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***In vitro* and *in vivo* degradation of poly(_{D,L}-lactide-co-glycolide)/amorphous calcium phosphate copolymer coated on metal stents**

Xiaodong Ma^{1,2,*}, Shizu Oyamada^{3,*}, Tim Wu^{1,2}, Michael P. Robich³, Hao Wu², Xingwei Wang¹, Bryan Buchholz¹, Stephen McCarthy¹, Cesario F. Bianchi³, Frank W. Sellke³, and Roger Laham⁴

¹Biomedical Engineering and Biotechnology Doctoral Program, University of Massachusetts, Lowell, Massachusetts 01854

²VasoTech, Inc., Lowell, Massachusetts 01854

³Division of Cardiothoracic Surgery, Brown University, Providence, Rhodes Island 02903

⁴Department of Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215

Abstract

The purpose of this study was to optimize a novel biodegradable polymer for drug eluting stent (DES) applications. Degradation profiles of different poly(_{D,L}-lactide-co-glycolide)/amorphous calcium phosphate (PLGA/ACP) composites coated on stents were studied both *in vitro* and *in vivo* for three months. For the *in vitro* study, stents were immersed into the phosphate buffered saline (37°C, pH 7.4) with constant shaking. The polymer weight loss was measured weekly and morphological changes were analyzed. The results demonstrated that approximately 60% of polymer was degraded within the three-month period and there was no significant difference between the different PLGA/ACP composites. However, the composite of 50% PLGA (65/35) with 50% ACP showed a slightly faster degradation rate than other composites. Morphologically, all stent surfaces changed from a micro-porous before degradation to a corrugated solid micro-net-like structure at two months post degradation. Based on *in vitro* results, 65% PLGA (65/35) with 35% ACP coated stents were selected and implanted into rat aortas ($n = 12$) for the *in vivo* study. Microscopic observation showed that no composite was found on any of the implanted stents at 12 weeks post implantation, which indicated the selected PLGA/ACP composite is desired for DES applications.

Keywords

poly(_{D,L}-lactide-co-glycolide); amorphous calcium phosphate; degradation; stent

INTRODUCTION

In-stent restenosis (ISR)¹⁻³ and thrombosis (subacute and late-stage)⁴⁻⁷ are the two major problems that exist in current coronary artery stent (CAS) technology. ISR can often be significantly reduced by revascularization with drug eluting stents (DES),⁸⁻¹⁰ and subacute

thrombosis can be effectively controlled with the use of dual antiplatelet therapy. However, sudden death associated with late-stage stent thrombosis (more than one year after placement), though a rare event, has become a great concern recently in clinical stenting. Although the precise mechanism of late stage stent thrombosis is unknown, it is generally believed that the combination of delayed endothelialization due to the anti-proliferative therapy and persistence of the nonerodable polymer contribute to the hypersensitivity reaction, possibly as a result of residual active drug that may not be eluted.^{11,12} Therefore, stents made or coated with biodegradable polymers are believed to be the future for the next generation of DES development.

Poly(lactides (PLA), polyglycolides (PGA) and their copolymer PLGA^{13,14} are the most well-known biodegradable synthetic polymers used widely in the medical field.¹⁵⁻¹⁹ PLGA is attractive for having lactic acid and glycolic acid as their degradation products, respectively. These natural metabolites are ultimately converted to water and carbon dioxide through the action of enzymes in the tricarboxylic acid cycle and are excreted via the respiratory system.^{20,21} Although PLGA has been used for coating drug-eluting stents (Biomatrix[®] stent, Biosensors International Group, Ltd, Singapore, www.biosensors.com), the major issue existing for the product is the arterial inflammatory response to the acidic products released during the PLGA degradation process.²²

Calcium phosphates (CaP), a family of inorganic biodegradable polymers, have been widely applied to the biological and medical fields.^{23,24} Of the family members, amorphous calcium phosphate (ACP) has become increasingly significant due to its high solubility and better remineralization compared to other CaP's.^{24,25} In addition, the ions released from ACP are thought to play roles in neutralizing the acidity resulting from polymer biodegradation, retarding the bioresorptive rate and eliminating inflammation occurrence.²⁶

We hypothesize that incorporating ACP into the PLGA polymer could neutralize the degraded acidic byproduct, prevent arterial inflammation resulting from those byproducts and therefore improve the PLGA/ACP copolymer's biocompatibility. Using a PLGA/ACP composite as the drug eluting polymer for the drug eluting stent has not been previously reported. The purpose of this study is to evaluate the PLGA/ACP copolymer's degradation behaviors when coated on metal stent surfaces in both *in vitro* and *in vivo* studies.

