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Biodegradable Polymers in Drug Delivery: Design, Degradation, and Drug Release Dynamics

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Abstract:

Biodegradable polymers have emerged as essential components in advanced drug delivery systems, enabling controlled, sustained, and site-specific therapeutic release while minimizing systemic toxicity. This comprehensive review covers the design principles, degradation mechanisms, and drug release dynamics of natural and synthetic biodegradable polymers such as PLGA, PCL, chitosan, and alginate. Their adaptability allows fabrication into nanoparticles, microspheres, hydrogels, and scaffolds tailored to various clinical needs, including cancer therapy, vaccine delivery, gene therapy, and tissue engineering. The review discusses hydrolytic and enzymatic degradation processes, surface versus bulk erosion behaviors, and factors influencing polymer degradation and drug release kinetics. Case studies highlight FDA-approved formulations leveraging these polymers for enhanced therapeutic efficacy and patient compliance. Challenges such as variability in degradation rates, formulation stability, manufacturing scale-up, and regulatory hurdles are addressed. Emerging frontiers in smart stimuli-responsive systems, hybrid polymers, AI-driven design, and personalized medicine underscore the future potential of biodegradable polymers as cornerstones of precision and sustainable therapeutics.

Keywords: Biodegradable Polymers, Drug Delivery, Controlled Release, Polymer Degradation, Nanoparticles, PLGA, Polymeric Microspheres, Stimuli-Responsive Polymers, Personalized Medicine, Pharmaceutical Formulation.

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1. Introduction

In the rapidly advancing field of pharmaceutical technology, polymer-based drug delivery systems have emerged as one of the most versatile and efficient platforms for improving therapeutic outcomes. These systems utilize polymeric materials to encapsulate, protect, and

control the release of active pharmaceutical ingredients (APIs), thereby enhancing drug stability, bioavailability, and patient compliance. Over the years, the transition from conventional dosage forms to polymeric carriers has marked a paradigm shift toward precision and sustained drug delivery [1].

Among the various classes of polymers, biodegradable polymers have gained significant attention due to their ability to degrade into non-toxic by-products after fulfilling their therapeutic purpose. This intrinsic degradability eliminates the need for surgical removal of the delivery system, making them particularly valuable in long-term treatments such as cancer therapy, chronic inflammation, and tissue regeneration. Moreover, the degradation kinetics of these polymers can be finely tuned by manipulating molecular weight, crystallinity, and copolymer ratios, allowing for precise control over drug release profiles [2].

Compared to non-degradable systems, biodegradable polymers offer numerous advantages, including reduced toxicity, improved patient compliance, and enhanced site-specific targeting. Materials such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), chitosan, and alginate have become staples in both research and clinical applications due to their proven safety and regulatory acceptance. These polymers provide versatile platforms for developing nanoparticles, microspheres, hydrogels, and scaffolds capable of encapsulating a wide range of therapeutic agents, from small molecules to proteins and nucleic acids [3].

This review aims to provide a comprehensive overview of biodegradable polymers in drug delivery, emphasizing their design principles, degradation mechanisms, and drug release dynamics. It explores recent advances in formulation strategies, discusses the underlying physicochemical and biological processes governing polymer degradation, and highlights case studies demonstrating their practical utility in controlled and targeted drug delivery applications. The goal is to underscore the pivotal role of biodegradable polymers in shaping the next generation of intelligent and sustainable therapeutic systems [4].

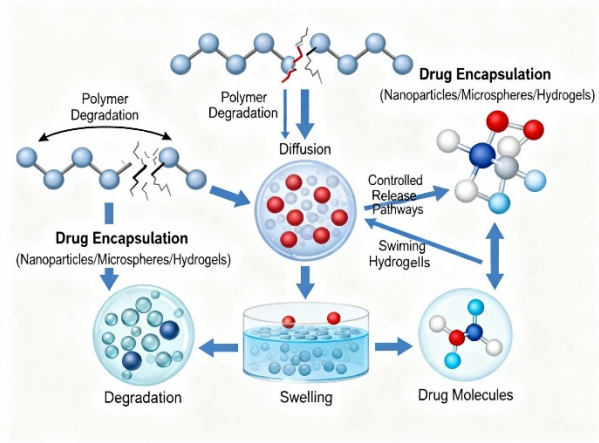

Figure 1: Schematic overview of biodegradable polymer-based drug delivery systems showing polymer degradation, drug encapsulation, and controlled release pathways

2. Classification of Biodegradable Polymers

Biodegradable polymers are broadly classified into two major categories—natural and synthetic polymers—based on their origin and method of preparation. Both types have found extensive applications in drug delivery due to their ability to degrade into non-toxic by-products while providing controlled and sustained release of therapeutic agents. However, they differ significantly in terms of their physicochemical properties, degradation behavior, and biological performance [5].

