

# Biodegradable Polymers for Drug Delivery Systems

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## Abstract

Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. Biodegradable polymers could be classified into synthetic and natural (biologically derived) polymers. Both synthetic and natural biodegradable polymers have been used for drug delivery, and some of them have been successfully developed for clinical applications. This entry focused on various biodegradable polymers that have been used in development of drug delivery systems. Advances in organic chemistry and nano/micro fabrication/manufacturing methods enable continuous progresses in better utilization of a wide range of novel biodegradable polymers in drug delivery.

## INTRODUCTION

Over the past few decades, a large number of polymers have been developed for application as drug delivery systems. In particular, biodegradable polymers with good biocompatibility have become increasingly important in the development of drug delivery systems.<sup>[1]</sup> There are many different types of biodegradable polymers that can be utilized to develop efficient drug delivery systems. Those biodegradable polymers might be classified into natural and synthetic polymers as listed in Table 1. Biodegradation of polymers involves enzymatic or hydrolytic cleavage of sensitive bonds in the polymer leading to polymer erosion.<sup>[2,3]</sup> While most of the natural biodegradable polymers undergo enzymatic degradation, synthetic polymers generally undergo hydrolytic degradation.

There are many useful natural biodegradable polymers such as protein-based polymers (e.g., collagen, gelatin, and fibrin), polysaccharides (e.g., chitosan, alginate, hyaluronic acid, and dextran), and microbial polymers (e.g., polyhydroxybutyrate). The use of natural biodegradable polymers remains attractive primarily because of good biocompatibility, easy availability, abundance in nature, and easy chemical modifications. However, due to their poor mechanical properties and possibility of an antigenic response, natural biodegradable polymers need to be purified or modified for drug delivery applications.<sup>[4]</sup>

There are a lot of synthetic biodegradable polymers, such as polyesters [e.g., polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone, and poly(lactic-co-glycolic acid) (PLGA)], polyamides, polyphosphazenes, polyorthoesters, and polyalkylcyanoacrylates. Synthetic biodegradable polymers are generally biologically inert, and they have no danger of immunogenicity or possibility of disease transmission. In addition, characteristics of synthetic

biodegradable polymers such as mechanical properties, degradability, and adhesiveness can be altered to facilitate clinical use.<sup>[5]</sup>

## POLYPEPTIDES AND PROTEINS

*Collagen.* Collagen is a main protein that is found in connective tissues such as skin, bones, and tendon. Collagen consists in more than 90% of the extracellular protein in the tendon and bone, and more than 50% in the skin.<sup>[6]</sup> Twenty-eight types of collagen protein have been described in literature to date.<sup>[7]</sup> Collagen is mainly isolated from animal sources, so one concern has been raised about safety of animal tissue-derived collagen.<sup>[8]</sup> To decrease the potential immunogenicity of animal tissue-derived collagen, atelocollagen has been used in drug delivery systems.<sup>[9,10]</sup> Atelocollagen produced by removing telopeptides, the major cause of foreign body response, from natural collagen molecules, resulting in reduction of antigenicity. Collagen is defined by good mechanical properties, good biocompatibility, low antigenicity, moldability, and easy modification. Therefore, collagen has been widely applied in drug delivery systems and tissue engineering.<sup>[11]</sup> The majority of collagen-based drug delivery systems are in the form of either implantable devices or injectable hydrogels.<sup>[12]</sup> The relevant applications of collagen in drug delivery systems are summarized in Table 2. Because of its unique structural properties, collagen has been fabricated into a wide variety of forms such as cross-linked sponges, meshes, injectable hydrogel, and particles in order to fully exploit the potential of collagen for drug delivery systems.<sup>[11]</sup>

*Gelatin.* Gelatin is a natural polymer that is obtained by the denaturation process of collagen<sup>[13]</sup> and is commonly

**Table 1** Representative list of biodegradable polymers used in drug delivery

Classification	Polymers
<i>Natural biodegradable polymers</i>	
Polypeptides and proteins	Collagen, gelatin, fibrin, serum albumin
Polysaccharides	Chitosan, alginate, hyaluronic acid, agarose, dextran
Microbial polymers	Poly(3-hydroxybutyrate)
<i>Synthetic biodegradable polymers</i>	
Aliphatic polyesters	Poly(lactic acid), Poly(glycolic acid), Poly( $\epsilon$ -caprolactone), Polydioxanones, Poly(lactic-co-glycolic acid)
Polyanhydrides	Poly(adipic anhydride), Poly(sebacic anhydride)
Phosphorous-based polymers	Polyphosphazenes, polyphosphates, polyphosphonates
Polyorthoesters	Poly(ortho ester)I, II, III, and IV
Polycyanoacrylates	Polyalkylcyanoacrylate