MATERIALS AND METHODS

Materials

Poly(D,L-lactide-co-glycolide) (PLGA, D, L lactide:glycolide, 100:0, 75:25, 65:35, and 50:50) and amorphous calcium phosphate nanoparticles (ACP, <150nm) were obtained from Sigma-Aldrich (St. Louis, MO). Tetrahydrofuran (THF) was bought from Fisher Scientific (Fair Lawn, NJ) as the solvent. The degradation medium was Dulbecco's phosphate buffered saline (DPBS, pH 7.4, Solon, OH). All metal stents (13 mm in length, made from 316L stainless steel) and stent delivery catheters used in the *in vivo* study were provided by VasoTech, Inc (Lowell, MA). Sprague-Dawley (SD) rats weighing from 400–500 g were purchased from Charles River Laboratory (Wilmington, MA).

Preparation of PLGA/ACP solution and stent coating

Different PLGA and ACP compositions were prepared according to the experimental design as shown in Table I. During the study, PLGA and ACP were dissolved/dispersed in THF solvent separately under constant sonicating (Branson 5210R-MT Ultrasonic Cleaner, Branson Ultrasonics Corporation, Danbury, CT) for one hour and then placed at room temperature overnight for full dissolving/dispersion. The final PLGA/ACP solution (1.5 mg/

mL) was made by vortex-mixing the dissolved PLGA and ACP for 1 min and then sonicating the solution constantly for 1 h.

Thirty-six metal stents (13mm, Vasotech, Inc.), divided randomly into nine groups were coated with different composites according to the experimental design shown in Table I. Before coating, all stents were ultrasonically cleaned for half an hour and then weighed by an Ultra Microbalance (Model: Cahn C-35, Thermo Fisher Scientific Inc., Waltham, MA). The prepared PLGA/ACP solutions were then spray-coated on the stent surface using a MediCoat DES 1000 Stent Coating System (Sono-Tek Corp., Milton, NY) under a class 100 laminar flow hood. After overnight curing at room temperature, all coated stents were weighed again and examined under a field emission scanning electron microscope (FE-SEM, JEOL JSM-7401F, JEOL USA Inc., Peabody, MA). The final coating on each stent was $260 \mu\text{g} \pm 10\%$ polymer with coating thickness of $30 \pm 10 \mu\text{m}$.

***In vitro* degradation**

All PLGA/ACP coated stents were individually placed into an Eppendorf tube with 1 mL DPBS solution (pH 7.4), and shaken constantly at 30 rpm in a 37°C water bath (Precision Scientific Inc., Chicago, IL). All tubes were tightly sealed during the study and the DPBS solution in the tube was replaced daily to keep the degradation medium fresh. At the end of each week, the shaking was stopped and stents were weighed after drying for 24 h in a vacuum oven at room temperature. The weight loss on each stent was calculated as following:

$$\text{Weight loss (\%)} = (W_0 - W_d) / W_0 \times 100\%$$

Where W_0 is the initial weight of a stent after coating, W_d is the weight of the stent at each time-point post degradation. The mean weight loss for the three stents in each group was reported.

Surface morphology observations

At specified points in time, all stent surfaces were examined under the JEOL JSM-7401F field emission scanning electron microscope (FE-SEM, JEOL USA Inc., Peabody, MA) after weighing. The morphological changes of each stent at different time points were compared with those predegradation.

***In vivo* degradation**

PLGA (65/35)/ACP copolymer at the ratio of 65:35 was selected for the further *in vivo* study. In this experiment, 12 polymer-coated stents were prepared as previously described in the *in vitro* study. The stents were premounted on VasoTech® miniature catheters (1.5 mm × 15 mm) and sterilized with Ethylene Oxide (ETO) for 60 min before implantation. All procedures involving animal use conformed with the “Guide for the Care and Use of Laboratory Animals” published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996), and the animal study protocol was approved by Institutional Animal Care Committee at the Beth Israel Deaconess Medical Center, Harvard Medical School.

