactones with low molecular weight has been prepared by direct copolycondensation (40).

Polylactic Acid

Lactic acid has a chiral center in its molecule; therefore, there are three forms of polylactic acid: *d* (+)−, *l* (−)−, and *dl* (+,−)− isomers. The polymers derived from the optically active *d* and *l* monomers are semicrystalline. Their degradation is similar to or slightly lower than polyglycolic acid due to the hydrophobicity provided by the extra methyl group and the restricted water uptake.

Poly(*dl*-lactic acid) is amorphous, and as it has only one morphological phase, it is a preferred candidate for drug matrix release. It does not have a high crystalline melting point (180°C), but it undergoes a solid melt transition in the region of 130°–150°C (41).

The degradation of poly(*dl*-lactic acid) occurs essentially by homogenous erosion over two stages. The first occurs by random hydrolytic chain scission of the ester groups and is accompanied by a linear loss in molecular weight. The second stage begins at a number-average molecular weight of 15,000, at which onset of the weight loss occurs, along with an increase in the chain breakdown. The duration of the first phase depends on the initial number-average molecular weight.

Biodegradable implants made from lactic acid have been used for the incorporation of various antibiotics, like gentamicin (42–44), sulfadiazine (45), adriamycin (46), and the like.

Both poly(*dl*-lactic acid) (42) and poly(*l*-lactic acid) (43,44) have been used to prepare amorphous matrix systems for the incorporation of gentamicin. The implant is in a powder or a thin-film form from which it gradually releases the antibiotic. The implant made from poly(*l*-lactic acid) was prepared by compressing the polymer-drug mixture containing about 10 mg of the drug (44). The in vivo and in vitro release characteristics have been investigated, and it has also been reported that both the molecular weight and the molecular weight distribution of the polymer affect the life of the device. The dependence of the release rate on the polymer molecular weight was demonstrated in the work on sustained release of sulfadiazine from polylactic acid (45). The release rate decreased as the molecular weight increased to 100,000. Beyond this, no difference was observed. It was also shown that lowering the polymer dispersity from 2.0 to 2.4 produced a system for the release of pyrimethamine, which had a reduced initial level of release and a constant release for a longer period (45).

Highly porous, biodegradable poly(*l*-lactic acid) fibers loaded with relatively low amounts of adriamycin were implanted next to a tumor. Effective destruction of the tumor and a long-term survival rate were obtained (46). Another anticancer drug, methotrexate, has been incorporated into films fabricated from both poly(*dl*-lactic acid) and poly(*l*-lactic acid) of different molecular weights. The drug release from these systems was observed to be

dependent on drug loading and molecular weight of the polymer (47).

A useful tool in locoregional chemotherapy is a solid cylinder containing cisplatin embedded in poly(*dl*-lactic acid), which releases the drug continuously for more than 4 weeks. When compared with a subcutaneously given drug solution, the implant maintained a higher concentration of the drug in the subcutaneous tissues for about 20 days (48). Cisplatin has also been incorporated into an in situ forming biodegradable implantable system called Atrigel. The formulation of poly(*dl*-lactide-*co*-caprolactone) or poly(*dl*-lactide-*co*-glycolide) dissolved in dimethyl siloxane exhibited sustained release of cisplatin, with the peak serum concentration being attained in about 2 days, followed by gradually decreasing levels up to 30 days (49). The last formulation was observed to be faster degrading and thus more suitable (50). Atrigel has also been investigated for the controlled delivery of proteins (51).

Apart from antibiotic-loaded implants, poly(*l*-lactic acid) implants in the form of needles and artificial testis have also been fabricated for the long-term delivery of LHRH analog leuprolide in conditions requiring hormone therapies (52).

Poly(*dl*-lactic acid) has also been used to prepare bioerodible implants with programmable release. Taking advantage of surface erosion, a polymer matrix was developed that allowed the release of either one drug in two phases or two drugs, one after the other. The first period of drug release from these implants lasts between 1 and 2 weeks and is followed by a second period of similar duration. The matrices consisted of several layers of the surface-eroding polymer. Generally, these polymers erode fast; therefore, it is necessary to incorporate bulk eroding polymers also to obtain implants with the desired release characteristics and yet at the same time keep the dimensions of the implant small (53).

Biodegradable parenteral dosage forms utilizing polylactic acid have traditionally been prepared by such various techniques as film casting (54), extrusion (55), molding (56), microencapsulation (57), and spray drying (58). The major drawback with all these procedures is that they are time consuming, dependent on many variables, difficult to scale up, and often make use of solvents and heat. To overcome these drawbacks, drug-containing pellets were prepared by direct compression of poly(lactide) (both *dl*- and *l*-lactide). The drug release from these poly(-lactide) pellets was independent of the pH of the dissolution media and could be increased by admixing sodium chloride before compression or decreased by dipping the pellets in methylene chloride for some time. In addition, the pellets also showed no drug-polymer interactions (59).

Poly(Orthoesters)

Poly(orthoesters) have been used to fabricate a new biodegradable implantable system. The active agents incorporated into the implants range from anticancer agents (60), to antibiotics (61), to anthelmentics (62), to steroidal contraceptives (63–65).

