Enhancing Ocular Drug Delivery Through Liposomal Systems

Ketan Chauhan[1], Tilotma Sahu[1]
[1]*Rungta Institute of Pharmaceutical Sciences, Bhilai, Chhattisgarh, India.*
Corresponding Author: tilu06sahu@gmail.com

Abstract— The major challenge faced by moment's pharmacist and expression scientist is optical medicine delivery. Topical eye drop is the most accessible and patient biddable route of medicine administration, especially for the treatment of anterior member conditions. Delivery of medicines to the targeted optical tissue is confined by colourful precorneal, dynamic and stationary optical walls. Also, remedial medicine situations aren't maintained for longer duration in target tissue. In the once two decades, optical medicine delivery exploration acceleratedly advanced towards developing a novel, safe and patient biddable expression and medicine delivery bias ways, which may surpass these walls and maintain medicine situations in tissue. Anterior member medicine delivery advances are witnessed by modulation of conventional topical results with saturation and density enhancers. Also, it includes development of conventional topical phrasings similar as dormancies, mixes and ointments. colourful nanoformulations have also been introduced for anterior member optical medicine delivery. On the other hand, for posterior optical delivery, exploration has been immensely concentrated towards development of medicine releasing bias and nanoformulations for treating habitual vitreoretinal conditions. These novel devices and/ or phrasings may help to surpass optical walls and associated side goods with conventional topical drops. Also, these novel devices and/ or phrasings are easy to formulate, no/ slightly prickly, retain high precorneal hearthstone time, sustain the medicine release, and enhance optical bioavailability of rectifiers. An update of current exploration advancement in optical medicine delivery necessitates and helps medicine delivery scientists to modulate their think process and develop new and safe medicine delivery strategies. Current review intends to epitomize the being conventional phrasings for optical delivery and their advancements followed by current nanotechnology grounded expression developments. Also, recent developments with other optical medicine delivery strategies employing in situ gels, implants, contact lens and microneedles have been bandied.

***Index Terms*— Nanomicelles, Ointments, Retina, Dormancies.**

1. Introduction

The eye is a complex organ with a unique deconstruction and physiology. The structure of eye can be divided into two main corridor anterior member and posterior member (Figure 1).

Manuscript revised April 10, 2024; accepted April 12, 2024. Date of publication April 25, 2024.
This paper available online at www.ijprse.com
ISSN (Online): 2582-7898; SJIF: 5.59

Anterior member of the eye occupies roughly one- third while the remaining portion is enthralled by the posterior member. tissue similar as cornea, conjunctiva, waterless humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior member of the eye include sclera, choroid, retinal colour epithelium, neural retina, optical whim-whams and vitreous humor. The anterior and posterior member of eye is affected by colourful vision hanging conditions. conditions affecting anterior member include, but not limited to glaucoma, antipathetic conjunctivitis, anterior uveitis and cataract. While, age- related macular degeneration (AMD) and diabetic retinopathy are the most current conditions affecting posterior member of the eye[1]

Topical instillation is the most extensively preferred non-invasive route of medicine administration to treat conditions affecting the anterior member. Conventional lozenge forms similar as eye drops account for 90 of the retailed ophthalmic phrasings. The reason may be attributed to ease of administration and case compliance1nevertheless, the optical bioavailability is veritably low with topical drop administration. multitudinous anatomical and physiological constraints similar as tear development, nasolacrimal drainage, kickback blinking, and optical static and dynamic walls pose a challenge and stymie deeper optical medicine saturation. Hence, lower than 5 of topically applied cure reaches to deeper optical tissue. Also, it's delicate to achieve remedial medicine attention into posterior member optical tissue following topical eye drops instillation because of the below mentioned walls. The medicine can be delivered to the posterior member optical tissue by different mode of administrations similar as intravitreal injections, periocular injections, and systemic administration. still, small volume of eye compared to whole body and presence of blood retinal walls; makes systemic administration an impracticable approach. Intravitreal injection is the most common and extensively recommended route of medicine administration to treat posterior optical conditions. Though, the need of repeated eye perforation with intravitreal injections causes several side goods similar as endophthalmitis, haemorrhage, retinal detachment and poor case forbearance. The transscleral medicine delivery with periocular administration route is evolved as an indispensable mode of medicine delivery to the posterior optical tissue. Although transscleral delivery is comparatively easy, less invasive and patient biddable, medicine saturation is compromised by optical static and dynamic walls. optical walls to transscleral medicine

delivery include static walls i.e., sclera, choroid and retinal colour epithelium (RPE), and dynamic walls, i.e., lymphatic inflow in the conjunctiva and episclera, and the blood inflow in conjunctiva and choroid. To overcome the optical medicine delivery walls and ameliorate optical bioavailability, colourful conventional and new medicine delivery systems have been developed similar as conflation, ointments, dormancies, waterless gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in situ thermosensitive gels for the earlier citation optical conditions. This review will give an overview on colourful conventional and new ophthalmic medicine delivery systems developed to deliver medicine to diseased optical tissue for the treatment of optical conditions[2].

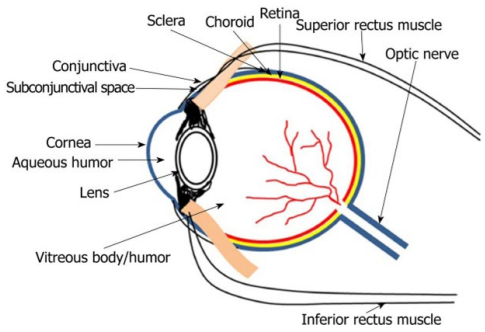

Fig.1. Structure of the eye.

2. Conventional Ocular Drug Delivery Systems

Topical drop instillation into the lower precorneal fund is a patient biddable and extensively recommended route of medicine administration. still, utmost of the topically administered cure is lost due to influx blinking and only 20(−7 µL) of inseminated cure is retained in the precorneal fund. attention of medicine available in the precorneal area acts as a driving force for its unresistant prolixity across cornea. still, for effective optical medicine delivery with eye drops, high corneal saturation with longer medicine cornea contact time is needed. Several sweats have been made toward perfecting precorneal hearthstone time and corneal penetration. To ameliorate corneal saturation iontophoresis, prodrugs, ion- brace forming agents and cyclodextrins are employed. There's a wide range of ophthalmic products available in the request out of which around 70 of conventions include conventional eye drops. The reasons may be due to ease of bulk scale manufacturing, high case adequacy, medicine product efficacity, stability and cost effectiveness.[3]

