Importance of Poly(lactic-co-glycolic acid) in Scaffolds for Guided Bone Regeneration: A Focused Review

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Total or partial tissue damage and loss of function in an organ are two of the most serious and costly issues in human health. Initially, these problems were approached through organ and allogenic tissue transplantation, but this option is limited by the scarce availability of donors. In this manner, new bone for restoring or replacing lost and damaged bone tissue is an important health and socioeconomic necessity. Tissue engineering has been used as a strategy during the 21st century for mitigating this need through the development of guided bone regeneration scaffold and composites. In this manner, compared with other traditional methods, bone tissue engineering offers a new and interesting approach to bone repair. The poly-α-hydroxy acids, which include the copolymers of lactic acid and glycolic acid, have been used commonly in the fabrication of these scaffolds. The objective of our article was to review the characteristics and functions of scaffold with biomedical applications, with special interest in scaffold construction using poly(lactic-co-glycolic acid) polymers, in order to update the current methods used for fabrication and to improve the quality of these scaffolds, integrating this information into the context of advancements made in tissue engineering based on these structures. In the future, research into bone regeneration should be oriented toward a fruitful exchange between disciplines involved in tissue engineering, which is coming very close to filling the gaps in our ability to provide implants and restoration of functionality in bone tissue. Overcoming this challenge will provide benefits to a major portion of the population and facilitate substantial improvements to quality of life.

Key Words: biopolymers, scaffold, PLGA, GTR, GBR, bone, regeneration, biomaterial

Introduction

Over the course of the past 30 years, the demands for biodegradable polymers for biomedical and pharmaceutical fields of application have increased considerably because of the notable improvements in the quality of these polymers.[1]

Tissue engineering has revolutionized the direction of orthopedic research, reorienting this field toward new materials with improvements on the nanometric scale, elaborating scaffolds that mimic the structural properties of the original tissues and provide stable support for the extracellular matrix.[2–4]

The current concept encompassed by the term *biomaterial* is any material, not necessarily biological in nature, that is tolerated by the organism and, as such, that could be used as a scaffold or induce a process of repair in order to achieve *restitutio ad integrum* of the damaged tissue.

This implies that the damaged tissue is replaced by another healthy tissue of identical characteristics, such that the final result is the original tissue and not a scar tissue that provides only reduced functionality and cannot restore the lost function.

The techniques elaborated for this purpose fall within the field of guided tissue regeneration (GTR) and are usually applied through the implantation of biocompatible or biodegradable scaffold for improved regeneration.[5,6]

In the case of odontology, this ability to improve bone regeneration through the implantation of these scaffolds is of major clinical applicability and importance.[5] The new strategies for bone regeneration made possible by tissue engineering[6] necessarily require the development and optimization of new biomaterials that are capable of fulfilling the ever-growing needs for morphological and functional repair.

The aim of our study was to review the characteristics and functions of scaffold for the biomedical field, with special interest in those derived from poly(lactic-co-glycolic acid) (PLGA) polymers, in order to update and modernize the current techniques used to produce and improve these scaffolds, integrating this with the advances made in tissue engineering based on these structures.

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Scaffold Functions and Characteristics

The primary function of scaffolds is to allow cells to join within and without the structure, as well as to facilitate the

proliferation and differentiation of cells. They also provide an environment in which cells can maintain their phenotype and synthesize all necessary molecules and proteins. The basic characteristics that all materials use to create the scaffold include high porosity, maximum surface area, superficial rigidity, specific 3-dimensional form, and biodegradability.

Since one of the primary functions of the scaffold is to direct cell growth, whether of the adjacent tissues or of cells seeded within it, the material must provide adequate cell adhesion and, in some cases, favor cell migration.

The porous structure provides the implanted material with two essential functions: first, the pore canals provide entry ports for cell migration; second, they provide maximum area for interactions between numerous specific cells.[7] For this reason, these characteristics will be explored more in depth in later sections.

