Chapter 6
Nanotechnology for Transcorneal Drug Targeting in Glaucoma: Challenges and Progress

Ameeduzzafar Zafar, Javed Ahmad, Sohail Akhter and Richard T. Addo

Abstract The eye is a highly protected organ, and designing ocular formulation for effective therapy, is challenging for drug delivery researcher. The anatomical and physiological barriers resulted in a low ocular bioavailability of administered drugs. Poor bioavailability of ocularly administered drugs is mainly due to factors responsible for precorneal loss (like tear dynamics, non-productive absorption, a transient residence time in the cul-de-sac, and relative impermeability of the corneal epithelial membrane). Due to these constraints, less than 5 % of the administered dose is absorbed from the conventional ophthalmic dosage forms. Vision-threatening diseases like glaucoma alter the physiology and molecular mechanism of vision. Ocular drug delivery in this dreadful condition is quite challenging. Though, the potential use of a nanoparticulate system as drug carriers has led to the development of many different colloidal delivery vehicles for targeted delivery in glaucoma. Drug loaded colloidal carriers associated with several favorable biological characteristics such as biodegradability, biocompatibility and mucoadhesiveness have been found to be effective in transcorneal drug targeting in glaucoma. These nanoparticulate systems exhibited better ocular drug efficacy by improving ocular bioavailability without blurring the vision in glaucoma. This

A. Zafar
Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard University, New Delhi 110062, India

J. Ahmad
Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Raebareli, Uttar Pradesh 229010, India

S. Akhter
LE STUDIUM® Loire Valley Institute for Advanced Studies, Centre-Val de Loire, France

S. Akhter
Nucleic Acids Transfer by Non-Viral Methods, Centre de Biophysique Moléculaire, CNRS, UPR4301 Orléans, France

R.T. Addo (✉)
Department of Pharmaceutical Sciences, School of Pharmacy, Union University, Jackson, TN 38305, USA
e-mail: raddo@uu.edu

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chapter aims to briefly discuss the ocular barriers to glaucoma drug delivery along with nanotechnology mediated transcorneal drug targeting.

Keywords Glaucoma · Bioavailability · Nanotechnology · Colloidal carrier · Transcorneal drug targeting

Introduction

Glaucoma is a group of eye sicknesses that is associated with damage to optic nerve. The optic nerve is the main nerve of the eye (posterior part of the eye), which are responsible for transmitting electrical impulses to the brain. It is also characterized by a progressive form of optic nerve damage associated with raised (>21 mmHg) intraocular tension and reduction of the visual field (Zimmerman 1993; Jarvinen et al. 2000; Langman et al. 2005; Quaranta et al. 2013a, b; Hyun et al. 2013). It occurs when an imbalance in production and drainage of ocular fluid (aqueous humor) that resulted in increased eye pressure (Van Buskirk and Cioffi 1992; Duijm et al. 1997; Casson et al. 2012; Rhee 2013). Usually patients with glaucoma, especially those suffering from normal tension glaucoma (NTG) or progressive high tension glaucoma (HTG), have slower blood flow velocity in the retina, (Langman et al. 2005) in the choroid (Duijm et al. 1997) and in the optic nerve head (Michelson et al. 1996). Blood flow is also reduced in the retrobulbar vessels, (Satilmis et al. 2003; Doina et al. 2004) carotid arteries, and particularly in the peripheral capillaries. In addition, it has also been observed that patients with glaucoma frequently suffer from ischemic lesions in other parts of the body such as the brain (Stroman et al. 1995) ear (Susanna and Basseto 1992) and heart. Glaucoma-like optic nerve head excavations have also been demonstrated in animals following induced ischemia. These reports suggest that the vascular mechanism of damage in glaucoma is at least in some respects a primary causative factor. Approximately 70 million people around the world are affected and estimated 7.5 million blind worldwide resulting from glaucoma. In India, at least 12 million peoples are affected with glaucoma. The disease is more common in old age, however approximately 2–3 persons per hundred are affected above the age of 40 years (Quigley 1996; Quigley and Broman 2006; Kowing et al. 2010; Jain et al. 2014).

Types of Glaucoma

There are many types of glaucoma, but the two most common types i.e., open-angle glaucoma and closed angle (angle closure) glaucoma.

Primary Open-Angle Glaucoma

Primary open-angle glaucoma (POAG) a chronic, slowly progressive optic neuropathy, characterized by progressive excavation of the optic nerve head and a distinctive pattern of visual field defects. It is about 90 % of all glaucoma cases. The disease is multifactorial in origin and is associated more closely with elevated intraocular pressure (IOP) resulting from reduced drainage of aqueous humor because trabecular meshwork becomes blocked and fluid cannot be transported to the normal drainage canals (Van Buskirk and Cioffi 1992; Piltz-Seymour et al. 2001; Doina et al. 2004; Gherghel et al. 2004; Ohtake et al. 2004).

Closed-Angle Glaucoma

It is also called acute glaucoma or angle closure glaucoma, accounts for about 9 % of all glaucoma cases and occurs when the opening between cornea and iris get narrows, such that the fluid cannot get to the trabecular meshwork and normal drainage channels (Fig. 6.1) (Shields 1992).

There are various anti-glaucoma drugs (Nathanson 1980; De-Santis 1994; Saxena et al. 2002; Tataru and Purcarea 2012) used for the treatment and available on the market, shown in Table 6.1. It acts on the aqueous humor dynamics to reduce the intraocular pressure mainly by three mechanisms.

- Decrease aqueous production in the ciliary body
- Increase aqueous humor outflow through the trabecular meshwork and
- Increase aqueous humor outflow via the uvea-scleral pathway.

