Science & Technology Development Journal – Engineering and Technology, 5(SI1):69-80

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Research Article

Injectable thermosensitive poly(ethylene glycol)–poly(ε-caprolactone)–poly(ethylene glycol) hydrogels: Optimal synthesis conditions and sol-gel-sol transition behaviour

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ABSTRACT

Hydrogels are polymeric materials containing amphiphilic networks that can absorb a large amount of physiological fluid without damaging their structure. By following the two-step procedure of e-caprolactone ring-opening reaction and coupling PEG-PCL blocks with hexamethylene diisocyanate (HMDI), injectable thermosensitive poly(ethylene glycol)–poly(e-caprolactone)–poly(ethylene glycol) (PEG–PCL–PEG, PECE) hydrogels are successfully fabricated. The PECE hydrogels are characterized in terms of physical-chemical properties and ``sol-gel-sol'' phase transition by Proton Nuclear Magnetic Resonance (^{1}H-NMR) and Fourier Transform Infrared spectroscopy (FT-IR). Effects of several factors (temperature, time reaction, and mole ratios of reactants) on the properties of the PECE hydrogels are also investigated to determine the optimal synthesis conditions. The results show that the structure and physical-chemical properties of the PECE are significantly affected by the investigated factors, especially the ratio of reactants. The optimal condition for the first stage is determined at 130 °C, 10 h, and a PEG/PCL mole ratio of 1:2; and for the second stage is 80 °C, 8 h, and HMDI/PEG mole ratio of 1:1. Furthermore, the PECE hydrogels are soluble at room temperature and become ``gel'' at human body temperature. The features of polymer structure such as the balance between hydrophilic and hydrophobic groups, and the length of PCL and PEG have a great impact on the phase transition behavior of the PECE.

Key words: Copolymer, Hydrogel, Sol-gel-sol Transition, Thermosensitive

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History

- Received: 25-4-2022
- Accepted: 25-8-2022
- Published: 30-9-2022

DOI : 10.32508/stdjet.v5iSI1.989

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INTRODUCTION

Scientists have recently focused on drug delivery systems because of their potential to improve drug concentration at the target site, prolong drug residence time for higher treatment efficiency, and reduce undesirable effects over conventional ones [1–3]. Thanks to the ability to not only reduce the toxicity of drug responses but also enhance therapeutic effects, the advanced drug delivery system can manage the limitations of traditional drug formulations. "Smart" materials responding specifically and flexibly to environmental stimuli like pH, temperature, enzyme activity, electric, magnetic, and ionic strength have been extensively exploited in local drug delivery [4,5]. Amongst them, hydrogels are a special material because they can retain a large amount of physiological fluid without destroying their structure in the aqueous medium [6]. For the last decades, stimuli-sensitive copolymer hydrogels with their outstanding ability to respond to physical stimuli and good biocompatibility have gained considerable attention and have been studied for numerous applications in biomedical fields and environmental treatment. [7,8]

Thermo-responsive hydrogels fabricated from both hydrophobic and hydrophilic polymers via physical cross-linking have been investigated in a form of injectable materials. [9,10] Such hydrogels having sol-gel transition behavior under physiological conditions allow ease of use to mix pharmaceuticals in liquid states at low temperatures and create gels when injected at the target location to release drugs in sustained manners [11].

Hydrogels are capable of drug delivery because they contain a lot of space, called meshes, between the cross-linked polymers that promote the diffusion of water and small solutes into and out of the system. Therefore, the absorption or release of drug molecules can be controlled by the mesh size of the hydrogel and the steric interactions between the drug and the polymeric substrate [12]. Regulating network degradation is one of the approaches to controlling the drug release rate of the hydrogel. The mesh size may increase when the hydrogel structure breaks down causing drugs contained in the material to move into the external environment. According to previous works, slow hydrolysis of ester bonds was utilized to syn-

Cite this article : Pham T H, Truong Q T, Do N H, Ha A C. **Injectable thermosensitive poly(ethylene glycol)–poly(ε-caprolactone)–poly(ethylene glycol) hydrogels: Optimal synthesis conditions and sol-gel-sol transition behaviour**. *Sci. Tech. Dev. J. – Engineering and Technology;* 5(SI1):69-80.

thesize biodegradable poly(ethylene glycol) hydrogels like polyesters poly(caprolactone) (PCL) for controlled protein release [12,13]. Besides, swelling is another behavior of the hydrogel when contacted with the physiological fluids to release entrapped drugs. Thanks to its excellent bearing structure, the hydrogel structure is not deformed and permeable when holding a large amount of water inside its network. An increase in mesh size results from the swelling of the hydrogel, thus the drug molecules are released [14].

Pluronic F127 as a triblock copolymer composed of poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG) is commonly used to fabricate thermosensitive hydrogels. PEG-PPG-PEG is also applied in producing emulsifiers, cellularized scaffolds, and other drug delivery carriers [15,16]. However, there is a disadvantage in high critical micelle concentration (CMC) of Pluronic F127 causing its gel state to become unstable for several hours. In addition, because of its non-biodegradability and accumulation in the human body, Pluronic F127 encounters some limitations in biomedical fields [17,18]. To handle this problem, the PPG replacement with polycaprolactone (PCL) in the Pluronic structure has been proposed and demonstrated its feasibility. The previous results demonstrated that a marked decline in the macromolecular weight of the hydrogel after degradation and a significant reduction of CMC are witnessed, thus the hydrogel exhibits improved biodegradability [19,20]. Moreover, both PCL and PEG are well-known FDA-approved for their biodegradability and biocompatibility, thus triblock copolymer PEG-PCL-PEG expresses plenty of potential in applications as biomedical materials [21].