**Table 2** Application of collagen for drug delivery system in biomedical engineering

Application form	Delivered biomolecule	Application area	Reference
Sponge	BMP-2	Bone regeneration	[135]
Injectable hydrogel	BMP-2 gene	Bone/cartilage regeneration	[136]
Collagen/PLLA	bFGF	Cartilage regeneration	[137]
Hydrogel	bFGF gene	Angiogenesis	[138]
Collagen/Heparan sulfate	bFGF	Angiogenesis	[139]
Injectable hydrogel	VEGF	Angiogenesis	[140]
Sponge	Antibiotic	Infection	[141]
Particle	Cyclosporine	Allograft implantation	[142]
Sponge	TGF- $\beta$	Wound healing	[143]

used for pharmaceutical and biomedical applications because of its biodegradability and biocompatibility in physiological environments.<sup>[13,14]</sup> Two different types of gelatin can be produced from collagen depending on the pretreatment method, prior to the extraction.<sup>[13,14]</sup> The alkaline process, through hydrolysis of amide groups of asparagine and glutamine, yields gelatin with a great proportion of carboxyl groups. In contrast, acidic pretreatment does little to affect the amide groups of collagen. As a result, alkaline-processed gelatin possesses negative charge and low isoelectric point (IEP, 5), while acid-processed gelatin possesses positive charge and high IEP

**Table 3** Application of gelatin for drug delivery system in biomedical engineering

Application form	Delivered biomolecule	Application area	References
Sponge	BMP-2	Cartilage regeneration	[144–146]
Hydrogel	TGF- $\beta$ 1	Bone regeneration	[147–150]
Hydrogel	BMP-2	Bone regeneration	[151–153]
Microsphere	bFGF	Angiogenesis	[154]
Hydrogel	VEGF	Angiogenesis	[155]
Styrenated microsphere	bFGF/Insulin/IGF	Adipogenesis	[156]
Injectable hydrogel	TGF- $\beta$ 1	Cartilage regeneration	[157]

(9), which is similar to collagen.<sup>[13–15]</sup> The different types of gelatin, negatively charged acidic gelatin or positively charged basic gelatin, allows for flexibility in terms of enabling polyion complexation of a gelatin with either basic protein or acidic protein. Basic gelatin with an IEP of 9.0 should be applicable as a carrier for acidic proteins, while basic gelatin with an IEP of 5.0 should be used for delivery of acidic proteins.<sup>[13]</sup> The main limitation of gelatin, as a drug delivery carrier, arises from its rapidly dissolving in aqueous environments leading to fast drug release at body temperature.<sup>[16]</sup> To overcome this problem, gelatin has been utilized by insoluble hydrogels through chemical cross-linking with water-soluble carbodiimides<sup>[17]</sup> or glutaraldehyde.<sup>[18]</sup> The relevant applications of gelatin in drug delivery system are summarized in Table 3. Because of its electrical and physical properties, gelatin has been fabricated into a wide variety of forms such as injectable microsphere, injectable hydrogel, and cross-linked sponge, in order to fully exploit the potential of gelatin for a drug delivery system.

**Fibrin.** Fibrin is a protein matrix produced from fibrinogen via cleavage by thrombin<sup>[19]</sup> and a major component of blood clots and plays a vital role in the subsequent wound healing response.<sup>[20]</sup> Unlike xenogenic gelatin and collagen, which may induce inflammatory and immune responses, fibrin can avoid the potential risk of a foreign body reaction when produced from patient's own blood.<sup>[21]</sup> Fibrin gel is formed when fibrinogen is activated by thrombin in the presence of  $\text{Ca}^{2+}$  ion and factor XIII. As a drug delivery carrier, fibrin could be implanted easily by injection through syringe, which could obviate invasive open surgery for treatment and reduce patients' pain.<sup>[22]</sup> The representative applications of fibrin in drug delivery system are summarized in Table 4. Due to fibrin's biochemical characteristics, mainly in cellular interactions, fibrin-based materials also found applications in the field of drug delivery with special focus in cell delivery, such as BMP-2 and human osteoblast,<sup>[23]</sup> bFGF and

**Table 4** Application of fibrin for drug delivery system in biomedical engineering

Application form	Delivered biomolecule	Application area	References
Fibrin gel	bFGF	Angiogenesis	[22,24,158]
Fibrin gel	VEGF	Angiogenesis	[159–162]
Fibrin gel	BMP-2	Bone regeneration	[163]
Fibrin/heparin-conjugated nanospheres	bFGF/BMP-2	Angiogenesis/bone regeneration	[84,164]
Fibrin–alginate–hydroxyapatite bead	bFGF, TGF- $\beta$ 1	Bone regeneration	[165]
Fibrin gel	NGF	Nerve regeneration	[166]
Fibrin gel	ENOS gene	Wound healing	[167]

human bone marrow-derived cell,<sup>[24]</sup> TGF- $\beta$ 1 and human fibroblast,<sup>[20]</sup> and NT-3 and ganglia cell.<sup>[25,26]</sup> These combined deliveries enhance the therapeutic efficacy of drug delivery.

