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Polymer-bioceramic composites for tissue engineering scaffolds

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Abstract Designing tissue engineering scaffolds with the required mechanical properties and favourable microstructure to promote cell attachment, growth and new tissue formation is one of the key challenges facing the tissue engineering field. An important class of scaffolds for bone tissue engineering is based on bioceramics and bioactive glasses, including: hydroxyapatite, bioactive glass (e.g. Bioglass®), alumina, TiO_2 and calcium phosphates. The primary disadvantage of these materials is their low resistance to fracture under loads and their high brittleness. These drawbacks are exacerbated by the fact that optimal scaffolds must be highly porous (>90% porosity). Several approaches are being explored to enhance the structural integrity, fracture strength and toughness of bioceramic scaffolds. This paper reviews recent proposed approaches based on developing bioactive composites by introducing polymer coatings or by forming interpenetrating polymer-bioceramic microstructures which mimic the composite structure of bone. Several systems are analysed and scaffold fabrication processes, microstructure development and mechanical properties are discussed. The analysis of the literature suggests that the scaffolds reviewed here might represent the optimal solution and be the scaffolds of choice for bone regeneration strategies.

Introduction

Tissue engineering is a discipline based on the principle that the living body has the potential of regeneration and combines engineering and cell biology concepts towards the creation (growth) of new human tissue [1].

One significant branch of tissue engineering involves the use of engineered materials with high porosity, termed scaffolds, which should act as (temporary) 3D templates for cell adhesion, proliferation, migration and ultimately the formation of new tissue [2]. The structure and properties of these scaffolds are pertinent to the tissue concerned and the loads it will experience in vivo. The generic requirements for ideal tissue engineering scaffolds have been discussed frequently in the literature [3–6]. Since scaffolds are intended as temporary artificial extra cellular matrix (ECM) to guide 3D tissue formation, materials that most closely resemble the intended tissue replacement are the most promising candidates. The challenges faced by tissue engineers are linked to the complex combination of properties required in an ideal scaffold. This is particularly significant in bone tissue engineering where the structural competence of the scaffold and its ability to sustain mechanical loads are essential.

An ideal scaffold for bone engineering should fulfil a number of criteria: (1) biocompatibility to enable cell attachment, differentiation and proliferation, (2) osteoconduction and osteoproduction (i.e. the material should induce strong bone bonding), (3) biodegradability at a rate matching the rate of new tissue formation, (4) mechanical competence, e.g. the strength of the scaffolds should be sufficient to provide mechanical stability in load bearing sites prior to regeneration of new tissue, and (5) interconnected porous structure with porosity >90% and pore size between 300 and 500 μm for cell penetration, tissue in growth and vascularisation [6, 7].

An important class of scaffolds for bone tissue engineering is based on biodegradable and bioactive ceramics and glasses, including: hydroxyapatite (HA) ($Ca_{10}(PO_4)_6(OH)_2$),

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bioactive silicate glasses and calcium phosphates. There are also research efforts in producing scaffolds from other oxide ceramics, notably alumina, titania and zirconia. Although these are not biodegradable ceramics, they find application in ex vivo approaches or in bioreactors. Bioceramic scaffolds exhibiting highly porous structures are being fabricated (with different degrees of success) by a variety of techniques, as reviewed elsewhere [8].

Since the inorganic component of bone is made of carbonated hydroxyapatite, many calcium phosphate-based scaffolds have been extensively studied [8]. These scaffolds are also bioactive, e.g. they induce a strong bond to bone when implanted. Bioactive glasses, discovered by Hench in 1969 [9], and related silicate glass–ceramics constitute another group of bioactive materials being highly considered in tissue engineering scaffold development [10–13] due to their high bioactivity. The primary advantage that makes bioactive glasses promising scaffold materials is their rapid rate of surface reactions which leads to fast tissue bonding without the formation of scar tissue. Moreover bioactive glass of composition 45S5 Bioglass® (in wt%: 45% SiO_2, 24.5% Na_2O, 24.4% CaO and 6% P_2O_5) exposes critical concentrations of Ca, Si, Na and P ions which have been shown to activate genes in osteoblast cells thus stimulating new bone formation in vivo [14].

The main advantage of inorganic scaffolds made of HA, bioactive glass or other bioceramics is their high biocompatibility. They suffer however from low mechanical strength and high brittleness. One approach being investigated to improve the mechanical properties of these brittle scaffolds is to coat them with polymer layers, in order to fill existing cracks in the bioceramic structure with a polymer phase. It is hypothesised that polymer filaments will bridge cracks during fracture thus increasing the scaffold toughness, in a similar manner as collagen fibres enhance the fracture toughness of bone [15]. The approach has been extended to include scaffolds with interpenetrating network structures, where the polymer is added not only as a surface coating but is also made to penetrate and infiltrate the pore walls (struts) of the scaffold via remaining porosity or microcracks. In addition, the polymer phase can have other functions, such as being a carrier for drugs and other biomolecules, e.g. growth factors, hence enhancing the functionality and bioactivity of the scaffolds.

