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Biodegradable cross-linked poly(trimethylene carbonate) networks for implant applications: Synthesis and properties

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ABSTRACT

In order to avoid the deformation of poly(trimethylene carbonate) (PTMC) in vivo applications, bis(cyclic carbonate) was synthesized and used as cross-linker to prepare PTMC based biodegradable networks via ring-opening polymerization of TMC and/or CL with stannous octanoate as catalyst. The effect of the cross-linking on the resulted networks was studied. The results showed that the crosslinker had high reactivity and efficiency to form stable polymeric networks with high gel percentage, high decomposition temperature and good mechanical properties. These obtained networks were amorphous and elastic, and the glass transition temperatures were below physiological temperature (37 °C), which were expected to be rubbery for in vivo applications. The properties of the networks could be predictably controlled and tailed by varying the polymer composition and cross-linker amount in feed. The cross-linked PTMC based networks showed a potential biomedical application of loading drugs for implanted devices.

1. Introduction

Synthetic biodegradable polymers such as polylactide (PLA), poly(ε-caprolactone) (PCL) and poly(trimethylene carbonate) (PTMC) have been studied extensively [1–9] for their excellent biocompatibility, good biodegradability and the avoidance of removal for in vivo implant. Nowadays, biodegradable polymers have been used as the biomaterials to fabricate drug delivery systems [10,11], nerve guides [12,13] and temporary three-dimensional (3D) scaffolds in tissue engineering [14,15], etc.

Among the members of these biodegradable polymers, aliphatic polycarbonates have attracted much interest as a bioresorbable material in the design of implanted drug delivery systems due to their non-acidic degradated products [16–18] to avoid aseptic inflammation. Poly(trimethylene carbonate) (PTMC) is one of the most important aliphatic polycarbonates. PTMC is an amorphous polymer at room temperature with a low glass transition temperature (approximately −16 °C) [19] and it shows a characteristic surface erosion degradation mechanism with a significant loss of mass in vivo. In one case, PTMC rod with a number average molecular weight of 457 × 10^3 g/mol implanted in the femur and tibia of rabbits showed a weight loss of 60% in 8 weeks [16]. However, the suitability of PTMC for the preparation of biomedical implants evaluated previously [20] indicates that PTMC has poor dimensional stability, tackiness and inadequate mechanical strength to maintain its original shape and dimension (Fig. 1), which is especially undesirable for implants. Its weak mechanical strength discouraged any practical application only when modification was carried out to improve the mechanical properties as well as modulate the rate of degradation [21].

It is well known that cross-linked polymers are normally stable because the networks are invulnerable to the breakage of a single bond [22] and could keep their original dimensions for longer time during degradation. Hence, biodegradable cross-linked networks (BCNs) have the virtues of a) stable 3D network structures and good dimensional stability, b) high flexibility and elasticity capable of providing excellent mechanical properties and c) tunable biodegradability that can be adjusted directly by cross-linking density [23]. Furthermore, another advantage of BCNs is that they often offer a homogenous degradation during degradation time [24,25], which would be favorable in the application of medical devices. In a word, BCNs are more suitable to localize drug delivery depots than linear polymers for implanted devices. Thus, in order to enhance

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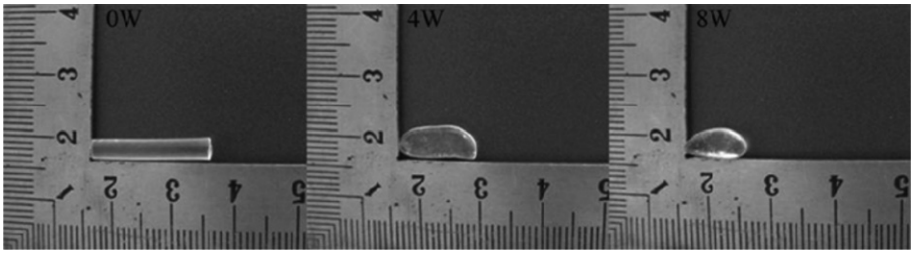

Fig. 1. Changes in shape and volume of PTMC rod implanted subdermally in rats.

the mechanical properties and biodegradability of PTMC to suit the requirements for the preparation of biomedical implants, great efforts have been devoted to the design and synthesis of BCNs derived from TMC-based polymers.

BCNs can be created by various methods including physical or chemical routes [24–39] and accomplished easily by means of high-energy radiation [40–44] and cross-linkers [45–49]. For biomedical applications, high-energy radiation has been widely used to modify the surface or bulk properties of polymeric biomaterials [50]. However, chain scission usually coexists with cross-linking and even predominates for some biodegradable polymers during the process of high-energy radiation cross-linking [51–54]. The adverse effects of high-energy radiation on the properties of the networks weakened the potential application in the preparation of BCNs. Therefore, the best way to prepare the BCNs is to incorporate suitable reactive cross-linking agents into the polymer chain.

