Applied Surface Science 262 (2012) 89–94

Contents lists available at SciVerse ScienceDirect

Applied Surface Science

journal homepage: www.elsevier.com/locate/apsusc

Characterization and morphology analysis of degradable poly(L-lactide) film in in-vitro gastric juice incubation

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ARTICLE INFO

Article history:
Available online 24 February 2012

Keywords:
Degradation
Poly(L-lactide)
Film
Hot melting
Gastric juice

ABSTRACT

The purpose of this study was to evaluate the use of the biodegradable poly(L-lactide) (PLLA) as a gastro-jejunal tube anchored in the duodenum for duodenal exclusion. PLLA film was fabricated using a hot melting process to a thickness of around 40–50 μm and was then immersed in human gastric juice to estimate the in vitro biodegradability behavior. PLLA film was more biodegradable in human gastric juice than in HCl and PBS. Measurements of weight loss indicated that 60% of original the PLLA was lost after 42 days of incubation. Surface functional group characterization, thermal stability, and surface morphology of the degraded PLLA film in human gastric juice showed that the decomposed sections of the PLLA film were primarily from the amorphous region. The degradation of the PLLA film in human gastric juice began with the erosion of continuous nanocavities in the range of 100–200 nm on the PLLA surface over the course of 21 days. The PLLA film collapsed and spiral PLLA fiber was obtained after 42 days of decomposing in human gastric juice.

1. Introduction

The number of overweight and obese is increasing at an alarming rate in both developing and developed country [1]. Obese have substantially increased morbidity and mortality from obesity-related complications, such as type 2 diabetes, cardiovascular disease, and several types of cancer [2–4]. Roux-en-Y gastric bypass (RYGB) is the most common and considered the gold standard weight loss surgery in United States. Diabetes blood sugar control can also be achieved after gastric bypass surgery by removing the duodenum from the nutrient flow (duodenal exclusion). Therefore, a lot of materials have been fabricated in tubular device anchored in the duodenum for duodenal exclusion has been investigated for exploring the mechanism of blood sugar control and weight loss after RYGB [5–7]. However, previously used materials have not been biodegradable and had to be removed when complications occurred. The development of a biodegradable tubular device may facilitate the understanding of the mechanism by which RYGB leads to weight loss.

Among broadly studied biopolymers, PLLA constitutes a class of biocompatible and biodegradable polyesters that already have extensive clinical uses as approved materials for implantable resorbable biomaterials such as sutures and screws [8]. PLLA degrades by the hydrolysis of ester linkages into low molecular weight molecules which can be either removed through the renal system [9]. Hydrolysis is a kind of chemical degradation, which occurs by the cleavage of chemical bonds in the main chain through a reaction with water. Hydrolysis is initiated by protonation by proton in the water [10] and then cleavage of the ester linkage. The hydrolytic degradation of bulk PLLA materials was reported to occur both by surface erosion and bulk erosion mechanisms. The surface erosion mechanism of polymer degradation occurs only at the interface of polymer and water. However, bulk erosion refers to uniform degradation throughout whole polymer [11,12]. In addition, the degradation of PLLA by enzymes has been widely investigated since 1981 [13]. It has been reported that proteinase K, one of the most commonly environmental enzymatic, can be used for studying the enzymatic degradation of PLLA. Moreover, the enzymatic degradation of PLLA occurred preferentially in the amorphous region of the PLLA [14], and the crystallinity of the PLLA had a significant effect on the degradation rate [15–19]. Although much has been reported on the degradation of PLLA in environmental enzymes and acidic hydrolytic surroundings, little has been reported on the biodegradation behavior of PLLA in digestive enzymes. Moreover, previous studies on degradable PLLA materials in digestive enzymes were focused on nanoparticles for application in oral drug carrier design [20], unrelated to PLLA film implantation in digestive organs.

