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Additional Information

**“The effect of beta-tricalcium phosphate on mechanical and thermal performance
of poly(lactic acid)”**

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Abstract

Orthophosphates are bioactive crystals with similar structure, in terms of elemental composition and crystal nature, to human bone. In this work, biocomposite materials were prepared with poly(lactic acid), PLA as matrix and beta-tricalcium phosphate, β -TCP, as osteoconductive filler by extrusion-compounding followed by conventional injection molding. The β -TCP load content was varied in the 10-40 wt.% range and the influence of the β -TCP load on mechanical performance of PLA/ β -TCP composites was evaluated. Mechanical properties of composites were obtained by standardized tensile, flexural, impact and hardness tests. Thermal analysis of composites was carried out by means of differential scanning calorimetry (DSC); degradation at high temperatures was studied by thermogravimetric analysis (TGA) and the effect of the β -TCP load on dynamical response of composites was studied by mechanical thermal analysis (DMTA) in torsion mode. The best-balanced properties were obtained for PLA composites containing 30 wt. % β -TCP with a remarkable increase in the Young's modulus. These materials offer interesting properties to be used as base materials for medical applications such as interference screws due to high stiffness and mechanical resistance.

Key words: beta-tricalcium phosphate; poly(lactic acid); thermal and mechanical properties; fasteners; bone tissue engineering

1. Introduction.

The use of joint devices such as screws, fasteners, anchor stitches, etc. for tendon and bone reconstruction or repairing has progressed in the last years; typical biocompatible and biostable materials based on high strength metallic alloys and insoluble ceramics have given way to new resorbable and biocompatible materials based on polymeric matrices. Today it is possible to find a wide variety of materials that could be potentially used in the biomedical sector. In the last years, important efforts have been done to develop new metallic, ceramics, polymeric and composite materials (1, 2) thus giving evidence of the need and importance of these materials in medicine.

With regard to metals, titanium based alloys (3-5) are widely used; in particular, Ti6Al4V alloy (6, 7) is one of the most used. Other alloys such as CoCr (8), CoCrMo (6) and stainless steels (9) are used. These metallic alloys are biocompatible but they are not able to induce bone tissue regeneration, so that, these alloys must be subjected to surface treatments to allow osteointegration (10-12). This costly and arduous procedure plays a key role in bone tissue regeneration among the bone-fixation interface to avoid potential rejection.

On the other hand, calcium phosphate ceramic materials such as hydroxylapatite (HA) are excellent candidates as fillers with osteoconductive properties. HA is a bio crystal that can be found in human bones in combination with collagen. HA and other calcium phosphates can be considered as biomimetic materials with no rejection

phenomena when in contact with connective tissue at physiological media pH (13). Nevertheless, due to its ceramic nature, HA is highly fragile.

For these reasons, the medical sector demands new materials with a balance between mechanical performance, density and cost. An additional attracting feature for biomaterials (in particular, materials for fixation devices and screws), is biodegradation/resorption in physiologic media. This allows controlled decomposition, gradual resorption and bone growth in the bone-fixation interface thus leading to total osteointegration. Biodegradable polymeric materials are an interesting choice due to their easy processing and potential degradation in physiological media (14, 15). An attracting approach is based on the fact that “*the best bone substitute is the regenerated bone itself*”. The polymeric material degrades-dissolves slowly and progressively and it is continuously resorbed and substituted by soft tissue and new specialized connective tissue. This fact leads polymers to an advantageous position if compared to conventional metallic and ceramic materials, since second surgery to remove fixation plates, screws, pins etc. once the bone has regenerated, can be avoided. Biodegradable polymers such as poly(glycolic acid)-PGA, poly(butylene succinate)-PBS, poly(ester amides)-PEA, poly(caprolactone)-PCL, poly(lactic acid) and their blends and/or copolymers are increasingly being used in biomedical applications (16-22). The different biodegradation rates of these polymers and their copolymers, allows tailoring the desired resorption times to ensure optimum recovery.

