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Advanced Composite Materials
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tacm20

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Published online: 04 Feb 2013.

To cite this article: Shusaku Yamaji & Satoshi Kobayashi (2013) Effect of in vitro hydrolysis on the compressive behavior and strain rates dependence of tricalcium phosphate/poly(L-lactic acid) composites, Advanced Composite Materials, 22:1, 1-11, DOI: 10.1080/09243046.2012.760437

To link to this article: http://dx.doi.org/10.1080/09243046.2012.760437

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Advanced Composite Materials, 2013
Vol. 22, No. 1, 1–11, http://dx.doi.org/10.1080/09243046.2012.760437

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Effect of *in vitro* hydrolysis on the compressive behavior and strain rates dependence of tricalcium phosphate/poly(L-lactic acid) composites

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(*Received 26 September 2012; accepted 17 December 2012*)

Bioactive ceramics/bioresorbable plastic composites have been expected as materials for the fracture fixations which have more biocompatibility than monolithic bioresorbable plastics. In this study, effects of strain rate on the mechanical properties of poly(L-lactic acid) (PLLA) and tricalcium phosphate/Poly(L-lactic acid) (TCP/PLLA) composites specimens were investigated experimentally. The TCP/PLLA composites containing three different TCP contents (5, 10 and 15 wt.%) were prepared by injection molding. The fabricated specimens were then immersed in the simulated body environment, such as phosphate buffered solution (pH = 7.4), to investigate effects of hydrolysis on the mechanical properties. In order to characterize the mechanical properties, compressive tests were performed at the strain rates ranging from 10^{-3} to 10^{-1}/s. Initial molecular weights (M_w) of non-annealing PLLA and TCP/PLLA composites were approximately 173,000 and 154,000. After 24 weeks immersion, M_w of 15 wt.% decreased to 91,000. In the results of these tests, TCP/PLLA composites showed that their Young's modulus has no dependence on the strain rate and their compressive strength increased with increasing strain rates. After 16 weeks immersion, compressive strength of 15 wt.% composites decreased slightly at a strain rate of 10^{-1}/s. After 24 weeks immersion, compressive strength of 5, 10, and 15 wt.% composites decreased.

Keywords: hydrolysis; tricalcium phosphate; poly(L-lactic acid); compressive behavior

1. Introduction

Bioresorbable bone fracture fixations made of Poly(L-lactic acid) (PLLA) are drawing attention as substitute materials for metallic devices due to non-necessity of second surgery, and have been used in clinical applications. In the previous study, various *in vitro* and *in vivo* characterizations had been conducted on PLLA.[1–5] However, monolithic PLLA do not have enough mechanical property for bone fracture fixations. Therefore, its coverage is limited. From the point of improvement in the mechanical properties, PLLA composites reinforced by bioactive ceramics with higher modulus have been expected. As the reinforcements (fillers) of the composites, bioactive ceramics, such as hydroxyapatite (HA) or tricalcium phosphate (TCP) have been used, and mechanical and *in vitro* and *in vivo* degradation properties of HA or TCP/PLLA composites have been evaluated experimentally.

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Verheyen et al. [6] prepared HA/PLLA composites, and investigated the mechanical properties of them. The composites contained 30 wt.% of HA showed improved strength and modulus. Shikinami and Okuno [7,8] developed unsintered-HA(u-HA)/PLLA composites. They reported that the composite denoted very high mechanical properties. In the studies using TCP as a filler, Kikuchi et al. [9] prepared TCP/copoly(L-lactic acid) (CPLA) composite containing 80 wt.% TCP. Ignatius et al. [10] investigated the mechanical properties of β-TCP/Poly(D,L-lactic acid) (PDLLA) composites contained 10 and 30 wt.% β-TCP.

