Review

Ocular prodrugs: Attributes and challenges

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Article history:
Received 27 January 2020
Revised 17 August 2020
Accepted 26 August 2020
Available online 28 September 2020

Keywords:
Bioavailability
Corneal permeability
Esterase
Stability
Lipophilicity
Ocular prodrugs

Abstract

Ocular drug delivery is one of the most attention-grabbing and challenging endeavors among the numerous existing drug delivery systems. From a drug delivery point of view, eye is an intricate organ to investigate and explore. In spite of many limitations, advancements have been made with the intention of improving the residence time or permeation of the drug in the ocular region. Poor bioavailability of topically administered drugs is the major issue pertaining to ocular drug delivery. Several efforts have been made towards improving precorneal residence time and corneal penetration, e.g. iontophoresis, prodrugs and ion-pairing, etc. Prodrug approach (chemical approach) has been explored by the formulation scientists to optimize the physicochemical and biochemical properties of drug molecules for improving ocular bioavailability. Formulation of ocular prodrugs is a challenging task as they should exhibit optimum chemical stability as well as enzymatic liability so that they are converted into parent drug after administration at the desired pace. This review will encompass the concept of derivatization and recent academic and industrial advancements in the field of ocular prodrugs. The progression in prodrug designing holds a potential future for ophthalmic drug delivery.

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1. Introduction

The foremost problem in the ocular drug delivery is the attainment of an optimal drug concentration at the site of action. The main route for the topically instillation of drugs into eyes is the cornea, whereas conjunctival and scleral route can also be utilized [1,2]. There have been number of positive attributes of topical administration due to which they are more preferred like expeditious onset of action, small dose, safety, patient compliance, non-invasive etc. On the other hand, negative attributes are also reported such as precorneal drop, restricted concentration of drug for lipophilic agents and physical barriers of cornea [3,4]. Despite of being easily accessible to eyes, topical ocular application inflicts a lot of constraints that are responsible for drainage of the drug that leads to rapid elimination which simultaneously affect bioavailability. The constraints include precorneal factors that rapidly remove drugs from the conjunctiva sac (where it is applied) and structure of the cornea that restricts the passage of drug molecules [5-7]. It becomes quite exigent to deliver drugs to the required site due to the presence of various constraints e.g. physiological limitations (blinking, nasolacrimal drainage, wash out by tears) and anatomical
limitations (blood aqueous and retinal barrier, physical membrane barrier, conjunctival blood and lymph flow) [8–10]. When dose instilled in the eye, some part of medication is expelled out by tear mechanism and remaining leftover dose resides for a small period of time to penetrate from cornea into the eye but poor permeability of cornea allows only small concentrations of active ingredient to pass through it [11, 12]. 1% or even less of applied drug is absorbed and eliminated by metabolic action [13]. Blood ocular barrier comprises of both blood aqueous and retinal barrier that restricts the movement of medicament into ocular compartments. Blood aqueous barrier limits the molecular motion to reach the aqueous humor via iris, ciliary capillaries from blood [14, 15]. Exterior surface of epithelial cells form tight junctions which act as corneal epithelium barrier. The presence of these tight junctions along with lipophilic property of epithelium, forms a highly structured barrier [16–18]. Ultimately small concentration of dose reaches at the site of action. Hence for effective delivery, attempts have been made to improve the bioavailability either by increasing the residence time in conjunctiva sac, or by improving the penetration across cornea. Regardless of ease of topical applied ocular drugs, the required amount of medication does not reach to the target site which in turn builds certain strategies to overcome the issue of bioavailability. Numerous strategies have been used to improve the bioavailability of topically instilled drugs. These strategies include the solubility enhancers improve solubility of drug in the formulation, penetration enhancers alter the drug permeation through corneal epithelium, retention strategies which consist of viscosity enhancing polymers, nanoparticles, in situ gelling system, mucoadhesives etc., ocular inserts and ocular implants etc. [19–26]. Numerous dosage forms e.g. solutions, ointments, gels, microparticles, nanoparticles, and micelles have been developed to tackle the issue of poor ocular bioavailability upon topical instillation of drugs [27]. There are several approaches to improve the bioavailability and corneal penetration but the most challenging and novel approach is prodrugs. The concept of prodrugs was introduced in 1958 by Albert for improving the corneal penetration [28]. The first commercial prodrug was methanamine available in 1899 by Schering [29]. Prodrug design is a chemical approach to transport parent drug molecule to the target site in order to achieve improved drug absorption [30–32]. It remains inactive until unless reach to target site and become active to exert its therapeutic action by altering the structure of drug.

Ocular prodrugs are designed in order to achieve one or more objectives, e.g. improving the efficacy of drugs, reducing side effects, alteration of duration of action or drug targeting, to ameliorate active drug solubility which may improve bioavailability, permeability as well as absorption and thus may alter the distribution profile of the drug that reaches to the target site. It mainly optimizes ADME (absorption, distribution, metabolism, excretion) profile [33]. The present review will be a revisit of utilization of prodrug strategy in ocular drug delivery. There are few imperative factors which are to be considered while formulating ophthalmic prodrugs e.g. the parent drug is required to possess a functional group amenable to chemical derivatization, the chemical modification at the functional group of parent drug must be reversible, prodrug or pro-moiety attached to parent compound must be safe and nontoxic, biological enzymes such as esterase and peptidase should be involved in bioreversion, prodrug should be safe and stable, log P value of prodrug is a significant parameter and lastly prodrug should exhibit high affinity and targeted delivery of parent drug.

2. Prodrug strategy – a novel developing approach

Prodrugs are the medicinal agents that remain inactive until they reach the target site. But when it reaches target site, becomes active to exert its required action [32, 34]. Prodrugs increase corneal drug permeability which is a major issue in ocular drug delivery by modification of hydrophilicity or lipophilicity of the drug. It involves different methods like alteration of chemical structure of drug moiety. Prodrug approach is used for the production of safe ocular drug delivery system that implicit action on the target site. Several factors such as instability, poor solubility, irritation, pain, low absorption, shorter duration of action, poor penetration and permeability are vanquished by the use of prodrugs [35]. The main objectives behind prodrugs in any delivery system are to ameliorate stability, intensify solubility, to improve patient compliance, decrease side effects, increase bioavailability, extended duration of action, and enhanced penetration and permeability [35–37]. The commonly used conventional opthalmic drug delivery include solutions [38, 39], suspensions [40], emulsions [41] and ointments [38, 40]. However, various new strategies that have been incorporated in ocular delivery are nanomicelles, liposomes, dendrimers, contact lens, nanoparticles, nanosuspension, implants etc. Ophthalmic formulation based on nanotechnology is a novel approach which is used for anterior as well as for posterior segment drug delivery. Several nano carriers are designed to ensure adequate bioavailability, low irritation and ocular tissue compatibility. These have been summarized in Table 1.

2.1. Consideration in prodrug designing

While considering prodrug derivatization, the important factors which are required to be considered are transport or mechanism of penetration of drugs, the presence of vulnerable or receptive functional group essential for derivatization, and enumeration of the characteristics or description of enzymes which will be responsible for bioconversion [59–61]. The derived prodrug should be stable in the finally designed dosage form, should possess optimum log P value in order to attain appropriate permeation across dynamic as well as static lipophilic ocular barriers. Parent drug must have the presence of functional group that is susceptible to chemical modification and derivatization at the site of parent drug attached with functional groups should be reversible. In addition, it is important that the parent drug and pro moiety linked with parent compound must be nontoxic and safe. The prodrug should manifest appropriate propinquity and should have targeted or site specific delivery of the parent drug. The significant factors
Table 1 - New strategies of ocular drug delivery system.

