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REVIEW

Ocular drug delivery systems: An overview

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Abstract

The major challenge faced by today's pharmacologist and formulation scientist is ocular drug delivery. Topical eye drop is the most convenient and patient compliant route of drug administration, especially for the treatment of anterior segment diseases. Delivery of drugs to the targeted ocular tissues is restricted by various precorneal, dynamic and static ocular barriers. Also, therapeutic drug levels are not maintained for longer duration in target tissues. In the past two decades, ocular drug delivery research acceleratedly advanced towards developing a novel, safe and patient compliant formulation and drug delivery devices/techniques, which may surpass these barriers and maintain drug levels in tissues. Anterior segment drug delivery advances are witnessed by modulation of conventional topical solutions with permeation and viscosity enhancers. Also, it includes development of conventional topical formulations such as suspensions, emulsions and ointments. Various nanoformulations have also been introduced for anterior segment ocular drug delivery. On the other hand, for posterior ocular delivery, research has been immensely focused towards development of drug releasing devices and nanoformulations for treating chronic vitreo-retinal diseases. These novel devices and/or formulations may help to surpass ocular barriers and associated side effects with conventional topical drops. Also, these novel devices and/or formulations are easy to formulate, no/negligibly irritating, possess high precorneal residence time, sustain the drug release, and enhance ocular bioavailability of therapeutics. An update of current research advancement in ocular drug delivery necessitates and helps drug delivery scientists to modulate their think process and develop novel and safe drug delivery strategies. Current review intends to summarize the existing conventional formulations for ocular delivery and their advancements followed by current nanotechnology based formulation developments. Also, recent developments with other ocular drug delivery strategies employing *in situ* gels, implants, contact lens and microneedles have been discussed.

Key words: Anatomy and physiology; Cornea; Contact lens; Drug delivery; Eye; Emulsions; Formulations; Implants; Liposomes; Nanomicelles; Ointments; Retina; Suspensions

Core tip: Drug delivery to targeted ocular tissues has been a major challenge to ocular scientist, for decades. Current review intends to summarize the existing conventional formulations for ocular delivery and their advancements followed by current nanotechnology based formulation developments. Also, recent developments with other ocular drug delivery strategies employing *in situ* gels, implants, contact lens and microneedles have been discussed.

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INTRODUCTION

The eye is a complex organ with an unique anatomy and physiology. The structure of eye can be divided into

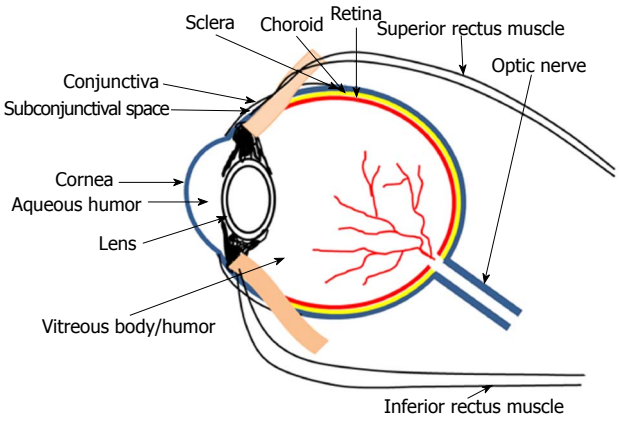

Figure 1 Structure of the eye.

two main parts: anterior segment and posterior segment (Figure 1). Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye.

Topical instillation is the most widely preferred non-invasive route of drug administration to treat diseases affecting the anterior segment. Conventional dosage forms such as eye drops account for 90% of the marketed ophthalmic formulations. The reason may be attributed to ease of administration and patient compliance[1,2]. Nonetheless, the ocular bioavailability is very low with topical drop administration. Numerous anatomical and physiological constraints such as tear turnover, nasolachrymal drainage, reflex blinking, and ocular static and dynamic barriers pose a challenge and impede deeper ocular drug permeation[3]. Hence, less than 5% of topically applied dose reaches to deeper ocular tissues[4]. Also, it is difficult to achieve therapeutic drug concentration into posterior segment ocular tissues following topical eye drops instillation because of the above mentioned barriers. The drug can be delivered to the posterior segment ocular tissues by different mode of administrations such as intravitreal injections, periocular injections, and systemic administration. However, small volume of eye compared to whole body and presence of blood retinal barriers; makes systemic administration an impractical approach. Intravitreal injection is the most common and widely recommended route of drug administration to treat posterior ocular diseases. Though, the need of repeated eye puncture with intravitreal injections causes several side effects such as endophthalmitis, hemorrhage, retinal detachment and poor patient tolerance[5]. The transscleral drug delivery with periocular administration route is evolved as an alternative mode of drug delivery to the posterior ocular tissues. Although transscleral delivery is comparatively easy, less invasive and patient compliant, drug permeation is compromised by ocular static and dynamic barriers. Ocular barriers to transscleral drug delivery include: static barriers *i.e.,* sclera, choroid and retinal pigment epithelium (RPE), and dynamic barriers, *i.e.,* lymphatic flow in the conjunctiva and episclera, and the blood flow in conjunctiva and choroid[6,7].

To overcome the ocular drug delivery barriers and improve ocular bioavailability, various conventional and novel drug delivery systems have been developed such as emulsion, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and *in situ* thermosensitive gels for the earlier mention ocular diseases. This review will provide an overview on various conventional and novel ophthalmic drug delivery systems developed to deliver drug to diseased ocular tissues for the treatment of ocular diseases.

CONVENTIONAL OCULAR DRUG DELIVERY SYSTEMS

Topical drop instillation into the lower precorneal pocket is a patient compliant and widely recommended route of drug administration. However, most of the topically administered dose is lost due to reflux blinking and only 20% (~7 μL) of instilled dose is retained in the precorneal pocket[8]. Concentration of drug available in the precorneal area acts as a driving force for its passive diffusion across cornea. However, for efficient ocular drug delivery with eye drops, high corneal permeation with longer drug cornea contact time is required. Several efforts have been made toward improving precorneal residence time and corneal penetration. To improve corneal permeation iontophoresis, prodrugs, ion-pair forming agents and cyclodextrins are employed[9-13]. There is a wide range of ophthalmic products available in the market out of which around 70% of prescriptions include conventional eye drops. The reasons may be due to ease of bulk scale manufacturing, high patient acceptability, drug product efficacy, stability and cost effectiveness.

Topical liquid/solution eye drops

Topical drops are the most convenient, safe, immediately active, patient compliant and non-invasive mode of ocular drug administration. An eye drop solution provides a pulse drug permeation post topical drop instillation, after which its concentration rapidly declines. The kinetics of drug concentration decline may follow an approximate first order. Therefore, to improve drug contact time, permeation and ocular bioavailability; various additives may be added to topical eye drops such as viscosity enhancers,

permeation enhancers and cyclodextrins. Viscosity enhancers improve precorneal residence time and bioavailability upon topical drop administration by enhancing formulation viscosity. Examples of viscosity enhancers include hydroxy methyl cellulose, hydroxy ethyl cellulose, sodium carboxy methyl cellulose, hydroxypropyl methyl cellulose and polyalcohol[14-16].

Permeation enhancers improve corneal uptake by modifying the corneal integrity. Other additives such as chelating agents, preservatives, surface active agents and bile salts were studied as possible permeation enhancers. Benzalkonium chloride, polyoxyethylene glycol ethers (lauryl, stearyl and oleyl), ethylenediaminetetra acetic acid sodium salt, sodium taurocholate, saponins and cremophor EL are the examples of permeation enhancers investigated for improving ocular delivery[17-19]. Addition of permeation enhancers to ocular solutions improves ocular drug bioavailability but few studies revealed a local toxicity with permeation enhancers[20]. Hence, research is still being conducted to modify the effect of permeation enhancers and evaluate their safety on corneal tissues. Hornof *et al*[21] evidenced that polycarbophil-cysteine as an excipient did not damage the corneal tissue integrity and suggested that it could be safe for ocular formulations. Cyclodextrins act as carriers for hydrophobic drug molecules in aqueous solution. This helps to deliver drugs to the surface of biological membrane. Highly lipophilic biological membrane has much lower affinity towards hydrophilic cyclodextrins. Therefore, cyclodextrins remain in aqueous solution and the hydrophobic drug is absorbed by the biological membrane. Optimal bioavailability was achieved for eye drops with cyclodextrins concentration of < 15%[22]. Other applications of cyclodextrins in eye drop formulation were recently reviewed and described in detail elsewhere by Cholkar *et al*[23].

