

Biodegradable synthetic polymers in biomedical application: A review

Polímeros sintéticos biodegradáveis em aplicação biomédica: Uma revisão

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ABSTRACT

Biotechnology associated with medical technology has allowed biodegradable synthetic polymers to have versatile and diversified biomedical applications due to interesting properties such as good cell adhesion, in vivo proliferation, and degradation without harmful effects to the human body. Thus, they are suitable for a variety of applications, especially those related to therapeutics or pharmaceuticals, for example, tissue engineering and drug delivery. This work aimed to revise the broad applications of the term biodegradation in different areas of science. We focused on the most recent biomedical applications of biodegradable synthetic polymers, revising the characteristics which have contributed to solving health-related problems. Actual, efficient, and consistent results have been introduced in the market as a result of the growing search for new technologies. They have been applied both at macro and nanometer scales, in isolated and conjugated forms, or even as encapsulating matrices. Biodegradable synthetic polymers present longer degradation periods when compared to natural polymers, they stand out in tissue engineering since they can be adjusted according to their composition, reaching various degrees of selectivity for specific clinical applications.

Keywords: antimicrobial, drug delivery, healing.

RESUMO

A biotecnologia associada à tecnologia médica tem permitido que os polímeros sintéticos biodegradáveis tenham aplicações biomédicas versáteis e diversificadas devido à propriedades interessantes como boa adesão celular, proliferação in vivo, e degradação sem efeitos nocivos ao corpo humano. Assim, eles são adequados para uma variedade de aplicações, especialmente aquelas relacionadas a terapêutica ou farmacêutica, por exemplo, engenharia de tecidos e entrega de drogas. Este trabalho teve como objetivo revisar as amplas aplicações do termo biodegradação em diferentes áreas da ciência. Focamos nas mais recentes aplicações biomédicas de polímeros sintéticos biodegradáveis, revisando as características que têm contribuído para a resolução de problemas relacionados com a saúde. Resultados reais, eficientes e consistentes foram introduzidos no mercado em decorrência da crescente busca por novas tecnologias. Eles têm sido aplicados tanto em escalas macro quanto nanométricas, de forma isolada e conjugada, ou mesmo como matrizes encapsulantes. Polímeros sintéticos biodegradáveis têm apresentado períodos de degradação mais longos quando comparados aos polímeros naturais, eles se destacam na engenharia de tecidos, pois podem ser ajustados de acordo com sua composição, atingindo vários graus de seletividade para aplicações clínicas específicas.

Palavras-chave: antimicrobiano, entrega de drogas, cicatrização.

1 INTRODUCTION

Synthetic polymers, popularly known as plastics, are materials produced by man in a laboratory or industrial scale, which emerged with reference to the composition of natural polymers. They are obtained by the addition of monomers to one another, the condensation of functional groups to form a second small molecule, or rearrangements between monomers; when formed by mixtures of two or more types of monomers, they are named copolymers. The emergence of these man-made polymers, whose monomers, in general, are extracted from

petroleum or its residues, had its importance recognized in several technological applications, such as health, textiles, electronic, and utensils; however, due to its large-scale production, the generation of high amounts of plastic waste increased environmental pollution. In the last decades, the global awareness of the society by minimizing this pollution encouraged the development of bio-based polymers, i.e., polymers with the extremely important characteristic of biodegradation.

As it is popularly known, the term biodegradable refers to naturally degradable materials, where degradation results mainly from the action of microorganisms, such as fungi, bacteria (with or without oxygen) and algae, generating CO₂, CH₄, cellular components, and other products; however, the term biodegradation has not been applied consistently in different areas of science. For example, for environmentally degradable plastics, the term biodegradation can be associated to fragmentation, loss of mechanical properties, or sometimes associated with the degradation by living organisms. For medical tools, such as sutures, implants, and drug carriers in drug delivery systems, the term biodegradation is used to indicate degradation into macromolecules that stay into the body, but migrate or hydrolysis into low molecular weight (MW) molecules. Polyethylene prostheses used in joints are those example of low MW molecules that are excreted from the body (bioresorption) or dissolved without molecular weight modification (bioabsorption) [1].