2.1 Natural Biodegradable Polymers

Natural biodegradable polymers are derived from biological sources such as plants, animals, or microorganisms. Common examples include chitosan, alginate, gelatin, collagen, and starch. These materials are inherently biocompatible and biodegradable, making them ideal for pharmaceutical and biomedical applications. Their chemical similarity to components of the extracellular matrix (ECM) enables excellent cell adhesion, proliferation, and tissue integration—properties that are especially valuable in wound healing, vaccine delivery, and tissue engineering.

Chitosan, a cationic polysaccharide obtained from chitin, exhibits mucoadhesive properties that enhance the absorption of drugs across mucosal surfaces. Alginate, derived from brown seaweed, forms hydrogels in the presence of divalent cations, making it an excellent carrier for proteins and vaccines. Gelatin and collagen, both derived from animal sources, are extensively used for controlled release of peptides and growth factors due to their natural biodegradability and ability to form crosslinked networks. Starch-based polymers offer an economical and renewable alternative with good mechanical properties and biocompatibility.

Despite their advantages, natural polymers suffer from certain limitations such as batch-to-batch variability, potential immunogenicity, and poor mechanical strength. Their degradation rate is often difficult to control, which can affect drug release kinetics and therapeutic efficiency. Nonetheless, they remain a cornerstone in biopolymer research due to their natural origin and low toxicity [6-7].

2.2 Synthetic Biodegradable Polymers

Synthetic biodegradable polymers, on the other hand, are chemically synthesized and offer greater control over molecular structure, composition, and degradation behavior. Notable examples include poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA), and poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) copolymers. These materials can be precisely engineered to achieve desired mechanical strength, degradation time, and drug release rates—making them highly versatile for a variety of pharmaceutical formulations.

PLGA is one of the most widely studied and FDA-approved synthetic polymers due to its predictable degradation profile and excellent biocompatibility. By altering the lactic to glycolic acid ratio, the degradation rate of PLGA can be finely tuned—from weeks to months—depending on therapeutic requirements. PLA and PCL are more hydrophobic and degrade slowly, making them suitable for long-term implants and sustained-release systems. PGA, being more hydrophilic, degrades faster and is used in applications requiring rapid drug release. Incorporating PEG into copolymers (e.g., PEG-PLA) enhances hydrophilicity, circulation time, and stealth properties, thus improving systemic delivery efficiency.

Synthetic polymers generally exhibit higher stability, reproducibility, and tunable degradation characteristics compared to their natural counterparts. However, they may lack inherent bioactivity and sometimes require surface modifications or blending with natural polymers to improve cellular interactions and reduce inflammation risk.

Overall, both natural and synthetic biodegradable polymers have their unique strengths and limitations. Natural polymers offer superior biological affinity, while synthetic polymers provide flexibility in design and performance control. The ongoing trend in drug delivery research focuses on hybrid systems that combine the biocompatibility of natural materials with the tunable properties of synthetic polymers, paving the way for more effective and predictable biodegradable delivery platforms [8-9].

3. Design and Fabrication Strategies

The design and fabrication of biodegradable polymer-based drug delivery systems are central to achieving precise control over drug loading, release kinetics, and biodegradation profiles. Depending on the therapeutic purpose and route of administration, these systems can be engineered into various structural forms such as nanoparticles, microspheres, hydrogels, films, and scaffolds. Each form provides unique advantages in terms of surface area, drug encapsulation efficiency, and release mechanisms [10].

