

# The degradation behavior of nanoscale HA/PLGA and $\alpha$ -TCP/PLGA composites

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**The aim of this work was to prepare and analyze the degradation properties of pure PLGA, homogeneous  $\alpha$ -tricalcium phosphate ( $\alpha$ -TCP)/PLGA and hydroxyapatite (HA)/PLGA composites for potential bone replacement applications.  $\alpha$ -TCP and HA powders were prepared in-house and 25 nominal wt% of calcium phosphate (CaP) powder was incorporated into commercially available PLGA pellets by twin screw extrusion. The degradation studies showed that pure PLGA had the fastest degradation rate followed by HA/PLGA and  $\alpha$ -TCP/PLGA. Overall, it was found that  $\alpha$ -TCP acted as a better buffering agent than HA, resulting in reduced acid group autocatalysis and hence a slower degradation rate.**

## 1. Introduction

In the last 30 years, a range of biomaterials have been used to replace bone including titanium and its alloys, bioactive glass, glass-ceramics, calcium phosphates (CaP) and bioresorbable polymers.<sup>1–4</sup> The mechanical behavior of metal implants, ceramics and also many polymers are a poor match to those of bone therefore composites of bioceramics and polymers were developed to produce materials with properties that match more closely those of bone and which might also eliminate the need of a secondary surgery.<sup>5</sup>

There is growing attention on the use of poly( $\alpha$ -hydroxyacids) in synthetic biomaterial composites. These composites transfer load gradually to the surrounding tissue while guiding new bone formation and eliminating the need for secondary surgery to remove the implants.<sup>6</sup> PLGA is an amorphous copolymer of polylactic acid and polyglycolic acid.<sup>7</sup> The degradation properties of PLGA can be tailored by varying the ratio of the copolymers. PLGA (50/50) has the fastest degradation rate among all the copolymers.<sup>3,8–15</sup>

In order to match the properties of poly( $\alpha$ -hydroxyacids) to those of bone, it is necessary to produce carefully designed composites combining these bioresorbable polymers with a suitable CaP. To this end, a large number of bioceramics have been incorporated into polymer matrices, including, amongst others: hydroxyapatite (HA), glass-ceramics, bioactive glasses,  $\alpha$ -TCP and  $\beta$ -TCP ( $\beta$ -tricalcium phosphate).<sup>16–20</sup> CaP increases the basicity of the environment and

reduces degradation rate by buffering acidic degradation products and thereby reducing the autocatalysis effect. Different CaP have different solubility rates over a range of pH levels. Therefore, they can influence the degradation rate of PLGA to different extents. Of the CaP, most frequently used in orthopaedic applications, the dissolution rates between pH 6.2 and 8.5 are as follows:

$$1. \quad \alpha\text{-TCP} \geq \beta\text{-TCP} \geq \text{HA}$$

Under physiological conditions, TCPs have higher dissolution rates than HA and  $\alpha$ -TCP dissolves much faster than  $\beta$ -TCP.<sup>21</sup>

Although the relative dissolution rates of CaP have been analyzed at different pH levels, the relative buffering effect of these CaP on PLGA are not well known. Therefore, in this study, nanometer scale HA and  $\alpha$ -TCP were prepared and added at 25 nominal wt% into a PLGA matrix. Then, the degradation behavior and % water uptake of HA/PLGA and  $\alpha$ -TCP/PLGA composites were compared. In this way, the buffering capability of HA and  $\alpha$ -TCP on the autocatalysis of PLGA was analyzed.

## 2. Experimental

### 2.1 Materials

PLGA (50/50) pellets with a molecular weight of 65 kDa and an inherent viscosity of 0.49 dl/g were purchased from SurModics Pharmaceuticals. CaP was produced in-house by a wet precipitation

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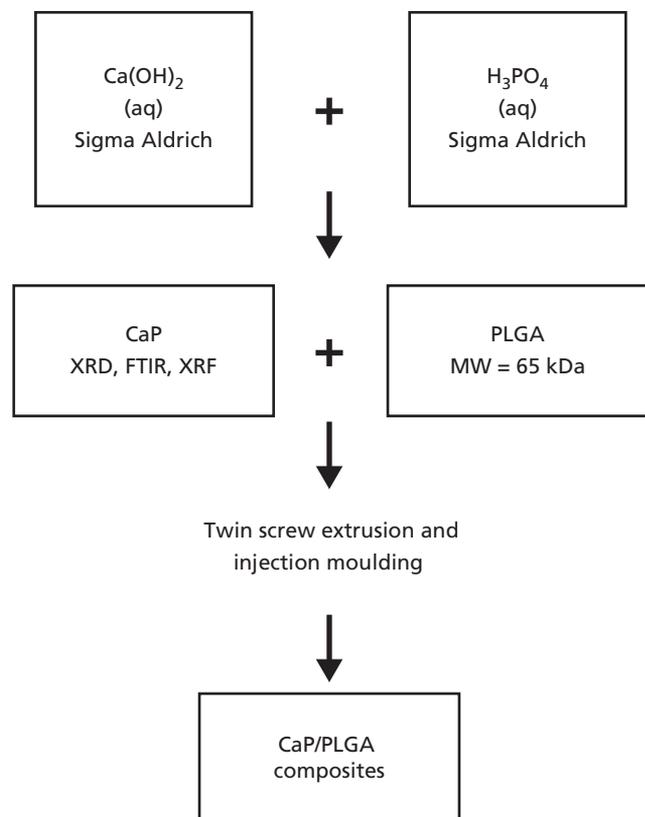
method as outlined below. CaP/PLGA composites were prepared and shaped by twin screw extrusion followed by injection moulding. Then, they were shaped into discs by an electronic saw.<sup>22,23</sup>