The scaffold can be fabricated from polymers, metals, ceramics, or composite materials. The techniques used to manufacture the scaffold depend on the properties of the material used and the final application, and it is important to know into what type of tissue the scaffold will be implanted, since this will determine the type of structure needed.

Normally, the scaffold is constructed of biodegradable materials so that it can be integrated into the host tissues and eventually be absorbed by the patient's body. Biodegradability allows for gradual and ordered replacement of the scaffold by functional tissue and also prevents the development of adverse responses (which are almost always chronic in nature) that arise from the artificial structures. In addition, the scaffold can be created to liberate active biological agents into the host tissue, for example, growth factors or genes. The material can also have intrinsic biological activity (which allows for a migration reaction or specific proliferation of neighboring cell populations). These are known as *nanocomposite enhancers*.

In addition to these characteristics of cell interaction, the structures also have specific physical properties: mechanical properties for specific tissues, macromolecular permeability, protein attraction or repulsion, tissue adhesion or lubricity, and facilitation of cell processes.[8]

These characteristics have produced the current availability of a wide range of applications for biopolymers used in the fabrication of scaffolds for biomedicine (Table 1).

Polyglycolic Acid, Polylactic Acid, and PLGA: Materials for Scaffold Construction

Several different types of biocompatible materials can be used to build the scaffold. In general, the most frequently used are polymers, and of these, biodegradable polymers are the most common, since these are gradually absorbed by the host body over an appropriate time scale.

When the ultimate goal of the intervention is restoring structure and function of the tissue architecture, the scaffold is considered to be a temporary support structure. Scaffold created from biodegradable polymers provides a cell support framework until the surrounding cells are capable of secreting their own extracellular matrix. In this manner, the ability to harmonize the velocity of degradation of the support structure, such that different profiles of consistency and properties are established during the progression of the recovery process, can vastly broaden the applications of the scaffold (Table 2).

Because of the wide variety in types of target tissues, the possibilities for different types of scaffold microstructures, and the techniques required, it is unlikely that a simple polymer could be sufficiently appropriate for the requirements of each tissue system. As such, a wide variety of polymers are under evaluation for application in tissue engineering, as well as new or modified materials that are under constant development, such as α-polyhydroxy acids and their derivatives.[9]

The first biodegradable polymers developed for the field of bioengineering, and the most commonly used currently, are those obtained from polyglycolic acid (PGA) and polylactic acid (PLA), which have been incorporated into a multitude of uses in the medical industry, starting with the biodegradable sutures that were first introduced in 1960. A study was published in 1990 explaining the principles of GTR for alveolar bone regeneration, in which researchers were already using barriers to prevent the appearance of recolonization by neighboring cell types foreign to bone tissues in the zone under treatment.[10,11]

The goal of tissue engineering is to overcome the limitations of conventional treatments based on organ transplantation and implantation of biomaterials in order to produce a source for artificial organs that are tolerated by the immune system and can replace native tissues and continue to mature and grow with the patient's body. Since then, several types of materials based on PGA and PLA have been developed in the form of copolymers, with a variety of uses as biomedical materials. The goal of these implants is to facilitate the permanent repair of damaged organs and tissues, without the need for supplemental therapies that can elevate the long-term costs of treatment. The use of this methodology could help mitigate many of the issues related to other types of techniques, such as second interventions that are costly and painful for extracting nonreabsorbable materials, interventions for extracting tissues for autografts, the scarce availability of organ donors, graft rejections (in the case of allografts), and the risk of infection and formation of fibrous tissue (associated with permanent implants).

We are currently in the development and utilization phase of the third generation of biomaterials. Materials designed in this generation are aimed at interacting in a specific manner with the host tissue through cellular and molecular stimuli and at combining properties of absorbability and biological activity within the same material. With each new development, we come closer to the ideal biomaterial.

