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Degradation of Poly(*D*,*L*-lactide-*co*-glycolide) 50:50 Implant in Aqueous Medium

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ABSTRACT

A liphatic polyesters are the source of the attractive polymeric matrices that are currently investigated for making controlled drug delivery devices. In spite of the large number of investigations dealing with LA/GA polymers which have been reported in the literature, only little is known about the degradation mechanism of these polyesters in solid state. In this study poly(*L*,*D*-lactide-*co*-glycolide) 50:50 (PLGA) was hydrolyzed at 37°C for periods up to 56 days. PLGA discs were prepared in 60°C and the results of their in vitro biodegradation behaviour are reported. We observed that hydrolysis of PLGA proceeds in 7 stages: surface hydrolysis, outer layers hydrolysis, outer layers water soluble oligomers formation, exiting water soluble oligomers, bulk hydrolysis and exiting degradation products, bulk catalyzed hydrolysis, and at the last step fragile porous structure formation. The remained porous structure is crystallized and shows more resistance to further degradation.

Key Words:

degradation; Poly(D,L-lactide-co-glycolide); implant; in vitro; lactic acid.

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INTRODUCTION

Within the last two decades, a variety of synthetic polymers have been reported to be degradable in mammalian organisms and, for some of them, to be resorbable, i.e., eliminated from the body either by kidney filtration or by metabolization. Those polymeric materials which undergo chemical degradation in body fluids, either by simple reactions or by enzymatic activity, are now currently designated as biodegradable. The prefix bio reflecting that degradation occurs on a living environment which always affects the degradation mechanism in one way or another. From a similar viewpoint, polymers which can be resorbed in the body are referred to bio-resorbable [1].

Aliphatic polyesters such as polyactic acid (PLA), poly glycolic acid (PGA) and poly(lactide-*co*-glycolide) (PLGA) are among the bio-degradable materials which have been most successfully used in medical applications [2]. Potential applications include suture materials [3], devices for bone surgery [4], reconstructive substitutes [5-7], scaffolds for tissue engineering [8-10], and blood vessel prostheses [11]. However, one of the most attractive potential applications of these polymers deals with the concept of controlled drug delivery via parenteral routes. Various systems are currently being investigated, namely implants [12], micro[13] and nano-particles [14], aggregates, micelles, macromolecular pro-drugs, and polymeric drugs [15].

Degradation of PLA, PGA, and PLGA in an aqueous environment occurs through simple hydrolysis of ester bonds which get auto-catalyzed by carboxylic groups and the hydrolysis rate increases exponentially with degradation time [16].

In mammalian organisms, PLGA polymers biodegrade into lactic acid and glycolic acid. Lactic acid enters the tricarboxylic acid cycle and metabolizes and subsequently eliminates from the body as carbon dioxide and water. Glycolic acid either excretes unchanged by the kidneys or it enters the tricarboxylic acid cycle and eventually eliminates as carbon dioxide and water [17].

Poly(*D*,*L*-lactide-*co*-glycolide) 50:50 among the PLGA copolymers has been most successfully used in drug delivery systems due to its amorphous morphology [18]. This polymer has been extensively characterized with respect to its water-uptake rate, degradation kinetics, and morphology changes after incubation in aqueous media. But only little is known about degradation mechanism including physical and chemical process and their relation, of this polyester in solid state.

These studies have examined the effect of environmental factors (temperature and medium) [19-20], polymer type (molecular weight, lactide/glycolide ratio, etc.) [16, 21] or device fabrication parameters [22]. Implantable large devices such as cylinders, pellets, slabs, discs, and films thicker than 0.1 mm are usually prepared by compression moulding [18, 22]. However, there is the risk of thermal degradation of polymer [18] or drug in implantable drug delivery systems [23].

