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The effect of tri-calcium phosphate (TCP) addition on the degradation of polylactide-co-glycolide (PLGA)

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Abstract This paper investigates the effects of α-tri-calcium phosphate (α-TCP) addition on the properties of polylactide-co-glycolide (PLGA). Samples with additions of 5, 10, 15, 20, 30 and 40 wt% α-TCP were prepared via a hotpressing method. Long-term in vitro studies (up to 60 days) were carried out in pH 7.4 phosphate-buffered saline (PBS). Degradation properties were investigated by monitoring pH, water uptake and mass loss. Dissolution of calcium was analysed with inductively coupled plasma spectroscopy (ICP). Internal changes of the sample structure were studied with X-ray microtomography (μCT). Change in the mechanical properties was assessed in tensile tests prior to degradation. With an addition of 40 wt% α-TCP, the onset of mass loss could be retarded by 18 days; at the end of the study the pH of the buffer solution was reduced to only 4.3 in comparison to 3 for pure PLGA. Although degradation properties seemed to be strongly dependent on the amount of α-TCP added, all samples appeared to show faster internal degradation when assessed with μCT.

Abbreviations

PLGA	Polylactide-co-glycolide
α-TCP	Alpha-tri-calcium phosphate
HA	Hydroxyapatite
PMMA	Polymethylmethacrylate
PDLLA	Poly-(D,L)-lactide
PLA	Polylactide
PBS	Phosphate-buffered saline
ICP	Inductively coupled plasma spectroscopy
*N*CT	X-ray microtomography
XRD	X-ray diffraction
FTIR	Fourier Transform Infrared Spectroscopy
wt%	Weight percentage
m_{loss}	Mass loss
w_{gain}	Water gain
w_{abs}	Water absorption
m_o	Original sample mass
m_d	Dry mass after degradation
m_w	Wet mass after degradation

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Introduction

After being implanted in the body, polyesters degrade through hydrolysis and their dissolved monomeric residues are removed by natural pathways. Besides their current main use as degradable sutures, polyesters are interesting materials for various other medical applications. Porous PLGA foam scaffolds could be used for the regeneration of various tissues and organs, such as bone and liver [1–4]. Their potential for bone-filling applications was shown in a study where PLGA implants increased the healing rate of cranial defects in rats with no infection or inflammation being reported [5]. Their main advantages over metal implants are avoidance of a second operation to remove the implant and a slow transfer of the load from the degrading polymer onto the regenerating bone instead of stress-shielding.

The mechanism of polyester degradation has been outlined by the degradation model of Li et al.[6–8]. First water diffuses into the sample. Polymer chains are degraded by hydrolytic scission of ester linkages in the polymer backbone. The carboxylic chain ends that are created during degradation can act as a catalyst and accelerate the degradation process. As aging increases, only oligomers close to the surface can diffuse out, whereas those in the middle of the sample remain entrapped and contribute to autocatalysis. This results in a slower degradation at the surface than in the center. A hollow shell may be left that is slowly degraded.

One of the main concerns with the use of polyesters as degradable medical materials is their degradation to acidic carboxyl end groups that decrease the pH of the surrounding medium. A low pH can cause inflammation in the host tissue [9]. The addition of neutralizing basic compounds to polyesters has the potential to overcome these effects. Such a composite has the potential not only to control the pH in the vicinity of the implants, but also to tailor degradation rate and to improve mechanical properties. Moreover, the addition of a biodegradable and bioactive material, would introduce osteoconductivity into the polyester. For example, the addition of 50 wt% bioactive glass particles to porous PLGA revealed that bioactive glass is a suitable material to retard degradation and at the same time to introduce class A bioactivity into the polymer [10]. Another study investigated the influence of different calcium compounds (calcium dihydrogenphosphate, calcium hydrogenphosphate, calcium phosphate, calcium carbonate) on the degradation of PLGA. The comparison revealed that calcium carbonate was most and calcium dihydrogenphosphate least effective in delaying the degradation of the sample by neutralizing the carboxyl end groups of the degradation products [11]. The addition of 30 wt% HA and sodium bicarbonate could reduce the fall in pH of the degradation solution during degradation of PLGA, however not as significantly as calcium carbonate [12].

