European Journal of Pharmaceutics and Biopharmaceutics 97 (2015) 30–38

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research Paper

Rapid and selective removal of preservative from ophthalmic formulations during eyedrops instillation

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ARTICLE INFO

Article history:
Received 11 June 2015
Revised 1 October 2015
Accepted in revised form 5 October 2015
Available online 13 October 2015

Chemical compounds:
Benzalkonium chloride (PubChem CID: 15865)
2-Hydroxyethyl methacrylate (PubChem CID: 13360)
Timolol maleate (PubChem CID: 5281056)
Dorzolamide hydrochloride (PubChem CID: 6918132)
Dexamethasone (PubChem CID: 5743)
Latanoprost (PubChem CID: 5311221)

Keywords:
Benzalkonium chloride
Preservative
Poly(2-hydroxyethyl methacrylate)
Macroporous hydrogel
Hydraulic permeability
Selectivity of separation

ABSTRACT

About 70% of eyedrops contain benzalkonium chloride (BAK) as a preservative to prevent the growth of microorganisms. While preservatives are mandated to maintain sterility, many patients exhibit irritation and toxicity to such compounds. We propose to mitigate the ocular toxicity in the ocular formulations without compromising sterility by designing a device that can be incorporated into an eyedrops bottle to selectively remove the preservatives during the process of drop instillation. Here, we specifically focus on macroporous poly(2-hydroxyethyl methacrylate) (pHEMA) gel due to its excellent biocompatibility and high partition coefficient for BAK. In addition to specific selectivity for BAK, the device also requires high hydraulic permeability to allow drop dispensing without excessive pressure drop. The pHEMA monolith can remove nearly 100% of contained BAK from a 25 ml, 0.012% BAK solution with negligible uptake of the hydrophilic drugs such as timolol and dorzolamide. The filter, however, had to be pre-equilibrated with hydrophobic drugs to reach a high separation of BAK without reducing the concentration of the active drug. The average hydraulic permeability of the filter was 0.025 Darcy, which is about 5-fold lower than the ideal value. Incorporation of a pHEMA macroporous gel into an eyedrops bottle can virtually eliminate the exposure of the eyes to the preservatives without compromising the sterility. Our novel design can eliminate the preservative induced toxicity from eyedrops thereby impacting hundreds of millions of patients with chronic ophthalmic diseases such as glaucoma and dry eyes.

1. Introduction

Ophthalmic diseases are most commonly treated by instillation of eyedrops with frequencies varying from one or two times a day for diseases such as glaucoma to as many as ten times a day for severe infections. The drug solutions in eyedrops bottles can get contaminated during use due to contact of the tip with hands, eyelids, lashes or tears while instilling the drops. In a recent study with 204 glaucoma patients, only 39% were able to instill the eyedrops without touching the bottle to the eye surface [1]. Additional risks of cross-contamination could be happened when multiple patients share the bottle such as in a family or in hospitals [2]. There is also the potential for contamination once the bottle has been opened by influx of air carrying a fungal or bacterial disease. The contamination could cause severe infection for the eye or vitiate the efficacy of the ophthalmic solutions. The high potential for the contamination after opening the bottles has led to regulations requiring addition of antimicrobial agent in multi-dose eyedrops formulations. Regulations require the ophthalmic preservatives to achieve 1.0 and 3.0 log reduction by days 7 and 14, respectively, along with no increase in survivors from days 14–28, and no increase in survivors for the fungi from day 0 to day 28 after inoculation with 10^6 colony forming units (cfu)/ml [3]. In addition to antimicrobial efficacy, the preservatives should have suitable properties for incorporation into the formulations such as chemical and thermal stability, compatibility with the eyedrops container and other compounds in the formulation, and more importantly, negligible toxicity to the ocular tissues [4]. Several preservatives have been explored in research and in commercial formulations including alcohols, parabens, EDTA, and chlorhexidine, and quaternary ammonium compounds [4–6].

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http://dx.doi.org/10.1016/j.ejpb.2015.10.004
0939-6411/

Due to the high antimicrobial efficacy and relatively low corneal toxicity, the quaternary ammonium compounds are preferred preservatives with benzalkonium chloride (BAK or BAC) (Fig. 1) being the most common choice [2]. BAK is actually a mixture of alkylbenzyldimethylammonium chlorides with alkyl group primarily being dodecyl and tetradecyl. The eyedrops formulations require BAK at concentrations ranging from 0.004% to 0.025% (w/w) to achieve the regulatory effectiveness. In spite of the good safety profile of BAK [7,8], it is not possible to achieve the targeted antimicrobial and antifungal effects without causing any toxic side effects to the ocular tissues. BAK can cause tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, and damage to deeper ocular tissues [2]. There are no evident ocular symptoms in short medication duration but require years to be clinically identifiable. Due to the fact that toxicity from the preservatives is in a time- and dose-dependent manner, the potential for ocular damage is particularly high for patients suffering from chronic diseases that require daily eyedrops instillations for long periods lasting years to decades such as glaucoma and dried eye patients [2,9,10]. Previous studies and clinical trials revealed consistent and solid data suggested that toxic side effects from preservative-free eyedrops are significantly lower than those from the preserved counterparts. A recent multicenter cross-sectional epidemiologic study with 9658 patients using preservative or preservative-free beta-blocking eyedrops showed that the patients on preservative-free eyedrops exhibit significantly less ocular symptoms and signs of irritation compared to those using preserved eyedrops [11]. Ishibashi et al. also showed that preserved glaucoma drug timolol caused significantly higher tear film instability and disruption of corneal barrier function than preservative-free timolol in healthy subjects [12]. Another study demonstrated goblet cell loss and increased cytoplasmic/nucleus ratio, two characteristics of dry eye disease, with use of BAK containing tear substitutes given eight times a day for 7 days [13].

