Chapter 6
Pharmacokinetics and Pharmacodynamics of Ocular Drugs

Vivek S. Dave and Suraj G. Bhansali

Abstract This chapter aims to provide the readers a systematic overview of the pharmacokinetics and pharmacodynamics of the drugs intended for ophthalmic use. The concepts of ocular pharmacokinetics and pharmacodynamics are briefly discussed in the introduction. The chapter begins with a discussion on the common anatomical and physiological factors such as blood–ocular and tear fluid–corneal barriers, as well as anterior segment drug loss; and the challenges these factor pose in describing ocular pharmacokinetics and pharmacodynamics. The biopharmaceutics of the ocular drugs describes common pathways of ocular drug absorption. Further, commonly employed routes of administration for ocular drugs are discussed with respect to the choice of the route, properties of the drug, the nature of the ocular disease, the targeted ocular tissue, and the pharmacokinetic behavior of the drugs administered through the route. The pharmacokinetic–pharmacodynamic models that describe the fate of ocular drugs are further reviewed. Finally, recent advances and current trends in understanding of the pharmacokinetics/pharmacodynamics of ocular drugs are discussed based on the reported findings of the scientific and medical community.

Keywords Ocular pharmacokinetics • Ocular pharmacodynamics • Biopharmaceutics • Ocular routes • Compartment models

6.1 Introduction

The treatment of ocular diseases by the means of drugs mainly involves optimizing the bioavailability of drugs in the ocular tissues. Thus, achieving and maintaining an optimum drug concentration at a specific ocular site requires a clear understanding of

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the anatomy/physiology of the eye, pathophysiology of the ocular disease, as well as the pharmacokinetics and pharmacodynamics of the drug. *Ocular pharmacokinetics* has been defined earlier as the study of mechanisms and extent of drug absorption, distribution, metabolism, and excretion in the eye [1]. The pharmacokinetics of a drug is influenced by several factors including patient-specific factors (age, gender, race, genetic makeup, disease condition, etc.) and drug-specific factors [2]. Ocular pharmacodynamics has been defined as the study of the biochemical and physiological effects of a drug in the eye, including mechanisms of action; and ocular toxicology has been defined as the study of unwanted, mild, or severe adverse effects of drugs on one or more ocular tissues [1]. Generally, there is a correlation between concentrations of a drug at the site of action and its effects, which can be driven by binding with receptors. Hence the pharmacodynamics of a drug is influenced by receptor density in addition to its pharmacokinetics. This chapter will provide a brief overview of the common challenges in ocular pharmacokinetics/pharmacodynamics, typical biopharmaceutical fate of ocular drugs, pharmacokinetic models used in ocular systems, and modern approaches utilized in studying ocular pharmacokinetics and pharmacodynamics.

6.2 Challenges in Ocular Pharmacokinetics and Pharmacodynamics

Characterization of pharmacokinetics and pharmacodynamics of ocular drugs is challenging due to the existence of anatomical and physiological barriers that are unique to ocular system. The main factors that influence the ocular bioavailability of drugs (e.g., instilled dose, tear turnover, drug absorption, metabolism, elimination, etc.) are shown in Fig. 6.1. Similarly, the typical fate of drugs delivered via ophthalmic routes is briefly represented in Fig. 6.2. These factors influencing the availability of the drugs to the ocular tissues can be broadly classified into three categories.

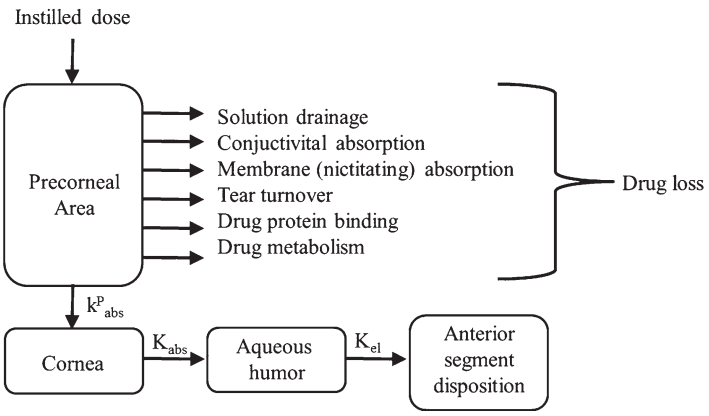

Fig. 6.1 Precorneal and intraocular drug movement following topical administration (Adapted from [3])

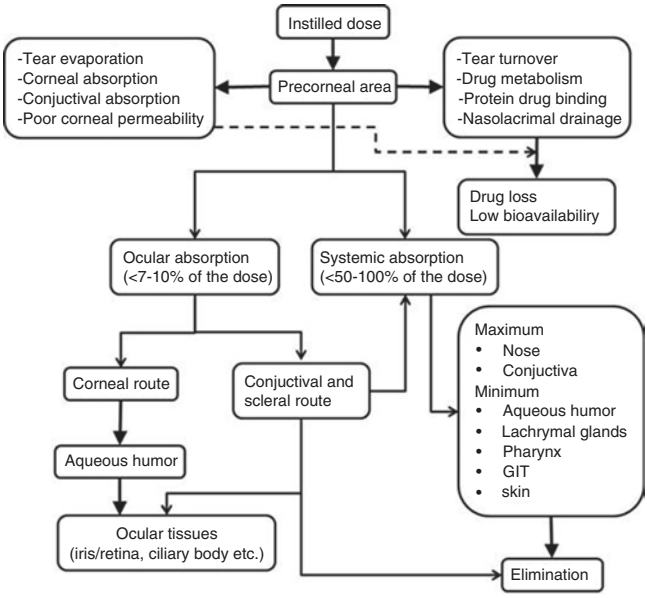

Fig. 6.2 Fate of a drug delivered via ophthalmic route (Adapted from Patel et al. [4])

