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Sustained Delivery of Amphotericin B and Vancomycin Hydrochloride by an Injectable Thermogelling Tri-Block Copolymer

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ABSTRACT: Because traditional drug delivery poses many disadvantages such as poor compliance of patients and a drug plasma level variation, novel drug delivery systems containing controlled release drug vehicles become attractive. In this study, a kind of tri-block copolymer consisting of polycaprolactone (PCL) and poly(ethylene glycol) (PEG), PCL-PEG-PCL, were synthesized by a rapid microwave-assisted and a conventional synthesis method to form an in situ gelling system that provides a controlled release of drugs over a long period of time. Copolymer characterization was performed using a gel permeation chromatography, the ^{1}H-NMR, and a phase transition behavior evaluation. Vancomycin hydrochloride and amphotericin B were used as drug models here. This study confirmed that the synthesis of the copolymer using microwave irradiation was the most effective method to prepare this smart copolymer. Results also demonstrated the better performance of the microwave-synthesized copolymer regarding its phase behavior. It was shown that gelatin temperatures were also affected by the hydrophilicity of the drug model, the copolymer concentration, and the media. It was indicated that the hydrogels could sustain the delivery of model drugs for about 17 to 20 days. As the drugs used in this study were both large molecules and the main release mechanism was copolymer bulk erosion rather than simple diffusion, the effect of drug and copolymer concentration on the drug release profile was not so significant.

KEYWORDS: Tri-block copolymer, PCL-PEG-PCL, Vancomycin, Amphotericin B, In situ forming gel, Drug release, Microwave

LAY ABSTRACT: Different studies have been carried out to improve drug delivery systems. Smart drug vehicles such as thermoresponsive and in situ forming hydrogels made of tri-block copolymers are promising systems in this field. Thermoresponsive hydrogels can release loaded molecules in response to the changing temperature. In situ forming hydrogels are the kind of thermoresponsive materials that are injectable fluid (sol) at room temperature and gel at body temperature. Pharmaceuticals release gradually from the gel over long periods of time. Here we investigated the in situ forming hydrogel based on poly(caprolactone)–poly(ethylene glycol)–poly(caprolactone) as a drug delivery system. Vancomycin hydrochloride and amphotericin B were used in this study as a model. The results indicated that this system can control release pattern of drug perfectly for approximately 20 days.

1. Introduction

In the past few decades, smart or stimuli-responsive copolymers have been demonstrated to be a promising new class of drug delivery systems, and they have received considerable attention because of their unique benefits (1–3). In particular, amphiphilic, thermosensitive ones (e.g., ABA and BAB tri-block or AB di-block) consisting of hydrophobic (B) and hydrophilic (A) blocks have been studied more than other smart systems due to their in situ gel-forming properties at body temperature (4–8).

Poly(caprolactone)–poly(ethylene glycol)–poly(caprolactone) (PCL-PEG-PCL) copolymers have been widely

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studied in different fields such as nanotechnology, tissue engineering, pharmaceutics, and medicinal chemistry due to their great biocompatibility, controlled biodegradability, and appropriate drug release behavior (9–14).

The extensively used method to synthesize PCL-PEG-PCL tri-block copolymers is the ring-opening polymerization from PEG and PCL with a catalyst (11). Mostly this has been done by conventional procedures using a two-necked flask or a stainless steel reactor (15–17). Here we compare a microwave-assisted polymer synthesis method for PCL-PEG-PCL, which was done before by Moretton and co-workers, with a conventional method (18). Microwave-assisted polymerization provides a reaction condition with higher temperature and sometimes pressure that shortens the time of reaction from hours and days to minutes and even seconds. By using microwave irradiation, the high-speed, reproducible, and scalable preparation of materials such as polymers with limited side reactions and byproducts and higher yields is possible. Also, this approach facilitates scale-up procedure and technology transfer from bench to industry (19–22).

In this study we prepared PCL-PEG-PCL in situ gel-forming copolymers composed of PEG (molecular weight 1500 and 2000) and PCL-to-PEG ratios of 1:1 and 2:1 using both conventional and microwave-assisted methods. The gels were then utilized for delivery of amphotericin B and vancomycin hydrochloride.

