Improved Ocular Drug Delivery: A Prodrug Approach

Malgope Ananya\textsuperscript{1} and Dey Sanjay\textsuperscript{2*}

\textsuperscript{1}Royal College of Pharmacy and Health Sciences, Andhapasara Road, Berhampur, Ganjam-760002, Orissa, India
\textsuperscript{2}Bengal College of Pharmaceutical Sciences and Research, S.S.B. Sarani, Bidhanagar, Dugapur-713212 West-Bengal, India.

Abstract: Topical application of eyedrops has been mainly used for treatment of ocular diseases. After instillation of an eyedrop, less than 5\% of the applied dose reaches the intraocular tissues. Rapid loss of the instilled solution from the precorneal area and poor corneal penetration of the drug results in low ocular bioavailability. However, ocular absorption of a drug can be improved by increasing its lipophilic properties. Prodrug derivatization is a suitable approach to achieve the desired goal. But unfortunately, stability and solubility problems in the resulting compounds as well as local irritation have limited their efficacy and clinical acceptability. This review summarizes the application of prodrugs designed to improve the ocular activity and to minimize the systemic and local toxicity of ocular drugs.

Keywords: Ocular prodrug; Ocular absorption; Corneal penetration; Lipophilicity.

Introduction

Various approaches have been developed during the last two decades to improve ocular drug absorption. Increase the contact time of the drug through vehicles and mechanical obstruction are the traditional approaches to improve ocular drug penetration. The various drug delivery systems like viscous solutions, suspensions, ointments, gels, thermosetting gels, polymeric inserts, micro and nanoparticles and liposomes are commonly used to prolong corneal retention of ocular drugs [1-2]. Prodrug, soft-drug and the chemical delivery system (CDS) are the chemical approaches that improve ocular drug delivery by improving drug penetration across the cornea.

The term prodrug refers to a pharmacologically inactive compound that is converted to an active drug by a chemical or enzymatic transformation which may occur prior during and after absorption or at specific target sites within the body [3]. Prodrugs have also been called reversible or bioreversible derivatives and latentiated drugs [4]. Unlike prodrugs, soft-drugs are active drugs which are designed to undergo a predictable and controllable activation in vivo. If the prodrug approach is applied to a soft-drug the resulting is known as a ‘pro-soft drug’ [5]. A CDS or site-specific CDS is an inactive drug derivative which undergoes several predictable enzymatic transformations and finally delivers the active drug to the site of action.

About 15 years ago, prodrugs were introduced into ophthalmology when ocular absorption of epinephrine was substantially improved by its prodrug, dipivefrine. Now a days, it has replaced epinephrine in treatment of the elevated intraocular pressure (IOP) associated with glaucoma. Since the prodrugs dipivefrine have been designed to improve the efficacy, to prolong their duration of action and/or to reduce the systemic side-effects. The drawback of prodrugs associated with the stability and solubility as well as local irritation have limited their efficacy and clinical acceptability. An ideal ocular prodrug should be stable and soluble in aqueous solutions.
to enable formulation, sufficiently lipophilic in order to penetrate through the cornea, non-irritative, and able to release the parent drug within the eye at a rate that meets therapeutic need. The present article primarily reviews the most recent literature on ocular prodrugs.

**Considerations for Ocular Prodrug Design**

Topical delivery of eyedrops into the lower cul-de-sac is the most common method of drug treatment in ocular diseases. The tightness of the corneal epithelium barrier, as well as the rapid precorneal drug elimination and systemic absorption from the conjunctiva limit ocular absorption of topically applied drugs [6].

**Ocular Absorption**

The cornea is generally considered as a major pathway for ocular penetration of topically applied drugs [7]. Hydrophilic and large molecules which show poor corneal permeability may primarily absorb via conjunctival and scleral route [8]. The cornea is anatomically composed of epithelium, Bowman’s membrane, stroma, Descemet’s membrane and endothelium, but only the epithelium, stroma, and endothelium represent barriers to drug absorption.

Usually, the lipophilic corneal epithelium, which is 6-7 cell layers thick, is the main barrier of drug absorption into eye. The stroma is a highly hydrophilic tissue which consists mostly of water. Due to a relatively open structure, drugs with molecular size up to 500 000 Dalton can diffuse in normal stroma [9]. Only for the most lipophilic drugs, hydrophilic corneal stroma represents the rate limiting barrier to ocular absorption. Tight junctions are present in corneal endothelium but they are not as tight as those in the epithelium [10]. It was estimated that drugs with molecular dimension up to about 20 nm can diffuse in normal endothelium [11].