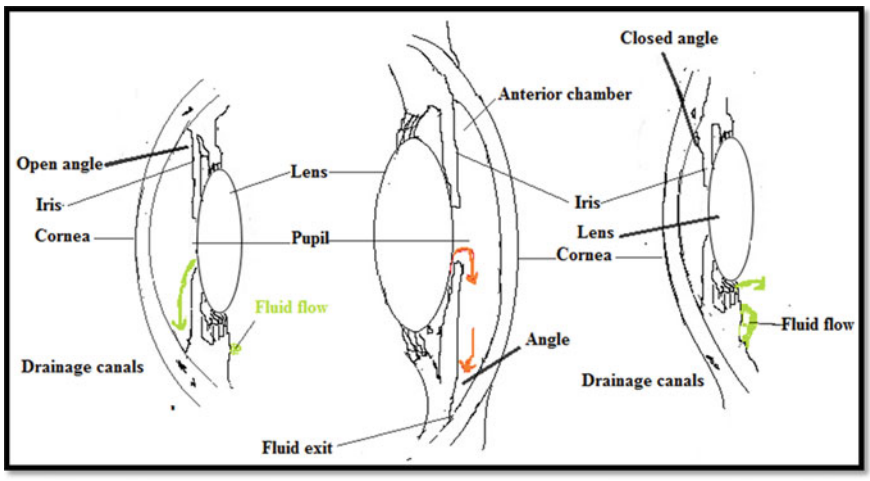

Fig. 6.1 Types of glaucoma

Table 6.1 Different drugs used in treatment of glaucoma

Drug	Dosage form	Action
Cholinergic agonist		
Pilocarpine	Eye drops (0.5–4 %)	It increases the trabecular outflow due to ciliary body contraction
Adrenergic agonists		
Dipivefrin (prodrug of epinephrine)	Eye drops (0.1 %)	It increases aqueous humor formation in the early phase presumably due to its α-adrenergic effect
		It also increases trabecular outflow probably by stimulating β2-adrenergic receptors in the trabecular meshwork
Epinephrine	Eye drops (0.25–2 %)	It decreases aqueous humor formation in the early phase presumably due to its α-adrenergic effect
		It also increases trabecular outflow probably by stimulating β2-adrenergic receptors in the trabecular meshwork
α_2-adrenergic agonist		
Apraclonidine	Eye drops (0.5–1 %)	Increasing trabecular meshwork outflow by reducing episcleral venous pressure and may also increase uvea-scleral outflow by an increase in prostaglandin synthesis
Brimonidine	Eye drops (0.2 %)	
Adrenergic antagonists		
Selective β1-blockers		
Betaxolol	Eye drops (0.5 %)	They act solely by reducing the aqueous humor production
Atenolol	Eye drops (4 %)	They block the β-receptors in the iris and ciliary body and thereby cause a significant reduction in IOP
Metoprolol	Eye drops (1–4 %)	
Non-selective β-Blockers		
Timolol,	Eye drops (0.25–0.5 %)	It reduces intraocular pressure by reducing Aqueous humor formation as well as by enhancing the outflow facility
Levobunolol	0.5 % eye drops	
Carteolol	1–2 % eye drops	
Carbonic anhydrase inhibitors		
Acetazolamide	250 mg tablets	It reversibly blocks the enzyme carbonic anhydrase in the ciliary body and thus suppresses aqueous humor production
Methazolamide	50 mg tablets	
Dorzolamide	Eye drops (2 %)	It penetrates cornea, inhibits carbonic anhydrase-II in the ciliary body, slows the production of local bicarbonates and thus decreases sodium and fluid transport which in turn reduces the secretion of aqueous humor
Brinzolamide	Eye drops (1 %)	
Prostaglandin analogs		
Latanoprost	Eye drops (0.005 %)	It undergoes enzymatic hydrolysis in cornea and gets activated by the acid of latanoprost
Travoprost	Eye drops (0.004 %)	It acts by enhancing uvea-scleral outflow rather than altering the conventional trabeculo-canalicular aqueous outflow
Unoprostone	Solution (0.12–0.15 %)	It acts by enhancing uvea-scleral outflow without affecting aqueous humor production

Ocular Drug Delivery in Glaucoma: Challenges and Opportunity

The development of drug delivery approach for the transportation of drug in a bio-available and safe manner to the target site is now becoming an exceedingly important area of biopharmaceutical researches.

There are various types of novel drug delivery techniques in every year and every part of the body has been attempted to deliver the active constituent to achieve the maximum bioavailability and minimum side effect as a potential target for the site of action. As a result, different smart drug delivery technologies with considerable outcomes have been reported for BCS class-II (low soluble) and class-IV (low soluble) drugs, proteins, peptides, herbal drugs, etc. among the novel techniques i.e., vesicular system, in situ gel system (temp, ion, pH and temp-ion dependent), bioadhesive, lipid system (solid lipid nanoparticles and nanostructured lipid carrier) nanotubes, dendrimers, emulsion (nanoemulsion, Microemulsion) and polymeric nanoparticles (biodegradable and non-biodegradable), implant, inserts etc. are currently under intensive exploratory studies (Akhter et al. 2011). Apart from that, drug delivery to the ophthalmic drug delivery has remained as one of the most challenging research for scientists, requires a series of specified characteristics on every step during the development of formulation according to the physiological and anatomical structure of the eye because it interferes with the fate of the administered drug and bioactive. To treat the local ophthalmic diseases, liquid eye drop (conventional) is the most considerable and desirable dosage forms for the treatment of most of the ocular diseases due to their ease of administration and clinical compliance of the patients. This conventional dosage form accounts for nearly about 90 % of dosage forms available in the market owing to their simplicity and good acceptance by patients. However, conventional eye drops, most of which are present in the solution form usually have quite a limited therapeutic efficacy due to low bioavailability (Jain et al. 2011). The conventional eye drop have some drawbacks (1) frequent instillation is required, to get the expected therapeutic effect, and this leads to growing inconvenience and adverse effects (Jain et al. 2011). (2) Only less than 5 % administered dose reaches into the active site. (3) The precorneal drug loss is due to blinking and high tear fluid turnover, which may pass into systemic circulation through nasolacrimal duct and conjunctiva (Bourlais et al. 1998). The objective of using the novel delivery system is based on these considerations thus enhancing the precorneal residence time, slow release of drug from a dosage form, slow removal of a drug from the therapeutic site and improvement of both intracellular and paracellular pathways of epithelial cells. It would be of enormous benefit to reduce the dose, dosing frequency and consequently, reduce the local side-effects and systemic side effect inborn to applied drugs. So, drug delivery in ocular therapeutics is a challenging concern and is a subject of interest to scientists working in the multidisciplinary areas pertaining to the eye (Akhter et al. 2011). In case of ocular drug delivery system most of the previous published research data on novel techniques (nano formulation) suggests many considerable