The objective of this study was to prepare PTMC based biodegradable cross-linked networks to maintain the shape during degradation as implant devices for drug delivery. 2,2′-bis(trimethylene carbonate-5-yl)- butylether (BTB) was used as a novel cross-linking agent for the formation of network via the ring-opening polymerization (ROP) of TMC and/or ε-caprolactone (CL) (Fig. 2). The effect of cross-linker on the resulting networks was given by the gel percentage and degree of swelling. The cross-linker amount and CL content were varied to investigate the thermal and mechanical properties of the PTMC-based networks.

2. Materials and methods

2.1. Materials

1,3-trimethylene carbonate (TMC) was obtained from Daigang Biomaterial Co., Ltd, recrystallized from ethyl acetate and dried to constant weight prior to use; ε-caprolactone (99%) was purchased from Sigma–Aldrich, freshly distilled over CaH_2 under reduced pressure before used; Di(trimethylolpropane) (97%), ethyl chloroformate (97%) and the catalyst stannous octoate ($SnOct_2$) (95%) were purchased from Sigma–Aldrich and used as received. All other solvents and reagents were analytical grads and used without any further purification. Toluene is dried by heating over sodium with benzophenone as indicator to produce anhydrous toluene.

2.2. Preparation of the cross-linking agent BTB

The solution of di(trimethylolpropane) (22.5 g, 0.09 mol) in 500 mL of THF was cooled below 0 °C. 57.0 g (0.53 mol) of ethyl chloroformate was added dropwise maintaining the reaction temperature at −3 to −10 °C. Triethylamine (56.0 g, 0.55 mol) was added under the same condition. The mixture was stirred at room temperature for 2 h. The precipitate was removed by filtration. The solvent was concentrated by rotary evaporator and precipitated in anhydrous ether to yield the crude product. The crude product was recrystallized in THF to obtain white crystals of six-membered bis(-cyclic carbonate) 2,2′-bis(trimethylene carbonate-5-yl)-butylether

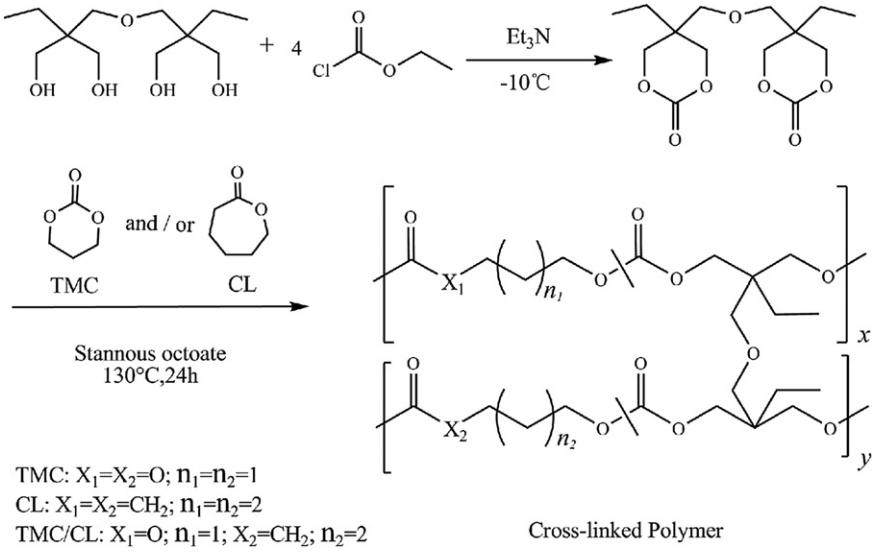

Fig. 2. The synthesis of cross-linking agent and the preparation of polymeric networks by ROP.

(BTB). Product yield was 20.0 g (74%) and the melting point of product was 103.9 °C.

^{1}H NMR ($CDCl_3$): 0.91(t, 6H, $-CH_3$), 1.50(m, 4H, $-CH_2-$), 3.50(s, 4H, $-CH_2OCH_2-$), 4.14(d, 4H, $-CH_2OCO-$), 4.29(d, 4H, $-CH_2OCO-$); IR (KBr): 2973–2883 (CH_3-, $-CH_2-$); 1746 (C=O); 1187 cm^{-1}(C–O–C).

2.3. Preparation of the cross-linked networks

Solvent free polymerization was carried out in sealed ampoules [21]. The mixture of monomers (TMC and/or CL) and cross-linker was charged into freshly dried glass ampoules and 2×10^{-4} mol of $Sn(Oct)_2$ per mol of monomer was added as a solution in anhydrous toluene in nitrogen atmosphere. The toluene was removed afterwards by evacuation. The ampoules were purged three times with dry nitrogen and heat-sealed under vacuum. The ampoules were put in an oil bath and reacted at 130 °C for 24 h. After reaction, the ampoules were quenched to room temperature and the polymers were received.