Nanoparticles (10–1000 nm) are one of the most widely explored polymeric carriers due to their ability to penetrate biological barriers, enhance drug stability, and provide controlled release. They are particularly valuable for targeted and intracellular delivery of anticancer drugs, proteins, and nucleic acids. Microspheres (1–1000 μm), on the other hand, are suitable for depot formulations and sustained release over weeks or months, often used in parenteral applications such as long-acting injectables. Hydrogels, composed of crosslinked hydrophilic polymer networks, offer high water content and biocompatibility, making them ideal for topical, transdermal, or tissue engineering uses. Films and scaffolds fabricated from biodegradable polymers provide mechanical support for localized delivery in wound healing, bone regeneration, and implantable drug systems [11].

The polymer composition and molecular architecture significantly influence the physicochemical characteristics of the formulation. Parameters such as molecular weight, crystallinity, copolymer ratio, and hydrophilicity determine the degradation rate, drug diffusion

profile, and mechanical strength of the system. For instance, increasing the glycolic acid content in PLGA enhances its hydrophilicity and accelerates degradation, while a higher lactic acid ratio slows it down. Branched or star-shaped polymers often show faster degradation than their linear counterparts due to increased surface area and water uptake. Hence, rational polymer design enables tailoring of release kinetics to meet specific therapeutic demands.

Several fabrication techniques are employed for developing biodegradable polymeric carriers, each offering distinct advantages for drug encapsulation and stability. The solvent evaporation method is a classic technique for forming nanoparticles and microspheres, where the polymer and drug are dissolved in an organic solvent followed by emulsification and solvent removal. Nanoprecipitation allows for the formation of small, uniform nanoparticles through controlled polymer precipitation in a non-solvent phase. Emulsion polymerization enables the synthesis of polymeric nanoparticles with high encapsulation efficiency and tunable particle size. Electrospinning, on the other hand, is widely used for creating nanofibrous mats and scaffolds, mimicking the extracellular matrix for tissue engineering and localized drug delivery applications [12-13].

The inclusion of additives and surfactants plays a vital role in enhancing formulation stability, drug encapsulation efficiency, and uniformity. Surfactants like polyvinyl alcohol (PVA), Tween 80, and Span 60 are commonly employed to stabilize emulsions and prevent particle aggregation during fabrication. Plasticizers such as glycerol or triethyl citrate improve polymer flexibility, while stabilizers like BSA (bovine serum albumin) can protect sensitive biomolecules like proteins or nucleic acids from denaturation during processing.

Overall, the successful design of biodegradable polymeric delivery systems hinges on a delicate balance between polymer chemistry, fabrication technique, and formulation additives. These parameters collectively determine drug release profiles, degradation behavior, and biocompatibility—key factors for translating laboratory formulations into clinically viable drug delivery systems [14-15].

4. Mechanisms of Polymer Degradation

The degradation of biodegradable polymers is a fundamental process governing the drug release profile, mechanical integrity, and biocompatibility of polymer-based drug delivery systems. Understanding the underlying degradation mechanisms is crucial for designing polymers that degrade in a predictable and controlled manner to meet specific therapeutic needs. Generally, degradation occurs through hydrolytic and/or enzymatic pathways, leading to the breakdown of polymer chains into smaller fragments, oligomers, and finally, biocompatible or metabolizable by-products such as carbon dioxide, water, or natural metabolites [16].

4.1 Hydrolytic Degradation

Hydrolytic degradation is the most common mechanism for synthetic biodegradable polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymer PLGA. It

involves the cleavage of ester bonds within the polymer backbone in the presence of water. This process begins with water penetration into the polymer matrix, followed by random scission of ester linkages, leading to molecular weight reduction and eventual mass loss. The degradation rate is influenced by the hydrophilicity, crystallinity, and molecular weight of the polymer. For instance, PGA, being more hydrophilic than PLA, degrades faster, while PLGA degradation can be fine-tuned by adjusting the lactic-to-glycolic acid ratio.

The hydrolytic degradation typically proceeds through two distinct phases—bulk erosion and surface erosion. In bulk erosion, water permeates the entire polymer matrix, and degradation occurs throughout the material, leading to a rapid decrease in molecular weight before noticeable mass loss. Surface erosion, on the other hand, occurs primarily at the polymer's exterior, resulting in gradual thinning of the matrix over time. PLGA usually exhibits bulk erosion, whereas polymers with hydrophobic or crosslinked structures often undergo surface erosion [17-18].

