WISELEAF SCIENTIFIC VENTURES

BIODEGRADABLE POLYMERS IN DRUG DELIVERY AND TISSUE ENGINEERING

CHAPTER-2

Synthetic Biodegradable Polymers: PLA, PLGA, PCL and Beyond

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Abstract

Synthetic biodegradable polymers are widely utilized in pharmaceutics and healthcare due to their unique properties such as biocompatibility, controlled degradability and versatility in advanced drug delivery systems. The present review highlights the various classes and pharmaceutical significance of major synthetic biodegradable polymers, including polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), polyanhydrides, polyorthoesters and poly(amino-acids) etc. and beyond. Various methods employed for their synthesis, physicochemical properties as well as mechanisms of action and degradation are discussed. The review further explores patented technologies and recent innovations associated with biodegradable polymeric systems. The recent approaches in the pharmaceutical applications of synthetic biodegradable polymers are also highlighted. These polymers are significant in the development of novel drug delivery systems and applications extending to 3D-printing, oncotherapy, gene delivery, tissue engineering and biomedical implants etc. The future prospects of these polymers in modern pharmaceutical research and therapeutic systems are also highlighted.

Keywords: Synthetic biodegradable polymers, drug delivery systems, PLGA, biocompatibility, advancements

1. Introduction

Biodegradable polymers are the substances that can be broken down into simpler units in the presence of physical, chemical or biological changes. The need for biodegradable polymers arose in the late 19th century due to expensive non-renewable resources and demand for cost-effective alternatives to existing polymers. The efforts to develop SBPs accelerated in the early 20th century (1). These polymers are broadly classified as natural or synthetic in nature based on their sources of origin. Natural biodegradable polymers are set of biodegradable agents which are obtained from natural sources. Cellulose, chitosan, starch, gelatin and alginate etc. are some of the well known natural biodegradable polymers (2). Synthetic biodegradable polymers (SBPs) form an important class of pharmaceutical excipients that have gained immense attention in the modern pharmaceutical research and healthcare sector. SBPs are macromolecules which are made up of homogenous or heterogenous monomers and are synthesized through artificial techniques. These substances possess unique properties such as biodegradability, biocompatibility, bioresorption, wide range of physicochemical properties and their tunability utilized in diverse applications (3).

The global market size of biodegradable polymers is estimated to be about USD 15.5 billion in 2026 and is expected to reach USD 90.39 billion by 2035 at a compound annual growth rate of 21.4% (4). The market size of Indian biodegradable polymers is around USD 435 billion in 2026 and can reach USD 956 million by 2033 at a CAGR of 11.9% (5). Some of the key market players in the field of SBPs are Evonik, Corbion, NatureWorks, Mitsubishi, DuPont, BASF etc (6).

2. Chemical Classification of SBPs

The following sections provide a comprehensive discussion of the major synthetic biodegradable polymers. Emphasis has been made regarding their composition, chemical structure, methods of synthesis, characterization techniques, mechanisms of action, physicochemical properties and applications etc. The general classification of SBPs is represented in **Fig.1.**