Twelve Sprague-Dawley (SD) rats weighing from 400 to 500 g were used in the study. Animals were fasted and treated with Aspirin 10 mg/kg orally commencing 12 h before the surgery and were maintained on aspirin through the studying period. After animals were fully anesthetized with constant inhalation of oxygen/isoflurane mixture (1.5:2 pressure/pressure), the left iliac arteries were exposed. Stents were inserted carefully into the

abdominal aortas 10 mm above the bifurcation through left iliac arterial incision, and were placed by inflating the balloon catheter to 10ATM pressure. At the predetermined time points of 1, 3, 6, and 12 weeks post implantation, the stented arteries ($n = 3/\text{group}$) were carefully harvested after rats were saline-perfused under anesthesia. After maximal removal of tissue surrounding the stent using a fine dissection forceps under a stereomicroscope (American Scope Inc., CA), the stents were then air-dried overnight and examined morphologically under a light microscope (Olympus America Inc., PA). The extent of polymer degradation was evaluated observationally using the following scoring system: 1, approximately 0-25% polymer was degraded; 2, 25-50% polymer was degraded, 3, 50-75% polymer was degraded, and 4, 75-100% polymer was degraded.

RESULTS

In vitro weight loss

As indicated in Figure 1, all experimental groups in the study have similar nonlinear degradation patterns. There were no significant differences in the degradation rates between different groups at different time points, although the group of 50% PLGA (65/35) with 50% ACP appeared to have a relative faster degradation rate. With a 50/50 ratio of PLGA/ACP, lactide/glycolide ratios of 65/35 and 75/25 appeared to have higher degradation rates than the other two PLGA ratios (100/0 and 50/50).

In vitro morphological changes

SEM examination demonstrated that the PLGA only coated stent has a rough corrugated surface (Fig. 2). With ACP in the formulation, the coated surface formed gradually into the micro-porous structure depending on the concentration of ACP in the formulation. As shown in Figure 2(d1), the stent surface coated with the group of PLGA/ACP at the ratio of 50/50 has the most uniform micro-porous structure. After two weeks of degradation, all polymer coated stent surfaces became polished and then changed to a solid net-like structure at two months. Fig. 3 is the SEM image on morphological change of 50/50 PLGA/ACP composites with different lactide/glycolide ratios before and one month after degradation, where the composites with 75/25 and 65/35 lactide/glycolide ratios appeared to be degraded more than the ones with both 100/0 and 50/50 PLGA, which will be discussed later.

In vivo degradation and morphology

The polymer *in vivo* degradation rate was estimated using a categorical scoring system: 1 = 0-25%, 2 = 25-50%, 3 = 50-75%, and 4 = 75-100% polymer degraded. As depicted in Figure 4, less than 25% of the total coated polymer was lost at the first week post stent implantation. At three weeks, ~40% of the coated polymer was degraded. By six weeks, ~80% of the polymer was degraded. At 12 weeks, there was essentially no polymer left on all implanted stents. There were no significant morphological changes of the stent surface at different time points besides the polymer losses. Figure 5 demonstrates the microscopic degradation of PLGA/ACP copolymer-coated stents at different time points post implantation. As shown in the images, before the implantation, the stent surface was formed in the microporous structure [Fig. 5(a)]. At one week post implantation, the stent was still covered mostly by polymer, however, the surface became a little smoother than pre-implantation [Fig. 5(b)]. At three weeks, additional polymer was degraded and some metal spots can be seen [Fig. 5(c)]. At six weeks, most of the polymer was degraded and only a few polymeric spots can be identified [Fig. 5(d)]. At 12 weeks, almost no polymer remains [Fig. 5(e)].