Amphotericin B is an antifungal drug administrated by infusion that takes at least 1 h (23). Because treatment duration of diseases using this drug takes almost 1–3 months and because of its poor oral absorption and half-life, which is about 24 h, daily infusion is currently the only way of its administration. In such cases, preparing a controlled or sustained drug delivery system that releases drug over a long time and provides an effective, safe, and stable drug concentration in the body is desirable. Such a system can also improve patient compliance, decrease the drug side effects, and reduce the cost of the treatment (24–26).

Vancomycin is a tri-cyclic glycopeptide antibiotic with a short half-life (6 h) and poor gastrointestinal absorption (27). Infusion of this drug, which is necessary in seriously ill patients, poses some drawbacks: first of all, the administration of the drug, depending on the disease, should be carried out every 8 or 12 h, and its infusion takes 1–2 h (28). This is really time-consuming and inconvenient for patients. Second, this administration procedure must be critically on time because a drug concentration fluctuation causes an ineffective and unsuccessful treatment of the infection and even a resistance to the antibiotic. Consequently, side effects increase with a higher concentration of drug (29–31). Finally, in some cases, the treatment must be continued for some days (28).

Separate study indicated the benefits of polymeric vehicles for the vancomycin hydrochloride administration. Using Poloxamer 407 as a vancomycin hydrochloride delivery system provides controlled release profiles, acceptable preservation of vancomycin activity, good tolerability in rats, and ease of administration (32). Vancomycin incorporated into a poly-L-lactide-co-caprolactone sheet was also effective for the prevention of prosthetic graft methicillin-resistant *Staphylococcus aureus* infection (33).

For all the above reasons, we proposed to evaluate the applicability of PCL-PEG-PCL thermoresponsive gels as a controlled release vancomycin hydrochloride and amphotericin B delivery system in this study.

2. Materials and Methods

2.1. Materials

The materials utilized in this study are PEG (Merck, Darmstadt, Germany), ε-caprolactone (Sigma Aldrich, St. Louis, MO, USA), stannous octoate [$Sn(Oct)_2$, Sigma Aldrich], Vancomycin hydrochloride (Sigma Aldrich), Amphotericin B (Cipla, Mumbai, India), high-performance liquid chromatography (HPLC)-grade acetonitrile (Duksan Pure Chemicals, Ansan-city, South Korea), HPLC-grade methanol (Duksan Pure Chemicals).

2.2. Tri-Block Copolymer Preparation

PCL-PEG-PCL (molecular weight 1500-1500-1500 and 1000-2000-1000) was synthesized by ring-opening polymerization using both conventional and microwave-assisted methods.

2.2.1. Conventional Method: The synthesis of copolymers in a stainless steel reactor and a two-necked, round-bottomed flask was carried out according to the protocol by Gong *et al.* (15, 16), with some minor modification. Briefly, PEG was dried and stirred at 110 °C for 2 h. Then adequate amount of PEG, ε-caprolactone, and $Sn(Oct)_2$ were loaded into the reac-

tor and the mixture was stirred at 130 °C under vacuum for 6 h. The product was degassed by a rotary vacuum drier for 30 min. With a two-necked, round-bottomed flask, the procedure was the same as synthesis using a reactor; the exception is that here the reaction was performed under a dry nitrogen atmosphere.

2.2.2. Microwave-Assisted Method: For synthesizing the copolymer 1500-1500-1500, 10 g dried PEG 1500, 20 g ε-caprolactone, and 1.8 g $Sn(Oct)_2$ were loaded in a glass flask fitted with a condenser and was transferred into a microwave. The mixture was kept at 130 °C, stirred, and irradiated at 800 w. The optimum irradiation time for the rapid preparation of the copolymer was determined by trying various irradiation duration (15, 20, 25 min).

2.2.3. Purification: To purify the product, it was dissolved in 20 mL dichloromethane. By adding 800 mL petroleum ether gradually, the copolymer precipitation was completed and the obtained copolymer was filtered. The purification procedure was done two times, and finally the product was dried in a freeze dryer for 24 h. The sample was then kept at 4 °C until usage (17).

