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Review

Ocular pharmacokinetics/pharmacodynamics

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Abstract

Delivering drugs to the front of the eye is an exceedingly complicated issue because of the numerous protective mechanisms that are present in the eye to shield the visual pathway from foreign chemicals. Design of modern ocular drug delivery systems is based on an understanding of the drug disposition pathways in the eye and the overall ocular pharmacokinetic/pharmacodynamic profile. Appropriate mathematical models to describe and predict drug disposition and response have evolved over the past twenty years and have become reasonably sophisticated. In this paper we review various ocular pharmacokinetic/pharmacodynamic models for different model drugs and drug delivery systems. © 1997 Elsevier Science B.V.

Keywords: Ocular; Ophthalmic; Pharmacokinetics; Pharmacodynamics; Compartment; Model; Drug delivery system; Rabbit; Human; Review

1. Introduction

The application of pharmacokinetic and pharmacodynamic modeling is taking on increasing importance in the drug approval process because in each phase of drug development the value of using pharmacokinetic and pharmacodynamic models is becoming increasingly evident [1]. Pharmacokinetic and pharmacodynamic modeling has been of significant interest in the field of therapeutics for more than four decades. Pharmacokinetics describes the quantitative relationship between administered dose and dosing regimen, and the observed plasma and/or tissue concentration of the drug, whereas pharmacodynamics can be defined as the quantitative relationship between observed plasma and/or tissue concentration of the active form of the drug and pharmacological effect [1,2]. These terms may also be defined as what the body does to the drug (pharmacokinetics) and what the drug does to the body (pharmacodynamics) [3].

Progress in ophthalmic pharmaceuticals during the last decade has been impressive [4,5]. Many products in this area have been or are being developed and include solutions [6], suspensions [7], ointments, gels [8,9], intravitreal injectables [10], subconjunctival injectables [11,12], iontophoretic systems [13], collagen shields [13], ocular inserts [14], etc. One of the most important tools to develop and assess these products is with accurate pharmacokinetic/pharmacodynamic models. The primary objective of a given pharmacokinetic and pharmacodynamic model must be to enhance the accuracy of estimates of the dynamic state of drug behavior in an actual clinical situation [5]. Many pharmacokinetic and pharmacodynamic models have been reported in the literature and represent varying levels of sophistication. Several excellent reviews on this subject are available [15–23]. In the present paper, pharmacokinetic and pharmacodynamic models for ophthalmic drug administration are reviewed.

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2. Pharmacokinetic models

Lee and Robinson [24] showed the numerous pathways accounting for drug loss from the precorneal area. This relatively primitive model, depicting precorneal and intraocular drug movement from topical dosing, is shown in Fig. 1 [15]. The major loss of drug is through solution drainage into the nose, which leads to systemic absorption as shown in Fig. 2 [16]. Other schematic models which show ocular penetration routes for topical ophthalmic drug administration are illustrated in Fig. 3 [25,26].

The simplest pharmacokinetic model for the eye is the single compartment model as shown in Fig. 4a [24,27]. The equation describing this process in terms of drug concentration is:

$$C = \left(\frac{FD}{V_d}\right)\left(\frac{k}{(k-K)}\right)(e^{-Kt} - e^{-kt})$$

where F is the fraction of dose absorbed, D is the dose, k and K are absorption and elimination rate constants, respectively, and V_d is the apparent volume of distribution.

It is well known that for most drugs the true absorption rate constant is much smaller than the elimination rate constant. This would normally lead to the classic 'flip-flop' pharmacokinetic model where the computed rate constant for the first portion of the pharmacokinetic profile would represent the elimination rate constant and the terminal line could be used to generate the absorption rate constant. What stops this from becoming a classic 'flip-flop' model is a kinetic scheme known as a parallel elimination pathway. In this process all rate constants describing loss of the instilled dose from the tear film are added together and the sum of these constants produces an apparent absorption rate constant that is larger than the elimination rate constant.

The model which incorporates the parallel elimination step from the precorneal area is shown in Fig. 4b [27]. The precorneal area basically consists of the tear film which covers the corneal surface with a uniform layer. In this case $F = k_{12}/(k_{12} + k_{10})$, then $k = k_{12} + k_{10}$ and $K = k_{23}$ which means that the apparent absorption rate constant into the compartment is the summation of the elimination rate constants from the precorneal area. The equation is:

$$C = \left(\frac{Dk_{12}}{V_d(k_{12} + k_{10} - k_{23})}\right)(e^{-k_{23}t} - e^{-(k_{12}+k_{10})t})$$

A two-compartment model which was used by Himmelstein and coworkers is shown in Fig. 5a [28]. The first compartment represents the tears and the second is the aqueous humor. The flow balance for pilocarpine in tear fluid at time zero was shown by the following equation.

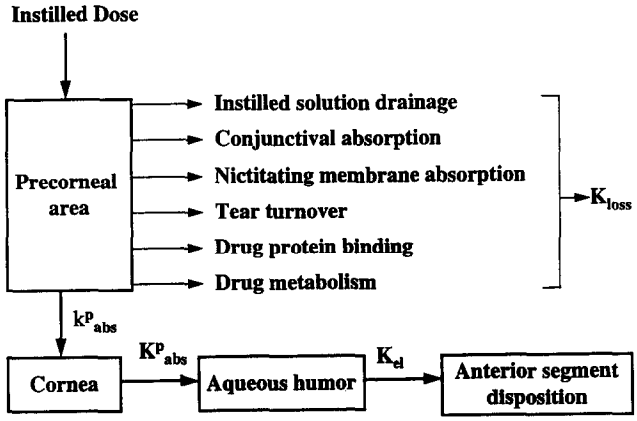

Fig. 1. Model depicting precorneal and intraocular drug movement from topical dosing.

$$\frac{dV_T}{dt} = Q_T - [Q_T + K(V_T - V_0)]$$

where V_T is the total volume in the precorneal area at any given time, T; Q_T is the normal tear production rate; K is a proportionality constant, that is a function of the instilled drop size, V_D; and V_0 is the normal resident tear volume.