Formulation of an osteoconductive, biocompatible, resorbable fixation device should be composed of two main components: a biodegradable polymeric matrix and an osteoconductive filler such as those derived from orthophosphates: oxyapatite (OXA), hydroxylapatite (HA), biphasic calcium phosphate (BCP), beta-tricalcium phosphate (β -TCP), or mixtures of all these phosphate materials as all they have similar composition to that of the human bone (23, 24). Orthophosphates can be classified in terms of their solubility in physiological media from the highest to the lowest (25) and the Ca/P ratio. As β -TCP particles solubilize, they supply calcium and phosphate in a controlled way and this leads to mineralization of the bone-fixation interface thus allowing formation of connective tissue and good osteointegration (26, 27). Osteointegration allows optimum bony growth and bone healing, which leads to stabilize the fracture of bone defect.

Connective tissue can be soft (cartilaginous) at the beginning and afterwards, hard bone tissue or simply fibrous-cartilaginous tissue if the fracture affected only tendons or ligaments. Several “*in vivo*” studies with composite materials based on PLA matrix and β -TCP showed a remarkable proliferation of mesenchymal stem cells (MSCs) which led to more adipose-derived stem cells differentiation (ASCs). The potential of rejection or inflammatory process with PLA/ β -TCP systems are extremely low. This is due to different phenomena: on the one hand the low degradation rate of PLA and on the other hand, the formation of a buffer solution with dissolved β -TCP

particles, which contributes to maintain constant pH. This occurs when alkaline salts such as phosphates (PO_4^{3-}) are present (28).

Manufacturing of polymeric fixation devices, interference screws, fixation pins, etc. by extrusion-injection molding processes is difficult to be substituted by other techniques due to an excellent balance between technical viability, costs and overall properties (29). Extrusion-injection techniques offer attracting advantages to obtain optimum particle dispersion that leads to high homogeneity (29). In addition, an increase in the residence time in the screw has a positive effect on particle dispersion. Furthermore, an increase in the applied pressure reduces porosity (29, 30). Foaming is one of the widely used techniques to mold polymers into shapes. The porous structure favors interaction with human tissues and, subsequently, osteointegration during the resorption process. In this work PLA/ β -TCP composite materials in the form of block materials with potential use as resorbable medical joint devices were prepared by the injection moulding process with previous extrusion-compounding. The extrusion is intended for improved particle dispersion and the injection moulding is intended for high quality end and cost-effective products that do not require further processing. The particle aggregation and dispersion has been tested by microscopic techniques by using selective extraction/dissolving of the β -TCP particles with HCl acid solution to reveal the real structure. The load content of β -TCP varied in the 0-40 wt. % range and the

effects of β -TCP content on mechanical and thermal properties of PLA/ β -TCP composites were evaluated.

2.- Experimental.

2.1.- Materials.

The base polymer was a poly(lactic acid), PLA, commercial grade Ingeo™ Biopolymer 6201D supplied by NatureWorks LLC (Minnetonka, USA), which is characterized by a content on D-lactic acid of about 2%. Its density is 1.24 g cm⁻³ and the melt flow index is in the 15-30 g/(10 min) range at 210 °C. The osteoconductive filler was beta-tricalcium phosphate (β -TCP) supplied by Sigma-Aldrich (Steinheim, Germany).

2.2.- Composite manufacturing.

Four different compositions based on PLA matrix and β -TCP osteoconductive reinforcement were manufactured by extrusion-compounding and subsequent injection molding. Table 1 summarizes the compositions and the reference material with their corresponding compositions. The β -TCP load varied in the 0-40 wt.% range. PLA was dried at 80 °C for 24 h to remove moisture. PLA/ β -TCP composites were compounded in a twin screw extruder at 60 rpm and a temperature profile of 170 °C (hopper), 175 °C, 180 °C and 185 °C (die). After cooling, compounds were pelletized and subsequently

injected in an injection molding machine Meteor 270/75 (Mateu&Sole, Barcelona, Spain) at an injection temperature of 180 °C.

Table 1

2.3.- Mechanical characterization of PLA/ β -TCP composites.

Mechanical properties of PLA/ β -TCP composites were evaluated in tensile and flexural conditions. Tensile and flexural properties were obtained in a universal test machine ELIB 30 (S.A.E. Ibertest, Madrid, Spain) at room temperature following ISO 527-5 and ISO 178:1993 respectively; a load cell of 5 kN was used and the crosshead rate was set to 10 mm min⁻¹ (tensile tests) and 5 mm min⁻¹ (flexural tests). Five different specimens were tested and average values of strength and modulus were calculated.

