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A Review on Ocular Drug Delivery System

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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.

KEYWORDS: Cornea; Emulsions; Implants; Liposome; Nanomicelles;

INTRODUCTON

Human eye is a complex structure, both anatomically and physiologically, that makes it a unique organ consisting of its physiologically independent functions. Its wide range of varied structures also challenges to develop drug delivery systems for it. The major problem in the conventional ocular drug delivery system with eye drops is their fast and extensive elimination from the eye, causing extensive loss of the drug [1, 2]. In eye drops, only a small portion of a drug penetrates through the corneal layer and arrives in the internal tissues present in the eye [3, 4]. Broad classification of ocular drug delivery results in two types, those concerned with the anterior and posterior segments. For vision-threatening ocular diseases, conventional drug delivery systems, such as eye drops, suspensions and ointments, cannot be used for optimal treatment [5]. About 90% of the ophthalmic formulations in the market are available in the form of eye drops and the sites of action are diseases occurring in the anterior segment of the eye [6]. Topical delivery of drugs through conventional approaches is unable to make it reach the posterior segment of the eye. Formulations like eye drops and ointments, when instilled into the cul-de-sac, are wiped away from eye region quickly because of the flow of tear and lachrymal nasal drainage. Most of the drug is drained away and only a small portion reaches the site of action; so, it needs frequent dosing to achieve a therapeutic effect. The eye's posterior segment includes the retina, vitreous humour and choroid; the diseases occurring in these regions can be cured by using intravenous and intravitreal drug delivery systems, implants or by administering drug through periocular route and needs high concentration of the drug as well. For ophthalmic drug delivery, the posterior segment of eye is frequently a choice of interest to locate drugs using novel approaches [7]. The rationale behind this review and novelty of this study are to highlight the newer developments in the pharmaceutical ophthalmic formulations, such as formulation of in situ gels, nanoparticles, liposomes, nanosuspension, microemulsion, ocular inserts and so on, and their progress to overcome the problems associated with the existing conventional dosage forms and also to improve the bioavailability as well as the sustained release of the drug at the target location [8].

Barriers for ocular drug delivery

Ocular drug delivery suffers from the following barrier effects:

Drug loss from the ocular surface

After using the dosage form of the drug in the ocular system, flow of lacrimal fluid wipes out a portion of the drug from its surface and its turnout rate is only about 1 µl/min, whereas, a major portion of the drug is wiped out through the nasolacrimal duct quickly within minutes. Other sources of drug removal include the systemic absorption of the drug, instead of being absorbed through the ocular route. Systemic absorption is mostly directed through the conjunctival sac to the local blood capillaries or takes place after the solution flows to the nasal cavity [9].

Lacrimal fluid-eye barriers

Absorption of the drug from the lacrimal fluid can be limited by the corneal epithelium present in the eye. Tight junctions formed from corneal epithelial cells limit the permeation of the drug paracellularly. Lipophilic drugs show higher permeability in the cornea as compared to hydrophilic drugs. In other terms, we can say that conjunctiva has leaky epithelium compared to that of the cornea and also has twenty times greater surface area than the cornea that supports rapid systemic absorption.

Blood-ocular barriers

Blood-ocular barriers are present in the bloodstream, which protect the eye from xenobiotics. It comprises of two parts, namely bloodaqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of endothelial cells in the uvea, i.e., the middle layer of the eye below sclera, iris, ciliary body and choroid. This barrier works to prevent the entry of hydrophilic drugs present in plasma to the aqueous humor and also limits the entrance of plasma albumin in aqueous humor. The posterior barrier which resides in between the eye and stream of plasma consists of retinal pigment epithelium (RPE) and retinal capillaries, resulting in tight wall junction. Choroid vasculature comprises of extensive blood flow and leaky walls, due to which easy access of drugs occurs in the choroidal extravascular space, but again their distribution in the retina is limited due to the presence of RPE and retinal endothelium [10]

Anatomy of the Eye:

