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# Performance of calcium deficient hydroxyapatite–polyglycolic acid composites: an in vitro study

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**Abstract** The strategic incorporation of bioresorbable polymeric additives to calcium-deficient hydroxyapatite cement may provide short-term structural reinforcement and modify the modulus to closer match bone. The longer-term resorption properties may also be improved, creating pathways for bone in-growth. The aim of this study was to investigate the resorption process of a calcium phosphate cement system containing either in polyglycolic acid tri-methylene carbonate particles or polyglycolic acid fibres. This was achieved by in vitro aging in physiological conditions (phosphate buffered solution at 37°C) over 12 weeks. The unreinforced CPC exhibited an increase in compressive strength at 12 weeks, however catastrophic failure was observed above a critical loading. The fracture behaviour of cement was improved by the incorporation of PGA fibres; the cement retained its cohesive structure after critical loading. Gravimetric analysis and scanning electron microscopy showed a large proportion of the fibres had resorbed after 12 weeks allowing for the increased cement porosity, which could facilitate cell infiltration and faster integration of natural bone. Incorporating the particulate additives in the cement did not provide any mechanism for mechanical property augmentation or did not demonstrate any appreciable level of resorption after 12 weeks.

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## 1 Introduction

Calcium phosphate cements (CPCs) were first proposed by Legros et al. [1] and Brown and Chow [2] more than two decades ago. The first commercial CPC product was introduced over a decade ago for treatment of maxillofacial defect, deformities [3] and bone defects [4]. Owing to its chemical and crystallographic similarity to apatitic calcium (Ca) phosphate (P) minerals found in human bone and teeth, hydroxyapatite (HA) has become one of the principal restorative materials used for the repair of human hard tissue [5]. CPCs can be delivered through a cannulated needle to an anatomical site or moulded to a desired shape to fill a bone defect and then self-cure to calcium deficient hydroxyapatite (CDHA). It is recognised for its low compressive strength and susceptibility to brittle fracture that has significantly limited the use of CDHA in load-bearing orthopaedic applications [6–8].

Another shortcoming of CDHA cement is its relative stability in vivo, several studies have reported that there is little clinical evidence of cement resorption following 4 years implantation [9–11]. To encourage new bone tissue to grow into the bone defects, pores are required in CDHA cements. Both, hydrogen peroxide solution [12] and emulsions [13] have been successfully used to create pores within apatitic cements, but both need treatments at high temperatures (>1000°C), which make it impossible to apply in injectable cements. These techniques could only be applied on pre-set materials. The incorporation of a resorbable phase material (e.g. sucrose [14, 15], mannitol [16], calcium sulphate dehydrate [17] and polylactic acid-co-glycolic acid [18]) within injectable CPC systems is another technique that has been adopted for the generation of porosity. While such additives have been successful in generating micro and macroporosity within the cement microstructure, their inclusion has had detrimental effects on the mechanical performance, setting reaction and injectability of the resultant CPC. Other groups have successfully improved the mechanical properties of CPC systems through the incorporated of ceramic particles (e.g. silicon nitride and silicon carbide [19], zirconica and alumina, silica [20]) and polymer fibres (bioresorbable grade of polyester [21] and polypropylene [22]). Xu et al. [21] reported that the incorporation of 8 mm long fibres improved the bending strength and the work to fracture of CPC. However, these fibres require pre-treatment prior to manual mixing with the CPC paste. Buchanan et al. improved the fracture behaviour of CPC through short fibre (2 mm long) reinforcement using polypropylene (PP) fibre without the requirement for additional steps during the mixing and delivery of the CPC [22]. However, one of the main drawbacks of using PP fibres is that they do not resorb and therefore will not facilitate the infiltration of cells or encourage new bone tissue to grow within the bone defect. The aim of this study was to investigate the resorption process of a CPC system containing either (i) polyglycolic acid tri-methylene carbonate (PGA-TMC) particulate additive or (ii) a PGA short fibre additive. This was achieved by simulating in vitro aging of the different resultant cements under physiological conditions. PGA-TMC copolymer was used in this study as they have been successfully used as a biomaterial in the application of sutures [23], tacks [24] and interference screws [25] demonstrating full resorption within 3–4 months [24]. Highly oriented PGA fibres were chosen because of their very high elastic anisotropy; tensile chain modulus of 294 GPa and a longitudinal shear modulus for a fibre of 6 GPa. [26]. These significant improvements in mechanical properties are largely attributed to the planar zigzag conformation of the molecular chains [26].