For the mechanical properties study, cylindrical cross-linked polymers were prepared by introducing clean and dry Teflon tubes with an inner diameter of 3 mm into the polymerization ampoules. After degassing, the polymerizations were performed under the same conditions as described above. After polymerization, the polymer rods were easily taken out of the Teflon tubes. The rods were cut to 40 mm in length and used without any further purification.

2.4. Characterizations

The ^{1}H NMR spectra were performed on a Bruker ARX 300 spectrometer (Bruker, Swiss) in deuterated chloroform ($CDCl_3$) solution with tetramethylsilane (TMS) as an internal standard. The DSC measurement was determined by a Netzsch DSC 200 F3 (Netzsch, Germany) equipped with a liquid nitrogen cooling system under nitrogen atmosphere. The samples were run at a heating rate of 10 °C/min from −100 °C to 100 °C to eliminate the thermal history and then a second scan was recorded, the glass transition temperature (Tg) was measured from the second heating cycle. The thermal stability of the polymers under nitrogen atmosphere was tested by a Netzsch TGA 209 F3 (Netzsch, Germany), the samples were heated from room temperature to 600 °C at a heating rate of 10 °C/min.

The degree of swelling of the network was determined gravimetrically at room temperature. A piece of network sample was weighed and kept in a sealed flask containing chloroform. At regular intervals, the sample was taken out and the excess solvent was removed from the surface with the help of a tissue paper. The sample was then weighed and returned to the medium. This procedure was continued until a constant weight was attained. The equilibrium degree of swelling (DS) was calculated according to Equation (1.1).

$$\mathrm{DS} = \frac{W - W_0}{W_0} \times 100 \tag{1.1}$$

where: W_0 is the initial weight of the dry sample and W is the final weight of the swollen sample.

The gel percentages were determined gravimetrically after the swollen gels were dried to constant weights. The gel percentage (GP) was calculated according to Equation (1.2).

$$\mathrm{GP} = \frac{W_0 - W_1}{W_0} \times 100 \tag{1.2}$$

where: W_0 is the initial weight of the dry sample and W_1 is the dry weight of the swollen sample. These measurements for DS and GP were done in triplicate for each network sample.

Table 1
Formulations of PTMC-based networks cross-linked by BTB at 130 °C for 24 h.

No.	Quantity of monomers (mol)		
	TMC	CL	BTB
1	100	0	0
2	100	0	0.05
3	100	0	0.1
4	100	0	0.5
5	100	0	1.0
6	90	10	0.05
7	70	30	0.05
8	50	50	0.05
9	50	50	0.1
10	50	50	0.5
11	50	50	1.0
12	0	100	0.05

Mechanical properties of the cyclical samples were measured on an Instron 1121 tensile testing machine (Instron, American) operated at a crosshead speed of 50 mm/min adopting the standard GB/T1040.1-2006. Five parallel specimens from the same sample were tested for the tensile strength, strain, and modulus.

3. Results and discussion

3.1. Preparation of the cross-linked polymers

Biomedical applications such as subcutaneous implants require elastic, flexible and form-stable polymers, which can withstand the specific requirements of these uses. When (co)polymers of TMC and CL were cross-linked during the ring-opening polymerization using BTB as the cross-linking agent, a strong elastomeric polymer network was formed, where tetra-functional crosslinkers were incorporated into the growing polymer chains. Polymeric samples with different cross-linking density and CL content were prepared by varying the molar ratio of the cross-link agent and CL mole fraction in monomer feed, as shown in Table 1.

The consumption of monomers and the incorporation of polymers into the cross-linked network were monitored by ^{1}H NMR with the variation of the intensity of the signals of α-methylene protons in monomers and polymers. For example, in Fig. 3, the intensity of the peak at 2.13–2.17 ppm [55] and 2.64–2.65 ppm [56] attributed to the protons in [$OCH_2-CH_2-CH_2O$] group of TMC

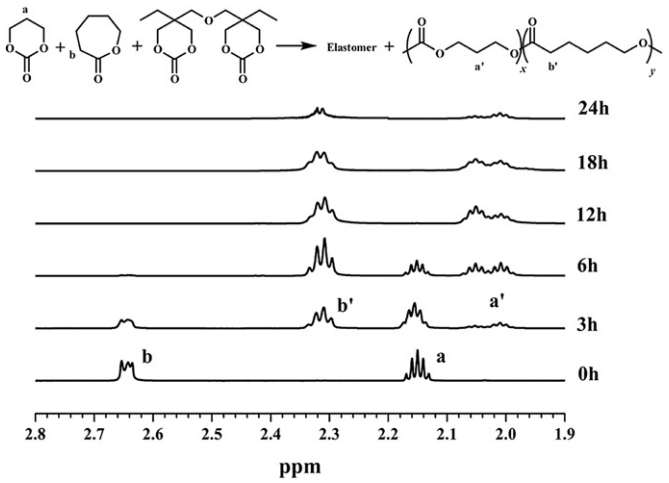

Fig. 3. ^{1}H NMR spectra of reaction mixture during cross-linking of TMC: CL (50:50) with 0.1 mol% BTB.