## POLYSACCHARIDES

**Chitosan.** Chitosan is a biodegradable and biocompatible polysaccharide obtained from deacetylation of chitin comprising  $\beta$ -(1,4)-linked *N*-acetyl-glucosamine.<sup>[27]</sup> Chitin is a natural polysaccharide found in the exoskeletons of insects and shells of crustaceans.<sup>[15,27]</sup> Chitosan has been used in a wide variety of biomedical applications since it has been proved to be biodegradable, biocompatible, and non-toxic.<sup>[28]</sup> Due to these favorable properties, the interest in chitosan as a carrier for drug delivery has increased in recent years.<sup>[29]</sup> The relevant applications of chitosan-based materials in drug delivery systems are summarized in Table 5. Chitosan and chitosan derivatives can easily form micro/nanoparticles. Therefore, chitosan micro/nanoparticles are being investigated as delivery systems for plasmid DNA in nonviral gene therapy.<sup>[30]</sup> Because it could open epithelial tight junctions to allow for an increased drug transport, chitosan has also been investigated as mucoadhesive natural polymer, as a permeation enhancer for drug delivery at mucosal epithelia.<sup>[31,32]</sup> Chitosan and chitosan derivatives are used as coating materials in drug delivery applications because of their good film-forming properties. Chitosan-coated microparticles have many advantages such as bioadhesive property, targeting property to specific tissue, and prolonged drug release properties compared to uncoated microparticles.<sup>[27]</sup>

**Alginate.** Alginate is one of the most versatile biopolymers with a wide range of pharmaceutical and biomedical applications such as tissue engineering and drug delivery

**Table 5** Application of chitosan-based materials for drug delivery system in biomedical engineering

Application form	Delivered molecule	Application area	Reference
Microspheres in chitosan scaffold	TGF- $\beta$ 1	Cartilage regeneration	[168]
Nanofibrous membrane	BMP-2	Bone regeneration	[169]
Photocrosslinkable hydrogel	bFGF	Angiogenesis	[170]
Chitosan/chitin tube with PLGA microparticles	EGF	Nerve regeneration	[171]
Galactosylated chitosan-graft-polyethyleneimine microparticles	pDNA	Gene therapy	[172]
pH sensitive <i>N</i> -succinyl chitosan/alginate hydrogel bead	PEDF plasmid	Bone regeneration	[173]
	Nifedipine	Treatment of hypertension	[174]

field. Alginate is a linear unbranched polysaccharide that contains the repeating units of 1,4-linked  $\beta$ -D-mannuronic acid and  $\alpha$ -L-guluronic acid.<sup>[33]</sup> Commercial alginates are isolated from three species of brown algae, such as *Laminaria hyperborea*, *Ascophyllum nodosum*, and *Macrocystis pyrifera*.<sup>[33]</sup> Bacterial alginates have also been extracted from *Azotobacter vinelandii* and *Pseudomonas species*.<sup>[15,34]</sup> Alginates have reversible gelling properties in aqueous solutions related to the interactions between the divalent cations, such as calcium, lead, and copper and carboxylic acid moieties.<sup>[35]</sup> Due to these properties of alginate hydrogel, many researches have been focused on the delivery of protein drugs, cell encapsulation, and tissue regeneration,<sup>[35]</sup> as summarized in Table 6. It is also possible to form an alginate hydrogel by lowering the environmental pH. Active biomolecules released from alginate hydrogel in low pH solutions is significantly reduced which could be advantageous in the development of drug delivery system. Theoretically, alginate shrinks in gastric environment and the encapsulated drugs cannot be released at low pH.<sup>[36]</sup> However, alginate undergoes a rapid dissolution at higher pH, which may result in burst release of active biomolecules. Therefore, chemical modification of alginate is needed for the sustained release of active biomolecules.<sup>[37]</sup>

**Hyaluronic acid.** Hyaluronic acid is a linear unsulfated glycosaminoglycan that consists of repeating disaccharide units of  $\alpha$ -1,4-D-glucuronic acid and  $\beta$ -1,3-*N*-acetylglucosamine linked  $\alpha$ -(1 $\rightarrow$ 4) and  $\beta$ -(1 $\rightarrow$ 3) respectively.<sup>[38]</sup> Hyaluronic acid is mainly found in the extracellular matrix of connective tissues such as cartilage, umbilical cord, vitreous of eye, and synovial fluid.<sup>[39,40]</sup> Hyaluronic acid is commercially obtained from rooster comb, synovial fluid, or umbilical

**Table 6** Application of alginate for drug delivery system in biomedical engineering

Application form	Delivered biomolecule	Application area	References
Beads	BMP-2, TGF- $\beta$ , or bFGF	Cartilage regeneration	[177–177]
RGD-modified hydrogel	BMP-2, TGF- $\beta$ 3	Bone regeneration	[178]
Beads	bFGF, VEGF, EGF	Angiogenesis	[179]
Hydrogel	VEGF, bFGF	Angiogenesis	[180]
Hydrogel	BMP-2 gene	Cartilage regeneration	[136]
Hydroxyapatite/collagen–alginate nanocomposites	BMP-2	Bone regeneration	[181]
Alginate/chitosan nanoparticle	Insulin	Oral delivery for diabetes	[182]

