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International Journal of Pharmaceutics 304 (2005) 165–177
international journal of pharmaceutics
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Sustained release of bovine serum albumin using implantable wafers prepared by MPEG–PLGA diblock copolymers

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Received 22 June 2005; received in revised form 14 August 2005; accepted 16 August 2005
Available online 27 September 2005

Abstract

MPEG–PLGA diblock copolymers, consisting of methoxy polyethylene glycol (MPEG) and poly(L-lactic-*co*-glycolic acid) (PLGA), were synthesized by ring-opening polymerization of L-lactide and glycolide in the presence of MPEG as an initiator. Implantable wafers, using diblock copolymers as a drug carrier, were fabricated by direct compression method after freeze milling of the diblock copolymers and bovine serum albumin–fluorescein isothiocyanate (BSA–FITC) as a model protein drug. The wafers prepared with MPEG–PLGA diblock copolymers exhibited initial burst in the release of BSA. The BSA release profiles from the wafers depended on MPEG–PLGA diblock copolymer compositions. The in vitro release of the BSA also correlated with the degradation rate of the PLGA part in the diblock polymers. The wafers prepared from diblock copolymers with an increased MPEG segment showed the more structural metamorphosis of crack form due to higher water absorption of MPEG inside the wafer, and induced faster BSA release. The wafers prepared by using MPEG–PLGA diblock copolymers in the presence of small intestinal submucosa (SIS) as a drug carrier additive exhibited controlled BSA release profiles, although the wafers exhibited release patterns with a lag time at the initial stage as the MPEG segment in diblock copolymer compositions increased. Thus, we confirmed that the MPEG–PLGA diblock copolymers could be used as a protein delivery carrier in implantable wafer form.

Keywords: Implantable wafer; Drug carrier; MPEG–PLGA; Bovine serum albumin

1. Introduction

Protein drugs delivered by oral route exhibit poor oral bioavailability (Fix, 1996; Mahato et al., 2003). To improve bioavailability of drugs, much effort has

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doi:10.1016/j.ijpharm.2005.08.004

been made to control and maintain the release of drugs for a long period through other administration methods in addition to the oral route (Bernkop-Schnurch and Walker, 2001; Owens et al., 2003; Torchilin and Lukyanov, 2003). The sustained protein delivery should release the loading drug at a continuous rate for a long period. It has become important to target research in order to develop a sustained and controlled delivery system for proteins.

Various natural and synthetic polymers have been explored as drug delivery carriers (Andrianov and Payne, 1998; Kopecek, 2003; Sinha et al., 2004). Among them, the biodegradable synthetic polymers have a greater potential as a drug delivery carrier (Raghuvanshi et al., 2001; Prabhu et al., 2002; Yoo et al., 2004; Lee et al., 2004a,b; Kim et al., 2005a). Additionally, the development of alternative administration methods to effectively deliver protein drugs is an important area of research. Many systemic administration forms such as microspheres, films, wafers, tablets, and scaffolds, which employed a variety of biodegradable synthetic polymers as the drug carrier, were examined in protein delivery. Among them, implantable administration forms can be considered as a candidate to enhance the effects of a protein drug through extending the period of drug release. Furthermore, it has been considered as one of the most convenient methods to capture drugs inside administration forms. In addition, it does not need to be removed by surgery after complete release of the drug because biodegradable carriers degrade into metabolic materials in vivo. Based on this view, implantable wafers using biodegradable synthetic polymers have been widely examined as administration forms with a strong impact on medical treatment over the past several years (Bromberg et al., 2001; Seong et al., 2002; Westphal et al., 2003; Kim et al., in press).

In terms of biodegradable drug carriers, aliphatic polyesters are one of the most attractive biodegradable polymers because their backbones easily cleave by hydrolysis and thereafter the non-toxic cleaved products are absorbed in and/or eliminated from tissue or cells (Abou-Zeid et al., 2001; Steinbuchel et al., 2001). Specially, polyesters like poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), or their copolyesters (PLGA) are biodegradable polymers commonly used as drug carriers (Jain et al., 1998; Thomasin et al., 1998; Khang et al., 2003).

Numerous studies have been carried out to examine the release behaviors of protein drugs from matrix prepared by PLGA. Some commercial products have been already industrialized into long time delivery systems for protein drugs (Heya et al., 1991; Furr and Hutchinson, 1992). However, a PLGA matrix shows some drawbacks resulting from its hydrophobic nature. Thus, some problems remain to be solved with respect to the establishment of the controlled release technology of proteins, including the problem of the initial burst.

Generally, the release behaviors of protein from administration forms based on PLGA polymers was carried out in at least two release phases. The initial phase of drug release is governed by diffusion of the protein through pores in the polymeric matrix and the later phase is correlated to an erosion of the polymeric matrix, which plays a more prominent role (Kissel et al., 2002). It is difficult to adequately control a release of protein from an implantable wafer prepared by using a PLGA polymer carrier alone, because of marked initial bursts.

The introduction of new block segments was proposed to overcome the problem of the PLGA polymer matrix. Poly(ethylene glycol) (PEG), which is already approved by the FDA, is widely used in biomedical research and applications. PEG may be considered as one of the most promising polymers due to prevention of protein absorption and improvement of biocompatibility for blood contact compound (Burnham, 1994; Greenwald et al., 2003). Based on their property, several PEG-conjugates have been used in practical biomedical applications as commercially available Oncaspar® or Neulasta™. Furthermore, some groups have introduced PEG segments into PLGA segments to modify the polymeric matrix (Beletsi et al., 1999; Jeong et al., 2000; Mosqueira et al., 2001; Li et al., 2001). In addition, PEG segment is a hydrophilic part that can change the physicochemical properties of hydrophobic and biodegradable PLGA block segments.