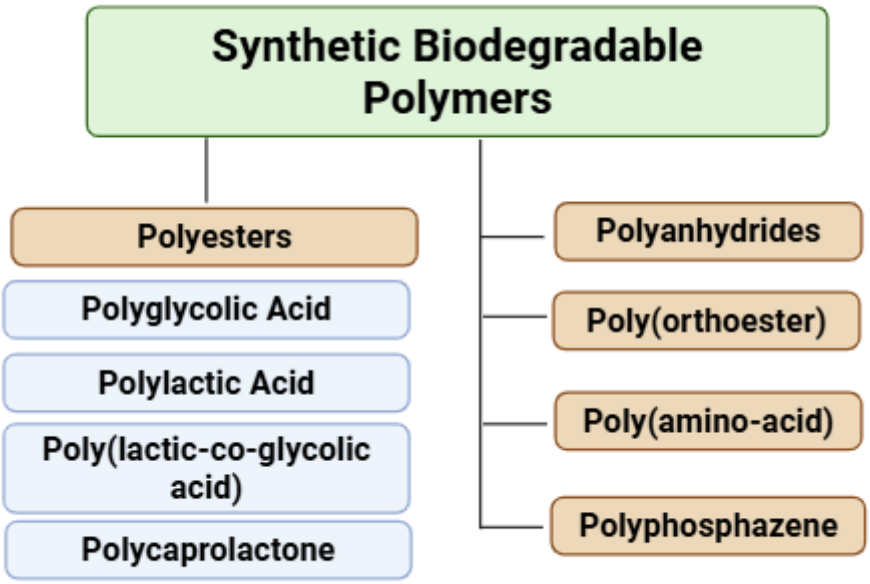

Figure 1. General Classification of SBPs

2.1 History of Polyesters

The important SBPs belonging to the class of polyesters include polylactic acid (PLA), polyglycolic acid (PGA) and poly(lactic-co-glycolic acid) (PLGA). All the three polymers are US FDA approved-aliphatic polyesters. PLA was first synthesized by Pelouze in 1845 by polycondensation (7). Dessaignes was the first to synthesize PGA, using hydroxyl-malonic acid, in 1854 (8). Carothers' group synthesized these polymers in 1930 and Du Pont patented the processes for synthesis of PGA and PLA in 1954 (9). In 1962, PGA became popular as the world's first SBP based-absorbable suture under the brand name "Dexon". PLGA was first synthesized in 1960s as a copolymer using varied proportions of PGA and PLA. US Food and Drug Administration approved PLGA-based, leuoprolin-containing formulation named Lupron Depot® (10). Vicryl®, a resorbable synthetic suture, made up of polyglactin 910 (90:10 glycolide: lactide), was developed by Ethicon and approved by FDA in 1974. Vicryl Plus, the first antibacterial suture, was cleared by FDA in December 2002 (11).

2.1.1 PLA and PGA

Ring open polymerization (ROP) of lactides is used in production of high molecular weight PLA, whereas decondensation of lactic acid is used to produce low to medium molecular

weight PLA. The microbial fermentation of sugar molecules, obtained from raw materials like corn, potato etc. in the presence of *Lactobacillus* strains produces lactic acid which further undergo chemical polymerization (12). PLA exhibits amorphous to semi-crystalline property with hydrophobic nature. The polymer degrades through hydrolysis of ester bonds, producing lactic acid as the primary degradation product. PLA exists in several stereochemical forms such as poly-L-lactic acid (PLLA), poly-D-lactic acid (PDLA) and poly-D,L-lactic acid (PDLLA). PLLA shows higher level crystallinity and mechanical strength whereas PDLLA is more amorphous and shows faster rate of degradation (13). PLA undergoes hydrolytic degradation by surface erosion or bulk degradation, making it suitable for long term, controlled drug release (14). PGA is linear and aliphatic polyester synthesized through ROP of glycolide in presence of stannous octanoate. PGA does not have methyl side groups, thus forming a highly crystalline structure and increased hydrophilicity. It has excellent tensile strength and superior fiber-forming capabilities and widely used for surgical sutures (15). PGA undergoes rapid hydrolysis to produce non-harmful glycolic acid and useful in short-term drug release.

2.1.2 PLGA

PLGA is a gold standard for the SBPs as it integrates the desired properties of both PLA and PGA. It is a co-polymer made up of varied proportions of lactic acid and glycolic acid. The ratio of lactide:glycolide determines the degree of hydrophilicity, degradation rate, melting point and drug release kinetics. A 50:50 ratio of lactide:glycolide containing PLGA generally degrades fastest due to reduced crystallinity, while increase in lactide content produces slow degradation due to enhanced hydrophobicity. Ratios such as 75:25 and 85:15 provide extended release durations suitable for long-term therapies (16,17). Low molecular weight PLGA weighs less than 1000 daltons whereas high molecular weight PLGA weighs greater than 1000 daltons. Ester-terminated, low molecular weight PLGA is synthesized by ROP using L-lactide and glycolic acid of suitable proportions in presence of stannous octonoate. Lactic acid and glycolic acid undergo condensation in presence of tin and diphenyl ether to yield acid- terminated high molecular weight PLGA (18,19).

2.1.3 Polycaprolactone

Polycaprolactone is also one of the foundational polymer synthesized by the Carothers' group in 1930s. It is a semi-crystalline aliphatic polymer synthesized using ROP of ε-caprolactone. Although, it is derived from petroleum-based feedstock, it is considered as an SBP, due to its biocompatibility with human body and environment and extremely slow degradation process. Coordination-insertion ROP of ε-caprolactone in presence of metal catalysts is useful in production of high molecular weight PCL. Transesterification of ε-caprolactone molecules during polymerization can lead to formation of low molecular weight PCL (20,21). Capronor, a levonorgesterol-containing, PCL-based subdermal contraceptive was developed by Research Triangle Institute and was patented in 1979 (22). The degradation of PCL occurs through hydrolysis of ester linkage and may require several months to years. This slow degradation profile differentiates PCL from the other three polyesters. It is ideal for applications which require structural support as well as long-acting, continuous therapeutic delivery over few years (23).

