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Mathematical and computational modeling of drug release from an ocular iontophoretic drug delivery device

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ABSTRACT

The advancement of computational technology has helped the modeling of controlled drug delivery into the biological tissues. One example is the modeling of the drug release into the human eye. Due to natural protective barriers of the eye, ocular drug delivery is considered as a major challenge in the development of treatments for diseases affecting different segments of the eye.

In this work, the drug release from a current-mediated drug delivery device into the human eye is mathematically modeled and numerically simulated. The heat conduction, the flow of the aqueous humor in the anterior and posterior cavities are considered in the modeling. The heat distribution in different segments of the eye in the standing and supine positions is considered to study the thermal safety of the device. The effect of the voltage strength on the heat elevation of the eye segments is investigated. Numerical experiments highlight that ocular iontophoresis drug delivery system does not produce significant thermal damage and it is thermally safe for the eye.

The mechanism of the drug release from the drug reservoir into different segments of the human eye is also studied. The observations show that the drug distribution in the standing position is asymmetric while the drug distribution in the supine position is symmetric.

1. Introduction

Ocular drug delivery is a significant challenge in the development of treatments for diseases affecting different segments of the eye. Dry eye syndrome is an eye problem that decreases the efficacy of the tear film and gradually damages the interpalpebral ocular surface. The disease is prevalent in 5–35% of individuals over age 50 years [1]. Conventional treatment of chronic dry eye requires multiple doses of eye drops over an extended period of time which takes weeks to months or even years. Topical eye drops are used to reduce signs and symptoms of the dry eye. By the way, the effectiveness of eye drops to treat the dry eye is limited by their low ocular bioavailability which is estimated to be 1–10% due to eye's natural protective barriers.

Restasis, the only FDA-approved drug for dry eye, is a treatment which is effective for only 15% of patients treated [1]. Therefore the need for adequate therapies to treat dry eye disease remains substantial. It is well-known that the eye is protected by a series of complex defense mechanisms which prevents drugs from entering the aqueous humor [2]. In order to improve the permeability of ocular drugs and their ocular bioavailability, several approaches including ointments, collagen shields, liposome carriers, prodrugs, penetration enhancers, mucoadhesive gels, polymeric inserts, and current-assisted drug delivery systems have been introduced [3,4].

Iontophoresis, a promising current-assisted drug delivery system, has been widely developed to deliver drugs or nucleic acids into the eye [5]. Iontophoresis is an ion delivery method in which a weak electric current is applied to enhance ionized drug penetration into tissue. It employs low voltages and currents over minutes to tens of minutes to provide a sustained and regulated driving force. In this technique, one electrode has the same charge of the ionized drug while the other one (the ground electrode) is placed elsewhere in the body to complete the circuit. Ocular iontophoresis has great significance in the treatment and diagnosis of eye diseases. Increased drug concentration and reduced systemic drug exposure are among benefits of ocular iontophoretic drug delivery [6].

The EyeGate II Delivery System (EGDS; Eyegate Pharmaceuticals Inc., Waltham, MA) utilizes transscleral iontophoresis to deliver optimal therapeutic levels of drug directly in the anterior and posterior segments of the eye [7]. It offers a potential alternative to current delivery modalities such as eye drops and ocular injections [1,6,8,9]. It uses an electrode to electrolyze water and produce the

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hydroxide or hydronium ions to move charged drug molecules. The device is equipped with an applicator containing a foam reservoir that houses the drug. It is placed just outside the limbus, the point where the cornea touches the sclera. The applicator is connected to a programmable generator connected to a ground electrode that is placed as close as possible to the former electrode to obtain minimal resistance. An electric field is generated inside the applicator to charge the electrode in order to push the drug into the eye.

Dexamethasone phosphate has shown safety and efficiency for ophthalmic symptoms. The efficacy of dexamethasone iontophoresis was studied in [10–12,3]. Clinical reports highlight that the transscleral iontophoresis using dexamethasone phosphate is safe, well tolerated, and easily applied for the treatment of severe ocular inflammation, and reduces the systemic side effects of corticotherapy [2]. EGP-437 is a novel 40-mg/mL dexamethasone phosphate developed by EyeGate for the treatment of dry eye using iontophoresis. When the drug is loaded into a charged reservoir, the drug molecules are driven by the electrical force of the like charges into the desired area. The safety, effectiveness, and iontophoretic dose(s) of EGP-437 is studied by Cohen et al. [12].

The technology of ocular iontophoresis for fast and safe delivery of drug in a specific ocular site is developed in the last years. The current work contributes to the computational study in the ocular iontophoresis drug delivery.