In the present paper we review the relevant previous work in the field of polymer-coated inorganic scaffolds and scaffolds with interpenetrating network microstructure. The review is organised in the following manner: section "Fabrication of inorganic scaffolds" includes a description of three typical fabrication technologies developed for production of bioceramic scaffolds, section "Bio-ceramic scaffolds combined with polymers" contains a detailed analysis of the available literature on polymer-coated and interpenetrating microstructure systems, while section "Recent developments: bioactive glass–ceramic/PDLLA composite scaffolds with interpenetrating microstructure" presents recent results on a Bioglass®/poly(D,L-lactide) (PDLLA) composite system, as an example of a novel scaffold with interpenetrating network structure.

Fabrication of inorganic scaffolds

This section will briefly review three methods which are widely used for fabrication of inorganic scaffolds. A more detailed description of these and other scaffold technologies, including computer assisted methods (e.g. rapid prototyping), has been presented elsewhere [8].

Foam replication method

The earliest production of macroporous ceramics by the foam replica method dates back to the early 1960s, when Schwartzwalder and Somers [16] used polymeric sponges as templates to prepare ceramic cellular structures of various pore sizes, porosities and chemical compositions. In the replica method approach, synthetic (e.g. polymer foams, typically polyurethane, PU [10]) and natural (e.g. coral, wood [17]) templates of desired macrostructure can be used to fabricate macroporous ceramics. The template is initially soaked into a ceramic suspension until the struts are homogeneously coated with the ceramic material. The coating should be viscous enough to avoid dripping by thixotropic effects. Thickening additives such as clays, colloidal silica, carboxymethyl cellulose and polyethylene oxide in combination with conventional dispersants can be used [17–20]. Moreover binders and plasticizers are added to the initial suspension in order to prevent cracking of the struts during the subsequent heat-treatment process. The ceramic-coated polymeric template is subsequently dried and the polymer template is burnt out through careful heating between 300 and 800 °C and finally densified by sintering in an appropriate atmosphere at temperatures between 1,000 to 1,500 °C, depending on the material. Highly porous ceramics can be produced reaching open and interconnected porosity levels in the range 40–95% with sizes of pores between 200 μm and 3 mm. One possible disadvantage of the method is the tendency to produce a hole in the centre of each strut resulting from the removal of the polymer skeleton on heating. The presence of this hole can negatively affect the mechanical properties of the foams [10]. However the approach of filling the hole with a polymer, as discussed below, leads to improved mechanical behaviour exploiting the interaction between the polymer and ceramic phases.

Alumina [21–23], titania [24, 25], zirconia [26, 27] and Bioglass® [10, 28] foams are examples of scaffolds produced by the replica method using polymer sponges as the synthetic templates. Figure 1 shows the typical structure of a Bioglass®- based glass–ceramic scaffold fabricated by the foam replica method [10].

A great variety of hydroxyapatite and calcium phosphate scaffolds have been also produced using both synthetic polymer templates as well as coral as natural templates [29–34]. The polymeric sponge method has been also proposed to manufacture macroporous calcium phosphate glass scaffolds of composition $CaO–CaF_2–P_2O_5–MgO–ZnO$ [35] and glass-reinforced HA foams [36]. Several approaches are being investigated to improve the mechanical properties of foams produced by replication methods. It has been reported for example that combination of replicating techniques with gelcasting of foams (discussed in [8, 37, 38]) leads to HA cellular structures of improved fracture strength [32].

Sacrificial template method

This method leads to porous materials having a negative replica of the original sacrificial template as opposed to the (positive) replica obtained with the method discussed above. The technique involves the preparation of a biphasic composite comprising a homogenously dispersed sacrificial phase in a continuous matrix of ceramic or glass particles [39]. The sacrificial phase is ultimately extracted from the partially consolidated matrix to generate pores within the microstructure. The removal of the sacrificial phase does not lead to flaws in the struts as is the case of positive replica methods. Therefore, the mechanical strength of the structures made by the sacrificial template method is usually higher than that of scaffolds fabricated by the replica method; however, porosity and pore interconnectivity are substantially lower [39, 40]. Hydroxyapatite porous bodies produced from PMMA particles, PVB beads, wax and starch particles, as well as naphatane and sucrose [41–45] as sacrificial materials have been made by this method.

