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Mathematical modelling of brimonidine absorption via topical delivery of microparticle formulations to the eye

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ABSTRACT

We developed a mathematical model to elucidate the absorption profile of an ocular drug, brimonidine, into the aqueous humour (AH) after its topical administration to the eye *via* microparticle formulations. For this, a compartment model with three distinct compartments of tear, cornea, and AH was proposed. The parameters were estimated, employing the experimental data of *in vitro* drug release, *in vivo* preocular retention, and drug concentration in the AH, which were obtained with four distinct microparticle types: (1) spherical microparticles without mucoadhesion, (2) spherical microparticles with mucoadhesion, (3) nanostructured microparticles without mucoadhesion, and (4) nanostructured microparticles with mucoadhesion. Our results showed that, for all microparticle types, the simulated and experimental profiles of drug concentration in the AH were in good agreement, as were the overall pharmacokinetic parameters, implying that the model is reliable. With this validated model, we predicted the drug concentration profile in the tear, where nanostructured, mucoadhesive microparticles showed greater than 1.9-fold increase in drug bioavailability, compared with the other microparticle types. This improvement at the preocular surface was reflected in the enhanced drug bioavailability in the AH: greater than 1.5-fold increase compared with the other microparticle types.

Introduction

Topically administered eye drops often disappear instantly from the surface of the eye, mainly due to extensive tear drainage and tear turnover [1]. Consequently, only a small amount of the drug can actually reach the action site, resulting in very low drug bioavailability (<5%) [2–4]. Therefore, multiple daily instillations are often required to obtain a therapeutically effective drug

Abbreviations: PLGA/PEG NM, mucoadhesive, nanostructured microparticles, which were made of poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG); PLGA, poly(lactic-co-glycolic acid); PEG, polyethylene glycol; AH, aqueous humour; PLGA MS, spherical microparticles without mucoadhesion (spherical microparticles of PLGA only); PLGA/PEG MS, spherical microparticles with mucoadhesion (spherical microparticles of PLGA and PEG); PLGA NM, nanostructured microparticles without mucoadhesion (nanostructured microparticles of PLGA only); PLGA/PEG NM, nanostructured microparticles with mucoadhesion (nanostructured microparticles of PLGA and PEG); PBS, phosphate buffered saline; D_M, amount of drug actually released into tear; t, time; D_r, cumulative drug release amount from all the initially administered microparticles; F_m, fraction of microparticles remaining in the preocular space; D_T, drug amount actually available in tear; D_C, drug amount actually available in the cornea; D_{AH}, drug amount actually available in the AH; Ke_T, drug elimination rate constant in tear; Ke_C, drug elimination rate constant in the cornea; Ke_{AH}, drug elimination rate constant in the AH; Ka_{TC}, drug absorption rate constant from tear to cornea; Ka_{CA}, drug absorption rate constant from cornea to AH; C_T, drug concentration in tear; C_{AH}, drug concentration in the AH; V_T, fluid volume in tear; V_{AH}, fluid volume in the AH; AUC, area under the curve; C_{max}, peak concentration; T_{max}, peak time; r^2, correlations of determination; RMSE, root mean square error; MS, spherical microparticles; NM, nanostructured microparticles.

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concentration; however, this often leads to poor patient compliance [5].

To resolve this, in our previous study we prepared mucoadhesive, nanostructured microparticles (*i.e.*, PLGA/PEG NM), which were made of poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) as a drug-diffusion wall and a mucoadhesive material, respectively, and proposed them as drug carriers for topical delivery to the eye [6]. The PLGA/PEG NM had a large specific surface area and thus the effect of the mucoadhesive material in the PLGA/PEG NM was synergistically enhanced. This led to better adherence of the PLGA/PEG NM to the mucosal layer of the eye surface, improving preocular retention. The PLGA/PEG NM was loaded with an anti-glaucoma drug, brimonidine, and it released the drug in the preocular region in a sustained manner. Therefore, we hypothesized that an effective drug concentration in the tear could be maintained for an extended period of time and thus the period for drug absorption could also be prolonged to improve drug bioavailability. In our previous work [6], drug bioavailability in the aqueous humour (AH) and period of lowered intraocular pressure of PLGA/PEG NM were increased by more than 2-fold compared with those of Alphagan P, a brimonidine medication already approved for clinical use.

However, elucidating the drug absorption profile in the eye proved more complicated because of the dynamic fate of the microparticles in the preocular space; for example, the microparticles were continuously cleared away from the eye surface. The drug was released in a sustained manner into the tear while at the same time the tear was continuously refreshed by turnover. The drug concentration in the tear thus varied over time. This variation would influence the actual amount of drug absorbed into the AH [7] and this amount is one of the representative pharmacokinetic parameters.