In this study, injectable PECE hydrogels are synthesized from poly(ethylene glycol) methyl ether (MPEG) and ε-caprolactone via ring-opening polymerization and coupling with hexamethylene diisocyanate [22]. To the best of our knowledge, there has been no study about finding the optimal reaction conditions, e.g. temperature, time reaction, and mol ratios of reactant for the synthesis of PECE hydrogels having the gelation region temperature suitable and low CGC for the desired condition of many applications. The features of PECE hydrogels including chemical properties of PEG and PCL blocks are also characterized. Moreover, the phase transition of the PECE is investigated using the test-tube-inversion method to expand our knowledge of the sol-gel transition of PECE via the structure-property relationship.

MATERIALS AND METHODS

Materials

MPEG (550 kDa) was purchased from Sigma, USA. e-caprolactone (e-CL), hexamethylene diisocyanate (HMDI), petroleum ether, dichloromethane (DCM), chloroform (CDCl3), tetramethylsilane (TMS), and stannous octoate $Sn(Oct)_2$ in high purity are all purchased from Sigma as well. All the chemicals were in analytical reagent (AR) grade.

Synthesis and Purification

PECE triblock copolymers were synthesized by two-step reactions. The first one is ring-opening copolymerization of e-CL initiated by MPEG and catalyzed by $Sn(Oct)_2$. The produced PEG-PCL di-block copolymer was coupled by HMDI. (Figure 1) [22].

The effects of temperature, reaction time, and mol ratio on the synthesis of PEG-PCL and PECE were studied. In the first stage, a mixture of å-CL, MPEG (M_n = 550), and $Sn(Oct)_2$ (0.5 wt% of total reactants) was prepared under a dry Ar atmosphere. The reaction system was kept at a specified temperature (110, 130, and 150 °C) for a defined time (8, 10, and 12 h). The mol ratio of ε-CL and MPEG was 1:1, 1:2, and 1:0.5 for each experiment. After that, HMDI was added to the reaction mixture, followed by stirring at (80, 100, and 120 °C) for (4, 6, and 8 h) and cooling to room temperature. The PECE block copolymers were dissolved in dichloromethane, followed by reprecipitation of the filtrate using cold petroleum ether.

Characterization

Chemical structure of PECE

Fourier Transform Infrared (FTIR) spectrum of the PECE was recorded by a BRUKER-TENSOR 27 spectrophotometer in the wavenumber range of 500-4000 cm^{-1}.

Nuclear Magnetic Resonance Analysis (^{1}H-NMR) spectra of the hydrogels were recorded by Bruker NMR Spectrometer at 500 MHz to characterize their chemical composition and macromolecular weight. The samples were dissolved in deuterated chloroform ($CDCl_3$) at room temperature; tetramethylsilane (TMS) was used as an internal reference standard. The average molecular weight of PECE and length of PEG/PCL blocks were determined by Eqs. 1-5 [22].

$$\frac{ID}{IA} = \frac{2\,(4\,(Y-1))}{4} \quad (1)$$

$$\frac{IB}{IA} = \frac{4X}{4} \quad (2)$$

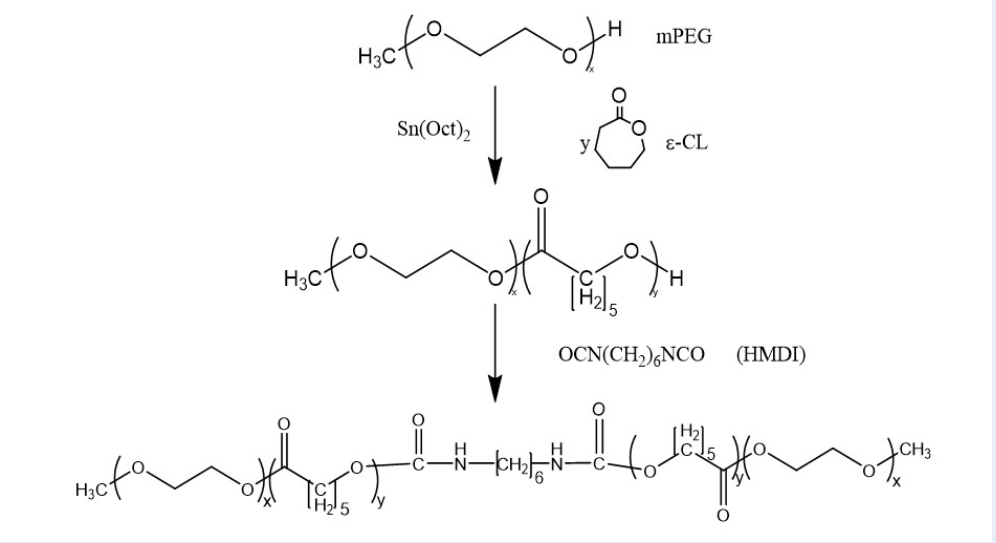

Figure 1: Synthesis scheme of PECE copolymers

$$M_{n(PEG)} = 2 \times (44Y + 31) \quad (3)$$

$$M_{n(PCL)} = 2 \times 114X \quad (4)$$

$$M_{n(PEG-PCL-PEG)} = M_{n(PEG)} + M_{n(PCL)} \quad (5)$$

Where IA, IB, and ID are respective integral intensities of peaks at 4.2, 4.06, and 3.6 ppm. 2X and 2Y are the block number of PCL and PEG in the structure of the hydrogel correspondingly.