Many experimental evaluations on mechanical properties were performed on bioactive ceramics/PLLA composites. Almost those evaluations have been carried out at alow strain rate (about 10^{-4}/s), whereas tibial bone undergoes a loading at strain rates up to 10^2/s [11] while walking. In the actual usage, it is expected that fracture fixations are subjected to dynamic and impact loading. Therefore, there is a probability of undergoing loading at strain rates up to 10^0–10^1/s. In general, mechanical properties of polymeric material are strongly influenced by strain rates.[12,13] The matrix material of the composites, PLLA, is a typical polymeric material. However, strain rate dependency of bioactive ceramics/PLLA composite has not been studied yet. Therefore, it is necessary to evaluate the mechanical properties of the composite at higher strain rates.

In a previous study, we investigated the effect of strain rate on tensile properties of TCP/PLLA composites after immersion in simulated body environments.[14] Considering the actual usage of bioabsorbable composites, compressive properties are more important. In this study, effects of *in vitro* hydrolysis and strain rates on the compressive properties of TCP/PLLA composite were investigated. In order to clarify the strain rate dependency of the matrix, PLLA, and TCP contents, the PLLA and TCP/PLLA composites with different TCP contents specimens were prepared by injection molding. Immersion tests in the simulated body environment and subsequent compressive tests were performed on the specimens as evaluation of the *in vitro* properties. In general, hydrolysis precedes in amorphous region, which results in increasing nominal crystallinity. Thus, the effect of matrix crystallinity on mechanical properties of hydrolyzed composites is also an important factor. Therefore, we also investigated the mechanical properties of PLLA with different crystallinities prepared by annealing and hydrolysis.

2. Materials and methods

2.1. Preparation of PLLA and TCP/PLLA composite specimens

PLLA pellet (Lacty#5000, Shimadzu Co., Ltd., Kyoto, Japan) and TCP powder (Taihei Chemical Industrial Co., Ltd., Osaka, Japan) were used in the preparation of PLLA and TCP/PLLA composite specimens. Specimens were prepared using an injection molding machine (NP7 Real Mini, Nissei Plastic Industrial Co., Ltd., Nagano, Japan). The geometry of the specimens was 100 mm × 10 mm × 4 mm.

In order to clarify the effect of crystallinity, the PLLA specimens fabricated were annealed at 70 and 130 °C for 24 h with a hot press system and cooled at room temperature. Non-annealed and annealed specimens at 70 and 130 °C are abbreviated as non-annealing, 70 °C-24 h, and 130 °C-24 h specimens, respectively.

Before injection molding, TCP and PLLA were dry-mixed at weight ratios 10.5:190, 21:180, and 32:170 (5, 10, 15 wt.%) in a polyethylene bottle. The mixture was put in the hopper of an injection molding machine and molded into rectangular-shaped specimens.

TCP contents in specimens (W_f) were calculated as follows:

Table 1. W_f [wt.%]calculated by Equation (1).

5 wt.%	4.7
10 wt.%	9.1
15 wt.%	13.3

$$W_\mathrm{f} = \frac{M_\mathrm{f} - R_\mathrm{f}}{M_\mathrm{m} + M_\mathrm{f} - R_\mathrm{f}} \times 100 \tag{1}$$

where M_f and M_m are the weights of TCP and PLLA, respectively, when mixed, and R_f is the weight of residual TCP in the polyethylene bottle. The specimens with TCP content 5, 10, and 15 wt.% are abbreviated as 5, 10, and 15 wt.% specimens, respectively. Table 1 shows real TCP contents calculated by Equation (1).

2.2. *In vitro hydrolysis*

The injection-molded specimens were immersed in phosphate buffer solution (PBS) of pH 7.4 at 37 °C to evaluate *in vitro* degradation. They were immersed for 8, 16, and 24 weeks. During immersion, measurement of water absorption were conducted. Specimens were picked up, swabbed to remove excess water, weighted, and returned in the PBS periodically. Amount of water absorption at time *t*, M_t, was calculated as follows:

$$M_\mathrm{t} = \frac{m_\mathrm{t} - m_\mathrm{t}}{m_\mathrm{t}} \times 100 \tag{2}$$

where m_t is the mass of the specimen at time *t*, and m_i is the mass of the specimen before immersion.