cord. Besides vertebrates, hyaluronic acid is produced in large scale from *Streptococci*, avoiding the risk of animal-derived pathogens.<sup>[40]</sup> It has a high capacity for lubrication, water sorption and retention, and a number of macromolecular functions.<sup>[38,41]</sup> These properties have allowed hyaluronic acid to be applied in ophthalmic surgery as a viscoelastic material<sup>[42]</sup> and in orthopedic surgery for treatment of articular cartilage defects.<sup>[43]</sup> Hyaluronic acid also plays a critical role as a signaling molecule in cell motility,<sup>[44]</sup> cell differentiation,<sup>[45]</sup> wound healing,<sup>[46]</sup> and cancer metastasis.<sup>[47]</sup> Recently, hyaluronic acid has been widely studied as a biocompatible and biodegradable carrier for drug delivery. The most relevant applications of hyaluronic acid in drug delivery are summarized in Table 7. As poor mechanical properties and rapid degradation of hyaluronic acid limit broader ranges of drug delivery systems, hyaluronic acid can be chemically modified or cross-linked to improve the mechanical properties and control the degradation rate.<sup>[41]</sup> Chemical modification of hyaluronic acid typically involves the carboxylic acid groups and/or the alcohol groups of its backbone. The carboxylic acid or alcohol groups have been modified by esterification<sup>[48]</sup> and by cross-linking with dihydrazide,<sup>[49]</sup> dialdehyde,<sup>[50]</sup> divinyl sulfone,<sup>[51]</sup> diglycidyl ethers,<sup>[52]</sup> or disulfide<sup>[53]</sup> cross-linkers.

**Dextran.** Dextran is a branched, high molecular weight glucose polymer, produced by bacteria from sucrose or by chemical synthesis.<sup>[54]</sup> Dextran consists of a substantial number of consecutive  $\alpha$ -(1 $\rightarrow$ 6) linkages in its main chains with some degree of branching via  $\alpha$ -(1 $\rightarrow$ 3) linkages. Because dextran is readily available in a wide range of molecular weight and it is biodegradable and biocompatible,<sup>[15]</sup> dextran has been clinically used for more than 50 years for plasma volume expansion and peripheral flow promotion.<sup>[54]</sup> Recently, dextran has been

**Table 7** Hyaluronic acid-based carriers for drug delivery system in biomedical applications

Application form	Delivered molecule	Application area	Reference
Hyaluronic acid–heparin conjugate hydrogel	bFGF	Angiogenesis	[183]
Hyaluronic acid–PCL scaffold	BMP-2	Bone regeneration	[184]
Gelatin–hyaluronic acid–chondroitin sulfate copolymer	TGF- $\beta$ 1	Cartilage regeneration	[185]
Hyaluronic acid-modified liposome	EGF	Wound healing	[186]
Hyaluronic acid/chitosan microparticles	Gentamicin	Bacterial infection	[187]
Hyaluronic acid hydrogel	BMP-2 gene	Bone/cartilage regeneration	[136]
Microsphere (HYAFF <sup>®</sup> )	Calcitonin	Vaginal delivery (hormone therapy)	[188]

actively investigated for sustained delivery of drugs and proteins as a potential carrier, in particular for injectable hydrogel and colon-specific drug delivery systems.<sup>[54]</sup> Dextran contains a large number of hydroxyl groups which can be easily modified by chemical reactions. Dextran, which contains double bond in the side chain, has been widely investigated because the photocrosslinking reactions allows the avoidance of the usual disadvantages of the chemically cross-linked hydrogel.<sup>[35,55,56]</sup> The release rate of drug from hydrogel is controlled by varying the cross-linking density of the network.<sup>[56]</sup> Dextran microspheres were also investigated for the potential delivery of drugs. The bioavailability of protein drug is improved in vivo due to the prolonged circulation time in the cavity, compared to the solution form.<sup>[57]</sup> Another interesting system is the exploding microgel.<sup>[58]</sup> Hydroxyethyl methacrylated dextran microspheres, which is called exploding microgel, have been used for pulsed drug delivery of protein and plasmid DNA.<sup>[58]</sup> Additionally, dextran-conjugated small molecule drugs and dextran–protein conjugates have also been studied to prolong the activity of drugs in vivo.<sup>[59–61]</sup>

## MICROBIAL POLYMER

**Polyhydroxyalkanoates.** Polyhydroxyalkanoates comprise a special group of polyesters that are synthesized by many bacteria as an intracellular carbon and energy compound, as a part of their survival mechanism.<sup>[62]</sup> The first polyhydroxyalkanoate, poly(3-hydroxybutyrate) was discovered in *Bacillus megaterium* by Lemoigne.<sup>[63]</sup> Polyhydroxyalkanoates became candidates as drug carriers

because they can be produced from a variety of renewable resources and they are biodegradable and biocompatible. Although a number of polyhydroxyalkanoate are produced, the use of polyhydroxyalkanoates in drug delivery system has been mainly restricted to poly(3-hydroxybutyrate) and poly(3-hydroxybutyrate-co-3-hydroxyvalerate). The brittleness of poly(3-hydroxybutyrate) was improved by copolymerization with 3-hydroxyvalerate.<sup>[64]</sup> Poly(3-hydroxybutyrate-co-3-hydroxyvalerate), which was first commercialized, is more flexible, less crystalline and a more readily processable material than poly(3-hydroxybutyrate).<sup>[15]</sup> Microspheres of poly(3-hydroxybutyrate) containing rifampicin were investigated for their use as a potential chemoembolizing agent.<sup>[65]</sup> Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) microspheres and microcapsules loaded with tetracycline were also used for the treatment of periodontal diseases.<sup>[66]</sup>