4.2 Enzymatic Degradation

In contrast to hydrolytic processes, enzymatic degradation is primarily observed in natural polymers such as chitosan, collagen, gelatin, and alginate. Specific enzymes, including lysozyme, collagenase, and amylase, catalyze the cleavage of glycosidic or peptide bonds within the polymer backbone. For example, chitosan undergoes depolymerization through the action of lysozyme, while collagen is degraded by collagenase into peptide fragments. The rate of enzymatic degradation depends heavily on the enzyme concentration, polymer surface accessibility, and local pH of the environment.

This enzymatic mechanism offers high specificity and tunability, allowing selective degradation in biological environments such as inflamed or tumor tissues where enzyme levels are elevated. Such responsiveness can be leveraged for stimuli-sensitive drug delivery, where the polymer matrix degrades faster in pathological sites, releasing therapeutic payloads in a controlled and targeted manner [19-20].

4.3 Surface vs. Bulk Erosion Mechanisms

The distinction between surface and bulk erosion is vital in understanding drug release behavior.

- In surface erosion, the polymer degrades from the outer layer inward, maintaining its internal structure but reducing in size over time. Drug release is generally linear and predictable, governed by surface area reduction. Examples include polyanhydrides and poly(ortho esters).
- In bulk erosion, degradation occurs throughout the matrix, leading to rapid molecular weight loss followed by sudden disintegration. This often results in an initial burst release of the drug followed by a slower, sustained phase—commonly seen in PLGA and PLA systems.

The dominant erosion mechanism depends on polymer properties such as hydrophilicity, diffusion coefficient, and geometry. Formulation scientists can manipulate these factors to tailor drug release kinetics for specific clinical applications [21].

4.4 Factors Influencing Polymer Degradation

Several physicochemical parameters affect the degradation rate and pattern of biodegradable polymers:

- pH: Acidic or basic environments accelerate hydrolysis of ester bonds. PLGA, for instance, exhibits autocatalytic degradation due to acidic degradation products.
- Temperature: Higher temperatures enhance molecular mobility and hydrolysis rates.
- Molecular weight: Lower molecular weight polymers degrade faster due to increased chain-end mobility and accessibility.
- Crystallinity: Amorphous regions degrade more rapidly than crystalline domains because of easier water penetration.

In addition, polymer morphology, drug loading, and formulation geometry (e.g., microsphere vs. film) also influence the degradation rate [22].

4.5 Kinetic Models of Degradation

To quantitatively describe polymer degradation, various kinetic models are applied, including first-order, zero-order, and autocatalytic models. The first-order model assumes degradation proportional to the remaining polymer concentration, while zero-order kinetics describe systems with a constant degradation rate over time. Autocatalytic models account for the accelerated degradation often observed in bulk-eroding polymers due to accumulation of acidic by-products. Advanced mathematical modeling helps predict degradation behavior and optimize polymer design for controlled release applications [23].

5. Drug Release Dynamics

Drug release dynamics from biodegradable polymer systems are governed by the interplay between diffusion, polymer degradation, and matrix swelling, which collectively determine the release rate, duration, and overall therapeutic performance. Understanding these mechanisms is essential for designing controlled-release formulations that maintain drug levels within the therapeutic window while minimizing side effects and dosing frequency [24].

5.1 Diffusion-Controlled Release

In diffusion-controlled systems, the movement of drug molecules through the polymer matrix is the primary mechanism of release. This process is typically dominant in non-degrading or slowly degrading polymers, where the drug diffuses through pores, channels, or microvoids formed

during polymer processing. The rate of diffusion depends on factors such as polymer porosity, crystallinity, molecular weight, and drug solubility.

For example, in PLGA nanoparticles, the encapsulated drug diffuses through aqueous channels created during polymer hydration, leading to a biphasic release profile—an initial burst phase followed by sustained diffusion-driven release. Hydrophilic drugs tend to diffuse faster through swollen matrices, while hydrophobic drugs exhibit slower, more controlled release. Optimizing polymer crosslinking density and drug loading helps modulate the diffusion rate to achieve the desired therapeutic profile [25].

5.2 Degradation-Controlled Release

In degradation-controlled systems, drug release is primarily dictated by polymer chain scission and mass loss. As the polymer undergoes hydrolytic or enzymatic degradation, the matrix structure weakens, allowing the entrapped drug to diffuse out. This mechanism is particularly important in biodegradable polymers such as PLGA, PCL, and polyanhydrides, where degradation kinetics directly correlate with drug release behavior.

