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Research paper

Morphological characterization of microspheres, films and implants prepared from poly(lactide-co-glycolide) and ABA triblock copolymers: is the erosion controlled by degradation, swelling or diffusion?

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Abstract

Erosion of biodegradable parenteral delivery systems (PDS) based on ABA copolymers consisting of poly(L-lactide-co-glycolide) (PLGA) A-blocks attached to polyethylene oxide (PEO) B-blocks, or PLGA is important for the release of macromolecular drugs. The degradation behavior of four types of PDS, namely extruded rods, tablets, films and microspheres, was studied with respect to molecular weight, mass, polymer composition and shape and microstructure of the PDS. For each device the onset time of bulk erosion (t_{on}) and the apparent rate of mass loss (k_{app}) were calculated. In the case of PLGA, the t_{on} was 16.2 days for microspheres, 19.2 days for films and 30.1 days for cylindrical implants and tablets. The k_{app} was 0.04 days^{-1} for microspheres, 0.09 days^{-1} for films, 0.11 days^{-1} for implants and 0.10 days^{-1} for tablets. The degradation rates were in the same range irrespective of the geometry and the micrographs of eroding PDS demonstrated pore formation; therefore, a complex pore diffusion mechanism seems to control the erosion of PLGA devices. In contrast, PDS based on ABA copolymers showed swelling, followed by a parallel process of molecular weight degradation and polymer erosion, independent of the geometry. The contact angles of ABA films increased either with decreasing PEO content or with increasing chain length of the PEO B-blocks. In summary, the insertion of a hydrophilic B-block leads to an erosion controlled by degradation of ABA copolymers, whereas for PLGA a complex pore diffusion of degradation products controls the rate of bulk erosion.

Keywords: ABA triblock copolymers; Poly(lactide-co-glycolide); Erosion mechanism; Degradation; Microspheres; Rod; Film

1. Introduction

During the past three decades, parenteral delivery for hydrophilic macromolecular drugs, e.g. peptides, proteins or DNA, has been an ambitious goal especially with regard to attaining constant release profiles [1]. Since the diffusivity of hydrophilic macromolecules like proteins in hydrophobic polymers like poly(lactide-co-glycolide) (PLGA) is negligible, the release profile is mainly controlled by pore diffusion and erosion of the polymer [2].

For both biomedical applications in surgery and drug delivery systems the degradation of the polymer, usually defined as a decrease in the molecular mass of the polymer, and the erosion, defined as mass loss of biomaterial from the implantation site, are important issues [3]. Although a heterogeneous degradation of PLGA devices seems likely, which is characterized by a higher rate of hydrolysis in the internal bulk phase rather than close to the surface [4,5], this phenomenon is discussed controversially in the literature [6]. A number of investigations dealing with the degradation mechanism of PLGA have been published, but the comparison of these results still remains problematic due to the use of different preparation techniques for implants [7], films [2] or microspheres [8]. Hypothetically, biodegradable polymers were classified with respect to a critical thickness, above which erosion proceeds mainly from the surface [9].

On one hand, the polyester hydrolysis can be described by an auto-catalytic degradation mechanism [6], since acidic degradation products are retained in the device leading to a decrease of the internal pH during degradation in vivo and in vitro [10,11]. In this case a larger device with a smaller surface to volume ratio should degrade faster than a smaller one of the same molecular mass [12]. On the other hand, an in vivo degradation study did not confirm an apparent spatial distribution of different degradation products between the surface and the center; in particular, PLGA

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Table 1
Characteristics of biodegradable polymers based on ABA triblock copolymers and PLGA (from Ref. [16])

Polymer	PEO (%)[a]	PEO Mn (g/mol)[b]	LA/GA/EO (%)[a]	Mw (g/mol)[c]	Mn (g/mol)[c]	Tg (°C)[d]
ABA 1	20	6000	57/21/22	42.000	21.400	45.0
ABA 2	30	6000	57/13/30	29.000	16.500	38.4
ABA 3	50	6000	40/9/51	17.800	11.800	33.0
ABA 4	30	3000	57/10/33	16.700	10.100	35.2
ABA 5	30	1000	57/12/31	5400	–	36.6
D,L-PLGA	–	–	50/50/0	29.300	15.800	40.8

[a] Calculated from ^{1}H-NMR spectra. LA, lactic acid; GA, glycolic acid; EO, ethylene oxide.
[b] Number average molecular weight (Mn) according to the specifications of the manufacturer.
[c] Weight average molecular weight (Mw) and number average molecular weight (Mn) from SEC.
[d] Glass transition temperature (Tg) from differential scanning calorimetry.

rods did not become hollow due to heterogeneous degradation [13]. This study addresses the influence of geometry affecting the degradation as well as the erosion according to the hypothesis of bulk degradation.

Additionally, ABA triblock copolymers, consisting of PLGA A-blocks attached to polyethylene oxide (PEO) B-blocks were investigated. Due to microphase separation and rapid swelling after exposure to water these polymers possess interesting properties for the encapsulation of hydrophilic macromolecules [14,15]. Since the pH inside ABA tablets remains relatively stable during incubation, an accelerating influence of auto-catalysis on the degradation rate is unlikely [16,17].

Implants and rods, prepared by melting techniques like ram-extrusion or compression molding, were compared to films and microspheres, prepared by solvent casting from dichloromethane (DCM) or coacervation from an oil in water (O/W) emulsion. Among the techniques of microsphere preparation, coacervation by phase separation has been widely used for the encapsulation of peptides and proteins [18]. The encapsulation process involves three phases: droplet formation in a water in oil (W/O) emulsion, coacervation/droplet stabilization in an W/O emulsion and hardening [18,19]. Due to its volatility and solvent properties for PLGA, DCM has often been used as an organic phase in emulsion techniques [20]. Since the emulsion processes generally require two different solvents – often water and DCM, which has to be removed in the final product [20] – microspheres prepared by an O/W technique served as a model to compare the degradation of PLGA and ABA triblock copolymers.

