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Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses

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ABSTRACT

Glaucoma is the second major cause of blindness in the world after cataract. Glaucoma management through eye drops that reduce the intraocular pressure (IOP) has major deficiencies including low patient compliance and low bioavailability. Extended wear contact lenses that deliver glaucoma drugs for extended periods could increase patient compliance, while also increasing the bioavailability. To develop extended wear contact lenses that can also provide extended glaucoma therapy, we disperse nanoparticles of PGT (propoxylated glyceryl triacylate) that contain a glaucoma drug timolol. The particles can also be loaded into prefabricated lenses by soaking the lenses in a solution of particles in ethanol. The particle loaded gels can release timolol in phosphate buffered saline (PBS) for about a month at room temperature. The most likely rate controlling mechanism is hydrolysis of the ester bond that links timolol to the PGT matrix, but other mechanisms such as water and drug diffusion, drug dissolution, drug-polymer chain cleavage, time-dependent drug permeability within the polymeric matrix, etc. may also be important. Nanoparticle incorporation in the silicone hydrogels results in reduction in ion and oxygen permeabilities, and an increase in modulus, and the impact on each of these properties is proportional to the particle loading. A gel with 5% particle loading can deliver timolol at therapeutic doses for about a month at room temperature, with a minimal impact on critical lens properties. Preliminary animal studies in Beagle dogs conducted with lenses in which particles are loaded by soaking the lenses in ethanol show a reduction in IOP.

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1. Introduction

Glaucoma is an ocular disease characterized by an increase in the intraocular pressure (IOP) and eventual damage of the optic nerve and loss of vision. The IOP is set by a balance between production of the aqueous humor fluid in the eye and its outflow through the trabecular and the uveoscleral pathways. Glaucoma sufferers are prescribed medications that reduce the IOP by either reducing the production of the aqueous humor or by increasing its outflow. Timolol a non-selective beta blocker is one such medication that decreases the IOP by reducing the production through blocking of the beta receptors in the ciliary body. Timolol and most ophthalmic drugs are delivered via eye drops that are instilled in the tear film. While eye drops are comfortable to instill, the low bioavailability of less than 5% is a major drawback [1,2]. Furthermore drug instillation through eye drops results in a burst delivery, which necessitates delivery of multiple drops each day [3]. All the factors listed above renders drug delivery by eye drops rather inefficient, with a possibility of side effects due to systemic uptake of drug [1,4,5].

Several approaches have been explored to overcome the disadvantages of eye drops including use of *in situ* forming gels [3] based on pH [4–7], temperature [8–10], and ionic [11,12] triggering, formulations with colloidal particles and collagen shields [13,14]. Also inserts such as puncta plugs, conjunctival inserts, bandage lenses, and contact lenses have been explored for ophthalmic drug delivery. Due to its location in the immediate vicinity of the cornea, contact lenses have some unique advantages for delivering drugs to the cornea. The limited mixing in the post lens tear film between the lens and the cornea leads to a residence time of more than 30 min for drugs released from the lenses [15,16] compared to about 5 min [17] for eye drops. The enhanced residence time leads to significant increases in bioavailability, to possibly as large as 50%, and thus reduces drug wastage [18]. There have been a number of attempts in the past to use contact lenses for ophthalmic drug delivery based on soaking hydrophilic lenses in a drug solution followed by insertion into the eye [19–26]. The major problem of loading drug by this method is that the loaded drug diffuses out in a very short time of a few hours, which is inadequate for extended drug delivery applications. We have proposed incorporating nanoparticles such as liposomes, micelles and microemulsions to increase the release duration from the contact lenses [23–27]. Also Danion et al. have proposed attaching drug loaded liposomes on the lens surface for extending

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the release duration [28]. Furthermore a number of researchers have focused on developing biomimetic and imprinted contact lenses and lenses with a drug containing polymer layer [29–35]. Recently vitamin E loaded contact lenses have been explored for extended drug delivery [36]. There are pros and cons associated with each of these delivery approaches including limitations on drug loading amounts and release durations, impact on critical lens properties such as transparency, modulus, and ion and oxygen permeability, lack of stability during processing, drug release during storage, etc. Several of the approaches cited above have been explored for extended delivery of timolol with varying degrees of success. Recently Jung and Chauhan developed nanoparticle loaded hydrophilic p-HEMA gels in which the drug molecules were crosslinked with the particles. The particle loaded gels released timolol for an extended duration ranging from about a month at room temperature to about a day at 80 °C. Contact lenses loaded with the particles could retain the drug during packaging in refrigerated conditions and provide extended release after insertion in the eyes. The particles were however loaded in p-HEMA gels which cannot be used for preparing extended wear contact lenses due to inadequate oxygen permeability [37].

In this study our aim is to develop particle loaded silicone hydrogel materials that can be used as extended wear contact lenses, while also providing extended drug release at therapeutic rates. To accomplish this objective we dispersed timolol loaded PGT nanoparticles in silicone hydrogel contact lenses. The nanoparticle loaded silicone hydrogel lenses are characterized to explore drug release profiles and all properties relevant to extended wear contact lenses including transparency, modulus, and ion and oxygen permeabilities. Furthermore, *in vivo* animal studies are conducted with Beagle dogs to establish safety and efficacy of glaucoma therapy by extended wear of nanoparticle loaded contact lenses.