α-Tri-calcium phosphate (α-TCP), a biodegradable and bioactive ceramic, has been investigated in composites with polymers (PLGA, PMMA, PDLLA, PLA) [13–17] and was found to improve dissolution properties and enhance formation of bone. α-TCP is commercially used in orthopaedics and dentistry, i.e. as bone filler, root canal filler, artificial tooth root and skull [18, 19]. α-TCP- addition up to 50 wt% to PDLLA increased the compressive strength, four point bending strength and Young's modulus [16]. The increase in strength was attributed to crack-deviation by the ceramic particles, plastic deformation around the particles or chemical bonding between α-TCP and PDLLA. In contrast to this, a study on TCP–PLGA–NaCl-compositions (80:10:10 and 60:20:20 wt%) showed that initial tensile strength increased as PLGA content increased [13]. This was related to a better filling of the voids between the ceramic particles as more polymer became available at the lower TCP fractions.

In this paper, the effect of the addition of different fractions of α-TCP powder to 50:50 PLA–PGA is examined. In an in vitro study, changes in polymer and ceramic mass, water gain and the pH of the degradation medium were investigated. The influence of α-TCP addition on mechanical properties of the undegraded material was assessed.

Materials and methods

Sample preparation

α-TCP was synthesized via an aqueous method. About 33.979 g calcium hydroxide (Aldrich) and 35.000 g orthophosphoric acid (BDH) were dissolved, then mixed and aged for 25 h. The mixture was filtered and dried in a drying cabinet for another 24 h. The solid thus obtained was crushed with mortar and pestle and sieved in order to obtain particles of a size <75 μm. The powder was sintered at 1200 °C for 4 h. XRD (Philips X-Pert PW3710) and FTIR (Bruker Optics Tensor 27 FT-IR) confirmed the material to be α-TCP.

Rod-shaped PLA50GA50 was purchased from Sigma Aldrich. PLAxGAy refers to the percentage of L-lactic acid units (x) and glycolic acid units (y). As there was only one type of polymer used in the experiments it will henceforth be termed PLGA.

PLGA and α-TCP-powder were weighed, and mixed to a homogenous composite on a hotplate at 200 °C. From the melt, small composite-spheres were formed (approximately 5 mm in diameter), which served as raw material for the subsequent hotpressing to sample shape. In order to minimize the degradation effect of heat on polymer, the mixing was finished within 15 min. A similar method was used in the study by Mellon [20] to form composites of PLGA and α-TCP.

Disk shaped samples were produced via hotpressing at 200 °C with moulds of 1.5 mm height and 10 mm diameter [21–23]. After removal from the hot press, samples were quenched in iced water in order to maintain their amorphous state.

The composites used in this study were made of PLGA with different weight-percent loadings (5, 10, 15, 20, 30 and 40 wt%) of α-TCP. They will be referred to within this paper as TCP5, TCP10 and so on. A pure PLGA sample served as control.

When storage before degradation was necessary, all samples and the mixed raw material were kept under vacuum to prevent reaction with the environment.

Tensile bars were produced for mechanical testing. Hotpressing into bar shaped moulds did not produce bars of sufficient quality for tensile testing. Therefore, sheets of 1.5 mm thickness were produced in the hot press and subsequently shaped via waterjet cutting to a size of 29 × 5 mm with a reduced section of 15 × 3 mm (OMAX 2626 Waterjet Machining Centre). However, the thicknesses of the sheets were not as uniform as those of the disks and the results of mechanical testing should therefore be treated with some caution.

Degradation studies

Following the method used by Hurrell et al. [21], the samples were degraded in 0.01 M phosphate buffered saline solution (PBS, Sigma Aldrich). A ratio of 6 mg of sample to 1 ml of buffer was used in all studies.

The bottles containing sample and PBS solution were placed in a water bath at 37 °C. Bottles were agitated at regular intervals. The duration of the dissolution experiments depended on the sample composition. For samples with a α-TCP content above 15 wt%, which were expected to degrade more slowly, the maximum dissolution time was 60 days. Controls and samples with 5 and 10 wt% α-TCP were degraded for maximum times of 20, 35 and 50 days, respectively. Intermediate time points were chosen with reference to the results of a similar study on PLGA and α-TCP carried out by Mellon [20].