Phase transition of PECE

The sol-gel-sol phase transition diagram of PECE was obtained by the test tube-inverting method. "Sol" and "gel" states were respectively defined as "flowing" and "non-flowing" witnessed in 1 min [16]. Each sample was dispersed in distilled water at room temperature and incubated at 10 °C for 10 min before being slowly heated to the gelation temperature with a heating rate of 0.5 °C/min.

RESULTS AND DISCUSSION

Characteristics of PECE hydrogel

The two-step procedure involving ring-opening copolymerization of ε–CL and coupling reaction catalyzed by HDMI has successfully synthesized PEG-PCL-PEG triblock copolymers. Their chemical structure is illustrated in Figure 2 and Figure 3.

As can be seen from Figure 2, peaks at 1105 and 1238 cm^{-1} are attributed to C–O–C stretching vibrations of PEG, and the –COO– bands stretching vibrations respectively. A strong C=O stretching band at 1734 cm^{-1} is attributed to ester bonds in carboxyl groups. In addition, there is no absorption band in the range of 2250–2270 cm^{-1}, which is attributed to the –NCO groups of HDMI, due to the presence of hydroxyl groups as a result of the coupling reaction of –NCO. The existence of the PECE is also confirmed by the absorption band at 3385 and 1527 cm^{-1} which corresponded to N–H stretching and bending vibrations, respectively.

To further confirm the structure of PECE, ^{1}H-NMR spectra (Figure 3) of PECE triblock copolymer are inspected and designated with the characteristic absorption peaks. The strong absorption peak (triplet) at 3.6 ppm and sharp peak (single) at 3.37 ppm are attributed respectively to methylene proton of the CH_2–CH_2–O– and CH_3-O- end group in the PEG block. The weak peaks (triplet) at 4.2 ppm and 3.7 ppm are assigned to methylene protons of –OCH_2CH_2– in the PEG end block that is linked with the PCL block.

Effect of Reaction Temperature on The Features of PECE Hydrogels

Table 1 also shows The molecular weight of the hydrogels and the length of PEG and PCL blocks in PECE at different reaction temperatures are summarized in Table 1.

According to Table 1, a significant difference is observed in the length of the PEG/PCL block and the total molecular weight of the obtained PECE hydrogel when changing the reaction temperature of the

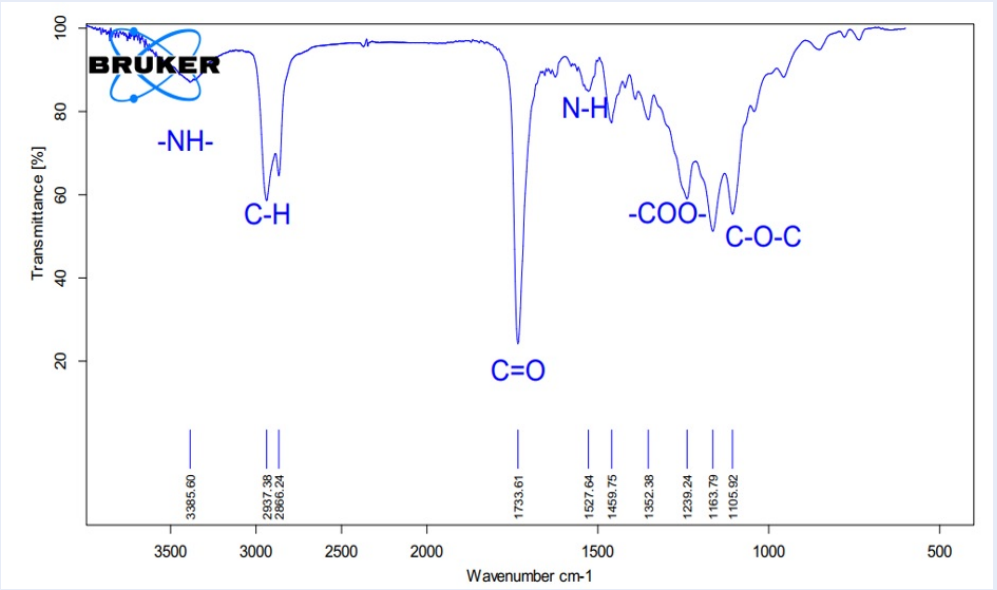

Figure 2: FTIR spectrum of PECE hydrogel.