The development of a simple and reliable administration form is important in the pharmaceutical industry (Jiang et al., 2005). Based on this purpose, the aim of our research was to try the development of drug administration forms fabricated by various drug delivery carriers. In this work, we chose the implantable wafer as a drug administration form in order to deliver bovine serum albumin (BSA), which is often used as a model

protein drug. We here describe the approach to evaluate the release behaviors of BSA from the implantable wafers prepared by MPEG–PLGA diblock copolymers with different compositions.

The second objective of this work is to add additives to suppress the initial burst. It is important that the matrix uniformly maintains the release of protein drug. The controlled release by the suppression of initial burst is important to establish further utilization of the implantable wafer form in the pharmaceutical industrial fields. Much research has been done to control the drug release using additives incorporated into polymer carriers. Among many additives, collagen has affinity with protein drugs, and the effects of this affinity on the release profiles cannot be ignored (Sano et al., 1998, 2003; Lee et al., 2001). Thus, collagen is considered to be a superior and promising material as a drug carrier or additive for carriers because it may influence the release profiles of protein drugs. Some groups (Palmer et al., 2002; Lee et al., 2004a,b) have recently reported that small intestinal submucosa (SIS) possess various benefits as natural products: easy preparation, lower cost, wide application, and thus it has been attempted in biomedical application (Campodonico et al., 2004; McCready et al., 2005; Kim et al., 2005b). We examined the effect of SIS as an additive in the release of protein from a wafer, assuming that it is effective to achieve the controlled release.

2. Materials and methods

2.1. Materials

Methoxy poly(ethylene glycol) (MPEG) (Aldrich, M_n ca. 550, 2000, and 5000 g/mol), carbitol (TCI), crosslinked polyvinylpyrrolidone (PVP, Aldrich), and carbopol (BF Goodrich) were used as received. L-Lactide (L-LA) and glycolide (GA) were recrystallized in ethyl acetate two times. Bovine serum albumin–fluorescein isothiocyanate (BSA–FITC, Sigma) was used under no light. SIS powder was prepared according to previously reported method (Palmer et al., 2002; Lee et al., 2004a,b).

2.2. Characterization

^{1}H NMR spectra were measured using a Bruker 300 and 500 MHz instrument with $CDCl_3$ in the presence of TMS as an internal standard. IR spectra were measured a with Magna-IR^{TM} spectrometer 550 Nicolet. Molecular weights of diblock copolymers were determined by ^{1}H NMR spectra and molecular weight distributions of MPEG–PLGA diblock copolymers were measured by a Futects At-3000 GPC system (Shodex RI-71 detector) using two columns (Shodex K-802 and Shodex Asahipak GF-510). $CHCl_3$ was used as the eluent at a flow rate of 0.6 mL/min. A scanning electron microscope (SEM, S-2250N, Hitachi, Japan) was used to examine the morphological change of the wafers before and after in vitro release of BSA. The wafers were mounted on metal stubs and coated with a thin layer of platinum using a plasma-sputtering apparatus (Emitech, K575, Japan) under argon atmosphere.

2.3. Synthesis of poly[(ethylene glycol)-block-(lactic-co-glycolic acid)] copolymers (MPEG–PLGA)

All glasses were dried by heating in vacuo and handled under a dry nitrogen stream. The typical process for the polymerization of P4 to give MPEG–PLGA with PLGA molecular weight (6000 g/mol) is as follows: MPEG (M_n = 2000 g/mol) (2 g, 1 mmol) and toluene (100 mL) were introduced into a flask. The MPEG solution was distillated by azeotropic distillation to remove water. Toluene was then distilled off to give 43 mL in final volume. LA (5.0 g, 34.7 mmol) and GA (1.0 g, 8.7 mmol) was added to MPEG solution at room temperature under nitrogen, followed by the addition of 0.6 mL of 0.1 M solution of stannous octoate in dried toluene. The mixture was stirred at 130 °C for 24 h. A reaction mixture was poured into a mixture of *n*-hexane and ethyl ether (v/v = 4/1) to precipitate a polymer, which was separated from the supernatant by decantation. The obtained polymer was redissolved in CH_2Cl_2 and then filtered. The polymer solution was concentrated by rotary evaporator and dried in vacuo to give a colorless polymer. The molecular weight of the PLGA segment in the diblock copolymers was determined by the comparison of the intensity for the terminal methoxy proton signal of MPEG at δ = 3.38 ppm and the methyl and methylene protons signals of PLGA at δ = 1.61 and 5.20 ppm, respectively, in ^{1}H NMR spectroscopy.

2.4. Preparation of BSA–FITC loaded wafers

Freeze milling of a mixture of 1 wt.% BSA–FITC for diblock copolymers with and without additive (10 wt.%) as a drug carrier was performed to uniformly disperse BSA–FITC in diblock copolymers. Ten milligrams of the mixed powder was compressed by mold with a 3 mm diameter using a Carver Press (MH-50Y CAP 50 t, Japan) at 20 kgf/cm^2 for 5 s at room temperature. The wafers were 3 mm × 1 mm in size with a flat surface and stored at 0 °C without light until use.