After immersion, they were washed with purified water, followed by drying in a vacuum desiccator for at least 14 days. Then, crystallinity, molecular weight, and compressive properties were measured.

2.3. *Crystallinity measurement*

Crystallinities of specimens were measured with differential scanning calorimeter (DSC) (DSC-60, Shimadzu Co., Ltd., Kyoto, Japan). DSC samples were cut out from the injection-molded specimens with a weight of 3–6 mg. The samples were heated with a heating rate of 10 °C/min up to 230 °C in the air.

The crystallinity of a PLLA sample (X_c1) was calculated as follows:

$$X_\mathrm{c1} = \frac{\Delta H_\mathrm{m} + \Delta H_\mathrm{c}}{\Delta H_{100\%}} \times 100 \tag{3}$$

where ΔH_c is the crystallization enthalpy, ΔH_m and $\Delta H_{100\%}$ are the enthalpy of melting of a PLLA sample and PLLA crystal having infinite crystal thickness, respectively. We used 135 J/g as $\Delta H_{100\%}$.[15]

The crystallinity of a TCP/PLLA composite sample (X_c2) was calculated as follows:

$$X_{c2} = \frac{\Delta H_{\mathrm{composite}}}{\Delta H_{100\%}} \times \frac{M_c}{M_m} \times 100 \tag{4}$$

where M_c is the weight of TCP/PLLA composite, and $\Delta H_{\mathrm{composite}}$ is the enthalpy of melting of a TCP/PLLA composite sample.

2.4. Molecular weight measurement

The weight average molecular weight (M_w) of a specimen was measured using a gel permeation chromatography (GPC) system. The system was composed of column (SHIMPACK GPC-804C, Shimadzu GLC Ltd., Tokyo, Japan), column oven (CTO-20A, Shimadzu Co., Ltd., Kyoto, Japan), and differential reflective index detector (RID-10A, Shimadzu Co., Ltd., Kyoto, Japan). GPC samples were cut out from the injection-molded specimens before and after immersion with a weight of about 0.5 g. The samples were dissolved with chloroform for 24 h. Then, the solution was filtered before being injected into the column.

2.5. Compressive tests

The specimens for compressive tests were cut from injection-molded specimens. The geometry of samples was 10 × 10 × 4 mm. The upper and lower surfaces were collimated with 180- and 800-grit abrasive papers. Then, strain gages were bonded on both sides of the specimens. These specimens were compressively tested at room temperature using a universal testing machine (Autograph AG-IS 50kNE, Shimadzu Co., Ltd., Kyoto, Japan) at cross-head rates of 1–1000 mm/min.

3. Results and discussion

3.1. Crystallinity of PLLA and TCP/PLLA composite specimens

Figure 1 shows crystallinity of PLLA specimens with three different annealing conditions and TCP/PLLA composite specimens with three different TCP contents. The X_c value of non-annealing specimen was approximately 5%. This denotes that non-annealing specimens are also amorphous. X_c increased with increasing annealing temperature, and X_c values of 70 °C-24 h and 130 °C-24 h specimens were approximately 28 and 49%, respectively.

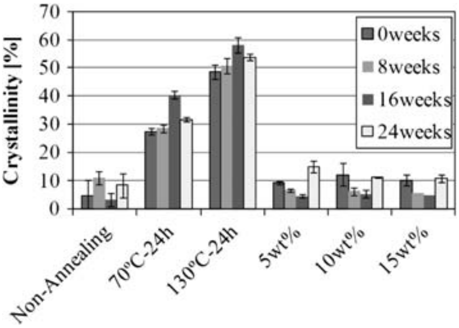


Figure 1. Crystallinity of PLLA and TCP/PLLA composites specimens.

After 16 weeks immersion, X_c of 70 °C-24 h and 130 °C-24 h specimens increased. The increasing X_c indicated a comparative increase in the crystalline region which results from the hydrolysis of the amorphous regions.