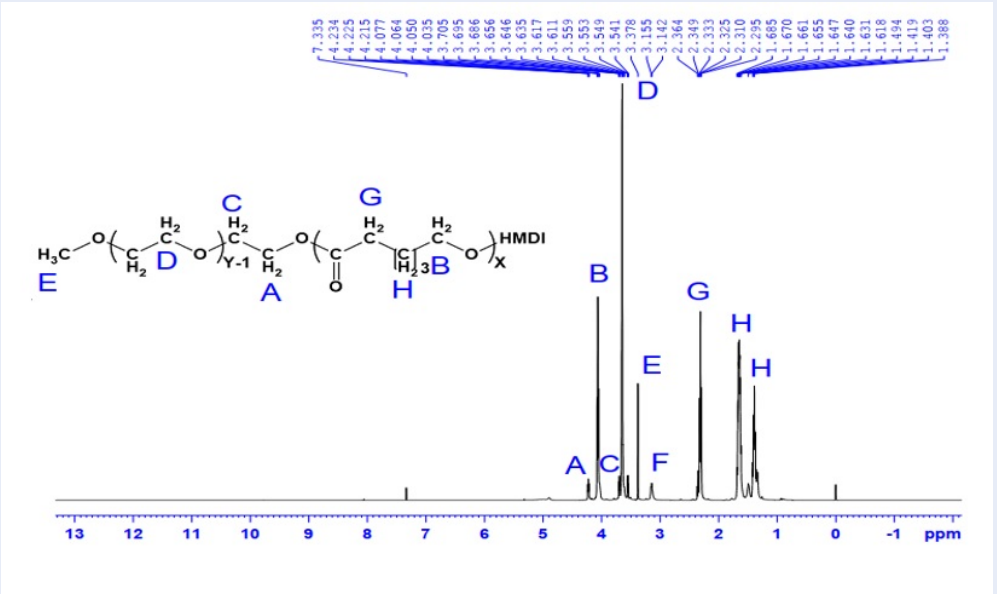

Figure 3: ^{1}H-NMR spectrum of the PECE hydrogel in $CDCl_3$

Table 1: Chemical properties of PECE at different reaction temperatures.

Stage reaction	Temperature (°C)	Y (PEG)	X (PCL)	$Mn_{(PEG-PCL-PEG)}$ (Da)
1	110	5.52	2.65	1152
	130	9.69	8.48	2848
	150	8.18	6.41	2243
2	80	11.6	16.6	4865
	100	11.5	16.9	4936
	120	10.4	17.4	4949

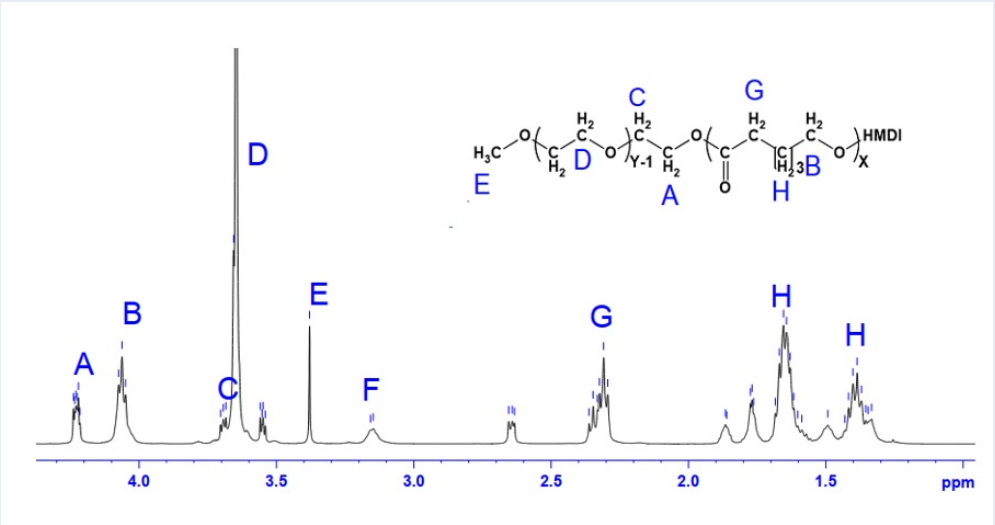

Figure 4: ^{1}H-NMR spectra of PECE synthesis at 110 °C (Stage 1) copolymer in $CDCl_3$.

first stage while other factors are kept constant. The difference in the ^{1}H-NMR spectrum of the hydrogels synthesized at 110 °C compared with the ones at 130 and 150 °C is the appearance of three peaks at 1.76 ppm, 1.87 ppm, and 2.65 ppm (Figure 4), which indicates that the synthesis reaction at 110 is not complete lead to the PECE is impurified and have low molecular weight. The molecular weight of the PECE hydrogel also increases from 1152 Da to 2848 Da when the reaction temperature rises from 110 to 130°C and declines to 2243 Da at the higher temperature of 150 °C, this is consistent with the maximum values of X and Y (8.48 and 9.69) in PECE hydrogel obtained when the reaction temperature is 130 °C. The difference in the structure of the PECE hydrogel can be explained by the effect of reaction temperature on the yield of the e-caprolactone ring-opening reaction. At 110 °C the polymerization reaction is not complete due to the required temperature is not reached. The reaction is sufficient at 130 °C, and the total molecular weight of the PECE is higher. However, the reaction temperature of up to 150 °C negatively affects the reactivity of the reactants and results in a lower molecular weight of the PECE hydrogel. Therefore, the temperature of 130 °C is chosen as the suitable temperature condition for the first stage of PECE synthesis.

Table 1 also shows that when the temperature of the second stage reaction is 80 °C, 100 °C, and 120 °C, while the first stage reaction is kept at 130 °C. The PCL/PEG block ratios (X/Y) are respectively 1.42, 1.47, and 1.55 when the reaction temperature is 80 °C, 100 °C, and 120 °C, but the total molecular weight of the PECE changes insignificantly. Therefore, the reaction temperature at this stage shows a negligible effect on the polymer network of the PECE. The temperature of the coupling reaction is chosen to be 80 °C for the PECE synthesis to save energy and easily control the temperature of the reaction.

