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Review Article

TARGETING DRUG MOLECULES TO THE BACK SIDE OF EYE

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ABSTRACT

Ocular drug delivery is the major challenge faced by the pharmaceutical researchers. Owing to unique anatomy, physiology and defence mechanism of the eye. Ocular diseases include the various anterior and posterior segment diseases. To obtain therapeutic drug concentration in the posterior segment of eye is quite challenging because of the ocular barriers like blood aqueous and blood retinal barriers as well as distance from the front to the back of the eye. Delivery of the drug to the vitreous humour is very low as compared to the aqueous humour after topical application. Hence there is a challenge to develop new formulation for the treatment of posterior segment eye diseases. Various routes of drug delivery to the posterior segment of the eye involves the topical, oral/ systemic, intravitreal, periocular routes. By preparing novel ophthalmic formulations we can minimize complications associated with drug delivery to the posterior segment of the eye. In this review, we highlight the recent attempts of nanotechnology –based systems for treating posterior ocular diseases. Nanotechnology based ocular formulations are one of the approaches which is now- a-days used for the both anterior as well as posterior drug delivery. These nanotechnology-based formulations with appropriate particle size can be designed to ensure low irritation, increases bioavailability, increases ocular tissue compatibility and enhances stability of the therapeutic entity. Novel approaches like nanoparticles, nanosuspension, nanoemulsion, liposomes, polymeric nanoparticles, cyclodextrin nanoparticles, penetration enhancers, prodrug approach, implants, contact lenses etc. are being used to formulate effective drug delivery system for ocular site.

KEY WORDS: Posterior segment of eye, ocular drug delivery, novel approaches, routes of administration, nanoparticles, barriers.

INTRODUCTION

Eye is the complex and unique organ of body in terms of its anatomical, physiological nature and defence mechanism. Drug delivery to the ocular site is one of the most challenging tasks faced by pharmaceutical researchers [Kumar et al. (2013)]. Now-a-days, the diseases affecting to the posterior part of the eye is increasing tremendously. Basically, structure of the eye is divided into two main segments that is anterior and posterior segment [Cholkar et al. (2013a)]. Delivery of the drug to the vitreous humour is very low as compared to the aqueous humour after topical application. Hence there is a challenge to develop new formulation for the treatment of posterior segment eye diseases. Bioavailability of the drug in the anterior and posterior part of eye is very limited due to precorneal residence time and various permeability barriers [Kompella et al. (2010)]. It takes a lot of potential to treat various disorders associated with the posterior segment of the eye [e.g.-retina, choroid, vitreous humour and optic nerve]. Delivery of the drug to the posterior part of the eye is crucial for treating several disorders such as age-related macular degeneration, diabetic retinopathy, glaucoma, uveitis,

macular edema, postoperative inflammation, proliferative vitreoretinopathy, retinitis pigmentosa etc. [Loftsson et al. (2008)]. The anterior portion comprises cornea, iris, lens, aqueous humour and posterior portion includes vitreous humour, retina, choroid, and back of sclera. The intraocular environment contains two main barriers i.e. blood- aqueous barrier and blood- retinal barrier, these two barriers restrict penetration of molecules into the intraocular chamber. Blood aqueous barrier is made up of the nonpigmented epithelium of the ciliary body. Blood retinal barrier is classified into two types i.e. inner blood retinal barrier (retinal vascular endothelium with tight junction) and outer blood retinal barrier (retinal pigment epithelium with tight junction) [Weng et al. (2016)]. Blood ocular barriers plays vital role in drug permeation into the eye and from eye to blood circulation. Ocular drug absorption is impeded by static, dynamic, and metabolic barriers. To obtain therapeutic drug concentration in the posterior segment of eye is quite challenging because of these ocular barriers as well as distance from the front to the back of the eye [Loftsson et al. (2008)]. Drug administration to the anterior and posterior segment of eye is often limited by clearance mechanism of the corneal surface and other precorneal factors, including eye blinking, tear turnover, tear film, drainage and lacrimation [Weng et al. (2016)]. Bioavailability of ocular drugs is hampered by these precorneal factors, clearance mechanism and ocular barriers that ultimately results in decreased efficacy of the total administered drugs which is less than 5% [Weng et al. (2016), Laddha and Mahajan; 2017].

