Advanced polymer-based composites and structures for biomedical applications

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ABSTRACT

A fast increasing demand of medical products based on biomaterials and tissue engineering has led to an extensive growth in biomedical research in the past two decades. A highly interesting class of biomaterials are polymer-based composites, which nowadays are widely used in biomedical applications due to their outstanding physical and mechanical properties. In this paper, we aim to summarize the advancement in polymer-based composites with regard to their properties, structure and fabrication using different techniques. Bioactive polymer-based composites, such as bone-forming, electrically conductive, magnetic, bactericidal and oxygen-releasing materials, as well as non-bioactive polymer-based composites containing reinforcing fillers and porogens are discussed. Amongst others, scaffold structures fabricated by particle leaching, electrospinning and additive manufacturing are described. In each section, significant and recent advances of polymer-based composites in biomedical applications are addressed.

1. Introduction

1.1. Overview

The biomaterials field has seen a strong growth in the past decades [1-4]. Biomaterials are used to prepare biomedical devices such as hydrogel contact lenses, polymer or metal stents, artificial heart valves, steel joint and hip replacements, knee and ligament implants, polymer vascular grafts, ceramic dental implants, polymer sutures, surgical adhesives, polymer barrier films, porous dialysis membranes, etc. [5-11]. Due to the fast increase of medical product demands caused by population expansion and aging, the numbers of both pre-clinical and clinical biomaterial studies are dramatically growing [12-14]. According to a global industry analysis report, the global biomaterials market was more than USD 94 billion in 2018 and is forecasted to be over USD 256 billion by 2025, *i.e.* an increase of more than 15% between 2019 and 2025 [15].

Instead of using non-degradable materials for tissue repair, degradable and absorbable biomaterials hold extensive capabilities to regenerate and reconstruct tissues such as bone, cartilage, muscle, skin, blood vessels, heart valves, nerves and many others [16-18]. These biomaterials are frequently used as scaffold materials for applications in tissue engineering and regenerative medicine [19]. In this strategy, specific cells are intended to grow into 3-dimensional (3D) biomaterials-

based porous scaffolds. After a while, native-like tissues or organs are formed which are used to replace and repair lost and failing tissues of patients. These engineered living tissues or organs could significantly reduce the replacement organ demand and offer new opportunities for therapy to accelerate the recovery of patients. Tissue engineering scaffolds contain a microenvironment which determines cell adhesion, growth, proliferation, differentiation and function. An ideal microenvironment supports cell growth and tissue formation, exchange of nutrients and waste products, and consists of extracellular matrix (ECM), growth factors, space for cell expansion, and external stimulation factors [20-23]. Scaffold materials are used as ECM and should be biocompatible, cell adhesive, biodegradable, and have proper mechanical properties. In addition, the materials may conduct electricity, release oxygen, and have magnetic or antibacterial properties. Scaffold structural parameters including pore size, porosity, and (patient-specific) 3D structure are important as well. Thus, scaffolds prepared from biocompatible and bioactive materials with an adequate 3D structure are essential for the formation of functional tissue [24-27].

In the early years, porous scaffolds were mainly prepared by solvent casting followed by particle leaching. As a result of technological developments, new techniques were applied in tissue engineering such as electrospinning, additive manufacturing, microfabrication and bioprinting [28,29]. These techniques enable to prepare porous scaffolds

with complex structures. Currently, processing of biomaterials to match the advanced manufacturing techniques is one of the most researched areas. In conclusion, bioactive scaffolds, implants, grafts and other biomedical devices with specific structures can be fabricated by modern processing and manufacturing technologies for the urgent demand of a variety of tissues and organs.

1.2. Materials for biomedical applications

Biomaterials can be divided into natural and synthetic polymers, metals and metal alloys, inorganic ceramics (natural and synthetic), carbon-based materials (graphite, graphene, carbon nanotube, carbon fiber, etc.), and composite materials [30-36]. The choice of materials for specific tissue repair is depending on the tissue characteristics and material properties, see Table 1.

Natural and synthetic polymers have been extensively used in tissue engineering and regenerative medicine because of their diverse properties, such as bioactivity, degradability, mechanical properties, processing ability. Natural polymers like silk fibroin, collagen, and gelatin are similar to the native ECM and generally show better cell adhesion and biocompatibility than synthetic polymers [37]. Even though scaffolds based on natural polymers hardly show chronic inflammation, toxicity or immunological reactions, which are frequently noticed in synthetic polymer scaffolds, poor mechanical properties are a drawback. On the other hand, synthetic polymers relatively easily allow tailoring of their molecular weight, degradation time, and mechanical properties for both hard and soft tissue engineering applications [38]. Biodegradable polymers such as poly(lactide) (PLA), poly(glycolide) (PGA), poly (lactide-co-glycolide) (PLGA), poly(ε-caprolactone) (PCL), poly(trimethylene carbonate) (PTMC) and their copolymers or blends are frequently used as scaffold materials in tissue engineering and regenerative medicine [39]. However, the utility of PLA and PGA as scaffold materials for implantation has been hampered by their acidic degradation products. Studies have shown a decrease in local pH caused by the acidic degradation products, which are harmful to cells, drugs, or proteins and can lead to tissue inflammation at the polymer/tissue interface [40,41]. Thus, scaffolds based on PLA, PGA, and their copolymers have sub-optimal degradation properties. In particular, PTMC has been suggested as an ideal polymer for biomedical applications [42,43]. As an amorphous polymer, PTMC has a low glass transition temperature (Tg) of $-17\,^\circ\text{C}$ [44 45]. The degradation products of PTMC are 1,3-propandiol and carbon dioxide. [46]. In contrast to the degradation of PLA and PGA, no acidic compounds are formed upon the degradation of PTMC [47,48]. Although the slow degradation rate of PCL does not lead to the rapid generation of large amounts of acidic degradation products, it degrades in bulk like PLA and PGA, which leads to abrupt scaffold fragmentation during tissue regeneration. PTMC degrades by surface erosion, resulting in prolonged mechanical strength during degradation

which is beneficial for tissue engineering applications [49]. PTMC degradation rate can be tuned by varying its molecular weight and by adjusting the crosslink density of networks [47,50]. PTMC-based polymer networks have been extensively studied and applied in various biomedical applications [51].

Up to now, plenty of biomedical products based on synthetic polymers have been produced such as nerve guide conduits, vascular grafts, and artificial skin. Although these polymers are biocompatible and have adjustable degradation rates and mechanical properties, a drawback is they do not present bioactivity. For the engineering of complex tissues like bone, the use of only polymers does not meet the requirements for a suitable microenvironment to form a functional tissue. This can be solved by using a polymer-based composite, see below.

Metals and metal alloys with designed load-bearing mechanical properties are being used for joint replacement (hip and knee) and dental implants. They are biocompatible and nearly all are non-biodegradable. Most implants made from metals and metal alloys are intended to have a long implantation time, which may lead to corrosion and metal ion toxicity [32,52]. Besides that, metallic implants are much stiffer than host bone, which may lead to stress shielding resulting in bone resorption [53]. It should be noticed that metal-based micro- and nano-particles (Au and Ag) display excellent conductivity, antimicrobial properties and other bioactive functions in medical applications [54].

