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Cyclodextrin-containing hydrogels for contact lenses as a platform for drug incorporation and release

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ABSTRACT

Poly(2-hydroxyethyl methacrylate) hydrogels containing β-cyclodextrin (pHEMA/β-CD) have been investigated as a platform for sustained release of ophthalmic drugs. First of all, pHEMA/β-CD hydrogel membranes and contact lenses were prepared by photopolymerization of HEMA, mono-methacrylated β-CD (mono-MA-β-CD) and trimethylolpropane trimethacrylate using a cast molding process. The hydrogels were characterized by Fourier transform infrared spectroscopy, equilibrium swelling ratio (ESR) and tensile tester. The results showed that the incorporation of β-CD in the hydrogels increased the ESR and tensile strength. Then, puerarin was used as a model to evaluate drug loading and in vitro and in vivo release behavior of the pHEMA/β-CD hydrogels. It was revealed that puerarin loading and in vitro release rate were dependent on β-CD content in the pHEMA/β-CD hydrogels. In rabbit eyes the pHEMA/β-CD hydrogel contact lenses exhibited longer mean residence times (MRT_F) of puerarin in tear fluid than that of pHEMA contact lenses and 1% puerarin eye drops. The puerarin concentration in the aqueous humor of rabbit reached a maximum of 0.81 μg ml^{-1} after wearing the pHEMA/β-CD contact lens, which had been presoaked in 0.802 mg ml^{-1} puerarin solution for 4.81 h. Also, the pHEMA/β-CD contact lenses had a higher drug bioavailability in aqueous humor than puerarin eye drops. The data demonstrate that pHEMA/β-CD hydrogel contact lenses can effectively deliver puerarin through the cornea.

1. Introduction

The ocular regions are an effective administration route, especially for topical ophthalmic diseases. Eye drops are the most popular treatment currently available for many ophthalmic diseases, such as glaucoma or infectious disease. Usually drugs dosed as eye drops are immediately eliminated due to lacrimation, tear turnover and drainage, and less than 1% of the dosed drug effectively reaches the affected part [1]. Therefore, frequent doses, extremely high concentrations or high viscosity are usually required. Frequent doses may lead to a decline in compliance and worsen the patient's quality of life. High concentrations of drug may cause severe side-effects to the eyes. Eye ointments can be adjacent to the cornea for much longer than eye drops, but they may affect the patient's sight and irritate eye tissues. Therefore, there are demands to develop novel drug delivery vehicles used to treat topical ophthalmic diseases.

Efficient ocular delivery relies on enhancing drug bioavailability by sustaining drug release on the ocular surface. In recent years hydrogel soft contact lens vehicles have attracted much attention for ophthalmic drug delivery owing to their high degree of comfort and a significant increase in drug residence time and bioavailability. Soft contact lenses can be loaded with the drug by simple immersion in a concentrated drug solution or direct instillation of eye drops. Usually, drug loading into soft contact lens is rapid, and a burst release of the loaded drug from the contact lens is observed within hours [2]. Nanoparticle and liposome laden [3,4], ion exchange [5], biomimetic and molecular imprinting [6] methods have been proposed to improve the drug reservoir and sustain release from contact lens vehicles. Danion et al. [7] immobilized liposomes on soft contact lenses for subsequent ophthalmic drug delivery to treat eye disease. A hydrogel containing cationic functional groups was loaded with an anionic drug which could be gradually released to the ocular environment [5]. Venkatesh et al. [8] incorporated receptor-based monomers into biomimetic soft contact lenses which showed six times the drug loading of a control lens and sustained release over 5 days.

Cyclodextrins (CDs) are a group of cyclic oligosaccharides with a hydrophobic cavity, which can form inclusion complexes with many small molecule drugs to increase aqueous solubility and the stability of poorly water soluble drugs [9]. Recent studies have shown that CDs are useful additives in ophthalmic formulations [10]. Hydrogels containing CDs have also been found to be useful

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for a variety of applications, including as drug loading carriers [11–15], stationary phases for separation science [16,17] and resin-based dental composites [18]. Dos Santos et al. obtained poly(hydroxyethyl methacrylate–co-methacrylated-β-cyclodextrin) hydrogels with drug loading/release properties [19]. They reported that drug molecules forming complexes with the CDs were efficiently loaded and their release could be sustained for several days. Liu and Fan [20] prepared a mono-acrylated CD monomer which co-polymerized with hydroxyethyl acrylate to produce a hydrogel network with CDs as pendent groups. The hydrogel showed a sustained release of *N*-acetyl-5-methoxytryptamine owing to the formation of drug/β-CD inclusion complexes.

Puerarin is a Chinese drug extracted from the radix of *Pueraria lobata* (Wild.) Ohwi. It is a white, needle-like crystal which is poorly soluble in water. Puerarin has been used as a drug to alleviate glaucoma and ocular hypertension because of its ability to block β-acceptors, to improve ocular blood flow and ameliorate retinal function and microcirculation. Puerarin eye drops of 1.0 wt.% are available commercially and can maintain intraocular hypotension for a longer time than timolol [21]. Puerarin can form inclusion complexes with β-CD molecules and β-CD can be used as a solubilizer for the preparation of puerarin solution [22].

Poly(2-hydroxyethyl methacrylate) (pHEMA)-based hydrogels are extensively used as soft contact lenses due to their excellent biocompatibility and mechanical properties. These hydrogels may be co-polymers of HEMA and other hydrophilic monomers such as *N*-vinyl pyrrolidone (NVP) and methacrylic acid (MAA), which are incorporated to increase the water content of hydrogel contact lens. In order to develop new ocular drug release vehicles and extend the applications of disposable soft contact lenses, pHEMA hydrogel membranes and contact lenses incorporating β-CD have been prepared and characterized in this report. Drug loading and the in vitro and in vivo sustained release behavior of the hydrogel membranes and contact lenses were evaluated using puerarin as a model drug for the treatment of ophthalmic disease.