2. Material and methods

2.1. Materials

N,N-Dimethylacrylamide (DMA), 1-vinyl-2-pyrrolidone (NVP), timolol maleate, and Dulbecco's phosphate buffered saline (PBS) were purchased from Aldrich Chemicals (St. Louis, MO). Propoxylated glyceryl triacrylate (PGT) was purchased from Sartomer; Benzoyl peroxide (BP) (97%) was purchased from Aldrich Chemicals (Milwaukee, WI). The macromer bis-alpha, mega-(methacryloxypropyl) polydimethylsiloxane (Macromer) was supplied by Clariant. 3-Methacryloxypropyltris(trimethylsiloxy)silane (TRIS) was a gift from Silar Laboratories (Scotia, NY). Methyacrylic acid (MAA) was purchased by Polysciences, Inc. (Wattingyon, PA). 2,4,6-Trimethylbenzoyl-diphenyl-phophineoxide (Darocur TPO) was kindly provided by Ciba (Tarrytown, NY). Vitamin E (D-alpha tocopherol, Covitol F1370) was a gift from Cogins Corporation.

2.2. Methods

2.2.1. Preparation methods

2.2.1.1. Preparation of drug containing PGT nano-particles. The drug loaded nanoparticles were prepared by thermal polymerization of a mixture of the timolol base and the PGT. The details of the process are available elsewhere. Briefly, timolol maleate was converted to the oily base form by increasing the pH of the aqueous solution. The timolol base was added to the crosslinker (PGT) and the initiator BP. The ratio of timolol base and PGT was varied to prepare particles with various drug loadings. The mixture was then added to 5 ml of DI water and then 1.65 ml of 2.08 M NaOH was added to the mixture. The mixture was purged with nitrogen for 15 min and then heated in an 80 °C hot water bath under stirring at 1100 rpm for 8 h. The thermal polymerization results in formation of drug loaded nanoparticles, which were separated from the suspension by centrifugation for 15 min.

2.2.1.2. Preparation of nanoparticle-laden silicone hydrogels by adding particles to the polymerization mixture. The particle-laden silicone gels were synthesized by free radical polymerization. To prepare the silicone hydrogel, 0.8 ml of macromer bis-alpha,omega-(methacryloxypropyl) polydimethylsiloxane and 0.504 g of the drug laden nanoparticle suspension were added to 0.56 ml of N,N-dimethylacrylamide (DMA), 0.24 ml of methylacrylic acid (MAA), 0.8 ml of 3-methacryloxypropyltris(trimethylsiloxy)silane (Tris), and 0.12 ml of 1-vinyl-2-pyrrolidone (NVP). This composition results in the formation of a gel with about 16.7% (w/w) particle loading. The mixture was purged by bubbling nitrogen for 15 min. After adding 0.012 g of the initiator Darocur® TPO with stirring for 5 min, the mixture was poured in between two glass plates separated by a 100 or 200 μm thick plastic spacer. The mold was then placed on Ultraviolet transilluminiator UVB-10 (Ultra·Lum, Inc.) and irradiated with UVB light (305 nm) for 50 min. The molded gel was cut into circular pieces (about 1.65 cm in diameter) with a cork borer and dried in air overnight before further use. Additionally, pure silicone gels used for controls were prepared by the same procedure as described above, except that particle suspension was not added to the mixture.

2.2.1.3. Loading timolol–PGT nanoparticles into commercial contact lenses. The timolol–PGT particles can be loaded into polymerized commercial contact lenses by soaking the lenses in a solution of particles in ethanol. Due to the small size of the particles and the increased pore size in the lens matrix, particles diffuse into the lenses. After equilibration, the lenses are withdrawn from the ethanol solution and soaked in PBS to extract ethanol. The particles are retained in the lenses due to the hydrophobicity and the larger size compared to ethanol. Specifically, contact lenses (Acuvue Oasys of −3.5 D power and 14 mm diameter) were soaked in the 3% (w/w) solution of the particles in ethanol for a period of 24 h. The lenses were then withdrawn and soaked in 100 ml PBS for extraction of ethanol for 24 h. The particle-loaded commercial lenses were then utilized in *in vitro* drug release studies and *in vivo* pharmacodynamics studies in Beagle dogs.

2.2.2. Characterization

2.2.2.1. Particle size distribution. The particle size distribution was determined by dynamic light scattering (DLS). The diameters of the particle suspensions were analyzed by Nanotrac Particle Size Analyzers (Microtrac Inc.).

2.2.2.2. Transmittance. The transmittance of nanoparticle-laden silicone hydrogels was measured using UV–Vis spectrophotometer (Thermospectronic Genesys 10 UV). The lenses were hydrated by soaking in PBS overnight, and then mounted on the outer surface of a quartz cuvette. The cuvette was placed in a spectrophotometer and the transmittance was measured at wavelengths ranging from 200 nm to 1000 nm.

2.2.2.3. Equilibrium water content (EWC). The dried lenses were weighed (W_{dry}) and then hydrated by soaking in 3.5 ml of PBS for 24 h. The hydrated gels were weighed (W_{wet}) and the equilibrium water content (EWC) was calculated as the percentage ratio of the weight gain during hydration and the dry gel weight.

2.2.2.4. Mechanical properties. Storage modulus of the gels was measured using a dynamic mechanical analyzer (DMA Q800, TA instruments). Hydrated rectangular gels 400 μm in thickness were mounted in the submersion tension clamp at room temperature. A preload force applied 0.01 N and force track was 115% used. Strain sweep tests were recorded to confirm the linear range at room temperature at 1 Hz. Subsequently, frequency dependent storage modulus was obtained by fixing the strain within the linear range.

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