Effect of Reaction Time on The Features of PECE Hydrogels

In Table 2, when the reaction time of the first stage increases, the total molecular weight of the PECE hydrogel and the length of the PEG and PCL block increase accordingly. After 10 h of reaction, the length of the PCL block is almost unchanged. This can be explained by increasing the reaction time, more e-CL molecules bond together in the ring-opening polymerization, which leads to a longer chain of PEG-PCL diblock[23]. The next step is coupling it will obtain a larger triblock copolymer with higher molecular weight. Thus, the ring-opening polymerization reaction occurs completely after 10 h and changes insignificantly after this time.

Moreover, the total molecular weight of the obtained copolymers increased with increasing reaction time in the second stage (the first stage is kept at 10 h) and highest at 8 h; the length of the PCL block increases while the PEG block changes undetermined. The mechanism of the second phase reaction is -N=C=O group of HMDI react with the –OH group of diblock PEG-PCL. When one group of –N=C=O is reacting, the other group is inactivated[24]. Therefore, the reaction time of 4 h is not enough for both –N=C=O groups of HMDI to take an addition reaction. As a result, the product at this condition has an incomplete triblock structure, leading to lower molecular weight compared to the other two products.

Effect of Amount of Initial Reactant on The Features of PECE Hydrogels

From Table 3, the length of PCL block in PECE obtained increases from 2.72, 8.48 to 20 with the PEG/PCL ratio of 1:0.5, 1:1 and 1:2, respectively. The molecular weight highest at the PEG: PCL ratio is 1:2; the length of the PCL block in this condition is higher than in other ratios. This can be explained by the increase in the initial amount of PCL inducing an increase in the number of PCL molecules participating in the polymerization reaction[25]. However, as the initial amount of PEG is increased, the PEG block in PECE triblock copolymers decrease. The reason may be due to the excess of PEG and lack of PCL leading to an unreacted amount of PEG and the formation of strange peaks at 2.63 ppm and 4.16 ppm (Figure 5).

The total weight of products, PEG, and PCL block are highest when HDMI/PEG ratio is 1:1 and lowest at the ratio of 1:2 because the PEG–PCL diblock chain is very long, and the probability for -OH and N=C=O groups to collide is low, reducing the reactivity. At the HMDI/PEG ratio of 1:0.5, the exceeding number of -N=C=O groups in HMDI over the hydroxyl groups in PEG-PCL, causes PEG-PCL to react with only -N=C=O groups, subsequently creating PEG-PCL-HMDI-NCO instead of PEG-PCL-PEG. Therefore, the molecular weight of the product is lower than that of the ones at the 1:1 ratio.

Thermo-sensitivity of PECE hydrogel

The PECE's aqueous solution is opaque and flows easily when its temperature is outside the gelation region. If the gelation temperature is reached, it will form a gel that is more opaque than the original solution and does not flow when the tube is inverted (Figure 6).

The phase transition diagram of the PECE hydrogel is shown in Figure 6. The X-axis represents different concentrations of hydrogel from 15 to 35 wt%. Y-axis indicates the lower critical gelation temperature (LCGT) and upper critical gelation temperature (UCGT) of the hydrogel. The gelation region is the region bounded by a line connecting the LCGT at each concentration and the other connecting the UCGT of hydrogels.

As can be seen, all studied hydrogels have LCGT, UCGT, and critical gelation concentration (CGC) depending on the concentration of PECE. When the PECE concentration is above the CGC, the sol hydrogel transforms to gel as the temperature increases. However, the hydrogel concentration in the solution increases leading to a decrease in LCGT and an increase in UCGT.

Figure 7a illustrates the effect of temperature reaction (Stage 1) on the thermo-sensitivity of the PECE; when this factor increases from 130 °C to 150 °C, the LCGT increases accordingly but both the UCGT and CGC decrease. The difference between the molecular weight of PECE triblock copolymer is mainly due to the length of the PCL block, so as the molecular weight of PCL is increasing, the gel region is more and more enlarged and the CGC becomes lower[26]. For hydrogels synthesized at 110 °C, no phase transition is observed; this is consistent with its molecular weight being much smaller than other products.

In Figure 7b, the CGC of an aqueous solution is 15% at 10 h reaction and is 20% for 8 h and 12 h. With increasing time reaction, UCGT of hydrogel increases accordingly, but LCGT changes unspecifically and is lowest at 10 h. Compare with the hydrogel synthesized at 8 h, the LCGT and UCGT values at 12 h are both higher, and the CGC values between the two hydrogels are also approximately the same due to the higher lengths of both PEG and PCL in this macromolecule. At 10 h and 12 h of reaction time, when the PEG block length increases along with an insignificant change in length of PCL, both LCGT and UCGT

Table 2: Chemical properties of PECE at different reaction times.

Stage reaction	Reaction Time (h)	Y (PEG)	X (PCL)	$Mn_{(PEG-PCL-PEG)}$ (Da)
1	8	8.53	6.29	2247
	10	9.69	8.48	2848
	12	11.0	8.30	2922
2	4	8.13	13.3	4347
	6	11.6	16.6	4809
	8	10.8	17.8	5071

Table 3: The molecular weight of PECE, length of PEG and PCL blocks in PECE at different reactant ratios.