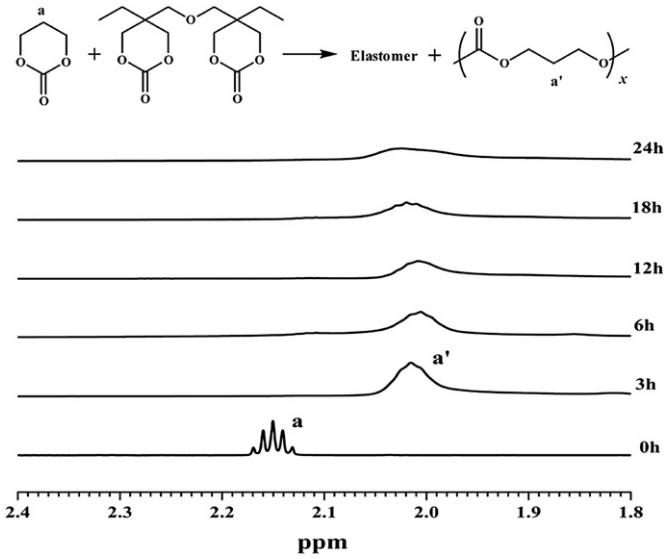

Fig. 4. ^{1}H NMR spectra of reaction mixture during cross-linking of TMC with 0.1 mol% BTB.

monomer and the [O–CO–CH_2] group of ε-CL unit decreased with increasing time and finally disappeared, indicating that the monomers were completely polymerized. It was important to note that CL reacted far more quickly and was virtually consumed within 6 h, whereas TMC was incorporated into the polymer at a slower rate within 12 h. It is attributed to the fact that CL has a higher reactivity ratio than that of TMC in the process of ROP catalyzed $SnOct_2$ [57].

Meanwhile, the α-methylene protons in PTMC and PCL appeared at 2.01–2.06 ppm [58] and 2.30–2.32 ppm [56], respectively. The intensity of these signals increased with increasing polymerization time firstly, which illustrated that more and more monomers were incorporated into the polymer chains. The intensity was then decreased due to the progressive non-availability of free polymer as the cross-linking reaction progressed. Once the polymer was completely cross-linked, there was no free polymer was dissolved in $CDCl_3$ and no proton signal was therefore observed by ^{1}H NMR.

Pure PTMC was also cross-linked by BTB in different reaction times and ^{1}H NMR was adopted to observer the signals intensity variations (Fig. 4). The results showed that the intensity of the peak at 2.13–2.17 ppm due to [OCH_2–CH_2–CH_2O] group of TMC monomer disappeared after 3 h, which was four times faster than that of P(TMC-CL) network, signifying the higher reaction reactivity of BTB to polymerize TMC than CL. As BTB has the similar structure and reactivity to that of aliphatic cyclic carbonates such as TMC, it is a promising cross-linking agent to form the TMC-based networks. The intensity of the signal at 2.0 ppm increased with increasing polymerization time firstly and then it decreased gradually, it illustrated the cross-linking reaction was progressed.

3.2. Gel percentage and swelling behavior of the cross-linked networks

The photographs of the (co)polymers extracted with chloroform were presented in Fig. 5. The volumes of the (co)polymers expanded greatly after the swelling. Both swelling crosslinked PTMC homopolymer and P(TMC-CL) copolymer were transparent solid. The swelling behaviors demonstrated that the obtained (co) polymers were cross-linked networks.

Fig. 6 shows the degree of swelling (DS) of the PTMC networks in chloroform. Increasing the percentage of the BTB in the monomer feeds resulted in a lower degree of swelling, which indicated the increasing of cross-linking density led to less space available for swelling of the network. For example, when the amount of cross-linker increased from 0.05 to 1.0 mol% in feed, the DS values of the cross-linked PTMC decreased from 2556 to 276%.

The cross-linking efficiency could be deduced by the gel percentage. Fig. 6 also displayed the relationship between the gel percentage and the cross-linker amount. As shown in Fig. 6, even for the lowest percentages of BTB (0.05 mol%), the gel percentage of