6.2.1 Anterior Segment Drug Loss

After topical administration, ocular drugs are rapidly removed from the surface of the eye by the lacrimal fluid. Within minutes a large fraction of the instilled formulation is transported to the nasolacrimal duct [5]. Such precorneal removal of the drugs is often referred to as *nonproductive* drug loss [4, 6]. In addition to the drug loss due to lacrimal fluid, instilled doses of ocular drugs may also be removed from the anterior segment due to systemic absorption. Systemic absorption of topically administered ocular drugs may occur either directly in the conjunctival sac from the local blood capillaries or from the nasolacrimal cavity [7, 8]. Thus, nonproductive drug loss as well as loss due to systemic absorption can result in a significant lowering, i.e., less than 10 % of ocular bioavailability of drugs [9].

6.2.2 Tear Fluid–Corneal Barriers

Corneal epithelium is a primary barrier to the transport of drugs from the lacrimal fluid into the eye [10]. The apical cells of the corneal epithelium form tight junctions and restrict the permeation of ocular drugs across the epithelial membrane [11]. Huang et al. studied the permeability characteristics of a group of beta-blocking agents on rabbit corneas [12]. The studies found that the lipophilic compounds penetrated the cornea more rapidly, whereas the corneal epithelium was rate limiting

for the most lipophilic compounds tested. As shown in Fig. 6.3, transcorneal permeation can still be considered as a predominant route for the transport of ocular drugs to the aqueous humor.

Prausnitz et al. and Hamalainen et al. in separate studies described that the conjunctiva has nearly 20 times greater surface area compared to the cornea and also demonstrates a significantly higher permeability to most ocular drugs due to the presence of hydrophilic pores [14, 15]. Owing to its high permeability to small and large molecules with a range of physicochemical properties, the study of drug transport across conjunctival membrane has been a focus of research in recent years [16]. The main mechanism of drug transport across the cornea and conjunctiva is thought to be passive diffusion, albeit the active transporters present in these membranes may play a role in drug absorption [13].

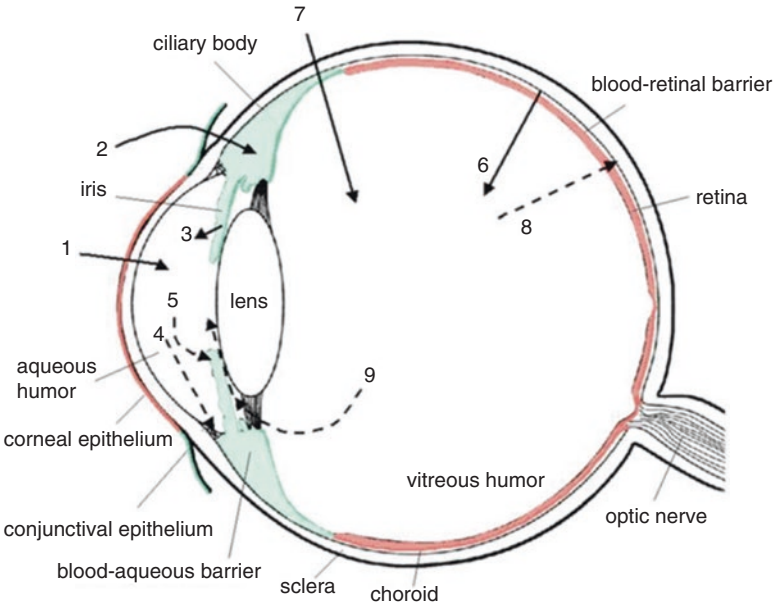

Fig. 6.3 Schematic of the ocular routes of drug transport: (*1*) transcorneal permeation from the lacrimal fluid into the anterior chamber, (*2*) non-corneal permeation across the conjunctiva and sclera into the anterior uvea, (*3*) distribution from the blood stream via blood–aqueous barrier into the anterior chamber, (*4*) elimination from the anterior chamber by the aqueous humor turnover to the trabecular meshwork and Schlemm's canal, (*5*) elimination from the aqueous humor into the systemic circulation across the blood–aqueous barrier, (*6*) distribution from the blood into the posterior eye across the blood–retina barrier, (*7*) intravitreal administration, (*8*) elimination from the vitreous via posterior route across the blood–retina barrier, and (*9*) elimination from the vitreous via anterior route to the posterior chamber (Adapted from Urtti et al. [13])

6.2.3 Blood–Ocular Barriers

Blood–ocular barriers exist to protect the ocular tissues from foreign, harmful molecules that may be present in the systemic circulation. As shown in Fig. 6.3, two types of blood–ocular barriers are present in the eye: (1) blood–aqueous barrier and (2) blood–retinal barrier. The blood–aqueous barrier is present in the anterior segment of the eye and consists of endothelial cells in the uvea. This barrier restricts the entry of albumin and other similar large biomolecules from the plasma into the aqueous humor. The blood–retinal barrier is present in the posterior segment of the eye and consists of retinal pigment epithelium (RPE). This barrier restricts the transport of drugs, ions, proteins, and water flux into and out of the retina and the choroid. Alterations of the blood–retinal barrier are known to play a crucial role in the development of retinal diseases [17]. For example, diabetic retinopathy and age-related macular degeneration (AMD) are known to be directly associated with alterations of the blood–retinal barrier [18–20].

