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Numerical simulation of Franz diffusion experiment: Application to drug loaded soft contact lenses

Kristinn Gudnason [a, *], Svetlana Solodova [b], Anna Vilardell [c], Mar Masson [b], Sven Sigurdsson [a], Fjola Jonsdottir [a]

[a] School of Engineering and Natural Sciences, University of Iceland, Iceland
[b] Center of Pharmaceutical Research, University of Iceland, Iceland
[c] Faculty of Pharmacy, University of Barcelona, Spain

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ABSTRACT

Drug loaded soft contact lenses (SCLs) have been considered as an alternative to drug administration via eye-drops to improve bioavailability and patient comfort. Understanding the drug delivery characteristics is key to the design of therapeutic drug delivery systems. In this study, Franz diffusion cell experiments were carried out in order to analyse such characteristics of hydrogel used in SCLs. Two types of experiments were carried out. In one case, the donor compartment was loaded with an initial concentration of diclofenac while in the other case the lens material was pre-loaded with diclofenac. Experiments were carried out with varied initial concentration and temperature. In order to simulate the experimental data and estimate relevant physical parameters of the SCL material, we introduce a general mathematical multi-layer model that takes into account diffusion within each layer as well as the effects of both partition and barriers between layers. The model includes a novel treatment of the discontinuity in drug concentration between layers in an accurate manner. We succeeded in simulating all these experiments. However, the donor-loaded experiments proved more consistent than the pre-loaded case as the same set of estimated parameters could consistently explain varied starting conditions in the simulation of donor-loaded experiments.

1. Introduction

Currently, more than 90% of ophthalmic drugs are delivered in the form of solutions or suspensions [1]. However, several factors influence the efficiency of such formulations, including low bioavailability, poor compliance, and rapid clearence by tear drainage. The low ocular bioavailability requires high drug concentrations in the eye drops, which can cause toxicity in the corneal tissues [2,3].

There is an increasing need to develop new devices for drug delivery to address ocular diseases. An optimal ocular drug delivery system needs to overcome the deficiencies of eye drops, while maintaining all the key requirements regarding physical properties, pharmacokinetics and pharmacodynamics. The system must be highly biocompatible, easy to administer, comfortable and should not have any adverse effect on vision or normal eye functions such as blinking. Furthermore, the device should provide extended drug release at therapeutic rates with increased corneal bioavailability [4–6].

Ophthalmic drug delivery by soft contact lenses (SCL) is more effective than eye drops due to direct contact with the cornea, that results in a high bioavailability of at least 50% compared to about 1 to 5% for eye drops [7–9].

In this study, the nonsteroidal anti-inflammatory drug (NSAID) diclofenac sodium was chosen as a model drug. It is well-known for its application for pain treatment due to its anti-inflammatory and analgesic properties because it inhibits the enzyme cyclooxygenase, which is essential in the biosynthesis of prostaglandins. Diclofenac sodium is indicated for the treatment of ocular diseases and postoperative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery. It has also demonstrated efficacy in chronic conjunctivitis treatment [10].

The topic of contact lenses as a drug delivery system is widely

* Corresponding author.
E-mail address: krg13@hi.is (K. Gudnason).

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covered in the literature [2–4,11–13]. However, the mechanisms of drug release from contact lenses are still not well understood and, hence, the release kinetics difficult to predict. In this respect, mathematical modelling provides a valuable tool to understand the combined action of these processes, and consequently to help devise optimization strategies for targeted drug delivery. Important aspects of such models include the appropriate interface conditions between the lens and the surrounding materials. These result both from partition effects and possible surface barriers, leading to discontinuities in drug concentration across such interfaces. These issues have received attention in recent modelling work on drug flow in the eye [14–16] as well as in some analogue situations [17–20].

We investigate the delivery properties of a hydrogel, a common type of SCL material, by in vitro Franz diffusion cell (FDC) experiment, which have evolved into one of the most important methods for researching drug administration [21]. Two types of FDC experiments were carried out. In the first case, the donor compartment was loaded with an initial concentration of diclofenac (donor-loaded) while in the other case the lens material was loaded with diclofenac beforehand (pre-loaded). An accurate multi-layer numerical model, based on a finite element approach, was developed to simulate the experimental data to estimate physical parameters of the hydrogel. As well as diffusion, the surface barrier effects of partitioning and mass transfer were considered. Additionally, extraction of samples taken from the receptor chamber during experiments was taken into account for more accurate parameter estimation.

The paper is organized as follows: First we describe the experiments that were carried out on SCLs in a FDC. We then present a multi-layer numerical model that describes the experimental setup. The fourth section presents a study of the model parameters to give insight into the effects of each parameter on the drug release curves. We then describe our parametrization of the model, based on the actual experimental data, and apply the results to validate the model using the experimental datasets. Finally, we draw conclusions about our results.