In this study, we prepared PLGA compressed-discs involving the use of low temperature and the results of their in vitro biodegradation behaviour are reported. Gel permeation chromatography (GPC), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), L-lactic acid assay and some other tests were employed to monitor the experiment. The purpose of this study is to investigate the degradation mechanism of Poly(D,L-lactide-co-glycolide) 50:50 in solid state. An extended new model based on experimental is also suggested. The results of this study will help us determining the mechanism of the drug release from PLGA implants and controlling it. The studies were performed in an aqueous buffer medium at 37°C (e.g., in-vitro) since only a significant difference was reported between in vivo and in vitro hydrolysis of PLA/PLGA polymers [24, 25].

This study is a part of a research for designing an implant based on PLGA 50:50 for Naltrexone release. The release data and other results will be published later.

EXPERIMENTAL

Materials

Poly(*D*,*L*-lactide-*co*-glycolide) 50:50 (RG 505, inherent viscosity = 0.54 dL/g in chloroform at 25°C, $M_w =$ 24000) was obtained from Boehringer-Ingelheim (Germany). Na(OH), Potassium phosphate monobasic (KH₂PO₄) and standard *L*-lactic acid were purchased from Merk, Aldrich, respectively.

PLGA Disc Preparation

Small discs of PLGA (0.2g and 13mm diameter and 1.4±0.1 mm thickness) were prepared using compression moulding at 60°C. A hydraulic press (SPECAC 15001, England) with maximum 15 tone force and cylindrical mould (13 mm in diameter) was used. The temperature of compression moulding depends on the morphological characteristics of the Polymer [18]. PLGA is an amorphous polymer and temperatures above the glass transition temperature (T_g) are usually sufficient for its forming. Thus, 60°C was selected.

Phosphate buffer saline (PBS) (0.1 M, Na_2HPO_4/KH_2 , pH 7.4) was prepared according to United State Pharmacope (USP) standard [26].

In Vitro Polymer degradation

The discs were weighed and then incubated in 10 mL phosphate buffer (pH 7.4) in 28 mL glass vial in an incubator at 37°C. Polymer discs were picked up at specified times and air dried to constant weight; water-uptake and weight loss were determined gravimetrically. Gel permeation chromatography (GPC) was used for polymer molecular weight determination.

Water Content and Mass Loss

Water uptake was calculated at each time using the following equation:

(%) H₂O uptake =
$$[(W_{wet} - W_t)/W_t] \times 100$$

 W_{wet} and W_t are the weight of polymer sample retrieved from PBS and the final constant weight after drying, respectively. The percent mass loss was calculated according to the following equation:

(%) Mass loss =
$$[(M_0 - M_f) / M_0] \times 100$$

Where M_0 and M_t are the initial mass is the final dry mass, respectively.

Molecular Weight Characterization

Polymer molecular weights were determined by gel permeation chromatography (GPC) (Waters-150°C, England). Dried samples were dissolved in tetrahydro-furan (THF) (5-10mg/mL) and filtered through a 0.22 μ m filters. GPC was conducted using a mixed column (300 × mm Polymer labs) eluted with THF. Detection was done by refractive index and molecular weights were calculated using Polystyrene (PS) standards (M_w from 580 to 950,000) and the universal calibration method.

Scanning Electron Microscopy (SEM)

The morphology of samples was characterized by scanning electron microscopy (SEM) using a Hitachi 510 electron microscope (Hitachi Pensi GmbH, Germany). Dried samples were cut and sputter-coated with the gold layer at 25 mA in Argon (Ar) atmosphere at 0.3 MPa for 2 min (sputter coater S150, Edward/ Klese, Germany).

L-Lactic Acid Assay

L-Lactic acid concentration in the aqueous medium was measured in Massoud clinical laboratory (Tehran, Iran) by an enzymatic method [27] using *L*-lactic acid assay kit (LACTATE, PAP) obtained from Randox (UK).

RESULTS AND DISCUSSION

In Vitro Degradation of PLGA

The time varying weight-average and number-average molecular weights (M_w and M_n , respectively) of residual polymer in in vitro degradation experiments are shown in Figure 1. The weight losses of samples as a function of hydrolysis time are shown in Figure 2. It



Figure 1. Molecular weight change as a function of hydrolysis time of PLGA Polymer.