## SYNTHETIC POLYMERS

### Polyesters

*Poly(lactic acid).* Polylactic acid or polylactide is biodegradable, thermoplastic, aliphatic polyester derived from lactic acid. Lactic acid is produced from the fermentation of agricultural by-products such as cornstarch or sugarcanes.<sup>[67]</sup> It is a chiral molecule with an asymmetric carbon atom and exists in two optically active configurations; D(-)-lactic acid and L(+)-lactic acid.<sup>[68]</sup> While poly(L-lactic acid) (PLLA) and poly(D-lactic acid) (PDLA) are semicrystalline polymers, poly(D,L-lactic acid) (PDLLA) is an amorphous polymer. Polylactic acid has a high tensile strength and modulus and hence, has been considered ideal biomaterials for load-bearing biomedical applications, such as orthopedic fixation implants (e.g., rod, plate, screw, and sheet). A wide range of mechanical properties and degradation rates can be achieved varying its molecular weights and composition in its copolymers.<sup>[69]</sup> While high molecular weight of PLA is used for orthopedic as augmentation devices, low molecular weight of PLA is used for pharmaceutical applications, such as a carrier for drug delivery systems. Polylactic acid undergoes hydrolytic degradation via the bulk erosion mechanism by the random scission of the ester bond.<sup>[3]</sup> It degrades into nontoxic lactic acid which is a normal human metabolic by-product and is broken down into water and carbon dioxide.<sup>[70]</sup> Due to good mechanical properties, biodegradability and biocompatibility, a large number of investigations have been carried out on PLA in sustained drug delivery system. The representative applications of PLA in drug delivery systems are summarized in Table 8.

*Polyglycolic acid.* Polyglycolic acid or Polyglycolide is one of the first biodegradable synthetic polymer investigated for biomedical applications. Polyglycolic acid is simply synthesized by ring-opening polymerization

**Table 8** The representative applications of PLA in drug delivery system

Application form	Delivered molecule	Application area	Reference
Nanoparticles	Paclitaxel		[189]
Microparticles	BMP	Bone regeneration	[190]
Microparticles	Nimesulide	Inflammatory disease	[191]
Microparticles	Morphine		[192]
PLA-PEG/hydroxyapatite composite	BMP-2	Bone regeneration	[193]
PLA/PEG hydrogel	CNTF, BDNF and NT-3	Spinal cord injury	[194]
Scaffold	VEGF	Angiogenesis	[195]

of the cyclic diester of glycolic acid or glycolide.<sup>[71]</sup> Polyglycolic acid is a highly crystalline polymer and has a high tensile strength and modulus.<sup>[68]</sup> Unlike other related polyesters such as PLA and polycaprolactone, PGA is insoluble in most organic solvents. Despite its low solubility, PGA was commercially used for the first synthetic absorbable suture due to its excellent fiber-forming properties.<sup>[3]</sup> Nonwoven PGA meshes have been extensively used as scaffold in tissue engineering due to their excellent biocompatibility and degradability, good mechanical properties, and cell binding compatibility. However, PGA has been limited for drug delivery carriers because of its low solubility and high melting point.

*Poly-ε-caprolactone.* Poly-ε-caprolactone (PCL) is biodegradable, biocompatible, and semicrystalline polyester with a low glass transition temperature (approximately -60°C) and low melting temperature (55-60°C), depending upon crystallinity of PCL.<sup>[3]</sup> PCL is soluble in a wide range of organic solvents, such as dichloromethane, chloroform, benzene, toluene, cyclohexanone, acetone, and ethyl acetate.<sup>[72]</sup> PCL is prepared by the ring-opening polymerization of the cyclic monomer ε-caprolactone. Stannous octoate and low molecular weight alcohols are usually used for the polymerization of ε-caprolactone as a catalyst and initiator, respectively.<sup>[68]</sup> Degradation of PCL is very slow because of its crystallinity and hydrophobicity. The PCL-based drug delivery carriers maintain their shape and weight during the initial phase of the biodegradation process, which covers a molecular weight range of 5,000 to 200,000.<sup>[72]</sup> The second phase of PCL degradation is characterized by a decrease in the rate of chain scission, which is associated with an increase in crystallinity, and the one set of weight loss. The chain cleavage of low molecular weight of PCL produces a fragment small enough to diffuse out of the polymer bulk.<sup>[72]</sup> Due to slow degradation PCL, several copolymers containing PCL have been investigated to control the degradation rate and mechanical