2.2 Polyanhydrides (PAs)

Bucher and Slade were the earliest scientists to synthesize polyanhydrides in early 20th century (24). In 1980s, Robert Langer utilized PAs in development of controlled released drug delivery systems (25). PAs are class of SBPs with anhydride group in their backbone which can be incorporated using various polymerization techniques. High molecular weight PAs are synthesized using melt condensation polymerization between respective dicarboxylic acids as monomers in presence of acetic anhydride (26). These substances exhibit surface erosion degradation mechanism i.e., penetration of water molecules into PAs occurs more slowly than bond breakage, causing degradation to occur predominantly at the surface.

2.3 A Brief Note on Emerging SBPs

Polyorthoesters (POEs) are a unique class of SBPs developed primarily for controlled drug delivery applications. They are made up of orthoester linkages in their polymer backbone and undergoes pH- sensitive hydrolytic degradation (27). Poly(amino acids)-based polymers are the agents derived from naturally occurring or synthetic amino acids. These polymers are considered highly attractive biomaterials as they show biomimetic properties as that of natural

proteins and extracellular matrix components. Some of the common examples include poly(L-lysine), poly(glutamic acid), poly(aspartic acid) etc. These molecules are synthesized using ROP of N-carboxyanhydrides derived from amino acids (28). Amino acids are basic biological building blocks and constitute the proteins in our body. These polymers can interact favorably with cells, tissues and physiological molecules due to presence of carboxyl and amino groups. The degree of hydrophilicity of the constituent amino acids determines the hydrophilicity of these SBPs (29). Polyproline, composed of proline units, exhibit high degree of strength, rigidity and restricted conformational changes (30). The first polyphosphazene molecule was synthesized by Stokes in late 1890s. Polyphosphazenes, also called as inorganic rubber, form a distinct class of SBPs due to the presence of inorganic phosphorus-nitrogen backbone (31). They are different from conventional polymers such as PLA, PGA and PLGA. Polyphosphazenes contain alternating phosphorus-nitrogen atoms with organic side groups attached to the phosphorus centers whereas the conventional polyesteric SBPs are composed of carbon chains (32).

3. Patent Landscape of SBPs

An analysis of 2862 patented biodegradable polymers- based inventions conducted by *Lee et.al. (2024)* reported that there has been an increased research interest with regard to biodegradable polymers, their technological advancements and applications across diverse sectors (33). **Table 1** discusses about some of the SBPs- based patented research works and innovations.

Table 1: SBPs- based patented works

S. No.	Type of the SBP	Patent Number	Crux of the Invention	Reference
1.	Polyester	US6592899B2	A PLA/PLGA oligomer- block copolymer systems in order to improve the aqueous solubility of poorly water-soluble drugs to enhance their delivery.	(34)

		US9957350B2	A novel efficient liquid-phase lactide polymerization using coordination catalyst, producing high-quality polylactide with enhanced kinetics.	(35)
		CA2825016C	A PLGA-based nanoparticle formulation for dermal and systemic delivery of drugs.	(36)
		WO2020077178 A1	A PLGA- polyethylene glycol based nanoparticle formulation for delivering nucleic acid components into cells	(37)
		US9925695B2	A bioresorbable PLGA scaffold incorporating magnesium wires to provide directional guidance and complete biodegradability.	(38)
		FR2557459A1	A PCL- based inert matrix dosage form for oral drug administration.	(39)
		RU2749803C1	A collagen peptide-encapsulated PCL- containing microsphere filler which promotes formation of collagen, tissue regeneration and wrinkle correction	(40)
2.	PAs	WO2008008387 A2	A biodegradable polyanhydride-based drug delivery system in which therapeutic agents are incorporated into the polymer backbone.	(41)
3.	POEs	US20220387595 A1	A biodegradable polyorthoester-based drug delivery system utilizing	(42)

			aprotic solvents for slow, controlled drug delivery.	
4.	Poly(amino-acids)	US20250236707 A1	A poly(amino-acids) based system for altering the rheological composition	(43)
5.	Polyphosphazenes	WO2017075483 A1	Multifunctional polyphosphazenes utilized as biodegradable drug carriers capable of improving pharmacokinetics and ensuring cellular drug delivery.	(44)
		US10940217B2	Biodegradable polyphosphazene nanoclusters-containing inorganic nanocrystals for medical imaging, biodistribution and gradual renal excretion of nanoparticles.	(45)