TCP/PLLA composite specimens denoted approximately the same values irrespective of TCP contents as each other. The X_c values were approximately 5–10% which were approximately the same value of non-annealing specimens. Thus, it is assumed that PLLA in the TCP/PLLA composites is amorphous.

After 24 weeks immersion, as in the case of non-annealing, marked change in X_c values of TCP/PLLA composites was not observed.

3.2. *Amount of water absorption*

Figure 2 shows the amount of water absorption, M_t. For the PLLA specimens (Figure 2(a)), M_t increased with increasing immersion time up to 42 days, and then saturated. M_t and water absorption rate of non-annealing were higher than other PLLA specimens. These results indicated that water absorption capacity and water absorption rate of crystalline region were lower than those of amorphous region.

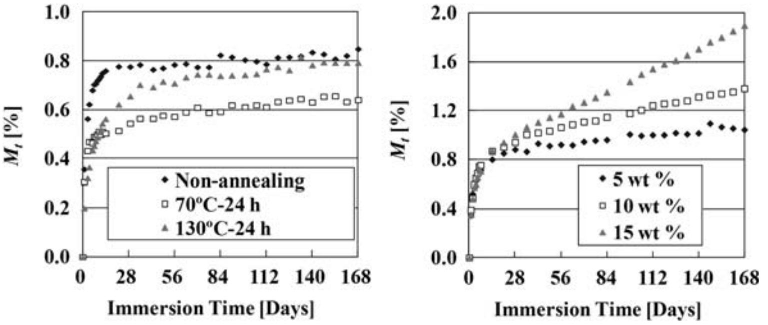
For the TCP/PLLA composite specimens (Figure 2(b)), all specimens showed approximately the same tendency, where M_t increased with increasing immersion time up to 168 days and TCP contents. These results indicated that water absorption capacity of TCP and/or TCP/PLLA interface was higher than PLLA.

According to the Fick's second law, the equation for the one-dimensional model of liner flow of mass in the solid bonded by two parallel planes, when the diffusion coefficient D is constant, is expressed as

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial^2 x}. \tag{5}$$

where C is the concentration of the diffusing species at time t and x is the distance of the diffusion.

For a plane sheet geometry, if the initial concentration of water is uniform and the surface kept at concentration C_0, Equation (5) has a solution in the following:



(a) PLLA (b) TCP/PLLA composites

Figure 2. Relationship between water absorption M_t and immersion time.

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp\left[-D\frac{(2n+1)^2\pi^2}{l^2}\right] \tag{6}$$

where l is the thickness of the specimen and M_∞ refers to water absorption at times ∞. We used the water absorption at 56 days as M_∞.

Accordingly, when M_t/M_∞ is small enough (<0.60) in the early stage, Equation (6) is reduced to the Stefan's approximation:

$$\frac{M_t}{M_\infty} = \frac{4}{l}\left(\frac{Dt^{\frac{1}{2}}}{\pi}\right) \tag{7}$$

From which, if one plots M_t/M_∞ against $t^{1/2}$, the diffusion coefficient can be calculated from the initial curve slope.

Table 2 shows D values calculated from experimental results. 70 °C-24 h specimen denoted the highest value of D and 130 °C-24 h specimen denoted the lowest value of D. Comparing non-annealing to 70 °C-24 h specimen, D value increased with increasing crystallinity. However, comparing 70 °C-24 h to 130 °C-24 h specimen, D value decreased with decreasing crystallinity. These results indicated the following. At first, interface between amorphous and crystalline region which has higher D value than that of amorphous and crystalline region increased with increasing crystallinity. Then, crystalline region which has the lowest value of D increased with increasing crystallinity. Therefore, 130 °C-24 h specimen which has the largest crystalline region denoted the lowest value of D. And it suggested that water absorption capacity of interface is higher than amorphous region. Because filled state of molecular chain becomes sparse in amorphous region between crystalline regions.[16] Therefore, amount of water absorption of 130 °C-24 h specimen, which has lower value of D and water absorption capacity results from the largest crystalline region, was lower than that of 70 °C-24 h specimen in the early stage of immersion. Then, the total water absorption of 130 °C-24 h specimen, which has higher water absorption capacity results from the largest interface between amorphous and crystalline regions, was higher than that of 70 °C-24 h specimen.