Figure 2. weight loss as a function of hydrolysis time of PLGA polymer.

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can be seen that weight loss of samples can be fitted with a polynomial equation with acceptable accuracy, which is so useful for prediction of weight changes. Decreases in M_w were seen immediately upon immersion in PBS while significant mass loss did not begin until 4 weeks later (Figure 2). These results indicated that in the first phase, significant amount of water soluble low-molecular-weight oligomers had been formed. When these compounds, were removed from the polymer matrix, mass losses began. In this regard the critical molecular weight average of the water soluble oligomers is approximately 6400.

It is likely that high molecular weight fraction, still remains water insoluble until a critical molecular weight is reached. Because of water solubility of this polymer fraction, mass loss and polymer erosion occur only long time after polymer degradation. Within 28 days, all PLGA discs did not degrade to polymer fractions with M_w <6400, thus weight loss is zero in this period (Figure 2). Changes of molecular weight distribution (MWD) (Figure 1) support this idea. It can be seen that the polydispersity becomes large at the early stage, the MWD decreases and a narrow peak formes when the weight loss reaches to 13.51%. Multimodal weight distribution was not seen due to amorphous nature of poly(*D*,*L*-lactide-co-glycolide) 50:50 [16, 28].

This observation agrees with previous studies of PLGA degradation, and is consistent with the interpretation that PLGA is bulk-degradable [14]. Figure 1 shows that M_w and M_n of PLGA discs decrease exponentially with time, which is in agreement with firstorder Polymer hydrolysis. First-order rate constants of M_w and M_n decreases were calculated and summarized in Table 1 along with previously reported in vitro studies [19, 29, 30]. The rate constant of M_n decrease is lower than the range of in vitro values literature in, while the rate constant of M_w decrease represents higher value in literature.

Water Uptaking by Degrading PLGA Discs

Figure 3 shows the time profile of water uptake. It can

Table 1. First order degradation constants (week⁻¹).

	This study	Ref. 27	Ref. 17, 28
M_{w}	0.624±0.034	0.517±0.136	0.656±0.0735
M _n	0.355±0.011	0.514±0.090	0.586±0.062



Figure 3. Time profile of water uptake.

be seen that upon immersion in PBS, an initial period of slow water uptake lasting about 2 weeks during which water content reaches 6%. During this period, PLGA discs changed from clear to opaque, and no significant swelling was observed (change appearance of discs are shown in Figure 4).

During the time periods of week 5th and 7th, water content increased rapidly from 20% to 100%; PLGA discs swelled visibly, damaged and divided into two completely opaque halves. These observations suggest that the discs underwent significant structural changes during this period. The rate of water uptake slowed in the remainder of the experiment and terminated after 8 weeks and reached 140%.

In the second phase, during the periods of week 3rd to week 5th, the water uptake rate increased from 6% to 20%. PLGA Discs softened and became completely opaque but no visible dimensional change was observed (Figure 4).

It seems that water could penetrate into PLGA discs during days 7th to 28th and chain scission due to hydrolysis caused molecular weight loss (Figure 1). Until day 28th molecular weight of polymer was more than its critical value and water soluble oligomers were not formed. Thus, no mass loss could be detected (Figure 2). From day 28th to day 42th mass loss due to exit of water soluble oligomers caused hole formation in surface of discs and more water penetration took place (Figure 3). This phenomenon continued in thes next day and rapid water uptake and weight loss could be detected (Figures 3 and 2).





Initial

after 1 week



after 2 weeks



after 3 weeks



after 4 weeks







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after 8 weeks

2 cm

after 5 weeks

after 6 weeks

after 7 weeks

Figure 4. Appearance changes of PLGA disc during degradation.

Morphology of Degrading PLGA

Figures 5a-5d show SEM photographs of PLGA before immersion in PBS and after 1-3 weeks of PBS exposure. PLGA discs were sliced to reveal the bulk structure. The magnification was selected 70 times for scanning both the surface and bulk structure of samples.

