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A novel pH-induced thermosensitive hydrogel composed of carboxymethyl chitosan and poloxamer cross-linked by glutaraldehyde for ophthalmic drug delivery

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ABSTRACT

In this work, a stimuli-responsive three dimensional cross-linked hydrogel system containing carboxymethyl chitosan (CMC) and poloxamer composed of a poly (ethylene oxide)/poly (propylene oxide)/poly (ethylene oxide) (PEO–PPO–PEO) block copolymer was constructed, and its aqueous solution was found to undergo a reversible sol-gel transition upon a temperature and/or pH change at a very low concentration. The hydrogels were synthesized via a cross-linking reaction using glutaraldehyde (GA) as the cross-linking agent. The structures of the hydrogels were characterized by FTIR, XRD, NMR and SEM studies and the swelling behaviour was studied in different buffered solutions. The results obtained indicated that cross-linked F127-CMC underwent discontinuous phase transition in different temperature and pH solutions. The hydrogels at 35 °C and pH 7.4 were found to have larger pores than at the other three conditions which resulted in greater swelling. The result of rheological studies showed that the gelation temperature was 32–33 °C and the viscosity of the hydrogel increased quickly after gelation. In an addition, the cytotoxicity and in vitro release was studied at different pH values and temperature. The results of a CCK-8 (Cell Counting Kit-8) assay showed that the hydrogel and its physical mixture solution were not cytotoxic to human corneal epithelial cells at a low concentration. Using the drug nepafenac (NP) as a model drug, the controlled drug release behaviour of these hydrogels was investigated. Owing to the formation of F127-CMC/NP retarding the diffusion rate of NP, a sustained release of NP from the hydrogel can be obtained. The release rate was found to be maximum at 35 °C and pH 7.4. From these preliminary evaluations, it is possible to conclude that the hydrogels have an excellent potential for application in ophthalmic drug delivery systems.

1. Introduction

The delivery of ophthalmic drugs to treat diseases of the anterior chamber is challenging in spite of the excellent accessibility and potential for targeted delivery of drugs directly into tears. Liquid ophthalmic formulations usually have a low bioavailability because of constant lacrimation and fast nasolacrimal drainage (Al Khateb et al., 2016; Kirchhof, Goepferich, & Brandl, 2015; Ma, Xu, Wang, Nie, & Pan, 2008). Specifically, eye drops account for about 90% of ophthalmic medications for front-of-the-eye diseases but the corneal bioavailability of drugs delivered via eye drops is less than 5%, much being absorbed systemically via conjunctiva and nasolacrimal ducts (Garcia-Millan, Koprivnik, & Otero-Espinar, 2015; Gause et al., 2015; Gonzalez, Tartara, Palma, & Alvarez Igarzabal, 2015; Makwana, Patel, & Parmar, 2016). As a result, short dosing intervals and high drug concentrations are needed to reach effective therapeutic levels. With regard to patient acceptability, improving pre-corneal drug retention is one of the main approaches to optimize topical ophthalmic drug delivery (Al Khateb et al., 2016; Gao, Lü et al., 2016; Hu & Gong, 2016; Nurettin Sahiner et al., 2009). One of the important classes of polymeric materials that have been used in a wide variety of biomedical and pharmaceutical applications is hydrogels (Ayyala, Duarte, & Sahiner, 2006; Gandhi, Paul, Sen, & Sen, 2015; Kirchhof et al., 2015; Liu & Fan, 2005; Sabaa, Abdallah, Mohamed, & Mohamed, 2015; Takeno & Sato, 2016; Zhao

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et al., 2016). Hydrogels are polymeric materials that have a three-dimensional network structure and can swell markedly in water or organic solvents without dissolving due to the presence of cross-links (Chen et al., 2004; Dutta, Samanta, & Dhara, 2016; Gao, Liu, Lu, & Zhou, 2016; Jabeen, Maswal, Chat, Rather, & Dar, 2016; Rui-Hong et al., 2016; Sabaa et al., 2015; Zhang, Yang, Zhang, Bian, & Yu, 2012; Zhu, Guo, Liu, & Zhao, 2016). Under physiological conditions, they are able to retain a large amount of water or biological fluids and are characterized by a soft rubbery consistency similar to living tissues, making them an ideal substance for a variety of applications. In recent years, environmentally responsive hydrogels that can produce an abrupt change in volume in response to external stimuli have attracted increasing attention due to their potential applications in many fields including drug delivery, control of enzyme activity, bioseparation and tissue engineering (Bian et al., 2016; Chen et al., 2010; Huh, Zhao, & Kim, 2015; Jabeen et al., 2016; Kirchhof et al., 2015; Liu & Fan, 2005; Rui-Hong et al., 2016; Wang & Gunasekaran, 2006; Zhang et al., 2012).