6.3 Biopharmaceutics of Ocular Drug Delivery

Due to the abovementioned barriers, ophthalmic drug delivery is challenging. Since the administration of drugs via systemic routes does not achieve an acceptable ocular bioavailability, the topical route remains the most commonly used approach for ocular drug delivery. Ocular drug absorption occurs mainly via two pathways: corneal and non-corneal. Corneal absorption is a major route of drug absorption. The transport of drugs across corneal epithelium is known to be the rate-limiting step for ocular bioavailability and is highly dependent on the physicochemical properties of the drugs [12]. The non-corneal route of absorption includes transport of drugs across the sclera and conjunctiva into the intraocular tissues. The drugs absorbed by this pathway reach the aqueous humor and may enter the systemic circulation via local capillaries and show higher clearance.

After transcorneal absorption, the drug is typically accumulated in the aqueous humor and then distributed to the other intraocular tissues via passive diffusion. The distribution of drugs to these tissues depends on the extent of drug–protein binding in the iris, ciliary body, and the aqueous humor and the elimination of the drugs due to the aqueous humor turnover. The ocular tissues express a wide range of enzymes; and these enzymes play a major role in the metabolism of ocular drugs. Among the commonly expressed ocular metabolic enzymes include esterases, oxidoreductases, lysosomal enzymes, peptidases, glucuronide-o-methyl-transferase, monoamine oxidase, and corticosteroid β-hydroxylase [21]. These enzymes are mainly found in the cornea, the iris–ciliary body, and the retina. Topically administered drugs are metabolized by the enzymes in the cornea and the ciliary body, whereas drugs administered by systemic or periocular routes are metabolized by the retinal enzymes. After absorption, most drugs are eliminated by the aqueous humor turnover. Other drugs are eliminated by metabolism and uptake by the blood vessels present in the anterior uvea or iris [21].

6.4 Ocular Routes of Drug Delivery

Drugs used for the treatment of ophthalmic diseases can be administered via different routes. The choice of a route for ocular drug delivery depends on a number of factors. These include physicochemical properties of the drug, the nature of the disease, and the specific ocular tissue to be targeted. Among the most commonly utilized routes for ocular drug delivery are topical, subconjunctival, and intravitreal. Conventionally topical and subconjunctival routes are used to treat the diseases of anterior segment of the eye. The intravitreal route is used mainly for the diseases of the posterior segment.

6.4.1 Topical Administration

Most topically administered ocular drugs are available in the form of ophthalmic solutions (e.g., eye drops). Due to several anatomical/physiological factors mentioned above and elsewhere in this book, the residence time of these dosage forms at the site of action is short. Several formulation approaches (e.g., gels, ointments, insert, etc.) have been explored to increase the ocular residence time of topically administered drugs [6, 22–26]. These approaches are described in detail in Chap. 7 of this book. As illustrated in Fig. 6.3, after topical administration to the corneal surface, the drug begins partitioning in the corneal epithelium. Depending on its lipophilicity, it either remains in the epithelium for an extended period or is slowly absorbed into the corneal stroma followed by its release in the anterior chamber [27]. The peak concentration in the anterior chamber after topical administration is typically reached in less than 30 min; however, only a small fraction of the administered dose is absorbed [9]. A fraction of topically administered ocular drugs may be absorbed from the conjunctival surface into the sclera, followed by the uvea and the posterior segment of the eye (Fig. 6.3). Drug absorption from the conjunctival surface is a slow process and dependent upon the physicochemical properties of the drugs. In the anterior chamber, the drug binds to the ocular protein *melanin*, thus forming a complex which may serve as a reservoir and provide a sustained drug release. The drug is then distributed to the uvea and the lens; the distribution to the lens is slower due to its tightly packed protein-rich composition [10].

The drug absorbed in the aqueous humor is mainly eliminated via two pathways. The first pathway is by the aqueous turnover through the chamber angle and Schlemm's canal (Fig. 6.3). The approximate elimination rate via this pathway is 3 μL/min and is independent of the nature of the drug [10]. The second pathway is via systemic circulation in the anterior uvea (Fig. 6.3). Elimination via this pathway is slower and depends on the ability of the drug to cross the endothelial walls of the blood vessels [10]. Thus, typically lipophilic drugs tend to clear faster from the anterior segment compared to hydrophilic drugs. In addition, due to the slow equilibration of the drugs in ocular tissues, determination of the volume of distribution is challenging. Animal studies have demonstrated a wide range (250 μL to 2 mL) of volume of distribution in aqueous humor [11].