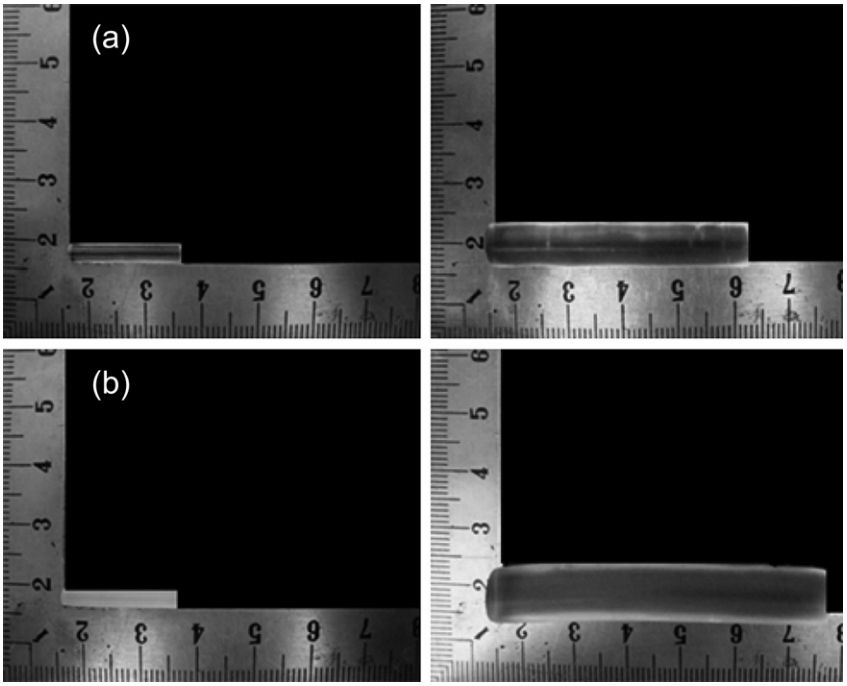

Fig. 5. The PTMC based networks were swollen in chloroform. The molar ratio of TMC to CL was (a) 100:0; (b) 30:70.

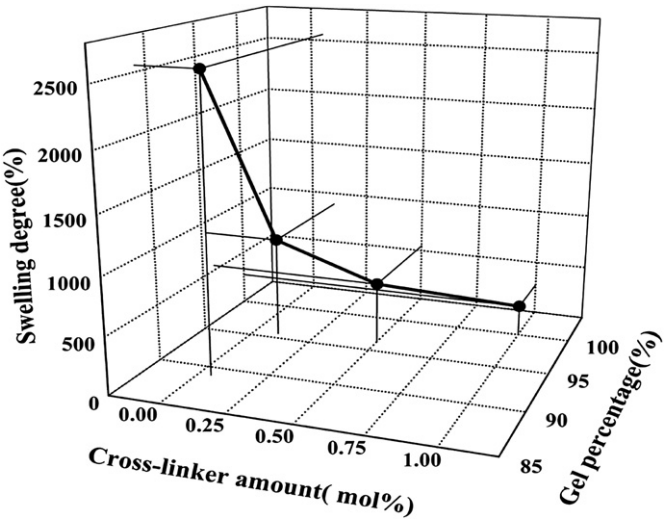

Fig. 6. Effect of cross-linker amount on the swelling degree and gel percentage of PTMC networks.

TMC network was 89% and the value of the gel percentage increased with the increasing of the cross-linker amount in feed. High gel percentage is obtained at small amounts of BTB indicates that BTB is a very efficient crosslinker.

Fig. 7 displays the gel percentage and swelling behavior of the P(TMC-CL) copolymer networks in chloroform. A similar trend to that of PTMC networks was discovered (Fig. 7). However, the P(TMC-CL) network exhibited a higher degree of swelling than that of the PTMC network with equal cross-linker amount, and the more CL in content resulted in the higher swelling degree (Fig. 8). This is in virtue of the fact that CL is a seven-membered ring and TMC is a six-membered ring, as a result the space between the cross-links is larger in the networks containing CL unit, where the diffusivity of solvent molecules is more, which leads to higher swelling values [47].

Meanwhile, the gel percentages of the P(TMC-CL) networks were lower than that of corresponding PTMC networks (Figs. 6 and 7) and they decreased with increasing CL content in compositions (Fig. 8). For instance, at the given cross-linker amount of 0.05 mol%,

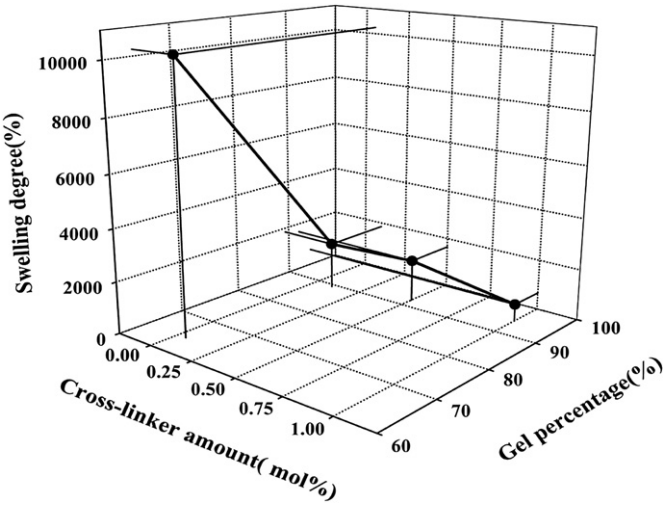

Fig. 7. Effect of cross-linking density on the swelling degree and gel percentage of P(TMC-CL) networks (molar ratio 50:50).

