A Pharmacokinetic Model for Ocular Drug Delivery

Kakuji Tojo

Faculty of Computer Science and Systems Engineering, Kyushu Institute of Technology; Iizuka, Fukuoka 820–8502, Japan.
Received May 17, 2004; accepted August 13, 2004

A pharmacokinetic model of ocular drug delivery has been developed for describing the elimination and distribution of ocular drugs in the eye. The model, based on Fick's second law of diffusion, assumes a modified cylindrical eye with three pathways for drug transport across the surface of the eye: the anterior aqueous chamber, the posterior aqueous chamber and the retina/choroids/scleral membrane covering the vitreous body. The model parameters such as the diffusion coefficient and the partition coefficient in various eye tissues can be evaluated from the *in vitro* membrane penetration experiments using a side-by-side diffusion cell system. The diffusion coefficient for a drug is also predicted by taking account of the effect of the molecular weight of model compounds. The present ocular pharmacokinetic model, which can predict the local concentration distribution in the eye, has well described the *in vivo* concentration profile in the various eye tissues, the lens, the aqueous humor and the vitreous body, following not only topical eye drop instillation but systemic administration as well. The present model also simulates the effects of binding and metabolism in the eye as well as the individual difference in ocular functions and structure such as cataract surgery and vitreous fluidity on the distribution and elimination of drug molecules in the eye.

Key words ocular pharmacokinetics; ocular drug delivery; elimination; distribution; virtual eye; drug diffusion

Pharmacokinetics of ocular drugs has frequently been analyzed by a conventional multicompartment model,[1] which assumes a homogeneous distribution of drugs in each ocular tissue. In spite of the usefulness and wide acceptance, this model may be limited in use. A major drawback of the compartment model is a lack of detailed information on the local concentration distribution in the eye. Pharmacological response is in general a function of the local tissue concentration at the site of action rather than the mean aqueous humor concentration monitored widely under *in vivo* conditions. Elimination routes in or on the eye also affect the local tissue concentration. Therefore the concentration in the aqueous chamber and in the vitreous body is not homogeneous but distribute complicatedly according to the elimination rate across the surrounding tissues. The animal data reported in the literature have often shown that the mean aqueous concentration, based on a simple compartment model, does not well correlate the pharmacological response because of an anti-clockwise hysteresis loop between the pharmacokinetic and pharmacodynamic relationship.[2] These phenomena were widely analyzed by an effective compartment model in the literature.[2] However the pharmacological response may directly be related with the local target concentration if we can evaluate the local concentration distribution.

Drug movement in the eye may be better described by diffusion model based on Fick's second law of diffusion, since the events taking place in the various eye tissues depend usually upon the local concentration instead of the mean concentration throughout ocular tissues. In the present study, we have developed a diffusion model assuming a modified cylindrical eye for the pharmacokinetics of ocular drug delivery. The present model can predict the time course of the local tissue concentration in the eye following a variety of ocular drug delivery including topical instillation, systemic administration, transdermal delivery and vitreous injection and implantable delivery. In the present ocular pharmacokinetic model, it is essential to evaluate the model parameters such as the diffusion coefficient and the partition coefficient in various ocular tissues. The model parameters have been determined from *in vitro* experiments designed independently from *in vivo* experiments.[3—6] The diffusion coefficient of a drug across ocular tissues may depend on the chemical structure and the physicochemical properties as well as the molecular weight of the drug. Maurice and Mishima, however, have found that the diffusion coefficient in ocular tissues is mainly influenced by the molecular weight of the drug.[1]

Spherical, Modified Cylindrical, Eye Model

The present pharmacokinetic model for ocular drug delivery assumes a spherical, modified cylindrical, eye as shown in Fig. 1. The diffusion coefficient of a drug varies not only among tissues but in each ocular tissue such as in the lens.[7] The drug elimination from the eye assumes to occur across three different diffusion routes of the eye: anterior chamber surface, poste-

