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Abstract

This review covers the development of bioresorbable polymeric composites for applications in tissue engineering. Various commercially available bioresobable polymers are described, with emphasis on recent bioresorbable composites based on natural and synthetic polymers. Bioresorbable polymers contain hydrolyzable bonds, which are subjected to chemical degradation via either reactive hydrolysis or enzyme-catalyzed active hydrolysis. For synthetic polymers, chemical hydrolysis is the most important mode of degradation. The degradation rate can be controlled by varying the molecular weight and crystallinity. Examples of bioresorbable polymers are: polyurethane, poly(D,L)lactide, poly(lactic-co-glycolic) acid, poly(α-hydroxy acids), cross-linked polyester hydrogels, poly(orthoesters), polyanhydrides and polyethylene glycol.

Keywords

Biodegradable polymer; bioresorbable; tissue engineering; composite

Introduction

One of the most frequent and devastating problems encountered in medicine is major injury or degeneration to various tissues or organs. Therapeutic approaches to replace or regenerate tissue using allografts, xenografts, autografts or implantation of biomedical devices have clear limitations, including donor availability, susceptibility to infection, poor integration, and potential rejection of the implant[[1]]. Nowadays, regenerative medicine includes different strategies for the creation of new or replacement tissue, including the cloning of isolated cells, fabrication of non-cellular structures, and biological constructs containing living cells. The latter approach, is usually referred to as tissue engineering (TE), and is regarded as highly promising for tissue regeneration.

Tissue engineering is a multidisciplinary field incorporating the principles and applications of engineering combined with biological sciences, in order to be able to replicate the structure-function relationship between the natural patient tissue and the laboratory-produced replacement tissues. This involves a combination of physical and chemical factors that aim to maintain tissue stability, improve the function of impaired tissue, or replace the biological function of lost or damaged tissue[[3]]. The term "tissue engineering" in its modern form was first introduced in 1985 by Fung in a proposal to the National Science Foundation[[6]]), and began to be used in 1988 by Vacanti et al.[[7]]. Recent advances in tissue engineering have been designed to overcome the limitations of conventional methods of repairing damaged tissue[[8]]. The overall goal is to construct replacement organs and tissues that can integrate, survive and grow within the recipient after the transplant. This would provide a permanent solution for the repair of damaged tissues, so that the need for continuing maintenance is avoided, and the cost of treatment could be greatly reduced[[11]].

Tissue engineering has been used to repair many different tissues, such as bone, cartilage, blood vessels and skin. Tissue requires the correct structural features and mechanical properties in order to fully perform its function. For example, in order to allow cells to survive and proliferate in

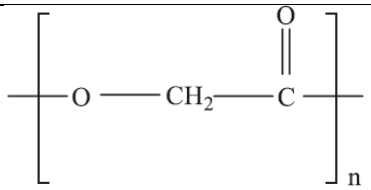
reconstructed tissue, it is necessary to recreate the complete three-dimensional environment that exists within the body (*in vivo*), by manipulating external conditions (*ex vivo*). To achieve these aims, the cells that will eventually form the replacement tissue are grown on scaffolds in the laboratory. These scaffolds are designed to mimic the naturally occurring extracellular matrix by using a porous material that encourages the adhesion and migration of the cells. An alternative approach, that does not require a permanent implant, is to implant scaffolds constructed from biomaterials that are biodegradable, and can be resorbed into the body when they have served their purpose[[12]].

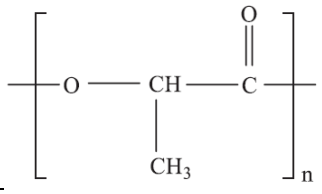
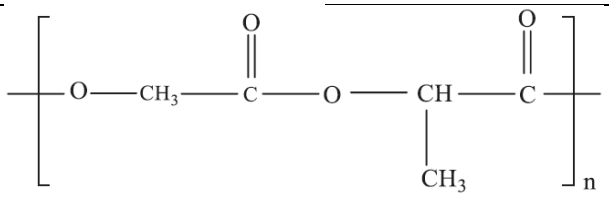
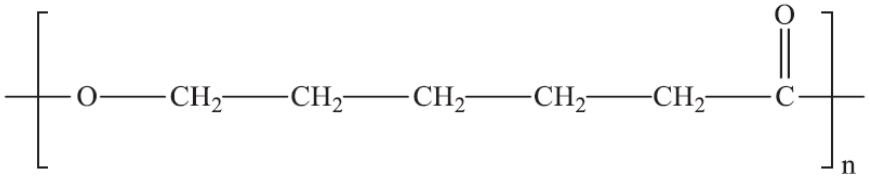
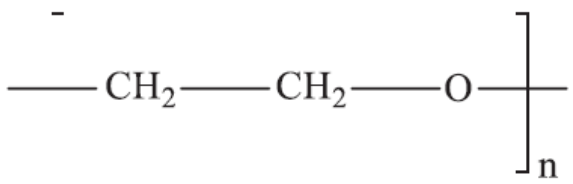
Biomaterials are compounds derived from natural or artificial origins (or a combination of both), which are used inside the human body. With the advancement in synthetic procedures, biomaterials, such as suture yarns, bone plates, replacement joints, heart valves, intraocular lenses and many more, are now widely used to replace and or restore the function of damaged tissue or organs. These implants help to repair, improve performance, correct and eliminate structural disorders, and thus improve the patient's quality of life. Currently, biomaterials used within the body can be divided into different types: metals, polymers, ceramics and composites. Biomaterials should above all, be biocompatible; in other words, the effect of the natural body environment on extraneous materials should not produce any toxic by-products or any excessive inflammatory or fibrotic reaction. For many years, researchers have been searching for materials that, after having served their purpose, are completely removed and absorbed by the body[[16]].

Among the various materials that have been investigated as implanted scaffolds, about 90% are based on polymeric materials. The relatively straightforward manufacturing process of these polymers, as well as the lower Young's modulus of these materials relative to metals, has favored their application. Polymers can provide a better transfer of tension to the bone surface, better repair of bone, and a longer useful life[[20]]. Polymers in general are divided into two classes: natural and synthetic materials. The best biomaterials derived from natural polymers are collagens, alginate and chitosan. Synthetic polymers can be further divided into two groups, non-biodegradable and biodegradable.

Biodegradable polymers are regarded as desirable in tissue engineering to avoid additional surgery for removal of the implants or scaffolds (Table 1). Due to the degradation of biodegradable materials over time, the cells continuously penetrate into the matrix where they produce structural proteins such as collagen and elastin that gradually replace the degradable materials. Vert et al.[[21]] classified biodegradable polymers into three different groups according to their properties and biomedical applications:

Table 1. Chemical structures of biodegradable polymers.