point related to formulation i.e., an appropriate particle size and a narrow size range (<200 nm), adequate bioavailability and compatibility with ocular tissues, ensuring low irritation, high residence time, and ensuring low systemic side effect, should be sought for every suspended drug (Sahoo et al. 2008). Thus, an optimum delivery system should be the one which can be delivered in the form of eye drops, causing no blurred vision or irritability and would need to be applied with low dosing frequency and better patient compliance. Despite numerous scientific efforts, efficient ocular drug delivery remains a challenge for the pharmaceutical scientists. Consequently, the design of a system with improved drug delivery properties to the ocular surface would be a promising step towards the management of external ocular diseases. Ophthalmic drug delivery, probably more than any other route of administration, may benefit from the uniqueness of nanotechnology-based drug delivery (Sahoo and Labhasetwar 2003). The use of nanocarriers provides attractive replacements for topical ocular drug delivery, mainly because of their capacity to protect the encapsulated molecule, along with its facilitated transport to the different compartments of the eye (Losa et al. 1993; Kayseri et al. 2005).

Additionally, nanoparticulate formulation may offer the possibility of controlling drug delivery (release of drug from formulation), thus being attractive vehicles for the treatment of some chronic ocular diseases like glaucoma

Anatomy and Physiology of Human Eye

The eye is characterized by its complex structure as well as high resistance to foreign substances including drugs. The anterior and posterior segments of the eye, although in juxtaposition to each other, and very different in their anatomical and physiological aspects, function both independently and in tandem upon application of an ocular preparation. While it has been known for long that conventional topical formulations are amenable to application to the anterior portion, most of the applied dose is lost due to the defensive mechanism of the eye. Consequently, a much concerted effort has been directed towards increased retention of the applied dose on the eye surface, with the hope that such increased retention will result in better therapeutic effect and lowered local and/or systemic effects. Since most drugs poorly penetrate the cornea, fulminating diseases of the posterior segment viz. vitreous, retina and choroid are required to be treated with either systemic administration or through intravitreal injections and vitreal implants. While therapy with systemic administration requires large doses due to strong blood-ocular tissue barrier, the other two routes are very invasive requiring skilled administration and are associated with a high degree of risk, such as the development of retinal detachment and endophthalmitis. Clearly, there is a strong case in favor of formulating ocular delivery systems by focusing on improved ocular bioavailability and extended drug effect in targeted tissues. Prolonging pre-corneal residence time through viscosity enhancers and gels has only a limited value because such liquid formulations are eliminated by the usual routes in the ocular domain. The selection

of enhancer to maximize drug transport requires great caution, because corneal/conjunctival tissues are highly sensitive towards penetration enhancers. An alternative approach is to develop a drug delivery system that would circumvent the problems associated with the conventional systems, and provide the advantages of targeted delivery of drugs for an extended period of time and be patient-friendly. The latter requisite becomes more crucial in cases where the patient has to use the drug preparation throughout his life, e.g. in glaucoma. These advantages have been reported in the literature through the use of nanoparticles.

Barriers in Ocular Drug Delivery

The different barriers in ocular drug delivery are discussed below.

Drug Loss from the Ocular Surface

After instillation, the flow of lacrimal fluid removes instilled formulation from the surface of the eye. Even though the lacrimal turnover rate is only about 1/min the excess volume of the instilled fluid is flown to the nasolacrimal duct rapidly in a couple of minutes (Schoenwald 1990). Another source of non-productive drug removal is its systemic absorption instead of ocular absorption. The systemic absorption of a drug from any dosage form may take place through two ways, first absorption directly from the conjunctival sac via local blood capillaries secondly by nasolacrimal duct or cavity (Ananthula et al. 2009). The systemic absorption of the drug through topical ocular routes depends on upon the particles size or molecular weight of the drug. The smaller particle size or very small molecular weight drug are absorbed into systemic circulation rapidly within few minutes, consequently decreasing the concentration of drug in lacrimal fluid extensively. This leads to lower bioavailability of drug i.e., less than 5 % (Schoenwald 1990; Lee and Robinson 1986). So the novel drug delivery has the capability to resist this loss of drug, which has been proved by many scientists.

Lacrimal Fluid-Eye Barriers

When the formulation is instilled in the eye surface it passes into the lacrimal fluid, then cornea. The drug absorption through the corneal epithelium is limited or lower because of the presence of the lacrimal fluid barrier. The corneal barrier is formed upon maturation of the epithelial cells. They migrate from the limbal region towards the center of the cornea and to the apical surface. The most apical corneal epithelial cells form tight junctions that limit the paracellular drug permeation. Therefore, the lipophilic drugs cross in high magnitude as compared to a hydrophilic drug because proximal part of corneal epithelium has more permeability for a lipophilic drug

(Machaand and Mitra 2003). Due to the tightness of the corneal epithelial layer, transcorneal permeation is the main route of drug doorway from the lacrimal fluid to the aqueous humor. In general, the conjunctiva is more permeable epithelium than the corneal epithelium and its surface area approx 20 times greater than that of the corneal epithelium. Drug absorption across the bulbar conjunctiva has gained increasing attention recently since conjunctiva is also quite permeable to the hydrophilic and large molecules weight or large particle size. Therefore, it may serve as a route of absorption for larger bio-organic compounds such as proteins and peptides. Clinically drugs used are generally small and fairly lipophilic. Thus, the corneal route is currently dominating as compared to other ocular routes for the treatment of glaucoma (Satilmis et al. 2003).