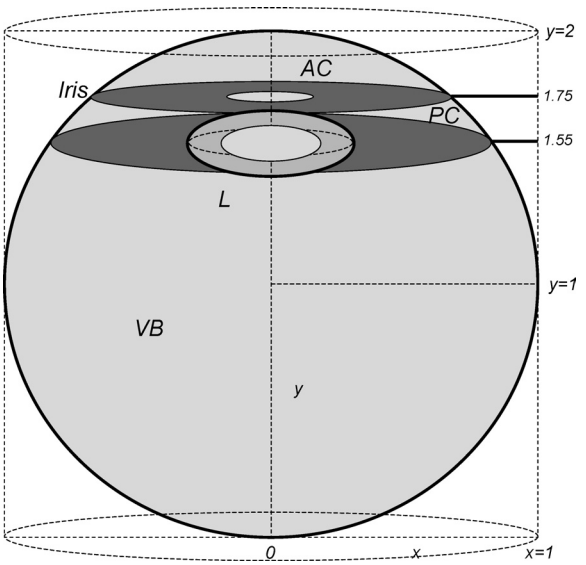

Fig. 1. A Spherical, Modified Cylindrical, Eye Model for Ocular Pharmacokinetics

AC: anterior chamber, PC: posterior chamber, L: lens, VB: vitreous body.

e-mail: tojo@bio.kyutech.ac.jp

Table 1. Diffusion Coefficient (cm^2/s) in Various Eye Tissues for Solving Eq. (1)

Vitreous body,[3] D_v	1×10^{-5} in Figs. 3, 4, 5, 7
Vitreous body, D_v	2×10^{-5} in Fig. 6
Anterior chamber, D_a	$10\times D_v$
Posterior chamber, D_p	$10\times D_v$
Lens capsule,[7] D_{lc}	$D_v/100$
Lens cortex,[7] D_c	$D_v/100$
Lens nucleus,[7] D_n	$D_v/250$
Iris body	$D_v/2$
Outside of inscribed sphere, D_0	$1000\times D_v$

rior chamber surface and vitreous body surface (Fig. 1). In order to approximate spherical eye, the diffusion resistance in the space between the circumscribed cylinder and the inscribed sphere is assumed to be negligible; when the diffusion coefficient between the outside cylinder and the inner sphere (Fig. 1) is 1000 times greater than that in the inscribed sphere of the eye, the diffusion resistance in the outside space becomes negligible.

The concentration of a drug in the eye based on this pharmacokinetic model is given by

$$\{1+B(x,y,t)\}\frac{\partial C}{\partial t}=\frac{1}{x}\frac{\partial}{\partial x}\left(xD\frac{\partial C}{\partial x}\right)+\frac{\partial}{\partial y}\left(D\frac{\partial C}{\partial y}\right)-R(x,y,t)+S(x,y,t) \quad (1)$$

where D is the diffusion coefficient in the eye, $B(x,y,t)$ is the binding term, $R(x,y,t)$ is the metabolism and degradation rate and $S(x,y,t)$ is the release rate of drug from the delivery system implanted or injected.[9] The diffusion coefficient D is not constant but varies in the ocular tissues as shown in Table 1. The diffusion coefficient in the eye was previously determined from the *in vitro* penetration experiment.[3—6] The diffusion coefficient in the aqueous humor is assumed to be 10 times of the vitreous diffusion coefficient since the aqueous humor has convective flow which enhances overall mixing of drug molecules. The partition coefficient inside the eye tissues such as the aqueous humor and the vitreous body is assumed to be unity because each tissue is basically hydrophilic.[7] The partition coefficient between the lens tissue and the aqueous humor was also found to be approximately unity from bovine lens.[7]

