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Review Paper

A Review on Biodegradable Polymer-Based Drug Delivery Systems

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ABSTRACT

When it comes to delivering drugs, traditional methods can be pretty limited. They often lead to the drug being eliminated from the body too quickly and can cause a lot of unwanted side effects. But biodegradable polymers are changing the game. These polymers are made from natural or synthetic materials like chitosan, alginate or PLGA. These are really good at releasing drugs in a controlled way. This means that the drug can be delivered exactly where it's needed and at the right time. Biodegradable polymers can be used to make all sorts of delivery systems, from tiny nanoparticles to larger implants and scaffolds. These are used to treat all sorts of diseases like cancer, diabetes, cardiovascular and neurological disorders. One of the best things about biodegradable polymers is that it can help in reducing the toxicity of drugs and even eliminate the need for surgery. With the advancement of new technologies like nanotechnology, 3D printing and artificial intelligence on the horizon, biodegradable polymer-based drug delivery systems are only going to get better. This is especially exciting for personalized medicine, where doctors can tailor treatments to individual patients' needs. Researchers may be able to create drug delivery systems that are more effective and have fewer side effects than ever before by combining biodegradable polymers with these new technologies.

INTRODUCTION

The field of drug delivery systems (DDS) has changed significantly in recent years. This shift has been driven by the need for precise, localized, and controlled transport of molecules [1]. Traditional methods of drug administration often face serious challenges. These include quick

removal from the body, early breakdown by enzymes, and unwanted distribution to healthy tissues [2]. These non-specific behaviors lead to the need for frequent, high-dose treatments, which increase systemic side effects and lower patient compliance [3]. To address these challenges, modern macromolecular chemistry has focused on designing advanced biodegradable polymers [4].

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These materials act as temporary, protective layers that safely hold therapeutic drugs, shielding them from harmful environments in the body while controlling their release at predictable rates [5]. Importantly, after the therapeutic agents are released, these polymers break down in the body into harmless, compatible building blocks that are easily removed through normal metabolic or excretory processes [6]. This self-removal mechanism prevents long-term reactions to foreign materials common with permanent implants and eliminates the need for additional surgeries to remove them [7]. As a result, the development of these polymeric structures has become essential for designing long-term treatments for chronic diseases that place a heavy burden on patients [8].

Concept of Biodegradable Polymers

- The basic use of a biodegradable polymer depends on its ability to break down predictably in a biological environment through hydrolysis, oxidation, or enzyme-driven cleavage of its macromolecular backbone [9]. While traditional biostable implants can cause chronic local inflammation, fibrous encapsulation, and ongoing macrophage activation, modern bioresorbable matrices adjust to changing physiological environments [10].
- To achieve successful clinical translation, these polymers must meet a strict set of biocompatibility and functional criteria [11]. First, neither the main macromolecule nor any of its intermediate or final breakdown products may cause an adverse immunogenic, cytotoxic, or thrombogenic response in host tissues [12]. Second, the mechanical properties and degradation rates must be consistent, ensuring that the rate of structural erosion aligns with either the biological healing timeline of the target tissue or the

planned drug release window [13]. Third, the polymer must be easy to process, allowing it to be reliably shaped into various forms, such as nanoparticles, micellar assemblies, injectable hydrogels, or electrospun scaffolds, without harming the chemical stability or structural integrity of the encapsulated therapeutic agents [14]. The right balance between the rate of water diffusing into the polymer matrix and the rate of chemical bond breakdown ultimately determines the performance and therapeutic value of the final dosage form [15].

Classification of Biodegradable Polymers

- Biodegradable polymers used in modern drug delivery are generally divided into natural and synthetic categories. Each category has its own structural, mechanical, and functional benefits [16].

Natural Polymers

- Natural polymers come directly from biological sources. They provide excellent biomimetic features and are biocompatible due to their similarities to the native extracellular matrix (ECM) [17].
- Chitosan: This linear, cationic polysaccharide is made from the partial deacetylation of chitin [18]. Its primary amine groups along the backbone give it a net positive charge under physiological conditions. This allows strong electrostatic interactions with negatively charged sialic acid residues on mucosal surfaces [19]. This mucoadhesive property makes chitosan very effective for drug delivery through mucosal, nasal, and ocular routes [20].
- Alginate: This unbranched, anionic polysaccharide is extracted from brown sea algae. Alginate consists of different sequences of beta-D-mannuronic and alpha-L-guluronic



acid residues [21]. It quickly forms a stable gel upon exposure to divalent cations, like Ca^{2+} , creating networks ideal for encapsulating delicate proteins and live cell therapeutics [22].

