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Synthesis and characterization of MeO–PEG–PLGA–PEG–OMe copolymers as drug carriers and their degradation behavior in vitro

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Abstract The objective of this study was to characterize the methylpoly (ethylene glycol)–poly (lacticacid-co-glycolicacid)–poly (ethylene-glycol) (**MeO–PEG–PLGA–PEG–OMe**, abbreviation as PELGE) copolymers as intravenous injection drug delivery carriers and their degradation behavior in vitro. A series of **MeO–PEG–PLGA–PEG–OMe** copolymers with various molar ratios of lactic to glycolic acid and various molecular weights and different MeO–PEG contents were synthesized by ring-opening polymerization in the presence of MeO–PEG with molar masses of 2000 and 5000, using stannous octoate as the catalyst. The hydrophilicity of PELGE copolymers, evaluated by contact angle measurements, was found to increase with an increase in their MeO-PEG contents. Methylpoly (ethylene glycol)–poly (lacticacid-co-glycolicacid) (MeO-PEG-PLGA, abbreviation as PELGA) nanoparticles and PELGE nanoparticles were prepared using the emulsion-solvent evaporation technique (o/w) with Pluronic® F68 (Poloxamer 188 NF) as emulsifier in the external aqueous phase. The degradation behavior of the nanoparticles was evaluated by the lactate generation with time upon their in vitro incubation in PBS (pH 7.4). The rate of in vitro degradation of the PELGE or PELGA nanoparticles depended on their composition, increasing with an increase in the proportion of MeO–PEG or LA in the copolymer chains. The degradation rate was slower at higher lactide: glycolide ratio. The lower the molecular weight of PELGE; the higher the degradation rate of the nanoparticles.

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Introduction

Synthetic polymers have long been of major importance for targeting delivery of drugs to the diseased lesions is one of the most important aspects of the drug delivery system (DDS) [1]. To convey a sufficient dose of drug to the lesion, suitable carriers of drug are needed. It isf required for the carrier systems containing a drug to be retained in the blood stream for a long time in aiming at the passive trageting of the drug. The blood compatibility is an important property for drug carriers directly injected into the blood stream. Poly (lactic acid-co-glycolic)(PLGA) polymers are considered as an acceptable carrier to meet the above requirements. However, they are clearly not the optimal carriers for the applications of intravenous injection drug delivery. Many problems still remain such as long-term incompatibility with blood cells and non-zero-order release behaviors and the PLGA as well as other particulate systems tend to disappear from the upkate by the phagocytic cells in the reticuloendothelial system(RES)[2, 3]. Many researchers have shown that circulation time of the particulate system, e.g. PLGA, depends on the particle size and surface characteristics of the carriers. Therefore, the surface modification of the nanoparticles with a blood compatible material is important in order to improve the potential of nanoparticles in the intravenous injection drug delivery systems. Poly (ethylene glycol) (PEG) modified biodegradable polymers may be used for the intravenous drug delivery [3]. It has been suggested that MeO–PEG modified nanoparticles

provides protection against interaction with the blood components, which induce removal of the foreign particles from the blood. It prolongs, thus, their circulation in the blood stream. In present study we have synthesized MeO–PEG–PLGA–PEG–OMe polymers with characteristics of biocompatibility, blood compatibility, drug compatibility and suitable biodegradation kinetics. Also, We have studied the behavior and mechanism of the degradation of PEG–PLGA nanoparticles(PELGA-NP) and PELGE nanoparticles (PELGE-NP). Because of the important role of degradation of the PELGE polymers in the drug delivery application, the selection of PELGE with desired composition and molecular weight is critical in the formulation of controlled-release drug delivery systems. The results reported here could be useful to ration MeO–PEG–PLGA–PEG–OMe nanoparticles by choosing the composition and the molecular weight of the polymeric matrix. Therefore, the drug release kinetics from the nanoparticles can be controlled. The information provided by this study could be useful to the pharmaceutical scientist working on the development of controlled drug delivery or drug targeting systems or intravenous injection drug delivery based on MeO–PEG–PLGA–PEG–OMe copolymers.

Experimental and methods

Materials

DL-lactide and glycolide were recrystallized twice from ethyl acetate and dried under vacuum at room temperature before use. Monomethoxypoly (ethylene glycol) (MeO–PEG, molecular weight 2000 and 5000) was obtained from Sigma and dried under vacuum at room temperature before use. Stannous octoate and hexamethylene diisocyanate (HMDI) were also obtained from Sigma.