2. Materials and methods

2.1. Materials

Boric acid, glycerin, β-CD and *p*-toluenesulfonyl chloride (*p*-TsCl) were purchased from Sinopharm Chemical Reagent Co. Boric acid glycerin ester was synthesized from boric acid and glycerin by the method described in the literature [23]. Anhydrous ethylene diamine (EDA) was obtained from Shanghai Lingfeng Chemical Reagent Co. Glycidyl methacrylate (GMA) was supplied by NCM Hersbit Chemical Co. HEMA was obtained from the Tianjin Chemical Reagent Research Center and distilled under vacuum before use. Darocur 1173 was provided by Ciba Specialty Chemicals Holding Inc. (Switzerland). Trimethylolpropane trimethacrylate (TMPTMA) was purchased from Sartomer Co. Puerarin was provided by Jiangsu Tiansheng Pharmaceutical Co. Puerarin eye drops (1 wt.%) were purchased from Zhejiang Shapuaisi Pharmaceutical Co. Contact lens polypropylene molds with the diameter of 11.4 mm were supplied by Hydron Contact Lenses Co.

2.2. Synthesis of mono-methacrylated β-CD

Mono-methacrylated β-CD (mono-MA-β-CD) was synthesized by the conventional method as described in the literature [24]. Briefly, 60 g β-CD was dispersed in 500 ml water. Then 20 ml of a 25 wt.% aqueous solution of sodium hydroxide was added, followed by drop-wise addition of a solution of 10 g *p*-TsCl in 30 ml acetonitrile over 30 min. The mixture was stirred for 2 h at room temperature, followed by filtration. The filtrate was allowed to precipitate at 4 °C overnight. A white precipitate of mono-(6-O-tolylsulfonyl-β)-CD was obtained, which was repeatedly washed with 1 M HCl and then dried at room temperature under vacuum. Mono-6-(6-O-tolylsulfonyl-β)-β-CD (5.0 g) was mixed with an excess amount of EDA (30 ml) and the mixture was kept in a water bath at 75 °C for 4 h. The mixture was cooled to room temperature and then acetone was added. The crude product, mono-EDA-β-CD was obtained as a white precipitate. The crude mono-EDA-β-CD was purified by dissolution in a water–methanol mixture and precipitation in acetone several times. The purified mono-EDA-β-CD was dried under vacuum at room temperature.

Mono-methacrylated β-CD was further synthesized by the reaction of mono-EDA–β-CD with glycidyl methacrylate (GMA) at 60 °C in 30 ml *N*,*N*-dimethylformamide for 6 h. The product, mono-methacrylated β-CD (mono-MA-β-CD), was obtained as a white powder after drying at room temperature under vacuum. The infrared (IR) (Bruker Vector 22 FTIR spectrometer) and NMR (Avance AV-300 Hz) data for mono-MA-β-CD are as follows. IR (KBr): 3386 cm^{-1} (OH), 2927 cm^{-1} (CH_2), 1713 cm^{-1} (C═O), 1030 cm^{-1} (C—O). ^1H NMR (D_2O): $\delta = 6.05$ p.p.m. (1H, C*H*═), 5.69 p.p.m. (1H, CH*H*═), 4.94 p.p.m. (7H, C(1)—*H*, β-CD protons), 3.83–3.72 p.p.m. (28H, C(3)—*H*, C(6)—*H*, C(5)—*H*, β-CD protons), 3.52–3.27 p.p.m. (14H, C(2)—*H*, C(4)—*H*, β-CD protons), 2.91 p.p.m. (2H, CH_2NH–β-CD), 1.87 p.p.m. (3H, —CH_3).

2.3. Preparation of pHEMA/β-CD hydrogel membranes and contact lenses

HEMA, mono-MA-β-CD, TMPTMA, Darocur 1173 and boric acid glycerin ester diluent were mixed as the formulations described in Table 1. The mixture was injected into the cavity of a polypropylene plate mold separated by a polypropylene frame with a thickness of 0.2 mm and then exposured to UV irradiation (30 mW cm^{-2} at 365 nm) for 7 min at room temperature. Hydrogels of pHEMA/β-CD1–3 and pHEMA were obtained as transparent membranes. The membranes were immersed in water at 70 °C for 6 h to extract the diluent and unreacted monomers and were hydrated in distilled water for at least 24 h at room temperature. Finally, pHEMA/β-CD1–3 and pHEMA hydrogel membranes were obtained as listed in Table 1 for the evaluation of drug loading and in vitro release.pHEMA/β-CD3 and pHEMA hydrogel contact lenses were prepared by a method similar to the preparation of pHEMA/β-CD3 and pHEMA hydrogel membranes, with the formulations described in Table 1, using polypropylene contact lens molds. The pHEMA/β-CD3 hydrogel contact lenses were obtained with a weight of 0.02964 ± 0.00623 g and a thickness of 0.053 ± 0.0051 mm. The pHEMA hydro-

Table 1
Formulations of pHEMA/β-CD hydrogel membrane and contact lens.

Sample	Monomers (wt.% of total monomers)			Darocur 1173 (wt.% of total monomers)	Boric acid glycerin ester (wt.% of total solution)
	HEMA	Mono-MA-β-CD	TMPTMA		
pHEMA	99.8		0.2	0.4	60
pHEMA/β-CD1	91.57	8.23	0.2	0.4	60
pHEMA/β-CD2	83.24	16.56	0.2	0.4	60
pHEMA/β-CD3	69.46	30.34	0.2	0.4	60