Effects of Polymer Degradation on Drug Release from PLGA-mPEG Microparticles: A Dynamic Study of Microparticle Morphological and Physicochemical Properties

Jin Li, Guoqiang Jiang, Fuxin Ding

Department of Chemical Engineering, Tsinghua University, Beijing 100084, People's Republic of China

Received 11 September 2007; accepted 20 November 2007
DOI 10.1002/app.27823
Published online 19 February 2008 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: *In vitro* degradation and drug release of poly (DL-lactide-*co*-glycolic acid)-methoxypoly(ethyleneglycol) (PLGA-mPEG) microparticles were performed through a dynamic monitoring process, to investigate the effect of degradation on drug release from microparticles and to elucidate the dominant factor that governed the drug release kinetics. Methotrexate (MTX), an antirheumatic drug, was employed as the model drug. Drug release showed a triphasic pattern: an initial burst release followed by a lag period and subsequently a second burst release. The initial burst release was mainly caused by dissolution and diffusion of drugs at/near the surface of microparticles. During the following lag period, microparticles suffered little morphological changes, whereas the physicochemical changes of the polymer contributed to the increasing mobility of drug molecules, and then provided transport pathways for drug release. Later on, the erosion of the polymer matrix became significant. Morphology study showed that the trend of porosity change was in accordance with last phase release profile, indicating that porosity played an extremely important role in controlling drug release. The liberation pattern of mPEG was elucidated. The more pores formed, the more mPEG chains were exposed to the aqueous medium and disengaged from the polymer. Scanning electron micrography observation further confirmed these conclusions. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 108: 2458–2466, 2008

Key words: poly(DL-lactide-*co*-glycolide)-methoxypoly(ethyleneglycol) microparticles; drug release kinetics; degradable polymers; morphological changes; porosity

INTRODUCTION

Poly(DL-lactide-*co*-glycolic acid) (PLGA)-based microparticles have been widely applied for sustained/controlled drug release, because they have been shown not to cause adverse tissue reaction and can be hydrolyzed in the body to form products that are easily resorbed or eliminated. Most importantly, they can control the resulting drug release kinetics over periods of days or months. These microparticles could promote the therapeutic efficiency and reduce side effects of medical treatments.[1]

However, knowledge available concerning the controlled drug release from polyester-based microparticles is still limited. Many factors can be involved in the control of drug release from these erodible microparticles. In addition to drug diffusion in the matrix, polymer degradation, which undertakes both morphological and physicochemical changes, should also be considered. Recently, many studies on the degradation behavior of PLGA microparticles in aqueous media under conditions mimicking those found in biological fluids have been reported. The initial porosity, drug loading, polymer molecular weight, as well as the degradation products were investigated,[2–5] and mathematical models were established.[6,7] However, the changes of drug release controlling factors such as porosity during polymer degradation have been rarely addressed. It is well known that the porosity of erodible particles can strongly influence the resulting drug diffusion release kinetics.[4,8]

On the other hand, since the hydrophobic drawback of PLGA polymer, the incorporation of methoxypoly(ethyleneglycol) (mPEG) domain has several advantages over PLGA. Low-molecular weight mPEG is a nontoxic, water-soluble polymer which has been widely used to improve the biocompatibility of the blood contacting materials.[9] It is not degraded and could be easily excreted out of human body. The hydrophilic effect of mPEG on accelerating drug release rate has been approved by many investigators.[10,11] The mPEG chains of PLGA-mPEG acting as a surface modifier of hydrophobic PLGA

Correspondence to: F. Ding (dingfx@tsinghua.edu.cn).
Contract grant sponsor: National Natural Science Foundation of China; contract grant number: 20576057.
Contract grant sponsor: Tsinghua Basic Research Foundation; contract grant number: JCqn2005033.

network, could enhance the permeation of water into the center of microparticles, thus increase the polymer degradation rate, reduce the acidic microenvironment because of the diffusion of acidic breakdown products, and accelerate the diffusion of drug in the matrix. As compared with PLGA microparticles, the PLGA-mPEG microparticles exhibited ability to increase both the encapsulation efficiency (EE) and drug release rate. This block copolymer could be more facilitate the hydrophobic small drugs[12] and hydrophilic biomolecular drugs, such as proteins and antigens.[11,13–15] *In vivo* tests have shown that PLGA-PEG based systems exhibited improved biological properties such as stability in gastrointestinal (GI) tract and specific disposition to reach the lymphatic system after oral and nasal administration, thus favoring the drugs to transport through physiological barriers for target delivery.[16] They are very promising systems for future biomedical applications. However, the disengagement of mPEG from the polymer matrix during microparticles degradation remained unclear. The investigation of mPEG release pattern is necessary for determining the way that mPEG present in the polymer matrix and its relationship with the polymer degradation kinetics.

The purpose of this article was to characterize the degradation pattern of the erodible PLGA-mPEG microparticles and to monitor the effects of dynamic morphological changes of porosity, particle shape, size, and surface character during microparticles degradation on the drug release, so as to elucidate dominant factors that govern the drug release from microparticles. Physicochemical changes of polymer molecular weight, mass loss, as well as glass transition temperature (T_g) were also investigated to adequately analyze polymer degradation behavior. Additionally, the liberation of mPEG was detected to specify its correlation with polymer degradation in this system. Methotrexate (MTX), one of the most frequently used antirheumatic drugs in the treatment of rheumatoid arthritis (RA), was employed as the model drug. The relationship between drug release and polymer degradation kinetics was characterized to specify the dominant factors by a critical analysis of experimental data. The effect of MTX on polymer degradation was also examined by comparing drug-loaded and drug-free microparticles.