Polymer	Chemical structure
PGA	

PLA	
PLGA	
PCL	
PEG	

I. **Biodegradables** are solid polymeric materials that are broken down in the body to produce macromolecular degradation products, without being completely removed. One example is polyurethane. (This definition excludes environmental, fungal or bacterial degradation).

II. **Bioresorbables** are solid polymeric materials that undergo bulk degradation and are completely resorbed *in vivo*. The polymers are eliminated through excretion of degradation by-products, or after their further metabolization. Bioresorption reflects total elimination of the initial foreign material and of the degradation by-products (low molecular weight compounds) with no residual material remaining. One example is poly-D,L-lactide.

III. **Bioerodibles** are solid polymeric materials that undergo surface degradation that continues uninterrupted until the material is totally eliminated. Bioerosion also reflects total elimination of the initial foreign material and of the surface degradation by-products (low molecular weight compounds) with no residual material remaining. The principal types of erodible polymers include poly(α-hydroxy acids), crosslinked polyester hydrogels, poly(orthoesters), polyanhydrides.

IV. **Bioabsorbables** are solid polymeric materials, which can slowly dissolve in body fluids without any cleavage of the polymer chain, or any decrease in the molecular mass. One example is polyethylene glycol[[23]]. A bioabsorbable polymer can also be bioresorbable if the dissolved macromolecules are excreted[[26]].

Many of the scaffolds used in bone tissue engineering are composed of composite materials based on polymers. Composites contain two or more components that when used in combination, compensate for the deficiencies of each one used alone. This is appropriate in that all the hard tissues in the human

body, except perhaps tooth enamel, can be regarded as composite nanostructures. The resorption rate of the composite materials in the body should match the formation rate of new tissue. The composite should also have improved mechanical properties compared to either polymer used alone, providing better structural integrity and flexibility than brittle ceramics[[29]].

Here we provide a comprehensive review of bioresorbable composite polymeric materials for tissue engineering, including the mechanisms of biodegradation, design strategies, and covering recent progress on the types of bioresorbable polymers and their applications in tissue engineering.

Bioresorbable polymers

Bioresorbable polymers were first used as bioresorbable suture threads to replace non-absorbable sutures used in surgery. Bioresorbable polymers have now been used for a wide range of applications, such as arterial stents[[31]], screws for bone repair[[32]], drug delivery[[26]], and guided tissue regeneration[[33]]. The breakdown of bioresorbable polymers can be accomplished by simple chemical hydrolysis of the bonds connecting the monomeric units, or by enzyme-catalyzed degradation that occurs in the body over time. The long polymer chains are split into monomers or oligomers, which are then are excreted from the body or further metabolized through biochemical pathways.

Three broad strategies have been adopted to stimulate the formation of new tissues: (1) use of autogenous cells directly injected into the damaged site; (2) tissue culture on matrices for subsequent implantation to replace damaged tissues; or (3) use of implantable substances that induce the regeneration of damaged tissue[[34]]. Bioresorbable polymer composites should possess the correct intrinsic properties for tissue regeneration; chemical structure and composition; hydrophilicity or hydrophobicity; crystalline/amorphous ratio; the initial molecular weight. Physical factors, structural factors, and environmental conditions, such as pH and enzyme activity, also influence the degradation rate[[36]]. Most bioresorbables are fabricated from biomaterials such as chitosan, collagen, aliphatic poly(esters), poly(anhydrides), poly(orthoesters), poly(amides), poly(aminoacids), and poly(phosphazenes). These polymers are attractive due to their availability and ease of manufacture for tissue engineering applications, along with their chemistry and rigid/elastic properties depending on the required application. The family of aliphatic poly(esters) are the most studied biodegradable polymers in biomedical applications due to their lower toxicity and better biocompatibility. These include poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA) copolymer[[38]].

Degradation of bioresorbable polymers

Degradation is a process whereby polymer chains are broken down by hydrolysis into oligomers and eventually to monomers. Erosion may occur at the surface, or degradation may occur throughout the bulk polymer. The penetration of water into the polymer matrix initates the degradation process. The erosion of polymers is carried out in two ways (Figure 1): (a) bulk erosion, where diffusion of water into the matrix is faster compared to hydrolysis; and (b) when water uptake is slower than hydrolysis, then erosion mainly occurs at the matrix surface[[40]]. Increasing the polymer molecular weight (with more covalent bonds) will increase the time required for resorption/degradation. Bioresorbable polymers contain hydrolyzable bonds thats are subject to chemical degradation, via either chemical hydrolysis reactions or enzyme-catalysed hydrolysis[[42]]. Passive hydrolysis is more likely to occur in amorphous

regions of polymers compared to crystalline regions. Bioresorbable polymers allow the polymer to be completely eliminated from the body either via metabolism (to CO_2 and H_2O), or because the oligomers are degraded to a size allowing the products to be excreted via the kidneys. Moreover, degradation should occur via producing the least toxic products, that can be metabolized and cleared from the body[[43]].

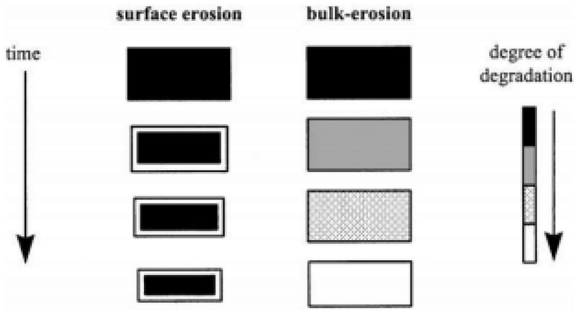


Figure 1. Schematic illustration of degradation by surface erosion or bulk erosion in a polymer matrix [[40]]. Copyright Elsevier, reproduced with permission.

Bioresorbable composites based on natural polymers

Natural polymers have been used for various TE applications (bone, skin, cartilage, blood vessels, ligaments). The main advantages of natural polymers are their excellent biocompatibility, biodegradability, and that some of them naturally occur in extracellular matrix. They are prepared from biological sources and are therefore suitable for cell adhesion, proliferation and differentiation. The main limitations of these polymers are poor mechanical properties and limited processability, which may hinder their widespread use in clinical applications[[44]].