2.2.4. Yield of Reaction: The yield of the reaction was calculated by dividing the weight of the purified PCL-PEG-PCL to the weight of initial materials used in the copolymer synthesis.

2.3. Characterization of PCL-PEG-PCL Copolymer

Nuclear magnetic resonance (^{1}H-NMR, AC 80 Brucker, Rheinstetten, Germany) analysis at 80 MHZ and 25 °C in $CDCL_3$ was used to determine the copolymer structure, PCL-to-PEG ratios, and the number average molecular weight (Mn) (16). Gel permeation chromatography (GPC)—Agilent GPC-Addon apparatus (California, USA) and RID-A refractive index signal detector (Agilent Technology, California, USA) coupled to Plgel® columns (Agilent Technology, California, USA)—was performed to determine the weight average molecular weight (Mw), Mn, and the polydispersity of tri-block copolymers. In this study tetrahydrofuran was used as the solvent and polystyrene was used as the standard sample for the calibration curve. The eluent had a rate of 1 mL/min (17).

2.4. Gelation Behavior of the Copolymer

Sol-gel and gel-precipitant transition temperatures were investigated using two different formulations, the copolymer dissolved in distilled water and in the dextrose solution of 20% w/w concentration. Five milliliters of the copolymer solution in distilled water or dextrose 20% with the concentrations of 25, 30, 35, 40, and 45% (w/v) was poured in to each vial and kept in a reciprocal water bath (NB-304, N-Biotec, Gyeonggi-do, South Korea). The temperature increased at a rate of 1 °C/3 min from 20 ± 0.1 to 70 ± 0.1 °C. After every 3 min, the vials were inverted to evaluate the flow ability of the content. The sol-gel transition temperature was recorded when the content of the inverted vial did not flow at all, showing a gel was formed. By increasing the temperature, the point at which the copolymer was phased out and precipitated was also measured (16). This measurement was also repeated after drug loading to evaluate the effect of the drug on the phase transition temperatures. The reversibility of the gelation was also investigated by decreasing the temperature. All the experiments were carried out in triplicate.

2.5. In Vitro Drug Release

According to the result of the phase transition evaluation, the two most appropriate concentrations of each copolymers, 35 and 40% (w/v), which were synthesized by the microwave-assisted method in 15 min, were chosen as drug delivery vehicles for in vitro drug release studies. To prepare drug-loaded hydrogels, the solutions of the adequate amount of the copolymers and drugs (0.1 and 0.5% w/v) in different media were prepared. Drug-free hydrogels (35 and 40% w/v) were used as blanks. The samples were prepared in triplicate. Two milliliters of each formulation were loaded in tubes and transferred to a reciprocal water bath at 37 °C until the gel was completely formed. Then 4 mL of phosphate-buffered solution (PBS, pH = 7.4) was added to each sample as a release media and the samples were shaken 60 times/min in the 37 °C reciprocal water bath. Every 48 h, an aliquot of 0.5 mL was withdrawn from the release media and replaced by 0.5 mL of fresh buffer. The amount of the drug in the samples was measured using HPLC [Acme 9000, Young Lin, Anyang-city, South Korea, C18 (3.9 × 150 mm, 5 μm) column]. The mobile phase for amphotericin B was composed of 450 mL acetonitrile, 450 mL methanol, and 600 mL sodium acetate 0.05 mol/L (34). For vancomycin hydrochloride, the mobile phase was a mixture of 100 mL ammonium acetate, 90 mL acetonitrile, and 810 mL deionized water (35). Flow rate in both analyses was 1 mL/min and UV detection wavelength was set at 382 and 210 nm for amphotericin B and vancomycin hydrochloride, respectively.