A. Topical liquid/solution eye drops

Topical drops are the most accessible, safe, incontinently active, patient biddable and on-invasive mode of optical medicine administration. An eye drop result provides a palpitation medicine saturation post topical drop instillation, after which its attention fleetly declines. The kinetics of medicine attention decline may follow an approximate first order. thus, to ameliorate medicine contact time, saturation and optical bioavailability; colourful complements may be added to topical eye drops similar as density enhancers, saturation enhancers and cyclodextrins. density enhancers ameliorate precorneal hearthstone time and bioavailability upon topical drop administration by enhancing expression density. exemplifications of density enhancers include hydroxy methyl cellulose, hydroxy ethyl cellulose, sodium carboxy methyl cellulose, hydroxypropyl methyl cellulose and polyalcohol.[4]

Saturation enhancers ameliorate corneal uptake by modifying the corneal integrity. Other complements similar as chelating agents, preservatives, face active agents and corrosiveness mariners were studied as possible saturation enhancers. Benzalkonium chloride, polyoxymethylene glycol ethers (lauryl, stearyl and oleyl), ethylenediamine tetra acetic acid sodium swab, sodium taurocholate, saponins and chromophore EL are the exemplifications of saturation enhancers delved for perfecting optical delivery. Addition of saturation enhancers to optical results improves optical medicine bioavailability but many studies revealed a original toxin with saturation enhancers. Hence, exploration is still being conducted to modify the effect of saturation enhancers and estimate their safety on corneal tissue. Hornof et al substantiated that polycarbophil- cysteine as an excipient didn't damage the corneal towel integrity and suggested that it could be safe for optical phrasings. Cyclodextrins act as carriers for hydrophobic medicine motes in waterless result. This helps to deliver medicines to the face of natural membrane. largely lipophilic natural membrane has much lower affinity towards hydrophilic cyclodextrins. thus, cyclodextrins remain in waterless result and the hydrophobic medicine is absorbed by the natural membrane. Optimal bioavailability was achieved for eye drops with cyclodextrins attention of< 15. Other operations of cyclodextrins in eye drop expression were lately reviewed and described in detail away by Cholkar et al. Among these approaches, density enhancers and cyclodextrins suffer from the disadvantage of precorneal loss. In the case of penetration enhancers, care should be taken in the selection due to high perceptivity of optical tissue. Hence, it leads to development of other conventional phrasings approaches with inert carrier systems for optical delivery of rectifiers. Conventional optical phrasings similar as mixes, dormancies, and ointments are developed to ameliorate solubility, precorneal hearthstone time and optical bioavailability of medicines. In the current period of nanotechnology, these conventional phrasings still retain their place, significance and prisoner the request at large. still, these phrasings are associated with colourful side goods similar as optical vexation, redness, inflammation, vision hindrance and stability issues. presently, exploration is being conducted to ameliorate in vivo performance of these carrier systems and to minimize their side goods. Several attempts are also being made to deliver medicines to posterior optical tissue with conventional phrasings. In the ensuing sections, attempts have been made to describe the recent sweats made to ameliorate in vivo performance of conventional optical expression and reduce their side goods.[5]

B. Emulsions

An conflation grounded expression approach offers an advantage to ameliorate both solubility and bioavailability of medicines. There are two types of mixes which are commercially exploited as vehicles for active Medicinals oil painting in water (o/ w) and water in oil painting (w/ o) conflation systems. For ophthalmic medicine delivery, o/ w conflation is common and extensively preferred over w/ o system. The reasons include lower vexation and better optical forbearance of o/ w conflation. Restudies, Refresh Endura (anon-medicated conflation for eye lubrication) and Aza Site are the exemplifications of presently retailed optical mixes in the United States. Several studies have demonstrated connection of mixes in perfecting precorneal hearthstone time, medicine corneal saturation, furnishing sustain medicine release and thereby enhancing optical bioavailability. In a recent study, Tajika et al demonstrated betteredanti-inflammatory exertion of prednisolone outgrowth,0.05 (3H) difluprednate, with conflation as vehicle. Results verified that in the rabbit eye, conflation could deliver medicine to the anterior optical tissue with small quantum of medicine reaching posterior tissue following single and multiple topical drop instillation. Single and multiple topical drop instillation studies revealed loftiest radioactivity in cornea followed by iris- ciliary body> retina- choroid> conjunctiva> sclera> waterless humor> lens> and vitreous humor. Post single drop administration, Tmax for cornea, conjunctiva, lens, iris- ciliary body, waterless and vitreous humor was0.5 h while for retina- choroid was 1h. Negligible quantum of medicine was quantified in systemic rotation. With repeated cure instillation, Tmax for lens and retina- choroid was 8 and0.5 h, independently. After 168 h, a total cure of roughly99.5 of radioactivity was excreted in urine and feces. This study suggests difluprednate conflation as an implicit seeker for treating anterior optical inflammations. Emulsions with lipid complements similar as soyabean lecithin, stearylamine were estimated as carrier systems for azithromycin to demonstrate better optical performance and bioavailability. A relative study for azithromycin result vs conflation at different doses (3, 5 and 10 mg/ mL azithromycin) was studied for gash elimination characteristics. In vivo studies were conducted in rabbits with topical drop administration. Emulsion, not only observed to bear as a vehicle for azithromycin but also braked medicine release, bettered its chemical stability and precorneal hearthstone time. also, conflation expression bettered the chemical stability (t1/2) of azithromycin at pH5.0 and7.0 relative to waterless results. Altogether, results suggest that lipid conflation could be a promising vehicle for optical medicine delivery.[5,6]

Also, another new approach is to derivatize active pharmaceutical constituents (API), and ameliorate its optical bioavailability with conflation as carrier system. This strategy may help to reduce optical irritancy and ameliorate the effect of API. To test this thesis, Shen et al made attempts to ameliorate conflation biocompatibility for the flurbiprofen. In this study outgrowth of flurbiprofen, flurbiprofen axetil, with castor oil painting and tween- 80 was used to prepare conflation. Four different mixes with varying rates of castor oil painting (0.1 wt –2.5 wt) and tween 80(0.08wt – 4wt) were prepared and label as F1, F2, F3 and F4 independently. In vivo studies were conducted in manly New Zealand albino rabbits with a topical drop instillation. Waterless humor pharmacokinetic studies showed F2 conflation (castor oil painting to tween 80 wt rate of0.50.4) to be better relative to other conflation phrasings and result. The F2 conflation translocated high medicine attention into waterless humor, post topical drop administration, relative to0.03 flurbiprofen sodium eye drops. also, optical vexation studies with F2 conflation demonstrated better biocompatibility relative to other mixes (F1, F3 and F4).

