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SYNTACTIC AND COMPOSITE FOAMS

TiO_2 foams with poly-(D,L-lactic acid) (PDLLA) and PDLLA/Bioglass® coatings for bone tissue engineering scaffolds

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Abstract TiO_2 foam-like scaffolds with pore size ~300 μm and >95% porosity were fabricated by the foam replication method. A new approach to improve the structural integrity of the as-sintered foams, which exhibit extremely low compression strength, was explored by coating them with poly-(D,L-lactic acid) (PDLLA) or PDLLA/Bioglass® layers. The PDLLA coating was shown to improve the mechanical properties of the scaffold: the compressive strength was increased by a factor of ~7. 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 formed on the surface of the foams upon immersion in simulated body fluid for 1 week.

Introduction

"Third generation" biomaterials [1], rather than merely replacing body tissue or replicating their functions, should actually assist the body's self repair mechanisms, promoting new tissue growth and regeneration. These effects can be achieved by tissue engineering strategies, which involve the implantation of a highly porous scaffold populated with relevant cells, providing a three-dimensional environment in which new tissue can grow. After tissue repair has been accomplished, the ideal biomaterial will then either be resorbed and removed by the body itself or integrated within the new tissue, without the need for further surgery [2].

One of the important requirements for the success of bone tissue engineering is the availability of a suitable scaffold to support and direct the growth of new bone and much current biomaterials research is concerned with developing and optimising such scaffolds [3, 4]. Titania is a promising material for this application as it possesses suitable mechanical and biocompatibility properties [5, 6]. Titania has been implanted in the human body many times, as it is in fact a naturally occurring oxide covering titanium implants. Hence, the biocompatibility of titania has been proved [7] and the incorporation of TiO_2 nanoparticles into biodegradable polymer scaffolds has been investigated to influence the scaffold mechanical properties and surface nanotopography [8]. It has also been suggested that TiO_2 could have bioactive properties, e.g. TiO_2 can lead to the formation of a strong bond to bone upon implantation via the formation of a hydroxyapatite layer [9, 10]. The influence of surface topography on the bioactive properties of titania has also been investigated [11]. Moreover, Polonchuck et al. [12] have shown that ceramic scaffolds made of TiO_2 are conducive to cellular organisation by growing cardiac muscle cells. The fact that cardiac muscle cells could be grown on TiO_2 suggests that it should also be possible to engineer other tissues, such as bone, using TiO_2 scaffolds.

A very important requirement for tissue engineering scaffolds is porosity. In particular, highly interconnected 3D-porous structures with pores larger than 100 μm in diameter are necessary to allow penetration of cells and for vascularisation [3, 4, 13]. However, the optimum porosity and pore dimensions of a scaffold for bone tissue

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engineering result from a compromise between the suitability for cell growth and the best possible mechanical properties that can be achieved.

The aim of the present work was to fabricate novel highly porous (90% porosity) and bioactive titania foam-like scaffolds for bone tissue engineering with pores of at least 300 μm in diameter. There has been only limited work published in the literature on the manufacturing of highly porous TiO_2 for tissue engineering scaffolds [5] with no special consideration given to the bioactivity and mechanical properties of the scaffolds.

The possibility to improve the mechanical properties of TiO_2 scaffolds by coating the foams with poly-(D,L-lactic acid) (PDLLA) was investigated. Moreover, the ability of the TiO_2 foams to form surface layers of hydroxyapatite, which are important in the first stage of integration with bone, was verified by immersion studies in simulated body fluid (SBF). A PDLLA/Bioglass® composite coating was also developed to enhance the bioactivity of the TiO_2 foams.

Experimental

The foam replication technique was used to manufacture the foams using PDLLA (Purac Biochem, Gorinchem, Netherlands) as a binder. This is a traditional process for fabricating ceramic foams (patented by K. Schwartzwalder in 1963 [14]) and it was adapted according to the procedure described by Chen et al. [15]. Commercially available polyurethane foams (Reticel, Corby, UK) were soaked in a slurry consisting of titanium dioxide nanopowder with mean particle size of 23 nm (Aeroxide® P25, Degussa, Frankfurt a. M., Germany), PDLLA binder and dimethyl carbonate (DMC). The slurry recipe consisted of 1.5 g PDLLA, which was dissolved in 50 ml DMC by magnetically stirring for an hour. Subsequently, approximately 12 g of the titanium dioxide nanopowder was added. After removing the excess slurry by squeezing the foams, the green bodies were dried in normal air for at least 12 h before being subjected to a heat treatment to burn out the PU foam and to sinter the ceramic. The heat treatment involved heating the foams to 450 C at 0.5 K min^{-1} and held them for 1 h at that temperature to burn out the sacrificial polymer template. The foams were then heated further at 3 K min^{-1} to sintering temperatures of 1,150 or 1,300 °C. The effect of holding at the sintering temperature for 1 h compared to using no hold time was also investigated. After sintering, the samples were cooled to room temperature at a rate of 5 K min^{-1}.

