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ORIGINAL ARTICLE

PLGA–PEG–PLGA hydrogel for ocular drug delivery of dexamethasone acetate

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Abstract

Aim: This study aims to investigate the suitability of thermosensitive triblock polymer poly-(DL-lactic acid-co-glycolic acid) (PLGA)–polyethylene glycol (PEG)–PLGA as a matrix material for ocular delivery of dexamethasone acetate (DXA). *Methods*: The copolymer was synthesized and evaluated for its thermosensitive and gelation properties. DXA in situ gel-forming solution based on PLGA–PEG–PLGA copolymer of 20% (w/w) was prepared and evaluated for ocular pharmacokinetics in rabbit according to the microdialysis method, which was compared to the normal eye drop. *Result*: The copolymer with 20% (w/w) had a low critical solution temperature of 32°C, which is close to the surface temperature of the eye. The C_{max} of DXA in the anterior chamber for the PLGA–PEG–PLGA solution was 125.2 μg/mL, which is sevenfold higher than that of the eye drop, along with greater area under the concentration–time curves (AUC). *Conclusion*: These results suggest that the PLGA–PEG–PLGA copolymer is potential thermosensitive in situ gel-forming material for ocular drug delivery, and it may improve the bioavailability, efficacy of some eye drugs.

Key words: *Dexamethasone; in situ gelling; ocular drug delivery; PLGA–PEG–PLGA; thermosensitive copolymer*

Introduction

Topically applied drugs that penetrate into the eye across the cornea first enter the aqueous humor and are subsequently distributed to the surrounding tissues, that is, iris, ciliary body, lens, vitreous, and choroid-retina. The extent of absorption of an ophthalmic therapeutic drug is severely limited by physiological constraints. The cornea is the primary location for drugs to penetrate into eyes. Human cornea generally consists of three layers: epithelium, stroma, and endothelium. The epithelium as the external layer is composed of a number of well-organized and tightly packed cells and serves as a selective barrier for the penetration of ophthalmic drugs. The stroma beneath the epithelium is a highly hydrophilic layer making up 90% of the cornea with limited ionic and hydrophilic transports, and the endothelium is responsible for maintaining normal corneal hydration. The tight junctions of the epithelium serve as a selective barrier for small molecules, and they prevent the diffusion of macromolecules through the paracellular route. It is commonly recognized that a high drug concentration at the cornea membrane surface is required for most of the hydrophilic drugs to ensure their essential delivery through the ocular barrier[1]. Another major problem encountered with drug solutions is the rapid and extensive elimination of drugs from the precorneal lachrymal fluids by solution drainage, lachrymation, and nonproductive absorption by the conjunctiva, which may cause undesirable side effects. Consequently, the ocular residence time of conventional solutions is limited to a few minutes, and the overall absorption of a topically applied drug is limited to 1–10%. Various approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs have been reported and discussed[2].

Dexamethasone acetate (DXA) has demonstrated to be an efficient anti-inflammatory drug in the treatment of acute and chronic posterior segment eye diseases

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such as uveitis or affections that involve neovascularization, such as proliferative vitreoretinopathy or subretinal neovascularization[3]. It is a challenge to improve its bioavailability and safety through various pharmaceutical approaches. The most common way is to increase the residential time at the corneal surface by using polymers to increase solution viscosity. Excipients such as hyaluronic acid sodium salt (HA-Na) have been chosen to form formulations because of its high viscosity that prolongs drug contact with the cornea and thus increases the bioavailability. Thermosensitive polymer solution behaves as a liquid below its low critical solution temperature (LCST) whereas it forms gel when the environmental temperature reaches or exceeds the low critical solution temperature. There are various thermosensitive gel-forming polymeric systems such as poloxamers, cellulose derivatives, and xyloglucan, among which poloxamer hydrogels represent the most extensively studied systems because they are commercially available in a wide range of molecular weights and block ratios[4]. Nevertheless, the main drawbacks associated with poloxamer gels for drug delivery applications are their large toxicity[5,6] and nonbiodegradability[4].

Recently, a novel biodegradable and water-soluble amphiphilic triblock copolymer of poly-(DL-lactic acid-co-glycolic acid) (PLGA)–polyethylene glycol (PEG)–PLGA (PLGA–PEG–PLGA) has been applied to thermosensitive gel-forming formulations and has been widely used in injectable drug delivery systems[7,8]. However, it is seldom used in ocular drug delivery. Therefore, in this study, PLGA–PEG–PLGA was investigated as a thermosensitive gel-forming formulation of DXA for ocular delivery. The copolymer was synthesized and characterized. Furthermore, the ocular pharmacokinetics of the in situ gel-forming solution was compared with the eye drop.

