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Adjustable degradation and drug release of a thermosensitive hydrogel based on a pendant cyclic ether modified poly(ε-caprolactone) and poly(ethylene glycol)co-polymer

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ABSTRACT

The convenient and precise fabrication of drug–hydrogel formulations with satisfactory degradability and a well-controlled drug release profile are crucial factors for injectable hydrogel formulations in clinical applications. Here a new injectable thermosensitive hydrogel formed from poly(ε-caprolactone) (PCL)–poly(ethylene glycol)–poly(ε-caprolactone) amphiphilicco-polymers with 1,4,8-trioxa[4.6]spiro-9-undecanone (TOSUO) moieties incorporated in the poly(ε-caprolactone) (PCL)block (PECT) was constructed to provide a route to tailor the degradation and drug release behavior. The effect of hydrophilic cyclic ether moieties on the degradation of and drug release by PECT hydrogels were evaluated in vitro and in vivo. The results indicated that a freeze-dried powder of paclitaxel-loaded PECT nanoparticles rapidly dissolved in water at ambient temperature with slightly shaking and formed a stable injectable in situ drug–hydrogel formulation at body temperature, which is convenient for clinical operations because it avoids the need for pre-quenching or long-term incubation. The paclitaxel distribution was also more quantitative and homogeneous on entrapping paclitaxel in PECT nanoparticles. Further, the small number of pendant cyclic ether groups in PCL could decrease the cystallinity and hydrophobicity and, as a result, the in vitro and in vivo retention time of PECT hydrogels and the release of entrapped paclitaxel could be tuned from a few weeks to months by varying the amount of PTOSUO in the hydrophobic block. Significantly, paclitaxel-loaded PECT nanoparticles and free paclitaxel could be simultaneously released during the in vitro paclitaxel release from PECT hydrogels. A histopathological evaluation indicated that in vivo injected PECT hydrogels produced only a modest inflammatory response. Thus pendant cyclic ether modification of PCL could be an effective way to achieve the desired degradation and drug release profiles of amphiphilicco-polymer thermosensitive hydrogels and PECT hydrogels may be suitable for local drug delivery.

1. Introduction

In the past two decades biodegradable thermosensitive in situ hydrogels have been investigated as local drug delivery systems [1–13]. An injected aqueous solution of thermosensitive polymer immediately forms a gel at the target location in the body, acting as a sustained drug delivery depot. Compared with systemic delivery, in situ hydrogels are expected to deliver drugs at a predetermined locus for predefined periods, which could enhance and maintain the local drug concentration, prolong local drug residence times and reduce systemic toxicity and side-effects [14–20]. The convenience of fabrication of the drug formulations, the satisfactory biodegradability and controlled drug release have been focused on to optimize the hydrogel systems and improve clinical application.

Thermosensitive hydrogels of amphiphilic block co-polymers based on different kinds of poly(ethylene glycol) (PEG) treated biodegradable polyesters have attracted much attention as injectable in situ drug delivery systems [10,16,21–23]. Poly(lactic acid-co-glycolic acid) (PLGA)–PEG–PLGA (1500–1000–1500) was the first thermogellingco-polymer (commercially available as ReGel®) approved by the FDA as a local controlled drug release formulation. Other biodegradable hydrophobic polymers, such as poly(lactic acid) (PLA), PLGA, poly(ε-caprolactone) (PCL), poly(ε-caprolactone-co-glycolic acid), poly(trimethylene carbonate) (PTMC), and polyanhydrides have also been used to construct thermosensitive co-polymers with a PEG segment [12,22,24–29].

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It is known that the chemical structure of the hydrophobic segments is an important factor in defining the thermogelling behavior, degradation, drug loading and release properties of thermosensitive PEGylated polyester co-polymers. ReGel® shows a viscous semi-solid morphology at room temperature and persists for less than 4 weeks in vivo, leading to the inconvenience of weighing and transferring it, and unsuitability for long-term application [11,16,30]. Another promising injectable hydrogel composed of PCL–PEG–PCL has the advantages of being easy to weigh and handle because it is a solid powder at ambient temperature. However, to prepare drug–hydrogel formulations it is necessary to initially dissolve the drug and PCL–PEG––PCL in water at a higher temperature (above the melting point of PCL) or age the mixture at 4 °C for more than 24 h [31–33], which is inconvenient and especially unsuitable for formulations containing protein drugs. The quantity and homogeneity of drug loaded into PCL–PEG–PCL hydrogels is also limited. A more critical issue related to the drug delivery properties of PCL–PEG–PCL hydrogels is the slow degradation and drug release due to the high crystallinity and strong hydrophobicity of PCL, which is not always desirable, depending on the desired time scale and location of the hydrogel device [31,34]. The incorporation of lactic acid (LA) or glycolic acid (GA) into PCL segments can improve the gelation and degradation, however, initial heating of the co-polymer solution or incubation for 12 h at 4 °C is still necessary for gelation and degradation is still too slow to achieve the preferred drug release profile [35–37]. Thus a more efficient route needs to be developed to manipulate the chemical composition of PCL, so that subsequently the degradation and drug release behavior of PCL–PEG–PCL hydrogels can be tailored accordingly.