2.5. In vitro release of BSA–FITC

BSA–FITC loaded wafers were individually placed in vial with 10 mL of phosphate buffered saline solution (PBS, pH 7.4). The vial was constantly shaken at 100 rpm and 37 °C. At the set time, 1 mL of solution was taken out from the vial and then 1 mL of PBS added to the vial. The taken solution was immediately measured by fluorescence spectroscopy (F-4500, Hitachi, Tokyo, Japan). The amount of cumulatively released BSA was calculated by the standard calibration curves predetermined with BSA–FITC. The release experiment was individually performed for three wafers and then calculated as average value.

2.6. Water uptake ability

The wafers in PBS solution were taken out at 1 day, followed by the removal of water from the wafer using soft KIM wipes. The obtained wafers were weighed to determine the water uptake of the wafer during the release test. The wafers were dried by the freeze-dryer for 3 days and weighed to determine the mass loss from the original wafer.

2.7. pH measurements of medium

At the set time, the pH variations of the PBS taken out from the solutions with wafers were measured by a pH meter (Corning 340, USA) equipped with a combined glass electrode at room temperature.

2.8. Degradation of polymer carriers

The wafers were incubated under release condition for 30 days. Triplicate wafers were lyophilized and used to determine the molecular weight of PLGA parts through measuring with ^{1}H NMR.

3. Result and discussion

3.1. Synthesis of MPEG–PLGA diblock copolymers as drug carriers

To synthesize MPEG–PLGA diblock copolymers as drug carriers, the polymerization of LA and GA by the terminal alcohol of carbitol (M_n, 134 g/mol) or MPEG (M_n, 550, 2000, and 5000 g/mol) as an initiator was performed with various feed ratios of monomer with regard to initiator in the presence of stannous octoate. The obtained MPEG–PLGA diblock copolymers were summarized in Table 1. The MPEG–PLGA diblock copolymers were prepared by changing in MPEG and PLGA ratios. Moreover, the polydispersities of the MPEG–PLGA diblock copolymers have maintained a narrow distribution (1.24–1.35) compa-

Table 1
Synthesis of MPEG–PLGA diblock copolymers

Number	Molecular weight of initiator[a] (g/mol)	$([LA]+[GA])_0$[b]/$[I]_0$	MPEG–PLGA[c] (M_n, g/mol)	M_w/M_n[d]
P1	134	56.8	$MEPG_3$–$PLGA_{57}$ (134–8400)	1.24
P2	550	53.8	$MPEG_{13}$–$PLGA_{54}$ (550–7800)	1.32
P3	2000	68.6	$MPEG_{45}$–$PLGA_{69}$ (2000–9800)	1.35
P4	2000	43.3	$MPEG_{45}$–$PLGA_{43}$ (2000–6000)	1.27
P5	2000	25.3	$MPEG_{45}$–$PLGA_{25}$ (2000–3200)	1.19
P6	5000	23.7	$MPEG_{113}$–$PLGA_{24}$ (5000–3100)	1.30

Condition: $[Sn(oct)_2]/[initiator]$= 0.6, [LA] + [GA]/[toluene] = 1 M, 130 °C, 24 h.
[a] MPEG = 550 g/mol (M_w/M_n = 1.10), 2000 g/mol (M_w/M_n = 1.17), 5000 g/mol (M_w/M_n = 1.12).
[b] [LA]/[GA] = 8/2 (mole ratio).
[c] Determined by ^{1}H NMR.
[d] Measured by gel permeation chromatography (based on standard polystyrene).