Materials and methods

Materials

PEG1000 and PEG1500 were purchased from Guoyao Group Chemical (Beijing, China). DL-Lactide and glycolide were obtained from Beijing Yuanshengrong Tech. (Beijing, China) and used without further purification. Tin(II) octanoate was obtained from Sigma (St. Louis, MO, USA) and used as received. DXA was provided by Tianjin Tiancheng Pharmaceutical Co., Ltd. (Tianjing, China). HA-Na 95% (MW 1500 kDa) was from Dajiang Group (Shanghai, China). All other chemicals used were of analytical grade. Dialysis system was from CMA (Stockholm, Sweden). Dialysis membrane (MD-2005) was from BAS (Baltimore, MD, USA). The New Zealand white rabbits weighing 2.0–2.5 kg were obtained from the Shanghai Baomu Animal Center.

Synthesis and characterization of the copolymers

Triblock copolymer of PLGA–PEG–PLGA [lactic acid (LA):glycolic acid (GA) = 5:1, PEG : PLGA = 3:7] was synthesized through ring-opening polymerization of DL-lactide and glycolide in the presence of PEG (PEG1000: PEG1500 =1:1) and the catalyst tin(II) octanoate as described by Zentner et al.[9]

The structure of PLGA–PEG–PLGA was confirmed by ^{1}H-NMR. Spectra were recorded at 300 MHz on a Varian spectrometer at 25°C. The solvent used was deuterated chloroform ($CDCl_3$). A tetramethylsilane signal was taken as the zero chemical shift. Lactide-to-glycolide ratio was determined using ^{1}H-NMR by integrating the signals pertaining to each monomer such as the peaks from CH and CH_3 of LA, CH_2 of ethylene glycol, and CH_2 of GA.

The molecular weight and molecular weight distribution of the copolymer were determined using gel permeation chromatography (GPC). An Agilent 1100 series (Agilent, Colorado Springs, CO, USA) apparatus equipped with a refractive index detector and three Phenogel® H-3259-KO, H-0445-KO, and H-0442-KO columns was used. The analyses were performed at 35°C, using tetrahydrofuran as the eluant at the flow rate of 1 mL/min and polystyrene as standards.

Phase diagram of the copolymers

The phase transition of sol (flow)–gel (nonflow) of the triblock copolymers in water was recorded using the inverting test method in a 4-mL vial with heating in increments of 1°C from 20°C to 60°C. Briefly, samples at given concentrations of 15%, 17%, 20%, 23%, 25%, 27%, and 30% (w/w) were prepared in distilled water at 4°C, and the gel–sol transition was determined by inverting the vial horizontally after keeping the sample at a constant temperature for 10 minutes to allow the establishment of equilibrium, as described previously[10].

Viscosity of measurements

The viscoelastic properties of PLGA–PEG–PLGA gels of 20% (w/w) were investigated using a Thermo Haake C25p Rheometer (Newington, NH, USA). The plates were equilibrated to the starting temperature of 10°C, and temperature sweep tests were carried out within the temperature range of 10°C–45°C at the heating rate of 0.5°C/min. Controlled shear strain with an amplitude of deflection angle φA of 6 rad/s was employed.

Preparation of thermosensitive gel-forming formulations

DXA (0.1%, w/v) was added to 20% (w/w) PLGA–PEG–PLGA copolymer aqueous solution and homogenized at 8000 rpm for 40 seconds to form a homogeneous clear solution at room temperature or below to get the polymer formulation. To form the DXA gel-forming solution, 0.7% NaCl and 0.01% benzalconium chloride were added.

DXA (0.1%, w/v) was added to 0.5% (w/v) HA-Na and homogenized at 8000 rpm for 40 seconds to form a homogeneous solution at room temperature. To obtain the DXA eye drop solution, 0.7% NaCl and 0.01% benzalconium chloride were added to the solution.

Pharmacokinetics study in rabbits' anterior chamber by the microdialysis technique

Probe characterization

The theory of probe characterization was described previously[11,12]. In vitro probe calibration was performed by placing the probe in aqueous solution containing 200 and 2000 ng/mL DXA, respectively. The probe was perfused with distilled water at a flow rate of 2 μL/min. After equilibrating for 60 minutes, the dialysate was collected every 20 minutes and analyzed using liquid chromatography–tandem mass spectrometry (LC/MS/MS) to determine the DXA in vitro recovery ($R_{\text{in vitro}}$), which was calculated by the following equation: Recovery = C_p/C_s, where C_p is the dialysate concentration and C_s is the known concentration of DXA.