2. Materials and experimental methods

2.1. Materials

We model the specific scenario of a soft contact lens (SCL) in a Franz diffusion cell (FDC), both the pre-loaded case, where initially the drug is contained within the lens material, and the donor-loaded, where the drug is initially located in the FDC donor chamber. Measurements were taken periodically to obtain data on the drug diffusion through the lens material. This section describes the scenario modeled, as well as the experimental setup used to obtain the data that we use later for the parameter estimation of the numerical model.

Potassium dihydrogen phosphate and sodium phosphate dibasic were obtained from AppliChem (Darmstadt, Germany). Sodium chloride was purchased from Riedel-de Han (AG Seelze, Germany). Diclofenac sodium, methanol, High-performance Liquid Chromatography (HPLC) grade acetonitrile and acetic acid were purchased from Sigma-Aldrich (San Louis, MO, USA). Deionised water was produced with a Mili-Q purification system (Millipore A/S, Copenhagen, Denmark). The commercial soft contact lenses used in this study are Etaficon A (1-Day acuvue moist, Johnson and Johnson Vision Care (Limerick, Ireland)) with diopter −0.50, based curve 8.5 *mm* and diameter 14.2 *mm* whose detailed composition is proprietary information. The thickness of the lens is 0.084 *mm*.

2.2. Franz diffusion cell equipment

In vitro drug diffusion and drug release studies were conducted by standard unjacketed Franz diffusion cells (PermeGear, Inc., Hellertown, PA, USA); see Fig. 1, with receptor volume 12 *ml* and inner diameter 9 *mm*.

2.3. HPLC analysis

HPLC analyses were carried out using a Dionex Ultimate 3000 HPLC, HPG-3400 pump with degasser, WPS 3000 TSL autosampler, TCC 3100 thermostatted column compartment, PDA 3000 detector and Chromeleon chromatography workstation (Thermo Scientific, Sunnyvale, CA). OnyxTM Monolithic C18 column (4.6100 mm^2, 5 μm, Phenomenex, Torrance, CA) with a flow rate of 1.5 mL/min was used. The mobile phase for diclofenac consisted of 60% acetonitrile, 40% acetic acid. The detection wavelength was 281 *nm*, the retention time average was 2.10 *min* and the detection limit was 0.1 $\mu g/mL$.

2.4. Release studies by in vitro experiments

2.4.1. Donor-loaded SCLs

Na-diclofenac solutions with four different concentrations (5 mg/cm^3; 1 mg/cm^3; 0.5 mg/cm^3; 0.2 mg/cm^3) in PBS pH7.4 were prepared. Pure SCL was clamped between donor and receptor chambers of a FDC; (see Fig. 1a). 1 *ml* of each concentration were used in donor compartment. The receptor compartment was filled with PBS and was stirred at 400 *rpm*. Experiments were carried out at two temperatures 25°*C* and 35°*C*, respectively. A constant climate chamber HPP-110 was used for experiments at 35°*C* . At predeterminated time intervals, samples were taken from FDCs through the sampling port, 0.20 *ml* each time, and replaced with an equal volume of fresh PBS. The samples were analyzed by HPLC to determine the quantity of drug that had penetrated through the SCL.

2.4.2. Pre-loaded SCLs

Diclofenac solutions with four different concentrations (5 mg/cm^3, 1 mg/cm^3, 0.5 mg/cm^3 and 0.2 mg/cm^3) were prepared in PBS pH7.4. The SCL was soaked with each different diclofenac solutions for at least 24*h* at room temperature. The contact lenses were dried carefully with filter paper to remove the excess drug solution from the surface, and subsequently, used for the drug release experiments. The donor chamber was removed from the FDC setup and replaced by a plexiglass sheet in these cases; (see Fig. 1b). The drug loaded contact lens was placed on the top of vertical FDC which was previously completely filled with PBS (pH = 7.4) with stirring at 400 *rpm*. The plexiglass plate prevents the air diffusion through the drug-containing lens. Samples of 0.2 *ml* were taken from the receptor compartment at predetermined time intervals with equal volume of fresh medium. The samples were analyzed by HPLC to determinate the quantity of drug that had been released from the SCL. As in the previous case, the experiments were carried out at two temperatures, 25°*C* and 35°*C*, and a HPP110 chamber used for samples at 35°*C*.

3. Numerical model

We present the one dimensional multi-layer mathematical model on which our finite element numerical model is based. The goal of the model is to accurately predict drug release characteristics in the setting of the experimental setup of the previous section. In particular, we take care to distinguish between the role of the partition coefficient and the mass transfer coefficient in the