By assuming that the densities of the tear fluid and drug solution are that of water, and also assuming that the amount of pilocarpine diffusing through the cornea does not significantly affect the tear fluid volume the model can be used. It is possible to solve this differential equation by noting that at the time of instillation, the total volume in the eye is equal to the volume of tears normally present plus the size of the instilled drop. Therefore the total volume of the eye fluid as a function of time is represented by the equation:

$$V_T = V_D e^{-Kt} + V_0$$

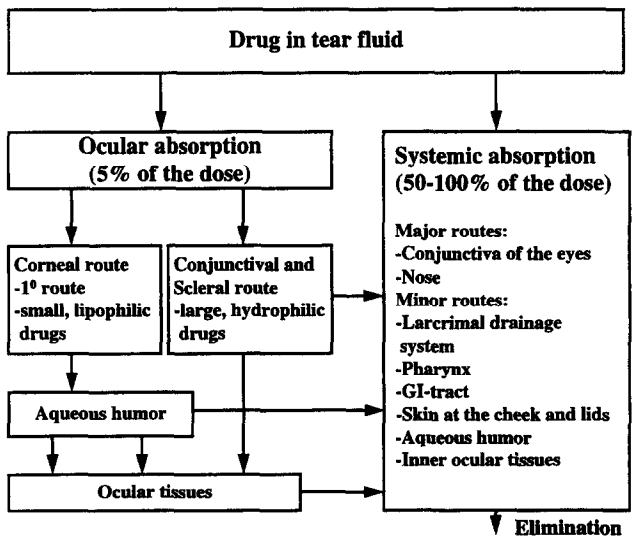

Fig. 2. Schematic diagram of ocular absorption.

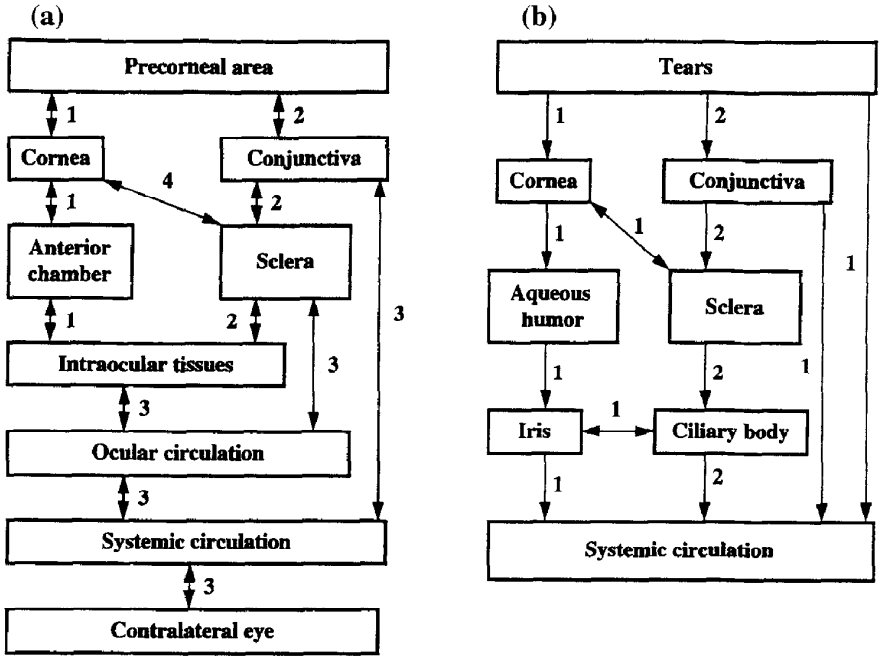

Fig. 3. Ocular penetration routes for topical ophthalmic drugs administration, (a) 1, transcorneal pathway; 2, noncorneal pathway; 3, systemic return pathway; 4, lateral diffusion. (b) 1, corneal route; 2, conjunctival/scleral route.

The mass balance in the tear fluid is expressed mathematically as:

$$\frac{dV_T C_T}{dt} = 0 - [Q_T + K(V_T - V_0)]C_T - \left(\frac{K_D A}{L}\right)(C_T - C_{AH})$$

where C_T is the concentration of pilocarpine in the tear fluid; K_D is the permeability coefficient; A is the cornea area; L is corneal thickness and C_{AH} is the concentration of pilocarpine in aqueous humor.

Then taking the indicated derivative and substituting for the value of V_T, a simplified relationship is shown as:

$$\frac{dC_T}{dt} = \frac{\left[-Q_T C_t - \left(\frac{K_D A}{L}\right)(C_T - C_{AH})\right]}{(V_D e^{-Kt} + V_0)}$$

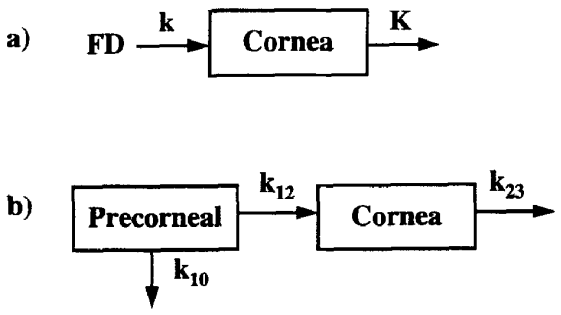

Fig. 4. (a) Schematic of one-compartment model, (b) Schematic of two-compartment model consisting of precorneal area and cornea.

This assumes, there is no appreciable loss to the conjunctiva and that diffusion into the aqueous humor is linear. A similar mass balance for the aqueous humor compartment is also shown as:

$$V_{AH}\left(\frac{dC_{AH}}{dt}\right) = \left(\frac{K_D A}{L}\right)(C_T - C_{AH}) - K_{el} C_{AH}$$

where V_{AH} is the aqueous humor volume and K_{el} is the lumped first-order clearance parameter from the aqueous humor.

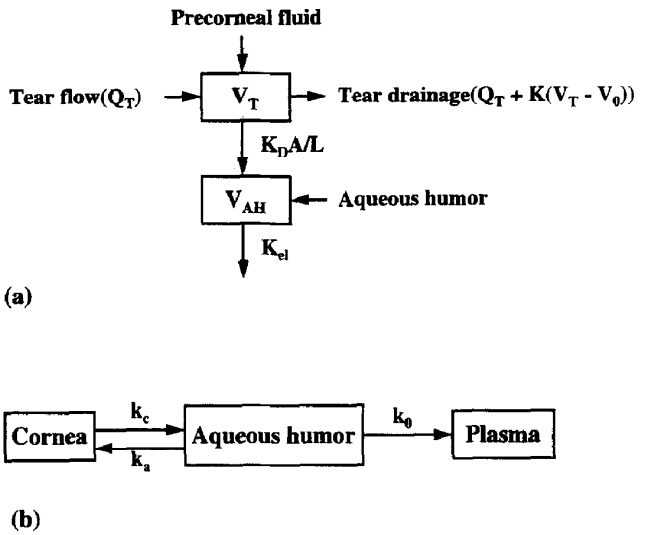

Fig. 5. (a) Schematic of two-compartment model consisting of precorneal area and aqueous humor, (b) Schematic of three-compartment model consisting of cornea, aqueous humor and plasma.