Poloxamers are biocompatible synthetic long chain polyethylene glycol-*b*-polypropylene glycol-*b*-polyethyleneglycol block-copolymers, widely used as emulsifiers, solubilizers and wetting agents in drug delivery systems for different routes of administration (Al Khateb et al., 2016; Dewan et al., 2015; Djekic, Krajisnik, Martinovic, Djordjevic, & Primorac, 2015; Jindal & Mehta, 2015; Korolenko, Pisareva, Filyushina, Johnston, & Machova, 2015; Scheeren et al., 2016). Poloxamer 407 (F127) is commercially available and contains hydrophilic block poly (ethylene oxide) (PEO, 70%) and hydrophobic block poly (propylene oxide) (PPO, 30%). Poloxamer 407 not only can self-assemble to form micelles but is also known to form gels in situ in response to a temperature increase (Al Khateb et al., 2016; Bujnakova, Dutkova, Balaz, Turianicova, & Balaz, 2015; De Souza Ferreira, Moco, Borghi-Pangoni, Junqueira, & Bruschi, 2015; Dewan et al., 2015; Gao, Wang et al., 2016; Kojarunchitt et al., 2015; Zeng et al., 2015). However, they generally have a high critical gelation concentration (CGCs) and poor resilience (Loh, Goh, & Li, 2007).

Chitosan is a copolymer of D-glucosamine and Nacetylglucosamine derived from chitin. For drug delivery applications, chitosan needs to be cross-linked due to its hydrophilic nature. Also, an acidic environment is usually required to dissolve chitosan (Chen et al., 2004) and some researchers have reported that incorporation of polysaccharides such as carboxymethyl chitosan into the hydrogel system markedly changed the characteristics of the gel (Chen, Zhang et al., 2016; Tang, Du, Hu, Shi, & Kennedy, 2007; Zhao, Xu, Mitomo, & Yoshii, 2006). Carboxymethyl chitosan (CMC) is an attractive biocompatible, non-toxic and biodegradable polymer which is a water-soluble chitosan derivative, prepared by the reaction of chitosan with monochloroacetic acid and, in alkaline condition, has been investigated in some applications, such as pharmaceuticals, foods and cosmetics (Bukzem, Signini, Dos Santos, Liao, & Ascheri, 2016; Dumont et al., 2016; He, Wang, Zhong, Ding, & Zhang, 2015; Huang et al., 2015; Lv, Zhou, Zhi, Gao, & Wang, 2016; Medeiros Borsagli, Mansur, Chagas, Oliveira, & Mansur, 2015; Vaghani, Patel & Satish, 2012; Wang et al., 2016; Yang, Bremner, Tao, Li, Hu & Zhu, 2016; Zhu & Zhang, 2016). There have been many reports that incorporation of CMC and other polymers produces a pH-sensitive hydrogel with good mechanical strength (Chen et al., 2004; Jaikumar et al., 2015; Zhao et al., 2006). Although hydrogels are commercially available and widely used, improving their properties, response rate, developing a superabsorbent hydrogel, and increasing their structure-property controllability, remain the key issues in their study (Chen, Tang, Liu, & Tan, 2016; Friedrich, Tieke, Stadler, & Bailly, 2011). To improve the response rate and high mechanical strength of the hydrogels to meet the requirements of specific applications, a novel gel involving poloxamer 407 (F127) and carboxymethyl chitosan (CMC) was synthesized via a crosslinking reaction using glutaraldehyde as the crosslinking agent. The reaction processes are shown in Fig. 1a.

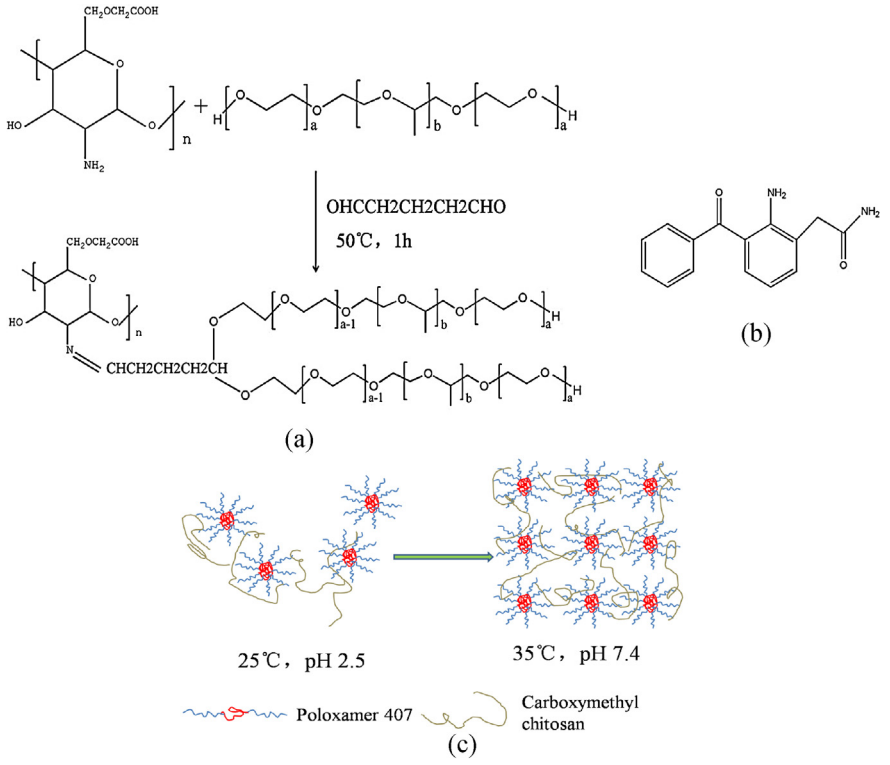

Fig. 1. (a) synthetic route of F127-CMC hydrogel; (b) chemical structure of nepafenac; (c) schematic representation of hydrogel.