The appropriate initial and boundary conditions are described by assuming the pseudo-steady state approach (PSSA)[8,9]:

$$t>0,\quad x=0;\qquad dC/dx=0 \quad (2)$$

$$t>0,\quad x=R;\quad \frac{dC}{dx}=\frac{D_a}{D_0}\frac{K_a}{l_a}(C-C_a)\quad (1.75<y/R<2.0) \quad (3)$$

$$\frac{dC}{dx}=\frac{D_p}{D_0}\frac{K_p}{l_p}(C-C_p)\quad (1.55<y/R<1.75) \quad (4)$$

$$\frac{dC}{dx}=\frac{D_r}{D_0}\frac{K_r}{l_r}(C-C_r)\quad (0<y/R<1.55) \quad (5)$$

$$t>0,\quad y=0;\quad \frac{dC}{dx}=\frac{D_r}{D_0}\frac{K_r}{l_r}(C-C_r) \quad (6)$$

$$y=H;\quad \frac{dC}{dx}=\frac{D_a}{D_0}\frac{K_a}{l_a}(C-C_a) \quad (7)$$

where R and H ($=2R$ for human eyeball) are the effective radius and height of the eyeball, respectively. K, D and l are the membrane partition coefficient, the diffusion coefficient through the boundary membrane and its thickness, respectively. D_0 is the diffusion coefficient in the space between the outside cylinder and the inscribed sphere. The subscripts, a, p, r refer to the anterior chamber membrane, the posterior chamber membrane and the RCS membrane, respectively.

The diffusion coefficient and the partition coefficient of a drug in the vitreous body can be determined by an *in vitro* permeation experiment using the vitreous gel membrane of rabbit.[3] The diffusion coefficient and the partition coefficient across the boundary membrane, the RCS membrane and the cornea, were also determined by the *in vitro* side-by-side membrane permeation experiments.[5,6] The diffusion coefficient in the lens was evaluated by using sliced lens tissue layer prepared from the bovine lens.[7] In the present analysis, the lens is assumed to consist of two parts, cortex and nucleus, as follows:

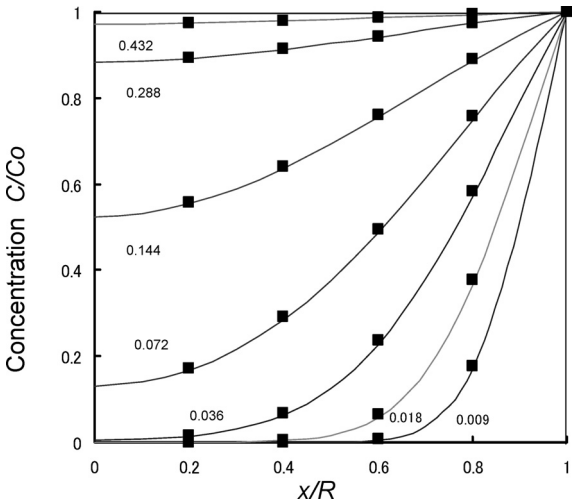

Fig. 2. Comparison between the Analytical Solution for Spherical Eye Model Eq. (9) and the Present Spherical, Modified Cylindrical Model

Lines: analytical solution, squares: calculated from the present model. The numbers with the curves are the dimensionless time defined by Dt/R^2.

For the lens cortex:

$$\frac{x^2}{0.20^2}+\frac{(y-1.55)^2}{0.11^2}>1,\quad \frac{x^2}{0.35^2}+\frac{(y-1.55)^2}{0.1925^2}<1 \quad (8)$$

For the lens nucleus:

$$\frac{x^2}{0.20^2}+\frac{(y-1.55)^2}{0.11^2}<1 \quad (9)$$

The thickness of the iris and the radius of the iris opening are assumed to be 0.05 and 0.25, respectively (Fig. 1).

The mean concentration in the aqueous humor, lens and vitreous body, was calculated by numerical integration of the concentration profile throughout each ocular tissue in the spherical eyeball.