## 2.2 Synthesis of CaP particles and CaP/PLGA composites

Scheme 1 shows the generic procedure to prepare the CaP and the composites.

### 2.2.1 Preparation of HA

HA was prepared in-house by a wet precipitation reaction between 0.5 moles of commercially available 98%  $\text{Ca}(\text{OH})_2$  and 0.3 moles of commercially available 85% ortho- $\text{H}_3\text{PO}_4$  (BDH Laboratory Supplies, UK) pH was maintained at 10.5 by the addition of ammonium hydroxide solution. After 2 hours mixing, the suspension was aged overnight. The aged mixture was filtered and the filter-cake was dried. The dried filter-cake was ground to fine powder with a pestle and mortar. HA was calcined using heating rate of  $2.5^\circ\text{C}/\text{min}$  to  $1200^\circ\text{C}$ , a dwell of 2 h at  $1200^\circ\text{C}$  and a cooling rate of  $20^\circ\text{C}/\text{min}$  to  $20^\circ\text{C}$ .<sup>24,25</sup> HA was then broken down using a pestle and mortar, then it was sieved with a  $75\text{-}\mu\text{m}$  gauge sieve.



**Scheme 1.** The schematic diagram of the CaP/PLGA composite preparation

### 2.2.2 Preparation of $\alpha$ -TCP

$\alpha$ -TCP was prepared in-house by a wet precipitation reaction between commercially available 98%  $\text{Ca}(\text{OH})_2$  and 85% ortho- $\text{H}_3\text{PO}_4$  (BDH Laboratory Supplies, UK) in deionized water at a molar ratio of 3:2.  $\text{Ca}(\text{OH})_2$  and  $\text{H}_3\text{PO}_4$  were dissolved into solution under continuous stirring and reacted according to the following reaction.<sup>26</sup>



After adding the orthophosphoric acid solution, the mixture was stirred continuously for 2 h, and then it was left to age for 1 d. The aged slurry was then filtered to obtain a filter-cake and dried. The dried TCP filter-cake was ground into fine powder using a pestle and mortar and calcined with a heating rate of  $2.5^\circ\text{C}/\text{min}$  to  $1400^\circ\text{C}$ , a dwell of 4 h at  $1400^\circ\text{C}$  and quenching in air to room temperature to obtain the  $\alpha$ -TCP.<sup>27</sup> The  $\alpha$ -TCP was then broken down using a pestle and mortar and sieved with a  $75\text{-}\mu\text{m}$  gauge sieve.<sup>28</sup>

### 2.3 Preparation of CaP/PLGA composites

A mini ( $5\text{cm}^3$ ), corotating twin screw extruder (DSM, The Netherlands) was used to disperse the CaP powder in PLGA matrix. PLGA pellets and the CaP particles were fed into the extruder simultaneously without any premixing. The nominal wt% of the CaP in PLGA was 25%. This composition was chosen to attain high levels of bioactivity while maintaining the homogeneity of the composites.

After cutting the extruded rods into cylinders of approximately 10 cm in length, the samples were fed into a piston type mini injection moulder (DSM, Xplore, Geleen, The Netherlands) with a capacity of  $5\text{cm}^3$ . After injection moulding, samples were obtained with a diameter of 0.6 cm and a length of 12 mm. Pure PLGA and 25 nominal wt% of CaP/PLGA composites were injection moulded with a flow temperature of  $130^\circ$ , a mould temperature of  $23\text{--}25^\circ\text{C}$  with an injection pressure of 5 bar. Samples were cooled and hardened at a holding pressure of 2 bar and a holding time of 3 s, which compensated for material shrinkage. After this, the injection moulded composites were shaped into discs with a 2-mm thickness by Accutom saw.

### 2.4 X-ray diffraction

X-ray diffraction (XRD) was carried out on about 50 mg of CaP powder with a Philips PW1730 diffractometer. The X-ray generator was operated at 40 kV and 40 mA using  $\text{CuK}\alpha$  ( $\lambda = 0.15404\text{nm}$ ). These data were collected over a  $2\theta$  range of  $10\text{--}50^\circ$  using a step size of  $0.04^\circ$  with a dwell time of 10 s. The slit sizes used were  $1^\circ$  divergence,  $0.2^\circ$  receiving and  $1^\circ$  antiscatter.