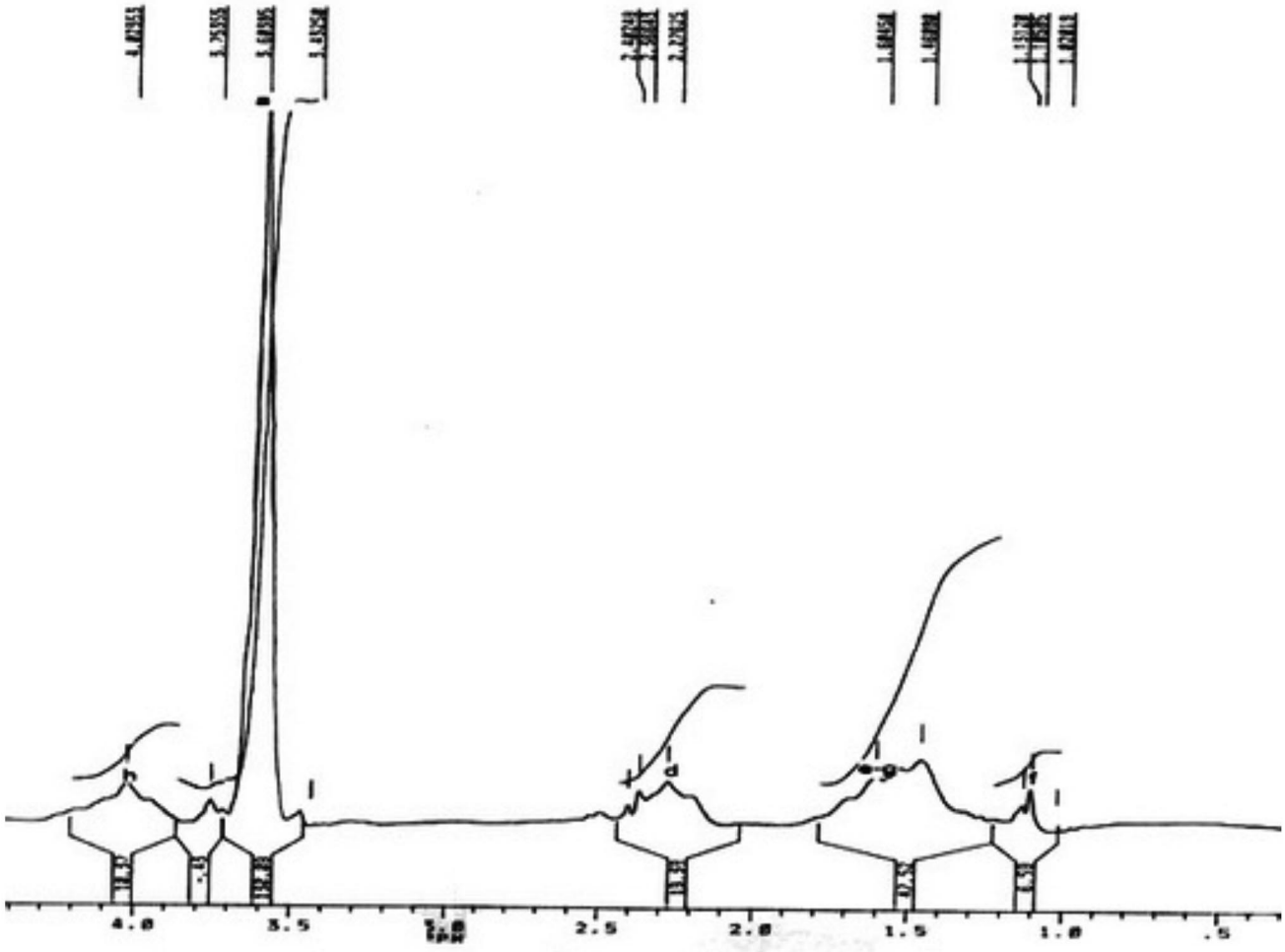

Figure 1

^{1}H NMR spectrum of the PCL-PEG-PCL (1000-2000-1000) prepared using the conventional method (by a reactor); the signal A pertains to the protons of PEG (A) and others (h, d, e, f, g) to the CH_2 groups of caprolactone.

2.6. Statistical Analysis

The results were reported as mean ± standard deviation (SD) (n = 3). Paired *t*-test and one-way analysis of variance (ANOVA) were used as the analysis method. In all cases, a significance level of $P < 0.05$ denoted statistical significance.