In general, an erosion process involves three steps: the penetration of water into the device, the hydrolysis of ester bonds in the polymer main chain leading to water soluble degradation products, and the mass loss of polymer from the device through transport of cleavage products into the surrounding medium [21]. To compare the erosion properties of ABA triblock copolymers and PLGA, the present study investigates the wetting properties of the polymers preceding a swelling process. In a further set of experiments the degradation and erosion of different devices were investigated for ABA and PLGA devices with respect to the geometry and the morphology during the proceeding breakdown of the polymer matrix.

2. Materials and methods

2.1. Polymers

PLGA (Type Resomer RG 503) was purchased from Boehringer Ingelheim (Germany). Linear ABA triblock copolymers consisting of PLGA A-blocks attached to central PEO B-blocks were synthesized and characterized as previously described [22]. The properties of the polymers used in this study are summarized in Table 1. All other materials were of analytical purity. The polymer molecular weights were determined by size exclusion chromatography (SEC) as described in Ref. [22].

2.2. Determination of glass transition temperatures

Glass transition temperatures (Tg) were measured using differential scanning calorimetry (DSC7, Perkin Elmer, Germany). Polymer samples (5 mg) were sealed in aluminum pans and heated twice in a nitrogen atmosphere. Thermograms covering a range of 0–120°C were recorded at a heating and a cooling rate of 10°C/min. The midpoint of the second run was used for Tg calculation. Calibration of the system was performed using gallium and indium standards.

2.3. Determination of polymer molecular weights

Polymer molecular weights were determined by SEC using Merck size exclusion columns (Lichrogel PS mix and Lichrogel PS 40, 10 mm) at 25°C (Merck, Germany). Three samples were dissolved in methylene chloride (20 mg/ml); the injection volume was 20 ml. A differential refractometer served as a detector (Merck RI 71). Weight average molecular weights (Mw) were calculated using polystyrene reference materials: Mw 3250, 5100, 19 600, 34 700 and 87 000 Da (Merck, Germany) and the Millennium software (Waters, Eschborn, Germany).

2.4. Preparation of implants with different shapes

The extrusion of the polymers was carried out at a temperature of 80°C as described in Ref. [16]. The die had a diameter of 1 mm and the rods were cut into implants of 100 mg weight. The rods prepared from PLGA were 54.0 mm in the average length and the diameter was 1.44 mm. The average length of ABA 2 rods was 87.00 mm and the average diameter was 1.04 mm. Compression molding of tablets was carried out under appropriate pressure using a thread press at a temperature of 70°C. About 100 mg of the polymer was compressed using two flat punches and stored at +4°C in a desiccator. The average diameter of tablets was 7.3 mm and the height was 2.1 mm in the case of both polymers.

2.5. Preparation of microspheres and films

For the O/W microspheres 300 mg of the polymer dissolved in 1.6 ml DCM was homogenized in 150 ml of an aqueous solution containing 0.1% (w/v) polyvinyl alcohol (Mowiol 18/88 from Hoechst, Germany). The homogenization was carried out using a propeller stirrer (model RW 18, Janke & Kunkel, Germany) at 300 rev./min to obtain large microspheres that could be cut using a razor blade. The particle size and size distribution of the microspheres were analyzed by laser light diffraction using a Malvern Mastersizer X (Malvern Instruments, UK). A 300 mm lens covered a particle size of 1.2–600 μm. The calculation of the particle sizes was carried out using the Malvern software based on the Fraunhofer approximation [23]. The weighted average of the volume distribution D (4.3) was used to describe the mean particle size. The microspheres prepared from PLGA had a diameter of 157 ± 50 μm, and ABA microspheres had a diameter of 287 ± 113 μm. After stirring for 3 h the microspheres were isolated by centrifugation, washed, subsequently lyophilized (Edwards Freeze Dryer Modulyo, UK, 15 h, 3.3 mbar) and stored at +4° under desiccation. Films were cast from a DCM solution (10% (w/v)) on Teflon plates, and then cut into discs of diameter 1.3 cm and thickness 0.3 mm. The films were dried for 3 days in a desiccator and further in a drying chamber under reduced pressure at room temperature until constant weight was obtained.

2.6. Determination of the composition of ABA copolymers during incubation

Polymer compositions were determined by ^{1}H-NMR spectroscopy. ^{1}H-NMR spectra (500 MHz) were obtained from $CDCl_3$ solutions containing tetramethylsilane as a reference at 25°C (JNMR-GX500 spectrometer, Jeol, Tokyo, Japan). The molar compositions were calculated by comparing the PEO methylene signal resonating at $d =$ 3.65 ppm, the lactic acid methine signals centered at $d =$ 5.15 ppm and the glycolic acid methylene groups observed at $d = 4.8$ ppm [22].

2.7. Contact angle measurements

Three dry films per sample were placed in an air-tight Plexiglas chamber at 25°C as described in Ref. [24]. A known volume of liquid was added using an assembly consisting of a syringe (gas-tight Luer-lock syringe Hamilton Co., Switzerland) fitted to a Steinmeyer micrometer head and holder (Desaga, Germany). A drop of phosphate buffer pH 7 was viewed through a glass window using a goniometer telescope (Leitz, Germany), and contact angles were read directly to the nearest 1.0° from each side of the drop, exactly 10 s after contact with the film.

2.8. Scanning electron microscopy

The morphology of all devices was analyzed by scanning electron microscopy (SEM) using a Hitachi S 510 scanning electron microscope (Hitachi Densi GmbH, Germany). Lyophilized pieces were cut using a razor blade and then mounted on aluminum pins using double-sided adhesive tape. Prior to microscopical examination the samples were sputter-coated with a gold layer at 25 mA in an argon atmosphere at 0.3 mPa for 2 min (Sputter Coater S 150, Edwards/Kiese, Germany).