Bio-glass is the first used bioactive inorganic ceramic able to induce bone formation and has been commercialized [55]. As components of native bone, calcium phosphate-based ceramics such as hydroxyapatite (HA), tricalcium phosphate (TCP) and biphasic calcium phosphate (BCP) are frequently used for bone tissue engineering as well [56]. Even though these ceramic materials resemble the natural inorganic component of bone and possess osteo-conductive and osteo-inductive properties, they are brittle and do not match the mechanical properties of bone [57].

Carbon-based biomaterials have been researched for decades and attract very much attention in biomedical applications due to excellent conductivity, unique structure and mechanical properties [58]. Graphene (single or multilayers) and carbon nanotubes (cylindrical carbon structure) are the mostly used carbon materials in neuronal, cardiac and bone tissue engineering. Moreover, they have also been used as secondary structural reinforcements to enhance the mechanical properties of tissue engineering scaffolds [59]. Graphene and carbon nanotubes express bioactivity in multiple processes like neurite outgrowth and extension, stem cell differentiation, osteogenic differentiation, and display antibacterial activity [35]. However, carbon materials are not able to be resorbed when applied *in vivo*.

The term "composite material" refers to the combination, on a macroscopic scale, of two or more materials, that differ in composition or morphology, in order to obtain specific chemical, physical and mechanical properties [60,61]. The advantage of using composite materials for biomedical applications is that a composite material may possess a combination of the best properties of the constituents. Composite materials offer useful properties such as bioactivity, electrical conductivity, oxygen supply and magnetic and antimicrobial properties. Polymer-based composites are composed of a polymer matrix and one or more fillers which provide physical, chemical or biological properties. As mentioned before, synthetic polymers generally lack bioactivity compared to bioactive ceramics, metal nano-particles, and carbon-based materials. A polymer/ceramic composite for bone grafting may present improved mechanical properties compared to either the neat polymer or the ceramic. This means that reinforced scaffolds with enhanced bioactivity and controlled resorption rates can be obtained by combining suitable polymers and ceramics [62]. A different application of composites in biomedical engineering is the use of composites with leachable components for the preparation of porous scaffolds. Leachable components include salt, sugar and crystallized solvent particles [63].

In this review, we summarize the properties of bioactive and non-bioactive polymer-based composites and their processing into

Table 1

Advantages and disadvantages of different classes of materials for tissue engineering and regenerative medicine.

	Advantages	Disadvantages
Polymers	Biocompatible, biodegradable, bioresorbable, low toxicity, mechanical properties for both soft and hard tissue engineering.	Lack of bioactivity.
Metals	Tough, high load bearing, good mechanical properties.	Too stiff causing tissue degeneration, corrosion, toxic ion release.
Ceramics	Bioactive such as osteo-conductive and osteo-inductive.	Brittleness, fragmentation.
Carbon-based materials	Conductive, low weight.	Not able to be degraded and resorbed.
Composite materials	Combination of advantages of the separate components.	Processing in such a way that the advantages are properly expressed.

structures for biomedical applications. Bioactivity of the composites includes osteo-conduction and -induction, electrical conductivity, magnetization, oxygenation, and antibacterial properties. Non-bioactive components of the composites include reinforcing and leachable fillers. Manufacturing techniques for the preparation of advanced structures using polymer-based composites are discussed as well.

2. Polymer-based composites for biomedical applications

Polymer-based composites can be divided into two main types regarding the filler incorporated in the polymer matrix. The first type are bioactive polymer-based composites, which contain bioactive fillers or particles. The second type are non-bioactive polymer-based composites, which contain *e.g.* reinforcing fillers or porogens (sacrificial particles added during processing for preparation of porous structures).

2.1. Bioactive polymer-based composites

2.1.1. Polymer/bioactive ceramic and -glass particle composites

Bioactive glass and bioactive calcium phosphate-based ceramics are synthetic bone graft materials widely used in bone tissue engineering [64]. Bioglass®, invented by Hench and co-workers, was the first synthetic material found to interact with bone [65]. This degradable glass is composed of Na_2O, CaO, SiO_2 and P_2O_5. When used for bone regeneration in animal models, it was found that bioactive glass-based implants could not be removed without breaking the bone. This discovery inspired research on bioactive inorganic materials, resulting in the development of other types of bioactive glass and calcium phosphate ceramics. Bone is a natural composite consisting of inorganic ceramics such as hydroxyapatite, calcium sulfate ($CaSO_4$) and calcium carbonate ($CaCO_3$), and the polymer matrix collagen [66]. The collagen matrix facilitates cellular interactions and tissue formation, while the inorganic materials provide mechanical strength and support the regeneration of bone. The inorganic phase releases calcium ions which benefit bone cell proliferation and differentiation.

CaP, $CaSO_4$, and $CaCO_3$ have been used separately or as composite fillers in a polymer matrix to fabricate substrates and scaffolds for bone regeneration [67]. CaP in the form of hydroxyapatite is a main component of native bone and can be resorbed by bone cells *in vivo*. CaP can be divided into the following types: hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), biphasic calcium phosphate (BCP) and amorphous calcium phosphate (ACP). CaP ceramics show bone forming activity (osteoconductivity or osteoinductivity), determined by their physical/chemical characteristics and surface structures [68]. Bone forming activity of CaP has been mostly shown in non-load bearing clinical situations involving orthopedic, dental, ear, nose and throat surgeries using compressed ceramic particles. CaP particles are inherently brittle and difficult to process, and not able to withstand load bearing conditions. Although synthetic polymers are generally easy to be processed into structures with tunable mechanical properties, they do not show satisfactory bone forming capacity. By combining the polymers and CaP particles, the resulting polymer-based ceramic composites can be used to fabricate bone grafts with suitable mechanical properties and bone forming activity [69].

Nano-HA has been frequently used as filler in polymer-based scaffolds for bone formation. Both synthetic polymers like PLA, PCL, PGA, PLGA, PTMC, and natural polymers such as gelatin and collagen have been used [70,71]. The presence of HA in the polymer matrix is important as it affects protein adsorption and bone cell adhesion. Nano-HA fillers with a high aspect ratio enhance the mechanical properties of polymer-based bone grafts. PTMC scaffolds containing 40 wt% HA nanoparticles showed more bone formation than PTMC scaffolds with 20 wt% HA upon implantation in calvarial defects in rabbits [72]. Moreover, this study indicated that surface enrichment of the HA nanoparticles in the PTMC-based ceramic composites was a key factor in the osteogenic potential of the bone grafts.

PCL/β-TCP composite scaffolds were manufactured by Park *et al.* using extrusion-based 3D printing [73]. Highly porous scaffolds were obtained with a high β-TCP content. *In vitro* studies showed that the scaffolds effectively promoted cell growth and osteogenic differentiation of mouse mesenchymal stem cells. Konopnicki *et al.* also 3D-printed PCL/β-TCP composite scaffolds for bone regeneration, which were seeded with porcine bone marrow progenitor cells and implanted into porcine mandibular defects. The results showed good bone penetration depth with angiogenesis in the center of the constructs [74].

PCL/BCP composite scaffolds for bone regeneration were prepared as well. By means of a solvent casting and salt leaching method, porous PCL/BCP scaffolds, with 200–500 μm pore size, were obtained. After 7 days culturing of human mesenchymal stem cells, the PCL/BCP composite scaffolds showed 4 times higher alkaline phosphatase activity than control PCL scaffolds [75]. Peroglio *et al.* used PCL to infiltrate brittle BCP scaffolds for bone engineering. The composite scaffolds were cytocompatible with human bone marrow stromal cells. Moreover, the mechanical properties of the scaffolds significantly improved by incorporation of PCL [76].