In summary, biodegradable polymers can be degraded into the human body and their products remain in living tissues for a long time. When called bioabsorbable polymers, the products of degradation are non-toxic and can be metabolized or eliminated from the body. At this point, it is possible to observe that the term biodegradable has been used interchangeably with other terms, including absorbable, resorbable, and bioabsorbable [2]. Also, biodegradation has been replaced by the terms bioresorption or bioabsorption [3].

Considering the above, there is no single ideal method to determine the biodegradation of polymeric materials, since the degradation process of a material is not determined only by its chemical composition and the corresponding physical properties; also, the degradation environment in which the material is exposed affects the rate and degree of biodegradation [1].

Focusing on the already mentioned bio-based polymers, these biodegradable materials obtained from renewable sources have a minimal impact on the environment when compared to those obtained by chemical synthesis methods. As a result of this new class of bio-based synthetic polymers, the most widely used in the biomedical field is the polylactic acid (PLA), a polyester obtained by the polymerization of lactic acid (LA) monomers whose isolation occurs from renewable natural sources through bacterial fermentation. Due to its chirality, LA exists

as two stereoisomers, L- and D-lactic acid, resulting in the formation of poly-D-lactic acid (PDLA) and poly L-lactic acid (PLLA).

Biodegradable synthetic polymers have been constantly evaluated due to their high biocompatibility, as well as bioactive properties such as antimicrobial activity, immunomodulatory activity, high cell proliferation capacity, and angiogenesis. Considering the harsh environment of the human body, these polymers must achieve basic criteria (biocompatibility, non-toxicity or mutagenicity) and exhibit chemical resistance [4]. Another important property is the ability to be spun into fibers, through electrospinning, mimicking the extracellular matrix, thus allowing their use in different biomedical applications [5]. The example of implants explains the main reason for using biodegradable synthetic polymers in this field: their excellent elasticity, chemical stability, and, in most cases, low or non-toxicity.

Various medical devices, mainly polyester-based ones, are commercially available, and new models are introduced into the market each year. Their mechanical performance and the wide range of degradation properties allow several degrees of selectivity for specific clinical applications of these polymers. In tissue engineering, for example, biodegradable synthetic polymers are the most used for the construction of scaffolds as they degrade slowly and the process could be adjusted according to the material composition [6]. Some examples of biodegradable synthetic polymers applied in biomedical field are shown in Table 1.

Table 1. Some biodegradable synthetic polymers used in biomedical applications.

Polymer	Applications	References
Polyglycolic acid (PGA)	Tissue engineering	[7]
Poly lactic acid (PLA)	Tissue engineering; Healing; Antimicrobial	[8-10]
Poly (L-lactic acid) (PLLA)	Tissue engineering	[11]
Poly (D, L-lactic acid) (PDLA)	Drug delivery	[12]
Poly (lactic-co-glycolic acid) (PLGA)	Tissue engineering; Antimicrobial	[13,14]
Polyesteramide (PEA)	Tissue engineering; Drug delivery	[15,16]
Polycaprolactone (PCL)	Tissue engineering; Healing; Antimicrobial; Drug delivery	[17-20]
Poly (glycerol sebacate) (PGS)	Tissue engineering; Healing; Antimicrobial; Drug delivery	[21-23]
Polyurethane (PU)	Tissue engineering; Drug delivery; Antimicrobial	[24-26]

One of the first biodegradable synthetic polymers studied in biomedical applications was polyglycolic acid (PGA); however, its intrinsic characteristics, such as high hydrophilicity, fast degradation, insolubility in most organic solvents, and fragility have hampered its practical use. Thus, PGA has been used mainly in the form of copolymers [28, 29]. Some studies have reported that the rapid degradation of PGA decreases its mechanical strength and increases glycolic acid levels; this acidic environment has also been associated with an exacerbation of the inflammatory response [30, 31].

In turn, PLA is a very promising biodegradable synthetic polymer. Regarding its synthesis, a multi-step fermentation process starts with the biosynthesis of lactic acid, which is then converted to cyclic lactide and then polymerized by a metal catalyst. As it is produced from renewable and non-toxic raw materials, PLA has emerged as an important polymeric material for biomedical applications due to its biocompatibility, biodegradability, mechanical strength, and easy processing. However, characteristics including low degradation rate, hydrophobicity, and low mechanical strength can impact and limit its use [32, 33]. PLA is presented in the following forms: poly (L-lactic acid) (PLLA), poly (D-lactic acid) (PDLA), poly (D, L-lactic acid) (PDLLA), and meso-poly (lactic acid) (PMLA); however, only PLLA and PDLLA have shown promising potential in biomedical applications [28].