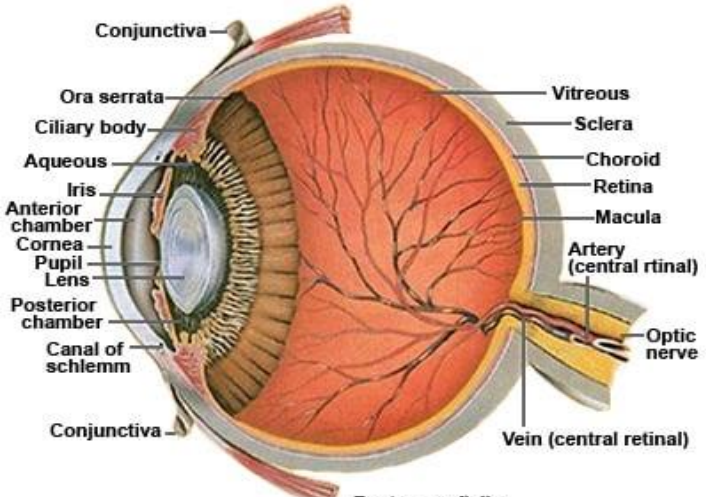

Figure 1. Anatomy of The Eye

The human eye, elegant in its detail and design, represents a gateway to the process we call vision. The eyeball is spherical in shape and about 1 inch across. It houses many structures that work together to facilitate sight. The human eye is comprised of layers and internal structures, each of which performs distinct functions. The detailed description of each eye part is given below.

1. Sclera

The sclera (white portion of the eye) is the tough white sheath that forms the outer-layer of the ball. It is a firm fibrous membrane that maintains the shape of the eye as an approximately globe shape. It is much thicker towards the back/posterior aspect of the eye than towards the front/anterior of the eye.

2. Conjuctiva

The conjunctiva is a thin transparent mucous epithelial barrier, lines the inside of the eyelids, and covers the anterior one-third of the eyeball. The respective portion of conjunctiva is referred to as the palpebral and bulbar conjunctiva. The conjunctiva is composed of two layers: an outer epithelium and its underlying stroma (substantia propria)..

3. Cornea

The cornea is a strong clear bulge located at the front of the eye. Surface of the adult cornea has a radius of approximately 8mm. It has an important optical function as it refracts light entering the eye which then passes through the pupil and onto the lens (which then focuses the light onto the retina)..

4. Aqueous humor

The aqueous humor is a jelly-like substance located in the outer/front chamber of the eye. It is a watery fluid that fills the "anterior chamber of the eye" which is located immediately behind the cornea and in front of the lens..

5. Pupil

Pupil generally appears to be the dark "centre" of the eye, but can be more accurately described as the circular aperture in the centre of the iris through which light passes into the eye. The size of the pupil (and therefore the amount of light that is admitted into the eye) is regulated by the pupillary reflex (also known as the "light reflex").

6. Iris

The iris is a thin circular contractile curtain located in front of the lens but behind the cornea. The iris is a diaphragm of variable size whose function is to adjust the size of the pupil to regulate the amount of light admitted into the eye. It is the coloured part of the eye (shades may vary individually like blue, green, brown, hazel, or grey).

7. Ciliary muscle

The ciliary muscle is a ring of striated smooth muscles in the eye's middle layer that controls accommodation for viewing objects at varying distances and regulates the flow of aqueous humour into schlemm's canal. The muscle has parasympathetic and sympathetic innervation. Contraction and relaxation of the ciliary muscle alters the curvature of the lens. This process may be described simply as the balance existing at any time between two states: Ciliary Muscle relaxed (This enables the eye to focus on distant objects) and Ciliary Muscle contracted (This enables the eye to focus on near objects).

8. Lens:

The lens is a transparent structure enclosed in a thin transparent capsule. It is located behind the pupil of the eye and encircled by the ciliary muscles.

9. Vitreous Humor:

The vitreous humour (also known as the vitreous body) is located in the large area that occupies approximately 80% of each eye in the human body..

10. Retina

The retina is located at the back of the human eye. The retina may bedescribed as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, ,lens, and finally the vitreous humour before reaching the retina.

11.Macula:

The center of the retina is called the macula. The macula contains a high concentration of photoreceptor cells which convert light into nerve signals. Because of the high concentration of photoreceptors, we are able to see fine details such as newsprint with the macula. At the very center of the macula is the fovea, the site of our sharpest vision.

12. Choroid:

The choroid layer is located behind the retina and absorbs unused radiation and nourishes the outer portions of the retina.

13. Optic nerve:

The optic nerve (a bundle of over 1 million nerve fibers) is responsible for transmitting nerve signals from the eye to the brain. These nerve signals contain information on an image for processing by the brain. The front surface of the optic nerve, which is visible on the retina, is called the optic disk.

