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Research paper

Feasibility of corneal drug delivery of cysteamine using vitamin E modified silicone hydrogel contact lenses

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ABSTRACT

Cystinosis is an inherited genetic disease characterized by the accumulation of cystine crystals in several tissues including the cornea. The corneal manifestations of cystinosis are treated by hourly instillation of cysteamine eye drops each day while awake. The high frequency of eye drop instillation along with the long duration of treatment leads to poor compliance in many patients. We have combined *in vitro* experiments with mathematical modeling to investigate the feasibility of daily use of cysteamine loaded contact lenses to replace the hourly instillation of drops. Our approach was based on incorporation of vitamin E diffusion barriers into commercially available contact lenses to increase the duration of drug release. Contact lenses were first soaked in a solution of vitamin E in ethanol. Subsequently, the lenses were soaked in an aqueous solution of cysteamine to load the drug. The drug release profiles from vitamin E treated lenses were measured under sink conditions. In addition, drug oxidation rates were measured after exposing drug loaded contact lenses to humidified room air. To study further the feasibility of using contact lenses for the delivery of cysteamine, a mass transfer model was used to determine the rates at which the drug loaded in the lens is delivered to the cornea. The results show that vitamin E loading increases the release duration from 10 min to about 3 h in solution, thus allowing the possibility of extended drug delivery. In addition to improving the release profiles, vitamin E loading also improved the drug stability by reducing the oxidation rates. The mathematical modeling of drug transport in the eye suggested that the vitamin E loaded contact lens can provide the daily therapeutic dose without causing toxicity, while significantly increasing the bioavailability compared to eye drops. Based on the *in vitro* experimental results and the mathematical modeling, it is likely that a single contact lens worn for about 2 h could achieve the same therapeutic effects as hourly instillation of eye drops.

1. Introduction

Cystinosis is a metabolic disease caused by mutations in *CTNS* gene and characterized by loss of the cystine efflux pathway in lysosomes leading to crystal formation and cell death. Cystinosis patients appear normal at birth, but exhibit growth retardation and renal tubular Fanconi syndrome at an early age, followed by further complications during pre-adolescence such as renal failure, renal osteodystrophy, and hypothyroidism [1–4].

Cystinosis leads to complications in several organs including the liver, kidneys, brain, and eyes. Cystine crystals accumulate in the cornea and other ocular tissues such as the iris, conjunctiva, and retinal pigment epithelium to cause irreversible damage to the eye [4–6]. Cystinosis is commonly treated with cysteamine (β-mercaptoethylamine) [7,8], which reacts with intralysosomal cystine to produce mixed disulfide cysteine–cysteamine dimers. These are transported out of the lysosome via the lysine transport system, bypassing the damaged cystinosis transporter [9,10]. The oral dose of cysteamine achieves therapeutic effects in several organs, but its concentration in corneal tissue is inadequate to reduce crystal accumulation [11]. Cysteamine eye drops, delivered hourly, are utilized for treating the ocular complications of cystinosis [2,12,13].

While the eye drop based therapy is effective, it suffers from potential problems related to drug stability and compliance. Cysteamine drug solutions must include stabilizers and are stored at 4 °C to prevent oxidation of the free thiol group. Other factors such as concentration of oxygen, presence of metal ions, and pH value of the solution can impact the rate of oxidation of cysteamine [14–16]. The oxidized form of the drug cystamine does not have clinical efficacy [10], and so, researchers have focused on developing new formulations which are more stable and yet therapeutically effective [5,14]. While the lack of stability limits the duration for which

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the drug remains effective, it does not reduce efficacy. A more severe problem with the eye drop based cysteamine therapy is the potential for poor compliance. Compliance is a problem intrinsic to chronic ocular diseases treated with eye drops [17]. Topical drug delivery via eye drops has a short residence time in the tear film of about 2 min resulting in a low bioavailability (<5%) [18]. Cysteamine eye drops are not effective at three or four times daily dosing regimens [19] and must be administered six times a day to every hour while awake [12,20–22]. This high frequency of drop instillation often leads to poor compliance and thus limitation of the therapeutic benefits and disease progression [4].

Several different devices could potentially be utilized for extended delivery of ophthalmic drugs including gel based formulations, fornix inserts, punctal plugs, sub-conjunctival inserts, and contact lenses. Among these, contact lenses are uniquely suited for cysteamine therapy due to the high corneal bioavailability (estimated to be as large as 50%) [23,24]. Cysteamine loaded contact lenses could potentially replace eye drops in adults and children as young as 8 years of age [25–28]. Another limitation of contact lenses particularly for small molecules like cysteamine is the short duration of release [29]. To prolong drug release durations, Peng et al. [30–34] proposed the possibility of incorporating vitamin E into commercial silicone hydrogel contact lenses as diffusion barriers. In addition to improving the drug release characteristics, vitamin E incorporation has some additional benefits which could be useful to cystinosis patients such as blocking of UV radiation [30]. Contact lenses loaded with 20% vitamin E have been shown to retain all critical lens properties including adequate ion and oxygen permeabilities [30] and have also been shown to be safe and therapeutically effective in a Beagle dog model of glaucoma [33,34].