Two deficiencies of this model have been discussed [24]: (1) the cornea is considered as a homogeneous membrane, with no apparent role in the disposition process, and (2) all precorneal drug disposition constants are lumped into one large rate constant. Another model considering the anterior segment of the eye as two separate compartments, the cornea and aqueous humor [17,29] is illustrated in Fig. 5b. The assumptions are:

1. Loss of drug to the tears from the cornea, i.e. back diffusion, is negligible;
2. Entry into the aqueous humor from the tears other than through the cornea is negligible;
3. Exchange between the cornea and blood at the limbus are important;
4. Exchange of the aqueous humor with the posterior reservoir is negligible.

From Fig. 5b, k_c and k_a are transfer coefficients between the cornea and aqueous humor, and k_0 is the loss coefficient from the aqueous to the plasma. The concentration of a drug in the aqueous humor will obey the equation:

$$C_a = C_A[e^{-A(t-t_0)} - e^{-B(t-t_0)}]$$

where A and B are the elimination and absorption coefficients defined as:

$$A + B = k_c + k_a + k_0 \qquad AB = k_c k_0$$

and t_0 is the lag time.

A three-compartment model, representing ophthalmic pharmacokinetics of topically applied aqueous eyedrops, is shown in Fig. 6a [30]. Since this simplified model is not a complete representation for pilocarpine disposition in ocular tissues, it is useful to describe limited data. Another three-compartment model has been developed to describe the pharmacokinetics of systemic absorption of various peptide drugs such as insulin, glucagon, luteinizing hormone-releasing hormone (LHRH), and leu-enkephalin through ocular routes [31]. The major compartments are the precorneal area, the peripheral regions, and the systemic circulation (Fig. 6b). Most of the drug is absorbed into the systemic circulation via the conjunctival membrane and the nasolacrimal drainage system. Finally, the drug is absorbed into the blood circulation and distributed to other parts of the body (peripheral compartment), or metabolized and excreted. The excellent agreement between model outputs and experimental data was obtained by fitting only one of five pharmacokinetic parameters, i.e. the transport constant between the precorneal compartment and the bloodstream compartment (k_{12}) with various concentrations of peptide solution while keeping the other parameters (k_{pc}, k_{23}, k_{32}, k_{el}) constant.

Makoid and Robinson [27] used a four-compartment model, shown in Fig. 7, to fit the data for both cornea and aqueous humor obtained after topical administration of pilocarpine to the Albino rabbit eye. The mathematical derivation of this pharmacokinetic model was also reported. However, the model does not distinguish specific roles for the corneal epithelium and corneal stroma [32]. However, the results demonstrated that the corneal epithelium acted as a barrier to drug penetration and as a reservoir for pilocarpine, and the corneal stroma and endothelium are kinetically homogeneous with aqueous humor. The model which corrected this deficiency is shown in Fig. 8a [24]. The major assumptions for this model are:

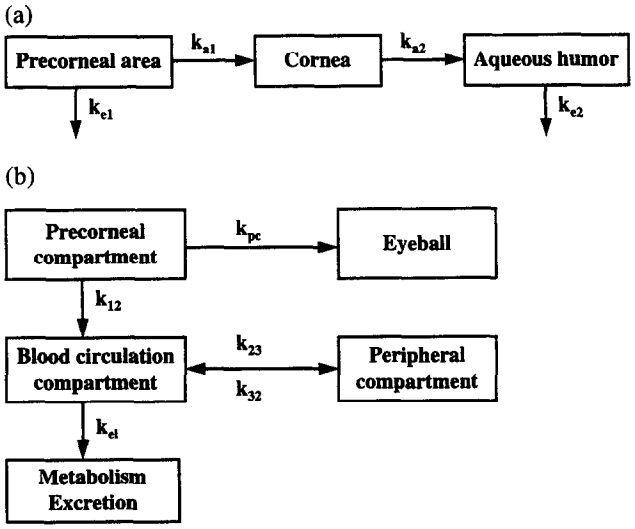

Fig. 6. (a) Schematic of three-compartment model consisting of precorneal area, cornea and aqueous humor; in which k_{a1} and k_{a2} represent the apparent absorption constants into the cornea and aqueous humor, respectively; k_{e1} represents elimination of drug from the precorneal area through drainage and nonproductive absorption; and k_{e2} represents elimination of drug from the aqueous humor, (b) Schematic of three-compartment model for describing the pharmacokinetic of systemic absorption of peptide drugs.

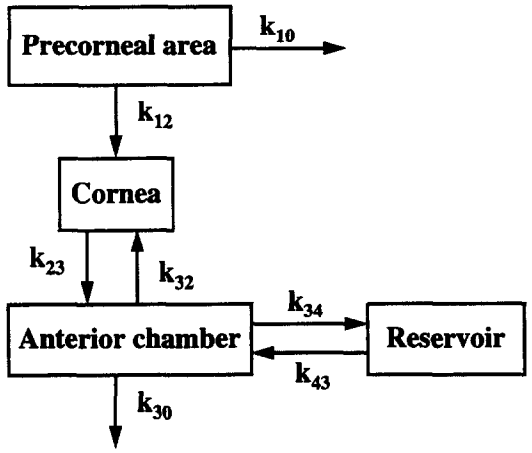

Fig. 7. Schematic of four-compartment model in which anterior chamber excludes lens and cornea, reservoir consists of the lens and vitreous, and k_{ij} is the rate constant for drug transport into and out of the various area.

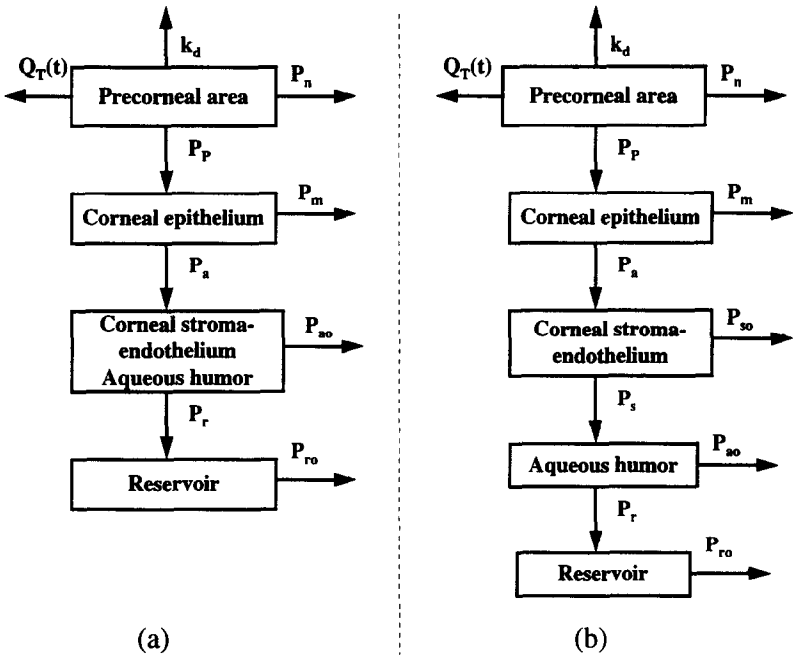

Fig. 8. (a) Schematic of four-compartment model which consider corneal stroma-endothelium and aqueous humor as one compartment, (b) Schematic of five-compartment model which consider corneal stroma-endothelium and aqueous humor are separated into two compartments.