Selected samples were coated with PDLLA or with PDLLA/Bioglass® composite layers, following the slurry dipping procedure introduced by Chen et al. [16]. A Bioglass® powder of composition 45S5 (in weight percentage: 45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5 [17]) and mean particle size <5 μm was used. For the coating procedure, two grams of PDLLA were dissolved in 40 mL of dimethyl carbonate, by mixing on a magnetic stirrer for 2 h. Then, the titania foams that had been sintered at 1,150 °C were soaked in the resulting mixture for 15 min. The mixture was manually agitated periodically through the soaking period. The samples were then removed from the slurry and allowed to dry at room temperature in normal air. Samples were also coated with a PDLLA/Bioglass® composite coating. The recipe for the coating was that given elsewhere [16] as follows: 0.4 g of PDLLA was dissolved in 10 mL of dimethyl carbonate by magnetic stirring for an hour. Then, Bioglass® powder was added such that Bioglass® comprised 40 wt% of the mixture. As the densities of PDLLA and DMC can be taken to be $\sim$1 g cm^{-3}, this required approximately 6.9 g of Bioglass®. In an attempt to reduce the amount of excess slurry in the foam, and to try to balance out the fact that it was not possible to squeeze out the excess slurry, the foams were allowed to stand on absorbent paper for 30 s on each face. The slurry was seen to be drawn out of the foams by a combination of gravity and absorbency of the tissue.

Bioactivity of the samples was characterised in acellular simulated body fluid (SBF) according to the protocol of Kokubo [18]. Briefly, samples were immersed in the fluid for durations of either 1 or 2 weeks, with the fluid being changed every three days to maintain the intended concentrations of ions and pH. Once the samples had been immersed in SBF for the desired time, they were removed and each was cut in half for microstructural analysis. Samples before and after immersion in SBF were characterised by X-ray diffraction (XRD) analysis (Phillips PW1700) and scanning electron microscopy (SEM) coupled with Energy Dispersive X-ray (EDX) analysis (LEO 1525 Gemini Field Emission Gun SEM and JEOL JSM-5610LV).

Compressive strength testing was performed using a Zwick/Roell Z010 machine, at a compressive strain rate of 0.5 mm min^{-1}. All tests were either continued to approximately 80% strain, or stopped prematurely after the onset of the densification regime. Prismatic samples were used with nominal dimensions: 13 mm × 7 mm × 7 mm. The exact dimensions of the foam samples were measured to an accuracy of 0.01 mm with electronic callipers. Three samples per data point were measured. This number of samples does not allow for a fully statistically significant study of the mechanical behaviour of these foams, which would require testing at least 15 foams per treatment; however, it will indicate typical ranges for the compressive strength values of different samples.

Results and discussion

Foam microstructure and mechanical properties

Figure 1a and b show typical SEM images of the "green" (as-dried) and sintered titania foams, respectively. From SEM micrographs, several dimensions were measured to characterise the structure of the foams, namely, strut thickness, pore diameter and mean particle size. The porosity was calculated by a geometric method, comparing the bulk density to the theoretical density of titanium dioxide, which is 4.27 g cm^{-3} for rutile titania. Using the density of rutile is justified by the fact that the XRD results on sintered samples, as shown below, revealed the presence of only this crystalline form. Porosity was calculated to be in the range 95–97% independently of the sintering temperature or holding time at temperature used. For samples sintered at 1,300 °C, the average pore size was ~300 μm and the average strut thickness was in the range of 30–45 μm, as determined from SEM images. It is believed that this observed pore diameter will be wide enough for the application of the foams in bone tissue engineering, i.e. to allow osteoblast cell migration, transport of nutrients and removal of waste, whilst not being so wide that cells simply would fall through the structure during seeding, as reported by Haugen et al. [5]. The SEM images also confirm that the foams have a very high pore interconnectivity as required for optimal tissue engineering scaffolds. Figure 2 shows a high magnification SEM micrograph indicating the grain structure of TiO_2 struts after sintering (sample sintered at 1,150 °C). It is observed that most grains have size <1 μm. Results of EDX showed the presence of Ti and O only (not shown here).

