A MODEL FOR EXTRAOCULAR FLUID DYNAMICS

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A compartment model (side-capacity-parallel-flow model) is used to explain the extraocular fluid dynamics that affects markedly the bioavailability of drugs in ophthalmic delivery. The SCPF model well describes the clinical profile of drug concentration after topical application not only in the open eye with normal blinking but in the closed eye as well.

Introduction

The human eye, with various barrier functions, protects the internal tissues against the entry of xenobiotics from the environment.[6,9,15] A drug applied topically is subject mainly to physical barriers, such as tear flow drainage and corneal resistance to diffusion, before entering the aqueous humor although some drugs undergo enzymatical degradation during corneal penetration.[18] The bioavailability of drugs for internal eye diseases, such as cataract, is therefore extremely low in most topical medication. A publication previously indicated that only 0.1 percent of pilocarpine placed on the eye of rabbits in saline vehicle reached the aqueous chamber after transcorneal penetration.[3] Recent advancements in biotechnologies may bring new pharmacologically active compounds for the treatment of eye diseases. We can,

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however, use these compounds only with great difficulty unless we develop an optimum delivery system for ocular drugs.

During the last two decades, researchers have investigated various delivery systems for ophthalmic drugs to improve their bioavailability after topical application.[1,17,18] Most frequently studied is the prolongation of the retention time of drug molecules in the extraocular fluid (tears). This approach involves the use of viscous solution,[13] ointment,[7] drug-containing soft contact lens,[21] reservoir-type polymeric delivery,[5] liposome or microsphere delivery[16] and biodegradable polymeric delivery.[14] The release of a drug from delivery systems into the extraocular fluid is strongly influenced by tear secretion rate, blinking, lacrimal drainage and formulation vehicle, which factors are the cause of great variability among individual humans and represent the large difference between man and rabbit. Extraocular fluid dynamics, therefore, deserves particular attention.

In this communication, I propose a mathematical model for extraocular fluid dynamics by which the time course of drug concentration in the tear fluid after topical instillation can be described. The effect of the extraocular fluid dynamics on the aqueous humor concentration is also discussed.

1. Extraocular Fluid Dynamics

It was previously found that the time course of the concentration of a drug in the tear fluid after topical instillation is significantly influenced by physicochemical properties of formulation vehicles as well as physiological factors like blinking and posture.[2] Generally speaking, however, the drug concentration in the tear fluid decreases markedly during the first 5 minutes after instillation and thereafter less rapidly, which biphasic profile may indicate the early efficient removal of drug molecules from the cornea surface by lacrimal drainage and the late pumping or recoating capacity of blinking from the conjunctival sac.

Lee and Robinson[8] observed, using albino rabbits, that the pilocarpine concentration in the tear fluid decreased exponentially during the initial 5 minutes after instillation. Mishima[11] assumed a first-order elimination kinetics to describe his clinical data on ocular pharmacokinetics. In spite of the widely accepted assumption of first-order elimination kinetics to simplify the data treatment, it is not clear how accurately this assumption can describe the pharmacokinetics in ophthalmic drug delivery, particularly that in the late period after instillation.

Fraunfelder[2] extensively studied the tear fluid dynamics using a radioactive compound, ^{99m}Tc, which is highly water-soluble, isotonic and nonabsorbable into the cornea. He found that the tear flow pattern was dictated in a complicated manner by various factors including gravity, blinking, lid closure, head position, formulation vehicle and so on.

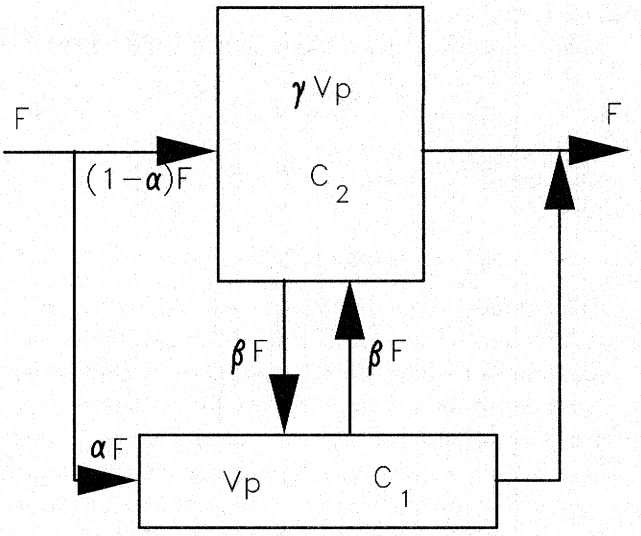

Fig. 1. Side-capacity parallel-flow (SCPF) model for extraocular fluid (tear) dynamics. The notations are listed in Nomenclature.