The probe was placed in water and was perfused at a flow rate of 2 μL/min with aqueous solution containing 200 and 2000 ng/mL DXA, respectively. After equilibrating for 60 minutes, the dialysate was collected every 20 minutes. The delivery loss in vitro ($D_{\text{in vitro}}$) is given by $1 - C_p/C_s$, where C_p is the dialysate concentration and C_s is the known concentration of DXA. If the $R_{\text{in vitro}}$ is nearly equal to $D_{\text{in vitro}}$ of the microdialysis probe, the $D_{\text{in vivo}}$ can be used to determine the $R_{\text{in vivo}}$.

The recovery in vivo was evaluated by the retrodialysis method after probe implantation[13]. The dialysis membrane was put into the anterior chamber of rabbits. DXA solutions of 200 and 2000 ng/mL at a rate of 2 μL/min serve as the perfusate. After equilibrating for 60 minutes, dialysis sample (P) was collected every 20 minutes and the delivery loss in vivo ($D_{\text{in vivo}}$) was determined according to the following equation:

$$D_{\text{in vivo}} = 1 - C_p/C_s.$$

Animal model and topical administration

Male rabbits were anesthetized with Urethane (25%, 4 mL/kg, intraperitoneal) by ear-vein injection. After local anesthesia and pupil enlargement of the eyes, the dialysis membrane was gently inserted into anterior chamber. The crevice between the dialysis membrane and the cornea was adhered by mucilage. After equilibrating for 60 minutes, the 0.1% (w/v) DXA in PLGA–PEG–PLGA thermosensitive gel-forming solution and the 0.1% (w/v) DXA eye drops at a dosage of 50 μL/kg were applied to both eyes of the rabbits, respectively. The probe was continuously perfused at a constant flow rate of 2 μL/min and the perfusates were collected before dosing and every 20 minutes post-dosing. The samples were stored at −20°C until analysis. All the in vivo studies of this research were complied with the 'Principles of Laboratory Animal Care' (NIH publication # 85–23, revised in 1985).

Analytical procedures and validation

The concentration of DXA in each dialysate (5 μL) was directly measured without any pretreatment using LC/MS/MS, which was composed of an high-performance liquid chromatography system (Waters, Milford, MA, USA) and triple quadruple tandem detector (Thermo Finnigan TSQ Quantum). The system work software was impower Pro (UPLC) and Xcalibur (MS).The mobile phase consisted of phase A of CH_3CN–H_2O (1:99; 0.02% HCOOH) and phase B of CH_3CN–H_2O (99:1; 0.02% HCOOH). The flow rate was 1 mL/min by gradient elution with a rapid gradient starting at 10% B and ending at 70% B within 4 minutes. A Luna Max-RP (2.0 ´ 50 mm, 4 μm; Phenomenex, Torrance, CA, USA) was used at 25°C. The MS was operated using electrospray ionization (ESI) source in the positive-ion detection.

Estimation of pharmacokinetic parameters

All relevant pharmacokinetic parameters were calculated using standard noncompartmental methods. The aqueous humor concentrations time data of an individual rabbit were analyzed. Maximum concentration ($C_{\max}$) and the time to reach $C_{\max}$ ($T_{\max}$) were determined using the concentration–time profiles. Area under the concentration–time curves (AUC) from zero to the last point (AUC_{0-t}) was calculated using the linear trapezoidal method.

Results

Synthesis and characterization of triblock copolymers

The typical ^{1}H-NMR spectrum of PLGA–PEG–PLGA (LA:GA = 5:1) with its chemical structure is presented in Figure 1. This spectrum was similar to that previously reported and all the signals were assigned on the spectrum[14]. The signals pertaining to PLGA–PEG–PLGA were found at δ = 5.20 ppm (CH of LA), 1.55 ppm (CH_3 of LA), 4.80 ppm (CH_2 of GA), 3.65 ppm (CH_2 of ethylene