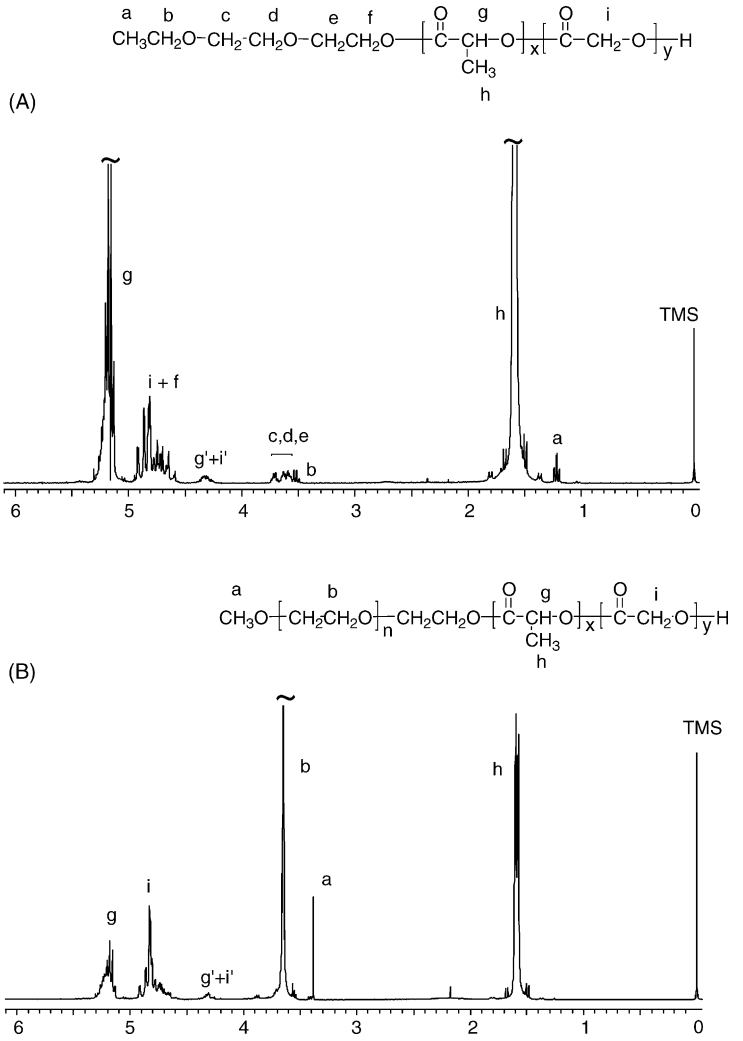

Fig. 1. ^{1}H NMR spectra of (A) carbitol–PLGA (P1) and (B) MPEG–PLGA (P3) diblock copolymers. (The g′ and i′ represented the peak assignable to the methine of LA and methylene of GA at polymer end, respectively.)

rable to those of MPEG (1.10–1.17). As shown in Fig. 1, carbitol–PLGA and MPEG–PLGA exhibited characteristic peaks of PLGA as well as those of carbitol or MPEG, respectively. IR spectroscopy of MPEG–PLGA diblock copolymers exhibited carbonyl peaks of PLGA at around 1768 cm^{-1}.

3.2. BSA releasing from wafers prepared by MPEG–PLGA diblock copolymers

We chose BSA as a model protein drug and employed an implantable wafer form as the administration form of BSA because it could be easily prepared. In general, water-soluble drug release from a wafer could depend on the penetrability of water or biologic fluid inside the wafer. Considering the water penetrability for polymers used as the carriers, the addition of hydrophilic segments into hydrophobic PLGA can change water penetrability and consequently the swelling property of the polymer carrier in the wafer, which is known to be of importance for the release of protein drug. Thus, it is firstly necessary to compare drug release from the wafers prepared by using various diblock copolymers. BSA–FITC was used to detect the

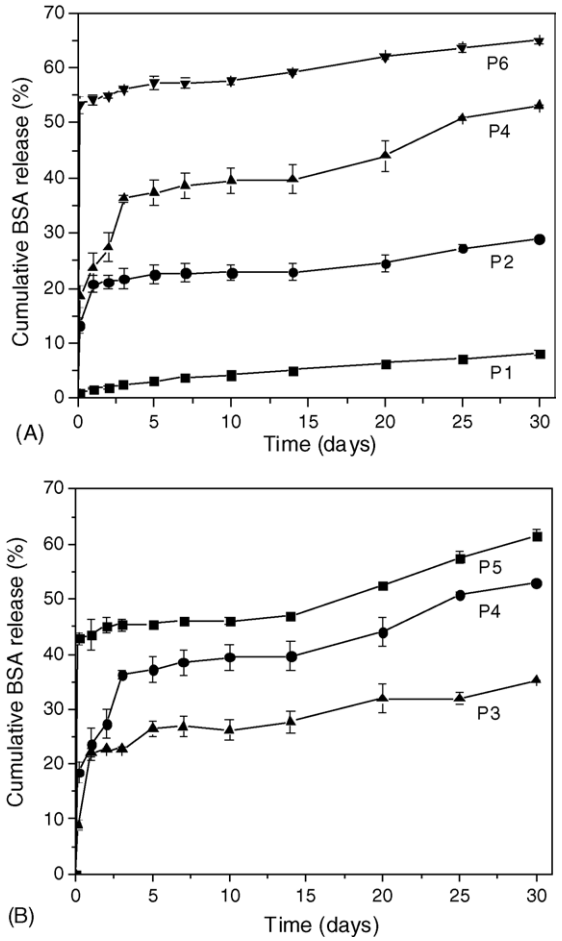

Fig. 2. BSA amount released from wafers prepared from diblock copolymers: (A) P1, P2, P4, and P6 (total molecular weight is 8000 g/mol) and (B) P3, P4, and P5 with various PLGA molecular weights and a constant PEG molecular weight (2000 g/mol).

amount of BSA released from wafer. The experiment to monitor BSA release from the wafers was performed at 37 °C for 30 days under shaking. The release profiles are shown in Fig. 2. The wafers, which were prepared by compression after freeze milling, loaded BSA without loss and exhibited small deviations in the release of BSA, indicating uniform dispersion of BSA in the diblock copolymer carriers. Fig. 2A shows the releasing behavior of BSA from wafers prepared from MPEG–PLGA diblock copolymers maintained at a total molecular weight of 8000 g/mol by changing the MPEG molecular weight (134, 550, 2000, and 5000 g/mol). The initial burst (percentage released in the first 1 day) from P1 was very small, and only exhibited a 7% release of BSA after 30 days. Meanwhile, P6 exhibited a 63% release of BSA after 30 days. As the relative MPEG segment in the diblock copolymers increased, the release amounts of BSA increased and a higher initial burst of BSA release was observed. The BSA release was bi-phasic with an initial burst at the first day and plateaued for 14 days, followed by a slower increase in release amount for the next 30 days. Fig. 2B also shows releasing amounts of BSA from wafers prepared by MPEG–PLGA diblock copolymers with different PLGA molecular weights and constant PEG molecular weight (2000 g/mol). In agreement with the results of Fig. 2A, the release amount of BSA increased as the relative PLGA segment decreased.