Contact lenses can increase bioavailability due to increased residence time of the drug in the tear film sandwiched between the lens and the cornea, but the increased contact time with the corneal epithelium could potentially cause toxicity. While *in vivo* models are required to assess toxicity, we here propose to utilize a mathematical model to design the contact lens based delivery system such that the potential for toxicity is minimized. The mathematical model combines the drug transport in the contact lens with mass transfer in the eye. This model uses the transport parameters obtained from the *in vitro* experiments and predicts the time dependent drug concentrations in the post-lens tear film (POLTF). We have used similar models in the past to determine the potential increase in bioavailability from contact lenses compared to eye drops [23,24]. Here, we use the model to design the contact lens such that the maximum concentration in the POLTF does not exceed the toxicity threshold for the drug, while the total mass of drug absorbed by the cornea reaches the therapeutic limit.

Our goal is to combine the *in vitro* experiments with mathematical modeling to develop a contact lens that can deliver at least the same amount of drug to the cornea as eight eye drops, so that a disposable contact lens worn for about 1–2 h and replaced every day could replace the current therapy of hourly instillation of eye drops. We also examine the possibility that contact lenses may have the additional benefit of reducing the oxidation rate of cysteamine.

2. Materials and methods

2.1. Materials

Four commercial silicone contact lenses and one conventional p-HEMA hydrogel (diopter −6.50) were used in this study and described in Table 1. Cysteamine hydrochloride (⩾98%), ethanol (⩾99.5%), and Dulbecco's phosphate buffered saline (PBS) were purchased from Sigma–Aldrich Chemicals (St. Louis, MO). Vitamin E (D-alpha tocopherol, Covitol® F1300) was kindly gifted by Cognis Corporation (Cincinnati, OH, USA). All chemicals were used as supplied without further processing.

2.2. Measurement of cysteamine and cystamine concentrations in solution

Cysteamine drug concentrations in this study were determined using UV–vis spectrophotometry (Thermospectronic Genesys 10 UV, Rochester, NY, USA). The absorbance spectrum of aqueous cysteamine in the range of 211–240 nm contains unique contributions from both cysteamine and its oxidative product cystamine. The measured spectrum was considered to be a linear combination of the reference spectrum of each form, and a least square fit was done to determine the individual concentrations according to the procedure described in Ref. [35]. The fitting procedure was robust and the fits were good with typical root mean square errors of less than 0.5% (results not shown).

2.3. Vitamin E loading procedure

Commercial lenses were rinsed with deionized water and then dried in air to measure their dry weight. Vitamin E was loaded into the lenses by soaking into 3 ml of a vitamin E-ethanol solution for 24 h, long enough to establish equilibrium between concentration of vitamin E in the lens and in the solution. There is a linear relationship between the concentration of vitamin E in the ethanol solution and the concentration loaded into the lens [30]. Based on the partition coefficient for each lens, appropriate concentrations of vitamin E in ethanol were selected to reach loadings of either about 10% or 20% in the lenses. Specifically, concentrations of 0.025 and 0.046 g/ml resulted in 10.22% and 22.24% loadings in 1-DAY ACUVUE® TruEye™ and a concentration of 0.04 g/ml resulted in a 19.14% loading in ACUVUE® OASYS®. Vitamin E was added to 100% ethanol to prepare the solutions, and all vitamin E loadings are based on the ratio of the weight of vitamin E loaded in the lens and the weight of the dried lens. After the 24 h loading, the lenses were taken out, gently blotted, and dried in air overnight. Pre- and post-soaking dry weights were compared to confirm the amount of vitamin E loaded into the lenses.

2.4. Drug loading procedure

50 mg/ml of cysteamine hydrochloride solution was prepared by using PBS as solvent and purged with nitrogen for 20 min to reduce the dissolved oxygen. Then, each lens with or without vitamin E was soaked in a vial containing 3 ml of cysteamine hydrochloride solution. Samples were purged with nitrogen for another 1 min to expel excess oxygen in the vials. These vials were then sealed and placed in the refrigerator for 24 h.

2.5. In vitro drug release experiments and modeling

The samples were taken out of the refrigerator and kept at room temperature for an hour. Then, the drug loaded lenses were taken out of the vials and gently blotted to remove excess cysteamine solution on the surface. The drug release experiments were carried out by soaking a drug loaded lens in 2 ml of PBS at room temperature of about 24 °C. UV spectra in the range 211–240 nm were periodically measured and utilized to determine the concentration of cysteamine and cystamine in the solution. Due to the high solubility of cysteamine in water, the release can be considered to occur under sink conditions, and thus, the % *release* (=cumulative mass released at time t/total mass released from the lens after infinite time) is given by the following equation [36]: