MPEG-PCL diblock copolymers as an in situ gel forming drug carrier

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Statement of Purpose: During the last decade, injectable polymers such as Poloxamers™ and Pluronics™ have attracted considerable attention as candidate materials for biomedical applications such as polymeric drug carriers, implants, and other medical devices. Aqueous solutions of these block copolymers undergo a reversible sol-gel transition as a function of temperature; this transition can be exploited for applications in which the solution is injected into a human or animal in the sol state to become a gel at body temperature.

In the present study we prepared MPEG-PCL diblock copolymer and examined whether aqueous solution of this copolymer could undergo sol-to-gel phase transition under physiological conditions. The efficacy of the thermo-responsive MPEG-PCL diblock copolymer for use as an in situ injectable gel-forming carrier studied the in vitro release of a model protein, BSA-FITC, loaded into a MPEG-PCL diblock copolymer carrier.

Methods: MPEG-PCL diblock copolymer (MW, ca. 750-2,500) were synthesized via the polymerization of ε-caprolactone using the terminal alcohol of MPEG as an initiator in the presence of HCl•Et2O as a monomer activator.

Five-milliliter solution of diblock copolymer in PBS was prepared in 10-ml vial and then dissolved by immersion in water at 80 °C. The solution was then left overnight in a refrigerator. Then, to determine their phase transition behavior, the solution was subjected to viscosity measurements as a function of temperature. For the protein release experiment, 1 wt% BSA-FITC was added to the diblock copolymer solution at room temperature and the mixture was gently mixed. A diblock copolymer solution containing BSA-FITC was incubated at 37 °C to form a gel. Then, 10 ml of PBS was added to the gel, and the vial was shaken at 100 rpm and 37 °C. At specified sample collection times, 1 mL of solution was removed from the vial and 1 mL of fresh PBS at 37 °C was added to the vial. Fluorescence spectroscopy was immediately performed on the removed solution. To study the formation of gel in vivo, we made MPEG-PCL copolymer gel in rat.

Results/Discussion: At room temperature, the MPEG–PCL diblock copolymer solution was a translucent emulsion. Figure 1 shows the viscosity versus temperature curve for the MPEG-PCL diblock copolymer solution. As the temperature of the polymer solution was increased from room temperature, the viscosity of MPEG–PCL diblock copolymer solution starts increasing at 28 °C and underwent a sol-to-gel phase transition.

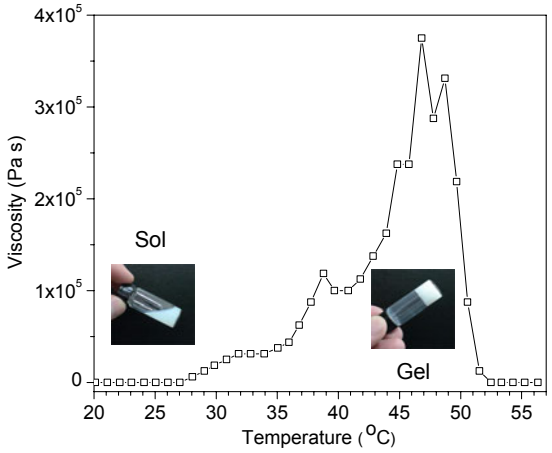

Figure 1. Viscosity versus temperature curve for MPEG-PCL diblock copolymer at 20 wt% concentration.

For in vitro release experiment, the BSA-FITC was added into the MPEG-PCL copolymer solution. The MPEG-PCL diblock copolymer gel exhibited prolonged release of BSA-FITC above 20 days. When the MPEG-PCL copolymer was injected at room temperature into live SD rats, they became gel almost immediately after injection. The injected MPEG-PCL gel was maintained at the injection site for the full 4-week experimental observation period. The MPEG-PCL gel was found to retain its original shape, and remain within the injected site with no signs of inflammation at the point of injection.

Conclusions: We prepared a MPEG-PCL diblock copolymer and examined its behavior in aqueous solution. Experiments examining the release of BSA-FITC from MPEG-PCL diblock copolymer gels under in vitro condition showed that the protein was released above 20 days. When BSA-loaded diblock copolymer solution at room temperature was subcutaneously injected into rats, it immediately became gels. We confirmed that MPEG-PCL diblock copolymer solution is thermo-responsive material.

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