3. Results

3.1. Tri-Block Copolymer Preparation

The copolymer was synthesized by two procedures: a conventional method, using a two-necked flask and a stainless steel reactor, which took longer time in comparison with the other method. The second method by which the copolymer was synthesized was under a microwave irradiation that took just a few minutes. The yield of the reaction by the conventional method using a two-necked flask and a stainless steel reactor was 60–65% and 81–84%, respectively, and by the microwave method it was 94–95%. By increasing the time of the reaction under a microwave irradiation from 15 to 25 min, no significant difference was found in the yield of reaction or the quality of the products. As the yield of the reaction using the two-necked flask was low, further studies were continued with the copolymers prepared by the stainless steel reactor and the microwave-assisted method.

3.2. PCL-PEG-PCL Copolymer Characterization

The ^{1}H-NMR spectrum of PCL-PEG-PCL (1000-2000-1000) synthesized by the reactor is presented in Figure 1. The signals that appeared in 3.6 (a), 4.1 (h), 2.2 (d), 1.5 (e, g) and 1 (f) ppm are related to the

TABLE I
The Copolymer Composition

PCL-PEG-PCL	Synthesis Method	Mn_a	PCL:PEG	Mn_b	Mw	Polydispersity
1000-2000-1000	Conventional, reactor	3137.7	0.568	-	-	-
1500-1500-1500	Microwave-assisted	4528	2.018	4575.7	7203.5	1.57

Mn_a and PCL: PEG obtained from ^{1}HNMR; Mn_b, Mw, and polydispersity (Mw/Mn) obtained from GPC.

protons of PEG (A) and the CH_2 groups of the caprolactone (h, d, e, f, g) (17). The Mn of the copolymer was calculated by the integration of the signals of ^{1}H-NMR spectrum pertaining to each monomer. Mn of the copolymer 1500-1500-1500, which was synthesized by the microwave method (15 min), 1000-2000-1000, which was synthesized by the reactor, and also the PCL-to-PEG ratios in the copolymers are shown in Table I.

Figure 2 illustrates the GPC chromatogram of 1500-1500-1500 copolymer prepared under a microwave irradiation. Mw, Mn, and the polydispersity (Mw/Mn) of the copolymer obtained from GPC are exhibited in Table I.

3.3. Phase Transition Behavior of the PCL-PEG-PCL Tri-Block Copolymer

The sol-gel transition temperatures of the PCL-PEG-PCL tri-block copolymers with various concentrations are listed in Table II. The copolymers synthesized using the conventional method (reactor) could not form gel in all concentrations in distillated water at body temperature. The solution of the copolymer

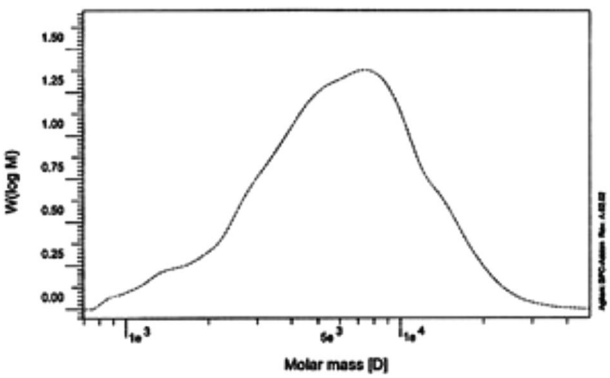

Figure 2

GPC chromatogram of the PCL-PEG-PCL (1500-1500-1500) synthesized by a microwave-assisted method.

1500-1500-1500 synthesized under a microwave irradiation (15 min) was prepared in dextrose solution 20% as well as distilled water. Adding dextrose caused a significant reduction in the sol-gel transition temperature of the system ($P < 0.05$). According to the results, when the solution was prepared in water, only the concentration of 45% copolymer could form gel at body temperature (37 °C), yet it posed very high viscosity and it did not have acceptable syringability when it was passed through a 25-gauge needle at room temperature. The copolymer concentrations of 35% and 40% in dextrose solution had the most appropriate gelation temperatures, which were around body temperature and were also syringible. There was no significant difference between the gel-forming temperatures of the copolymers prepared using microwave irradiation with different reaction times ($P < 0.05$, data not shown).

For the microwave-assisted synthesized copolymer, the sol-gel transition occurred in 30–50 s at 37 °C, which never happened with the copolymers synthesized by the conventional methods. Copolymer precipitation was also investigated for the microwave-synthesized copolymer, and the results are shown in Table III.