XRD studies were carried out for HA and  $\alpha$ -TCP and the XRD patterns were compared with the ICDD (Joint Committee of

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Powder Diffraction Standards (JCPDS)) standard patterns. ICDD standard patterns for HA and  $\alpha$ -TCP are (09–0432) and (29–0359), respectively. X'Pert Plus software based on the structural data of CaP was used to identify the phase composition of CaP.

## 2.5 Thermogravimetric analysis

Thermogravimetric analysis (TGA) was carried out using a TA Instrument Q500 TGA on approximately 50 mg of pure PLGA and composites. Changes in sample weight in relation to temperature were recorded at a rate of 10°C/min over a temperature range of 0–650°C in a nitrogen atmosphere. Initially, three repeats were performed for each sample however when TGA thermographs showed the same reading for all the samples, this was followed by characterization of one sample for each composition.

## 2.6 Scanning electron microscopy

Using a JEOL 6340 FEGSEM operating at 5 kV, in backscattered electron and secondary electron imaging mode, the morphology of the samples, the particle size distribution of CaP powder and the dispersion state of CHA particles within PLGA were analyzed. The cylindrical samples were cut into discs with a 2-mm thickness in order to analyze their cross-sections. The samples were mounted on an aluminum stub using double adhesive tape and sputter-coated with platinum in an argon-purged chamber. Using Java Image-J (1.42q/Java 1.6.0\_10 (32-bit)) software, for each sample, the particle size of CaP was analyzed for around 100 particles using around seven to ten micrographs taken from different regions. From the results, histograms of the particle size distribution were obtained.

## 2.7 Degradation studies

PLGA and CaP/PLGA composite discs with a 2-mm thickness were degraded in 0.01 M PBS (Sigma Aldrich) solution at 37°C

for progressive time periods. Using an electronic balance, the per cent weight loss and per cent water uptake were calculated using Equations 2 and 3.

$$2. \quad \% \text{weight loss} = 100 \times \frac{M_i - M_f}{M_i}$$

$$3. \quad \% \text{weight uptake} = 100 \times \frac{M_w - M_i}{M_i}$$

where  $M_i$  is initial dry mass,  $M_f$  is the final dry mass and  $M_w$  is the wet weight.

The pH value of the PBS solution was monitored during the degradation study using an electronic pH meter (HI-98230, HANNA Instruments).

## 3. Results and discussion

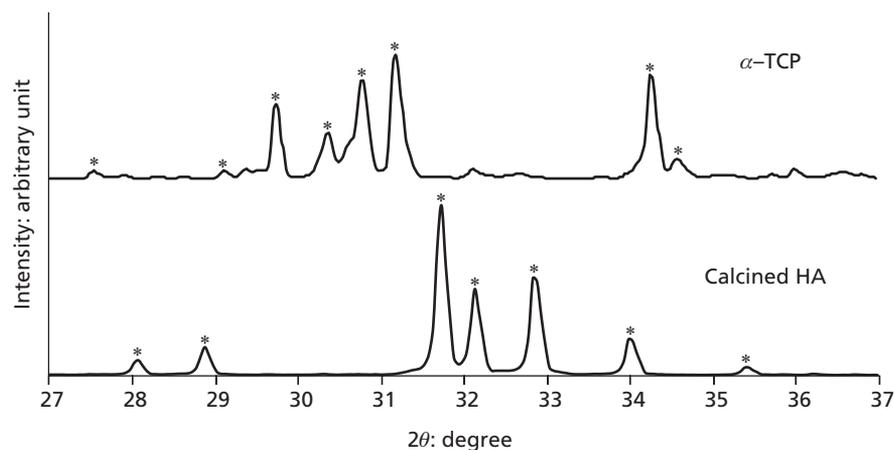
### 3.1 Phase purity of CaP composites

XRD was carried out to study the phase purity of  $\alpha$ -TCP and HA powders. Figure 1 shows the XRD patterns of the studied CaP.