Tobramycin sulfate in a bioerodible implant has been used as a local antibiotic therapy for the treatment of osteomyelitis. The earlier implants of tobramycin and gentamicin with polymethylmethacrylates had to be removed by a second surgery after about a 21-day implantation period. The drug release from these systems is only about 15% of the drug load. The newer systems in the form of disks (1-cm diameter) could release tobramycin over a 21-day period at the rate of 2 mg/day/g of implant. The disks without any adjuvants released 20–60% of the drug in 24 hr and an additional 10% in the subsequent 20 days. For achieving uniform and complete drug release over 21 days, lactic acid, sorbic acid, oleic acid, and palmitoleic acid were added in varying concentrations in the disks containing 8% tobramycin sulfate (61).

Other potential uses of implantable systems of poly(orthoesters) have been in the delivery of ivermectin (62) and pyrimethamine (66). In a study carried out by Zenter (62), the long-term delivery of ivermectin from a subcutaneous implant was investigated.

Cross-linked poly(orthoesters) have been used for the delivery of levenorgestrel (67,68) from polymeric disks that were implanted in rabbits. The effect of copolymerization on the polymer erosion and drug release rates was also studied in vivo (68).

Polyanhydrides

A hydrophobic polyanhydride polymer matrix is suitable for use after implantation for the controlled release and delivery of biologically active substances such as antibiotics, steroids, and the like. The implantable polyanhydride matrix has internal anhydride linkages, which are hydrolytic in nature in varying degrees, in accordance with the chemical composition of the polymer backbone, pH, and temperature of the environment. As the individual anhydride linkages become hydrolyzed, the matrix erodes, predominantly by surface erosion, into nontoxic and biocompatible degradation products and with the concomitant release of the active substance (69).

Implantable drug delivery systems composed of polyanhydrides can be modified to provide various rates of drug delivery (70). The mechanisms of drug release have been investigated by Park (71). Methotrexate-containing implants have been used for the treatment of cancer of the head and the neck. The polymer used for the fabrica-

tion of the device is a copolyanhydride based on the dimer uric acid and sebacic acid, and the methotrexate loading ranged from 2% to 20% (72).

A theoretical model was developed for the simulation of polyanhydride erosion that allows the prediction of release of two drugs for programmable drug delivery from polyanhydride implants. It is possible to release low molecular weight compounds from the same implants with a delay of days or weeks (73).

Polyurethanes

Polyurethanes have been used to prepare implantable matrices from which the release of drugs like lidocaine (74), 5-fluorouracil (75), and methotrexate (76) has been studied. A copolymer system of polyether and polyurethane segments has also been evaluated for drug release after implantation (77,78). Apart from matrix-type devices, reservoir devices with coatings of polyurethanes have also shown sustained-release effects (79). 5-Fluorouracil implants prepared with poly(phosphoester urethanes) are biocompatible and biodegradable (75).

Poly(E-Caprolactone)

Poly(E-caprolactone) is an aliphatic polyester and can be used as a biomaterial for sustained drug delivery (80,81). Films of the polymer were prepared using the solvent evaporation technique and were evaluated as a subdermally implantable drug delivery system for diclofenac sodium in rats with adjuvant-induced arthritic syndrome. It has been suggested by the group that, by employing polycaprolactone of high molecular weight and by selecting an appropriate drug-polymer ratio, subdermal implantable devices may be formulated to release the drug over a longer period of time (82).

Biodegradable films of poly(E-caprolactone) loaded with methotrexate were also prepared. Polyglycolic acid was incorporated into the films to effect the drug release and the in vivo polymer degradation. The release of the drug was found to be faster than the polymer degradation rate (83).

Imasaka et al. (84) have reported the in vivo degradation and the release for hydrophilic and hydrophobic drugs incorporated in poly(E-caprolactone) and poly(δ-valerolactone) and have found that, for hydrophobic drugs, the release and the degradation were almost the same. The slow degradation may be due to the poor ability of the hydrophobic drugs to form a porous structure in the polymer as they are not easily dissolved, leading to slow hydrolytic cleavage autocatalyzed by the carboxylic end groups of the polymer (85–87).

Random copolymers of caprolactone containing 5–25 mol% trimethylene carbonate were shaped into tubular devices to form cylindrical capsules for the sustained delivery of drugs after subcutaneous implantation (88).

Shenoy et al. (16) have prepared films of poly(E-caprolactone) alone and of poly(E-caprolactone) with carbopol, loaded with centchroman for use as an antifertility drug delivery system. The former gave a sustained-release effect for over 3 weeks, and both provided protection against implantation of the embryo. A subcutaneous implant of levenorgestrel contained in a biodegradable capsule of poly(E-caprolactone) has been evaluated by Darney (89) for efficacy, safety, and patient acceptance.

CONCLUSION

Implantable systems most closely meet the primary objectives of controlled delivery by maintaining optimal therapeutic levels of the drug for the duration of treatment. These ensure safe drug delivery at desirable rates, thus reducing adverse side effects and minimizing the frequency of dose intake. The biodegradable systems also alleviate the need for surgical removal of the polymeric device on culmination of therapy. Patient compliance and patient acceptability have therefore considerably improved because of these aspects.

It is expected that further investigations now in progress with other drugs will provide a better understanding of the potentials of biodegradable polymeric carriers in implantable controlled drug delivery.

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