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doi:10.1016/j.apsusc.2012.02.087

In order to design a suitable PLLA tubular device for RYGB application, a PLLA film was fabricated using a hot embossing method at 180 °C, and the degradation behavior was investigated by immersing this film in human gastric juice. The surface morphology, surface chemical structure, and thermal degradation of the degraded PLLA film were studied through scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), and thermal gravimetric analysis (TGA).

2. Experiment

2.1. Materials

Poly(L-lactide) pellets of commercial grade were purchased from Sigma–Aldrich. The Mn of this PLLA was between 85,000 and 160,000 Da. Phosphate buffer saline was purchase from Gibico®. Hydrochloric acid (32%) was purchased from Merck. All of materials were used without any purification. The major components of human gastric juice are gastric acid and digestive enzymes. The pH of gastric acid is between 1.35 and 3.5, and the acid can digest proteins by activating digestive enzymes. Pepsinogen is the main gastric digestive enzyme and is activated by gastric acid into its active form, pepsin. Pepsin can break down long protein chains into shorter chains of amino acids.

2.2. Preparation of PLLA film

PLLA films were fabricated by a melt-pressing technique using a carver press with preheating to 180 °C, and the PLLA pellets were placed between the two heated plates and allowed to heat to 180 °C for 10 min. The film was cooled to room temperature at the same pressure for approximately 6 h to maintain thickness. A pressure of 20,000 pounds was applied to the sandwich until the film cooled to room temperature. The resulting PLLA films had a thickness of around 40–50 μm and were suitable for use as tubular devices in the duodenum. The PLLA films were kept in a desiccator for future studies.

2.3. Degradation of PLLA film

Three PLLA films weighing 8 mg each were immersed in an aqueous solution of human gastric juice, HCl (pH 2.6), and phosphate buffer solution (PBS), then agitated in a warm-water bath maintained at a constant temperature of 37 °C for up to 2 months. The aqueous solutions were exchanged every week. Thereafter, the samples were withdrawn from the aqueous solutions for each time point, dried at room temperature for 24 h, and weighed until constant weights were obtained. Finally, the resulting PLLA samples were used to characterize variations in the weight loss, thermal stability, morphology, and chemical structures of the films.

2.4. Weight loss measurement

The percentage weight loss of the degraded PLLA films was calculated from the weights change before and after degradation according to the following equation:

$$W_{\text{loss}}(\%) = 100\% \times \frac{(W_{\text{before}} - W_{\text{after}})}{(W_{\text{before}})},$$

where W_{loss} (%) is the percentage weight loss of the degraded PLLA film.

W_{before} and W_{after} mean the weight of the pristine PLLA film before and after degradation.

3. Characterization of degradation of the PLLA film

3.1. ATR-FTIR

Identification of chemical structure of degraded PLLA film was examined by IR spectrum by using a Nicolet Magna 760 spectrometer. The spectra were collected using the attenuated total reflectance (ATR) mode with a resolution of 4 cm^{-1} and 64 scans per sample in the region of 3780–680 cm^{-1}.

3.2. TGA

TGA data were obtained using a TA Instruments Thermo gravimetric Analyzer, model Q500. 20 mg of PLLA film were heated at a rate of 10 °C/min from room temperature to 530 °C, under a dry nitrogen gas flow rate of 40 mL/min.

3.3. SEM

All the PLLA films were coated with a thin gold layer using a sputter coater and observed with a scanning electron microscope (FE-SEM, JSM-6500F, JEOL) at an accelerating voltage of 20 kV.

4. Results and discussion

4.1. PLLA film preparation

High molecular weight PLLA is a thermoplastic polymer with a glass transition around 60 °C and melting temperature in the range of 170–210 °C, making it suitable for thermal processing. Therefore, PLLA pellets were transformed into smooth, flat films using a hot melting process under a pressure of 20,000 pounds and at a temperature 180 °C maintained for 10 min. The resulting PLLA film is shown in Fig. 1(a), and the thickness of the film was around 40–50 μm. In order to maintain the thickness of the PLLA film, the PLLA film was slowly cooled to room temperature while maintaining a high pressure. PLLA can be crystallized by slowing from melt or annealing at temperature above glass transition and under strain. Moreover, semicrystalline polymers, such as PLLA, are known to crystallize by chain folding forming lamella perpendicular to the chain axis on the order of 10–30 nm [21]. Although it was not our intention to form the crystalline structure in the PLLA film, a rearrangement of the PLLA chain may have caused the crystalline structure formed inside the film during the slow cooling process.