Shore D hardness was obtained in a Shore durometer mod. 673-D (Instrumentos J. Bot S.A., Barcelona, Spain) as indicated in UNE-EN ISO 868.

The ability for energy absorption was estimated by using a 1 J Charpy's pendulum (Metrotec S.A., San Sebastian, Spain) as recommended in ISO179:1993 standard. Tests were carried out for five different unnotched samples and average values of energy absorption were calculated.

2.4.- Microscopic characterization of PLA/ β -TCP composites.

A scanning electron microscope (SEM) Phenom (FEI Company, Eindhoven, Netherlands) was used to characterize fractured surfaces from impact tests as well as raw β -TCP microparticles. Samples were previously subjected to a metallization process in a sputter coater EMITECH SC7620 (Quorum Technologies Ltd., East Susex, UK) with an Au-Pd alloy.

2.5.- Dynamic mechanical characterization of PLA/ β -TCP composites.

Dynamic mechanical characterization in torsion mode was conducted in an oscillatory rheometer AR G2 (TA Instruments, New Castle, USA), equipped with a torsion clamp accessory for solid samples. Rectangular samples sizing 40x10x4 mm³ were subjected to a heating program from -50 °C up to 110 °C at a constant heating rate of 2 °C min⁻¹; the frequency and the maximum deformation (γ) were set to 1 Hz and 0.1% respectively.

2.6.- Thermal analysis of PLA/ β -TCP composites.

Thermal properties of raw materials and PLA/ β -TCP composites were studied by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). TGA was carried out in a TGA/SDTA thermobalance mod. 851 (Mettler-Toledo Inc., Schwerzenbach, Switzerland) with a heating program from 30 °C to 700 °C at a heating rate of 20 °C min⁻¹ in nitrogen atmosphere (66 mL min⁻¹). Thermal transitions were

evaluated in a differential scanning calorimeter (DSC) mod. 821 (Mettler-Toledo Inc., Schwerzenbach, Switzerland); samples sizing 7-10 mg were placed into standard 40 μ L aluminum crucibles and subjected to a heating program from 30 $^{\circ}$ C to 350 $^{\circ}$ C at a heating rate of 10 $^{\circ}$ C min^{-1} in air atmosphere.

3.- Results and discussion.

3.1.- Effect of weight % β -TCP on mechanical properties of PLA/ β -TCP composites.

Fig. 1 & Fig. 2 show the plot evolution of the main parameters obtained from tensile and flexural tests respectively.

Figure 1

From observation of tensile test results (Fig. 1) we see a decrease in tensile strength values with regard to unfilled PLA. The tensile strength of unfilled PLA is close to 64 MPa and decreases up to values of 50.5 MPa for composites containing 40 wt.% β -TCP. Nevertheless, for a β -TCP content of 10 wt.%, the tensile strength decrease is less than 3%. This is related to low particle-polymer interactions; thus the osteoconductive filler acts as a stress concentrator but the poor interaction makes calcium and phosphate easy available during degradation and this is positive from a biomedical point of view. Intermediate compositions with 20 and 30 wt.% β -TCP

promote a decrease in tensile strength of about 12% and 15%. With regard to elongation at break the unfilled PLA is characterized by relatively low values around 8%. As the β -TCP content increases, we observe a clear decreasing tendency and minimum values of about 3.4% are obtained for PLA/ β -TCP composites with the highest β -TCP content, which represents a percentage decrease of almost 60%. As expected, the elastic modulus increases with β -TCP content thus leading to stiffer materials. This is in total agreement with the evolution of tensile strength and elongation at break. The elastic modulus represents the ratio between the stress and the elongation in the linear region. As abovementioned, we have observed a decrease in tensile strength but the decrease in elongation at break is still higher so that, the ratio between these values increases due to the lower values of elongation at break.