Targets which are present to the back of eye includes choroid, retinal pigment epithelium and retina [Kompella et al. (2010)]. Influx of drug molecule into the retina and vitreous humour is restricted because of the outer and inner blood- retinal barriers. Large doses of the drug are required in order to achieve therapeutic concentration and to maintain it, due to large doses, unwanted side effects are observed as the drug accumulates in other tissues of the body. For the drug to reach neural retina it has to cross the RPE (a monolayer of cells with tight junctions) i.e. outer blood retinal barrier. To reach the retina from systemic circulation, it has to cross the retinal blood vessels with a tight monolayer of endothelial cells (inner blood retinal barrier). Due to the presence of such barriers eye drops and systemic doses do not efficiently deliver a drug to the posterior segment of the eye [Shah et al. (2014)]. Another physiological barrier such as tear production and blink reflex. Blinking continuously displays the tear film and drifts the tears via nasolacrimal canal into the nose and further to GIT. Physiological barriers is one of the reason that limits the absorption of drug molecules [Dubald et al. (2018)].

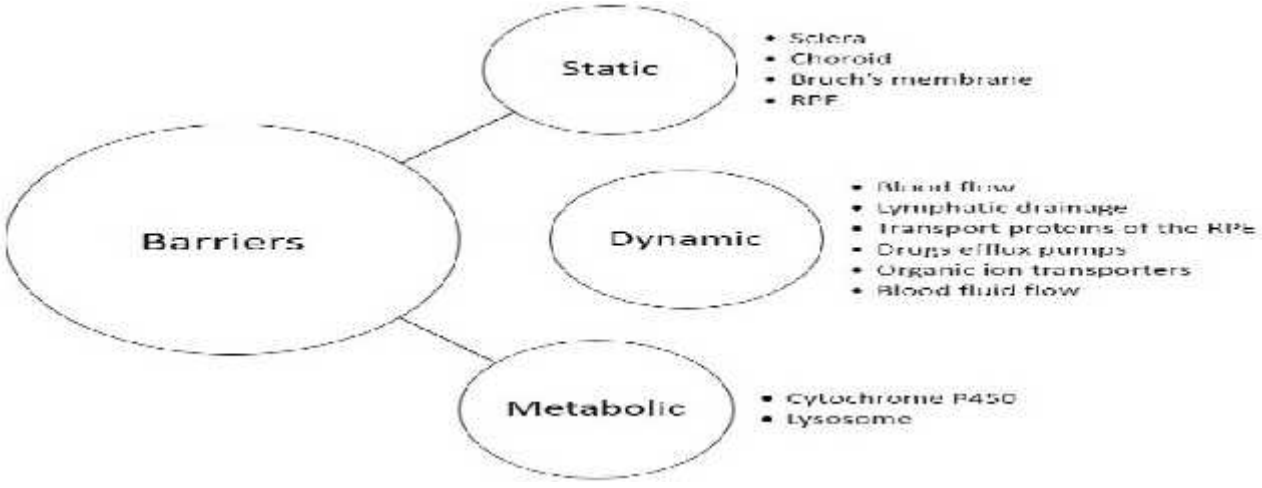


Fig.: Barriers to transscleral drug delivery

Various routes of drug delivery to the posterior segment of the eye involves the topical, oral/ systemic, intravitreal, periocular routes. The major challenge in ocular drug delivery is to achieve the therapeutic drug concentration in the posterior segment of the eye [Thrimawithana et al. (2011)]. Topical administration results in small amount of a drug penetrates the cornea, conjunctiva, and sclera due to the various barriers present in the eye. This route is inefficient in delivering therapeutic