Natural polymers can be classified on the basis of their origin: (a) polysaccharide based; (b) protein based; and (c) bacterial polyesters [e.g., polyhydroxyalkanoate (PHA)][[45]]. Polysaccharide-based polymers (e.g., chitosan, starch, alginate, hyaluronic acid, dextran) have advanatges, such as nontoxicity, good hemocompatibility, good interaction with cells, and lower cost compared to other biopolymers, such as collagen, thereby justifying their use as scaffold materials for TE applications. Protein-based polymers, namely collagen, gelatin, fibrin, and elastin have been widely investigated as potential materials for cell delivery in TE. Animal-sourced collagen has been used to develop several commercially avilable TE scaffolds. PHAs are another interesting class of biodegradable polymers, which are produced by bacterial fermentation of sugars (as a carbon and energy source) for TE applications. PHAs such as, poly(3-hydroxybutyrate), poly(3-hydroxybutyrate-co-3-hydroxyvalerate), poly(4-hydroxybutyrate), poly(3-hydroxybutyrate-co-3-hydroxyhexanoate), and poly(3-hydroxyoctanoate) have been used to develop resorbable implantable devices, such as adhesion barriers, sutures, and wound dressings, as well as tissue regeneration scaffolds. Collagen and chitosan have been shown to have intrinsic bioactivity, and materials based on these polymers have been used in tissue engineering[[16], [48]].

Among polysaccharides, chitosan has been the focus of many studies because it demonstrates antibacterial activity, biodegradability, biocompatibility, wound healing stimulation properties, bio-adhesive character, large-scale availability, and low cost[[13]]. Shavandi et al.[[51]] fabricated a biocomposite scaffold from squid pen chitosan, hydroxyapatite (HA) and beta-tricalcium phosphate β-

TCP, and examined the physiochemical properties for bone tissue engineering. They showed that in samples with a high percentage of HA/β-TCP, the rate of degradation increased, but also showed better mechanical properties. The scaffold morphology is important for encouraging vascularization and cell proliferation, and pore sizes from 30 to 1000 μm have been reported in the literature to be useful for bone tissue engineering. The Shavandi study indicated that an increase in the HA/β-TCP % led to a reduced pore size, more inhomogeneous pore size distribution, and an overall less homogenous pore structure of the scaffolds. Direct transfer of cells into damaged organs, secure engraftment, and tissue regeneration depend on the scaffold microenvironment and the type of cells.

Nerantzaki et al.[[52]] synthesized N-(2-carboxybenzyl)chitosan (CBCS) composite scaffolds containing different proportions of nanoTiO_2 and bioglass (BG) by a freeze-drying technique. The results of *in vitro* degradation studies showed that the degradation rate of the composite CBCS scaffolds declined significantly after 1 and 3 weeks of immersion in lysozyme solution (compared to pristine CBCS) because the acidic degradation products could be neutralized by alkali leaching out from nanoTiO_2 or BG leading to a reduced degradation rate.

Lowe et al.[[53]] investigated a composite containing fucoidan (a sulfated polysaccharide from seaweed) plus functionalized chitosan-natural nano-hydroxyapatite for its ability to encourage the differentiation of periosteum derived-mesenchymal stem cells (PMSCs) for applications in bone tissue engineering. Fucoidan has been used to improve the adhesion and proliferation of bone cells, and to up-regulate the expression of osteogenic genes such as, bone morphogenetic protein-2 (BMP-2), collagen-1, and osteocalcin. They found that the presence of the nHA groups led to improved cell survival and proliferation within the chitosan-nHA-fucoidan scaffold that could induce the differentiation of stem cells to produce bone minerals.

Bioresorbable composites based on synthetic polymers

Synthetic bioresorbable polymers have some advantages over natural polymers for the development of scaffolds for TE applications: (a) they can be produced using a reproducible method, at a large scale, and at low cost; (b) they are easier to process; (c) they have no risk of immunogenicity; and (d) their degradation kinetics and mechanical properties can be easily tailored for the required application. Their main weaknesses are that, they are less biocompatible than natural polymers, they typically do not present cell recognition sites, and their degradation products are not generally natural metabolites, and might cause problems if accumulated in the organism[[54]]. One of the major classes of synthetic bioresorbable polymers is aliphatic polyesters of poly(a-hydroxy acids). Poly(a-hydroxy acids) such as PGA, stereoisomers of poly(lactic acid) (PLA), poly(L-lactic acid (PLLA) and poly(D-lactic acid), and the poly(lactic-co-glycolic acid) (PLGA) copolymer are the most widely used bioresorbable polymers[[56]].

Bioresorbable polymers based on poly(lactic-co-glycolic) acid (PLGA)

Poly(lactic-co-glycolic) acid (PLGA) copolymer is a blend of polyglycolic acid (PGA) and polylactic acid (PLA) as shown in Figure 2. In recent decades, PLGA copolymer has been used in medical implants within the human body, cell scaffolds, and other tissue engineering materials for the promotion of cell growth and for organ repair[[58]]. This copolymer has some advantageous properties, such as mechanical strength and biocompatibility. Moreover PLGA copolymer degrades by non-enzymatic

hydrolysis, and the degradation products are eliminated from the body in the form of water and carbon dioxide[[60]].

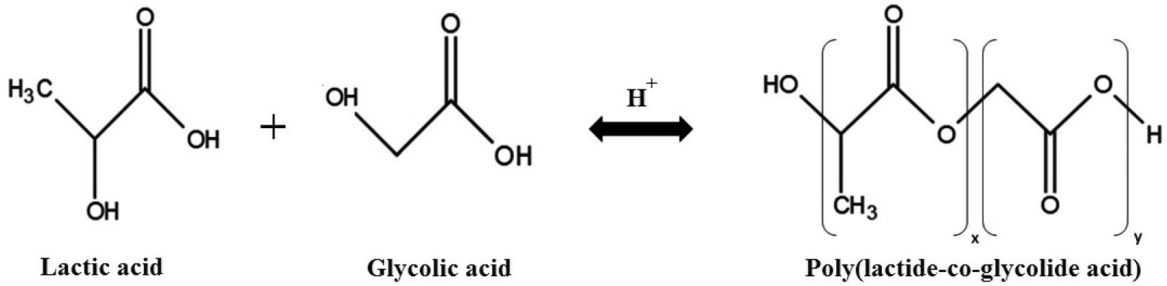


Figure 2. PLA, PGA and PLGA copolymer.

PLGA is used in preparation of skin substitutes because the mechanical properties and degradation rate of this polymer are tunable and controllable[[61]]. Zuber and coworkers[[62]] investigated PLGA thin films for use as cell carriers for skin tissue engineering. The proliferation, adhesion, motility and differentiation of primary human skin keratinocytes on PLGA thin films were analyzed, and compared with tissue culture polystyrene (regarded as the best material for cell culture). Results indicated that PLGA films did not affect the basic function of primary human skin fibroblasts and keratinocytes related to tissue regeneration. PLGA copolymer is a potential candidate for orthopedic applications, such as bone repair and bone fixation, because this copolymer has suitable mechanical properties and a biocompatible and biodegradable nature. In recent years, composite materials including PLGA copolymer have been widely used for bone tissue engineering scaffold applications, because they show an excellent balance between toughness and strength[[63]]. Jose and coworkers[[65]] synthesized PLGA/nano-hydroxyapatite (nano-HA) nanocomposite scaffolds using an electrospinning method for bone tissue engineering. The effects of different amounts of nano-HA were characterized (Figure 3). The results demonstrated that nano-HA acted as a reinforcement at lower concentrations (1% and 5%), but agglomeration of HA was observed at higher concentration. The highest storage modulus value of the scaffolds was found in the 5% concentration of nano-HA that was increased from 441 MPa to 724 MPa. Also, 1% concentration of nano-HA showed lowest mass loss and absorption.