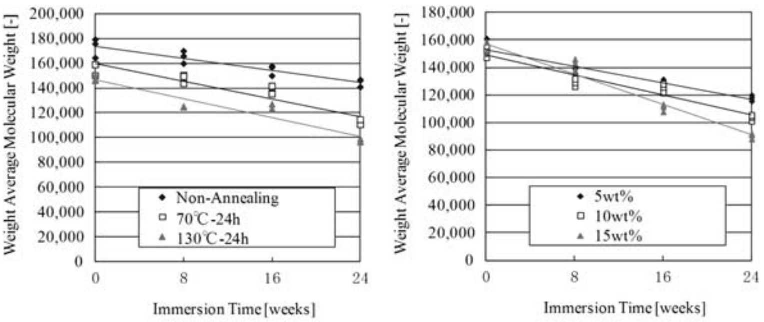
D values of TCP/PLLA composite specimens decreased with increasing TCP contents. The results suggested that TCP has lower D value than PLLA. In order to compare closely D value of PLLA to TCP/PLLA composite specimens, we will need to use the saturated water absorption of TCP/PLLA composite specimens as M_∞.

3.3. *Molecular weight of PLLA and TCP/PLLA composite specimens*

Figure 3 shows weight average molecular weight (M_w) of PLLA and TCP/PLLA composite specimens. For the PLLA specimens, M_w of non-annealing, 70 °C-24 h, and 130 °C-24 h spec-

Table 2. D values calculated from experimental results.

Non-Annealing	6.8×10^{-12}
70 °C-24 h	8.3×10^{-12}
130 °C-24 h	2.3×10^{-12}
5 wt.%	4.0×10^{-12}
10 wt.%	2.9×10^{-12}
15 wt.%	1.3×10^{-12}



(a) PLLA **(b) TCP/PLLA composites**

Figure 3. Relationship between weight average molecular weight and immersion time.

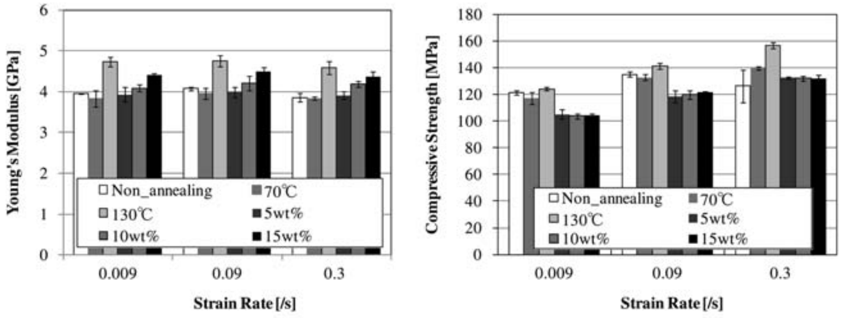
imens before immersion were approximately 173,000, 156,000, and 148,000, respectively (Figure 3(a)). After 24 weeks immersion, M_w of non-annealing, 70 °C-24 h, and 130 °C-24 h specimens decreased to approximately 144,000, 112,000, and 97,000, respectively. M_w decreasing became faster as the X_c was higher, when compared at the same immersion time. These results denoted higher hydrolysis rate at the amorphous region between crystalline regions, which has higher density hydrophilic end group increased with increasing X_c.[16,17]

In the TCP/PLLA composite specimens, these M_w before immersion denoted approximately the same values as each other. The M_w were approximately 151,000–156,000 (Figure 3 (b)). After 24 weeks immersion, M_w of 5, 10, and 15 wt.% specimens decreased to approximately 118,000, 104,000, and 91,000, respectively. And M_w decreasing became faster as the TCP content was higher, when compared at the same immersion time.