The increase of BSA release was probably caused by allowing the medium into the wafers after the initial burst, implying that the degradation of PLGA in diblock copolymer should be occurred. Degradation of the diblock copolymers depends on several factors, such as the type of chemical bonds, mobility of water within the polymer, and the pH of the polymer solution. Moreover, each block length, determined by the ratio change in MPEG and PLGA block segments, could affect physicochemical properties of degradation. Thus, molecular weight change was evaluated to examine the degradation of diblock copolymers at 37 °C for 30 days under shaking in PBS. Since no change in molecular weight of the MPEG part was observed under in vitro release conditions, molecular weight change of the PLGA part compared to the MPEG part was determined by ^{1}H NMR. The molecular weight of the PLGA part decreased as release time increased, as shown in Fig. 3. The initial slow degradation in the molecular weight of the PLGA part can be attributed to the compact structure of the wafers, leading to slower diffusion of the water. At 30 days, the PLGA part of P6 was decreased to 40% of its original molecular weight; meanwhile P1 only showed a slight change of molecular weight. An accelerated molecular weight loss was observed to be proportional to increasing the relative MPEG block in diblock copolymer, indicating that the incorporation of the MPEG segment as a hydrophilic part into the hydrophobic PLGA part led to faster erosion of the PLGA part due to better accessibility of water to the ester bonds of PLGA block. This result strongly indicates that the

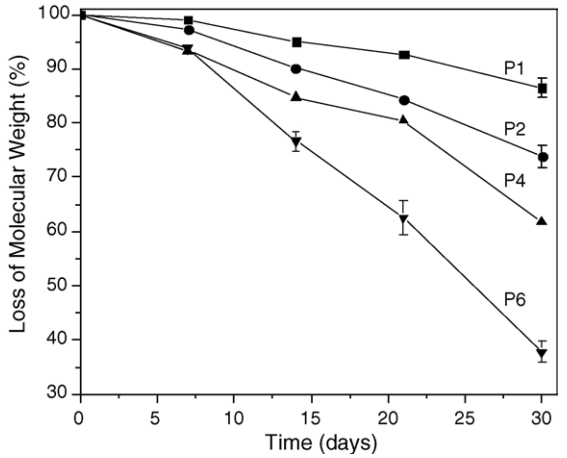

Fig. 3. Loss of molecular weight for the PLGA segment in the diblock copolymer carriers under in vitro release condition for 30 days.

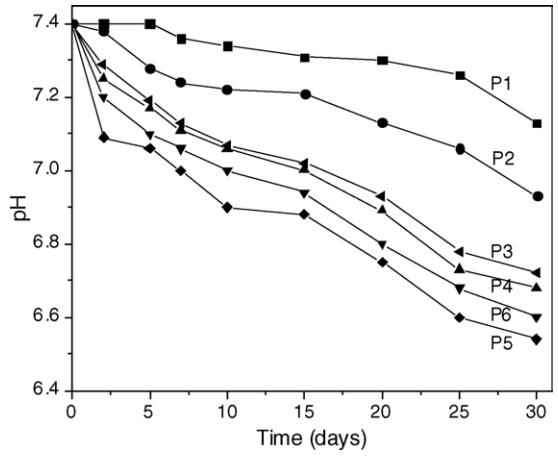

Fig. 4. pH change of medium of the wafers prepared from diblock copolymers (P1–P6) under in vitro release condition for 30 days.

MPEG ratio increase induced a faster incoming of water into the wafer due to swelling of the MPEG segment, resulting in the fast BSA release through PLGA degradation.

The PLGA segment in the MPEG–PLGA diblock copolymer changed to either lactic acid (LA) or glycolic acid (GA) by hydrolysis cleavage of an ester bond. The cleavage could induce a pH change in the media. Hence, the variation of pH in PBS as medium was also measured to estimate the degradation of PLGA for the wafers. The degradation media showed the decline in pH during 30 days, as shown in Fig. 4. The pH decrease of all media proceeded rapidly for the incubation time. The decrease shows a slow decrease during the initial 7 days, and exhibits an increase in pH drop slope for the following period. As previously described (Yoo et al., 2004), the degradation of PLGA could be accelerated by cleavage products, thus resulting in drastic drop of pH. The pH drop correlated with the degradation of PLGA. The pH drop of the wafer increased as content of the MPEG part increased. The pH of medium of the P5 wafers used dropped towards acidic faster than that of the P1 wafers used.

Fig. 5 shows a picture of wafers using diblock copolymers before and after BSA release for 30 days. The resulting color of the wafer was an indication of the amount of BSA released. The P6 wafer used changed to white from yellow, indicating larger release of BSA, while P4 wafer used was only a little yellow-

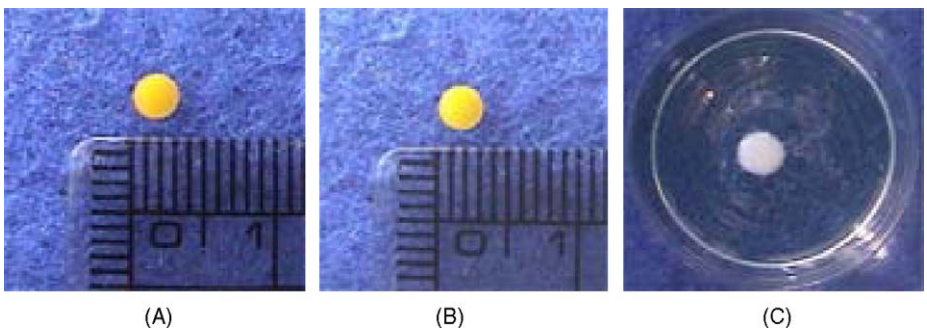

Fig. 5. Pictures of wafers (A) before and (B) after releasing of BSA from the P1 wafer used for 30 days and (C) after releasing of BSA from the P6 wafer used for 30 days.