PLLA is obtained from the methylation of PLA, which increases its hydrophobicity and also its stability against hydrolysis (even more than PGA). In view of this higher degradation rate, some studies are developed with the aim to modify this property, mixing or copolymerizing PLLA with other biodegradable polymers [28]. PDLLA is a racemic mixture of PLLA and PDLA, with a shorter degradation rate than PLLA and also associated with other biodegradable polymers to create copolymers; these mixtures form new materials with enhanced, more suitable properties for use in the biomedical field [28, 34].

Poly(lactide-co-glycolide) (PLGA), derived from the copolymerization of PLA and PGA, has controllable properties, well-defined formulation techniques (also easily replicated) and excellent biocompatibility and biodegradability; thus, it is considered the biodegradable synthetic polymer most researched for therapeutic applications. PLGA is being widely used in tissue engineering since it has demonstrated excellent cell adhesion and proliferation properties. Due to its rapid degradation when compared to other polyesters, PLGA has been applied in the

controlled distribution of drugs; depending on the composition of this copolymer, the release rate of the drug in the body may be then altered [32, 35].

Polyesteramides (PEAs) are polymers with ester-type and amide-type bonds in their main chain and thus combine the degradability of polyesters and the mechanical properties of polyamides. In view of this conformation, PEAs present susceptibility to enzymatic degradation by lipases; however, the increase in the number of amide groups decreases this characteristic. The extent of biodegradation appears to be dependent on the density and distribution of the polymer's hydrogen bonds, i.e., the length of the amide blocks present in copolyesteramides [36]. Thus, many studies have been focusing on polyesteramides, the obtainment of biodegradable plastics with improved properties (favorable to biodegradability), and potential biomedical applications.

Polycaprolactone (PCL) is a biodegradable, biocompatible polymer that has high elasticity and tensile strength. The slow rate of biodegradation of PCL produces fibers with excellent applicability in the area of tissue and artificial skin regeneration, in addition to application in other fields, for example in delivery systems [37].

Poly(glycerol sebacate) (PGS) is an elastomer polymer obtained from a simple polycondensation of glycerol and sebacic acid with important characteristics such as biocompatibility, biodegradability, and low inflammatory response when compared to other synthetic polymers; also, PGS has properties similar to collagen and elastin, which allowed its use for biomedical applications by the Food and Drug Administration (FDA) [38]. PGS properties can be modulated according to the parameters used during polymerization; for example, a fraction of glycerol can be lost with the process, thus causing significant changes in its properties [39]. For the processing of PGS, the presence of a carrier polymer is necessary, such as PCL, which is easily electrospun and able to produce uniform fibrous structures. The combination of PCL and PGS increases the viscosity of the mixture, the efficiency of the electrospinning process [40], and the adjustment of the degradation rate (by combining the concentration of each polymer in the proportion of the mixture) [39].

Polyurethanes (PUs) have been used in biomedical applications for decades due to its broad spectrum of physicochemical, mechanical, and structural properties. The development of new biologically based macromolecular architectures has allowed the development of PU structures for several suitable biomedical devices, such as for adhesion, proliferation, and differentiation of many cell types [41].