| Types          | Description                                                                 | Examples                                                                 | Ref.     |
|----------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------|----------|
| Nanomicelles   | Surfactant and polymeric in nature                                          | Dexamethasone loaded polyhydroxyethylaspartamide                          | [42, 43] |
|                | Small size, easily prepared, high drug encapsulation capacity               |                                                                          |          |
|                | Increase bioavailability of drugs in ocular tissues                        |                                                                          |          |
|                | Copolymers-poly (ethylene oxide), poly (propylene oxide), poly (ethylene oxide) used to build micelles as vehicle for gene therapy |                                                                          |          |
|                | Polymers are incorporated to form micelles that load drug to exhibit enhanced ocular bioavailability |                                                                          |          |
| Liposomes      | Multilamellar or unilamellar                                                | Acyclovir loaded liposome, Visudyne® containing verteporfin, Tears again® | [40, 44–48] |
|                | Cationic liposomes show better efficacy than anionic and neutral because of electrostatic interaction |                                                                          |          |
|                | Enhance residence time as well as enhance absorption                        |                                                                          |          |
| Dendrimers     | Highly branched nanosize polymeric system having functional groups attached | Poyl (amide amine) (PAMAM)                                               | [49, 50] |
|                | Terminal functional group- utilized for conjugating moieties                |                                                                          |          |
|                | Incorporate both hydrophilic and hydrophobic drugs                         |                                                                          |          |
|                | Disadvantage- critical selection of size, molecular geometry, functional groups |                                                                          |          |
| Contact lens   | Curved shape plastic disc that cover cornea                                 | Particle laden contact lenses for delivery of lidocaine.                 | [51, 52] |
|                | Enhance residence time, higher flux through cornea by less drug flow in nasolacrimal duct |                                                                          |          |
|                | To overcome inadequate drug loading, particle laden contact lenses available |                                                                          |          |
|                | Drug loaded in vesicles like liposomes, microemulsion are dispersed in contact lens material |                                                                          |          |
| Nanoparticles  | Size range: 10 to 1000 nm                                                   | Natamycin loaded chitosan                                                | [53, 54] |
|                | Bio adhesive polymer used to exhibit prolong residence                      | Lechitin nanoparticles, Dexamethasone loaded PLGA                       |          |
|                | Made of lipids, proteins, polymers                                         | (Poly lactide co glycolide)                                              |          |
| Nanosuspension | Colloidal dispersion of drug in polymer or surfactants                      | Glucocorticoids-prednisolone, dexamethasone, Fluribuprofen encapsulated in Eudragit RS 100® and RL 100® polymer | [55]     |
|                | Commonly used for delivery of hydrophobic drugs                            |                                                                          |          |
|                | Easy to formulate eye drops, less irritation, increase ocular bioavailability of insoluble drugs in tear fluid |                                                                          |          |
| Implants       | Intravitreal placed with incision by surgery that is posterior to lens and anterior to retina | Implant of gancicllovir (vitrasert)                                      | [56–58] |
|                | Avoids blood retina barrier                                                |                                                                          |          |
|                | Can be biodegradable and non-biodegradable device                          |                                                                          |          |
|                | Non-biodegradable possess long term release                                 |                                                                          |          |
|                | Polymer used in non-biodegradable implants are PVA, ethylene vinyl acetate, polysulfon capillary fiber |                                                                          |          |
|                | Polymer used in biodegradable implants are polyglycolic acid, polyactic acid |                                                                          |          |

which should be considered for ocular drug delivery are explained through Fig. 1 [62–66].

2.2. Consideration in ocular delivery

Nearly in all cases, prodrugs are the chemical derivatives which are one or more chemical or enzymatic steps away from the parent drugs. Many ophthalmic drugs have hydroxyl or carboxyl groups that can be esterified to ester-prodrugs which can be more lipophilic. The esterase activity in corneal epithelium is ~2.5 times higher than that in the stromal endothelium [67]. In addition, it is worth noting that acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) are absent in rabbit’s tears [68], this further ensures the absorption of intact ester-prodrug into the corneal epithelium. Hence, along with presence of enzymes, chemical structure of drugs play a significant role in designing and derivatization of ocular prodrugs.

2.2.1. Adrenergic agonist prodrugs

Epinephrine prodrugs: Epinephrine (EPI) is a choice used in the treatment of glaucoma by exerting its action by blocking beta adrenergic receptors. However, the major drawback associated is cardiovascular unenviable effects when the drug passes into systemic circulation through the tear duct [69]. Enhanced polarity manifests decreased transport across the corneal epithelium which is considered as lipoidal barrier. In consequence, resistance to the permeation occurs due to top two cell layers. Hence, to overcome this problem the prodrug had been designed. A prodrug of EPI is supposed to have an optimum water solubility and lipophilicity in order to deliver drugs to the target site in the eye. Dipivefrin (Dipivalyl
epinephrine) (Fig. 2) is a prodrug that diffuses quickly across ocular tissue and is bio transformed into epinephrine with the help of enzyme called of corneal esterase. It exhibits better therapeutic index than EPI [70, 71]. In addition the study elucidated that absorption and subsequent hydrolysis of dipivefrin takes place in the conjunctiva, which is accounted for ~60%−75% of instilled prodrug recovered in the eye. Furthermore, the investigation revealed the age and pigmentation related variation of esterase activity in case of rabbits [71]. Lipophilicity of Dipivefrin is approximately ~600 fold because of which it exhibits improved corneal penetration [71]. Table 2 summarizes the log P values of EPI and dipivefrin in different solvents. In another investigation, dipivefrin and related compounds have been reported to inhibit passive anaphylactic reactions in rat conjunctiva. The order of activity has been reported as isoproterenol > dipivefrin > EPI > Nor EPI. Dipivefrin was suggested to exert anaphylactic action due to activation of beta adrenergic receptors [72].

Phenylephrine prodrugs: Phenylephrine (PE) is a class of drug that is used for the dilation of pupil mainly during surgery and examination [73]. Its main drawback is lower ocular bioavailability because of high hydrophilicity (log P is −1.89) [74]. It does not permeate well across the cornea because of low lipophilicity. Hence, to overcome these limitations oxazolidines phenylephrine (OPE) was synthesized as a prodrug (Fig. 3) which enhanced lipophilic character and ultimately bioavailability. Oxazolidines are weaker bases (pKa= 6–7) and more lipophilic at physiological pH. Due to enhanced lipophilicity (log P = 1.38) it easily permeates across cornea [75]. OPE lead to ~2 fold more mydriatic effect as compared to PE. 10% suspension of OPE lead to ~8 fold enhanced bioavailability in the aqueous humor, which may
be the reason of faster transport of OPE across the cornea, which further may lead to decrease in the dose of PE [76]. In another study improved lipophilicity of OPE lead to ~3 fold more distribution coefficient and further exerted significant improved mydriatic effect (9 mm) with low dose (1% prodrug) as compared to PE [77].

2.2.2. Antiviral prodrugs

**Acyclovir**: Acyclovir (ACV) is mainly given in patients having herpetic keratitis and corneal disease. ACV has low penetration across the cornea due to its hydrophilicity (log P = −1.22) [78] which may be the reason of decreased ocular absorption and in turn lesser ocular bioavailability. In order to overcome decreased permeability, ACV was converted into prodrug. Biotinylated lipid ACV prodrug was developed to improve ocular bioavailability and absorption of ACV [79]. The most common means of increasing water solubility of drugs containing OH group is by the formation of water soluble ester prodrugs. The ideal characteristics of such prodrugs include high water solubility at pH of optimum stability leading to improved shelf life (more than 2 years) of ready to use solutions. However, practically this is demanding and un governable as generally they are hydrolyzed by enzymes very quickly leading to decreased stability.

Anand and Mitra investigated the permeation and enzymatic hydrolysis of valacyclovir (VACV) [80]. The corneal permeation of VACV (L-valyl ester of acyclovir) was ~3 fold more than ACV. β-lactam antibiotics and angiotensin converting enzyme inhibitors inhibited the transport of VACV which elucidated that the corneal permeation of VACV was dependent on carrier mediated transport system specific for peptides. The flux was pH dependent and was found to be 1.087 ± 0.05 nmole/cm²/min [80]. Numerous esters (valyl, benzoyl, acyl, amino, methyl, glycin, benzoate) of ACV have been synthesized to improve its corneal transport. It is well established that enzymatic process plays a more vital role than chemical processes in hydrolysis. Stability of different ester prodrugs of ACV was studied and stability was found to be in the order of EACV (γ-glutamate) > JACV (L-serine) > IACV (L-isoleucine) > VACV (L-valine) > AACV (L-alanine). Different ester prodrugs of ACV have been mentioned along with their structures that represent the moiety attached responsible for the prodrug activity (Fig. 4). In addition, half-lives of these prodrugs was significantly less and the only exception in this case was EACV whose half-life 82 ± 6 min, MRT (mean residence time) was 149 ± 11 min and Tₘ₉ (time to reach maximum concentration) was 160 ± 11 min. The reason of this was the lack of the amino terminus near the hydraulic site, i.e. the ester linkage [81]. Physiological data of various esters linked with ACV has been mentioned in Table 3.

**Ganciclovir**: It is also an antiviral drug that exhibits action against human cytomegalovirus that leads to infection to AIDS patient, and if remain untreated leads to blindness. Its bioavailability is less due to which it does not get rapidly penetrated into ocular tissues. Its partition coefficient is low (1.55) [78] which contribute towards low corneal bioavailability. Hence, to overcome this drawback, it has been modified into prodrug (Fig. 5). An investigation on ganciclovir (GCV) was carried out by Macha and Mitra in order to determine its intravitreal pharmacokinetics [85]. Acyl monoester prodrugs of GCV were being used to achieve improved and sustained concentration of GCV in the vitreous fluid. The metabolic enzymes responsible for the bioconversion are primarily acetylicholine esterase and butyrylcholine esterase. Hydrolysis of prodrug were found to increase with increase in ester chain length and it followed
timolol IOP decreased up to 4.5 to 4.8 mmHg [90] and 6.4–6.8, respectively [91]. This data clearly shows the efficacy of TVP in maintaining the IOP in comparison to combinational therapy. In addition, TVP was found to maintain the decreased IOP up to 63 h after the last dose. However, it was Suzuki, who suggested once in a day dosing of TVP as first line therapy and its fixed dose combination with Timolol to enhance IOP in case of failure of monotherapy [90]. Yucel and Ariturk compared efficacy of LTP (0.005%), TVP (0.004%) and bimatoprost (0.03%) in open angle glaucoma and ocular hypertension. The baseline IOP in case of LTP, TVP and BMP was found to be 26.50 ± 3.14, 25.58 ± 3.62 and 24.66 ± 3.62 mm Hg, respectively. However, the mean IOP was found to be similar in all the three cases. All the three drugs were found to be equipotent although LTP was considered to be the most preferred because of lesser side effects [92]. Structure of different prostaglandins and their conversion to prodrugs has been represented in Fig. 6.