4. Applications of SBPs

The various applications of SBPs that have been discussed in this section are listed as follows:

a. Novel Drug Delivery Systems

b. Oncotherapy

c. Vaccine Delivery and Tissue Engineering

d. Theranostics and Medical Imaging

e. 3D-printing and Bioprinting Technology

4.1 Novel Drug Delivery Systems

SBPs have improved controlled drug delivery systems by enabling the sustained and site-specific release of therapeutic agents over extended periods. Polymers such as PLA, PGA, PLGA, PCL and polyorthoesters can be fabricated to control the drug release through different types of processes such as diffusion, erosion or polymer degradation mechanisms. These polymers are extensively employed in the development of novel systems such as microspheres,

nanoparticles, implants etc. These kinds of dosage forms are helpful in ensuring therapeutic drug concentrations over a long period of time i.e, for weeks or even months. PLGA-based formulations have achieved significant commercial success and cleared by US FDA. Risperidal Consta ® is a long-acting, risperidone- containing injection which is used to primarily treat schizophrenia (46). Sandostatin LAR ® is a long-acting octreotide-containing injectable suspenion. It mimics the natural growth hormone and is used to treat acromegaly (47). The ability of these polymers to ensure prolonged drug delivery, protect the drugs from degradation while decreasing the dosing frequency has been crucial in improving the patient-compliance and therapeutic outcomes

4.2 Oncotherapy

SBPs have become an important part of modern cancer therapy. Polymeric novel platforms and implantable systems promote the targeted delivery of anticancer drugs, thereby improving drug entry at tumor sites and ensure the reduction in adverse effects. PLA copolymer- based nanocarriers with zwitterionic groups has been explored for chemotherapy (48). The nanoparticles synthesized from mPEG- PCL dual polymer have been combined with tamoxifen for the latter's prolonged release (49). PLGA- based nanoparticles drug delivery system has been used in modification of tumour microenvironment in colorectal cancer (50).

4.3 Vaccine Delivery and Tissue Engineering

Polymer based nanoparticle system have been extensively researched. DNA vaccine- loaded PLGA microspheres was found to provide protection against *Aeromonas* infection (51). PLA and PLGA- based aerosolized inhalable nanoparticles were found to provide enhanced immune response against Hepatitis B (52). These platforms are increasingly being explored for infectious diseases, oncovaccines and next-generation nucleic acid- based vaccines. Interestingly, PLGA- based vaccines have been promoted and explored for minimizing the infections in fishes, thereby improving the quality of aquaculture (53). PLGA- based composite was optimized for bone tissue engineering applications. It was enhanced using PCL, PLA and polyurethane (54). Vascular tissue engineering has gained importance in the treatment of diseased cardiovascular tissues. Apart from the conventional natural biodegradable polymers, SBPs such as PCL, PLA and PGA are used to make vascular grafts (55). Poly(L-lactide-co-ε-

caprolactone), a novel polymer derived from L-lactide and ε-caprolactone, is of great importance in biomedical engineering (56).

4.4 Theranostics and Medical Imaging

PLGA- containing pH-sensitive, nanoparticle system was used as a theranostic agent in treatment of mesothelioma (57). Polyphosphazenes are emerging agents that have gained immense importance as nanoparticulate contrasting agents (58). PLGA-based nanoparticles have the ability to interact with cancerous cells, thus can be used to load imaging and therapeutic agents against cancers (59). Disulfide bond linked- PCL and hyaluronic acid based nanosystems were reported to diagnose and treat tumours (60). Poly(aspartic acid) polymer and self assembled metallic particles based dual imaging and contrasting agent was found to improve the fficacy of the chemodynamic therapy against tumours (61). Axitinib-loaded POE based implant was found to be useful in treatment of macular degeneration the eye (62).

4.5 3D- Printing and Bioprinting Technologies

The integrated approaches of SBPs with 3D-printing and bioprinting technologies have facilitated newer opportunities for personalized healthcare. 3D-printed PLA scaffolds were found to be effective solutions for bone generation in animal models during pre-clinical studies (63). Silver nanoparticles-containing polyester SBPs such as PCL, PLGA can be explored as antibacterial substances and incorporated in implants (64). 3D- printed PGLA scaffold have been explored for healing of burn-related wounds (65). PLA, PGA, PLGA and PCL have been utilized in the making of bioresorbable stents (66). Using 3D-printing, SBPs are altered to form metallic particles containing biocompatible composites useful in orthopedic implants (67).