Synthesis of PELGEs

Prior to the polymer synthesis, all glassware was cleaned and dried at 120 °C in an oven overnight. The dried glassware was cooled to room temperature in sealed desiccators. The catalyst solution was prepared by dissolving the stannous octoate in the hexane immediately before use.

Lactide and glycolide at a molar ratio of 4/1 or 7/3 or 5/5 and specified amount of MeO–PEG were accurately weighed and put in 25-mL glass ampoules. The total weight of the feed was 10 g. Stannous octoate was added at a concentration of 0.05% (w%) by weight of the feed and the tubes were sealed under vacuum and heated in an oil bath at 150 °C for 5 h. Products were purified by dissolving them in dichloromethane (DCM) (10%) and then precipitating them in excess methanol. The purified copolymers were dried under vacuum. Then the coupling reaction of diblock copolymers was performed with HMDI in toluene at 60 °C for 12 h, followed by reflux for 6 h. The triblock copolymers were purified by methanol precipitation of polymer from methylene chloride using diethyl ether. The PELGEs having 70–30 or 80–20 or 50–50 molar ratio of lactic to glycolic acid moieties and 5% or 10% or 15% or 20% MeO–PEG but different molecular weights were synthesized.

PELGE characterization

Copolymers were characterized by various analytical techniques. The identity and purity of the copolymers were examined by IR (Nicolet 200SXV) and nuclear magnetic resonance (^{1}H-NMR) spectroscopy (UNITY INOVA–400, Varian, USA). The composition of the copolymers was determined from the integrals of the peaks in the ^{1}H-NMR spectra. Their molecular weight and molecular distribution were determined by gel permeation chromatography (GPC). The glass transition temperature (Tg) of the copolymers was examined by differential scanning calorimetric (DSC). The surface energy of the copolymers was evaluated by the contact angle formed by liquids droplets on the surface of copolymer films. Contact angles of test liquid on film of PELGE were measured using a contact angles goniometer (JY-82, China) by a sessile drop method.

Nanoparticle formulation

The nanoparticles were fabricated by using the emulsion-solvent evaporation technique (o/w) with F68 as emulsifier in the aqueous phase. The copolymer was dissolved in acetone/DCM (2/3) and was transferred to an aqueous solution of F68 and the mixture was sonicated at 360 w for 30 s. The resulted o/w emulsion was gently stirred at room temperature until the organic phase was completely evaporated. Orthogonal experiment design was adopted to select the optimal scheme by the experiment of the singular factor. The following six factors: the concentrations of PELGE, the ultrasonic time, the concentrations of F68, molecular weight of PELGE and the stirring time, were selected to investigate their influences on nano-particle sizes.

Characteristic of nanoparticles

Nanoparticles were examined on negative stain electron microscopy using a JEM 1200 EXII electron microscope (Jeol Ltd, Tokyo, Japan). The particle morphology was observed by TEM. The size distribution of nanoparticles was determined by laser diffractometry (Mastersize/2000, Malvern). The samples were diluted with distilled water and measured at room temperature with a scattering angle of 90°

Degradation of PELGA-NP and PELGE-NP

The degradation behavior of the nanoparticles was evaluated by the lactate and MeO–PEG generation and nanoparticle mass reduction with time upon their in vitro incubation in phosphate-buffered saline (PBS, pH 7.4) [4, 5]. Nanoparticles samples, enclosed in dialysis bags, were incubated in 40 mL PBS at 37 °C under mild agitation in a water bath. For lactate and MeO–PEG assay, 2 mL samples were withdrawn from the incubation medium at predetermined time intervals. The samples were replaced by equal volume of fresh PBS. The lactate formed during PELGA or PELGE hydrolysis was determined on a GBC UV cintra 10e Spectrophotometer. The absorbance of the samples was measured at 262 nm [6]. The release of MeO–PEG was measured according to a method described by Avgoustakis et al. [4] and Gref et al. [7]. Firstly a solution of 2 g potassium iodine in 100 mL deionized water was saturated by adding 1 g iodine and equilibrating overnight. 10 μL of this reagent was added to 250 μL of an aqueous sample containing MeO–PEG and after incubation of 5 min the absorbance at 500 nm was measured. The linearity of the method was verified up to a concentration of 1–20 μg/mL.

