BIODEGRADABLE POLYMER-BIOCERAMIC COMPOSITE SCAFFOLDS FOR BONE TISSUE ENGINEERING

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SUMMARY

Tissue engineering scaffolds with suitable mechanical properties and favourable microstructure based on composites of biodegradable polymers and bioactive ceramics are reviewed in this paper. These scaffolds are optimised in their chemical composition and pore structure to promote cell attachment and new tissue formation.

Keywords: Scaffolds, tissue engineering, bioactive glasses, biodegradable polymers, porosity

INTRODUCTION

Critical size bone defects due to trauma or disease are very difficult to repair via the natural growth of the host bone. Therefore, these defects must be filled with a bridging material (scaffold), which should also, in combination with relevant cells and signalling molecules, promote the regeneration of new bone tissue. In this context, bone regeneration is one of the most attractive areas in the tissue engineering field [1-3].

Bone tissue engineering scaffolds are fabricated with bioactive materials which are able to react with physiological fluids to form tenacious bonds to bone. Basic scaffold design requirements have been identified, as summarized in Figure 1 [4, 5]. The most common bioactive materials are bioceramics, including special compositions of silicate glasses and glass-ceramics, as well as hydroxyapatite (HA) and related amorphous or crystalline calcium phosphates [6]. The major disadvantage of bioactive ceramics is their low fracture toughness and brittleness. For applications as bone tissue scaffolds, bioceramics are thus often used in combination with biodegradable polymers to achieve the best possible mechanical and biological performance [7, 8]. Development of composite materials for tissue engineering is attractive since their properties can be engineered to suit the mechanical and physiologic demands of the host tissue by controlling the volume fraction, morphology and arrangement of the reinforcing phase. Not only the combination of the "right" biomaterials but also the structure and morphology of the scaffold, characterised by a highly interconnected, three dimensional (3D) pore network as well as tailored surface characteristics, determine the suitability of a scaffold for a

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given application. For bone tissue engineering, porosity of ~90% and pore size >100 μm are desirable, as well as high pore interconnectivity, in order to facilitate the attachment and proliferation of cells, the ingrowth of new tissue and the vascularisation of the new tissue formed [4]. In the development of composites for tissue engineering scaffolds, two main approaches are being followed; the first approach considers the incorporation of bioceramic particles as inclusions into polymer structures, e.g. foams, the second approach considers the incorporation of polymer coatings onto a 3D porous bioceramic [9].

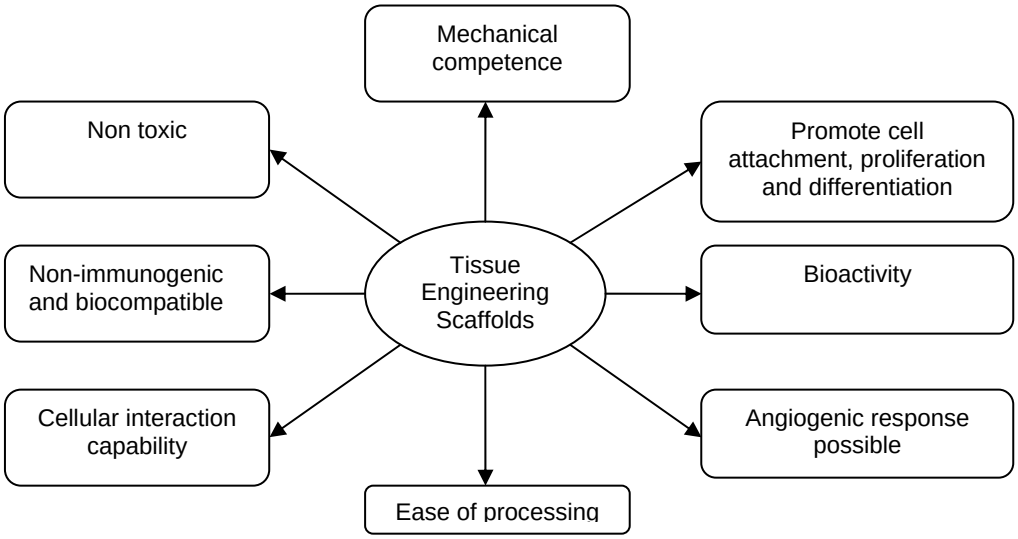

Figure 1 Requirements for tissue engineering scaffolds

The present review will thus focus on the composite material strategy for developing scaffolds for bone tissue engineering, including aspects of materials selection and processing technologies. Selected composite systems are described with emphasis on their structure, properties and applications in bone tissue engineering.