## 2 Materials and methods

The reinforced CPC specimens were obtained by mixing alpha-tricalcium phosphate (α-TCP), calcium phosphate ($CaHPO_4$), calcium carbonate ($CaCO_3$), HA and PGA-TMC particles or PGA fibres with an aqueous solution of disodium hydrogen phosphate ($Na_2HPO_4$). The α-TCP was prepared from calcium phosphate ($CaHPO_4$) and $CaCO_3$ as previously described [22]. X-ray diffraction (XRD) analysis was conducted using an X-Pert Pro X-ray diffraction system with an X'Celerator X-ray detector (Panalytical Ltd., UK). X'Pert High Score software was used to identify the phases present in the α-TCP powder and their respective quantities. Subsequently, the α-TCP was ground in ethanol using a planetary mill (Pulverisette 6; Frisch, Germany) in a 250 ml agate bowl with 50 × 10 mm agate balls for 30 min at 595 ± 5 revolutions per minute as described by Jack et al. [27]. The particle size distribution was measured using a laser diffraction technique (Sympatec HELOS BF particle sizer; Sympatec Ltd., UK).

The granular additive (G) used in this study were PGA-TMC copolymer (Smith & Nephew plc. UK), 67% PGA and 33% TMC. The particulate additives were produced from rod stock (Ø1 ± 0.2 mm) and initially pelletised (Strand Pelletiser CSG 171/1; Dr. Collin GmbH, Germany) followed by cryogenic grounding (Spex 6850 freezer mill; Spex CertiPrep, UK) using two cycles of 2 min and then sieved to between 106 and 425 μm (Endecotts Ltd. UK). PGA fibres (F) with a diameter of 0.2 ± 0.1 mm and length of 2–4 mm fibres were supplied by Smith and Nephew Research Centre, York, UK. The fibre were drawn at 110°C up to a draw ratio of 6 using the zone-drawing technique [28]. The fibres were cryogenically ground (Spex 6850 freezer mill; Spex CertiPrep, UK), which facilitated random distribution and better adhesion of the fibres with the CPC. Two different cycles were used, (i) one cycle of 1 min (F1) and (ii) two cycles of 2 min (F2). The additions examined were 5, 10 and 20 wt% for the PGA-TMC granules and 1 wt% for PGA fibres. An unreinforced CPC was used as the control. The control and reinforced CPC specimens were prepared by hand as described Buchanan et al. [22] using a bowl and spatula technique under atmospheric conditions (22 ± 1°C and 50 ± 2% relative humidity). The cement paste was then delivered and manually compacted into aluminium moulds, which yielded six cylindrical specimens (Ø6 ± 0.2 and 12 ± 0.2 mm height). A total of 36 specimens were prepared for each volume fraction and control specimen. The mould was then placed in a water bath (phosphate buffered solution (PBS), 37 ± 1°C) for 72 ± 0.5 h to complete the setting reaction. The majority of specimens ($n = 30$) were placed individually in sterilised PP containers of 40 ml PBS (37 ± 1°C) for 1, 3, 6, 9 and 12 weeks, the remaining six specimens were used as the control. The PBS solution was prepared in accordance with ISO 15814: 1999 using potassium dihydrogen phosphate ($KH_2PO_4$) and $Na_2HPO_4$ [29]. The pH of the PBS was between 7.4 and 7.5 at the beginning of the study and was not subsequently altered.

To investigate the resorption process of the unreinforced and reinforced CPC specimens a number of different techniques were used. Six specimens were removed at each time point and dried for 24 h at 37 ± 1°C. Gravimetric analysis was then conducted, which recorded weight differences as a function of time in PBS. The pH of the PBS was recorded at each time point using an Accumet 1003 portable pH meter (Fisher Scientific, UK). A sample of PBS was taken at each time point and examined for Ca and P ion concentration using inductively coupled plasma-optical emission spectrometry (ICP-OES) using a ThermoElemental Intrepid