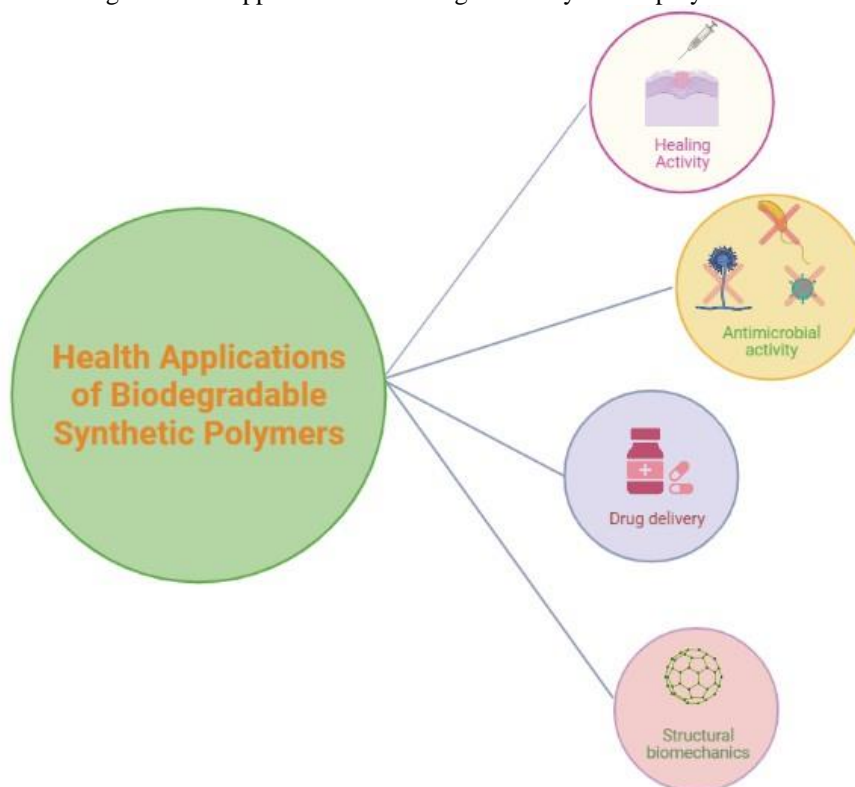
Polybutylene succinate (PBS) has been widely explored as a biodegradable packaging material since the 1990s; however, it has gained special attention recently, when the

regenerative medicine area discovered its many favorable properties. PBS has excellent mechanical and thermal properties, good processability, and low cost, which has highlighted PBS as an attractive material for various purposes, especially as a promising scaffolding material in bone tissue engineering applications [27].

1.1 APPLICATIONS OF BIODEGRADABLE SYNTHETIC POLYMERS IN THE HEALTH AREA

In this section, recent successful works with different objectives in the health area as healing, biomechanics, antimicrobial and drug delivery (Figure 1) are being presented.

Fig 1: Health applications of biodegradable synthetic polymers.