ACP nanoparticles also showed biocompatibility and bioactivity. PDLLA/ACP composite nanofibers were prepared and evaluated *in vitro* by Ma *et al.* Surface roughness of the composite nanofibers significantly increased with increasing content of ACP. Bio-mineralization of the composite nanofibers was found after 1 day in simulated body fluid, and further increased after 7 days. Osteoblast-like MG63 cells were seeded on PDLLA/ACP composite nanofiber scaffolds, and good cell adhesion and cell spreading behavior were obtained [77].

Likewise, polymer-based bioactive glass composites were developed [78,79]. Initially, micron-size bioactive glass particles were used, which was followed by application of nano-size bioactive glass particles and fibres as fillers in polymer-based composites. Hong *et al.* investigated PLA/nano bioactive glass composite scaffolds for bone regeneration. *In vitro* studies showed that bioactive glass containing lower phosphorous and higher silicon content had a better bioactivity than bioactive glass with lower silicon and higher phosphorous content [80].

$CaSO_4$ and $CaCO_3$ were also considered as fillers to form polymer-based composites for bone regeneration [81 82]. Silica (SiO_2) nanoparticles were investigated as well [83,84].

2.1.2. Polymer/electrically conductive filler composites

Electrically conductive materials have received increasing attention of academic and industrial researchers to explore potential biomedical applications, *e.g.* in the fields of biosensing, targeted drug delivery, and tissue engineering [85,86]. These materials could stimulate cell adhesion, proliferation, differentiation, migration, function, and further drive cell activities and tissue formation with or without exogenous electrical stimulation [87,88]. Native tissues such as nerve, muscle, lung, cardiac and skeletal muscle, have conductivity values between 0.03 and 0.6 S/m [89,90]. Therefore, tissue engineering scaffolds fabricated from electrically conductive materials are believed to accelerate tissue formation and regeneration [91].

Conductive polymers and composites of polymers and conductive fillers have been used as materials to fabricate electrically conductive scaffolds [92,93]. Conducting polymers such as polypyrrole (PPY), polyaniline (PAN), polythiophene (PTH) and poly (3,4-ethylene dioxythiophene) (PEDOT) were prepared for neuronal tissue engineering. However, for *in vivo* application, conductive polymers are not ideal due to poor suturability, brittleness, and long-term toxicity [88]. An alternative strategy is to use biocompatible and biodegradable polymers combined with conductive fillers. These are mainly divided in two classes: carbon-based nanofillers (carbon nanotubes, graphene derivatives) and metal particles (gold and silver particles). These fillers show high electrical conductivity and biocompatibility, and conductive polymer-based composites containing these fillers have been widely used for peripheral nerve regeneration and cardiac tissue engineering [94].

The conductivity of polymer/conductive filler composites is dependent on the formation of conductive paths of fillers distributed in the polymer matrix [95]. The formation of conductive paths is affected by the amount of fillers in the polymer matrix as well as the geometry and intrinsic properties of the fillers. In addition, interactions between filler and matrix are important for a homogenous distribution of the filler in the matrix. As shown in Fig. 1, the conductivity of a polymer-based composite initially shows a small increase with increasing amount of conductive filler. Upon reaching the percolation threshold, the conductivity dramatically increases and finally reaches a maximum [94,96]. When the amount of conductive filler is above the percolation threshold, a continuous conductive network is formed throughout the composite. A high aspect ratio (ratio of length to diameter) of conductive fillers was found to contribute to the conductivity of polymer-based composites [96,97].

Carbon nanotubes (CNTs) are hollow nanostructures consisting of carbon atoms with excellent mechanical properties and high electrical conductivity. Crowder *et al.* prepared electrically conductive PCL/CNT composite scaffolds by electrospinning for cardiac tissue engineering. The highest conductivity (0.035 S/cm) of this fibrous scaffold was obtained with 3 wt% incorporated CNTs. Differentiation of human mesenchymal stem cells in these scaffolds was found to be dependent on the substrate conductivity under DC electrical stimulation [97]. Other PCL/CNT composite scaffolds were prepared for nerve regeneration by Zhou *et al.* They showed improved PC-12 cell growth and differentiation in the conductive PCL/CNT composite scaffolds compared to neat PCL scaffolds. In addition, both proliferation and neuronal cell extension benefited from electrical stimulation, indicating the potential for application in nerve regeneration [98].

Single and multilayer graphene are known as high aspect ratio two dimensional nanosheets with ultra-high electrical conductivity and excellent mechanical properties. The common forms of graphene derivatives are graphene oxide (GO) and reduced graphene oxide (rGO). rGO is usually obtained by thermal or chemical reduction of GO, and has a higher conductivity than GO. rGO is more hydrophobic than GO and easily forms non-reversible aggregates because of van der Waals forces and π–π stacking interactions. Therefore, both small molecules and polymers were used to modify the surface of rGO particles in order to obtain homogenous dispersions in a polymer matrix. Recently, polymer-based composites with rGO as conductive filler have drawn a lot of attention for biomedical applications. Sayyar *et al.* prepared PCL/rGO composite materials, both by solvent mixing and covalent linking of PCL to rGO. The latter method resulted in higher conductivity with lower

amount of rGO than solvent mixing. In addition, well-dispersed rGO in the polymer matrix improved the mechanical properties of the PCL/rGO composites [99]. Shin *et al.* also used covalent linking to prepare gelatin/rGO composite scaffolds for cardiac tissue engineering. The electrical conductivity and mechanical properties of the scaffolds were significantly improved by incorporation of rGO filler. Excellent cardiomyocyte viability, proliferation, and maturation were observed on the gelatin/rGO composite hydrogels. Moreover, the cells showed stronger contractility and faster spontaneous beating on the gelatin/rGO composite hydrogels compared to gelatin hydrogels [100].

Gold nanoparticles are regarded as ideal materials for nanomedicine, and widely used in imaging, theranostics and controlled drug delivery owing to facile synthesis, modification, tunable structure (spheres, rods, nanoplate, etc.), physicochemical properties, and biocompatibility [101,102]. Gold nanoparticles have a high electrical conductivity and have been incorporated in polymer matrices for biomedical applications. Navaei *et al.* prepared gelatin/gold nanorod composite substrates by solvent mixing and photo-crosslinking for cardiac regeneration. Both electrical conductivity and mechanical properties were improved by incorporation of the gold nanorods. Good retention, spreading and distribution of cardiac cells were observed on the conductive gelatin/gold nanorod composite hydrogel. Notably, cell-cell coupling and robust synchronized (tissue-level) beating behavior were observed [103]. PCL-gelatin/gold nanoparticle composite fibrous scaffolds were also reported, showing that the assembly of a functional cardiac tissue was improved on the conductive surface [104].

Electrically conductive polymer-based composites offer opportunities to apply electrical stimulation to cells and tissues. Electrical stimulation could direct, concentrate and isolate cell responses. Furthermore, cells could grow aligned and tissue may orientate by using electrical stimulation. Encouraging results based on electrically conductive polymer-based composites were obtained with or without electrical stimulation in cardiac tissue engineering, wound healing and nerve regeneration. However, drawbacks of long-term toxicity and non-degradability of conductive fillers still remain as problems for future applications.