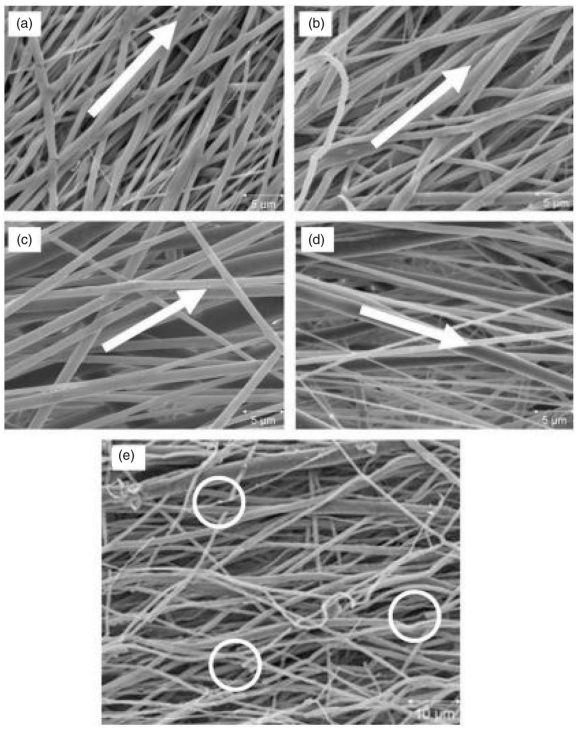


Figure 3. SEM micrographs of nanocomposite scaffolds: (a) neat PLGA; (b) PLGA + 1%; (c) PLGA + 5% HA; (d) PLGA + 10% HA; and (e) PLGA + 10% HA. The arrows indicate the orientation direction, while the circles indicate broken fibers [[65]]. Copyright Elsevier, reproduced with permission.

CieĞlik and coworkers[[66]] evaluated PLGA + HA and PLGA + carbon fiber (CF) composites in the bone tissue regeneration process. The *in vivo* and *in vitro* examinations showed that the PLGA + HA and PLGA + CF composites were biocompatible materials. These composites were nontoxic to bone-forming cells.

Some other PLGA-based composites with their potential applications and their Young's modulus are summarized in Table 2.

Table 2. Summary of PLGA-based composites, potential applications and Young's modulus.

Composite	Composite form	Potential application	Young's Modulus (MPa)	References
PLGA/CNT	Film (thickness 300 µm)	Hard and soft tissue engineering	7.8	[67]
PLGA/SBG	Film (thickness 110 µm)	Bone tissue engineering	2–4 × 10^3	[68]
PLGA/45S5 Bioglasss	Scaffold (pore size 10–100 µm, porosity >90%)	Hard and soft tissue engineering	22–27	[69]
PLGA/GO	Scaffold	Hard and soft tissue engineering	–	[70]
SBA-15/PLGA	Scaffold (pore size 3.7 nm)	Bone tissue engineering	–	[70]

As a naturally derived polymer, chitosan has many beneficial biological and physicochemical properties for use as a material in bone tissue engineering; however, it may trigger blood clotting. On the other hand, PLGA is a synthetic polymer used in tissue engineering and sustained drug delivery, but it can interfere with the healing process and cause tissue inflammation by release of acidic byproducts. One strategy to improve the biocompatibility of PLGA and chitosan is to use PLGA-chitosan based composites. Ignjatović and coworkers reported a chitosan-PLGA polymer composite as a coating for HA nanoparticles and investigated their antimicrobial properties, osteoconductivity, and regeneration of osseous tissues. They synthesized HA nanoparticles by a solvent/non-solvent precipitation method along with freeze-drying. Afterwards, they were coated with the chitosan-PLGA blend and with chitosan. The results of *in vivo* and *in vitro* analyses were compared between HAp/chitosan and HAp/chitosan-PLGA polymer blend. The results of immunohistochemistry analysis of the nanoparticle/cell interface illustrated that there were no adverse morphological effects on the osteoblastic cells with either HAp particles, HAp/chitosan or the HAp/chitosan-PLGA blend, and it is clear that all of these materials could be applied for *in vivo* repair of bone defects (Figure 4). Also, HAp/chitosan exhibited the highest antimicrobial activity against all four tested microbial strains (*S. aureus, S. epidermis, P. aeruginosa* and *E. coli.*) in this study, but it also caused an inflammatory reaction in the newly formed tissue where the material was implanted for the reconstruction of the bone defect. In contrast, the HAp/chitosan-PLGA polymer blend increased the quality of the newly formed bone tissue in the reconstructed defect without causing inflammation, but it lacked antimicrobial activity[[33]].

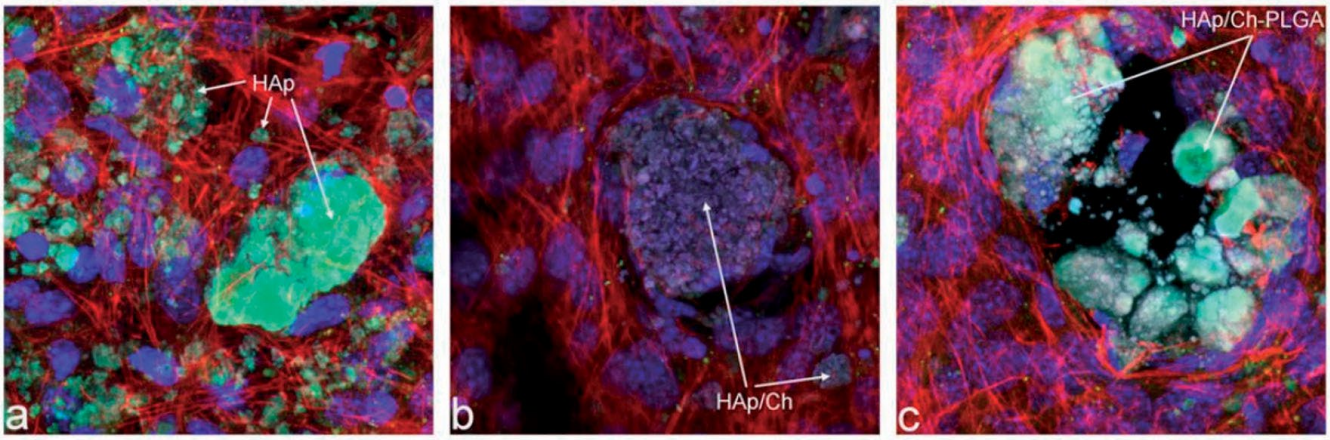


Figure 4. Confocal optical micrographs of fluorescently stained osteoblastic MC3T3-E1 cells following incubation with HAp (a), HAp/Ch (b) and HAp/Ch-PLGA. (c) Cell nuclei are stained in blue and f-actin microfilaments are stained in red [[33]]. Copyright Elsevier, reproduced with permission.

