The Effect of pH on the Polymer Degradation and Drug Release from PLGA-mPEG Microparticles

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ABSTRACT: *In vitro* drug release and degradation mechanism of Poly (*dl*-lactide-*co*-glycolic acid)- methoxypoly (ethyleneglycol) (PLGA-mPEG) microparticles were investigated under different pH conditions. Methotrexate(MTX), an antirheumatic drug, was employed as the model drug. In polyester-based microparticle system, two main issues involved in degradation were water uptake and the carboxylic groups produced by chain scission. Polymer composition was identified to be responsible for the odd degradation behavior in different releasing media. Because of the exposure of mPEG chains at the particle surface, microparticle degradation showed apparent different mechanism under the investigated releasing conditions. At pH 10.08, microparticles exhibited rapid weight loss but slower molecular weight decrease, and the degradation pattern was close to surface degradation. At pH 7.4, microparticles underwent heterogeneous bulk degradation. However, at pH 1.2, it showed fastest molecular weight decrease while slowest weight loss, and homogeneous degradation was observed. Particle agglomeration was also seen in acidic environment. Fourier transform infrared (FTIR) spectrum results indicated the crystallization of drugs under the low pH condition. Drug release was dependent on transport paths and drug property. These two factors were highly controlled by the polymer degradation and drug solubility in the releasing media as well as drug crystallinity. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 109: 475–482, 2008

Key words: PLGA-mPEG microparticles; release condition; polymer composition; degradation; hydrolysis; drug release kinetics

INTRODUCTION

Poly (*dl*-lactide-*co*-glycolic acid) (PLGA)-based microparticles have been widely applied for sustained/controlled drug release in drug delivery systems. These microparticles could promote therapeutic efficiency and reduce side effects of medical treatments.[1] Microparticles made of PLGA-mPEG block copolymers, with the incorporation of hydrophilic mPEG (methoxypoly(ethyleneglycol)) chain into the hydrophobic PLGA backbone, exhibited better ability to adjust the polymer degradation behavior and increase drug release rate as compared with PLGA microparticles.[2,3] mPEG is a nontoxic, water-soluble polymer which has been widely used to improve the biocompatibility of the blood contacting materials. It is not degraded and could be easily excreted out of human body.[4,5] *In vivo* tests have shown that PLGA-PEG based systems exhibited improved biological properties such as stability in gastro-intestinal (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.[6] They are very promising systems for future biomedical applications.

Because the *in vivo* tests were time consuming and were difficult to directly measure the drug release amount in the body fluid or target tissue, many studies were carried out *in vitro* under fluids that mimic the body environment. These studies demonstrated that the release condition such as pH, osmotic pressure and ionic strength could affect polymer degradation and thus affect the drug release kinetics.[7–10] Among these factors, pH is predominant and has been under concentrated investigation, but little knowledge is yet available for the importance of the pH conditions on elucidating the correlation between degradation and drug release kinetics. On the other hand, most of degradation studies were performed with strings, sutures, or matrix cylinders, but microparticles were seldom related. Besides, the degradation of block copolymer PLGA-mPEG, which showed different mechanism as compared with PELA or PLGA, has been rarely investigated. It has been pointed out that morphology and polymer composition could be responsible for the polymer matrix degradation behavior.[11,12]

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Our effort aims at providing the degradation mechanism of PLGA-mPEG microparticle under different pH release conditions and analyzing the impact of pH triggered polymer degradation on drug release kinetics. It is helpful for developing new products based on polyester block copolymers for different incubating-condition application. The degradation patterns under acid or basic catalysis, compared with those under pH 7.4 conditions, were investigated from polymer composition profile by measuring degradation products, weight loss, and molecular weight (M_w) change of the polymer matrix and etc. High performance liquid chromatography (HPLC), gel permeation chromatography (GPC), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and Fourier transform infrared (FTIR) spectrum were applied as analyzing tools. The model drug, methotrexate (MTX), one of the most frequently used antirheumatic drugs in the treatment of rheumatoid arthritis (RA), was employed as well to evaluate the release kinetics of small molecule drugs.