MATERIALS AND METHODS

Materials

PLGA (M_w = 50,000, LA : GA = 75 : 25)-mPEG (3000) and PLGA (M_w = 30,000, LA : GA = 75 : 25) were purchased from Jinan Daigang Biotech (Shandong, China). Poly(vinyl alcohol) (PVA) (hydrated, M_w = 13,000) was a gift from Prof. Tan (Tianjin University, Tianjin, China). MTX was purchased from Hubei Zhanwang Sanxin Chempharma (Hubei, China). mPEG (M_w = 3000) standard was supplied by Alfa Aesar (UK). Polystyrene molecular weight standards (M_w ranging from 1000 to 70,000) were supplied by Fluka.

All other solvents and chemicals used were of analytical grade.

Microparticle preparation

Drug-loaded microparticles were prepared by solid-in-oil-in-water solvent evaporation method. In brief, the polymer (1 g) was dissolved in methylene chloride (20 mL) and then MTX was suspended in it. The drug suspension was slowly dispersed into 100-mL PVA solution (1%) and magnetically stirred at 900 rpm for 5 min to form the primary O/W emulsion. This emulsion was then dispersed into 1-L external water phase with magnetic stirrer at 400 rpm for 4 h under room temperature and ambient pressure, till all the organic solvent evaporated. The solidified microparticles were recovered by filtration and washed three times with distilled water. The washed microparticles were lyophilized for 4 h and stored in a desiccator at room temperature. Drug-free PLGA-mPEG and PLGA microparticles were prepared using the same method as above, except for the drug suspension process.

As already reported, drug release and degradation kinetics highly depended on the particle size,[6,8,17,18] so that the microparticles were sieved to uniform size (average pore size of the sieves: 57 and 53 μm) throughout whole experiments.

Encapsulation efficiency

Ten milligrams of drug-loaded microparticles were dissolved in 2 mL of methylene chloride. MTX was then extracted with 10-mL phosphate buffered salines (PBS) (pH 7.4, 0.1*M*). The drug concentration in the aqueous phase was measured using a UV–vis spectrophotometer (TU-1810, Beijing Purkinje General Instrument) at 305 nm. The EE was calculated as follows: (the amount of MTX in the microparticles/the theoretical amount of MTX in the microparticles) × 100%.

In vitro drug release test

The *in vitro* MTX release test were conducted by suspending 60 mg sieved microparticles in 10 mL of PBS (pH 7.4, 0.1*M*) and maintained at 37°C under continuous shaking (100 rpm). All dissolution tests were performed in sink conditions, 4-mL aliquots of the medium were withdrawn and the same volume of fresh buffer was added at certain time intervals.

Triplicate samples were recovered. The concentration of MTX in the release medium was measured by UV–vis spectrophotometry.

Degradation study

Two hundred milligrams of sieved microparticles were incubated in 20 mL of PBS (pH 7.4, 0.1*M*), and maintained at 37°C under continuous shaking (100 rpm). At certain time intervals, microparticles were recovered by filtration and lyophilized. The collected microparticles were then applied for pore size distribution, surface area characterization, scanning electron micrography (SEM), gel permeation chromatography (GPC), and differential scanning calorimetry (DSC) analysis.

The mPEG liberated during PLGA-mPEG degradation was determined by a colorimetric assay.[19,20] Samples (1 mL of the drug release medium) were diluted with 2-mL PBS (pH 7.4, 0.1*M*) to this solution, 75 μL of potassium iodide solution (0.02 g/mL) saturated with iodine was added. The sample was mixed using a small glass rod, and after 5 min the absorbance was detected at 500 nm using UV–vis spectrophotometry. The linearity was established in the range of mPEG concentrations measured (1–15 μg/mL).

The weight–average molecular weights (M_w) of degraded polymers were determined by GPC. An apparatus was used in which a LC-20AT pump was connected to a RID-10A refractive index detector. The analytical column was TSK-GEL H Type from TOSOH. Assay conditions for the analysis of 1 mg/mL polymer dissolved in tetrahydrofuran were as follows: 20-μL sample injection, a mobile phase of tetrahydrofuran flowing at 1 mL/min. The standard curve was prepared using a series of polystyrene standards.

DSC was carried out from 25 to 120°C using a Seiko DSC6200 under nitrogen flow (50 mL/min) at 5°C/min.

Morphology characterization

SEM was performed on a JEOL JSM 7401F microscope operating at 1.0 kV, to observe the surface morphology of microparticles. The microparticles were coated with gold before applied to the SEM observation.

Macropore size distributions and intrusion volumes were recorded by mercury intrusion porosimetry using a micromeritics autopore IV 9510 porosimeter. Nitrogen adsorption–desorption isotherms were measured at 77 K using a Quantachrome Autosorb-1-C Chemisorption-Physisorption Analyzer after the samples were outgassed for about 30 min at 25°C. The Brunauer-Emmett-Tellern (BET) surface area was calculated from the adsorption branches in the relative pressure range of 0.05–0.25.

Particle size was determined by SEM. For each sample the diameter of 50–70 microparticles was measured and averaged by a SMILE VIEW software.

RESULTS

Surface morphology of microparticles before degradation

The SEM pictures of the morphology of drug-free microparticles were shown in Figure 1. The chains of mPEG twisted to form a network and covered the surface of the PLGA-mPEG microparticles. It was evident that some of mPEG chains were exposed at the surface because of their hydrophilic nature during the microparticles preparation process and rest of them were entangled within the matrix, whereas, our previous study showed that, drug-free PLGA microparticles displayed a relatively smooth and nonporous surface. Furthermore, Wang et al. pointed out that pores in the size range of 0.1–1.0 μm which were initially present at the surface of microparticles were probably correlated with the initial burst within their system (octreotide acetate-loaded PLGA microparticles).[21,22] In this study, it should be emphasized that the surface of PLGA-mPEG microparticles observed by SEM [Fig. 1(c)] could not indicate the existence of macropores (size $>$ 50 nm) because of the mPEG chain masking effect, and meso- and nanopores would not be visible with the applied SEM technique. The pore size distribution and surface area measurement were further determined by mercury porosimetry and N_2 adsorption technique.