concentration of a drug to the posterior part of the eye. It is least invasive method, shows the high patient compliance. Delivery of the drug to the posterior part of the eye is more challenging due to the longer diffusion distance and cellular nature of the vitreous body [Shah et al. (2014), Peptu et al. (2015), Thrimawithana et al. (2011)]. Systemic administration for ocular drug delivery involves intravenous injections and oral dosing. Blood retinal barrier limits the diffusion of systemically administered drug to the posterior part of the eye and from the administered drug only 1-2% of drug access to the retina and vitreous humour. Systemic administration of drugs also have a poor access to the eye tissue because of the blood- aqueous barrier, which prevents drug molecule from entering into the aqueous humour and blood retinal barrier which prevents drug molecule from entering into the retinal space and the vitreous humour [Weng et al. (2016), Shah et al. (2014), Peptu et al. (2015), Thrimawithana et al. (2011), Kaur and Smitha; 2002]. Intravitreal delivery-topical injections, drug solution or suspension is directly injected into the vitreous humour through pars plana using 27- or 30-gauge needle, which result in increased drug concentration at the retina and vitreous body. Due to frequent administration of drugs by this route results in various side effects like retinal detachment, retinal haemorrhage, endophthalmitis, and uveitis. To avoid these side effects novel drug delivery system has been developed in the form of biodegradable and nonbiodegradable implants [Weng et al. (2016), Shah et al. (2014), Peptu et al. (2015), Thrimawithana et al. (2011)].

Periocular injection overcomes drawbacks of systemic administration, periocular administration (retro bulbar, periocular, sub-Tenon and subconjuctival injection) are less invasive than intravenous injection. It is considered as most promising and efficient route for delivery of the drug to posterior part of eye. [Weng et al. (2016), Shah et al. (2014), Thrimawithana et al. (2011)].

NOVEL APPROACHES FOR DELIVERY OF THE DRUGS TO THE BACK SIDE OF EYE

The delivery of drug into the eye is very complicated because of the defense mechanism of the eye which makes it difficult to achieve the therapeutic concentration of drug to the target site of the eye. Due to these intricate defense mechanism of the eye, leads to a poor bioavailability of the drug to the site of action. After topical administration rapid precorneal loss is occur due to nasolacrimal drainage and high tear fluid turnover, results in poor bioavailability of the drug to the ocular site [Kaur and Smitha; 2002]. This problem can be overcome by preparing novel ophthalmic drug delivery system, by preparing novel ophthalmic formulations we can minimize complications associated with drug delivery to the posterior segment of the eye and to enhance patient compliance. This NDDS based preparations enhances the bioavailability to the back side of eye as well as stability of the therapeutic entity [Thrimawithana et al. (2011)].