Method of Solution

The drug concentration in the internal eye tissues, such as the anterior and posterior aqueous chamber, lens, iris and vitreous body, was computed by solving the governing equation Eq. (1) subject to the appropriate initial and boundary conditions as summarized in Eqs. (2) to (7). We have used a method of lines procedure to solve the partial differential equation.[8] A resulting set of ordinary differential equations are numerically solved by Gear's method.[9]

To test the accuracy of the present modified cylindrical approach for analyzing the drug transport in the spherical eye, the numerical solution is compared with the analytical solution for a special case where we assume the constant diffusion coefficient throughout the spherical eye tissue. The diffusion coefficient in the space between the outside cylinder and the inside sphere is assumed to be 1000 times larger than that in the vitreous body since the diffusion resistance outside the inscribed sphere can be neglected under this condition. If the concentration in the spherical eye is initially zero and thereafter the surface concentration remains a constant C_0, the solution becomes[10]:

$$\frac{C}{C_0}=1+\frac{2R}{\pi x}\sum_{n=1}^{\infty}\frac{(-1)^n}{n}\sin\frac{n\pi x}{R}\exp\left(-\frac{Dn^2\pi^2 t}{R^2}\right) \quad (10)$$

As can be seen from Fig. 2, the numerical solution agrees excellently with the analytical solution, and thus indicates the validity of the present modified cylindrical model for simplifying the spherical eye.

Results and Discussion

Topical Application Time course of mean aqueous humor concentration of terazosin after topical instillation in rabbit has been simulated and compared with the *in vivo*

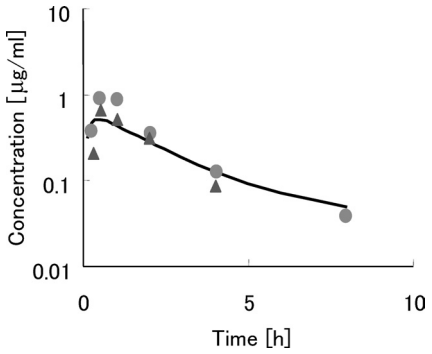

Fig. 3. Time Course of Concentration Changes of Terazosin in the Aqueous Humor after Instillation of 50 μl of 0.3% Terazosin HCl Solution in the Rabbit Eye

Line: calculated, triangles: experimental (aqueous humor concentration), circles: experimental (iris and ciliary body).[2] $Sh_v=2.0\times10^{-5}$, $Sh_a=1.6\times10^{-5}$, $Sh_p=2.0\times10^{-2}$, $D_v=1.0\times10^{-5}$ (cm^2/s), $C_a=1500\,\mu$g/ml, $C_v=C_p=0$. $k_1=0.00116$ (1/s), where $Sh_i=(D_i/D_0)(RK_i/l_i)$.

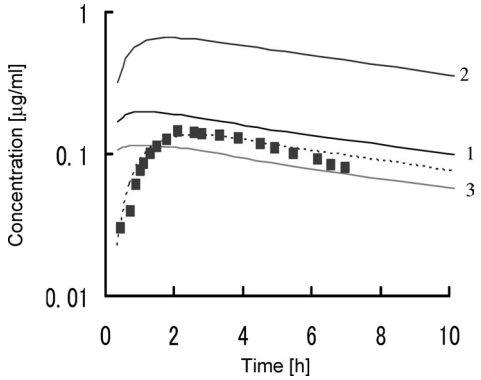

Fig. 4. Time Course of Fluorescein Concentration Changes in the Aqueous Humor of Human Eye after Instillation of 10% Solution.[16]

Lines: calculated, squares: experimental (Mishima[16]). Line 1: $k_1=0.00292$ (1/s), line 2: $k_1=0.00083$ (1/s), line 3: $k_1=0.005$ (1/s) and $k_2=10$ (1/s), dashed line: $k_1=0.00083$ (1/s), $k_2=0.001$ (1/s). $Sh_v=6.0\times10^{-7}$, $Sh_a=4.8\times10^{-7}$, $Sh_p=4.8\times10^{-7}$, $D_v=1.0\times10^{-5}$ (cm^2/s), $C_a=45000\,\mu$g/ml, $C_v=C_p=0$, where $Sh_i=(D_i/D_0)(RK_i/l_i)$.

