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Synthesis and Characterization of Biodegradable Polymers for Controlled Drug Delivery Systems

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ABSTRACT

Biodegradable polymers have emerged as important materials for the development of controlled drug delivery systems because they can provide sustained and site-specific drug release while gradually degrading into biologically acceptable products. Conventional drug administration often results in fluctuations in plasma drug concentrations, repeated dosing, poor patient compliance, and systemic adverse effects. Polymer-based delivery systems offer an opportunity to overcome these limitations by regulating drug encapsulation, protection, transport, and release. This review discusses the synthesis, characterization, and pharmaceutical applications of biodegradable polymers used in controlled drug delivery. Particular attention is given to naturally derived polymers, including chitosan, alginate, gelatin, collagen, and starch, as well as synthetic polymers such as poly (lactic acid), poly (glycolic acid), poly (lactic-co-glycolic acid), polycaprolactone, and related copolymers. Major synthesis approaches, including ring-opening polymerization, condensation polymerization, solvent evaporation, nanoprecipitation, emulsion techniques, and ionic gelation, are discussed. Characterization techniques such as Fourier-transform infrared spectroscopy, nuclear magnetic resonance, X-ray diffraction, differential scanning calorimetry, thermogravimetric analysis, scanning electron microscopy, particle-size analysis, and molecular-weight determination are important for establishing polymer structure and performance. Factors controlling drug release, including polymer composition, molecular weight, crystallinity, degradation rate, particle size, porosity, and drug–polymer interactions, are also considered. Recent advances in stimuli-responsive, nanoparticle-based, and targeted polymeric delivery systems are highlighted. Overall, biodegradable polymers provide a versatile platform for developing safer, longer-acting, and more effective drug delivery technologies.

Keywords: *Biodegradable polymers; controlled drug delivery; polymer synthesis; characterization; nanoparticles; sustained release; drug encapsulation.*

1. Introduction

Drug delivery plays a central role in determining the therapeutic effectiveness and safety of pharmaceutical agents. Conventional oral, injectable, and topical formulations frequently produce rapid changes in drug concentration, resulting in periods of subtherapeutic exposure or concentrations associated with adverse effects. Frequent administration may also reduce patient compliance, particularly in chronic diseases requiring long-term therapy. Controlled drug delivery systems have therefore been developed to maintain drug concentrations within an appropriate therapeutic window for an extended period. Polymeric materials are particularly attractive for controlled delivery because their chemical composition and physical structure can be modified to regulate drug loading, degradation, diffusion, and release.

Among these materials, biodegradable polymers have received substantial attention because they can progressively break down within the body and eliminate the need for surgical removal after completion of drug release. Biodegradable polymers may be obtained from natural sources or synthesized chemically [1]. Natural polymers such as chitosan, alginate, gelatin, collagen, and starch generally possess favorable biocompatibility and biological functionality. Synthetic polymers, including poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL), provide greater control over molecular weight, degradation kinetics, mechanical properties, and formulation characteristics. The selection and synthesis of an appropriate polymer are critical because polymer properties directly influence the performance of a drug delivery system. Molecular weight, monomer composition, crystallinity,

hydrophilicity, glass-transition temperature, surface characteristics, and degradation behavior can all affect drug release [2]. This review examines the major biodegradable polymers used for controlled drug delivery, their synthesis and characterization, mechanisms of drug release, formulation strategies, advantages and limitations, and emerging developments in this field.

2. Classification of Biodegradable Polymers

Biodegradable polymers used in pharmaceutical drug delivery can broadly be classified into natural and synthetic polymers based on their origin, chemical structure, and method of preparation. Natural biodegradable polymers are obtained from biological sources and generally exhibit favorable biocompatibility, biodegradability, and biological activity, making them attractive for pharmaceutical and biomedical applications. Important natural polymers include chitosan, alginate, gelatin, collagen, hyaluronic acid, starch, dextran, and cellulose derivatives. These polymers contain functional groups capable of participating in hydrogen bonding, ionic interactions, enzymatic degradation, and chemical modification, allowing their physicochemical and drug-release properties to be tailored according to therapeutic requirements. Chitosan, for example, possesses cationic and mucoadhesive properties, whereas alginate readily forms hydrogels through ionic crosslinking. Gelatin and collagen offer excellent biological compatibility and are particularly useful for protein, peptide, and tissue-related drug delivery applications. In contrast, synthetic biodegradable polymers provide greater control over molecular weight, polymer composition, crystallinity, mechanical properties, and degradation kinetics. Common synthetic polymers include poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), poly(trimethylene carbonate), and polyethylene glycol-containing biodegradable copolymers. Among these materials, PLGA is one of the most extensively investigated polymers for controlled drug delivery because its degradation rate and drug-release behavior can be modulated by altering the lactic acid-to-glycolic acid ratio, molecular weight, particle size, and polymer architecture [3]. The selection between natural and synthetic polymers therefore depends on the desired drug-release profile, route of administration, therapeutic agent, biodegradation requirements, and biological environment.