Blood-Ocular Barriers

The eye is a vital organ of the body which is protected from the xenobiotics in the blood stream by blood-ocular barriers. These barriers have two parts: blood-aqueous barrier and blood-retina barrier (BRB) which is shown in Fig. 6.2. The anterior blood-eye barrier is composed of the endothelial cells in the uvea. The anterior blood-eye barrier prevents the admittance of plasma albumin into the aqueous humor, as well as limits access of hydrophilic drugs from plasma into the aqueous humor. Inflammation may disrupt the integrity of this barrier causing unlimited drug distribution to the anterior chamber. In fact, the permeability of this barrier is poorly characterized for a hydrophilic drug. This barrier comprised of retinal pigment epithelium (RPE, inner BRB) and the tight walls of retinal blood capillaries (outer BRB, Langman et al. 2005; Quaranta et al. 2013a, b). There are no diffusional barriers between the extracellular fluid (ECF) of the retina and the adjacent vitreous, nor does the vitreous body itself extensively obstruct the diffusion of substances. Principally, the drug molecules may move in the vitreous by two

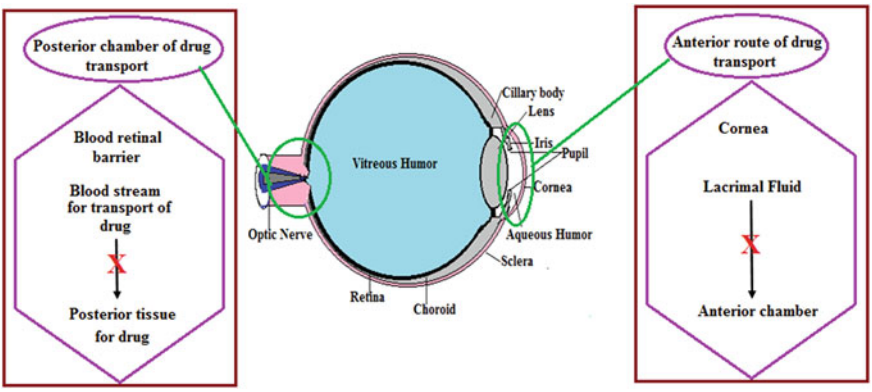

Fig. 6.2 Routes and barriers of eye

different mechanisms: diffusion or bulk flow. Unlike retinal capillaries, the vasculature of the choroid has extensive blood flow and leaky (permeable) walls. The drug molecules are easily interred to the choroidal extravascular space and distributed to the retina. But the distribution of drug molecules into the retina is limited by the RPE (inner BRB) and retinal endothelial cell (outer BRB) due to the tight junction (analog to brain vessels). The choroidal is highly vascularised but it constitutes only a small fraction of the entire blood flow in the body. Thus, without specific targeting systems only a small fraction drug of the oral or intravenous dose reached the retina and choroid (Maurice and Mishima 1984; Hornof et al. 2005). As per many researchers the outer and inner components of the BRB, having different kind of absorptive transport processes which are capable of removing potentially harmful substances from the extracellular fluid of the retina and vitreous (Rapoport 1976).

Drug Targeting Through Topical Transcorneal Route

Topical transcorneal route of drug administration was found to be a potential strategy in the management of glaucoma. Drug penetration through transcorneal route is mainly affected by the corneal barrier, physicochemical characteristics of the drugs as well as active ion transport system present at the cornea.

Anatomy and Physiology of Transcornea Route

The cornea is an optically transparent tissue. It acts as the principal refractive element of the eye. The diameter of cornea approx 11.7 mm with a radius of curvature of the anterior surface of about 7.8 mm (Sahoo et al. 2008). The thickness of the cornea is about 0.5–0.7 mm and it is thicker in the center than in the limbus (Urtti et al. 1990, 1994). The cornea is composed of epithelium, Bowman's membrane, stroma, Descement's membrane and endothelium. The relative thicknesses of corneal epithelium (50–90 μm), stroma and endothelium are about 0.l: l.0:0.0l (Maurice and Mishima 1984). Usually, the cornea1 epithelium is the main barrier of drug absorption into the eye (Jarvinen et al. 2000). Compared to many other epithelial tissues (intestinal, nasal, bronchial, tracheal), corneal epithelium is fairly impermeable, but it is more permeable compared to the stratum corneum of the skin (Liaw and Robinson 1992). The stratified corneal epithelium acts as a protective barrier to invasion of foreign substances and also as a barrier to ion transport. The corneal epithelium consists of a basal layer of columnar cells, two to three layers of wing cells and one or two outermost layers of squamous, polygonal shaped superficial cells (Maurice and Mishima 1984). The surface areas of superficial squamous cells of the rabbit corneal epithelium at central, paracentral and peripheral sites vary substantially. Cell divisions occur in the basal layer of epithelium and cellular differentiation occurs gradually as cells move towards the

corneal surface. In a healthy corneal epithelium, the intercellular tight junctions (zonula occludens) completely surround the most superficial cells, but the intercellular spaces are wider between wing cells and between basal cells (Maurice and Mishima 1984). This allows paracellular diffusion of large molecules like horseradish peroxidase (MW 40,000) through these layers of cells only (Hämäläinen et al. 1997). When the superficial cell layers of the epithelium in excised pigmented rabbit cornea was first devitalized, gradual formation of tight junctions between the epithelial cells was observed within 8 h (Geroski and Edelhauser 2001) and the complete reformation of the corneal epithelial barrier took place in 5 days following removal of the corneal epithelium of pigmented rabbits (Newell 1986). Perfusion studies have been done in an attempt to estimate the size range of the intercellular space in the epithelium. Small hydrophilic molecules, such as glycerol (MW 92, 0.6 nm) (Maurice and Mishima 1984) and polyethylene glycols 200 and 400 (Huang et al. 1989) are able to penetrate through intercellular spaces of the corneal epithelium, but inulin (MW 5000, 1.5 nm) (Maurice and Mishima 1984) and horseradish peroxidase (MW 40,000 about 3 nm) (Hämäläinen et al. 1997) molecules are too large for paracellular diffusion across the corneal epithelium. Corneal and conjunctival permeability coefficients of hydrophilic P-blockers with similar molecular weights (about 300) but different partition behaviors (octanol/buffer partition coefficients varied from −0.62 to 0.93) suggesting a paracellular penetration route into the eye. The stroma of the cornea is highly hydrophilic in nature because it contains mostly water molecule. Human stroma is composed mainly of collagen fibrils with a uniform diameter of 25–35 nm which runs parallel to each other to form collagen bundles with varying widths and thicknesses. The regular arrangement of collagen fibrils in collagen bundles is important for normal visual acuity. The corneal stroma constitute with corneal fibroblasts (keratocytes, major cellular component) that occupy 2–3 % of the total volume of the corneal stroma. Due to their comparatively loose structure, the drugs having molecular or particles size up to 500,000 can diffuse in the normal stroma (Jarvinen et al. 2000). But it is rate limiting barrier of ocular absorption for most lipophilic drugs (Langman et al. 2005). This is not due to the physical barrier of the stroma, but rather to the low partitioning between lipophilic compounds of lipoid epithelium and hydrophilic stroma. The corneal endothelium is accountable for maintaining normal corneal hydration. The corneal endothelium is a single layer of hexagonal cells covering the posterior surface of the cornea (Maurice and Mishima 1984). Junctional complexes between endothelial cells were seen in the New Zealand White rabbit from 13 days after birth (Kaye et al. 1973). Tight junctions are present in corneal endothelium but they are not as tight as those in epithelium as judged by its permeability to horseradish peroxidase (Liaw and Robinson 1993). It has been expected that drug molecules with dimensions up to approx 20 nm can diffuse across normal endothelium cell (Gaudana et al. 2009a, b).

