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Rapid loading and prolonged release of latanoprost from a silicone hydrogel contact lens

Ryan R. Horne, Kevin E. Judd, William G. Pitt*

[a] Chemical Engineering Department, Brigham Young University, Provo, UT 84602, USA

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ABSTRACT

Eye disorders are often treated with medicated eye-drops, a treatment system that suffers from patient non-compliance and drug delivery inefficiencies. Drug-eluting contact lenses could improve the rate of patient compliance and sustain the rate of delivery of the therapeutic. We report the technology to rapidly load hydrophobic drugs into silicone hydrogel contact lenses, loaded by 4 min or less of soaking the lens in a solution of the drug in n-propanol, followed by rapid deswelling in water. Using this loading system, the amount of hydrophobic drug placed into the lenses was controllable, with up to 450 μg per lens. Drug loading was proportional to the loading time and to the drug concentration in the solution. In vitro drug release from the lenses into artificial tear solution was proportional to total amount of drug loaded, appeared to be diffusion controlled for the first 3 days, and was completed by 4 days. Release into water was much slower. This method of rapid loading could be more feasible than conventional loading from aqueous solutions, particularly for hydrophobic drugs.

1. Introduction

Eye diseases leading to blindness afflict a tremendous number of people. For example, the estimate for glaucoma alone is that it will affect about 3.5% of the population ages 40–80, and perhaps 76 million people worldwide by 2020 [1]. Other eye diseases present similarly poor outcomes. Clinicians often prescribe medicated eye-drops for eye diseases, a treatment system that suffers from patient non-compliance and drug delivery inefficiencies. The inefficiency is directly related to the bolus delivery that occurs periodically throughout the day producing a short-lasting drug exposure at a relatively high concentration [2]. It is estimated that 90–99% of the instilled drug never makes it to the target site in the eye because lacrimation and blinking quickly sweep the majority of the instilled fluid from the eye. An often-proposed alternative to eye-drops is drug delivery via therapeutic contact lenses, which have the potential to bypass these problems of intermittent intense drug delivery, especially for patients who already wear contact lenses. Furthermore, development of continuous wear silicone hydrogel (SiHy) contact lenses presents the possibility of continual drug delivery both day and night.

Researchers have explored many avenues of using contact lenses to deliver biologically relevant molecules to the eye since soft contact lenses entered the market in 1965 [3]. Contact lenses are non-invasive, easy to use and replace, and relatively affordable – all distinct advantages for a drug delivery device [2,4]. Furthermore, the advent of silicone hydrogel contact lenses presents a delivery platform that can contain poorly soluble hydrophobic drugs – drugs that could not be considered for contact lens deliver 2 decades ago.

Despite these advantages therapeutic contact lenses are not common in treatment of eye diseases, with the exception of “bandage contact lenses” used for corneal protection, moisturizing and pain relief following corneal surgeries or in treatment of corneal ulcers [5].

Various methods have been explored to load therapeutics into contact lenses. Soaking is relatively easy to execute. For example, a SiHy lens was loaded with 40 μg timolol maleate by soaking at room temperature for 7 days in a 1.5 mg/mL drug solution in PBS [6]. Similarly, a less water soluble drug, ketotifen fumarate was loaded over 24 h into a SiHy lens [7]. Other “non-soaking” techniques for loading hydrophobic drugs tend to be highly specialized [8].

While not a drug, a hydrophobic comfort agent, 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) was loaded into an experimental silicone hydrogel (SiHy) contact lenses by a novel non-

* Corresponding author. 350 Clyde Building, Chemical Engineering Department, Brigham Young University, Provo, UT 84602, USA.
E-mail address: pitt@byu.edu (W.G. Pitt).

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aqueous approach [9]. This approach takes advantage of the solubility of the hydrophobic agent in n-propanol and the swelling of the lens in this solvent to load large quantities into the contact lens. Rather than simple diffusion of the hydrophobic molecule into the lens over several hours, the lens quickly absorbs the organic solvent, bringing dissolved therapeutic into the contact lens by convection of the solvent, not by diffusion of the therapeutic. When the swollen lens is placed in water or a buffer, it shrinks as the water replaces the alcohol. When the therapeutic is poorly water soluble, it gets trapped in the shrunken lens. Most importantly, loading of this hydrophobic therapeutic can occur on the order of minutes (not days) and provide sustained release over many days [10].

There are other reports of loading hydrophobic agents through similar exposure to an alcohol solution, such as loading vitamin E, dissolved in ethanol, into SiHy lenses over 24 h [6] and dexamethasone, dissolved in ethanol, into silicone hydrogels over 3 h [11].

There are many drugs used to treat ocular disease, both hydrophilic and hydrophobic. One commonly used drug for treating primary open-angle glaucoma is latanoprost, which is fairly hydrophobic, as it has a water solubility of about 40 μg/mL [12] and a *logP* (octanol/water) partition coefficient of 4.4 [13]. Other prostaglandin analogs used for glaucoma treatment are similarly hydrophobic (travoprost *logP* = 4.6, bimatoprost *logP* = 3.2); yet some anti-glaucoma drugs are fairly hydrophilic (timolol *logP* = 1.8; pilocarpine *logP* = 1.1). Because prostaglandin drugs are generally considered front-line treatments for primary open-angle glaucoma [14], many methods have been explored for loading them into contact lenses. However, the currently proposed methods either call for long loading times (anywhere from three hours [11] to four days [6]) or would require major restructuring of existing manufacturing processes [15]. If a more rapid drug-loading procedure were available on the order of minutes, medicated contact lenses would likely be much easier to produce.