Morphological changes of microparticles during degradation

Morphological changes of degraded PLGA-mPEG microparticles including porosity, particle size, and surface were monitored throughout the 49 days incubation in PBS (pH 7.4, 0.1*M*) at 37°C.

BET surface area

First, the BET surface area of PLGA-mPEG microparticles was measured by N_2 adsorption technique and calculated in the course of incubation, and data is rendered in Table I. Recent studies have demonstrated a bulk degradation and erosion heterogeneous mechanism in PLGA microparticles.[18] During the degradation process, plenty of pores were formed and acted as transport pathways for drug and water molecules, resulting in a growth of the surface area of the microparticles. However, the surface area calculated by BET method was considerably low ($<$10 m^2/g), as seen in Table I. As N_2

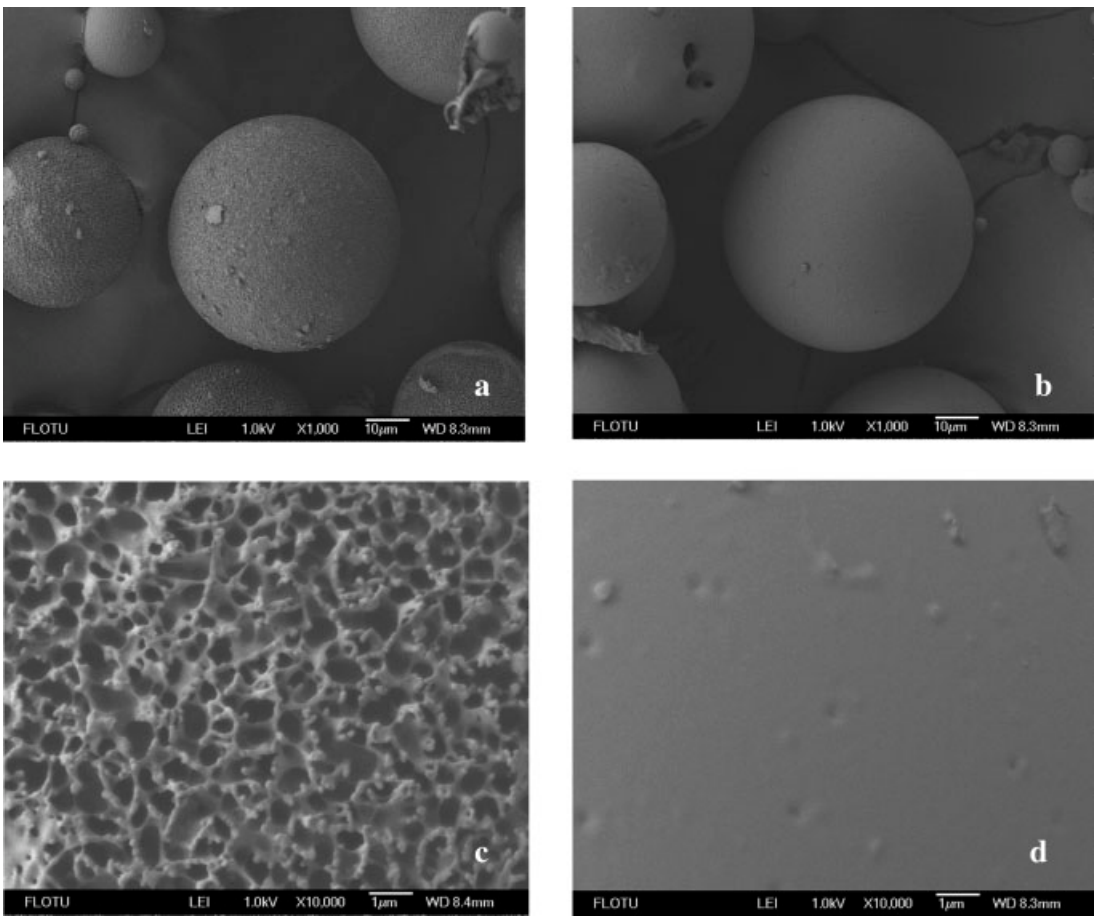

Figure 1 SEM photographs of PLGA-mPEG and PLGA microparticles before incubation in PBS (pH 7.4, 0.1*M*). (a) PLGA-mPEG microparticles with 1000 times magnitude. (b) PLGA microparticles with 1000 times magnitude. (c) Surface of PLGA-mPEG microparticles with 10,000 times magnitude. (d) Surface of PLGA microparticles with 10,000 times magnitude.

adsorption technique being applied in our experiment had accuracy only for meso- or micropores. The result suggested that there were no appreciable mesopores or micropores in the matrix in the dry state, and also did not form a remarkable amount during the degradation process,[23,24] indicating that meso- or micropores contributed little to the transport pathways for drug or water molecules. The macropores were further investigated by mercury porosimetry. Interestingly, drug-loaded microparticles showed a relatively higher BET surface area compared with drug-free microparticles (values in parentheses). This may be related to the existence of MTX. The release of MTX from the polymer left small pores for the matrix, and therefore, the drug-loaded microparticles exhibited higher BET surface area. It should also be noticed that with the incubation continued, the BET surface area of both drug-loaded microparticles and drug-free microparticles altered irregularly, and dropped to the lowest at the end of the 5th week. This might arise from a transition state of partial masking and forming meso- or micropores by degrading and dissolving phenomena. Based on our experiment results, the amount of meso- and micropores was far less than that of mac-