2.2.4. Beta adrenergic antagonist prodrugs
These are the hypotensive agents for ocular use that have the potential to diminish IOP. Timolol (TM) (Fig. 7), tiilsolol (Fig. 8), oxeprenolol (Fig. 9) are the commonly used beta adrenergic antagonist whose prodrugs have been synthesized. FDA approval to TM was granted in 1979 for ocular delivery, which was used as a gold standard for IOP reduction. Prodrugs of TM were synthesized with the aim to decrease the extent of systemic absorption of the drug following ocular administration, thereby decreasing side effects and improving the ratio of corneal versus conjunctival penetration. TM has low lipophilicity (log P = −0.04) at physiological pH, which is hostile for corneal absorption [93]. Esterification of the hydroxyl group of TM with aromatic/aliphatic acids increased the lipophilicity and thereby also corneal absorption. Half-lives and lipophilicity of various esters of TM has been mentioned in Table 4.

The penetration of TM esters across cornea was found to be more than the parent molecule due to increased lipophilicity, however, the magnitude of corneal penetration was not in parallel to that through conjunctiva membrane and ultimately to systemic absorption. The major challenge which is associated with delivery of TM esters is its stability in ophthalmic formulations for sufficient time which is required for enzymatic activity to ensure its complete bioconversion in the eye. Now investigations are being conducted by various researchers to overcome the limitation of the prodrug i.e. stability and also to further improve its action, e.g. for

| Table 3 – Physicochemical data of various esters of ACV. |
|---------------------------------------------------------|
| Esters (aromatica and aliphaticb) | Aqueous solubility (mM) | Corneal permeability (× 10⁻⁵ cm/s) | Ref. |
|------------------------------------|------------------------|----------------------------------|-----|
| Valtyb                               | > 30                   | 12                               | [82, 83] |
| Divalyb                              | > 30                   | 9.9                              | [82, 83] |
| O-Propionylb                         | 5.0                    | 4.3                              | [84] |
| O-Butyrylb                           | 4.6                    | 5.1                              | [84] |
| O-Pivaloylb                          | 4.8                    | 3.9                              | [84] |
| Valerateb                           | 1.5                    | 6.5                              | [84] |

Fig. 5 – Structure of ValGCV (prodrug) converted from GCV (parent drug).

the order as butyrate->valerate->propionate->acetate. Also the MRT increased ~ 3 to 4 folds with the administration of GCV. Their elimination rate was found to increase with the increase in their lipophilicity. This investigation had concluded that the prodrug approach is better than the use of sustained release implants in case of eyes [85]. Another investigation carried out by the same research group involved replacement of monooester prodrugs of GCV by diesters and then the hydrolytic rate followed the order as dibutyrate->dipropionate->diacetate and MRT was enhanced by ~2 folds following prodrug administration as compared to GCV [86].

2.2.3. Prostaglandins
The most common complication is glaucoma that leads to loss of vision, the destruction of the optic nerve and the use of prostaglandins can overcome this. Prostaglandins are the polar compounds that do not have enough penetration and possess several unwanted side effects. The major focus is given to PGF₂α, and its analogues. The initial PGF₂α prodrugs were PGF₂α-L-methyl and PGF₂α-L-isopropyl esters that inhibited increased corneal permeability [87]. Latanoprost (LTP) and travoprost (TVP) are isopropyl esters of PGF₂α analogue on which modification was done on one side of omega chain. LTP was approved by FDA in 1996 (marketed as Xalatan®) followed by bimatoprost (BMP) (Lumigan®), TVP (travatan) and unoprostone isopropyl (rescula®) by early 2000s [88]. The analogs possess lower side effects. LTP and TVP gets hydrolyzed to free acid by the enzymatic action of corneal esterases. TVP was found to decrease intraocular pressure (IOP) up to the levels of 6.5–9.0 mmHg [89], however, with a combination of timolol-dorzolamide and latanoprost-
Table 4 – Half-lives and partition coefficients of various esters of timolol [94].

| Esters              | Half-life at pH 7.4 and 37 °C (h) | Partition coefficient (log P) |
|---------------------|----------------------------------|-----------------------------|
| Timolol             | —                                | −0.04                       |
| O-acetyl            | 0.47                             | 1.12                        |
| O-propionyl         | 0.67                             | 1.62                        |
| O-butyryl           | 0.83                             | 2.08                        |
| O-isobutyryl        | 0.94                             | 2.19                        |
| O-valeryl           | 1.0                              | 2.67                        |
| O-pivaloyl          | 3.6                              | 2.68                        |
| O-2-ethylbutyryl    | 23                               | 3.26                        |
| O-3,3-dimethylbutyryl | 23                            | 3.09                        |
| O-hexanoyl          | 1.3                              | 3.35                        |
| O-octanoyl          | 1.2                              | 4.66                        |
| O-cyclopropanoyl    | 4.1                              | 1.74                        |
| O-1′-methylcyclopropanoyl | 9.9                          | 2.22                        |
| O-2′-methylcyclopropanoyl | 12.1                         | 2.26                        |
| O-cyclobutanoyl     | 0.35                             | 2.36                        |
| O-cyclopentanoyl    | 0.92                             | 2.75                        |
| O-cyclohexanoyl     | 1.6                              | 3.30                        |
| O-benzoyl           | 2.0                              | 2.55                        |
| O-2-methylbenzoyl   | 10                               | 3.02                        |
| O-4-methylbenzoyl   | 4.9                              | 3.11                        |
| O-2-methoxybenzoyl  | 4.1                              | 2.51                        |
| O-4-methoxybenzoyl  | 4.9                              | 2.65                        |
| O-2-acetoxybenzoyl  | 0.51                             | 1.21                        |
| O-2-benzoyloxybenzoyl | 4.5                         | 4.37                        |
| O-2-aminobenzoyl    | 36.6                             | 2.51                        |
| O-2-methylaminobenzoyl | 41.8                         | 3.04                        |
| O-3-thienyl         | 3.8                              | 2.27                        |

Fig. 6 – Structures of different prostaglandins (parent drug) and their prodrugs.

Fig. 7 – Synthesis of O-pivaloyl (prodrug) from timolol (parent drug).

Fig. 8 – Synthesis of O-acetyl tilisolol (prodrug) from tilisolol (parent drug).

sustained effect/depot effect in order to improve the efficacy and patient compliance. Such novel drug delivery systems have been summarized in Table 5.

O-Palmitoyl tilisolol (PaTL) were synthesized as its prodrug by Kawakami et al. [99]. They have reported enhanced transit time as well as increased retention of PaTL in precorneal
areas as compared to the parent drug in ocular tissues. Hence improved effects with prodrugs have been demonstrated [99]. The same group has reported O-butyliden (BuTL) and O-palmitoyl (PaTL) derivatives of tilisolol as prodrugs. Ocular inserts of tilisolol prodrug were formulated in order to achieve sustained release/controlled release of drug through the cornea. Lipophilic index of tilisolol, BuTL and PaTL have been reported as 1.56, 2.18 and 3.75, respectively [100]. Number of prodrugs of oxeprenolol (OPL) were also investigated for determining the stability profile. O-acetyl, O-propionyl, O-butyliden, O-valeryl and O-pivaloyl were synthesized as prodrugs and their half-lives in buffer at physiological pH were determined and found to be 9.1, 10.4, 19.1, 21.1 and 2035.5 h, respectively and half lives were found to be 1.4, 1.5, 2.9, 3.1 and 308.4 h, respectively. It was concluded that O-pivaloyl exhibited the maximum stability, which is reflected from its shelf life that determines quality and efficacy over a specific period of time. O-acetyl was considered to be unstable amongst the rest of the prodrugs of OPL [101].

2.2.5. Cholinergics
Pilocarpine prodrugs: Pilocarpine is well known cholinergic agent used in the treatment or management of glaucoma. It exhibits low level of absorption in the corneal site due to which it cannot penetrate into ocular tissues to exhibit its effect. Its log P value is −0.15 [102]. So the answer to the above problem was in the synthesis of pilocarpine prodrug (Fig. 10) that would improve the corneal absorption of parent drug and prove beneficial in ocular drug delivery. Bispilocarpic diesters (BPD) prodrug is one of the best examples to elaborate the effect of pilocarpine prodrug over parent drug. BPD prodrug exhibits unimpeachable amount of water solubility and lipophilic character due to esterification of lactone which is required for the better corneal penetration which further aids in releasing Pilocarpine at predetermined rate [103]. During investigations permeability coefficients of bispilocarpic acid diesters was found to be (6.5–20.2) × 10⁻⁶ cm/s more than the pilocarpine. Lipophilicity of the ester was improved from −0.77 to 2.49 at pH 5.0 which leads to augmented corneal permeation [104]. Double prodrug is an auspicious means to overcome the stability issues with the help of derivatization of prodrug. In such a way that enzymatic release approach became necessary antecedent to release prodrug spontaneously e.g. pilocarpic acid diesters (double prodrug) by the action of ocular esterase, which further hydrolyzed into pilocarpic monoesters (prodrug) and ultimately leads to the cyclization of pilocarpine (parent drug) without enzymatic action (Fig. 11) [105].