The manner of drug loading and the drug state in thermosensitive gels are other key factors in clinical application. Normally drug–hydrogel formulations are prepared by directly dispersing the powdered drug in thermogelling co-polymer aqueous dispersions, in which precipitation of the hydrophobic drug readily occurs when the drug loading efficiency is high because of its poor solubility and incompatibility with the hydrogel, affecting the drug release behavior and stability of the drug–hydrogel formulation.

In a previous work a new kind of triblock co-polymer of PEG and modified PCL with cyclic ether pendant groups, i.e. poly(ε-caprolactone-co-1,4,8-trioxa[4.6]spiro-9-undecanone)-poly(ethylene glycol)-poly(ε-caprolactone-co-1,4,8-trioxa[4.6]spiro-9-undecanone) (PECT) were prepared [38]. We found that the introduction of cyclic ether pendant groups into PCL segments by co-polymerization of 1,4,8-trioxa[4.6]spiro-9-undecanone (TOSUO) with ε-caprolactone could improve and control the gelation performance by affecting crystallization of the PCL segments. PECT and its freeze-dried nanoparticle powder readily dissolves in water at ambient temperature without any prequenching treatment and the thermal gelation behavior can be conveniently adjusted by altering the TOSUO content. In this paper we try to further elucidate the effect of the hydrophilic cyclic ether pendant groups on drug–hydrogel formulation fabrication, the morphology of loaded paclitaxel, the in vitro and in vivo degradation, and the release of paclitaxel. Whether subcutaneously implanted PECT hydrogels provoke an in vivo inflammatory response was also studied.

2. Materials and methods

2.1. Materials

PEG (M_n 1500 g mol^{-1}) was provided by Jiangtian Co. (Tianjin, China). ε-Caprolactone from Sigma–Aldrich was dried over CaH_2 for 48 h at room temperature and distilled under reduced pressure prior to use. Stannous octoate was used as received from Sigma–Aldrich (Milwaukee, WI). TOSUO was prepared by our laboratory following the literature [39]. Paclitaxel was purchased from Shenyang Tianfeng Biological Pharmaceutical Co. Ltd. All other reagents were from the Jiangtian Co., were of analytical grade and were used as received without further purification.

2.2. Preparation of PECT and static contact angle measurement

The detailed preparation and characterization of PECT were discussed in a previous paper [38] and a series of the triblock co-polymers synthesized is shown in Table 1. Static contact angle measurements were performed using a DSA 10 MK2 (Krüss) drop shape analysis system at room temperature. PECT was dissolved in methylene dichloride and then cast on a glass plate. After the methylene dichloride had evaporated a drop of deionized water (3 μl) was dropped onto the surface of the film, which had a thickness of 0.2 mm, and images of the water menisci on the sample surface were recorded using a digital camera and analyzed using DSA software to obtain contact angle values. A total of five measurements on different areas of the film were performed.

2.3. Calculation of the solubility parameter of co-polymers

The solubility parameter δ was obtained by Hansen's approach, which uses the partial solubility parameters to calculate the total solubility parameter according to Eq. (1), where δ_d, δ_p, and δ_h are the partial solubility parameters for van der Waals dispersion forces between atoms, dipole–dipole interactions between molecules, and hydrogen bonding between molecules, respectively

$$\delta = \left(\delta_d^2 + \delta_p^2 + \delta_h^2\right)^{1/2} \quad \delta_d = \sum F_d/V, \; \delta_p = \sqrt{\sum F_p^2}/V, \quad \delta_h = \sqrt{\sum F_h}/V \tag{1}$$

The partial solubility parameters for the hydrophobic blocks were estimated using the Hansen theory of solubility group contribution method (GCM) compiled by Beerbower [40].

2.4. Characterization of co-polymer aggregates in hydrogel solution and viscosity measurements

The PCL–PEG–PCL aqueous solution was prepared by dissolving PCL–PEG–PCL at 60 °C followed by quenching at 0 °C. The PECT aqueous solution was prepared by directly dissolving PECT in water at room temperature to give a concentration of 25 wt.%. All solutions were liquid at room temperature. The aggregate of PECT in aqueous solution was examined by transmission electron microscopy (TEM) (JEOL 100CX-II) and dynamic light scattering (DLS) (BI200SM, Brookhaven) at a scattering angle of 90° at room temperature by diluting the PECT aqueous solution from a concentration of 25 wt.% to 0.5 wt.%.

The viscosity of each polymer solution was measured using a fluids rheometer (Stress Tech, Rheological Instruments AB). The polymer aqueous solution (25 wt.%) was placed between parallel plates 25 mm in diameter with a gap of 0.5 mm at 20 °C for 60 min. The heating rate was 0.5°C min^{-1}. The data were collected under controlled stress (0.01 Pa) at a frequency of 1.0 rad s^{-1}.

2.5. In vitro and in vivo degradation of PECT hydrogel

The aqueous solution of PCL–PEG–PCL or PECT (25 wt.%, 1 ml) was placed in a test tube and immersed in a water bath at 37 °C for 12 h to produce a stable gel. Then 10.0 ml of 0.01 M phosphate-buffered saline (PBS), pH 7.4 was added to the test tube. In vitro degradation was conducted under shaking (70 rpm) at 37 °C. The medium was replaced by a 10 ml aliquot of fresh PBS every