Ocular Drug Transporter

The conventional approach to improving ocular bioavailability of drug molecules exploited some chemical modification to accomplish the desired solubility and lipophilicity characteristics in the drug molecule. But this approach is very complicated and expensive. However, a more rational approach would be a transporter-targeted modification of the drug i.e., drug molecule bound with a transporter. Transporters are membrane-bound proteins that play a vital role in the active transport of nutrients and drug molecules across biological ocular membranes. The various transporters present are on various ocular tissues, it is reported by various investigators. However, in the present article, we have focused on the transporters that are localized in the epithelia of the cornea. These ocular transporters may be agreeable to bind and transport specific-targeted ligands attached to drug moieties. Mainly two types of transporter systems are of interest in ocular drug delivery i.e., efflux and influx transporters (Gaudana et al. 2009a, b; Mannermaa et al. 2006; Dey et al. 2003a, b).

Efflux transporter

Efflux transporters belong to the ATP-binding cassette superfamily. This transporter decreases the bioavailability of the drug by effluxing the molecules out of the cell membrane and cytoplasm of the eye. Prominent efflux transporters identified in ocular tissues include P-gp. The other transporter is multidrug resistance protein (MRP), and BCRP. The P-gp efflux transporters have an affinity to efflux lipophilic compounds in normal as well as in cancerous cells, possibly leading to the emergence of drug resistance. Expression and functional activity of P-gp were identified on various ocular cell lines and tissues such as the cornea, conjunctiva as well as a retinal epithelial cell (Kawazu et al. 1999; Dey et al. 2003a, b). The functional activity of MRP transporter are similar to P-gp, but it effluxes only organic anions and conjugated compounds. There are mainly nine isoforms MRP, only three were recognized in ocular tissues i.e., MRP1, MRP2, and MRP5. MRP1 was present in rabbit conjunctival epithelial cells. The efflux pump inhibition can be caused by the following mechanisms (Dey et al. 2004) (Figs. 6.3 and 6.4).

- By blocking of drug binding sites competitively, noncompetitively or allosterically
- By interfering with ATP hydrolysis
- By altering integrity of cell membrane lipids

Influx Transporter

Influx transporters belong to the solute carrier (SLC) superfamily. The amino acid (SLC1, SLC6, and SLC7) and peptides are most commonly pertinent influx

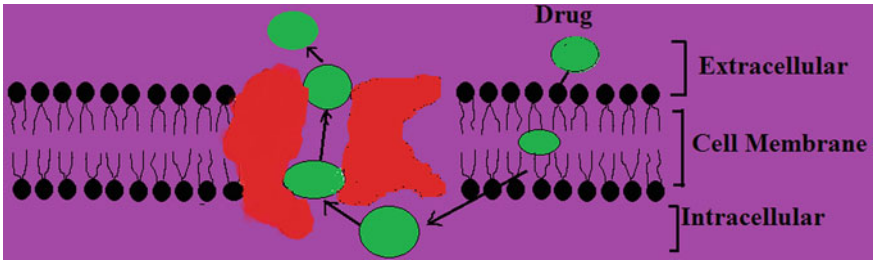

Fig. 6.3 Transportation of drug molecule into the cell

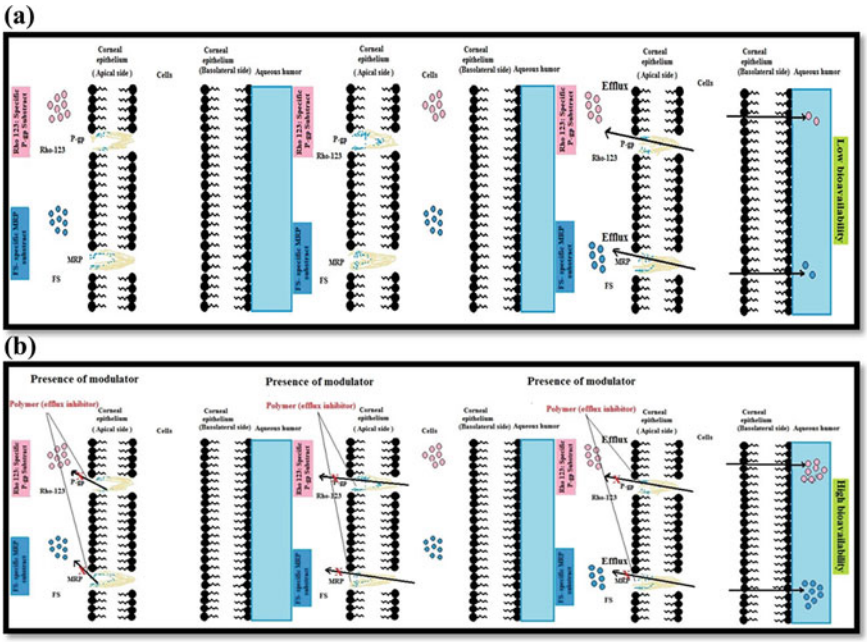

Fig. 6.4 Proposed mechanism of ocular drug transport **a** absence of modulator **b** presence of modulator

transporters for ocular drug delivery. Other types of transporter includes vitamins, glucose, lactate, and nucleoside/nucleobases. These proteins transporter may have a putative role in ocular drug delivery along with their physiological role of transporting various amino acids and nutrients into ocular tissues. Influx transporters assist the transportation of essential nutrients and xenobiotics across biological membranes of the eye.

Nanotechnology Exploited for Transcorneal Drug Delivery

The development of a wide spectrum of nanoscale technologies is beginning to change the scientific landscape in terms of disease diagnosis, treatment, and prevention. These technological innovations, referred to as nanomedicines by the National Institutes of Health, have the potential to turn molecular discoveries arising from genomics and proteomics into a widespread benefit for patients. Nanoparticles can mimic or alter biological processes (e.g., infection, tissue engineering, de novo synthesis, etc.).