### 3.2 TGA, morphology and particle size distribution

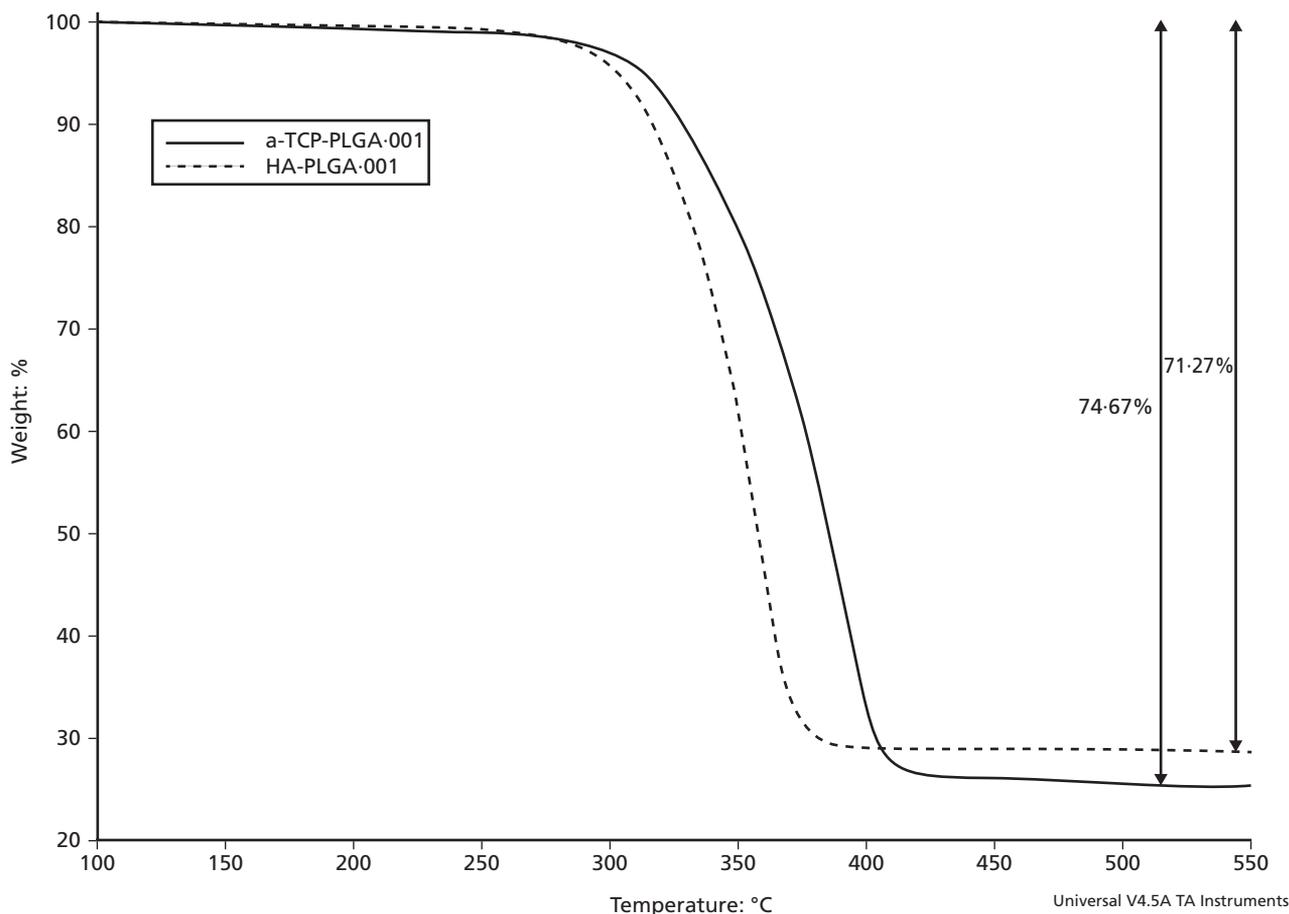
In Figure 2, TGA thermograms reveal the actual CaP content in the composites.

From TGA studies, the actual weight fraction of HA and  $\alpha$ -TCP in PLGA were found to be 29 and 25 wt%, respectively. Figure 3 and Figure 4 show the scanning electron microscopic (SEM) images of CaP/PLGA composite discs after they were extruded and injection moulded and CaP particle size distribution in the polymer matrix.



**Figure 1.** X-ray diffraction pattern of calcium phosphate powders  
(\* shows the calcium phosphate peaks)

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**Figure 2.** Thermogravimetric analysis thermograms of the CaP/PLGA composites

The SEM studies show that the particles were quite well distributed within the polymer matrices. In Figure 3, a large population of particles can be clearly observed, which are well dispersed and mainly below 500nm in diameter. Figure 4 also shows good dispersion of particles with most particle sizes again in the range of 50–250nm. Figure 4 shows the particle size distribution in the 25 wt%  $\alpha$ -TCP/PLGA composites.

### 3.3 % water uptake, % weight loss and pH changes

Figure 5 shows the % mass loss of the CaP/PLGA composites in PBS solution.