For most ocularly applied drugs, passive diffusion is thought to be the main transport process across cornea. Drug penetration across cornea occurs via transcellular and paracellular pathways. Physicochemical properties of drug, such as lipophilicity [12], solubility, molecular size and shape [13], drug charge [14] and degree of ionization [15], affect the transport pathway and transport rate of drug across the tissue.

Lipophilic drugs prefer the transcellular pathway. Hydrophilic drugs penetrate primarily through the paracellular pathway that involves passive or altered diffusion through intercellular spaces [16]. The optimum apparent partition coefficient ($P_{app}$) in octanol/buffer (pH 7.4) for corneal drug penetration was found to be in the range of 100 to 1000 [17]. The rate-limiting barrier for ocular penetration of highly hydrophilic drugs is a lipophilic corneal epithelium.

**Biotransformation of Ocular Prodrugs**

Enzymatic transformation of prodrugs in ocular tissues is often utilized for releasing the active drug. Usually, enzymatic bioconversion of prodrugs has been studied only in rabbits. The ocular tissues of rabbit contain true esterases, such as acetyl cholinesterase (AChE) [18] and butyrylcholinesterase (BuChE) [19], carbonic anhydrase [20] which has some esterase activity [21], peptidases [22] and phosphatases [23]. Esterases are present in several ocular tissues [24], but not in tears [25]. Many ophthalmic drugs contain hydroxyl or carboxyl groups that can be esterified to lipophilic ester-prodrugs. AChE and BuChE are considered to be critical in the enzymatic hydrolysis of ester-prodrugs. Absence of AChE and BuChE in tears [26] ensures the absorption of intact ester-prodrug into the corneal epithelium.

**Prodrugs of Adrenergic Agonist**

**Epinephrine Prodrugs**

Dipivefrine, a dipivalyl prodrug-ester of epinephrine, has currently replaced epinephrine in the treatment of glaucoma. Dipivalyl epinephrine (dipivefrine) is a dipivalic acid diester of epinephrine which releases epinephrine after corneal absorption [27]. Dipivefrine penetrates the human cornea 17 times better than epinephrine [28] due to fact that dipivefrine is 600 times more lipophilic (at pH 7.2) than epinephrine [29]. As compared to the conventional 2% epinephrine hydrochloride eyedrop, a 0.1% dipivefrine eyedrop is slightly less effective on IOP lowering effect, while side-effects are greatly reduced [30].
**Phenylephrine Prodrugs**

Phenylephrine is an alpha-adrenergic agent used clinically for pupil dilation. The ocular bioavailability of phenylephrine is low due to its hydrophilic nature ($\log P_{\text{app}} = -1.89$) [31]. Due to systemic absorption, the large topical dose of phenylephrine may cause systemic side-effects, such as severe hypertension, ventricular arrhythmia, and possible myocardial infraction [32]. Phenylephrine oxazolidine is a lipophilic ($\log P_{\text{app}} = 1.38$) prodrug of phenylephrine [33]. The oxazolidine prodrug converts to phenylephrine very quickly in aqueous solution at pH values ranging from 1 to 7.4 ($t_{1/2} = 6-13$ min). Thus, oxazolidine prodrug eye drops are formulated in non-aqueous solution (sesame oil). Compared to 10% phenylephrine eyedrops, 10% oxazolidine prodrug eyedrops increased phenylephrine levels in aqueous humor 6-8 fold and improved mydriatic activity 4-fold in rabbits [34].

**Prostaglandins**

Topical administration of PGs increases Intraocular pressure (IOP). However, the effect of topical PGs on IOP depends on the applied dose. Many PGs decrease IOP, major attention has been focused to PGF$_{2\alpha}$ and its analogs. PGF$_{2\alpha}$ is an effective ocular hypotensive agent in humans [35] but is not clinically acceptable due to the adverse ocular side effects [36]. Thus the main objective of PGF$_{2\alpha}$ research is to design a non-irritating ophthalmic drug delivery system. The prodrug technique is one suitable approach to achieve this goal.