For this reason, mathematical models have been proposed to explain the time-varying drug concentration in the eye after its topical administration [8–15]. In most of those models, the cornea was considered as a major diffusion barrier against drug absorption into the eye, and the eye was considered to be composed of several individual compartments, such as the tear, cornea and AH [8–14]. The drug absorption was mathematically elucidated at each of the compartments to predict the drug absorption up to the targeted site of interest within the eye [8–14]. Such mathematical models emphasized that the time-varying drug concentration in the preocular region was important, as the tear dynamically cleared the instilled drug *via* its turnover and drainage [9,11–13]. The drug could also be absorbed into untargeted tissue in the eye [10–13]. It was reported that the preocular drug elimination rate constant was subject to change, depending on the volume of the added fluid in the tear [11].

In this work, we propose a compartment model to mathematically elucidate the brimonidine concentration profile in the eye specifically for the topically administered microparticle formulation. We define three major compartments: tear, cornea, and AH. The drug is released from the microparticles into the tear, the drug in the tear is then absorbed into the cornea, and the drug in the cornea is then absorbed into the AH. As in the previous study [12], the time-varying amount of drug actually released in the tear was simulated with the known variables from the experiments, where we empirically mathematized the *in vitro* drug release and *in vivo* preocular retention profiles of the microparticles.

To find the best-fit model, we compared the simulated drug concentrations in the AH with those known from the actual experiments in our previous work [6]. For this, the simulated drug concentration profiles in the AH were each compared with those obtained with the four distinct microparticles in this work: (1) spherical microparticles without mucoadhesion (spherical microparticles of PLGA only, PLGA MS), (2) spherical microparticles with mucoadhesion (spherical microparticles of PLGA and PEG, PLGA/PEG MS), (3) nanostructured microparticles without mucoadhesion (nanostructured microparticles of PLGA only, PLGA NM), and (4) nanostructured microparticles with mucoadhesion (nanostructured microparticles of PLGA and PEG, PLGA/PEG NM). Those microparticles each exhibited the distinct profiles of *in vitro* drug release, *in vivo* preocular retention and *in vivo* drug concentration in the AH.

Experimental

Microparticle preparation and characterizations

In this study, we prepared a new batch of four different microparticles loaded with brimonidine, following the same method employed in our previous study [6]: PLGA MS, PLGA/PEG MS, PLGA NM and PLGA/PEG NM. Further details of microparticle fabrication and their characterization can be found in our previous work [6]. With those newly prepared microparticles herein, we examined *in vitro* drug release profiles and *in vivo* preocular retention properties to examine microparticle reproducibility.

In vitro *drug release experiments*

In vitro drug release experiments were performed with the new batch of microparticles prepared in this work. For this, the microparticles were immersed in phosphate buffered saline (PBS; pH = 7.4) at 37 °C for 48 h. For each type of microparticles, the experiments were performed at least four times using the same procedure in our previous work [6].

In vivo *evaluation of preocular retention*

We evaluated *in vivo* preocular retention properties with a new batch of microparticles prepared in this study. For this, *in vivo* animal experiments were carried out with male New Zealand White rabbits (2.5–3.5 kg, Cheonan Yonam College, Korea) under approval from the Institutional Animal Care and Use Committee (IACUC No. 13-0101) at Seoul National University Hospital Biomedical Research Institute. For this test, the microparticles were loaded with a fluorescent tracer, Nile Red, instead of brimonidine. At scheduled sampling times after topical administration of a microparticle formulation, microparticles were collected from the preocular space and quantified fluorophotometrically (FS2, Scinco, Korea) and the percentage of remaining microparticles was calculated. To generate sufficient data for statistical analysis, at least four experiments were performed for each microparticle type at each sampling time. Details of the *in vivo* experimental procedure are described in our previous work [6].

In vivo *pharmacokinetic evaluation*

In this work, we used the data of the profiles of drug concentration in AH, obtained from our previous work [6]. For this, briefly, at scheduled times after administration of the microparticles, each rabbit was anesthetized and approximately 100 μl of AH was aspirated. The resulting liquid was assayed with high performance liquid chromatography. The limit of detection and limit of quantification are 30 ng/ml and 100 ng/ml, respectively. Only one sample was taken per animal at each time and at least three experiments were performed for each type of the microparticles. The procedures are detailed in our previous work [6].