Among these approaches, viscosity 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 sensitivity of ocular tissues. Hence, it leads to development of other conventional formulations approaches with inert carrier systems for ocular delivery of therapeutics. Conventional ocular formulations such as emulsions, suspensions, and ointments are developed to improve solubility, precorneal residence time and ocular bioavailability of drugs. In the current era of nanotechnology, these conventional formulations still retain their place, importance and capture the market at large. However, these formulations are associated with various side effects such as ocular irritation, redness, inflammation, vision interference and stability issues[24]. Currently, research is being conducted to improve *in vivo* performance of these carrier systems and to minimize their side effects[25]. Several attempts are also being made to deliver drugs to posterior ocular tissues with conventional formulations. In the following sections, attempts have been made to describe the recent efforts made to improve *in vivo* performance of conventional ocular formulation and reduce their side effects.

Emulsions

An emulsion based formulation approach offers an advantage to improve both solubility and bioavailability of drugs. There are two types of emulsions which are commercially exploited as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion systems[26]. For ophthalmic drug delivery, o/w emulsion is common and widely preferred over w/o system. The reasons include less irritation and better ocular tolerance of o/w emulsion. Restasise™, Refresh Endura® (a non-medicated emulsion for eye lubrication) and AzaSite® are the examples of currently marketed ocular emulsions in the United States. Several studies have demonstrated applicability of emulsions in improving precorneal residence time, drug corneal permeation, providing sustain drug release and thereby enhancing ocular bioavailability[27].

In a recent study, Tajika *et al*[28] demonstrated improved anti-inflammatory activity of prednisolone derivative, 0.05% [^{3}H] difluprednate, with emulsion as vehicle. Results confirmed that in the rabbit eye, emulsion could deliver drug to the anterior ocular tissues with small amount of drug reaching posterior tissues following single and multiple topical drop instillation. Single and multiple topical drop instillation studies revealed highest radioactivity in cornea followed by iris-ciliary body > retina-choroid > conjunctiva > sclera > aqueous humor > lens > and vitreous humor. Post single drop administration, T_{max} for cornea, conjunctiva, lens, iris-ciliary body, aqueous and vitreous humor was 0.5 h while for retina-choroid was 1 h. Negligible amount of drug was quantified in systemic circulation. With repeated dose instillation, T_{max} for lens and retina-choroid was 8 and 0.5 h, respectively. After 168 h, a total dose of approximately 99.5% of radioactivity was excreted in urine and feces. This study suggests difluprednate emulsion as a potential candidate for treating anterior ocular inflammations.

Emulsions with lipid additives such as soyabean lecithin, stearylamine were evaluated as carrier systems for azithromycin to demonstrate better ocular performance and bioavailability[29]. A comparative study for azithromycin solution *vs* emulsion at different doses (3, 5 and 10 mg/mL azithromycin) was studied for tear elimination characteristics. *In vivo* studies were conducted in rabbits with topical drop administration. Emulsion, not only observed to behave as a vehicle for azithromycin but also slowed drug release, improved its chemical stability and precorneal residence time. Additionally, emulsion formulation improved the chemical stability ($t_{1/2}$) of azithromycin at pH 5.0 and 7.0 relative to aqueous solutions. Altogether, results suggest that lipid emulsion could be a promising vehicle for ocular drug delivery.

Similarly, another novel approach is to derivatize active pharmaceutical ingredients (API), and improve its ocular bioavailability with an emulsion as carrier system. This strategy may help to reduce ocular irritancy and improve the effect of API. To test this hypothesis, Shen *et al*[25] made attempts to improve emulsion biocompatibility for the flurbiprofen. In this study, a derivative of flurbi-

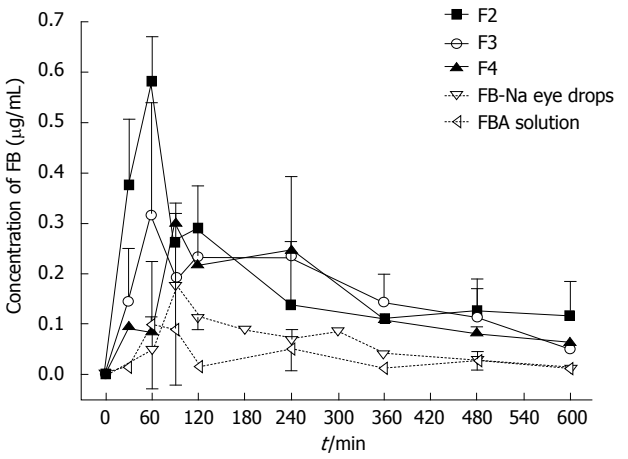

Figure 2 Concentration-time profiles of flurbiprofen (in the aqueous humor after instillation of flurbiprofen axetil emulsion F2-F4, FB-Na eye drops and flurbiprofen axetil-oil solution in rabbits. F1 = 0.1 wt% of castor oil, 0.08 wt% of tween-80; F2 = 0.5 wt% of castor oil, 0.4 wt% of tween-80; F3 = 1.0 wt% of castor oil, 0.8 wt% of tween-80; and F4 = 2.5 wt% of castor oil, 4.0 wt% of tween-80 with 2.2 wt% and 0.1 wt% of glycerol and flurbiprofen respectively. Reproduced with permission from reference Shen *et al*[25]. FB: Flurbiprofen; FBA-EM: Flurbiprofen axetil emulsion.

profen, flurbiprofen axetil, with castor oil and tween-80 was used to prepare emulsion[30]. Four different emulsions with varying ratios of castor oil (0.1 wt%-2.5 wt%) and tween 80 (0.08 wt%-4 wt%) were prepared and labeled as F1, F2, F3 and F4 respectively. *In vivo* studies were conducted in male New Zealand albino rabbits with a topical drop instillation. Aqueous humor pharmacokinetic studies showed F2 emulsion (castor oil to tween 80 wt% ratio of 0.5:0.4) to be better relative to other emulsion formulations and solution. The F2 emulsion translocated high drug concentrations into aqueous humor, post topical drop administration, relative to 0.03% flurbiprofen sodium eye drops (Figure 2). Similarly, ocular irritation studies with F2 emulsion demonstrated better biocompatibility relative to other emulsions (F1, F3 and F4).

Several researchers have introduced mucoadhesive polymers such as chitosan and hydroxypropyl methyl cellulose ether for emulsion coating. Studies concluded that chitosan surface coating improves precorneal residence time of API and thereby ocular bioavailability. Indomethacin loaded o/w emulsion was prepared employing castor oil and polysorbate-80 and the resultant emulsion was surface coated by chitosan[31]. A comparative *in vivo* study for chitosan coated *vs* non-coated indomethacin emulsions were conducted in male albino rabbits with topical drop instillation. Tear fluid pharmacokinetic study showed that emulsion surface coating with chitosan improves emulsion mean residence time and also half-life by 1.5 and 1.8 times, respectively relative to non-coated emulsion. Indomethacin concentrations were quantified in cornea, conjunctiva and aqueous humor, post 1 h of emulsion instillation. Indomethacin concentrations with emulsion system were found to be about 5.3 and 8.2 times higher in cornea relative to conjunctiva and aqueous humor.