2.1.3. Polymer/magnetic particle composites

Magnetic nanoparticles (MNPs) have been regarded as one of the most attractive and important nanomaterials for biomedical applications in the fields of hyperthermia, magnetic resonance imaging, tissue engineering, targeted drug and gene delivery, biosensors and labs on chip owing to their chemical and physical properties [105,106]. Both metal (*e.g.* Fe, Ni, Co) and metal oxide (Fe_3O_4, Fe_2O_3) particles were considered as magnetic fillers. However, pure metal particles are extremely sensitive to oxidation in conditions of high magnetization [107]. Therefore, iron oxide particles with a low sensitivity to oxidation and relatively strong magnetic response have been applied *in vitro* and *in vivo* for many years. Fe_3O_4 and Fe_2O_3 particles are biocompatible and relatively easy to be synthesized and functionalized [108].

MNPs and application of magnetic forces have been introduced in targeted drug delivery and tissue engineering research. Drugs or bioactive compounds can be loaded on MNPs. Using an external magnetic field, the particles can be directed to the target area. Likewise, cells loaded with magnetic particles can be adhered on a substrate or scaffold using an external magnetic field. Magnetizable scaffolds have been developed as well. When a scaffold is magnetic, an external magnetic field generates much higher magnetic field gradients as compared to a non-magnetic scaffold. Moreover, when superparamagnetic iron oxide particles are used (size <20 nm), the magnetism of the scaffold can simply be turned off by removing the external magnetic field. Such a magnetizable scaffold could be used to attract MNPs loaded with bioactive compounds multiple times to the scaffold after implantation, with varying payloads in time [109]. Moreover, by using an alternating external magnetic field, the temperature of the scaffold increases which could be applied for drug release or cancer treatment [110].
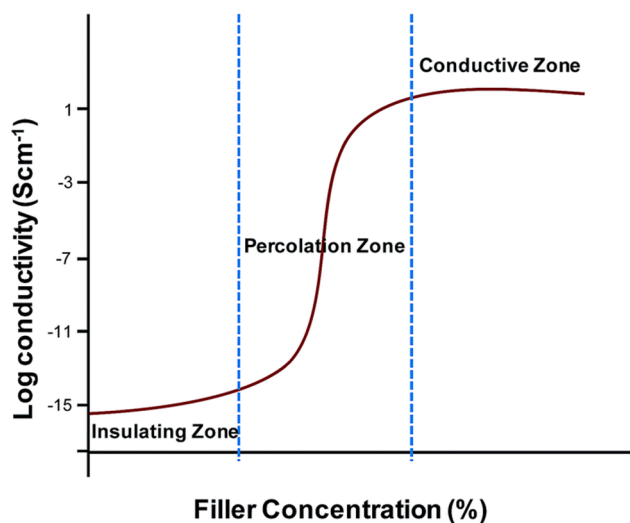
Fig. 1. Percolation curve of electrically conductive filler in polymer matrix [94].

Zhang *et al.* prepared novel fibrous polymer/magnetic particle composite scaffolds by electrospinning, composed of the tri-block copolymer poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL or PCEC) and Fe_3O_4 nanoparticles with an average size of 18 nm, see Fig. 2. Without an external magnetic field, PCEC/Fe_3O_4 scaffolds with 2–10 wt% nanoparticles showed improved NIH 3T3 cell adhesion and proliferation as compared to neat PCEC scaffolds. Moreover, the PCEC/Fe_3O_4 composites showed low cytotoxicity and hold great potential for skin tissue engineering [111].

Cai *et al.* prepared PLLA/superparamagnetic Fe_3O_4 nanoparticle composite scaffolds by electrospinning. Compared to PLLA scaffolds, composite scaffolds with 2.5–5.0 wt% NPs stimulated the proliferation and differentiation of MC3T3-E1 osteoblasts, which further increased by application of a 100 mT external magnetic field [112].

Panseri *et al.* implanted collagen-HA/Fe_3O_4 nanoparticle composite scaffolds in bone defects in rabbits. The NP content was 7 wt% and the particles had a size <50 nm. In some cases, a NdFeB magnet was co-implanted in contact with the scaffold, generating a 1.2 T magnetic field. With and without magnetic field, the extent of bone formation in the scaffolds was the same. With magnetic field, however, both the scaffold and newly formed bone were oriented, which may shorten remodeling and more quickly generate mature bone [113].

The above concepts could also be applied for magnetic scaffold fixation after implantation, or for development of scaffolds with intrinsic ability to stretch or move. Furthermore, magnetically responsive surfaces and hydrogels are currently being investigated [114].

2.1.4. Polymer/oxygen-generating particle composites

Oxygen is one of the most important factors for tissue growth and survival. Even though a promising tissue engineering scaffold with porous channels could provide nutrients and oxygen by diffusion, in the early stages after implantation of a construct the lack of vasculature to support an adequate supply of nutrients and oxygen limits tissue survival which is a challenge for clinical translation [115]. For example, during implantation of a tissue-engineered construct for a large bone defect, the *in situ* vasculature is damaged and disrupted. The implanted cells on the scaffold will suffer anoxia and nutrient deficiency in the concurrent wound bed before generation of new vasculature. Methods to vascularize engineered tissue and to connect the vasculature to the host circulation are still in development and not able to solve the oxygen demand of implanted constructs. An emerging approach is the use of oxygen-generating scaffolds to provide the initial oxygen supply. Calcium peroxide, magnesium peroxide, and sodium percarbonate are very suitable as oxygen-generating materials and have been successfully applied in tissue engineering [116]. The mechanism of oxygen generation is based on formation of hydrogen peroxide upon hydrolysis or dissolution in water, which will subsequently release oxygen. The reaction equations are as follows:

$$CaO_2 \text{ (calcium peroxide)} + 2H_2O \rightarrow Ca(OH)_2 + H_2O_2$$

$$MgO_2 \text{ (magnesium peroxide)} + 2H_2O \rightarrow Mg(OH)_2 + H_2O_2$$

$$(Na_2CO_3)_2 \cdot 3H_2O_2 \text{ (sodium percarbonate)} \rightarrow 4Na^+ + 2CO_3^{2-} + 3H_2O_2$$

$$2H_2O_2 \rightarrow O_2 + 2H_2O$$
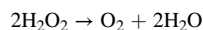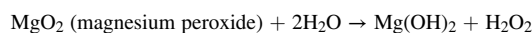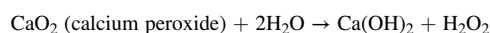
Polymer/oxygen-generating particle composites have been used to prepare 'breathing scaffolds' for the engineering of bone, cardiac, muscle and skin tissue. The polymer matrix properties affect the oxygen-release kinetics, which influence cell viability, proliferation and differentiation. Hydrophobic polymers can prevent water absorption and slow down the rate of oxygen release, while hydrophilic polymers may increase the oxygen release rate by rapid diffusion of water into the polymer structure, thus decreasing the sustainability of oxygen release. The solubility of the oxygen-generating compounds in water affect the oxygen release as well. CaO_2 has a higher solubility in water than MgO_2 (calcium peroxide 1.65 g/L and magnesium peroxide 0.86 g/L at room temperature) [117]. Therefore, CaO_2 has been frequently investigated as oxygen-generating compound in polymer-based composites for tissue engineering.