Routes of ocular drug delivery

The various possible routes for ocular drug delivery are described below:

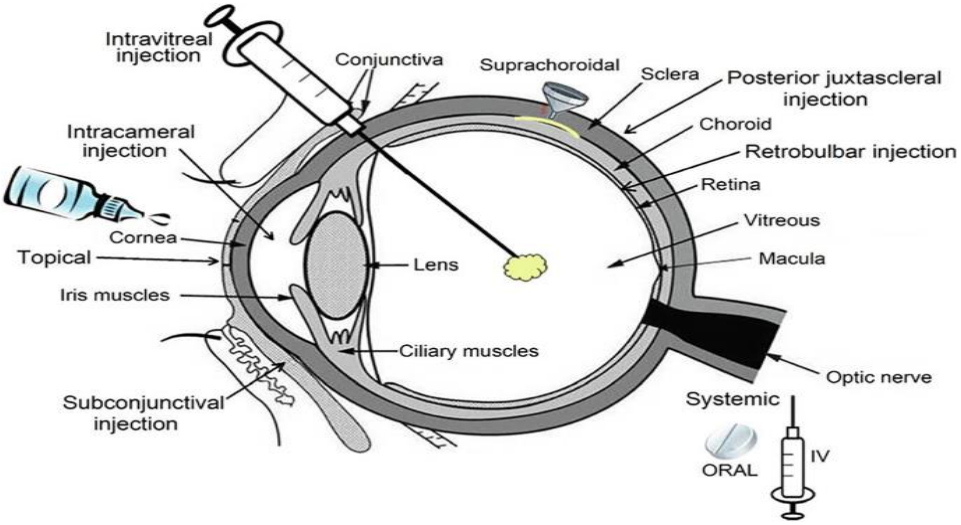

Figure3 : Routes of ocular drug delivery

1.Intravitreal route

In this route, the medication is delivered through injections in the vitreous humor of the eye. This route of administration is used to cure a number of eye disorders; the delivery through this ocular route is shown in fig. 2

2. Intracameral route

Anterior or posterior chambers of the eye are the sites of action for a drug in this route of administration. It can be demonstrated by injecting an anesthetic agent into the anterior chamber of the eye, usually during surgery.

3.Perilocular route

The drug is administered around the eye in this route of administration. It can be explained by peril ocular steroid injection involving the placement of steroids around the eye to treat intraocular inflammation or swelling [11].

4.Suprachoroidal route

Supra choroid region of the eye is the target in this route of administration. The space existing between the sclera and the choroid is termed as suprachoroidal space.

5.Subconjunctival route

In this route, the drug is administered to the mucus membrane, comprising of the open space of the eyeball and the inner surface of the eyelids.

6.Topical route

Eye drops are the best examples of ophthalmic dosage forms used for topical administration of drugs in the eye as compared to ointments, gels and emulsions, which are used to cure the diseases of the anterior segment of the eye. It is the most convenient method drug delivery to eye, due to ease of administration and lower cost.

7.Systemic route

Common barriers to the systemic delivery of ophthalmic drugs are blood-aqueous barrier and blood-retinal barrier (BRB) for the anterior segment and posterior segments of eye, respectively.[14]

CONVENTIONAL OCULAR DRUG DELIVERY SYSTEM

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 [12] . 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 [13–15] . 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 noninvasive 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[16-18] .

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 [19] . Currently, research is being conducted to improve in vivo performance of these carrier systems and to minimize their side effects[20] . 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. For ophthalmic drug delivery, o/w emulsion is common and widely preferred over w/o system [21]. 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.

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[22]. 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[23] 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 Tobra-Dex® (66%). Ocular distribution studies showed higher tissues concentrations of dexamethasone and tobramycin in rabbits treated with TobraDex ST® relative to Tobra-Dex®.

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.

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 °C). The choice of hydrocarbon is dependent on biocompatibility. Ointments help to improve ocular bioavailability and sustain the drug release .[24]

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 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..

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[25–27] . Formulations with preservatives also induce adverse reactions upon systemic absorption[28,29] . 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 have been developed for ocular drug delivery (Figure 2). Some of them have shown promising results for improving ocular bioavailability.

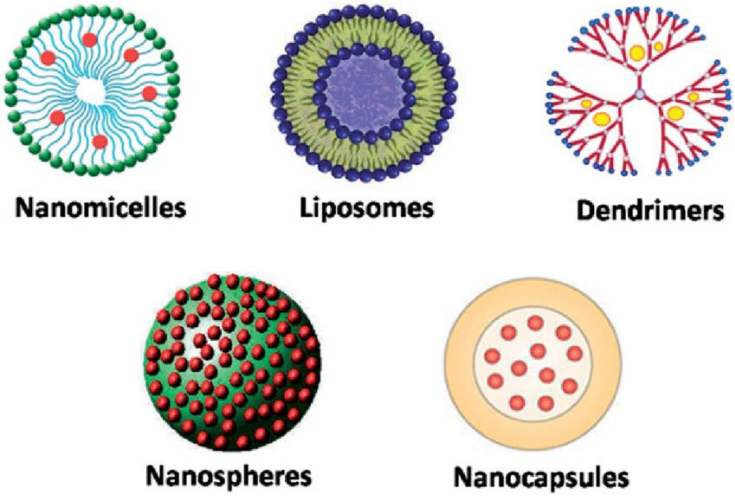

Figure 3. Nanocarriers for ocular drug delivery.