3. Natural Biodegradable Polymers

Natural biodegradable polymers have attracted considerable attention in controlled drug delivery because of their biological origin, biodegradability, biocompatibility, and structural similarity to components of the extracellular environment. Chitosan is one of the most extensively investigated natural polymers and is obtained primarily through the deacetylation of chitin. The presence of amino groups gives chitosan a positive charge under acidic conditions, enabling electrostatic interactions with negatively charged biological membranes and mucosal surfaces. Its mucoadhesive, antimicrobial, and film-forming properties make it suitable for oral, nasal, ocular, transdermal, and localized drug delivery systems. Chitosan can be formulated into nanoparticles, microparticles, hydrogels, films, and nanofibers, while ionic gelation using agents such as sodium tripolyphosphate provides a relatively mild approach for nanoparticle preparation.

Alginate, a polysaccharide mainly obtained from brown seaweeds, is another important natural polymer that can form hydrogels through ionic crosslinking with divalent cations, particularly calcium ions. Alginate-based systems have been investigated for encapsulation and controlled delivery of small molecules, proteins, peptides, and other sensitive therapeutic agents. However, rapid swelling, relatively weak mechanical strength, and ion-exchange behavior may influence its long-term stability and release characteristics. Gelatin and collagen, which are derived from collagenous biological materials, possess excellent biocompatibility and contain functional groups suitable for chemical and physical modification. Gelatin nanoparticles, microspheres, and hydrogels have been explored for the delivery of anticancer drugs, antibiotics, proteins, and growth factors. Collagen is particularly attractive for localized delivery and tissue-engineering applications because of its biological recognition properties, although its relatively rapid enzymatic degradation and limited mechanical stability may require crosslinking or combination with other polymers. Hyaluronic acid is another naturally occurring polysaccharide with excellent biocompatibility and water-retention capacity. Its interaction with cell-surface receptors such as CD44 has encouraged its investigation in targeted drug delivery, particularly for cancer therapy [4]. Similarly, starch, dextran, and cellulose derivatives provide abundant functional groups that permit chemical modification and formulation into hydrogels, nanoparticles, films, and microspheres. Despite their advantages, natural polymers can exhibit batch-to-batch variation, source-dependent composition, relatively unpredictable degradation, and limited mechanical stability. Consequently, chemical modification, blending, crosslinking, or combination with synthetic polymers is frequently employed to improve their physicochemical and drug-release characteristics.

4. Synthetic Biodegradable Polymers

Synthetic biodegradable polymers provide greater control over molecular weight, chemical composition, crystallinity, mechanical properties, and degradation kinetics than many naturally derived materials. Poly(lactic acid) (PLA) is an important biodegradable polyester produced from lactic acid or its cyclic dimer lactide. It possesses good mechanical strength, biocompatibility, and relatively slow degradation, making it suitable for long-term drug delivery, implants, microspheres, and nanoparticle formulations. However, its hydrophobic nature can restrict water penetration and may limit the delivery of highly hydrophilic drugs. Poly(glycolic acid) (PGA) is another biodegradable polyester with comparatively higher hydrophilicity and faster degradation than PLA. Although its rapid degradation can be advantageous for certain applications, excessive degradation may lead to accumulation of acidic products and undesirable changes in the local microenvironment. Poly(lactic-co-glycolic acid) (PLGA) is a copolymer produced by combining lactic acid and glycolic acid and is among the most widely investigated synthetic polymers for controlled drug delivery. The ratio of lactic acid to glycolic acid, together with molecular weight, polymer end groups, crystallinity, particle size, and formulation architecture, can be manipulated to regulate degradation and drug-release behavior. PLGA has been extensively used for nanoparticles, microspheres, injectable depots, implants, and localized delivery systems. Polycaprolactone (PCL) is a semicrystalline biodegradable polyester characterized by good flexibility, biocompatibility, and relatively slow degradation.