2.2.6. Carbonic anhydrase inhibitors (CAIs)
Ethoxzolamide, methazolamide and acetazolamide are CAIs that have been exploited for derivatization in order to improve aqueous solubility and permeability, and to reduce unwanted side effects of the parent molecule [106]. As mentioned earlier, reduced lipophilicity is the main culprit in the reduced permeation of this category of drugs. During the early periods, to overcome the limitation of these parent drugs different formulations were prepared like suspension, soft contact lenses, etc. Afterwards to surmount the same, chemical modification of existing CAIs was carried out to synthesize prodrugs with appropriate and desired physicochemical properties. However, it was further reported that the moiety which was considered to be amenable for derivatization was

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**Table 5 – Novel formulations of prodrugs of timolol.**

| NDDS (Novel Drug Delivery System) | Remarks | Ref. |
|----------------------------------|---------|------|
| Nanoparticle                     | Sustained release, 30% in 1 h and 63% within 12 h implies better retention of TM maleate, reduced dose frequency, side effects and improved patient compliance. | [95] |
| Liposome hydrogels               | Permeability and flow rate of TM liposome with transcutol P was 2.19 times as compared to commercialised eye drops. Enhanced drug action, reduced dosing frequency, improved retention time and stability. | [96] |
| Hydrogel                         | Sustained reduction of IOP for up to 24 h instillation. Increased bioavailability of timolol maleate hydrogel. | [97] |
| Cubosome                         | Decreased IOP from 27.8–39.7 to 21.4–32.6 mmHg. Longer retention time (86.6 ± 2.9 min) | [98] |

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**Fig. 9 – Synthesis of O-acetyl oxeprenolol (prodrug) from oxeprenolol (parent drug).**

**Fig. 10 – Conversion of pilocarpic acid monoester (prodrug) into pilocarpine (parent drug).**
not appropriately amenable for prodrug synthesis, however, on the other side, it mainly emphasized on molecular manipulation of CAIs in order to improve physicochemical properties with the help of tail and ring approach [106]. In continuation to this synthesis based problem, it was found in vivo experiments that substitution on sulphonamide nitrogen either diminishes or completely nullifies CAI activity. Because of these limitations, the progress of work on synthesis of a prodrug of CAIs was not appreciated by the researchers.

2.2.7. Steroids
The steroid is the first class of drugs on which concept of prodrug was practically applied by researchers [107]. The posterior segment of eye has always faced a challenge for efficient drug delivery. Dexamethasone has been used for treating anterior as well as posterior segment ocular problems [107]. The ester prodrugs of steroidal class have been synthesized to improve their absorption through cornea and also to improve the hydrophilicity of parent molecules which build a possible way for the preparation of aqueous eye drops solution, leading to improved patient compliance as well as the instillation of an accurate dose [108]. However, the data of few steroids suggest that there is no correlation of permeability through the cornea with a partition coefficient against the normal principle of permeation. Dexamethasone acetate possesses log P value of 2.4 (highly lipophilic) however, its corneal permeation is low [105]. In a study, concentrations of dexamethasone following sub conjunctival administration of dexamethasone disodium phosphate were lower at initial time points (15 min), however, higher concentrations were achieved at 2 h time period, which revealed its lower residence time or depot effect in ocular tissues [109]. Structures of dexamethasone disodium phosphate (prodrug) and dexamethasone (parent drug) are represented in Fig. 12. Barot and co-researchers developed a transporter targeted prodrug strategy which could be recognized by peptide transporter in retina. They synthesized amino acid and peptide prodrugs of dexamethasone and studied their physicochemical properties. The water solubility of Valine–Valine dexamethasone, a peptide prodrug has been reported as 7.07 ± 1.86 mg/ml, which is significantly greater than that of dexamethasone (0.14 ± 0.09 mg/ml). In addition, stability studies revealed the fast bioconversion of parent drug from the prodrug [110]. Data on some of steroids has been mentioned below in Table 6.

3. Patents
Ocular drug therapy has been considered to be a major challenge in the turf of drug delivery. The presence of blood ocular barriers and efflux pumps has always been of a great concern. Pharmaceutical industries and research institutes have embraced a collaborative way to meet the contemporary challenges which is demonstrated by the progression in the published and filed patents. Various approaches have been employed to achieve sustained and targeted delivery in the segments of the ocular diseases. Prodrug strategy has been implied to overcome ophthalmic challenge and obstacles which is evident from an increasing number of patents filed in this field. Patents are essential for promoting new directions in the research as well as for illuminating possibilities for future prospective in the field of ophthalmic. Few ocular drugs along with their prodrugs have been summarized in Table 7 and few patents on ocular prodrugs have been enlisted with their respective data in Table 8. Quinidine is a known substrate of efflux transporters due to which it leads to a significant decrease in the permeation. Valine conjugated prodrugs of the quinidine (Val-quinidine and Val-Val-quinidine) depicted higher affinity for the peptide transporters and lesser affinity for the efflux transporters.
| Drug                  | Functional groups | Modification              | Prodrug                | Remark                                                                 | Use                       | Ref.  |
|----------------------|-------------------|---------------------------|------------------------|------------------------------------------------------------------------|---------------------------|-------|
| **Adrenergic agonists** |                   |                           |                        |                                                                        |                           |       |
| Epinephrine          | Hydroxyl          | Two esters group          | Dipivalyl epinephrine  | Corneal permeability increased up to 17 times 10% phenylephrine oxazolidine enhanced ~8 fold ocular bioavailability and mydriatic activity up to 4 fold. | Glaucoma [111]            |       |
| Phenylephrine        | Ketone and aldehyde | Pivalyl Ester            | Phenylephrine oxazolidine, |                                           | Papillary dilation (during ocular surgery) | [112] |
| Fadolmidine          | Pivalyl           | Ester                     | Pivalyl fadolmidine    | Increased IOP lowering effect due to increased lipophilicity of pivalyl group (1.8 at pH 5.0); Improved stability and prolonged duration of action. | Glaucoma [113]            |       |
| **Adrenergic antagonists** |                   |                           |                        |                                                                        |                           |       |
| Nadolol              | Diacetyl          | Ester                     | Diacetyl nadolol      | Lipophilicity is 20 fold greater than nadolol, 10 folds improvement in ocular bioavailability. | Glaucoma (reduction of IOP) | [114] |
| Timolol              | Butyryl           | Aliphatic ester           | O-butyryl timolol     | 4-6 fold enhancement of timolol absorption in cornea. It increased extent of action. | Glaucoma [115]            |       |
| Timolol and other beta blockers | Amine and carboxylic | Ester | Carbamate derived timolol | Increased corneal penetration and better therapeutic index. | Glaucoma [116]            |       |
| Tilisolol            | Butyryl           | Ester                     | O-butyryl tilisolol   | Lipophilic index 2.18 greater than parent drug. The ratio of $\text{AUCaq/AUCplasma}$ was 3.1 fold and 3.8 fold greater than TL as well as PaTL. It has a lipophilic index around 3.75 higher than parent drug. Increased retention time and ocular absorption. | Glaucoma [100]            |       |
| Propranolol          | Ketone and secondary hydroxyl | Oxime | Propranolol ketoximes | Controlled IOP reduction, better therapeutic index | Glaucoma                   |       |
| **Cholinergics**     |                   |                           |                        |                                                                        |                           |       |
| Pilocarpine          | Methyl, Ethyl, Butyl, 4-Chlorobenzyl $R_1=$Benzyl and $R_2=$Benzoyl | Monoester diester | Mono ester pilocarpic acid Pilocarpic diesters | Monoesters exhibit highly lipophilic character than pilocarpine, enhanced ocular absorption. Stability complication of monoesters overcome by developing diesters. It maintains protract action from 2 to 2.5 folds. Diesters hydrolyzed by enzymes into monoesters comprise half-lives of 3 to 330 min in the 75% plasma solution of human with pH 7.4 at 37°C. | Glaucoma (maintain the fluctuated intraocular pressure) | [117–119] |
|                      |                   |                           |                        |                                                                        |                           | [118,119] |

(continued on next page)
A carrier-mediated transport of the quinidine prodrug resulted in improved permeation (1.5 and 3 times higher permeability of val-quinidine and Val-Val-quinidine in comparison to quinidine) [143]. This approach was further exploited by scientists of Allergan Inc. These researchers anticipated glycyl and tryptophyl ester prodrug of bimatoprost (targeting amino acid transporters); glycylsarcosine ester of bimatoprost (targeting peptide transporters), succinate ester of bimatoprost (targeting monocarboxylic acid transporter), uridine di-ester of bimatoprost (targeting nucleoside transporters), and D-glucopyranosyl ester of dexamethasone (targeting glucose transporter) [134]. These types of researches build the gap between academic and industry based research and proves to be beneficial for the society.
### Table 8 – Patented ocular prodrugs.

