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Research paper

Drug delivery to the eye anterior chamber by intraocular lenses: An *in vivo* concentration estimation model

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ABSTRACT

Drug loaded intraocular lenses have been proposed as an alternative to the conventional post-cataract removal prophylaxis through topical drug administration, since the drug or combination of drugs released from the lenses are delivered directly to the target site. In this work, a mathematical model to estimate the concentration of drug released from such lenses in the eye aqueous humor was developed. To attain these estimated concentration profiles, partition and effective diffusivity coefficients for the specific lens material were obtained from standard *in vitro* release experiments. The model was validated by comparing the predicted aqueous humor concentrations with those obtained in *in vivo* studies where hydrophilic acrylic intraocular lens loaded with an antibiotic (moxifloxacin) were implanted in rabbits. Subsequently, other partition and effective diffusivity values were determined for levofloxacin, diclofenac and ketorolac in the same hydrophilic acrylic and in a second material, a silicone hydrogel. Predicted drug concentrations in the aqueous humor allowed an initial screening and evaluation of the most promising system for post-cataract removal prophylaxis, with the hydrophilic acrylic material presenting promising results, especially for moxifloxacin and diclofenac controlled release.

1. Introduction

From the first reported cataract extraction in 1747 [1], this type of ophthalmic surgery has evolved and became one of the most succeeded medical procedures, with positive impact in the thousands of patients intervened each day. However, it may entail risks, such as postoperative endophthalmitis (POE) which is one of the most feared complications. Endophthalmitis is an inflammation of the intraocular tissues that can occur in an acute phase after surgery (up to 2 weeks) but also in a later stage [2,3], with a reported incidence in the last decade ranging from 0.04 to 0.2% [4–6]. To avoid POE, prevention of infection becomes a priority during pre and post-operative period. Usually, it involves topical application of antibiotic drugs, through eye drops placed in the external part of the eye and afterwards absorbed by the cornea and conjunctiva to deeper ocular tissues. This drug delivery route offers numerous advantages, namely ease of procedure and patient compliance, however, it presents low bioavailability (1–5%) due to rapid precorneal clearance [7–9]. A cost-effectiveness analysis of POE prophylaxis reported that topical application of antibiotics was among the most expensive options, compared with intracameral or subconjunctival delivery routes [10].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are also prescribed postoperatively for management of the inflammatory response and prevention of cystoid macular edema (CME) [11]. Cystoid macular edema is a painless disorder in which swelling develops in the macula. As the swelling increases, multiple fluid filled cysts develop in the macula, causing vision loss and distortion. Inflammation after cataract removal surgery is one of the mechanisms responsible for the development of CME [12]. Published studies suggest that topical application of nonsteroidal anti-inflammatory drugs (NSAIDs) bring benefits to early visual recovery and decrease the prevalence of postoperative CME [11].

Drug loaded intraocular lenses (IOLs) could potentially be used as a promising alternative to topical administration of ophthalmic drugs, since they are implanted *in situ,* where infection and/or inflammation may be developed, being able to ensure an high bioavailability of the drug. In the work herein presented, we aimed (1) to develop a mathematical tool to estimate the *in vivo* efficacy of drug eluting IOLs, and (2) to predict the performance of commercially available materials used in intraocular lenses manufacturing in what concerns the delivery of

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antibiotic and anti-inflammatory drugs. The development of a mathematical model arises since *in vivo* conditions, where the IOLs are implanted, are different from those commonly used in laboratorial essays to study drug release kinetics. The application of animal models is not always an alternative, due to economical and/or ethical reasons [13]. Therefore, this mathematical tool is a first step for selection of the most promising drug delivery systems that can, then, be further tested and optimized.

To validate the simulation results obtained from the mathematical model, data from two independent *in vivo* studies were used. In both cases, IOLs manufactured from a hydrophilic acrylic were implanted in rabbits after loading in moxifloxacin solution and aqueous humor samples were collected at given times and analyzed to determine the drug concentration. The obtained values were compared with those predicted by the model.

Two different materials were then selected for the case study: besides the hydrophilic acrylic based material, a silicone hydrogel was also used. Concerning the drugs, two antibiotics (moxifloxacin and levofloxacin) and two nonsteroidal anti-inflammatories (diclofenac and ketorolac) were chosen. *In vitro* drug release studies under static sink conditions were performed to characterize the partition and diffusivity of drugs in the studied materials. The efficacy of the systems was predicted using the model.

2. Materials and methods

2.1. Materials

Discs (thickness 1 mm), made from (1) poly[(2-hydroxyethyl methacrylate)-co-(methyl methacrylate)]-based copolymer with 26% equilibrium water content with average dry weight of 20 mg (from this point on mentioned as 26Y) and (2) Definite50-Contamac® with 50% equilibrium water content with average dry weight of 15 mg (from this point on mentioned as DEF50) were provided by PhysIOL S.A. (Belgium) and cut into 5 mm diameter samples with a cork borer.

