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Design, Degradation Mechanisms, and Drug Release Kinetics of Biodegradable Polymers in Advanced Drug Delivery Systems: Applications, Challenges, and Future Perspectives

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Abstract:

Biodegradable polymers have stood out among other templated macromolecular materials as fundamental components of advanced drug delivery systems, providing controllable, sustained and site-specific release of therapeutics with lower toxic side effects. We present a comprehensive review of the design concepts, degradation principles, and drug-release kinetics of natural and synthetic biodegradables such as PLGA, PCL, chitosan, and alginate. The adaptability of naturally occurring substances allows them to be fabricated into nanoparticles, microspheres, hydrogels and scaffolds for different clinical applications such as cancer therapy, vaccine delivery, gene therapy and tissue engineering. This review covers hydrolytic and enzymatic degradation mechanisms, surface or bulk erosion behavior of polymers, and parameters affecting polymer degradation and drug release kinetics. These polymers have been used in FDA-approved formulations, which are shown in a few case studies to result in both improved therapeutic efficacy and patient compliance. It discusses challenges including inter- and intra-protein degradation rate variability, formulation stability issues, scale-up of manufacturing process difficulties, and regulatory hurdles. The continuing advances at the emerging frontiers of smart, stimuli-responsive systems, hybrid polymers, AI-assisted design, and personalized medicine suggest a bright future for biodegradable polymers in engineering 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

Polymer-based drug delivery systems have become an efficient and versatile platform in the ever-evolving field of pharmaceutical technology aimed at ameliorating therapeutic efficacy. Such system utilize polymeric materials to encapsulate, protect, and modulate the liberation of active pharmaceutical ingredients (APIs), improving drug stability, bioavailability and patient compliance. Since then, the transformation to polymeric carriers from traditional dosage forms has been a paradigm shift toward precision and sustained drug delivery[1].

One of the classes of polymers of interest today is biodegradable polymers, which can be broken down into non-toxic products upon completion of their therapeutic activity. Inherent degradability of the delivery systems avoids any surgical removal, and thus these nanocarriers are especially useful in long-term treatments like those for cancer therapy, chronic inflammation, tissue regeneration etc. Furthermore, polymer degradation kinetics can be readily varied via molecular weight, crystallinity, and copolymer composition[2].

Biodegradable polymers have many advantages such as lower toxicity, improved patient compliance and better site-specific targeting compared to non-degradable systems. Biomaterials like poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), chitosan, and alginate have established a prominent position in research as well as clinical applications owing to their safety and regulatory history. These polymers create versatile platforms to develop nanoparticles, microspheres, hydrogels and scaffolds that can encapsulate diverse therapeutic modalities ranging from small molecules to proteins and nucleic acids[3].

This review summarizes biodegradable polymers in drug delivery, including design principles, degradation mechanisms, and release kinetic behaviors over the past few decades. This review covers recent developments in formulation strategies and biological approaches for pharmaceutical polymer degradation, while also featuring case studies exemplifying their applications in controlled and targeted drug delivery systems. It aims to highlight the importance of biodegradable polymers in the development of next-generation smart, sustainable therapeutic systems[4].

2. Classification of Biodegradable Polymers

Biodegradable polymers are classified into two main classes, natural and synthetic, based on their source and formulation approach. Both drug delivery types have been widely exploited as they degrade into non-toxic by-products while allowing controlled and sustained release of therapeutic agents. Despite the aforementioned similarities, they are also distinct structurally, with very different physicochemical properties, degradation mechanisms, and biological behaviour[5].

Biodegradable Polymers derived from natural, biological sources like plants/animals/microorganisms. Most common examples are chitosan, alginate, gelatin, collagen and starch. On the other hand, these

materials are naturally biocompatible and biodegradable, which makes them promising candidates for pharmaceutical and biomedical applications. They act not only as extracellular matrix (ECM) mimetics; this chemical similarity to components of the ECM leads to superior cell adhesion, proliferation and tissue integration, making them especially useful in wound healing, vaccine delivery and tissue engineering applications[6].

Chitosan is a cationic polysaccharide found from chitin, and has mucoadhesive properties that promote drug absorption in the mucosa. Brown seaweed alginate can easily form hydrogels when combined with divalent cations, making it an excellent stabilising carrier material for proteins and vaccines. Additionally, these proteins can crosslink into networks and are natural biodegradable materials that have been widely used for peptide or growth factor-controlled release from matrices such as gelatin and collagen. Starch polymers have inherent low cost and renewable nature, good mechanical properties and biocompatibility.