properties. Copolymers of  $\epsilon$ -caprolactone with lactide have yielded materials with faster degradation and elastomeric properties.<sup>[72–74]</sup> Similarly, copolymers of  $\epsilon$ -caprolactone with glycolide resulted in scaffolds that were elastic compared to those made of PGA alone.<sup>[75,76]</sup> Due to its slow degradation, high permeability to many drugs, and nontoxicity, the PCL is ideally suitable for long-term delivery over a period of more than 1 year.<sup>[72,77]</sup> Extensive research is ongoing to develop various delivery systems in the form of microspheres, nanospheres, and implants. The representative applications of PCL in drug delivery systems are summarized in Table 9. PCL also has the ability to form compatible blends with other polymers, such as PLA,<sup>[78]</sup> PMMA,<sup>[79]</sup> PLGA,<sup>[80]</sup> and polysaccharides,<sup>[81]</sup> which provide opportunities to manipulate the drug release rate from carriers.<sup>[77]</sup> *Poly(lactic-co-glycolic acid)*. Poly(lactic-co-glycolic acid) copolymers have been most widely used as carriers for controlled delivery of macromolecular therapeutics such as proteins, peptides, genes, vaccines, growth factor, and antigens, because their mechanical properties and degradation rate can be precisely controlled by varying the lactide/glycolide ratio and the molecular weight of the copolymers.<sup>[82]</sup> Poly(lactic-co-glycolic acid) copolymers are easily prepared by polycondensation reactions with lactic and glycolic acid<sup>[83]</sup> and by ring-opening polymerization of lactide and glycolide.<sup>[84]</sup> Poly(lactic-co-glycolic acid) copolymers are cleaved to monomeric acids (e.g., lactic and glycolic acid) that are eliminated from the body as carbon dioxide and water.<sup>[4]</sup> Poly(lactic-co-glycolic acid) copolymers undergo bulk erosion through simple hydrolysis of the ester bond linkage and the degradation

rate of PLGA depends on a variety of parameters, such as molecular weight, the monomer ratio, hydrophilicity, and the shape and structure of the matrix.<sup>[85]</sup> In the composition range of 25–50% of glycolic acid, PLGA copolymers form amorphous polymers and degrade more rapidly.<sup>[3]</sup> The degradation of low molecular weight of PLGA copolymers becomes faster than that of high molecular weight of PLGA copolymer because of the higher concentration of carboxylic acid, which accelerate the acid-catalyzed degradation, at the end of PLGA.<sup>[77]</sup> Poly(lactic-co-glycolic acid) copolymers are well suited for drug delivery systems since PLGA can be fabricated into various forms such as microspheres, nanospheres, films, rods, beads, pellets, and porous scaffolds by solvent casting, spray drying, compression molding, solvent evaporation, and salt leaching.<sup>[86,87]</sup> The representative applications of PLGA for drug delivery system in biomedical engineering are summarized in Table 10. Among all PLGA applications in drug delivery, the injectable micro/nanospheres have been extensively investigated as carriers for drug delivery systems. Micro/nanospheres have some advantages, such as ease of fabrication with good reproducibility, good biocompatibility, ease of incorporation of various kinds of drugs, ease of administration, and controllable drug release behavior.<sup>[87]</sup> However, due to the bulk erosion of the PLGA copolymers, it has been difficult to achieve a zero-order release kinetic from PLGA micro/nanospheres. Another concern with using PLGA copolymers as a protein

**Table 9** The representative applications of PCL in drug delivery system

Application form	Delivered molecule	Application area	Reference
Microparticles	Nifedipine and propranolol HCl	Antihypertensive	[196]
Microspheres	Cyclosporine	Immunosuppression	[197]
PCL or PCL/PLGA	NGF	Nerve regeneration	[198]
microspheres			
Microspheres	Insulin	Diabetes	[199]
Heparin-conjugated micelle	bFGF	Angiogenesis	[200]
Hyaluronic acid/PCL scaffold	BMP-2	Bone regeneration	[184]
PEG/PCL nanospheres	Paclitaxel	Cancer therapy	[201]
PCL nanofiber mat	Heparin	Vascular injury	[202]

**Table 10** The representative applications of PLGA in drug delivery system

Application form	Delivered molecule	Application area	Reference
Microspheres/ millicylinders	BSA/bFGF/ BMP-2		[203]
Microsphere	Hepatitis B vaccine	Immunization	[204]
Microspheres- embedded hydrogel	TGF- $\beta$ 1	Cartilage regeneration	[205]
Micro/ nanospheres	Gentamicin		[206]
Nanosphere	bFGF	Angiogenesis	[84]
Nanosphere	VEGF gene	Angiogenesis	[207]
Nano-fibrous scaffold	BMP-7	Bone regeneration	[208]
Nanospheres	Rapamycin	Maturation of cell	[209]
Microsphere- based scaffold	IGF-I and TGF- $\beta$ 1		[210]
Heparin- conjugated scaffold	BMP-2	Bone regeneration	[211]
Discs	NGF		[212]
Nanospheres	Dexamethasone	Vascular injury	[213]

delivery carrier is the possibility of protein denaturation within the PLGA micro/nanospheres because of bulk erosion mechanism of the PLGA copolymer and the acidic degradation of by-products.<sup>[3]</sup> To overcome the problem associated with protein denaturation, many efforts have been made to modify the properties of PLGA copolymers and blend the PLGA with other polymers, such as alginate and chitosan,<sup>[88]</sup> gelatin,<sup>[89]</sup> poly(vinyl alcohol),<sup>[90]</sup> and poly(ortho esters).<sup>[91]</sup>

