Instant Preparation of Biodegradable Injectable Polymer Formulation Exhibiting Temperature-responsive Sol-gel Transition

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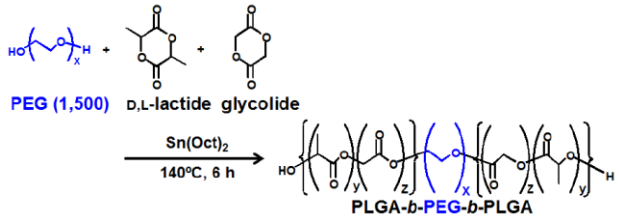
Introduction: Biodegradable polymers exhibiting temperature-responsive sol-gel transition between room temperature and body temperature are expected to be applied as injectable polymer (IP) systems in biomedical applications. IP solution containing drugs or living cells can be injected by simple syringe injection at the target site in the body to form a hydrogel acting as sustained drug releasing depot or scaffold for tissue regeneration. For example, Lee and coworkers reported ABA-type triblock copolymer of poly(lactide-*co*-glycolide) and poly(ethylene glycol), PLGA-*b*-PEG-*b*-PLGA, as biodegradable injectable polymer exhibiting temperature-responsive sol-gel transition between room temperature and body temperature[1]. We also reported several biodegradable IP systems exhibiting temperature-responsive sol-gel transition and relatively high mechanical strength in gel state using block copolymers of polylactide and branched PEG[2]. However, these copolymers are usually sticky paste in dry state at room temperature, and inconvenient for storage and weighing. Moreover, it takes a long time (usually more than 5 hours) to be dissolved in aqueous solution. On these issues, Jeong *et al.* reported solidification of the triblock copolymers containing poly(ε-caprolactone), PCL-*b*-PEG-*b*-PCL, exhibiting temperature-responsive sol-gel transition[3]. However, the copolymers must be heated above melting temperature upon dissolution. In this study, in order to provide convenient IP system for instant use at clinical scene, which is solid state in dry condition and can be dissolved in short time, we synthesized a triblock copolymer of poly(ε-caprolactone-*co*-glycolide) and PEG, PCGA-*b*-PEG-*b*-PCGA, and investigated the effect of some additives on dissolution time of IP formulation. Then, we succeeded to develop an IP formulation quickly preparative at room temperature.



Scheme 1. Synthesis of PLGA-*b*-PEG-*b*-PLGA triblock copolymer.

Methods: A series of triblock copolymer of poly(ε-caprolactone-*co*-glycolide) and PEG, PCGA-*b*-PEG-*b*-PCGA, was synthesized by ring-opening polymerization of ε-caprolactone and glycolide using PEG and $Sn(Oct)_2$ as an initiator and a catalyst, respectively (Scheme 1). Temperature-responsive sol-gel transition behavior of PCGA-*b*-PEG-*b*-PCGA solution was investigated by a test tube inverting method and by a dynamic rheometer (HAAKE, Thermo HAAKE RS600). Then, we investigated the effect of additives (hydrophilic polymers or saccharides) on the dissolution time for the mixture of PCGA-*b*-PEG-*b*-PCGA and these additives in aqueous solution.

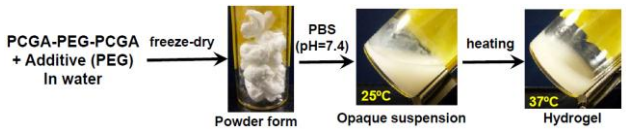


Figure 1. Preparation of PCGA-*b*-PEG-*b*-PCGA + additive (PEG) formulation: from powder from in dry state, to PBS solution (suspension) at 25°C, and then to the hydrogel form at 37°C.

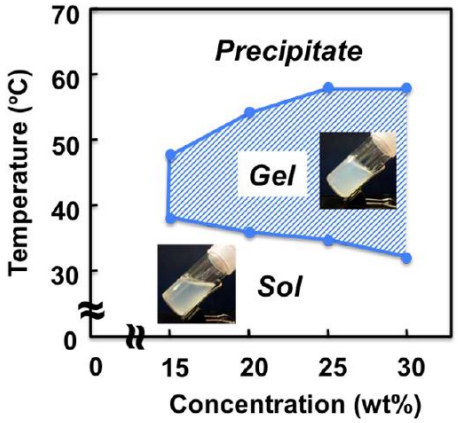


Figure 2. The phase diagrams of PCGA-*b*- PEG-*b*-PCGA solution at various temperature and concentrations.

Results: The obtained PCGA-*b*-PEG-*b*-PCGA could be freeze-dried to show powder form morphology in dry state at room temperature (Fig. 1). Its aqueous solution exhibited temperature-responsive sol-gel transition between room temperature and body temperature (Fig. 2). We found that formulations composed of PCGA-*b*-PEG-*b*-PCGA and PEG as additives could be distributed in PBS to give suspension within 1 min at room temperature (Fig.1). The obtained suspension was opaque, but could be sucked by syringe, and exhibited temperature-responsive sol-gel transition between room temperature and body temperature.

Conclusions: We found instantly preparative IP/additive system, which can be distributed in PBS within 1 min. This system should be convenient for instant preparation of IP formulation at clinical scene.

References

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3) Jeong B et al. Macromolecules. 2005;38;5260-5265.