Its prolonged degradation makes it particularly useful for long-term drug delivery and implantable systems [5]. However, its hydrophobicity can influence drug loading and release, especially for hydrophilic therapeutic molecules. Other synthetic biodegradable polymers, including poly(trimethylene carbonate), polydioxanone, polyhydroxyalkanoates, and biodegradable polyethylene glycol-containing copolymers, have also been investigated to achieve specific combinations of hydrophilicity, degradation, mechanical strength, and biological responsiveness. The major advantage of synthetic polymers is their ability to be rationally designed and reproducibly manufactured with defined physicochemical properties. Nevertheless, residual solvents, degradation products, manufacturing conditions, polymer purification, and potential inflammatory responses must be carefully evaluated before clinical application. The selection of an appropriate synthetic polymer therefore requires consideration of the drug's physicochemical characteristics, desired duration of therapy, administration route, degradation profile, and required release kinetics.

5. Synthesis of Biodegradable Polymers

The synthesis of biodegradable polymers is a critical step because polymerization conditions determine molecular weight, molecular-weight distribution, monomer composition, crystallinity, chain architecture, and ultimately degradation and drug-release behavior. Condensation polymerization is one of the conventional approaches used for preparing biodegradable polymers and involves reactions between functional groups, commonly with the elimination of small molecules such as water or alcohol. The molecular weight obtained through condensation polymerization depends strongly on monomer purity, stoichiometric balance, reaction temperature, catalyst concentration, and removal of reaction by-products.

Ring-opening polymerization (ROP) is particularly important for the synthesis of biodegradable polyesters such as PLA, PGA, and PCL. In this approach, cyclic monomers such as lactide, glycolide, or ε-caprolactone undergo ring opening in the presence of suitable catalysts or initiators to produce polymer chains. ROP provides considerable control over molecular weight, composition, and polymer architecture and is therefore widely used in the preparation of pharmaceutical-grade biodegradable polymers. Copolymerization can further modify polymer characteristics by combining two or more monomers with different hydrophilicities and degradation behaviors. PLGA is a prominent example in which adjustment of the lactic acid-to-glycolic acid ratio allows modulation of water uptake and degradation. Crosslinking is particularly important for natural polymers such as chitosan, gelatin, collagen, and alginate because it improves structural stability and enables the formation of three-dimensional networks. Crosslinking may occur through ionic interactions, covalent bonds, physical interactions, or enzymatic mechanisms. The extent and type of crosslinking influence swelling, porosity, mechanical strength, degradation, and drug diffusion. In addition to conventional chemical synthesis, increasing attention is being directed toward environmentally sustainable polymer-production approaches involving renewable feedstocks, low-toxicity catalysts, solvent-minimized processing, and green chemistry principles. After synthesis, purification is essential to remove unreacted monomers, catalysts, solvents, and other low-molecular-weight impurities that could compromise biological safety [6]. Therefore, optimization of polymer synthesis must balance chemical reproducibility, biodegradation behavior, pharmaceutical performance, and biocompatibility to produce materials suitable for controlled drug delivery.

Table 1. Representative biodegradable polymers and their applications in controlled drug delivery

Polymer	Source/type	Major characteristics	Common delivery applications
Chitosan	Natural	Biodegradable, mucoadhesive, cationic	Oral, nasal, ocular, transdermal
Alginate	Natural	Hydrogel-forming, hydrophilic	Oral, protein and peptide delivery
Gelatin	Natural	Biocompatible, easily modified	Nanoparticles, microspheres, tissue delivery
PLA	Synthetic	Hydrophobic, relatively slow degradation	Long-term drug delivery
PGA	Synthetic	Relatively rapid degradation	Shorter-duration delivery systems
PLGA	Synthetic copolymer	Tunable degradation	Nanoparticles, microspheres, implants
PCL	Synthetic	Flexible, slow degradation	Long-term and implantable systems

Table 2. Major characterization techniques for biodegradable polymers

Technique	Major information obtained
FTIR	Functional groups and chemical interactions
NMR	Molecular structure and copolymer composition
XRD	Crystalline/amorphous characteristics
DSC	Glass transition and melting behavior
TGA	Thermal stability and degradation
SEM	Surface morphology and porosity
TEM	Nanoparticle morphology and size
GPC/SEC	Molecular weight and polydispersity
DLS	Particle-size distribution
Zeta potential	Surface charge and colloidal stability