## Polyanhydrides

Polyanhydrides are one of the useful biodegradable polymers as carriers of drugs to various tissues, such as brain, bone, blood vessels, and eyes.<sup>[92]</sup> The main chain of polyanhydrides is composed of either aliphatic or aromatic groups connected by a highly labile anhydride linkage. Polyanhydrides are hydrolyzed in aqueous solution into nontoxic dicarboxylic acids that are eliminated from the body as metabolites,<sup>[92]</sup> resulting in polymer degradation and subsequent erosion. Because water does not penetrate into bulk of hydrophobic polyanhydrides, degradation and erosion occur at the surface of polyanhydrides rather than in bulk.<sup>[93]</sup> The degradation rate of polyanhydrides can be controlled by varying the length of alkyl chains in polyanhydrides such as poly[bis-(p-carboxyphenoxy)alkane anhydride].<sup>[94]</sup> The degradation rate can be increased by incorporating hydrophilic sebacic acid into the polyanhydrides such as poly[bis(p-carboxyphenoxy)propane anhydride].<sup>[95]</sup> Because desirable release kinetics of drug can be obtained by combining polyanhydrides with different erosion rates, surface erodible polyanhydrides are particularly well suited for sustained release and drug stabilization.<sup>[96]</sup> Especially, polyanhydride microsphere-based drug delivery systems have been formulated by hot-melt microencapsulation technique,<sup>[97]</sup> microencapsulation by solvent removal,<sup>[98]</sup> or spray drying.<sup>[99]</sup> The release rate of incorporated drug was affected by the surface erosion rate of the polyanhydrides. The incorporated drugs were released at a near-constant rate for more than 25 days without any large initial burst, irrespective of the molecular weight of the polymer and protein loading amount.<sup>[100,101]</sup> Recently, the use of polyanhydrides for sustained delivery of DNA for the potential to enhance long-term gene therapy has been reported.<sup>[102,103]</sup>

## Polyphosphazenes

Polyphosphazenes are one of the most rapidly developing classes of biomedical polymers due to their synthetic flexibility and versatile adaptability for applications.<sup>[104]</sup> Polyphosphazenes consist of alternating phosphorus and nitrogen atoms linked by alternating single and double bonds with two side groups attached to each phosphorus atom.<sup>[105]</sup> Since Allcock et al. synthesized the linear polydichlorophosphazene by ring-opening polymerization,<sup>[106]</sup>

a large number of polyphosphazenes have been developed by changing the side groups to obtain biodegradability.<sup>[177]</sup> Biodegradable polyphosphazenes are hydrolyzed in aqueous solution to nontoxic, low molecular weight products such as phosphates, ammonia, and corresponding side groups. A large number of biodegradable polyphosphazenes have been investigated as potential carriers for drug delivery systems including polyphosphazenes containing amino acid ester,<sup>[107]</sup> imidazolyl,<sup>[108]</sup> ethylamino,<sup>[109]</sup> lactic or glycolic acid ester,<sup>[110]</sup> and glucosyl amino groups.<sup>[111]</sup> The representative applications of polyphosphazenes are summarized in Table 11. Most studies using biodegradable polyphosphazenes have been focused on development of pellets or films as drug delivery carriers, which are usually fabricated by solvent casting or compression molding.<sup>[104]</sup> In addition, microencapsulation methods, such as emulsion solvent evaporation and spray drying, are also used for drug delivery systems.<sup>[112,113]</sup>

## Poly(ortho esters)

Poly(ortho esters) are synthetic bioerodible hydrophobic polymers which can undergo an erosion process confined to the polymer–water interface. Poly(ortho esters) were developed by Heller and coworkers, since the 1970s, and have been designated as poly(ortho esters) I, poly(ortho esters) II, poly(ortho esters) III, and poly(ortho esters) IV.<sup>[114]</sup> Poly(ortho esters) can be synthesized by the reaction of diols with diketene acetals via a transesterification reaction. Poly(ortho ester) I has been developed at the Alza Corporation and is hydrolyzed in an aqueous environment, thus producing  $\gamma$ -butyrolactone which is rapidly changed to  $\gamma$ -hydroxybutyric acid. To avoid an uncontrollable autocatalytic hydrolysis reaction, the polymer should be stabilized with a base such as  $\text{Na}_2\text{CO}_3$ .<sup>[114,115]</sup> Poly(ortho ester) I has been used in the delivery of the narcotic antagonist naltrexone<sup>[114,116]</sup>, in the delivery of the steroid levonorgestrel,<sup>[117]</sup> and in the delivery of indomethacin for orthopedic application.<sup>[118]</sup> However, the autocatalytic hydrolysis reaction of poly(ortho ester) I has limited its applications in drug delivery systems.