Depending on the degradation mechanism, two main patterns are observed:

- Bulk-degrading polymers (e.g., PLGA) exhibit an initial burst release due to surface desorption, followed by a sustained phase as degradation progresses throughout the matrix.
- Surface-eroding polymers (e.g., polyanhydrides) offer a more predictable and nearly linear release, as the outer layers gradually erode, continuously exposing new surfaces for drug diffusion.

The degradation rate can be precisely tuned by modifying polymer composition (e.g., lactic/glycolic ratio), molecular weight, and crystallinity. This tunability makes degradation-controlled systems ideal for long-acting injectables and implantable formulations [26-27].

5.3 Swelling-Controlled Release

Swelling-controlled release is observed in hydrophilic polymers and hydrogels, where the matrix absorbs water, expands, and facilitates the diffusion of encapsulated drugs. The rate and extent of swelling depend on the polymer's crosslinking density, hydrophilicity, and environmental conditions (such as pH and ionic strength). Natural polymers like chitosan and alginate, as well as synthetic hydrogels such as PEG-based networks, exhibit swelling-mediated release behavior [28].

This mechanism is particularly useful for peptides, proteins, and hydrophilic small molecules, allowing a sustained and pH-sensitive release profile. For example, pH-responsive hydrogels can swell more in acidic or basic environments, making them suitable for site-specific drug delivery in the gastrointestinal tract or tumor microenvironments [29].

5.4 Role of Polymer–Drug Interactions and Physicochemical Compatibility

The strength and nature of polymer–drug interactions—including hydrogen bonding, hydrophobic interactions, and ionic attractions—strongly influence release kinetics. A drug with high affinity for the polymer matrix may exhibit slower release due to strong binding, while weakly interacting drugs may diffuse rapidly. The physicochemical compatibility between polymer and drug also affects encapsulation efficiency, drug stability, and release uniformity. For instance, hydrophobic drugs are better retained in PLA or PCL matrices, whereas hydrophilic drugs are more compatible with hydrogels or PEG-based systems [30].

5.5 Mathematical Models for Drug Release

To describe and predict drug release profiles, several mathematical models have been established:

- Higuchi Model: Describes diffusion-controlled release, where the amount of drug released is proportional to the square root of time.
- Korsmeyer–Peppas Model: A semi-empirical model that characterizes release mechanisms using an exponent ‘n’; values of *n* help distinguish between Fickian diffusion, anomalous transport, or case-II relaxation.
- First-Order Kinetic Model: Assumes that the release rate is proportional to the remaining drug concentration within the matrix, suitable for degradation-controlled systems.

These models are widely applied to optimize formulation parameters and to understand the contribution of diffusion, degradation, and swelling in the release process [31].

5.6 Influence of Particle Size, Porosity, and Polymer Composition

Drug release dynamics are heavily influenced by particle size, porosity, and polymer composition. Smaller particles have a higher surface-to-volume ratio, leading to faster release due to shorter diffusion pathways. Conversely, larger particles or denser matrices provide more sustained release. Porosity determines water ingress and drug diffusion; highly porous structures facilitate rapid drug escape, while compact matrices slow down release. Adjusting polymer composition—for example, increasing glycolic acid in PLGA—enhances hydrophilicity and accelerates degradation, whereas increasing lactic acid content slows it [32].

5.7 Case Examples of Sustained-Release Formulations

Numerous sustained-release systems utilize these principles for clinical success. For instance, Lupron Depot® (leuprolide acetate) employs PLGA microspheres for month-long hormone release, while Gliadel® wafers use a biodegradable polyanhydride matrix for local chemotherapy in brain tumors. Similarly, PLGA-based nanoparticles are extensively used for controlled delivery of anticancer drugs such as paclitaxel and doxorubicin, achieving prolonged plasma circulation and reduced toxicity.

Collectively, understanding drug release dynamics is critical for designing biodegradable delivery systems that offer predictable, sustained, and therapeutically efficient release patterns tailored to the pharmacokinetic demands of modern therapeutics [33-34].

6. Applications of Biodegradable Polymers in Drug Delivery

Biodegradable polymers have revolutionized modern drug delivery systems by offering controlled release, targeted delivery, and improved biocompatibility, minimizing systemic side effects. Their versatility allows them to be tailored for specific therapeutic needs through chemical modification, molecular weight adjustment, and nanostructuring. These polymers are widely explored in cancer therapy, vaccine formulations, gene delivery, and tissue engineering applications due to their ability to degrade safely within biological environments [35].