A polydimethylsiloxane (PDMS)/CaO_2 composite was prepared by Pedraza *et al.* [118]. Although they showed an effectively slow release of oxygen, PDMS is a non-degradable polymer which is not ideal as scaffold material for tissue engineering. Steg *et al.* prepared PLA/CaO_2 and PLGA/CaO_2 composites for the controlled release of oxygen [119]. However, oxygen release from both composites was faster than from control CaO_2 particles. This was explained by a relatively low pH
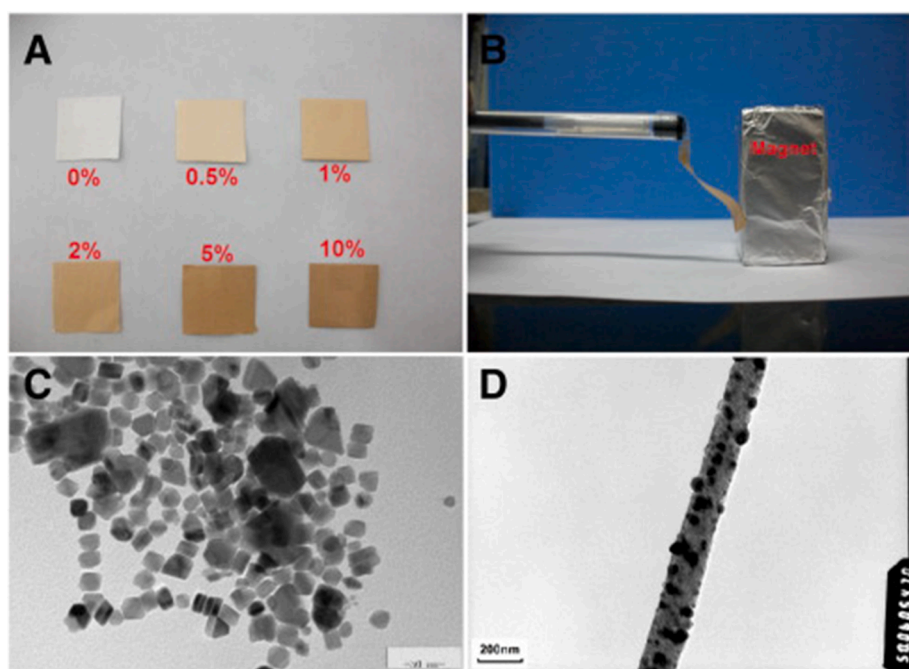

Fig. 2. Photograph of PCEC/Fe_3O_4 fibrous membranes with increasing Fe_3O_4 content (A), magnetic response of a PCEC/Fe_3O_4 composite membrane with 10 wt% Fe_3O_4 particles (B), TEM images of the Fe_3O_4 particles (C) and the PCEC/Fe_3O4 fiber containing 10 wt% Fe_3O_4 particles (D) [111].

induced by hydrolysis of the lactide-based polymers, leading to a higher solubility of the intermediate $Ca(OH)_2$, which accelerated the reaction towards H_2O_2 formation. Therefore, they prepared $PTMC/CaO_2$ composite microspheres which were able to release oxygen for a few weeks and promote mesenchymal stromal cell proliferation under hypoxic conditions *in vitro* [120]. Harrison *et al.* prepared PLGA/sodium percarbonate composite films for wound healing. The composite films released oxygen for a period of approximately 70 h. Subcutaneous implantation of the composite films in a mouse model for ischemic skin, showed significantly lower skin necrosis and higher skin viability after 7 days compared to implantation of control PLGA films [121].

Sustainable oxygen-releasing scaffolds were prepared from a PU/CaO_2 composite by Siekh *et al.* The scaffolds released oxygen over a period of 10 days and *in vitro* cardiomyoblast cell viability on the composite scaffolds under hypoxic conditions was better than on control PU scaffolds. Subcutaneous implantation of the composite scaffolds in a mouse model for ischemic skin, showed that skin necrosis could be prevented up to 9 days [122].

Oxygen deficiency after myocardial infarction leads to massive cardiac cell death. Re-introduction of oxygen into the infarcted area may protect cardiac cells and promote cardiac repair. Fan *et al.* prepared core-shell microspheres based on PLGA covered with a PVP/H_2O_2 complex. The microspheres released oxygen for 28 days and supported cardiac cell survival under hypoxic conditions *in vitro* [123].

2.1.5. Polymer/antibacterial particle composites

Bacterial infection of biomedical implants during surgical procedures remains challenging. Adhesion of bacteria on the implants may result in the formation of biofilms which are difficult to remove and may lead to failure of patient recovery [124-126]. Bacterial infection of the implant can occur simultaneously with implantation, or spread from the blood or a nearby infection site present in the patient [127]. Therefore, the availability of biomedical materials with antibacterial properties is of great importance. Various polymer-based composites with antibacterial particles have been developed [128]. Silver nanoparticles (AgNPs), magnesium oxide (MgO), and zinc oxide (ZnO) are frequently used and show activity against antibiotic-resistant bacteria [129-131].

There are two potential antibacterial mechanisms of AgNPs: direct contact of the particles with the bacterial cell membrane leading to leakage of cellular contents, and interaction of Ag^+ ions with cellular structures and biomolecules such as enzymes, lipids and DNA. For the development of biocompatible polymer/AgNP composites with antibacterial properties, the dose-dependent toxicity of Ag to tissue cells has to be taken into account. Fortunati *et al.* prepared PLGA/AgNP composite films, which started to show weight loss due to degradation of PLGA after 25 days incubation in PBS at 37 °C. This time point coincided with an increase of Ag^+ release from the films, probably due to increased water influx in the films promoting Ag oxidation [132]. PLCL/AgNP composite scaffolds were fabricated by electrospinning with 0.5 mg or 1.0 mg Ag loading per g scaffold. The biocompatibility of the scaffolds was evaluated by culturing of human epidermal keratinocytes, and antibacterial properties were investigated with staphylococcus aureus and escherichia coli cultures. Although both scaffolds were able to inhibit bacterial cell growth, the scaffold with the higher Ag content was also toxic to the keratinocytes [133]. Madhavan *et al.* prepared electrospun PCL/AgNP composite scaffolds for vascular tissue engineering. Scaffolds with 0.1 wt% AgNPs showed antibacterial properties without toxicity to cultured endothelial cells [134].

Bakhsheshi-Rad *et al.* fabricated electrospun PCL/MgO-Ag composite nanofibers as coating on biodegradable Mg alloy implants. Nanofibers containing 1–3 wt% MgO and 1 wt% Ag showed efficient antibacterial behavior toward Escherichia coli and Staphylococcus aureus [135]. PLA/ZnO nanoparticle composite scaffolds were electrospun by Rodríguez-Tobías *et al.* Tensile strength, toughness and Young's modulus of the scaffolds increased by addition of ZnO, and reached a maximum at 3 wt% ZnO. The scaffolds showed antibacterial properties when they contained more than 1 wt% ZnO [136]. MgO and ZnO have been shown to generate reactive oxygen species, leading to lipid peroxidation and bacterial membrane leakage [137,138].

2.2. Non-bioactive polymer-based composites

2.2.1. Polymer/reinforcing micro- and nano-fiber composites

Mechanical properties of tissue engineering scaffolds are one of the most important parameters, especially in the case of load bearing applications. Inorganic, organic, and carbon fillers and fibers have been used as reinforcements to improve the mechanical properties of polymer-based scaffolds for biomedical applications. Bioactive fillers that improve mechanical properties of scaffolds were discussed in 2.1.1. Concerning non-bioactive fillers, polymer fibers are mostly being used to reinforce polymer-based scaffolds. Zhang *et al.* prepared tough biodegradable materials consisting of polymer-polymer composites. A PTMC matrix was reinforced by electrospun PLA fibers. Incorporation of a small amount (5 wt%) of PLA fibers, resulted in an increase of Young's modulus and tensile strength [139].