This result might be attributed to the increasing matrix–filler interface, which promoted hydrolysis by enhancing water diffusion with increasing TCP content.

3.4. Results of compressive tests

Figure 4 shows the Young's modulus and compressive strength for PLLA and TCP/PLLA composite specimens over a range of strain rates.



(a) Young's Modulus **(b) Compressive Stremgth**

Figure 4. The results of compressive tests with strain rate.

For PLLA specimens, Young's modulus of non-annealing and 70 °C-24 h denoted approximately the same values as each other. And Young's modulus of 130 °C-24 was higher than those of other PLLA specimens.

For TCP/PLLA composite specimens, Young's modulus of 5 wt.% specimen denoted approximately the same values as that of non-annealing. On the other hand, Young's modulus of 10 and 15 wt.% specimens increased with increasing TCP content. In all specimens, no dependency on strain rates was observed for Young's modulus up to a strain rate of 0.3/s (Figure 4(a)). On the other hand, in the previous study, tensile Young's modulus increased with increasing strain rate.[14] Difference in strain rate dependence has been shown between tension and compression.

For compressive strength, non-annealing and 70 °C-24 h denoted approximately the same values as each other and that of 130 °C-24 h was higher than other specimens. For TCP/PLLA composite specimens, compressive strength of TCP/PLLA composite specimens denoted approximately the same values as each other. In terms of strain rate dependency, compressive strength of the all specimens other than non-annealing increased with increasing strain rate up to 0.3/s. For non-annealing specimens, compressive strength increased with increasing strain rate up to 0.09/s, and decreased at strain rate of 0.3/s. At strain rate of 0.3/s, brittle fracture behavior were observed with some of non-annealing specimens. As a result, compressive strength of non-annealing specimens decreased.

As observed above, less dependency on strain rates was observed for Young's modulus of PLLA and TCP/PLLA composite specimens up to strain rate of 0.3/s before immersion. On the other hand, compressive strength of specimens increased with increasing strain rate. And