6.1. Cancer Therapy: Polymeric Nanoparticles for Targeted Drug Delivery

In cancer treatment, biodegradable polymers like PLGA, PEG-PLA, and PCL are engineered into nanoparticles that encapsulate anticancer agents such as paclitaxel, doxorubicin, and cisplatin. These systems provide controlled release and enhanced permeability and retention (EPR) effects, leading to selective accumulation in tumor tissues. Surface functionalization with ligands such as folic acid, antibodies, or peptides further enhances tumor-specific targeting. The gradual degradation of the polymer matrix enables sustained intracellular drug release, improving therapeutic efficacy while minimizing cytotoxicity to normal tissues [36].

6.2. Vaccine Delivery: PLGA-Based Antigen Encapsulation Systems

Biodegradable polymers, particularly PLGA, are widely used in vaccine delivery due to their ability to protect antigens from premature degradation and facilitate controlled antigen release. PLGA microspheres and nanoparticles can deliver antigens to antigen-presenting cells (APCs), promoting both humoral and cellular immune responses. These systems can also eliminate the need for multiple booster doses. Additionally, chitosan-based formulations enhance mucosal immunity through nasal or oral administration, making them suitable for non-invasive vaccination strategies [37].

6.3. Gene Delivery: Biodegradable Polycations for DNA/RNA Transport

Gene therapy requires safe and efficient delivery of genetic material, which can be achieved using biodegradable cationic polymers such as poly(β-amino esters), PEI derivatives, and

chitosan. These polymers condense DNA or RNA into stable nanoparticles that protect against nuclease degradation and facilitate cellular uptake through endocytosis. Once inside cells, the polymers degrade into non-toxic byproducts, releasing the nucleic acids to the target site. This biodegradable approach reduces cytotoxicity and enhances transfection efficiency compared to non-degradable carriers [38].

6.4. Tissue Engineering and Regenerative Medicine: Biopolymer Scaffolds for Cell Growth

In tissue engineering, biodegradable polymers like collagen, gelatin, alginate, and PLGA serve as scaffolds that mimic the extracellular matrix (ECM), providing mechanical support and biochemical cues for cell adhesion, proliferation, and differentiation. These scaffolds gradually degrade as new tissue forms, allowing natural regeneration. For instance, PLGA-based scaffolds are widely used for bone and cartilage regeneration, while collagen and chitosan are employed in skin and nerve tissue repair. The degradation rate and porosity of these materials can be fine-tuned to match tissue growth dynamics, promoting effective integration with the host tissue [39].

6. Applications of Biodegradable Polymers in Drug Delivery

Biodegradable polymers have significantly transformed modern drug delivery systems by enabling controlled release, targeted delivery, and superior biocompatibility while minimizing systemic side effects. Their structural versatility allows fine-tuning for specific therapeutic purposes through chemical modification, molecular weight adjustment, and nanostructuring. Due to their safe degradation profiles and adaptability, these polymers have found broad applications in cancer therapy, vaccine formulation, gene delivery, and tissue engineering [40].

6.1. Cancer Therapy: Polymeric Nanoparticles for Targeted Drug Delivery

In oncology, biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), poly(ethylene glycol)-polylactic acid (PEG-PLA), and polycaprolactone (PCL) are formulated into nanoparticles encapsulating anticancer agents like paclitaxel, doxorubicin, and cisplatin. These nanocarriers exploit the enhanced permeability and retention (EPR) effect for selective tumor accumulation while enabling sustained and localized drug release. Surface modification with ligands (e.g., folic acid, monoclonal antibodies, or peptides) further enhances active targeting. The polymer matrix gradually degrades under physiological conditions, providing prolonged intracellular drug exposure, improving therapeutic efficacy, and reducing toxicity to healthy tissues [41].