These figures show that PLGA discs were initially rigid with rough broken surface, but after 3 weeks, they became smooth due to water penetration.

Figure 6 shows SEM photograph of PLGA samples surface after 3 weeks with 5 times of the magnification of the Figure 5d (i.e., 350 times). It could be seen the micro pores in the surface and deep holes (about 200 μ m depth and 25 μ m diameter) in outer layer of each sample.

Figures 7a and 7b show SEM photographs in weeks 4^{th} and 5^{th} , respectively. It can be seen that the top layers of disc have porous structure while inner layer (about 650µm in thickness) is smooth and non-porous. Porous layers propagate during hydrolysis, after 5 weeks (Figure 7b) no significant differences were seen between bulk and surface. At this time, sample is completely soft and due to soft structure of samples, we could not analyze them by SEM.

These observations are not similar to those of Chiu

et al. [15]. According to them, PLGA was initially smooth and non-porous which became porous after 4 days and pores volume fraction as well as pores diameter increase with degradation time. They also reported that no differences were seen between surface and bulk morphologies at any of the examined times. Our observation showed that water penetration in the first two weeks is enough to change rough structure to smooth, but for more water uptaking, pores should be induced in samples and after 3 weeks outer layers became porous. In week 4th this process continued, but after 5 weeks when mass loss was observed, degradation products exited form the samples. It caused increment in pores diameter and depth.

After 6 weeks, very significant structural changes happened and discs divided into two halves, with very porous and fragile structure. It can be seen that 90% of mass loss occurs in 56 days and 10% of samples mass remained undegradable. We hardly could take a SEM photograph of these samples after 7 weeks. Figures 8 a and 8b shows SEM of one half of PLGA disc after 7 weeks with magnification of 35 and 70, respectively. It can be seen that pore size in the center side is smaller than the surface side due to degradation propagation from the surfaces. It seems some rigid and crystalline

1, **(5**7)



Figure 5. Morphology changes of PLGA discs in the first 3 weeks of degradation (magnification = 70): (a) before degradation (b) after 1 week, (c) after 2 weeks and (d) after 3 weeks.

mer. M. Vert et al. reported the same phenomena [30].

structure formed during the degradation of PLGA poly-



Figure 6. Morphology changes of the surface and outer layers in week 3^{rd} (magnitication = 350).

Schematic representation of the morphological changes of PLGA polymers during degradation is given in Figure 9 [31]. The triangle can be divided into two types of zones: C Zones are composed of intrinsically crystalline polymers and A zones of intrinsically amorphous polymers. In the case of amorphous polymers, three sub-zones can be distinguished: Al, A2, and A3. For A1 polymers, degradation leads to hollow structures that remain amorphous due to the high irregularity of polymer chain structure. For A2 polymers, degradation also leads to hollow structures that is partially crystallized, the crystalline structure depending on the initial composition. For A3 polymers no hollow structure can be obtained, both the surface and interior were crystallized. It is likely that in this study, morphology of PLGA discs would be in zone A2 (point 1) and change during the degradation, but the LA/GA ratio



(a)



Figure 7. Morphology changes of PLGA disc during the degradation (magnification = 70): (a) after 4 weeks; and (b) after 5 weeks.

increased with degradation of PLGA copolymers after

6 weeks and morphology at the end of 65 days was in zone C corresponding to low molar mass crystalline zones contained *L*-lactic acid or glycolic acid (points 2 or 3). Crystallization mainly resulted from low molar mass chains whose T_g (glass transition temperature) would be lower than that of longer chains. The resulting crystallized polymers were more resistance to further degradation [1,18].

