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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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