In all cases, gel formation was irreversible, and decreasing the temperature did not lead to a gel-sol transition. Elevating the temperature as high as the copolymer precipitates and then rapidly cooling the precipitant caused the mixture become the sol again.

As indicated in Tables II and III, by increasing the copolymer concentration, the sol-gel transition reduced noticeably ($P < 0.05$) and a slight increase in precipitation temperature was observable, but it was not significant.

Finally, the effect of loaded drugs on the phase transition behavior of the microwave-irradiated (15 min) copolymer 1500-1500-1500 (35% and 45% w/v in 20% dextrose) was determined. This system was se-

TABLE II
Sol-Gel Transition Temperatures (Mean °C ± SD) of copolymers with various concentrations

Copolymer Concentration (% w/v)	Copolymer 1500-1500-1500 in Dextrose Solution (Microwave)	Copolymer 1500-1500-1500 in Water (Microwave)	Copolymer 1500-1500-1500 in Water (Reactor)	Copolymer 1000-2000-1000 in Water (Reactor)
%25	No gel	No gel	No gel	No gel
%30	41 ± 2.4	48 ± 3.1	56 ± 1.9	No gel
%35	36 ± 1.2	41 ± 1.9	51 ± 0.71	59 ± 3.1
%40	32 ± 0.71	38 ± 1.9	45 ± 1.5	51 ± 1.9
%45	26 ± 1.2	34 ± 1.5	40 ± 2.4	45

lected for the in vitro drug release study because of its best phase behavior and characterization results in comparison with the others. As it is shown in Table IV, adding vancomycin hydrochloride (0.5%) and amphotericin B (0.5%) caused an increase and a decrease in gel formation temperatures, respectively ($P < 0.05$). This result was not observed with lower concentrations of drugs.

3.4. In Vitro Drug Release

In vitro drug release study was performed on microwave-assisted, synthesized PCL-PEG-PCL (1500-1500-1500) in concentrations of 35% and 40% w/v in 20% dextrose solution. Two various concentrations of amphotericin B (Amp) and vancomycin hydrochloride (Van), 0.1 and 0.5% w/v was investigated to determine the effect of drug concentration on the release profile. Comparisons between the formulations consisting of the same amount of the drug but different concentrations of the copolymer are shown in Figure 3. According to the statistical results and their *P*-values, no difference was found between the release profiles of the formulations of different copolymer concentrations in this concentration range (35% and 40% w/v). As indicated in Figure 4, in the formulations of 35% copolymer and different concentrations of the drugs, the rate of drug release was independent of the drug concentration. A significant difference ($P < 0.05$) was found for the formulations of different kinds of drug.

TABLE III
Precipitation Temperatures of 1500-1500-1500 Copolymer Solutions Synthesized by the Microwave Irradiation (Mean °C ± SD)

Copolymer Concentration (% w/v)	Precipitation Temperature (°C) in Water	Precipitation Temperature (°C) in Dextrose Solution
25	Not identified	Not identified
30	55 ± 1	51
35	57 ± 2	54 ± 2
40	60 ± 2	56 ± 1
45	60 ± 2	56 ± 1

4. Discussion

Drug delivery systems have evolved to keep pace with new therapeutic molecules such as peptides, nucleic acids, and others. Additionally, some of these systems provide a stable concentration of drug in the blood for a long period of time that is desirable for treatment of some diseases, and there is concrete evidence of patients' compliance improvement during such treatment. PCL-PEG-PCL, an in situ gel-forming and thermoresponsive copolymer, was synthesized by a conventional method and has been studied as a drug delivery system and in tissue engineering before (36–38). In this study, we investigated a kind of microwave-assisted method to hasten the preparation of the copolymer as well. The comparison between the conventional and the microwave-assisted methods confirmed that the microwave-assisted method was prefererable to the conventional method because it had a higher yield and a shorter time of reaction (about a few minutes). Moreover, this situation caused a limited generation of by-products and therefore needs fewer purification steps (20).