4.2. Weight loss measurement of degraded PLLA film

In order to produce a suitable biodegradable RYGB tubular device, the PLLA film was first immersed in human gastric juice

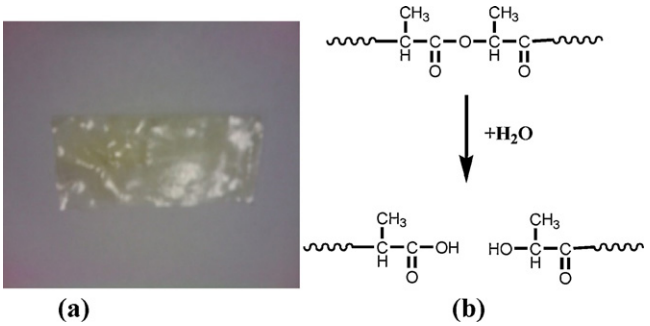

Fig. 1. (a) PLLA fabricated from hot melting method (b) hydrolytic reaction of PLLA film.

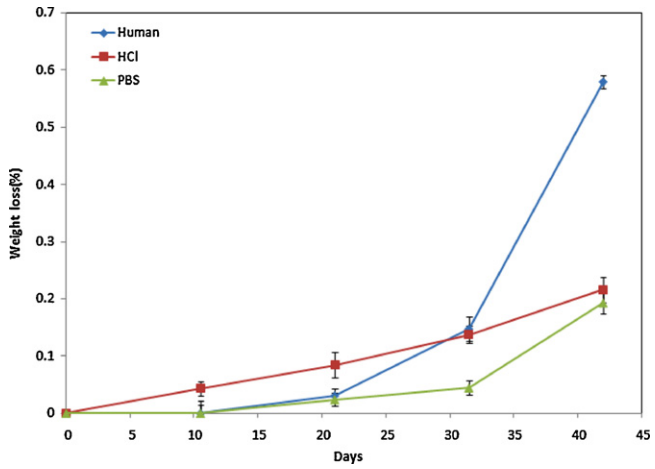

Fig. 2. Weight loss of PLLA film immersing in human gastric juice, HCl and PBS.

in vitro for further investigation. Weight change is one of the results of polymer degradation. In this process, long polymer chains are cleaved to shorter chains that are able to migrate away from the film. Therefore, the weight of the original film is reduced. The degradability of the PLLA film was measured directly after collecting the experimental pieces from an incubator. The weight change measurements of the PLLA film during in vitro degradation are shown in Fig. 2. Here, PLLA was incubated with human gastric juice, PBS and HCl solution to evaluate degraded behavior PLLA film at different condition. In addition, PBS and HCl solution were act as control group for study the effect of digestive enzymes on degradation of PLLA film. The degradation of PLLA is primarily due to the hydrolysis of ester linkages, which occurs more or less randomly along the backbone of the polymer. Fig. 1(b) also demonstrates the necessity of water to cleave the bonds in the PLLA main chain and degrade the film. For the nonenzymatic degradation, the degradation rate could be enhanced in acidic or alkaline condition. It might be the reason why the weight loss of PLLA immersed in the HCl solution showed much more pronounced than in the PBS solution before day 32. On the other hand, the digestive enzymatic degradation occurred only on the surface of materials. The hydrophilic digestive enzyme must react with the hydrophobic PLLA surface and then degradation of PLLA might work. The result indicated that the hydrolytic scission process might change the hydrophobic surface of PLLA and the effective enzyme activity happened on day 21. Therefore, the degradation rate of PLLA film in human gastric juice accelerated at day 21 when compared with the PLLA film in HCl and