albino rabbit experiment in Fig. 3. The concentration in the iris is also plotted. According to Maurice and Mishima,[1] the iris in albino rabbits is porous, and drug molecules dissolved in it freely communicate with the aqueous humor across its anterior surface, and therefore, the iris may be regarded as a part of the anterior chamber compartment from the point of view of pharmacokinetics. The mean concentration was evaluated by integrating the concentration distribution throughout the aqueous humor. The model parameters required for this simulation were determined independently from the *in vitro* penetration experiment.[5—7] The figure shows good agreement between the simulated profile and the *in vivo* experiment. The clinical data for fluorescein concentration after 10% solution instillation are also compared with the experimental data by Mishima in Fig. 4. With respect to the clinical data of fluorescein instillation, Mishima previously indicated that the elimination rate constant after instillation of fluorescein solution ranges from 0.0008 to 0.005 s^{-1} under clinical conditions. In Fig. 4, the effect of the rate constant is also demonstrated together with the average elimination rate constant of 0.00292 s^{-1}. We can find that the clinical data fall approximately between the two extreme values of elimination rate constants. However initial deviation before reaching the peak concentration is appreciable; the calculated peak value is higher than the clinical data before reaching the peak value. This can be attributed to the pseudo-steady state approach (PSSA) in applying the boundary conditions on the surface of the eye. In general, PSSA may initially overestimate the surface concentration on the cornea, and therefore the rate of absorption from the anterior portion is overestimated. On the other hand, under the elimination period after the peak time, PSSA becomes a reasonable assumption. PSSA can also be applied to sustained or controlled release formulations because of the surface concentration maintained nearly constant during the drug administration.

By considering the time lag across the corneal surface shortly after topical instillation, the concentration on the surface of the cornea can be approximated by the following equation:

$$C_s=A(e^{-k_1t}-e^{-k_2t}) \tag{11}$$

where k_1 and k_2 are the apparent elimination rate constant and the apparent absorption rate constant in the surface layer of the cornea, respectively. The dashed line in Fig. 4, which is evaluated by Eq. (11), well represents the time course of clinical fluorescein concentrations.

The drug concentration profile in the eye at different time intervals, 12 and 48 h after topical instillation, was compared in Fig. 5. The drug molecules initially reach the front of the lens tissue and then diffuse laterally along the surface of the lens. In the late stage after 48 h, however, the drug molecules accumulated in the lens tissue give rise to a typical reservoir function due to a slow elimination of drug molecules; Kaiser and Maurice have found[11] that the dye spreads laterally in the lens cortex more rapidly than it penetrates, and it forms a colored shell beneath the surface of the tissue. The behavior of a lipid-soluble dye has also been directly observed and it appears to be similar to that of fluorescein. Some of the dye that enters the lens diffuses out again two days after topical application.[11] The concentration profile simulated from the present mathematical model agreed reasonably well with the observation of *in vivo* rabbit study.

Systemic Application Kinsey reported the concentration of radio-labeled chloride ion following the parenteral administration distributes in a complicated manner throughout the eye[12]; the ions enter mainly through the posterior chamber while the drug transport across the retina/choroids/scleral membrane was much less than that across the posterior chamber wall although this is not negligible. As a result, the concentration in the eye shortly after administration (35 min) becomes typical stadium-like distribution as shown in Fig. 6. The simulated concentration profile is in good agreement with the experimental observation obtained by Kinsey. It is indicated that the drug molecules after systemic administration enter the eye mainly across the posterior chamber wall and then distribute both anterior chamber and the vitreous body. However, the drug molecules hardly penetrate in the lens nucleus.

Local Injection and Implants Drug delivery from a biodegradable polymer device is simulated by the present ocular pharmacokinetic model in which we assume the device is implanted at the center of the vitreous body. The advantage of biodegradable polymer is the fact that no surgery is required in order to remove the device after med-