Natural polymers hold lots of advantages; however, they have major limitations such as batch-to-batch variability compared to synthetic equivalents. They also show the risk of bioactive material-induced protein response (immunogenicity) and have poor mechanical strength. Their degradation rate is often challenging to control with respect to drug release kinetics and therapeutic efficiency. However, they are not replaced in biopolymer research due to their abiotic nature and low toxicity[6–7].

2.1 Synthetic Biodegradable Polymers

In contrast, synthetic biodegradable polymers are chemically synthesized and allow for a more precise control of molecular structure, composition, and degradation behaviour. Common polymers such as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA), and poly(ethylene glycol)-poly(lactic acid) (PEG–PLA) copolymers fit in this category. They can be tailored for specific mechanical strength, degradation time and drug release rates, making them suitable for many pharmaceutical formulations. PALGA is a well-studied and FDA-approved synthetic polymer most frequently used due to its predictable degradation profile and ideal biocompatibility[8]. PLGA is biodegradable, and its degradation rate can be adjusted through the lactic to glycolic acid ratio, ranging from weeks to months depending on therapeutic needs. PLA and PCL are hydrophobic, degrade slower, and work well in long-term implants or sustained-release systems. PGA, which is more hydrophilic and leads to faster degradation, is applied in rapid drug release scenarios. Addition of PEG to copolymers (e.g., PEG-PLA) increases hydrophilicity, blood circulation time, and stealth properties thus improving efficiency for systemic delivery[9].

The synthetic polymers are usually more stable, reproducible and have a more tenable degradation than the natural polymer. However, they are usually bioactive in nature and may need to be surface modified or blended with natural polymers so as to augment the cellular interactions of the tissues around it and reduce the risk of inflammation. In Conclusion, as illustrated here, both natural and synthetic biodegradable polymers possess their own unique strengths and weaknesses. Natural polymers have better biological affinity, Synthetic polymer has more flexibility in designing and controlling performance. A hot area of research in drug delivery continues to be the development of hybrid systems where a combination of the biocompatibility seen with natural materials, along with the tenable

properties afforded by synthetic polymers allows for more efficient and reproducible biodegradable delivery platforms[10].

3. Design and Fabrication Strategies

Biodegradable polymer-based drug delivery systems can be developed to elicit precise control of the linkages employed throughout the controlled drug loading and time kinetics and biodegradation profile. Depending on the therapeutic applications and delivery route, these systems can be designed into multiple formats including nanoparticles, microspheres, hydrogels, films or scaffolds. These forms offer unique advantages concerning the surface area, drug encapsulation efficiency, and release mechanisms[11].

Many researchers are searching polymeric carriers such as nanoparticle (with a size range of 10–1000 nm) which cannot only permeate biological barriers but also increase the stability of drug and control its release. They would be especially useful for the intracellular and specific delivery of anticancer agents, proteins and nucleic acids. In contrast, microspheres (1–1000 μm) are appropriate for depot formulations and longer-term release over weeks or months and used in parenteral applications including long-acting injectables Hydrogels are networks composed of crosslinked hydrophilic polymers able to retain high levels of water and are biocompatible, making them useful for topical, transdermal or tissue engineering applications. For localized delivery in wound healing, bone regeneration and implantable drug systems[11], films and scaffolds fabricated from biocompatible and biodegradable polymers provide physical mechanical support[12].

The polymer diffusion and molecular architecture play a vital role in the physicochemical properties of the composition. The molecular weight, crystallinity, copolymer ratio and hydrophilicity influence the degradation rate, drug diffusion profile and mechanical strength of the system. For example, an increase in the glycolic acid content of PLGA increases its hydrophilicity and degradation rate, whilst a higher lactic acid ratio reduces it. Branched or star-shaped polymers typically exhibit faster degradation when compared to their linear counterparts, providing increased surface area and uptake of water. As such, rational polymer design facilitates control over release kinetics for specific therapeutic requirements[13].

Different fabrication techniques are used for biodegradable polymeric carriers, each of which offers their specific advantages on the encapsulation and stability of drugs. The solvent evaporation method is widely used to prepare nanoparticles and microspheres, where the polymer and drug are dissolved in an organic solvent, which then undergoes emulsification before the solvent is removed. What really changes is nanoprecipitation, which allows the formation of small-sized, uniform nanoparticles by controlled precipitation, inside a non-solvent phase, of polymers. With the method of emulsion polymerization, both high encapsulation efficiency of nanoparticles and tunable particle size can be obtained. Conversely, the first technology is called electrospinning, widely formulated for the production of nanofibrous mats and scaffolds specific to mimic the extracellular matrix applied in tissue engineering and localized drug delivery applications [14-15].