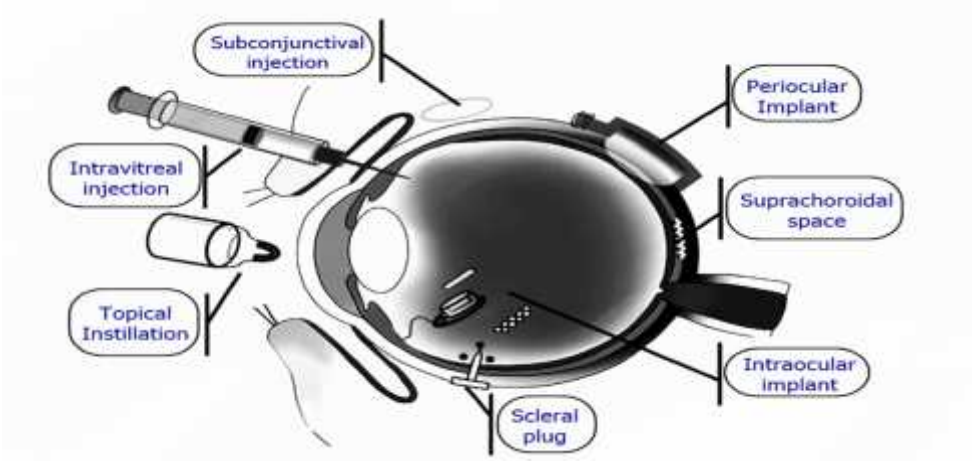
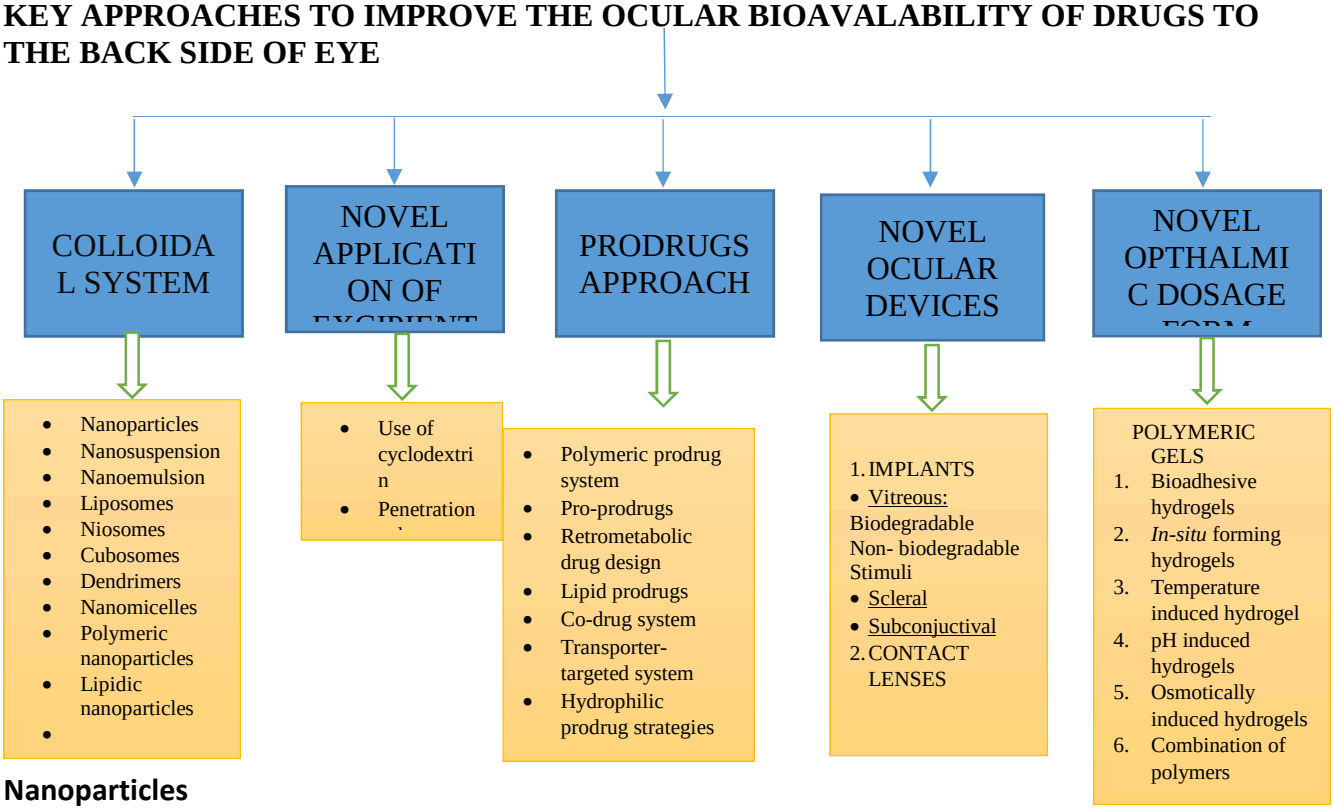


Fig. Routes of drug administration to posterior segment of eye

Novel approaches involves hydrogels, nanoparticles, liposomes, niosomes, micro-emulsions, dendrimers, nanomicelles, implants, nanosuspension etc. many other ocular delivery approaches includes prodrugs, penetration enhancers, ocular inserts, cyclodextrin etc. [Laddha and Mahajan; 2017]. Nanotechnology based ocular formulations are one of the approaches which is now- a-days used for the both anterior as well as posterior drug delivery. These nanotechnology-based formulations with appropriate particle size can be designed to ensure low irritation, increases bioavailability and increases ocular tissue compatibility [Cholkar et al. (2013a)]. Various nanocarriers' i.e. colloidal dosage form includes nanoparticles, nanosuspension, nanoemulsion, liposomes, niosomes, dendrimers, nanomicelles, cyclodextrin nanoparticles etc. Conventional ophthalmic formulations such as ointments, gels, and other viscous formulations are focus on improving the retention time on the surface of the eye and could hardly reach the posterior segment. These colloidal dosage forms overcomes drawbacks associated with conventional ocular drug delivery systems. It offers advantages like sustained and tissue targeted drug delivery, ability to overcome drug efflux, increase drug stability and reduces dosing frequency. The recent advances in nanotechnology based ocular formulations provides a great opportunity to overcome drawbacks of conventional drug delivery system. [Cholkar et al. (2013b)].