In this paper, the mathematical model of ocular iontophoresis by EGDS is represented using a coupled systems of partial differential equations describing the transport of drug from drug reservoir into different segments of the human eye. Heat conduction, flow of aqueous humor in the anterior and posterior cavities and the flow of the vitreous humor in the vitreous cavity are convective contributors of the drug transport. Mixed convection heat and mass transfer is investigated in the literature as for example [13,14]. Bioheat transfer in the human eye is extensively studied in the literature [15–22]. In this study, we focus on the effect of voltage strength on the heat elevation of the eye segments in standing and supine positions in order to evaluate the thermal safety of the iontophoretic ocular devices. The effect of different eye orientations on the temperature distribution are also studied. The mechanism of the drug release from the drug reservoir into different segments of the human eye is also studied when an eclectic field is applied. The observations show that the drug distribution in the standing position is asymmetric and more drug leaves through the lower part of the anterior cavity, while the drug distribution in the supine position is symmetric.

To best of our knowledge, this is the first time that the mathematical model of the drug release from an iontophoretic ocular drug delivery by taking into account of electric, convective and thermal fields is studied. The paper is organized as follows. In Section 2, we describe the mathematical model of the drug release from drug reservoir into different segments of the human eye. Mathematical descriptions of the electric potential, fluid flow in the anterior and vitreous cavities and heat conduction are included in this section. The next section is devoted to studying the influence of effective parameters such as voltage strength, duration of the applied charge and permeability of the sclera on the drug release in different segments of the eye. In Section 4 some comments and conclusions are addressed.

2. Mathematical model

In this study, a two-dimensional model of the eye, containing different segments including cornea (C), anterior cavity (A), sclera (S), lens (L) and vitreous cavity (V) is developed (see Fig. 3). The geometrical model is based on physiological dimensions of the human eye [23].

This section presents a mathematical model that describes the integrated process of the drug release enhanced by an electric field (Section 2.1) from a drug reservoir into different segments of the eye. The fluid flow in the anterior and vitreous cavities are described in Section 2.2 and the subsequent heat conduction and drug delivery into eye segments are represented in Sections 2.3 and 2.4 respectively.

Due to the complexity of the model, our study is limited to some restrictions.

- As the choroid and retina (see Fig. 1) are relatively thin compared to the sclera, for simplification these layers are modeled as part of the sclera.
- It is assumed that each eye segment is homogeneous and electrically as well as thermally isotropic.
- As the iris and the sclera have similar biomechanical properties, they are modeled together as one homogeneous region.
- The trabecular meshwork as well as the Schlemm's canal and the collector's channel have not been included in the geometrical model.
- Zonules anatomically are ligaments that connect the ciliary muscle with the lens. For the sake of simplicity, they are represented as tissues connected to the lens with the properties of the iris.

2.1. Electric field

EGDS comprises a power source and two electrodes. It is an annular-shaped silicone probe for transscleral iontophoresis contacted to the sclera with an opening to avoid contact with the cornea (Fig. 2). The basic electrical principle that oppositely charged ions attract and same charged ions repel is the central idea of the iontophoresis. The ionized substances are driven into the tissue by electrorepulsion either at the anode for positively charged drug or at the cathode for negatively charged drug.

The electrical potential distribution in each eye segment (ϕ_i) induced by EGDS is obtained through the solution of the steady-state Laplace equation

$$-\nabla \cdot (\sigma_i \nabla \phi_i) = 0, \quad i = D, C, A, L, V, S, \tag{1}$$

where D represents the drug reservoir and σ_i (S/m) is the electric conductivity of each eye segment (see Table 1).

Eq. (1) is completed with initial, boundary and interface conditions. The electric field is assumed to be non-zero on $\Gamma_{\text{electrode}}$. Electrical potentials and electric fields are assumed to be continuous at the interfaces of the eye segments ($\Gamma_{\text{device-sclera}}$, $\Gamma_{\text{sclera-cornea}}$, $\Gamma_{\text{cornea-anterior}}$, $\Gamma_{\text{sclera-anterior}}$ and $\Gamma_{\text{vitreous-sclera}}$) while other boundaries are isolated for the electrical potential (see Fig. 3). The electric field influences the heat conduction in the eye segments (Section 2.3) as well as the drug release from the drug reservoir into eye segments (Section 2.4).

2.2. Fluid flow in the eye

The eye contains two separated cavities: the anterior (A) and the vitreous (V) which are separated by zonules. The anterior cavity of the eye is comprised of two chambers, the anterior chamber which is located between the iris and the cornea, and the posterior chamber which is the region behind the iris and the anterior to the lens (Fig. 4). The anterior cavity is filled with a transparent fluid similar to water called aqueous humor (AH), while the vitreous is filled with a clear gel called vitreous humor, composed of 99% water and 1% collagen and hyaluronic acid.

The presence of natural circulation of AH is evident from clinical, experimental and simulated observations. The present section