For each time point at least two samples were investigated to ensure reproducibility of results.

Characterisation of degraded samples

The sample mass was first measured before degradation. After a specific time, the samples were taken out of the solution, dabbed dry with a paper towel and their wet mass weighed immediately to minimise water evaporation (Sartorius BP61 balance ±0.1 mg). The samples were then put into a vacuum drying cabinet at 44 °C (below the glass transition temperature of the dry polymer [24]) and their dry mass was recorded after three days of drying (Gallenkamp vacuum oven).

The percentage of mass loss (m_{loss}), water gain (w_{gain}) and water absorption (w_{abs}) were calculated from the original mass (m_o), the dry mass after degradation (m_d) and the wet mass (m_w) as displayed in Eqs. 1–3. Dividing the mass of water in the wet sample ($m_w - m_d$) by the original mass (m_o) allows comparison of all samples by normalising for initial weight variation (Eq. 2). Dividing the mass of water in the wet sample ($m_w - m_d$) by the sample mass remaining (m_d) gives information about the actual water content of a sample at a given time (Eq. 3).

$$m_{loss} = (m_d - m_o)/m_o \cdot 100 \quad (1)$$

$$w_{gain} = (m_w - m_d)/m_o \cdot 100 \quad (2)$$

$$w_{abs} = (m_w - m_d)/m_d \cdot 100 \quad (3)$$

The initial pH of the buffer solution was 7.4. The pH was measured at intervals during degradation (Camlab ISFET pH meter KS723).

Inductively coupled plasma spectroscopy (ICP) (Varian Liberty ICP AES) was used to determine the calcium content ($C_{Ca,measured}$) of the degradation medium at intervals during the degradation. To ensure complete dissolution of the calcium in the degradation medium, one part of the latter was mixed with nine parts of 2.2% nitric acid solution. Six standard solutions were prepared, containing the maximum amount of calcium leachable from the sample into the degradation media ($C_{Ca,max}$). It was assumed that the release of calcium is representative of the release of α-TCP. This allowed the mass of α-TCP and PLGA remaining to be calculated as follows (Eq. 4a and b).

$$m_{TCP\,remaining}\ [mg] = m_{Ca(x)} - m_{TCP\,dissolved} \quad (4a)$$

$$m_{PLGA\,remaining}\ [mg] = m_d - m_{TCP\,remaining} \quad (4b)$$

where $m_{Ca(x)}$, the mass of calcium in the original sample, and $m_{TCP\ dissolved}$, the mass of α-TCP dissolved, are given by

$$m_{Ca(x)} = 0.387 \cdot m_o \cdot x \quad (5)$$

$$m_{TCP dissolved}\ [mg] = C_{Ca,measured}[ppm]/C_{Ca,max}\ [ppm] \cdot (x \cdot m_o) \quad (6)$$

In Eq. 5, the value of 0.387 is the relative amount of calcium in α-TCP ($Ca_3(PO_4)_2$) as calculated from atomic masses and m_o the original sample mass with α-TCP weight fractions x ($0 < x < 1$). In Eq. 6 $C_{Ca,measured}$ is the calcium concentration in the solution as measured with ICP. $C_{Ca,max}$ is the maximum concentration of calcium dissolvable. The latter is the fraction of the original mass of calcium and the volume of PBS used. About 1 ml of PBS was used per 6 mg of sample [21].

X-ray microtomography (μCT) analysis was performed on samples of composition 40 wt% α-TCP before and after degradation ("Skyscan 1072"). Samples were wrapped in cling film to keep them moist during acquisition. Data was collected at 100 kV and 98 μA with a 1 mm aluminium filter. Transmission images were obtained by rotating the sample through 180° with a rotation step of 0.9°. Images with a pixel size of 16.49 μm were reconstructed with Cone Beam Reconstruction software (Skyscan, Belgium) with density ranges set to 0.053–0.171 and beam hardening

correction of 25%. Thus obtained cross-sectional images were analysed with CTAn software (Skyscan, Belgium).