KEY APPROACHES TO IMPROVE THE OCULAR BIOAVALABILITY OF DRUGS TO THE BACK SIDE OF EYE



Nanoparticles

The particle size which ranges from 10-1000 nm are referred as nanoparticles and particles over 1000 nm are referred as microparticles. Nanoparticles are colloidal carriers, prepared in the form of the spheres or capsules in which drug is dissolve, encapsulated or entrapped or absorbed or adsorbed. In the spherical form of the particles, active ingredient is dispersed into the polymer matrix. Whereas, in capsule form of particles active ingredient is present in a core and which is surrounded by a polymer layer (resembles the reservoir) [Cholkar et al. (2013a), Janoria et al. (2007), Kompella et al. (2013)]. Nanoparticles for ocular delivery are usually composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide- co-glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. Now -a -days most widely used polymer are PLGA and PLA, which are approved by FDA and biodegradable in nature [Cholkar et al. (2013a), Diebold and calong; 2010].

Recently researchers focused on drug loaded nanoparticles for delivery to both anterior and posterior segment of eye. Nanoparticles becomes a promising candidate for ocular drug delivery because of its nanosize. This nanosize leads to low irritation and sustained release of the drug which avoids frequent administration [Cholkar et al. (2013a)]. However, like aqueous solutions nanoparticles may be eliminated rapidly from precorneal space and only 1-10% of topically applied drug get absorbed due to precorneal factors [Cholkar et al. (2013a), Laddha and Mahajan; 2017]. This rapid elimination of nanoparticles can be reduce by addition of a mucoadhesive properties, and these properties shows improve in precorneal residence time [Cholkar et al. (2013a), Kompella et al. (2010)]. The topical ocular formulations containing mucoadhesive or viscous materials sustains and enhances the drug delivery to ocular site. Excipients like gellan gum, polycarbophil, carbopol, poly (styrene-divinyl benzene) sulfonic acid are used in ophthalmic formulations for enhancement of viscosity and mucoadhesion. The viscosity of an ocular formulation can range up to 20-30 cps [Kompella et al. (2010)]. Excipients like polyethylene glycol (PEG), chitosan, hyaluronic acid are commonly used to improve precorneal residence time of nanoparticles [Cholkar et al. (2013a)]. Various preclinical studies demonstrated that, nanoparticles are efficient in delivering drugs to the posterior segment of the eye via periocular and intravitreal route of administration [Thrimawithana et al. (2011)]. Jayamanti pandit, et.al, developed the chitosan coated PLGA nanoparticles of bevacizumab as novel drug delivery to target retina. Chitosan is mucoadhesive polymer on PLGA nanoparticles and expected that, it might be interact with negatively charged barrier i.e. sclera and hence induces trans-scleral uptake and prolongs precorneal residence time and decreases clearance [Cholkar et al. (2013a)]. Kohei Tahara, et.al, they developed surface modified PLGA nanoparticles and proved that delivery of the drug to the posterior segment of eye by non- invasive topical instillation is enhance by surface modification [Tahara et al. (2017)]. Targeting the drug molecule to the retinal site by the non-invasive topical instillation is the novel approach, where researchers trying to reduce the complications associated with the multiple injections [Shah et al. (2010)].