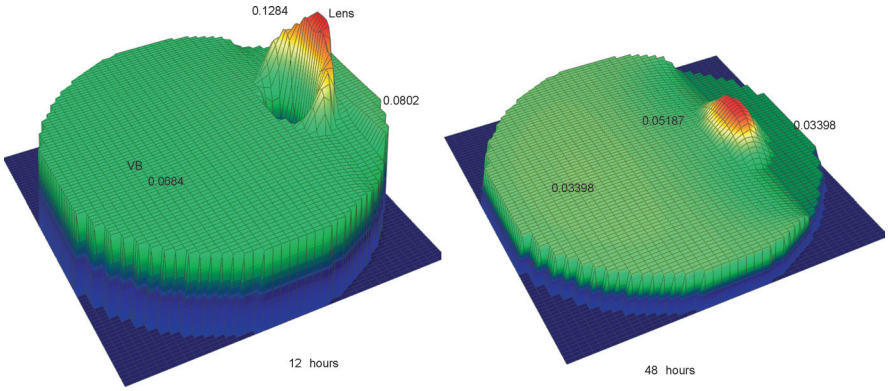

Fig. 5. The Drug Concentration Profile in the Eye Following Topical Instillation

Left: 12 h, right: 48 h after instillation. The model parameters are the same as in Fig. 3. The numbers on the profile are the dimensionless concentration (C/C_0: $C_0=1$ at $t=0$).

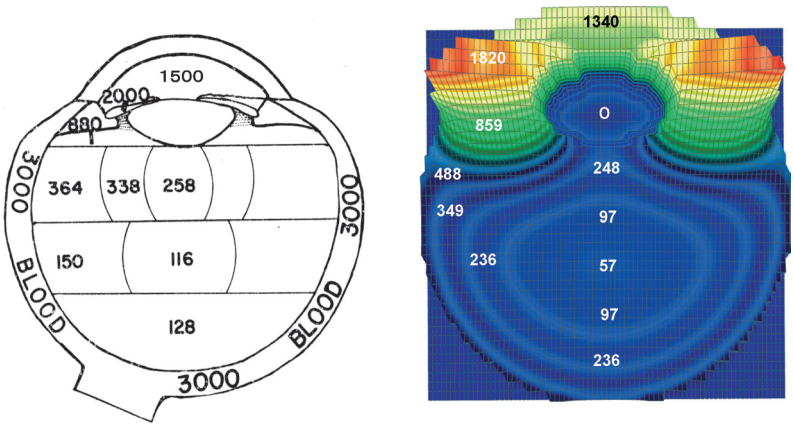

Fig. 6. Concentration Distribution in the Rabbit Eye at 35 min after Parenteral Administration

Left: *in vivo* rabbit data, right: calculated from the present model. $Sh_v=8.3\times10^{-4}$, $Sh_a=6.6\times10^{-4}$, $Sh_p=6.6\times10^{-4}$, $D_v=2.0\times10^{-5}$ (cm^2/s), $C_a=0$, $C_v=C_p=3000$. $k_1=0.00116$ (1/s), where $Sh_i=(D_i/D_0)(RK_i/l_i)$.