TABLE I
Characterization Data for MTX-Loaded PLGA-mPEG Microparticles During 49 Days Incubation in PBS (pH 7.4, 0.1*M*) at 37°C

Sample ID	Incubation time (day)	BET surface area (m^2/g)[a]	Intrusion volume (mL/g)[b]
0	0	9.4948 (5.5227)	0.6408
1	7	6.2323 (1.7542)	0.5093
2	14	6.7859 (2.9994)	0.642
3	21	4.7793 (5.3442)	1.0391
4	28	6.4188 (7.3385)	1.0291
5	35	1.6333 (0.3132)	1.3043
6	42	8.3218 (3.5947)	2.7962
7	49	8.3404 (7.4537)	4.2506

[a] As characterized by N_2 sorption–desorption and calculated by Brunauer-Emmett-Teller(BET) method. The values in parentheses refer to drug-free microparticles.

[b] Measured by mercury porosimetry over the pore size range from 20 nm to 100 μm.

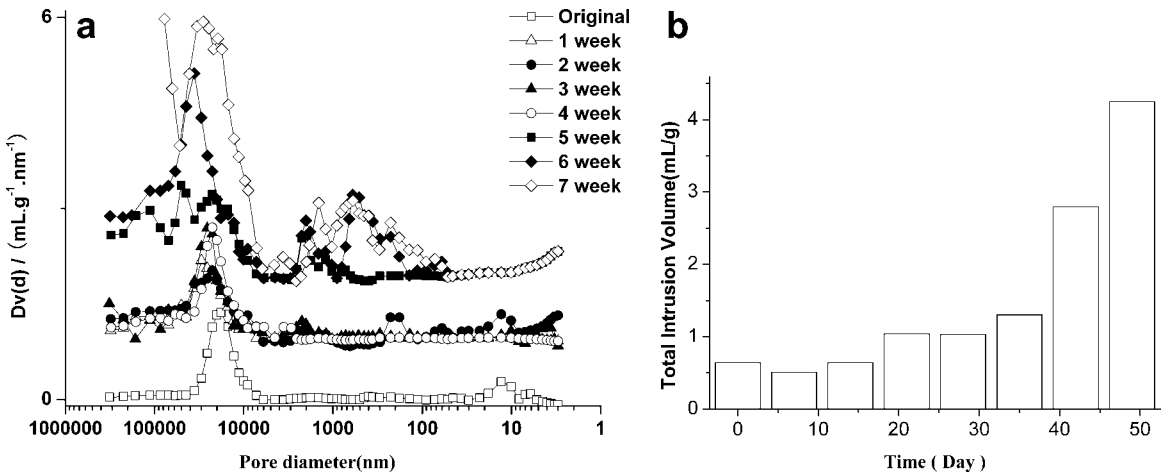

Figure 2 Macroporosity of MTX-loaded PLGA-mPEG microparticles measured by mercury porosimetry for each week during 49 days incubation in PBS (pH 7.4, 0.1*M*) at 37°C. (a) Pore size distribution of microparticles after lyophilized for each week. (b) The change of intrusion volume as a function of incubation time.

ropores. And also, they were much more easily to be blocked than macropores. So a small fluctuation would lead to a remarkable change of BET surface area. However, this change would not have significant impact on the other microparticle changes such as weight loss.

Macropore size distribution

Secondly, macropore size distribution during incubation was characterized by mercury porosimetry and the experimental data is shown in Figure 2(a). Before incubation, the macropore size distribution of microparticles was relatively narrow, with the peak macropore size of 18 μm. The pore size distribution was kept narrow for 4 weeks, except that the peak pore size rose up to 29 μm. During this period, the intrusion volume (macropore volume) dropped slightly at the beginning and then increased by 61% at the 3rd week, seen in Figure 2(b). From the 5th week to the end of incubation time, the macropore size distribution broadened largely and many smaller macropores formed, with size ranging from 800 nm to 50 μm (the pore size greater than 50 μm was caused by the interspace of microparticles and was out of consideration), whereas the intrusion volume increased little in the 5th week, and increased dramatically in the 6th week and 7th week. As it could be seen from Figure 2(a), in the 5th week, although the pore size distribution started to broaden, the amount of pores did not increase dramatically compared with the amount of pores in the 6th and 7th weeks. This could explain the discrepancy of intrusion volume increase between the 5th week and the following weeks.

Particle size

Particle size alteration during incubation was also investigated in this study. Many investigations focused on the size influence on the drug release and degradation behavior, for it induces a diffusion path length effect and plays a crucial role for the occurrence of autocatalytic effect, which rises from the decrease in micro-pH within the system.[6,7,25,26] It is necessary to specify whether the particle size changes during drug release and polymer degradation, especially for the simulating and modeling studies. Several mathematical models considering polymer degradation/erosion were established, and the radii of the microparticles within the models were set as time dependent.[6,7] In this study, microparticles were sieved before incubation and the particle size was controlled within 53–57 μm. Several studies had approved the accuracy of SEM technique on particle size measurements,[27] so the SEM technique was applied in our study. We also measured particle size using a Mastersizer 2000 and evaluated by a volume concentration (data was not shown), but the result was imprecise because of many disturbances such as particle aggregation and the existence of impurities. The particle size was monitored throughout the 7-week-drug release period, and the result is shown in Figure 3. The particle size remained unchanged and no particle collapse occurred till the end of 7th week when drug was completely released. The same phenomenon emerged with the drug-free microparticles. This is important for simulating studies, which correlate both drug release and polymer degradation processes. The model can be greatly simplified as the radius of microparticle being considered to be time independent. Nonetheless, it could not be concluded