| Date       | Class                                      | Disease                                  | Enzymes                                      | Description                                                                                                           | Ref.  |
|------------|--------------------------------------------|-------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-------|
| 14-4-1992 | 2-amino-3-methyl-delta-A4-1,3,4-           | Glaucoma                                  | Acetyl cholinesterase, serum cholinesterase,  | Hydrolytic cleavage bond exists between water soluble group and carbonic anhydrase inhibitor.                         | [128] |
|            | thiazidazoline-5-sulfonamides              |                                            | glycolase                                    | Enhanced penetration through cornea and releasing parent compound to exert action.                                     |       |
|            | Carbonic anhydrase inhibitors              |                                            |                                              |                                                                                                                     |       |
| 6-7-1993  | Methazolamide derived carbonic anhydrase   | Glaucoma                                  | Esterase                                    | Enhance Carbonic anhydrase inhibitory results to prevent ocular hypertension.                                        | [129] |
|            | inhibitors                                  |                                            |                                              | Reduced side effects by directly accessing drug to the required site of action.                                       |       |
|            |                                            |                                            |                                              | Enhanced water solubility and so thus penetration power.                                                            |       |
| 7-9-1993  | Thiazole sulfonamide carbonic anhydrase    | Glaucoma and for estimating corneal       | Cornea epithelial esterases                  | Enhanced aqueous solubility and lipophilic character to allowed efficacious corneal penetration that helped in producing the action. | [130] |
|            | inhibitors                                  | performance                               |                                              |                                                                                                                     |       |
| 26-2-2002 | Ocular antihypertensive agents and         | Ocular hypertension and glaucoma          | Acetylcholine esterases                      | Enhanced both aqueous solubility and lipophilic character to allow efficacious corneal penetration.                   | [131] |
|            | anti-glaucoma agents                        |                                            |                                              | Conversion of Prodrug to hydrophilic parent drug by enzyme action in corneal site.                                    |       |
| 11-1-2007 | Pyrrolidinones based methyl ester prodrugs  | Glaucoma and ocular hypertension          | Esterase                                    | The invention is based on Pyrrolidinones based ester prodrugs that are used for the treatment of ocular hypertension and glaucoma. | [132] |
| 12-6-2007 | Antibacterial, Antiviral, cyclosporine,    | Ocular infections                          | —                                            | Drug linked with delivery enhancer transporters formed linkage that gets cleaved when transported in the ocular tissues due to solvent action. | [133] |
|            | ascomycins, corticosteroids.                |                                            |                                              |                                                                                                                     |       |
| 28-11-2007 | Ester based (2R)-propyloctanoic acid       | Ophthalmic diseases such as Glaucoma,     | —                                            | The invention is based on the ester based propyloctanoic prodrug used in ophthalmic diseases.                        | [134] |
|            | prodrugs                                    | muscae volitantes, age-related macular    |                                              |                                                                                                                     |       |
|            |                                            | degeneration, diabetic retinopathy,       |                                              |                                                                                                                     |       |
|            |                                            | macular edema etc                         |                                              |                                                                                                                     |       |
| 11-8-2009 | Steroidal quinols                           | Glaucoma, cataract, diabetic retinopathy  | Phosphatase and Esterase                    | Maintains balance between hydrophilic and lipophilic character.                                                      | [135] |
|            |                                            | and conjunctivitis and posterior segment  |                                              | Increased penetration through cornea.                                                                               |       |
|            |                                            | related eye diseases                      |                                              |                                                                                                                     |       |
| 11-5-2010 | Prostamides, corticosteroids, alpha and    | —                                          | Esterases                                   | Therapeutic agent attached with carrier through covalent bond and released drug by breaking bond when drug reached close to the target site by enzymatic action only in posterior segment. | [136] |
|            | beta adrenergic agents.                     |                                            |                                              |                                                                                                                     |       |

(continued on next page)
### Table 8 (continued)

| Date     | Class                                | Disease                                                                 | Enzymes              | Description                                                                                           | Ref.  |
|----------|--------------------------------------|------------------------------------------------------------------------|----------------------|-------------------------------------------------------------------------------------------------------|-------|
| 5-10-2011 | Antiangiogenic agent, steroids, anti-inflammatory agent (NSAID), antibiotic, anti-viral, anti-fungal agents, anti-neoplastic agents | Retinoblastoma, diabetic macular edema, age related macular degeneration and inflammatory disorders. | Cellular esterases | Parent drug with carotenoid formed covalent bond which got cleaved by enzymatic action and thus yielded parent drug to exhibit required action. Carotenoid aided in enhancing Lipophilic character for easy corneal penetration. | [137] |
| 24-7-2012 | Corticosteroid                        | Posterior segment eye diseases                                         | Esterase             | Use of one prodrug preferably corticosteroid for ophthalmic composition intended in ocular disease of human being or animal. | [138] |
| 21-6-2012 | Retinoid, prostaglandins, alpha-2-adrenergic agonists, beta-adrenoreceptor antagonists, dopaminergic agonists, cholinergic agonists, antihistamines. | Retinitis pigmentosa, proliferative vitreal retinopathy (PVR), age-related macular degeneration (ARMD), diabetic retinopathy, diabetic macular edema, cytomegalovirus retinitis | Esterase             | Sustained delivery method of active drug to posterior segment of eye preferably with ester prodrug by subconjunctivally or periocularly. | [139] |
| 5-6-2014  | Triazole based amide prodrug (Carbonic anhydrase inhibitors) | Cytomegalovirus retinitis, ophthalmononyiasis, diabetic retinopathy | Proteases and Esterases | The prodrug of invention provide carbonic anhydrase inhibitors and formulation and methods for their use in the treatment of non-lifethreatening diseases with a little or no side effects. | [140] |
| 24-11-2015 | Corticosteroid                        | Posterior segment eye diseases                                         | Pseudo cholinersterase, Acetyl cholinersterase | Prodrug for the manufacture of medicament used in the treatment of ocular diseases affecting posterior segment of eye. In vivo sustained release of active agent through intraocular invasive delivery. | [141] |
| 27-4-2017  | Anti-inflammatory, anti-infective, antiviral, anti-glucoma, steroids, anti-cataract, mydriatic agent | Macular degeneration, diabetic macular edema | Esterase             | Invention related to the pharmaceutical composition containing hydrogel linked prodrug used for the treatment, prevention and diagnosis of eye related conditions. | [142] |

### 4. Conclusion

Drug development for ocular prodrug is extremely exigent approach for the researchers, as prodrugs have to pass defined basic standards like adequate solubility, stability, rational bioconversion into parent drug, optimum lipophilia, safety etc. for the fortunate target drug delivery. Unfortunately, only a few of them are optimized for ocular absorption considering pharmacokinetic properties, and in addition poor water solubility that present a censorious pace in preclinical phases. Constraints of ocular drug delivery include short residence time, narrow pH range that can be tolerated, highly impermeable cornea, small surface area for corneal absorption, and large surface area for systemic drug loss. Attempts to improve ocular bioavailability have focused primarily on improving precorneal drug retention. Overcoming of poor permeability of the cornea
and providing a possible alternate for the refinement of undesirable ADME properties and done with the help of prodrug approach. Due to flexibility in prodrug approach, many drug molecules are approved by FDA in the market for clinical use and are classified under prodrug. The rational prodrug derivatization has become an integral part in drug designing and development as illustrated by increasing number of approved prodrugs and patents.

5. Current and future developments

Effective topical administration of drugs using ocular drug delivery systems has always been a challenging task for scientists, researchers and industries. The paramount challenge is because of membrane barriers (reduce drug transport/permeation) and contact time. The extensive research in ocular drug delivery system has been going on since last many years and numerous new approaches like prodrug solution, implants and nana carriers have been developed. Gene therapy has also emerged as an interesting area of research in the field of ocular delivery recently. The reason behind this is that the eye is easily accessible, highly compartmentalized and immune privileged organ. However, this technique also faces extracellular and intracellular challenges. Hence it is expected that still there is a need of designing and synthesizing new molecules with expected physicochemical and pharmacokinetic properties, which can be achieved by in silico screening. Furthermore, if one approach is not proving to have desirable effects, then the combination of approaches might solve the issue.

Conflict of interest

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2020.08.002.