6.4.2 Subconjunctival Administration

Ocular drugs are administered via subconjunctival route to improve their bioavailability in the uvea. The main drivers for the use of this route in recent years are (1) the need to deliver newly developed drugs or dosage forms to the retina and choroid in the treatment of macular degenerative diseases and (2) the exponential progress made in fields of ophthalmic formulations and drug delivery systems to deliver the drugs to the posterior segment of the eye [28–30].

The sclera is known to have a higher permeability compared to the cornea, and its permeability to the drugs is independent of the drug lipophilic character [15, 31]. Thus, compared to the cornea and conjunctiva, sclera demonstrates a higher permeability to a wide range of molecules. This makes subconjunctival administration of drugs a more feasible approach to deliver the drugs to the choroid [32]. However, due to the presence of blood vessels, there is a significantly high systemic clearance of the drugs from the choroid. Pitkanen et al. also demonstrated that retinal pigment epithelium may be the rate-limiting factor in the retinal delivery of hydrophilic drugs and macromolecules through the transscleral route [31]. A comprehensive understanding of the scleral and choroidal pharmacokinetics is essential to optimize the drug bioavailability in the posterior segment of the eye.

Several researchers have reported the advantages of subconjunctival administration of ocular drugs over other routes. In a clinical study, Behren-Baumann et al. carried out a comparative investigation of the ocular pharmacokinetics of azlocillin between intravenous and subconjunctival routes of administration [33]. The study results revealed a superior bioavailability of azlocillin in aqueous humor with subconjunctival route compared to intravenous application. Moreover, the half-life of azlocillin in aqueous humor was also found to be longer with subconjunctival administration compared to intravenous route. In a series of studies following this study, Behren-Baumann et al. evaluated the ocular pharmacokinetics of a variety of drugs in animals and humans and demonstrated the superiority of subconjunctival route compared to other modes of drug administration in improving ocular drug bioavailability [34–37].

6.4.3 Intravitreal Administration

Intravitreal drug administration involves injecting a drug solution directly into the vitreous via pars plana to increase the vitreal bioavailability of drugs compared to the drugs delivered via topical or systemic routes [4]. This approach of drug delivery has an inherent advantage of ensuring highest vitreal and retinal bioavailability while avoiding systemic toxicity, since the drug is delivered directly into the posterior segment of the eye. The reduced systemic toxicity is attributed to the presence of retinal pigment epithelium (RPE), which serves as a barrier to the transport of drugs, particularly large, positively charged molecules to the choroid [38, 39]. In addition to passive diffusion, convection resulting from eye movements is known to play a role in the

drug transport process across the vitreous [40]. As shown in Fig. 6.3, drugs administered via intravitreal route may be eliminated in the anterior segment and/or the posterior segment [10]. Elimination in the anterior segment occurs via aqueous turnover and uveal blood flow for most drugs. Elimination in the posterior segment is restricted to small, lipophilic molecules and occurs via passive diffusion across the blood–retinal barrier (BRB). Thus, an extended half-life is observed for large, hydrophilic drugs in the vitreous.

The pharmacokinetics and the pharmacodynamics of the drugs administered via intravitreal routes have been well researched. Shen et al. investigated the pharmacokinetics and safety of caspofungin, a potent antifungal agent, after intravitreal injection (50 μg/0.1 mL) in rabbits [67]. The results showed that caspofungin had a half-life of 6.28 h with the mean vitreous concentration of 6.06 ± 1.76 μg/mL. Detectable concentration of caspofungin was found up to 24 h. In addition, intravitreal injection of caspofungin was found to be safe and devoid of any focal necrosis or other abnormalities in retinal histology. Haller et al. studied the pharmacodynamics of intravitreal ocriplasmin in the treatment of vitreomacular adhesion and vitreomacular traction in human patients [41]. This multicenter, randomized, placebo-controlled, double-masked, 6-month clinical trial consisting of 652 randomized patients confirmed the positive effects of ocriplasmin across relevant subpopulations. Inoue et al. evaluated the pharmacodynamics of intravitreal injection of ranibizumab for the treatment of age-related macular degeneration in humans, as measured by the visual function and vision-related quality of life [42]. The study results demonstrated the tolerability, efficacy, and compliance with intravitreal ranibizumab in the test patients. Intravitreal injections are known to be associated with some specific drawbacks. Ausayakhun reported several short-term complications including retinal detachment, endophthalmitis, and intravitreal hemorrhages after intravitreal injection of ganciclovir in AIDS patients when used to treat cytomegalovirus retinitis [43]. Ornek et al. evaluated the corneal and the conjunctival sensitivity changes measured using the Cochet-Bonnet esthesiometer, following intravitreal ranibizumab (IVR) injection in patients with diabetic retinopathy [44]. The study found significantly increased sensitivities in the central, temporal, and nasal corneas after a single intravitreal ranibizumab injection; and the corneas remained sensitive up to a week. Aslan et al. reported hypersensitivity reaction in the form of marginal keratitis in a single patient after receiving an intravitreal injection of ranibizumab for the treatment of diffuse diabetic macular edema [45].