MATERIALS AND METHODS

Materials

PLGA (M_w = 85,000, LA : GA = 75 : 25)-mPEG (5000) was purchased from Jinan Daigang Biotech Co., Lid (Shandong, China). Poly (vinyl alcohol) (PVA) (hydrated, M_w = 13,000) was a gift from Prof.Tan (Tianjin University, Tianjin, China). MTX was provided by Hubei Zhanwang Sanxin chempharma, Ltd (Hubei, China). mPEG (M_w = 5000) standard was supplied by Alfa Aesar (UK). Polystyrene molecular weight standards (M_w ranging from 1000 to 70,000) were supplied by Fluka (Sigma-Aldrich, US). All other solvents and chemicals used were of analytical grade.

Micropaticle 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 of 1% PVA solution and magnetically stirred for 5 min to form the primary O/W emulsion. This emulsion was then dispersed into 1 L external water phase with magnetic stirrer for 4 h under room temperature and ambient pressure, till all the organic solvent evaporated. The solidified microparticles were recovered by filtration and washed thrice 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.

Drug release and degradation kinetics were found to be highly depended on the particle size,[13–15] so that the were sieved to uniform size before further analysis (average pore size of the sieves: 57 and 53 μm).

Encapsulation efficiency

The encapsulation efficiency was determined as following extraction process: 10 mg drug-loaded microparticles were dissolved in 2 mL of methylene chloride in test tube. MTX was then extracted by adding 10 mL of phosphate buffered salines (PBS) (pH 7.4, 0.1*M*) to the test tube and the test tubes were shaken vigorously for the complete MTX extraction. The drug concentration in the aqueous phase was measured using a UV-Vis spectrophotometer (TU-1810) at λ = 305 nm. The EE was calculated as: (the amount of MTX in the microparticles/the theoretical amount of MTX in the microparticles) $\times$100%.

In vitro drug release test

The *in vitro* MTX release test were conducted by suspending 60 mg sieved microparticles in 10 mL release medium and maintained at 37°C under continuous shaking (100 rpm). All dissolution tests were performed in sink conditions according to the solubility characteristics of the drug, 4 mL aliquots of the medium were withdrawn and the same volume of fresh buffer were added at defined time intervals. Triplicate samples were recovered. The concentration of MTX in the release medium was measured by UV-Vis spectrophotometry.

Release medium with different pH values were prepared according to literature: Hydrochloric acid (0.1*M*, pH 1.2), phosphate buffer (0.1*M*, pH 7.4), and carbonate buffer (0.1*M*, pH 10.08).

In vitro degradation study

Sixty milligram sieved microparticles were incubated in 20 mL release medium with different pH and maintained at 37°C under continuous shaking (100 rpm). The erosion media were replaced regularly as to maintain the pH of incubation media. At defined time intervals, microparticles were recovered by filtration and lyophilized. The collected microparticles were then applied for SEM, GPC, and FTIR analysis.

The mPEG liberated during PLGA-mPEG degradation was determined by a colorimetric assay.[16,17] Samples (1 mL of the drug release medium) were diluted with 2 mL corresponding release medium to this solution, 75 μL of a potassium iodide solution (0.02 g/mL) saturated with iodine was added. For degradation

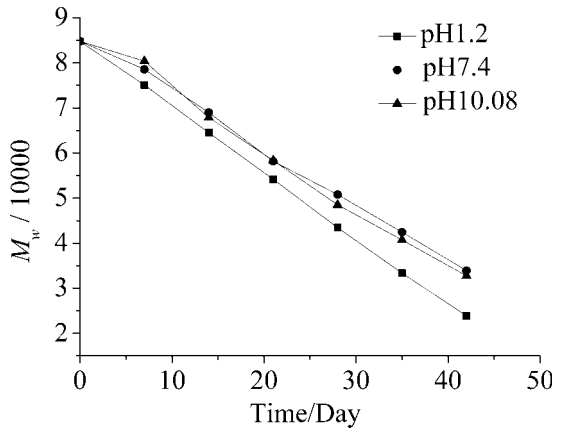

Figure 1 Dependence of M_w on degradation time during microparticle incubated in different pH conditions (0.1*M*).

under pH 10.08, the pH of medium was neutralized with hydrochloric acid. The sample was mixed using a small glass rod and after 5 min the absorbance was detected at 500 nm using an UV-Vis spectrophotometer. The linearity was established in the range of mPEG concentrations measured (1–15 μg/mL).