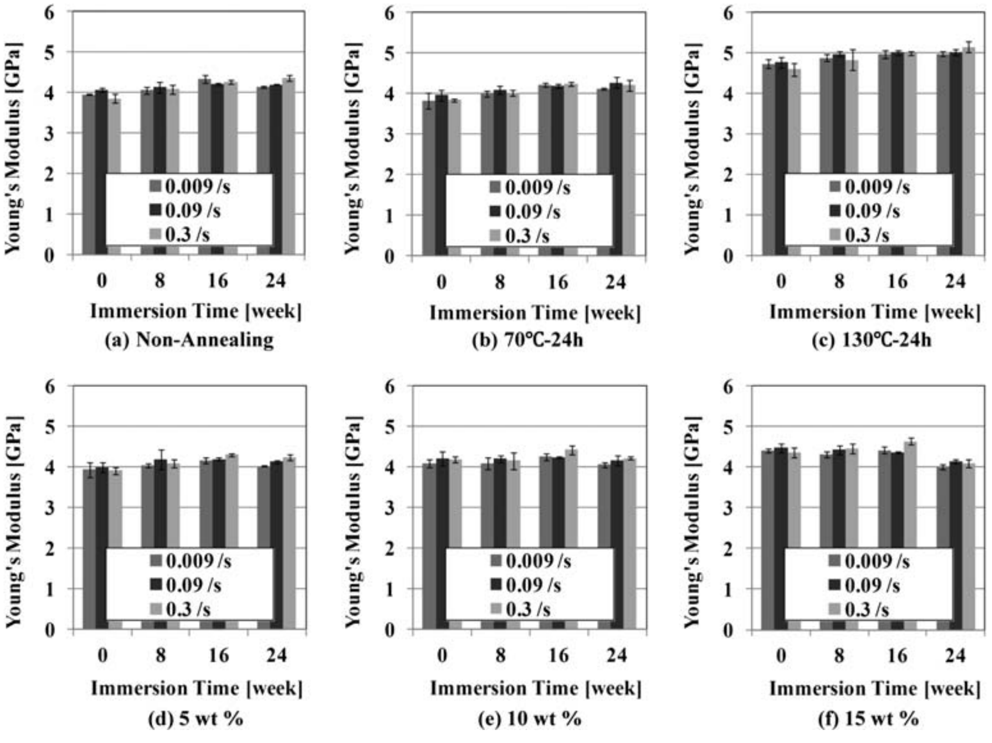
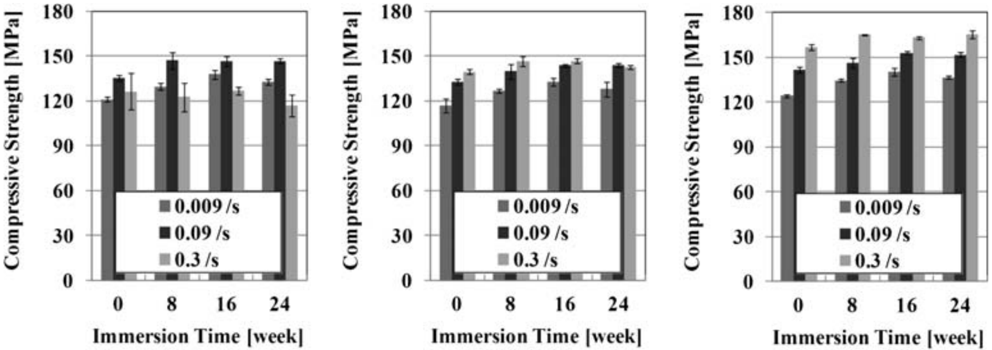
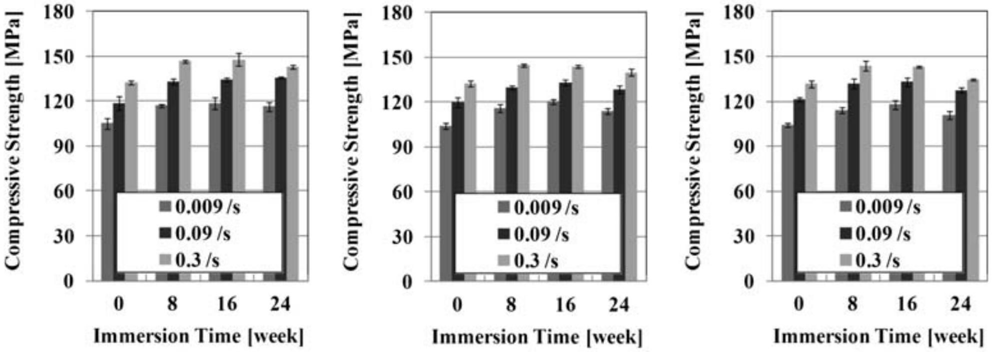


Figure 5. Relationship between Young's modulus and immersion time.



(a) Non-Annealing (b) 70°C-24h (c) 130°C-24h



(d) 5 wt. % (e) 10 wt. % (f) 15 wt. %

Figure 6. Relationship between compressive strength and immersion time.

decrease in compressive strength of non-annealing caused by brittle fracture behavior was observed at strain rate 0.3/s.

3.5. *Results of In vitro hydrolysis*

Figure 5 shows relationships between Young's modulus and immersion time. For all specimens, Young's modulus denoted approximately the same values as each immersion time. And no strain rate dependency was observed for Young's modulus up to a strain rate 0.3/s. On the other hand, in the previous study, decrease in tensile Young's modulus caused by the damages such as the interface debonding between TCP and PLLA and/or hydrolysis of PLLA near the TCP/PLLA interface was observed.[14] From these results, it is suggested that loss of the load-carrying capacity of TCP particles result from hydrolysis does not occur under the compressive stress.