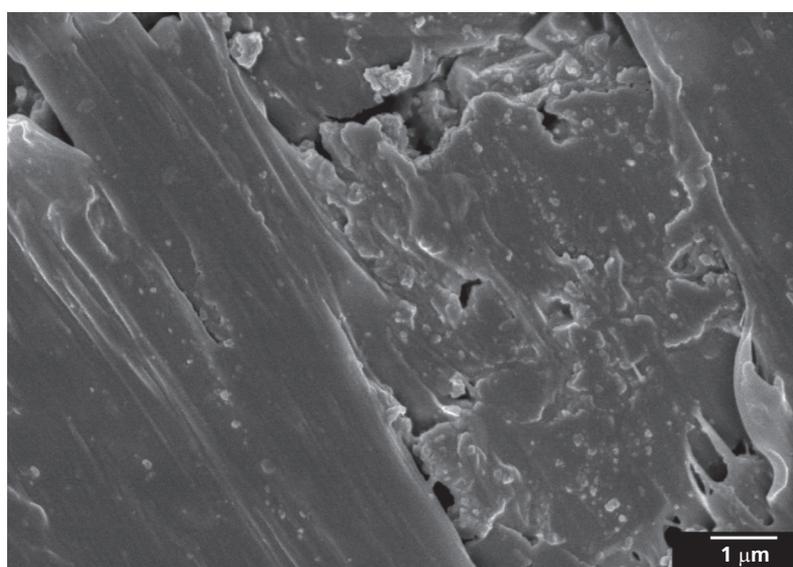
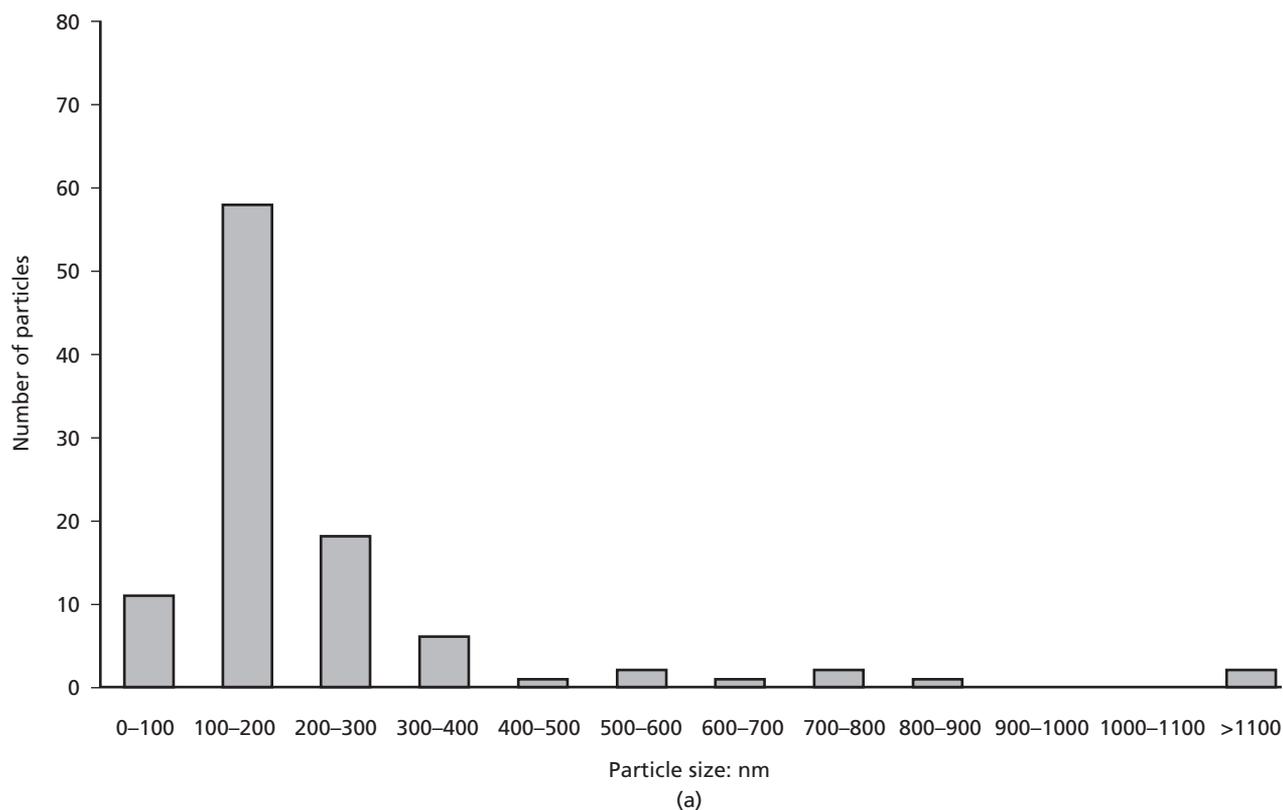
On day 56, some debris of the composite was found at the bottom of all the containers. However, it was not in measurable quantities, so the degradation is assumed to be 100% completed. Per cent weight loss results show that PLGA has the fastest mass loss. This is followed by HA/PLGA and  $\alpha$ -TCP/PLGA composites. PLGA loses all of its mass by day 21 whereas the composites lose all their mass by day 56.