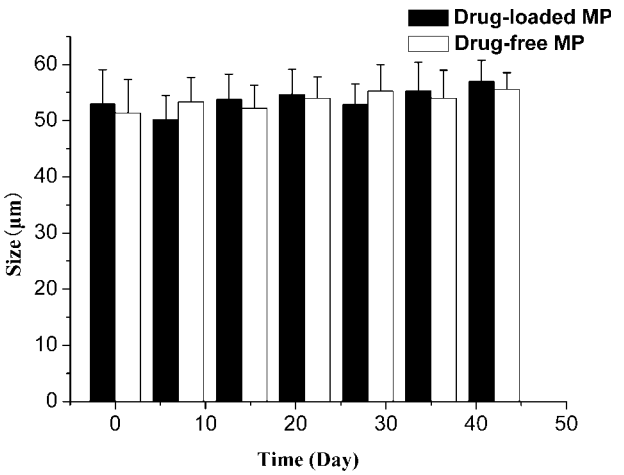

Figure 3 Particle size changes versus incubation time during PLGA-mPEG microparticles being exposed to PBS (pH 7.4, 0.1*M*) at 37°C. Samples were lyophilized before measurement. MP, microparticles.

that the particle size was unchanged till all the polymer was completely degraded, and it might also not be adaptable for other drug-loaded systems such as carrying drugs with a big molecule volume.

Surface morphology

The surface morphology of microparticles during incubation is shown in Figure 4. The sphericity of microparticles maintained well, and there was no collapse or breakdown occurred, except for a little aggregation in the 6th and 7th week. However, the aggregation broken up during microparticles filtration and lyophilization process, so it could not be seen in the SEM image. The surface of microparticles changed from spinous to smooth and became obvious porous at the end of 5th week, which corresponded well to the degradation data obtained from mPEG liberation (see section ''mPEG Liberation'') and porosity: mPEG at the surface of microparticles degraded foremost, and the pore intrusion volume increased dramatically in the 6th week.

mPEG liberation

The introduction of mPEG enhanced the hydrophilicity of hydrophobic PLGA polymer. The liberation of mPEG was measured to specify its liberation pattern and its correlation with polymer degradation. Figure 5 showed that the mPEG liberation appeared to start soon after microparticles were incubated in the degradation medium. To compare with pore volume increases, concomitant increases were also observed in the liberation of mPEG during degradation. It suggested that due to its hydrophilic characteristic, the mPEG at the surface of matrix which exposed to the aqueous surroundings was firstly disengaged from the polymer chains. As the pore volume increased, the mPEG which intertwisted within the PLGA chains began to expose at the pore walls. The more pore formed, the more mPEG exposed and liberated as being contacted with water. Additionally, there was no significant difference in mPEG liberation between drug-loaded and drug-free microparticles in the first 6 weeks, indicating that small MTX molecules had little effect on the mPEG libera-

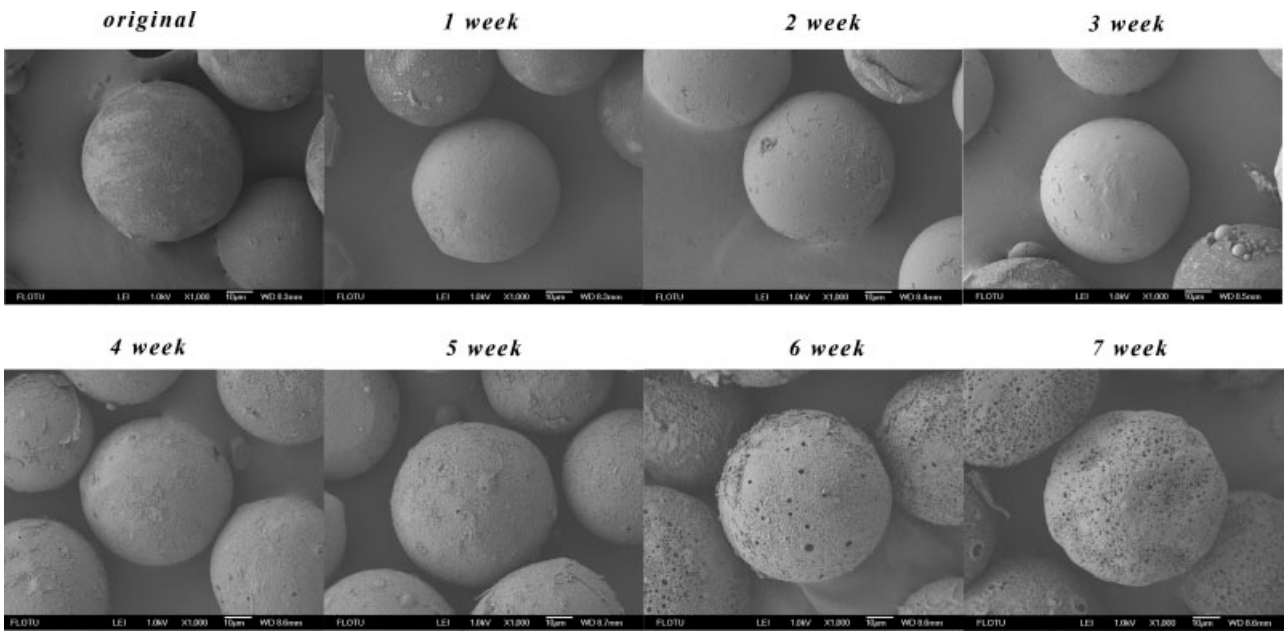

Figure 4 SEM photographs of PLGA-mPEG microparticles for each week during incubation in PBS (pH 7.4, 0.1*M*) at 37°C.