1. Instantaneous and complete mixing of instilled drug solution and tears;
2. Pilocarpine metabolism in the tear fluid is negligible;
3. The tissues comprising the compartments are homogeneous;
4. The iris, ciliary body, lens and vitreous humor constitute the reservoir.

For fluorometholone [33], an oil soluble drug, the corneal stroma-endothelium and aqueous humor are logically separated as illustrated in Fig. 8b. The model parameters are shown in Table 1, and more detail about the mathematical equations are described in the original article.

Eller et al. [34] considered a pharmacokinetic model (Fig. 9a) in which a constant rate of administered drug is made to the corneal surface from a reservoir and then passively transported across the cornea into the aqueous humor. From the aqueous humor, drug may reversibly distribute to adjacent tissues, particularly the iris/ciliary body, or be eliminated from the eye into the body via the aqueous humor. The assumption of this model is that the cornea acts as a net barrier to absorption and not as a compartment, since a quantity of drugs which resides in the cornea during the infusion time period is constant. This model was used for the lipophilic drugs: ethoxolamide [34], ibuprofen and ibufenac [35].

A similar model was modified by Rao et al. [35] and used for hydroxyethoxy analogs of ibuprofen and ibufenac. This model represents the epithelium and endothelium as barriers and the stroma as a separate compartment (Fig. 9b).

The figure of an expanded pharmacokinetic model for the intraocular disposition of pilocarpine is shown in Fig. 10 [36,37]. This model depicts the eye as consisting of five major compartments (precorneal area, cornea, aqueous humor, iris-ciliary body and lens) and assumes that drug movement between compartments is a reversible process. Moreover, drug elimination from the eye, i.e. loading to the systemic circulation, was assumed to occur only from the aqueous humor and iris-ciliary body.

Table 1
Parameters of the models described in Fig. 8

Parameter	Coefficient associated with
P_p	Transfer of drug between precorneal area and corneal epithelium
P_n	Nonproductive loss
K_d	Drainage
$Q_T(t)$	Tear flow
P_a	(a)Transfer of drug between corneal epithelium and corneal stroma-endothelium-aqueous humor (b) Transfer of drug between corneal epithelium and corneal stroma-endothelium
P_m	Drug loss via metabolism in or lateral diffusion from corneal epithelium
P_{ao}	Drug elimination from aqueous humor
P_r	(a) Transfer of drug between corneal stroma-endothelium-aqueous humor and reservoir(b) Transfer of drug between aqueous humor and reservoir
P_{ro}	Drug elimination from reservoir
P_s	Transfer of drug between corneal stroma-endothelium and aqueous humor
P_{so}	Drug elimination from corneal stroma-endothelium

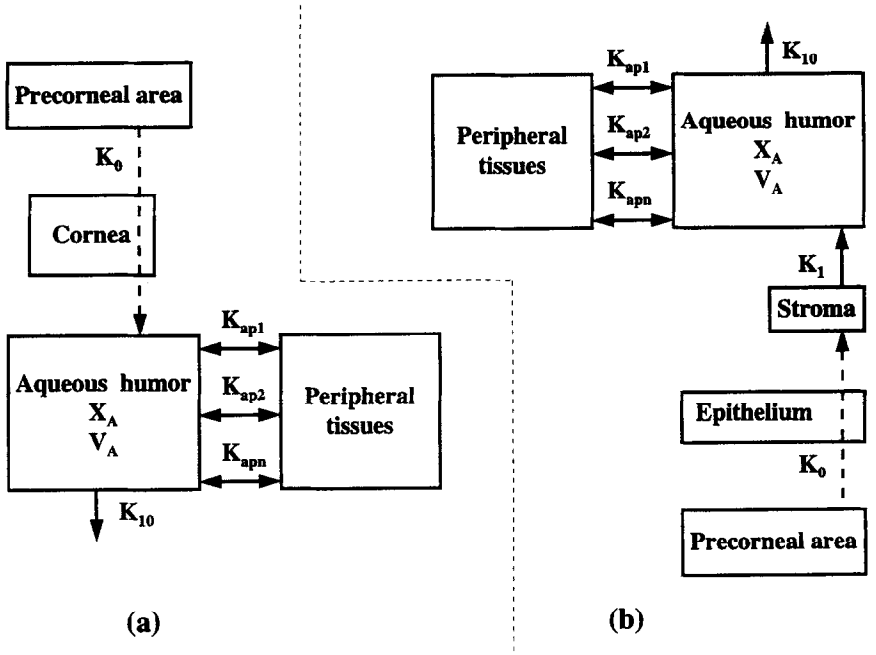

Fig. 9. (a) The pharmacokinetic model which used for lipophilic drug, (b)The pharmacokinetic model which used for ibufenac and ibuprofen analogs in which K_0 is the apparent constant (zero-order) input rate from the precorneal area to the aqueous humor and to the stroma for Fig. 9(a) and (b), respectively, K_1 represents transfer of drug across the endothelium into aqueous humor, K_{10} is the elimination rate constant out of aqueous humor by aqueous humor turnover and uptake by vessels, and $K_{(ap1\ldots n)}$ represent the first order transfer rate constants from aqueous humor to peripheral tissues.

A multi-compartment model (Fig. 11) was developed to simulate the pharmacokinetic data obtained from injection of cyclosporine into the anterior chamber [38]. The model described cyclosporine concentration in various ocular tissues and fluids by providing separate compartments for each of the aqueous humor, conjunctiva, sclera, lens and iris-ciliary body, and two subcompartments for cornea (lipophilic cellular layers and hydrophilic stroma). The concentration within each compartment was assumed uniform. In addition, potential pathways for the elimination of cyclosporine from the aqueous humor to the vitreous, and from the cornea, conjunctiva and sclera to the systemic circulation were not included in this model.