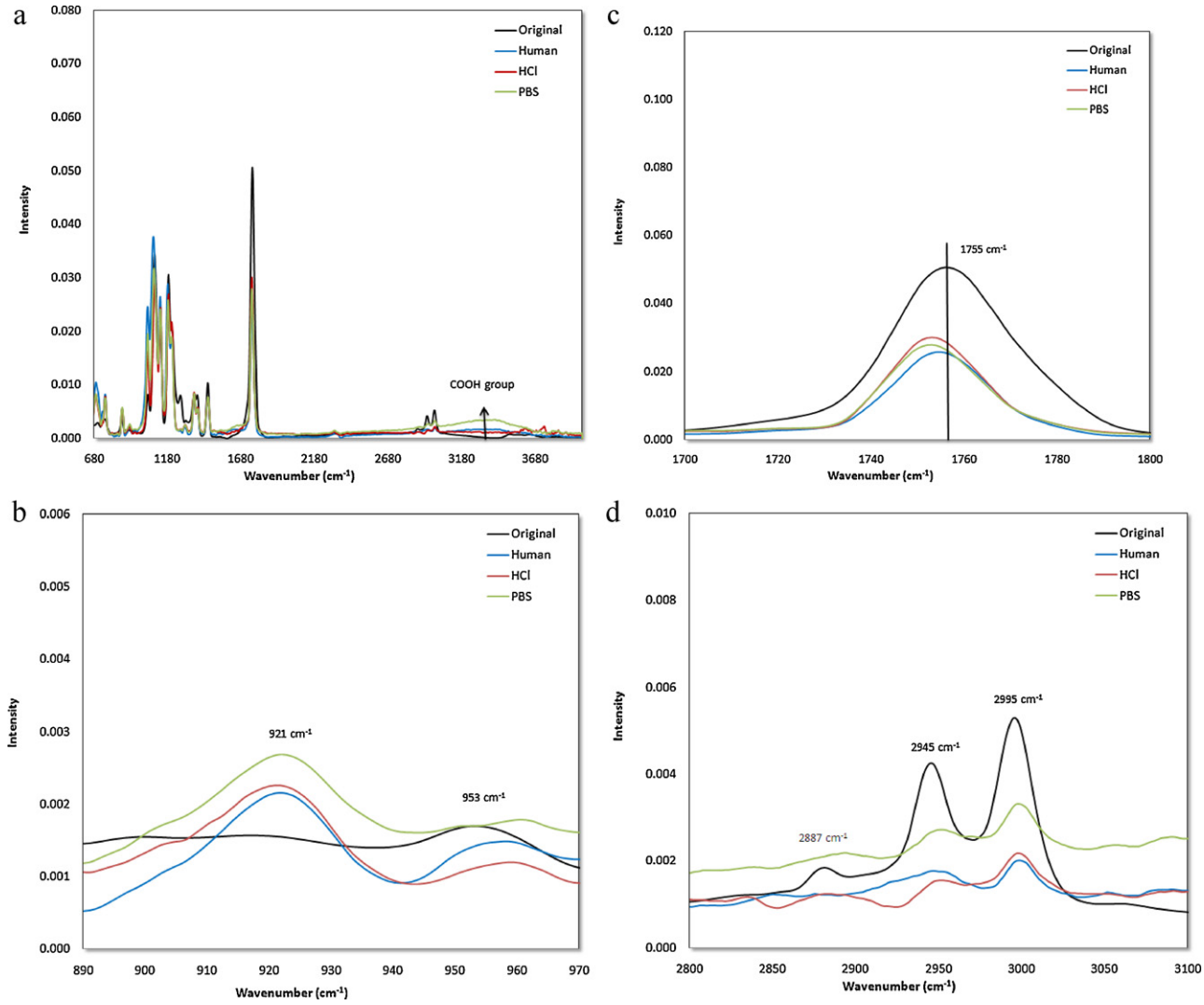

Fig. 3. ATR-FTIR spectra of pristine PLLA film and degraded film for immersing in solution for 21 days (a) 680–3780 cm^{-1} (b) 890–900 cm^{-1} (c) 1700–1800 cm^{-1} (d) 2800–3100 cm^{-1}.

PBS solution. Finally, the data showed that the overall weight loss of PLLA film in human gastric juice (57.9 wt%) was higher than that for PLLA film in PBS (19.3 wt%) and HCl (21.6 wt%) solution after being immersed for 42 days.

Polymer degradation occurs mainly through the scission of the main chains or side chains of macromolecules. However, the degradation of a polymer can be activated through hydrolysis, thermal activation, biological activity, oxidation, or photolysis [22]. Gastric juice is acidic (pH 1–3), and its main components are HCl, renin, pepsinogen gelatinas, and gastric amylase. Although no research has been done on the effects of gastric juice on PLLA, it has been reported that the enzymatic degradation of PLLA is more efficient than hydrolytic degradation.

4.3. Analysis of the surface characteristics of PLLA film by ATR-FTIR

The influence of a biological environment on changes on chemical structure of biomaterials can be investigated by infrared spectra. FTIR analyses can provide further information of degradation properties. ATR-FTIR is used for surface characterization; therefore, the surface properties of PLLA films degraded in various solutions were studied by ATR mode. Degraded PLLA films become brittle and are not easily measured by ATR-FTIR. We chose 21-day degraded film for the ATR-FTIR measurement. All four samples exhibited similar FTIR spectra, as shown in Fig. 3(a). For all degraded PLLA films, the appearances of a broad band in the 3000–4000 cm^{-1} region was confirmed to be the hydroxyl group in the carboxylic acid. Such a carboxylic acid peak results from the hydrolysis of the PLLA ester bond.

As shown in Fig. 3(b) for pristine PLLA film, a wide band at 953 cm^{-1} is detected before degradation. In contrast, a new band at 921 cm^{-1} appeared after 3 weeks of degradation. It has been reported that an absorption band at 921 cm^{-1} is characteristic of the helix conformation in an alpha PLLA crystal state and that a 953 cm^{-1} band represents the amorphous state of PLLA [23–25]. Therefore, the hydrolytic(nonenzymatic) and enzymatic degradation of the amorphous regions between lamellae stacks likely influences the chain stretching and CH_3 rocking in the PLLA lamellae resulting in the changing of crystalline and amorphous band of PLLA. Similar results, where varied crystal morphologies were obtained after the enzymatic hydrolysis of PLLA with proteinase K, have been reported [26,27]. Fig. 3(c) illustrates changes to the C=O stretching band region (1800–1700 cm^{-1}), where a shift to a higher frequency corresponds with increasing crystallization. Also, changes to the C=O band are connected with an increased number of carboxylic end groups in the polymer chain that form during hydrolytic degradation and during the cycle of enzymatic changes. Similar results have been reported that relate shifts in the C=O band refer to the crystallization of PLLA [27]. The absorption bands at 2995, 2940, and 2877 cm^{-1} (due to the stretching of CH_3) are representative of the amorphous structure of the PLLA film as shown in Fig. 3(d). The amorphous structure of the PLLA film seemed to be reduced after degradation, an observation that is consistent with previous reports.