The first PGF$_{2\alpha}$ prodrugs involved esterification of the 1-carboxylic acid group. These PGF$_{2\alpha}$-l-methyl and PGF$_{2\alpha}$-l-isopropyl esters greatly enhanced the corneal uptake of PGF$_{2\alpha}$ where they released the free acid, PGF$_{2\alpha}$ [37]. Compared to ocular administration of PGF$_{2\alpha}$ itself, PGF$_{2\alpha}$-1-esters increased concentration of PGF$_{2\alpha}$ in intraocular tissues (aqueous humor, ciliary body, iris) and improved its ocular hypotensive potency [38]. Unfortunately, their therapeutical use was limited by ocular side-effects [39].

Recently a novel series of PGF$_{2\alpha}$ prodrug esters with the acyl group at the 9-, 11- and 15-positions, has been reported [40]. PGF$_{2\alpha}$-9-acyl esters did not convert to PGF$_{2\alpha}$ but 11-mono, 15mono, and 11,15-diesters were converted. All the prodrugs that converted to PGF$_{2\alpha}$ decreased IOP in rabbits. These new PGF$_{2\alpha}$ esters (e.g. PGF$_{2\alpha}$-11-pivaloyl, PGF$_{2\alpha}$-9,11-dipivaloyl, PGF$_{2\alpha}$-11,15-diisovaleryl) seem promising since they lowered IOP efficiently with mild ocular side-effects. PGF$_{2\alpha}$-1,11-lactone and PGF$_{2\alpha}$-1,15-lactone both decreased IOP in rabbits but only PGF$_{2\alpha}$-1,11-lactone lowered IOP without substantial ocular side-effects.

**Prodrugs of β-adrenergic Antagonists**

β-Antagonists are effective ocular hypotensive agents which decrease IOP by decreasing the formation of aqueous humor [41]. Currently, timolol is one of the most frequently prescribed drugs for the reduction of the elevated IOP. In addition to timolol, betaxolol, levobunolol and metipranolol are in clinical use. Also various other beta blockers, such as atenolol, carteolol, labetalol, metoprolol, nadolol, pindolol and propranolol, have been evaluated for their topical ocular hypotensive activity. The clinical acceptance of eyedrops containing a beta blocker, especially a nonselective beta blocker, is limited mostly by the systemic side effects associated with ocular therapy.

**Timolol Prodrugs**

Timolol is a base with a pKa value of 9.2 [12]. The log $P_{\text{app}}$ value for timolol at pH 7.4 being -0.04 [42]. The low lipophilicity of timolol hinders its corneal absorption and less than 5% of the instilled dose gains access to internal eye structures [43]. Various alkyl, cycloalkyl, aryl esters and a carbamate ester have been prepared by esterifying the hydroxyl group of timolol [44]. All the studied prodrugs were more lipophilic than timolol and the most promising examples penetrated the cornea substantially better than timolol [45]. Compared to an equivalent timolol solution, O-butyryl timolol increased the corneal absorption of timolol 4-6 times but did not affect systemic absorption of timolol via nasal mucosa and conjunctiva of the eye [46].

**Nadolol Prodrugs**

Nadolol is a hydrophilic ($\log P_{\text{app}} = -0.82$, pK$_a$ 9.39) nonselective beta blocker [47]. The low corneal
permeability of nadolol is probably the main reason for its poor clinical efficacy. Diacetyl
nadolol, a prodrug of nadolol, is about 20 times more lipophilic than nadolol and enhanced the
ocular absorption of nadolol in rabbits in vivo about 10-fold compared to nadolol [48].

**Tilisolol Prodrugs**

Tilisolol is a nonselective, hydrophilic (log \( P_{app} = -0.27 \)) beta blocker [49]. As with other interesting prodrugs of beta blockers, tilisolol prodrugs are more lipophilic than the active drug itself. The corneal penetration of tilisolol prodrugs was 3-6-fold higher than that of tilisolol in vitro but the prodrugs did not increase the conjunctival and scleral penetration of tilisolol.

**Oxprenolol Prodrugs**

Oxprenolol (log \( P_{app} = 0.32 \)) has not been reported to decrease IOP in animals or human. However, lipophilic oxprenolol ester prodrugs have been developed for ocular use [50], but their corneal permeabilities or effects on IOP have not been established.