Additives and surfactants are crucial in improving formulation stability, drug core encapsulation efficacy, and homogeneity. Surfactants used to stabilize emulsions in order to avoid particle

agglomeration during fabrication include polyvinyl alcohol (PVA), Tween 80 and Span 60. Plasticizers, including glycerol or triethyl citrate, enhance polymer flexibility, while stabilizers such as BSA (bovine serum albumin) prevent the denaturation of sensitive biomolecules (e.g. proteins and nucleic acids) during the processing phase of Generation II scaffolds.

In summary, the engineering of robust biodegradable polymeric delivery systems inherently requires a careful design continuum that spans polymer chemistry, fabrication technique and formulation excipients. Together, these parameters control drug release profiles, degradation behaviours and biocompatibility, which are critical for translating successful laboratory formulations into clinically applicable drug delivery systems[16-17].

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[18].

4.1 Hydrolytic Degradation

Dissolution can occur through chemical or physical processes and is the most common mechanism by which synthetic biodegradable polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymer PLGA undergo hydrolytic degradation. It consists of the cleavage of ester bonds in the polymer backbone with water. This process starts with water ingress into the polymer matrix and random scission of ester linkages, resulting in mass loss through a decrease in its molecular weight. The degradation rate is related to the hydrophilicity, crystallinity and molecular weight of the polymer. For example, PGA is a hydrophilic polymer that degrades rapidly compared to PLA; PLGA's degradation can be adjusted by modifying the lactic-to-glycolic acid ratio [19].

Hydrolytic degradation is characterized as bulk erosion and surface erosion over time. Bulk erosion, in which water permeates into the polymer as a whole, on the other hand, causes degradation throughout the bulk material, resulting in quick loss of molecular weight before observable mass loss occurs. Surface erosion is the other way which operates mainly on the outside of the polymer, leading to a gradual thinning of the matrix with time. PLGA typically has bulk erosion, while hydrophobic or crosslinked polymers undergo surface erosion [20-21].

4.2 Enzymatic Degradation

In contrast to hydrolytic processes, enzymatic degradation is primarily observed in natural polymers such as chitosan, collagen, gelatine, and alginate. Specific enzymes, including lysozyme, collagenase, and amylase, catalyse 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 enzyme concentration, polymer surface accessibility, and local pH.

This enzymatic mechanism offers high specificity and tunability, allowing selective degradation in biological environments such as inflamed or tumour 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[22-23].

4.3 Surface vs. Bulk Erosion Mechanisms

The distinction between surface and bulk erosion is essential for understanding the drug release behavior of biodegradable polymer systems. In surface erosion, the polymer gradually degrades from the outer surface toward the inner core while maintaining its internal structural integrity. As erosion proceeds, the size of the polymer matrix decreases over time, resulting in a relatively linear and predictable drug release profile that is primarily governed by the reduction in surface area. Polymers such as polyanhydrides and poly(ortho esters) are typical examples that exhibit surface erosion characteristics. In contrast, bulk erosion involves degradation occurring uniformly throughout the entire polymer matrix rather than being limited to the surface. This process leads to a rapid reduction in molecular weight within the polymer bulk, followed by sudden structural disintegration. Bulk erosion systems often display an initial burst release of the drug due to rapid diffusion, followed by a slower and sustained release phase. This behavior is commonly observed in polymers such as poly(lactic-co-glycolic acid) (PLGA) and polylactic acid (PLA). The dominant erosion mechanism depends on intrinsic polymer properties such as hydrophilicity, diffusion coefficient, and geometric configuration. By carefully modifying these parameters, formulation scientists can tailor drug release kinetics to meet specific therapeutic and clinical requirements[24-25].

