

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.

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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 bio-resorbable material in the design of implanted drug delivery systems due to their non-acidic degraded 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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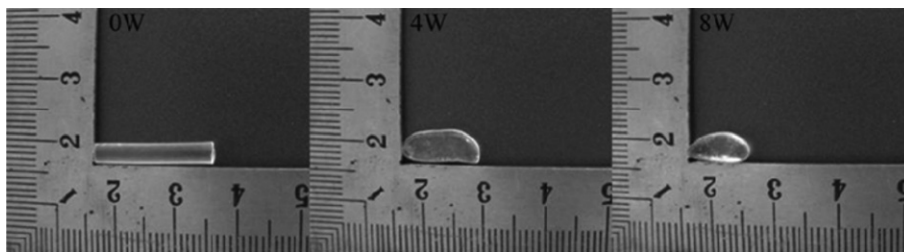


Fig. 1. Changes in shape and volume of PTMC rod implanted subdermally in rats.

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

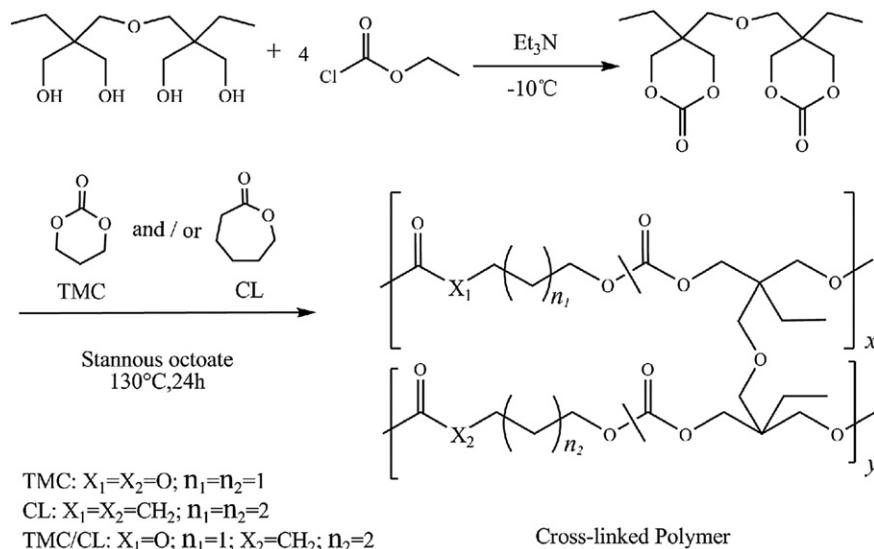


Fig. 2. The synthesis of cross-linking agent and the preparation of polymeric networks by ROP.

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