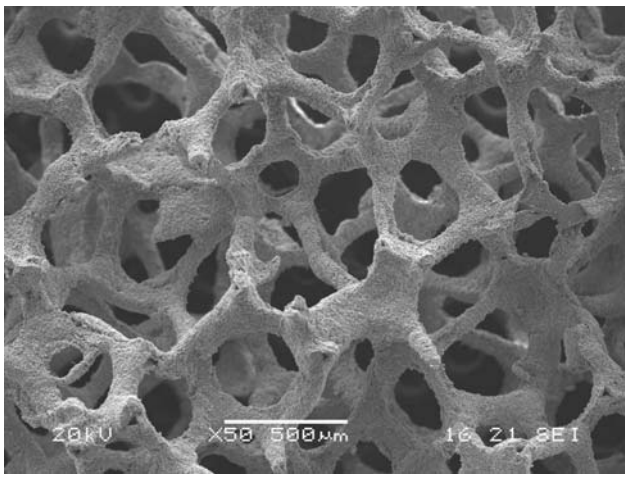

Fig. 1 Macroporous structure of a Bioglass®-based glass–ceramic scaffold fabricated by the foam replica method using PU sponge as sacrificial template [10]

Direct foaming methods

In the direct foaming method approach, air is incorporated into a ceramic suspension which is then set in order to create a structure of air bubbles [46, 47]. In most cases, the consolidated foams are afterwards sintered at high temperatures to produce a high-strength porous ceramic. Stabilisation of air bubbles in the initial suspension is the most critical process. The stability of the air bubbles can be achieved by various surfactants and particle stabilisers. The foam structures prior to solidification are important because they influence the total porosity, pore size, wall thickness and microstructure of the final products. The porosity of foams produced by this method typically varies between 40% and 93%, whereas the average pore size can change from 10 to 300 μm.

Examples of scaffolds produced from the direct foaming technique are hydroxyapatite and calcium phosphate scaffolds [48, 49] obtained by gel-casting setting process as well as sol–gel derived bioactive glass scaffolds [46, 50].

Bioceramic scaffolds combined with polymers

The basic process developed to fabricate both polymer-coated inorganic scaffolds and polymer–ceramic scaffolds with interpenetrating network microstructures consists of infiltrating a sintered or partially sintered bioceramic scaffold with the polymer phase [51], as schematically shown in Fig. 2. In most cases, a biodegradable synthetic polymer is used. This approach is inspired by the fact that nearly 60 wt% of bone is constituted of an inorganic phase (hydroxyapatite) and the rest is the organic phase (collagen) and water. It is well known that the fracture behaviour of mineralised tissues such as bone (and dentin) is influenced by the optimal interaction of the inorganic and organic phases, and the toughening mechanisms induced by the presence of collagen fibrils in bone are starting to be elucidated [52, 53]. Thus, the addition of a polymer phase to a porous ceramic scaffold is expected to enhance the fracture toughness of the composite and to allow the functionalisation of the surface to induce enhanced bioactivity. Investigations on dense materials have also shown improved mechanical properties of the interpenetrating polymer/ceramic composites as compared to those of

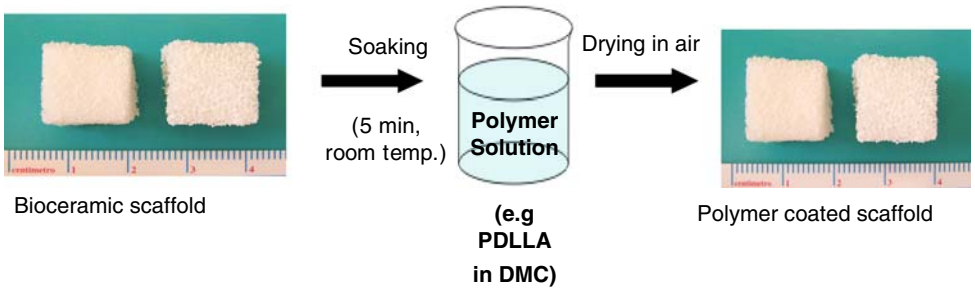

Fig. 2 The polymer solution dipping method developed to coat bioceramic scaffolds with biodegradable polymers, e.g. PDLLA solution in dimethyl carbonate (DMC) [25]

monolithic brittle ceramics or glasses [54]. In the following paragraphs, specific polymer-coated bioceramic scaffolds and polymer–bioceramic scaffolds with interpenetrating network microstructure are discussed. The alternative of fabricating hybrid polymer–ceramic composite scaffolds, e.g. exploiting the molecular mixing of inorganic and organic phases for example in sol–gel based approaches, has also been explored [55, 56]; however those hybrid materials will not be considered in the present review.

Calcium phosphate-based scaffolds

As mentioned above, calcium phosphates including hydroxyapatite (HA), tricalcium phosphate (TCP) and calcium phosphate cements (CPC) play an important role in the development of scaffolds for bone tissue engineering. Miao et al. [57] have produced porous calcium phosphate ceramics with interconnected macropores (>200 μm) and microporosity (~5 μm) as well as high porosities (~80%) by firing polyurethane (PU) foams coated with calcium phosphate cement at 1,200 °C. The open micropores of the struts were infiltrated with poly(lactic-co-glycolic acid) (PLGA) to achieve an interpenetrating bioactive ceramic/biodegradable polymer composite structure. This work followed from earlier work by the authors [58], where PLGA-coated porous CPC scaffolds were developed exhibiting compressive strength values of up to 4 MPa. In their most recent investigation Miao et al. [57] further coated the PLGA filled struts with a 58S bioactive glass (33 wt%)-PLGA composite coating. The resulting scaffolds proved to be bioactive and exhibited even higher compressive strength values (up to 7.7 MPa) and compressive moduli of up to 3 GPa, these values being comparable to those of natural spongy bone. Miao et al. [59] have also developed highly porous HA/TCP composite scaffolds (87% porosity) infiltrated with PLGA to form ceramic–polymer interpenetrating microstructures. In these composites the addition of PLGA led to a significant improvement of the compressive strength [59]. The mechanism based on crack bridging, previously investigated by Pezzotti et al. [60], was proposed to explain the strengthening and toughening in the composites, evident by the presence of polymer ligaments that were stretched upon crack opening along the wake of the crack [59].