Several experimenters have introduced mucoadhesive polymers similar as chitosan and hydroxypropyl methyl cellulose ether for conflation coating. Studies concluded that chitosan face coating improves precorneal hearthstone time of API and thereby optical bioavailability. Indomethacin loaded o/ w conflation was prepared employing castor oil painting and polysorbate- 80 and the attendant conflation was face carpeted by chitosan. A relative in vivo study for chitosan carpeted vsnon-coated indomethacin mixes were conducted in manly albino rabbits with topical drop instillation. Tear fluid pharmacokinetic study showed that conflation face coating with chitosan improves conflation mean hearthstone time and also half- life by1.5 and1.8 times, independently relative tonon-coated conflation. Indomethacin attention was quantified in cornea, conjunctiva and waterless humor, post 1 h of conflation instillation. Indomethacin attention with conflation system were set up to be about5.3 and8.2 times advanced in cornea relative to conjunctiva and waterless humor.6

C. Suspensions

Dormancies are another class of non-invasive optical topical drop medicine carrier systems. suspense may be defined as dissipation of finely divided undoable API in an waterless detergent conforming of a suitable suspending and dispersing agent. In other words, the carrier detergent system is a logged result of API. suspense patches retain in precorneal fund and thereby ameliorate medicine contact time and duration of action relative to medicine result. Duration of medicine action for suspense is flyspeck size dependent. lower size flyspeck replenishes the medicine absorbed into optical tissue from precorneal fund. While on the other hand, larger flyspeck size helps retain patches for longer time and slow medicine dissolution. therefore, an optimal flyspeck size is anticipated to affect in optimum medicine exertion. Several suspense phrasings are retailed worldwide to treat optical bacterial infections. TobraDex suspense is one of the extensively recommended marketable products for subjects responding to steroid remedy. TobraDex is a combination product of antibiotic, tobramycin (0.3%), and steroid, dexamethasone (0.1%). The major debit of this marketable product is high density. lately, Scoper et al made attempts to reduce the density of TobraDex and to ameliorate it's in vivo pharmacokinetics along with bactericidal exertion. The explanation behind

developing this expression was to ameliorate the suspense expression characteristics similar as quality, tear film kinetics and towel saturation. The new suspense (TobraDex ST) consists of tobramycin (0.3%), and steroid, dexamethasone (0.05%). suspense settling studies showed that new expression had veritably low settling over 24 h (3) relative to retailed Tobra-Dex (66). optical distribution studies showed advanced apkins attention of dexamethasone and tobramycin in rabbits treated with TobraDex ST relative to Tobra-Dex. New suspense expression was set up to be more effective than TobraDex against Staphylococcus aureus and Pseudomonas aeruginosa. Clinical studies in mortal subjects showed high dexamethasone attention in waterless humor than TobraDex. These results suggest that new suspense expression to be a volition to retailed suspense. This is because the new suspense possesses better expression characteristics, pharmacokinetics, bactericidal characteristic and patient compliance than retailed TobraDex suspense.[7]

In another study, to treat dry eye, 4wk, randomized, double masked, multi-center phase II clinical trials were conducted with rebamipide (OPC- 12759) suspense. suspense expression at two different boluses, i.e., 1%and 2% rebamipide were employed for this study, where placebo served as control. The efficacity and safety of suspense expression were determined in mortal subjects following topical instillation. A cure dependent response was observed for placebo, 1and 2 rebamipide suspense for both fluorescein corneal staining and Lissamine green conjunctival staining studies at 2 and 4 wk. Tear product showed no significant difference from birth from day 1 to week4.But, the gash film breaks up time showed significant change in 1% and 2% rebamipide relative to placebo. All the subjects entering treatment with suspense rebamipide expression reported enhancement of 64.1% and 54.9% independently than subjects entering placebo. Dysgeusia, optical vexation and nasopharyngitis adverse events were constantly observed in27.2% ,29.1% and 30.4% cases entering placebo,1%and 2% suspense, independently. medicine convinced adverse goods similar as eye vexation was observed in3.9,2.9 and2.0 subjects entering placebo, 1% rebamipide and 2% rebamipide independently. All these adverse goods were set up to recover without any fresh treatment. This 4 wk studies revealed that suspense phrasings were well permitted and both phrasings were effective in treating dry eye. In some measures, of the two phrasings, 2% rebamipide suspense was set up to be more effective relative to 1% suspense.[7,8]

D. Ointments

Ophthalmic ointments are another class of carrier systems developed for topical operation. optical ointment comprises of admixture of circumfluous and a solid hydrocarbon (paraffin) that has a melting point at physiological optical temperature (34 °C). The choice of hydrocarbon is dependent on biocompatibility. Ointments help to ameliorate optical bioavailability and sustain the medicine release.

In another study by Eguchi et al, four different ointment expression of vancomycin with varying attention (0.03%,0.10%,0.30% and1.00%) were prepared in 14 fusions of liquid paraffin and vaseline. The efficacity of phrasings was estimated in rabbit model of MRSA keratitis infection after topical operation. It was observed that at low medicine attention, i.e.,0.03% and0.10%, multitudinous infiltrates were set up in corneas with abscesses. On the other hand, creatures treated with0.3 expression showed no rush of keratitis in any eye over 14 d study period. thus,0.3 vancomycin ointment was suggested to be acceptable and effective to resolve corneal MRSA keratitis.

Though considerable trouble is being put into exploration to ameliorate efficacity, still there's a need to overcome certain downsides associated with conventional phrasings. The below mentioned phrasings conflation, suspense, and ointment are known to beget optical adverse goods similar as vexation, redness of eye and hindrance with vision. Also, habitual administration may increase systemic API vacuity which may lead to severe systemic complications. phrasings with preservatives also induce adverse responses upon systemic immersion thus, to overcome expression grounded adverse goods and to deliver remedial quantities of medicine in optical tissue exploration is now being concentrated on exploring and developing other new strategies of optical medicine delivery. In the ensuing sections, we've bandied about the recent developments made in nanotechnology and controlled release bias in once decade to ameliorate optical medicine delivery.[8]

3. Novel Ocular Drug Delivery Systems

A. Nanotechnology based ocular drug delivery

In a last many decade, numerous approaches have been employed for the treatment of optical conditions. Nanotechnology grounded ophthalmic phrasings are one of the approaches which is presently being pursued for both anterior, as well as posterior member medicine delivery. Nanotechnology grounded systems with an applicable flyspeck size can be designed to insure low vexation, acceptable bioavailability, and optical towel comity. Several nanocarriers, similar as nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have been developed for optical medicine delivery. Some of them have shown promising results for perfecting optical bioavailability.[8]