DISCUSSION

In vitro degradation

The *in vitro* degradation profile of PLGA has been investigated extensively.²⁷⁻³⁰ The *in vitro* degradation of the PLGA/ACP copolymer, which is believed to be much more complex than that of PLGA only, has been previously reported for bone tissue engineering,^{31,32} but to our knowledge, this study is the first attempt to use the PLGA/ACP copolymer in coated stents for cardiovascular purposes.

Our data show that the PLGA/ACP copolymer-coated stent surface has nonlinear *in vitro* degradation kinetics. Several reasons may contribute to this nonlinear phenomena: (1) As the pore surface of PLGA was filled with ACP, water penetration into the polymer may be retarded and the release of PLGA degradation products may be delayed;³³ (2) The ACP may have been coated with the polymer, thus the degradation of the polymer resulted in a mass of ACP nanoparticles dropped into degradation media leading to further weight loss. However, according to the literature,³² ACP was completely transformed to apatite after 1-h soaking in PBS at pH 7.4 and calcium ion concentration was unchanged after 3-h soaking in PBS at pH 7.4. The nanoparticles of apatite crystallites were easily readsorbed by the polymer surface, which could explain the weight increase. To confirm the hypothesis, we washed the stents at two months during the degradation by sonication in deionized water and found that there were significant decreases of the stent body weight (Fig. 1) indicating that the degraded products may accumulate on the polymer surface. The Ca and PO₄ ions released from ACP were considered to have the roles of neutralizing the acidity from the polymer degradation, which would slow the rate of the hydrolysis process by decreasing autocatalysed reactions. In addition, the acidic environment affected the solubility of the apatite. With the increasing degradation time, the percentage crystallinity of the lactide was increased due to the accelerated hydrolysis process and degraded amorphous regions,³⁴ which would be another reason for the weight loss. The different ratio of lactide/glycolide in PLGA affects the degradation rate absolutely. It is generally believed that the lower ratio of lactide/glycolide the PLGA has, the faster the PLGA is degraded, but 65/35 and 75/25 PLGA had faster degradation rates than both 100/0 and 50/50 PLGA when they were blended with the same amount of ACP [Figs. 1(b) and 3]. The reason is unknown. It maybe caused by the dynamic equilibrium reaction between ACP and acidic products of PLGA.

In vivo degradation

The results from the *in vitro* degradation study showed clearly that the 50% PLGA (65/35) with 50% ACP and the 75% PLGA (65/35) with 25% ACP have better microporous structures compared with the other two groups at all degradation time points. However, the higher ratio of ACP in the composite will reduce the viscosity of PLGA/ACP which is prone to cracking and peeling and the higher lactide ratio in PLGA copolymer results in the longer degradation time. Therefore, the ideal ratio of PLGA/ACP in the final product should be the one having a balance between degradation, neutralization and viscosity. For this reason, an intermediate composite between the 50% PLGA (65/35) with 50% ACP and the 75% PLGA (65/35) with 25% ACP, the 65% PLGA (65/35) with 35% ACP, was selected for the *in vivo* degradation investigation.

The PLGA/ACP degraded dramatically faster *in vivo* than it did *in vitro*. Our results corresponded well with a previous report which described that the mechanism for *in vivo* degradation is different from that for *in vitro* degradation.³⁵ Many studies have attempted to find the explanation for the difference, for example, lipids or other biological compounds that act as plasticizers *in vivo* facilitating the uptake of water into the polymer,³⁶ and the foreign body response (free radicals, acidic products, enzymes, local temperature, or pH

changes) may also contribute to the faster degradation *in vivo*.³⁷⁻³⁹ Degradation time is the core factor in engineering a biodegradable polymer for drug eluting purposes. The function of the polymer on the stents is just for drug delivery; therefore, the ideal polymer should “do their job, and then disappear.”⁴⁰ The current commercially available drug-eluting stents have drug eluting profiles of approximately one month. For example, 79.5% of total loading everolimus in Xience V[®] is released at 28 days; 95% of total loading zotarolimus in Endeavor[®] is released at 14 days.⁴¹⁻⁴³ Thus, a biodegradable polymer with degradation profile of between one and three months is clinically meaningful. The composite of 65% PLGA (65/35) with 35% ACP has an *in vivo* degradation profile falling into this window and is a potential polymer for drug-eluting stent applications.