TABLE IV
Influence of Drugs and Their Concentrations on the Sol-Gel Transition Temperatures (Mean °C ± SD)

Copolymer Concentration (w/v %)	Gelation Temperatures before Drug Loading (°C)	Gelation Temperatures after Drug Loading			
		Amphotericin B (w/v %)		Vancomycin (w/v %)	
		0.1	0.5	0.1	0.5
35	36 ± 1.2	36 ± 1	37	35	33 ± 1
40	32 ± 0.71	34 ± 2	36 ± 1	31 ± 2	29

Furthermore, copolymer characterization results demonstrated the superiority of the microwave-assisted copolymerization because the copolymer (1000-2000-1000) prepared by the conventional method had a lower Mn (3137) and PCL:PEG ratio (0.568) than the theoretical values (Mn = 4000 and PCL:PEG ratio: 1). In spite of these results, the copolymer (1500-1500-1500) prepared under microwave irradiation had a Mn (4528) and PCL:PEG ratio (2.018) that were very close to the expected values (Mn = 4500 and PCL: PEG ratio: 2) (Table I). Moreover, a symmetric peak in the chromatogram of microwave-assisted, synthesized copolymer (Figure 2) indicated a low polydispersity of the copolymer. Thus it is shown that the microwave-assisted method provided a better control of the reaction, and this has also been indicated in some previous studies for different kinds of polymers (39–42).

As surprisingly indicated in Table II, the gelation temperature of the microwave-synthesized copolymer was much lower than the reactor-synthesized one (1500-1500-1500). Gelation of the microwave-synthesized copolymer solutions occurred instantaneously at body temperature (37 °C), whereas conventionally synthesized copolymers could not form gel at this temperature. As mentioned, because of a lower Mn and consequently shorter PCL blocks (the hydrophobic block) of the conventionally prepared copolymers, higher temperatures were needed to form gel according to the mechanism of the gel formation (16, 17).

Table II shows that the sol-gel transition temperature of the copolymer (1000-2000-1000) was higher than the copolymer (1500-1500-1500) because of its shorter PCL segments and consequently a lower PCL: PEG ratio. This means a decrease in hydrophobic to hydrophilic interaction caused a lower driving force for the gelation. Sol-gel transition temperature was also shown to depend on the copolymer concentration. By increasing the copolymer concentration and consequently enhancing the number of hydrophobic interactions, the gel formed at lower temperatures (43).

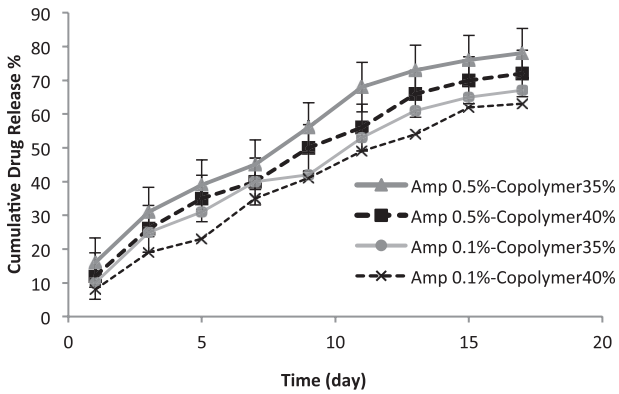

Figure 3

Effect of the copolymer and drug concentration on the in vitro release profile of amphotericin B (Amp) (mean ± SD).

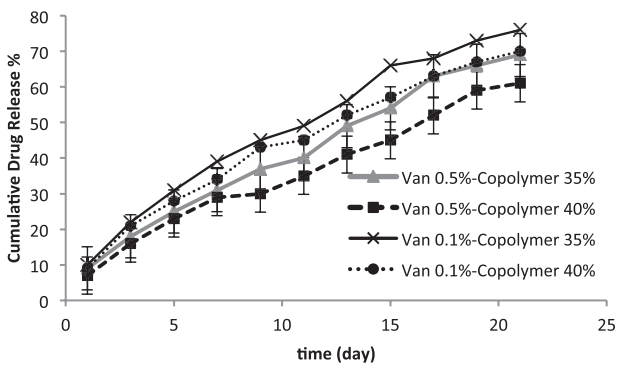

Figure 4

Effect of the copolymer and drug concentration on the in vitro release profile of vancomycin hydrochloride (Van) (mean ± SD).