Different tendency can be observed by following the evolution of the flexural properties of the PLA/ β -TCP system. The unfilled PLA is characterized by a flexural strength of about 110 MPa and the flexural strength values in terms of the β -TCP content decreases up to values in the 90-100 MPa range. It is clear that increasing β -TCP filler increases flexural strength and flexural modulus. However, the resistance is lower in all cases compared to the virgin PLA. The smallest resistance value is obtained for PLA composites containing 10 wt.% β -TCP. This may be due to the presence of small particle aggregates that promote crack initiation prematurely thus leading to fracture. However with increasing β -TCP load we observe stiffer materials and,

therefore, an increase in resistance, but always less than virgin PLA due to particle aggregation. On the other hand, the flexural modulus increases in a remarkable way from 3.24 GPa for unfilled PLA up to 5.02 GPa for composites containing 40 wt.% β -TCP. Once again, the flexural results indicate that addition of β -TCP provides stiffer materials with slightly lower resistance. Compositions in the 10-20 wt.% β -TCP represent a good balance between overall mechanical response as they offer high stiffness materials with similar resistance and deformation ability to unfilled PLA. The evolution of the Shore D hardness is similar to other mechanical resistant properties with a clear increase with the β -TCP load.

Figure 2

Another desirable attracting property in materials for fixation devices is the ability to absorb energy during fracture. Table 2 shows the absorbed energy (Charpy's test) as a function of the β -TCP load content. PLA is a quite fragile material as indicated by the relatively low energy absorption values close to 1.85 J m^{-2} . Addition of β -TCP leads to a slight decrease in absorbed energy. For compositions comprised between 10 and 20 wt.% β -TCP, the absorbed energy is reduced up to values of 1.68 J m^{-2} (percentage decrease of 10%) and 1.40 J m^{-2} (percentage decrease of about 24%) respectively. These values indicate that the ability of PLA for energy absorption is

highly sensitive to presence of stress concentrators such as the case of the osteoconductive β -TCP filler. So that, compositions with more than 20 wt.% β -TCP would not be recommended (31) for fixation devices unless additional surface treatments are carried on the filler to minimize the loss on mechanical performance.

Table 2

The morphology of the fractured surfaces from impact tests of PLA/ β -TCP composites was observed by SEM analysis. Fig. 3a shows typical fracture of unfilled PLA(32); as the β -TCP content increases we observe more rough surfaces due to presence of filler. Presence of β -TCP leads to a fracture process with a typical flake formation which is representative for a fragile fracture. Increasing flake structure is representative for more fragile materials as observed in Table 2 with absorbed energy values.

Figure 3

Figure 4 clearly shows the typical distribution β -TCP particles in the PLA matrix. It can be observed good particle dispersion among the PLA matrix. Although some particle-polymer interaction can be observed in Fig. 4a (low particle-polymer

gap), in general terms, interaction is not high as previous mechanical characterization has revealed with a decrease in both strength and deformation ability. Fig. 4b shows a FESEM image of a PLA composite containing 30 wt.% β -TCP subjected to a treatment with 6M HCl for 12 hours. The voids and holes correspond to removed/dissolved β -TCP and the overall void size and distribution also indicate good particle dispersion.

Figure 4

3.2.- Effect of weight % β -TCP on thermal properties of PLA/ β -TCP composites.

Thermal transitions of PLA/ β -TCP composites were evaluated by means of differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Table 3 shows melt temperature, glass transition temperature (T_g), cold crystallization peaks and normalized values for the cold crystallization. We observe a slight decrease in the melt peak from 173 °C to 170-172 °C but it is not relevant. Similar behavior can be observed for the cold crystallization process with a peak at 116 °C (unfilled PLA) up to values in the 113-116 °C for PLA/ β -TCP composites. The crystallization of PLA/ β -TCP composites decreases in all formulations compared to the virgin PLA. In addition, the glass transition temperature is slightly lower but it is not relevant as it changes from 65 °C (unfilled PLA) to 62-63 °C for PLA/ β -TCP composites. This could be related to

partial hydrolysis of PLA polymer chains due to the presence of a highly hydrophilic filler such as β -TCP which could contribute to hydrolyze (33) some poly(lactic acid) chains and promote a plasticization process with the formed lactic acid oligomers. Fig. 5 shows a comparative plot of the DSC curves for PLA/ β -TCP composites with different β -TCP loads in which, the different transitions can be observed. In addition, a double melt peak is detected, which is directly related to a crystalline polymorphism due to presence of small amounts of D-lactide (34). The change in the peak shape corresponding to PLA with 30 wt.% β -TCP is due to increased melting of spherulites D-lactide crystallization. The osteoconductive particles promote this type of crystallization.