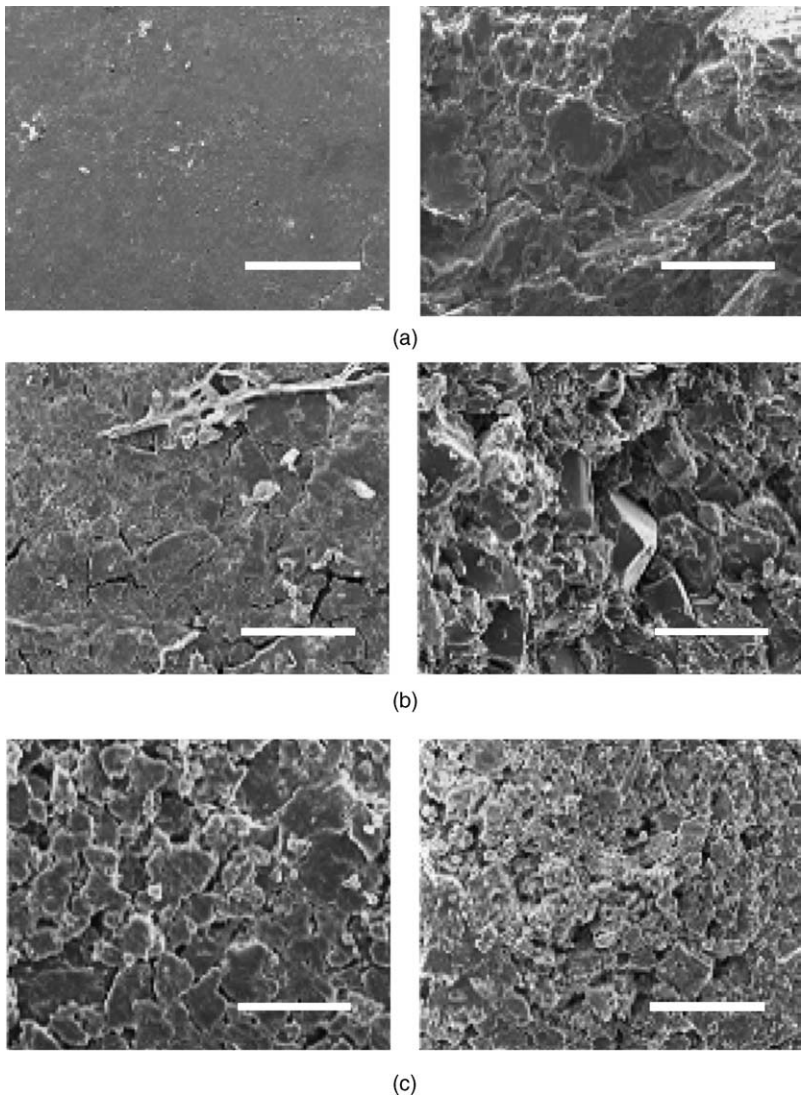

Fig. 6. SEM microphotographs of BSA-loaded wafers after release for 30 days: (a) P1, (b) P4, and (c) P6. (left: surface, right: cross section, magnification is 200×, scale bar represents 200 μm.)

ish even after releasing for 30 days. Before and after the BSA release test, the morphological changes of the wafer were also observed by SEM, as shown in Fig. 6. The P4 wafer used showed the more structural metamorphosis of crack form compared with the P1 wafer used, probably due to higher water absorption of MPEG inside the wafer. This result indicates that the structure change of the wafer induced faster BSA release.

3.3. BSA releasing from wafers prepared by MPEG–PLGA diblock copolymers in the presence of additives

First, the wafers were prepared by the addition of hydrophilic additives (10%) such as MPEG (MW, 2000 g/mol), PVP (MW, 30 kg/mol), carbopol, and SIS, into the P1 polymer to compare the release of BSA (Fig. 7). The P1 wafer exhibited only 7% release of

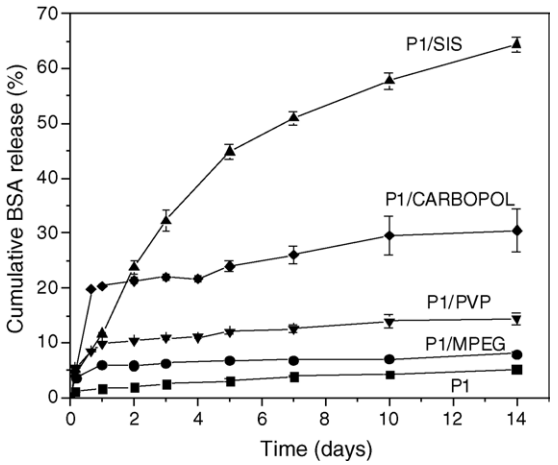

Fig. 7. BSA amount released from wafers prepared by P1 in the absence and presence of additives (10%).

BSA for 30 days. Slight increase in the release amount of BSA has been detected for wafers prepared by using P1 with MPEG or PVP when compared with that using only P1 polymer. In the case of the addition of a carbopol, the wafer exhibited slow release after a higher initial burst at 1 day. Meanwhile, the SIS added wafer showed the controlled release profile and greater enhancement in the release amount of BSA at 14 days. In addition, no initial burst for release of BSA was observed.