B. Nano micelles

Nano micelles are the most generally used carrier systems to formulate remedial agents in to clear waterless results. In general, these nano micelles are made with amphiphilic motes. These motes may be surfactant or polymeric in nature. lately, Cholkar et al have reviewed in detail about optical walls and operation of nano micelles grounded technology in optical medicine delivery.

presently, tremendous interest is being shown towards development of nano micellar expression grounded technology for optical medicine delivery. The reasons may be attributed due to their high medicine encapsulation capability, ease of medication, small size, and hydrophilic nano micellar nimbus

generating waterless result. In addition, micellar expression can enhance the bioavailability of the remedial medicines in optical apkins, suggesting better remedial issues. So far, several attestations of conception studies have been conducted to probe the connection of nanomicelles in optical medicine delivery. For case, Civiale et al developed dexamethasone loaded nanomicelles by employing copolymers of polyhydroxyethylaspartamide (PHEAC (16)) and pegylated PHEAC (16) for anterior member delivery. In vivo dexamethasone attention time biographies were studied and determined in rabbits with waterless humor slice. Results showed that dexamethasone loaded PHEA micelles have advanced optical bioavailability relative to dexamethasone suspense. The area under the wind for dexamethasone micellar expression was 40 advanced than that of control suspense. Results suggest that nanomicellar phrasings are a feasible option for topical optical delivery of small motes. Experimenters have also employed nanomicelles for optical gene delivery. In a study, Liaw et al made attempts to deliver genes by topical drop administration to cornea. Copolymer, poly (ethylene oxide)- poly (propylene oxide)- poly (ethylene oxide) (PEO- PPO- PEO) was used to develop micelles as a vehicle for gene delivery. This polymeric system efficiently transferred plasmid DNA with LacZ gene in rabbit and mice optical tissue. Results were promising and indicated the implicit operation of copolymers in DNA transfer. farther studies were conducted with the copolymer to deliver two cornea specific promoters, i.e., keratin 12 (K12) and keratocan. Transgene expression was quantified with β- girl exertion. Significant elevated situations were quantified following six boluses of eye drop of pK12- Lac Z- PM three times a day in both mouse and rabbit corneas. The probable medium of transfection was endocytosis and flyspeck size dependent paracellular transport of polymeric micelles. Several attempts are also being made to use nanomicelles for the posterior optical medicine delivery. lately, the authors have made a significant stride to deliver remedial medicines to the posterior optical tissue with the aid of topical drops of mixed nanomicellar phrasings. To bolster the thesis that the nanomicelles can deliver the medicine to the posterior optical tissue, in vivo studies were carried out in rabbits using voclosporin loaded nanomicelles. Interestingly, the nanomicelle phrasings were suitable to efficiently cut optical tissue and deliver medicine to back of the eye tissue. optical tolerability of nanomicelles was estimated against Restasis as control in New Zealand White rabbits. A detailed 72 h study with Hackett- McDonald scoring with bitsy optical examination was included for two voclosporin (0.02 and0.2) micellar and Restasis phrasings. Post 1 h- topical drop administration of Restasis loftiest optical vexation was observed relative to two micellar voclosporin phrasings. It was demonstrated that the new mixed nanomicellar phrasings were well permitted and convinced markedly low vexation than Restasis. Further, authors also prepared dexamethasone and rapamycin mixed nanomicellar phrasings at a attention of 0.1 and 0.2wt, independently. optical towel distribution studies with single drop instillation showed that nanomicellar expression recapitulating voclosporin, dexamethasone and rapamycin was suitable to deliver remedial attention of medicine to back of the eye tissue post topical drop instillation. These studies suggest that small size, hydrophilic nanomicellar nimbus help to shirk optical walls and deliver medicine weight to posterior optical tissue. Anon-corneal pathway of medicine delivery has been hypothecated for reverse of the eye medicine delivery. made attempts to deliver fluorescein isothiocyanate-labeled poly- L- lysine (FITC- P(Lys)) to back of the eye tissue via intravenous medicine administration to treat back of the eye towel neovascularization. In vivo studies with unformulated FITC- P(Lys) redounded in death of creatures post 1 h of administration. On the contrary recapitulating the FITC- P(Lys) in polyehthylene glycol- block- poly-- aspartic acid micelles redounded in no death. This indicates no free medicine was available in nanomicellar expression. Micellar expression showed a Cmax at 4 h in retina- choroid and medicine was detected up to 7 d following single intravenous administration. Dragged micellar rotation was achieved by controlling polymer to medicine charge rates. Authors suspected that longer systemic micellar rotation may prop in enhanced saturation and retention (EPR) effect at neovascularization point. Micellar constructs were observed to widely accumulate at the pathologic neovascular point to a lesser extent than in normal tissue.[9,10]

C. Nanoparticles

Nanoparticles are colloidal carriers with a size range of 10 to 1000 nm. For ophthalmic delivery, nanoparticles are generally composed of lipids, proteins, natural or synthetic polymers similar as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. medicine loaded nanoparticles can be nanocapsules or nanospheres (Figure 3). In nanocapsules, medicine is enclosed inside the polymeric shell while in nanospheres; medicine is slightly distributed throughout polymeric matrix. From once many decades, nanoparticles have gained attention for optical medicine delivery and several experimenters have made attempts to develop medicine loaded nanoparticles for delivery to both anterior and posterior optical apkins (Table 1).

Nanoparticles represents a promising seeker for optical medicine delivery because of small size leading to low vexation and sustained release property avoiding frequent administration. still, like waterless results, nanoparticles may be excluded fleetly from precorneal fund. Hence, for topical administration nanoparticles with mucoadhesive parcels have been developed to ameliorate precorneal hearthstone time. Polyethylene glycol (cut), chitosan and hyaluronic acid are generally employed to ameliorate precorneal hearthstone time of nanoparticles.[10]

Chitosan coating is most extensively explored for perfecting precorneal hearthstone of nanoparticles. The chitosan is appreciatively charged and hence it binds to negatively charged

corneal face and thereby improves precorneal hearthstone and decreases concurrence. For case, natamycin loaded chitosan/ lecithin nanoparticles displayed high optical bioavailability at reduced cure and dosing frequence in rabbit eye compared to retailed suspense. Following topical administration, the attention- time wind (AUC) (0 – 8) was increased up to1.47 fold and concurrence was dropped up to7.40 fold in case of chitosan/ lecithin nanoparticles compared to retailed suspense. In another study, Musumeci et al reported that melatonin loaded PLGA-PEG nanoparticles were most effective and demonstrated significant intraocular pressure (IOP) lowering effect compared with melatonin loaded PLGA nanoparticles and waterless result of original attention in the rabbit eye. It was suspected that the reduced zeta eventuality of nanoparticles fabricated from PLGA- cut than the PLGA allowed better and longer commerce between the nanoparticles and eye face leading to advanced hypotensive effect for prolonged period.