Scaffold Fabrication From Biopolymers

Porous polymeric structures can be obtained through several different methods. Each technique for elaborating these materials confers different structural characteristics to the final scaffold, which requires careful selection of the appropriate material for the final mode of application.[12–14]

Some of the most commonly used fabrication methods today include gel casting, particle dissolution and release, membrane lamination, phase separation, gas saturation, high-pressure foamed particle release, lyophilization, fiber bonding, and 3-dimensional printing.

TABLE 1

Main applications and functions of biopolymers for biomedical scaffold

Biopolymers	Applications
Synthetic, nondegradable polymers	
Polymethyl methacrylate	Bone cement, artificial teeth, intraocular lenses
Polymethyl hydroxyethylmethacrylate	Soft contact lenses
Epoxies	Protective materials, fiber composites
Fluorocarbons	Vascular grafts, catheters, and periodontal and abdominal patches
Hydrogels	Catheters and anti-adhesives
Polyacetals	Heart valves, structural components
Polyamides	Sutures
Polyamide elastomers	Catheters and wound covers
Polycarbonates	Oxygenation and hemodialysis membranes, connectors
Polyesters	Vascular grafts, angioplasty balloons, sutures, and hernia repair
Polyester elastomers	Catheters
Poly-etheracetones	Structural components and orthopedics
Polyamides	Structural components and catheters
Polymethylpentene	Protective materials for extracorporeal devices
Polyolefins	Sutures, angioplasty balloons, catheters, syringes
Polyolefin elastomers	Tubes, artificial hearts, catheters
High crystalinity polyolefin films	Angioplasty balloons
Polysulfones	Structural components and orthopedics
Polyurethanes	Catheters, artificial hearts, vascular prostheses, wound covers, and blood-compatible coatings
Polyvinyl chloride	Blood bags and tubes
Silicones	Plastic surgery implants, catheters, heart valves, oxygen-permeable membranes, facial prostheses, and ear prostheses
Ultra-high-molecular-weight polyethylene	High-resistance tissues
Styrene and acrylonitrile copolymer (SAN)	Breast prostheses
Polystyrene	Diagnosis kits, disposable laboratory materials
Polyacrylonitrile	Dialysis membranes
Bioabsorbable	
Poly-amino acids	Controlled release, cell adhesion peptides
Polyanhydrides	Controlled release
Polycaprolactones	Sutures and controlled release
Lactic acid and glycolic acid copolymers	Sutures, controlled release, bone discs
Polyhydroxybutarates	Controlled release, bone discs
Polyorthoesters	Controlled release
Collagen	Tissue reconstruction and coatings
Biologically derived macromolecules	
Cross-linked albumin	Coatings for vascular grafts and a contrast dye for ultrasound
Cellulose acetates	Hemodialysis membranes
Copper ammonia cellulose	Hemodialysis membranes
Cytosine	Coatings and controlled release
Collagen	Coatings and hybrid organs
Elastin	Coatings
Cross-linked gelatin	Coatings for artificial hearts
Hyaluronic acid	Coatings, anti-adhesives, ocular and auricular anti-inflammatory agents
Phospholipids	Liposomes
Silk	Sutures, experimental silk protein coatings
Passive coatings	
Albumin	Thrombo-resistance
Alkyl chains	Absorbs albumin for thrombo-resistance
Fluorocarbon	Reduces catheter chaffing
Hydrogels	Reduces catheter chaffing
Silica-free silicones	Thrombo-resistance
Silicone oils	Lubrication for needles and catheters
Bioactive coatings	
Anti-coagulants (eg, heparin)	Thrombo-resistance
Antimicrobials	Resistance against infection
Cell adhesion peptides	Improves cell adhesion
Cell adhesion proteins	Improves cell adhesion
Tissue adhesives	
Cyanoacrylates	Microsurgery
Fibrin glue	Coatings for vascular grafts and microsurgery