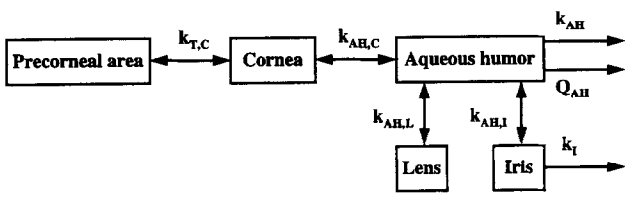

Fig. 10. Five-compartment model which assumed that drug movement between compartments are reversible process and drug elimination from the eye occurs only from the aqueous humor and iris-ciliary body;in which Q_{AH} represents aqueous humor turnover, k_{AH} is the facilitated drainage due to the pharmacologic action of pilocarpine on outflow, k_I is the drug loss from the iris-ciliary body, attributed to intraocular venous circulation, $k_{x,y}$ is the transfer rate between compartment x and y.

There are some reports which try to explain the pharmacokinetics of drugs in the posterior segment of the eye. In the case of topical ophthalmic drug administration, the possibility of scleral absorption was evaluated by Ahmed et al. [39] for the lipophilic drugs: propanolol, timolol, nadolol and penbutolol and the hydrophilic drugs: sucrose and inulin. The results showed that resistance to penetrability for all compounds tested in the outer layer of the sclera is much less than the corneal epithelium.The cornea offered

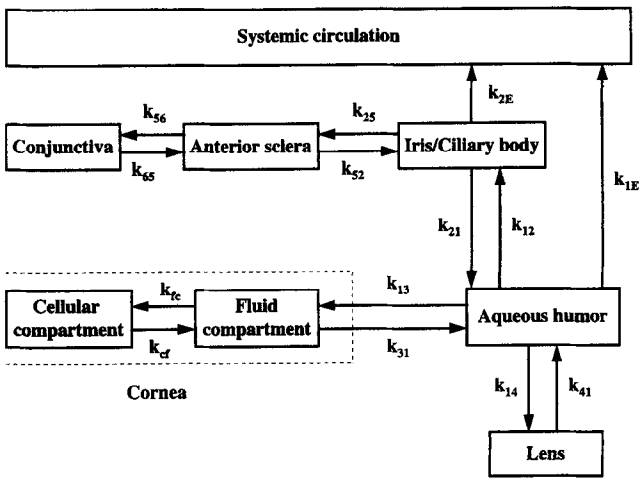

Fig. 11. Schematic of multi-compartment model using for cyclosporine pharmacokinetics in the eye.

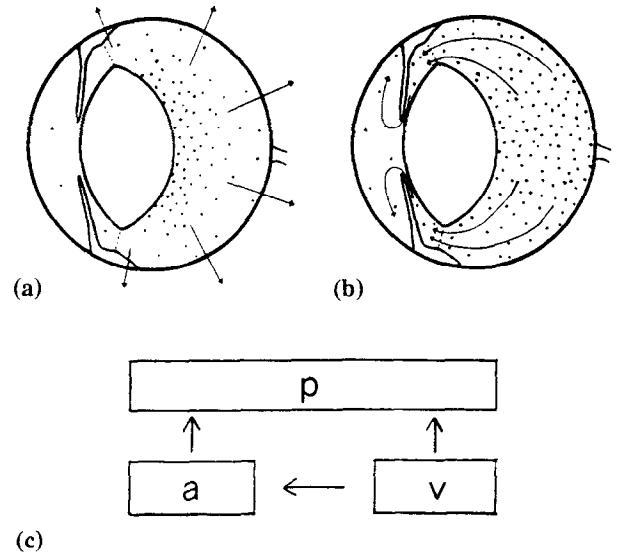

Fig. 12. Exit pathways from the vitreous body, (a) across the retinal surface and (b) via drainage out of the anterior chamber; (c) represents the compartments concerned: a, anterior chamber; p, plasma; v, vitreous.

substantially more resistance to inulin (a hydrophilic drug) than did the conjunctiva, i.e. hydrophilic drugs penetrate the sclera more rapidly than lipophilic drugs [25]. However, the cornea and conjunctiva offered comparable resistance against timolol (a lipophilic drug) [39]. In addition, Schoenwald et al. [40] have shown that the conjunctival/scleral route of entry produced higher iris/ciliary body concentrations for methazolamide analogs and 6-carboxyfluorescein, but not for rhodamine B (a lipophilic dye). The explanation of this phenomena is that hydrophilic drug is absorbed into the ciliary body through vessel uptake into the sclera and deposit within the ciliary body, while lipophilic drug penetration across the cornea diffuses through the pupil against aqueous flow to enter the posterior chamber.

Drugs which are introduced into the vitreous humor by intravitreal injection will spread through the vitreous humor and into the anterior chamber at the same rate that they diffuse in free solution [17]. Two pathways of exit from the vitreous chamber were predicted (Fig. 12): Through the anterior hyaloid membrane into the posterior chamber and out of the eye with aqueous drainage, and directly across the retinal surface. The loss of drug from the vitreous chamber can be characterized by assuming that diffusion across the iris is negligible.

$$k_v = \left(\frac{f}{V_v}\right)\left(\frac{C_a}{C_v}\right)$$

In which k_v is the transfer coefficient, f is the aqueous humor flow rate, V_v is the volume of vitreous humor, C_a and C_v are drug concentrations in aqueous humor and vitreous humor, respectively.

A more recent study uses computer simulation to evaluate the in vivo/in vitro pharmacokinetic correlation of dexamethasone sodium following intravitreal injection of m-sulfobenzoate in rabbits [41]. The mathematical model was developed based on Fick's second law of diffusion by assuming that the vitreous body was a cylinder with three major pathways for elimination: The posterior aqueous chamber, the retina/choroid/scleral membrane and the lens (Fig. 13). Results showed that the major route of elimination of the drug was through the posterior aqueous humor because of an absence of a barrier membrane between the boundaries. By using the ratio of the product of the diffusion coefficient and the effective area for the posterior chamber, the retina/choroid/scleral membrane and the lens (50:4:0.1), the authors concluded that most hydrophilic drugs, following intravitreal injection, are eliminated via the annular gap between the lens and the ciliary body, and the retina/choroid/scleral membrane may act as a major route of elimination for lipophilic drugs.