Mechanical testing

The tensile deformation of undegraded samples of each composition was tested (Hounsfield 5 kN universal test machine along with LabVIEW 7.1 software). The surface of the sample ends were slightly roughened with sandpaper in order to prevent slipping from the rubber grips during the test. The experiments were performed at a speed of 1 mm/min. About 5 runs were performed on each type of sample.

The tensile modulus E was calculated from maximum stress and strain as described in Eq. 7. The maximum stress σ was calculated from the maximum load F_{max} and the cross-sectional area at the site of breakage $A_{breakage}$.

$$E = \sigma/\varepsilon \quad \text{with} \quad \sigma = F_{max}/A_{breakage} \tag{7}$$

Results

pH

Figure 1 shows the changes in pH of the degradation medium as a function of degradation time and sample composition. Two features of these graphs are affected by the α-TCP-content in the sample. Firstly, the onset of pH reduction is later for samples with higher α-TCP content. A decrease in pH was measured for the first time after 15 days of dissolution for pure PLGA samples, and after 30 days for both TCP30 and TCP40. Secondly, it was observed that an increase in α-TCP content led to a higher pH in the solution at the end of the study when almost the entire sample was degraded: the pH stabilized at around pH 3 for samples with α-TCP additions up to 15 wt%. Further additions of α-TCP buffered the pH at higher values, with a maximum buffering level of pH 4.3 for TCP40.

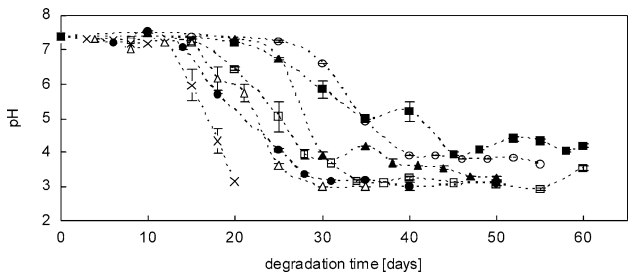

Fig. 1 Changes in pH of the dissolution media (PBS) as a function of degradation time and sample composition: pure PLGA (×), TCP5 (△), TCP10 (●), TCP15 (□), TCP20 (▲), TCP30 (○), TCP40 (■)

Mass loss and water gain

Figures 2 and 3 show changes in sample composition as a function of degradation time and initial composition. The columns represent the amounts of PLGA, α-TCP and water at given time points, expressed as a percentage of the initial sample mass (*y*-axis 1). *Y*-axis 2 refers to the amount of water absorbed expressed as a percentage of the dry sample mass remaining after a certain degradation time, as calculated according to Eq. 3.

Key points in the mass loss curves for all compositions are summarized in Table 1. It reveals that the onset of mass loss occurred at later time points for samples with higher α-TCP loadings: between 12 days for pure PLGA and 30 days for TCP40. Correspondingly, the time required to dissolve 60% of the original sample mass, increased with α-TCP content from only 20 days for pure PLGA to 52 days for TCP40.

Figure 4 shows the changes in water absorption, expressed as a percentage of dry remaining mass, as a function of time and composition. Shortly after the onset of water absorption, the graphs exhibit peaks for samples with no or small (up to 15 wt%) levels of α-TCP. For TCP20, TCP30 and TCP40 samples a plateau is seen. The higher the α-TCP content, the later the peak or plateau is reached. The amount of water absorbed by the sample at this stage of degradation was higher for composites with a low ceramic content (TCP5, TCP10, TCP15). However, pure PLGA showed the lowest water absorption. Towards the end of the experiment a sharp increase in water absorption was observed for all compositions. This final rise occurs later for samples with higher α-TCP content: between 18 days for pure PLGA and 48 days for TCP40.

X-ray microtomography

Changes in internal sample structure were analysed visually with μCT (Fig. 5). Cross-sectional images of the samples showed white regions of faster internal mass loss. The white circles are pores, which were present initially. Black dots are α-TCP particles which have a higher density than the surrounding polymer.

Mechanical testing

A small set of mechanical tests were performed on undegraded samples of all compositions. The tensile strength for pure PLGA was measured at 3.4 ± 0.44 GPa which is within the range of published data (1–4.34 GPa [25]). Due to the addition of up to 40 wt% α-TCP tensile modulus increased by approximately 75% to 5.9 ± 1.22 GPa.