Li et al. [61] have produced macroporous HA ceramics with nanoporous struts. Then, a commercially available biopolymer, Polyactive™, was incorporated into the struts by vacuum infiltration. As a result, the mechanical properties of the porous composites with interpenetrating organic/inorganic phases were found to improve significantly. Similar results were achieved in earlier investigations by Tencer et al. [62, 63], who found that coating the internal surfaces of porous HA with a biodegradable polymer (PDLLA) improved the compressive strength significantly, but the coated material was shown to lack bioactivity.

Since bioactive silicate glasses exhibit higher bioactivity [64] or have faster rates of apatite formation than crystalline HA, bioactive glasses have been combined with HA scaffolds in bioactive composite coatings. Huang and Miao [65], for example, have used tetracalcium phosphate ($Ca_4(PO_4)_2O$; TTCP) and dicalcium phosphate anhydrous ($CaHPO_4$; DCPA) macroporous ceramics and PLGA/Bioglass® composite to coat HA scaffolds. The bioactive glass addition to the polymer coating increased the bioactivity of the scaffolds. The replication technique was combined with H_2O_2 (hydrogen peroxide) pore forming method to produce the macroporous HA scaffolds which resulted in an increase in porosity and smaller size of the pores [65]. The HA scaffolds were first coated with 40 wt% PLGA and further coated with bioactive glass/PLGA to increase the bioactivity as well as the compressive strength (5.8 MPa). Figure 3a shows a SEM micrograph of the microstructure of Huang and Miao's composites [65] showing that the PLGA phase fills the open micropores in the struts of the hydroxyapatite foam. It was observed that PLGA also filled the large defects (central hole) in the struts, as shown in Fig. 3b.

Nakahira et al. [66] investigated hybrid hydroxyapatite/polymer composites by the infiltration of nylon into porous hydroxyapatite prepared from whisker-like powder at sintering temperatures between 800 and 1,000 °C. These HA/nylon composites were shown to have fracture toughness (K_{IC}) of 1.65 $MPam^{1/2}$, and also they showed good bioactivity according to the results of SBF immersion tests.

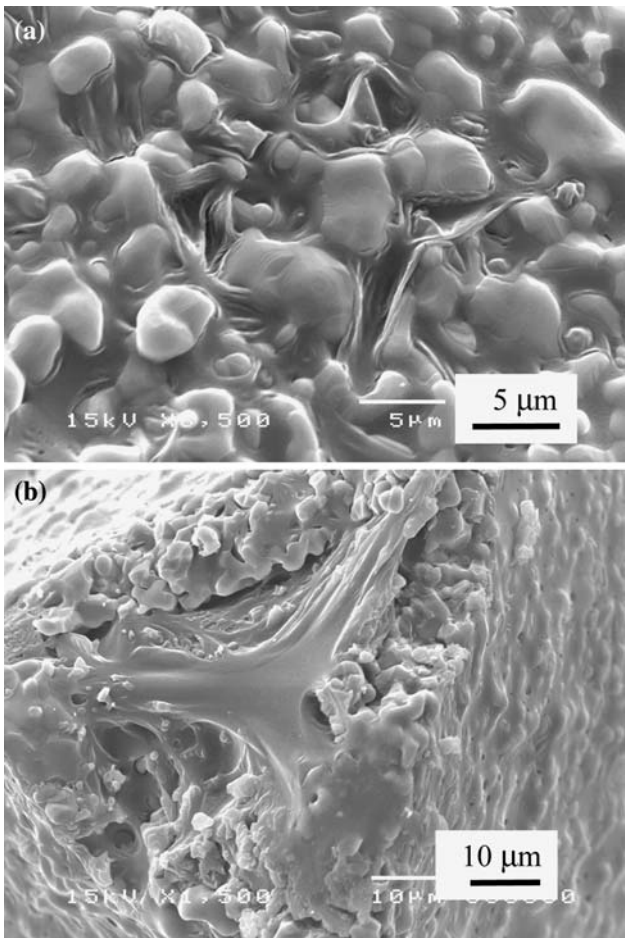

Fig. 3 SEM micrographs showing the microstructure of PLGA/HA composite scaffolds fabricated by Huang and Miao [65]: (**a**) PLGA phase (dark) filling open micropores in a HA strut (bright) and (**b**) PLGA phase filling the large defect in the centre of a strut

A related study was published by Pezzotti et al. [54] who produced HA composites with relative porosity of 32% by cold-isostatic pressing followed by sintering. The HA structures containing percolated submicron porosity channels were infiltrated with 6-nylon to produce composites with improved fracture properties. The results of this investigation also demonstrated the effect of different types of polymers with different mechanical properties on the overall fracture behaviour of the composites.