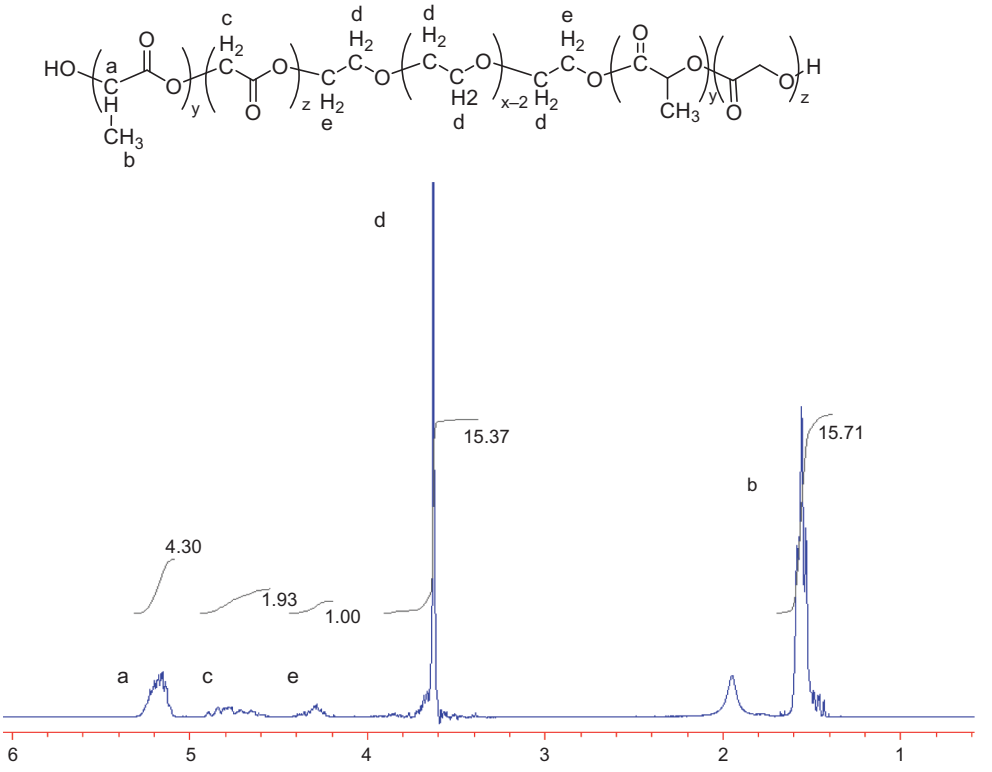

Figure 1. Typical ^{1}H-NMR spectra of PLGA–PEG–PLGA copolymer (a) CH of LA, (b) CH_3 of LA, (c) CH_2 of GA, (d and e) CH_2 of ethylene glycol.

glycol), and 4.20 ppm (CH_2 of ethylene glycol). The complicated split in these peaks was due to the random copolymerization of glycolide and lactide. The molar ratio of LA:GA was shown in Table 1 as calculated according to the work of Jeong et al.[14]

GPC was used to determine the weight–average molecular weight (M_w), the number–average molecular weight (M_n), and molecular weight distribution (M_w/M_n). The polydispersity of the copolymer was found to be about 1.25, which showed a symmetric peak and a relative narrow molecular weight distribution. Unimodal GPC trace with a low polydispersity value confirmed the formation of triblock copolymers that suggested a sufficiently high purity to study their physical properties. All the quantitative data on M_w and polydispersity of the copolymers are listed in Table 1.

Table 1. Characterization of PLGA–PEG–PLGA copolymer.

^{1}H-NMR		GPC		
Theoretical ratio (LA:GA)	Actual ratio (LA:GA)[a]	M_n[b]	M_w[b]	M_w/M_n[b]
5:1	4.8 : 1	4872	6105.5	1.25

[a]Determined by ^{1}H-NMR.
[b]Measured by GPC.

Phase diagram of PLGA–PEG–PLGA

In this study, a typical phase diagram of PLGA–PEG–PLGA triblock copolymers is shown in Figure 2, which demonstrated a thermoreversible sol–gel transition characteristic. The sol–gel transition temperature was found to be dependent on both the concentration and the composition of the block copolymers. From 10°C to 60°C, all hydrogels presented three physical states: solution, gel, and precipitate. Transition between solution and gel is defined as sol–gel transition and transition

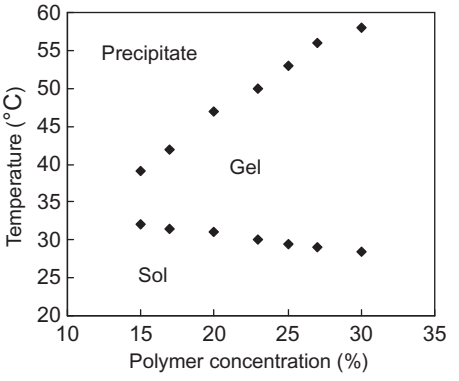

Figure 2. Phase diagram of PLGA–PEG–PLGA copolymer.

between gel and precipitate is defined as gel–sol transition. When the copolymer concentration increased from 15% to 30% (w/w), the sol–gel transition temperature was decreased by 0.5–3°C and the gel–sol transition temperature was increased by 1.5–12.5°C for the copolymers.

