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Sustained *in vivo* release from imprinted therapeutic contact lenses

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ABSTRACT

In this paper, we demonstrate the successful *in vivo* extended release of a small molecular weight therapeutic, ketotifen fumarate (MW = 425), from molecularly imprinted, therapeutic contact lenses. This is the first time that a steady, effective concentration of drug is maintained in the tear film from a contact lens for an extended period of time for the entire duration of lens wear. Poly(HEMA-co-AA-co-AM-co-NVP-co-PEG200DMA) soft contact lenses were prepared (100 ± 5 μm thickness, diameter 11.8 mm, power zero), and a constant tear film concentration of 170 ± 30 μg/mL was measured for up to 26 hrs in a New Zealand white rabbit model. The results showed a dramatic increase in ketotifen mean residence time (MRT) and bioavailability compared to topical drop therapy and drug soaked lenses. The MRT for imprinted lenses was 12.47 ± 3.99 hrs, ~4 and 50 fold greater than non-imprinted lenses and 0.035% eye drops (Zaditor®), respectively. Furthermore, $AUC_{0-26hrs}$ was 9 and 94 fold greater for imprinted lenses than non-imprinted lenses and eye drops, respectively. The results indicate that molecular imprinting provides an exciting rational engineering strategy for sustained release. It is clear that imprinted lenses are very promising combination devices and are much more effective and efficient delivery devices than eye drops.

1. Introduction

Ocular tear flow poses a significant challenge to effective and efficient delivery of drugs to the eye. Continuous tear production reduces the residence time of topically applied drugs within the tear fluid, often 30 min or less [1]. Typically, less than 1–7% of drug delivered through eye drop formulations is absorbed, and most is lost to systemic circulation resulting in very low drug bioavailability [2]. However, eye drops and ointments account for 90% of ophthalmological formulations on the market today [3]. Increased variability in the effectiveness of topically applied drugs is introduced through patient noncompliance when patients fail to follow the dosage regimen [4]. A typical ocular drug concentration profile for eye drops is presented in Fig. 1. A high concentration of drug is applied via eye drops and is quickly reduced. To maintain effective concentration of drug, eye drops must be applied often. If the dose is missed during waking hours and/or sleep, long periods of zero drug concentration can occur. Thus, there exists a considerable unmet need and strong motivation for more efficacious delivery of ocular therapeutics.

To meet this need, our group has developed therapeutic contact lenses capable of controlled release of drugs [5–9]. A significant improvement in both drug loading and a sustained, delayed drug release can overcome ocular transport limitations and poor patient compliance. The motivation for this work was to design a contact lens that allows a steady, effective concentration of drug in the tear film for an extended period of time for the entire duration of lens wear. The objectives were to compare the *in vivo* release of ketotifen fumarate from molecularly imprinted therapeutic contact lenses and topical eye drop administration. We have successfully demonstrated that therapeutically relevant amounts of drug can be released *in vitro* over multiple days from a contact lens platform [5]. This included relatively constant release in artificial lacrimal solution with ocular flow rates [6]. Since conditions within the eye are difficult to match *in vitro*, *in vivo* studies are needed to confirm the increased efficacy and efficiency of this delivery method.

Thus far, most data involving drug release from contact lenses has been from drug soaked contact lenses, which lack a controlled release mechanism. Drug release from drug soaked lenses is purely a diffusion process, depending on differences in drug concentration, steric hindrance, drug partitioning, and drug solubility in the lens. However, drug soaked lenses have been produced for a variety of drugs and used in a number of *in vitro* and *in vivo* studies. In the overwhelming majority of these cases, the drug is released very quickly with no control over the release profile and only slight improvements over topical eye drops have been demonstrated [10–18].

To emphasize the low potential for drug soaked lenses, the uptake and the *in vitro* release of cromolyn sodium, ketotifen fumarate, keterolac tromethamine, and dexamethasone sodium phosphate were compared between silicone hydrogel lenses and traditional hydrophilic lenses [10]. This paper contained overwhelming evidence

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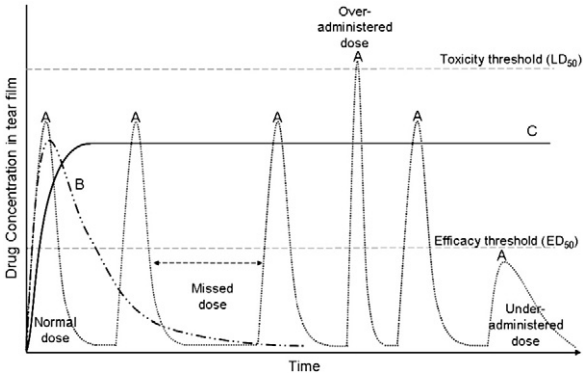