Nanoparticles have also been successfully employed as an indispensable strategy for long term medicine delivery to the posterior member optical tissue. For posterior member delivery, disposition of nanoparticles depends on the size and face property. Following, periocular administration in to Sprague-Dawley rats, 20 nm patches were cleared fleetly from periocular tissue. The rapid-fire concurrence can be due to junking by conjunctival, episcleral or other periocular circulatory systems. On the other hand, patches in the range of 200 – 2000 nm were retained at the point of administration for at least two months. also, due to the rapid-fire concurrence and fast medicine release, small size nanoparticles couldn't sustain retinal medicine position. thus, it can be concluded that for dragged transscleral medicine delivery to the reverse of the eye, nanoparticles with slow medicine release and low concurrence by blood and lymphatic gyrations are suitable medicine delivery campaigners.[11]

Following intravitreal injection, nanoparticles resettle through the retinal layers and tend to accumulate in the RPE cells. The PLA nanoparticles were present in rat RPE tissue up to 4 following single intravitreal injection which suggest that nanoparticles have great eventuality for achieving steady and nonstop delivery to the reverse of the eye. Zhang et al delved the pharmacokinetics and forbearance of dexamethasone (DEX) loaded PLGA nanoparticles in rabbits following intravitreal injection. Authors concluded that DEX when reprised in nanoparticles displayed sustained release for 50 d. The constant DEX situations were maintained in vitreous over 30 d with a mean attention of 3.85 mg/L. Contrary, only trace quantities of DEX being detected on the 7th day after injection of DEX result. These results indicate that intravitreal injection of dexamethasone nanoparticles may be employed for sustained delivery of medicines for the treatment of posterior member eye conditions.

The face property of nanoparticles is a crucial factor affecting their distribution from vitreous humor to retinal layers. Koo et al studied correlation between face parcels of the nanoparticles and their distribution in the vitreous and retina after intravitreal injection.

Table 1
Summary of recent developments with nanoparticles as ocular drug delivery vehicles

DRUG	POLYMER	FEATURES
Carboplatin	CH, SA	Carboplatin loaded NPs demonstrated elevated and sustained anti-proliferative activity in a retinoblastoma cell line (Y-79), with IC_{50} of 0.56 and 0.004 µg/mL for free carboplatin and carboplatin loaded NPs, respectively[13]
5-FU	CH,SA	CH coated SA-CH nanoparticles (CH-SA-CH NPs) loaded with 5-FU showed significantly higher concentration of 5-FU in aqueous humor as compared to SA-CH 5- FU loaded NPs and 5-FU solution. The higher C_{max} was achieved in case of CH-SA-CH NPs (24.67 µg/mL) compared to 5-FU solution (6.14 µg/mL)
Sparfloxacin	PLGA	After topical application, sparfloxacin-loaded nanoparticles were retained for a longer duration on the corneal surface as compared to an aqueous solution, which was drained rapidly from the corneal surface. Also, *in vitro* release studies revealed an extended release of sparfloxacin[13]
BT	Sodium algimate	BT-loaded nanoparticles provided prolong drug release over a period of 8 h after topical instillation to albino rabbits
levofloxacin	PLGA	The nanosuspensions was retained for the longer time on rabbit eye surface and drained out slowly compared to marketed formulation. Results of *ex-vivo* transcorneal permeation study across excised goat cornea revealed that levofloxacin from the marketed formulation was permeated 36.9% in 4 h whereas levofloxacin from PLGA nanoparticles was permeated 47.43% in 4 h across cornea
DS	PLGA	An extended DS release was observed from the nanoparticles under *in vitro* conditions. The developed polymer nanoparticles formulation was non-irritant to cornea, iris, and conjunctiva for as long as 24 h after application[14]
Pilocarpine	PLGA	The *in vivo* miosis studies showed that the duration of miotic response increased by 40% for the nanoparticles compared to the eye drops
Gatifloxacin/Prednisolone	Eudragit RS 100 and RL 100, coating with hyaluronic acid	*In vitro* release studies revealed prolonged drug release compared to the free drugs with no burst effect Nanoparticles formulation showed better bioavailability of gatifloxacin in rabbit eye with 1.76 fold increase in C_{max} of gatifloxacin in the aqueous humor in comparison to the eye drops
Cloricromene (AD6)	Eudragit	Nanosuspension enhanced stability of the ester drug for several months as compared to an AD6 aqueous solution
Brimonidine Tartrate	Eudragit RS 100 Eudragit RL 100	The AUC (ΔIOP *vs* time) for the selected nanoparticles formulations were about seven times higher `than that of eye drop formulations in rabbit eye[15]

Miscellaneous polyethyleneimine/ glycol chitosan (PEI/ GC), mortal serum albumin (HSA)/ GC, and HSA/ hyaluronic acid (HA) nanoparticles were prepared by blending two polymers.

The value of zeta eventuality of these nanoparticles were20.7 ±3.2−1.9 ±4.1 and−23.3 ±4.4 for PEI/ GC, HSA/ GC, and HSA/ HA nanoparticles, independently. The nanoparticles were fitted into vitreous depression of Long Evans rats and vitreous/ retinal distribution was estimated by confocal microscopy. shows vitreal and retinal distribution of intravitreally administered miscellaneous nanoparticles. It can be depicted from the that PEI/ GC nanoparticles fluently entered the vitreal hedge and reached at the inner limiting membrane. still, PEI/ GC nanoparticles didn't access through the physical pores of inner limiting membrane into the deeper retinal layers and also some addition, nanosuspension can also be incorporated into hydrogels or optical inserts for achieving sustained medicine release for quested time period.[12]

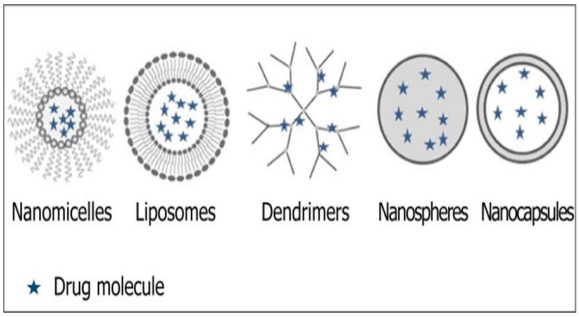

Fig.2. Nanocarriers for ocular drug delivery.