REFERENCES

[1] Das S, Suresh PK. Drug delivery to the eye: special reference to nanoparticles. Int J Drug Deliv 2010;2:12–21.
[2] Schoenwald RD, Deshpande GS, Rethwisch DG, Barfknecht CF. Penteration into the anterior chamber via the conjunctival/scleral pathway. J Ocul Pharmacol Ther 1997;13(1):41–59.
[3] Bourlais CL, Aacar I, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems – recent advances. Prog Retin Eye Res 1998;17(1):33–58.
[4] Bachu RD, Chowdhury P, Al-Saedi ZH, Karla PK, Boddhu SH. Ocular drug delivery barriers—role of nanocarriers in the treatment of anterior segment ocular diseases. Pharmaceuticals 2018;10(1):28.
[5] Agrahari V, Mandal A, Agrahari V, Trinh HM, Joseph M, Ray A, et al. A comprehensive insight on ocular pharmacokinetics. Drug Deliv Transl Res 2016;6(6):735–754.
[6] Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: an overview. World J Pharm-Co 2013;2(2):47–64.
[7] Du Toit LC, Pillay V, Choonara YE, Govender T, Carmichael T. Ocular drug delivery – a look towards nanobioadhesives. Exp Opin Drug Deliv 2011;8(1):71–94.
[8] Tseng CL, Chen KH, Su WY, Lee YH, Wu CC, Lin FH. Cationic gelatin nanoparticles for drug delivery to the ocular surface: in vitro and in vivo evaluation. J Nanomater 2013:238351.
[9] Gupta H, Aqil M, Khan RK, Ali A, Bhatnagar A, Mittal G. Sparfloxacin-loaded PLGA nanoparticles for sustained ocular drug delivery. Nanomedicine 2010;6(2):324–33.
[10] Yasukawa T, Tabata Y, Kimura H, Ogura Y. Recent advances in intraocular drug-delivery systems. Recent Pat Drug Deliv Formul 2015;5(1):1–10.
[11] Kumaran KG, Karthika K, Padmapreetha J. Comparative review on conventional and advanced ocular drug delivery formulations. Int J Pharm Sci 2010;2(4):1–5.
[12] Lee VHl, Robinson JR. Mechanistic and quantitative evaluation of precorneal pilocarpine disposition in albino rabbits. J Pharm Sci 1979;68:673–84.
[13] Patel JK, Sutarla V, Kanwar JR, Pathak YV. Drug delivery for the retina and posterior segment disease. 1st ed. Switzerland: Springer; 2018.
[14] Achouri D, Alhannout R, Picerelle P, Andrieu V. Recent advances in ocular drug delivery. Drug Dev Ind Pharm 2013;39(11):1599–617.
[15] Ghate D, Edelhauser HF. Ocular drug delivery. Exp Opin Drug Del 2006;3(2):275–87.
[16] Rojanasakul Y, Robinson JR. Transport mechanisms of the cornea: characterization of barrier perme selectivity. Int J Pharm 1989;55:237–46.
[17] Washington N, Washington C, Wilson CG. Transdermal drug delivery. Physiological pharmaceutics: barriers to drug absorption. 2nd ed. London: Taylor and Francis; 2001.
[18] Jain-Vakkalagadda B, Pal D, Gunda S, Nashed Y, Ganapathy V, Mitra AK. Identification of a Na+ -dependent cationic and neutral amino acid transporter, B0+, in human and rabbit cornea. Mol Pharm 2004;1(5):338–46.
[19] Kulkarni S, Gupta SP, Upmanyu N, Tonpay SD. Solubility enhancement of water insoluble drug for ophthalmic formulation. Int J Drug Deliv 2011;3:141–8.
[20] Liu R, Liu Z, Zhang C, Zhang B. Gelucire44/14 as a novel absorption enhancer for drugs with different hydrophobicities: in vitro and in vivo improvement on transcorneal permeation. J Pharm Sci 2011;100(8):3186–95.
[21] Shahwali VK. Ocular drug delivery: an overview. Int J Biomed Adv Res 2011;2(5):167–87.
[22] Gratieri T, Gelfuso GM, Rocha EM, Sarmiento VH, De Freitas O, Lopez RFV. A poloxamer/chitosan in situ forming gel with prolonged retention time for ocular delivery. Eur J Pharm Biopharm 2010;75(2):186–93.
[23] Yadav VK, Gupta AB, Kumar R, Yadav JS, Kumar B. Mucoadhesive polymers: means of improving the mucoadhesive properties of drug-delivery system. J Chem Pharm Res 2010;2(5):418–32.
[24] Rathore KS, Nema RK. Review on ocular inserts. Int J Pharm Tech Res 2009;1(2):164–9.
[25] Nagarwal RC, Kant S, Singh PN, Maiti P, Pandit JK. Polymeric nanoparticulate system: a potential approach for ocular drug delivery. J Control Release 2009;136(1):2–13.
[26] Zhang G, Feng X, Wabner K, et al. Intraocular nanoparticle drug delivery: a pilot study using an aerosol during pars plana vitrectomy. Invest Ophthalmol Vis Sci 2007;48(11):5243–9.
[27] Baranowski P, Karolewicz B, Gajda M, Pluta J. Ophthalmic...
drug dosage forms: characterisation and research methods. Sci World J 2014;861904.

[28] Albert A. Chemical aspects of selective toxicity. Nature 1958;182(4633):421–3.

[29] Huttunen KM, Raunio H, Rautio J. Prodrugs from serendipity to rational design. Pharmaco! Rev 2011;63(3):750–71.

[30] Han HK, Amidon GL. Targeted prodrug design to optimize drug delivery. AAPS PharmSci 2000;2(1):48–58.

[31] Stella VJ, Ni-Addae KW. Prodrug strategies to overcome poor water solubility. Adv Drug Deliv Rev 2007;59(7):677–94.

[32] Stella VJ, Charman WN, Naringrekar VH. Prodrugs. Drugs 1985;29(5):455–73.

[33] Notari RE. Theory and practice of prodrug kinetics. Method Enzymol 1985;12):309–23.

[34] Testa B, Mayer JM. Hydrolysis in drug and prodrug metabolism chemistry, biochemistry, and enzymology. Switzerland: Verlag Helvetica Chimica Acta; 2003.

[35] Testa B, Mayer JM. Pharmacokinetic optimization in drug research: biological, physicochemical, and computational strategies. Germany: Wiley-VCH; 2001.

[36] Stella V, Borchardt R, Hageman M, Oliyai R, Maag H, Tilley J. Prodrugs: challenges and rewards. 1st ed. New York: Springer; 2007.

[37] Mueller CE. Prodrug approaches for enhancing the bioavailability of drugs with low solubility. Chem Biodivers 2005;6(11):2071–83.

[38] Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: an overview. World J Pharmace! 2013;2(2):47–64.

[39] Dubald M, Bourgeois S, Andrieu V, Fessi H. Ophthalmic drug delivery systems for anti-inflammation a review. Pharmaceutics 2018;10(1):10.

[40] Kaur IP, Kanwar M. Ocular preparations: the formulation approach. Drug Dev Ind Pharm 2002;28(5):473–93.

[41] Tamilsan S, Benita S. The potential of lipid emulsion for ocular delivery of lipophilic drugs. Eur J Pharm Biopharm 2004;58(2):357–68.

[42] Cholkar K, Patel A, Vadlapudi DA, Mitra AK. Novel nanomicellar formulation approaches for anterior and posterior segment ocular drug delivery. Recent Pat Nanomed Nanotech! 2012;6(2):82–95.

[43] Courtney L, Pierre PDK, Yahya EC, Lisa CDT, Naseer A, Viness P. Advances in biodegradable nano-sized polymer-based ocular drug delivery. Polymers 2019;11(8):1371–95.

[44] Kaur IP, Garg A, Singla AK, Aggarwal D. Vesicular systems in ocular drug delivery: an overview. Int J Pharm 2004;269(1):1–14.

[45] Law SL, Huang KJ, Chiang CH. Acyclovir-containing liposomes for potential ocular delivery: corneal penetration and absorption. J Control Release 2000;63:135–40.

[46] Kean SJ, Scott LJ, Curran MP. Verteportin: a review of its use in the management of subfoveal choroidal neovascularisation. Drugs 2003;63(22):2521–54.

[47] Dieter D, Suwan L, Sabine D, Chan KJ, Gregor S, Wanda M. Comparative study of treatment of the dry eye syndrome due to disturbances of the tear film lipid layer with lipid-containing tear substitutes. Klin Monatsbl Augenh 2006;223:974–83.

[48] Lee S, Dausch S, Maierhofer G, Dausch D. A new therapy concept for the treatment of dry eye-the usefulness of phospholipid liposomes. Klin Monbl Augenh 2004;221(10):825–36.

[49] Fischer M, Vöttle F. Dendrimers: from design to application: a progress report. Angew Chem Int 1999;38(7):884–905.

[50] Abdellaher H, Alany RG. Controlled and continuous release ocular drug delivery systems: pros and cons. Curr Drug Deliv 2012;9(4):421–30.

[51] Gupta H, Agli M. Contact lenses in ocular therapeutics. Drug Discov Today 2012;17:522–7.

[52] Kim J, Chauhan A. Dexamethasone transport and ocular delivery from poly (hydroxyethyl methacrylate) gels. Int J Pharm 2008;353(1–2):205–22.

[53] Bu HZ, Guksayan HJ, Goulet L, Lou XJ, Xiang C, Koudriakov T. Ocular disposition, pharmacokinetics, efficacy and safety of nanoparticle-formulated ophthalmic drugs. Curr Drug Metab 2007;8(2):91–107.

[54] Zhang L, Li Y, Zhang C, Wang Y, Song C. Pharmacokinetics and tolerance study of intravitreal injection of dexamethasone-loaded nanoparticles in rabbits. Int J Nanomed 2009;4:175–83.

[55] Patravale VB, Date AA, Kulkarni RM. Nanosuspension: a promising drug delivery strategy. J Pharm Pharmacol 2004;56(7):827–40.

[56] Bourges J, Bloquel C, Thomas A, Foussart F, Bochat A, Azan F, et al. Intraocular implants for extended drug delivery: therapeutic applications. Adv Drug Deliv Rev 2006;58(11):1182–202.

[57] Lee SS, Hughes P, Ross AD, Robinson MR. Biodegradable implants for sustained drug release in the eye. Pharm Res 2010;27(10):2043–53.