CONCLUSION

Degradation behaviors of different PLGA/ACP composites were compared initially *in vitro* and then a selected PLGA/ACP composition was further investigated in *in vivo*. All studied PLGA/ACP compositions had a nonlinear *in vitro* degradation profile. The results of the *in vitro* and the *in vivo* studies suggested that PLGA/ACP compositions with the ratios ranging from 50:50 to 75:25 have a desired degradation profile for drug eluting applications. The ultimate selection for the composition in drug eluting stent applications should be balanced among the polymer's degradation time, acidic neutralization capacity and coating viscosity.

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References

1. Schofer J, Schlüter M, Gershlick AH, Wijns W, García E, Schampaert E, Breithardt G. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: Double-blind, randomised controlled trial (E-SIRIUS). *Lancet*. 2003; 362:1093–1099. [PubMed: 14550694]
2. Muramatsu T, Tsukahara R, Ho M, Ito Y, Ishimori H, Hirano K, Nakano M, Matsushita M, Leung W. Clinical outcome of stent implantation in small coronary arteries using different type of coronary stents. *J Invasive Cardiol*. 2001; 13:634–639. [PubMed: 11533501]
3. Iijima R, Ikari Y, Miyazawa A, Nakajima H, Hara K. Predictors of restenosis after implantation of 2.5 mm stents in small coronary arteries. *Circ J*. 2004; 68:236–240. [PubMed: 14993779]
4. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airolidi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005; 293:2126–2130. [PubMed: 15870416]
5. Ong ATL, McFadden EP, Regar E, De Jaegere PPT, Van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol*. 2005; 45:2088–2092. [PubMed: 15963413]
6. Ong ATL, Hoye A, Aoki J, Van Mieghem CAG, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, Van Der Giessen WJ, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol*. 2005; 45:947–953. [PubMed: 15766834]
7. McFadden EP, Stabile E, Regar E, Cheneau E, Ong ATL, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004; 364:1519–1521. [PubMed: 15500897]
8. Tanabe K, Regar E, Regar E, Lee CH, Smits PC, van-der-Giessen WJ. Sirolimus-eluting stent for treatment of in-stentrestenosis: One-year angiographic and intravascular ultrasound follow-up. *J Am Coll Cardiol Suppl A*. 2003; 41:12A.