Table 2

Time to degradation of the primary polymers used in biomedical research

Polymer	Time to Elimination, mo
D-lactic polyacid	12–16
L-lactic polyacid	18–24
Poly(lactic-co-glycolic acid)	6–12
Polycaprolactone	18–24
Polyglycol	2–4
Polyhydroxybutarate	18–24
Phosphate polyester	12–24
Polyorthoester	12–24
Alkane polyanhydrides	0.2–4
Aromatic polyanhydrides	6–12
Gelatin	0.2–1
Oxidized cellulose	0.2–1
Collagen	0.2–1
Pseudo-poly-amino acids	2–24
Polyaminocarbonates	4–12
Polyphosphazenes	6–18
Polyprophylene fumarate	12–24

Whereas PLA-PGA polymers have been used primarily with bone and cartilaginous tissue, other polymers have been applied in other tissue types (polyanhydrides: controlled medication release and bone scaffold; polyorthoesters: controlled medication release; polycaprolactone: biodegradable devices for structural fixation; polycarbonate: fixation devices, bone scaffold, controlled medication release; polyfumarate: bone scaffold, etc).

Reinforcement

In most scaffold applications, the polymeric portion is supplemented with an inorganic component. Three fundamental reasons exist for the addition of an inorganic factor as a facilitator for establishing the polymeric matrix as a substrate for tissue engineering:

- The incorporation of this second phase modifies the mechanical properties of the material, bolstering the structural integrity of the scaffold.
- The inorganic component increases the bioactivity of the polymer.
- The inorganic component can also positively affect the degradation pattern of the polymer.[9]

Some of the most commonly used and well-known compounds for tissue engineering and their reinforcing inorganic components include hydroxyapatite and calcium nitrate for polycaprolactone; hydroxyapatite, tricalcium phosphate, and nanohydroxyapatite for poly-L-lactide; bioactive crystals and calcium nitrate for PLA; tricalcium phosphate and calcium phosphate glasses for chitosan; carbonated apatite and calcium nitrate for PGA; bioactive crystals for PDLA; and nanohydroxyapatite for collagen.

Porosity and pore size

As we have seen, the scaffold constructed using PLGA and its reinforcing materials are usually used for integration into bone tissue. Scaffold for osteogenesis must mimic bone morphology, structure, and function in order to optimize integration into the implanted bone tissue. In this sense, the porosity of the material and pore size play a critical role in in vitro and in vivo bone formation.

Bone tissue has a trabecular morphology with 50%–90% porosity. The pores are necessary for the formation of bone tissue, since they facilitate migration and proliferation of osteoblasts and mesenchymal cells, as well as vascularization. In addition, a porous surface improves mechanical interlocking between the implanted biomaterial and the natural surrounding bone tissue, providing better mechanical stability at this critical interface.

Porosity is defined as the percentage of empty space within a solid and is a morphological characteristic that differs with each type of material. This variable, total porosity (P), is measurable through gravimetry. The minimum pore size required for regenerating mineralized bone is generally considered to be approximately 100 μm, although it has been shown that osteogenesis is best at pore sizes greater than 300 μm, since this facilitates better vascularization and oxygenation of the tissues. A smaller pore size (75–100 μm) provokes internal demineralization, and at even smaller sizes (10–44 μm and 44–75 μm), the structures become blocked by fibrous tissue.

Pore sizes and densities within the scaffold can be controlled by modifying temperature and time intervals in the fabrication of solvents, as well as by varying the density and viscosity of polymer solutions.[15]

The most commonly used techniques for establishing a set porosity in a biomaterial are based on the material used for constructing the scaffold: sintering, phase transformation, salt leaching, freeze drying, gas foaming, or cross-linking.

Main nanocomposite enhancers

To promote optimal osteointegration, and above all in the case of membranes, researchers have explored modifications that do not affect the internal structure of the biomaterials but that modify their surfaces.

These modifications include coating with inorganic layers of metallic oxides with potentially bioactive properties in an attempt to create surfaces capable of forming a direct chemical bond between the biomaterial and the native bone (active fixation, equivalent to the concept of osteointegration used for the first time by Branemark to describe the behavior of titanium dental implants in contact with native bone).