Measurement of the water uptake amount for the wafers was performed to examine the change of BSA release amount from the wafers in the presence of additives. Water uptake of P1 wafer was below 5% at 1 day and that of the P1/MPEG blend wafer used was 10%. After 1 day in PBS, ^{1}H NMR spectrum of the wafer prepared by using the P1/MPEG blend, which was lyophilized, showed almost P1 peaks with a few MPEG. This indicates that MPEG dissolves easily out of the wafer.

The water absorption amount of the wafers prepared by using P1/PVP, P1/SIS and P1/carbopol blend was approximately 12, 50 and 130%, respectively, even at 1 day; although the exact amount could not be determined due to the slight dissipation of the wafers. PVP, SIS, and carbopol as additives for diblock copolymers were only swelled and remained inside wafers. The SIS added wafer changed to a white color and maintained its original shape for 14 days, while the carbopol added

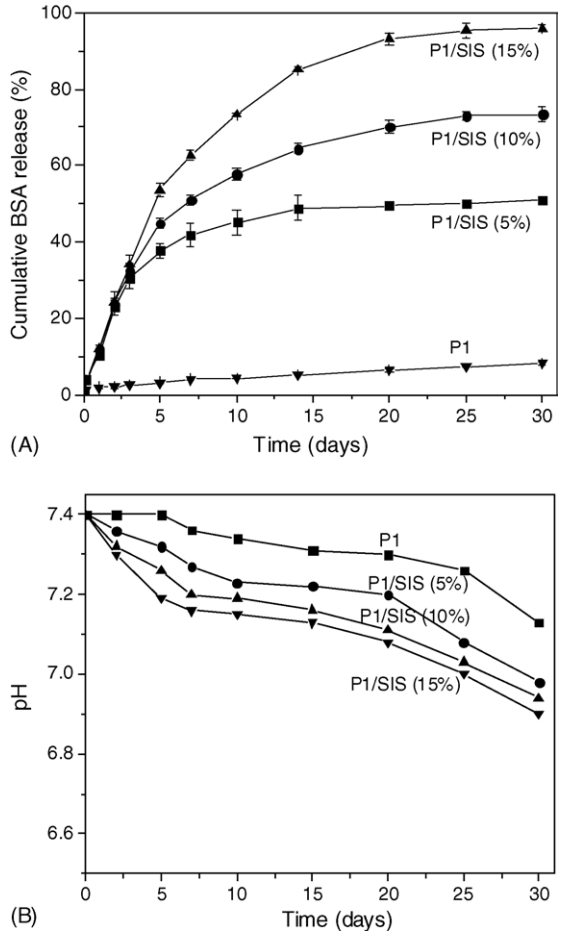

Fig. 8. (A) BSA amount released from wafers prepared by P1 in the absence and presence of SIS powder (5, 10, and 15%) and (B) pH change of medium.

wafer kept the yellow color and did not completely maintain the shape, probably because carbopol induced the crack of the wafer through larger water absorption. These results indicate that BSA release could depend on the water uptake ability of wafer.

Fig. 8A shows the release profiles of the wafers manufactured by using P1 with variation of SIS content. BSA release showed similar profiles for all wafers until 3 days, even though there are the changes in SIS content and there was no initial burst from the wafers. After 3 days, the release of BSA increased as SIS content increased. This indicated that the addition of SIS into the wafer contributed to controlled release.

Maeda et al. (1999) have already reported that the diffusion of a protein drug occurs through the pore type mechanism according to the relationship between the porous collagen structure and BSA permeation characteristics inside the wafer. The addition of SIS can affect the release behaviors of BSA, assuming that BSA in the wafers has affinity with collagen in SIS due to adsorption and ionic interactions between BSA and collagen in SIS (Bodmer et al., 1992). SIS is swollen after administration. BSA drug is believed to be released by diffusing into the swollen SIS in the wafer because SIS can induce variation in the balance between inflow and outflow of release media into the wafer. Thus, it appears that the above reasons contributed to suppression of the initial burst release of BSA from the wafer. Fig. 8B shows the pH changes measured in the absence and presence of SIS (5–15%) for 30 days. The pH value for the wafers drops from 7.4 to around 7.0 according to increasing SIS contents. After the BSA release from the wafer in the presence of SIS, SEM pictures of the wafer were observed, as shown in Fig. 9. The P1/SIS wafer showed the more structural crack form when compared with the P1 alone used wafer (Fig. 6a).

Fig. 10 shows releasing behaviors of BSA from wafers prepared from MPEG–PLGA diblock copolymers in the presence of 10% SIS. All wafers have a lag time for the release of BSA. Since swelling of the matrix by SIS occurred after infiltration of release medium inside the wafer, the diffusion of BSA was retarded at the initial stage of release by interaction with the swelled SIS. But, abrupt burst of BSA was observed at 2 days. Swelling of the MPEG segment in the diblock copolymer induced further infiltration of the release medium after a lag time. The high degree of swelling due to SIS and the MPEG segment in the diblock copolymer made the wafer porous and induced the burst of BSA. The BSA diffuses continually from the wafer after the swelling of the MPEG segment at approximately 2 days.

