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Thermo-sensitive and biodegradable hydrogels based on stereocomplexed Pluronic multi-block copolymers for controlled protein delivery

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Abstract

Injectable sol–gel transition hydrogels based on thermo-sensitive polymers are of great interest as potential biomaterials for sustained delivery of therapeutic molecules. A novel temperature-sensitive and *in-situ* forming hydrogel system based on Pluronic F127 was developed and evaluated. A series of multi-block Pluronic copolymers linked by D-lactide and L-lactide oligomers with different spacer lengths were synthesized. A pair of multi-block copolymers having the corresponding enantiomeric D- or L-lactide oligomer spacer was blended to form stereocomplexed hydrogels. The resultant physically crosslinked Pluronic hydrogels exhibited significantly altered sol–gel phase transition behaviors with much lower critical gelation concentrations and temperatures, compared to the uncomplexed multi-block or Pluronic homopolymer hydrogels. The stereocomplexed hydrogels also had far increased mechanical strength with high resistance to rapid dissolution in aqueous medium. When human growth hormone (hGH) was incorporated in the strereocomplexed multi-block Pluronic copolymers, hGH was released out in a sustained and zero-order fashion for 13 days by a diffusion/erosion coupled mechanism.

Keywords: Hydrogel; Multi-block; Stereocomplex; Injectable; Thermo-sensitive; Protein delivery

1. Introduction

Injectable and biodegradable hydrogels are of great interest as potential materials for protein delivery and tissue engineering [1]. Especially, thermo-sensitive and sol–gel transition water soluble polymers can provide *in-situ* forming hydrogels for delivery of therapeutic molecules upon injection into the body without an invasive surgical procedure [2]. Physically cross-linked hydrogels self-assembled from intermolecular ionic interaction, hydrogen bonding, and hydrophobic interaction are advantageous for macromolecular delivery systems, since they provide a more benign environment for encapsulation of proteins and cells, compared to chemically crosslinked hydrogels [3]. Various synthetic thermo-sensitive polymers such as poly(*N*-isopropylacrylamide) [4], polyphosphazenes [5,6], poly (ethylene oxide) (PEO)/poly(propylene oxide) (PPO) tri-block copolymers [7–9], and PEO/poly(D,L-lactide-co-glycolide) (PLGA) tri-block copolymers [10,11] have been extensively studied for use as injectable sol–gel transition hydrogel systems for pharmaceutical and biomedical applications.

Among these, a series of PEO–PPO–PEO tri-block copolymers (e.g. Pluronics and Poloxamers) has been widely exploited as *in-situ* forming drug delivery carriers because they exhibit unique sol–gel transition behaviors in response to temperature in aqueous solution [12]. These tri-block copolymers form spherical micelles in aqueous solution by hydrophobic interaction between the middle PPO segments [13]. Above a critical gelation temperature and concentration, the self-assembled micelles are closely packed to produce a physically crosslinked gel structure. However, the Pluronic hydrogels are very soft and easily disintegrated and dissolved out upon contact with excess amount of buffer solution. This is due to the fact that the concentration of Pluronic copolymers is immediately diluted to below the critical gelation concentration, resulting in the dis-assembling of the micellar structure [7,8]. Thus, when a highly concentrated aqueous solution of Pluronic copolymer is injected into the body tissue as a sol state, the *in-situ* formed gel structure cannot be maintained for the desired period to achieve sustained release of

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encapsulated proteins or support the proliferation of cells to induce new tissue formation.

Recently more robust physical hydrogels with improved gel stability have been prepared by introducing stereocomplexed crystalline domains in the hydrogel structure, which can crosslink water soluble polymers in a more stable manner than any other physical hydrogels prepared traditionally by the aforementioned noncovalent interactions [3,14–17]. Biodegradable poly(lactic acid) having a chiral carbon atom in the monomer structure exhibits such stereocomplex crystalline behavior. It is well known that a pair of enantiomeric poly(L-lactic acid) and poly(D-lactic acid) produces a stereocomplexed crystalline structure different from the crystalline structure of the respective homopolymer. Various water soluble polymers grafted with enantiomeric oligo D- and L-lactic acid chains can form more stable hydrogels based on stereocomplex formation. We have previously reported that a pair of poly(2-hydroxylethylmethacrylate, HEMA) grafted with enantiomeric oligo D- or L-lactic acid was stereocomplexed to form physically crosslinked hydrogels [18]. Similarly, de Jong et al. [16] reported that *in-situ* forming stereocomplexed dextran hydrogels could be prepared by grafting D-lactic acid and L-lactic acid oligomers to the backbone of dextran. The stereocomplexed dextran hydrogels exhibited superior rheological properties, compared to dextran or dextran grafted with a single enantiomeric oligo(lactic acid), and also demonstrated potential sustained release applications for therapeutic proteins [19,20]. Hydrogels and microparticles based on stereocomplex formation of tri-block copolymers of PEG end-capped with D-lactic acid and L-lactic acid oligomers have also been reported in various studies [21–23]. More recently, the incorporation of star-shaped PEG or crosslinking by photopolymerization has produced stereocomplexed hydrogels with enhanced gelation characteristics [24,25]. The synthesis of multi-block hydrogels has also been suggested as another approach to form more mechanically strong hydrogels. Cohn et al. [26] designed a series of multi-block copolymers based on Pluronic F127, which showed much enhanced stability and delayed degradation behaviors compared to the homopolymer. We and others also studied physically crosslinked multi-block copolymers by introducing stereocomplex crystalline domains [27,28]. Tri-block copolymers of poly(L-lactic acid)-PEG-poly(L-lactic acid) and poly(D-lactic acid)-PEG-poly(D-lactic acid) were able to form stereocomplexed multi-block hydrogels with improved mechanical properties even at low concentrations [28].