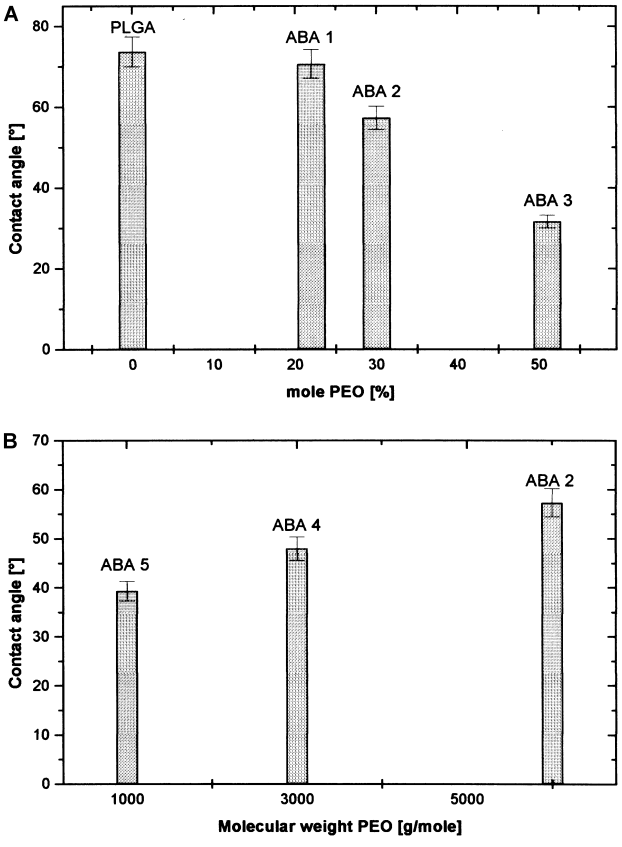

Fig. 1. (a) Contact angles of ABA films as a function of PEO content (%). The number average molecular weight (Mn) of PEO was 6000 g/mol. (b) Contact angles of ABA films as a function of molecular weight of PEO. The mol content of PEO in the ABA was 30%.

2.9. In vitro degradation study of the devices

The devices were incubated in 10 ml phosphate buffer (pH 7.4) in glass vials in an incubator at 37°C. At defined time intervals the buffer was replaced, washed with demineralized water and subsequently lyophilized. The buffer solution was changed every 3 days. The degree of degradation was measured by SEC and SEM. Mass loss was estimated gravimetrically. Each sample was measured in triplicate. The volumes of swollen implants were measured using light microscopy.

2.10. Calculation of kinetic constants of erosion

The erosion of PLGA can be described by two parameters [7], namely the onset time of erosion (t_{on}) and the apparent pseudo-first order rate of erosion (k_{app}). According to Eq. (1) the k_{app} was calculated using the least square regression of the decay phase of the relative mass loss profiles:

$$\ln(\%\ \text{mass remaining}) = \text{intercept} - k_{app} \times t \quad (1)$$

The t_{on} was obtained from Eq. (2):

$$t_{on} = (\text{intercept} - \ln 100)/k_{app} \quad (2)$$

3. Results

An important prerequisite for the hydrolytic degradation of different polymeric devices is their wetting behavior. The contact angles at the phosphate buffer/film/air interface showed that a higher content of PEO in the ABA triblock copolymer resulted in a lower contact angle (Fig. 1a) compatible with an increase in hydrophilicity of the polymer film. Apart from the PEO content the chain length of PEO had an impact on the contact angle as well (Fig. 1b). A longer hydrophilic B-chain in the ABA triblock copolymer increased the contact angle, indicating that the relative PEO proportion at the surface was reduced compared to PEO with a lower molecular weight. In contrast, a relative increase of the swelling agent PEO inside the matrix of the ABA films resulted in an increasing volume extension of the films. Thus, during the first 2 days incubation the swelling of the ABA films containing 30% PEO increased with increasing chain length of the B-block (data not shown).

The morphology of microspheres (O/W emulsion technique) during degradation is shown in Fig. 2. After 1 day of incubation the surface of PLGA microspheres (Fig. 2a) appeared smooth without pores and the matrix did not