Figure 6 shows the pH change for the composites during their degradation in the PBS medium. Figure 6 shows the pH change in the PBS solution during the degradation of the samples. For pure PLGA, the pH started to drop after day 15. This correlates with the time of the start of the mass loss. The pH dropped to 3.3 when the degradation was complete. The initial pH drop was delayed for HA/PLGA and  $\alpha$ -TCP/PLGA. The final pH value for HA/PLGA and  $\alpha$ -TCP/PLGA were 3.8 and 4.9, respectively.

In this study, PLGA lost mass faster than the composites, because of the buffering effect of the CaP.  $\alpha$ -TCP was observed to be the most effective buffer followed by HA, and indicated by delayed pH drop, and a slower mass loss. In addition,  $\alpha$ -TCP was observed to have the greatest final pH. This effect was seen, even though the measured fraction of  $\alpha$ -TCP in the composites was slightly lower than that of the HA composites. For composites with exactly equal particle weight fractions, the effect would be expected to be even more marked.

Figure 7 shows the % water uptake for pure PLGA and CaP/PLGA composites. As described by Ehrenfried *et al.*, the results indicate

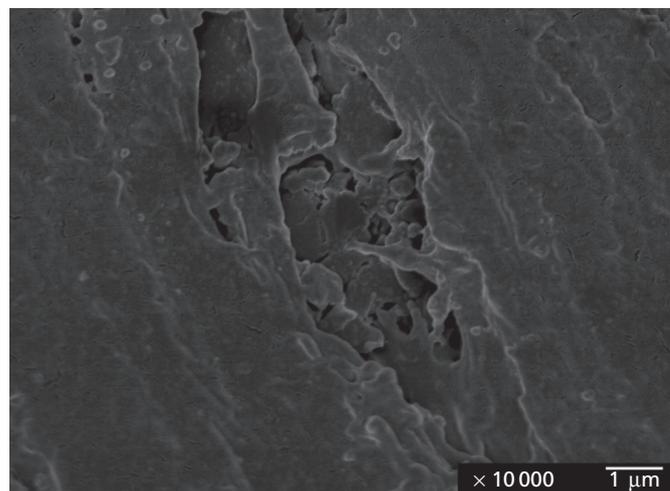
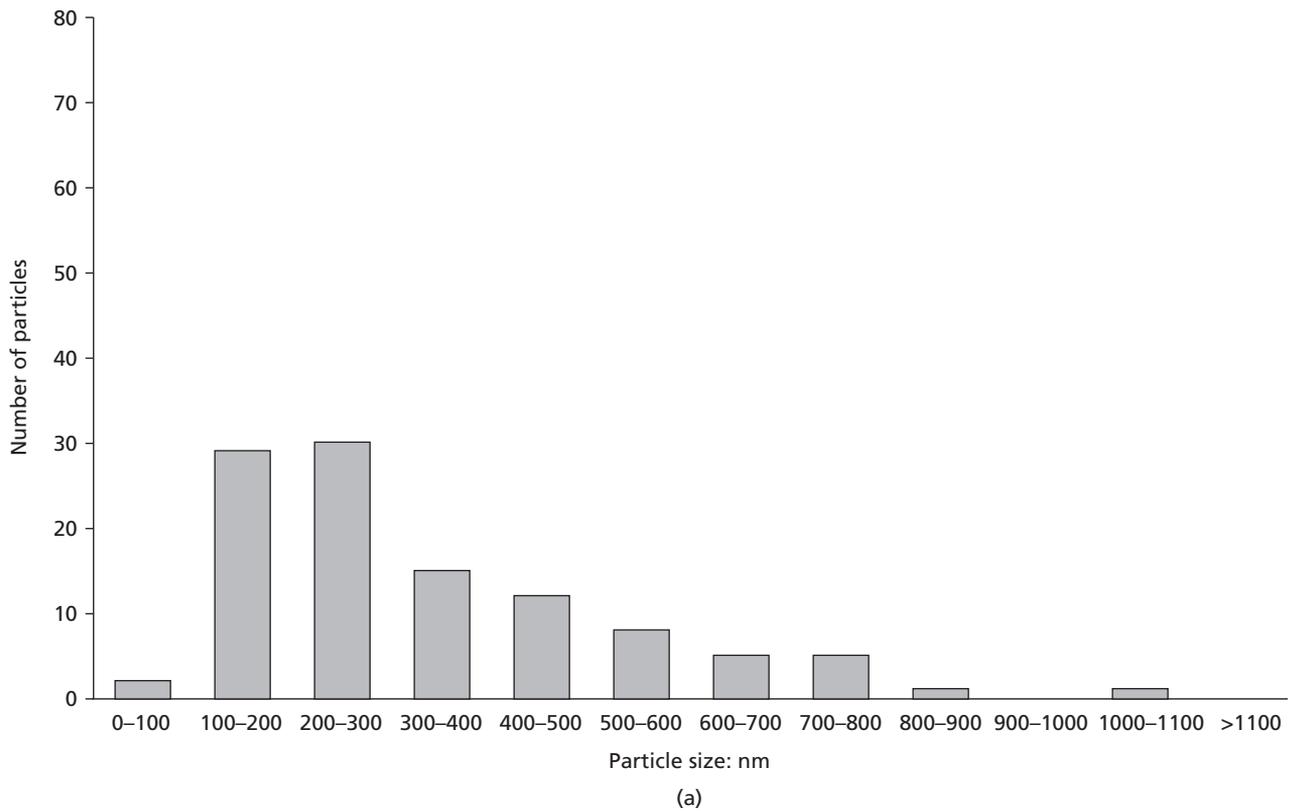
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(b)