6.5 Ocular Pharmacokinetic–Pharmacodynamic Models

Pharmacokinetic–pharmacodynamic models consist of compartments that represent physiology of various tissues/organs to characterize and predict drug disposition and pharmacological response using mathematical expressions. Pharmacokinetic models describe relationship between administered dose and drug concentrations in blood/plasma and or tissues/organs. Pharmacodynamic models describe dose–/concentration–response relationships. Combined, pharmacokinetic–pharmacodynamic models can establish and

predict effect-time course resulting from a dose of drug. The application of pharmacokinetic–pharmacodynamic models in drug development has become very critical as they provide valuable information during each phase of development. Worakul et al. have extensively reviewed several pharmacokinetic–pharmacodynamic models for drugs administered via ocular route [46]. One of the basic models that describe precorneal and intracorneal drug movement following topical administration is shown in Fig. 6.1. In this model, as described by Lee et al., the dose is instilled in the precorneal area from where fraction of drug can be absorbed to the cornea then to aqueous humor from where it can be eliminated. Also, the drug may be directly eliminated or lost from the precorneal area as shown in Fig. 6.1 [3].

Schematic of another model describing the ocular absorption is shown in Fig. 6.2. For topically administered drugs or dosage form (e.g., eye drops), there is very limited ocular absorption (only 5–7 %), which is absorbed via the cornea, sclera, or aqueous humor to ocular tissues. Majority of drug is lost through conjunctiva of the eye and nose which results in systemic absorption [6]. Based on the mechanisms of ocular absorption described above, several ocular pharmacokinetic models have been reported in the literature [3, 27, 47–56].

One compartment model is the simplest model where the eye is represented as a single compartment (Fig. 6.4). The drug concentration (C) using this model can be estimated by the following equation, where F is fraction of absorbed dose (D), K_a and K_{el} are rate constants for absorption and elimination, and apparent distribution volume is described by V_d [3, 52]:

$$C = \left(\frac{FD}{V_d}\right)\left(\frac{K_{el}}{K_a - K_{el}}\right)\left(e^{-K_{el}t} - e^{-K_a t}\right)$$

Makoid et al. described a two-compartment model representing the precornea (compartment 1) and cornea (compartment 2) as shown in Fig. 6.5a [52]. The model depicted elimination from both the compartments. The concentration in the cornea was estimated using the following equation:

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

A model developed by Himelstein et al. for pilocarpine consisted tears and aqueous humor as two compartments (Fig. 6.5b), which incorporated input to and elimination

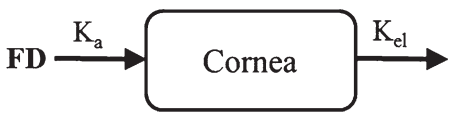

Fig. 6.4 Schematic of a one-compartment model to describe ocular pharmacokinetics

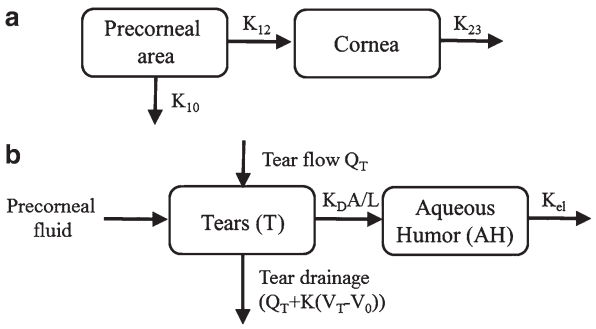

Fig. 6.5 Schematics of different types of two-compartment models ((**a**) Adapted from [52] (**b**) Adapted from [50])

from both the compartments [50]. The concentration in the tear fluid (T) was characterized by the following equation:

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

The concentration in the aqueous humor (AH) was characterized by the following equation:

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

where C_T represents the concentration in tear fluid; C_{AH}, the concentration in aqueous humor; Q_T, the normal rate of tear production; V_D, the volume of drop; V_0, the normal tear volume; V_{AH}, the aqueous humor volume; K_D, the coefficient of permeability; K_{el}, the first-order elimination constant from the aqueous humor compartment; and A and L, the area and thickness of the cornea, respectively. In this model, the cornea was assumed to be homogeneous membrane with no contribution to drug disposition. Also, the entire disposition from the precornea was explained by one rate constant.

A three-compartment model is described in Fig. 6.6a where anterior of the eye was divided into two compartments, the cornea and aqueous humor. Another three-compartment model with precorneal area, cornea, and aqueous humor is shown in Fig. 6.6b.

In a four-compartment model, Makoid et al. incorporated both the cornea and aqueous humor (Fig. 6.7a), but the role of stroma was not captured separately [52]. Stroma and endothelium were combined and described as a single compartment. This was corrected in another four-compartment model by Lee et al. as shown in Fig. 6.7b, with an assumption that instilled drug mixes completely and instantaneously and the

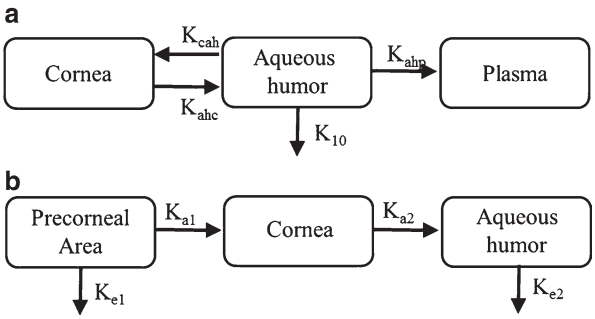

Fig. 6.6 Schematics of different types of three-compartment models ((**a**) Adapted from [51] (**b**) Adapted from [53])