Figure 3 photographically demonstrates the sol–gel transition of the copolymers present. Just as it was taken out of the cold chamber at room temperature, PLGA–PEG–PLGA solution was in a transparent sol state (Figure 3a). In contrast, after the temperature was elevated from room temperature to 32°C, the copolymer solution became a transparent gel state (Figure 3b). As the temperature further increased above 37°C, it became a turbid gel (Figure 3c), and finally a precipitate (Figure 3d) was obtained at 45°C.

Viscosity measurements

Figure 4 illustrates the viscoelastic profiles of the 20% (w/w) PLGA–PEG–PLGA copolymer solution. The shear storage or elastic modulus (G') as well as the shear loss or viscous modulus (G'') were measured as a function of temperature. G' represents the elastic behavior or the energy stored in the sample during the deformation, whereas G'' denotes the viscous character or the energy dissipated as heat. In the sol state of the sample (liquid state), G'' dominated over G', and both G'' and G' began to noticeably increase at about 29°C (Figure 4a). The sol–gel transition temperature was observed at ~32°C when the G'' and G' curves intersected. In the gel state, G' dominated over G'', and G'' and G' values further increased with increasing temperature, reaching their highest values of 247 Pa (at ~37°C) and 369 Pa (at ~36°C), respectively. Increasing the temperature to 45°C and above resulted in precipitation of the polymer from the solution (turbid sol) and hence the gel strength was lost.

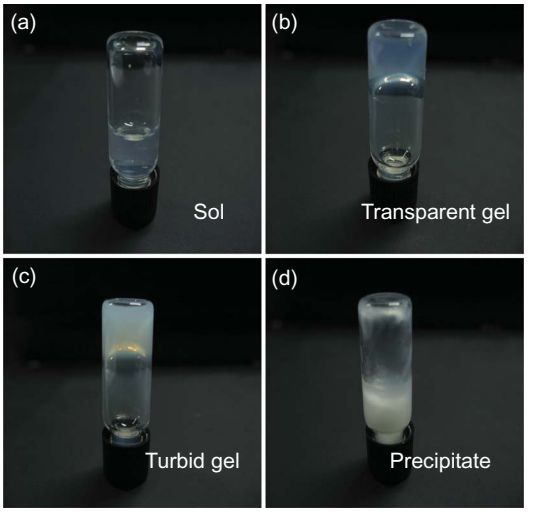

Figure 3. Sol–gel transition of PLGA–PEG–PLGA (20%, w/w) copolymer in aqueous solution observed as temperature gradually increased. (a) Transparent sol; (b) transparent gel; (c) turbid gel; (d) precipitate.

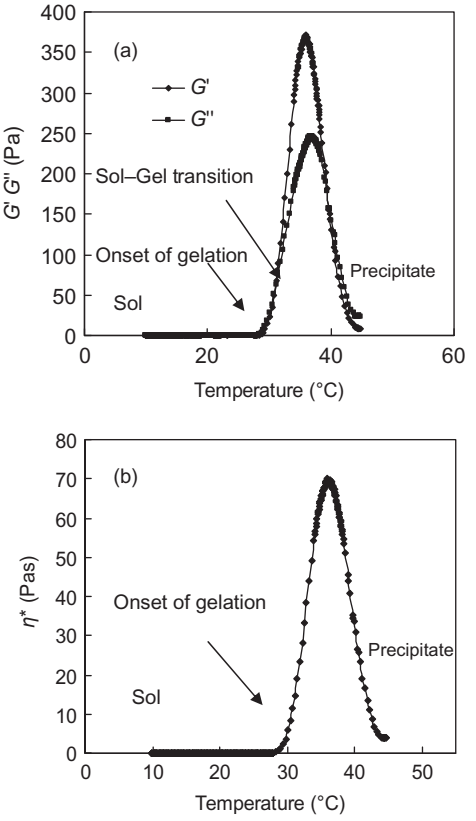

Figure 4. Viscoelastic profile of PLGA–PEG–PLGA copolymer 20% (w/w) aqueous solution. (a) G' and G'' as a function of temperature; (b) η^* as a function of temperature.

In the sol state, below gelation temperature, the complex viscosity η^* was independent of temperature (Figure 4b). During the onset of gelation, the complex viscosity was temperature-dependent, in that an increase in temperature led to rapid augmentation in the complex viscosity.