The aim of targeted drug delivery and controlled release is to manage better drug pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity and biorecognition of systems in the quest for improved efficacy.

Nanoparticles (NPs), as the very name implies, are particles varying in size from 10 to 1000 nm and depending on the end use, may or may not contain a drug molecule. The drug may be attached to a nanoparticle matrix, or dissolved, encapsulated and entrapped, giving rise to different terminologies as nanoparticles, nanospheres or nanocapsules. All these terms signify their most general characteristic, i.e. they are nanosize particles. Drug loaded nanoparticles (DNPs) constitute an almost versatile drug delivery system, with their ability to overcome physiological barriers and guide the drug to specific cells or intracellular compartments either by passive or ligand-mediated targeting mechanisms (De compose et al. 2001; Quaranta et al. 2013a, b). For ophthalmic applications, properly formulated DNPs are reported to provide ease of application just like eye drop solutions, with the added advantage of being patient friendly, due to less frequent application and extended duration of retention in the extraocular portion. Although the size of the nanoparticles is in the colloidal range which is more precisely accepted to fall between 1 nm and 0.5 μm for ophthalmic formulations, such a preparation may contain larger particles albeit within the colloidal range stated earlier. Terminologies like lyophilic and lyophobic have been used to characterize the dispersion medium, lyophilic systems are usually easier to prepare and have greater stability. Thus, DNPs being organic molecules disperse readily upon addition to the dispersion medium to form colloidal dispersions.

Polymeric Nanoparticles

Polymeric nanoparticles have attracted the interest of many research groups and have been utilized in an increasing number of fields during the last decades. The polymeric nanoparticle enhanced the corneal permeation through enhancing precorneal residence time of the drug. Different polymers can be used to fabricate polymeric NPs such as biodegradable polymers like polylactide (PLAs), poly (D,L-lactides), polylactic-co-glycolic acid, E-caprolactone, (Fessi et al. 1989; Kumari et al. 2010; Addo et al. 2010, 2015; Aksungur et al. 2007; Gupta et al. 2011),

polyacrylamide, polycyanoacrylate and polymethylmethacrylate (Zimmer et al. 1991; Wenger et al. 2011) and natural polymers like chitosan (Jain et al. 2013), gelatin (Vandervoort and Ludwig 2004), sodium alginate (Zhu et al. 2012), albumin (Zimmer et al. 1994; Merodio et al. 2002) and tamarind kernel polysaccharide (Kaur et al. 2012) can be used effectively for efficient drug delivery to the ocular tissues. Many researchers conducted the study on nanoparticulate drug delivery system and found that it prevents the degradation of the drug in the ocular environment and release of drug over an extended period of time which gives the desired effect (Gupta et al. 2010; Javadzadeh et al. 2010).

Poly (Alkyl Cyanoacrylate) (PACA) Nanoparticles

Poly (alkyl cyanoacrylate) nanoparticles particles possess properties of biodegradation and bioadhesion, making them of considerable interest as possible drug carriers for controlled ocular drug delivery and drug targeting.

Zimmer et al. (1994) developed pilocarpine nitrate loaded polybutylcyanoacrylate nanoparticles. The pharmacokinetic study in the eyes of New Zealand white rabbits showed that pilocarpine nitrate loaded polybutylcyanoacrylate nanoparticles exhibited an increase of 23 % in pilocarpine levels in aqueous humor and prolonged $t_{1/2}$ compared to the aqueous control solution.

In another study, adsorption of pilocarpine onto polybutylcyanoacrylate nanoparticles enhanced the miotic response by about 22 % compared to the control aqueous drug solution (Harima et al. 1986).

Diepold et al. incorporated pilocarpine into polybutylcyanoacrylate nanoparticles and evaluated the aqueous humor drug levels and the intraocular pressure-lowering effects using three models (the water-loading model, the alpha-chymotrypsin model, and the betamethasone model) in rabbits. Pilocarpine loaded polybutylcyanoacrylate nanoparticles exhibited about 33 % increment of miotic response while the miotic time increased from 180 to 240 min compared to the control solution (Diepold et al. 1989).

Vidmar et al. studied the intraocular pressure-lowering effects of pilocarpine hydrochloride loaded poly (lactic acid) microcapsules. Developed poly (lactic acid) microcapsules of pilocarpine hydrochloride prepared by a solvent precipitation method prolonged miosis about 4 h in comparison to control solution in Female albino rabbits (Vidmar et al. 1985).

A significant improvement in the bioavailability of pilocarpine was attained by co-administering the pilocarpine-loaded albumin nanoparticles with the viscous bioadhesive polymer mucin (Zimmer et al. 1995).

In a clinical study with Piloplex (latex emulsion of pilocarpine hydrochloride), a lower level of the drug with less fluctuation compared to the corresponding control solution was observed on the third day of treatment. This study involving nine subjects showed a reduction by 5.25 mmHg of the average diurnal intraocular pressure (IOP) value compared to the control. Only one out of 30 patients

complained of a local sensitivity reaction with Piloplex in the yearlong study (Ticho et al. 1979a, b).

Similar results were obtained in yet another study involving 50 patients, where 67.6 % of the eyes treated with the formulation were under control, while only 45.2 % were under control with the pilocarpine solution (Ticho et al. 1979a, b).

Poly-E-caprolactone nanocapsules also showed good performance in increasing the ocular availability of drugs such as metipranolol (Losa et al. 1993) and betaxolol (Marchal-Haussler et al. 1992) while suppressing their systemic absorption.

Losa et al. developed PECL nanocapsules of metipranolol. The developed nanocapsule exhibited a significant reduction in the intraocular pressure similar to the commercial ophthalmic solution of the drug, but the systemic side effects, studied by evaluation of the cardiovascular effects, were significantly suppressed with the nanocapsules. The heart rate reached normal values within an hour of administration of nanocapsules versus the commercial eye drops, which showed pronounced bradycardia for more than 2 h (Losa et al. 1992).