3. The rabbit model

Since many anatomical and physiological factors of the rabbit and human eye are similar (Table 2), and the animal is relatively inexpensive and easy to handle, rabbits have been used as an animal model in most ocular experiments. However, some differences between the rabbit and human eye could affect drug kinetics. For example: The blinking rate in humans (6–15 times/min) is higher than in rabbits (4–5 times/h) and could allow the penetration of drug through the cornea of the rabbits more than that of human because of high drug

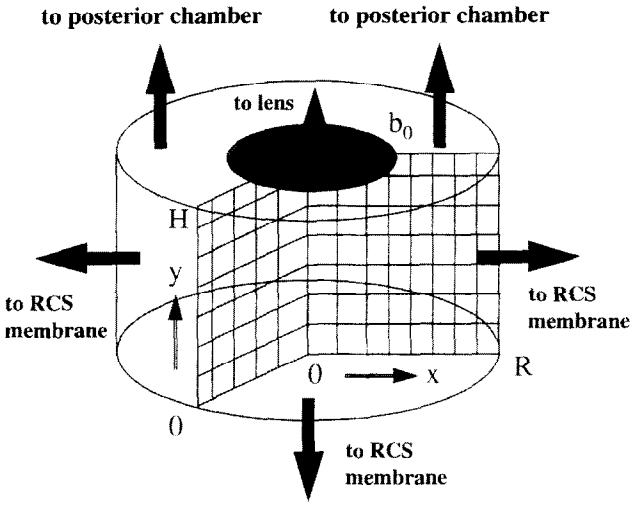

Fig. 13. Cylindrical model of the vitreous body of rabbits for analyzing the pharmacokinetics of intravitreal drug delivery; the surface of the vitreous body is divided into three areas of elimination pathways: the posterior aqueous chamber, the RCS membrane and the lens.

Table 2
Comparison of pharmacokinetic factors between rabbit and human eye [5,15,17,20,21,23,42–52]

Pharmacokinetic factors	Rabbit	Human
Tear volume (μl)	5–10	7–30[a]
Tear turn over rate (μl/min)	0.5–0.8	0.5–2.2
Spontaneous blinking rate[b]	4–5 times/h	6–15 times/min
Lacrimal punctum/puncta	1	2
Bowman's membrane	Partially absent	Present
Nictitating membrane[c]	Present	Absent
pH of lacrimal fluids	7.3–7.7	7.3–7.7
Turnover rate of lacrimal fluids (% min^{-1})	7	16
Larcrimal volume (μl)	7.5	7.0
Buffering capacity of lacrimal fluids	Poor	Poor
Milliosmolarity of tear (mOsm/l)	305	305
Initial drainage rate constant (min^{-1})	0.55	1.6
Corneal thickness (mm)	0.35–0.45	0.52–0.54
Corneal diameter (mm)	15	11–12
Corneal surface area (cm^2)	1.5–2.0	1.04
pH of aqueous humor	8.2	7.1–7.3
Aqueous humor volume (ml)	0.25–0.3	0.1–0.25
Aqueous humor turnover rate (μl/min)	3–4.7	2–3
Protein content of tear (%)	0.5	0.7
Protein content of aqueous humor (mg/ml)	0.55	30
Ratio of conjunctival surface and corneal surface	9	17

[a] Range depending on blinking rate and conjunctival sac volume.
[b] Occurs during normal waking hours without apparent external stimuli.
[c] Significance of nictitating membrane from precorneal area is small relative to overall loss rate.

concentration at the corneal surface [44,53] and low drug solution drainage in the rabbit eye [23]. Moreover, rabbits appear to be less sensitive than humans to moderate increases of vehicle viscosity, especially for a suspension-type paraffin ointment which gave better results in humans, probably because shear effects facilitate drug release [45]. Therefore, clinical trials in humans must always be used to confirm data from rabbits.

4. Pharmacodynamic models

Ophthalmic pharmacological responses such as miosis and mydriasis [45,54–56], light reflex inhibition [12,57] and intraocular pressure [58–62] have been used as parameters for investigating the effectiveness of ocular drug administration.

The miotic response of the eye was used to show the effect of cholinergic drugs [17,18,63,64]. The general equation, shows a linear relationship as:

$$m_r = -k_{dm}t + m_0$$

where m_r describes the miotic response at time t, m_0 is a value for the theoretical miosis at time $t = 0$, and k_{dm} is the decrease of the miosis coefficient, i.e. pupil response coefficient, which is equivalent to the slope of the curve determined by linear regression [64].

By using the curve plotted between miotic response versus time, one can also calculate d_{max} and M_{max}; in which d_{max} is the maximal duration of the miotic effect (the time axis intercept), and M_{max} is the maximal miotic effect at t_{max}.

Another mathematical model for miotic response and mydriasis response of the pupil from pilocarpine and carbachol, respectively [17,18] was reviewed as follow:

$$R_1 = \frac{R}{(R_{max} - R)}$$

For miotic response, $R = D_0 - D$ and $R_{max} = D_0 - D_{min}$, whereas mydriatic response, $R = D - D_0$ and $R_{max} = D_{max} - D_0$. The maximum and minimum diameter of the pupil was also defined as 8.5 and 1 mm, respectively. D_0 is a pupil diameter before use of the drug and D is a pupil diameter at time of administration. Therefore, the response parameter can be rewritten as:

For miotic response, $R_1 = \frac{(D_0 - D)}{(D - 1)}$

For mydriatic response, $R_1 = \frac{(D - D_0)}{(8.5 - D)}$

Plots of response and drug concentrations on a logarithmic scale, show that a correlation slope of the regression line is very close to unity. Thus the relation can be expressed as:

$$R_1 = \frac{R}{(R_{max} - R)} = q'C$$

where C is the drug concentration and q' is the proportionality constant.

The linearized response, R_1, may be calculated for pupil diameter at various time intervals after instillation and plotted against time after instillation. These plots were expressed as similar curves for pilocarpine and tropicamide as shown in Fig. 14 [6,18]. The following equation describe the curves.

$$R_1 = R_L(e^{-A(t - t_0)} - e^{-B(t - t_0)})$$

where R_L is the value of R_1 at the intercept of the A and B components of the curves, t_0 is the lag time between instillation and the first response, A and B are apparent elimination and absorption rate constants which are related to the rate of drug release from the cornea into the anterior chamber and to the rate of loss from the anterior chamber.