Suspensions

Suspensions are another class of non-invasive ocular topical drop drug carrier systems. Suspension may be defined as dispersion of finely divided insoluble API in an aqueous solvent consisting of a suitable suspending and dispersing agent. In other words, the carrier solvent system is a saturated solution of API. Suspension particles retain in precorneal pocket and thereby improve drug contact time and duration of action relative to drug solution. Duration of drug action for suspension is particle size dependent. Smaller size particle replenishes the drug absorbed into ocular tissues from precorneal pocket. While on the other hand, larger particle size helps retain particles for longer time and slow drug dissolution[32]. Thus, an optimal particle size is expected to result in optimum drug activity. Several suspension formulations are marketed worldwide to treat ocular bacterial infections. TobraDex® suspension is one of the widely recommended commercial products for subjects responding to steroid therapy. TobraDex® is a combination product of antibiotic, tobramycin (0.3%), and steroid, dexamethasone (0.1%). The major drawback of this commercial product is high viscosity. Recently, Scoper *et al*[33] made attempts to reduce the viscosity of TobraDex® and to improve its *in vivo* pharmacokinetics along with bactericidal activity. The rationale behind developing this formulation was to improve the suspension formulation characteristics such as quality, tear film kinetics and tissue permeation. The new suspension (TobraDex ST®) consists of tobramycin (0.3%), and steroid, dexamethasone (0.05%). Suspension settling studies showed that new formulation had very low settling over 24 h (3%) relative to marketed TobraDex® (66%). Ocular distribution studies showed higher tissues concentrations of dexamethasone and tobramycin in rabbits treated with TobraDex ST® relative to TobraDex®. New suspension formulation was found to be more effective than TobraDex® against Staphylococcus aureus and Pseudomonas aeruginosa. Clinical studies in human subjects showed high dexamethasone concentrations in aqueous humor than TobraDex®. These results suggest that new suspension formulation to be an alternative to marketed suspension. This is because the new suspension possesses better formulation characteristics, pharmacokinetics, bactericidal characteristic and patient compliance than marketed TobraDex® suspension.

In another study, to treat dry eye, 4 wk, randomized, double masked, multicenter phase Ⅱ clinical trials were conducted with rebamipide (OPC-12759) suspension[34]. Suspension formulation at two different doses, *i.e.,* 1% and 2% rebamipide were employed for this study, where placebo served as control. The efficacy and safety of suspension formulation were determined in human subjects following topical instillation. A dose dependent response was observed for placebo, 1% and 2% rebamipide suspension for both fluorescein corneal staining and Lis-

samine green conjunctival staining studies at 2 and 4 wk. Tear production showed no significant difference from baseline from day 1 to week 4. But, the tear film break up time showed significant change in 1% and 2% rebamipide relative to placebo. All the subjects receiving treatment with suspension rebamipide formulation reported improvement of 64.1% and 54.9% respectively than subjects receiving placebo. Dysgeusia, ocular irritation and nasopharyngitis adverse events were frequently observed in 27.2%, 29.1% and 30.4% patients receiving placebo, 1% and 2% suspension, respectively. Drug induced adverse effects such as eye irritation was observed in 3.9%, 2.9% and 2.0% subjects receiving placebo, 1% rebamipide and 2% rebamipide respectively. All these adverse effects were found to recover without any additional treatment. This 4 wk studies revealed that suspension formulations were well tolerated and both formulations were effective in treating dry eye. In some measures, of the two formulations, 2% rebamipide suspension was found to be more effective relative to 1% suspension.

Ointments

Ophthalmic ointments are another class of carrier systems developed for topical application. Ocular ointment comprises of mixture of semisolid and a solid hydrocarbon (paraffin) that has a melting point at physiological ocular temperature (34 ℃). The choice of hydrocarbon is dependent on biocompatibility. Ointments help to improve ocular bioavailability and sustain the drug release[35].

Vancomycin HCl (VCM) is a glycopeptides antibiotic with an excellent activity against aerobic and anaerobic gram positive bacteria and methicillin and cephem resistant *Staphylococcus aureus* (MRSA). Inspite of better activity of VCM, no appropriate topical formulation was available in the market. Better ocular tissue permeability of VCM was not expected in a normal eye but few clinical effects of VCM solution were reported in ocular disease treatment. The reason for the observed effects was hypothesized due to broken ocular barrier system, which might have improved drug permeation. Fukuda *et al*[36] studied the intraocular dynamics of vancomycin hydrochloride ophthalmic ointments in rabbits. Thus, authors made attempts to demonstrate ocular dynamics of VCM ophthalmic ointment (TN-011) with indications limited to extraocular MRSA infections. The minimum growth inhibitory concentration to treat MRSA bacterial infections was found to be 1.56 μg/g. *In vivo* studies were conducted in rabbits [normal *vs Bacillus subtilis* (BS) group]. The BS group was developed in cornea by injecting BS solution into the central portion of parenchyma. Treatment was by topical ocular ointment (1% VCM) administration to normal and BS group rabbit eye. In normal group, after 15 min, VCM concentration in cornea of 12.04 ± 4.73 μg/g was attained at 30 min which was decreased to 0.49 ± 0.97 μg/g at 120 min. On the other hand, VCM concentrations in BS group cornea was 25.60 ± 11.01 μg/g after 15 min and 3.68 ± 1.38 μg/g after 240 min of administration. The concentrations of VCM were maintained above MIC levels, in MRSA infection induced BS group, a considerable benefit to the patients from TN-011 is expected.

In another study by Eguchi *et al*[37], four different ointment formulation of vancomycin with varying concentrations (0.03%, 0.10%, 0.30% and 1.00%) were prepared in 1:4 mixtures of liquid paraffin and vaseline. The efficacy of formulations was evaluated in rabbit model of MRSA keratitis infection after topical application. It was observed that at low drug concentrations, *i.e.,* 0.03% and 0.10%, numerous infiltrates were found in corneas with abscesses. On the other hand, animals treated with 0.3% formulation showed no recurrence of keratitis in any eye over 14 d study period. Therefore, 0.3% vancomycin ointment was suggested to be adequate and effective to resolve corneal MRSA keratitis.

Though considerable effort is being put into research to improve efficacy, still there is a need to overcome certain drawbacks associated with conventional formulations. The above mentioned formulations: emulsion, suspension, and ointment are known to cause ocular adverse effects such as irritation, redness of eye and interference with vision. Also, chronic administration may increase systemic API availability which may lead to severe systemic complications[38-40]. Formulations with preservatives also induce adverse reactions upon systemic absorption[41,42]. Therefore, to overcome formulation based adverse effects and to deliver therapeutic amounts of drug in ocular tissues, research is now being focused on exploring and developing other novel strategies of ocular drug delivery. In the following sections, we have discussed about the recent developments made in nanotechnology and controlled release devices in past decade to improve ocular drug delivery.

NOVEL OCULAR DRUG DELIVERY SYSTEMS

Nanotechnology based ocular drug delivery

In a last few decades, many approaches have been utilized for the treatment of ocular diseases. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have been developed for ocular drug delivery (Figure 3). Some of them have shown promising results for improving ocular bioavailability.

Nanomicelles

Nanomicelles are the most commonly used carrier systems to formulate therapeutic agents in to clear aqueous solutions. In general, these nanomicelles are made with amphiphilic molecules. These molecules may be surfac-

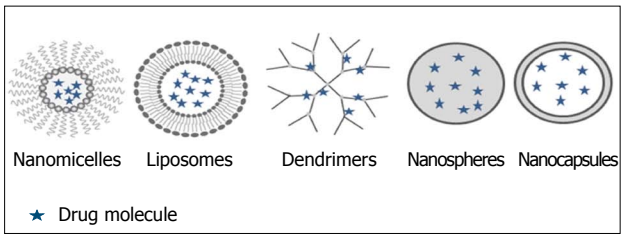

Figure 3 Nanocarriers for ocular drug delivery.

tant or polymeric in nature. Recently, Cholkar *et al*[43] have reviewed in detail about ocular barriers and application of nanomicelles based technology in ocular drug delivery.

