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Analytical prediction of hydrolysis behavior of tricalcium phosphate/poly-L-lactic acid composites in simulated body environment

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Analytical prediction of hydrolysis behavior of tricalcium phosphate/poly-L-lactic acid composites in simulated body environment

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Bioactive ceramics/poly-L-lactic acid (PLLA) composites have been expected as a material for bone fracture fixations which have more biocompatibility than monolithic PLLA. In this study, monolithic PLLA and β-tricalcium phosphate (β-TCP)/PLLA composites containing three different β-TCP contents (5, 10, 15 wt%) were prepared by injection molding and hydrolysis behavior in simulated body environment was characterized. The specimens were immersed in phosphate buffered solution to measure water absorption and molecular weight of the specimen. Water absorption in monolithic PLLA increased with increasing immersion time up to 14 days, and then saturated, whereas water absorption in composites increased with increasing immersion time up to 168 days. The composites with higher β-TCP content showed larger water absorption. Degradation of number averaged molecular weight for the composites became faster with β-TCP content at the same immersion time. Number averaged molecular weight of 15 wt% composites decreased from 60,000 to 39,000 after 24 weeks immersion. Two layers and three layers models were proposed to predict water absorption and number average molecular weight variation, respectively. To predict hydrolysis behavior of bioactive ceramics/PLLA composites more precisely, effect of water diffusion was considered in the proposed models. Predictions based on the present models were in good agreement with experimental results and the effectiveness of the models was confirmed.

Keywords: biomaterials; composite material; hydrolysis; poly-L-lactic acid; tricalcium phosphate

1. Introduction

Metallic bone fixation devices have been widely used in clinical practice. However, the metallic fixations may cause stress shielding which weaken bones because of their higher stiffness. In addition, tissue inflammation may be promoted around the fixations. Thus, reoperation to remove the fixation is necessary after complete recovery. This reoperation is a burden to a patient physically, mentally, and economically. Recently, bio-resorbable poly(L-lactic acid) (PLLA) with no necessity of reoperation is drawing much attention from the view point of Quality of Life. In the previous studies, various *in vitro* and *in vivo* characterizations have been conducted on PLLA. Elastic modulus and bending strength for PLLA are 3.4–6.9 GPa and 117–180 MPa,[1–3] respectively. The values are lower especially for modulus comparing with the values of elastic

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modulus (17 GPa) and bending strength (131 MPa) for tibia bone for human.[4] Therefore, the coverage is limited to lower loaded region, such as maxillofacial region.

From the point of improvement in mechanical properties, PLLA composites reinforced by bioactive ceramics with higher modulus have been investigated. For such composites, reduction in the time of hydrolysis and improvement in bio-safety are also expected. In the past, hydroxyapatite (HA), main inorganic constituent of bone, and β-tricalcium phosphate (β-TCP), bio-resorbable calcium phosphate, have been utilized as bioactive fillers, and mechanical and *in vivo* and *in vitro* hydrolysis properties of the composites have been investigated.[5–12]

Verheyen et al. [5] prepared HA/PLLA composites, and investigated the mechanical properties of them. The composites containing 30 wt% of HA showed improved strength and modulus. They also conducted *in vitro* and *in vivo* tests on the composites. Bending strength of the composites decreased to 50% of initial values within three weeks and decreased rapidly under *in vitro* condition than *in vivo* condition. Shikinami and Okuno [6] developed unsintered-HA(u-HA)/PLLA composites. They reported the composite denoted very high mechanical properties in the case of filler content 50%. *In vitro* and *in vivo* tests were also conducted on the composites. From *in vivo* test results, no inflammation reactions were observed for 5–7 years because of bio-resorbable u-HA filler and the composite proved to have physiological bio-safety.[7–9] These composite has been used in the clinical application.

In the studies using TCP as a filler, Kikuchi et al. [10,11] prepared TCP/copoly(L-lactic acid) composite containing 80 wt% TCP. They also prepared TCP/PLLA composites from TCP with different calcination temperature and evaluate mechanical properties in saline. Ignatius et al. [12] investigated the mechanical properties of β-TCP/poly(D,L-lactic acid) composites containing 10 and 30 wt% β-TCP in phosphate buffered solution up to 78 weeks.