The recommended eye-drop dosage for latanoprost eye-drops is a once-a-day dose of one drop (per eye) with about 1.5 μg of latanoprost per drop [16]. However, only 1–7% [17] of the drug of eye-drops reaches the aqueous humor of the eye for therapeutic effect. In a rabbit model, single daily dosing from eye drops created cyclic concentration fluctuations in the aqueous humor from a high value of 54 ng/mL to a low of 1 ng/mL, with an average of 13 ng/mL; while continuous release from a contact lens produced a steady humoral concentration of about 6 ng/mL [15].

In the absence of detailed pharmacokinetic information for latanoprost, a conservative range for a therapeutic effect from a contact lens could conceivably lie between 1% and 10% of this daily dose delivered continuously, as perhaps not all of the continuously released latanoprost may enter the eye. While this target is wide (0.015–0.15 μg per day), preliminary research would show whether an alcohol-loading technique is within a range that could give promise for further therapeutic development.

In this paper we demonstrate a fast and efficient novel method of loading a hydrophobic ocular drug into a commercial SiHy contact lens, using latanoprost as an example. Latanoprost is actually a prodrug, the isopropyl ester of the biologically active prostaglandin acid analog.

We also present the *in vitro* release of this drug into an artificial tear solution over several days, showing delivery within the conceivable therapeutic range stated above.

2. Materials and methods

2.1. Lenses

Dailies Total1® commercial lenses were kindly donated by Alcon (Fort Worth, Texas) in sterile blister packs. These are made from a silicone hydrogel (delefilcon A) that contains 33% water, and the lens is reported to have a "water gradient" on the surface. The lens power was −3.0 diopters and the diameter was 14 mm.

2.2. Latanoprost and other reagents

Latanoprost (9a, 11a, 15R-trihydroxy-17-phenyl-18,19,20-trimax-prost-5E-en-1-oic acid isopropyl ester) was obtained from Puho Pharmaceutical (Shanghai, China) and was used without further purification. Its chemical structure was confirmed by ^{1}H NMR (data not shown). Tritium-labeled latanoprost in ethanol was purchased from American Radiolabeled Chemicals (St. Louis, MO).

Deionized water was distilled to produce DDH_2O used in the experiments. Salts used to prepare phosphate buffered saline and n-propanol were purchased from SigmaAldrich (St. Louis, MO) or Fisher Scientific (Pittsburgh, PA).

2.3. Convective loading of latanoprost

2.3.1. Loading by swelling in n-propanol

A 5.5-mL loading solution of n-propanol was prepared with various concentrations of tritiated latanoprost in 20-mL glass scintillation vials. Approximately 0.5 mL of the loading solution was transferred to n-propanol and DDH_2O to make radioactive standards for calibrations.

The contact lenses were handled with plastic tweezers, rinsed in a stream of DDH_2O, and blotted dry on a KimWipe®. The contact lens was then immersed into 5.0 mL loading solution for a predetermined length of time (60, 120 or 240 s) with gentle swirling of the vial to prevent the contact lens from adhering to the glass vial. The contact lens began to swell immediately. The lens was then removed from the loading solution precisely on time using rubber-tipped plastic tweezers and immediately transferred into a series of three rinses of 5–10 s each, with each rinse consisting of gentle swirling of the contact lens in about 15 mL of fresh DDH_2O. After 3 rinses the contact lens was transferred into a small beaker of about 8 mL of DDH_2O, and left to sit without stirring. During these rinses, the lens shrank back to its original size. After 15 min the lens was processed for either quantitative extraction or release of latanoprost (elution) into water or into artificial tear solution (ATS).

In similar swelling experiments, the lenses were removed from the blister pack, lightly blotted and weighed. After immersion in n-propanol solution, they were removed after 60, 120, 240 or 360 s, lightly blotted and weighed. From the lens masses, the swelling was calculated as the change in mass of the swollen lens divided by the original mass of the hydrated lens: Swelling = $(m_{swollen} - m_{hydrated})/m_{hydrated}$. In a few cases, the diameter of the lens was measured before swelling upon removal from the blister pack, and then again after deswelling.

2.3.2. Quantitation of latanoprost in a lens

The amount of latanoprost in a lens was determined by "extracting" and measuring the amount of latanoprost using scintillation counting as follows. The contact lens was removed from its solution of origin (following loading or following elution into artificial tear solution or water), rinsed thoroughly with DDH_2O to wash away any soluble radioactivity in liquid on the contact lens surface, and lightly blotted on a KimWipe®. The lens was then immersed into a 20-mL glass scintillation vial containing a 2.0 mL solution of n-propanol. The glass vial was capped and placed in a 35 °C incubator under gentle shaking (30 rpm) for one hour. Then the contact lens was removed, suspended over its vial with tweezers, and rinsed with 1.0 mL of n-propanol which was intended to drain into the its vial below to provide a total volume of 3.0 mL in