Chien and co-workers [55] showed another mathematic equation (an E_{max} model) for mydriatic activity

of phenylephrine and its prodrug. The relation between drug concentration in aqueous humor corresponding to the mydriatic response was predicted by a Michaelis–Menten relationship.

$$\Delta E(t) = \frac{(E_{max} C_a(t))}{(K'_m + C_a(t))}$$

where $\Delta E(t)$ is the mydriatic response at time t; ΔE_{max} is the maximum mydriatic response of the drug; K'_m is the drug concentration in aqueous humor required to produce half of the maximum mydriatic response ($1/2\Delta E_{max}$), which is equal to the drug concentration in iris required to produce $1/2\Delta E_{max}$ divided by the partition coefficient of the drug between the iris and the aqueous humor; $C_a(t)$ is drug concentration in the aqueous humor at time t, which can be calculated by the equation:

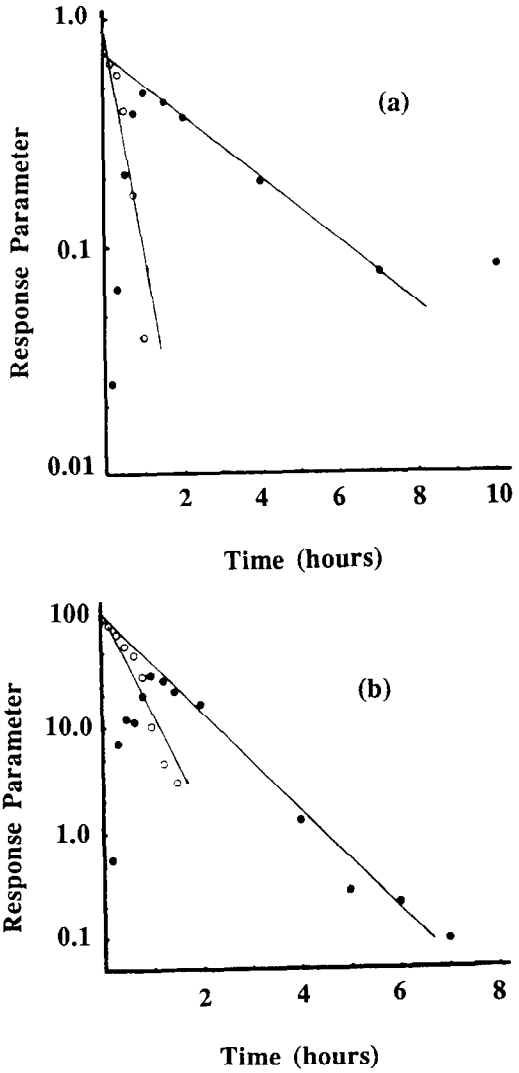

Fig. 14. (a) Time course of the response parameter after instillation of 0.5% pilocarpine solution, (b) Time course of the response parameter after instillation of 0.4% tropicamide solution; two line for calculating the absorption and elimination rate constants.

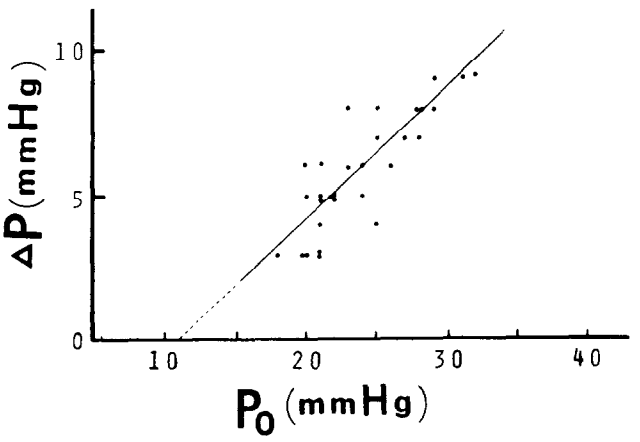

Fig. 15. Relationship between IOP-reduction and the baseline IOP 2 h after instillation of 1% bupranolol solution.

$$C_a(t) = M(e^{-A_1(t-t_0)} - e^{-B_1(t-t_0)})$$

where M is the value of C_a at the interception of the A_1 and B_1 components of the curve and depends on the initial dose of the drug, the fraction absorbed, and the kinetic parameters, A_1 and B_1.

Since mydriatic tolerance was developed by phenylephrine, K'_m was changed and calculated at a set time interval by the following equation:

$$K'_m(t) = \left[\left(\frac{\Delta E_{max}}{\Delta E(t)}\right) - 1\right] C_a(t)$$

Another biological response which can be assessed from a kinetic point of view is intraocular pressure (IOP) reduction. One can use this respose compared with the miotic effect for investigating ophthalmic preparations containings cholinergic drugs [8]. By plotting IOP versus time, the pharmacodynamic coefficients of the IOP response, area under the curve (AUC), t_{max}, I_{max}, and $\Delta 1/2$, can be calculated. I_{max} is determined as the maximal IOP reduction at t_{max}. $\Delta 1/2$ is a value calculated from the width of the IOP response at half of the height. $\Delta 1/2$ values shows the duration of IOP-reduction response [64].

An E_{max} model can be modified for IOP-reduction response as described by the same equation for mydriatic response [65]:

$$\Delta E = E - E_0 = \frac{(E_{max} C)}{(EC_{50} + C)}$$

In which ΔE is a corresponding IOP-reduction effect; E_0 is the baseline IOP, and the aqueous humor concentration (C) that produced 50% of the maximum effect (E_{max}) is EC_{50}.

The expression of IOP-reduction in different ways was reviewed by using the relationship between the drug-induced IOP reduction and the control level of the IOP [18]. This relationship showed a linear relation (Fig. 15) which can be represented by:

$$\left[\frac{\Delta P_i}{(P_i - 9)}\right] = X$$

where ΔP_i is the IOP-reduction, P_i is the control level IOP, and X is the value which varied with changes in the drug concentration.

The results showed that the slope of the relation increased with increasing concentration of the drug without significantly altering the intercept. Therefore, X can be used to express the drug effect on the IOP response.

Zimmer [64] used this relative enhancement to compare the pharmacodynamic effects (miosis and IOP-reduction) between aqueous solutions and nanoparticle preparations with different doses of pilocarpine. This value is useful to develop an appropriate drug delivery preparation. The relative enhancement was calculated by the equation:

$$\text{Relative enhancement}(\%) = \left[\frac{PD(NP)}{PD(AS)}\right] \times 100$$

In the case of light reflex inhibition (LRI) which is the amplitude of reflex responses to 0.5 s light flashes can be calculated by equation:

$$\text{LRI}(\%) = \left[\frac{((RAU_t - RAT_t) - (RAU_0 - RAT_0))}{(RAU_t)}\right] \times 100$$

where RAT and RAU are the reflex amplitude of treated eye, and untreated eye, respectively (each at time t or time $t = 0$).

Using the LRI to investigate the relative bioavailability of pilocarpine, the results showed that it was inhibited in parallel with miosis [12].