2.2.2. Polymer/porogen particle composites

Porous scaffolds with a proper porosity, pore size, and pore shape are essential for successful tissue engineering. Current methods to fabricate porous scaffolds include particle leaching, thermally induced phase separation, gas foaming, electrospinning, and additive manufacturing. Among these methods, particle leaching is the easiest technique to obtain 3D scaffolds with varying pore size and porosity [20,140]. Sodium chloride, sugar and other leachable particles are being used. Sodium chloride is most popular as porogen, owing to its low cost, easy way of fractionation in different sizes, and the convenience of using water as leaching solution [141].

To prepare a porous scaffold, leachable particles are mixed in a polymer solution, thus forming a polymer/leachable particle composite. For a fully leachable scaffold, the particle content should be high enough to allow interconnection of the particles. By adjusting particle content and particle size, 3D scaffolds can be fabricated with varying porosity and pore size, which affect cell seeding in the scaffolds. Song *et al.* used sodium chloride particles as porogen to prepare PTMC scaffolds for vascular tissue engineering and showed that a pore size around 150 μm was favorable for smooth muscle cell proliferation [142].

Pore interconnectivity is also important for tissue formation. Using a salt fusion method, the interconnectivity of pores in a scaffold can be improved [143]. Pore shape can be tuned by the shape of the particles. Liang *et al.* prepared quasi-spherical particles as porogen to fabricate porous PLGA scaffolds, by wobbling small sodium chloride particles in melted sucrose [63]. Compared to the use of cubic salt particles, using the quasi-spherical particles resulted in higher pore interconnectivity, less time for porogen leaching, and less residual porogen present in the scaffolds after leaching. Moreover, the latter scaffolds showed improved proliferation of mesenchymal stem cells, probably due to a rougher surface of the pores.

Tissue engineering scaffolds with designed porosities and pore structures can be fabricated by additive manufacturing. Among the various additive manufacturing techniques, stereolithography (SLA) is the most accurate and allows printing at the highest resolution, see also section 3.3. Using currently available laser-based and digital light processing SLA machines, structures can be built at a resolution of 10–150 μm [144,145]. Although pores of these sizes suffice many tissue engineering applications, it can be advantageous if the scaffold contains (sub)micron pores in the struts of the polymer structure. This can be accomplished by printing a polymer/leachable particle composite. Mu *et al.* fabricated poly(ethylene glycol) scaffolds by digital light processing with rectangular macro-pores of 2 mm and micro-pores of 75–180 μm by inclusion of sacrificial sodium chloride particles during printing [146].

3. Preparation of polymer-based composite structures for biomedical applications

3.1. Porous tissue engineering scaffolds prepared by particle leaching

Particle leaching is a very convenient method to prepare porous TE scaffolds. It has been used for decades due to its simplicity and low cost. A polymer solution is combined with uniformly distributed leachable particles of a certain size range, after which the mixture is cast on a mold or template. The solvent is either evaporated or extracted, yielding a polymer/leachable particle composite [147]. Subsequently, the polymer/leachable particle composite is immersed into a solvent for the particles, to extract the porogen and obtain a porous scaffold with a specific structure. The amount of particles in the composite has to be higher than a threshold value, otherwise the particles cannot be completely leached from the polymer matrix. The main benefits of this method include the ability to adjust the porosity by tuning the amount of leachable particles, and to vary the pore size by selecting the size of the particles [148].

Song et al. developed a porous tubular PTMC scaffold for vascular TE by solvent casting of a mixture of PTMC and NaCl particles on a glass rod. After drying, the PTMC was crosslinked by gamma-irradiation and the particles were leached in water [149]. As determined by micro computed tomography (μCT), the interconnected porous scaffold had an average pore size of 110 μm, and a porosity of 85%. Human smooth muscle cells (SMCs) were seeded into the pores of the tubular scaffolds and cultured for 14 days in a pulsatile flow bioreactor. The porous structure facilitated the proliferation of the SMCs. The radial tensile strength of the constructs increased from 0.16 to 0.47 MPa, due to the presence of SMCs and deposition of extracellular matrix in the structures. A tubular PTMC scaffold, its porous structure as well as histology after culturing with SMCs are shown in Fig. 3.

Particle leaching can also be combined with other techniques such as extrusion-based 3D printing. This enables the fabrication of more complex 3D structures, as compared to solvent casting on a mold. By using a photo-crosslinkable polymer-based and particle-containing resin, a designed porous structure can be printed. The polymer struts contain the particles, which can subsequently be leached to obtain a dual porous structure. Mu et al. used this fabrication method to prepare 3D PEG structures, containing 2 mm rectangular macropores by printing and 75–180 μm micropores by leaching of NaCl particles [146].

3.2. Fibrous tissue engineering structures prepared by electrospinning

Electrospinning (ES) has been widely used in TE to develop micro- or nano-fibrous scaffolds with a large surface area and high porosity. ES equipment is composed of a syringe pump, a metal needle, a high-voltage power supply, and a grounded collector. The latter can be of various shapes, such as a flat plate or a mandrel, depending on the desired shape of the scaffold. A polymer solution or melt is driven through the charged needle, resulting in a charged liquid jet that is attracted by the grounded collector. During its travel to the collector, the jet solidifies due to solvent evaporation or cooling. This results in the deposition of micro- or nano-fibers on the surface of the collector yielding porous structures very high porosities in which the pore structure is fully interconnected [150]. Electrospun fibrous mats based on biodegradable polymers such as PLA and PCL showed better cell adhesion than non-fibrous substrates of the same materials [151]. To combine the benefits of synthetic polymers and functional fillers, fibrous polymer-based composite scaffolds were prepared by ES of mixtures of polymers and fillers. Successful incorporation of functional fillers in electrospun polymer fibers is dependent on the size of the fillers. Graphene sheets, carbon nanotubes, nano-hydroxyapatite and silver particles of either nano- or sub-micron size are suitable fillers for polymer fibers to obtain bioactive scaffolds [152].

Yu et al. fabricated PCL-collagen/carbon multi-walled nanotube (MWNT) composite fibrous nerve guides by ES for peripheral nerve regeneration [153]. Fig. 4 shows the carbon MWNTs, composite fibers, a conduit, and implantation of the conduit. Upon loading with carbon MWNTs, the hydrophilicity of the scaffolds increased due to carboxyl groups present in the MWNTs. The mechanical properties of PCL-collagen fibrous meshes, in terms of Young's modulus, elongation at break and maximum strength, increased by incorporation of carbon MWNT filler. The degradation rate of the composite scaffolds was lower than that of the PCL-collagen scaffolds. Schwann cell adhesion and elongation were enhanced on the electrospun composite scaffolds. *In vivo* studies demonstrated that PCL-collagen/carbon MWNT composite conduits effectively promoted sciatic nerve regeneration in rats and prevented muscle atrophy, without serious chronic inflammation.