Currently, tremendous interest is being shown towards development of nanomicellar formulation based technology for ocular drug delivery. The reasons may be attributed due to their high drug encapsulation capability, ease of preparation, small size, and hydrophilic nanomicellar corona generating aqueous solution. In addition, micellar formulation can enhance the bioavailability of the therapeutic drugs in ocular tissues, suggesting better therapeutic outcomes. So far, several proofs of concept studies have been conducted to investigate the applicability of nanomicelles in ocular drug delivery. For instance, Civiale *et al*[44] developed dexamethasone loaded nanomicelles by employing copolymers of polyhydroxyethylaspartamide [PHEAC(16)] and pegylated PHEAC(16) for anterior segment delivery. *In vivo* dexamethasone concentration time profiles were studied and determined in rabbits with aqueous humor sampling. Results showed that dexamethasone loaded PHEA micelles have higher ocular bioavailability relative to dexamethasone suspension. The area under the curve for dexamethasone micellar formulation was 40% higher than that of control suspension. Results suggest that nanomicellar formulations are a viable option for topical ocular delivery of small molecules. Researchers have also utilized nanomicelles for ocular gene delivery. In a study, Liaw *et al*[45] 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 ocular tissues. Results were promising and indicated the potential application of copolymers in DNA transfer. Further 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-Gal activity. Significant elevated levels were quantified following six doses of eye drop of pK12-Lac Z-PM three times a day in both mouse and rabbit corneas. The probable mechanism of transfection was endocytosis and particle size dependent paracellular transport of polymeric micelles[46].

Several attempts are also being made to utilize nanomicelles for the posterior ocular drug delivery. Recently, the authors have made a significant stride to deliver therapeutic drugs to the posterior ocular tissues with the aid of topical drops of mixed nanomicellar formulations. To bolster the hypothesis that the nanomicelles can deliver the drug to the posterior ocular tissues, *in vivo* studies were carried out in rabbits using voclosporin loaded nanomicelles[43]. Interestingly, the nanomicelle formulations were able to efficiently traverse ocular tissues and deliver drug to back of the eye tissues. Ocular tolerability of nanomicelles was evaluated against Restasis® as control in New Zealand White (NZW) rabbits. A detailed 72 h study with Hackett-McDonald scoring with microscopic ocular examination was included for two voclosporin (0.02% and 0.2%) micellar and Restasis® formulations. Post 1 h-topical drop administration of Restasis® highest ocular irritation was observed relative to two micellar voclosporin formulations. It was demonstrated that the novel mixed nanomicellar formulations were well tolerated and induced markedly low irritation than Restasis®. Further, authors also prepared dexamethasone and rapamycin mixed nanomicellar formulations at a concentration of 0.1 and 0.2 wt%, respectively. Ocular tissue distribution studies with single drop instillation showed that nanomicellar formulation encapsulating voclosporin, dexamethasone and rapamycin was able to deliver therapeutic concentrations of drug to back of the eye tissues post topical drop instillation. These studies suggest that small size, hydrophilic nanomicellar corona help to evade ocular barriers and deliver drug cargo to posterior ocular tissues. A non-corneal pathway of drug delivery has been hypothesized for back of the eye drug delivery. Ideta *et al*[47] made attempts to deliver fluorescein isothiocyanate-labeled poly-L-lysine [FITC-P(Lys)] to back of the eye tissues *via* intravenous drug administration to treat back of the eye tissue neovascularization. *In vivo* studies with unformulated FITC-P(Lys) resulted in death of animals post 1 h of administration. On the contrary encapsulating the FITC-P(Lys) in polyehthylene glycol-block-poly-α,β-aspartic acid micelles resulted in no death. This indicates no free drug was available in nanomicellar formulation. Micellar formulation showed a C_{max} at 4 h in retina-choroid and drug was detected up to 7 d following single intravenous administration. Prolonged micellar circulation was achieved by controlling polymer to drug charge ratios. Authors speculated that longer systemic micellar circulation may aid in enhanced permeation and retention (EPR) effect at neovascularization site. Micellar constructs were observed to selectively accumulate at the pathologic neovascular site to a greater extent than in normal tissues.

In another study, Ideta *et al*[48] made attempts to encapsulate dendritic photosensitizer (DP) in PEG-b-P(Lys) micellar construct for the treatment of exudative AMD with photodynamic therapy. *In vitro* cytotoxicity studies were performed under dark and light irradiation for DP alone and DP loaded polyionic complex (PIC) micelles to be more cytotoxic in light irradiated conditions. This higher cytotoxic effect of polymeric ion complex micelles under light irradiation was utilized for the treatment of exudative AMD. Photocoagulation was induced in rat eye. DP

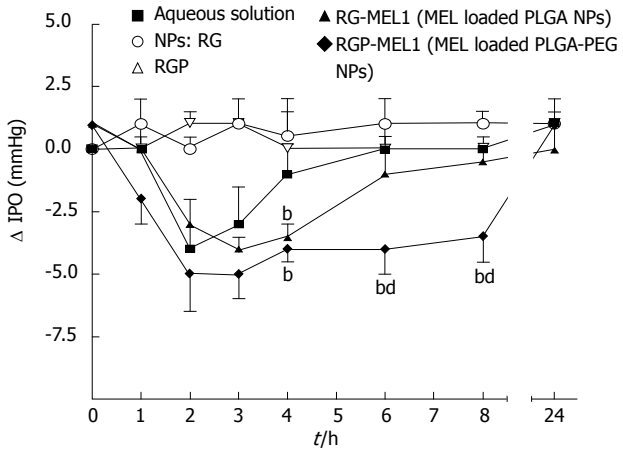

Figure 4 Intraocular pressure in normotensive rabbit eyes after topical instillation of melatonin (MEL). $^{b}P < 0.01$ *vs* melatonin; $^{d}P < 0.001$ *vs* RGP-MEL1. Reproduced with permission from Musumeci *et al*[61]. IOP: Intraocular pressure.

loaded PIC micelles were administered by intravenous injection and DP accumulation in choroidal neovascular site was observed. Application of mild laser light treatment destroyed/choked the abnormal vasculature. This new technology prevents further drug leakage. Histological studies revealed accumulation of PIC micelles at ocular lesion site. Reason may be attributed due to EPR effect. Administered free DP was eliminated within 24 h. On the other hand, PIC micelles encapsulated DP were detected after 24 h indicating micellar construct accumulation at lesion site with slow cell uptake. A reduction in fluorescence was observed post 25 min intravenous administration of DP loaded PIC micelles, due to chocking of abnormal vasculature. Hypofluorescence of DP micelles was increasing with time indicating increased vascular chocking. Normal endothelial cell destruction was not observed, possibly due to lower DP accumulation. Results suggest that small size and hydrophilic negatively charged micellar corona resulted in considerable EPR effect. This resulted in selective drug accumulation in the choroidal neovascular tissues with minimal/no drug induced adverse effects on normal cells.

Ocular research is currently focused to non-invasively deliver therapeutic levels of drugs to both anterior and posterior ocular segments. Advent of nanomicellar technology to delivery drugs in a non-invasive route, topical drop, is gaining interest. Due to their extremely small size and hydrophilic corona, nanomicelles may be retained in systemic circulation for longer time and accumulate at the diseased tissue *via* EPR effect. Thereby, non-specific drug accumulation in to normal tissues may be minimized. Proper selection of surfactant/polymer and engineering technique may aid in delivery of drugs to both anterior and posterior eye segments.

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 such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. Drug loaded nanoparticles can be nanocapsules or nanospheres (Figure 3). In nanocapsules, drug is enclosed inside the polymeric shell while in nanospheres; drug is uniformly distributed throughout polymeric matrix. From past few decades, nanoparticles have gained attention for ocular drug delivery and several researchers have made attempts to develop drug loaded nanoparticles for delivery to both anterior and posterior ocular tissues (Table 1)[49-58].

Nanoparticles represents a promising candidate for ocular drug delivery because of small size leading to low irritation and sustained release property avoiding frequent administration. However, like aqueous solutions, nanoparticles may be eliminated rapidly from precorneal pocket. Hence, for topical administration nanoparticles with mucoadhesive properties have been developed to improve precorneal residence time[59]. Polyethylene glycol (PEG), chitosan and hyaluronic acid are commonly employed to improve precorneal residence time of nanoparticles.