D. Liposomes

Liposomes are lipid vesicles with one or further phospholipid bilayers enclosing a waterless core. The size of liposomes generally range from 0.08 to10.00 µm and grounded on the size and phospholipid bilayers, liposomes can be classified as small unilamellar vesicles (10 – 100 nm), large unilamellar vesicles (100 – 300 nm) and multilamellar vesicles (contains further than one bilayer). For ophthalmic operations, liposomes represent ideal delivery systems due to excellent biocompatibility, cell membrane like structure and capability to synopsize both hydrophilic and hydrophobic medicines. Liposomes have demonstrated good effectiveness for both anterior and posterior member optical delivery in several exploration studies. Recent advancements in liposomal optical medicine delivery are epitomized in Table 2. In a recent study, for delivery of latanoprost to anterior member optical tissue. liposomal expression was developed by Natarajan et al. The single subconjunctival injection of latanoprost/ liposomal expression in rabbit eye produced sustained IOP lowering effect over a period of 50 d with IOP reduction similar to diurnal eye drop administration. For medicine delivery to anterior member of the eye, sweats are substantially put toward perfecting precorneal hearthstone time by incorporating appreciatively charged lipids or mucoadhesive polymer in liposomes. The appreciatively charged liposomes i.e., cationic liposomes have displayed better efficacity in optical delivery than negatively charged and neutral liposomes due to binding with negatively charges of corneal face.

Didodecyldimethylammonium platitude, stearylamine, and N-(1-(2,3- dioleoyloxy) propyl)-trimethylammonium chloride are generally employed for fabricating cationic liposomes.[16]

Acyclovir loaded cationic and anionic liposomes were prepared by incorporating stearylamine and dicetylphosphate (DP), as cationic and anionic charge- converting agents, independently. In rabbit eyes, the acyclovir attention in the cornea at2.5 h after topical administration of appreciatively charged liposomes was lesser than those of negatively charged liposomes and free acyclovir. ACV attention in cornea were253.3 ±72.0,1093.3 ±279.7 and571.7 ±105.3 ng/ g for ACV result, ACV loaded appreciatively and negatively charged liposomes, independently. Also, the extent of ACV immersion through cornea was advanced from appreciatively charged liposomes which can be observed from ACV attention in waterless humor at 2.5 h after instillation. The suggested reason was the advanced list of appreciatively charged liposomes with negatively charged corneal face via electrostatic commerce which eventually lead to an increase of hearthstone time and increase in acyclovir immersion. In another study, when Coenzyme Q10 (CoQ10) loaded liposomes was carpeted with mucoadhesive trimethyl chitosan, there was a4.8 fold increase in the precorneal hearthstone time in the rabbit eye was observed.

For posterior member delivery, liposomes development is more focused toward perfecting half- life of medicine by lessening concurrence from vitreous humor, guarding labile motes similar as peptides and oligonucleotides from declination and furnishing sustained medicine release. For case, the vitreal half- life of fluconazole in rabbit eye was increased from3.08 to23.40 h after formulating into liposomes. In another study, tacrolimus loaded liposomes were developed for the treatment of uveoretinitis. Following single intravitreous administration, tacrolimus vitreous position above 50 ng/ mL was sustained for 14d. The tacrolimus liposomal expression demonstrated further effectiveness in suppressing uveoretinitis relative to medicine alone and there was also reduced toxin to inner retinal cells.17

Several liposomal phrasings for optical medicine delivery are being exploited, many are inpre-clinical and clinical study stage and many are commercially available. Visudyne and Gashes again are the exemplifications of commercially available liposomal phrasings for the treatment of optical conditions. Visudyne (QLT Ophthalmics, Inc, Menlo Park, CA, United States) is a liposomal expression containing photosensitizer, verteporfin. It's used in photodynamic remedy for sub foveal choroidal neovascularization in age related macular degeneration, presumed optical histoplasmosis and pathological diplopia. Gashes again (Optima Pharmaceutical GmbH, Germany) is a phospholipid liposomes spot approved for the treatment of the Dry Eye pattern. In clinical studies, this liposomal spray demonstrated significant advantages when compared with triglyceride- containing eye gel and a balanced swab result.

Table 2
Recent advancements in liposomal ocular drug delivery

Drug	Type of Liposomes	Result
Acetazolamide	Multilamellar, unilamellar	Multilamellar liposomes produced a more significant lowering in IOP in comparison with REVs liposomes
Ciprofloxacin	Multilamellar	The mean residence time of ciprofloxacin was three fold higher for the CS-coated liposomes (3.85 h) compared to commercially available eye drops Ciprocin® (1.39 h)[18]
Cytochrome C	Cardiolipin-containing-liposomes	The cytochrome C loaded freeze-dried liposomes exhibited significant efficacy in retarding the onset and progression of cataract formation in rat eye
VIP	Pegylated liposomes	After intravitreal injection, VIP concentration in ocular fluids was 15 times higher for liposomal formulation (155 ± 65 ng/mL) than the solution (10 ± 1 ng/mL), at 24 h
Coumarin-6	Multilamellar	After topical administration in mice, the intensity of coumarin-6 in the retina was much higher with PLL modified liposomes[19]
Fluorescence probe (coumarin-6)	Submicron-sized liposomes (ssLips) and multilamellar	After topical instillation of submicron-sized liposomes (ssLips), drug was delivered to the posterior segment ocular tissues including retina
Fluconazole	Multilamellar	Antifungal activity of fluconazole in liposomal formulation was better than that of fluconazole solution[20]
Edaravone	Submicron-sized liposomes	Topical administration of edaravone-loaded ssLips protected retina against light-induced dysfunction in mice eye while there was no marked protection found in the group treated with free edaravone
Bevacizumab (Avastin)	Multivesicular	Vitreous concentration of bevacizumab after 42 d of administration was 16 and 3.3 µg/mL in the eyes for liposomal and non-liposomal bevacizumab, respectively. The AUC (conc *vs* time) for liposomal bevacizumab was 1.5 fold higher compared with non-liposomal bevacizumab
Diclofenac	Multilamellar	Topical administration of diclofenac loaded PVA-R modified liposomes lead to improved retinal delivery in rabbit eye. Concentration of diclofenac in the retina–choroid was enhanced by 1.8 fold in case of drug loaded PVA-R modified liposome compared to that of the diclofenac solution[20]

E. Dendrimers

Dendrimers are characterized as nanosized, largely fanned, star shaped polymeric systems. These fanned polymeric systems are available in different molecular weights with terminal end amine, hydroxyl or carboxyl functional group. The terminal functional group may be employed to conjugate targeting halves. Dendrimers are being employed as carrier systems in medicine delivery. Selection of molecular weight, size, face charge, molecular figure and functional group are critical to deliver medicines. The largely fanned structure of dendrimers allows objectification of wide range of medicines, hydrophobic as well as hydrophilic. In optical medicine delivery, many promising results were reported with these fanned polymeric systems.[21]