**Pilocarpine Prodrugs**

Pilocarpine is a direct-acting cholinergic agonist used for the control of the elevated IOP associated with glaucoma. Pilocarpine shows a low ocular bioavailability (1-3% of instilled dose) due to poor absorption into the cornea. Consequently, concentrated pilocarpine eyedrops must be administered 3-4 times daily resulting in undesirable side-effects and poor patient compliance. The absorption of pilocarpine is mainly limited by its low lipophilicity (log \( P_{app} = -0.15 \)) [51] and its short duration of action is due to rapid elimination. Thus lipophilic prodrugs of pilocarpine providing controlled release and improved ocular delivery have been developed.

**Carbonic Anhydrase Inhibitor Prodrugs**

Carbonic anhydrase inhibitors (CAIs) like acetazolamide, methazolamide, ethoxzolamide and diclofenamide, are used systemically in the treatment of glaucoma [41]. The limited aqueous solubility of active CAIs has been thought to hinder their topical use. Recently, the prodrug approach and CD technology [52] have been applied to increase their aqueous solubility. A series of O-acyl derivatives of 6-hydroxybenzothiazole-2-sulphonamide (L-643, 799) were evaluated as a topically active CAI [53].

**Anti-viral Prodrugs**

**Acyclovir**

Acyclovir is a potent and selective anti-herpes drug [54]. Formulation of acyclovir eyedrops is hampered by its low aqueous solubility (-0.2% at 25 °C) [55]. N-substituted (aminomethyl)benzoate ester prodrugs of acyclovir are weak bases (\( pK_a = 8 \)) and showed high aqueous solubility in weakly acidic solutions [56]. These prodrugs also showed high aqueous stability [57] and may be suitable prodrugs of acyclovir for topical and parenteral applications.

**Idoxuridine**

Idoxuridine (5-iodo-2’-deoxyuridine) is a halogenated pyrimidine derivative used in topical treatment of herpes simplex keratitis. Various aliphatic 5A-ester prodrugs of idoxuridine have been developed to improve the ocular absorption of the drug [58]. The most promising prodrug, 5’-butyryl ester, improved the ocular absorption of idoxuridine about 4 times in rabbits.

**Steroids**

Steroids applied into the lower conjunctival sac (dexamethasone, fluorometholone, hydrocortisone, prednisolone) are used clinically to treat inflammations of the eye. The acetate ester prodrugs have been prepared in order to increase the lipophilicity and the corneal absorption of the steroids [59]. Phosphate esters of steroids have been developed in order to increase the aqueous solubility of steroids which makes it possible to prepare aqueous ophthalmic eyedrop solutions containing steroids [60].

**Other Ocular Prodrugs**

**Albuterol Prodrugs**

Albuterol (salbutamol) is a \( \beta \)-adrenergic agonist. Topical albuterol decreased IOP but some side-effects (irritation, tachyphylaxis) were observed [61]. Albuterol triesters were synthesized in order
Improved Ocular Drug Delivery: A Prodrug Approach

to increase the therapeutic index (i.e. the aqueous humor/plasma absorption ratio) of ocularly applied albuterol and the decrease its side effects.

5-Fluorouracil Prodrugs

5-Fluorouracil (5-FU) has been administered subconjunctival and topically into the eye in order to prevent scarring of filtering blebs following glaucoma surgery. Prodrugs of 5-FU improved the corneal penetration of 5-FU 10-50 times due to increased lipophilicity and the protection of 5-FU from metabolism during ocular absorption and later.

Conclusions

Development of an effective ophthalmic prodrug is very challenging task for the researchers, since the prodrug must satisfy certain key criteria (adequate aqueous solubility and stability, reasonable bioconversion to the parent drug, sufficient lipophilicity, adequate safety, etc.) for successful therapy of diseases. Preliminary reports revealed that the physicochemical properties and therapeutic activities of many prodrug derivatives have been very promising in the field of research. However, they are not sufficient effective in humans as they are irritating or produce some undesirable side-effects. So far, now a day dipivefrin and steroid esters are the only ophthalmic prodrugs available in the market. In future, the extensive research on this particular field and an increasing comprehension of ophthalmic drug delivery should produce new commercial and therapeutically effective prodrugs.

References


[51] Loftsson T., Fridriksdottir H., Thorisdottir S., Stefansson E., Sigurardottir A. N., Gudmundsson G.
Improved Ocular Drug Delivery: A Prodrug Approach

55