6.2. Vaccine Delivery: PLGA-Based Antigen Encapsulation Systems

PLGA remains the gold-standard biodegradable polymer in vaccine delivery systems due to its exceptional biocompatibility and antigen protection capability. PLGA-based micro- and nanoparticles shield antigens from premature enzymatic degradation and allow sustained release, thereby stimulating both humoral and cellular immune responses. These systems can minimize or eliminate the need for booster doses. Moreover, chitosan-based formulations have gained

prominence in mucosal vaccine delivery (nasal or oral), enhancing antigen uptake by mucosal immune cells and promoting strong local immunity with improved patient compliance [42].

6.3. Gene Delivery: Biodegradable Polycations for DNA/RNA Transport

For gene therapy, biodegradable cationic polymers—such as poly(β-amino esters), polyethyleneimine (PEI) derivatives, and chitosan—serve as efficient non-viral vectors. These polymers form electrostatic complexes with nucleic acids, condensing DNA or RNA into nanosized particles that protect genetic cargo from nuclease degradation. After cellular internalization, the polymer backbone undergoes biodegradation, releasing genetic material in a controlled manner. Compared to conventional non-degradable carriers, these systems exhibit reduced cytotoxicity, improved biocompatibility, and enhanced transfection efficiency [43].

6.4. Tissue Engineering and Regenerative Medicine: Biopolymer Scaffolds for Cell Growth

In tissue engineering, biodegradable polymers such as collagen, gelatin, alginate, and PLGA act as scaffolding materials that replicate the extracellular matrix (ECM), providing essential structural and biochemical cues for cell attachment, proliferation, and differentiation. These scaffolds degrade in synchrony with new tissue formation, ensuring a seamless transition between the implanted material and the regenerating tissue. PLGA scaffolds are commonly used for bone and cartilage engineering, while collagen and chitosan are employed in skin, vascular, and neural tissue regeneration. The degradation rate, porosity, and mechanical properties of these materials can be precisely tuned to support specific tissue repair requirements [44].

7. Challenges and Limitations in Biodegradable Polymer-Based Drug Delivery

Despite the remarkable potential of biodegradable polymers in controlled and targeted drug delivery, several scientific and practical challenges still limit their widespread clinical translation. These challenges stem from material variability, complex degradation behavior, formulation instability, and stringent regulatory requirements. Understanding and overcoming these barriers are essential for optimizing therapeutic efficacy and ensuring patient safety [45].

7.1. Inconsistent Degradation and Release Profiles

One of the most persistent challenges is achieving predictable and reproducible degradation rates. Factors such as polymer crystallinity, molecular weight, and copolymer composition can significantly alter hydrolysis and erosion kinetics. For example, PLGA degradation is influenced by the lactic-to-glycolic acid ratio, leading to batch-to-batch variability in drug release. This inconsistency can affect therapeutic outcomes, particularly for long-term implantable systems [46].

7.2. Stability and Encapsulation Efficiency Issues

Many bioactive compounds—especially proteins, peptides, and nucleic acids—are sensitive to the harsh conditions used during polymer processing, such as organic solvents or high shear

forces. This often leads to low encapsulation efficiency or loss of bioactivity. Maintaining the stability of the active ingredient during formulation, storage, and administration remains a major concern [47].

7.3. Limited Drug Loading Capacity and Burst Release

The drug loading capacity of biodegradable polymers is often limited by their chemical compatibility with the active ingredient. In some cases, an undesirable "burst release" occurs, where a large fraction of the drug is released prematurely, compromising sustained delivery. This issue is particularly significant for hydrophilic drugs encapsulated in hydrophobic polymer matrices like PLA or PCL.

7.4. Scale-Up and Manufacturing Constraints

Translating laboratory-scale polymer formulations to industrial production poses numerous challenges. The reproducibility of particle size, morphology, and drug distribution across large batches requires precise process control. Additionally, the use of organic solvents and complex purification steps increases production costs and complicates compliance with Good Manufacturing Practice (GMP) standards [48].

7.5. Biocompatibility and Immunogenic Concerns

Although biodegradable polymers are generally considered safe, their degradation products—such as lactic acid or glycolic acid—can lead to local pH changes and mild inflammation. Moreover, natural polymers like chitosan or gelatin may trigger immune reactions in sensitive individuals. Ensuring complete biocompatibility and eliminating immunogenic residues remains a crucial safety consideration [49].

7.6. Regulatory and Standardization Barriers

The regulatory approval process for biodegradable polymer-based drug delivery systems is often slow due to the need for extensive biocompatibility, toxicity, and long-term degradation studies. Lack of standardized testing protocols across countries further delays commercialization.