4.4 Factors Influencing Polymer Degradation

The degradation rate and pattern of biodegradable polymers are strongly influenced by several physicochemical parameters that determine how quickly the polymer matrix breaks down under physiological conditions. One of the most critical factors is pH, as acidic or basic environments can significantly accelerate the hydrolysis of ester bonds within polymer chains. For example, polymers such as poly(lactic-co-glycolic acid) (PLGA) demonstrate autocatalytic degradation due to the formation of acidic by-products that further promote hydrolysis. Temperature also plays an important role in polymer degradation, as higher temperatures increase molecular mobility and enhance the rate of hydrolytic reactions. Molecular weight is another key determinant, with lower molecular weight polymers generally degrading more rapidly due to greater chain-end mobility and improved accessibility of reactive sites. Additionally, the degree of crystallinity within a polymer influences its degradation profile, since amorphous regions are more susceptible to water penetration and hydrolysis than highly ordered crystalline domains. Beyond these primary factors, polymer morphology, drug loading capacity, and the physical geometry of the formulation, such as microspheres, nanoparticles, or

thin films, also contribute significantly to the overall degradation behaviours and rate of drug release[26-27].

4.5 Kinetic Models of Degradation

To understand polymer degradation quantitatively, mathematical and kinetic models of the behaviour of the polymer matrix over time are needed. First-order, zero-order, and autocatalytic kinetic models are a few of the modelled degradation mechanisms. In the first-order model, the degradation rate is directly proportional to the intact polymer concentration; therefore, mass data for polymers show a gradual decrease in degradation rate. Zero-order kinetics, on the other hand, are characteristic of systems whereby the degradation rate is constant with time and result in a uniform and predictable polymer degradation/drug release rate. This makes autocatalytic models very useful for describing bulk-eroding polymers, as degradation becomes more rapid with increasing matrix acidification over time. These acids then catalyse additional hydrolysis, leading to a feedback loop that accelerates the degradation. The application of advanced mathematical modelling techniques allows researchers to relate polymer degradation behaviours with various environmental and formulation conditions, which in turn facilitates the rational design of controlled/sustained release polymer-based drug delivery systems[28-29].

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 [30].

5.1 Diffusion-Controlled Release

For diffusion-controlled systems which release the drug from a polymer matrix, the primary mechanism of release is the movement of drug molecules through the polymer. In the case of non-degrading (or very slowly degrading) polymers, this process is normally predominant, involving diffusion of drug through pores, channels, or microvoids generated during polymer processing. The diffusion rate is a function of polymer porosity, crystallinity, molecular weight and drug solubility[31].

For instance, in PLGA nanoparticles, the drug diffuses through aqueous channels that form as the polymer hydrates and large molecules diffuse out, producing a biphasic release profile with an initial burst phase followed by sustained diffusion-driven release. For example, hydrophilic drugs would diffuse faster compared to swollen matrices as opposed to the case of hydrophobic drugs, which show a slow and sustained release. Polymer crosslinking density and drug loading can be optimized to modulate the diffusion rate to confer the desired therapeutic profile [32].

5.2 Degradation-Controlled Release

In degradation-controlled systems, drug release is mostly dominated by scission of polymer chains and mass loss. The matrix structure is gradually weakened due to the hydrolytic or enzymatic degradation of the polymer, so that the diffusive delivery of the enclosed drug can occur [33]. This process is especially prominent in PLGA, PCL and polyanhydrides (biodegradable polymers), since the degradation kinetics are directly related to drug release profiles. Two main degradation patterns are observed based on the mechanism of degradation: Bulk-degrading polymers (PLGA, for instance) display burst release due to surface desorption followed by a sustained phase as degradation proceeds throughout the matrix. Polymers that degrade at the surface level (e. g., polyanhydrides) tend to provide a more consistent and almost linear drug release, because as the top layers of polymer slowly erode, new surfaces are continuously created through which diffusion of the drug occurs. The degradation most importantly proceeds at a controllable rate, which we can easily adjust by altering the polymer composition (e.g., lactic/glycolic ratio), molecular weight & crystallinity. This tunability makes the degradation-controlled systems ideal for a platform of long-acting injectables and implantable formulations [34-35].

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 behaviours.

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 [28].

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 [29].

5.5 Mathematical Models for Drug Release

To describe and predict drug release profiles from polymeric systems, several mathematical models have been developed and widely applied in pharmaceutical research. Among these, the Higuchi model

is one of the earliest and most commonly used approaches for diffusion-controlled drug release systems. This model assumes that the amount of drug released from the matrix is directly proportional to the square root of time, reflecting a diffusion-driven mechanism where drug molecules migrate through a porous matrix. Another important model is the Korsmeyer–Peppas model, which is considered a semi-empirical approach used to analyze drug release from polymeric systems when the mechanism is not well understood or when multiple processes occur simultaneously. In this model, the release mechanism is characterized by an exponent value denoted as 'n', where different values of n indicate distinct transport mechanisms, such as Fiskian diffusion, anomalous (non-Fiskian) transport, or case-II relaxation behaviours. Additionally, the first-order kinetic model assumes that the rate of drug release is proportional to the concentration of the drug remaining within the polymer matrix, making it particularly suitable for systems where degradation or dissolution governs the release process. Collectively, these mathematical models play a significant role in optimizing formulation parameters and enhancing the understanding of how diffusion, degradation, and swelling processes contribute to the overall drug release mechanism [30-32].