DUO HR (Thermal Elemental, UK) in argon. Mechanical assessment of six specimens was conducted at each time point using compression testing as per the ISO 5833 (2002) standard [30] using a EZ50 universal materials test system (Lloyds Instruments, UK) with a 5kN load cell at a rate of displacement of 1 mm min$^{-1}$. Scanning electron microscopy (SEM) analysis of as moulded and fractured specimens surfaces was conducted for each of the different time points using a JEOL 6500 FEG SEM (Advanced Microbe am, Inc., USA) with operating voltages of 5.0 kV. Specimens were mounted on aluminium discs using a cold cure resin (Extec Corp, Enfield, CT, USA) and allowed to cure for 24 h. The specimens were subsequently sputtered with gold prior to SEM examination. Data collated for all experimental tests were evaluated for statistical significance using a one-way analysis of variance with $P < 0.05$ denoting significance. Post-hoc tests were conducted using the Student–Newman–Keuls and Duncan methods. All the tests were conducted using commercially available software (SAS 8.02; SAS Institute, Cary, NC).

## 3 Results and discussion

The α-TCP had a particle size D50 of 3.61 ± 1.1 μm after planetary milling. The α-TCP produced by sintering and air quenching was confirmed by XRD analysis to be 'pure' α-TCP (Fig. 1). Significant changes in the XRD patterns between 25°2$\theta$ and 35°2$\theta$ were observed for the unreinforced CPC when immersed in PBS over a 12 week period (Fig. 1). The principal peaks for α-TCP were observed at 24°2$\theta$ and 31°2$\theta$ for specimens not immersed in PBS at counts greater than 1,300 and 1,000, respectively. The α-TCP peaks were no longer apparent after 1 week immersion in PBS, indicating that the reaction of α-TCP to CDHA was complete. Peak search and identifications showed that three main constituents in the CPC after the 12 week period; (i) $CaHPO_4$ (or monetite), $CaCO_3$ and HA. The main $CaHPO_4$ peaks appeared at 26°2$\theta$ and 30°2$\theta$, the intensity of these peaks decreased as the PBS immersion period increased. The two main HA peaks occurred at 26°2$\theta$ and 32°2$\theta$, the latter peak being the more significant. The HA peak intensity increased as a function of PBS immersion, signifying the HA content within the CPC increased. The $CaCO_3$ peak (29.9°2$\theta$) was very prominent after CPC was immersed for 1 week in PBS, however as the immersion time increased the $CaCO_3$ peak decreased and beyond 9 weeks was no longer visible on the XRD spectra. SEM analysis of the unreinforced CPC concurred with the XRD findings (Fig. 1). Needle-like HA crystals were observed on the cement surface after 1 week PBS immersion, which are synonymous with CDHA. After