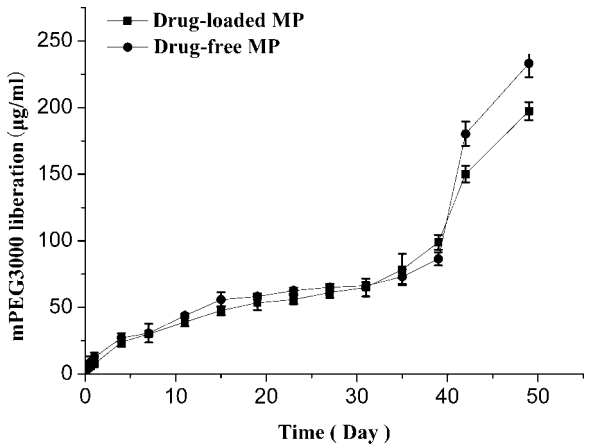

Figure 5 mPEG liberation from PLGA-mPEG microparticles as a function of incubation time in PBS (pH 7.4, 0.1*M*) at 37°C. MP, microparticles.

tion and thus had little effect on the water uptake rate, though they might contribute a little bit to the formation of small pores.

Physicochemical changes of microparticles during degradation

Polymer molecular weight, mass loss, and glass transition temperature (T_g) were measured during PLGA-mPEG microparticles incubation in PBS (pH 7.4, 0.1*M*) at 37°C, to investigate the effect of physicochemical changes on drug release kinetics.

For polyester-based microparticles, the hydrolization of polymer occurred when water was imbibed into the polymer matrix. The decrease of molecular weight could significantly increase the mobility of the drug molecules, which altered to the drug release kinetics. Previous studies have shown that PLGA degradation experimentally followed pseudo first-order kinetics.[8,18,28] The decrease of polymer

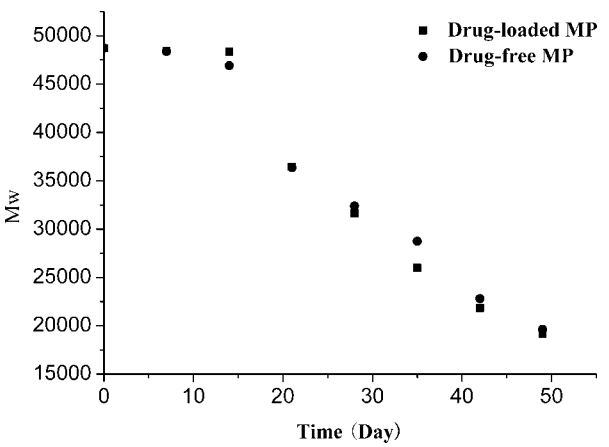

Figure 6 Dependence of M_w on degradation time during microparticle incubated in PBS (pH 7.4, 0.1*M*) at 37°C.

weight–average molecular weight (M_w) can be calculated as follows:

$$M_w(t) = M_{w0} \exp(-k_{\text{degr}} t), \quad (1)$$

where M_{w0} is the polymer molecular weight before exposure to the release medium and k_{degr} is the pseudo first-order degradation rate constant of the polymer.

In this degradation study, it was found that the M_w remained approximately unchanged for 14 days before an apparently pseudo first-order degradation began, as shown in Figure 6. This phenomenon have been reported in other degradation studies,[7,29,30] in which an explanation was given that the observed lag phase might be due to the washing out of low-molecular weight fraction of the polymer. The experimental data excluding the first three data points were plotted versus time and the curve were fitted with eq. (1) to determine the k_{degr}. The linear regression results are shown in Table II. Good agreement between theory and experiment was obtained for both drug-loaded and drug-free microparticles. The existence of MTX in some sort accelerated the degradation of the polymer, which was consistent with the former morphological changes analysis.

The change of M_w undertook a steady decrease kinetic and was not correlated with that of pore volume, which showed burst patterns. The dry weight of microparticles during degradation was calculated as follows, to further analyze the polymer degradation behavior:

$$\text{Dry weight } (\%)(t) = \text{dry weight } (t) \times 100\%/\text{dry weight } (t = 0) \quad (2)$$

The result is shown in Figure 7. It exhibited a negligible loss during the first 30 days and lost quickly when the burst pore volume occurred. This was in consistence with the morphological changes of microparticles, revealing that the erosion not polymer chain hydrolization was predominant in the degradation for the rest of incubation period.

The decrease in glass transition temperature (T_g) indicated the polymer matrix physically changed from a glassy state to a rubbery state owning to the water uptake (water acting as a plasticizer upon exposure to the release medium) and the M_w

TABLE II
Pseudo First-Order Kinetics Describing PLGA Degradation in the Investigated Drug-Loaded and Drug-Free Microparticles Calculated by Eq. (1)

Sample	k_{degr}	r^2
Drug-loaded	0.026	0.99
Drug-free	0.024	0.99

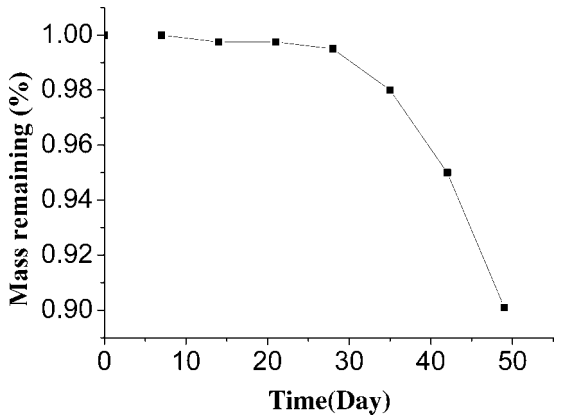

Figure 7 Dependence of weight mass loss on degradation time during microparticle incubated in PBS (pH 7.4, 0.1*M*) at 37°C. Samples were lyophilized before measurement.