8. Future Perspectives

The future of biodegradable polymer-based drug delivery is incredibly promising, driven by advances in materials science, nanotechnology, and computational modeling. Researchers are now designing "intelligent" biodegradable systems that not only release drugs in a controlled manner but also respond dynamically to physiological stimuli or disease-specific conditions. These next-generation systems aim to achieve precision therapy with minimal side effects and maximal therapeutic benefit [50].

8.1. Smart and Stimuli-Responsive Polymers

Emerging "smart" polymers can alter their structure and release profiles in response to environmental triggers such as pH, temperature, enzymes, redox potential, or light. For example, pH-sensitive poly(ortho esters) and enzyme-responsive peptide–polymer conjugates enable site-specific drug release in tumor microenvironments or inflamed tissues. These materials combine therapeutic control with adaptability, enhancing both efficacy and patient compliance.

8.2. Hybrid and Composite Polymer Systems

Future research is increasingly focused on hybrid materials that integrate the advantages of natural and synthetic polymers. These systems offer improved mechanical strength, tunable degradation, and biofunctionality. For instance, PLGA–chitosan and PEG–gelatin composites merge biodegradability with biological recognition, making them ideal for gene delivery and tissue engineering. Hybrid nanostructures incorporating lipids or inorganic nanoparticles are also being explored for combined drug delivery and imaging applications [51].

8.3. AI-Driven Design and Predictive Modeling

Artificial intelligence and machine learning are transforming polymer design and formulation optimization. AI algorithms can predict degradation kinetics, drug–polymer compatibility, and optimal formulation parameters, drastically reducing experimental workload. Integrating AI with pharmacokinetic (PK) and pharmacodynamic (PD) modeling allows for precise prediction of in vivo performance, enabling the creation of patient-specific biodegradable drug delivery systems.

8.4. Personalized and Regenerative Medicine Applications

The shift toward personalized medicine is driving the customization of polymer-based carriers for individual patients. Biodegradable systems can be tailored based on genetic, metabolic, or disease-specific profiles to achieve optimal therapeutic response. In regenerative medicine, 3D bioprinting of biodegradable scaffolds loaded with growth factors or stem cells promises revolutionary outcomes in tissue and organ repair.

8.5. Sustainable and Green Polymer Development

With growing environmental awareness, future formulations will increasingly rely on eco-friendly polymers derived from renewable sources. Innovations in green chemistry and solvent-free fabrication methods aim to reduce toxicity and waste generation while maintaining clinical-grade performance [52].

9. Conclusion

Biodegradable polymers have fundamentally transformed the field of drug delivery, offering a safe, efficient, and environmentally responsible approach to therapeutic management. Their

inherent ability to degrade into non-toxic byproducts eliminates the need for surgical removal, making them ideal for both short- and long-term biomedical applications. By enabling precise control over drug release kinetics, improving bioavailability, and reducing systemic toxicity, these polymers bridge the gap between traditional formulations and modern precision medicine.

Over the past few decades, polymers such as PLGA, PLA, PCL, and chitosan have demonstrated remarkable versatility in encapsulating small molecules, peptides, proteins, and nucleic acids. The evolution of polymer chemistry, combined with advancements in nanotechnology, has led to sophisticated delivery platforms like nanoparticles, hydrogels, and scaffolds tailored for targeted and sustained release. Moreover, integration with imaging agents and biosensors is pushing the boundaries toward theranostic systems—capable of both therapy and diagnosis.

Despite these achievements, challenges persist, particularly in scalability, reproducibility, and regulatory standardization. The degradation behavior of polymers can vary under physiological conditions, influencing drug stability and therapeutic outcomes. Addressing these complexities requires a multidisciplinary effort encompassing materials science, pharmacology, and data-driven modeling.Looking forward, the next generation of biodegradable polymer systems will focus on stimuli-responsive, patient-personalized, and AI-optimized formulations, marking a shift from conventional drug delivery toward adaptive and precision-oriented therapeutics. Sustainable, bio-based polymer innovation will further align drug delivery research with environmental stewardship.In essence, biodegradable polymers represent not only a technological advancement but also a paradigm shift in how drugs are designed, delivered, and experienced by patients—paving the way for safer, smarter, and more effective healthcare solutions in the decades to come.

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