**Table 11** Application of polyphosphazenes for drug delivery system in biomedical engineering

Application form	Delivered molecule	Application area	Reference
Micelle	Indomethacin	Arthritis	[214]
Microsphere	Insulin	Diabetes	[112]
Cationic polyphosphazenes	Plasmid DNA	Gene delivery	[215]
Hydrogel	Human growth hormone		[216]
Microsphere	Naproxen	Inflammation	[113]
Films	Colchicine		[217]

Poly(ortho ester) II was developed at the Stanford Research Institute by the addition of a diol to the diketene acetal. Polymer synthesis is very simple and highly reproducible, and molecular weights can be easily controlled by adjusting the stoichiometry.<sup>[77,114]</sup> Because the initial product of hydrolysis is neutral, the erosion of poly(ortho ester) II is very slow in an aqueous environment.<sup>[119]</sup> Desired erosion rate of polymer can be achieved by addition of acidic excipient, such as adipic acid or suberic acid, into the polymer matrix.<sup>[120]</sup> Poly(ortho ester) II has been investigated as a carrier for the delivery of 5-fluorouracil which is used as an antiproliferative agent. The release rate of 5-fluorouracil from poly(ortho ester) II can be controlled by varying the amounts of suberic acid.<sup>[121]</sup> Poly(ortho ester) III was also developed at the Stanford Research Institute by reacting triols with two vicinal hydroxyl groups.<sup>[122]</sup> Poly(ortho ester) III is a very flexible, viscous, and gel-like material at room temperature. This viscous nature of poly(ortho ester) III allows incorporation of therapeutic agents by a simple mixing at room temperature without the need of using organic solvents or elevated temperatures.<sup>[120]</sup> Moreover, the initial hydrolysis of the poly(ortho ester) III is followed by a much slower hydrolysis of the monesters to produce a carboxylic acid and a triol. Although poly(ortho ester) III offers a number of advantages, its biomedical applications have been limited by difficulties in synthesis and reproducibility.<sup>[114]</sup> Poly(ortho ester) IV was recently developed by Heller et al. using a triol, 1,1,4-cyclophencanetrimethanol, and trimethyl orthoacetate.<sup>[123]</sup> Poly(ortho ester) IV can be readily prepared by a well-developed synthesis that has been scaled up under GMP. Because poly(ortho ester) IV has excellent potential as a drug delivery carrier, many therapeutic agents including proteins, peptides, and DNA have been delivered from poly(ortho ester) IV. Poly(ortho ester) IV has also potential for treating ocular diseases, as a viscous, injectable material or solid, implantable matrix.<sup>[120]</sup>

### Polyalkylcyanoacrylates

Alkylcyanoacrylates have been used in tissue adhesives such as surgical glue because of their excellent adhesive properties resulting from the high bond strength with most polar substrates.<sup>[124]</sup> Polyalkylcyanoacrylates have also been used for biomedical applications since the polyalkylcyanoacrylates have been found to be biodegradable and biocompatible.<sup>[125]</sup> The degradation rate of polyalkylcyanoacrylates can be controlled by changing alkyl group chain lengths.<sup>[126]</sup> Recently, a phase I clinical trial test for the polyalkylcyanoacrylate nanoparticles containing doxorubicin was carried out successfully in the treatment of refractory solid tumors,<sup>[127]</sup> polyalkylcyanoacrylate nanoparticles have been extensively studied to deliver anticancer drug or peptides.<sup>[128,129]</sup> However, polyalkylcyanoacrylate nanoparticles have a major problem which is their nonspecific uptake by macrophages after intravenous

administration.<sup>[124]</sup> To reduce nonspecific uptake, polyalkylcyanoacrylate–polyethylene glycol copolymers or polyethylene glycol-coated polyalkylcyanoacrylate nanoparticles have been investigated for drug delivery systems.<sup>[130,131]</sup> Polyethylene glycol-coated polyalkylcyanoacrylate nanoparticles result in a lower uptake by macrophages and a longer circulation time in the blood.<sup>[132]</sup> Polyalkylcyanoacrylate nanoparticles have recently passed a phase II clinical trial and have now reached the status of phase III clinical trials for resistant cancers.

### CONCLUSIONS

Drug delivery systems aim to improve the therapeutic efficacy of drug using natural and synthetic biodegradable polymers. We have focused on biodegradable polymers developed recently for drug delivery systems in this entry. Most of the biodegradable polymers, such as collagen, gelatin, PLA, PLGA, etc. are currently on the market. Future advances in organic chemistry, polymer science, and biotechnology are enabling the development of a wide range of novel biodegradable polymers as candidates for drug delivery carriers. Furthermore, new fabrication and manufacturing processes, such as nanofabrication<sup>[133]</sup> and molecular imprinting,<sup>[134]</sup> will lead to development of new drug delivery systems.

### ACKNOWLEDGMENTS

This study was supported in part by the National Institute of Health through GM065284 and HL078715 and the Showalter Trust Fund from Purdue University.

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