Reactant	Mole Ratio	Y (PEG)	X (PCL)	$Mn_{(PEG-PCL-PEG)}$ (Da)
PEG: PCL	1:0.5	7.73	2.72	1362
	1:1	9.69	8.48	2848
	1:2	12.8	20.0	5748
HDMI: PEG	1:0.5	9.36	14.3	4142
	1:1	10.8	17.8	5066
	1:2	7.00	12.5	3528

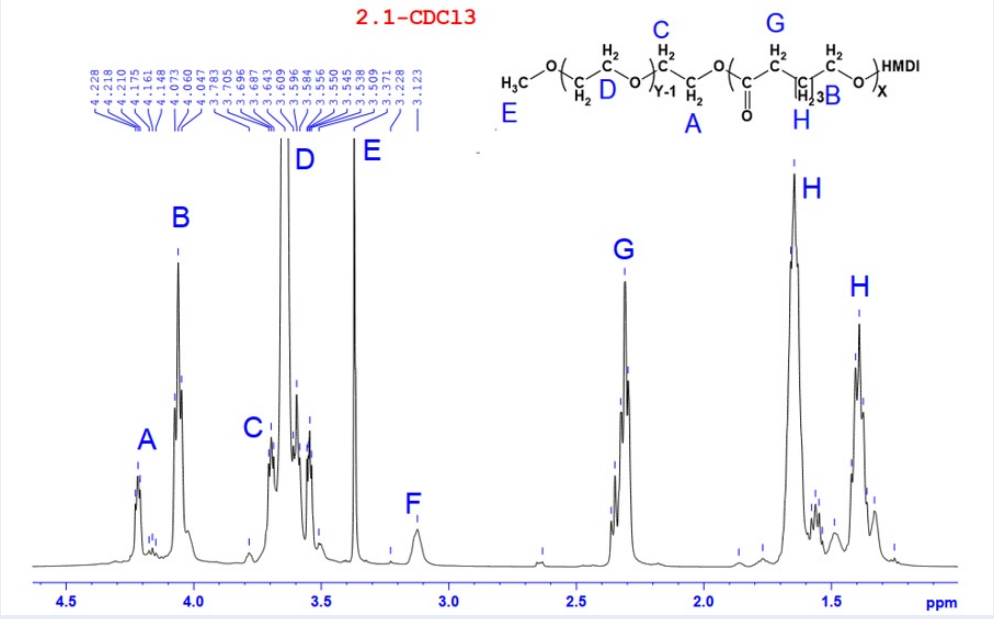

Figure 5: ^{1}H-NMR spectra of PECE synthesis at PEG: PCL (1:0.5) copolymer in $CDCl_3$.

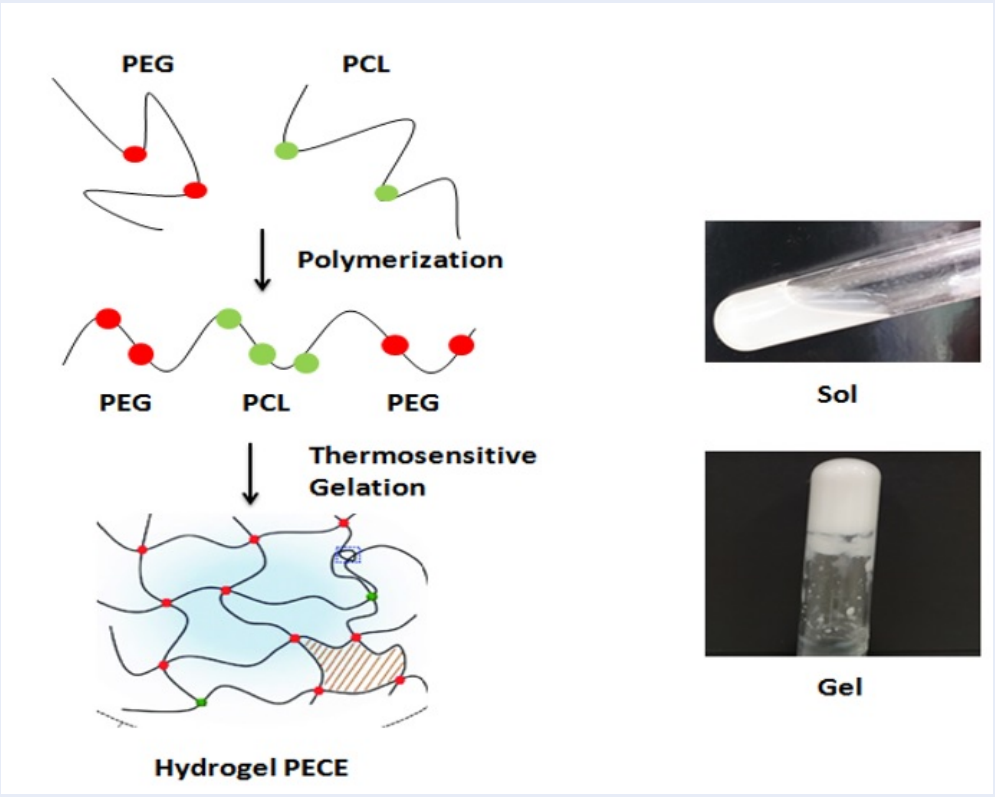

Figure 6: PECE hydrogel at 15°C (Sol) and 37°C (Gel).

of the hydrogel increase, and the gelation region shifts to a higher temperature[27].