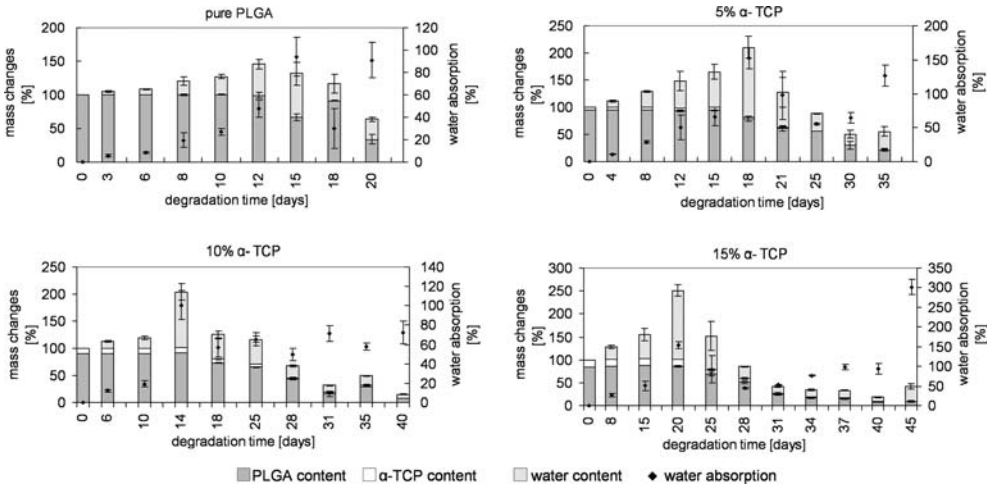

Fig. 2 Compositions of samples with low initial α-TCP-content (i.e. 0–15 wt%). Columns show the mass of PLGA, α-TCP and water as a percentage of the initial sample mass. On the second *y*-axis the water absorption (◆) is given as percentage of the dry sample mass remaining, giving a measure of the actual water content of a sample at different degradation time points

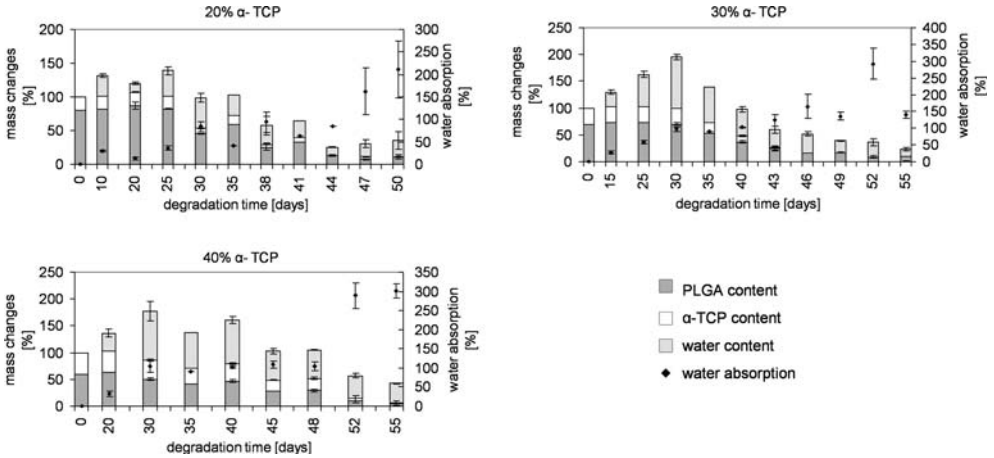

Fig. 3 Compositions of samples with high initial α-TCP-content (i.e. 20–40 wt%). Columns show the mass of PLGA, α-TCP and water as a percentage of the initial sample mass. On the second *y*-axis the water absorption (◆) is given as percentage of the dry sample mass remaining, giving a measure of the actual water content of a sample at different degradation time points

Table 1 Summary of the key changes in mass loss for all samples showing degradation time until first mass loss was measured (t ($m < m_0$)) and degradation time when less than 40% of the initial sample mass remained (t ($m < 0.4\ m_0$))

	Pure PLGA	TCP5	TCP10	TCP15	TCP20	TCP30	TCP40
t ($m < m_0$)	12	15	15	20	25	30	30
t ($m < 0.4\ m_0$)	20	30	30	30	38	43	52

Discussion

The purpose of this paper is to investigate the buffering effect of α-TCP addition on the degradation of PLGA. α-TCP is thought to buffer the acidic degradation products of PLGA, thus reducing autocatalysis in the centre of the sample. The overall results indicate that, with an increasing addition of α-TCP, mass loss of the samples can successfully be delayed.