4.4. Thermal properties of degraded PLLA film

Fig. 4 shows the weight loss of the PLLA film after the thermal degradation study. From these data, it is possible to precisely determine the thermal stability and kinetic parameters for the degraded PLLA films. It was observed the all the TGA curves presented a sigmoidal shape, and it was clear that the decomposition proceeded according a unique reaction within a narrow temperature range. Table 1 shows the characteristic temperatures of thermal decomposition including T_{s5}, the temperature at which 5% of the initial mass is lost; T_{s50}, the temperature at which 50% of the initial mass is lost; and T_{s95}, the temperature at which 95% of the initial mass is lost. The temperature of thermal stability (T_{s5}) was 236 °C for pristine PLLA film, whereas the degraded PLLA films were more stable. Therefore, degraded PLLA film has a thermal stability higher than that of pristine PLLA film. Thermal degraded at 5 wt% is similar with materials melting process which was responsible for a certain depolymerization processing. Indeed, it can be expected that crystalline PLLA in the film surface can withstand a given load up to a higher temperature since the crystalline region should maintain the stiffness of materials during the melting depolymerization process. T_{s50} was 358 °C for pristine PLLA film and between 336–349 °C for degraded PLLA film. T_{s95}, which essentially conveys the quasi destruction of materials, was 385 °C for pristine PLLA film and between 365–375 °C for degraded PLLA film. Therefore, an inversion of thermal stability behavior was observed for T_{s50} and T_{s95} and thermal stability was significantly higher in degraded PLLA than in pristine PLLA. From this, we can conclude that the degradation process can actually damage the chemical structure of the PLLA film to produce total decomposition at a slightly higher temperature. Moreover, it was observed that degrading the PLLA film in HCl and PBS could slightly improve thermal stability when compared with the PLLA film degraded in human gastric juice.

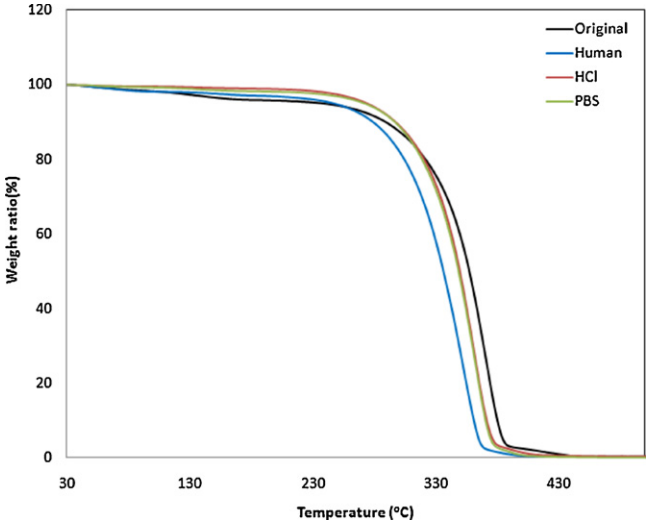

Fig. 4. TGA analysis of pristine PLLA film and degraded PLLA film for immersing in solution for 21 days.

4.5. Analysis of the morphology characteristics of PLLA film by SEM

Fig. 5 shows the SEM image of PLLA film made using a hot melting process and degraded by several solutions over 21 days. Before degradation, the PLLA film appeared rather smooth and without specific defect, which is commonly observed with hot-melting film formation, as shown in Fig. 5(a). After 3 weeks of degradation, the PLLA film was slightly eroded, and the amorphous domain was partially removed, as shown in Fig. 5(b–d). Micro cracks and tiny

Table 1
Characteristic temperatures of the thermal stability of PLLA film.

	T_{s5} (°C)	T_{s50} (°C)	T_{s95} (°C)
Pristine PLLA film	236	358	385
Human Gastric juice[a]	246	336	365
HCl[a]	274	349	375
PBS[a]	272	348	374