Chitosan coating is most widely explored for improving precorneal residence of nanoparticles. The chitosan is positively charged and hence it binds to negatively charged corneal surface and thereby improves precorneal residence and decreases clearance. For instance, natamycin loaded chitosan/lecithin nanoparticles exhibited high ocular bioavailability at reduced dose and dosing frequency in rabbit eye compared to marketed suspension. Following topical administration, the concentration-time curve (AUC) (0-∞) was increased up to 1.47 fold and clearance was decreased up to 7.40 fold in case of chitosan/lecithin nanoparticles compared to marketed suspension[60]. In another study, Musumeci *et al*[61] 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 aqueous solution of equivalent concentration in the rabbit eye (Figure 4). It was speculated that the reduced zeta potential of nanoparticles fabricated from PLGA-PEG than the PLGA allowed better and longer interaction between the nanoparticles and eye surface leading to higher hypotensive effect for prolonged period.

Nanoparticles have also been successfully employed as an alternative strategy for long term drug delivery to the posterior segment ocular tissues. For posterior segment delivery, disposition of nanoparticles depends on the size and surface property. Following, periocular administration in to Sprague-Dawley rats, 20 nm particles were cleared rapidly from periocular tissues. The rapid clearance can be due to removal by conjunctival, episcleral or other periocular circulatory systems. On the other hand, particles in the range of 200-2000 nm were

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[49]
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)[50]
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[51]
BT	Sodium alginate	BT-loaded nanoparticles provided prolong drug release over a period of 8 h after topical instillation to albino rabbits[52]
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[53]
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[54]
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[55]
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[56]
Cloricromene (AD6)	Eudragit	Nanosuspension enhanced stability of the ester drug for several months as compared to an AD6 aqueous solution[57]
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[58]

CH: Chitosan; SA: Sodium alginate; 5-FU: 5-Fluorouracil; PLGA: Poly (lactide-co-glycolide); IOP: Intraocular pressure; AUC: Area under the curve; BT: Brimonidine tartrate; DS: Diclofenac sodium.

retained at the site of administration for at least two months. Moreover, due to the rapid clearance and fast drug release, small size nanoparticles could not sustain retinal drug level. Therefore, it can be concluded that for prolonged transscleral drug delivery to the back of the eye, nanoparticles with slow drug release and low clearance by blood and lymphatic circulations are suitable drug delivery candidates[62,63].

Following intravitreal injection, nanoparticles migrate through the retinal layers and tend to accumulate in the RPE cells. The PLA nanoparticles were present in rat RPE tissues up to 4 mo following single intravitreal injection which suggest that nanoparticles have great potential for achieving steady and continuous delivery to the back of the eye. Zhang *et al*[64] investigated the pharmacokinetics and tolerance of dexamethasone (DEX) loaded PLGA nanoparticles in rabbits following intravitreal injection. Authors concluded that DEX when encapsulated in nanoparticles exhibited sustained release for 50 d. The constant DEX levels were maintained in vitreous over 30 d with a mean concentration of 3.85 mg/L. Contrary, only trace amounts of DEX being detected on the 7th day after injection of DEX solution. These results imply that intravitreal injection of dexamethasone nanoparticles may be employed for sustained delivery of drugs for the treatment of posterior segment eye diseases.

The surface property of nanoparticles is a key factor affecting their distribution from vitreous humor to retinal layers[65]. Koo *et al*[66] studied correlation between surface properties of the nanoparticles and their distribution in the vitreous and retina after intravitreal injection. Heterogeneous polyethyleneimine/glycol chitosan (PEI/GC), human serum albumin (HSA)/GC, and HSA/hyaluronic acid (HA) nanoparticles were prepared by blending two polymers. The value of zeta potential of these nanoparticles were 20.7 ± 3.2, -1.9 ± 4.1 and -23.3 ± 4.4 for PEI/GC, HSA/GC, and HSA/HA nanoparticles, respectively. The nanoparticles were injected into vitreous cavity of Long Evans rats and vitreous/retinal distribution was evaluated by confocal microscopy. Figure 5 shows vitreal and retinal distribution of intravitreally administered heterogeneous nanoparticles. It can be depicted from the Figure 5 that PEI/GC nanoparticles easily penetrated the vitreal barrier and reached at the inner limiting membrane. However, PEI/GC nanoparticles did not penetrate through the physical pores of inner limiting membrane into the deeper retinal layers and also some aggregates were observed in vitreous. Similar to PEI/GC nanoparticles, HSA/GC nanoparticles reached to inner limiting membrane but could not penetrate to the deeper retinal layers which might be due to inhibition of the interaction between HSA and the Müller cells in retina by GC. On the other hand, negatively charged HSA/HA nanoparticles, could penetrate the whole retina structures and reach the outer retinal layers such as the photoreceptor layer and RPE which was attributed to interaction between anionic surface and Müller cells. In another study, HSA-NPs penetrated the whole retina and localized inside the RPE of the normal retina after intravitreal injection in rat eyes. Furthermore, in the laser photocoagulated retina,

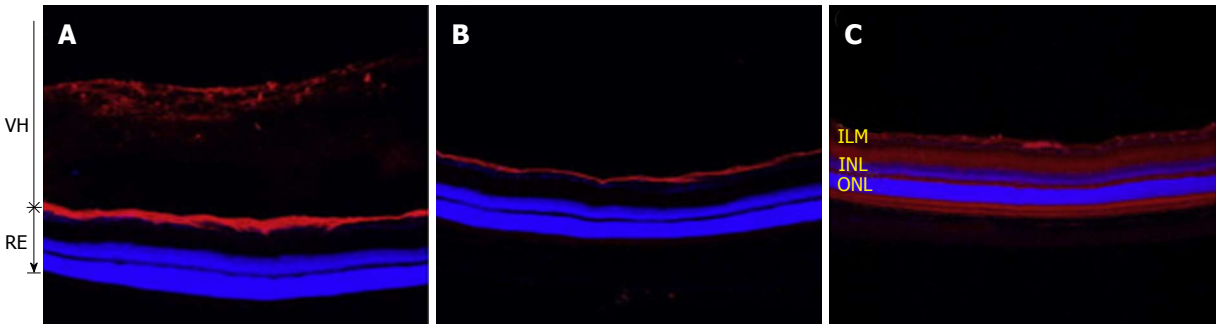

Figure 5 Vitreal and retinal distribution of intravitreally administered. A: Polyethyleneimine/glycol chitosan heterogeneous nanoparticles; B: Human serum albumin/glycol chitosan heterogeneous nanoparticles; C: Human serum albumin/ hyaluronic acid heterogeneous nanoparticles 6 h post-injection. Red color = FPR-552 conjugated nanoparticles, blue color = DAPI staining of retinal cell nuclei. VH: Vitreous; RE: Retina; ILM: Inner limiting membrane; INL: Inner nuclear layer; ONL: Outer nuclear layer, respectively. All images were captured at × 10 magnification. Reproduced with permission from reference Koo *et al*[66].

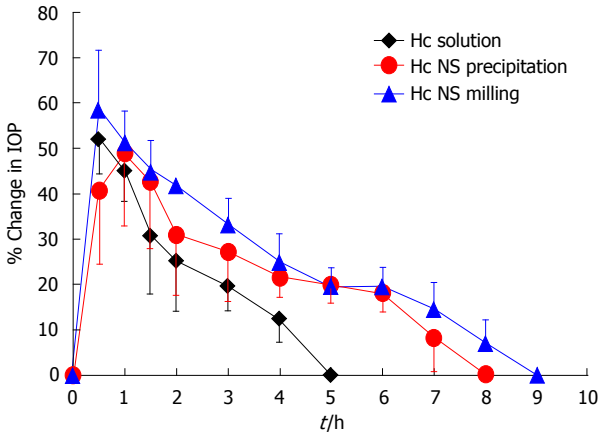

Figure 6 Changes in intraocular pressure of rabbits eyes following administration of hydrocortisone solution and nanosuspensions produced by milling and precipitation. Reproduced with permission from reference Ali *et al*[70]. IOP: Intraocular pressure; Hc: Hydrocortisone; NS: Nanosuspension.