As mentioned above, various experimental investigations have been conducted. Remarkable characteristics of bioactive ceramics/PLLA composites are controllable mechanical and hydrolysis properties by adjusting the content of bioactive ceramics as fillers. These characteristics enable an optimum material design to provide proper mechanical and hydrolysis properties for the composites depending on degree and location of diseases. From this view point, analytical studies also have been conducted. Especially, analytical models on hydrolysis behavior have been proposed for bio-resorbable polyester, including hydrolysis behavior of PLLA.[13] One of the models is a hydrolysis model considering the auto-catalytic effect due to carboxyl group included in polyester.[14] Based on this model, hydrolysis rate constants for polyglyconate [15] and PLA-Poly(caprolactone) fiber [16] have been calculated. Variations in molecular weight for PLA/poly(butylene succinate) (PBSU) blend was also predicted based on the model.[17] For bioactive ceramics/bioresorbable plastic composites, Pan proposed a numerical model considering acceleration of hydrolysis due to acid dissociated from carboxyl group and buffer reaction of phosphate ions ionized from TCP.[18]

For the proper design of bio-resorbable composites and bone fixation devices, predictions for hydrolysis were necessary. The investigations mentioned above neglect water diffusion into the material and assumed water concentration, which contributes hydrolysis, as constant. In the case of larger volume, such as a bone fixation, these models may not give a precious prediction because of longer water diffusion distance in the volume. Kobayashi and Naito predicted variations in water absorption and molecular weight for PLA/PBSU polymer blend considering auto-catalytic effect based on the experimental results for monolithic PLA and PBSU. However, their prediction for molecular weight did not consider water concentration. Therefore, they suggested the possibility to underestimate the decrease in molecular weight.[17]

In the present study, we proposed an analytical method to predict molecular weight change in PLLA in bioactive ceramics/PLLA composites considering water concentration change which enables the optimum material design with a proper biodegradation property. In order to clarify the hydrolysis behavior of bioactive ceramics/PLLA composites, β-TCP with higher biocompatibility and bio-resorption property was used as a filler. β-TCP/PLLA composites were fabricated by injection molding. Experimental characterizations included immersion of the specimen in phosphate buffered solution for 8, 16, and 24 weeks followed by measurement of weight and molecular weight changes. Based on the experimental results, the effectiveness of the proposed analytical method was confirmed.

2. Materials and methods

2.1. Preparation of PLLA and β-TCP/PLLA composite specimens

PLLA pellet (Lacty#5000, Shimadzu Co., Ltd., Kyoto, Japan) and β-TCP powder (Taihei Chemical Industrial Co., Ltd., Osaka, Japan) were used in preparation of PLLA and β-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.

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

β-TCP contents in specimens (W_f) were calculated as follows

$$W_f = \frac{M_f - R_f}{M_m + M_f - R_f} \times 100 \tag{1}$$

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

2.2. Crystallinity measurement

Crystallinities for specimens were measured with a differential scanning calorimeter (DSC) (DSC-60, Shimadzu Co., Ltd., Kyoto, Japan). DSC samples were cut out from the injection-molded specimens with a weight 3–7 mg. The samples were heated with a heating rate 10 °C/min up to 230 °C in the air.

Table 1. W_f and particle diameter in β-TCP/PLLA composites.