9. Grube E, Silber S. Six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation*. 2003; 107:38–42. [PubMed: 12515740]
10. Eisenberg MJ, Babapulle MN. Coated stents for the prevention of restenosis. I. *Circulation*. 2002; 106:2734–2740. [PubMed: 12438301]
11. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tsepili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent should we be cautious? *Circulation*. 2004; 109:701–705. [PubMed: 14744976]
12. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skoriya K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006; 48:193–202. [PubMed: 16814667]
13. Gunatillake PA, Adhikari R. Biodegradable synthetic polymers for tissue engineering. *Eur Cells Mater*. 2003; 5:1–16.
14. Hollinger JO. Preliminary report on the osteogenic potential of a biodegradable copolymer of polylactide (PLA) and polyglycolide (PGA). *J Biomed Mater Res*. 1983; 17:71–82. [PubMed: 6298242]
15. Heller J. Chemically self-regulated drug delivery systems. *J Control Release*. 1988; 8:111–125.
16. Daniels AU, Chang MKO, Andriano KP, Heller J. Mechanical properties of biodegradable polymers and composites proposed for internal fixation of bone. *J Appl Biomater*. 1990; 1:57–78. [PubMed: 10148987]
17. Langer R, Vacanti JP. Tissue engineering. *Science*. 1993; 260:920–926. [PubMed: 8493529]
18. Fraser RK, Cole WG. Osteolysis after biodegradable pin fixation of fractures in children. *J Bone Joint Surg Br*. 1992; 74:929–930. [PubMed: 1332975]
19. Middleton JC, Tipton AJ. Synthetic biodegradable polymers as orthopedic devices. *Biomaterials*. 2000; 21:2335–2346. [PubMed: 11055281]
20. Iwasaki Y, Sawada S-I, Ishihara K, Khang G, Lee HB. Reduction of surface-induced inflammatory reaction on PLGA/MPC polymer blend. *Biomaterials*. 2002; 23:3897–3903. [PubMed: 12164195]
21. Loo SCJ, Ooi CP, Boey YCF. Radiation effects on poly(lactide-co-glycolide) (PLGA) and poly(lactide) (PLLA). *Polym Degrad Stab*. 2004; 83:259–265.
22. van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HMM, Serruys PW, Holmes DR, Ellis SG, Topol EJ. Marked inflammatory sequelae to implantation of biodegradable and non-biodegradable polymers in porcine coronary arteries. *Circulation*. 1996; 94:1690–1697. [PubMed: 8840862]
23. Amjad, Z. *Calcium Phosphates in Biological and Industrial Systems*. Boston: Kluwer Academic Publishers; 1998.
24. Skrtic D, Antonucci JM, Eanes ED. Amorphous calcium phosphate-based bioactive polymeric composites for mineralized tissue regeneration. *J Res Natl Inst Stand Technol*. 2003; 108:167–182.
25. Park M, Eanes E, Antonucci J, Skrtic D. Mechanical properties of bioactive amorphous calcium phosphate/methacrylate composites. *Dent Mater*. 1998; 14:137–141. [PubMed: 10023203]
26. Stamboulis A, Hench LL, Boccaccini AR. Mechanical properties of biodegradable polymer sutures coated with bioactive glass. *J Mater Sci Mater Med*. 2002; 13:843–848. [PubMed: 15348548]
27. Catiker E, Guemesderelioglu M, Guener A. Degradation of PLA. PLGA homo- and copolymers in the presence of serum albumin: A spectroscopic investigation. *Polym Int*. 2000; 49:728–734.
28. Park TG. Degradation of poly(lactic-co-glycolic acid) microspheres: Effect of copolymer composition. *Biomaterials*. 1995; 16:1123–1130. [PubMed: 8562787]
29. Yuan X, Mak AFT, Yao K. In vitro degradation of poly(L-lactic acid) fibers in phosphate buffered saline. *J Appl Polym Sci*. 2001; 85:936–943.
30. Zhu JH, Shen ZR, Wu LT, Yang SL. In vitro degradation of poly-lactide and poly(lactide-co-glycolide) microspheres. *J Appl Polym Sci*. 1991; 43:2099–2106.
31. Navarro M, Ginebra MP, Planell JA, Barrias CC, Barbosa MA. In vitro degradation behavior of a novel bioresorbable composite material based on PLA and a soluble CaP glass. *Acta Biomater*. 2005; 1:411–419. [PubMed: 16701822]

32. Gao Y, Weng W, Cheng K, Du P, Shen G, Han G, Guan B, Yan W. Preparation, characterization and cytocompatibility of porous ACP/PLLA composites. *J Biomed Mater Res A*. 2006; 79:193–200. [PubMed: 16826600]
33. Furukawa T, Matsusue Y, Yasunaga T, Shikunami Y, Okuno M, Nakamura T. Biodegradation behavior of ultra-high-strength hydroxyapatite/poly (-lactide) composite rods for internal fixation of bone fractures. *Biomaterials*. 2000; 21:889–898. [PubMed: 10735465]
34. Burg KJL, Shalaby SW. Physicochemical changes in degrading polylactide films. *J Biomater Sci Polym Ed*. 1997; 9:15–29. [PubMed: 9505200]
35. Tracy MA, Ward KL, Firouzabadian L, Wang Y, Dong N, Qian R, Zhang Y. Factors affecting the degradation rate of poly(lactide-co-glycolide) microspheres in vivo and in vitro. *Biomaterials*. 1999; 20:1057–1062. [PubMed: 10378806]
36. Menei P, Daniel V, Montero-Menei C, Brouillard M, Pouplard-Barthelaix A, Benoit JP. Biodegradation and brain tissue reaction to poly [D L-lactide-co-glycolide] microspheres. *Biomaterials*. 1993; 14:470–478. [PubMed: 8507795]
37. Ali SA, Doherty PJ, Williams DF. Molecular biointeractions of biomedical polymers with extracellular exudate and inflammatory cells and their effects on the biocompatibility, in vivo. *Biomaterials*. 1994; 15:779–785. [PubMed: 7986942]
38. Williams DF, Mort E. Enzyme-accelerated hydrolysis of polyglycolic acid. *J Bioeng*. 1977; 1:231–238. [PubMed: 210160]
39. Tokiwa Y, Suzuki T. Hydrolysis of polyesters by lipases. *Nature*. 1977; 270:76–78. [PubMed: 927523]
40. Waksman R. Biodegradable stents: They do their job and disappear. *J Invasive Cardiol*. 2006; 18:70–74. [PubMed: 16446520]
41. Nakazawa G, Finn AV, Kolodgie FD, Virmani R. A review of current devices and a look at new technology: Drug-eluting stents. *Expert Rev Med Devices*. 2009; 6:33–42. [PubMed: 19105778]
42. Serruys PW, Ruygrok P, Neuzner J, Piek JJ, Seth A, Schofer JJ, Richardt G, Wiemer M, Carrie D, Thuesen L. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: The SPIRIT II trial. *EuroIntervention*. 2006; 2:286–294. [PubMed: 19755303]
43. Kandzari DE, Leon MB. Overview of pharmacology and clinical trials program with the zotarolimus-eluting endeavor stent. *J Interv Cardiol*. 2006; 19:405–413. [PubMed: 17020565]