[a] PLLA film was incubated at solution for 21 days

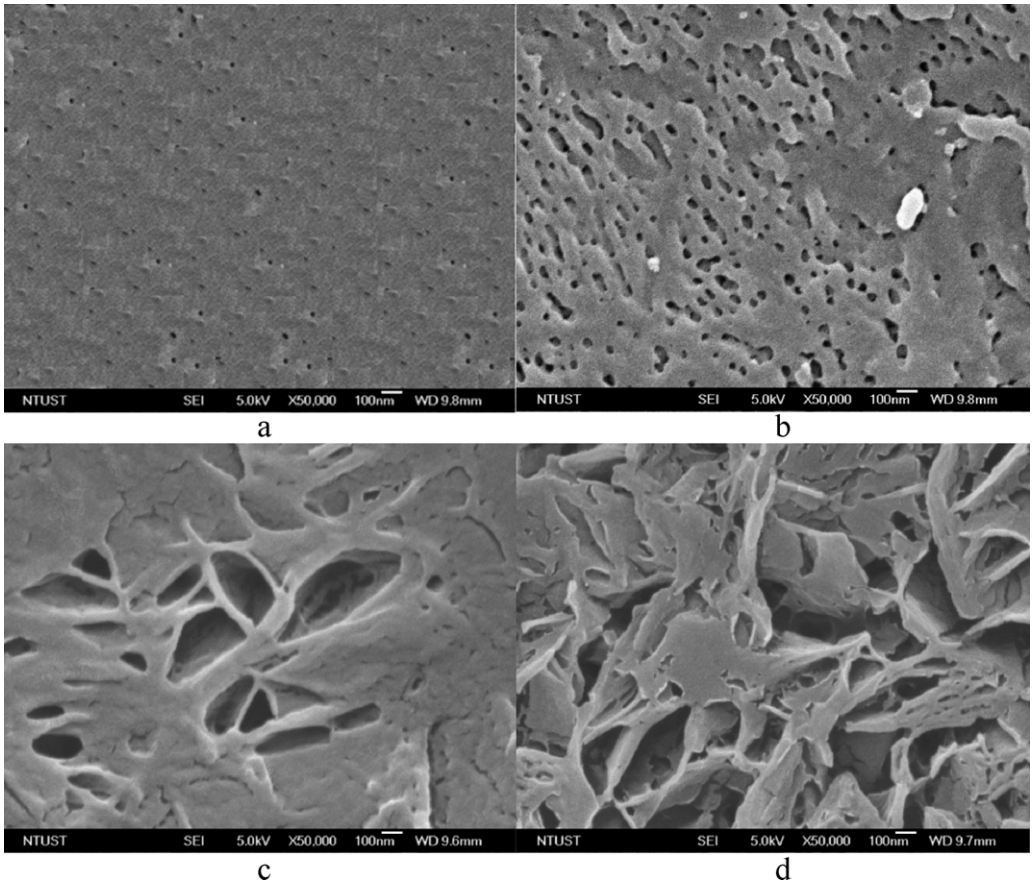

Fig. 5. SEM micrograph of the surface of (a) pristine PLLA film and degraded PLLA film for immersing in (b) PBS (c) HCl and (d) human gastric juice for 21 days.

pinholes were observed in all the degraded PLLA films. It has been reported that the degradation of aliphatic polyester begins with the diffusion of water into the amorphous zone of the polymer creating random ruptures in the ester bonds [28]. Hydrolysis degradation of PLLA chains are randomly cleaved in PBS incubation and resulted in small hole erosion in the surface as shown in Fig. 5(b). Under acidic condition, the degradation of PLLA can be accelerated by OH end catalyzed hydrolysis [29]. Therefore, larger holes were formed for the PLLA incubated in HCl solution (Fig. 5(c)). In addition, enzymatic degradation easily occurred on the amorphous region of PLLA surface [30]. Therefore, the effect much more pronounced for PLLA film immersed in human gastric juice so that the process is characterized as accelerated degradation. In Fig. 5(d), degraded PLLA film at 21 days shows a continuous nanostructure of inter-connected pores, 100–200 nm in length.

After immersing the PLLA film in human gastric juice for 42 days, surface cracks in the PLLA film were found, as shown in Fig. 6(a), and a spiral-fiber structure was obtained, as shown in Fig. 6(b). This may explain why the PLLA films became brittle after being immersed in human gastric juice for 42 days. These observations led to the conclusion that the PLLA film was not degraded by surface erosion, but rather by bulk erosion. Degradation likely began at individual points on the film's surface and then propagated inside the film. Therefore, the cracking on the film resulted in a fiber like structure on the surface. The bulk erosion of aliphatic polyesters has been supported by other findings [31–33].