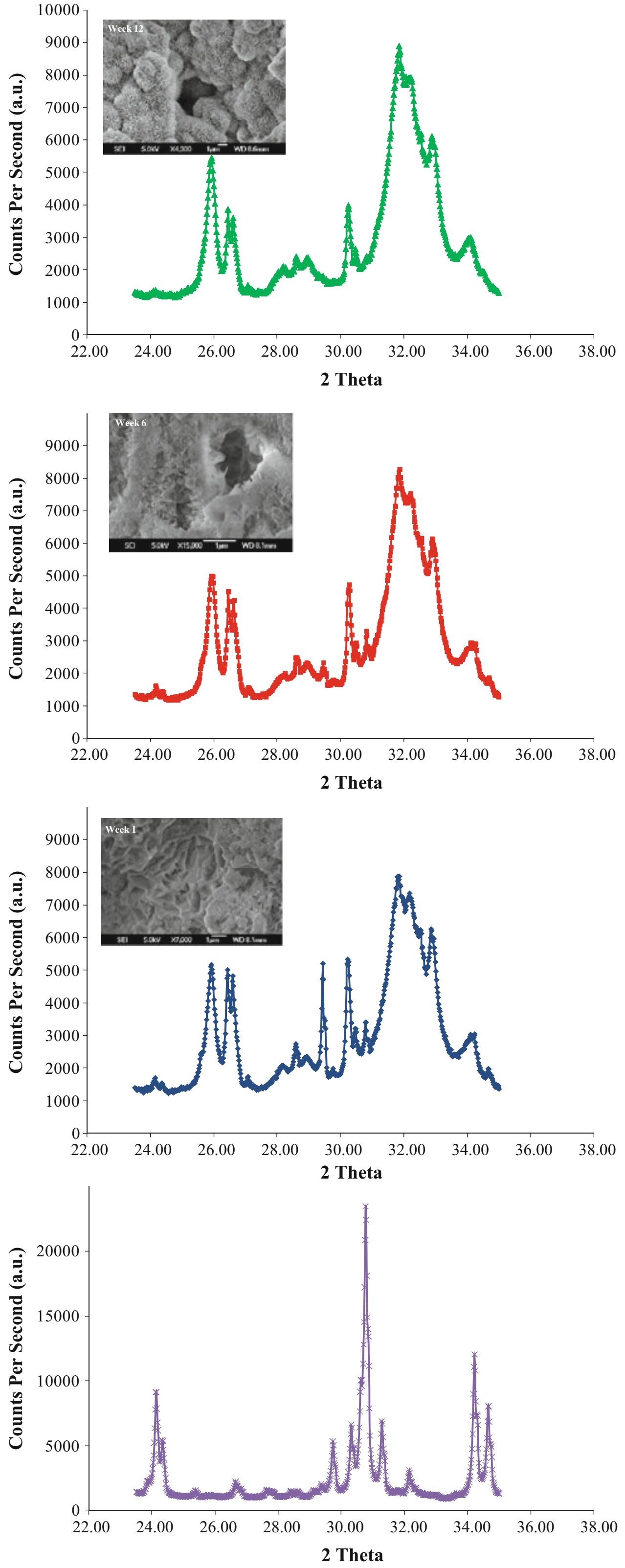


**Fig. 1** XRD spectra for CPC and SEM micrographs showing progressive HA precipitate formation over 12 week PBS immersion. *Note*: CPC specimen after 72 h post-setting reaction is also shown

6 weeks immersion in PBS crystals of typical apatite morphology were evident in the majority of pores on the cement surface [31–33]. By week 12 the apatite formation was clearly defined and a highly crystalline layer of HA precipitate covered the majority of the external and internal surface of the CPC. XRD data also showed that the HA content in the CPC specimens was approx. 64% initially and increased to 89% after 12 weeks PBS immersion. da Silva et al. [34] reported that monetite readily dissolves and re-precipitates as HA when immersed in a solution with a pH of 7.4–8.0. In our study the pH of the PBS was alkaline after week one and levelled to pH8 ± 0.1. ICP-OES analysis of the PBS recorded that the Ca and P ion levels of the starting PBS were 1.203 and 2.793 counts, respectively. The normalised Ca ion levels increased up to 6 weeks (12 counts at week one to 32 counts at week six) and then decreased thereafter (7 counts at week 12), while the P ion levels decreased for the 12 weeks ($-30$ counts at week one to $-310$ at week 12). The ICP-OES data are supported by the XRD spectra, which show that the $CaCO_3$ was leached from the CPC during the first 6 weeks allowing the Ca ions to react with the P ions to form an insoluble apatite layer. The decreasing P levels are symptomatic of steady HA precipitate formation throughout the 12 weeks. The compressive strength (Fig. 2a) and compressive modulus (Fig. 2b) of the unreinforced CPC was found to decrease ($P$-value $> 0.05$) up to 9 weeks and then increase ($P$-value $> 0.05$) due to the continued setting reaction and the formation of HA precipitate within the cement microstructure. Observing the gravimetric results it was found that the mass of the unreinforced CPCs significantly increased ($P$-value $< 0.05$) after one week due to water uptake for the $\alpha$-TCP to CDHA reaction (Fig. 3). Small increases ($P$-value $> 0.05$) were noted thereafter due to the balance of $CaCO_3$ loss and HA precipitate formation. Camiré et al. reported similar findings when they immersed