6. Fabrication of Biodegradable Polymeric Drug Delivery Systems

The fabrication of biodegradable polymers into appropriate drug delivery systems is essential for achieving predictable drug loading, protection, transport, and controlled release. Depending on the physicochemical properties of the therapeutic agent and the desired route of administration, biodegradable polymers can be formulated as nanoparticles, microparticles, microspheres, hydrogels, films, nanofibers, implants, and injectable depots. Polymeric nanoparticles are generally prepared using techniques such as nanoprecipitation, emulsification–solvent evaporation, solvent diffusion, and ionic gelation. Nanoprecipitation is particularly useful for hydrophobic polymers and involves dissolving the polymer and drug in an appropriate organic phase followed by controlled addition to an aqueous phase, resulting in spontaneous formation of nanoscale particles. Emulsion-based methods are widely employed for PLGA and related polymers and can produce particles with relatively high encapsulation efficiency. Microspheres and microparticles provide a larger polymeric matrix within which drug molecules can be dispersed or encapsulated, allowing sustained release over extended periods. The emulsion–solvent evaporation method is commonly employed for their preparation, particularly when biodegradable polyesters are used.

Hydrogels represent another important class of delivery systems and consist of three-dimensional polymeric networks capable of absorbing substantial quantities of water while retaining their structural integrity [7]. Natural polymers such as chitosan, alginate, gelatin, and hyaluronic acid can be converted into hydrogels through physical or chemical crosslinking, while synthetic polymers can be designed to provide specific mechanical and degradation characteristics. Hydrogels are particularly useful for localized delivery because their swelling and degradation can be adjusted to regulate drug diffusion. Films and nanofibers can provide high surface area and flexibility and have been investigated for transdermal, wound, buccal, and localized drug delivery. Electrospinning is frequently used to fabricate biodegradable polymeric nanofibers with tunable morphology and drug-loading capacity. Implants and injectable polymeric depots can provide prolonged drug release for weeks or months and are particularly valuable when continuous exposure to a therapeutic agent is required. The fabrication process must be carefully optimized because parameters such as polymer concentration, solvent characteristics, stirring rate, temperature, surfactant concentration, phase ratio, drying conditions, and drug-to-polymer ratio can substantially influence particle size, morphology, encapsulation efficiency, surface properties, and release kinetics.

7. Characterization of Biodegradable Polymers and Polymeric Delivery Systems

Comprehensive physicochemical and pharmaceutical characterization is necessary to establish the structural integrity, stability, safety, and functional performance of biodegradable polymeric delivery systems. Fourier-transform infrared spectroscopy (FTIR) is widely used to identify characteristic functional groups and investigate chemical interactions between polymers and incorporated drugs. Shifts, broadening, or changes in characteristic absorption bands may indicate hydrogen bonding, ionic interactions, crosslinking, or other molecular interactions. Nuclear magnetic resonance (NMR) spectroscopy provides detailed information regarding the chemical structure, monomer composition, degree of substitution, and copolymerization of biodegradable materials and is particularly useful for confirming the successful synthesis of polymeric systems. X-ray diffraction (XRD) is employed to determine the crystalline and amorphous characteristics of polymers. Crystallinity can influence water penetration, mechanical properties, degradation rate, and drug diffusion and therefore represents an important parameter in controlled-release formulations. Differential scanning calorimetry (DSC) provides information regarding glass-transition temperature, melting point, crystallization, and other thermal transitions, whereas thermogravimetric analysis (TGA) evaluates thermal stability and mass loss associated with polymer degradation. Morphological characteristics are commonly examined using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). SEM can reveal surface morphology, porosity, particle aggregation, and structural integrity, while TEM provides higher-resolution information regarding nanoparticle morphology and internal structure [8]. Dynamic light scattering (DLS) is frequently used to determine the hydrodynamic particle-size distribution and polydispersity of polymeric nanoparticles, while zeta-potential analysis provides information regarding surface charge and colloidal stability.

Molecular weight and molecular-weight distribution are important determinants of polymer degradation and drug release and can be evaluated using gel permeation chromatography or size-exclusion chromatography. Pharmaceutical characterization additionally includes determination of drug-loading capacity, encapsulation efficiency, moisture content, swelling behavior, degradation rate, and in vitro drug-release kinetics. Stability studies under different temperature and humidity conditions are also required to determine whether particle size, polymer structure, drug content, and release characteristics remain consistent during storage. Collectively, these characterization techniques provide complementary structural, thermal, morphological, chemical, and pharmaceutical information necessary for establishing the quality and reproducibility of biodegradable polymeric drug delivery systems.