The lactic acid (LA) released into the incubation medium was determined by HPLC using a SHMADZU apparatus (LC-10ATvp pump and RF-10AXL detector, SHMADZU, Tokyo, Japan) linked to an injection valve (SIL-10ADvp; SHMADZU, Tokyo, Japan) and an VP-ODS column (150 × 4.6 μm; SHMADZU, Tokyo, Japan) maintained at a constant temperature of 30°C with a SDC15 Space Column Heater (YAMATAKE, Japan). The mobile phase was phosphate buffer (0.025*M*, pH 2.5). Chromatography was performed at a flow-rate of 0.6 mL/min and the eluent absorbance was monitored at 210 nm.

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 Corp. Assay conditions for the analysis of 1 mg/mL polymer dissolved in tetrahydrofuran were: 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.

Morphology characterization

SEM were performed on a Hitachi *S*-450 microscope operating at 20 kV and 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.

A Perkin–Elmer Spectrum GX FTIR spectrometer was used to obtain the spectra (resolving power 0.3 cm^{-1}) of the degraded microparticles under acidic condition, over the 4000–400 cm^{-1} range.

RESULTS

pH effects on the polymer degradation

In degradation studies, molecular weight (M_w) and dry weight of the microparticles were monitored during 6 weeks incubation under different pH conditions. Degradation products released into the incubation media were detected as further evidence. SEM and FTIR were also applied for monitoring morphological changes of microparticles.

Molecular weight (M_w) change and weight loss

M_w decrease and weight loss were illustrated in Figures 1 and 2. M_w decrease was followed pseudofirst-order kinetics.[18,19] The decrease of polymer M_w could be calculated as follows:

$$M_w(t) = M_{w0}e^{-k_{\mathrm{deg}r}t} \tag{1}$$

where M_{w0} is the polymer molecular weight before exposure to the release medium and $k_{\mathrm{deg}r}$ is the pseudofirst-order degradation rate constant of the polymer.

The weight loss (*WL*) percent of microparticles during degradation was calculated as follows:

$$WL(\%) = \frac{W(t)}{W(t=O)} \times 100\% \tag{2}$$

where $W(t)$ is the dry weight of microparticles at time t.

From the calculated $k_{\mathrm{deg}r}$ data (shown in Table I), the decrease of M_w was the fastest in acidic condition, but almost the same at pH 10.08 and pH 7.4.

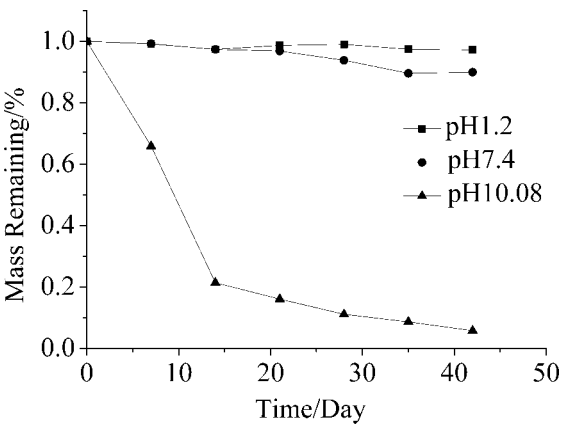

Figure 2 Dependence of weight loss on degradation time during microparticle incubated in different pH conditions (0.1*M*). Samples were lyophilized before measurement.

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

Condition	k_{degr}	R^2
pH 1.2	0.030	0.97
pH 7.4	0.022	0.98
pH 10.08	0.023	0.98

R^2, correlation coefficient.

Contrarily, weight loss rate increased with the growth of pH value of the release medium. A pronounced weight loss occurred in the basic medium at the first 2 weeks and then the loss of water-soluble degradation oligomers continued at a reduced rate. To the end of incubation, only trace of degradation residues remained in contrast to the degradation at pH 1.2 and 7.4. At pH 7.4, the erosion onset was observed at the end of the third week but no more than 10% in total, whereas, microparticles hardly lost any weight under acidic condition.