Miao et al. [67] have studied a composite consisting of three interpenetrating networks: tricalcium phosphate (TCP), HA and PLGA. Firstly, the porous TCP network was produced by coating a PU foam with hydrolysable α-TCP slurry. Then, a HA network was derived from calcium phosphate cement (CPC) filled in the porous TCP network. Finally, the remaining open pore network in the HA/TCP composites was infiltrated with PLGA. These composites feature three phases with different degradation behaviour. It was postulated that bone would grow on the fastest degrading network (PLGA), while the remaining phases would remain intact thus maintaining their geometry and load bearing capability. The achieved compression strength of the PLGA coated material was remarkable at 30 MPa; however the final porosity of the coated foams was not reported in the original study [67].

In other developments targeted to improve bone ingrowth and osseo integration, HA scaffolds have been coated with HA particles and polycaprolactone (PCL). The PCL matrix also acted as carrier for the antibiotic drug tetracycline hydrochloride which was entrapped within the coating layer [68, 69]. HA scaffolds have been also coated with PLLA and compressive strength values of ~3 MPa were achieved however for a pore volume fraction of 70%, which can be considered lower than what is ideal for bone tissue scaffolds [70]. With the PCL/HA composite coating, on the other hand, the mechanical properties such as compressive and elastic modulus were improved by several orders [68, 69]. The release rate of the drug sustained for prolonged periods was found to be dependent on the degree of coating dissolution. In a parallel study by the same group [71], HA porous scaffolds were coated with polymer (PCL)-HA hybrids for use as wound healing and tissue regeneration substrates. The antibiotic Vancomycin was incorporated in the PLC matrix in different concentrations and the drug release profile was determined. The encapsulated drug within the coated scaffold was released in a highly sustained manner as compared to the rapid release of drugs directly adsorbed on the pure HA scaffold [71]. These studies were the first to show the enhanced function of a scaffold achieved by applying a polymer coating. Not only are the mechanical properties improved but the scaffold also becomes a vehicle for targeted drug delivery.

Bioactive glass-and calcium silicate-based scaffolds

Chen et al. [72] have investigated the mechanical properties and bioactivity of Bioglass®-based scaffolds, before and after applying a PDLLA coating on the foam struts. They found that the bioactivity of scaffolds upon immersion in simulated body fluid (SBF) was maintained in the PDLLA-coated foams, while the transformation of the crystalline phase ($Na_2Ca_2Si_3O_9$) to amorphous calcium phosphate, which is a typical feature in Bioglass® derived glass–ceramic scaffolds [10], was retarded by the PDLLA coating. The compressive and three-point bending strengths were slightly increased by the PDLLA coating, and the toughness was considerably enhanced, e.g. the work-of-fracture of the foams after PDLLA coating was 20 times higher than the value without PDLLA coating. The polymer layer was made to cover and fill the microcracks in the strut, improving the mechanical stability of the scaffold as the polymer layers induced a crack bridging

mechanism, as mentioned above. The mechanical strength of as-sintered foams decreased to a large extent (from 0.3 to 0.03 MPa) upon immersion of the foams in SBF when the crystalline phase $Na_2Ca_2Si_3O_9$ transformed to amorphous calcium phosphate. However the mechanical performance was shown to be maintained in the polymer-coated foams even after immersion in SBF for 8 weeks [72]. The surface of the foams developed a nanostructured composite layer upon immersion in SBF formed by newly grown HA nanocrystals onto the polymer coating layer. It is expected that this in situ formed nanostructured layer will further improve the mechanical integrity of the constructs as well as serving as nanoscaled surface topography for the efficient attachment and proliferation of osteoblast cells [73]. PDLLA was the first biodegradable polymer considered to coat Bioglass® scaffolds [72]; however, more recently, a new polymer based on a polyhydroxyalkanoate has been investigated as alternative coating material [74]. The polymer chosen, poly(3 hydroxybutyrate), PHB, is a natural thermoplastic polymer produced by many types of micro-organisms which can be extracted as a stereoregular, optically active, isotactic polyester with high purity and without any inclusion of catalyst residues [75]. In addition to its biocompatibility and biodegradability PHB has been reported to have piezoelectric properties, which can stimulate bone growth and aid in healing. Bretcanu et al. [74] used for the first time bacteria-derived PHB to infiltrate 45S5 Bioglass® scaffolds. These scaffolds are intended for applications in cancellous bone substitution after trauma incidents. The pore morphology and macrostructure of the scaffolds before and after coating with PHB as well as the coating homogeneity were investigated. It was found that polymer coating did not affect the interconnectivity of the pore structure; however, the coating was not fully homogeneous, as shown in Fig. 4. The compressive strength of the coated and uncoated scaffolds was measured and it was found that the polymer coating considerably increased the compressive strength of the scaffolds ($\sim$1.5 MPa at 85% porosity). The formation of HA crystals on the scaffolds' surface was investigated confirming the high bioactive character of the scaffolds, as after 2 weeks of immersion in SBF, a uniform layer of HA crystals formed. The high exposure of the bioactive glass surface to SBF, due to the partial disruption of the polymer layer (shown in Fig. 4), is thought to have led to this result, which indicates that, as the polymer has a long degradation time, a composite HA/P(3HB) coating layer can form in situ on the scaffold surfaces [74].