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 surfactant or polymeric in nature. Recently, Cholkar et al[30] 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 e Civiale et al[31] 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[32] 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[33] .

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[30] . 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 t wo 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[34] 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 glycolblock-poly-α,β-aspartic acid micelles resulted in no death. This indicates no free drug was available in nanomicellar formulation. Micellar formulation showed a Cmax at 4 h in retinachoroid 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[41] 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 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.

Nanosuspensions

Nanosuspensions are generated for poorly water-soluble drugs suspended at nano size range in a suitable dispersion medium. This technology can be utilized in a good way for drug moiety that forms crystals with high energy content, due to which they are insoluble in organic (lipophilic) or hydrophilic media. Polymeric nanoparticle suspensions are being formulated using inert polymeric resins, which can be used as vital drug delivery vehicles, having the capacity to increase drug release as well as improve its bioavailability. The carriers having such type of properties can be used as inert carriers for ophthalmic drugs, because they donot cause any irritation to the cornea, iris or conjunctiva. An example of such carrier is polymeric nanoparticle suspension having flurbiprofen (FLU) as an active ingredient and eudragit RS 1001 and RL 1001 are polymers used. Nanodispersions of alginate chitosan produced for sustained drug delivery and improved transcorneal permeation have been reported by Morsi et al. (2015) [35,36].

Nanoparticles

These are polymeric colloidal particles, size varying from 10 nm to 1 nm, where the drug is being dissolved, entrapped, encapsulated, or adsorbed [31]. It consists of a number of biodegradable substances, like natural or synthetic polymers, lipids, phospholipids and metals. To obtain nanoparticles, the drugs can be formulated in many ways as by integrating with the matrix or by attaching to the surface of biodegradable polymers used for the preparation. Nanoparticles used in delivering drug to ocular tissues are polylactides (PLAs), polycyanoacrylate, poly (D, L-lactides) and natural polymers such as chitosan, gelatine, sodium alginate and albumin. Approximately,

since last 10 y, nanoparticles have been used as carriers in delivering drug for ocular disorders and given promising results. A specific type of nanoparticles can be classified as small capsules having a central cavity surrounded by a polymeric membrane and solid matrix spheres, known as nanocapsules and nanospheres, respectively. Marchal et al. (1993) have reported that the nanocapsules exhibit better effect as compared to that of the nanospheres, because drug (betaxolol, carteolol) present in unionized form in the oily core, diffuses at a higher rate into the cornea [44]. A number of authors have reported that the nanocapsules are more efficient due to the presence of mucoadhesive property in it that shows a rise in the residence time and biological responses [45]. So, these can enhance the bioavailability of drugs at ocular site and also decrease the frequency of dosing. Alonso et al.

(1995) have reported in their study that the nanoparticles made from poly-e-caprolactone having cyclosporine exhibit better corneal absorption with respect to the drug's oily solution [34].

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, 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)[39] . 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. In a recent study, for delivery of latanoprost to anterior segment ocular tissues, 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.

n-situ gelling systems

. Researchers have found the new concept of in situ gel in the early1980s. Delivery of drug to ocular system through in situ gel is mainly for enhancing viscosity to decrease drug drainage from the cornea. The pourable gels are in liquid form when applied, after which they undergo a phase transition, when reaches to cul-de-sac of eye and converted into a visco-elastic gel giving rise to a response to changes environmentally, thereby increasing the bioavailability of the drug automatically. The major disadvantages of the in situ gels are that they get affected by temperature, pH or ions. Bazzaz et al. (2018) reported that in situ gelling system provides better and prolonged effect of a drug rather than conventional eye drops [37].

Dendrimers

Dendrimers are symmetric structures made from repetitive branched molecules surrounding a central core, proposed recently as topical ocular drug delivery systems [38]. Frequently used dendrimers for delivery in ocular system are poly-(amidoamine) (PAMAM), PLL, polypropylenimines (PPI) and phosphorus dendrimers. These are used as carriers to deliver nucleic acid-based drugs, mostly in ocular delivery system [38], but sometimes used for drugs with low molecular weight that can be hydrophilic (antibiotics) or lipophilic (anti-glaucoma) drugs as well [32,37]. According to the reported methods, it has been found that the carrier's performance can be increased by making a change on their surface using methods like PEGylation or acetylation, which also help in reducing their toxicity factors [38,39,40]. So, the advantages of using dendimers as carrier of drugs for topical applications are enhancement of the drug residence time in the pre-corneal area, increase in bioavailability of drugs and prolonged therapeutic effect [40,41].