Marchal-Heussler et al. developed carteolol loaded PECL nanoparticle and nanocapsule (with a TiO_5 oily core) for the treatment of glaucoma. Both formulations demonstrated a pronounced decrease in the intraocular pressure (IOP) compared to the commercial aqueous solution in rabbits with induced intraocular hypertension. The PECL carriers increase the residence time of the drug, enhance the corneal uptake of the drug in unionized form, and decrease the systemic side effects (Marchal-Heussler et al. 1993).

Chitosan Nanoparticles

Kao et al. developed pilocarpine-loaded chitosan/Carbopol nanoparticles. Pilocarpine loaded in nanoparticles showed an initial burst release followed by a continuous and sustained release for 24 h. The in vivo miotic study of developed nanoparticle in New Zealand albino rabbits exhibited the excellent extended miosis effect of pilocarpine (Kao et al. 2006).

Wadhwa et al. developed dorzolamide hydrochloride (DH) and timolol maleate (TM) loaded hyaluronic acid (HA) modified chitosan (CS) nanoparticles (CS-HA-NPs) for the management of glaucoma. Hyaluronic acid provides a synergistic effect for mucoadhesion in association with chitosan. CS-NPs and CS-HA-NPs exhibited a significant reduction in IOP level compared to a plain solution of a drug when administered in glaucomatous male albino rabbits (Wadhwa et al. 2010).

Singh and Shinde developed brimonidine tartrate (BT) loaded chitosan nanoparticles (BT-CS-NPs) for controlled delivery of BT to the ocular membrane. BT-CS-NPs exhibited a significantly higher reduction in IOP compared to marketed formulation (alphagan® P) in glaucomatous female New Zealand rabbits. Draize eye test showed no redness or sign of irritation after instillation of the BT

nanoparticles. Furthermore, BT-CS-NPs exhibited initial burst release followed by a prolonged release of BT (Singh and Shinde 2011).

Jain et al., developed betaxolol hydrochloride loaded chitosan nanoparticles (CS-NPs) for ocular delivery and studied their anti-glaucoma efficacy. In vivo pharmacodynamic study in dexamethasone-induced glaucoma model in Male New Zealand albino rabbits showed that betaxolol hydrochloride loaded CS-NPs exhibited gradual reduction of IOP reaching peak value of 9.9 ± 0.5 mm Hg, equivalent to 36.39 ± 1.84 % reduction in IOP compared to control at the end of 5 h which was significant compared to marketed formulation (Jain et al. 2013).

Lin et al. developed pilocarpine-loaded chitosan-PAA nanosuspension using template polymerization of acrylic acid (AA) in a chitosan solution. Both in vitro and in vivo studies in New Zealand albino rabbits revealed that the prepared nanoparticle suspension exhibited better sustained release of pilocarpine than either simulated tear fluid or commercial eye drops (Lin et al. 2007).

Singh et al. prepared pH-triggered polymeric nanoparticulate in situ gel for ophthalmic delivery of acetazolamide by nanoprecipitation method and Carbopol 934P as a gelling agent. The optimized formulation exhibited 3.5-fold (74.50 μg/cm^2) higher permeation than eye drops (20.08 μg/cm^2), prolonged pre-corneal residence time, significant decrease in IOP in comparison to eye drops and sustained drug release along with higher in vitro efficacy, safety and patient compliance (Singh et al. 2014).

Eudragit Nanoparticles

Bhagav et al., developed brimonidine tartrate loaded Eudragit nanoparticles by double emulsion-solvent evaporation technique for the treatment of open-angle glaucoma. The developed nanoparticles were subjected to in vivo intraocular pressure-lowering efficacy studies by administering aqueous dispersion of nanoparticles into the lower cul de sac of glaucomatous rabbits. The selected nanoparticle upon in vivo ocular irritability and tolerability tests were well tolerated with no signs of irritation. The nanoparticle formulations showed a reduction in the elevated IOP in rabbits with glaucoma for a longer period of time. Selected nanoparticles exhibited 7 folds higher AUC (ΔIOP vs. t) value compared to the eye drop preparations (Bhagav et al. 2011).

Poly (DL-Lactide-Co-Glycolide) Nanoparticles

Musumeci et al. developed Melatonin loaded poly (D,L-lactide-co-glycolide) (PLGA) and PLGA-poly(ethylenglycole) (PEG) nanoparticles (NPs) to prolong the pharmacological effects of melatonin to modulate the IOP. The hypotensive effect was evaluated by measuring IOP during 24 h after instillation in the eye of Male albino rabbits of the New Zealand strain in comparison with a melatonin aqueous solution at the same concentration (0.08 %, w/v). Their developed NPs showed

good ocular tolerability in rabbit eye using biomicroscopy. Melatonin-loaded PLGA-PEG NPs exhibited 5 mmHg IOP reduction up to 8 h (Musumeci et al. 2013).

Warsi et al. developed dorzolamide (DZ)-loaded PLGA nanoparticle by using two different emulsifying agents (PVA and vitamin E TPGS) for the treatment of glaucoma. Nanoparticles emulsified with vitamin E TPGS (DZ-T-NPs) were found to have higher encapsulation efficiency (59.8 ± 6.1 %) when compared to PVA as emulsifier (DZ-P-NPs). Y-Scintigraphy studies showed the reduced corneal clearance, as well as nasolacrimal drainage in comparison to drug solution. Also, efficacy study revealed that DZ-P-NPs and DZ-T-NPs markedly reduced the intraocular pressure after a single topical instillation into the eye (Warsi et al. 2014) (Table 6.2).

Lipid-Based Nanoparticles

The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size. However, the scarcity of safe polymers with regulatory approval and their high cost have limited the widespread application of nanoparticles to clinical medicine.

To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs) which are attracting the wide attention of formulators world-wide.

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) were introduced in 1991, are used as alternative carrier systems to traditional colloidal carriers for treatment of glaucoma, such as emulsions, liposomes and polymeric micro- and nanoparticles (Uner and Yener 2007; Zhang et al. 2010; Hu et al. 2005; Wasutrasawat et al. 2013; Parhi and Suresh 2010). SLNs indicate lipids, which are used in the development of nanoparticles; it is solid at room temperature and body temperature. They are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interfaces, and are attractive for their potential to improve the performance of pharmaceuticals, nutraceuticals and other materials (Kalam et al. 2010; Seyfoddin et al. 2010).