The crystallinity of sintered TiO_2 foams (sintering temperature 1,150 °C) was assessed by XRD, as shown in Fig. 3. In this figure, the XRD pattern corresponding to the

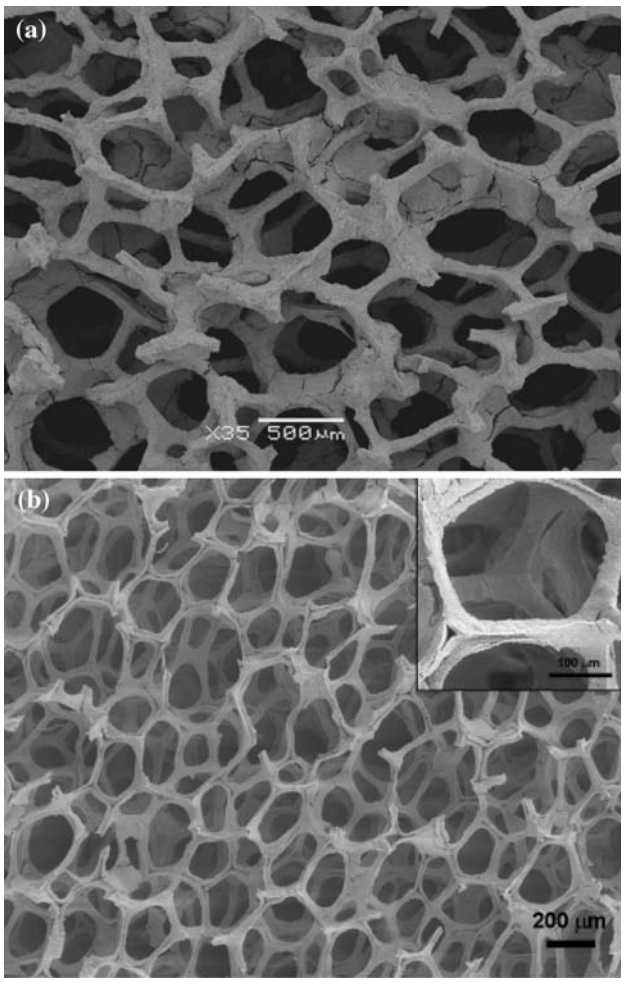

Fig. 1 SEM images showing TiO_2 green body after slurry dipping (**a**) and the sample sintered at 1,300 °C, 1 h (**b**). The inset shows the microstructure of the sintered struts in more detail

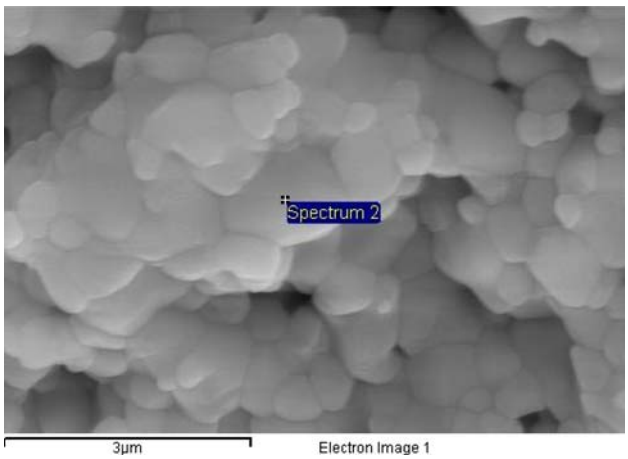

Fig. 2 High magnification SEM image of a TiO_2 foam strut after sintering at 1,150 °C showing that the mean grain size is <1 μm. The EDX spectrum (not shown here) demonstrated the presence of Ti and O