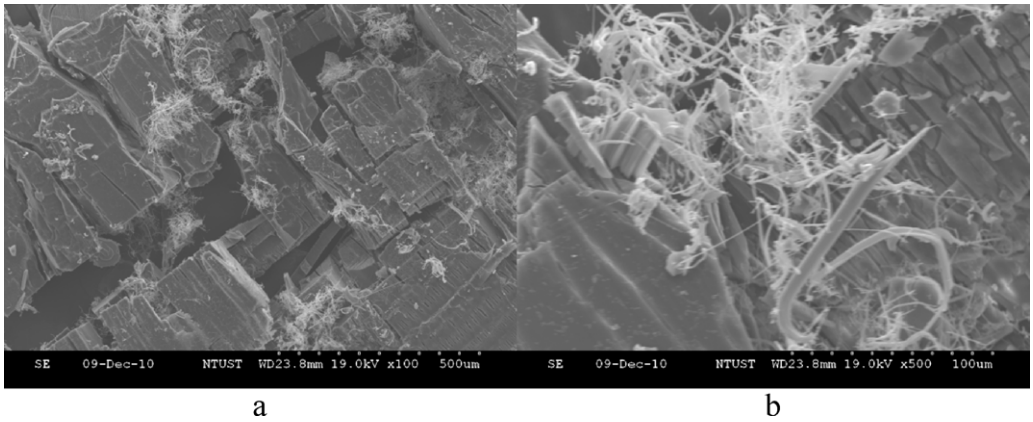

Fig. 6. SEM micrograph of PLLA surface immersing in the human gastric juice for 42 days. (a) Crack region (b) fiber-like region.

The enzymatic degradation progressed on the surface of the PLLA films, because the polymer chains were water-insoluble and the enzyme molecules were water-soluble. It was concluded that the enzymatic degradation proceeded mainly via a surface erosion mechanism [34]. Amorphous regions hydrolyzed more readily than crystalline regions. The observed degradation product indicated that film structure could be described two phase contaminations. PLLA film was made using a hot melt-pressing method and was slowly cooled while maintaining pressure. Therefore, the reorientation or rearrangement of the molecular chains of PLLA may have occurred during the cooling process. This seems to have caused alternating crystalline and amorphous regions within the thin PLLA film. After degradation in gastric juice, a collapse of the film structure could completely separate the two independent segments.

5. Conclusion

We have reported for the first time a degradation study of PLLA film in human gastric juice. A thin polymer film is required for use as a gastro-jejunal tube anchored in the duodenum for duodenal exclusion. Therefore, we fabricated a PLLA film using a hot meting process, which is common technique used in the plastic industry. The fabricated PLLA film contained amorphous and crystalline regions, and the degradation behavior of the PLLA film was strongly dependent upon these two phases. ATR-FTIR spectroscopy was used for investigating surface functional groups, and the presence of alpha-crystalline PLLA was discovered in PLLA film degraded for 21 days in a human gastric juice solution. Further investigations using TGA and SEM supported the results found with ATR-FTIR. Decomposition of the PLLA film began with surface erosion in human gastric juice, after which water diffused into the swelling PLLA film for the next step of degradation. Eventually, the pristine PLLA film was degraded into fragments, and the films became very brittle after incubating in vitro for 42 days in human gastric juice. The next stages of our work will focus on producing crosslinking PLLA, and providing the mechanical properties of duodenal wriggle when the PLLA film is initially implanted and anchored in the duodenum.

Acknowledgments

The authors would like to thank the National Science Council of the Republic of China, Taiwan NSC 100-2511-S-011-006-MY2 and Tri-Service General Hospital TSGH-C100-106 for financially supporting this work.

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