	Weight fraction (%)	Particle diameter (μm)
5 wt%	4.7	2.22
10 wt%	9.1	2.40
15 wt%	13.3	2.68

The crystallinity of a PLLA sample (X_{c1}) was calculated as follows

$$X_{c1} = \frac{\Delta H_m + \Delta H_c}{\Delta H_{100\%}} \times 100 \tag{2}$$

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. We used 135 J/g as $\Delta H_{100\%}$.[19]

The crystallinity of a β-TCP/PLLA composite sample (X_{c2}) was calculated as follows

$$X_{c2} = \frac{\Delta H_{\text{composite}}}{\Delta H_{100\%}} \times \frac{M_c}{M_m} \times 100 \tag{3}$$

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

2.3. Immersion test in simulated body environment

The injection-molded specimens were immersed in phosphate-buffered 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, measurements of water absorption were conducted. Specimens were picked up, swabbed to remove excess water, weighted, and returned in the PBS periodically. The amount of water absorption at time t, M_t was calculated as follows

$$M_t = \frac{m_t - m_i}{m_i} \times 100 \tag{4}$$

where m_t is the mass of the specimen at time t, 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, the crystallinity and the molecular weight were measured.

2.4. Molecular weight measurement

The number averaged molecular weight (M_n) 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 specimens with a weight about 0.5 g. The samples were dissolved in chloroform for 24 h. Then, the solution was filtered before injection in the column.

3. Results and discussion

3.1. Crystallinity of PLLA and β-TCP/PLLA composite specimens

Figure 1 shows crystallinity of monolithic PLLA and β-TCP/PLLA composite specimens with three different β-TCP contents. The X_c value of monolithic PLLA was

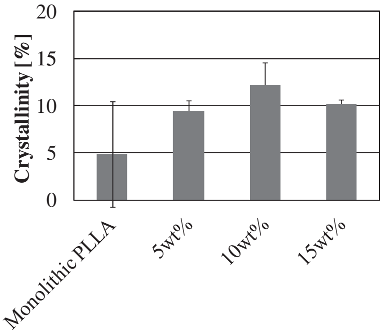


Figure 1. Crystallinity of PLLA and β-TCP/PLLA composites.

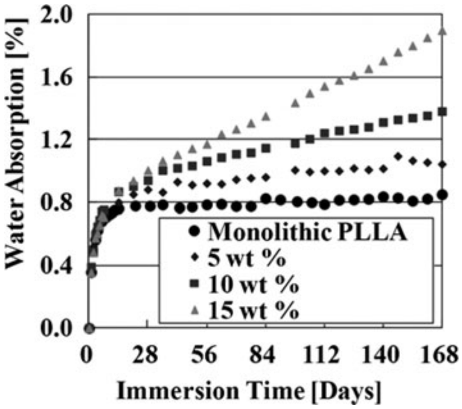


Figure 2. Relationship between water absorption M_t and immersion time.

approximately 0–10%. This denotes that monolithic PLLAs are also amorphous. The β-TCP/PLLA composite specimens denoted approximately the same values irrespective of β-TCP content as each other. The X_c values were approximately 10% which were approximately the same value of monolithic PLLA. Thus, it is assumed that PLLA in the β-TCP/PLLA composites was almost amorphous as same with monolithic PLLA.

3.2. *Amount of water absorption*

Figure 2 shows the amount of water absorption, M_t. For the monolithic PLLA, M_t increased with increasing immersion time up to 14 days, and then saturated. For the β-TCP/PLLA composite specimens, all specimens showed approximately the same tendency, where M_t increased with increasing immersion time up to 168 days and with β-TCP content. These results indicated that the water absorption capacity of β-TCP and/or β-TCP/PLLA interface was higher than PLLA.

Further, an increase was seen after 24 weeks immersion in 5 wt% specimens, while a tendency to converge to a constant value was observed for monolithic PLLA. In the specimen with higher β-TCP content, particularly 15 wt%, water absorption increased monotonically in latter immersion period. These results suggest that water absorption increased because of increasing total filler surface area and resultant increasing degraded region around the matrix–filler interface, which absorbed water.

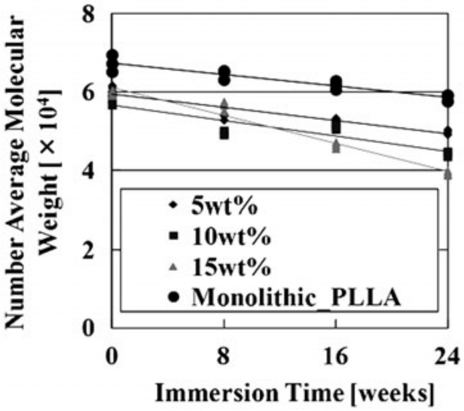


Figure 3. Relationship between number-average molecular weight and immersion time.