According to Figure 7c, the PECE copolymer has a lower CGC when PEG: PCL ratio is 1:2 compared with the 1:1 ratio. This is a newly observed for PEG-PCL-PEG hydrogel when achieving a low CGC (10%) that has not been reported in any studies. Low CGC of the hydrogels can reduce their concentrations when applied, leading to a lower breakdown time and reduced amount of degradation products as well as lower toxicity and enhanced biocompatibility. As the amount of PCL reactant increases, both LCGT and UCGT increase accordingly; the gelation region shifts to a higher temperature. For hydrogels synthesized with an initial PEG: PCL ratio of 1:0.5, the sol-gel-sol phase transition was not observed with temperature change; the problem may be that increasing the initial PEG ratio reduces the total molecular weight of the hydrogel.

Figure 8a shows the influence of temperature reaction (Stage 2) on the phase transition of the PECE. In all aqueous solutions of PECE copolymer at 15% concentration, no phase transition is observed. At 20-35% concentration, the LCGT and UCGT of each hydrogel are insignificantly different. Thus, the reaction temperature in the second stage has an insignificant influence on the molecular structure and thermo-sensitivity of the hydrogel.

According to Figure 8b, the sol-gel-sol transition of the PECE under different reaction times is different. The PECE copolymer has a lower CGC when the reaction time is 6 h and 8 h (20%) compared with 4 h (25%). The hydrogel synthesized at 4h has a higher LCGT, and the gelation region is smaller than in other conditions. With increasing time reaction from 6 h to 8 h, both LCGT and UCGT of hydrogels increase accordingly, and the gelation region shifts to a higher temperature. In addition, the PECE's aqueous solution synthesized at 8h has a wider gelation region than others. This is explained by the long PCL chain, so hydrophobic interactions form more easily.

In Figure 8c, when the HMDI: PEG ratio is changed from 1:2, 1:0.5 to 1:1, the gelation region of hydrogels becomes wider, respectively; and both the LCGT and CGC increase accordingly, but the UCGT decreases. When the HMDI: PEG ratio is 1:2, both the length of PEG and PCL blocks in the copolymer is lower than under other conditions, so the gelation area is smaller;

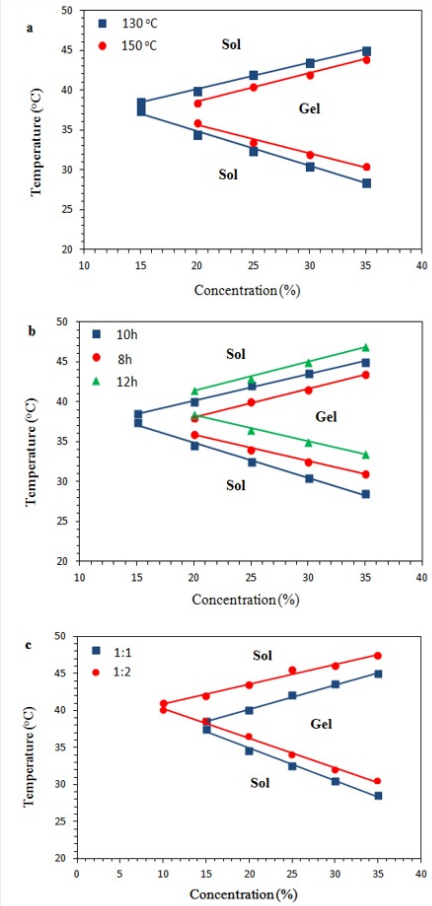

Figure 7: Phase transition diagram of thermo-sensitive PECE hydrogel (Stage 1 reaction conditions).

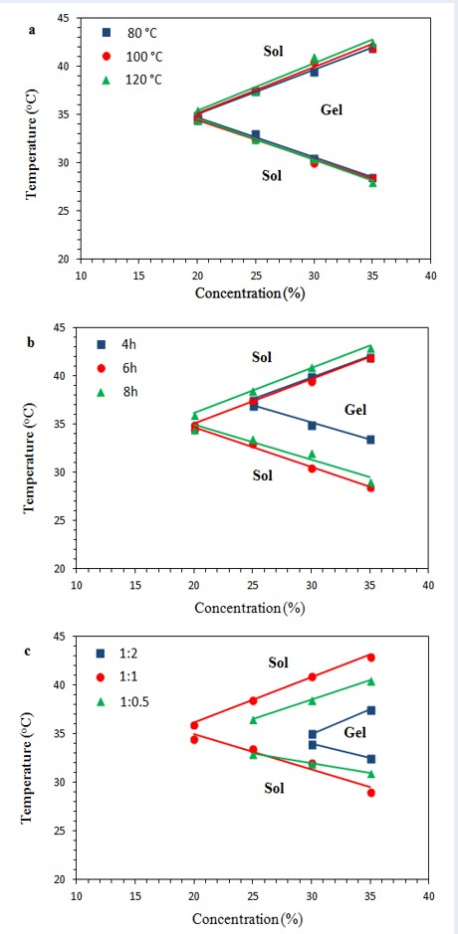

Figure 8: Phase transition diagram of PECE hydrogel (Stage 2 reaction conditions).

the opposite is reported when this ratio is 1:1. Therefore, the reactant ratio in the second stage influences the phase transition of the obtained hydrogel, and the 1:1 ratio is the optimal condition.