Ocular pharmacokinetics

Assay performance and validation

The chemical structure, ion mass spectra, and their proposed rationalizations in terms of fragmentation patterns of DXA are illustrated in Figure 5, which showed predominant fragment ions at *m/z*: 236.91, 146.97, 393.12(m^+). As shown in Figure 6, there was no significant direct interference of endogenous substances at the retention time of the analyte.

The seven-point calibration curve was linear over the concentration range 1.37–1000 ng/mL. The best linear fit and least squares residuals for the calibration curve

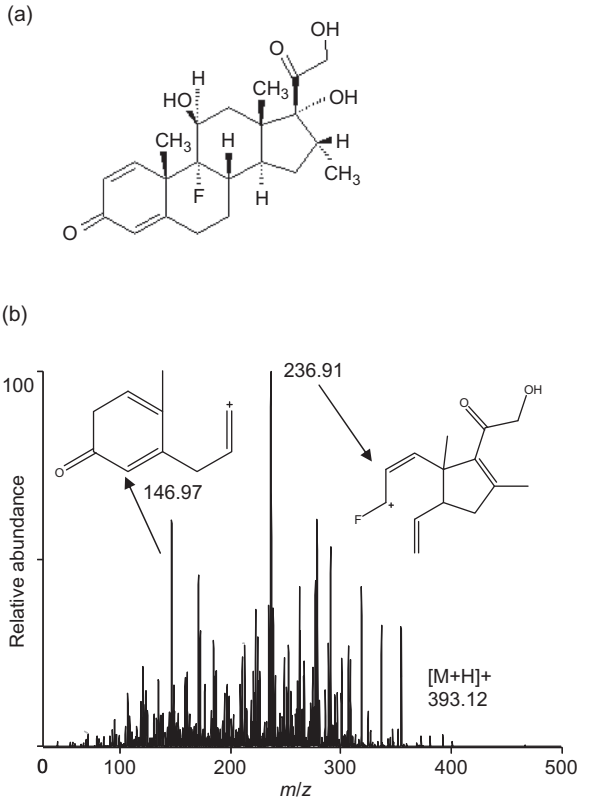

Figure 5. (a) Chemical structures and (b) chromatograph of MS/MS for DXA.

were achieved with a 1/× weighing factor, giving a mean linear regression equation for the calibration curve of $Y = 2096X + 472$ (Y, the area of peak; X, the concentration of DXA in dialysis). The mean correlation coefficient of the weighted calibration curve generated during the validation was 0.999. For the experiments the precision ranged from 0.2% to 14.8% and the accuracy from 103% to 107 %. The precision and accuracy for the analyte met the acceptance criteria (≤ ±15%).

Probe recovery in vitro and in vivo

It is well known that some ocular drugs have rapid absorption and elimination rates, which result in relatively short period for the local concentration measurements. To fully utilize the microdialysis technique, the probe recovery needs to be determined in advance, which is defined as the estimation for the in vivo extractable fraction of the testing compound from the space.

Table 2 shows that the calculated $R_{\text{in vitro}}$ was close to 28.1% at the flow rate of 2.0 μL/min and $D_{\text{in vitro}}$ was 24.8% that was similar to $R_{\text{in vitro}}$, thus providing an experimental proof for the in vivo recovery measurement by the microdialysis method. $D_{\text{in vivo}}$ was calculated to be 35.5%.

Ocular pharmacokinetics in anterior chamber

Microdialysis is a useful technique for continuously monitoring the trace substances in vivo[13,15]. Currently, there is a growing interest in using the technique for pharmacokinetic and biopharmaceutics studies. By means of the sampling technique, the ocular pharmacokinetic behaviors of DXA were studied after the gel-forming solution and eye drop were administered.

The concentration–time curves of DXA in the anterior chamber for the gel-forming solution and eye drop are illustrated in Figure 7. For the eye drop, the $C_{\max}$ in the anterior chamber was 17.6 ± 2.18 ng/mL, and $T_{\max}$ was about 1.67 hours. In comparison, the $C_{\max}$ was 125.2 ± 8.87 ng/mL detected at 1.61 hours for the gel-forming solution, which is sevenfold higher than that of the eye drop, along with a 7.89-fold larger AUC. Such result indicated that the PLGA–PEG–PLGA thermosensitive gel-forming solution could significantly enhance the bioavailability and therefore enhance the effectiveness of DXA compared with the eye drops (Table 3).

Discussions

The potential of PLGA–PEG–PLGA triblock copolymer as a thermosensitive gel-forming matrix material for ocular delivery of DXA has been assessed. And the evidence for improving the efficacy, bioavailability, and pharmacokinetic properties of water-insoluble eye drugs such as DXA is been provided.