Liberation of LA and mPEG

The liberation data was expressed in terms of mPEG or LA molar percentage of total mPEG or LA content in the polymer, seen in Figures 3 and 4. The composition and structure of PLGA-mPEG block copolymers, focusing on the end repeating unit of each block, was schematically showed in Figure 5. mPEG acted as cap located at the end of PLGA chains. The cleavage of either ester linkage between mPEG and PLGA or between LA and GA unit could produce the carboxylic group. During the degradation, carboxylic group exposed more and resulted in local low pH environment, which was considered to be the main cause of autocatalytic effect.[19]

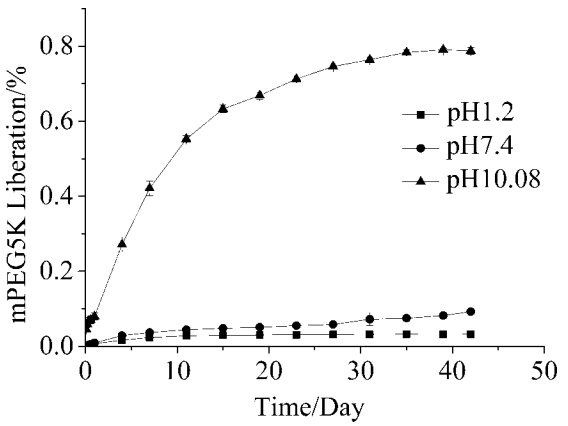

Figure 3 mPEG liberation from PLGA-mPEG microparticles as a function of incubation time in different pH conditions (0.1*M*).

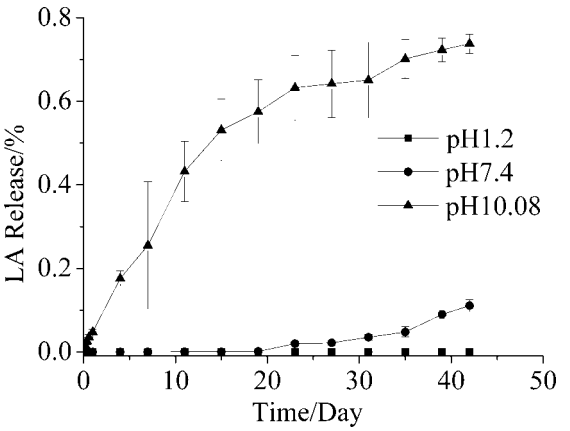

Figure 4 LA liberation from PLGA-mPEG microparticles as a function of incubation time in different pH conditions (0.1*M*).

The introduction of mPEG chain caused some local interference in the PLGA crystalline region, and the hydrophilic nature made the end units of polymer very susceptible to water molecule attacks.[20,21] Consequently, the ester linkage between PLGA and mPEG was more vulnerable to hydrolysis than that between LA and GA. This could be concluded from the liberation data: In all pH conditions, mPEG was first detected from the liberation media, and the liberation rate was faster than that of LA. In addition, the higher pH led to the faster the mPEG fragments liberated into the medium. The release of LA monomer also showed the same pattern as that of mPEG. This also provided another evidence for analyzing matrix erosion mechanism besides the weight loss data as LA made up of the most part of the polymer. At pH 10.08, LA release was the fastest at the beginning and showed an inflection point on the 15th day. At pH 7.4, an onset of LA release was also observed in the third week compared with the onset of weight loss. However, at pH 1.2, there was hardly any LA detected in the releasing medium.

Morphology analysis

Figure 6 exhibited the SEM images of degraded microparticles after 4 weeks incubation. The images of microparticles before incubation were taken as the control. Before incubation [see Fig. 6(a,b)], mPEG chains twisted to form a network and covered the surface of the microparticles due to their hydrophilic nature during the microparticles fabrication (O/W

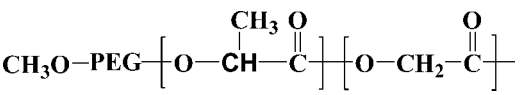

Figure 5 Basic structure of PLGA-mPEG block copolymer.