In another PLGA-based composite study, Lee and coworkers fabricated a polypyrrole-coated electrospun PLGA (PPy–PLGA) scaffold using a simple method involving nano-thick deposition for a neural tissue engineering application. The PPy–PLGA scaffold demonstrated nanofibrous features and good electrical activity. In this study, two types of neurons, PC12 cells and rat embryonic hippocampal neurons, were chosen for *in vitro* neuronal cell culture. Moreover, the electrical stimulation of PC12 cells growing on these cytocompatible electroconductive nanofibers was performed. Electrical stimulation studies showed that PC12 cells on PPy–PLGA scaffolds, could be stimulated with a potential of 10 mV/cm, and demonstrated 40–90% more neurite formation, and 40–50% longer neurites than

unstimulated PC12 cells on the same scaffold. In conclusion, the PPy–PLGA nanofibrous scaffold could be a potential material for the regeneration of injured peripheral and central nerves[[71]].

Bioresorbable polymers based on poly(lactic acid)/HA

PLA is a bioresorbable material, which has been extensively used in dental and orthopedic applications[[72]]. However, some adverse clinical effects have been observed when PLA polymer was used alone[[74]]. Therefore the incorporation of additional biocompatible materials, such as tricalcium phosphate (TCP) or hydroxyapatite (HA), into the PLA matrix may eliminate or reduce the allergic or inflammatory reactions of PLA[[75]]. PLA-based composites, such as PLA/TCP composite, have been widely studied in tissue engineering. Yanoso-Scholl and coworkers investigated the mechanical and microstructural properties of dense PLA and PLA/β-TCP scaffolds by a rapid volume expansion phase separation technique. The volumetric porosity of PLA was in the range of 30–40%. The embedding of β-TCP mineral particles into PLA reduced the porosity (20.1 ± 11.9%), whereas it significantly increased the torsional and compressive properties.

The properties of scaffolds as delivery vehicles have been investigated for the optimized controlled release profile of osteogenic and angiogenic factors *in vitro* and *in vivo*. The results showed that these scaffolds culd be used as a potential material for the localized delivery of therapeutic factors[[78]]. In a similar work, Dong and coworkers synthesized PLA/tetracalcium phosphate (TTCP) with high mechanical strength by a melt compounding method. In order to modify the surface of TTCP, N-(2-aminoethyl)-3-aminoproplytrimethoxysilane (AEAPS) was used. Pyromellitic dianhydride (PMDA) was also incorporated into the matrix to enhance the interfacial adhesion properties. Results indicated that AEAPS and PMDA improved the interfacial adhesion between TTCP and PLA and enhanced the mechanical properties of the PLA/TTCP composite. The tensile strength was improved by the addition of AEAPS, from 51.5 MPa for the PLA/TTCP composite to 68.4 MPa for the PLA/TTCP-AEAPS composite. According to the dynamic mechanical analysis, a 51% improvement in the storage modulus was observed by adding 0.2 wt% PMDA into the PLA/TTCP-AEAPS composite (5 wt% of TTCP). The PLA/TTCP bioresorbable composite, showed improved mechanical properties, and could reduce the inflammatory or allergic effects caused by the acidic degradation products arising from PLA[[79]].

Hydroxyapatite (HA) is one of the most common bioactive materials used to increase the osseointegration and mechanical properties of PLA polymer used for bone reconstruction[[80]]. Mathieu and coworkers prepared PLA/HA composites by a supercritical foaming method for bone tissue engineering, and compared them with PLA/β-TCP composite. The effect of the foaming parameters and the biocompatibility of the scaffold with human bone cells was investigated in this study. Results indicated that a more homogenous structure was obtained with β-TCP compared to HA due to the tendency of HA particles to agglomerate when distributed in a PLA matrix. Moreover, the optimal content of HA in the polymer matrix was 5%. Biocompatibility studies with human bone cells illustrated that both composites were biocompatible[[83]]. Shikinami and coworkers examined various mechanical properties of u-HA/poly l-lactide (PLLA) composite and studied the osteological bioactivity, such as direct bonding to bone, osteoconductivity, radioopacity and total resorbability, and evaluated their utility for oral-maxillo and craniofacial, plastic reconstructive surgery compared to titanium only or PLLA-only implants. In this study, the composites were used to manufacture miniscrews (30 wt% of u-HA particles) or miniplates (40 wt% of u-HA particles) and measured bioactivity and total mechanical

strength. The results indicated that the PLLA-only devices had slightly different mechanical properties compared to the composite devices. Moreover, comparison between the fatigue resistance after alternating bending of the composites and titanium miniplates, showed that the composite miniplates retained 70% of their initial strength after 60 repetitions of bending (without showing any damage), but the titanium devices showed structural failure after 8 times. In conclusion, u-HA/PLLA composite had good osteological bioactivity and radioopacity, and could be a suitable candidate for use in cranial, oral, and maxillo-facial, plastic reconstructive surgeries. Figure 5 shows a clinical application of a u-HA/PLLA composite in bone tissue engineering[[29]]

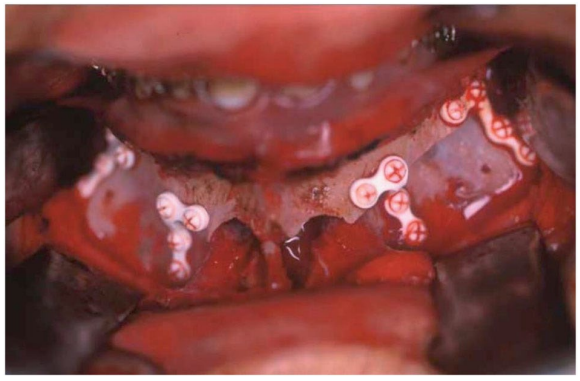


Figure 5. A clinical application of u-HA/PLLA composite to Le Fort I osteotomy [[29]]. Copyright Elsevier, reproduced with permission.