The growing body of evidence for BAK toxicity and the demands from regulatory bodies has led to several attempts by the pharmaceutical companies to design new approaches for eliminating or minimizing the toxicity from the preservatives. The industry has developed more efficacious glaucoma therapies or fixed combination therapies containing multiple drugs in one single bottle to reduce the dose of preservatives expose to patients' eyes [14,15]. However, still the cumulative effect of preservatives over long periods of years could lead to toxicity. The use of preservatives can be avoided by packaging a single dose in a vial [2]. While this approach can certainly eliminate the exposure to preservatives, it increases the manufacturing costs and environmental impact because of the significant increase in the amount of packaging material. Additionally, the single dose formulations contain about 0.3–0.4 ml of the formulation which is significantly more than the typical eyedrops volume of 30 μl leading to wastage or possibly misuse by using the same bottle for multiple days. Alternatives have been proposed to replace BAK such as Purite®, a stabilized oxychloro complex, and Sofzia®, composed of boric acid, propylene glycol, sorbitol, and zinc chloride and polyquaternium compounds, some of which are used in contact lens care solutions [2]. While these "new" preservatives show promising results in reducing toxic reaction [16–18], still more studies are required to confirm the long term impact of using these preservatives, the potential interaction with active drugs or excipients and the antimicrobial efficiency. Companies have also developed preservative-free formulations by redesigning the eyedrops bottle. The ABAK® (Laboratoires Théa, France) design introduces a filter at the top of the bottle to filter out bacteria from the re-entering solution, thereby preventing contamination. The COMOD® (Ursapharm, Germany) system combines an air free pump and an inner lining that retracts as the liquid is pushed out to avoid contamination of the contents of the bottle [19]. These designs are innovative and useful but cannot protect against any microorganisms introduced due to errors in the manufacturing processes causing loss of sterility. Also, neither of these are approved in the United States.

We are developing a novel approach to mitigate the toxicity in the ocular formulations by selectively separating the preservatives at the point of application, i.e., during the process of drop instillation. The preservative removal is accomplished in a monolith integrated into the neck of the eyedrops bottle to sequester BAK as the eyedrops formulation passes through the device. By this approach we eliminate the toxic effects of the preservative while retaining the beneficial effects of ensuring that the formulation in the bottle is safe. The current focus is on preservative removal from the eyedrops, but the concept can be broadly applied to other liquid formulations containing preservatives such as oral and intravenous drugs, personal care products, and food, particularly for babies. There are three critical challenges in this project: 1. Material design to achieve selectivity for the preservatives over the drugs, and sufficient uptake capacity to bind the preservatives in the entire volume of the eyedrops, 2. Structure design to ensure that the monolith has adequate hydraulic permeability to allow passage of the fluid without excessive pressure drop, and finally 3. Controlling the pore size such that the time required for radial diffusion and adsorption of the preservative on the walls of the pores is less than the convective time through the device.

This manuscript proves the feasibility of our proposed concept. In this study, we show that poly(2-hydroxyethyl methacrylate) (pHEMA) is a suitable material for this concept due to a high affinity for the BAK and well-established biocompatibility and history of use in ocular applications [20]. We also show that porous monoliths of pHEMA can be designed with high hydraulic permeability and rapid uptake of the preservative allowing selective removal of BAK as an ocular formulation is pushed through the monolith. In the eventual design, the monolith will be incorporated into the neck of the eyedrops bottle (Fig. 2), but here we incorporate it into the base of a 3 ml syringe to facilitate measurements of the hydraulic permeability and the separation efficiency. We focus

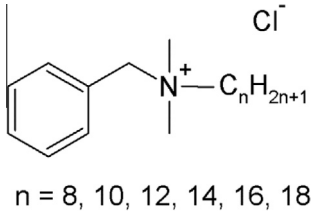

Fig. 1. The molecular structure of BAK.

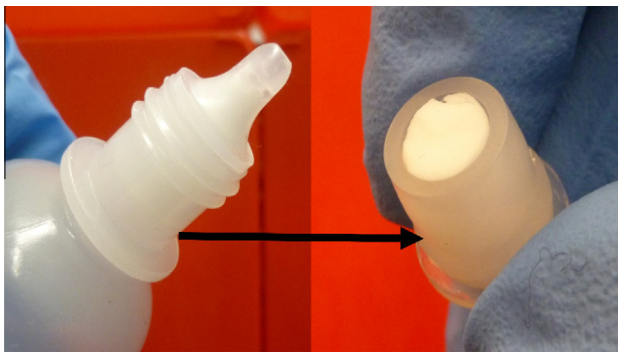

Fig. 2. The incorporation of pHEMA macroporous gel in the neck of an eyedrops bottle.