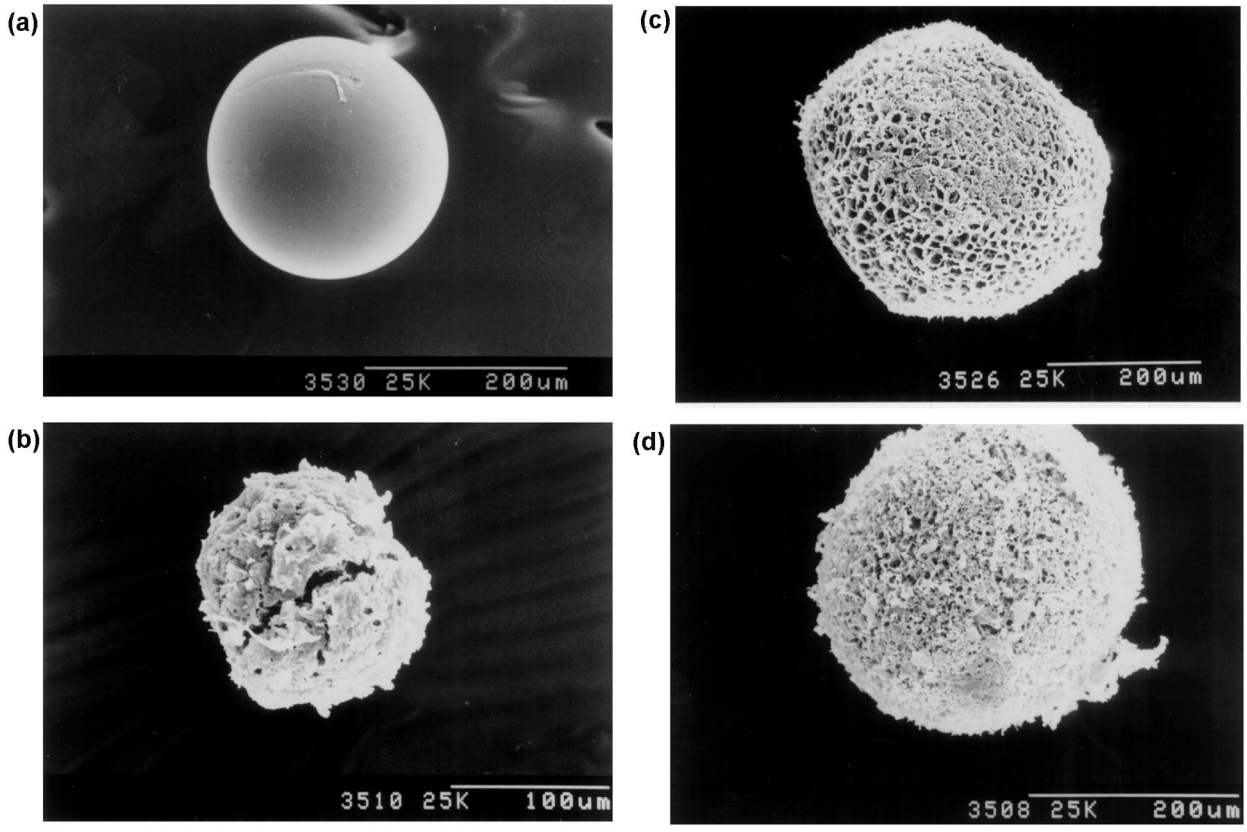

Fig. 2. Typical scanning electron micrographs of microspheres. (a) PLGA microspheres after 1 day of incubation (scale bar, 200 μm; magnification, 200-fold; acc. volt., 25 kV). (b) PLGA microspheres after 40 days of incubation (scale bar, 100 μm; magnification, 300-fold; acc. volt., 25 kV). (c) ABA microspheres after 1 day of incubation (scale bar, 200 μm; magnification, 150-fold; acc. volt., 25 kV). (d) ABA microspheres after 40 days of incubation (scale bar, 200 μm; magnification, 200-fold; acc. volt., 25 kV).

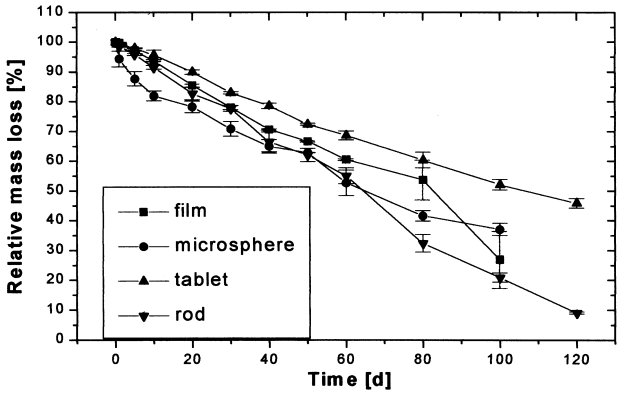

Fig. 3. Erosion of ABA 2 as a function of the device (each sample was measured in triplicate).

show any channel-like structures, allowing diffusion of water soluble products. After 40 days of incubation (Fig. 2b) the PLGA microspheres showed a rough and porous surface, indicative of the ongoing erosion. A different picture was obtained for the ABA microspheres (Fig. 2c) with a sponge-like structure at the beginning of incubation, where a diffusion of water soluble products was possible. For this type of polymer the structure of the microspheres did not change during 40 days of erosion (Fig. 2d).

As a consequence of the swollen structure, the erosion of the ABA devices (Fig. 3) started immediately after incubation without any lag phase. The rate of mass loss gave the following rank order: rods > films and microspheres > tablets. The surface to volume ratios were 3.8 mm^{-1} for rods and 1.5 mm^{-1} for tablets. Besides the use of a solvent during processing, films and microspheres had a larger relative surface, namely the ratio surface/volume was 6.2 mm^{-1} in the case of films and for microspheres >21 mm^{-1}.

In Fig. 4 the changes in the molar composition of eroding ABA 2 as a function of the device are shown. The relative PEO content decreased inside the eroding ABA 2. After 50 days only 50% of the initial PEO content was retained in each of the devices, whereas the content of PLGA in ABA 2 increased to over 85%.

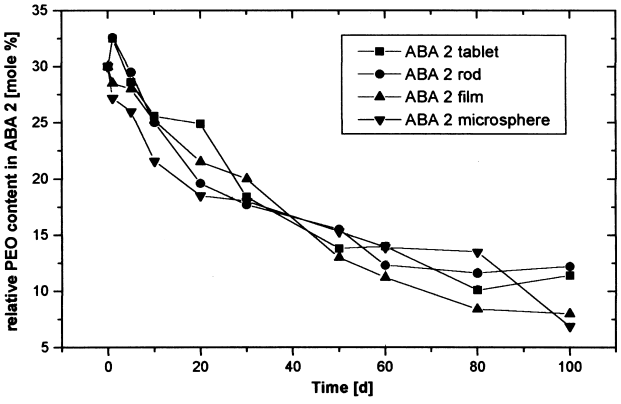

Fig. 4. PEO content inside eroding ABA 2 as a function of the device.