HSA-NPs were observed to reach the choroid through the disruption site of the RPE and Bruch's membrane. Therefore, the anionic HSA-NP could be promising drug delivery carrier for the treatment of AMD which required drug distribution to the choroid region in order to inhibit choroidal neovascularization[67].

Nanosuspensions

Nanosuspensions are colloidal dispersion of submicron drug particles stabilized by polymer(s) or surfactant(s). It is emerged as promising strategy for delivery of hydrophobic drugs. For ocular delivery, it provides several advantages such as sterilization, ease of eye drop formulation, less irritation, increase precorneal residence time and enhancement in ocular bioavailability of drugs which are insoluble in tear fluid[68]. The efficacy of nanosuspensions in improving ocular bioavailability of glucocorticoids has been demonstrated in several research studies.

Glucocorticoids such as prednisolone, dexamethasone and hydrocortisone are widely recommended for the treatment of inflammatory conditions affecting anterior segment ocular tissues. The current therapy with these drugs requires frequent administration at higher doses which induce cataract formation, glaucoma, and damage optic nerve. Efforts have been made toward improving ocular bioavailability of glucocorticoids by formulating as nanosuspensions. For instance, Kassem *et al*[69] compared ocular bioavailability of various glucocorticoids (prednisolone, dexamethasone and hydrocortisone) from nanosuspensions, solutions and microcrystalline suspensions. The formulations were instilled into the lower cul-de-sac of the rabbit eye and intraocular pressure (IOP) was measured at frequent time intervals up to 12 h. The area under percentage increase in IOP *vs* time curve (AUC) values for all the suspensions were higher than that for the respective drug solutions. In addition, higher extent of drug absorption and more intense drug effects were observed for all steroids form nanosuspensions compared with solutions. In another study, Ali *et al*[70] compared ocular bioavailability of hydrocortisone (Hc) nanosuspensions prepared by precipitation and milling method with HC solution in rabbits post topical instillation. Nanosuspensions prepared by both the precipitation and milling method achieved significantly higher AUC (0-9 h) values of 28.06 ± 4.08 and 30.95 ± 2.2 μg/mL than that of HC solution (15.86 ± 2.7 μg/mL). A sustained drug action which was represented in terms of changes in intraocular pressure was maintained up to 9 h for the nanosuspensions compared to 5 h for the drug solution (Figure 6).

From the results of above research studies, it can be concluded that nanosuspensions could be an efficient ophthalmic drug delivery system for delivery of poorly soluble drugs. In addition, nanosuspension can also be incorporated into hydrogels or ocular inserts for achieving sustained drug release for stipulated time period.

Liposomes

Liposomes are lipid vesicles with one or more phospholipid bilayers enclosing an aqueous core (Figure 3). The size of liposomes usually range from 0.08 to 10.00 μm and based on the size and phospholipid bilayers,

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[72]
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)[73]
Cytochrome C		The cytochrome C loaded freeze-dried liposomes exhibited significant efficacy in retarding the onset and progression of cataract formation in rat eye[74]
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[75]
Coumarin-6	Multilamellar	After topical administration in mice, the intensity of coumarin-6 in the retina was much higher with PLL modified liposomes[76]
Bevacizumab (Avastin)		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[77]
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[78]
Fluconazole		Antifungal activity of fluconazole in liposomal formulation was better than that of fluconazole solution[79]
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[80]
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[81]

REVs: Reverse phase evaporation; PLL: Poly-L-lysine; VIP: Vasoactive intestinal peptide; PVA: Polyvinyl alcohol; IOP: Intraocular pressure; AUC: Area under the curve.

liposomes can be classified as small unilamellar vesicles (10-100 nm), large unilamellar vesicles (100-300 nm) and multilamellar vesicles (contains more than one bilayer)[71]. For ophthalmic applications, liposomes represent ideal delivery systems due to excellent biocompatibility, cell membrane like structure and ability to encapsulate both hydrophilic and hydrophobic drugs. Liposomes have demonstrated good effectiveness for both anterior and posterior segment ocular delivery in several research studies. Recent advancements in liposomal ocular drug delivery are summarized in Table 2[72-81]. In a recent study, for delivery of latanoprost to anterior segment ocular tissues, liposomal formulation was developed by Natarajan *et al*[82]. The single subconjunctival injection of latanoprost/liposomal formulation in rabbit eye produced sustained IOP lowering effect over a period of 50 d with IOP reduction comparable to daily eye drop administration. For drug delivery to anterior segment of the eye, efforts are mainly put toward improving precorneal residence time by incorporating positively charged lipids or mucoadhesive polymer in liposomes. The positively charged liposomes *i.e.,* cationic liposomes have exhibited better efficacy in ocular delivery than negatively charged and neutral liposomes due to binding with negatively charges of corneal surface. Didodecyldimethylammonium bromide, stearylamine, and *N*-[1-(2,3-dioleoyloxy)propyl]-*N,N,N*-trimethylammonium chloride are commonly employed for fabricating cationic liposomes.

Acyclovir loaded cationic and anionic liposomes were prepared by incorporating stearylamine and dicetylphosphate (DP), as cationic and anionic charge-inducing agents, respectively. In rabbit eyes, the acyclovir concentration in the cornea at 2.5 h after topical administration of positively charged liposomes was greater than those of negatively charged liposomes and free acyclovir. ACV concentrations in cornea were 253.3 ± 72.0, 1093.3 ± 279.7 and 571.7 ± 105.3 ng/g for ACV solution, ACV loaded positively and negatively charged liposomes, respectively. Also, the extent of ACV absorption through cornea was higher from positively charged liposomes which can be observed from ACV concentrations in aqueous humor at 2.5 h after instillation (Figure 7). The suggested reason was the higher binding of positively charged liposomes with negatively charged corneal surface *via* electrostatic interaction which ultimately lead to an increase of residence time and increase in acyclovir absorption[83]. In another study, when Coenzyme Q_{10} (CoQ_{10}) loaded liposomes was coated with mucoadhesive trimethyl chitosan, there was a 4.8 fold increase in the precorneal residence time in the rabbit eye was observed[84].

For posterior segment delivery, liposomes development is more focused toward improving half-life of drug by lessening clearance from vitreous humor, protecting labile molecules such as peptides and oligonucleotides from degradation and providing sustained drug release[5,85,86]. For instance, the vitreal half-life of fluconazole in rabbit eye was increased from 3.08 to 23.40 h after formulating into liposomes[86]. In another study, tacrolimus loaded liposomes were developed for the treatment of uveoretinitis. Following single intravitreous administration, tacrolimus vitreous level above 50 ng/mL was sustained for 14 d. The tacrolimus liposomal formulation demonstrated more effectiveness in suppressing

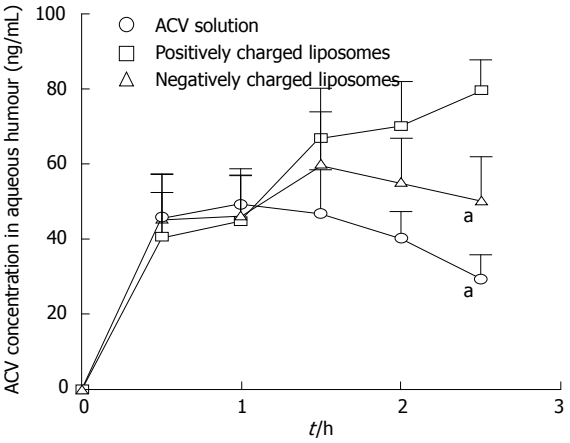

Figure 7 Acyclovir concentrations in aqueous humor after topical administration of Acyclovir solution and Acyclovir-containing liposomes. $^{a}P < 0.05$ *vs* positively charged liposomes ($n = 6$). Reproduced with permission from reference Law *et al*[83]. ACV: Acyclovir.

uveoretinitis relative to drug alone and there was also reduced toxicity to inner retinal cells[87].