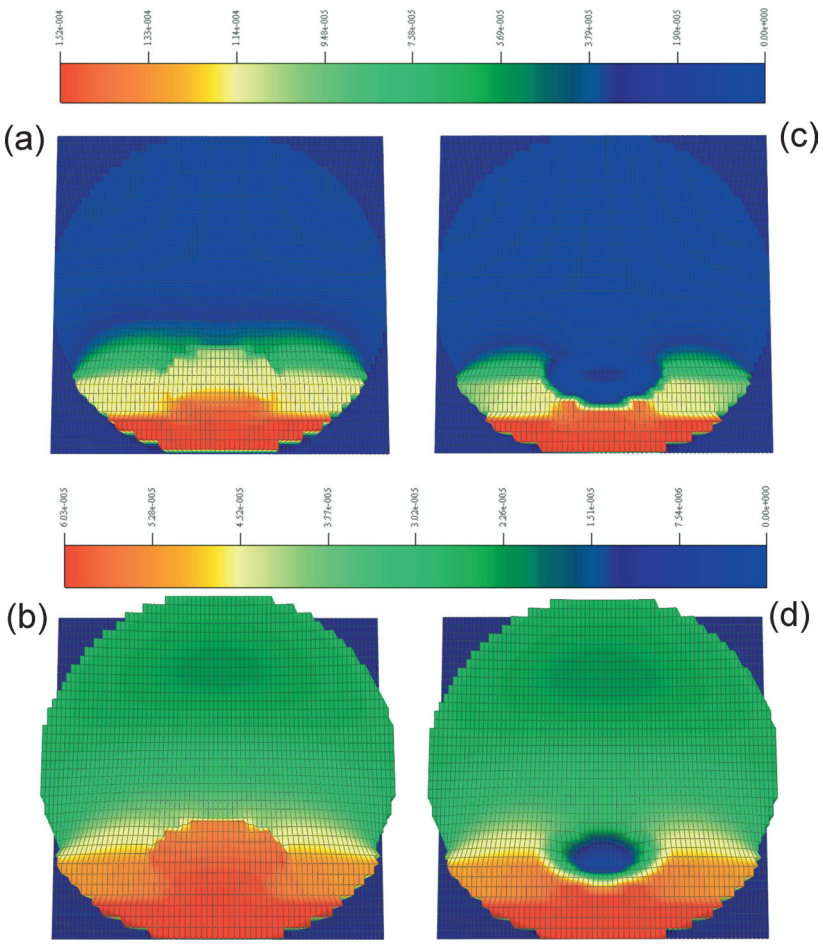

Fig. 7. Concentration Distribution of Ocular Drugs after Topical Instillation

(a), (b): cataract treated eye; (c), (d): normal eye; top: 2 h; bottom:12 h. The model parameters are the same as in Fig. 3.

ical treatment. This is particularly attractive for diseases in the internal segment of the eye. The biodegradable polymers, however, may cause exceedingly high rates of release in the late period due to bulk erosion of the polymer matrix.[13,14] In order to avoid this drawback, we have developed a new approach to formulate a constant-release PLA rod device which can release the active agent at a constant rate for extended period of time without occurring bursting release due to polymer bulk erosion.[15] We have found that the concentration in the vitreous body is approximately proportional to the constant release rate of drug from the device implanted. We have also found that the vitreous body concentration near the site of device implanted becomes extremely high, approximately 4 to 5 times higher than the mean vitreous body concentration. On the contrary, the concentration in the lens hardly increases because of a rapid elimination of the drug across the posterior chamber. This may suggest that the drug delivery to the lens is quite difficult to achieve under normal physiological conditions.

Effect of Cataract Surgery Drug concentration profile in the eye after cataract surgery is compared with that in the normal eye in Fig. 7 where we assume the cataract treated lens has the diffusion coefficient same as in the vitreous body since the contents of the lens, lens cortex and nucleus, are completely removed and replaced by the stagnant aqueous fluid, which enters from a small opening in the anterior lens capsule. The IOL situated in the empty lens capsule was neglected in this simulation because of its small volume fraction. In spite of the great difficulty of drug diffusion in the lens of normal eye, the overall concentration profile is little influenced by the cataract surgery excepting in the lens and its surrounding; the concentration in the aqueous humor and in the vitreous body is almost unchanged by cataract surgery. This finding implies that the posterior lens capsule controls the drug diffusion in the posterior segment of the eye for both normal and cataract treated eyes. Therefore the drug molecules mainly penetrated into the vitreous body across the anterior hyaloid membrane from the posterior chamber.

Effect of Iris Binding Both drug binding and its slow diffusion in the ocular tissues may cause reservoir function and slow elimination of drugs from the eye, which is attributed either to extremely slow diffusion in the lens or drug binding in the iris pigments.[16] In spite of a similar phenomenon of slow elimination, drug binding in the iris should be clearly distinguished from the reservoir function of the lens due to slow diffusion.