L-Lactic Acid Concentration and pH Assay During Degradation

Figures 10 and 11 show pH changes and lactic acid concentration vs. degradation time, respectively. It can be seen that pH shows no significant changes during the first week. Then it is observed a period of slow pH decrease lasting about 2 weeks during which pH reaches 7 form 7.4. In the next two weeks pH decreases rapidly from 7 to about 4.5, then decrease more slowely in the remainder of the experiment time. It confirms the release of acidic materials from polymer matrix. It seems that in the first stage, pH was decreased due to water soluble oligomer formation and in the next stage aqueous hydrolysis reaction of these oligomers produced the difference in monomers (L-lactic acid, D-lactic acid, and glycolic acid) concentration. Since degradation products are retained in the solution, this leads to pH decreasing. Increment of L-lactic acid in degradation medium after 28 days (Figure 10) supports this idea. It can be seen that in the first phase (21th day), Llactic acid concentration is approximately zero although in the next 4 weeks increased dramatically and reached about 140 mg/dL due to auto-catalyzed



Figure 8. Morphology changes of PLGA disc after 7 weeks: (a) magnification = 35; and (b) magnification = 70.





Figure 9. Schematic presentation of the morphological changes of PLGA polymer via degradation [31].

hydrolyses reaction of water soluble oligomers.

A Schematic Model for Samples Degradation

Figure 12 shows our suggested schematic model for degradation of samples. Seven steps can be seen in this model:

Step 1- Upon immersion in PBS, up to day 7th water molecules absorbed to the surface of samples due to hydrophilic nature of PLGA. Water molecules caused initiation of hydrolysis reactions on the surface and polymer chains brokedown to water insoluble smaller chain. Thus molecular weight decreased and molecular weight distribution became broader but no significant water uptake and mass loss were detected.

Step 2- In second week, water molecules penetrated



Figure 10. pH Changes during degradation of PLGA Polymer.



Figure 11. *L*-Lactic acid concentration in medium versus degradation time.

into the outer layer of sample through surface micro pores making it smooth and opaque. During this step, water causes hydrolysis reaction and more formation of water insoluble low molecular weight polymers and oligomers in outer layers. In this step, water uptake increased and molecular weight decreased.

Step 3- In third week, water penetrates into the sample and volume increasing (swelling) of implant is detected. During this step due to water penetration, pores diameter and depth increased and hydrolysis reaction caused more formation of water insoluble low molecular weight polymers and oligomer in inner layers and water soluble oligomers in outer layers. In this step, due to more formation of low molecular polymer and oligomer, molecular weight distribution became narrower.

Step 4- In week 4th, water molecules in the samples caused initiation and propagation of hydrolysis reaction between PLGA and water molecules. Therefore some water soluble oligomer exited the sample and pH of aqueous medium decreased due to (COOH) end group of these oligomers. In this step big pores formed in the sample and swelling was completely detected.

Step 5- In week 5th, mass loss due to exit of degradation products (lactic acid and glycolic acid) was detected and increased during this step. The exiting of these molecules increased the diameter and the depth of pores very dramatically and decreased the pH of aqueous medium. *L*-Lactic acid concentration increased in this step. It is likely that among the low molecular weight materials which exited the sample in this step, glycolic acid was more than lactic acid because pH decreased





(•)H₂O (•) Glycolic acid (•)

Lactic acid

(vvv) water soluble oligomers

Figure 12. A schematic model for samples degradation.

from 6.2 to 4.2. But the large change in *L*-lactic acid concentration occured in the next step. Faster degradation rate of glycolide-rich polymers reported in literature supports this idea [31].

Step 6- In week 6^{th} , water uptake and mass losses rate increased and *L*-lactic acid concentration changed dramatically. It seems that lactic acid and glycolic acid catalyzed the hydrolysis reaction and increased the rate of exiting of these molecules (degradation products) that, in turn, caused the increase in diameter and depth of pores.

Step 7- After 7 weeks, degradation from the surface to inner layers caused the disc devides into two halves, with very porous and fragile structure. The rates of water uptake and mass loss decreased. It seems that the LA/GA ratio increased and the low molar mass crystallize zones remained that were more resistance to future degradations. At the end of 56 days period about 10% of mass remained undegrade.