Several liposomal formulations for ocular drug delivery are being exploited, few are in pre-clinical and clinical study stage and few are commercially available. Visudyne® and Tears again® are the examples of commercially available liposomal formulations for the treatment of ocular diseases. Visudyne® (QLT Ophthalmics, Inc., Menlo Park, CA, United States) is a liposomal formulation containing photosensitizer, verteporfin. It is used in photodynamic therapy for subfoveal choroidal neovascularization in age related macular degeneration, presumed ocular histoplasmosis and pathological myopia[88]. Tears again® (Optima Pharmaceutical GmbH, Germany) is a phospholipid liposomes spray approved for the treatment of the Dry Eye syndrome. In clinical studies, this liposomal spray demonstrated significant advantages when compared with triglyceride-containing eye gel and a balanced salt solution[89,90].

Dendrimers

Dendrimers are characterized as nanosized, highly branched, star shaped polymeric systems. These branched polymeric systems are available in different molecular weights with terminal end amine, hydroxyl or carboxyl functional group. The terminal functional group may be utilized to conjugate targeting moieties[91]. Dendrimers are being employed as carrier systems in drug delivery. Selection of molecular weight, size, surface charge, molecular geometry and functional group are critical to deliver drugs. The highly branched structure of dendrimers allows incorporation of wide range of drugs, hydrophobic as well as hydrophilic. In ocular drug delivery, few promising results were reported with these branched polymeric systems[4,92,93].

Poly (amidoamine) (PAMAM) dendrimers are widely employed in ocular drug delivery[92]. Vandamme *et al*[94] demonstrated application of PAMAM dendrimers as ophthalmic vehicles for delivery of pilocarpine nitrate and tropicamide, for miotic and mydriatic activity. In this study, mean ocular residence time for fluorescein in saline and in PAMAM solutions were studied in rabbit eye. Fluorescein in 0.2% w/v Carbopol solution was used as reference bioadhesive polymer. The mean ocular residence time was significantly higher in case of PAMAM solutions and 0.2% w/v Carbopol solution compared to saline. Therefore, the use of dendrimers could be another option for increasing ocular residence time and therapy enhancing ocular bioavailability and achieving better therapeutic outcomes. For instance, PAMAM dendrimers when co-administrated with pilocarpine nitrate and tropicamide, showed higher miotic and mydriatic activity in albino rabbits[94].

In order to avoid scar tissue formation after glaucoma filtration surgery, conjugates of modified PAMAM dendrimers with glucosamine (DG) and glucosamine 6-sulfate (DGS) were synthesized to exert immunomodulatory and anti-angiogenic activities, respectively. 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 consequently reduced scar tissue formation. The results obtained from the experiment indicated that the ocular administration of DG and DGS might be effective and safe in clinical practice in avoiding scar tissue formation post glaucoma filtration surgery[95].

In-situ gelling systems

In-situ hydrogels refer to the polymeric solutions which undergo sol-gel phase transition to form viscoelastic gel in response to environmental stimuli. Gelation can be elicited by changes in temperature, pH and ions or can also be induced by UV irradiation. For ocular delivery, research studies have been more focused toward development of thermosensitive gels which respond to changes in temperature[96]. Several thermogelling polymers have been reported for ocular delivery which includes poloxamers, multiblock copolymers made of polycaprolactone, polyethylene glycol, poly (lactide), poly (glycolide), poly (*N*-isopropylacrylamide) and chitosan. These thermosensitive polymers form temperature dependent micellar aggregates which gellify after a further temperature increment due to aggregation or packing[96,97]. For drug delivery, these polymers are mixed with drugs in the solution state and solution can be administered which forms an *in situ* gel depot at physiological temperature. These thermosensitive gels demonstrated promising results for enhancing ocular bioavailability for both anterior and posterior segment. Gao *et al*[98] have evaluated suitability of thermosensitive gel made of triblock polymer PLGA-PEG-PLGA (poly-(DL-lactic acid co-glycolic acid)-polyethylene glycol-poly-(DL-lactic acid co-glycolic acid) as a ocular delivery carrier for dexamethasone acetate (DXA). It was formulated as either 0.1% w/v DXA solution or 0.1%, w/v DXA in 20% PLGA-PEG-PLGA *in situ* gel forming solution and administered topically in rabbit eye. Following topical

administration, the C_{max} of DXA in the anterior chamber was significantly higher for the PLGA-PEG-PLGA solution (125.2 μg/mL) relative to the eye drop (17.6 ± 2.18 ng/mL) along with higher AUC values. The increment in both C_{max} and AUC was approximately 7.00 and 7.98 fold for PLGA-PEG-PLGA *in situ* gel compared to the solution eye drops. These results suggest potentiality of PLGA-PEG-PLGA thermosensitive gel forming solution in enhancing ocular bioavailability.

Rieke *et al*[99] have reported applicability of ReGel™ (biodegradable and thermosensitive triblock copolymer consisting of PLGA and PEG, in providing sustained release of a large molecule ovalbumin to the choroid and retina following subconjunctival administration in the rat eye. The ovalbumin concentrations were maintained at measurable levels in the sclera, choroid, and retina of rats over a period of 14 d. These results suggest feasibility of thermosetting gel system in providing sustained delivery of macromolecules to the posterior segment ocular tissues such as choroid and retina. Cross linked poly (*N*-isopropylacrylamide) (PNIPAAm)-poly (ethylene glycol) diacrylate hydrogels were also synthesized for sustained release of macromolecules such as bovine serum albumin (BSA) and immunoglobulin G (IgG)[100]. The gel system has provided nearly 3 wk of sustained BSA release under *in vitro* condition. The results of research studies clearly signify the advantages of thermosensitive gels in providing sustained drug release, prolong contact time of drugs with the cornea, less frequency of applications, reduced side effects and higher ocular bioavailability over aqueous drops. In conclusion, the thermosensitive gels may be a viable option for the delivery of drugs for treating chronic ocular diseases.

Contact lens

Contact lenses are thin, and curved shape plastic disks which are designed to cover the cornea[101]. After application, contact lens adheres to the film of tears over the cornea due to the surface tension. Drug loaded contact lens have been developed for ocular delivery of numerous drugs such as β-blockers, antihistamines and antimicrobials. It is postulated that in presence of contact lens, drug molecules have longer residence time in the post-lens tear film which ultimately led to higher drug flux through cornea with less drug inflow into the nasolacrimal duct. Usually, drug is loaded into contact lens by soaking them in drug solutions. These soaked contact lenses demonstrated higher efficiency in delivering drug compared to conventional eye drops. Kim *et al*[102] observed much higher bioavailability of dexamethasone (DX) from poly (hydroxyethyl methacrylate) (PHEMA) contact lenses in comparison to eye drops. Indeed, efficient than topical drops, these soaked contact lenses suffers from disadvantages of inadequate drug loading and short term drug release. To overcome these obstacles, particle-laden contact lenses and molecularly imprinted contact lenses have been developed. In particle-laden contact lenses, drug is first entrapped in vesicles such as liposomes, nanoparticles or microemulsion and then these vesicles are dispersed in the contact lens material. Gulsen *et al*[103,104] developed particle-laden contact lenses for ocular delivery of lidocaine. In two different studies, they have prepared particle-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 8 d. Indeed, particles-laden contact lenses look promising for extended ocular drug delivery; it needs to be stored in drug saturated solutions to avoid drug loss during storage. The designing of stimuli responsive such as pH or temperature sensitive "smart" particles which can release drug only in the eye could eliminate this problem. The imprinted contact lenses have also showed benefit in terms of both drug loading and drug release[105]. It has been demonstrated that soft contact lenses fabricated by the molecular imprinting method have 1.6 times higher timolol loading capacity than the contact lenses prepared by a conventional method and also provided sustained timolol delivery[106]. In another study, ketotifen fumarate loaded imprinted lenses have revealed higher tear fluid bioavailability compared to drug soaked lenses or ketotifen fumarate marketed eye drops. The relative bioavailability for the imprinted lenses was 3 times greater than that of non-imprinted lenses. The AUC value of ketotifen fumarate for imprinted 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, respectively[107]. The results clearly demonstrate more effectiveness of imprinted lenses over non-imprinted lenses and eye drops.