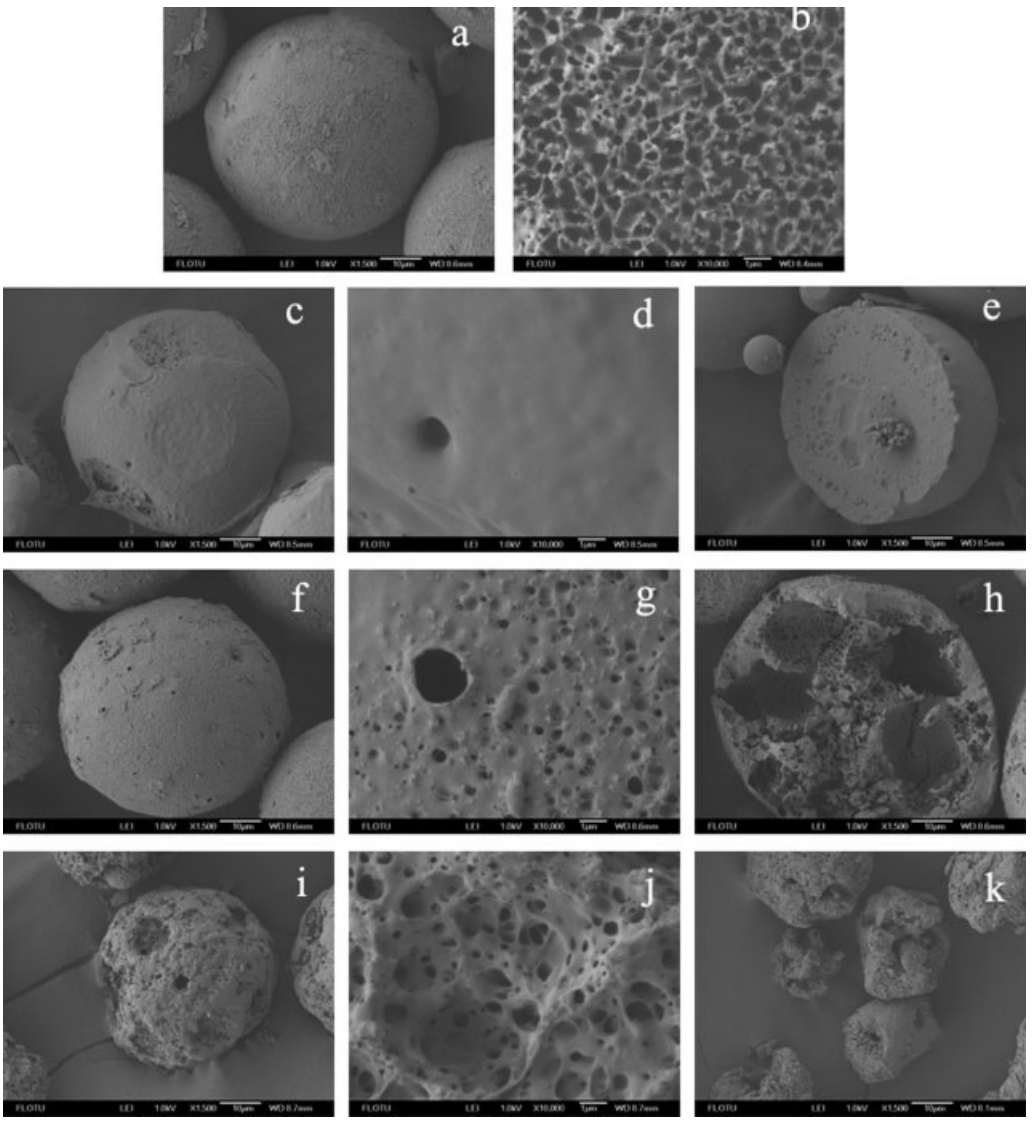

Figure 6 SEM Figures of PLGA-mPEG microparticles in different pH conditions (0.1*M*) after 4 weeks' incubation. Figure 6(a,b) represent the microparticles before incubation; 6(c–e) (cross section) represent the microparticles incubated at pH 1.2; 6(f–h) (cross section) represent the microparticles incubated at pH 7.4; 6(i–k) represent the microparticles incubated at pH 10.08.

emulsification solvent evaporation process). It was an important phenomenon for elucidating degradation mechanism of PLGA-mPEG microparticles, because the quick mPEG liberation led to the exposure of carboxylic end groups on the surface, and thus affected the degradation behavior of the polymer matrix. The function of carboxylic end groups will be discussed in the discussion and conclusion section. After 4 weeks incubation, in all conditions, the surface of microparticles became smooth, indicating that the PEG chains firstly fell off the surface. Pores could be seen on the particle surface. At pH 10.08 [see Fig. 6(i–k)], significant erosion was observed on the surface and plenty of pores were formed on the tunnel wall. The morphology was irregular and microparticles tended to collapse. Besides, the size became smaller compared with the particle size before degradation. At pH 7.4 [see Fig. 6(f–h)], plenty of pores were presented at the surface and hollow structure was observed in the cross section image, which represented an obvious heterogeneous degradation mechanism.[19] The whole morphology kept well and no breakdown or agglomeration occurred. At pH 1.2 [see Fig. 6(c–e)], hardly any pores were seen on the surface, and cross section image also showed few pores inside. One odd phenomenon under pH 1.2 was the particles agglomeration (see Fig. 7. the aggregated particles formed to be hard and solid. This picture imaged the particles after broken up by physical strength before being applied on SEM), and we supposed whether there might be any chemical interactions