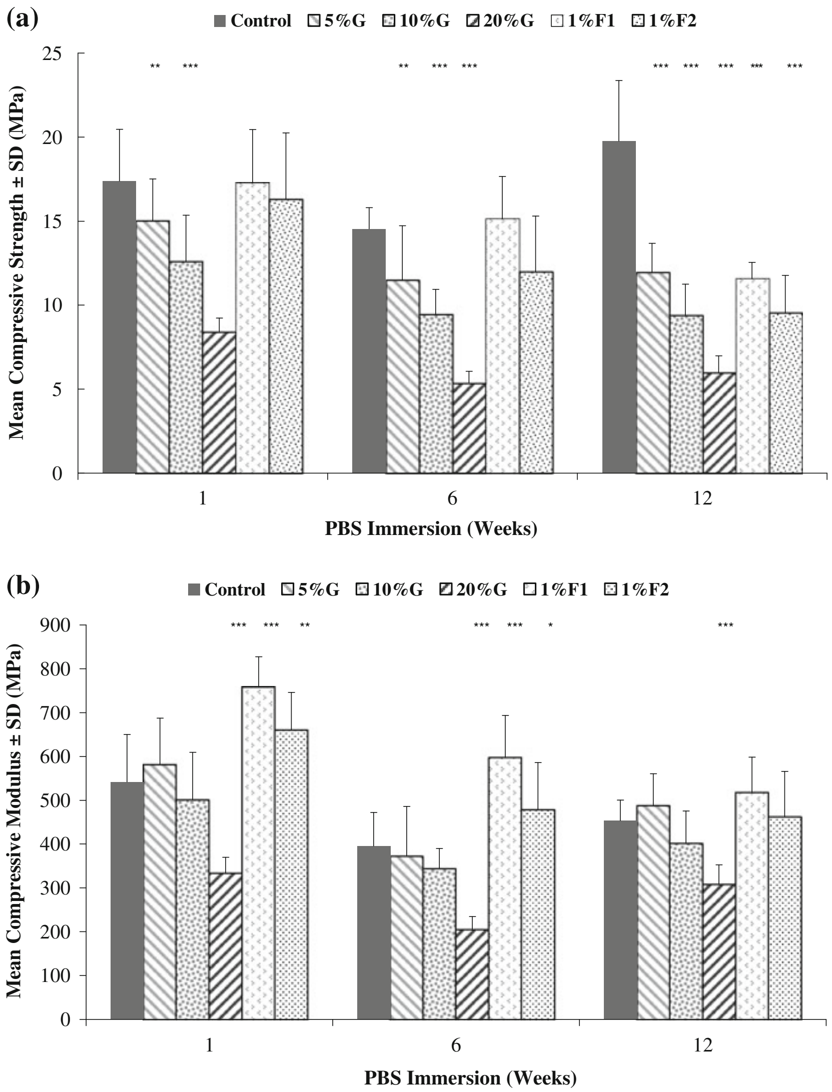
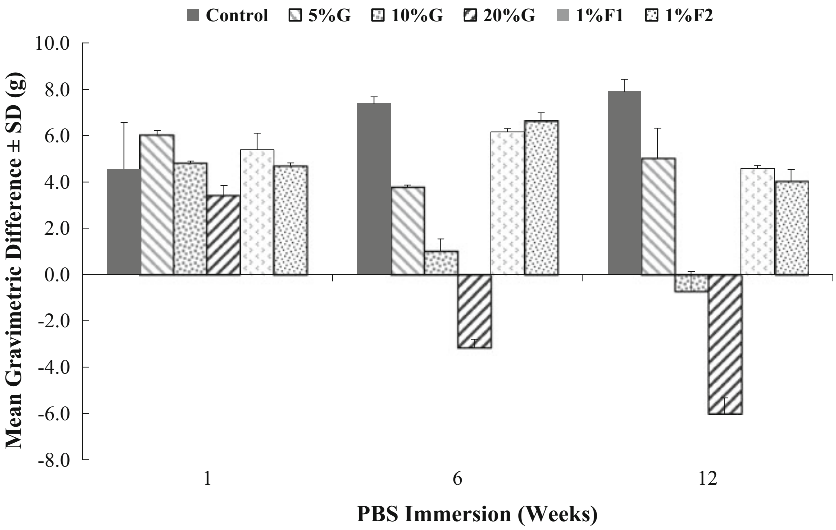


**Fig. 2** Mean compressive strength (**a**) and compressive modulus (**b**) with standard deviation for unreinforced and reinforced CPC after 1, 6 and 12 weeks immersion in PBS. ***, ** and * indicate *P* values less than 0.001, 0.01 and 0.05, respectively, demonstrating a statistically significant difference between unreinforced and reinforced CPC

**Fig. 3** Mean gravimetric differences with standard deviation for unreinforced and reinforced CPC after 1, 6 and 12 weeks immersion in PBS. ***, ** and * indicate *P* values less than 0.001, 0.01 and 0.05, respectively, demonstrating a statistically significant difference between unreinforced and reinforced CPC



silicon substituted α-TCP in simulated body fluid for 4 weeks; with a thin dense layer of bone-like apatite forming on the cement surface [35].