POLYMER COMPOSITES WITH BIOCERAMIC INCLUSIONS

Advantages of polymer composite scaffolds

Composites for tissue engineering applications must exhibit specific properties such as high initial strength and tailored initial elastic modulus close to the elastic modulus of bone. Polymers by themselves exhibit relative low mechanical strength and stiffness, whereas inorganic materials such as ceramics and glasses are known to be stiff and brittle. Polymers can be easily fabricated into complex shapes and porous structures however, in general, they lack a bioactive function (e.g. strong bonding to bone), being too flexible and weak to meet the mechanical demands in bone regeneration

applications. The combination of polymers and bioceramic inclusions leads to composite materials with improved mechanical properties due to the inherent higher stiffness and strength of the inorganic material. Moreover bioactive inorganic particles such as hydroxyapatite, Bioglass® or tricalcium phosphate, provide an extra function to scaffolds: they allow the composite to interact effectively with the surrounding bone tissue by forming a tenacious bond via the growth of a carbonate hydroxyapatite layer [7,8]. Moreover, addition of bioactive phases to bioresorbable polymers can change the polymer degradation behaviour by buffering the pH of the nearby solution, thus preventing the autocatalytic effect of the acidic end groups resulting from hydrolysis of polymer chains, e.g. in polylactic acid. In addition, incorporation of bioactive phases in biodegradable polymers should enhance water ingress due to the internal interfaces formed between the polymer and the more hydrophilic bioactive inclusions, hence enabling the control of the degradation kinetics of scaffolds [10].

Fabrication technologies

The mechanical properties and structural integrity of scaffolds are related to their porosity, e.g. pore volume, size, shape, orientation and connectivity. Several fabrication methods have been developed to fabricate 3D polymer-ceramic scaffolds with controlled porosity [7,8]. A minimum pore size is required for tissue ingrowth and high 3D interconnectivity is necessary for access of nutrients, transport of waste products, better cell spreading and vascularisation [11]. There is a high number of polymer-bioceramic composite scaffold manufacturing techniques, covering the use of porogens, chemical segregation and rapid prototyping. Techniques such as solvent casting, particulate leaching, three dimensional printing, thermally induced phase separation (TIPS) and fused deposition modeling are among the most used for fabricating 3D structures with variable porosity [8]. Each of these techniques has the ability to produce scaffolds with different pore architecture with their own advantages and disadvantages. For example, solvent casting in combination with particulate leaching is one of the simplest and common methods used for scaffold preparation. Solvent casting involves the dissolution of the polymer in an organic solvent, mixing with ceramic particles and casting the solution into a predefined 3D mould. The solvent is subsequently allowed to evaporate. The main advantage of this technique is the ease of manufacturing and ability to incorporate drugs (e.g. antibiotics, antioxidants) within the scaffold. The main disadvantages are that only simple shapes, e.g. flat sheets and tubes, can be formed and that pore interconnectivity is low. Another method for scaffold production is microsphere sintering. In this process, ceramic/polymer composite microspheres are fabricated first, using an emulsion/solvent evaporation technique. Sintering the composite microspheres yields a 3D porous scaffold. Lu et al. [12] have developed PLGA/ Bioglass® scaffolds using this method. The mechanical properties of these composites were found to be similar to those of cancellous bone. TIPS is a method that can produce homogeneous and highly porous (~95%) scaffolds with highly anisotropic tubular morphology and extensive pore interconnectivity [13]. This technique allows controlling the macro and microstructures of the scaffolds. The membranes obtained usually exhibit oriented tubular pores of diameters >100μm and an isotropic pore network of smaller pore size (~ 10 μm) connecting the large tubular pores. Finally, solid freeform fabrication techniques (SFFT), such as fused deposition modelling, have been employed to fabricate scaffolds with highly interconnected pore networks [14-16]. SFFT offer the possibility to fabricate polymer composite scaffolds with well-defined

architecture because local composition, macrostructure and microstructure can be specified and controlled at high resolution. This method was applied for scaffolds containing calcium phosphates as the bioactive phase [17]. Moreover Taboas et al. [18] have produced PLA scaffolds with computationally designed pores (500-800μm) and solvent-derived local pores (50-100μm). A shortcoming of this route is increased scaffold fabrication time and complex equipment requirement and costs compared with direct methods.