Most of the processes used to incorporate these nanocomposite enhancers take place at room temperature and so do not affect the integrity of the polymeric membrane. Intermediate treatments with oxygen plasma are also used to promote cell contact with the biological polymer and to modify its degradation coefficient.[16]

Currently, a variety of functionalizations are in use for favoring induction of osteoblasts in the area of surgical insertion, so as to facilitate the synthesis of mineral materials and regenerate the bone defect with newly formed autologous bone.

Some of these modifications or improvements to the scaffold surface based on extracellular signaling, regulation, metabolism, proliferation, differentiation, and function in bone regeneration that are currently being studied are shown in Table 3.[15–19]

TABLE 3

Main nanocomposites used for providing functionality to biopolymer scaffold*

Growth Factors: TGF-b, PDGF, BDGF, VEGF, hsGF, FGF, IGF	Collagen, Hyaluronic Acid, Calcium, Chitosan, Hormones: PTH, Vitamin D_3
Proteins: BMP, osteogenin Peptides: RGD	β-TCP
Gene fragments, anti-tumor agents, activators, inhibitors, and RNA_i	Metallic oxides TiO_2, SiO_2; HA

*TGF-b indicates transforming growth factor beta; PDGF, platelet-derived growth factor; BDGF, bone-derived growth factor, VEGF, vascular endotelial growth factor; hsGF, heparin sulfate growth factor; FGF, fibroblast growth factors; IGF, insulin-like growth factor; BMP, bone morphogenetic protein; RGD, arginylglycylaspartic acid; PTH, parathyroid hormone; TCP, tri-calcium phosphate; HA, hydroxyapatite.

PLGA structural designs based on macroscopic morphology

Several different macroscopic designs have been applied in PLGA for the fabrication of scaffold, which primarily involve 2-dimensional membranes (which can be created through creating fiber networks, carpets, or meshes, through a layer network or through porous structure), 3-dimensional discs and cylinders, and 3-dimensional spheres.

Two-Dimensional Membranes

These are fine-scale scaffold layers structured in micro/nano-metric-dimensional fibers. These fibers, linked to form sheets, establish a substrate that favors cell growth and adhesion and are created through nanotechnological methods based on the use of cold plasma and magnetron sputtering, among other advanced techniques. One example of this type of structure is shown in Figure 1 and Figure 2.

Three-Dimensional Discs and Cylinders

These are polylactic cylindrical masses for filling preimplant bone cavities. The size and curvature of the structures depend on the area of application.

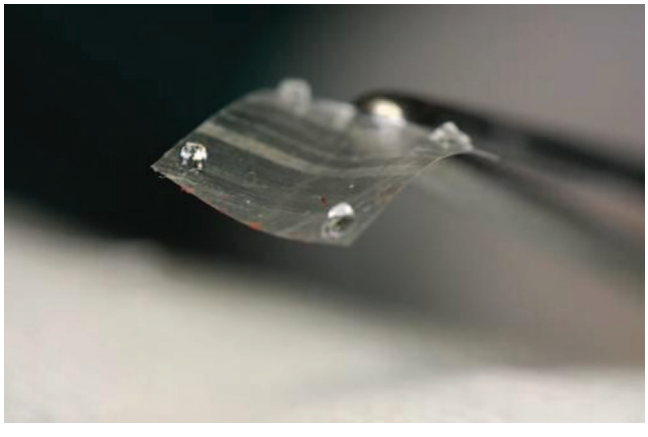

FIGURE 1. Two-dimensional membrane fabricated using poly(lactic-co-glycolic acid).