CONCLUSION

Our results showed that the degradation of PLGA copolymer proceeds in seven stages:

- Hydrolysis reaction on the surface due to absorbed water molecules to the surface of sample

- Hydrolysis reaction in outer layers due to water penetration

- Formation of water soluble oligomers in outer layers

- Exiting water soluble oligomers of the sample

- Hydrolysis reaction in the bulk of the sample and exiting of the degradation product (lactic acid and glycolic acid)

- Catalyzed hydrolysis reaction due to formation of lactic and glycolic acids

- Disc divided into two halves with very porous and fragile structure and with higher LG/GA ratio, that is crystallized and more resistance to degradation.

At the end of the 56 days period about 10% of mass remained undegradable.

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REFERENCES

- Vert M., Li S., Garreau H., More about the degradation of LA/GA- derived matrices in aqueous media, *J. Con. Rel.*, 16, 15-26 (1991).
- Zhang Y., Zale S., Sawyer L., Bernstein H., Effect of metal salts on poly(*D*,*L*-lactide-*co*-glycolide)polymer hydrolysis, *J. Biomed. Mat. Res.*, 34, 531-538 (1997).
- Heino A., Naukkarinen A., Kulju T., Törmälä P., Pohjonen T., Mäkelä E.A., Characteristics of poly(*L*-)lactic acid suture applied to fascial closure in rats, *J. Biomed. Mat. Res.*, **30**, 187-192 (1996).
- Otto T.E., Nulend J.K., Patka P., Burger E.H., Haarman H.J.Th.M., Effect of (poly)-*L*-lactic acid on the proliferation and differentiation of primary bone cells in vitro, *J. Biomed. Mat. Res.*, **32**, 513-518 (1996).
- Bessho K., Carnes D.L., Cavin R., Ong J.L., Experimental studies on bone induction using low molecular weight poly(*D*,*L*-lactide-*co*-glycolide) as a carrier for recombinant human bone morphogenetic protein-2, *J. Biomed. Mat. Res.*, **61**, 61-65 (2002).
- Goldstein A.S., Joarez T.M., Helmke C.D., Gostin M.C., Antonios G., Effect of convection on osteoblastic cell growth and function in biodegradable polymer foam scaffolds, *Biomaterials*, 22, 1279-1288 (2001).
- Sherwood J.K., Reily S.L., Palazzole R., Brown S.C., Monkhoose D.C., Coates M., Eriffith L.G., Landeen L.K., Ratcliffe A., A three-dimensional osteochondral composite Scaffold for particular Cartilage repair, *Biomaterials*, 23, 339-4751 (2002).
- Widmer M.S., Gupta F., Li L., Meszenyi R.K., Evans G.R.D., Brandt K., Savel T., Gorlek A., Patrick C.W., Manufacture of porous biodegradable polymer conduits by an extrusion process for guided tissue regeneration, *Biomaterials*, **19**, 1945-1955 (1998).
- Thomson R.C., Mikos A.G., Beahm E., Lemon J.C., Satterfield W.C., Aufdemort T.B., Miller M.J., Guided tissue fabrication from Eriostemon using preformed biodegradable polymer scaffolds, *Biomaterials*, 20, 2007-2018 (1999).
- Mayer J., Karamuk E., Akaike T., Winter-Mantel E., Matrices for tissue engineering Scaffold structure for a bioartificial liver support system, *J. Cont. Rel.*, **64**, 81-90 (2000),
- Elazer E.R., Arona N., Katada M., Gates J., Karnovsky M.J., Perivasculor graft heparin delivery using biodegradable polymer warps, *Biomaterials*, 21, 2279-2286

(2000).