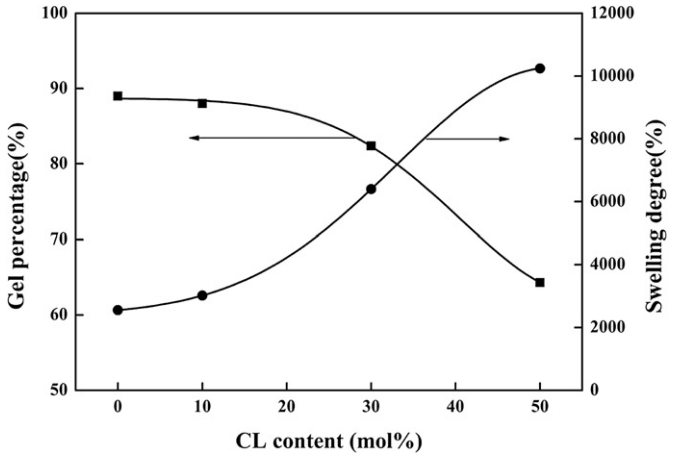

Fig. 8. Effect of CL content on the swelling degree and gel percentage of P(TMC-CL) networks with 0.05% cross-linker amount.

the gel percentage of the P(TMC-CL) networks was decreased from 88.02% to 64.28% when the CL content in feed increased from 10 mol% to 50 mol%. What is particularly worth mentioning is that the pure PCL could not be cross-linked by BTB with 0.05 mol% cross-linker amount, which also verified that BTB is lower efficient in copolymerization with CL than to TMC (Fig. 4), thus a product of non-crosslinked polymer and no swelling behavior was observed.

3.3. Thermal properties of the networks

The glass transition temperature (*Tg*) is an important parameter in connection with structures and properties. In general, chemical cross-linking imposes additional constraints on the motion of chain segments and reduces the available free volume. *Tg* is thus expected to increase with the increasing of cross-linker amount. A summary of the corresponding *Tg* for the PTMC networks is provided in Table 2. The data shows that the glass transition temperature of the PTMC networks was essentially dependent on cross-linker amount, and it increased as cross-linker amount increased. The *Tg* was changed from −16.2 °C to −11.7 °C when the amount of BTB ranged from 0 to 1 mol%. The *Tg* of the extracted PTMC networks cross-linked by 0.05 mol% and 0.1 mol% BTB were −13.8 °C and −13.2 °C, respectively. However, there was no significant difference in the value of *Tg* when the cross-linker amount in feed increased. That was because of the restricted motion of some chain segments affected by cross-linking action of BTB incorporated into the polymer chain, which led to the increase in *Tg* of PTMC network with a low gel percentage of 89% when BTB amount in feed was 0.05 mol%.

The *Tg* of the P(TMC-CL) networks also increased with increasing the BTB amount (Fig. 9) and decreased with increasing the CL content in a linear fashion (Fig. 10). What's more important is

Table 2
The glass transition temperatures (before and after solvent extraction) of PTMC networks.

No.	Quantity of monomers (mol)			*Tg* (°C)	
	TMC	CL	BTB	Un-extracted	Extracted
1	100	0	0	−16.2	−16.2
2	100	0	0.05	−14.1	−13.8
3	100	0	0.1	−13.7	−13.2
4	100	0	0.5	−13.3	−12.4
5	100	0	1	−12.5	−11.7

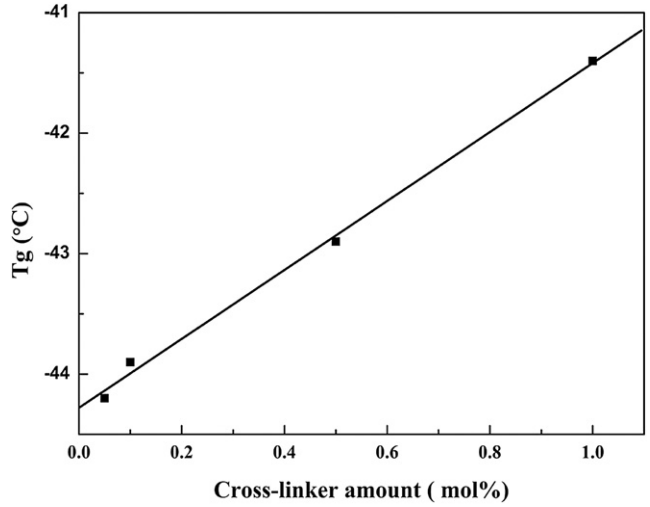

Fig. 9. Effect of cross-linker amount on *Tg* of P(TMC-CL) networks (molar ratio 50:50).

that all the polymer networks were amorphous and the *Tg* values were below body temperature, making these flexible elastomeric networks to be rubbery and suitable in subcutaneous implant applications.