[58] Choorna YE, Pillay V, Danckwerts MP, Carmichael TR, Du Toit LC. A review of implantable intravitreal drug delivery technologies for the treatment of posterior segment eye diseases. J Pharm Sci 2010;99(S):2219–39.

[59] Shirke S, Shewale S, Satpute M. Prodrug design: an overview. Int J Pharm Chem Bio Sci 2015;5(1):332–41.

[60] Balant LP. Metabolic considerations in prodrug design. In: Abraham DJ, editor. Burger’s medicinal chemistry and drug discovery. John Wiley & Sons, Inc.; 2003. p. 499–532.

[61] Yang YH, Aloysius H, Inoyama D, Chen Y, Hu LQ. Enzyme-mediated hydrolytic activation of prodrugs. Acta Pharma Sin B 2011;1(3):143–59.

[62] Kumar KS, Bhowmik D, Paswan S, Srivastava S. Recent challenges and advances in ophthalmic drug delivery system. J Pharm Innov 2012;1(4):1–15.

[63] Ghate D, Edelhauser HF. Barriers to glaucoma drug delivery. J Glaucoma 2008;17(2):147–56.

[64] Kaur IP, Kanwar M. Ocular preparations: the formulation approach. Drug Dev Ind Pharm 2002;28(5):473–93.

[65] Rawas-Qalaji M, Williams CA. Advances in ocul! drug delivery. Curr Eye Res 2012;37(5):345–56.

[66] Duvvuri S, Majumdar S, Mitra AK. Role of metabolism in ocular drug delivery. Curr Drug Metab 2004;5(6):507–15.

[67] Lee VH, Morimoto KW, Stratford RE Jr. Esterase distribution in the rabbit cornea and its implications in ocular drug bioavailability. Biopharm Drug Dispos 1982;3(4):291–300.

[68] Petersen RA, Lee KJ, Donn A. Acetylicholinesterase in the rabbit cornea. Arch Ophthalmol 1965;73(3):370–7.

[69] Gupta K, Niranjani GD, Agrawal SS, Srivastava S, Saxena R. Recent advances in pharmacotherapy of glaucoma. Indian J Pharmacol 2008;40(5):197–203.

[70] Wei CP, Anderson JA, Leopold I. Ocular absorption and metabolism of topically applied epinephrine and a dipivalyl ester of epinephrine. Invest Ophthalmol Vis Sci 1978;17(4):315–21.

[71] Redell MA, Yang DC, Lee VH. The role of esterase activity in the ocular disposition of dipivalyl epinephrine in rabbits. Int J Pharm 1983;17(2–3):299–312.

[72] Iso T, Uda K, Yamachi H, Nakajima N, Suda H. Antianaphylactic effects of dipivalyl epinephrine and related compounds in rat conjunctiva. Invest Ophthalmol Vis Sci 1980;19(7):824–6.

[73] Ananya M, Sanjay D. Improved ocular drug delivery: a prodrug approach. Int J Pharmagenesis 2011;2(1):49–55.

[74] Schoenwald RD, Folk JC, Kumar V, Piper JG. In vivo
comparison of phenylephrine and phenylephrine oxazolidine instilled in the monkey eye. J Ocul Pharmacol Ther 1987;3(4):333–40.

[75] Chien DS, Schoenwald RD. Improving the ocular absorption of phenylephrine. Biopharma Drug Dispos 1986;7(5):453–62.

[76] Chien DS, Schoenwald RD. Ocular pharmacokinetics and pharmacodynamics of phenylephrine and phenylephrine oxazolidine in rabbit eyes. Pharm Res 1990;7(5):476–83.

[77] Miller-Meeks MJ, Farrell TA, Munden PM, Folk JC, Rao C, Schoenwald RD. Phenylephrine prodrug: report of clinical trials. J Ophthalmol 1991;98(2):222–6.

[78] Krishnamoorthy R. Ocular pigmentation effects on the intravitreal disposition of novel acylguanosine analogs PhD Dissertation part 2. Thesis. Purdue University; 1995.

[79] Vadlapudi AD, Vadiapalita RK, Earlra R, Srimullapena S, Bailey JB, Pal D, et al. Novel biotinylated lipid prodrugs of acyclovir for the treatment of herpetic keratitis (HK): transporter recognition, tissue stability and antiviral activity. Pharm Res 2013;30(8):2063–76.

[80] Anand BS, Mitra AK. Mechanism of corneal permeation of L-valyl ester of acyclovir: targeting the oligopeptide transporter on the rabbit cornea. Pharm Res 2002;19(8):1194–202.

[81] Katragadda S, Gunda S, Hariharan S, Mitra AK. Ocular pharmacokinetics of acyclovir amino acid ester prodrugs in the anterior chamber: evaluation of their utility in treating ocular HSV infections. Int J Pharm 2008;359(1–2):15–24.

[82] Anand BS, Katragadda S, Gunda S, Mitra AK. In vivo ocular pharmacokinetics of acyclovir dipetide ester prodrugs by microdialysis in rabbits. Mol Pharm 2006;3(4):431–40.

[83] Anand BS, Nashed YE, Mitra AK. Novel dipetide prodrugs of acyclovir for ocular herpes infections: bioereversion, antiviral activity and transport across rabbit cornea. Curr Eye Res 2003;28(3–4):151–63.

[84] Hughes PM, Mitra AK. Effect of acylation on the ocular disposition of acyclovir II: corneal permeability and anti-HSV 1 activity of 2-esters in rabbit epithelial keratitis. J Ocul Pharmacol Ther 1993;9(4):299–309.

[85] Macha S, Mitra AK. Ocular disposition of ganciclovir and its monoester prodrugs following intravitreal administration using microdialysis. Drug Metab Dispos 2002;30(5):570–5.

[86] Macha S, Duvvuri S, Mitra AK. Ocular disposition of novel lipophilic diester prodrugs of ganciclovir following intravitreal administration using microdialysis. Curr Eye Res 2004;28(2):77–84.

[87] Bito LZ, Baroody RA. The ocular pharmacokinetics of eicosanoids and their derivatives. 1. Comparison of ocular eicosanoid penetration and distribution following the topical application of PGA20, PGA20-1-methyl ester, and PGF20-1-isopropyl ester. Exp Eye Res 1987;44(2):217–26.

[88] Järvinen T, Niemi R. Prodrug approaches to ophthalmic drug delivery. In: Valentino J, Stellon Donald T, BorchardMichael J, HagemanReza O, Maag H, Tilley JW, editors. Prodrugs challenges and rewards. Springer; 2007. p. 125–55.

[89] Suzuki ER, Suzuki CL. Efficacy and safety of travoprost alone or in combination with other agents for glaucoma and ocular hypertension: patient considerations. Clin Ophthalmol 2010:4:1165–71.

[90] Suzuki ER, Franklin LM, Silva LJ, Figueiredo CR, Netto JA, Batista WD. Comparison of the efficacy and safety of travoprost with a fixed-combination of dorzolamide and timolol in patients with open-angle glaucoma or ocular hypertension. Curr Med Res Opin 2006;22(9):1799–805.

[91] Franks WA, Renard JP, Cunlife IA, Rojanapongpun P. A 6-week, double-masked, parallel-group study of the efficacy and safety of travoprost 0.004% compared with latanoprost 0.005%/timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. Clin Ther 2006;28(3):332–9.

[92] Yucel OE, Ariturk N. A comparison of the efficacy of latanoprost, travoprost and bimatoprost in open angle glaucoma and ocular hypertension. Int J Clin Exp Med 2012;29(2):89–92.

[93] Bundgaard H, Buur A, Chang SC, Lee VH. Prodrugs of timolol for improved ocular delivery: synthesis, hydrolysis kinetics and lipophilicity of various timolol esters. Int J Pharm 1986;33:15–26.

[94] Bundgaard H, Buur A, Chang SC, Lee VH. Timolol prodrugs: synthesis, stability and lipophilicity of various alkyl, cycloalkyl and aromatic esters of timolol. Int J Pharm 1988;46:77–88.

[95] Agnihotri SA, Aminabhavi TM. Chitosan nanoparticles for prolonged delivery of timolol maleate. Drug Dev Ind Pharm 2007;33(11):1254–62.

[96] Zhang HH, Luo QH, Yang ZJ, Pan WS, Nie SF. Novel ophthalmic timolol maleate liposomal-hydrogel and its improved local glaucomatous therapeutic effect in vivo. Drug Deliv 2011;18(7):502–10.

[97] Karavasili C, Konnenou A, Katsamenis OL, Charalampidou G, Kofidou E, Andreidis D, et al. Self-assembling peptide nanofer hydrogels for controlled ocular delivery of timolol maleate. ACS Biomater Sci Eng 2017;3(12):3386–94.

[98] Huang J, Peng T, Li Y, Zhan Z, Zeng Y, Huang Y, et al. Ocular cubosome drug delivery system for timolol maleate: preparation, characterization, cytotoxicity, ex vivo, and in vivo evaluation. AAPS Pharm Sci Tech 2017;18(8):2919–26.

[99] Kawakami S, Nishida K, Mukai T, Yamamura K, Kobayashi K, Sakaeda T, et al. Ocular absorption behavior of palmitoyl tilisolol, an amphiphilic prodrug of tilisolol, for ocular drug delivery. J Pharm Sci 2001;90(12):2113–20.