decrease in the polymer backbone.[18,31,32] The transition of polymer from glassy state to a rubbery state can also enhance the mobility of drug molecules. T_g of the microparticles during degradation was measured by DSC after lyophilization, seen in Figure 8. In the first 5 weeks, it showed an initial increase and a following continuous decrease in T_g for both drug-loaded and drug-free microparticles. The increase of T_g at the beginning could be attributed to the rapid loss of a low-molecular weight fraction of polymer from the matrix as previously discussed. In the following days, the T_g of both drug-loaded and drug-free microparticles decreased in a steady trend. And T_g of drug-loaded microparticles decreased faster than that of drug-free microparticles. However, in the 6th week, the T_g of drug-loaded microparticles increased dramatically, which might involved two mechanisms. On one hand, the remaining MTX might crystallize as being contacted with water for a long time, it acted as bond which caused the polymer to form a more rigid physical state, and the T_g of the polymer increased as such. On the other hand, since the degradation happened earlier in amorphous region than in crystal region of the polymer, it was common that at the end of degradation, the elimination of the amorphous region could also to some extent made contribution to the increase of T_g.[33] Whatever, the increase of T_g more or less hindered the degradation rate of the polymer, but without a significant effect.

In vitro drug release kinetics

The release kinetic of MTX from PLGA-mPEG microparticles (EE = 81.18%) incubated into PBS (pH 7.4, 0.1*M*) at 37°C is presented in Figure 9. The *in vitro* release of MTX exhibited an apparent triphasic release pattern: an initial burst release, followed by a lag period, and subsequently a second burst release. On the first day, ~ 16% of MTX was released; the following lag period lasted for 34 days, and about 35% of drug was released at a relative slow rate; at the end of the 4th week, the drug release accelerated dramatically, till the complete MTX release after 7 weeks of incubation. This was in agreement with the release pattern observed with PLGA and PELA microparticles,[13,34,35] indicating that the introduction of mPEG did not alter the release profiles of PLGA microparticles.

Drug release kinetics highly depended on the morphological and physicochemical properties changes during degradation. The initial burst of drug release was mainly attributed to the dissolution and diffusion of drugs at or near the surface of microparticles. During the following 34 days of incubation, microparticles suffered little morphological changes, whereas the weight–average molecular weight of the polymer began to decrease and the matrix physically

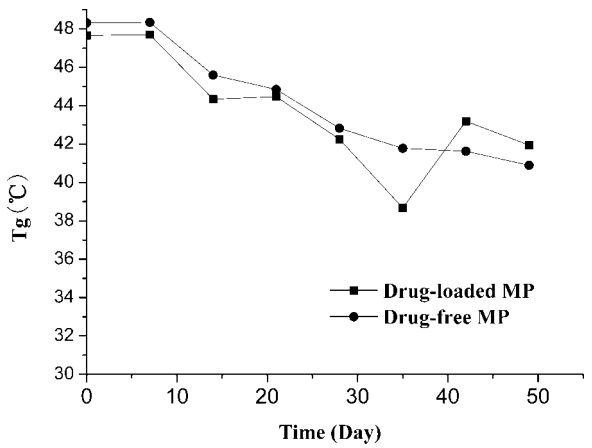

Figure 8 Decrease in the glass transition temperature (T_g) of PLGA-mPEG microparticles as a function of incubation time in PBS (pH 7.4, 0.1*M*) at 37°C.

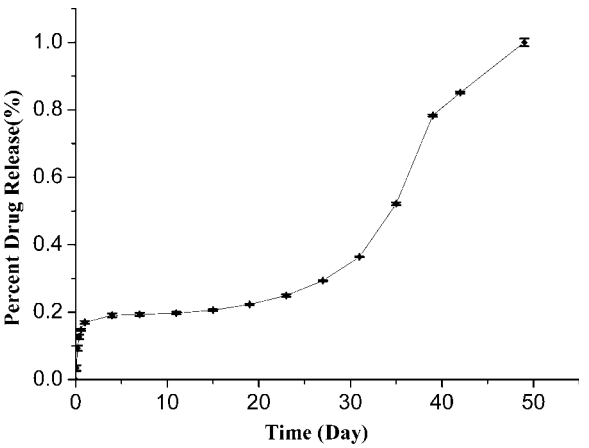

Figure 9 *In vitro* release profile of MTX-loaded PLGA-mPEG microparticles incubated in PBS (pH 7.4, 0.1*M*) solution at 37°C.

changed to a more rubbery state as the water was imbibed into the polymer phase. These physicochemical changes enhanced the mobility of the drugs, and then the drug transport pathways were mainly provided by the polymer phase. The morphology changes became obvious at the end of 5th week. At this time, the changes of pore volume and weight mass exhibited a shift pattern that was synchronous with the *in vitro* drug release. That is, during the first 5 weeks, the pore volume changed steadily. From the end of 5th week, the pore volume increased considerably and the volume of water uptake began to rise. This enhanced the diffusion (due to concentration gradients) and increased drug release rate, thus the second drug burst release emerged. The correlation between pore volume change and drug release pattern indicated that, to some point, the pores became the dominant transport pathways during the last drug release phase.