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

Figure 3 shows number-averaged molecular weight (M_n) of monolithic PLLA and PLLA in β-TCP/PLLA composite specimens. For the monolithic PLLA, M_n before immersion was approximately 67,000. After 24 weeks immersion, M_n for monolithic PLLA decreased to approximately 59,000. In the β-TCP/PLLA composite specimens, M_n before immersion denoted approximately the same values as each other, and the values were approximately 58,000–61,000. However, the number-averaged molecular weight was reduced compared with that of monolithic PLLA. That is, the amount of heat transferred during injection molding increased and thermal decomposition was accelerated, because of incorporation of filler with higher heat conductivity and lower heat capacity.

After 24 weeks immersion, M_n of 5, 10, and 15 wt% specimens decreased to approximately 50,000, 44,000, and 39,000, respectively. The decrease in M_n became faster with the β-TCP content comparing with 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 β-TCP content. This is consistent with the results of Figure 2.

4. Analytical prediction

4.1. *Prediction of water absorption*

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 plane sheet geometry, concentration of water at time t (C_t) is obtained as follows by the principle of superposition of Equation (5)

$$\frac{C_t}{C_\infty} = 1 - \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{1}{2n+1}\exp\left[-D\frac{(2n+1)^2\pi^2}{l^2}t\right]\sin\left[\frac{(2n+1)\pi}{l}x\right] \tag{6}$$

where C_∞ is concentration of water at times ∞ and l is the thickness of the specimen. When M_t are the water absorption at time t, it is required the following equation using the Equation (6).

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\exp\left[-D\frac{(2n+1)^2\pi^2}{l^2}t\right] \tag{7}$$

where M_∞ are the water absorption at times ∞. Accordingly, when M_t/M_∞ is small enough (<0.60) in the early stage, Equation (6) is reduced to the Stefan's approximation

$$\frac{M_t}{M_\infty} = \frac{4}{l}\left(\frac{Dt}{\pi}\right)^{\frac{1}{2}} \tag{8}$$

From which, if one plots M_t/M_∞ against $t^{1/2}$, the diffusion coefficient can be calculated from the initial curve slope. Diffusion coefficient of monolithic PLLA obtained from the above equation was 5.8×10^{-12} with $M_\infty = 0.8\%$. Since the water absorption into composites continued to increase in 168 days immersion and equilibrium could not be confirmed for the composites, it was not possible to determine the diffusion coefficient.

In order to predict water diffusion in the composites, we propose a simplified two-phase model. Figure 4 shows a simplified water absorption model for a β-TCP/PLLA composite. The one-dimensional diffusion in the Fick's second law and independent water diffusion in each phase, matrix, and β-TCP, were assumed.

From crystallinity measurements, it is assumed that PLLA in the β-TCP/PLLA composites is almost amorphous similar to the monolithic PLLA. In this study, we used the prediction for the amount of water absorption in monolithic PLLA as those of matrix in the composites. The amount of water absorption into β-TCP was calculated from the difference between the experimental results of β-TCP/PLLA composites and matrix, considering filler content. Then, prediction of water absorption in β-TCP was performed. Water absorption in β-TCP did not saturate after 24 weeks immersion and saturation of water absorption was unknown. Therefore, experimental results for initial absorption were approximated as a single curve using variable parameters of diffusion coefficient D and saturation of water absorption M_∞. Water absorption obtained is shown in Figure 5. The prediction in the initial stage is in good agreement with the experimental results independent of β-TCP content. D and M_∞ used for β-TCP are

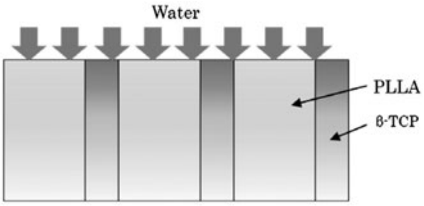


Figure 4. Water absorption model of β-TCP/PLLA composites.