Results and discussion

Synthesis of PELGE

Stannous octoate has been approved by the U.S.FDA for surgical and pharmacological application. This compound is the most widely used initiator. It provides high reaction ratio, and high molar mass even under relatively mild conditions. Synthetic scheme of block copolymer was showed in Fig. 1.

The yield of the polymerization

The yield of the polymerization increased with the increase of polymerization time, and the higher the MeO–PEG content of the feed the lower the yield. The yield of the final polymers was 90–95%. According to the reaction mechanism proposed by Dunn et al. [8] and Li et al. [9] for the polymerization of lactide in the presence of MeO–PEG, an active intermediate should be formed from the reaction of lactide/glycolide, stannous octoate and MeO–PEG in the initiation phase. The tin of this intermediate may coordinate either with the terminal OH group of the intermediate (intramolecular reaction leading to chain growth) or with the terminal OH group of another molecule, such as a MeO–PEG molecular or another copolymer chain (intermolecular reaction leading to chain transfer growth). The

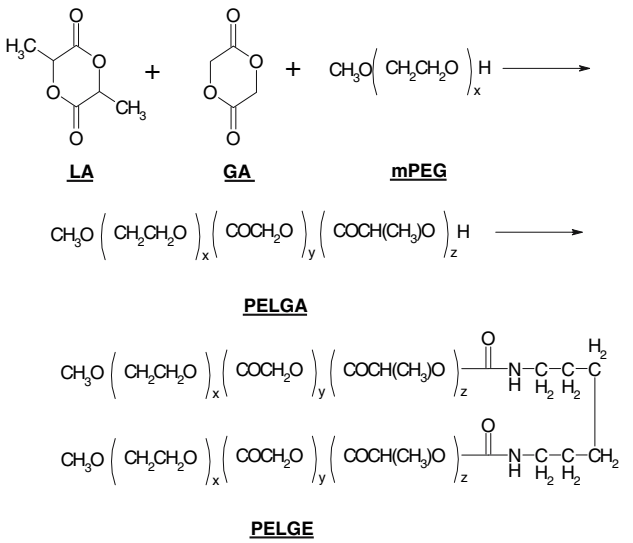

Fig. 1 Synthetic scheme of block copolymers

higher the MeO–PEG content of the feed the higher the probability that the active intermediate formed would react with a MeO–PEG molecule. This would result in the formation of a relatively large number of small chains characterized by a high MeO–PEG/PLGA ratio which probably did not precipitate in methanol with the rest of the copolymer during copolymer purification. Thus, increasing the MeO–PEG content of the feed decreased the polymerization yield. In fact, the higher the molar mass of MeO–PEG, the fewer the hydroxyl endgroups or initiation sites and the lower the conversion ratio of lactide/glycolide under the same reaction condition.

Composition of the copolymers

The identity and purity of the copolymers were investigated by IR and ^{1}H-NMR spectroscopy. A IR spectrum of a MeO–PEG–PLGA–PEG–OMe copolymer. The major peaks assigned to the structure of MeO–PEG–PLGA–PEG–OMe were: 2900–3000 cm^{-1}(C–H stretching), 1750 cm^{-1}(ester C=O stretching), and 1080 cm^{-1} (O–CH_2 stretching).

The comparison of the IR spectrum of MeO–PEG–PLGA–PEG–OMe with that of MeO–PEG confirmed that the reaction between PLGA and MeO–PEG had been effective. It is characteristic that the broad absorption band at 3500 cm^{-1} in the spectrum of MeO–PEG, assigned to O–H stretching, was practically eliminated from the spectrum of MeO–PEG–PLGA–PEG–OMe, indicating that the free hydroxyl groups of MeO–PEG had reacted with the carbonyl groups of lactide/glycolide.