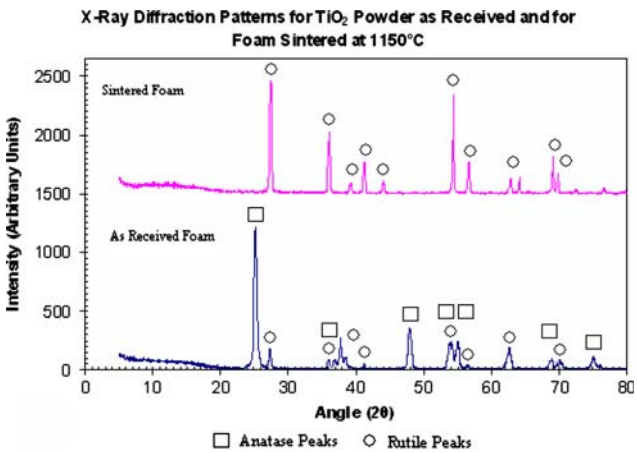

Fig. 3 X-ray diffraction patterns for as-received TiO_2 powder and sintered TiO_2 foam (sintering temperature: 1,150 °C)

as-received titania powder is shown, indicating the presence of both rutile and anatase crystalline forms. A change in the XRD pattern is observed for the sintered foam. This is due to the anatase phase present in the supplied powder fully transforming to a rutile phase at the sintering temperature. It is well known that anatase transforms to rutile at temperatures ~700 °C, but for particles <50 nm, anatase is more stable, and so higher temperatures may be required for the transformation to become energetically favourable [19]. In the present scaffolds, the complete transformation to rutile at the sintering temperature is shown by the disappearance of the peaks at 25°, 38° and 49° 2θ and an increase in intensity of the peaks for rutile, which were also present for the initial powder, but in a much lower proportion. Similar crystallinity (rutile) was determined for the foams sintered at 1,300 °C. Initial observations of the foams post-sintering were promising; the foams retained their structure during sintering and were strong enough to be handled and removed from the furnace without crumbling. However, although the foams could be handled without damage, they were not particularly strong. The compressive strength of the foams was extremely low and it was determined to be in the range (0.030–0.045 MPa) for all sintering conditions (temperature, holding time) tested. This is most probably a consequence of the microcracks in foam struts that are observed in both unsintered and sintered samples (e.g. Fig. 1a and b, respectively), implying that the cracks appeared already during the drying process and were not closed during the sintering stage. This suggests the need to dry the foams in a controlled manner after slurry dipping, i.e. at a lower drying rate. Moreover, as the strut thickness is most probably the predominant factor determining the strength of the foams, future development might require that the thickness be increased to improve mechanical strength without significantly affecting the porosity and pore connectivity. Alternative advanced methods to coat sacrificial polymer sponges with ceramic particles to fabricate ceramic foams by the replica technique are available, which should lead to foams with more homogeneous microstructures and higher mechanical strength [20–22]. A very convenient method is electrospraying, which has been demonstrated to lead to stronger foams, e.g. made from zirconia [22], in comparison to foams made by the simple slurry dipping technique used in the present investigation.

In this work, however, the alternative approach of coating the TiO_2 foams with a thin polymeric layer was investigated, following our previous successful developments on PDLLA-coated Bioglass® scaffolds [16] and also considering recent literature results on alumina [23], calcium phosphate [24–26] and hydroxyapatite [26] foams.

By coating the TiO_2 foams with PDLLA or PDLLA/Bioglass® layers, the mechanical properties of the foams

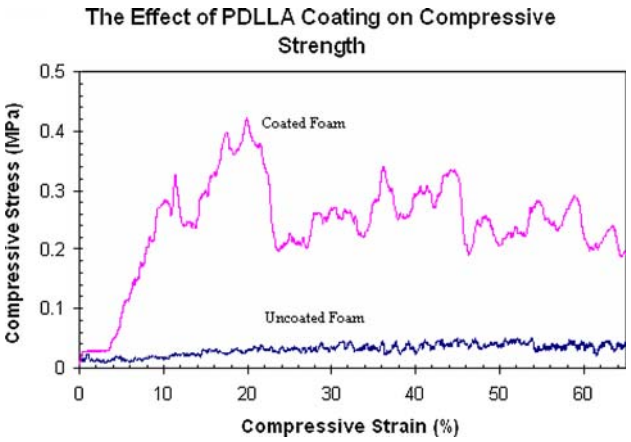

Fig. 4 Effect of PDLLA coating on the stress–strain behaviour of TiO_2 foams in compression

were substantially improved, i.e. the compressive strength increased by a factor of around seven, from 0.045 to ~0.3 MPa. The composite scaffolds thus achieved compression strength values close to the lower bound strength value for spongy bone [27] and comparable to the compression strength of similar highly porous polymer-ceramic scaffolds described in the literature, as reviewed recently [28]. From a practical point of view, experience indicates [16] that strength values of 0.3–0.4 MPa are sufficient for the foams to be handled with, such as manipulating during SBF tests and cutting of samples for mechanical tests. Figure 4 shows typical stress-displacement curves for uncoated and coated foams indicating the dramatic increase of both the compression strength and the work of fracture, which is related to the area under the stress displacement curve. It is also evident that the curve for the coated foam is much less jagged, and the shape more resembles the ideal curve for highly porous foams [27]. The coating process appears to have resulted in an average six-fold increase in the area under the stress–strain curve.

The most likely reason explaining why the coating process improved the compressive strength of the foams is that it both filled the cracks in the struts of the foams and made them thicker. Also, assuming that the "jagging" in the compression curve for the untreated samples is due to microcracks in the struts, then from the fact that the compression curves for the coated samples are smoother (without the jagging), it can be inferred that the coating process enabled PDLLA to fill the cracks, and crack bridging by the polymer occurs. This is also confirmed by SEM images of PDLLA-coated foams (discussed below), which showed a smooth surface of the struts and no large microcracks present. In the previous investigation on bioactive glass foams [16], we have estimated the thickness of the PDLLA coating to be in the range 1–5 μm. As a consequence of the coating, the porosity decreased to ~90%,

which is however still within the desired range for bone tissue engineering scaffolds [3, 4, 13]. While the thickness of the PDLLA layer was not measured in the present composites, it is suggested that a similar thickness as in the previous study [16] has been achieved (1–5 mm) since the same coating method and conditions were applied. The deposition of such thin polymer layer would indicate a slight reduction of porosity, which would however still lie within the porosity range required for bone tissue engineering scaffolds (~90%). As also indicated in our previous investigation [16], the interconnectivity of the scaffold porosity would not be compromised by the presence of such thin polymer layer and the reduction of pore size (with a mean value of ~300 μm, see Fig. 1b) would be negligible. On the other hand, the observed increase in compression strength can be ascribed to the filling of the voids and microcracks on the foam struts by the polymer layer. An alternative mechanism, which has been proposed in the literature [23], considers the effect of crack bridging by the polymer phase, which substantially increases the fracture energy of the foams in a similar manner as collagen fibres enhance the fracture toughness of bone [29, 30]. 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 in bone are induced by the presence of collagen fibrils [30].

Bioactivity study

It has been shown in previous studies that PDLLA can be bioactivated by the inclusion of Bioglass® particles [31, 32] and that PDLLA/Bioglass® composites exhibited higher cell densities when osteoblasts were cultured on the surfaces [33]. The presence of bioactive glass particles also decreases the degradation rate in vivo as the alkaline Bioglass® dissolution products can buffer the acidic effect produced by hydrolytic degradation of PDLLA, thus reducing its autocatalysis [34]. In the present scaffolds, in contact with body fluid, the PDLLA layer will dissolve, resulting in the time-dependent decrease of the mechanical strength of the foam. It is anticipated, however, that the PDLLA/Bioglass® coatings on TiO_2 foams will degrade at a slower rate than the neat PDLLA coatings, because the mentioned dissolution products of the Bioglass® acting to buffer against the acid dissolution by hydrolysis of the polymer [34]. Thus, the presence of Bioglass® particles will reduce the auto-catalysis effect of PDLLA and it can be used to control the degradation kinetics of the coatings and hence the time-dependant mechanical properties of the coated scaffold. The optimisation of the PDLLA/Bioglass® composition should be such that enough time is available for cells to grow into the pores of the scaffold, secrete collagen and form new tissue to compensate for the loss of strength due to the polymer coating degradation. If the rate of PDLLA degradation is higher than the rate of formation of any compensating phase (including crystalline HA, see below), a decline in mechanical properties will follow. In a worst case scenario, but as a logical explanation, if the whole of the PDLLA coating was resorbed without being replaced by a new compensating phase, the foam would be returned to its initial state without the surface cracks being filled, and thus the mechanical properties would decline.