Table 3

Figure 5

Fig. 6 shows thermogravimetric curves (TGA) for PLA/ β -TCP composites with different β -TCP content. PLA is highly stable to temperature; nevertheless, PLA/ β -TCP composites show a slight decrease in the degradation onset due to hydrolysis processes (35, 36). As we have described previously, β -TCP is highly hydrophilic and this fact leads to hydrolytic scission of poly(lactic acid) chains thus leading to formation of lactic acid oligomers. The percentage residue is directly related to the total content on β -TCP

inorganic filler; so that, composites with 20 wt.% β -TCP show a residual percentage weight of 22% which corresponds to the β -TCP filler plus residual ashes from PLA.

Figure 6

With regard to dynamic mechanical thermal behavior of PLA/ β -TCP composites, Fig. 7 shows a comparative plot of the storage modulus (G') as a function of temperature for different β -TCP loads. As we can see, the storage modulus moves to higher values as the β -TCP content increases which is representative for stiffer materials as described previously. The storage modulus remains almost constant up to values of about 60 °C. A remarkable decrease in G' occurs in the 60-80 °C range which is directly related to the glass transition temperature (T_g) of . A new increase in storage modulus (G') is detected at temperatures higher than 90-100 °C; this is related to the cold crystallization process which leads to increased crystallinity and, subsequently, an increase in stiffness is achieved. As we can clearly detect, the crystallization moves to lower temperatures as the β -TCP content increases due to the nucleating effect of finely dispersed β -TCP into the PLA polymeric matrix (37).

Figure 7

4. Conclusions.

In this work we developed biocompatible and resorbable composites based on PLA matrix and beta tri-calcium phosphate (β -TCP) as osteoconductive filler. PLA with 20-30 wt.% β -TCP shows an increase in Young's modulus and flexural modulus up to 35 and 53%, respectively. Higher β -TCP loads (>20-30 wt.%), produce a significant loss of resilience or ability for energy absorption. A reduction on **crystallinity** and the degradation onset temperature are observed by adding β -TCP to PLA. Due to the high hydrophilic character of the β -TCP particles, PLA/ β -TCP composites are more hydrophilic than neat PLA. This is due to degradation caused by thermal hydrolysis processes. The softening temperature of the composites decreases compared to the polymer without osteoconductive load. This is also due to the lower crystallinity. An increase in the Young's modulus of composites is observed at temperatures below the T_g in comparison with PLA. The Young's modulus increases as the percentage of osteoconductive load rises. Considering that the working temperature of the composites will be lower than the softening point, it can be stated that the PLA composites containing 20-30 wt.% β -TCP show a necessary improvement in mechanical properties to prevent breakage in interference screws made from this material.

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Table captions

Table 1.- Compositions and labelling of PLA/ β -TCP composites.

Table 2.- Shore D hardness values and Charpy's absorbed energy of PLA/ β -TCP composites in terms of the β -TCP weight %.

Table 3.- Summary of the main thermal parameters of PLA/ β -TCP composites, obtained by differential scanning calorimetry (DSC).

Figure legends

Figure 1.- Plot of the evolution of mechanical properties from tensile tests as a function of the weight % β -TCP.

Figure 2.- Plot of the evolution of mechanical properties from flexural tests as a function of the weight % β -TCP.

Figure 3.- SEM images of fractured surfaces from impact tests corresponding to PLA/ β -TCP composites with different wt.% β -TCP, a) unfilled PLA, b) 10 wt.% β -TCP, c) 20 wt.% β -TCP, d) 30 wt.% β -TCP, e) 40 wt.% β -TCP.

Figure 4.- FESEM images of fractured surfaces from impact tests of PLA composite with 30 wt.% β -TCP, a) untreated and b) treated with 6M HCl for 12 hours.

Figure 5.- Comparative plot of DSC graphs corresponding to PLA/ β -TCP composites with different wt.% β -TCP.

Figure 6.- Comparative plot of TGA graphs corresponding to PLA/ β -TCP composites with different wt.% β -TCP.

Figure 7.- Evolution of the storage modulus (G') of PLA/ β -TCP composites with different wt.% β -TCP.