In recent years, HA derived from natural sources such as the waste bones of animals, has gained attention as a material for bone fillers and grafts. Lee and coworkers investigated the biocompatibility and toxicity of a PLA-based composite containing HA derived from waste backbones of the dolphin *Neophocaena asiaeorientalis* (HA_{NA}). The PLA/HA_{NA} composite was subcutaneously implanted in SD rats for up to 8 weeks for investigation of possible toxicity or inflammation of the composite. The results showed that PLA/HA_{NA} composite was biocompatible and nontoxic; therefore, HA_{NA} could be a suitable material for bone tissue engineering[[82]]. In a similar study, Rakmae and coworkers reported the cytotoxicity and physical properties of surface-modified bovine bone-based HA (bHA)/PLA composites. In this study, bovine bone was prepared and thermally treated to form carbonated HA and then incorporated into PLA. The properties of silane-treated HA and untreated HA were also compared. The results indicated that the thermal stability of silane-treated HA/PLA composite was better than the untreated HA/PLA composite. Moreover, the mechanical and morphological properties of the PLA composites showed that silane-treated HA enhanced the interfacial adhesion between the two phases, and the dispersion of HA in the PLA matrix. *In vitro* cytotoxicity testing of bHA/PLA showed that this composite was nontoxic for human osteoblast cells[[77]].

Table 3 provides a summary of the properties of PLA/HA composite scaffolds.

Table 3. Summary of PLA/HA composite scaffold properties.

Amount of HA	Fabrication method	Porosity (%)	Tensile (T), compression (C), flexural (F) strength (MPa)	Young's modulus (MPa)	Cell type in vitro	References

0–50 wt%	Particulate leaching	86–92%	0.29–0.44 (C)	4.72–9.87		[78]
5 wt%	Supercritical gas foaming	79.2%		133	Human fetal bone cells	[79]
0–6 wt%	Electrospinning	–		400–600		[80]
30–50 wt%	Solvent casting			150–570	Osteoblasts, CRL-1213	[81]
0–20 wt%	Extrusion/injection molding	–	47.4–65.3	–		[82]

The HA/ poly-D/L-lactide (PDLLA) composite can act as a bioresorbable scaffold. Akagi and coworkers studied the utility of an HA/PDLLA composite scaffold implanted into bone in vivo, by analyzing the remodeling process compared with a β-TCP scaffold. In this study, dogs underwent surgery for replacement of a section of tibial bone with the aforementioned scaffolds (Figure 6). The results showed that the HA/PDLLA scaffold was similar to the β-TCP scaffold in terms of biodegradation and new bone formation. The results of immunohistochemistry staining demonstrated that the HA/PDLLA scaffold showed better cell infiltration than the β-TCP scaffold. Also, the risk of any residual scaffold remaining with the HA/PDLLA scaffold was less than the β-TCP scaffold[[84]].

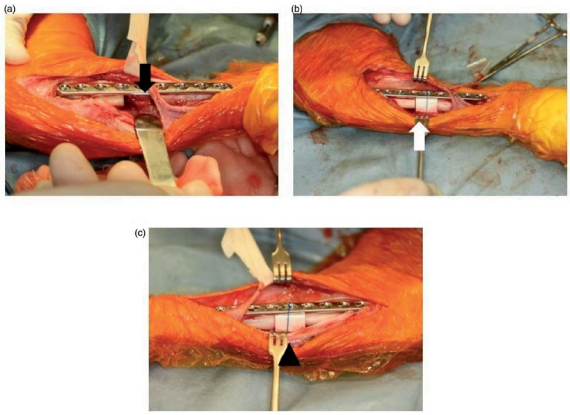


Figure 6. Images of surgery. (a) The central region of the tibia was removed using an oscillating bone saw (black arrow). (b) The HA/PDLLA composite was inserted into the space created (white arrow). (c) The β-TCP composite was inserted into the space created (black arrow) [[84]]. Open access no permission necessary.

Carbon fibers (CF) have been used in recent PLA and PLA/CF composite biomedical studies, specifically for osteosynthesis, because CF has specific properties, such as excellent tensile strength, high thermal and chemical stability, low density and other features[[85]]. Morawska-Chochół and coworkers investigated the influence of the preparation method of intramedullary nails on the degradation rate and mechanical properties. In this study, two groups of composite nails were manufactured, comprising PLA reinforced with Mg alloy wire and incorporating gentamicin sulfate (GS) (PLA/Mg/GS) and PLA reinforced with CF and long calcium alginate (Alg) fibers. Hot pressing, injection molding and solution methods were used for construction of the intramedullary nails. The PLA/CF composite was manufactured by a hot pressing method. The results demonstrated that the fabrication method clearly influenced the degradation behavior and mechanical properties of polymer-based nails. Moreover, the

hot pressing method was suitable for fiber-reinforced nails because it allowed better impregnation of fibers into the polymer matrix, and higher volume fractions. The PLA/CF composite was shown to have more suitable mechanical properties (bending strength = 380 MPa, elastic modulus = 400 MPa) than other manufactured composites[[87]]. CF has also been used as a reinforcement material in HA/PLA composites in order to improve the mechanical properties while retaining the advantages of HA/PLA composite materials.

Shen and coworkers[[88]] investigated the mechanical properties of CF-reinforced HA/PLA biocomposites, which were prepared by hot pressing a "prepreg" consisting of PLA, HA and CF. The *in vitro* degradation behavior of the composite was investigated, including the attenuation of the modulus, mass loss, strength of the material, water absorption, and the change in pH value during soaking in certain solutions for 3 months. The results indicated that the CF/HA/PLA composites possessed suitable mechanical properties. The effect of varying the HA content on the mechanical properties of CF/HA/PLA composites was investigated. Increasing the HA content led to values of flexural modulus, shear strength and flexural strength being 22 GPa, 212 MPa and 430 MPa, respectively. The flexural modulus and flexural strength of the composites decreased by 5.4% and 13.2%, respectively, and the shear strength of the composites remained at 190 MPa after degradation *in vitro* solution for 3 months. The SEM images of the fracture faces of the composites showed that there were gaps between the CF and the PLA matrix after degradation (Figure 7). The pH values of the phosphate buffer solution (PBS) changed less than 0.1 pH unit, because the alkalinity of the HA neutralized the acidic degradation products from PLA, therefore preventing any acidic damage when used in bone tissue engineering.