Implants

Intraocular implants are specifically designed to provide localized controlled drug release over a extended period. These devices help in circumventing multiple intraocular injections and associated complications[108,109]. Usually for drug delivery to posterior ocular tissues, implants are placed intravitreally by making incision through minor surgery at pars plana which is located posterior to the lens and anterior to the retina. Though implantation is invasive procedure, these devices are gaining interest due to their associated advantages such as sustained drug release, local drug release to diseased ocular tissues in therapeutic levels, reduced side effects and ability to circumvent blood retina barrier[109,110]. Several implantable devices have been developed for ocular drug delivery especially for the treatment of chronic vitreoretinal diseases.

Ocular implants are available as biodegradable and non-biodegradable drug releasing devices. Non-biodegradable implants offer long-lasting release by achieving near zero order release kinetics[110]. Polymers such as polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA), and polysulfone capillary fiber (PCF) are being employed for fabricating non-biodegradable implants[108]. Vitrasert® and Retisert® are the examples of marketed non-biodegrad-

able implants.

Vitrasert® (Bausch and Lomb Inc., Rochester, NY, United States) is a controlled-release intraocular implant of ganciclovir approved by Food and Drug Administration (FDA) for the treatment of acquired immune deficiency syndrome-associated cytomegalovirus retinitis. It is composed of a ganciclovir tablet of 4.5 mg surrounded by PVA/EVA that slowly release the drug over an extended period of 5-8 mo. The device provides long term sustained release without systemic toxicity at reduced cost[108,110,111]. Retisert® (Bauschnd Lomb Inc., Rochester, NY, United States) is approved by FDA for the treatment of chronic uveitis which affects the posterior segment of the eye. It is the first marketed silicone laminated PVA implant. It provides sustained release of fluocinolone acetonide up to 3 years. The implant had effectively controlled inflammation, reduced uveitis recurrences and improved vision acuity. The associated side effects are cataracts and elevated IOP[110-113]. Long term drug release may be achieved with these non-biodegradable implants but are associated with certain short comes. These devices have to be surgery implanted and removed after drug depletion, which makes the treatment expensive and patient non-compliance. Also, adverse events such as endophthalmitis, pseudoendophthalmitis, vitreous haze and hemorrhage, cataract development and retinal detachment limit their applications.

Another category of ocular implant includes biodegradable implants. These implants are gaining much attention and are being studied at large due to their biocompatible property and sustained drug release properties. Because of biodegradable nature, these implants are not required to be surgically removed which signify a distinctive advantage over the non-biodegradable implants. Polylactic acid (PLA), polyglycolic acid (PGA), PLGA, and polycaprolactones are the most commonly used polymers for the fabrication of biodegradable implants[108]. Examples of biodegradable implants for ocular delivery include Surodex™ and Ozurdex® which are designed for the sustained delivery of dexamethasone for the treatment of intraocular inflammation and macular edema (ME), respectively[110]. Surodex™ (Allergan, Inc., Irvine, CA, United States) composes PLGA and hydroxypropyl methylcellulose enclosing dexamethasone. The implant is inserted in the anterior chamber of eye to control postoperative inflammation in cataract patients. It provides sustained dexamethasone release for a period of 7-10 d with improved anti-inflammatory effect comparable to topical steroid administration[110].

Ozurdex® (Allergan Inc., Irvine, CA, United States) is another biocompatible and biodegradable intravitreal implant. It was approved by FDA in June 2009 for the treatment of macular edema. It employs Allergan's NOVADUR® technology for delivering dexamethasone. The NOVADUR® system contains a PLGA polymer matrix which degrades slowly to lactic acid and glycolic acid allowing prolonged release of dexamethasone up to 6 mo. Randomized clinical trials have demonstrated its potency in reducing vision loss and improving vision acuity in eyes with macular edema associated with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Also, clinical studies with Ozurdex® for treatment of diabetic retinopathy, and Irvine-Gass syndrome proved it as a promising treatment and drug delivery candidate[110].

Microneedles

Microneedle based technique is an emerging and minimally invasive mode of drug delivery to posterior ocular tissues. This technique may provide efficient treatment strategy for vision threatening posterior ocular diseases such as age related macular degeneration, diabetic retinopathy and posterior uveitis. This new microneedle based administration strategy may reduce the risk and complications associated with intravitreal injections such as retinal detachment, hemorrhage, cataract, endophthalmitis and pseudoendophthalmitis. Moreover, this strategy may help to circumvent blood retinal barrier and deliver therapeutic drug levels to retina/choroid. Microneedles are custom designed to penetrate only hundreds of microns into sclera, so that damage to deeper ocular tissues may be avoided. These needles help to deposit drug or carrier system into sclera or into the narrow space present between sclera and choroid called "suprachoroidal space" (SCS). Puncturing of sclera and depositing drug solution or carrier systems in sclera or SCS may facilitate diffusion of drug into deeper ocular tissues, choroid and neural retina[114]. For intraocular delivery of drugs Jason et al. investigated the application of microneedles surface coated with drugs[115]. Cadaver eyes were used to evaluate the role and scleral penetration of microneedle and intrascleral dissolution of microneedle surface coated drug (sulforhodamine). Results demonstrated that surface coated drug was rapidly dissolved in scleral tissue indicating high scleral sulforhodamine deposition within microneedle hole. In another study, Jiang *et al*[116] made attempts to evaluate the performance of microneedles to infuse drug solutions, nanoparticles and microparticles into scleral tissues. By use of microneedles, authors were able to infuse approximately 10-35 μL of fluid in to tissues. Nanoparticles suspensions and microparticles were also delivered into sclera by microneedles however; microparticles were delivered only in the presence of collagenase spreading enzymes and hyaluronidase. Study demonstrated that hollow microneedles may be employed for scleral infusion of drug or micro/nanoparticles with minimal invasive route.

Further, in another study Patel *et al*[117] made attempts to deliver drug solution, nanoparticles and microparticles in the SCS of rabbit, pig, and cadaver eyes with microneedles. Authors hypothesized that microneedle based minimally invasive strategy may help to deliver high level of both drug and nanocarriers to retinal tissues from SCS. Parameters for suprachoroidal delivery with microneedles such as microneedle length, pressure, and particle size were studied and optimized. Results demon-

strated the strategy to be safe, minimally invasive and may sustain drug release. But, the study did not provide any evidence of drug reaching the inner retinal tissues from SCS. Same group made further attempts to study *in vivo* pharmacokinetics of SCS deposited solution/suspension post microneedle infusion. Results demonstrated that microneedle may provide a safe, reliable and targeted approach to chorio-retinal tissues[117].

CONCLUSION

Drug delivery to targeted ocular tissues has been a major challenge to ocular scientist, for decades. Administration of drug solutions as topical drop with conventional formulations was associated with certain drawbacks which initiated the introduction of different carrier systems for ocular delivery. Tremendous efforts are being put into ocular research toward the development of safe and patient compliant novel drug delivery strategies. Currently, researchers are thriving hard to improve *in vivo* performance of conventional formulations. On the other hand, advent of nanotechnology, new techniques, devices and their applications in drug delivery is developing immense interest to ocular scientists. Drug molecules are being encapsulated into nanosized carrier systems or devices and are being delivered by invasive/non-invasive or minimally invasive mode of drug administration. Several nanotechnology based carrier systems are being developed and studied at large such as nanoparticles, liposomes, nanomicelles, nanosuspensions and dendrimers. Few of these are commercially manufactured at large scale and are applied clinically. Nanotechnology is benefiting the patient body by minimizing the drug induced toxicities and vision loss. Also, these nanocarriers/devices sustain drug release; improve specificity, when targeting moieties are used, and help to reduce the dosing frequency. However, there is still need of developing a carrier system which could reach targeted ocular tissue, including back of the eye tissues, post non-invasive mode of drug administration. With the current pace of ocular research and efforts being made and put in, it is expected to result in a topical drop formulation that retains high precorneal residence time, avoids non-specific drug tissue accumulation and deliver therapeutic drug levels into targeted ocular tissue (both anterior and posterior). In near future, this delivery system may replace invasive mode of drug administration to back of the eye such as periocular and intravitreal injection.

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