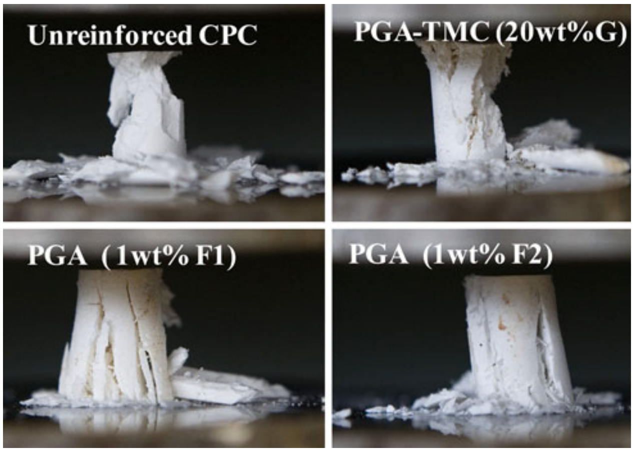


**Fig. 4** Unreinforced (control) and reinforced CPC after compression test

Incorporating PGA-TMC granules into the CPC system significantly ($P$-value $< 0.001$) reduced the compressive strength irrespective of the reinforcement content for each time point up to 12 weeks when compared with the compared with the unreinforced CPC (Fig. 2a). Observing the compressive modulus data, adding 20 wt% of PGA-TMC granules demonstrated a significant reduction ($P$-value $< 0.001$) in the compressive modulus for all time points tested (Fig. 2b). In contrast, incorporating 1 wt% PGA fibre reinforcement in the CPC did not significantly affect ($P$-value $> 0.05$) the compressive strength up to the 6 week time point (Fig. 2a). Beyond 6 weeks immersion in PBS there was a significant reduction ($P$-value $< 0.001$) in compressive strength of the fibre reinforced CPC, irrespective of the cryogenic grinding time of the fibres. Improvements in the compressive modulus of the fibre reinforced CPC were observed for all PBS immersion time points, however the increase in compressive modulus was only significant ($P$-values $< 0.001$–$0.05$) up to six weeks (Fig. 2b). Figure 4 shows a series of CPC specimens (i.e. unreinforced CPC, CPC reinforced with 20 wt% PGA-TMC granules, CPC reinforced with 1 wt% PGA fibres) after compression testing to a 25% strain. The characteristic brittle behaviour of the unreinforced CPC can be observed, as the specimen exhibited catastrophic failure after critical loading and subsequently broke into fragments. Observing a compression specimen of CPC reinforced with 1 wt% PGA fibres (Fig. 4) post-testing, it can be seen that the mechanism of failure is different as the specimen maintains a degree of cohesive structure and is capable of supporting load. The ability of the fibre reinforced CPC to support a load of approx. 5 MPa was observed, while a dramatic decrease in stress after failure was recorded for the unreinforced CPC specimen. A similar observation was noted for the CPC reinforced with PGA-granules post-compression testing. Buchanan et al. [22] reported that PP polymer fibres significantly reinforced the CPC, allowing the cement to retain its structure beyond critical loading providing a bridging mechanism across cracks. Wang et al. [36] described the ability to support load after peak loading as ‘pseudoductile’ behaviour. Prior to grinding the fibre cross-section shape was relatively circular. The fibre length after cryogenic grinding was found to be 2 ± 1 mm as measured using SEM analysis. The grinding process also changed the cross-sectional shape of the fibres to a more flattened, fibrous profile with split and splayed ends. The extent of this change in fibre structure increased with cycle duration. SEM analysis showed the PGA fibres are embedded in the