2. Mathematical Model

A side-capacity parallel-flow (SCPF) model as shown in **Fig. 1** is used to describe the time-course of drug concentration after topical application. The model parameters, parallel flow ratio α, side flow rate β and side-capacity volume ratio γ, are influenced by the physicochemical properties of formulation as well as blinking and tear flow rate. The model parameters, α, β, γ, may be time-dependent rather than constant as a result of physiological response to topical instillation. The time-dependent parameters may be important when the eyes are irritated by either the drug or its instilling vehicle. In this study, however, all model parameters are assumed to be constant during the entire period of medication.

The concentration of a drug in the tear fiim on the corneal surface C_1 and that in the surrounding precorneal area C_2 are given by

$$V_p \frac{dC_1}{dt} = -(\alpha+\beta)FC_1 + \beta FC_2 \quad (1)$$

$$\gamma V_p \frac{dC_2}{dt} = \beta FC_1 - (1-\alpha+\beta)FC_2 \quad (2)$$

The initial condition for Eqs. (1) and (2) is

$$C_1 = C_2 = C_0 \quad \text{(constant)} \quad (3)$$

where C_0 is the initial concentration in the tear fluid immediately after instillation and is approximately 50% of the drug concentration for eyedrops[12] because of the volume of one drop instilled from most applications (about 20 μl) and the volume of tear fluid

(20–30 μl).

The concentration in the tear film is then given by

$$\frac{C_1}{C_0}=\frac{(A-a)e^{-a\tau}-(A-b)e^{-b\tau}}{b-a} \tag{4}$$

where $\tau=tF/V_p$, $A=(1-\alpha+\beta+\beta\gamma)/\gamma$ and a, b are the roots of

$$m^2-(A+\alpha)m+(\alpha+\beta-\alpha^2)/\gamma=0 \tag{5}$$

The clinical data reported by Hardberger *et al.*[4] are analyzed by the present SCPF model, the model parameters of which can be determined by non-linear least-squares curve fitting. The results for the open eye with normal blinking and for closed eye are plotted **Figs. 2** and **3**, respectively. The good agreement suggests that the SCPF model is feasible for describing the tear flow dynamics after topical instillation.

In the normal blinking eye, the parallel tear flow ratio α decreases with increasing vehicle viscosity, while the side-capacity volume ratio γ increases with increasing vehicle viscosity. The higher the solution viscosity, the more tear fluid is entrapped in the conjunctival sac. The exchange rate β is, however, found to be approximately the same order of magnitude for all formulations investigated. In the closed eye, on the other hand, the parallel flow ratio α is much smaller than that in the normal blinking eye, indicating that the tear flow on the cornea surface in the closed eye remains almost stagnant. This is particularly the case for viscous ointment ($\alpha=0.024$). The exchange rate β also decreases significantly when the eye is closed. The side-capacity volume ratio γ, however, increases substantially when the eye is closed, probably because the tear fluid volume entrapped in the surrounding area beside the cornea surface increases in the closed eye.[2]

In Fig. 2, the concentration profile of pilocarpine in the anesthetized rabbit eye[8] is also plotted for comparison (dashed line). Since tear flow characteristics differ significantly between human and rabbit eyes, the values of model parameters were found not to be a good predictor for the human eye. Mishima[12] reported as a rule of thumb that the concentration of a drug instilled in the human eye is reduced to 50% at about 2 minutes and to 10% at about 10 minutes after eyedrop instillation (dotted line). The values of the model parameters for this rule-of-thumb criterion are also determined ($\alpha, \beta, \gamma=0.36$, 0.054, 12, in Fig. 2). Lee and Robinson[8] found first-order elimination kinetics of pilocarpine in rabbit tear fluid with a half-life of about 2 minutes. Their finding does not agree with the data by Hardberger *et al.*[4] This is probably due to the difference in the drug and the vehicle used. The average tear secretion rate in the human eye is 1 to 1.5 μl/min under normal blinking conditions. The tear flow rate may, however, increase a hundredfold when the eyes are irritated.[10]