Finally, the acellular bioactivity of the foams was verified by immersing them in simulated body fluid for different periods of time. As is customary in the biomaterials literature [17, 18, 31, 32], bioactivity (or bioreactivity) is considered to be related to the formation of hydroxyapatite (HA) crystals on the surface of materials upon immersion in SBF. The microstructure of an uncoated titania foam sample after it had been immersed in SBF for 2 weeks is shown in Fig. 5a. There is no evidence of the formation of hydroxyapatite. Similar appearance was observed for the PDLLA-coated foams, as seen in Fig. 5b. This agrees with the results of previous studies on the absence of HA formation on pure PDLLA or PDLLA filled with TiO_2 nanopowder when immersed in SBF [35]. Hence, the PDLLA-coated TiO_2 scaffold is confirmed not to be conducive to the formation of hydroxyapatite in contact with SBF and thus the scaffold is non-bioactive.

In contrast, hydroxyapatite crystals were observed on the surface of the Bioglass®/PDLLA-coated TiO_2 foam, as shown in Fig. 5c. The presence of Ca and P elements was confirmed by EDX analysis (Fig. 5d). In the EDX spectrum, peaks indicating the presence of calcium, sodium, silicon and phosphorous, which are the constituent elements of Bioglass® are confirmed. The gold peak is present because of the coating required for the preparation of the sample for SEM. The atomic ratio of calcium to phosphor found by EDX in the present specimens was 1.58, which can be considered to be within the limits of the non-stoichiometry of hydroxyapatite (the value for stoichiometric HA is 1.67).

The presence of HA on the Bioglass®/PDLLA-coated foams was also confirmed by XRD analysis. From Fig. 6, presenting the XRD diffraction patterns obtained for uncoated and coated TiO_2 foams after immersion in SBF for a week, a rather distinctive peak corresponding to hydroxyapatite (JCPDS file No: 09-0432) is evident in the spectra of PDLLA/Bioglass®-coated samples.

There is an extended debate in the literature as to whether there is any significant difference in biocompatibility between the different crystal structures of titanium dioxide [10, 36, 37]. However, it is generally recognised that anatase is more effective in promoting the formation of hydroxyapaptite in contact with SBF [36]. Our results