[100] Kawakami S, Nishida K, Mukai T, Yamamura K, Nakamura J, Sakaeda T, et al. Controlled release and ocular absorption of tilisolol utilizing ophthalmic insert-incorporated lipophilic prodrugs. J Control Release 2001;76(3):255–63.

[101] Jordan CCM. How an increase in the carbon chain length of the ester moiety affects the stability of a homologous series of oxpropenol esters in the presence of biological enzymes. J Pharm Sci 1998;87(7):880–5.

[102] Bundgaard H, Falch E, Larsen C, Mosher GL, Mikkelsen TJ. Pilocarpine prodrugs II. Synthesis, stability, bioconversion, and physicochemical properties of sequentially labile pilocarpine acid diesters. J Pharm Sci 1986;75(8):775–83.

[103] Järvinen T, Poikolainen M, Suohon P, Vespiäinen J, Alaranta S, Urtti A. Comparison of enzymatic hydrolysis of pilocarpine prodrugs in human plasma, rabbit cornea, and butyrylcholinesterase solutions. J Pharm Sci 1995;84(5):656–60.

[104] Suohon P, Järvinen T, Rytkönen P, Peura P, Urtti A. Improved corneal pilocarpine permeability with O,O-[(4,4-Xylylene) bis(hydroxyacetic acid ester double prodrugs. Pharm Res 1991;8(12):1539–42.

[105] Lee VL, Bundgaard H. Improved ocular drug delivery with prodrugs. J Drugs Pharm Sci 1992;53:221–97.

[106] Sugre MF. Pharmacological and ocular hypertensive properties of topical carbonic anhydrase inhibitors. Prog Retin Eye Res 2000;19(1):87–112.

[107] Shirasaki Y. Molecular design for enhancement of ocular penetration. J Pharm Sci 2008;97(7):2462–96.

[108] Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced glaucoma: an avoidable irreversible blindness. J Curr Glaucoma Pract 2017;11(2):67–72.

[109] Hosseini K, Matsushima D, Johnson J, Widera G, Nyak K,
Kim L, et al. Pharmacokinetic study of dexamethasone disodium phosphate using intravitreal, subconjunctival, and intravenous delivery routes in rabbits. J Ocul Pharmacol Ther 2008;24(3):301–8.

[110] Barot M, Gaudana R, Samantha S, Earla R, Mitra AK. Development and evaluation of dexamethasone prodrugs for the treatment of ocular ailments. Invest Ophthalmol Vis Sci 2009;50(13):4998.

[111] Mandell AI, Stenzt F, Kitabchi AE. Dipivalyl epinephrine: a new pro-drug in the treatment of glaucoma. J Ophthalmol 1978;85(3):268–75.

[112] Chien DS, Schoenwald RD. Ocular pharmacokinetics and pharmacodynamics of phenylephrine and phenylephrine oxazolidine in rabbit eyes. Pharm Res 1990;7(5):476–83.

[113] Niemi R, Huuskonen J, Laine K, Järvinen T. Synthesis, hydrolysis, and intraocular pressure lowering effects of fadomidine prodrugs. Int J Pharm 2005;295(1–2):121–7.

[114] Duzman E, Chen CC, Anderson J, Blumenthal M, Twizer H. Diacetyl derivative of nadolol: I. Ocular pharmacology and short-term ocular hypotensive effect in glaucomatous eyes. Arch Ophthalmol 1982;100(12):1916–19.

[115] Schoenwald RD, Huang HS. Corneal penetration behavior of β-blocking agents I: physicochemical factors. J Pharm Sci 1983;72(11):1266–72.

[116] Barot M, Bagui MR, Gokulgandhi M, Mitra AK. Prodrug strategies in ocular drug delivery. Med Chem 2012;8(4):753–68.

[117] Järvinen T, Suohon T, Auriola S, Vepsäläinen J, Uritti A, Peura P. Bispirolac acid monoesters as prodrugs of pilocarpine: I. Preparation and identification. Int J Pharm 1992;79(1–3):233–42.

[118] Järvinen T, Suohon T, Auriola S, Vepsäläinen J, Uritti A, Peura P. O,O’–(1, 4-xylylene) bispirolac acid esters as new potential double prodrugs of pilocarpine for improved ocular delivery. I. Synthesis and analysis. Int J Pharm 1991;75(2–3):249–58.

[119] Järvinen T, Poikolainen M, Suohon T, Vepsäläinen J, Alaranta S, Uritti A. Comparison of enzymatic hydrolysis of pilocarpine prodrugs in human plasma, rabbit cornea, and butyrylcholinesterase solutions. J Pharm Sci 1995;84(5):656–60.

[120] Larsen JD, Bundgaard H, Lee VH. Prodrug forms for the sulfonamide group. II. Water-soluble amino acid derivatives of N-methylsulfonamides as possible prodrugs. Int J Pharm 1988;47(1–3):103–10.

[121] Dias C, Nashed Y, Alturi H, Mitra A. Ocular penetration of acyclovir and its peptide prodrugs valacyclovir and val-valacyclovir following systemic administration in rabbits: an evaluation using ocular microdialysis and LC-MS. Curr Eye Res 2002;25(4):243–52.

[122] Tirucherai GS, Dias C, Mitra AK. Corneal permeation of ganciclovir: mechanism of ganciclovir permeation enhancement by acyl ester prodrug design. J Ocul Pharmacol Ther 2002;18(6):535–48.

[123] Shen W, Kim JS, Mitchell S, Kish P, Kijek P, Hilfinger J. S-OD-Valyl ara A, a potential prodrug for improving oral bioavailability of the antiviral agent vidarabine. Nucleos Nucleot Nucl 2009;28(1):43–55.

[124] Sheng Y, Yang X, Pal D, Mitra AK. Prodrug approach to improve absorption of prednisolone. Int J Pharm 2015;487(1–2):242–9.

[125] Patane MA, Schubert W, Sanford T, Gee R, Burgos M, Isom WP, et al. Evaluation of ocular and general safety following repeated dosing of dexamethasone phosphate delivered by transcleral iontophoresis in rabbits. J Ocul Pharmacol Ther 2013;29(8):760–9.

[126] Samtani MN, Jusko WJ. Stability of dexamethasone sodium phosphate in rat plasma. Int J Pharm 2015;361(1–2):262–6.

[127] Wang W, Bundgaard H, Buur A, Lee VH. Corneal penetration of 5-fluorouracil and its improvement by prodrug derivatization in the albino rabbit: implication in glaucoma filtration surgery. Curr Eye Res 1991;10(1):87–97.

[128] Schoenwald RD, Barftknecht CF. Topical ophthalmic imino substituted 2-imino-3-methyl-delta4-1, 3, 4-thiadiazoline-5-sulfonamides carbonic anhydrase inhibitors. USA, 5104887[P]. 1992.

[129] Schoenwald RD, Barftknecht CF. Methazolamide-derived carbonic anhydrase inhibitors. US 5,225,424[P]. 1993.

[130] Pierce Jr WM. Topically active ophthalmic sulfonamide carbonic anhydrase inhibitors. US 5,242,937[P]. 1993.

[131] Garst ME, Adorante JS. Methods and compositions for drug delivery. USA, 6350780[P]. 2002.

[132] Old, DW. Pyrrolidinones for the treatment of glaucoma and ocular hypertension. WO, 2007005176 AI[P]. 2007.

[133] Rothbard JB, Wender PA, McGrane PL, Sista LV, Kirschberg TA. Compositions and methods for enhancing drug delivery across and into ocular tissues. USA, 7229961[P]. 2007.

[134] Maegawa H. Therapeutic agent for ophthalmic disease. USA, 11/90818[P]. 2009.

[135] Prokai L, Prokai K, Simpkins J, Agarwal N. Prodrugs for use as ophthalmic agents. USA, 7572781[P]. 2009.

[136] Hughe PM, Olejnik O, Chang-Lin JE. Compositions and methods for the intraocular transport of therapeutic agents. USA 7714024[P]. 2010.

[137] Michael MD, Chu CK. Methods and compositions for treatment of macular and retinal disease. USA, 8058266[P]. 2011.

[138] Rabinovich-Guilatt L, Lambert G. Use of a steroid prodrug for the treatment of disease of the posterior segment of the eye. USA, 8227452[P]. 2012.

[139] Hughe PM, Olejnik O. Delivery of an active drug to the posterior part of the eye via subconjunctival or periorcular delivery of a prodrug. USA, 13/407906[P]. 2012.

[140] Robinson G, Shapiro G, Franklin AJ, Jurczik S. Cai-based systems and methods for the localized treatment of ocular and other diseases. USA 14/174080[P]. 2014.

[141] Rabinovich-Guilatt L, Lambert G. Method for treating eye disease or conditions affecting the posterior segment of the eye. USA, 9192567[P]. 2015.

[142] Knappe T, Laufer B, Rau H, Sproge K, Voight T, Weisbrod S. Prevention and treatment of ocular conditions. USA 5/400887[P]. 2017.

[143] Mitra AK, Majumdar S, Jain R, Nashed Y. Peptidyl prodrugs that resist P-glycoprotein mediated drug efflux. USA, 7214664[P]. 2007.