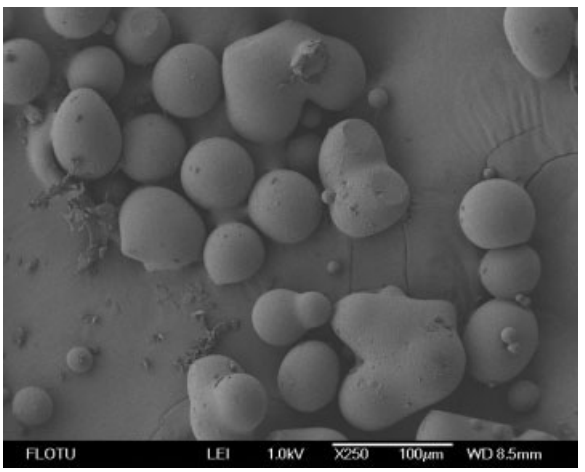

Figure 7 SEM image of microparticle agglomeration under acidic condition.

between polymer and drug or polymer chains themselves. However, the agglomeration also happened with the drug-free microparticles (image or data not shown), suggesting drug was not the cause of particle agglomeration. This hypothesis was further investigated by FTIR in the next section.

FTIR was applied for analyzing the agglomeration phenomenon observed in acidic condition. Figure 8 showed the IR spectrum of pure drug (MTX), PLGA-mPEG microparticles before and after 4 weeks incubation at pH 1.2. Compared with the undegraded microparticles, the spectrum of degraded microparticles exhibited almost the same spectrum except that an apparent carbonyl band was apparent at 1758 cm^{-1}, indicating the exposure of carboxylic groups caused by degradation. We could conclude from the almost unchanged spectra that there was no chemical reaction between polymer chains or between polymer and drug molecules. Another clearly contrasting was that the peaks at 1642 and 1604 cm^{-1}, known to be related to characteristic peaks of MTX, appeared in the spectrum of degraded microparticles. This demonstrated that drugs began to crystallize and phase separation between drug and polymer occurred. It is generally accepted that drug release rate from microparticles is dependent on drug dispersion state, so our observation could be another evidence for explaining the drug release mechanism under acidic condition.

pH effects on *in vitro* drug release

The pH of the release medium could fundamentally affect the resulting drug release patterns of the investigated PLGA-mPEG microparticles, seen from Figure 9(a). At pH 7.4, it showed apparently trimodal release pattern: an initial burst release (almost 25% drug content) on the first day, following a lag period lasted for 30 days, and subsequently a second burst release, till the complete MTX release after six weeks. However, this trimodal release pattern was not seen under the acid or basic conditions. At pH 10.08, MTX release was the fastest and completed within 15 days. The release pattern experimentally fitted pseudofirst-order kinetics kinetic (correlation coefficient $R^2 = 0.98$) [see Fig. 9(b)], which indicated that drug release was mainly controlled by pass diffusion through the polymer matrix. Whereas, at pH 1.2, MTX release showed the slowest: an initial 7% burst release at the beginning, and an uncompleted lag release (12% in all) till the end of six- weeks incubation. Faisant et al.[10] also observed that drug showed the slowest release from PLGA microparticles in acidic environment, but the mechanism was not efficiently elucidated on polymer degradation profile.

DISCUSSION AND CONCLUSION

It could be concluded from the experimental data, that the pH of releasing medium has great effect on microparticles degradation and drug release behavior. The release of small drug molecules from biodegradable matrix was considered to be matrix-diffusion and polymer-degradation controlled.[22–24] In some cases, drug property such as crystalline nature and solubility in the releasing medium also played an important role on drug release kinetics.[10] The solubility of MTX in the investigated release media at 37°C were given in Table II.