FIGURE 1.

In vitro PLGA/ACP degradation kinetics curves: (a) 65/35 PLGA with different proportions ACP; (b) 50% PLGA 50% ACP with different proportions of lactide and glycolide in the PLGA. Note that the final significant weight loss was caused by the sonication. [Color figure can be viewed in the online issue, which is available at <http://www.wileyonlinelibrary.com>.]

FIGURE 2.

SEM micrographs of different PLGA/ACP copolymer-coated stents (a1-a3: PLGA/ACP = 100/0; b1-b3: PLGA/ACP = 85/15; c1-c3: PLGA/ACP = 75/25; d1-d3: PLGA/ACP = 50/50) at different degradation time courses *in vitro* (a1, b1, c1, d1 = before, a2, b2, c2, d2 = two weeks, and a3, b3, c3, d3 = eight weeks). Note that PLGA/ACP ratio of 50/50 (d1) has the most uniformly formed microporous structure among all the groups. All copolymer coated stent surfaces were changed from microporous at the beginning (d1) to a solid net-like structure after two months of degradation (d3) (Scale bar = 10 μ m).

FIGURE 3.

SEM micrographs of stent surfaces coated with different lactide/glycolide ratios (a1-a2: lactide/glycolide = 100/0; b1-b2: lactide/glycolide = 75/25; c1-c2: lactide/glycolide = 65/35; d1-d2: lactide/glycolide = 50/50) in 50/50 PLGA/ACP copolymer at before (a1, b1, c1, d1) and one month after degradation (a2, b2, c2, d2) (Scale bar = 10 μ m).

FIGURE 4.
The *in vivo* degradation profile of PLGA/ACP copolymer (65/35) in the rat aorta stenting model.

FIGURE 5.

Light microscopy images of stents coated with (65/35) PLGA/ACP copolymer (65/35) at baseline (0 week, a1, a2), and 1 week (b1, b2), 3 weeks (c1, c2), 6 weeks (d1, d2), and 12 weeks (e1, e2) postimplantation in rat aorta arteries. (Scale bar = 500 μ m). Note that there were only a few polymeric spots can be found at six weeks post implantation (d1, d2). At 12 weeks, all polymers were degraded (e1, e2). [Color figure can be viewed in the online issue, which is available at <http://www.wileyonlinelibrary.com>.]

TABLE I
PLGA/ACP Copolymer Compositions for *In Vitro* and *In Vivo* Degradation Studies

Group	Number	Ratio of PLGA (%mw/mw)		Ratio of PLGA/ACP (%w/w)	
		Lactide	Glycolide	PLGA	ACP
A	1	65	35	100	0
	2			85	15
	3			75	25
	4			50	50
B	5	100	0	50	50
	6	75	25		
	7	65	35		
C	8	50	50		
	9	65	35	65	35

Groups A and B were for the *in vitro* study and group C was for the *in vivo* study.