BIOCERAMIC SCAFFOLDS WITH BIODEGRADABLE POLYMER COATING

The biopolymer coating approach

An important class of scaffolds for bone tissue engineering is based on biodegradable and bioactive ceramics and glasses, including: hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), bioactive silicate glasses and calcium phosphates. Since the inorganic component of bone is made of carbonated hydroxyapatite, these scaffolds are also bioactive, e.g. they induce a strong bond to bone when implanted. Bioactive glasses and related silicate glass-ceramics constitute another group of inorganic materials being considered in bone tissue engineering due to their high bioactivity [19, 20]. The primary advantage that makes bioactive glasses promising scaffold materials is their rapid rate of surface reactions which leads to fast tissue bonding. One approach being investigated to improve the mechanical properties of these brittle scaffolds is to coat them with biodegradable polymer layers, in order to fill existing cracks in the bioceramic structure with the polymer. The approach can be expanded to include scaffolds with interpenetrating network structures. In this case the polymer will infiltrate the pore walls (struts) of the scaffold entering through open porosity or microcracks [9]. A further advantage of this approach is that the polymer phase can act as carrier for drugs and other biomolecules, e.g. growth factors, hence enhancing the functionality and bioactivity of the scaffolds.

It is anticipated that polymer layers will bridge cracks during fracture leading to increased scaffold toughness, which should mimic the behaviour of collagen fibres in bone [21]. This approach is therefore inspired by the fact that nearly 60wt% 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 is influenced by the optimal interaction of the inorganic and organic phases and the tough character of bone is related to this effective interaction between collagen and HA phase [21].

Processing technologies

Processes developed to fabricate both polymer coated bioceramic scaffolds and polymer-ceramic scaffolds with interpenetrating network microstructures are based on infiltrating a sintered (or partially sintered) bioceramic scaffold with the biodegradable polymer [9]. A novel method recently developed to coat 3D scaffolds with polymers is Matrix Assisted Pulsed Laser Evaporation (MAPLE). This technique is often preferred over other film deposition methods since it provides high control over film

characteristics. It was shown that this technique can be used to produce PDLLA (poly(D,L lactide)) coated Bioglass® scaffolds [22]. 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 [23], however those hybrid materials will not be considered in the present paper.

Bioceramic scaffolds exhibiting highly porous structure are being fabricated by a variety of techniques [24]. The earliest production of macroporous ceramics by the foam replica method was presented by Schwartzwalder and Somers [25]. The technique involves the use of polymeric sponges as templates to prepare ceramic cellular structures of various pore sizes, porosities and chemical compositions. The sacrificial template, e.g. a polyurethane foam, is initially soaked into a ceramic suspension until the struts are homogeneously coated with ceramic particles. Binders and plasticizers are added to the initial suspension in order to prevent cracking of the struts during the subsequent heat-treatment. The ceramic-coated polymeric template is subsequently dried, the polymer template is burnt out by a controlled heat treatment and the ceramic (or glass) structure is finally densified by sintering at high temperatures. Highly porous ceramics can be produced exhibiting open and interconnected porosity in the range 40%-95% with pore sizes between 200μm and 3mm. Bioactive glass-ceramic [26, 27] foams have been produced by the replica method using polymer sponges as synthetic templates. Figure 2a shows the cross section of a Bioglass® based glass-ceramic scaffold fabricated by this technique [9]. Several hydroxyapatite and calcium phosphate scaffolds have been also produced using both synthetic polymer templates as well as coral as natural templates [28, 29].