**Figure 3.** (a) Particle size distribution of hydroxyapatite particles in the 25 nominal wt% HA/PLGA composite; (b) FEGSEM (SE) micrographs illustrating the cross-section of 25 nominal wt% HA/PLGA. Scale bar is 1  $\mu\text{m}$

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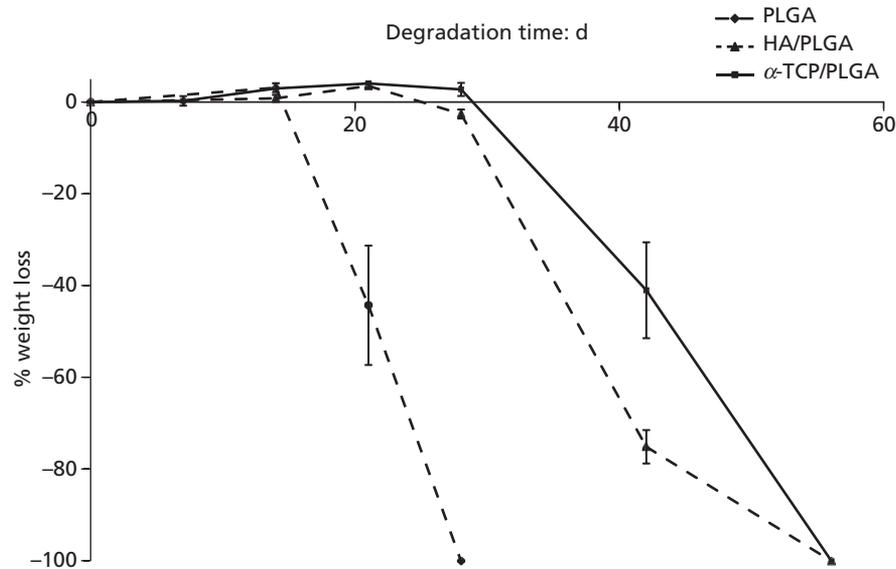
(b)

**Figure 4.** (a) Particle size distribution of  $\alpha$ -TCP particles in the 25 nominal wt%  $\alpha$ -TCP/PLGA composite; (b) FEGSEM (SE) micrograph illustrating the cross-section of 25 nominal wt%  $\alpha$ -TCP/PLGA. Scale bar is 1  $\mu$ m

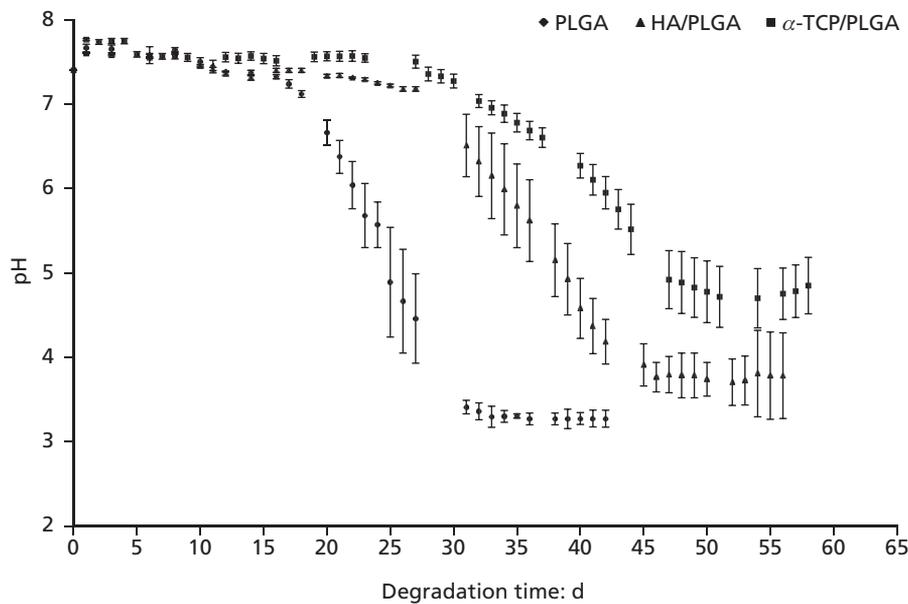
that for all the samples, water uptake takes place in a number of stages. Firstly, water penetrates into the polymer leading to swelling. In the second stage, optimum water uptake takes place. This is when the first sufficiently degraded oligomers diffuse from

the inner layer of the sample to the solution. In the third stage, significant polymer loss takes place due to degradation of some of the oligomers below a threshold size. This results in a reduced level of water content in the sample.<sup>4</sup>