PCL/GO composite fibrous scaffolds were prepared by Chaudhuri *et*
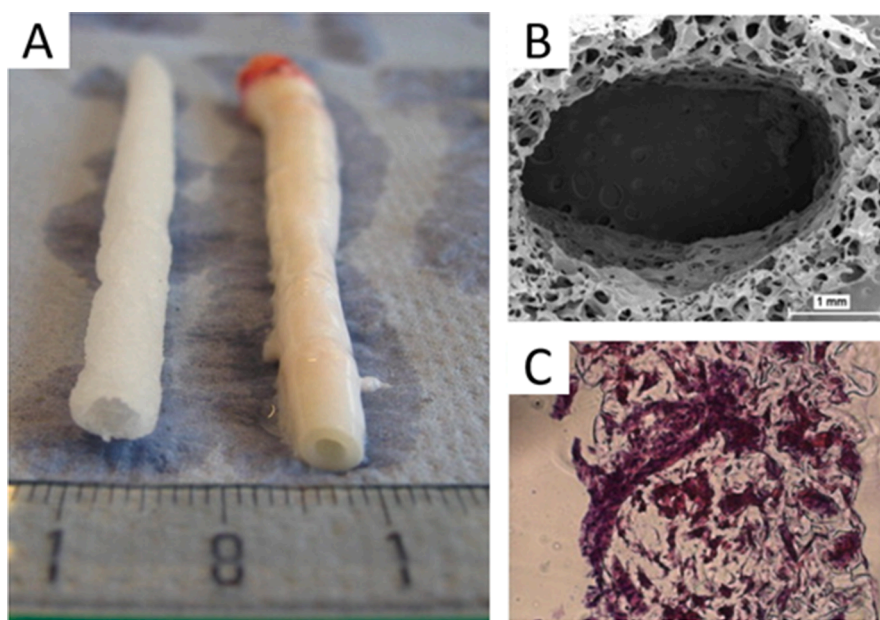
Fig. 3. A, Photograph of a porous tubular PTMC scaffold (left) and a porcine carotid artery (right). B, SEM image of a cross-section of a tubular PTMC scaffold. C, SMCs cultured for 7 days in a porous tubular PTMC scaffold in a pulsatile flow bioreactor. Cross-section stained with hematoxylin and eosin, magnification 100x.
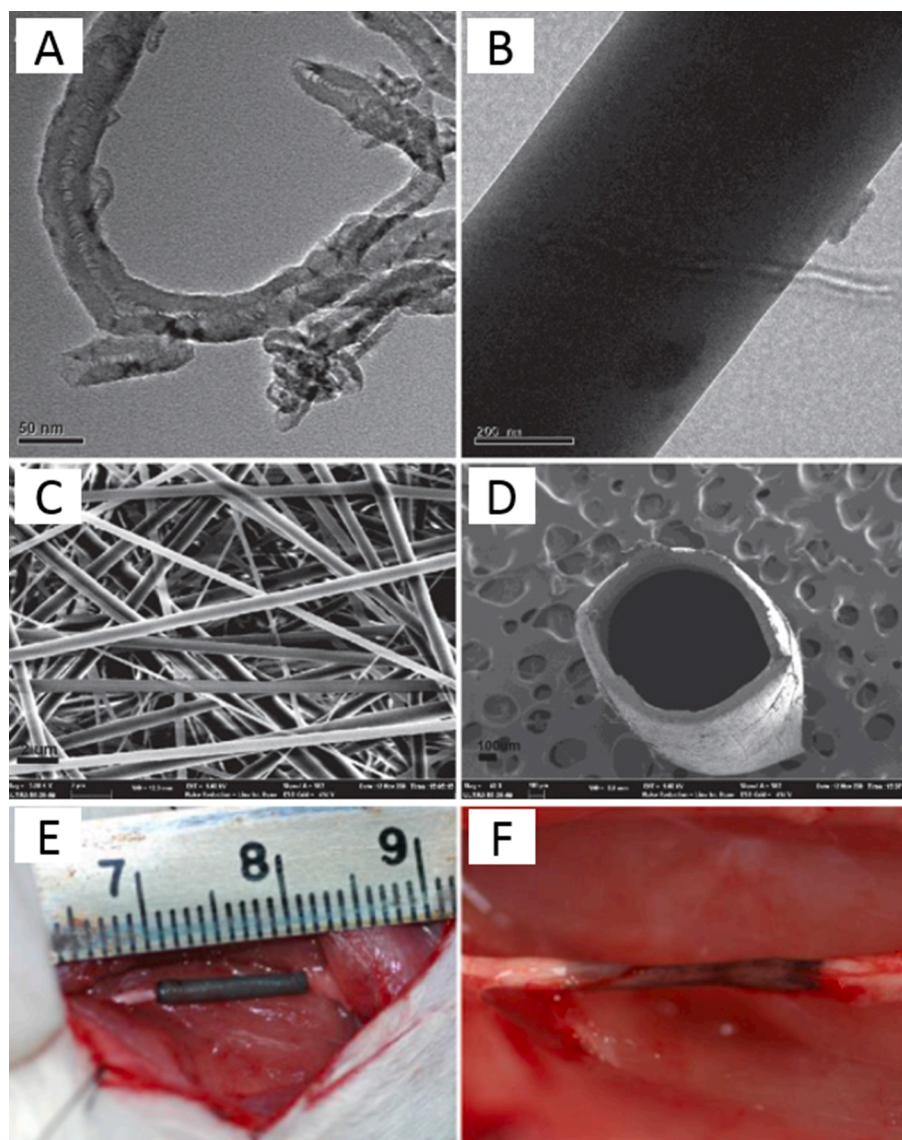
Fig. 4. TEM images of carbon MWNTs (A) and electrospun PCL-collagen/carbon MWNT composite fiber (B); SEM images of PCL-collagen/carbon MWNT composite fiber mesh (C) and nerve guide conduit (D). Surgical implantation of PCL-collagen/carbon MWNT composite nerve guide conduit to bridge an 8 mm sciatic nerve defect in a rat (E) and macroscopic image of the regenerated nerve four months postoperatively. The bar in A = 50 nm, in B = 200 nm, in C = 2 μm, in D = 100 μm [153].

al. by means of ES. The electrical conductivity of PCL scaffolds was enhanced by incorporation of GO particles. The composite scaffold exhibited excellent properties for myoblast differentiation, and has potential to be applied for skeletal muscle regeneration [154].

Even though ES is a relatively simple and quick method to manufacture fibrous scaffolds that support cell adhesion and proliferation, fabrication of complex structures with load bearing architectures is still a challenge and limits its biomedical applications [155].

3.3. Patient-specific porous structures and implants prepared by additive manufacturing

Additive manufacturing (AM), also known as 3D printing, offers an engineering route to build complex structures in a rapid and cost-effective way. A wide range of biomaterials such as polymers, metals, ceramics have been processed to become 3D printable for AM applications, according to the requirement and mechanism of the printing equipment [23]. AM techniques include stereolithography (SLA) using laser-based systems and digital light processing (DLP), fused deposition modeling (FDM), selective laser sintering (SLS), and extrusion-based 3D printing [156,157]. AM is widely used for biomedical applications, *e.g.* to fabricate tissue engineering scaffolds, bone implants, and microfluidic

chips for organ models. In contrast to traditional fabrication approaches such as solvent casting and ES, AM involves layer by layer printing of virtual slices of a designed 3D structure. It is a rapid manufacturing method to obtain complex scaffolds and patient-specific implants [158]. Synthetic polymers such as PCL, PEG, PDLLA, PTMC and natural polymers such as gelatin and cellulose have been used to prepare scaffolds by AM for a variety of biomedical applications. Polymer-based composites with bioactive properties are interesting materials for the fabrication of functional structures by means of AM [159 160].