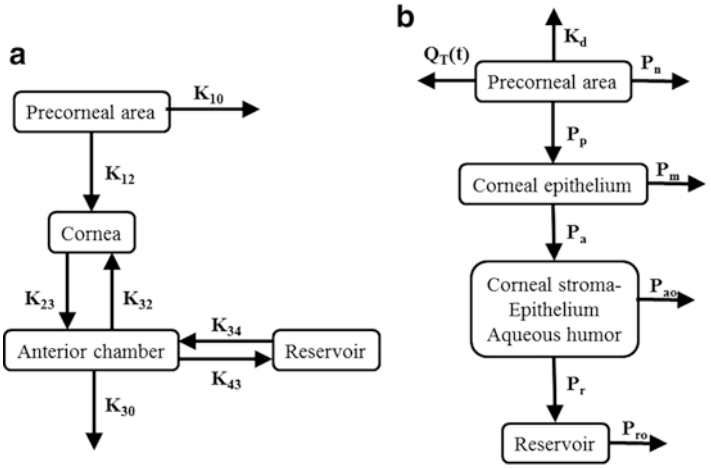

Fig. 6.7 Schematics of different types of four-compartment models ((**a**) Adapted from [52] (**b**) Adapted from [3])

reservoir compartment contains the iris, lens, vitreous humor, and ciliary body [3]. The group extended the model to separate stroma and aqueous humor to make it a five-compartment model (Fig. 6.8a), where drug loss or transfer occurred from each of the compartments. This model was used for a lipophilic drug, fluorometholone [56]. A five-compartment model was also used to describe the pharmacokinetics of pilocarpine as shown in Fig. 6.8b, where the five compartments were precorneal area, cornea, aqueous humor, lens, and iris [54]. The movement of drug to/from each compartment was considered reversible. In this model, elimination of drug was considered to be only from the aqueous humor and iris.

Sakanaka et al. developed one of the first ocular pharmacokinetic–pharmacodynamic (PK/PD) models for timolol (a beta-blocker), after topical administration or

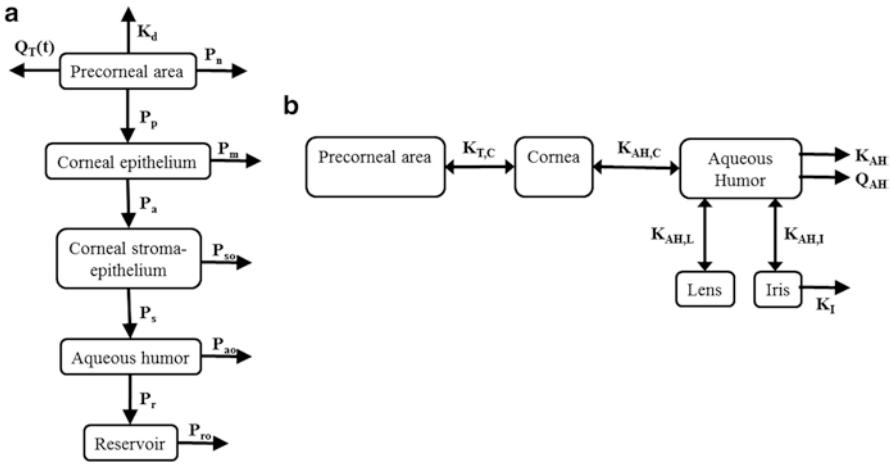

Fig. 6.8 Schematics of different types of five-compartment models ((**a**) Adapted from [56] (**b**) Adapted from [54])

injection into the anterior chamber in rabbit eyes [57]. Timolol concentrations in the tear fluid, aqueous humor, cornea, and iris–ciliary body were measured by high-performance liquid chromatography (HPLC). In addition, intraocular pressure (IOP) was measured by a telemetry system. The PK/PD parameters were estimated by fitting the concentration-time profiles and the ocular hypotensive effect-time profiles. A six-compartment PK model described the concentration-time profile; and the PD model which consisted of aqueous humor dynamics, i.e., timolol lowering of IOP by suppressing aqueous humor production, described the ocular hypotensive effect-time profiles of timolol (Fig. 6.9). Similarly, a model for bunazosin with seven compartments where cornea compartment was divided into two compartments, corneal epithelium and stroma, was developed [58]. All the other processes and parameters were similar to timolol model. Sakanaka et al. were also the first to develop a combined ocular PK/PD model for multidrug therapy (Fig. 6.10) [59]. This model considered mechanism of action of two drugs, timolol and bunazosin. The model was used to simulate the concentrations in aqueous humor and intraocular pressure-lowering effects following instillation of combination of timolol and bunazosin. The reliability of this model was verified with observed drug concentrations in aqueous humor and measurement of ocular hypotensive effects using telemetry. For further details including derivations of equations, readers are encouraged to refer to the original publication [59].