CONCLUSION

The optimal factors for the e-caprolactone ring-opening reaction (first stage) are 130 °C, 10 h, and PEG: PCL ratio is 1:2; and for the coupling reaction (second stage) is 80 °C, 8 h, and HDMI: PEG ratio is 1:1. With increasing temperature, PECE hydrogels perform a sol-gel-sol transition. The PEG/PCL ratio and the PECE molecular weight significantly influence the sol-gel-sol transition of the hydrogel. The temperature range of the phase transition can be modified, and the PECE hydrogel can become "gel" at around body temperature. The CGC of our PECE hydrogel reaches 10 wt% which has not been reported before. Low CGC allows degradation-controlled release, furthermore, hydrogels can transform to gel and swell to diffuse the entrapped drugs. Based on these findings, a solvent-free injectable hydrogel system like PECE can be useful in delivering drugs.

ACKNOWLEDGEMENT

This research is funded by Ho Chi Minh City University of Technology (HCMUT) under grant number SVKSTN-2021-KTHH-22. We acknowledge Ho Chi Minh City University of Technology (HCMUT), VNU-HCM for supporting this study.

ABBREVIATION

PEG: Poly(ethylene glycol)
PCL: Poly(caprolactone)
PECE: Poly(ethylene glycol)–poly(e-caprolactone)–poly(ethylene glycol)
HMDI: Hexamethylene diisocyanate

^{1}H-NMR: Proton Nuclear Magnetic Resonance
FT-IR: Fourier Transform Infrared spectroscopy
CGC: Critical gelation concentration
LCGT: Lower critical gelation temperature
UCGT: Upper critical gelation temperature

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Thinh H. Pham: Investigation, Analysis, Writing – original draft. **Quyen T. Truong**: Characterization. **Nga H.N. Do**: Data curation, Writing – review & editing. **Anh C. Ha**: Conceptualization, Visualization, Writing – review & editing, Project administration.

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Tạp chí Phát triển Khoa học và Công nghệ – Engineering and Technology, 5(SI1):1-1

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Bài nghiên cứu

Hydrogel nhạy nhiệt Poly(ethylene glycol)–poly(ε-caprolactone)–poly(ethylene glycol): Tối ưu điều kiện tổng hợp và quá trình chuyển pha Sol-gel-sol

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TÓM TẮT

Hydrogel là nhóm các vật liệu được tạo thành từ mạng lưới polyme lưỡng tính, có thể hấp thụ một lượng đáng kể chất lỏng mà không ảnh hưởng đến cấu trúc của chúng trong các điều kiện sinh lý. Trong nghiên cứu này, hydrogel nhạy nhiệt poly(ethylene glycol)–poly(e-caprolactone)–poly(ethylene glycol) (PEG–PCL–PEG, PECE) đã được tổng hợp thành công qua hai giai đoạn là mở vòng trùng hợp (caprolactone ring-opening) và phản ứng ghép đôi (coupling PEG-PCL) dựa vào chất liên kết là hexamethylene diisocyanate (HMDI). Các tính chất hóa lý về khối lượng phân tử, chiều dài khối PEG/PCL và khả năng chuyển pha sol-gel-sol đã được kiểm tra thông qua phổ cộng hưởng từ hạt nhân (^{1}H-NMR), phổ hồng ngoại (FT-IR) và phương pháp đảo ngược ống nghiệm. Ảnh hưởng của các yếu tố như nhiệt độ, thời gian và tỉ lệ tác chất phản ứng đã được khảo sát để tìm ra điều kiện tối ưu. Nghiên cứu đã cho thấy các yếu tố này có ảnh hưởng đến cấu trúc và tính chất của sản phẩm thu được, đặc biệt là tỉ lệ tác chất phản ứng. Đối với phản ứng giai đoạn 1 điều kiện tối ưu là 130 °C, 10 h, và tỉ lệ mol PEG/PCL 1:2; và đối với phản ứng giai đoạn 2 là 80 °C, 8 h, và tỉ lệ mol HMDI/PEG 1:1. Hơn nữa, các biểu đồ chuyển pha sol-gel-sol được ghi lại bằng phương pháp đảo ngược ống nghiệm cho thấy rằng các hydrogel thu được có thể chuyển pha từ dạng sol (chảy được) sang dạng gel (không chảy được) ở nhiệt độ cơ thể. Nhiệt độ chuyển pha của hydrogel có thể thay đổi tùy thuộc vào sự cân bằng ưa nước / kỵ nước trong cấu trúc polyme và bằng cách thay đổi chiều dài của khối PCL và PEG.

Từ khoá: Copolymer, Hydrogel, Chuyển pha Sol-gel-sol, Nhạy nhiệt

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Lịch sử

- Ngày nhận: 25-4-2022
- Ngày chấp nhận: 25-8-2022
- Ngày đăng: 30-9-2022

DOI : 10.32508/stdjet.v5iSI1.989

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Trích dẫn bài báo này: Thịnh P H, Quyên T T, Nga D N H, Anh H C. **Hydrogel nhạy nhiệt Poly(ethylene glycol)–poly(ε-caprolactone)–poly(ethylene glycol): Tối ưu điều kiện tổng hợp và quá trình chuyển pha Sol-gel-sol**. *Sci. Tech. Dev. J. - Eng. Tech.;* 5(SI1):1-1.