In separate developments, Wu et al. [76] have produced a highly porous interconnected ($\sim$99.9%) calcium silicate scaffold coated with PDLLA by the sponge replica technique. They reported compressive strength values of up to 1.45 MPa in air and 1.10 MPa in PBS. The PDLLA

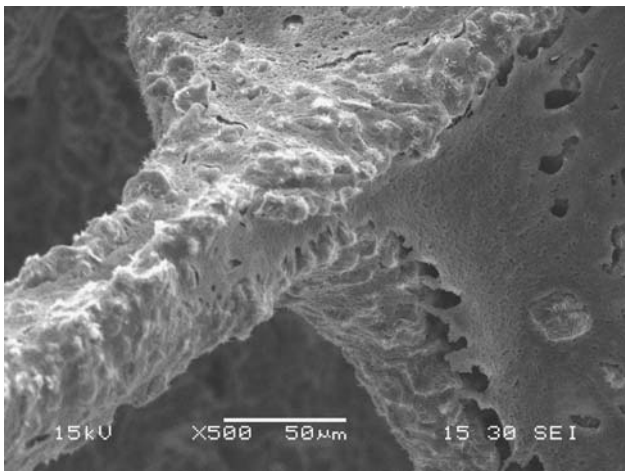

Fig. 4 SEM image showing the microstructure of a Bioglass® scaffold coated by P(3HB) polymer [74]

modification was found to decrease the dissolution ratio of the calcium silicate scaffolds, while maintaining their apatite forming ability in SBF. In addition, the studies showed that PDLLA-modified scaffolds had a more uniform and continuous network of inner connectivity compared to non-modified scaffolds, in agreement with other investigations using Bioglass® [72] or HA [70], while also increasing the spreading and viability of human bone derived cells.

Polymer-coated scaffolds based on alumina and titania

The concept of polymer coating and formation of interpenetrating polymer–ceramic microstructures has also been applied to scaffolds made from "bioinert" ceramics, such as alumina and titania. Peroglio et al. [77] have recently investigated alumina scaffolds coated with PCL. The coating was obtained by infiltrating the scaffolds with either a PCL solution or PCL nanodispersion. A typical fracture surface of a scaffold strut is shown in Fig. 5, which exhibits the presence of the polymer phase on the surface and penetrating cracks in the alumina microstructure. It was found that the elastic behaviour is controlled primarily by the ceramic scaffold, while the fracture energy mainly depends on the polymer phase. Addition of 10–20% of PCL to the alumina scaffolds led to a 7- to 13-fold increase of the apparent fracture energy, in agreement with the results of Chen et al. for PDLLA-coated Bioglass® scaffolds [72]. The toughening mechanisms were discussed [77] and crack bridging by polymer fibrils was identified as being the most likely. The authors also showed that infiltrating PCL by nanodispersion did not result in significant improvement of the mechanical behaviour of the scaffolds.

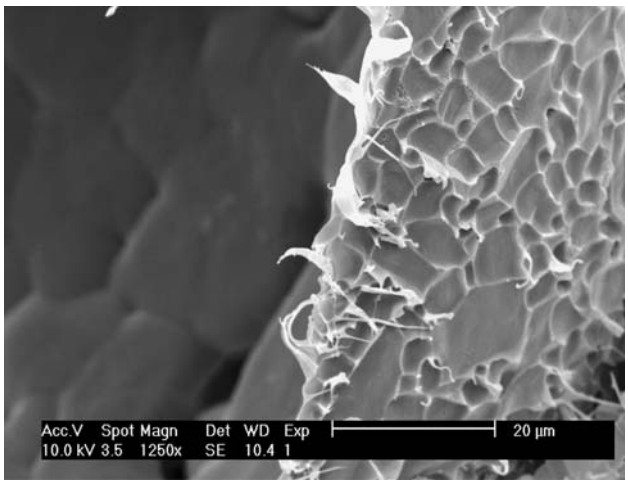

Fig. 5 SEM image of the fracture surface of a PCL/alumina composite scaffold obtained by infiltrating alumina foams with a PCL solution [77]. The polymer phase is seen to coat the strut and to penetrate cracks in the alumina microstructure

TiO_2 foam-like scaffolds with pore size ~300 µm and >95% porosity were fabricated by the foam replication method by Novak et al. [25]. In order to improve the structural integrity of the as-sintered foams, which exhibited extremely low compression strength (<0.045 MPa), PDLLA or PDLLA/Bioglass® coatings were developed. The PDLLA coating of a few microns in thickness was shown to improve the mechanical properties of the scaffold: the compressive strength was increased by a factor of ~7 (0.3 MPa). Moreover the composite coating involving Bioglass® particles was shown to impart the rutile TiO_2 scaffold with the necessary bioactivity for the intended applications in bone tissue engineering. A dense hydroxyapatite layer was shown to form on the surface of the foams upon immersion in SBF for 1 week [25].