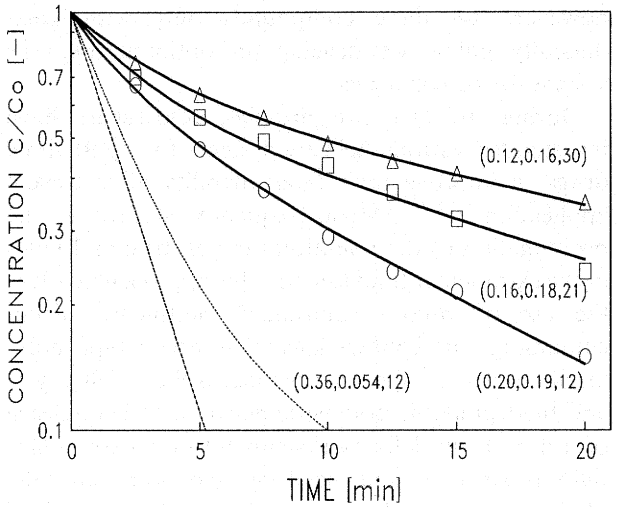

Fig. 2. Time course of drug concentration in tear film in the open eye with normal blinking after topical application. Circles, squares and triangles are clinical data with vehicle of saline, polyvinyl alcohol and ointment, respectively.[4] (——) SCPF model ($F=1$ μl/min, $V_p=1$ μl). Numbers with lines are values of model parameters (α, β, γ). (------) rule of thumb for eyedrop,[12] (– – –) rabbit with pilocarpine.[8]

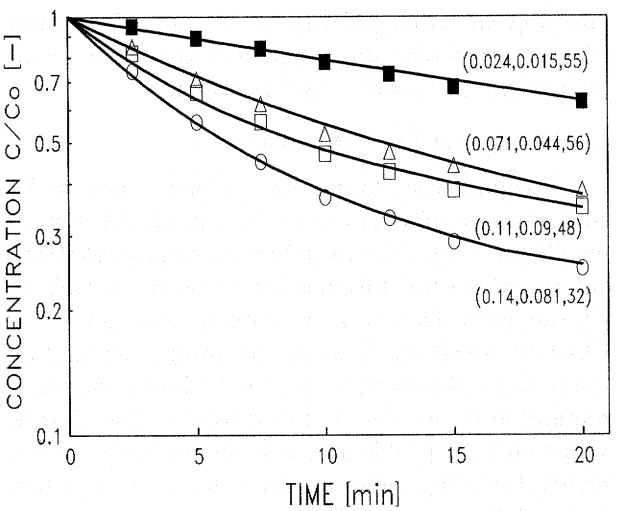

Fig. 3. Time course of drug concentration in tear film in the closed eye after topical application. Circles, squares, triangles and closed squares are clinical data with vehicle of saline, polyvinyl alcohol, methylcellulose and ointment, respectively.[4] (——) SCPF model ($F=1$ μl/min, $V_p=1$ μl). Numbers with lines are values of model parameters (α, β, γ).

3. Aqueous Humor Concentration

The time course of drug concentration in the aqueous humor following topical instillation was simulated by an ocular pharmacokinetic model which consists of the present tear fluid dynamics (SCPF model), bilayer diffusion/partitioning for transcorneal transport[18] and multicompartment elimination/distribution in the internal eye tissues.[19] Simulated profiles are plotted in **Fig. 4**, in which the solid lines