Table 6.2 Polymeric nanoparticles exploited for ocular delivery in glaucoma

Drug molecules	Polymer used	Formulation	Inferences	References
Betaxolol	Chitosan	Nanoparticles	Marked reduction in IOP	Jain et al. (2013)
Dorzolamide hydrochloride (DH) or timolol maleate	Hyaluronic acid + chitosan	Nanoparticles	Formulation showed significantly decrease in intra ocular pressure (IOP) due to bioadhesive nature of polymer, which enhanced the corneal contact time	Wadhwa et al. (2010)
Dorzolamide HCl and Pramipexole HCl	Chitosan	Nanoparticles	Formulation showed good mucoadhesion and sustained in vitro release	Papadimitriou et al. (2008)
LCS-NP complex	Chitosan	Nanoparticles	Formulation showed no cytotoxicity on conjunctival epithelial cell line IOBA-NHC and strong cellular uptake by corneal epithelium due to bioadhesive nature of polymer	Diebold et al. (2007)
Metipranolol	Chitosan	Nanoparticles	Decreases the systemic side effect because it decreases or inhibits the nasolacrimal drainage	Losa et al. (1993)
Pilocarpine	Albumin	Nanoparticles	Increased the bioavailability of pilocarpine by about 50–90 % (miosis), and decreased IOP 50–70 %, when compared to pilocarpine solution due to high surface of nanoparticles, it enhanced the corneal contact time and decreases nasolacrimal drainage of drug	Zimmer et al. (1994)
Melatonin	PLGA	Nanoparticles	Formulation showed significant decrease in intraocular pressure due to high surface area of particles and minimizes the drainage of drug through tear fluid	Musumeci et al. (2013)
Brimonidine and timolol maleate	PLGA	Hybrid hydrogel Dendrimer	Formulation showed sustained release of drug over a day. Significantly reduced the intraocular pressure	Yang et al. (2012)

(continued)

Table 6.2 (continued)

Drug molecules	Polymer used	Formulation	Inferences	References
Carteolol	Polyalkylcyanoacrylate (PACA)	Nanoparticles and Nanocapsules	Decrease in IOP was much more pronounced with carteolol incorporated into the colloidal carriers than with the commercial eye drops	Heussler et al. (1993)
Metipranolol	PBCA/PECL	Nanocapsules	10 % reduction in IOP in 6 h	Losa et al. (1993)
Acetazolamide	Lipid	Liposomes	The positively charged and neutral liposomes exhibited greater lowering in IOP and a more prolonged effect than the negatively charged ones in rabbit eye	Hathout et al. (2007)
Acetazolamide	Lipid	liposome	Significant and prolonged decrease in IOP compared to the solution of free drug and plain niosomes	Guinedi et al. (2005)
Acetazolamide	Lipid	Liposome	Strong and sustained reduction in IOP in rabbits	Omaima and Ahmed (1997)
Pilocarpine	Lipid	Liposome	Prolonged duration of the miotic effect as compared to aqueous solutions and non-coated vesicles	Durrani et al. (1992)
Penicillin G	Lipid	Liposome	More than four-fold flux increase across isolated rabbit cornea	Kaur et al. (2004)
Timolol maleate	Non-ionic surfactant	Niosome	It showed 1.7 times higher peak concentration of drug in aqueous humor when compared to timolol maleate solution with 2.34 times AUC	Kaur et al. (2010)
Acetazolamide	Span 60	Niosome	Formulation showed higher aqueous humor drug concentration due to enhanced corneal permeation	Aggarwal et al. (2007)

Nanostructured Lipid Carriers

NLCs were introduced to overcome the potential difficulties with SLNs. The goal was to increase the drug loading and prevent drug expulsion. This could be visualized in three ways. In the first model, spatially different lipids (like glycerides) composed of different fatty acids are mixed. The use of spatially different lipids leads to larger distances between the fatty acid chains of the glycerides and general

imperfections in the crystal and thus provides more room for accommodation of guest molecules. The highest drug load could be achieved by mixing solid lipids with small amounts of liquid lipids (oils) (Kalam et al. 2010; Wang et al. 2014a, b).

Wang et al. developed and evaluated Methazolamide (MTZ) loaded solid lipid nanoparticles modified with low molecular weight chitosan for the treatment of glaucoma. In vitro release profile of MTZ from CS-SLN-MTZ exhibited prolonged release pattern. CS-SLN-MTZ exhibited excellent permeation in excised New Zealand albino rabbit cornea. In vivo studies revealed that the CS-SLN-MTZ exhibited significantly higher IOP-lowering effect of (245.75 ± 18.31 mmHg × h) compared to both SLN-MTZ (126.74 ± 17.73 mmHg × h) and commercial product Brinzolamide Eye Drops AZOPT® (171.17 ± 16.45 mmHg × h). CS-SLN-MTZ showed no ocular irritancy sign to the Draize method and the histological examination (Wang et al. 2014a, b).

Chen et al. developed methazolamide loaded phosphate (CaP) nanoparticles for local delivery of methazolamide to the eye. In vitro release study of methazolamide loaded CaP-NPs exhibited release as diffusion-controlled from the CaP-NPs over a period of 4 h. In vivo study indicated that the intraocular pressure (IOP)-lowering effect of the inorganic nanoparticle eye drops lasted for 18 h, which was significantly better than the effect of 1 % brinzolamide eye drops (6 h) (Chen et al. 2010).

Tuomela et al. developed brinzolamide (BRA) loaded nanocrystal formulation. The intraocular pressure (IOP) lowering effect was investigated in vivo using a modern rat ocular hypertensive model and elevated IOP reduction was seen in vivo with all the formulations. The developed nanocrystal exhibited significantly decreased intraocular pressure values in rat ocular hypertension model. Furthermore, all formulations showed advantageous dissolution and absorption behavior.

Leonardi et al., developed melatonin (MEL) loaded cationic solid lipid nanoparticles. The ocular hypotensive effect was evaluated by measuring the intraocular pressure (IOP) during 24 h in Male albino rabbits of the New Zealand strain. MEL loaded SLNs exhibited a significant IOP reduction in the rabbit eye. All the formulations tested in vivo demonstrated a good tolerability. The nanocarrier containing stearic acid was the most effective in terms of IOP reduction (maximum IOP reduction: −7 mmHg), and its effect lasted approximately 24 h (Leonardi et al. 2014).

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