The composition of the copolymers was determined from the integrals of the peaks in the ^{1}H-NMR spectra. ^{1}H-NMR spectra of PELGE triblock copolymers with their chemical structure are presented in Fig. 2. To obtain the

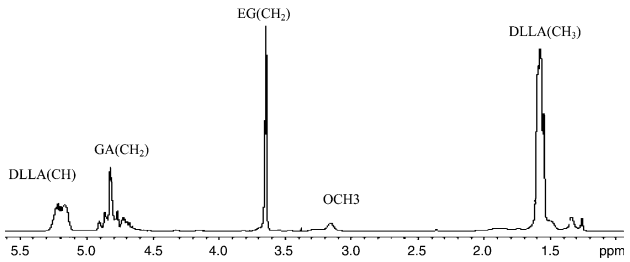

Fig. 2 ^{1}H-NMR spectra of PELGE in $CDCl_3$: LA:GA molar ratio in PLGA was 70:30, MeO–PEG was 10%

number average molecular weight, the peaks at 5.20 ppm (CH of DLLA), 4.83 ppm (CH_2 of GA), 3.65 ppm (CH_2 of ehtylene glycol), 3.38 ppm (CH_3 of PEG end group), 1.55 ppm (CH_3 of DLLA were used. Similar results were reported by other researcher e.g.He et al. [6]. The resluts of following equations were used to calculate the number average molecular weight of PELGE triblock copolymers by end group analysis.

$$\mathrm{CH_3O[CH_2CH_2O]_x[COCH_2O]_y[COCH(CH_3)O]_z\ CONH(CH)_6 \times NHCO\ [OCH_2CO]_y[OCH(CH_3)]CO]_z\ [OCH_2CH_2]_xOCH_3}$$

$$[4(x-1)+2]/3 = A_{3.65}/A_{3.38}$$
$$2y/[4(x-1)+2] = A_{4.83}/A_{3.65}$$
$$3z/[4(x-1)+2] = A_{1.55}/A_{3.65}$$

$A_{3.38}$, $A_{3.65}$, $A_{4.83}$, and $A_{1.55}$ are integration values at 3.38, 3.65, 4.83, and 1.55 ppm, respectively in ^{1}H-NMR spectra. x–1 indicates the connecting methylene group between PLGA and PEG appears at a different position (4.3 ppm) to the other methylene group of PEG [10]. Molar ratio of DLLA/GA in the PLGA block is 70/30 and the mole ratio is in agreement with feed. The composition of the synthesized polymers are well correlated to the feeding composition of the lactide and glycolide.

The glass transition temperature of the PELGA and PELGE

The glass transition temperature (Tg) of the PELGA or PELGE were determined by DSC. The Tg of the lactic/glycolic polymers ranges from 30 °C to 50 °C. The Tg increased when the molecular weight of the polymers increases. The glass transition temperature study of the lactic/glycolic polymers also shows that the Tg increases with increasing molar percentage of lactide in the lactic/glycolic polymers. This phenomenon have also been observed by other researchers e.g. Wang et al. [11]. The Tg may play a role in the drug release. If the Tg of a polymer is below the body temperature, the polymer is in a rubbery state. In contrast, if the Tg of a polymer is above the body temperature, the polymer will be in a glassy state. A rubbery polymer matrix has a higher permeability to water and the loads more drugs than a glassy polymer, which results in faster polymer hydration, degradation, and drug release. A glassy polymer will gradually become a rubbery polymer due to the Tg decrease caused by hydration. The hydration for a glassy polymer results in a longer time lag for drug release and for polymer degradation.

The molecular weight of the PELGA and PELGE

Molecular weight of the PELGA and PELGE raw coplymers were determined by a gel permeation chromatography method. For molecular weight determination, tetrahydrofuran (THF) was the mobile phase at a flow rate of 1 mL/min and a temperature of 30 °C. Polymers were dissolved in THF (0.25 wt% polymer sample in THF), filtered, and then injected (20 (μL) into a set of four μ-Styragel columns with nominal pore sizes of 10^5,10^4,10^3 and 100 Å. Average molecular weights were calculated using a series of polystyrene standards [12]. The average molecular weights of PELGE were determined in Table 1.

Surface energy

The surface energy of the copolymers was evaluated by the contact angle formed by liquid droplets on the surface of copolymer films. The six test liquids are ethylene glycol (surface energy γ—48.3 mJ/m^2), glycerol (γ—63.4 mJ/m^2), double-distilled water (γ—72.8 mJ/m^2), formamide (γ—58.2 mJ/m^2), tritolyl phosphate (γ—40.9 mJ/m^2), diiodomethane (γ—50.8 mJ/m^2). The surface energy values of the samples were obtained from the plots of the Owens-Wendt-Kaeble's equation [13]:

$$\gamma_{LV}(1+\cos\theta) - 2(\gamma_L^d.\gamma_s^d)^{1/2} + 2(\gamma_L^p\gamma_s^p)^{1/2} \quad (1)$$