5. Models derived from drug delivery

In order to improve the development of drug delivery devices, a five-compartment model was developed [66], which can be used to study the mechanisms involved in transcorneal permeation. The five compartments consist of the tear film, epithelium, stroma, endothelium and aqueous humor which were assumed to be perfectly mixed and adequately represented by plane sheet barriers of known physical thickness with constant surface area. In this model, four routes of drug loss: lacrimal drainage, conjunctiva absorption, aqueous drainage and iris-ciliary body absorption, were included as shown in Fig. 16. By using simple mass balances and flux relationships, the investigators could convert the compartment model to a series of mathematical expressions. More details about the mathematical equations and assumptions, can be found in the published paper. The model was validated by using the experimental in vivo data compared with predicted aqueous humor drug concentrations from the model. The results showed an excellent correlation and it was also possible

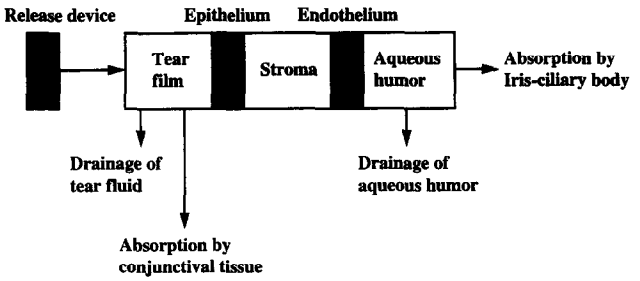

Fig. 16. Schematic of five-compartment model which was developed for drug delivery devices (composes of tear film, epithelium, stroma, endothelium and aqueous humor).

to predict the amount of drug lost through each of the four elimination pathways. Modification of this model by adding the compartments for the conjunctiva and the iris-ciliary body was done to compare pharmacokinetic differences between ocular inserts and eyedrops of timolol [67]. Moreover, two other modifications to the model were added to account for conditions that occured as a result of the experimental methods which are:

1. A reduction in tear flow, caused by the anesthetic during the period devices were sutured in place,
2. The unexpected corneal epithelial abrasion that occured as a result of contact between the cornea and the suture.

The results indicated that the model parameters required to predict ocular drug levels following administration via a controlled release ocular insert are different from eyedrop administration.

A multi-compartments model was constructed to describe ophthalmic drug delivery with nanoparticle preparations by expanded the three-compartment model (Fig. 6a), and is shown as Fig. 17 [64]. This model was constructed from the data which showed that nanoparticle preparations might be able to create a precorneal depot [68]. This can enhance drug penetration directly to its site of action, the trabecular meshwork [64], through the scleral or non-corneal pathway [25,69].

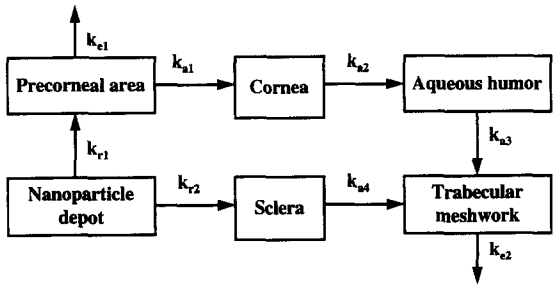

Fig. 17. Schematic of multi-compartment model describing ophthalmic drug delivery with nanoparticles in which k_a and k_e are absorption and elimination constants; k_{r1} is the pilocarpine release constant from the nanoparticles into the tear film; k_{r2} shows the drug release into the scleral tissue.

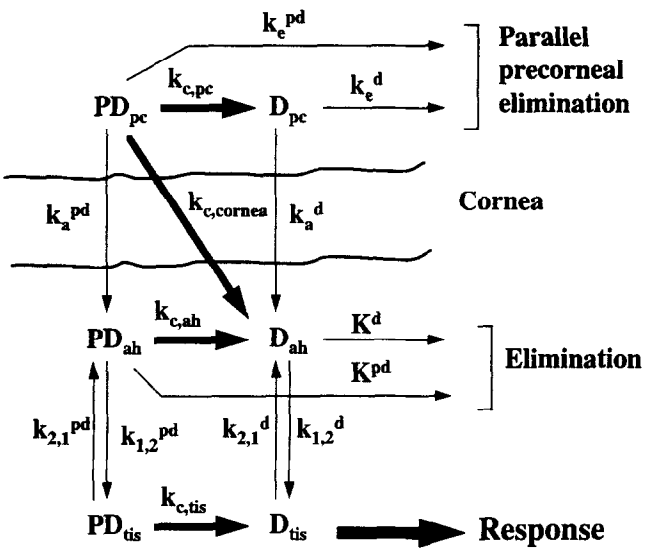

Fig. 18. Schematic diagram of the ocular disposition of prodrug (PD, pd) and drug (D, d) following the topical instillation of a prodrug (pc, precorneal; ah, aqueous humor; tis, tissue; k_c, prodrug-to-drug conversion rate constant; k_e, rate constant of parallel precorneal elimination; k_a, rate constant of productive corneal absorption; K, rate constant of drug elimination; →, mass transfer pathway; ⇒, enzymatic or chemical reaction pathway.

A four-compartment model can be assumed to describe the pharmacokinetics of a prodrug following topical instillation (Fig. 18). The objective of using a prodrug is to get a more intense response or a response of extended duration which can be dose-saving or can lead to more favorable absorption, distribution, or elimination [70]. From Fig. 18, an optimum prodrug can be achieved by various design considerations. For example:

Improved physicochemical properties resulting in a greater extent of absorption which mean that corneal membrane permeability of the prodrug would be greater than that of the drug alone ($K_a^{pd} > K_a^d$).

A prodrug designed in such a way that its properties result in a decreased elimination rate constant ($K^{pd} < K_a^d$) which would extend the duration of drug effect.

A prodrug designed in such a way that its distribution into receptor-containing tissues is more favorable and would result in a lower dose demand.

Grass and Lee [71] described and developed methods for constructing a pharmacokinetic model which can be used to predict the effect of increasing drug retention in the conjunctival sac, and varying the drug release rate from a controlled drug delivery device, on the ratio of drug concentration in aqueous humor and plasma after topical dosing in rabbits. The pharmacokinetic model simulating timolol kinetics in both aqueous humor and plasma after topical dosing in the eye was constructed in separate segments and then linked in a stepwise manner. Validation of this model in each segment was done by using previous published data on intraveneous, nasal, and ocular dosing. From this model, the investigators concluded that a model may be useful in designing drug delivery strategies to improve the safety of topical eye medications by minimizing systemic absorption and maximizing drug delivery to ocular tissues. Moreover it may be possible to scale the data obtained in rabbits to humans.

6. Conclusion

The pharmacokinetic and pharmacodynamic data of ophthalmic drugs can be very useful to evaluate the bioavailability of drugs in ocular tissues. Therefore, pharmacokinetic and pharmacodyamic models which are appropriate for specific cases must be chosen and developed. These models should be simple enough to express in mathematical terms, and also incorporate all the important pharmacokinetic factors of the process in which the data produced by the models can conform to known data.

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