In this study, a novel type of thermo-sensitive and biodegradable stereocomplexed hydrogels composed of multi-block Pluronic copolymers was synthesized by combining the ideal hydrogel characteristics for sustained release of protein drugs: thermo-sensitivity, biodegradability, biocompatibility, and *in-situ* gel forming ability. A series of multi-block Pluronic copolymers linked by D-lactide and L-lactide oligomers was synthesized to form *in-situ* forming stereocomplexed hydrogels upon mixing the pair of two corresponding enantiomeric Pluronic multi-block copolymers (Fig. 1). It was hypothesized that the spontaneous formation of stereocomplex crystalline domains in the thermo-sensitive self-assembling hydrogel structure provided additional crosslinking points, thereby substantially increasing the gel strength of Pluronic based micellar hydrogels. The sol–gel transition behaviors and rheological properties of the hydrogels formed by stereocomplexation were examined. Furthermore, the stereocomplexed Pluronic

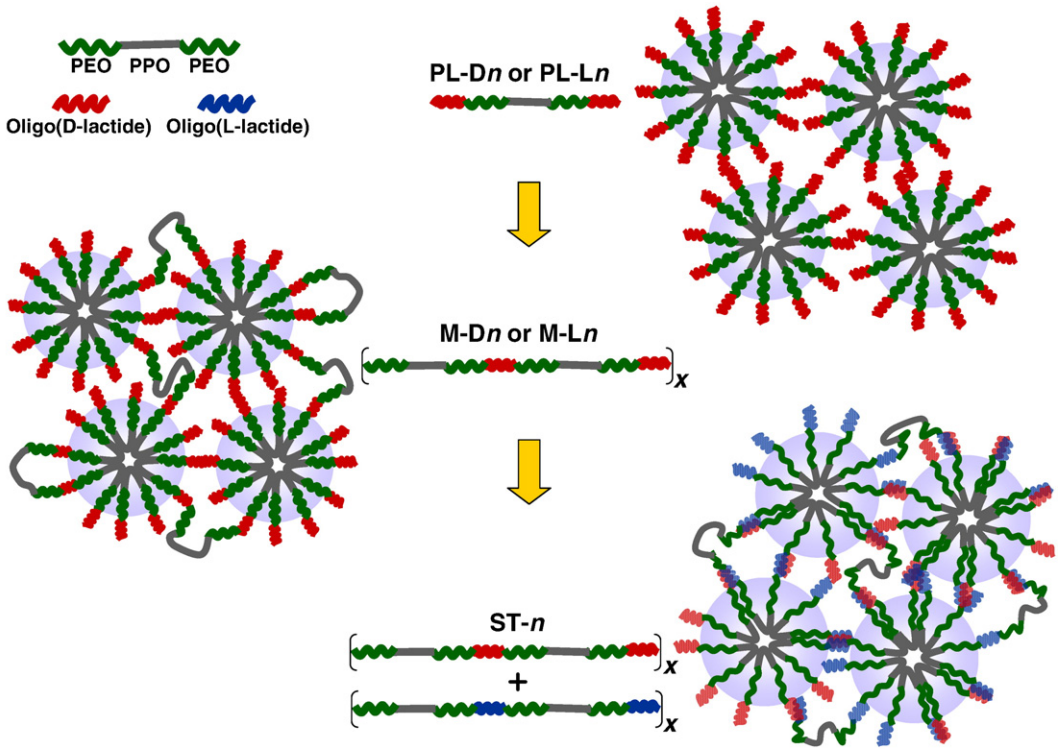

Fig. 1. Schematic illustration for molecular structure of hydrogels formed by PL copolymer end-capped with oligolactide (PL-D*n* or PL-L*n*), multi-blocks (M-D*n* or M-L*n*), and stereocomplexed multi-blocks (ST-*n*).