In pharmacodynamic models, measurements of pharmacological responses like miosis and mydriasis and intraocular pressures have been considered [46]. For cholinergic drugs, miotic response m_r was used to measure the effect at time t and was expressed as shown below [60]:

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

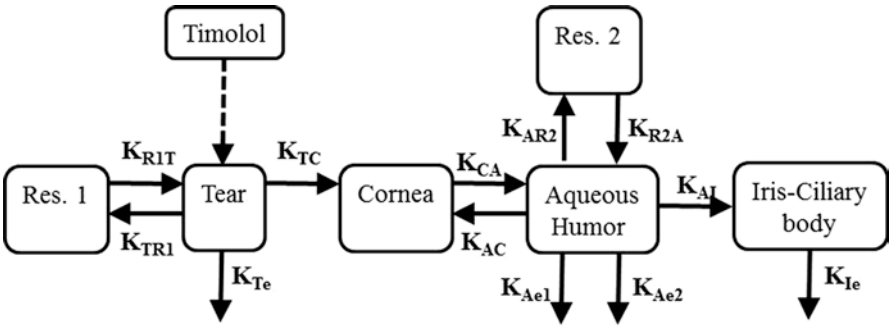

Fig. 6.9 Schematic of a six-compartment model for the ocular pharmacokinetics of timolol [57]

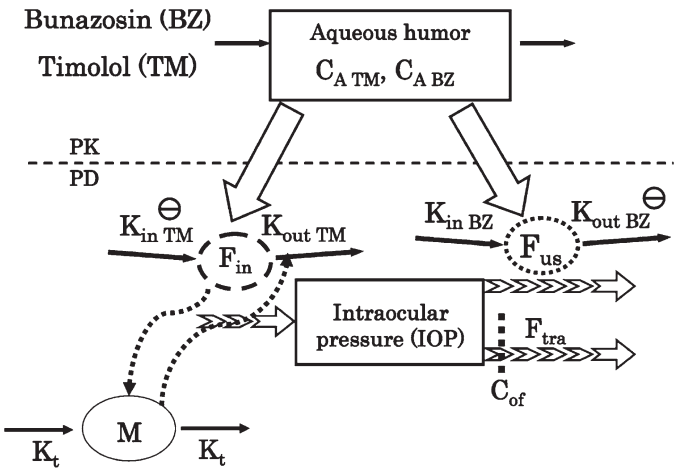

Fig. 6.10 Combined pharmacokinetic–pharmacodynamic model for bunazosin and timolol (Adapted from [59])

where m_0 is baseline miosis and k_{dm} is the decrease in miosis coefficient.

To describe miotic or mydriatic response of pilocarpine or carbachol, the following general model was used [46]:

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

For the miotic response, $R = D_0 - D$ and $R_{\max} = D_0 - D_{\min}$, and for the mydriatic response, $R = D - D_0$ and $R_{\max} = D_{\max} - D_0$, where D_0 is baseline pupil diameter prior to treatment and D is pupil diameter after drug administration.

For measurement of mydriatic response at time t, ΔE_t, a simple Emax model has been used for phenylephrine:

$$\Delta E_t = \left(\frac{E_{\max} Ca_t}{K_m + Ca_t} \right)$$

where $E_{\max}$ is the maximum response of the drug, K_m is the concentration of drug in the aqueous humor that produces half the maximum response, and Ca_t is the concentration of drug in aqueous humor at time t.

Further, modified $E_{\max}$ model was used for the measurement of intraocular pressure (IOP) reduction [61]:

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

Here, ΔE is the reduction in IOP, E_0 is the baseline IOP, and EC_{50} is the concentration C in aqueous humor that produced half of maximum effect, $E_{\max}$.

In recent years, additional mechanistic models have been utilized by researchers. Durairaj et al. developed a mechanism-based translational pharmacokinetic–pharmacodynamic (PK/PD) model for intraocular pressure (IOP)-lowering drugs, brimonidine in rabbits and latanoprost in dogs [62]. The physiologically based population model was used to predict the IOP following treatment in patients with glaucoma or ocular hypertension (OHT), which can be useful for dose and regimen selection for designing clinical trials. Luu and coworkers developed a physiologically relevant population PK/PD model for an EP4 agonist CP-734432 and its metabolite PF-04475270 [63]. Population PD models characterized the IOP-lowering profiles. An indirect-response model with a response-driven positive feedback loop that accounted sensitization of PD captured the response adequately.

In a clinical study by Zhang et al., a nonlinear mixed-effect population model was developed to characterize PK of ranibizumab after intravitreal administration in patients with retinal vein occlusion (RVO) or diabetic macular edema [64, 65]. PK was described by a one-compartment model with first-order absorption and first-order elimination and was found to be similar in patients with RVO, DME, and age-related macular degeneration (AMD). Although the authors did not use the concentrations in the ocular tissues, they postulated that intravitreal injection of ranibizumab may result in similar intraocular concentrations and eventually similar concentrations in the serum irrespective of the disease.

Most of the comprehensive modeling work is done in preclinical species based on animal data as it is challenging to obtain drug concentrations in the human eye or ocular tissues. Due to simplification of the processes, the models have certain limitations but are adequate to characterize and describe the data. The application of appropriate model depends on drug properties, mode of application, and available information (observed data).

6.6 Current Trends in the Pharmacokinetics and Pharmacodynamics (PD) of Ocular Drugs

The studies of pharmacokinetics and pharmacodynamics of drugs used to treat ophthalmic diseases have gained a lot of interest among researchers in recent years [9]. Due to the uniqueness of the drug delivery systems as well as the therapeutic targets, these studies bring significant and synergistic contributions to the knowledge base in ocular therapeutics. Several research studies focusing on PK/PD of ocular drugs have been carried out using a variety of biological models including cells, tissues, animals, and humans.