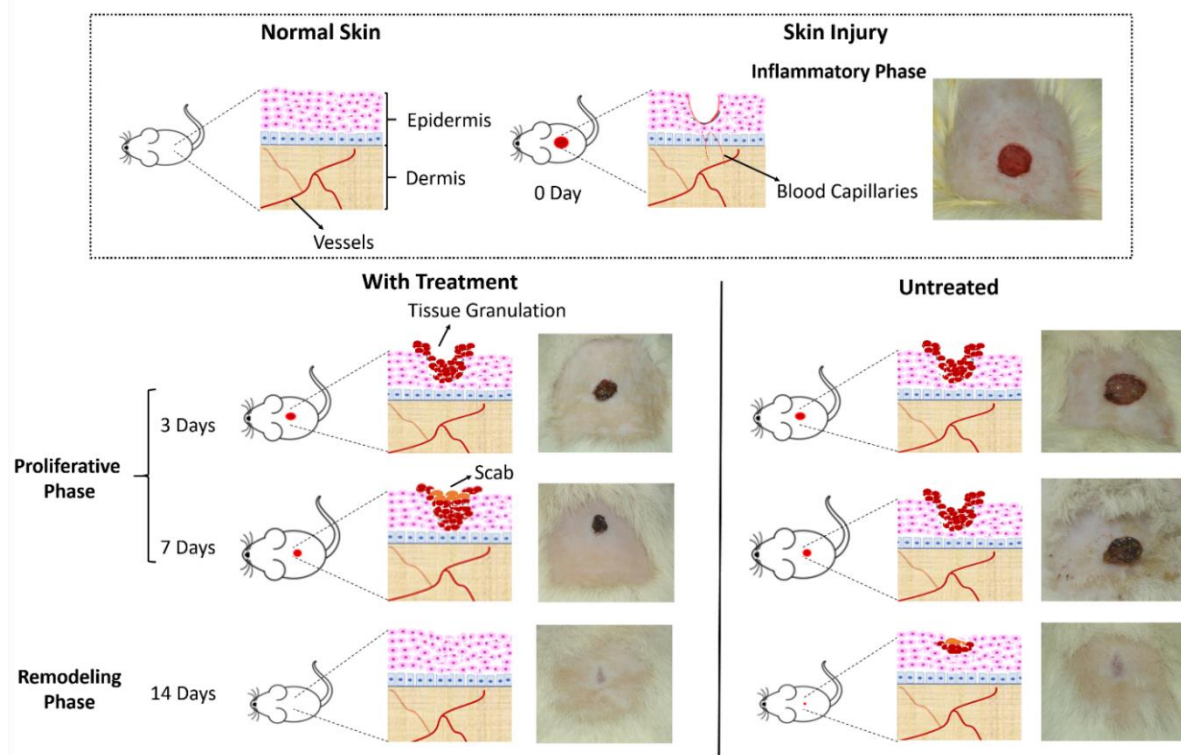
1.1.1 Healing activity

A wound results in any tissue injury with disruption of anatomical integrity and functional loss, i.e., an interruption in the continuity of a body tissue. The wound healing process is a physiological reaction that begins after the injury and extends weeks or years to be completed, depending on the severity of the injury and various biological factors. This process involves an interaction between diverse molecular, humoral, and cellular mechanisms, occurring in three overlapping stages known as inflammatory, proliferative, and remodeling phases [42,43]. The use of biodegradable polymers has been described as a promising

alternative for wound treatments. In Figure 2, it is possible to compare the effects of using biodegradable polymers on the healing process of topical wounds produced in male rats.

The growing dependence of the society for modern and efficient biomaterials, in this case those able to accelerate the healing process, encouraged the development of a large number of recent, successful studies, for example: PLA membrane by electrospinning, isolated or associated with the *S. dendrodeum* extract, favored the healing process of second-degree burns in Wistar rats, with an increase in fibroblasts, collagen fibers, and blood vessels [44]. Nanoporous membrane of electrospun PLA incorporated with nanoparticles of niobium pentoxide (Nb₂O₅) showed biocompatible properties with adequate porosity, in addition to facilitated properties of cell fixation and proliferation by allowing the diffusion of oxygen and nutrients. The system was considered a potential candidate for drug application and dressings [45]. L-arginine-modified PGS films showed a low water vapor transmission rate and antimicrobial effect, being reported as a new dressing for the treatment of dermal wounds [46].

Fig 2: Comparative diagram between the wound healing phases (3, 7 and 14 days) with the respective images of skin lesions in rats without and with treatment with polymeric formulation, which were photographed to a constant distance at the indicated times.



1.1.2 Structural biomechanics

One of the most critical challenges for regenerative medicine is the *in vitro* recreation of a similar structure to cartilaginous tissue; the absence of fast and economical techniques for

the construction of 3D fibrous scaffolds, with precise anisotropic properties, encouraged the development of composite materials suitable for these applications. Thus, the use of new biomaterials in tissue engineering aims to regenerate and restore damaged human organs and tissues by using biocompatible supports that can mimic native tissues.

Currently, the use of biodegradable and biocompatible synthetic polymers has been widely explored for applications in the area of prostheses. Its clinical application is widely used as polymeric membranes, as they present different levels of flexibility, which is an essential characteristic for cutaneous implantation.

According to the characteristics of different tissues, PCL can be modified by changing its functional groups or combining its monomers with other materials in order to improve the physicochemical, mechanical, and biological properties of the polymer, allowing the scaffolds to achieve the requirements of different engineering and regenerative medicine tools [47]. For example, PCL microspheres suspended in a carboxymethylcellulose gel, after injection at the site of action, acted as a collagen stimulator with an immediate volumizing effect, contributing to the creation of a unique 3D structure, demonstrating potential for aesthetic applications [48]. Also, multifunctional PCL/silver nanoparticles (NP) scaffolds also showed cytocompatibility and interconnected porous structure with well-defined mechanical and antibacterial properties, with potential use in bone tissue engineering [49].