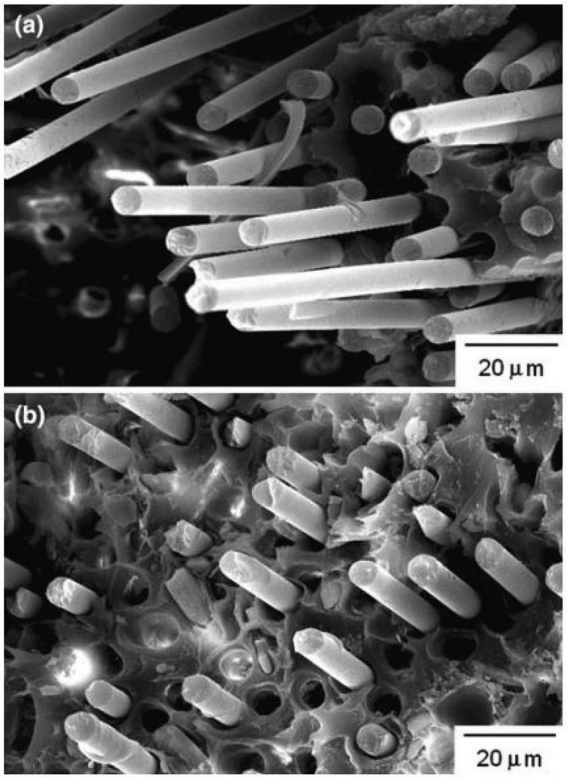


Figure 7. SEM photos of fracture faces of the CF/PLA/HA composites degraded in PBS for (a) 1 week and (b) 12 weeks [[88]]. Copyright Springer Nature, reproduced with permission.

Titanium dioxide (TiO_2) nanoparticles have also been used as a filler in PLA-based composite scaffolds for regenerating bone damage arising from cancer or other bone diseases and trauma. Gerhardt and coworkers[[89]] synthesized poly(D,L lactic acid) (PDLLA)/TiO_2 composites by a solvent casting method with different contents of TiO_2 nanoparticles (5 and 30 wt%). Results showed that an increase in the TiO_2 nanoparticle content increased the surface roughness, which led to improved adhesion of osteoblast cells. In order to investigate the bioactivity, the free TiO_2 nanoparticles and PDLLA/TiO_2 composite films were immersed in simulated body fluid (1.5 SBF) for up to 3 weeks, and the formation of hydroxyapatite (HA) on the material surface was evaluated. At a low content of TiO_2 (5 wt%), only a trace amount of HA nano-crystals (ns-HA) formed on the composite films after 21 days immersion in 1.5 SBF, while at high TiO_2 content (30 wt%), ns-HA formed on the composite films after 14- and 21-days immersion. Moreover, TiO_2 nanoparticles had no adverse effect on MG-63 osteoblast-like cell viability.

Bioglass is a bioactive material that reacts with physiological fluids and forms strong bonds to soft and hard tissues mediated via cellular activity. Macroporous PDLLA foams and bioglass particles were developed as bioresorbable and bioactive materials in recent tissue engineering studies. Roether and coworkers[[90]] synthesized and characterized polylactide foam/bioglass composites for bone tissue engineering. In this study, homogeneous and stable bioglass coatings on the surface of PDLLA foams were obtained by a slurry-dipping technique in conjunction with pretreatment of the foams in ethanol. *In vitro* studies incubated the PDLLA/bioglass composites in SBF to test for formation of HA on the surface. The results of this study indicated that increasing time in SBF rapidly increased the thickness of the HA layer. The PDLLA/bioglass composite was proposed to be a bioactive and resorbable scaffold for bone tissue engineering.

Polycaprolactone (PCL)-based composites

PCL is a biodegradable aliphatic polyester that has been used as a scaffold in various tissue engineering applications[[91]]. While the PCL polymer alone has some advantages, such as biocompatibility, excellent thermal stability and chemical inertness, however PCL alone also has disadvantages such as, poor cell attachment and proliferation when used *in vivo* because of its hydrophobic properties. Therefore, surface modification of PCL polymer and blending with other materials may improve its performance[[92]]. Park and coworkers reported the use of a PCL/β-TCP composite scaffold that was fabricated by a 3 D-printing (bioprinting) technique for bone tissue engineering. The effects of increasing the β-TCP content (from 0 to 30 wt%) on the strength of the PCL/ β-TCP scaffold, and its ability to allow osteogenic differentiation were investigated. The results indicated that increasing the β-TCP content increased the mechanical strength. The PCL/β-TCP scaffold containing 30 wt% of β-TCP was most suitable for use in bone tissue engineering.

PCL-HAp has been investigated as a material for replacing bone tissue. Lebourg and coworkers[[96]] synthesized a hybrid PCL-HAp scaffold using biomimetic apatite growth obtained via a mixed porogen leaching/phase inversion process. Investigation of the *in vitro* mineralization of the scaffolds in SBF was performed with or without a nucleation treatment[[97]]. Incorporation of HAp into the PCL matrix enhanced its *in vitro* bioactivity, while addition of a nucleation treatment improved the mechanical properties. The results of mechanical testing after *in vitro* biomineralization indicated that the PCL-HAp composite scaffold could be used as a promising material for bone tissue engineering.

Heip and coworkers[[98]] synthesized a co-polymer PLGA/PCL blend with different percentages of PLGA using electro-spinning, and investigated its biocompatibility for tissue engineering The MTT assay results indicated that increasing the percentage of PLGA increased cell attachment, cell proliferation and improved the biocompatibility of the electro-spun co-polymer. Figure 8 shows the SEM images of cell proliferation 24 h after seeding the cells, and it is evident that cell growth on the control increased with increasing of amount of PLGA. Moreover, the mechanical strength of PLGA/PCL electro-spun blend was higher than PCL alone.

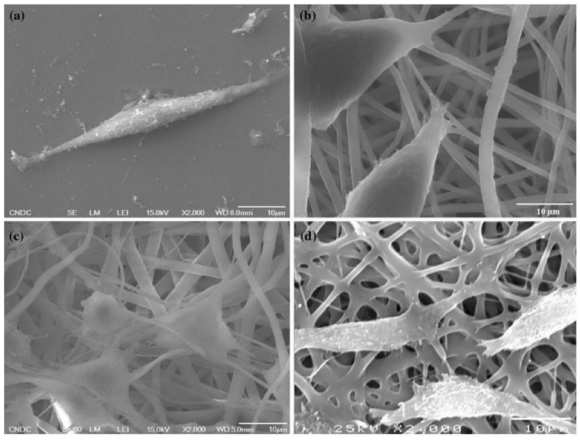


Figure 8. SEM morphology of fibroblast cells grown on the control (a) blend PLGA/PCL (10/90), (b) PLGA/PCL (20/80) (c) and PLGA/PCL (30/70) and (d) electro-spun after seeding cell 1 day [[98]]. Copyright Springer Nature, reproduced with permission.

Gautam and coworkers[[99]] fabricated a PCL/gelatin/chitosan ternary composite nanofibrous scaffold using an electrospinning method. The fiber morphology of the composite scaffold was related to the concentrations of PCL, gelatin and chitosan in the polymer solution, and a bead-free fiber morphology was obtained when the PCL polymer content was increased up to 16%. The L929 mouse fibroblasts were seeded directly onto the scaffold. The cell proliferation rate, cell viability and cell adhesion were measured by DNA quantification, MTT assay and FE-SEM analysis of the cell-scaffold cultures. The PCL/gelatin/chitosan composite scaffold could be used in some tissue engineering applications. In a similar study, Gomes and coworkers evaluated nanofibrous scaffolds prepared from chitosan, PCL and gelatin for skin tissue engineering. Physico-chemical characterization, such as porosity, wettability, dimensional stability and mechanical properties, was carried out for the scaffolds.