Comparison of the data for mass loss and buffer pH shows that the onset of pH drop was either at the same day or shortly after the first mass loss of the samples for all compositions. The interdependence of mass loss and pH originates from the release of acidic degradation products during mass loss which contributes to a decrease in buffer pH [7]. With increasing α-TCP content in the sample, the absolute amount of solubilised α-TCP increased faster and reached higher final concentrations (Figs. 2, 3). As a consequence, pH was buffered at higher values (pH ≈ 4 for TCP40 and TCP30; pH ≈ 3 for TCP5, TCP10 and TCP15) and at earlier stages (i.e. pH stabilized after only 50% of the initial mass was dissolved for TCP40, in contrast to 80% for TCP5, TCP10 and TCP15) (Fig. 1).

Analysis with μCT gave an insight into internal changes in the sample. The pictures provided evidence that degradation is faster in the centre of the sample (Fig. 5). Hence, the degradation model of polyesters which was described by Li et al. [6–8] seems to be applicable even for TCP40 composites, when buffering within the sample might be expected to reduce the internal autocatalysis.

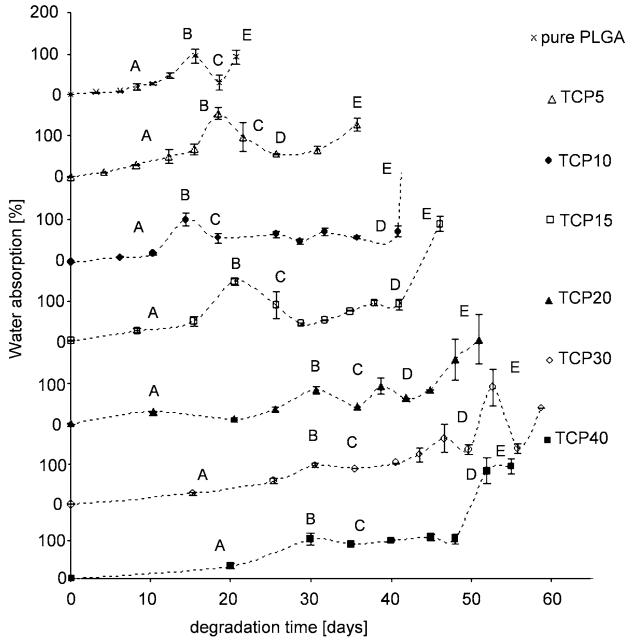

Fig. 4 Water absorption to a sample at a given time, showed in percentage of sample mass remaining (Eq. 3). Curves are offset, as indicated, for clarity

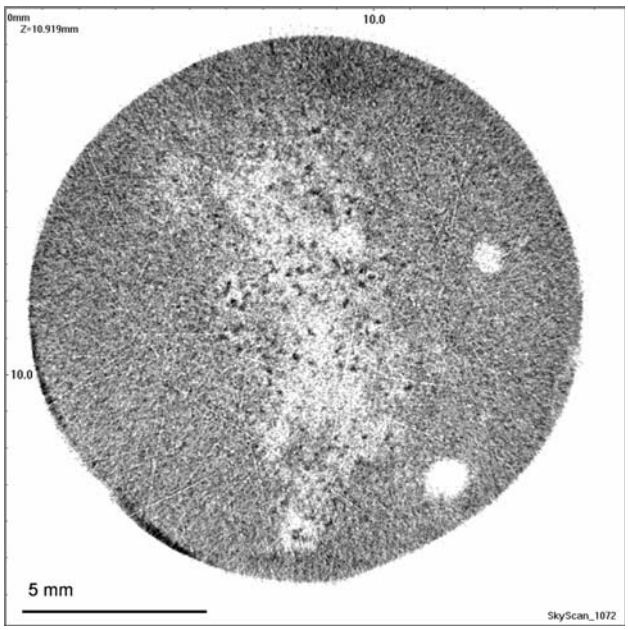

Fig. 5 μCT cross-sectional pictures of a TCP40 sample which was degraded for 30 days. Note white regions of faster internal degradation and black dots representing the α-TCP