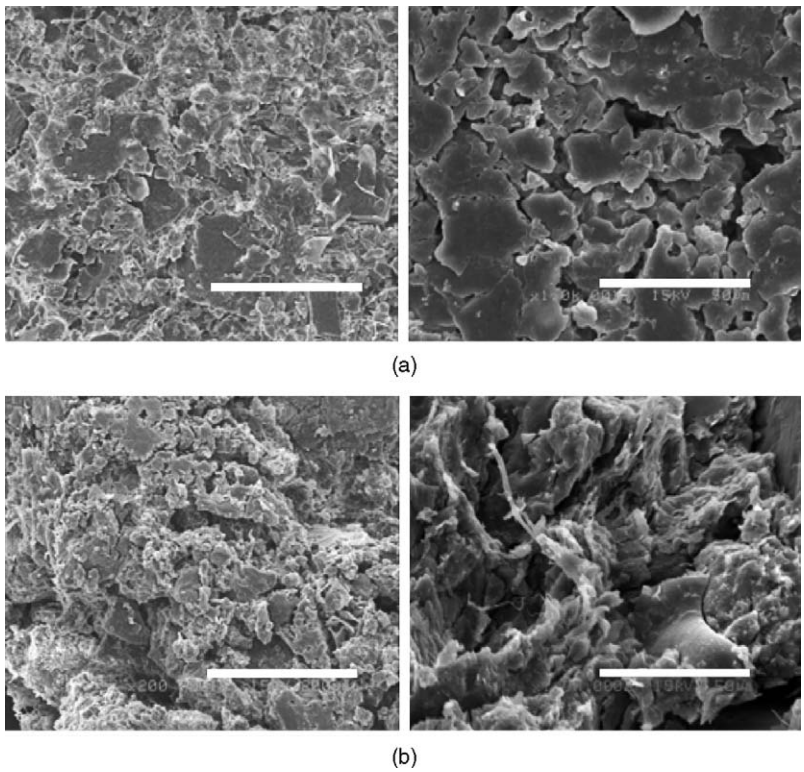

Fig. 9. SEM microphotographs of BSA-loaded wafers with SIS (10%) after release for 30 days: (a) surface and (b) cross section. Magnifications of left and right are 200× and 1000×, scale bar represents 200 and 50 μm, respectively.

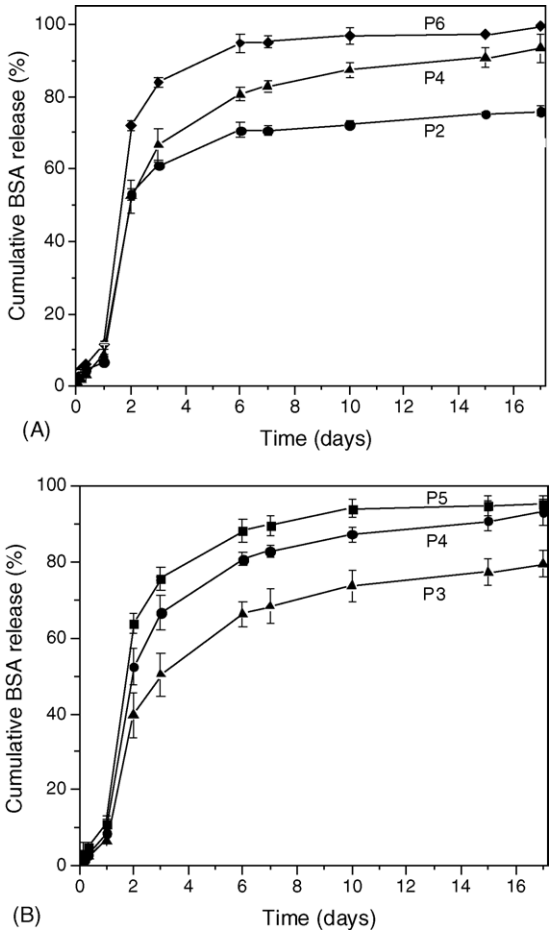

Fig. 10. BSA amount released from wafers prepared from diblock copolymers: (A) P2, P4, and P6 (total molecular weight is 8000 g/mol) and (B) P3, P4, and P5 changed by PLGA molecular weight in a constant PEG molecular weight (2000 g/mol).

4. Conclusion

We prepared successfully MPEG–PLGA diblock copolymers with various compositions. BSA-loaded implantable wafers were easily prepared by direct compression method after freeze milling of the diblock copolymers and BSA. The prepared implantable wafers exhibited release patterns with a dependence on MPEG–PLGA diblock copolymer compositions, although the release of BSA from the wafers exhibited initial burst. The in vitro release of BSA also correlated with the degradation rate of the PLGA part in diblock polymer. The wafers prepared from the diblock copolymers with the increased MPEG segment showed more structural metamorphosis of crack form due to the higher water absorption of MPEG inside the wafer, resulting in inducing faster BSA release. Generally, zero-order release of drug is desirable for a long-term releasing formulation. However, the implantable wafers prepared from the diblock copolymers showed a bi-phasic release behavior, i.e., an initial burst, a lag time, and a subsequent steady release. The problem of initial burst, which may have serious side effects, was solved by the addition of SIS. The SIS added wafers showed the controlled release profile, although the wafers prepared from diblock copolymers with increasing MPEG exhibited release patterns with lag time at the initial stage.

In view of the results so far obtained, we confirmed the possibility that MPEG–PLGA diblock copolymers as protein carriers for implantable wafer possess many advantages such as simple manufacture, long-term delivery, and controlled release. Further research on the biodegradability and the biocompatibility for tissue of the diblock copolymers according to changing of MPEG and PLGA compositions is now in progress.

Acknowledgement

This work was supported by KMOCIE (grant no. N11-A08-1402-05-1-3).

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