The characteristic decomposition temperatures and percentage weight losses depend on the backbone structure of the networks. A representative thermogravimetric analysis trace of P(TMC-CL) network is shown in Fig. 11 and the decomposition of PTMC network occurred in the temperature range of 250 °C–350 °C. Within this temperature range, the temperature of the maximum rate of weight loss T_{max} and the percentage weight loss at T_{max} were determined from the differential thermogravimetric (DTG) traces. They are plotted against CL content in P(TMC-CL) networks with BTB amount of 0.05 mol% in Fig. 12, and a linear relationship between the T_{max} or the percentage weight loss and the CL content was observed. A linear relationship was also observed when T_{max} and the percentage weight loss of the networks were plotted against cross-linker amount in feed (Fig. 13). The increase of CL content and cross-linking density led to more stable networks, which was shown as the increase in T_{max} and decrease in percentage weight in Figs. 12 and 13.

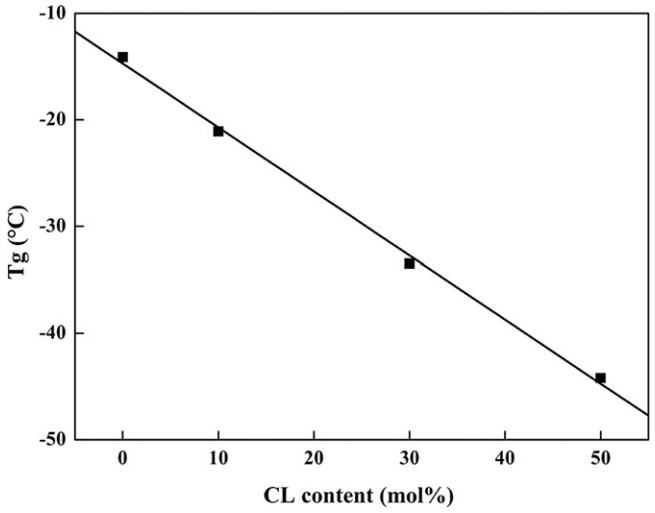

Fig. 10. Effect of CL content on *Tg* of P(TMC-CL) networks with cross-linker amount of 0.05 mol%.

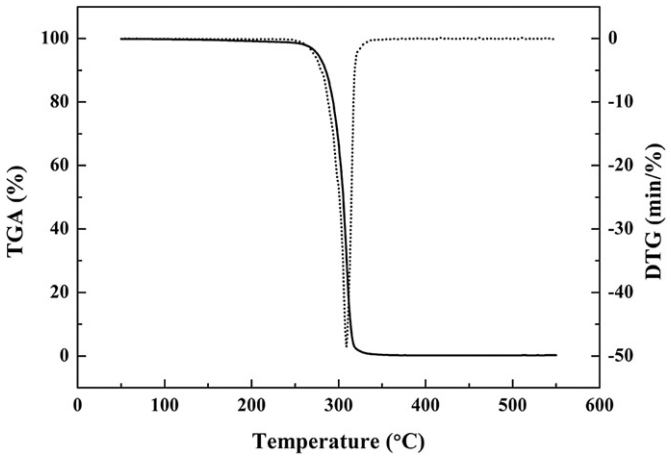

Fig. 11. Thermogravimetric trace of PTMC network: TGA (–), DTG (…).

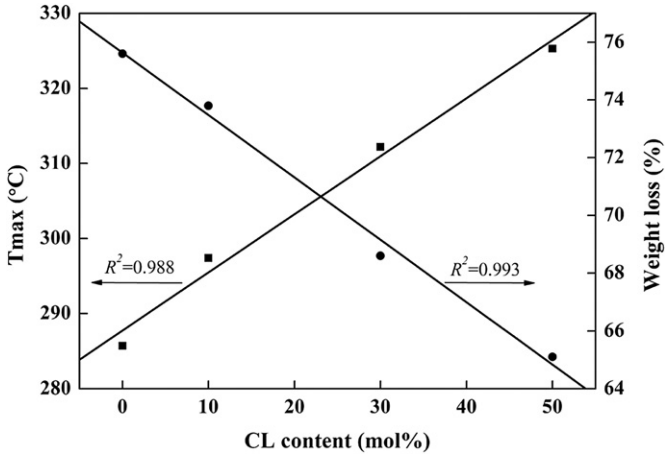

Fig. 12. Effect of CL content on decomposition temperature, T_{max} (■) and percentage weight loss (●) of P(TMC-CL) networks with cross-linker amount of 0.05 mol%.