Figure 4 shows that samples with low α-TCP content (≤15 wt%) have high initial water uptake rates. This finding can be attributed to the hydrophilic character of PLGA and its degradation products, which will take up water more readily than α-TCP does. Therefore, both the maximum amount of water absorbed and the absorption rate decrease as α-TCP content increases. In this context, it is interesting to find that pure PLGA shows the lowest water gain peak. Similar results were made by Ara et al. [11]. They investigated water gain behaviour of PLA50GA50 with additions of various calcium phosphates and calcium carbonate. Pure PLGA showed the smallest water absorption peak. The authors attributed this finding to the lack of buffering inorganic phases within the pure PLGA sample, which resulted in the dissolution of the oligomers being much quicker than the water uptake of the residual material. The result is a lower peak water content, as highly hydrated degraded material is lost from the sample at an earlier stage.

The understanding of the degradation process might be enhanced by Figs. 2 and 3, which compare water absorption with mass changes for samples with low TCP-content (i.e. 0–15 wt%) and a high TCP-content (i.e. 20–40 wt%), respectively.

Comparing Figs. 2–4 leads to the identification of five characteristic points (A–E) in the water absorption graph which seem to be related to the degradation process in the sample. We will discuss these for composites of PLGA with the addition of (i) equal and less than 15% α-TCP and (ii) 20–40% α-TCP. For both groups of samples the explanations given in the next two paragraphs are illustrated by an individual schematic diagram in Fig. 6.

≤15 wt% α-TCP (Fig. 2)

Within region A water penetrates the polymer, leading to polymer swelling. The level of water uptake is higher than for samples with high α-TCP addition because of the hydrophilic nature of PLGA. Water uptake is further increased by hydrophilic end groups that are created during degradation of the polymer.

At B, the water absorption graph reaches its peak (after approx. 20 days), which is just after the onset of PLGA and α-TCP release. As the first sufficiently degraded oligomers diffuse from the bulk into solution, pores may be left in the sample structure that give way for more water to enter the as yet unsaturated sample.

In region C, some oligomers are degraded below a threshold size and significant polymer loss takes place. At the same time, a decrease in the water content of the sample can be observed. The level of water in the sample is reduced because the mass being lost is more hydrated than the bulk remaining. It was concluded from studies on PLGA with the addition of various calcium compounds [11] and bioactive inorganic fillers (bioglass, wollastonite) [26] that water content reflects the balance between hydrated oligomers going into solution and the water uptake to the residual material. The water content increases as