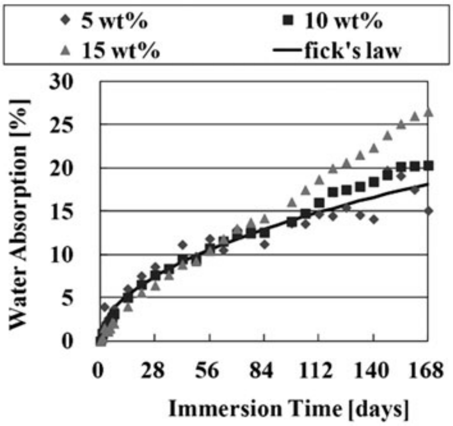
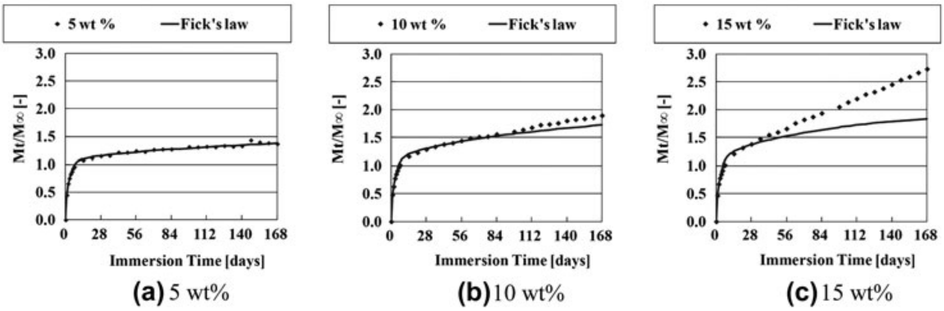


Figure 5. Water absorption into β-TCP in PBS and analytical curve with Fick's law.



(a) 5 wt% **(b)** 10 wt% **(c)** 15 wt%

Figure 6. Water absorption into β-TCP/PLLA composites in PBS and analytical curve with Fick's law.

22.8% and 8.0×10^{-14}, respectively. Figure 6 shows the water absorptions into the composites calculated based on the rule of mixture. D and M_∞ for matrix in the composites used were identical value for monolithic PLLA. Prediction for 5 wt% is in good agreement with the experimental result; however, discrepancies appear with filler content. Especially, water absorption continued to increase at a later stage for immersion. This is attributed to variations in D and M_∞ due to hydrolysis. Nevertheless, initial water absorptions for the composites based on the rule of mixture are in good agreement with the experimental results. These results suggest that initial water absorption is predictable using D and M_∞ for monolithic PLLA and β-TCP.

4.2. Prediction of number averaged molecular weight

In general, hydrolysis of polyester is accelerated in the presence of acid or alkaline. For polyester, autocatalytic reaction has been confirmed since polyester include hydrophilic carboxyl group at the end of the molecular chain. Hydrolysis rate due to autocatalytic reaction is expressed as [14]

$$\frac{d[\mathrm{COOH}]}{dt} = k_1[\mathrm{COOH}][\mathrm{ester}][\mathrm{H_2O}] \tag{9}$$

where, [COOH], [ester], and [H_2O] are concentration of carboxyl group, ester bond, and water, and k_1 is a rate constant. Since $[\mathrm{COOH}] \ll [\mathrm{ester}][\mathrm{H_2O}]$, [ester][$H_2O$] is assumed to be constant. Then, integrating Equation (9) with a relation, $[\mathrm{COOH}] \propto M_n^{-1}$ results in,

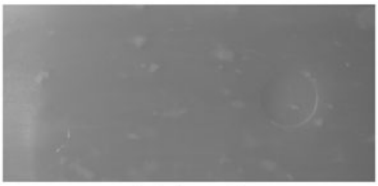
$$\ln M_n(t) = \ln M_n(0) - k_2 t \tag{10}$$

where $M_n(t)$ and $M_n(0)$ are number-averaged molecular weight M_n at hydrolysis time t and 0 and $k_2 = k_1[\mathrm{ester}][\mathrm{H_2O}]$. From Equation (10), k_2 is obtained from the slope of relation between ln M_n (t) and t.