- 12. Wanga F., Leeb T., Wong C.H., PEG modulated release of etaindazole from implantable PLGA/PDLA, *Biomaterials*, **23**, 3555-3566 (2002).
- Cao X., Shoicheta M.S., Delivering nauru-active molecules from biodegradable micro spheres for application in central nervous system: Disorders, *Biomaterials*, 20, 329-339 (1999).
- Panyam J., Labhasetwor V., Biodegradable nano-particles for drug and gene delivery to cells and tissue, *Adv. Drug Del. Rev.*, 55, 329-347 (2003).
- Chiu L.K., Chiu W.J., Cheng Y.L., Effect of Polymer degradation on drug release a mechanistic study of morphology and transport properties in 50:50 poly(*dl*-lactide*co*-glycolide), *Int. J. Pharma.*, **125**, 169-178 (1995).
- Hakkarainen M., Albetsson A.C., Karlsson S., Weight losses and molecular weight changes correlated with the evolution of hydroxy-acids in simulated in vivo degradation of homo- and copolymers of PLA and PGA, *Polym. Deg. Stab.*, **52**, 283-291 (1996).
- Wise D.L., Trantolo D.J., Altbelli D.E., Yaszemski M.J., Gresser J.D., Schwartz E.R., (Eds.), *Encyclopedic Handbook of Biomaterials and Bioengineering*, Marcel Dekker, 2, 1047 (1995).
- Mathinwitz E., (Ed.), Encyclopedia of Controlled Drug Delivery, Biodegradable Polymers, John Wiley, New York, 71 (1999).
- Reed A.M., Gilding D.K., Biodegradable polymers for use in surgery-poly(glycolic)/poly(lactic acid) homo and copolymers: 2- In Vitro degradation, *Polymer*, 22, 494-498 (1981).
- Li S., Gorreau H., Vert M., Structure-property relationships in the case of the degradation of massive poly(α-hydroxy acids) in aqueous media. Part 2: Degradation of lactide-glycolide copolymers. PLA37.5GA25 and PLA75GA25, *J. Mater. Sci. Mater. Med.*, **1**, 131-139 (1990).
- Park T.G., Degradation of poly(*D*,*L*-lactic acid) microsphere: Effect of molecular weight, *J. Con. Rel.*, **30**, 161-173 (1994).
- Meikel M.C., Mark W.Y., Papaioannou S., Davies E.M., Bone-derived growth factor release from poly(α-hydroxy acid) implants in vitro, *Biomaterials*, 14, 177-183 (1993).
- 23. Michaeli W., Pfannschmidt O., Microporous, resorbable implants produced by the CESP process, *Adv. Eng. Mat.*, 1, 206-208 (1999).
- 24. Tsuji M., Ikada Y., Properties and morphology of poly(L-

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lacide) 4. Effect of structural parameters on long term hydrolysis of poly(L-lactide) in phosphate buffer solution, *Polym. Deg. Stab.*, **67**, 179-189 (2000).

- 25. Cam D., Hyon S.H., Ikada Y., Degradation of high molecular weight poly(*L*-lactide) in alkaline medium, *Biomaterials*, **16**, 833-843 (1995).
- 26. USP (The United States Pharmacopeias), Webcom Ltd, Ontario, **2**, 2340 (2002).
- 27. Shimojo N., Fujino K., Lactate analyzer with continuous blood sampling for monitoring blood lactate during physical exercise, *Clin. Chem.*, **37**, 1978-1980 (1991).
- Wang S., Luo A., Beiand J., Cai Q., Biodegradation behaviour of poly(lactide-*co*-glycolide) induced by microorganism, *Polym. Deg. Stab.*, **71**, 243-251 (2001).
- 29. Kenley R.A., Lee M.D., Mahoney T.K., Sanders L.M., Poly(glycolide-*co*-lactide) decomposition kinetics in vivo and in vitro, *Macromolecules*, **20**, 2398-2403 (1987).
- Li S., Vert M., Girod-Holland S., Hydrolytic degradation of poly(*D*,*L*-lactic acid) in the presence of caffeine base, *J. Cont. Rel.*, 40, 41-53 (1996).
- Li S., Hydrolitic degradation characteristics of aliphatic polyesters derived from lactic and glycolic acid, J. Biomed. Mater. Res. Appl. Biomater., 48, 342-355 (1999).

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