3.4. Mechanical properties

To further confirm the formation of elastomeric and strong network, tensile tests were performed. The results were shown in

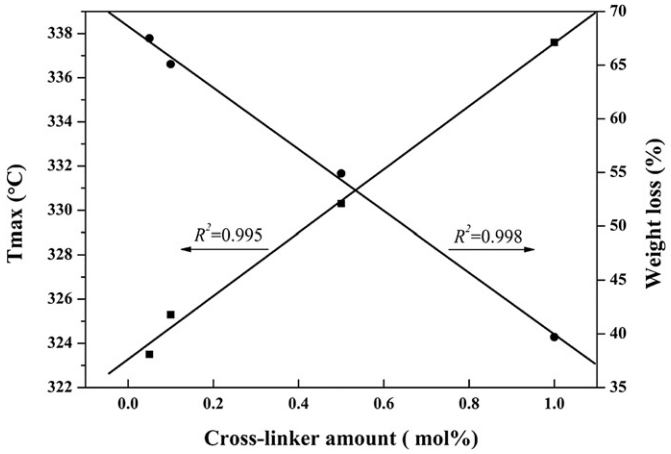

Fig. 13. Effect of cross-linker amount used on the decomposition temperature, Tmax (■) and percentage weight loss (●) of P(TMC-CL) networks (molar ratio 50:50).

Table 3
Mechanical properties of the PTMC based networks.

No.	Quantity of monomers (mol)			E (MPa)	σ_b (MPa)	ε_b (%)
	TMC	CL	BTB			
1	100	0	0	3.19 ± 0.50	3.06 ± 0.40	4767 ± 58
2	100	0	0.05	5.60 ± 0.49	4.58 ± 0.93	2100 ± 75
3	100	0	0.10	6.34 ± 0.50	5.67 ± 0.12	1200 ± 27
4	70	30	0.05	3.44 ± 0.15	3.35 ± 0.20	3953 ± 61
5	50	50	0.05	1.62 ± 0.24	0.35 ± 0.15	5067 ± 47

Values are means ± standard deviation ($n = 4$).

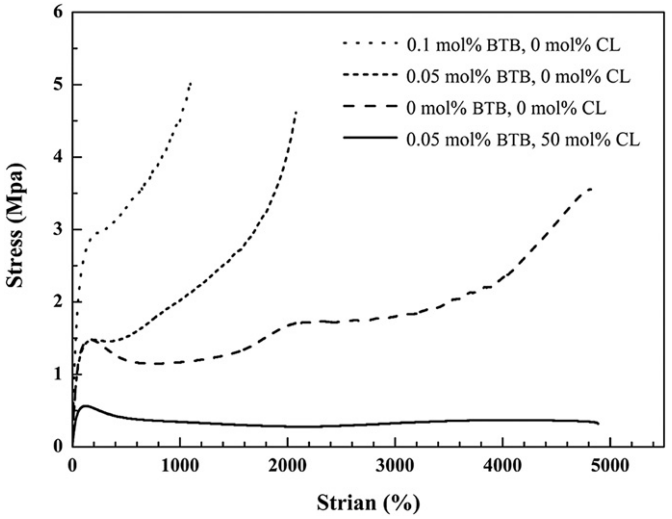

Fig. 14. Effect of CL content and cross-linker amount on stress–strain behavior of the obtained networks.

Table 3 and the typical stress-strain curves were presented in Fig. 14. In the P(TMC-CL) networks, the modulus decreased gradually with increasing CL content. At the same time, an increase in elongation at break was determined. These findings were attributed to the low activity of the BTB to CL monomer, which resulted less cross-linking points and low gel percentage in the network.

As expected, the increase of cross-linker amount led to the increase of modulus and decrease in elongation at break (Table 3). Incorporating higher amounts of the cross-linker BTB resulted in a stronger elastomer when the cross-linker amount increased from 0 to 0.1 mol%, which was indicated in higher modulus (6.34 MPa), higher stress (5.67 MPa) and lower strain at break (1200%). The physical properties suggest that the network is an elastic and flexible biomaterial potentially for subcutaneous implants.

4. Conclusion

Our goal of this work was to prepare amorphous networks that could maintain their form stability for an extended time period and have a *Tg* below body temperature. The copolymers of trimethylene carbonate and ε-caprolactone were cross-linked via crossl-inking agent 2,2′-bis(trimethylene-carbonate-5-yl)-butylether (BTB). The properties of the crosslinked network were tested. The increase of BTB concentration in feeding dose resulted in the increase of gel percentage and the decrease of swelling degree of the received networks. While the increasing of the CL content in the copolymers led to the decrease in gel percentage and the increase in swelling degree at a given cross-linking density. The *Tg* viriation was proportional to the content of the cross-linker, which decreased in a linear fashion as the CL content increased, and all the *Tg* of the networks were below physiologic temperature, which were suitable to be used as flexible implants in vivo. Moreover, increasing the CL content and cross-linker amount could produce more stable polymers with higher decomposition temperature. The mechanical and thermal properties of the networks can be varied through the manipulation of the polymer composition and crosslink agent content in feed. The obtained materials are elastomeric biomaterials and the degradation properties of these materials will be further evaluated when the specific application in long-term implants is envisaged.

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