Table 1 Molecular weight and polydispersity of the PELGE block compolymers

Sample	LA/GA (molar ratio)	mPEG(%)	Mw	Mn
PELGE1	80:20	5	46,875	31,449
PELGE2	80:20	10	40,200	28,549
PELGE3	80:20	15	32,823	23,959
PELGE4	70:30	5	26,827	19,121
PELGE5	70:30	10	40,329	27,579
PELGE6	70:30	15	23,288	17,319
PELGE7	50:50	15	26,863	18,299

where, subscripts L and S represent solid and liquid surfaces respectively, γ^d stands for dispersion component of total surface energy (γ) and γ^p is polar component, γ may be expressed as the sum of dispersion component and polar component:

$$\gamma = \gamma^d + \gamma^p \quad (2)$$

The surface energy of the samples was showed in Fig. 3. PELGE had the highest surface energy. The change of the surface energy was attributed to the increase of MeO–PEG content. The results showed the surface energy of copolymers increased with the increasing of MeO–PEG contents.

Preparation of nanoparticles

PELGA nanoparticles and PELGE nanoparticles were prepared using the emulsion-solvent evaporation technique (o/w) with F68 as emulsifier in the external aqueous phase, where the MeO–PEG fraction migrated to the surface of the nanoparticles forming a protective cover. Nanoparticles were formed by the following steps: when the polymeric solution was added, emulsion droplets were formed in the aqueous phase; acetone quickly diffuses out form each emulsion droplet, drastically reducing its size to nanograde and the consequent ''solvent-evaporation'' process, in which the remaining dichloromethane was removed from the system, makes the droplets solidify to finally form polymeric nanoparticles [14].

Orthogonal design was applied to optimize the preparation technology on the basis of the single factor evaluation. The optimal conditions for nanoparticle preparation were as follows: 10 mg/mL was the concentration of PELGE or PELGA, the ratio of DCM/acetone was 3/2, the concentration of F68 was 3% and the volume ratio of o/w is 1/6 (v/v).

Morphology and particle size of nanoparticles

A transmission electron microphotograph (TEM) of freeze-dried nanoparticles prepared with the acetone/DCM system was showed in Fig. 4 as a typical example. The PELGA and PELGE nanoparticles were spherical, discrete particles without aggregation, and smooth in surface morphology. The average diameter of PELGA and PELGE nanoparticles were 127 nm and 138 nm respectively.

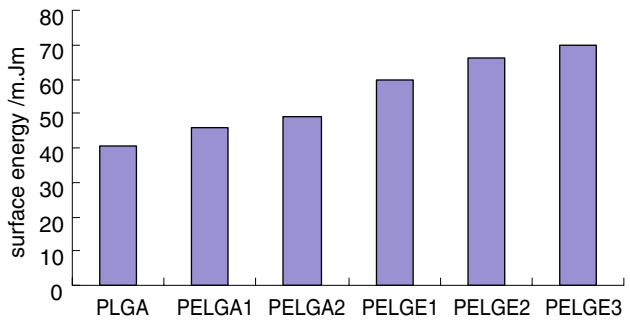

Fig. 3 Surface energy of the samples film: the ratio is 50:50 of LA:GA in the copolymers, the contents of MeO–PEG was 5% in PELGA1 and PELGE1, 10% in PELGA2 and PELGE2, and 15% in PELGE3

Degradation of PELGA-NP and PELGE-NP

The degradation mechanism of PELGA-NP and PELGE-NP

In general, PELGE or PELGA degradation is considered as a hydroxylation process. The cleavage of an ester bond leads to a COOH end group and an OH one. The thus formed COOH end groups are capable of catalyzing hydrolysis of other ester bonds, a phenomenon called autocatalysis [15, 16]. When a polymer specimen was placed in an aqueous medium, water penetrates the specimen and ester bonds are cleaved hydrolytically, thus producing COOH end group which can, in principle, catalyze the reaction by autocatalysis. Microspheres less than 300 microns in diameter undergo a homogeneous degradation with the rate of degradation of the core being equivalent to that at the surface [14, 17]. The heterogeneous hydrolytic degradation of PELGE or PELGA at 37 °C and pH 7.4 has been hypothesized as being due to (1) the diffusion of the soluble oligomers from the surface and (2) neutralization of carboxylic end groups located at the surface by the external buffer solution. The basic sizes of the nanoparticles involved in the degradation studies were from 60 nm to 200 nm. The degradation of the nanoparticles appeared to start immediately after their immersion in the degradation medium. The final in vitro degradation products of PELGE nanoparticles are oligomers of lactic acid, oligomers of glycolic acid, lactic acid, glycolic acid and MeO–PEG. Similar results have been reported by other researcher's e g. Avgoustakis et al. [4].