Tang-Liu et al. carried out a comprehensive investigation of the ocular pharmacokinetics and safety of 0.05 % cyclosporine ophthalmic emulsion, approved by the US FDA for treatment of keratoconjunctivitis sicca (dry-eye disease) [66]. The initial results from the cell culture studies showed that cyclosporine had no adverse effects on human corneal endothelial and stromal cells in vitro. Furthermore, long-term ocular administration of cyclosporine (up to 0.4 %) in rabbits (6 months) and dogs (1 year) was also found to be devoid of any systemic or ocular toxicity. The formulation was also found to be safe in the safety studies in human patients with dry eye. Bucolo et al. evaluated the ocular pharmacokinetics of two marketed ocular formulations, i.e., a suspension containing hydroxypropyl methylcellulose (IND-HPMC) and a solution with hydroxypropyl-beta-cyclodextrin (IND-CD) of indomethacin following topical administration in rabbits [67]. Indomethacin levels were measured in aqueous humor, vitreous humor, and the retina of the animals at regular intervals between 0 and 240 min by liquid chromatography–mass spectrometry (LC-MS). The results showed that the peak concentrations in the vitreous and humor were achieved within 30 and 60 min for IND-HPMC and IND-CD, respectively. The total bioavailability in the retina, vitreous, and humor as obtained from the area under the curve (AUC) was found to be significantly higher (three-fold to fourfold) with IND-HPMC compared to that with IND-CD. Overall, the data indicated the importance of formulation composition in achieving therapeutically relevant pharmacokinetics of the drug.

Yuan et al. in a series of studies investigated the safety and pharmacokinetics of FK506 (*tacrolimus hydrate*, a macrolide immunosuppressant used to prevent graft rejection after organ transplantation) following topical administration in rabbits [68, 69]. The preliminary results indicated that FK506 had acceptable ocular safety profile. Moreover, the drug concentration in the cornea and aqueous humor measured after single-dose and multiple-dose administration at various time points indicated that the therapeutic concentration of FK506 required for treating corneal allograft rejection was achieved. Asena et al. studied the ocular pharmacokinetics, efficacy, and endothelial toxicity of moxifloxacin after a single intracameral bolus injection of 500 μg/0.1 ml in rabbit eyes [70]. Moxifloxacin concentrations in aqueous humor and vitreous samples were determined at 0.5, 1, 3, 6, 12, and 24 h by HPLC and compared with the minimum inhibitory concentrations and mutant prevention concentrations for endophthalmitis pathogens. The results showed that moxifloxacin

exceeded the minimum inhibitory concentrations and mutant prevention concentrations of all common endophthalmitis pathogens in the aqueous humor for 6 h. The half-life of moxifloxacin in the aqueous humor was found to be 2.2 h.

In a recent study, Lin et al. investigated the ocular pharmacokinetics of 1 % naringenin (4′, 5, 7-trihydroxy flavanone) eye drops following topical administration to rabbits [71]. The authors analyzed the concentrations of naringenin in the ocular tissues and plasma using specific electrospray ionization liquid chromatography–tandem mass spectrometry method. The results found highest ocular bioavailability of naringenin in the cornea, followed by the aqueous humor, retina, and vitreous body, as measured by the area under the curve ($AUC_{0\text{-}t}$). The half-lives of naringenin were found to be 9.37 h (cornea), 0.65 h (aqueous humor), 1.17 h (vitreous), and 4.62 h (retina). The plasma levels of free naringenin and total naringenin were found to be similar based on the C_{max} and T_{max}. The study revealed the utility of naringenin in the treatment of several ocular diseases like age-related macular degeneration and retinitis pigmentosa. In another study, Shen et al. compared ocular and systemic pharmacokinetics of brimonidine and dexamethasone following a single intravitreal dose in rabbits and monkeys [72]. The results were also compared between healthy animals and those with chemical- or laser-induced breakdown of the blood–retinal barrier (BRB). The results showed that in both animals, the ocular bioavailability (as measured by AUC) was found to be lower in animals with damaged BRB compared to healthy animals. This was attributed to increased systemic clearance of the drugs due to the absence of BRB. There was no significant difference in the plasma concentrations of the drugs. The study emphasized the importance of the PK/PD data obtained and analyzed from healthy vs. disease models and suggested caution when extrapolating PK data from these models.

6.7 Summary

Optimizing ocular therapeutics via targeted drug delivery to specific ocular tissues is a challenge due to the unique anatomical and physiological constraints present in the eye. The rate and extent of absorption, distribution, metabolism, and elimination of ocular drugs may vary significantly depending on the physicochemical properties of the drugs, the route of drug administration, as well as the pathophysiology of the ocular disease state. The design and development of pharmacokinetic and pharmacodynamic models is of great help in evaluating the bioavailability, efficacy, and safety of ocular drugs. A robust ocular PK/PD model should include all relevant physiological/pharmacological processes and should have reliable predictive value. These models then form the basis of the theoretical understanding of the pharmacokinetics, pharmacodynamics, and toxicokinetics of the ocular drugs. Such an understanding is essential in identifying the challenges, predicting drug response, as well as implementing appropriate formulation and other interventional strategies to optimize ocular drug therapy.

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