Poly (amidoamine) (PAMAM) dendrimers are extensively employed in optical medicine delivery. Vandamme et al demonstrated operation of PAMAM dendrimers as ophthalmic vehicles for delivery of pilocarpine nitrate and tropicamide, for miotic and mydriatic exertion. In this study, mean optical hearthstone time for fluorescein in saline and in PAMAM results were studied in rabbit eye. Fluorescein in0.2 w/ v Carbopol result was used as reference bioadhesive polymer. The mean optical hearthstone time was significantly advanced in case of PAMAM results and0.2 w/ v Carbopol result compared to saline. thus, the use of dendrimers could be another option for adding optical hearthstone time and remedy enhancing optical bioavailability and achieving better remedial issues. For case, PAMAM dendrimers when co-administrated with pilocarpine nitrate and tropicamide, showed advanced miotic and mydriatic exertion in albino rabbits.[22]

In order to avoid scar towel conformation after glaucoma filtration surgery, conjugates of modified PAMAM dendrimers with glucosamine (DG) and glucosamine 6- sulfate (DGS) were synthesized to ply immunomodulatory and anti-angiogenic conditioning, independently. The subconjunctival administration of these modified conjugates in rabbit model of glaucoma filtration surgery have shown significant inhibition of pro-inflammatory and pro-angiogenic responses and accordingly reduced scar towel conformation. The results attained from the trial indicated that the optical administration of DG and DGS might be effective and safe in clinical practice in avoiding scar towel conformation post glaucoma filtration surgery.[23]

F. Contact lens

Contact lenses are thin, and twisted shape plastic disks which are designed to cover the cornea. After operation, contact lens adheres to the film of gashes over the cornea due to the face pressure. medicine loaded contact lens have been developed for optical delivery of multitudinous medicines similar as β-blockers, antihistamines and antimicrobials. It's supposed that in presence of contact lens, medicine motes have longer hearthstone time in the post-lens tear film which eventually led to advanced medicine flux through cornea with lower medicine flux into the nasolacrimal conduit. generally, medicine is loaded into contact lens by soaking them in medicine results. These soaked contact lenses demonstrated advanced effectiveness in delivering medicine compared to conventional eye drops. Kim et al observed much advanced bioavailability of dexamethasone (DX) from poly (hydroxyethyl methacrylate) (PHEMA) contact lenses in comparison to eye drops. Indeed, effective than topical drops, these soaked contact lenses suffers from disadvantages of shy medicine lading and short term medicine release. To overcome these obstacles, flyspeck- laden contact lenses and molecularly ingrained contact lenses have

been developed. In flyspeck- laden contact lenses, medicine is first entangled in vesicles similar as liposomes, nanoparticles or microemulsion and also these vesicles are dispersed in the contact lens material. Gulsen et al developed flyspeck- laden contact lenses for optical delivery of lidocaine.23 In two different studies, they've prepared flyspeck- laden contact lenses by dispersing lidocaine loaded microemulsion drops or liposome in poly-2-hydroxyethyl methacrylate (p- HEMA) hydrogels. Results of both the studies demonstrated the extended release of lidocaine over a period of 8d. Indeed, patches- laden contact lenses look promising for extended optical medicine delivery; it needs to be stored in medicine impregnated results to avoid medicine loss during storehouse. The designing of stimulants responsive similar as pH or temperature sensitive "smart" patches which can release medicine only in the eye could exclude this problem. The ingrained contact lenses have also showed benefit in terms of both medicine lading and medicine release. It has been demonstrated that soft contact lenses fabricated by the molecular imprinting system have1.6 times advanced timolol lading capacity than the contact lenses prepared by a conventional system and also handed sustained timolol delivery.24 In another study, ketotifen fumarate loaded ingrained lenses have revealed advanced gash fluid bioavailability compared to medicine soaked lenses or ketotifen fumarate retailed eye drops. The relative bioavailability for the ingrained lenses was 3 times lesser than that of non-imprinted lenses. The AUC value of ketotifen fumarate for ingrained lenses, non-imprinted lenses and eye drops were 4365 ± 1070 µg/ h per milliliter, 493 ± 180 µg/ h per milliliter,46.6 ±24.5 µg/ h per milliliter, independently. The results easily demonstrate more effectiveness of ingrained lenses overnon-imprinted lenses and eye drops.[25]

G. Implants

Intraocular implants are specifically designed to give localized controlled drug release over a extended period. These bias help in circumventing multiple intraocular injections and associated complications. generally, for drug delivery to posterior optic tissue, implants are placed intravitreally by making incision through minor surgery at pars plana Ozurdex (AllerganInc, Irvine, CA, United States) is another biocompatible and biodegradable intravitreal implant. It subsisted approved by FDA in June 2009 for the treatment of macular edema. It employs Allergan's technology for delivering dexamethasone.[26] The NOVADUR system contains a PLGA polymer matrix which degrades slowly to lactic acid and glycolic acid allowing dragged release of dexamethasone up to 6 mo. Randomized clinical trials have demonstrated its energy in reducing vision loss and perfecting vision perceptivity in eyes with macular edema associated with branch retinal tone occlusion (BRVO) or central retinal tone occlusion (CRVO). Also, clinical studies with Ozurdex for treatment of diabetic retinopathy, and Irvine- Gass pattern proved it as a promising treatment and drug delivery candidate.[27]

H. Microneedles

Microneedle grounded fashion is an arising and minimally invasive mode of medicine delivery to posterior optical tissue. This fashion may give effective treatment strategy for vision hanging posterior optical conditions similar as age related macular degeneration, diabetic retinopathy and posterior uveitis. This new microneedle grounded administration strategy may reduce the threat and complications associated with intravitreal injections similar as retinal detachment, hemorrhage, cataract, endophthalmitis and pseudo endophthalmitis. also, this strategy may help to circumvent blood retinal hedge and deliver remedial medicine situations to retina/ choroid. Microneedles are custom-made designed to access only hundreds of microns into sclera, so that damage to deeper optical tissue may be avoided. These needles help to deposit medicine or carrier system into sclera or into the narrow space present between sclera and choroid called "suprachoroidal space" (SCS). Puncturing of sclera and depositing medicine result or carrier systems in sclera or SCS may grease prolixity of medicine into deeper optical tissue, choroid and neural retina. For intraocular delivery of medicines Jason etal. delved the operation of microneedles face carpeted with medicines. Cadaver eyes were used to estimate the part and scleral penetration of microneedle and intrascleral dissolution of microneedle face carpeted medicine (sulforhodamine). Results demonstrated that face carpeted medicine was fleetly dissolved in scleral towel indicating high scleral sulforhodamine deposit within microneedle hole.28 In another study, Jiang et al made attempts to estimate the performance of microneedles to inoculate medicine results, nanoparticles and microparticles into scleral tissue. By use of microneedles, authors were suitable to inoculate roughly 10 – 35 µL of fluid in to tissue. Nanoparticles dormancies and microparticles were also delivered into sclera by microneedles still; microparticles were delivered only in the presence of collagenase spreading enzymes and hyaluronidase. Study demonstrated that concave microneedles may be employed for scleral infusion of medicine or micro/ nanoparticles with minimum invasive route.[29,30]