The drug solubility was increased as the pH of media increased. This was partially responsible for the differences of drug release in alterant pH condition. However, it could not be the factor dominating the drug release, as there was little difference

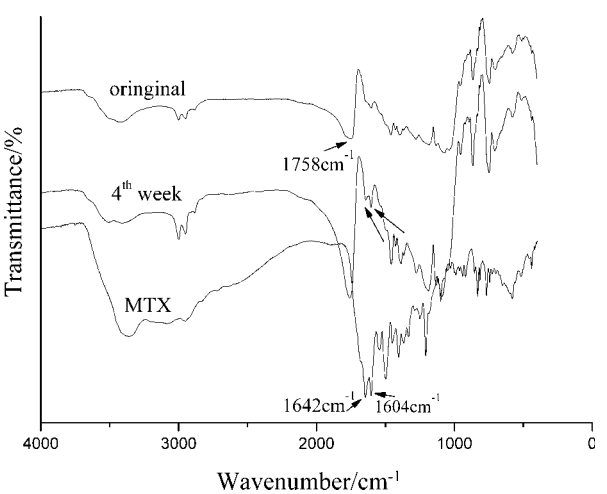

Figure 8 IR spectra of MTX and *in vitro* degrading PLGA-mPEG microparticles under acidic condition.

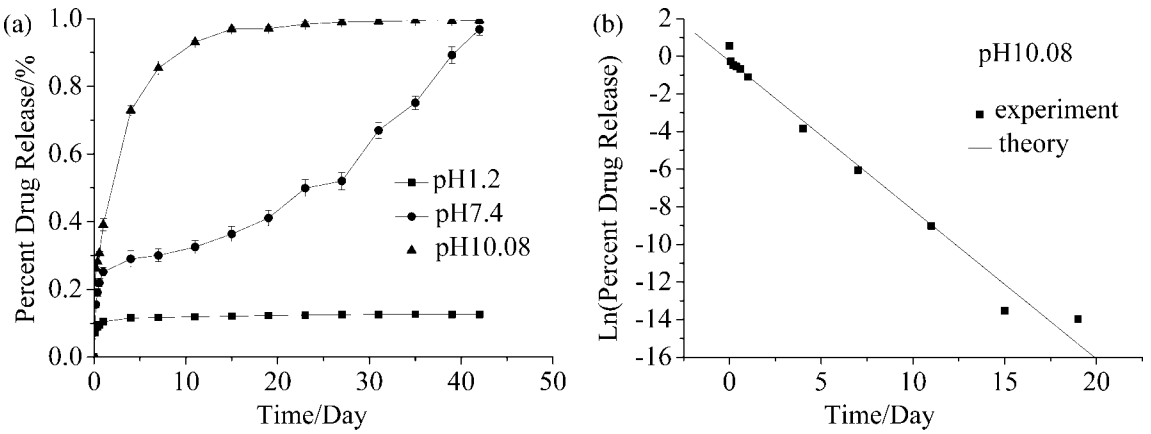

Figure 9 (a) *In vitro* release profile of MTX-loaded PLGA-mPEG microparticles incubated in different pH conditions (0.1*M*). (b) pseudofirst-order release kinetics at p10.08. Solid curve: theory. Dots: experiment data.

between the solubility at pH 7.4 and 1.2, but great difference in drug release kinetics. Thus, we inferred the fundamental drug release mechanism from the microparticle degradation profile. In polyester-based microparticle system, degradation was due to the ester bond hydrolysis in polyester backbone, in which, two main hypothesized issues involved were water uptake and the carboxylic groups produced by chain scission. In the course of degradation process, pores and interspaces of polymer chains accommodated transport paths for water, degradation oligomers and drug molecules.

When microparticles were incubated at 37°C, PBS (pH 7.4), water diffused through the pores from the microparticle surface and penetrated into the interspaces of polymer chains due to the osmotic effect (initial pores were formed during the solvent evaporation process). This induced random cleavage of the polymer chain and therefore a steady decrease of M_w. In addition, the existence of hydrophilic mPEG from the surface enhanced water uptake.[25] As the fast liberation of mPEG fragments, carboxylic group was exposed at the surface and also acted as a hydrophilic terminal for enhancing the water absorbing rate. This composition-induced mechanism made PLGA-mPEG unique from other block polymers such as end-capped PLGA or PELA. At this time, drug at or near the particle surface diffused quickly into the medium, and then drug inside particle began to diffuse through the extended interspaces of degraded polymer chains. These could be considered as the first and second drug release periods. As the chain scission went on, more carboxylic end groups were produced. However, the diffusion of external buffer into the interior was limited by the shell and acidic degradation oligomers accumulated to form a micro low pH environment. H+ attacked the ester bond and triggered the autocatalysis effect, which has so far been identified to be responsible for the bulk degradation mechanism.[7] In the meanwhile, the carboxylic end groups located at the surface could be neutralized by the external buffer solution. So the degradation proceeded more rapidly in the center than at the surface and hollow structure formed. As degradation proceeded, pores appeared more. They began to provide much more transport paths for the accumulated degradation products and drug molecules. We could observe from this period that there were onsets for both weight loss and drug release.