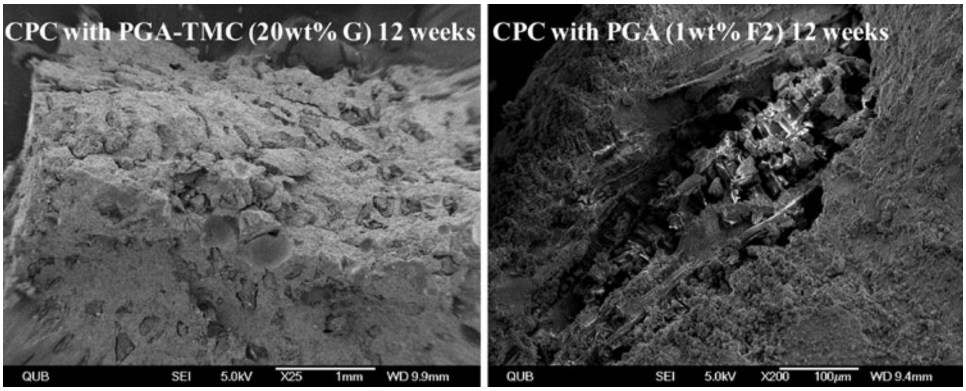


**Fig. 5** Scanning electron micrographs of reinforced CPC microstructure after 12 weeks PBS immersion

matrix and exhibit good adhesion within the CPC cement. The split and splayed ends of the ground PGA fibres led to better interfacial adhesion strength at the fibre-cement interface, which facilitated the CPC retaining its cohesive structure during loading. The same phenomenon was not observed with the SEM micrographs of the particulate reinforced CPC, the PGA-TMC granules of randomly distributed throughout the CPC and there was some evidence of holes within the cement microstructure, which could be attributed to particulate fall-out. Sabir also reported that fibrillated PP fibres were effective in controlling post-cracking behaviour in concrete, thereby preventing catastrophic failure [37].

Observing the gravimetric data for the particulate reinforced CPC cement (Fig. 3), it can be observed that there was a reduction ($P$-value $< 0.001$) in mass for the PGA-TMC reinforced CPC as the PBS immersion time increased. SEM analysis of the PGA-TMC granule reinforced CPC showed a similar level HA precipitate formation as with the unreinforced CPC. Moreover, micropores (<100 µm) were evident on the surface of the PGA-TMC granule reinforced CPC specimens after 1 week, the size of which increased (>300–900 µm) after 12 weeks PBS immersion. Examination of the internal microstructure showed that the majority of PGA-TMC granules were largely intact within the cement matrix, albeit shrinkage gaps were observed at the granule-cement interface (Fig. 5). Simon et al. [38] and Habraken et al. [18] reported the development of macro and micropores pathways within CPC microstructure after 12 weeks immersion in PBS at 37°C when 10–20 wt% PLGA microspheres were used as the resorbable polymer additive. An in vivo study of α-TCP cement with 20 wt% PLGA granules implanted in a rat cranial defect showed the polymeric additive completely absorbed after eight weeks implantation, facilitating an increased cement-bone interface and increased bone in-growth [39]. To generate a similar porous network in CPC using PGA-TMC microparticles may require a PBS immersion beyond the 12 weeks. Notwithstanding this, the particulate additives used in this study did not contribute significantly to augmenting the mechanical properties of the CPC.

The fibre reinforced CPC cement recorded a significant increase ($P$-value $< 0.01$–$0.001$) in mass during the first 6 week when immersed in PBS (Fig. 3). It is postulated this increase in mass was due to PGA fibres absorbing water. The mass of the fibre reinforced CPC specimens significantly decreased ($P$-value $< 0.001$) thereafter due to hydrolytic degradation of the PGA fibres. SEM analysis of the PGA fibre reinforced CPC showed that the fibres were largely intact within the CPC after 6 weeks; however after 9 weeks a significant proportion of the fibres had resorbed as there evidence of cylindrical channels within the cement matrix indicative of where the fibres previously were embedded (Fig. 5). Surface porosity was also evident for the PGA fibre reinforced CPC specimens, the extent of micropore development increased as the duration in PBS increased. Xu et al. [21] reported an average degradation time of 56 days when using longer bioresorbable polyester fibres (Vicryl Rapide$^{\text{TM}}$) in CPC, which required pre-treatment prior to manual mixing with the CPC paste.

## 4 Conclusions

In vitro resorption tests of CPC showed increasing precipitate formation over 12 weeks. An increase in CPC compressive strength was shown at 12 weeks due to the continued setting reaction of the cement and the development of a highly crystalline HA layer. However the CPC exhibited catastrophic failure under compressive loads. The fracture behaviour of CPC was improved by the incorporation of short-fibre reinforcement. The typical brittle nature associated with CPCs was significantly enhanced and the cement retained its intrinsic structure after critical loading. Moreover, a large proportion of the PGA fibres had resorbed after 12 weeks allowing for the increased cement porosity, which could facilitate cell infiltration and faster integration of natural bone. Incorporating PGA-TMC particulate additives in the CPC did not provide any mechanism for mechanical property augmentation. Moreover the majority of the PGA-TMC granules remained in the CPC after 12 weeks.

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