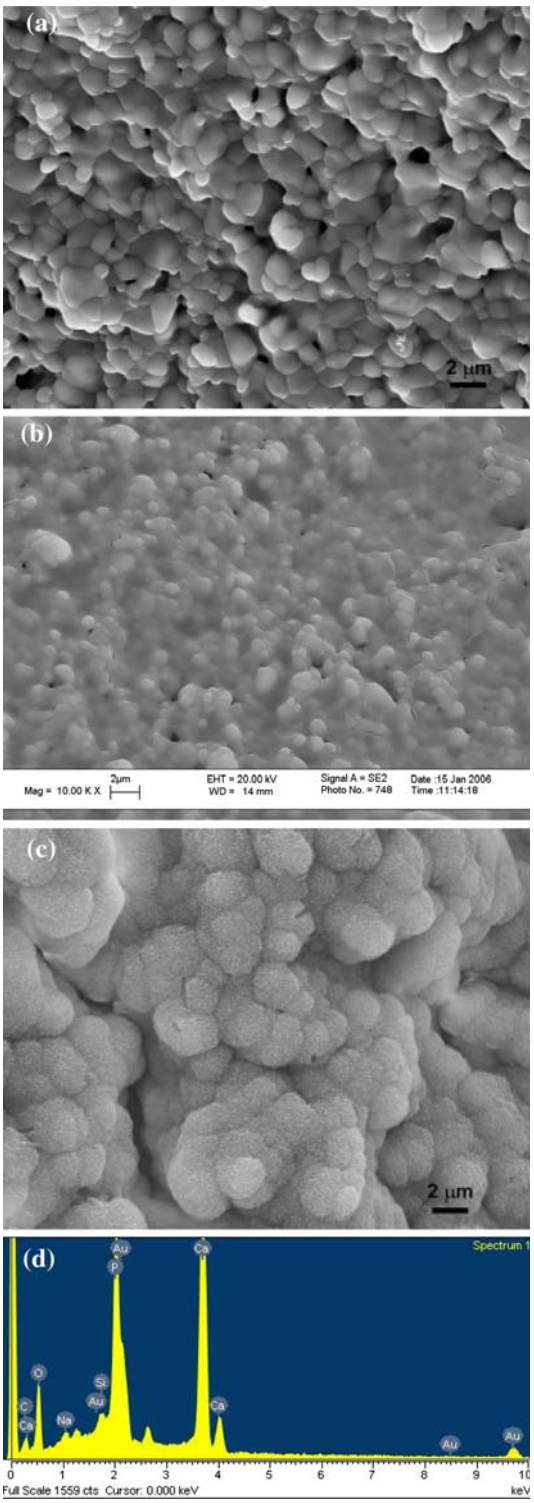

Fig. 5 SEM images of (**a**) as-sintered (uncoated) and (**b**) PDLLA-coated TiO_2 foam struts after 2 weeks immersion in SBF, (**c**) Bioglass®/PDLLA-coated TiO_2 foam strut after 1 week immersion in SBF. The formation of a uniform layer of hydroxyapatite crystals on the surface of the PDLLA/Bioglass®-coated strut is evident and the presence of Ca and P was confirmed by EDX results (**d**)

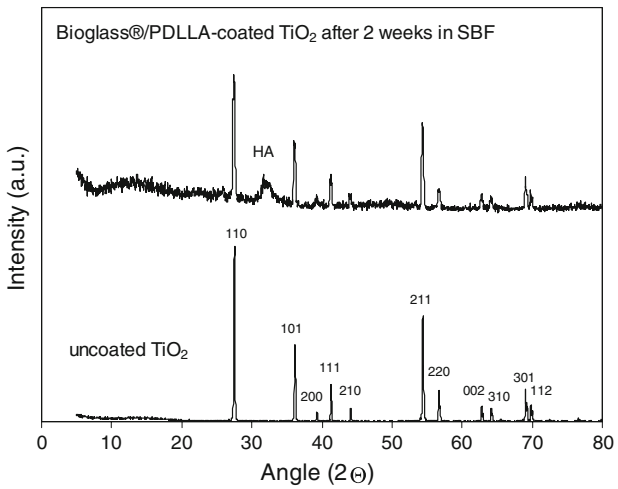

Fig. 6 XRD patterns for uncoated (lower diagram) and Bioglass®/PDLLA-coated TiO_2 foams (upper diagram) after immersion in SBF for 1 week, showing hydroxyapatite (HA) (JCPDS file No: 09-0432) and TiO_2 rutile peaks (indexed)

support the opinion that rutile exhibits unfavourable bioactivity, but we also confirmed that the bioactivity can be significantly improved by the Bioglass®/PDLLA coating. This bioactive coating renders the rutile TiO_2 foam potentially useful as a scaffold for bone tissue engineering. Future research will focus on comparing the relative biological performance, both in vitro and in vivo, of Bioglass®-based scaffolds developed earlier [15] and the novel TiO_2/PDLLA/Bioglass® foams fabricated in this investigation. Further work must also concentrate on determining the minimum amount of Bioglass® required to impart an appropriate degree of bioactivity, without sacrificing too much porosity, and on assessing the possibility of adding growth factors or other biomacromolecules to the polymer coating to further functionalise the scaffold surfaces.

Conclusions

It was shown that TiO_2 foams formed by using the sponge replica method displayed a macrostructure suitable for their application as bone tissue engineering scaffold. The large pore size ($\sim$300 μm) and high porosity (>95%), however, led to poor mechanical properties. By developing a method to dip coat the foams with PDLLA, the compressive strength was increased by a factor of around seven, from 0.045 to 0.3 MPa, and the work of fracture also increased significantly. This improvement was probably mainly due to the filling of microcracks in the struts of the foam by the polymer, but may also be in part due to the thickening

effect of the PDLLA coating on the struts and a crack bridging mechanism by the polymer fibrils. Neither uncoated TiO_2 foams nor PDLLA coated TiO_2 foams possessed sufficient bioactivity to form hydroxyapatite layers after 2 weeks of immersion in SBF. However, TiO_2 foams coated with a Bioglass®/PDLLA composite layer were bioactive, i.e. after only 1 week immersion in SBF, extensive hydroxyapatite formation was observed on the surface of Bioglass®/PDLLA-coated TiO_2 foams, thus indicating the potential of these scaffolds for bone tissue engineering applications. It is noted that the polymer phase can have other functions, such as being a carrier for drugs and other biomolecules, e.g. growth factors, thus enhancing the functionality and bioactivity of the scaffolds.

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