4. Conclusion

Ocular drug delivery systems play a pivotal role in addressing the unique challenges associated with treating eye disorders. As the eye presents a highly complex and sensitive organ, traditional drug delivery methods often fall short in providing effective and sustained therapeutic outcomes. ocular drug delivery systems represent a transformative frontier in the field of ophthalmology, offering the potential to revolutionize the treatment landscape for various eye disorders.

References

[1]. Bourlais CL, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems--recent advances. Prog Retin Eye Res. 1998.

[2]. Gulsen D, Chauhan A. Ophthalmic drug delivery through contact lenses. Invest Ophthalmol Vis Sci. 2004.

[3]. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. AAPS J. 2010.
[4]. Gaudana R, Jwala J, Boddu SH, Mitra AK. Recent perspectives in ocular drug delivery. Pharm Res. 2009.
[5]. Bochot A, Fattal E. Liposomes for intravitreal drug delivery: a state of the art. J Control Release. 2012.
[6]. Kim SH, Lutz RJ, Wang NS, Robinson MR. Transport barriers in transscleral drug delivery for retinal diseases. Ophthalmic Res. 2007.
[7]. Lee SJ, He W, Robinson SB, Robinson MR, Csaky KG, Kim H. Evaluation of clearance mechanisms with transscleral drug delivery. Invest Ophthalmol Vis Sci. 2010.
[8]. Schoenwald RD. Ocular drug delivery. Pharmacokinetic considerations. Clin Pharmacokinet. 1990.
[9]. Vaka SR, Sammeta SM, Day LB, Murthy SN. Transcorneal iontophoresis for delivery of ciprofloxacin hydrochloride. Curr Eye Res. 2008.
[10]. 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.
[11]. Gunda S, Hariharan S, Mitra AK. Corneal absorption and anterior chamber pharmacokinetics of dipeptide monoester prodrugs of ganciclovir (GCV): in vivo comparative evaluation of these prodrugs with Val-GCV and GCV in rabbits. J Ocul Pharmacol Ther. 2006.
[12]. Gallarate M, Chirio D, Bussano R, Peira E, Battaglia L, Baratta F, Trotta M. Development of O/W nanoemulsions for ophthalmic administration of timolol. Int J Pharm. 2013.
[13]. Tirucherai GS, Mitra AK. Effect of hydroxypropyl beta cyclodextrin complexation on aqueous solubility, stability, and corneal permeation of acyl ester prodrugs of ganciclovir. AAPS PharmSciTech. 2003.
[14]. Vulovic N, Primorac M, Stupar M, Brown MW, Ford JL. Some studies on the preservation of indometacin suspensions intended for ophthalmic use. Pharmazie. 1990; 45:678–679.
[15]. Meseguer G, Buri P, Plazonnet B, Rozier A, Gurny R. Gamma scintigraphic comparison of eyedrops containing pilocarpine in healthy volunteers. J Ocul Pharmacol Ther. 1996.
[16]. Gebhardt BM, Varnell ED, Kaufman HE. Cyclosporine in collagen particles: corneal penetration and suppression of allograft rejection. J Ocul Pharmacol Ther. 1995.
[17]. Saettone MF, Chetoni P, Cerbai R, Mazzanti G, Braghiroli L. Evaluation of ocular permeation enhancers: in vitro effects on corneal transport of four beta-blockers, and in vitro/in vivo toxic activity. Int J Pharm. 1996.
[18]. Van der Bijl P, van Eyk AD, Meyer D. Effects of three penetration enhancers on transcorneal permeation of cyclosporine. Cornea. 2001.
[19]. Burgalassi S, Chetoni P, Monti D, Saettone MF. Cytotoxicity of potential ocular permeation enhancers evaluated on rabbit and human corneal epithelial cell lines. Toxicol Lett. 2001.
[20]. Keister JC, Cooper ER, Missel PJ, Lang JC, Hager DF. Limits on optimizing ocular drug delivery. J Pharm Sci. 1991.
[21]. Hornof MD, Bernkop-Schnürch A. In vitro evaluation of the permeation enhancing effect of polycarbophil-cysteine conjugates on the cornea of rabbits. J Pharm Sci. 2002.
[22]. Kurz D, Ciulla TA. Novel approaches for retinal drug delivery. Ophthalmol Clin North Am. 2002.
[23]. Cholkar K, Patel SP, Vadlapudi AD, Mitra AK. Novel strategies for anterior segment ocular drug delivery. J Ocul Pharmacol Ther. 2013.
[24]. Mannermaa E, Vellonen KS, Urtti A. Drug transport in corneal epithelium and blood-retina barrier: emerging role of transporters in ocular pharmacokinetics. Adv Drug Deliv Rev. 2006.
[25]. Shen J, Gan L, Zhu C, Zhang X, Dong Y, Jiang M, Zhu J, Gan Y. Novel NSAIDs ophthalmic formulation: flurbiprofen axetil emulsion with low irritancy and improved anti-inflammation effect. Int J Pharm. 2011.
[26]. Vandamme TF. Microemulsions as ocular drug delivery systems: recent developments and future challenges. Prog Retin Eye Res. 2002.
[27]. Liang H, Brignole-Baudouin F, Rabinovich-Guilatt L, Mao Z, Riancho L, Faure MO, Warnet JM, Lambert G, Baudouin C. Reduction of quaternary ammonium-induced ocular surface toxicity by emulsions: an in vivo study in rabbits. Mol Vis. 2008.
[28]. Tajika T, Isowaki A, Sakaki H. Ocular distribution of difluprednate ophthalmic emulsion 0. 05% in rabbits. J Ocul Pharmacol Ther. 2011.
[29]. Liu Y, Lin X, Tang X. Lipid emulsions as a potential delivery system for ocular use of azithromycin. Drug Dev Ind Pharm. 2009.
[30]. Karasawa F, Ehata T, Okuda T, Satoh T. Propofol injection pain is not alleviated by pretreatment with flurbiprofen axetil, a prodrug of a nonsteroidal antiinflammatory drug. J Anesth. 2000.