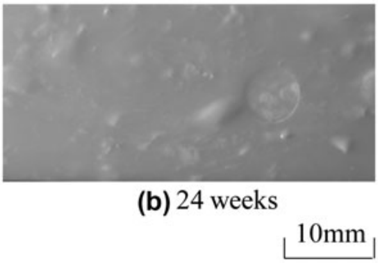
k_2 determined for the present experimental results are shown in Table 2. k_2 increased with filler content. This is due to the accelerated hydrolysis caused by increasing water absorption around increasing interface region between filler and matrix. Figure 7 shows surface morphology for a 15 wt% specimen during a immersion test. Blisters around filler aggregations were observed after 24 weeks immersion, which indicates increasing water absorption with filler content. Figure 8 shows cryogenic fracture surfaces. Clearance gap which was not observed for specimen without immersion existed in the specimen after 24 weeks immersion. This result also indicated accelerated hydrolysis around interface.

Table 2. k_2 values calculated from experimental results.

Monolithic PLLA	9.5×10^{-9}
5 wt%	1.4×10^{-8}
10 wt%	1.9×10^{-8}
15 wt%	2.9×10^{-8}



(a) 0 weeks



(b) 24 weeks

Figure 7. Surface view of 15 wt% β-TCP/PLLA composites.

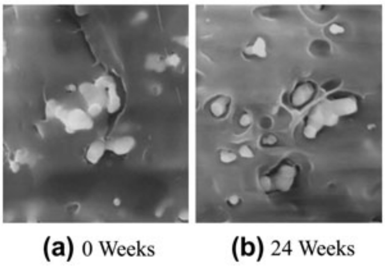


Figure 8. Cryogenic fracture surfaces of 15 wt% β-TCP/PLLA composites before and after immersion.

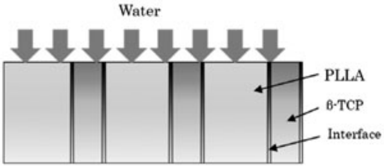


Figure 9. Hydrolysis model of β-TCP/PLLA composites.

In the above, k_2 have been obtained under the assumption of constant water concentration in matrix. On the other hand, water concentration changed over time from the experimental results as mentioned before. Especially, water concentration in composites is considered to increase after 24 weeks immersion. In addition, a variation in molecular weight for the composite is considered to occur by hydrolysis of matrix only. Therefore, the difference in hydrolysis rate with filler content is due to difference in water concentration.

In the present study, 3-phase model, which consists of matrix, filler, and interphase, is proposed for hydrolysis of composites, as shown in Figure 9. Matrix in the composite is assumed to absorb and to hydrolyze as monolithic PLLA. Difference in the amount of water absorption between monolithic PLLA and the composite is considered to diffuse into the interphase. That is, water concentration is higher in interphase than in PLLA matrix. Interphase is also assumed to hydrolyze as monolithic PLLA. Molecular weight is predicted base on Equation (10) as,

$$\frac{\mathrm{d}[\mathrm{COOH}]}{\mathrm{d}t} = k_2[\mathrm{COOH}][\mathrm{H_2O}] \tag{11}$$

In the present study, k_2 value for monolithic PLLA as shown in Table 2 was used. Substituting a variation in water concentration with time calculated with Equation (7) into Equation (11), [COOH] in PLLA and the interphase around a β-TCP particle are obtained numerically. In the present analysis, the gradient of water diffusion in the thickness is neglected and the value of k_2 for monolithic PLLA as shown in Table 2 is used. Next, unknown interphase region is assumed as Figures 9 and 10. [COOH] for interphase region was calculated to approximate the experimental results by varying the diameter of interphase region D_i. Number-averaged molecular weight for matrix of the composites was calculated using the relation [COOH] $\propto M_n^{-1}$.