The degradation behaviors of PELGE-NP or PELGA-NP

The degradation of PELGE or PELGA nanoparticles having different composition was studied by measuring the lactate and MeO–PEG generated with time upon nanoparticle incubation in PBS (pH 7.4). The results were shown in Fig. 5–Fig. 7. The glycolate, which is also produced during PELGE or PELGA hydrolysis, did not interfere with the lactate analysis [4]. In the case of PELGE, lactic acid could be detected at the 8th hour. Then the concentration of lactic acid in the medium increased continuously. The increase with time was similar to that found for PELGA.

Figure 5 showed the Lactate accumulated generation from PELGA-NP or PELGE-NP of different molecular weight in PBS. Results indicated the degradation rates of PELGA or PELGE decreased with an increase molecular

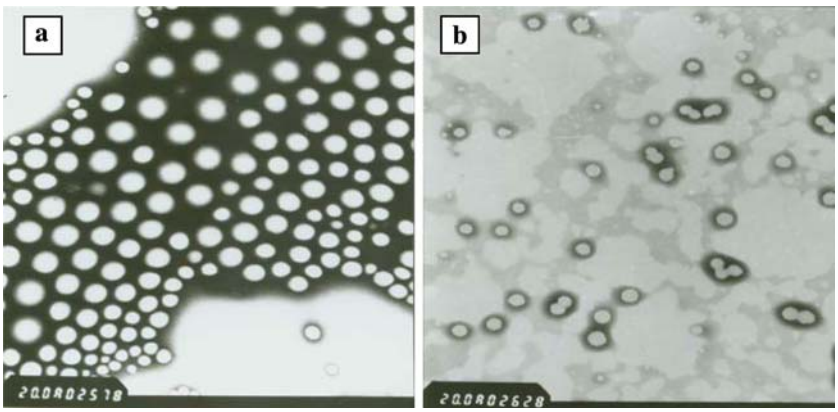

Fig. 4 TEM micrograph of PELGE2–NP (**a**) before degradation; (**b**) after degradation for 7days (20KX)

weight. The molecular weight and molecular weight distribution may play a role in the degradation behavior. In fact, the higher the Mw, the lower the COOH end group concentration and the slower the degradation.

Although the molecular weight of a sample decreases immediately upon contacting with media, the weight loss does not start until a critical point of oligomer formation in the sample is reached.

In the case of PELGE systems, weight loss could occur from the release of water soluble oligomers whenever such oligomers were formed within the degraded nanoparticles. Total weight loss was calculated from the following relationship: weight loss% = (Wi–Wr)/Wi, in which Wi and Wr represent the initial and remaining weights of the specimens, respectively. Data showed that no weight loss occurred during the first 1 day. Avgoustakis reported that the MeO–PEG liberated was coordinated with that of the lactate generated: the rate of lactate formation and MeO–PEG liberation depended on nanoparticle composition, increasing with higher MeO–PEG proportion in the nanoparticles and rates of mass loss from the nanoparticles. In all cases, high rates of mass loss were associated with high rates of formation of degradation products. The percent mass loss during the period of 15 days investigated was 85% for the PELGA nanoparticles and 90% for the PELGE.

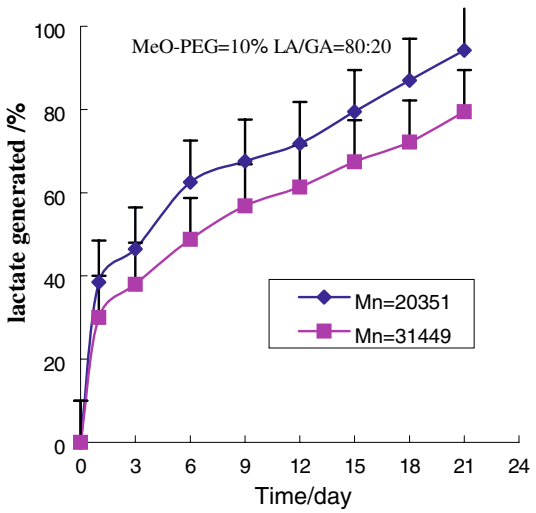

Fig. 5 Lactate accumulated generation from PELGE–NP different molecular weight in PBS

The composition of polymer chains greatly determines the degradation rate of PELGA and PELGE polymers. PELGE (LA/GA: 50/50) degrades the most rapidly, whereas PELGE (80:20) is the most stable of the series. Altering the chemical composition by increasing the glycolide molar ratio in the copolymer increases the rate of biodegradation. The results were showed in Fig. 6. Similar results were reported by other researchers [18].