Phase transition temperature is an important parameter for in situ gel-forming polymer, which determines the potential utilization of the polymer in ocular drug delivery[16]. It is also well noted that polymer concentration may alter the phase transition property of its solution. Based on the block length and the copolymer concentration, different phase diagrams were achieved and discussed previously[17,18]. The data represented here demonstrated that the thermosensitive triblock copolymer PLGA–PEG–PLGA possessed desirable viscoelastic properties that would undergo gelation upon application to the eye. The copolymer was stored in the solution form before use. Upon contact with the ocular hydrogel, the sol state of the polymer solution underwent gelation. On the basis of the phase transition data, we proposed a gelation mechanism for the polymer solution. The polymer aqueous solution with the concentration higher than the critical concentration may have four distinct phases depending on its temperature. The polymer solution at room temperature was clear, and it had a fully expanded coil state in water (Figure 3a). As temperature was raised, the polymer solution became more and more viscous, and a transparent gel

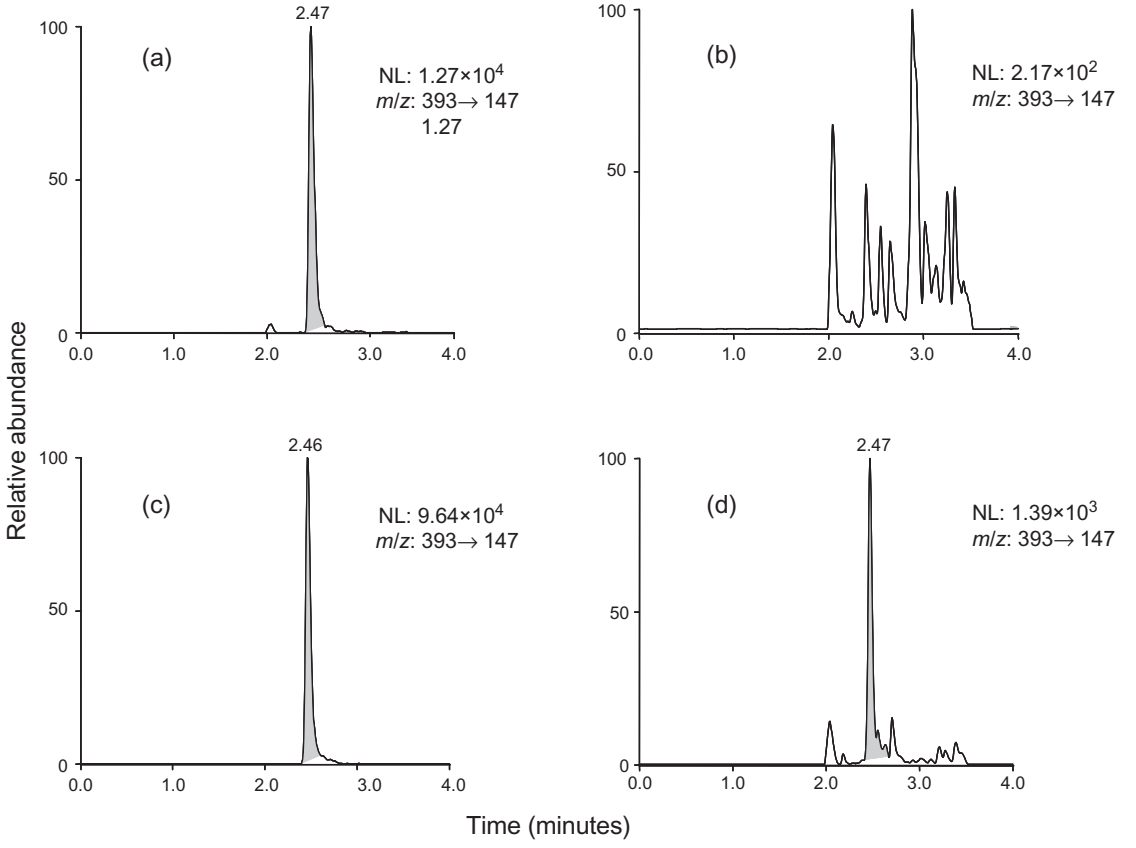

Figure 6. LC/MS/MS Chromatograms of DXA dialysis samples from rabbit anterior chamber (a) DXA standard; (b) blank dialysis sample; (c) blank dialysis sample spiked with DXA standard; (d) dialysis samples post-dosing.

Table 2. Results of $R_{\text{in vitro}}$, $D_{\text{in vitro}}$, and $R_{\text{in vivo}}$ of DXA ($n = 4$) (mean ± SD).