TABLE V
Kinetic Profile of Drug Release

Drug	Drug Concentration % (w/v)	Copolymer Concentration % (w/v)	R^2 Zero order	R^2 Higuchi
Amphotericin B	0.1	35	0.999	0.986
		40	0.982	0.987
	0.5	35	0.960	0.985
		40	0.975	0.993
Vancomycin hydrochloride	0.1	35	0.976	0.995
		40	0.979	0.996
	0.5	35	0.994	0.980
		40	0.987	0.974

The parameters that caused the water molecules to disperse from the copolymer chains elevated micelle formation due to an increase in the chance of hydrophobic interactions among PCL segments and a decrease in the hydrogen bonds between water molecules and PEG chains, and as a result a reduction in the sol-gel transition temperature was observed (44). Dextrose repelled the water molecules from the copolymer chains, inducing gel formation at lower temperatures (16).

Above the precipitation temperature, which may be different depending on the structure, molecular weight, and the concentration of the tri-block copolymer solution, phase separation occurred and the copolymer was phased out (43). As illustrated in Table III, adding dextrose significantly reduced the precipitation temperatures as well as the gelation temperatures. This may be a result of water activity reduction in the gel network in the presence of water-soluble materials such as dextrose (44).

Loaded drugs could also change the phase transition temperature of the systems depending on their molecular weights and their hydrophilicity. In contrast to amphotericin B, vancomycin hydrochloride is a water-soluble molecule. The migration of water toward vancomycin hydrochloride must lower the activity of water and favor the hydrophobic interactions between PCL segments of the copolymers. Also, because of its hydrophilic nature, vancomycin hydrochloride bound to the hydrophilic segments of the copolymer (PEG) and decreased the number of PEG–water hydrogen bonds. Because the hydrophilic positions were occupied by drug molecules and the formation of the hydrophobic bonds became more probable, the gel formed at lower temperatures. Conversely, amphotericin B, which is attracted to the inner part of the PCL-PEG-PCL micelles, that is, PCL, occupied the hydrophobic positions and consequently decreased the chance of PCL–PCL interactions so that the gelation occurred at higher temperatures.

The most appropriate copolymer, 1500-1500-1500, which was synthesized using a microwave irradiation, was evaluated here as a drug delivery system in concentrations of 35% and 40% w/v copolymer in 20% w/w dextrose solution. Surprisingly, neither drug concentrations nor copolymer concentrations had a significant effect on the drug release profile (Figures 3 and 4). In the release rate of the formulations with different copolymer concentrations, this insignificancy may be due to the limited range of the concentration that could gel in the body temperature but was sol and injectable in the room temperature (35–40% w/v). Drugs release from polymeric matrix occurred by two main mechanisms: diffusion, and surface and bulk erosion. To investigate the main mechanism of the drug release from the hydrogel, data was fitted according to the zero-order (release by gel surface erosion) and the Higuchi kinetic models (release by diffusion or bulk erosion). As indicated in Table V, the R^2 of both models were similar in the entire formulations. Although most formulations fitted a little better to the Higuchi model, both mechanisms must be considered. Given that both drugs are large molecules, it seems that drugs were mainly released by copolymer bulk erosion, which is independent of the copolymer and drug concentration in spite of the diffusion rate,

which depends on both the copolymer and drug concentration (3, 45).

5. Conclusion

PCL-PEG-PCL (1500-1500-1500) synthesized under microwave irradiation, which is a fast, simple, and cost-effective method and causes higher yield of reaction, forms gel in body temperature with low concentration of polymer and appears to be an appropriate in situ–forming drug delivery system. The physicochemical properties of drug molecules are a critical determinant of drug release profile and release mechanism. When the drug is a very large molecule and/or there is a possibility of interaction between drug and vehicle, drug releases by polymer degradation rather than by diffusion; consequently, drug or polymer concentration do not have a significant effect on release profile, as we demonstrated in this study.

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Conflict of Interest Declaration

Authors declare that they do not have any financial or nonfinancial competing interests related to this paper.

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