Human fetal fibroblasts (cell line HFFF2) were used for an *in vitro* study of the scaffolds. The results showed that the chitosan/PCL/gelatin scaffolds had improved physical properties. Comparison of cell adhesion between the different blends showed that PCL/gelatin > chitosan/gelatin > chitosan/PCL/gelatin > chitosan/PCL. All these blends had some properties that made them useful for skin tissue engineering[[100]].

Gentile and coworkers[[101]] synthesized a PCL-collagen graft-copolymer for tissue engineering. The results indicated that the combination of the biodegradability and good mechanical properties of PCL, with the biological properties of type I collagen provided a functional material for tissue engineering. Moreover, good metabolic activity and biocompatibility was obtained for PCL-graft-collagen films compared to PCL and blend controls. Figure 9 shows the collagen staining results for PCL, PCL/collagen and PCL-graft-collagen, and a higher collagen content was observed for the PCL-graft-collagen

substrates. The viability of L929 fibroblast cells cultured on the PCL-graft-collagen, PCL/collagen and PCL only films, indicated a spindle-like morphology, spreading homogeneously on the PCL-graft-collagen film surface after 3 days of culture.

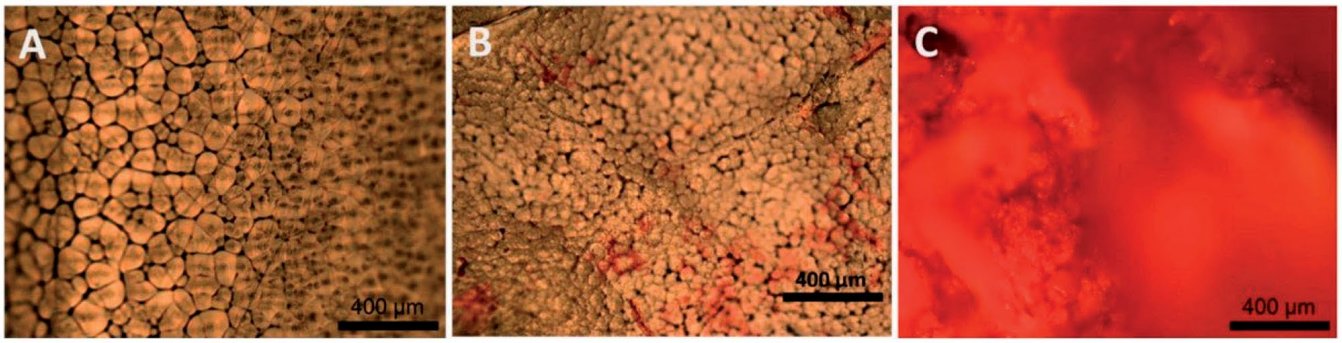


Figure 9. Collagen staining of (A) PCL; (B) PCL/ collagen blend and (C) PCL-graft-collagen with Sirius Red assay. Scale bars correspond to 400 µm[[101]]. Open access no permission necessary.

A summary of PCL-based composite scaffolds that have been used for various tissue engineering applications is presented in Table 4.

Table 4. Summary of PCL-based composites for different tissue engineering applications.

Composite	Fabrication technique	Cell type	Application	References
PCL/ZnO	Thermally induced phase separation and freeze extraction method for solvent removal	Simulated body fluid (SBF)	Tissue engineering	[102]
PCL/PLGA/HA	Melt blending and particle leaching	hMSCs	Bone tissue engineering	[103]
PCL-HAp and PCL-bioglass	Mixed particle leaching/ freeze extraction process	MC3T3-E1 (an osteoblast-like cell line from mouse Osteosarcoma)	Bone tissue engineering	[104]
PCL/HAp	Selective laser sintering	Rat MSCs	Tissue engineering for osteochondral defects	[105]
PCL/β-TCP	rapid-prototyped (RP)	Osteoblast-like cells (MG63)	Bone tissue engineering	[106]

Conclusions

In recent years, bioresorbable polymers have undergone considerable investigation in the field of tissue engineering. However, this approach is only beginning to be developed, and only a few of these materials are in clinical use. The use of bioresorbable polymers for internal fixation has the advantage of eliminating the need for a second surgical intervention for their removal after healing has occurred. Bioresorbable or biodegradable composites are of growing interest because of their ability to provide the necessary mechanical properties for the tissue reconstruction process and allowing cells to attach

and grow. The optimized degradation rate of bioresorbable materials should be in a sustainable range for the specific function that the material serves within the body. Poly(lactic acid) can fulfill these criteria for many different applications, thanks to its chiral structure and its ability to undergo copolymerization with other polymers to form composites. One of the important challenges of nanocomposites, is the absorption of biological materials and possible migration of nanoparticles into surrounding tissues. In addition, a multidisciplinary approach is necessary for the comprehensive investigation of bioresorbable polymers before they are widely available for implantation into patients. Moreover, composite nanomaterials will need to be manufactured reproducibly, on a large scale and in a cost-effective manner to be widely used in tissue engineering.

Disclosure Statement

MRH declares the following potential conflicts of interest. Scientific Advisory Boards: Transdermal Cap Inc, Cleveland, OH; BeWell Global Inc, Wan Chai, Hong Kong; Hologenix Inc. Santa Monica, CA; LumiThera Inc, Poulsbo, WA; Vielight, Toronto, Canada; Bright Photomedicine, Sao Paulo, Brazil; Quantum Dynamics LLC, Cambridge, MA; Global Photon Inc, Bee Cave, TX; Medical Coherence, Boston MA; NeuroThera, Newark DE; JOOVV Inc, Minneapolis-St. Paul MN; AIRx Medical, Pleasanton CA; FIR Industries, Inc. Ramsey, NJ; UVLRx Therapeutics, Oldsmar, FL; Ultralux UV Inc, Lansing MI; Illumiheal & Petthera, Shoreline, WA; MB Lasertherapy, Houston, TX; ARRC LED, San Clemente, CA; Varuna Biomedical Corp. Incline Village, NV; Niraxx Light Therapeutics, Inc, Boston, MA. Consulting; Lexington Int, Boca Raton, FL; USHIO Corp, Japan; Merck KGaA, Darmstadt, Germany; Philips Electronics Nederland B.V. Eindhoven, Netherlands; Johnson & Johnson Inc, Philadelphia, PA; Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany. Stockholdings: Global Photon Inc, Bee Cave, TX; Mitonix, Newark, DE.

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