	Concentration (ng/mL)		
	200	2000	Mean
$R_{\text{in vitro}}$ (%, mean ± SD)	29.3 ± 2.0	26.9 ± 3.5	28.1
$D_{\text{in vitro}}$ (%, mean ± SD)	25.3 ± 3.8	24.3 ± 5.2	24.8
$R_{\text{in vivo}}$ (%, mean ± SD)	36.3 ± 3.5	34.7 ± 9.0	35.5

(Figure 3b) was formed owing to the physical association of the pendant hydrophobic groups of amino acid esters like ethyl ester on the polymer backbone. We presumed that the hydrophobic interaction between the side chain fragments of amino acid esters acted as a physical junction in the aqueous polymer solution, resulting in the formation of hydrogel. The transparent gel became an opaque gel (Figure 3c) as temperature was further increased, subsequently leading to a shrunken gel by expelling water. At higher temperature, the gel was broken to become a turbid sol (Figure 3d).

Based on our experience concerning the viscoelastic properties of PLGA–PEG–PLGA, the 20% (w/w) copolymer solution that displayed a satisfactory gelation temperature and gel strength was used for viscosity measurements, and it remained a gel after application to the ocular surface. It was also easier to formulate in comparison with the more concentrated

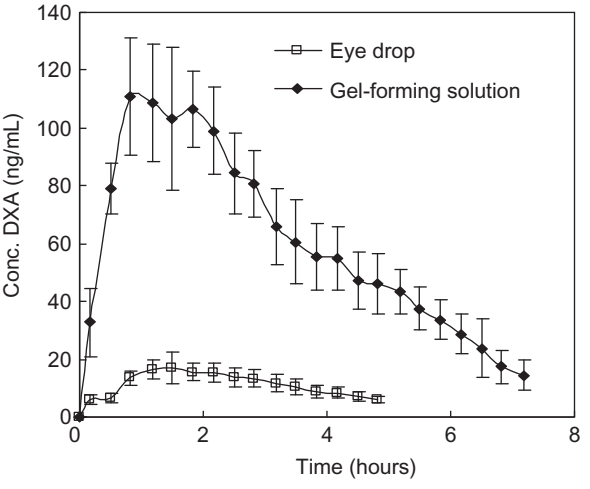

Figure 7. DXA concentration in aqueous humor after instillation of 0.1% (w/v) DXA PLGA–PEG–PLGA gel-forming solution and 0.1% (w/v) DXA eye drop ($n = 5$).

Table 3. Pharmacokinetic parameters of DXA PLGA–PEG–PLGA gel-forming solution and eye drop in rabbit aqueous humor (noncompartment model, $n = 5$) (mean ± SD).

Group	C_{max} (ng/mL)	T_{max} (hours)	AUC_{0-t} (ng h/mL)
Gel-forming solution	125.2 ± 8.87	1.61 ± 1.21	436.0 ± 52.60
Eye drop	17.61 ± 2.18	1.67 ± 0.41	55.17 ± 9.89

counterparts. The 25% and 30% (w/w) polymer solutions were more difficult to handle as they were too viscous and sticky with lower temperature of gel–sol transition.

The thermosensitive properties of the copolymer resulted in the prolonged precorneal retention of DXA because the water-insoluble drug was readily embedded in the gel and its elimination from the aqueous humor by tear was effectively inhibited. In addition, the PLGA–PEG–PLGA could enhance the corneal permeability and absorption of DXA because of its hydrophobic–hydrophilic and adhesive characteristics. This is the first time that this has been demonstrated with the PLGA–PEG–PLGA hydrogel as a matrix material for improving ocular availability and enhancing the eye drug effectiveness. Supporting findings have been reported for other injectable applications such as those for lysozyme[17] delivery and ophthalmic applications as a biosynthetic bandage for corneal wound repair[19], where hydrogels show good compatibility.

Conclusions

In conclusion, we have successfully synthesized the triblock PLGA–PEG–PLGA by the method of ring-opening polymerization. The thermosensitive gelation properties were illustrated through rheological studies and the copolymer solution was sensitive to the temperature. It was simple to prepare the formulation for DXA. The results of rabbit ocular pharmacokinetics indicated that the PLGA–PEG–PLGA thermosensitive gel-forming solution could achieve significantly enhanced bioavailability of DXA than eye drops in the anterior chamber. This research supported the possible role of thermosensitive PLGA–PEG–PLGA for the delivery of therapeutic agents in the treatment of acute and chronic posterior segment and other eye diseases.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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