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**Figure 5.** Per cent weight loss of pure PLGA, 25 nominal wt% HA/PLGA and 25 nominal wt%  $\alpha$ -TCP/PLGA during degradation (results mean  $\pm$  standard error,  $n = 3$ )

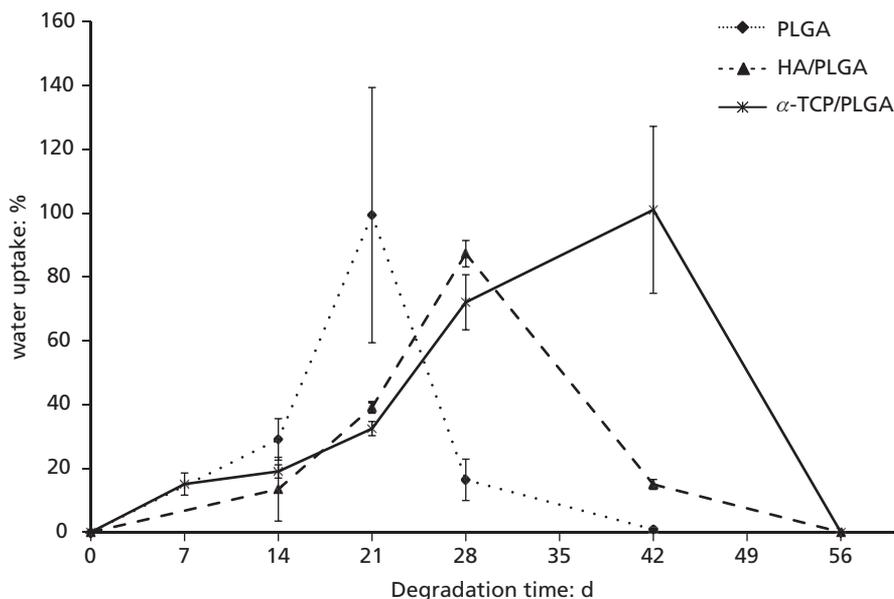


**Figure 6.** pH of pure PLGA, 25 nominal wt% HA/PLGA and 25 nominal wt%  $\alpha$ -TCP/PLGA during degradation (Results mean  $\pm$  standard error,  $n = 3$ )

For pure PLGA, maximum water uptake was reached on day 21 whereas for HA/PLGA, it was reached on day 28. The  $\alpha$ -TCP/PLGA reached the maximum water uptake the latest, 21 d later than pure PLGA at day 42. The maximum water uptake were  $99 \pm 40\%$ ,  $87 \pm 4\%$  and  $101 \pm 26\%$  for pure PLGA, HA/PLGA and  $\alpha$ -TCP/PLGA, respectively. These results were

similar with Ehrenfreund *et al.* and Yang *et al.* where they observed delayed water uptake of 20, 30 and 40 wt%  $\alpha$ -TCP/PLGA composites compared to pure PLGA. The slower water uptake of CaP/PLGA compared to PLGA resulted from the enhanced diffusion pathways for the oligomers and the buffering effect of the CaP.<sup>4,26</sup>

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**Figure 7.** Per cent water uptake of pure PLGA, 25 nominal wt% HA/PLGA and 25 nominal wt%  $\alpha$ -TCP/PLGA during degradation (results mean  $\pm$  standard error,  $n = 3$ )

The maximum water uptake is related to point at which mass loss occurs from the sample and can be correlated with the pH drop point (Figure 6). The first mass to be lost is also the most hydrated and therefore remaining mass has a lower water content.<sup>4</sup> The maximum water uptake of each composite type was similar despite the different timescale over which it was observed.

#### 4. Conclusions

Twenty-five nominal wt% of CaP/PLGA composites were produced via twin screw extrusion, including HA/PLGA,  $\alpha$ -TCP/PLGA. The technique resulted in a good dispersion of the filler particles within the PLGA matrix. The degradation studies showed that PLGA had the fastest degradation rate followed by HA/PLGA and  $\alpha$ -TCP/PLGA. The addition of HA and  $\alpha$ -TCP delayed the maximum water uptake by 7 and 21 d, respectively. The final pH value of  $\alpha$ -TCP/PLGA composites was greater than HA/PLGA composites. These results suggest that CaPs with greater solubility are more effective at buffering acidic end groups within the degradation of the polymers thereby slowing autocatalysis and delaying the bulk effects of degradation.

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