However, under basic or acidic catalytic condition, polymer degradation behaviors were quite different from that in neutral environment. Both OH^- and H^+ were nucleophilic and could catalyze the hydrolysis reaction of ester bond. When in the basic environment, microparticle exhibited the fastest weight loss but the second slowest M_w decrease. Apparently, there was accelerated hydrolysis of ester groups in the terminal but not in the middle of polymer chains. At least two hypotheses could explain this phenomenon. (1) the enhanced nucleophilicity of the attacking species (OH^-) and the neutralization rate of carboxylic end groups located at the particle surface. The autocatalysis effect was replaced by the fast OH— hydrolysis and neutralization effect. (2) The enhanced hydrolysis and neutralization rate was much higher than the water penetration rate. Water molecules were mostly trapped at the entrance for hydrolysis. So the fastest degradation happened at the terminal of the polymer chains where carboxylic

TABLE II
Effects of the Type of Release Medium on the Solubility of MTX at 37°C

pH	Type of media	Solubility (g/L)
pH 10.08	Carbonate	40
pH 7.4	Phosphate	5
pH 1.2	Hydrochloric acid	2

group located. Therefore, reduced size of microparticles and significant erosion starting from the surface were observed. This degradation mechanism was similar to surface degradation.[26] On the other hand, although the amount of pores increased during degradation, they only played a less important role as transport paths than in neutral or acidic environments, because degradation and erosion primarily happened at the surface. Burkersroda et al.[7] studied PLGA matrices' degradation behavior under pH 13. Their results showed an unchanged M_w. However, our results exhibited a steady M_w decrease. Here, the function of pores might account for the difference. The matrices they used were nonporous cylindrical plate, while ours were porous microparticles in which pores were created during the fabrication process. Water could still penetrate into the matrix and induced random chain cleavage, although this process was confined as discussed earlier. Accordingly, drug release under basic condition might be explained by the degradation mechanism. The pseudofirst-order kinetic was mainly caused by the fast diffusion of drug molecules from the fast eroding surface.

At pH 1.2, as shown by SEM images, the hollow structure was not seen and fewest pores were exhibited in either cross section or surface image. Clearly, a homogenous hydrolytic degradation pattern came into being. In the meanwhile, hardly any weight of microparticles was lost but the fastest M_w decrease was observed. Because of the few pores formed during microparticle incubation, the transport paths for water, degradation products and drug molecules were mainly provided by the interspaces of polymer chains. Furthermore, as microparticle agglomerated and became compact as incubation proceeded, the transport paths were restrained as well. We hypothesized that the fastest decrease of M_w was due to the water penetration at the foremost of incubation and enhanced H^+ catalysis effect provided by the acidic media. An abundant of H^+ replaced carboxylic end groups to accelerate the ester hydrolysis. Then the pH gradient that developed by the acidic degradation products was greatly reduced. The whole polymer matrix degraded equally. Since the autocatalysis effect played no crucial role in microparticle degradation under low pH condition, the composition of the polymer then had less impact on the degradation behavior, so the degradation result was similar with other polymers such as PLGA or PELA.[7,27] For the drug release profile, because of the restrained transport paths and homogenous matrix degradation, microparaticles showed the slowest drug release rate and none-second-burst release. FTIR analysis also indicated enhanced drug crystallinity, which was another factors hindering the drug release. Therefore, drug release was stagnant as the incubation went on.

Overall, based on the study on PLGA-mPEG microparticles, polymer composition and releasing conditions play crucial roles in polyester-based microparticle degradation and drug release mechanism. Thus, by selection of the manufacturing procedures, the type of polymer and the releasing media, it is possible to design a controlled drug delivery system.

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