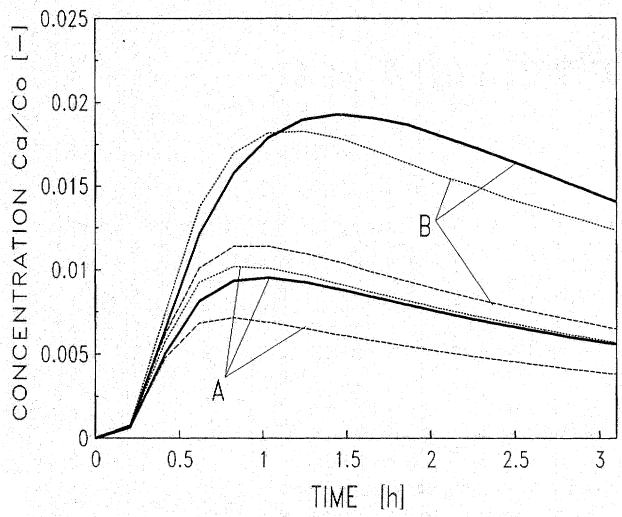

Fig. 4. Simulated profiles of aqueous humor concentration of catalin, an anticataract drug, after topical application. Pharmacokinetic model: bilayer corneal diffusion/multi-compartment tissue distribution model.[18,19] Key: (A) saline; (B) ointment; C_a=drug concentration in aqueous humor. (——) SCPF model. (– – –) First-order elimination rate constant k [s^{-1}] (2.5×10^{-3} for saline and 1.5×10^{-3} for ointment) determined from concentration at 5 min. (------) First-order elimination rate constant k [s^{-1}] (1.7×10^{-3} for saline and 8.8×10^{-4} for ointment) determined from concentration at 20 min. Diffusion coefficient [cm^2/s]: 6.6×10^{-9} in corneal epithelium and 3.2×10^{-7} in stroma. Total corneal thickness [cm]: 0.040, epithelium thickness [cm]: 0.0035. Partition coefficient between epithelium and stroma: 0.031. Volume of distribution in aqueous chamber [ml]: 0.30. Volume of distribution in lens [ml]: 0.40. Effective corneal surface area [cm^2]: 1.0. Elimination rate constant in aqueous humor [s^{-1}]: 0.01. Elimination rate constant in lens [s^{-1}]: 5×10^{-4}. Mass transfer coefficient in aqueous humor/corneal endothelium boundary [cm/s]: 3×10^{-4}. Transfer rate constant from aqueous humor to lens [s^{-1}]: 3×10^{-4}. Transfer rate constant from lens to aqueous humor [s^{-1}]: 1×10^{-4}.

and dashed lines are, respectively, based on the SCPF model and the simplified first-order elimination kinetics for tear flow dynamics. The physiocochemical properties and the pharmacokinetic parameters were obtained from the *in vivo* and *in vitro* experiments for a model drug, catalin, using albino rabbits.[18,20] The dashed lines in Fig. 4 indicate that the simplified tear flow dynamics assuming first-order elimination kinetics may appreciably underestimate the aqueous humor concentration after topical instillation if the elimination rate constant is evaluated from the slope of tear fluid concentration during the initial 5 minutes after instillation. If the elimination rate constant is, however, determined from the concentration at 20 minutes (dotted lines), the underestimation is within 12% for both saline and ointment. Therefore, the simplified first-order elimination kinetics based on the concentration at 20 min can be used approximately to analyze the ocular bioavailability following topical instillation of drugs with physicochemical properties similar to those for the present model drug, catalin. This would not be always the case for other drugs and hence a biphasic profile of extraocular drug concentration must correctly be taken into account using a proper model like the present one to analyze the bioavailability of drugs after topical instillation.

Nomenclature

a	=	root of Eq. (5)	[—]
A	=	$(1-\alpha+\beta+\beta\gamma)/\gamma$	[—]
b	=	root of Eq. (5)	[—]
C_a	=	concentration in aqueous humor (Fig. 4)	[g/ml]
C_0	=	initial concentration in tear film	[g/ml]
C_1	=	concentration in tear film on cornea surface	[g/ml]
C_2	=	concentration in conjunctival sac	[mg/ml]
C_a	=	concentration in queous humor	[mg/ml]
F	=	tear secretion rate	[ml/min]
t	=	time	[min]
V_p	=	volume of tear film on cornea surface	[ml]
α	=	parallel flow ratio (Fig. 1)	[—]
β	=	exchange rate (Fig. 1)	[—]
γ	=	side-capacity volume ratio (Fig. 1)	[-]

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