Moxifloxacin hydrochloride (MFX), levofloxacin (LVF), diclofenac sodium salt (DCF) and ketorolac tromethamine (KETO) were purchased from Carbosynth Limited (UK). Phosphate saline buffer (PBS, pH 7.4) was purchased from Sigma-Aldrich (USA).

2.2. Drug loading procedure

Drug loaded samples were prepared by soaking discs into 1 mL of drug solution (5 mg mL^{-1}) for 15 days at room temperature. This period is enough to ensure drug equilibrium (data not show). All drug solutions were prepared with PBS. After the loading period, samples were immersed in deionized water (approximately 10 s) and blotted to remove drug in the samples surface.

2.3. In vitro drug release experiments and determination of K and D_e

Drug release was performed by placing the samples in 10 mL of PBS at room temperature and under mild shaking. At predetermined times drug concentration in the supernatant medium was measured in a Thermo Scientific™ GENESYS™ 10S UV–Vis spectrophotometer (USA), in the range 190–320 nm or in an UV–VIS MultiscanGO from ThermoScientific® spectrophotometer in the range 200–400 nm. The sampling solutions were returned to the vials after measurement.

The partition coefficient, K, defined as the ratio between the drug concentrations in the gel and in the aqueous phase, can be calculated for the loading or the release experiments [14], in this work the partition coefficient was calculated based on the release data. Since the volume of the samples is much lower than the volume of the release solution and the drugs used present high solubility limits, it can be assumed that the release occurs in sink conditions. More, it is also assumed that all the loaded drug is released during the experiments that were conducted until no changes of the concentration of the release medium occurred (3–25 days, depending on the drug/material system). In these conditions, the partition coefficient may be determined through the following equation:

$$K = \frac{V_r C_{f,r}}{V_{gel} C_{f,l}} \quad (1)$$

where $C_{f,r}$ is the final concentration of the release medium, V_r is the volume of the release medium, V_{gel} the volume of the fully hydrated gel sample and $C_{f,l}$ the equilibrium concentration in the loading solution.

Concerning, the effective diffusivity, D_e, it can be determined with an analytically model based on the one-dimensional diffusion equation when fitted to experimental release data. Briefly, the drug transport can be described through a uniform thickness film through the Fick's second law:

$$\frac{\partial C}{\partial t} = D_e \frac{\partial^2 C}{dy^2} \quad (2)$$

where C is the concentration of the drug in the lens, which depends on y, the spatial coordinate, and t, the time. The boundary conditions for the drugs release experiments are the following, for the center of the lens (y = 0) and the surface of the lens whose thickness is 2 h:

$$\frac{\partial C}{\partial y}(y = 0, t) = 0 \quad (3)$$

$$C(y = h, t) = 0 \quad (4)$$

The first boundary condition accounts for the symmetry at the center of the lens and the second boundary condition is based on the sink assumption. The known initial condition is the concentration of drug in the lens C_i

$$C(y, t = 0) = C_i \quad (5)$$

which is constant in any point for a lens in equilibrium.

A mass balance on the aqueous release phase yields:

$$-2D_e A_{surface} \frac{\partial C}{\partial y}|_{y=h} = V_r \frac{dC_r}{dt} \quad (6)$$

where $A_{surface}$ is the surface area of the lens, C_r is the release medium drug concentration and V_r the release medium volume, as defined above. The diffusion based problem can be solved and, through the fitting to the experimental data, D_e can be determined.

2.4. In vivo drug release model

A mathematical model was developed to predict the drug concentration in the aqueous humor released from a soaked intraocular lens placed in the eye as substitute of a cataract. In Fig. 1, a representation of an IOL placement in the eye is shown, as well as the model geometry herein used.

The aqueous humor is represented as a flat, two-dimensional film bounded by a non-deformable cornea and a non-deformable IOL. The IOL is treated as a two-dimensional object with a half-thickness of h. The assumption of a two-dimensional geometry has been made to simplify the problem. Considering that the diffusion of the drug through the IOL gel matrix is a purely diffusive process, it can be described with Eq. (2). To solve the diffusion problem, it is necessary to represent mathematically the boundary conditions between both the vitreous-IOL (B1 on Fig. 1) and the aqueous humor-IOL (B2 on Fig. 1).

Regarding the first boundary, with the common use of the extracapsular cataract extraction technique, the elastic capsular bag that covers the lens is left in the eye partially intact after surgery. This capsule remains between the implanted IOL and the vitreous. Published reports suggest that this thin envelop (thickness ranging from 3.5 to 16 μm [15]) is permeable to small molecules, but that capsule permeability can be also dependent on other factors, besides size, such as the