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 [31].

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 [32-33].

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 [34]. 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 [35]. 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 [36]. 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 [37].
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 [38].

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 [39].

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 [40].

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 [41].

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 [42].

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 [43].

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.

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 [44].

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 [45].

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 [46].

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 [47].

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

Basic and practiced exploration into biodegradable polymer-based drug delivery systems may be unprecedentedly auspicious, propelled fundamentally by never-ending advances in materials science, nanotechnology, and computational modeling. For these reasons, we see a shift towards the design of smart biodegradable systems that not only achieve controlled drug release but also responsively act to perturbations in physiology or disease specific signals. Advances in this field are aimed at achieving precision therapy, whereby drugs will be administered within the right location, in the right dosage, and time frame so that side effects will be limited while therapeutic efficacy maximised. These innovations will likely advance both treatment outcome and patient safety in the coming years. Probably, one of the more relevant advances achieved in this field are smart and stimuli-responsive polymers. The advanced materials can change their structure and prescription release characteristics in response to environmental triggers including changes in pH, temperature, enzyme concentration, redox potential or light exposure [48]. An example of this is pH-sensitive poly(ortho esters) that are under investigation for localized drug release in environments such as tumor tissues or sites of inflammation, and enzyme-responsive peptide–polymer conjugates [26]. This responsiveness is only elicited if the biological signal triggers adaptation, which grants these smart materials better therapeutic control, improved precision in treatment protocols and increased patient adherence due to lower dosing frequency and side effects. The other key direction for future research relates to the development of hybrid and composite polymer systems that harness the advantages of both natural and synthetic polymers. Such hybrid materials not only give mechanical stability, but also have tunable degradation rates and increase biological function. Composite systems such as PLGA–chitosan and PEG–gelatin, which integrate the biodegradability of synthetic polymers with the biological compatibility and recognition properties of natural polymers[49]. These systems are particularly useful in gene delivery or tissue engineering applications. Furthermore, hybrid nanostructures containing lipids or inorganic nanoparticles have received much attention for their application in dual therapeutic delivery and diagnostic imaging (theragnostic) to simultaneously treat and monitor disease progression. And here is where are tees similar systems such as Artificial intelligence and machine learning technologies come into picture the design and optimization of bio-degradable polymer systems. AI-driven models can analyse large datasets to predict polymer degradation behaviour, drug–polymer compatibility and optimal formulation conditions. This shortens formulation development time, costs and the labour involved in experiments. In addition, the combination of AI with pharmacokinetic and pharmacodynamic modelling can help researchers simulate in vivo drug behaviour more closely. Such capability endows extreme optimisation and patient-specific drug delivery platforms to be developed for tailored therapy based on the individual therapeutic requirements. The interest in personalized medicine is making polymer based drug delivery systems more customized and this process is getting stronger with the ever emerging need of people. Biodegradable carriers, when customized according to genetic profiles, metabolic characteristics or specific conditions of the disease, can lead to much better therapeutic responses. The regenerative medicine field is using previously developed biodegradable polymers in advanced technologies, such as three-dimensional bioprinting, for use in regenerating tissues and organs. Work is also being done with bioprinter scaffolds infused with either growth factors, cells or stem cells intended to assist in tissue repair and regeneration which could provide innovative treatments for debilitating diseases that were previously untreatable[50]. Eco-Friendliness – Lastly, eco-friendliness is slowly becoming a question to be asked when our biodegradable polymers of the future are being created. Green polymers

from renewable natural resources and green chemistry methods to reduce solvent usability and waste production are of growing interest. The intention of these sustainable fabrication strategies is to achieve performant clinical behaviours coupled with reduced ecological footprints in line with the global 'green' vision towards safe, efficacious and environmentally friendly drug delivery technologies[51].

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 theragnostic systems capable of both therapy and diagnosis. Despite these achievements, challenges persist, particularly in scalability, reproducibility, and regulatory standardization. The degradation behaviours 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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