Figure 11 show the prediction of the number-averaged molecular weight for 15 wt% composite at a variation in D_i from 1.0 *d* to 2.0 *d*, where D_i = 1.0 *d* and D_i = 2.6 *d* correspond to no interphase and interphase of entire PLLA, respectively. At 24 weeks, molecular weight is five times larger for D_i = 2.6 *d* comparing to D_i = 1.0 *d*, which indicate molecular weight is extremely sensitive to the volume of interphase region.

Figure 12 shows the simulation results for averaged molecular weight as a function of time for each specimen based on three-phase model and the prediction for water absorption. In the simulation, interphase thickness is assumed as 0.7 times the filler radius, irrespective of filler content. Good agreements are obtained between simulation

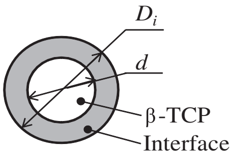


Figure 10. Interface model of β-TCP/PLLA composites.

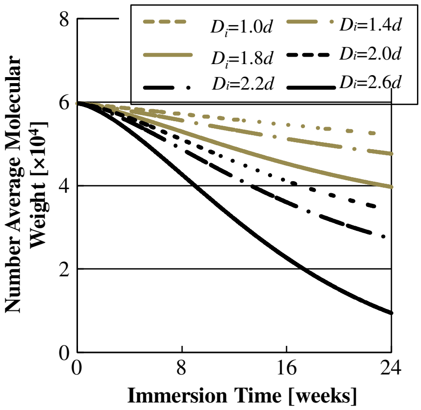
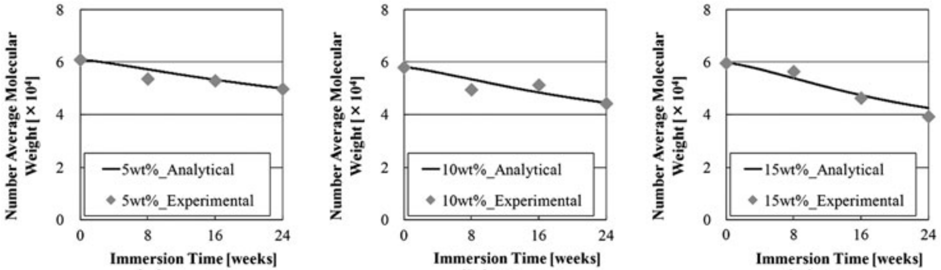


Figure 11. Analytical curve of 15 wt%. (D_i = 1.0–2.6 *d*).



(a) 5 wt% **(b)** 10 wt% **(c)** 15 wt%

Figure 12. Number-average molecular weight of β-TCP/PLLA composites in PBS and analytical curve.

and experimental results. These results suggest that hydrolysis is accelerated in the interphase region whose thickness is 0.7 times the filler radius, i.e. about 0.8–0.9 μm thick. The possibility for prediction of molecular weight considering water absorption is also confirmed.

5. Conclusions

Immersion tests in simulated body environment were conducted on monolithic PLLA and β-TCP/PLLA composites to measure water absorption and molecular weight variations of PLLA. Based on the experimental results, an analytical model for hydrolysis was proposed considering a variation in water concentration with time. The conclusions obtained are as follows:

(1) Water absorption into monolithic PLLA saturated at 14 days immersion. Water absorption into β-TCP/PLLA composites became larger with β-TCP content. It indicates the existence of β-TCP accelerates water absorption.
(2) M_n for β-TCP/PLLA composites without immersion were independent of filler a content. In contrast, reduction in M_n was more significant with filler content. These results suggest that the interface between β-TCP and PLLA accelerate hydrolysis of PLLA in composites.
(3) The effectiveness of the proposed model for hydrolysis prediction was confirmed by comparing the analytical results with experiments. The interphase thickness is independent of filler contents.

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