Advantages of AM techniques to create biomimetic tissue structures include the formation of highly interconnected pores to facilitate tissue formation, and tuning of the mechanical strength by adjusting the design of the structure. Scaffolds built by AM can be based on a computer design or on imaging data, *e.g.* obtained by CT scanning. Among all AM techniques, laser-based SLA and DLP are most suitable for scaffold fabrication due to their high resolution, ability to build complex structures, and ease of tailoring the scaffold properties by adjusting the liquid resin formulation [161,162].

Dienel *et al.* fabricated bioresorbable implants based on a PTMC/TCP composite resin for repair of damaged bone tissue [163]. 3D composite scaffolds containing up to 60 wt% β-TCP could be built by DLP. By using a slightly lower β-TCP content of 51 wt%, a large-size patient-specific

implant was manufactured at high resolution based on imaging data. The mechanical properties of the structure significantly increased by addition of β-TCP. The porous implant containing bioactive TCP and biodegradable PTMC perfectly matched the defect shape of the patient. Fig. 5 shows the imaging-based defect model and the porous PTMC/β-TCP composite implant.

Geven *et al.* used PTMC/HA composites to fabricate patient-specific orbital floor implants by DLP based on CT imaging data [164]. Photo-crosslinkable PTMC-based resins were formulated with 20 wt% and 40 wt% nano-HA. Mechanically stable orbital floor implants were precisely prepared using these composite resins, and shown to support the culturing of human bone marrow mesenchymal stem cells.

Although AM is able to improve the performance of biomaterial-based structures for medical applications, there are still challenges. Optimal scaffold structures for specific biomaterials are not well known, as relevant mechanical, physical and biological properties of the biomaterials should be considered during the design phase. The optimal shape, pore size and structure for specific applications still need to be determined. There are limited biomaterials available for processing by AM techniques. Commercial materials with the best accuracy in AM are not biocompatible, not biodegradable and lack bioactivity. Therefore, development of novel biomaterials for use in AM and improvement of AM techniques for currently available biomaterials are both required [165].

4. Conclusions and future perspectives

Polymer-based composites are highly promising materials to be used as biomedical implant materials for diverse biomedical applications. There are several advantages of using polymer-based composites, such as low cost of available natural and synthetic polymers and ease and tunability of manufacturing techniques. Several fillers with bioactive or non-bioactive properties hold opportunities in the engineering of suitable scaffolds or implants for tissue engineering and regenerative medicine applications.

The current techniques, applying polymer-based composites, need in general fine-tuning to optimize the structure required in the specific application. Polymer-based composite scaffolds already showed not only high cell adhesion, biocompatibility, and biodegradability but also outstanding bioactivities in terms of tissue formation, function, stimulation, survival and antibacterial properties during *in vitro* and *in vivo* experiments.

However, there are still challenges because of the limited choice of bioactive and functional fillers, control of the bioactive expression in the polymer matrix, and manufacturing techniques of suitable structures. Polymer-based composites should be adapted to the biological micro-environment, thereby accelerating tissue repair and regeneration. Studies on the relationship between the material properties of a specific polymer-based composite, its structure, physical and mechanical properties and biological response for specific biomedical applications remain necessary.

Two developing trends in the field of polymer-based composites for biomedical application are summarized below.

1) Combination of different functional fillers in a polymer matrix provides opportunities to enable multifunctional expression. Modugno *et al.* reported that the combined use of carbon nanomaterials, metal nanoparticles and polymers showed good results for diagnosis, imaging, therapy and theranostic applications, thanks to the extraordinary structural, optical, chemical and thermal properties of the resulting materials [166]. It is to be expected that more polymer/multifunctional filler composites will be developed as materials for the engineering or repair of tissues.

2) Polymers express tunable characteristics due to their wide range of physical and chemical properties. Some polymers show 'intelligent' characteristics such as stimuli-responsive behavior. This causes shape changes by stimulative factors such as temperature, humidity, solvent, pH, light, and others. These controlled shape changes provide opportunities for the manufacturing of complex structures by so-called 4D printing, in which time is the fourth dimension. 4D printing uses AM technologies to fabricate stimuli-responsive 3D parts that can form novel structures when subjected to appropriate
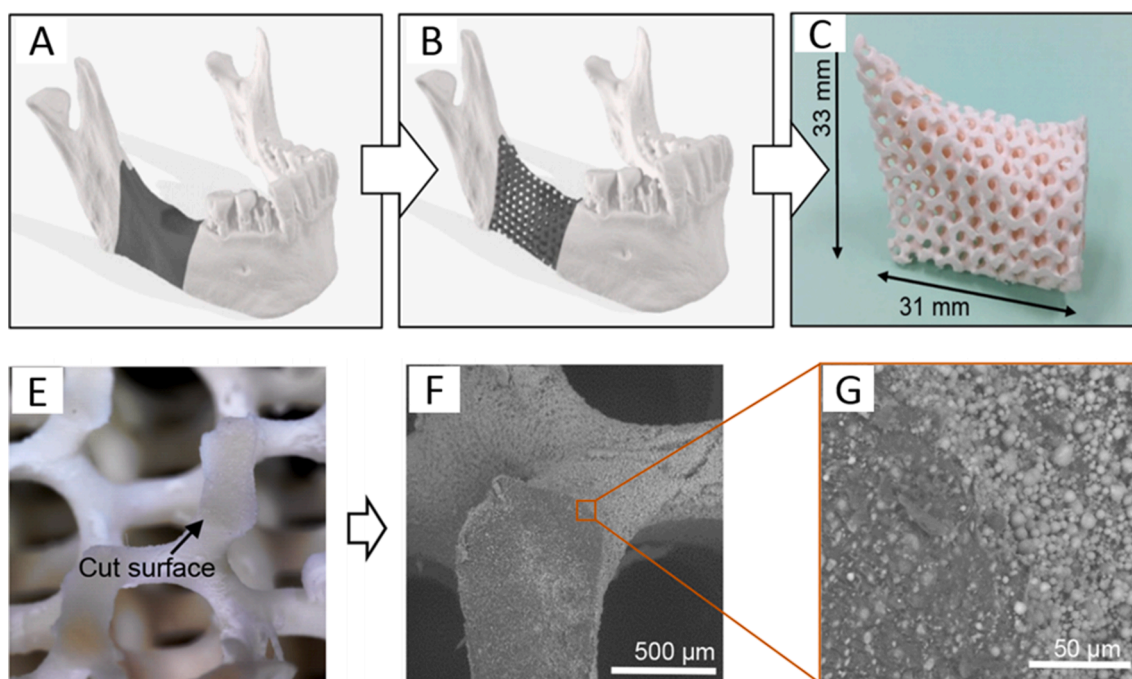

Fig. 5. A, imaging data (grey) to fix a defect in a human jaw; B, defect model of porous patient-specific implant; C, PTMC/TCP composite implant printed by DLP. E, macroscopic image of a cut PTMC/TCP implant with gyroid pore architecture; F, SEM image of the cut surface of this scaffold; G, high magnification of this cut surface, where polymer matrix and TCP filler can be observed clearly [163].

stimuli [167]. As this involves multi-material printing, it is to be expected that polymer-based composites will be used in the 4D printing of complex and multifunctional structures for biomedical applications.

Declaration of Competing Interest

The authors state that they do not have any conflict of interest.

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