Recent developments: bioactive glass–ceramic/PDLLA composite scaffolds with interpenetrating microstructure

In order to exploit the effect of interpenetrating network microstructures in scaffold optimisation, current work is investigating the infiltration of a biodegradable polymer phase (e.g. PDLLA) into partially sintered Bioglass® glass–ceramic scaffolds prepared by the foam replica technique. In order to leave partially sintered, e.g. relative porous, strut structures, sintering was stopped at temperatures below 1,000 °C or sintering time was reduced considerably. The results showed that the mechanical properties of the interpenetrating microstructure of the 45S5 Bioglass®/PDLLA composites significantly increased; the compressive strength of the coated scaffold was up to 7 times higher than the value for the non-coated scaffolds, as shown in Fig. 6. This result indicates that PDLLA films have effectively infiltrated the micropores of the partially sintered struts, as shown in Fig. 7. A preliminary qualitative analysis of fracture surfaces has shown that the PDLLA phase can increase the toughness of the 3D glass–ceramic scaffolds by the presence of uncracked polymer fibrils bridging the cracks, but the detailed toughening mechanism is still under investigation. Work by Nalla et al. [52, 53] has investigated the toughening mechanisms in bone and dentin by collagen interaction with microcracks in the inorganic phase. The role of collagen fibrils providing a crack bridging mechanism was postulated [53]. This toughening effect of collagen would explain the apparent relationship between bone toughness and collagen denaturation, which appears to weaken bone. Moreover a detailed analysis of fracture paths in human bone indicating how cracks interact with the microstructure has been provided by Nalla et al. [52], and the effect of

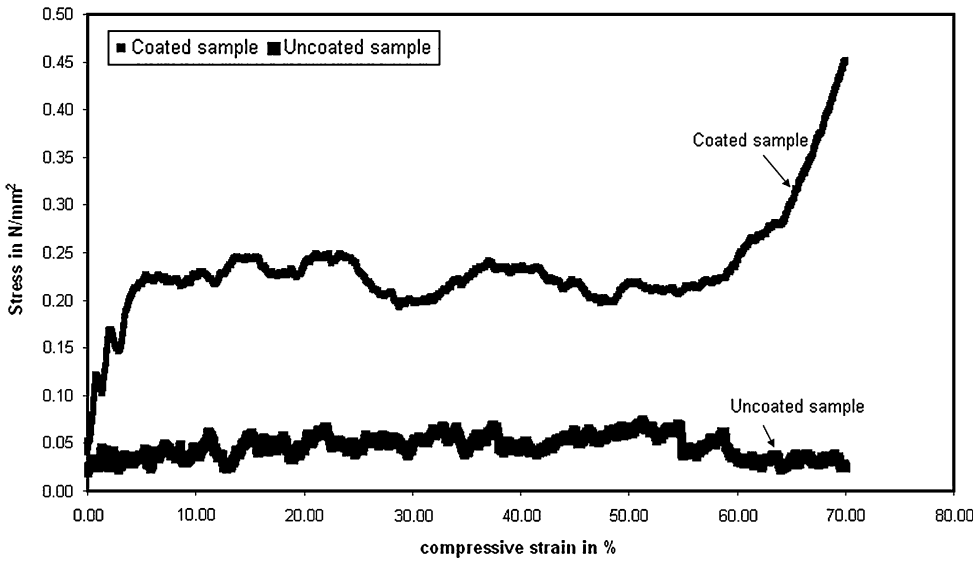

Fig. 6 Typical compressive stress-strain curves of an as-sintered 45S5 Bioglass® scaffold and a poly(D,L-lactic acid)-coated Bioglass® scaffold

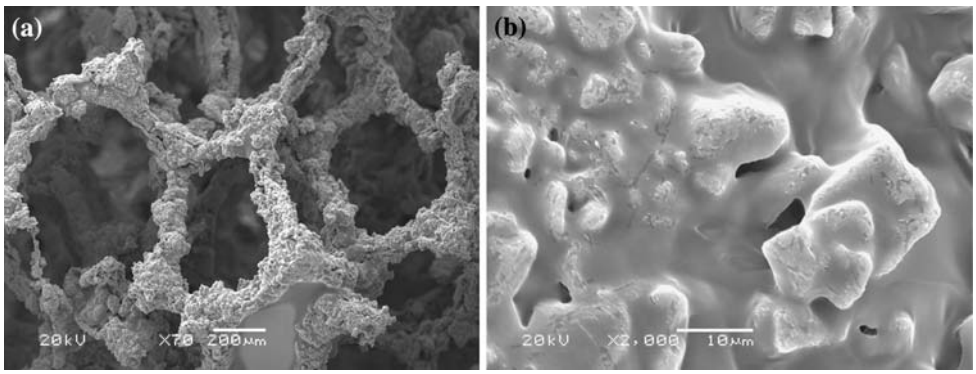

Fig. 7 SEM images showing the microstructure of the 45S5 Bioglass® scaffold struts after coating with PDLLA at (**a**) low and (**b**) high magnifications