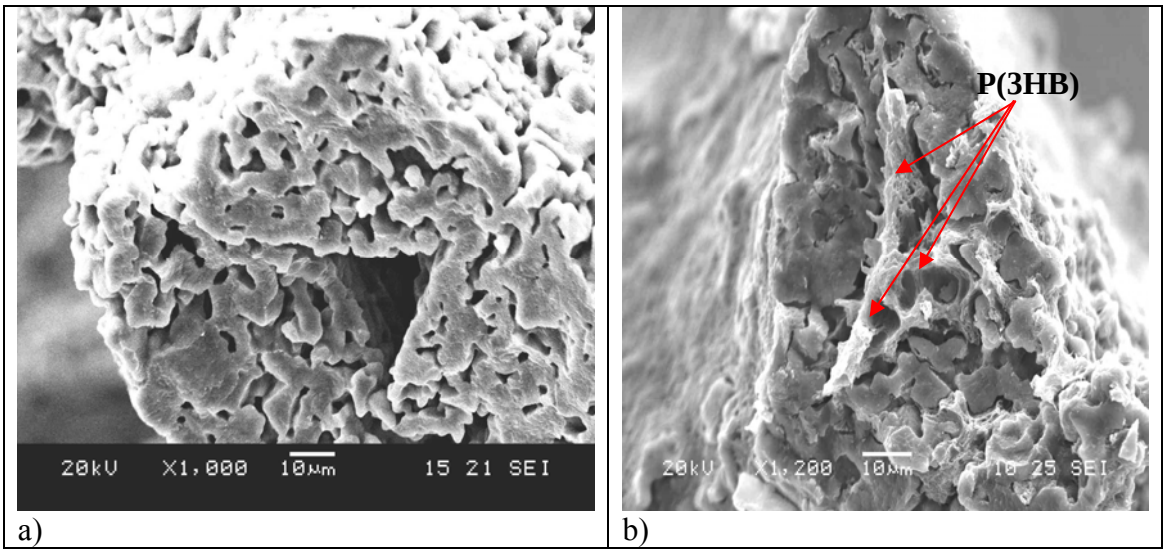

Fig.2. SEM images showing the microstructure of the strut cross-section of a) as-sintered 45S5 Bioglass®-based glass-ceramic scaffold and b) P(3HB) coated 45S5 Bioglass® scaffold sintered at 1000ºC for 2 hours.

Another method developed to produce porous scaffolds is the sacrificial template technique. This method involves the preparation of a composite comprising a sacrificial phase mixed with a continuous matrix of ceramic or glass particles [30]. The sacrificial phase is extracted from the partially consolidated matrix to generate pores within the microstructure. The mechanical strength of 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 [30]. A final method to be considered for production of highly porous scaffolds is the direct foaming method. In this case, air is incorporated into a ceramic suspension in order to create a structure of air bubbles [31, 32]. The consolidated foams are 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 stabilizers. The porosity of foams produced by this method typically varies between 40% and 95%; whereas the average pore size can change from 10 to 300 microns [33].

As mentioned above, calcium phosphates including HA, tricalcium phosphate (TCP) and calcium phosphate cements (CPC) play an important role in the development of scaffolds for bone tissue engineering. Porous calcium phosphate ceramics with interconnected macropores (> 200 μm) and microporosity (~5 μm) as well as high porosities (~ 80%) have been produced by firing polyurethane (PU) foams coated with calcium phosphate cement at 1200°C [34]. 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. Miao et al. [35] 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 [44]. In related investigations, HA scaffolds have been coated with HA particles and polycaprolactone (PCL) [36]. The PCL matrix acted also as carrier for the antibiotic drug tetracycline hydrochloride. Chen et al. [37] have developed Bioglass®-based scaffolds coated with PDLLA. It was found that the bioactivity of scaffolds upon immersion in simulated body fluid (SBF) was not impaired by the PDLLA coating. Polyhydroxyalkanoate (P(3HB) has been investigated in parallel investigations as an alternative coating material for tissue engineering scaffolds [38]. Bretcanu et al. [38] used bacteria-derived P(3HB) to infiltrate 45S5 Bioglass® glass-ceramic scaffolds. Fig. 2b shows the cross section of a P(3HB) coated Bioglass® based glass-ceramic scaffold fabricated in our laboratory, demonstrating that the polymer has infiltrated the open pores of the foam strut, which should lead to enhance fracture toughness, as mentioned above. The mechanical properties of these novel scaffolds are being investigated but qualitatively, it has been shown that the work of fracture increases dramatically with the P(3HB) coating [9].

CONCLUSIONS

The development of bone tissue engineering scaffolds based on biopolymer-bioceramic composites was reviewed. Two families of composite systems were considered: i) polymer scaffolds containing bioceramic particle inclusions and ii) bioactive ceramic based scaffolds with biopolymer coating. The potential for improving the biological

behaviour and mechanical properties of bioceramics/polymer composite scaffolds by the composite approach has been demonstrated in several systems. In optimised composites, the compressive strength of scaffolds of high porosity (> 90%) has reached values in the range of values for cancellous bone. In coated bioceramic scaffolds significant toughening effect by the polymer incorporation, especially in scaffolds exhibiting interpenetrating network microstructure, has been confirmed. The addition of a polymer phase has extra functions since the biodegradable polymer can act as vehicle for biomolecules, growth factors and antibiotics, hence improving the overall performance of tissue engineering constructs.

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