5. Conclusion

SBPs have revolutionized modern pharmaceutical sciences, biomedical engineering, regenerative medicine and advanced healthcare technologies. Each polymer has unique physicochemical characteristics which are characterized for its suitability for varied biomedical purposes. PLA provides higher degree of mechanical strength as well as undergoes slow degradation, thus making it a better option for implants, orthopedic devices and tissue engineering scaffolds. PGA shows rapid rate of degradation and high tensile strength and are highly used in development of absorbable sutures and medical devices. PLGA is a gold-

standard biodegradable polymer because of mainly because of its adjustable rate of degradation, biocompatibility and regulatory compliance. It is versatile and used in commercial products and various novel platforms. PCL undergoes extremely slow degradation and has maximum flexibility, thus making it ideal for long-acting implants, regenerative medicine and 3D-printed biomedical structures.

Specialized polymers such as polyanhydrides, polyorthoesters and polyphosphazenes have widened the possibilities of targeted and controlled drug delivery. Polyanhydrides exhibit surface erosion behavior thus producing convenient drug release rate. Polyorthoesters provide pH-sensitive degradation and controlled-release characteristics and are useful in localized therapies and injectable depots. Polyphosphazenes have a different framework of inorganic backbone and side groups in its structure. It can be controlled for biodegradation, immune responses and therapeutic activities in a precise manner. Poly(amino acid) polymers show biomimetic properties. Thus, it has been utilized in various applications such as protein delivery, tissue engineering, gene therapy and regenerative medicine.

Between 2021 to 2026, the field of SBPs has witnessed vast range of advancements. Nanotechnology-based formulations, improved systems that help in theranostics smart drug delivery systems, gene delivery techniques and personalized medicine approaches have significantly expanded the applications of these polymeric substances. Polymeric nanoparticles have also improved therapeutic efficacy of drugs while reducing systemic toxicity.

In the field of medical devices and implants, SBPs have reduced the need for secondary surgeries by eliminating need for incorporating permanent foreign materials after tissue healing. In tissue engineering, these polymers produce temporary scaffolds; which is important and supports cell growth and tissue regeneration; and slowly degrades as the new tissue forms. 3D printing and bioprinting technologies have improved so much that these materials have further enhanced the ability to fabricate patient-specific implants, drug delivery systems and regenerative medicine using SBPs. Regulatory agencies such as USFDA and international organizations such as ICH support the development of biodegradable polymer-based medical devices and implants (ISO 10993 series), their chemical characterization, degradation products and their nature through well-established guidelines and evaluation frameworks. The extensive

clinical success of the above discussed polymers demonstrates their safety, efficacy and commercial scalability.

5. Future Perspectives

The future of SBPs is associated with the fast growing sectors such as smart polymers, 3D-printing, personalized and precision medicine and material sciences. The tunability of the SBPs to incorporate compatible set of drugs, produce controlled degradation and suitable drug release kinetics and ensuring the efficacy and stability provided to the formulation are of great interest. The next generation of SBPs represents the development of stimuli-responsive or "smart" polymeric systems. These belong to the class of advanced polymers that can respond to various internal and external stimuli such as pH, temperature, light, enzymatic action and redox conditions. These systems possess the ability to recognize and react to specific physiological and pathological signals and better therapeutic efficacy with minimum adverse effects. These polymers can also be crucial in treatment of chronic diseases, targeted oncotherapy. 3D printing and bioprinting technologies enable the fabrication of patient-specific implants, scaffolds and medical devices with accurate specifications. In regenerative medicine, biodegradable polymer-based scaffolds incorporating stem cells, growth factors and bioactive molecules facilitate tissue repair, organ regeneration and patient-centric therapeutic interventions. Artificial intelligence and machine learning are playing an important role in transforming design of polymer and formulation. Advanced computational tools such as Schrödinger's digital chemistry and material sciences platform can predict critical polymer characteristics, including physicochemical properties, degradation kinetics, drug-release behavior and biocompatibility, prior to experimental synthesis.

Theranostic systems that combine diagnosis and therapy within a single biodegradable novel drug delivery system are gaining prominence. Emerging omics technologies provides insights into monitoring of disease progression and biological variations, thus guiding in the rational design of drug delivery. Eco-friendly approaches to in synthesis of SBPs are becoming highly valued. Principles of green chemistry, renewable starting resources and solvent-free manufacturing methodologies reduce environmental burden while improving the sustainability of industrial-level production. These advancements serve as an indication that SBPs will

definitely play a transformative role in the future of pharmaceutical sciences and advanced healthcare systems.

Acknowledgement

The author sincerely thanks the editors and publishers for providing the opportunity to contribute this book chapter. The work was independently researched and written by the author.

Conflict of Interest: None

Financial Support: None

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