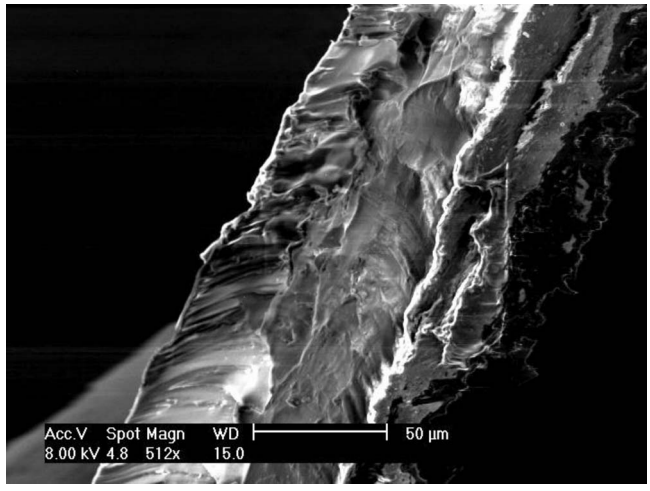

FIGURE 2. Cryofracture of a two-dimensional poly(lactic-co-glycolic acid) membrane showing its internal structure.

Three-Dimensional Spheres

In recent years, there has been an increase in the use of PLGA polymers in the form of injectable microspheres. These microspheres are homogeneous, and during the process of degradation, when placed in contact with body fluids, they are capable of producing smaller polymer fragments. The benefits of this system are increased biocompatibility along with excellent reproducibility both in terms of microencapsulation processes and in the release of active compounds.

Using this system, researchers have elaborated an injectable contraceptive that contains steroid-filled microspheres. In cases such as luteinizing hormone, very positive results have been obtained, since low-molecular-weight polypeptides are extremely stable in the presence of copolymers and their residues from bioerosion.[9]

Certain issues have arisen in other uses involving the release of certain proteins, peptides, and antigens. For example, in the case of materials containing growth hormone, a notable loss of activity occurs after only a few days, which is attributed to interactions between the polymer and the hormone.

DISCUSSION

Total or partial tissue damage and loss of organ function are two of the most serious and costly problems for human health. Initially, these problems were approached through allogenic tissue and organ transplantation. However, this option is severely limited by the scarce availability of donors.[2,20–23]

The need for new bone for restoring or replacing lost and damaged bone tissue is an important clinical and socioeconomic concern, and tissue engineering has produced strategies for furnishing these components during the 21st century through the use of scaffold and composite materials for guided bone regeneration (GBR).[24]

The development of biopolymers has constituted a major scientific and technological advancement for the field of medicine by facilitating improvements over conventional treatment strategies. In the field of clinical biomedicine,

biopolymers such as PLGA and its functionalized derivatives are under development for a wide array of applications in biomedical research to combat issues of high demand and global morbidity rates, in addition to GTR and GBR.[12,13,16,25,26]

The family of poly-α-hydroxy acids, which includes the copolymers of lactic acid and glycolic acid, have been integrated into the creation of scaffold for use in the release of steroids, anticancer agents, peptides, proteins, antibiotics, anesthetics, and vaccines, as well as for scaffold used in the process of bone repair.

The requirements for scaffold used in GBR are very complex, since these must involve precise values for a multitude of variables necessary for proper functioning of the material within the implanted bone tissue and for ensuring proper functioning for the designed purpose.[6]

One of the developments that we will see in the future will be antibiotic and drug release by polymeric scaffolds. This can improve notably the results of the healing processes, because it can prevent and control infections that might interfere in regeneration. This is interesting especially in patients with a predisposition to these kind of complications: smokers, patients with diabetes mellitus, and so on.[27,28]

Research into bone regeneration must be oriented toward a fruitful exchange between the scientific disciplines involved in tissue engineering, a partnership that is coming very close to combating effectively the issues in implantation and restoration of functionality in bone tissue. Overcoming this challenge would signify incredible benefits to a large portion of the world's population and an enormous improvement to patient quality of life.[19,29,30]

Abbreviations

GBR: guided bone regeneration
GTR: guided tissue regeneration
PGA: polyglycolic acid
PLA: polylactic acid
PLGA: poly(lactic-co-glycolic acid)

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