Wounds and implanted tissues are commonly harmed by circulatory problems and insufficient angiogenesis. Oxygen release scaffolds composed of PGS/PCL/NP of calcium peroxide were developed and characterized with the aim to solve this oxygen supply deficiency in patient-derived bone-marrow-derived mesenchymal stem cells (BM-MSCs). The results revealed a significant improvement of cellular metabolic activity due to alleviation of hypoxic environment around primary BM-MSCs in addition to inhibiting the growth of bacterial pathogens associated with surgical infections. The results pointed out these scaffolds as potential tools for diverse applications in tissue engineering, especially in ischemic conditions and wound-healing [38]. Scaffolds obtained by the electrospinning of polyglycolic acid (PGA) seeded with human dermal fibroblasts showed versatile properties when exposed to mechanical circumferential stretching; when combined with a biomimetic culture system, the scaffolds were also suggested as efficient tools for vascular graft applications [50].

According to Zeng et al. [51], hybrid silk-based scaffolds reinforced with porous PLLA microspheres with a multi-hierarchical porous structure showed good performance in promoting chondrogenesis for auricular cartilage regeneration, being considered promising in areas related to plastic surgery. In turn, PLLA membranes obtained by the modified diffusion-

induced phase separation method, which controls the surface morphology and membrane permeability, responded to the pro-inflammatory stimulus, showing a promising potential for application in lung tissue engineering [52]. Regarding the results obtained by Babilotte et al. [53], porous 3D scaffolds obtained by mixing medical grade PLGA copolymer with hydroxyapatite NP showed biocompatibility, limited inflammatory reaction, and relevant response for bone tissue engineering applications.

1.1.3 Antimicrobial activity

PLA-based antimicrobial materials have received considerable attention as promising systems to control microbial growth [54]. For example, PLA-based functional films containing curcumin exhibited excellent UV barrier properties, antioxidant activity, and discrete antibacterial activity, being suggested as active food packaging [55]. It is possible to consider that the development of materials based on PLA, with antimicrobial agents incorporated, depicts new perspectives to the food industry with the emergence of the next generation of ecological packaging materials that prolong the shelf life of food, thus ensuring consumer health. Additionally, PLA-based antimicrobial systems can also be used in drug delivery systems or other biomedical applications due to properties associated with dose-dependent side effects and reduction of antimicrobial resistance phenomena [54].

PLGA/TiO₂ scaffolds showed a high antibacterial effect (100%) against *E. coli* strains [56]. Linezolid-loaded PLGA fiber mats also demonstrated antibacterial activity, in this case against methicillin-resistant *S. aureus*, when a 37-fold lower dose of the antibiotic was evaluated in infected rats with prosthetic implant after bone fracture [57].

PCL fibers containing copper oxide NP, which are simple and inexpensive to prepare, were shown to be suitable as an antifungal dressing [58]. PCL nanofibers with adsorbed resveratrol nanocrystals also showed effective antimicrobial activity against *Propionibacterium acnes*, thus suggesting its advantage in the preparation of dermal patches [59].

1.1.4 Drug delivery

Smart drug delivery systems have promising potential for clinical applications and provide well-controlled designs for combination tissue engineering and pharmaceuticals. For example, MPEG/PCL microspheres loaded with bone morphogenetic protein-2 showed high biocompatibility, strongly induced osteogenesis, and sustained drug release (with statistical activity) *in vivo*, demonstrating beneficial therapeutic effects for treated patients [60]. PDLLA-PEG-PDLLA-based hydrogel containing different drugs (bevacizumab – antiangiogenic - and

doxorubicin -anticancer) proved to be efficient in tumor suppression for up to 36 days without damage to vital organs, demonstrating to be a promising efficient strategy for a local and sustained chemotherapy [61].

Another successful drug delivery system for cancer treatment was developed with thermosensitive PLGA – PEG – PLGA hydrogels containing corilagin and chitosan [62]; furthermore, photothermally driven biodegradable nanomotors based on PEG-PDLLA coated with gold were able to penetrate tumor tissues, allowing the active transport of molecules or macromolecules, either by encapsulation or co-delivery, that is, offering opportunities for their application in tissue penetration and drug delivery [34].

2 CONCLUSION

Biodegradable synthetic polymers have contributed immensely to solving health-related problems in recent years. Actual, efficient, and consistent results have been introduced in the market as a result of the growing search for new technologies. They have been applied both at macro and nanometer scales, in isolated and conjugated forms, or even as encapsulating matrices. Also, as they present longer degradation periods when compared to natural polymers, they stand out in tissue engineering since they can be adjusted according to their composition, reaching various degrees of selectivity for specific clinical applications.

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