Fig. 1. Ocular tear film drug concentration based on delivery method. (A)Tear film drug concentration quickly reaches a maximum value when applied by eye drops. Lacrimation, drainage and absorption of the drug quickly reduce the concentration below therapeutic levels until another drop is applied. To maintain effective concentration of drug, eye drops must be applied multiple times a day. (B) Drug release from drug soaked lenses has been shown to load small amounts of drug and release drug quickly. However, (C) an unmet need exists for a drug delivery device that provides a controlled and sustained drug release where a constant concentration of drug can be achieved for an extended period of time.

that drug soaked lenses lack significant control over drug release rates and load insufficient drug concentrations necessary for use as therapeutic contact lenses, regardless of material. Drug release was performed in 2 mL of saline and the uptake of cromolyn sodium, ketorolac tromethamine, and dexamethasone sodium phosphate was rapid and release was complete in less than an hour. Ketotifen fumarate demonstrated slower uptake and release was complete in approximately 5 hrs from drug soaked alphafilcon A (PHEMA) lenses [10]. An *in vivo* release of ketotifen fumarate from silicone hydrogels lenses was recently demonstrated with the majority of drug being released in less than 5 hrs without control over the release [19]. The lens released an effective dose (ED50) of ~30 μg/mL [20] for approximately 8 hrs, which is considerably much shorter than the duration of wear for a silicone contact lens.

The duration of lens wear is an important metric when considering release methods. Drug soaked lenses clearly do not extend release for sufficient times, and topical eye drops have remained the 'go to' products. It is important to note that drug soaking has been around as long as soft contact lenses have existed [21]. The most telling fact of their non-superiority to topical therapy is that after 46 years, no contact lens product that loads or releases drug this way has made it to market.

For molecularly imprinted networks, macromolecular framework or memory for the drug is produced during polymer synthesis. Imprinted networks have been shown to improve loading and considerably extend and control release. Excellent review articles give background of the field [22–24] with some specifically written in regard to contact lenses [25,26]. In 2006, our group produced biomimetic hydrogel contact lenses for the enhanced loading and extended release of the anti-histamine, ketotifen fumarate [27,5,28]. Such lenses could be worn with comfort by allergic conjunctivitis patients to relieve itching and discomfort due to seasonal or perennial allergies [29]. In biomimetic imprinting, monomers chosen to mimic receptors in the drug's biological binding molecule are complexed non-covalently to the drug and crosslinked into a hydrogel matrix. The drug's heightened interaction with these memory pockets slows its release from the hydrogel.

This type of network formation—with a proper optimization of drug affinity relating to number and strength of functional monomer interactions, crosslinking structure, and mobility of polymer chains—has a strong potential to influence a number of hydrogel systems and add to the variables one can alter to control the release profile. Multiplicity of monomer–template interactions was achieved with four functional monomers chosen from an analysis of histamine ligand-binding pockets leading to significantly enhanced loading and an increased duration of release compared to less functionalized systems [5]. The results described herein are the first *in vivo* study of these lenses.

To date, there has only been one published study of *in vivo* release from imprinted contact lenses. It was published in 2005 showing the release of timolol in rabbit eyes using 14 mm wide diameter, 80 μm thick lenses [30]. Imprinted lenses showed higher timolol concentration in the tear layer of the rabbits but did not manage to extend release past 90 min. Thus, these imprinted lenses showed marginal improvement over conventional eye drops with enhanced bioavailability, but only loaded 35 μg of timolol/lens [30].

The technology represented by controlled release imprinted contact lenses is one of the most promising areas in ocular drug delivery. Afocal or non-correcting cosmetic lenses can be used by non-lens wearing patients and elute drug for the duration of wear. Controlled, sustained delivery will remove patient non-compliance as a hindrance to effective delivery and represents a more convenient and comfortable platform for drug delivery than traditional topical delivery.

2. Experimental materials and methods

2.1. Rabbit purchase, handling, and ophthalmic evaluation

Male New Zealand white rabbits, approximately 3 months old and weighing between 2.3 and 2.5 kg, were purchased from Myrtles Rabbitry (Thompsons Station, TN). Upon arrival, rabbits were acclimatized for at least 7 days to reduce stress and achieve psychological, nutritional, and physiological stability. All animal facilities used in this project were certified and inspected by AAALAC and the USDA. All rabbits were treated according to the ARVO Statement for the use of Animals in Ophthalmic and Vision Research and NIH standards. Prior to experimental work, protocols were reviewed and approved by the Auburn University Institutional Animal Care and Use Committee (IACUC). Care was taken to assure animals were acclimated to the handling in this study. Prior to experimental manipulation, rabbits were handled on a regular basis starting on the second day after arrival in a non-threatening situation (e.g. petting, giving food treats) [31]. The rabbits were individually housed in a light controlled room (12 hr light–dark cycle) maintained at 20 ± 2 °C with a relative humidity of $50 \pm 3\%$ with no restriction of food and water intake.

Procedures were non-painful and a commercially available rabbit restrainer (Otto Environmental, LLC) was used. The rabbits were adapted to the restraint device. The rabbits were placed in the device for successively longer intervals until the maximum time of restraint was achieved without causing distress to the rabbit. Rabbits in restraints were also continuously monitored. Rabbits were housed in