- Collagen and Gelatin: Collagen is the main structural protein in human connective tissues. It has natural cell-signaling motifs that encourage cell adhesion and tissue remodeling [23]. Gelatin, which comes from partially denatured collagen, keeps these important biocompatible sequences while having lower immunogenicity and adjustable thermal gelation properties [24].
- Hyaluronic Acid (HA): This is a naturally occurring, non-sulfated glycosaminoglycan found in synovial fluid and loose connective tissues [25]. HA binds specifically and strongly to CD44 receptors, which are commonly overexpressed on many cancer cells. This makes it a valuable material for developing drug delivery systems that target cancer cells [26].

Synthetic Polymers

- The synthesis of polymers involves the use of a number controlled chemical polymerisation routes, which deliver consistency of the batch to batch properties, adjustable strength properties and very predictable degradation kinetics [27].
- Poly (lactic-co-glycolic acid) (PLGA): the most familiar copolymer for a broad spectrum of clinically approved drugs/formulation [28]. The degradation (between a couple of weeks to a few months) can be controlled by systematic adjustment of the molar ratio of the hydrophobic lactic acid and the hydrophilic glycolic acid monomers [29].
- Polylactic Acid (PLA) and Polyglycolic Acid (PGA): PLA has a pendant methyl group

that makes a highly hydrophobic and crystalline 3-D system which limits the access of water and thereby prolongs the hydrolytic degradation time period [30]. PGA which does not possess the methyl side chain becomes 100 times more hydrophilic and experiences a 10 times faster hydrolytic degradation of mass loss [31].

- Polycaprolactone (PCL): Aliphatic (crystalline), highly hydrophobic polymer with low melting point [32]. Very slow chain-scission degradation processes renders PCL so that the long term subdermal contraceptive or structural tissue engineering scaffolds implants degrade over a one-two year period [33].
- Polyanhydrides: Highly reactive anhydride links between the hydrophobic groups present along the polymer backbone allow surface erosion in a linear fashion, suitable for localized therapy which requires a zero order, constant release [34].

Properties of Biodegradable Polymers

The spatial and temporal drug release profiles of the encapsulated drug are directly controlled by the inherent intrinsic physicochemical and mechanical properties of the hosting polymer matrix [35].

Glass transition temperature (T_g): It is determined the glass or rubbery state at 37 degrees C [36]. A high T_g polymers (above 37 degrees C) will have high mechanical stability and low mobility [37], while low T_g polymers will have relaxing chains and therefore increase of drug diffusion.

Crystallinity: The polymer matrices are formed by both amorphous and crystalline regions of structures present [38]. The amorphous regions are loosely packed areas where water molecules penetrate, leading to increased hydrolysis rates as compared to the crystalline areas where structural integrity is maintained for longer periods.



Hydrophilicity and Hydrophobicity: The quantity of functional groups, which are push-side versus pull-side distributed along the polymer chain dictates the degree of water sorption available [39]. For example, a hydrophilic backbone will lead to rapid, even sorption of water while a highly hydrophobic chemistry limits water interaction to the outside surface of the device [40].

Molecular Weight (Mw): polymers with higher molecular weights result in more entangle chains and cohesive mechanical strengths that delay the beginning of polymer dissolution, mass loss, and matrix erosion [41].

Important properties of biodegradable polymers include:

- **Biocompatibility** – They do not produce significant toxic or inflammatory reactions when administered into the body [42].
- **Biodegradability** – These polymers undergo hydrolysis or enzymatic degradation and are eliminated naturally from the body without surgical removal [43].
- **Controlled Drug Release** – They can provide sustained and targeted drug delivery over weeks or months, improving patient compliance in chronic diseases [44].
- **Mechanical Strength** – Biodegradable polymers possess suitable flexibility and durability for use in implants, sutures, orthopedic devices, and stents [45].
- **Thermal Properties** – Properties such as glass transition temperature (T_g) and crystallinity influence degradation and drug release behavior [46].
- **Solubility and Water Uptake** – Water absorption affects polymer swelling, erosion, and degradation kinetics [47].
- **Tailorable Properties** – Polymer composition, molecular weight, and copolymer ratio can be

modified to obtain desired degradation and release profiles [48].

Mechanism of Biodegradation

Conversion of a solid polymeric matrix to water-soluble, excretable monomers is normally achieved through two separate physical modes of erosion at rates controlled by the relative rate of water diffusion into the matrix as compared to the rate of backbone chemical cleavage [49].

Bulk Erosion: This mode of degradation occurs when water molecules diffuse into the whole of the core material of the polymer matrix at a rate significantly higher than the rate of chemical hydrolysis of the polymer bonds [50]. As a result, polymer degradation occurs uniformly through the entire volume of the polymer device [51]. This mode of internal structural decay often results in the catastrophic loss of mechanical strength of the device, resulting in a distinct ‘burst release’ of the remaining drug payload [52]. Polyester matrices such as PLGA and PLA are primarily susceptible to bulk erosion processes [53].

Surface Erosion: this pattern is observed where cleaving of the chemical bonds at the interface of the water and polymer occurs much faster than the rate at which water molecules permeate the interior of the polymer [54]. The device compresses in size from the outside to inside, with its dense interior structure and composition remaining largely unaltered [55]. This type of structural response can yield reliably predictable, zero order drug release from the device [56]. Surface eroding biomaterials include the polyanhydrides and polyorthoesters of old [57].

Drug Delivery Systems Using Biodegradable Polymers

Micro and nanoscale morphologies of the biodegradable polymers can be achieved through the use of sophisticated engineering processes for desired pharmacokinetics [58].



Microparticles and Nanoparticles Polymer-based nanoparticles (generally 10 to 200 nm) greatly enhance the apparent solubility of poorly water-soluble small molecules, prolong circulation half-lives and protect sensitive biologics from premature systemic elimination [59].

Polymeric Micelles: When amphiphilic block copolymers are dissolved in water, a supramolecular assembly of these molecules occurs, composed of a hydrophobic core surrounded by a hydrophilic “shell”. These micelles are used to entrap hydrophobic drugs in the core and their hydrophilic shell prevents recognition by the mononuclear phagocyte system [60].

Hydrogels: 3-dimensional cross-linked network capable of tremendous swelling in water without dissolution [61]. Can be tailored to be smart in situ gel forming systems that are injected as a liquid and get solidified in specific location as a local depot in response to biological triggers such as body temperature, pH [6].

Types of delivery devices: Implants and electrospun scaffolds: Solid (macro-scale) devices or porous nanofibrous meshes produced to provide local continuous delivery at specific sites for prolonged periods of time. They are often implanted in post-operative regions or defect zones (e.g., tissues) [63].

Role in Chronic Diseases

Chronic disease management with therapeutics involves prolonged, tightly regulated drug exposures that inhibit disease progress and minimize systemic side effects [64].

Cancer

Maintaining and utilizing a laboratory database of information on cell lines and cytogenetics to avoid repeated laboratory procedures, maintain quality control and make cell lines and samples readily available.

Systemic administration of cytotoxic agents results in extensive toxicity due to the non-specific distribution to other tissues [65]. Polymeric nanoparticles are able to use the EPR effect to passively localize to the unorganized and leaky vasculature of solid tumors [66]. To increase the specificity of tumor localization, the surface of the nanoparticle can be functionalized with an antibody, aptamer or folate binding ligand to recognize an overexpressed receptor on the surface of the tumor cell [67]. In addition, once the nanoparticle has isolated within the cell cytoplasm, it can be designed to rapidly destabilise and release its cytotoxic payload in response to a specific feature within the tumor cell (i.e. Acidic lysosomal pH, high glutathione concentration) [68].

Diabetes

Diabetes mellitus management necessitates accurate, routine monitoring of blood-glucose levels and responsive insulin delivery to prevent catastrophic hypo- or hyperglycemic conditions [68]. Recently developed glucose responsive, ‘smart’ polymeric delivery devices have been demonstrated, where the enzyme glucose oxidase has been successfully loaded into a pH- or hypoxia-responsive polymeric hydrogel [69], which respond to the localized microenvironment acidity as a result of Glucose oxidase catalyzed oxidation of glucose to gluconic acid, by initiating local swelling, drug release, or structural transitions, thus closely eluting insulin or other secretagogues on demand [70].

Cardiovascular Diseases

In restenosis and coronary artery disease, permanent metallic stents have been associated with chronic arterial inflammation and late stent thrombosis [71]. Drug-eluting stents (DES) coated with biodegradable polyesters (e.g., PCL or PLGA) release the drug needed to combat



restenosis (e.g., sirolimus, paclitaxel) onto the injured vascular tissue over a controlled period of time [72]. As the blood vessel reestablishes a layer of endothelium, the polymeric matrix is resorbed, leaving nothing but a healthy vessel behind and reducing long-term clinical risks [73].

Bone and Joint Disorders

Chronic joint pathologies such as rheumatoid arthritis and osteoarthritis would benefit greatly from prolonged local delivery [74]. To achieve this, injectable biodegradable polymer microspheres containing high concentrations of anti-inflammatory drugs can be injected in the joint (intra-articularly), keeping therapeutic concentrations in the synovial fluid for months without adverse systemic effects [75]. Similarly, in large bone defects, porous biodegradable scaffolds would provide immediate structural support for osteoblasts, while providing a steady delivery of BMPs until the scaffold safely disintegrates into new bone [76].

Neurological Disorders

The BBB tightly regulates CNS homeostasis excluding over 98% of small-molecule drugs from penetration into the brain parenchyma [77]. Biodegradable nanoparticles may be surface-conjugated with targeted ligands (e.g., transferrin or polysorbate-80) for receptor-mediated transcytosis through the brain into brain capillary endothelial cells [78]. For more localized brain CNS abnormalities such as glioblastoma multiforme, surgery-placed polyanhydride carmustine wafers (Gliadel (R)) provide a continuous post-surgical application of chemotherapeutic without the BBB and without off-target damage [79].

Advantages

➤ **Sustained and Controlled Release:** Allows plasma drug levels to stay within a narrow safe therapeutic range, strongly suppressing

dangerous peaks of toxicity and sub-therapeutic troughs [80].

- **No Secondary Extraction Surgery:** Fully degraded in vivo into natural metabolites results in no expenditure of clinical cost or trauma on specialists removal of biostable devices [81].
- **Anatomical targeting:** improves local drug accumulation at the diseased tissue site, which permits to use lower total doses and dramatically reduces systemic side effects [82].
- **Payload protection:** Protects the sensitive macromolecular therapeutics (siRNA, monoclonal antibodies, peptides etc.) against the destructive enzymes found in the body [83].

Limitations and Challenges

- **Initial Burst Release:** A common surface-erosion polymeric system is characterized by an unintentional and near instantaneous burst release of the drugs contained on the surface of the device when the system encounters aqueous conditions. Such behavior may be problematic in the context of targeted dose-dumping [84].
- **Local Acidic Microenvironments:** Aliphatic polyesters such as PLGA also produce highly concentrated acidic monomer degradation products (lactic and glycolic acid) [85]. These micro-environments reduced pH within the matrix could induce denaturation of encapsulated biologic payloads or induce localized tissue inflammation [86].
- **Industrial Scaling Bottlenecks;** Converting multi-component system of polymeric nanomedicines from largely small-scale, bench-top synthesis to reliably reproducible, sterile, cGMP-compliant industrial manufacturing lots is still a major bottleneck [87].



- Comprehensive Regulatory Requirements: Approval process for thoroughly defining the multi-phase in vivo toxicity, clearance, and metabolic profiles of the intact polymer as well as all intermediate degradation fragments is extremely complex and lengthy [88].

Recent Advances

The immediate advances are centered around the use of stimuli responsive polymeric architecture where the physical state change occurs in response to a specific altered endogenous environment (e.g. increased level of certain enzymes, redox potential) or external physical trigger (e.g. Near-infrared, ultrasound, magnetic field.[89] Additionally, the novel approaches of 3D and 4D Printing Technologies build up the functionality of customized implants by producing specified external geometries on a layer-by-layer basis as well as through constructing intricate multi-phasic internal drug delivery matrices [90]. 4D Printing techniques utilize time-dependent shape-memory attributes of polymers so that miniature delivery devices can be delivered via keyhole surgery before unfurling on reaching body temperature into their determined functional forms [91].

FUTURE PROSPECTS

The prospects for biodegradable polymer-guided drug delivery are greatly dependent upon future developments in the field of personalized medicine [92]. The application of artificial intelligence (AI) and machine learning algorithms is facilitating the de novo design of new synthetic polymer chains which are formulated to precisely align with each individual patients specific physiologico-metabolic profile [93]. Moving from simple mono-therapies toward highorder,mult-stage, sequential release platforms will permit simultaneous control over the delivery of synergistic drug cocktails [94]. Simultaneously, the implementation of continuous manufacturing

platforms such as microfluidics will greatly reduce batch-to-batch inconsistencies and address many of the industry scale-up bottlenecks associated with traditional manufacturing technology [95].

CONCLUSION

Biodegradable polymers have progressed from dead, passive delivery vehicles into sophisticated, high performance systems [96], allowing for rigorous control over the drug release temporal and spatial profile. Thus overcoming the pharmacodynamic and pharmacokinetic constraints of traditional therapeutics, especially in high-burden diseases requiring chronic treatment regimens [97]. Although challenges with initial burst release, acidic degradation products, and industrial scale production design persist, ongoing synergistic research between polymer chemists, nanotechnologists, and process engineers ensures these materials will persist as the gift that keeps on giving in future targeted therapeutics and personalized medicine [98]

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