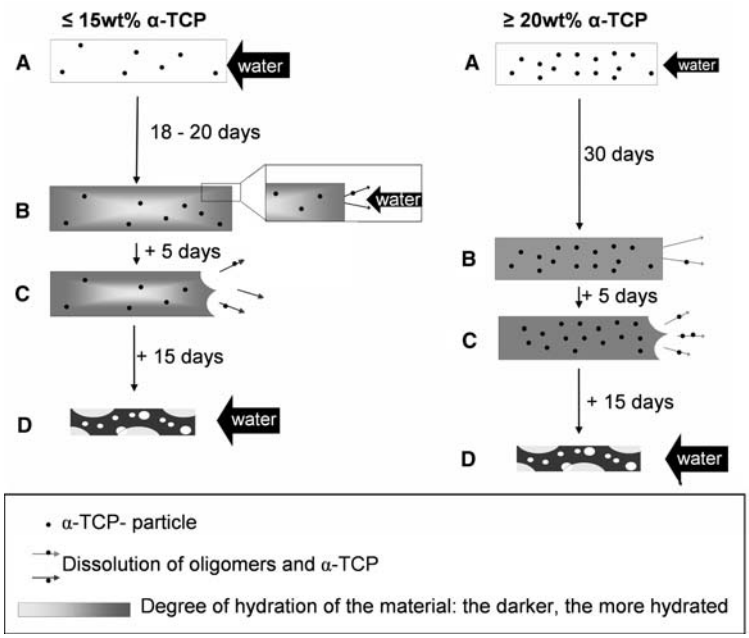

Fig. 6 Schematic diagram of degradation of samples with α-TCP additions ≤15 wt% and ≥20 wt%: (**A**) Water diffuses into the sample. (**B**) Onset of dissolution of oligomers. Samples with low α-TCP additions are not yet saturated and further water ingress can be observed. (**C**) Massive degradation of oligomers takes place. For samples with low α-TCP content, the mass lost is much more hydrated than the bulk remaining. For samples with high α-TCP content the degree of hydration of the mass lost and bulk remaining is the same. (**D**) α-TCP has dissolved completely from the sample. A very open and porous structure is left which water can easily access

long as accumulation of hydrolytic degradation products is the predominating mechanism. It decreases when an increasing number of oligomers is degraded enough to dissolve.

In addition to this, the strong decrease in water absorption may be due to mechanisms that hinder water access to the sample at later time points. A study on PLGA films suggests that at these advanced stages of degradation the highly degraded polymer chains are able to flow into the spaces created by the mass lost [27]. This results in reduced surface area and less space available for water ingress.

D indicates the point when α-TCP has dissolved completely. Due to the lack of buffer, hydrolysis of PLGA is accelerated. Furthermore, the remaining sample is already highly degraded and features a very open and porous structure that allows rapid water ingress. This results in the sharp final rise in water absorption depicted in region E.

≥20 wt% α-TCP (Fig. 3)

Within region A water penetrates the polymer, leading to polymer swelling. Due to the decreased fraction of PLGA compared with the low α-TCP samples, the samples are less hydrophilic in general. Carboxylic endgroups are neutralized by basic compounds—α-TCP in the presented study—and thus the degradation rate is decreased [28]. With less hydrophilic end groups being created, the tendency to water absorption is further reduced in comparison to the samples with α-TCP content below 15 wt%. Lin et al. suggested from a study on sintered PDLLA–TCP composites that the reduced water gain rate was attributed to TCP particles which limited the access of water to the surface of the sample at earlier degradation stages [16].

At B the water content graph reaches a plateau (after approx. 30 days), which is just after the onset of PLGA and α-TCP release. The existence of a plateau rather than a peak may be explained by the longer time that the samples have been degrading compared with the low α-TCP composites at the equivalent point. By the time the oligomers are small enough to dissolve, the samples may already be saturated which results in no further increase in water absorption in region B. As there is no difference in the water content of the oligomers leaving and the sample remaining, water absorption does not decrease in region C but stays constant.

D indicates the time point when α-TCP has dissolved completely. Due to the lack of buffer, the hydrolysis of PLGA is accelerated. Furthermore, the remaining sample is already highly degraded and features a very open and porous structure that allows rapid water ingress. This results in the sharp final rise depicted in region E.

Future work should investigate the degradation process with magnetic resonance imaging to confirm or correct these assumptions.

Mechanical testing

Tensile modulus increased from 3.4 ± 0.44 GPa for pure PLGA to 5.9 ± 1.22 GPa for TCP40 samples. This finding is in agreement with Lin et al. who reported an increase in compressive strength for PDLLA samples with α-TCP-additions up to 50 wt% [16]. They attributed the increase in strength to crack-deviation by the ceramic particles,

plastic deformation around the particles or chemical bonding between α-TCP and PLGA.

Conclusion

The addition of α-TCP to PLGA is a suitable method of buffering the pH to higher levels in vicinity of the sample. This would decrease the risk of inflammation in vivo, which can be triggered by low pH values. In addition, degradation of the sample was significantly delayed. Therefore, the addition of α-TCP to PLGA might be a means to obtain a fully resorbable sample with degradation properties that match in vivo requirements. Furthermore, the mechanical properties of pure PLGA could be improved by the addition of α-TCP.

Future work should confirm the improvement of biocompatibility with in vivo studies. It is hoped that the addition of an osteoconductive material will enhance bioactivity and osseointegration of the sample in situ. Analysis of the degrading samples with magnetic resonance imaging might give a better understanding of the degradation process.

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