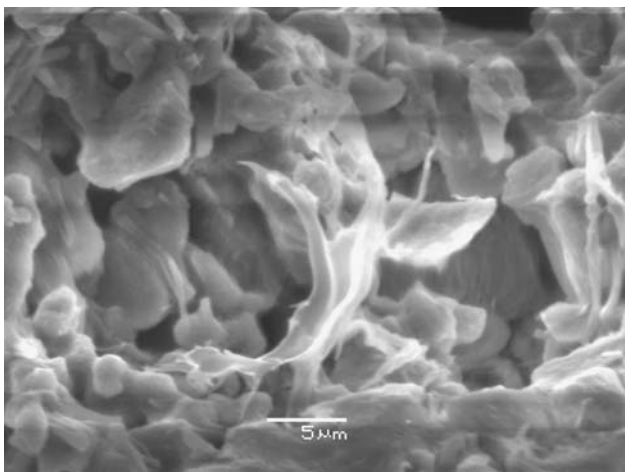

Fig. 8 SEM image showing the fracture surface of a Bioglass®/PDLLA scaffold strut with interpenetrating network microstructure. The uncracked polymer fibrils are seen to bridge the major crack, in notable similarity with the collagen bridged cracks in bone, as reported in the literature [52]

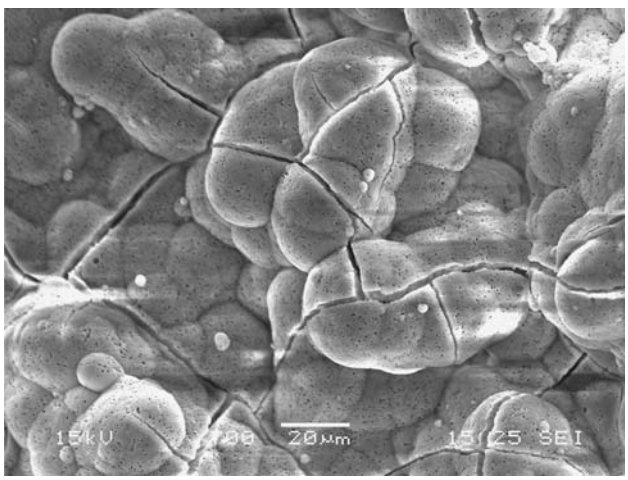

Fig. 9 SEM image of the surface of a 45S5 Bioglass® sintered scaffold coated with PDLLA after immersion in 1.5SBF for 28 days showing the formation of a continuous hydroxypaptite surface layer

crack bridging by collagen fibrils on toughening has been quantified for the first time. Figure 8 shows the fracture surface of a Bioglass®/PDLLA scaffold strut with interpenetrating network microstructure, where the uncracked polymer fibrils are seen to bridge the major crack, in notable similarity with the collagen bridged cracks in bone reported by Nalla et al. [52].

The bioactivity of the PDLLA-coated 45S5 Bioglass® scaffolds was investigated by immersion in acellular 1.5SBF and by subsequently determining the formation of hydroxyapatite on the surfaces. HA was clearly detected after 7 days of immersion in concentrated SBF (1.5SBF) and the layer thickness increased with increasing time in the medium, reaching a dense, continuous HA layer after 28 days in 1.5SBF, as shown in Fig. 9. This result suggests that the PDLLA coating does not affect negatively the bioactive character of the 45S5 Bioglass®-based scaffolds, as also discussed elsewhere [72].

Conclusions

An overview of the literature on the development of tissue engineering scaffolds based on polymer-coated bioceramics and interpenetrating polymer/bioceramic microstructures has been presented. The potential for improving the mechanical properties of bioceramics/polymer composite scaffolds by this approach has been demonstrated in several systems, which have achieved mechanical properties, in particular compression strength, in the range of values for cancellous bone. A significant toughening effect by the polymer incorporation, especially in scaffolds exhibiting interpenetrating network microstructure, has also been found. The addition of a polymer phase might have extra functions, e.g. the biodegradable polymer can act as carrier for biomolecules, growth factors and antibiotics, hence increasing the capability of tissue engineering constructs. Moreover addition of nanoparticles or carbon nanotubes to the polymer coating will induce nanotopographical surface features which should be relevant for enhancing cell

attachment and subsequent cellular behaviour in contact with the scaffold.

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