Contact lens

Contact lenses are thin, and curved shape plastic disks which are designed to cover the cornea[41] After application, contact lens adheres to the film of tears over the cornea due to the surface tension.

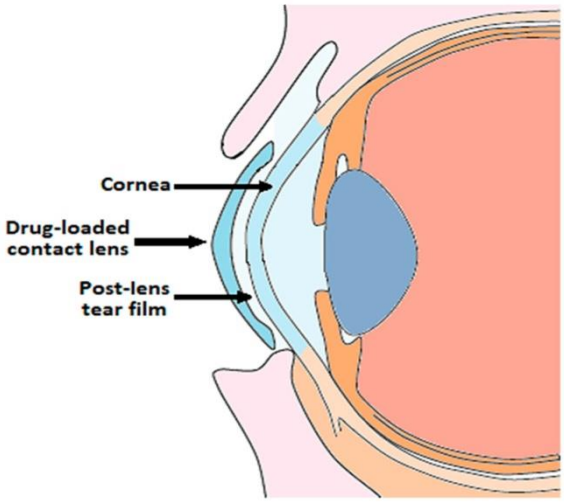

Figure 4 . Ophthalmic drug delivery from Contact lenses.

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[41] 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[39,40] developed particle-laden contact lenses for ocular delivery of lidocaine. In two different studies, they have prepared particleladen 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[41] .

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[39] . 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[41] . The results clearly demonstrate more effectiveness of imprinted lenses over non-imprinted lenses and eye drops.

Implants

The aim of designing an intraocular implant is to prolong the activity of the drug, along with its controlled release by using a polymer or polymer system. An injectable delivery system of drug, like liposomes and nanoparticles, is easy to administer, but having limitation that after insertion, it becomes difficult to retract those particles during any complication, like toxic responses. So it is beneficial to use implants for balancing the rate and duration of drug release. Removal of ocular implants is easy and can be removed by surgical intervention. [40]

Advantages of ocular drug delivery systems

- They impart accuracy and uniformity in dosing rate. Pulsed• dosing of conventional systems can be avoided.
- Sustained and controlled release of drugs can be achieved.
- By increasing corneal contact time, they cause enhancement in the ocular bioavailability of drugs and it is achieved by effective adherence of the drug to the corneal surface.
- For the prevention of loss of ocular tissues, targeting within the ocular globe is to be done.
- They bypass the protective ophthalmic barriers, such as drainage, lacrimation and conjunctival absorption.
- They bypass the protective ophthalmic barriers, such as drainage, lacrimation and conjunctival absorption.
- They also improve patient's compliance, offer comfort and enhance therapeutic drug performance.
- They provide better housing of delivery systems.
- The make self-administration of drugs possible.
- Systemic and visual side effects are lower and absorption is faster [11].

Disadvantages of ophthalmic drug delivery systems

The major drawbacks of ophthalmic drug delivery systems are as follows:

- Short contact time of drug solution and eye surface.
- Poor bioavailability.
- Instability for dissolved drugs.
- Use of preservatives [12]

hallenges and Future Perspectives for Ocular Drug-Delivery Technologies

The shortcomings of the current ocular drug-delivery system, such as lower drug bioavailability for topically administered drugs and the invasive nature of posterior implants, create challenges, allowing novel technologies to rise with superior and effective treatment of ocular disorders. Ocular disorders such as cataract, dry eye disease, wet and dry AMD, glaucoma, DR, and DME are predicted to escalate in the next two decades. For a majority of the anterior segment disorders, eye drops are regarded as the safest and most convenient dosage form. Eye drops face the challenge of having low drug bioavailability at the target tissue. Controlled drug delivery with the help of nanoformulations such as nanomicelles, nanoparticles, liposomes, dendrimers, nanowafers, and microneedles can achieve high bioavailability of drugs at the anterior tissues, such as the conjunctiva and cornea. Currently, all treatments for back of the eye disorders are invasive in nature. Frequent intravitreal injections can lead to retinal detachment, hemorrhage, and discomfort to the patients. Design of a noninvasive sustained drug-delivery system for the posterior segment is challenging for ocular drug-delivery scientists. Thus, there is an urgent need for the development of novel noninvasive drug-delivery systems that can overcome ocular barriers, sustain drug release, and maintain effective drug levels at the back of the eye.

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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