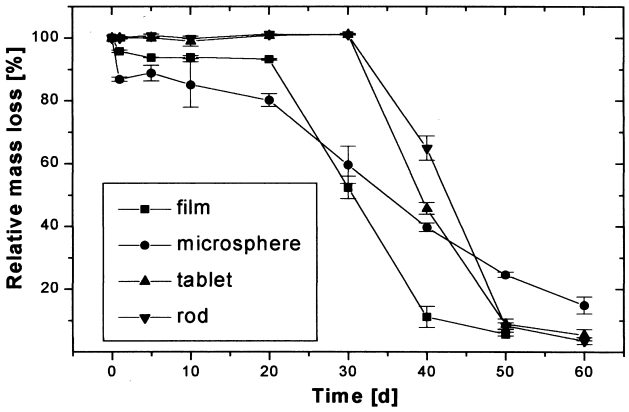

Fig. 5. Erosion of PLGA as a function of the device (each sample was measured in triplicate).

The erosion of the PLGA devices is shown in Fig. 5. The typical pattern of lag phase followed by a more or less rapid erosion was obtained. According to the method of Kenley et al. [7] we calculated the kinetic constants for the erosion of different devices, as shown in Table 2. In the case of all four ABA devices, the onset time for erosion was zero, confirming the immediate mass loss after contact with the aqueous medium. The erosion rates of the ABA devices ranged between 0.0065 and 0.0096 $days^{-1}$, whereas in the case of PLGA the absolute erosion rates were higher than for ABA.

The rates of PLGA erosion decreased with increasing surface to volume ratio from tablets (1.5 mm^{-1}) and rods (2.8 mm^{-1}) to films (7.3 mm^{-1}) and microspheres (38.2 mm^{-1}). This finding was confirmed by the Tg of the different PLGA devices. During the first 3 weeks the Tg of implants and films showed only a slight decrease. Parallel to the immediate onset of erosion, the Tg of PLGA microspheres decreased from 39.2 to 29.1°C after 30 days of incubation, while the PLGA implant showed a Tg decay from 40.8 to 35.0°C. In general, the erosion of PLGA was finished after 7 weeks while ABA took about 14 weeks, although the initial molecular weights were identical.

The characterization of the morphology using SEM of rods and films during erosion is given in Figs. 6 and 7.

Table 2
Apparent erosion rates (k_{app}) and onset times of erosion (t_{on}) as a function of the polymer and the device

Device	k_{app} ($days^{-1}$)	R^a	t_{on} (days)
ABA 2 tablets	0,0065 ± 0.00009	0.991	0
ABA 2 rods	0.0098 ± 0.00028	0.997	0
ABA 2 films	0.0092 ± 0.00033	0.995	0
ABA 2 microspheres	0.0096 ± 0.00038	0.993	0
PLGA tablets	0.1035 ± 0.009	0.992	30.1
PLGA rods	0.115 ± 0.006	0.997	30.1
PLGA films	0.093 ± 0.002	0.999	19.2
PLGA microspheres	0.041 ± 0.002	0.995	16.2

[a] From least square regression of ln(% mass remaining) = intercept − $k \times t$.

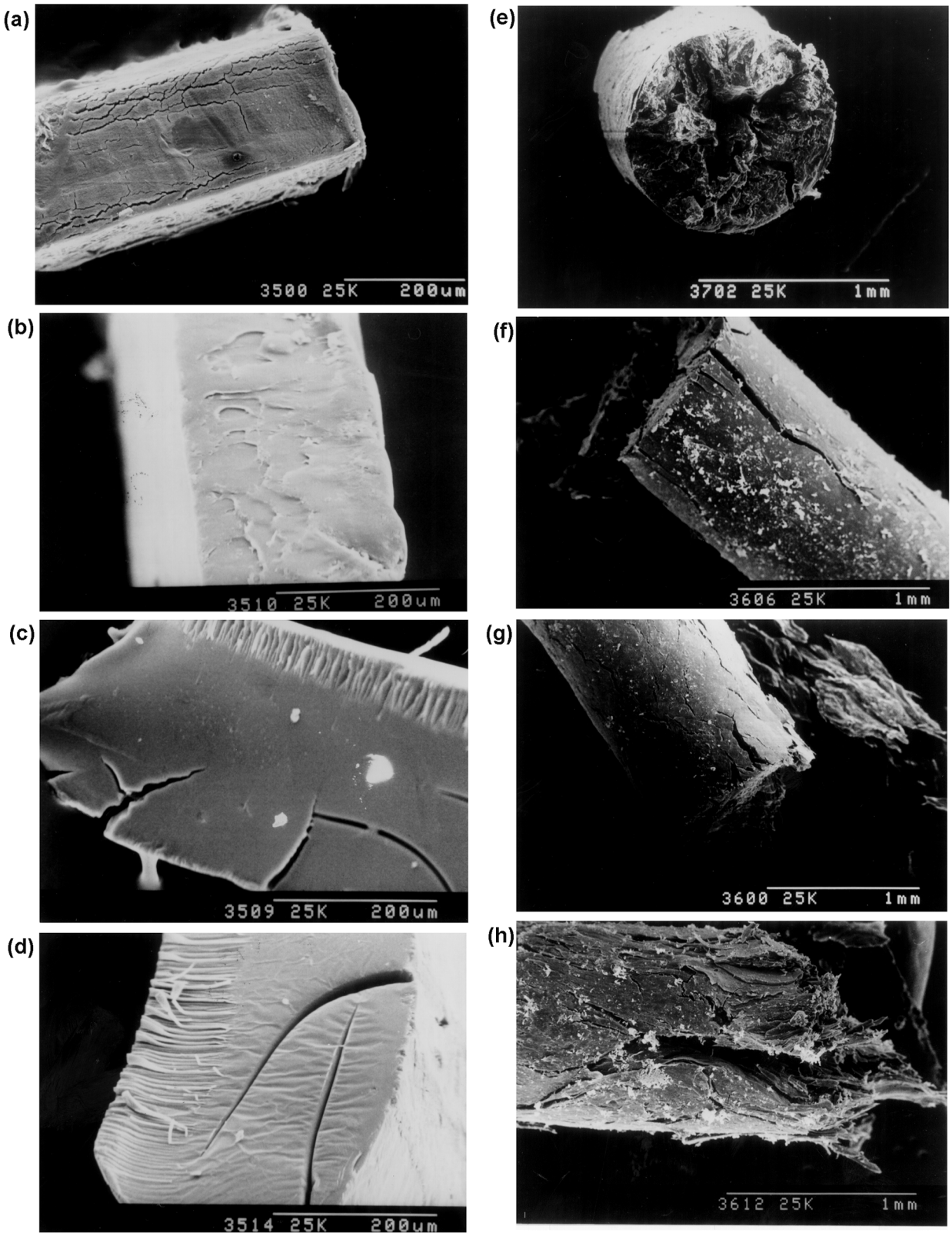

Fig. 6. Typical scanning electron micrographs of eroding ABA 2 films (a–d: scale bar, 200 μm; a: magnification, 200-fold; acc. volt., 25 kV) and rods (e–h: scale bar, 1 mm; e,f,h: magnification, 50-fold; g: magnification, 40-fold; acc. volt., 25 kV) after 10 days (a,e), 20 days (b,f), 30 days (c,g) and 40 days (d,h) of incubation.

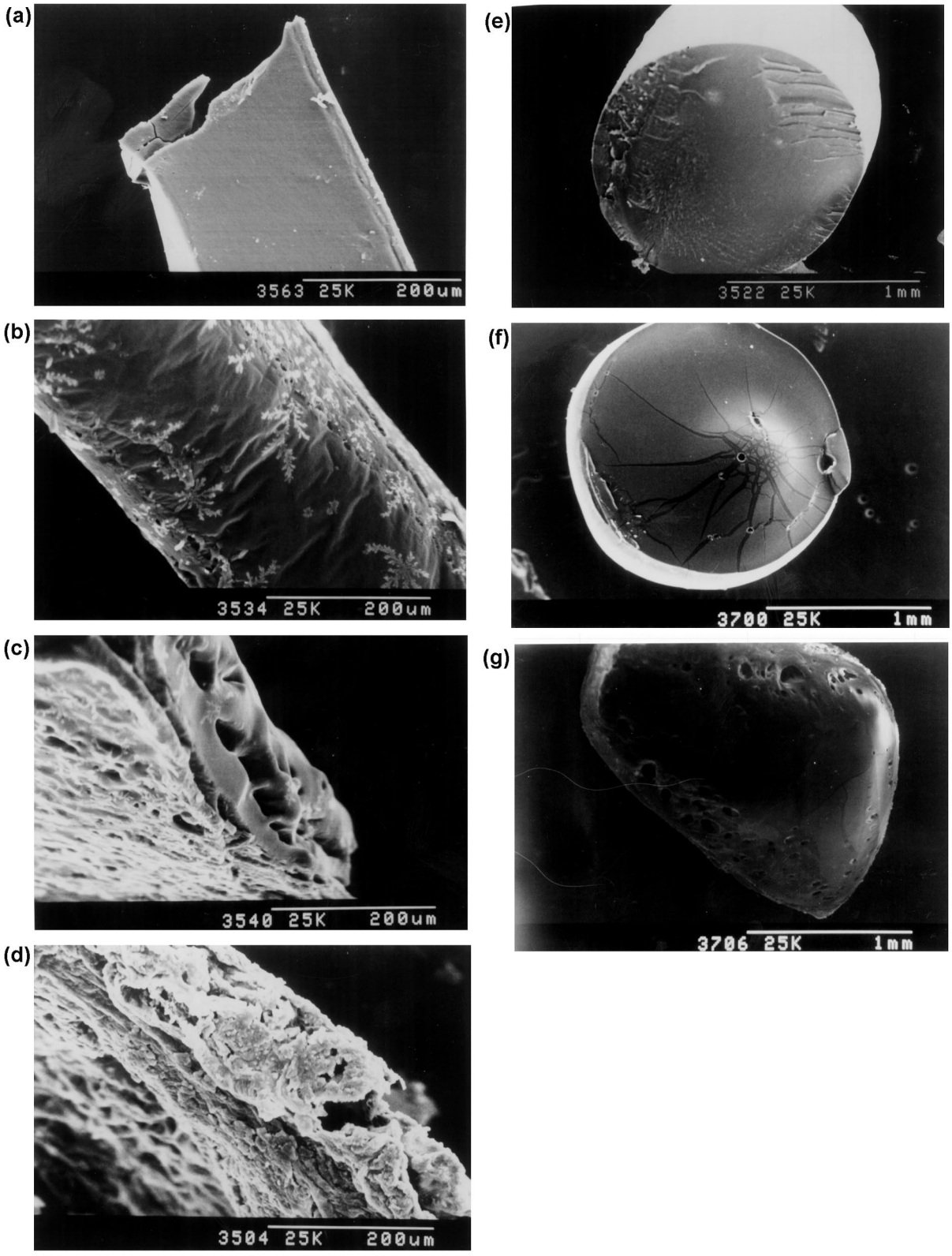

Fig. 7. Typical scanning electron micrographs of eroding PLGA films (a–d: scale bar, 200 μm; a: magnification, 150-fold; b–d: magnification, 200-fold; acc. volt., 25 kV) and rods (e–g: scale bar, 1 mm; e,f: magnification, 50-fold; g: magnification, 40-fold; acc. volt., 25 kV) after 10 days (a,e), 20 days (b,f), 30 days (c,g) and 40 days (d) of incubation.

After 10 days of incubation, the ABA film (Fig. 6a) was smooth, showing some cracks close to the surface. While their compact structure was retained even after 20 days (Fig. 6b), the drying process for the SEM preparation led to cracks of the films. On the surface pores were seen (Fig. 6c) growing slowly into the film (Fig. 6d), but the compact structure of the films remained even after 40 days of incubation. The rods (Fig. 6e–h) demonstrated that the ongoing mass loss of the ABA devices was not accompanied by a smaller volume of the device. During observation the cracks increased, indicating a loose structure of the matrix. The investigation of PLGA films after 10 days of incubation (Fig. 7a) demonstrated that there was no difference between surface and bulk. After 20 days (Fig. 7b) pores were visible close to the surface of the film. During the next 10 days the diameter decreased and the typical picture of a bulk eroding device was obtained: pores and large holes inside the film while the surface disclosed smaller pores. The breakdown was visible after 40 days (Fig. 7d) of incubation; the initially compact film had become a damaged network. By contrast, the PLGA rods (Fig. 7e–g) demonstrated a more or less compact matrix up to 20 days without pores on the surface. After 30 days, at the time point when the Tg decreased below the incubation temperature, a deformation of the implants was observed which was indicative of a polymer flow (Fig. 7g). The structure of PLGA rods was completely broken down after 40 days of incubation (data not shown), confirming the observation of the rapidly ongoing mass loss (see also Fig. 5).

The molecular weight decay of PLGA devices preceding mass loss (or erosion) was faster than for ABA (Fig. 8a,b). Regardless of the preparation method, the degradation of ABA copolymers started immediately after incubation in the aqueous medium and proceeded subsequently with a decreasing rate. Also all the PLGA devices started to degrade with incubation revealing a sigmoid profile of molecular weight decay. From the least square fit of ln Mw against time we calculated degradation rates (k_{deg}) for the different PLGA devices as inserted in Fig. 8b.

4. Discussion

Drug delivery systems prepared from PLGA or ABA triblock copolymers control the release of proteins both by pore diffusion and an erosion mechanism [25–27]. For the first step of the erosion process, namely the water penetration, the contact angle is an important factor, describing the 'wetting' of the device. The absolute range of the contact angles for PLGA films is comparable to data obtained by analysis of flotation profiles of microspheres [28]. An effect of the PEO content on the contact angle became evident >20 mol% PEO. In the case of films prepared by solvent evaporation, the hydrophobic PLGA A-blocks were preferably located at the surface [29]. The contact angles decreased with increasing molar PEO content in the ABA triblock copolymers. PEO blocks seem to reduce protein adsorption on the surface of microspheres [30]. With ABA nanoparticles PEO loops on the surface were found, which may be easier formed by shorter PEO chains [31]. Thus, we observed decreasing contact angles with decreasing PEO chain length, although the molar PEO content was constant. An important effect of water penetration was visualized by SEM, namely the swelling of different polymer devices. Comparing the volume extension of films and rods during the first 2 days of incubation, the hydrophilic B-blocks in the ABA copolymers seem to be responsible for water uptake [16].

The erosion of the ABA triblock copolymers started with incubation in the aqueous medium regardless of the geometry of the devices. Due to the swollen structure during the entire degradation process, a transport of degradation products from the site of formation into the surrounding medium seemed to have occurred immediately. The molecular weight decay proceeded parallel to the erosion, and there was no evident lag phase between the formation and the release of water soluble degradation products confirming previous findings [16]. Regardless of the device geometry the PEO content decreased during the initial erosion phase. Furthermore, the pH inside the ABA matrix remained stable according to a previous study [16], and there was no accumulation of acidic degradation products inside the

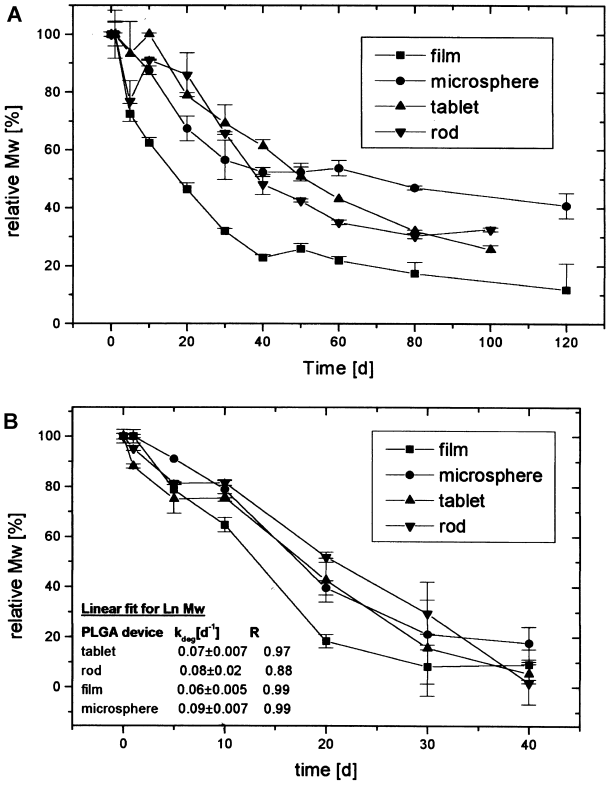

Fig. 8. (a) Degradation of ABA 2: influence of geometry on the relative molecular weight (Mw) decay. (b) Degradation of PLGA: influence of the geometry on the relative molecular weight (Mw) decay.

device. Despite these characteristics of a diffusion-controlled erosion, the geometry of the device had a negligible influence on the erosion of ABA triblock copolymers. In general, diffusion processes are influenced by geometry, but here the rate limiting effect of diffusion of degradation products on the erosion of ABA devices is negligible. Thus, other mechanisms apart from diffusion through a bi-coherent hydrogel have to be considered, e.g. microphase orientation due to the processing. The erosion of ABA copolymers still proceeded after the degradation rate slowed down after day 60. Therefore, the erosion of ABA is rather controlled by the degradation of the polymer chain than by the diffusion of water soluble degradation products consisting of PEO and PLGA oligomers.