CONCLUSIONS

This study exhibited the dynamic degradation behavior of PLGA-mPEG microparticle and its correlation with drug release kinetics. The pattern of mPEG liberation was also elucidated to show how it worked on polymer degradation as a water-uptake enhancer. From the experimental results, drug release showed a triphasic pattern as same as the reported PLGA microparticles, indicating that the introduction of mPEG into the hydrophobic PLGA polymer did not alter the drug release pattern of PLGA microparticles. For each drug release phase, polymer degradation induced both physicochemical and morphological changes of microparticles, and these changes played important roles in drug release kinetics. Compared with the hydrophobic and smooth surface of PLGA microparticle, some of the mPEG chains covered the surface of PLGA-mPEG microparticle and acted as a water-sopping shell. The others were entangled within the polymer matrix. In the course of degradation process, concomitant mPEG liberation was observed as the pore volume increased. The more pore formed, the more mPEG chains were exposed to the aqueous medium. Besides, the particle sizes of microparticles remained unchanged throughout the whole drug release period. SEM observation further confirmed these conclusions. The existence of drug accelerated the degradation of matrix somewhat, because of the complicated interaction of drug and polymers.

References

1. Jiang, W.; Gupta, R. K.; Deshpande, M. C.; Schwendeman, S. P. Adv Drug Delivery Rev 2005, 57, 391.
2. Belbella, A.; Vauthier, C.; Fessi, H.; Devissaguet, J. P.; Puisieux, F. Int J Pharm 1996, 29, 95.
3. Giunchedi, P.; Conti, B.; Scalia, S.; Conte, U. J Controlled Release 1998, 56, 53.
4. Sant, S.; Nadeau, V.; Hildgen, P. J Controlled Release 2005, 107, 203.
5. Yoo, J. Y.; Kim, J. M.; Seo, K. S.; Jeong, Y. K.; Lee, H. B.; Khang, G. Biomed Mater Eng 2005, 15, 279.
6. Berkland, C.; Kim, K.; Pack, D. W. Pharm Res 2003, 20, 1055.
7. Raman, C.; Berkland, C.; Kim, K.; Pack, D. W. J Controlled Release 2005, 103, 149.
8. Klose, D.; Siepmann, F.; Elkharraz, K.; Krenzlin, S.; Siepmann, J. Int J Pharm 2006, 314, 198.
9. Peter, J. P.; Lucie, B.; Bohdana, D.; Frank, S. B.; Dennis, E. D. J Controlled Release 2003, 90, 323.
10. Zhu, K. J.; Lin, X.; Yang, S. J Appl Polym Sci 1990, 39, 1.
11. Huang, Y. Y.; Chung, T. W.; Tzeng, T. W. Int J Pharm 1997, 156, 9.
12. Ruan, G.; Feng, S. S. Biomaterials 2003, 24, 5037.
13. Li, X.; Deng, X.; Yuan, M. L.; Xiong, C.; Huang, Z.; Zhang, Y.; Jia, W. Int J Pharm 1999, 178, 245.
14. Li, X.; Deng, X.; Yuan, M. L.; Xiong, C.; Huang, Z.; Zhang, Y.; Jia, W. J Appl Polym Sci 2000, 78, 140.
15. Li, X.; Deng, X.; Huang, Z. Pharm Res 2001, 18, 117.
16. Palakurthi, S.; Vyas, S. P.; Diwan, P. V. Int J Pharm 2005, 290, 55.
17. Berkland, C.; King, M.; Cox, A.; Kim, K.; Pack, D. W. J Controlled Release 2002, 82, 137.
18. Siepmann, J.; Elkharraz, K.; Siepmann, F.; Klose, D. Biomacromolecules 2005, 6, 2312.
19. Burkersroda, F. V.; Gref, R.; Giipferich, A. Biomaterials 1997, 18, 1599.
20. Avgoustakis, K.; Beletsi, A.; Panagi, Z.; Klepetsanis, P.; Karydas, A. G.; Ithakissios, D. S. J Controlled Release 2002, 79, 123.
21. Wang, J.; Wang, B. M.; Schwendeman, S. P. In Proceedings AAPS Annual Meeting, Indianapolis, 2000a.
22. Wang, J.; Wang, B. M.; Schwendeman, S. P. In Proceedings AAPS Annual Meeting, Indianapolis, 2000b.
23. Zhang, H.; Hardy, G. C.; Rosseinsky, M. J.; Cooper, A. I. Adv Mater 2003, 15, 78.
24. Zhang, H.; Hardy, G. C.; Khimyak, Y. Z.; Rosseinsky, M. J.; Cooper, A. I. Chem Mater 2004, 16, 4245.
25. Berkland, C.; Kim, K.; Pack, D. W. J Controlled Release 2001, 73, 59.
26. Li, L.; Schwendeman, S. P. J Controlled Release 2005, 101, 163.
27. Ruan, G.; Feng, S. S.; Li, Q. T. J Controlled Release 2002, 84, 151.
28. Siepmann, J.; Faisant, N.; Akiki, J.; Richard, J.; Benoit, J. P. J Controlled Release 2004, 96, 123.
29. Kenley, R. A.; Lee, M. O.; Randolph, I. T.; Mahoney, T. R.; Sanders, L. M. Macromolecules 1987, 20, 2398.
30. Liang, L. S.; Jackson, J.; Min, W.; Risovic, V.; Wasan, K. M.; Burt, H. M. J Pharma Sci 2004, 93, 943.
31. Jamshidi, K.; Hyon, S. H.; Ikada, Y. Polymer 1988, 29, 2229.
32. Faisant, N.; Siepmann, J.; Benoit, J. P. Eur J Pharm Sci 2002, 15, 355.
33. Park, T. G. Biomaterials 1995, 16, 1123.
34. Chiu, L. K.; Chiu, W. J.; Cheng, Y. L. Int J Pharm 1995, 126, 169.
35. Duvvuri, S.; Janoria, K. G.; Mitra, A. K. Pharm Res 2006, 23, 215.