Figure 6 shows relationships between compressive strength and immersion time. In all specimens, compressive strength increased with increasing immersion time up to 16 weeks. It is supposed that cause of the increase in strength is the plasticization of PLLA result from water absorption. And then in 24 weeks immersion, compressive strength of non-annealing, 10 and 15 wt.% decreased. As a result, compressive strength of TCP/PLLA composite specimens decreased with increasing TCP content in 24 weeks immersion.

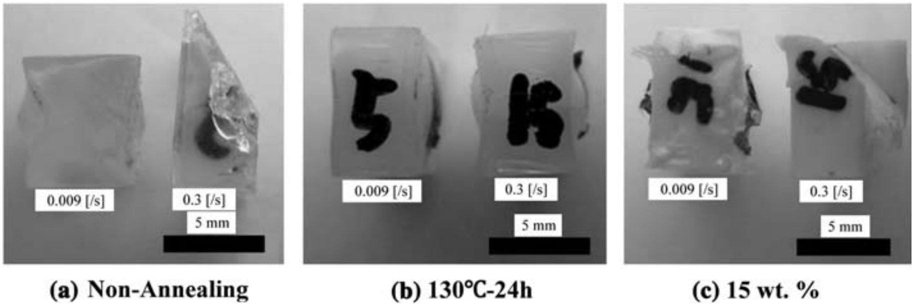


Figure 7. Specimens of PLLA and TCP/PLLA composites after compressive tests.

From the results of molecular weight measurement, M_w decreased with increasing immersion time, and the lowest M_w observed at 24 weeks immersion was approximately 91,000. On the other hand, Migliaresi et al. reported that PLLA which had the initial M_w of 177,000 maintained its bending strength at constant value after 327 days immersion, where its M_w decreased to 32,000.[1] Considering their results, it seemed that the reason of decreasing compressive strength is not due to decreasing M_w but degradation of matrix-filler interface strength.

As observed above, fewer changes were observed for Young's modulus of PLLA and TCP/PLLA composite specimens up to a strain rate of 0.3/s and 24 weeks immersion. Meanwhile, compressive strength of non-annealing and TCP/PLLA composite specimens decreased at strain rate 0.3/s and 16–24 weeks immersion, where brittle fracture behavior were observed (Figure 7). This is due to the embrittlement caused by strain rate dependency of amorphous PLLA and hydrolysis of amorphous PLLA. Therefore, it is supposed that compressive strength of TCP/PLLA composite which has higher X_c value than 70 °C-24 h increased with increasing strain rate up to 0.3/s. And it is considered that fracture morphology of TCP/PLLA composite became more brittle as the TCP contents increased because of stress concentration in TCP particle.

4. Conclusions

Biodegradable PLLA and TCP/PLLA composites specimens were prepared by injection molding, and compressive tests were performed up to a strain rate of 0.3/s. Strain rate dependency of PLLA and TCP/PLLA composites specimens immersed in the simulated body environment on mechanical properties were evaluated experimentally. As a result, we obtained the conclusions as follows:

(1) Amorphous region of PLLA has higher water absorption capacity and diffusion coefficient D than crystalline region. And existence of interface between amorphous and crystalline regions which has higher D value than that of amorphous and crystalline regions was suggested. Whereas it is supposed that TCP has the highest water absorption capacity but lower diffusion coefficient D.

(2) In all specimens before immersion, no dependency of strain rates on compressive Young's modulus up to strain rate 0.3/s was observed. Compressive strength of all specimens increased with increasing strain rate. For only non-annealing specimens, decrease in compressive strength caused by brittle fracture behavior was observed at

strain rate 0.3/s. It denoted that compressive strength decreased at certain level of strain rate.

(3) In the results of *in vitro* hydrolysis, weight average molecular weight decreased with increasing immersion time. And the M_w decreasing became faster as the X_c and TCP content became higher, when compared at the same immersion time. In all specimens, compressive Young's modulus denoted approximately the same values at each immersion time. Compressive strength of non-annealing and TCP/PLLA composite specimens decreased at a strain rate 0.3/s and 16–24 weeks immersion, where they denoted brittle fracture behavior resulting from the effect of strain rate and hydrolysis.

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