By contrast, PLGA is more hydrophobic than ABA, as demonstrated by the contact angle measurements. The bulk erosion of PLGA can be described by two kinetic parameters, the onset time of erosion and the erosion rate [7]. According to the present study the hydrophobic surface of implants remained smooth after 20 days of incubation, whereas the degradation commenced shortly after incubation. During the onset time of erosion an almost negligible release of acidic degradation products from the interior of the matrix was reported leading to a pH drop and autocatalytic acceleration of degradation [6]. The second kinetic parameter, the erosion rate, describes the mass loss from the biodegradable device.

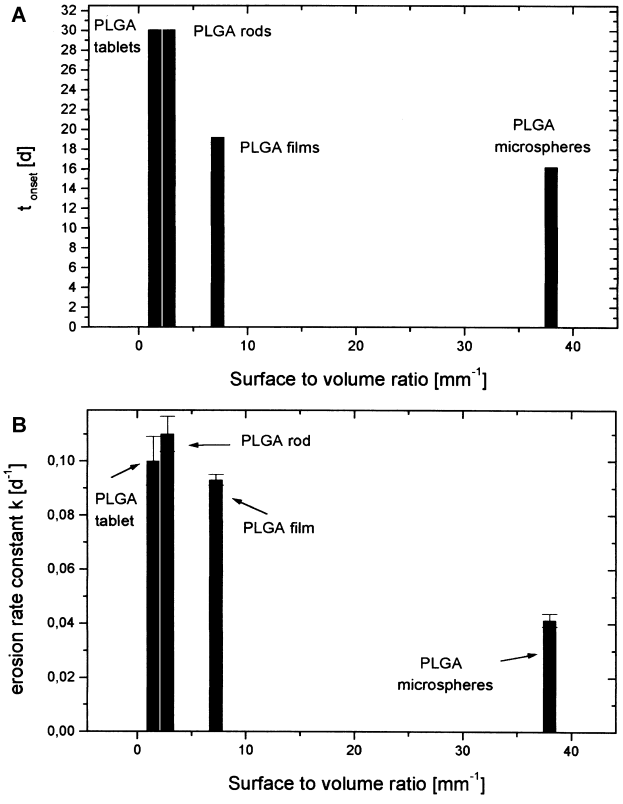

Fig. 9. (a) Influence of the geometry on the onset time (t_{on}) of erosion. (b) Influence of the geometry on the erosion rate (k_{app}).

Interestingly, the kinetic parameters were affected by device geometry as shown in Fig. 9. In the case of microspheres, the high surface to volume ratio led to a shorter onset time of erosion (Fig. 9a). This is expected from an erosion process that proceeds from the inside to the outside, as shown in the micrographs of eroding microspheres or even film samples. In the case of rods a bulk erosion kinetic was observed, although the SEM study did not demonstrate a hollow structure during erosion. Similar results were also obtained under in vivo conditions, where implants prepared by injection molding of poly(lactic acid) (PLA) only occasionally showed a hollow structure [13].

The rate of erosion decreased in the rank order rods and tablets > films > microspheres (Fig. 9b). Since the degradation rates did not follow this order, the direct correlation of the degradation and erosion rate is potentially misleading, as shown under in vivo conditions as well [7]. In this context it is worth mentioning that the in vivo erosion rate is in excellent agreement with our findings. For cylindrical PLGA implants $k = 0.153 \pm 0.04$ (days^{-1}) was reported [7]. The difference between in vivo and in vitro erosion of PLGA could be identified as the earlier onset of erosion, namely after 22 days. In the case of films the scanning electron micrographs showed a pore formation at day 20, according to previous findings in Ref. [2]. Interestingly, the time point of pore formation correlates with the onset time of erosion in the case of films, suggesting a diffusion process of degradation products. Indeed, the observations of porous microspheres after 40 days and pore-free implants after 30 days confirm this observation. Therefore, the different erosion rates are the result of pore diffusion inside eroding PLGA devices. A quantification of the release of degradation products by pore diffusion from a PLGA matrix requires further investigations, since this is a complex steady state process [25] which is influenced by the rigidity of the polymer chains, the concentration gradient, the pore size and the rate of pore formation.

In summary, the morphological characterization of different PLGA and ABA devices demonstrated that the erosion is controlled by the degradation in the case of ABA triblock copolymers, whereas a complex pore diffusion process is the rate limiting step for the erosion of PLGA. These findings point to the fact that parenteral delivery systems prepared from ABA triblock copolymers seem to be more appropriate for the proteins and acid-sensitive molecules than those from PLGA. Moreover, the degradation mechanism of polyesters on a micro-morphological scale requires further investigations.

5. Conclusions

Among the factors affecting erosion of biodegradable drug delivery systems the geometry and the swelling properties were investigated for ABA triblock copolymers and PLGA.

In the case of ABA copolymers, the PEO content is responsible for the wetting of films and for the extent of swelling of the device. The micrographs of eroding ABA devices confirmed the swollen structure of the matrix during the entire degradation. The different devices prepared from ABA demonstrated comparable profiles of degradation and erosion; conclusively, the device geometry is not a rate limiting factor for the continuous erosion process.

PLGA degraded faster than ABA but nevertheless polymer hydrolysis proceeded regardless of the geometry. In the case of PLGA, the geometry of the devices had a strong influence on the bulk erosion profile. While demonstrating the shortest onset time and the lowest rate of erosion PLGA microspheres provided the most favorable bulk erosion profile with regard to a continuous release system. The micrographs of eroding films and microspheres clearly showed pores and therefore the kinetic of PLGA erosion is rather influenced by a complex pore diffusion process than by the degradation of the polymer chain.

Conclusively, the current study demonstrated two different approaches to obtain a continuous erosion profile for biodegradable drug delivery systems: variation of the PLGA geometry or chemical insertion of a hydrophilic B-block leading to ABA triblock copolymers.

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