Drug binding in the ocular tissues can be analyzed by a dual sorption model.[17] Assuming an equilibrium state between the bound and unbound drug molecules in the iris based on the Langmuir isotherm, the governing equation Eq. (1) can be modified as[18]

$$\left\{1+\frac{\beta}{(1+\alpha C)^2}\right\}\frac{\partial C}{\partial t}=\frac{1}{x}\frac{\partial}{\partial x}\left(xD\frac{\partial C}{\partial x}\right)+\frac{\partial}{\partial y}\left(D\frac{\partial C}{\partial y}\right)-R(x,y,t)+S(x,y,t) \quad (12)$$

Equation (12) indicates that the effective diffusion coefficient, D_e, is given by the following equation with binding:

$$\frac{D_e}{D}=\frac{1}{1+\beta/(1+\alpha C)^2} \quad (13)$$

By solving Eq. (12), we have analyzed the effect of iris binding on the concentration in the aqueous humor. The reservoir function of iris binding was found to be effective for the order of hours and days, while that caused by the slow diffusion in the lens may affect the aqueous concentration for longer than a day. The sustained concentration profile due to iris binding depends obviously not only on the physicochemical properties of the drug but on the binding mechanism between drugs and tissues.

Conclusion

A mathematical model for analyzing ocular pharmacokinetics has been developed assuming a spherical, modified cylindrical, eye. The concentration distribution in various ocular tissues was simulated following various routes of drug delivery including topical, systemic and implantable application.

The drug concentration distribution in the eye was well described by the present model for both topical instillation and systemic administration. The diffusion coefficient and the partition coefficient in the ocular tissues were determined from the *in vitro* penetration experiment using animal models including rabbit, bovine and pig. Since the parameter values are generally influenced by the animal model used, a reliable method has to be established for the prediction of the model parameters in human from animal data. With the model parameters in human, the present ocular pharmacokinetic model can be used for evaluating the clinical performance of various ocular drug delivery systems on the basis of the animal data.

The present computational "virtual eye" approach is useful to simulate the effects of various factors not only for the delivery system design but for the physiological or individual differences of the eye. Using this computer model, we may be able to reduce significantly the clinical trials by designing a rational and effective protocol for clinical studies.

References

1) Maurice D. M., Mishima S., "Pharmacology of the Eye," ed. by Sears M. L., Springer, Berlin, 1984, pp. 19—116.
2) Ohtori A., Deguchi T., Tojo K., *J. Eye* (*Atarashii Ganka*), **13**, 1263—1266 (1996).
3) Uno K., Ohtori A., Tojo K., *J. Eye*, **11**, 607—609 (1994).
4) Kurita T., Nakagawa K., Yamashita A., Tojo K., *J. Eye*, **15**, 391—394 (1998).
5) Ohtori A., Tojo K., *J. Eye*, **10**, 589—593 (1993).
6) Tojo K., *Drug News Pers.*, **3**, 409—416 (1990).
7) Tojo K., *J. Jpn. Soc. Cataract. Res.*, **13**, 5—12 (2001).
8) Aoyagi H., Isowaki A. Tojo K., *J. Chem. Eng. Jpn.*, **35**, 450—455 (2002).
9) Tojo K., Isowaki A., *Adv. Drug Del. Rev.*, **52**, 17—24 (2001).
10) Crank J., "The Mathematics of Diffusion," 2nd ed., Oxford Univ. Press, Oxford, 1975, pp. 89—103.
11) Kaiser R. J., Maurice D. M., *Exp. Eye Res.*, **3**, 156—165 (1964).
12) Kinsey V. E., *Circulation*, **21**, 968—987 (1960).
13) Tojo K., Nakagawa K., Morita Y., Ohtori A., *Eur. J. Pharm. Biopharm.*, **47**, 99—104 (1999).
14) Tojo K., "Drug Delivery Systems," Biocom Systems Inc., Fukuoka, 2002.
15) Tojo K., Fujikawa Y., Jpn. Patent Application 2001-53035 (2001).
16) Mishima S., *Invest. Ophthalmol. Vis. Sci.*, **21**, 504—541 (1981).
17) Vieth W. R., "Membrane Systems, Analysis and Design," Chapt. 2, Oxford Univ. Press, New York, 1988.
18) Tojo K., "Mathematical Models of Transdermal and Topical Drug Delivery," Biocom Systems Inc., Fukuoka, 2003.