8. Mechanisms of Controlled Drug Release

Drug release from biodegradable polymeric systems is governed by several interconnected mechanisms, primarily diffusion, swelling, polymer degradation, and erosion. In diffusion-controlled systems, drug molecules migrate through water-filled pores, channels, or polymeric regions toward the surrounding biological environment. Diffusion is particularly important during the initial phase of release and is strongly influenced by polymer porosity, drug solubility, molecular size, particle dimensions, and polymer–drug interactions. In degradation-controlled systems, water or biological enzymes progressively cleave susceptible polymeric bonds, resulting in a gradual reduction in molecular weight and structural integrity. Hydrolysis is particularly important for biodegradable polyesters such as PLA, PGA, PLGA, and PCL. As degradation proceeds, the polymer matrix becomes increasingly permeable, facilitating drug liberation. Erosion-controlled release occurs when polymer material is progressively lost from the surface or throughout the bulk matrix, thereby exposing and releasing the incorporated therapeutic agent. The relative contribution of surface erosion and bulk degradation depends on polymer chemistry, hydrophilicity, molecular weight, crystallinity, and environmental conditions. Swelling-controlled release is especially relevant to hydrophilic polymers and hydrogel systems. Following water absorption, the polymer network expands and creates diffusion pathways through which drug molecules can migrate. In many practical delivery systems, these mechanisms do not operate independently; instead, diffusion, swelling, degradation, and erosion occur simultaneously and influence one another. The release profile may therefore demonstrate an initial burst caused by surface-associated drug, followed by a slower sustained-release phase associated with diffusion and progressive polymer degradation [9]. The therapeutic objective is generally to minimize undesirable burst release while maintaining a predictable drug concentration over the intended treatment period. Mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models can be applied to experimental release data to provide insights into the dominant release mechanism. Optimization of polymer composition, molecular weight, particle size, porosity, drug loading, crosslinking density, and polymer architecture can consequently provide considerable control over the temporal profile of drug release.

9. Factors Affecting Drug Release from Biodegradable Polymers

The rate and extent of drug release from biodegradable polymeric systems depend on a complex interaction between polymer characteristics, drug properties, formulation architecture, and physiological conditions. Polymer molecular weight is a major determinant because higher-molecular-weight polymers generally possess longer degradation times and may consequently provide prolonged drug release. Polymer composition is equally important, particularly in copolymers such as PLGA, where changes in monomer ratio influence hydrophilicity, water penetration, hydrolysis, and matrix erosion. The chemical structure and solubility of the drug also strongly affect release behavior. Hydrophilic drugs may diffuse relatively rapidly through hydrated polymeric matrices, whereas hydrophobic drugs may exhibit stronger interactions with hydrophobic polymers and therefore demonstrate slower release. Particle size and surface area influence the rate at which water penetrates the delivery system and degradation products are removed; smaller particles generally provide greater surface area and may exhibit faster drug release. Porosity and pore size determine the accessibility of water and the pathways available for drug diffusion. Increased porosity may accelerate water penetration and drug liberation but can also contribute to undesirable initial burst release [10]. Polymer crystallinity affects water permeability and degradation because crystalline regions are generally more resistant to molecular penetration than amorphous regions. Drug loading and distribution within the polymer matrix can also influence release kinetics, with excessive loading potentially causing drug accumulation near the particle surface and increasing the initial burst effect. In hydrogel systems, crosslinking density regulates swelling and mesh size, thereby controlling the movement of drug molecules through the polymer network. Physiological parameters, including pH, temperature, ionic strength, enzymatic activity, and fluid composition, can further modify polymer degradation and drug diffusion after administration [11]. Consequently, rational formulation design requires simultaneous consideration of polymer properties and drug characteristics rather than optimization of a single parameter. Careful control of these factors can produce biodegradable delivery systems capable of maintaining therapeutic drug concentrations while minimizing premature release and reducing dosing frequency.

10. Conclusion

Biodegradable polymers provide a versatile and highly adaptable platform for controlled drug delivery. Natural polymers such as chitosan, alginate, gelatin, and collagen offer valuable biological properties, whereas synthetic polymers including PLA, PGA, PLGA, and PCL provide greater control over molecular structure and degradation behavior. Advances in polymer synthesis, particularly ring-opening polymerization and controlled copolymerization, have enabled the development of materials with increasingly predictable pharmaceutical characteristics. Comprehensive characterization using spectroscopic, thermal, microscopic, structural, and molecular-weight techniques is essential for establishing polymer quality and understanding its influence on drug-release performance. Depending on polymer composition and formulation architecture, drug release can occur through diffusion, swelling, degradation, and erosion.

Future biodegradable delivery systems are likely to combine controlled degradation with targeting, stimuli responsiveness, nanotechnology, and personalized therapeutic approaches. Although challenges related to manufacturing, stability, toxicity, reproducibility, and clinical translation remain, continued advances in polymer chemistry and pharmaceutical engineering are expected to expand the clinical applications of biodegradable polymer-based drug delivery systems.

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