Figure 7 showed the higher degradation rates of the nanoparticles with a higher MeO–PEG contents. The pH of the degradation medium remained stable for the first 7 days. It decreased slightly at day 10. Between 10 and 20 days, the pH dropped down to 6.8, which is in agreement with the release of oligomers into the aqueous medium. Afterwards, it remained relatively stable.

Conclusions

The hydrophilicity of PELGE or PELGA copolymers, evaluated by contact angle measurements, was found to increase with an increase in their MeO–PEG content. The rates of in vitro degradation of the PELGE or PELGA nanoparticles depended on their composition, increasing with an increase of the MeO–PEG proportion in the copolymer chains. The degradation rates of PELGA or PELGE decreased with an increase of molecular weight. The degradation rates of PELGA increased with an increase of lactic ratios. The degradation rates of these polymers were found to increase as follows: MeO–PEG–$PLA_{80}GA_{20}$–PEG–OMe < MeO–PEG–$PLA_{70}GA_{30}$–PEG–OMe < MeO–PEG–$PLA_{50}GA_{50}$–PEG–OMe. Release rates could be altered over a wide range

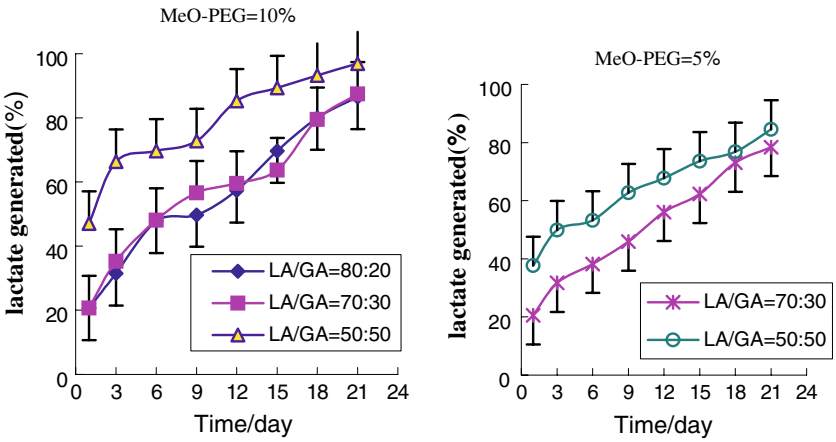

Fig. 6 Lactate accumulated generation from PELGA–NP of different ratio LA/GA in PBS

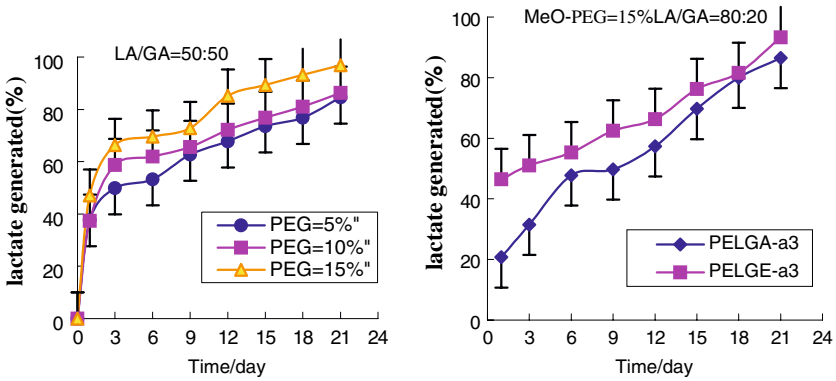

Fig. 7 Lactate accumulated generation from PELGA–NP (left) or PELGE-NP of different MeO–PEG content in PBS

by changing molar mass and composition of copolymers. The degradation rates could be adjusted by varying the proportion of LA to GA.

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