Nanosuspension

Nanosuspension is a colloidal dispersion consists of poorly water- soluble drug which is suspended in an appropriate dispersion medium and stabilized by addition of a surfactants [Cholkar et al. (2013b), Gaudana et al. (2009)]. Nanosuspension technology is a promising strategy for delivery of hydrophobic drugs. It is favoured for compounds that are poorly water soluble (but soluble in oil) with high log P value, high melting point and high doses [Shid et al. (2013)]. This system comprises of nanosize particles and these particles helps to cross the barriers which are present in eye. To cross this barriers is the most challenging task in ocular drug delivery [Cholkar et al. (2013b)]. For ophthalmic drug delivery, it provides no. of benefits such as sterilization, ease of eye drop formulation administration, less irritation, increase precorneal residence time and enhancement in ocular bioavailability of drugs which are insoluble in tear fluid [Cholkar et al. (2013a)]. Nanosuspension have particle size less than 1 um, it has been recommended that particles size less than 10 um to minimize particle eye irritation to the eye, decreases tearing and drainage of instilled dose and therefore increases efficacy of an ocular treatment. The size of the particles determines the uptake and distribution of the nanoparticles [Kassem et al. (2007), Shende and Godbole; 2016]. Such formulation can be prepared by media milling, high pressure homogenisation, precipitation technique, emulsion diffusion method, microemulsion template, supercritical fluid technology melt emulsification method, dry co-grinding etc. [Cholkar et al.(2013b), Shid et al. (2013)]. The nanosize represents a state of matter characterized by higher solubility, higher surface area available for dissolution, higher dissolution rate, higher bioadhesion, and corneal penetration [Kassem et al.

(2007)]. Nanosuspension comprises of various biodegradable or non- biodegradable polymers, lipids, phospholipids or metals. It is classified into two types i.e. nanospheres (where the drug has been uniformly dispersed) and nanocapsules (where drug has been coated with polymeric material) [Kassem et al. (2007), Shende and Godbole; 2016]. Number of studies have proved the efficacy of nanosuspension in improving ocular bioavailability of glucocorticoids [Dubald et al. (2018)].

Nanoemulsions

Nanoemulsion is a heterogeneous system, thermodynamically stable colloidal dispersion, usually consist of oil droplets in an aqueous medium and which is stabilized by addition of the mixture of surfactant and co-surfactant. The system in which droplets of less than 200nm in size are referred as nanoemulsion and these are also considered as promising candidates for ophthalmic drug delivery. It basically includes two classical forms i.e. o/w and w/o emulsion. [Mahboobian et al. (2017), Achouri et al. (2012)]. Nanoemulsion provides several benefits in ophthalmic drug delivery such as stability, improves bioavailability, ease of production and high solubilising capacity which render them attractive systems for drug delivery. This system provides main benefits in ophthalmic drug delivery is that delivering the hydrophilic and lipophilic drugs [Cholkar et al. (2013b), Mahboobian et al. (2017)]. Emulsion droplets are prepared by mixing oil phase containing surfactant, whose energy input is lower. Small droplets size exhibits high drug loading absorption and enhanced pre-corneal permeation [Wang et al. (2018)]. The surfactant used in nanoemulsion formulation can also act as penetration enhancers, thereby improving drug permeability across the cornea [Cholkar et al. (2013b)]. The amount and selection of surfactant and co-surfactant used to bring down the surface tension of colloidal dispersion is the critical step, because inadmissible surfactant may stimulate ocular irritation. Other than surfactant, some another factors like viscosity, pH, toxicity and surface charge also makes an enormous difference in the use of emulsion for ophthalmic drug application [Wang et al. (2018)]. Nanoemulsion formulation have been investigated for enhancing ocular bioavailability, increasing drug stability, reducing adverse effects, and providing sustained release of ophthalmic drugs. A study by Mohammad M. Mahboobian et al. evaluated the therapeutic efficacy with the NE formulation and it is higher for NE formulation [drug conc.0.4%] as compared to the commercial product of brinzolamide [1%] [Mahboobian et al. (2017)].

Nanomicelles

Nanomiceller formulation is the most commonly utilized carrier system to formulate therapeutic agent into a clear aqueous solution [Cholkar et al. (2013a), Wang et al. (2018)]. Nanomiceller systems such as surfactant nanomicelles and polymeric nanomicelles is the emerging trend for the drug delivery to the posterior segment of eye. Surfactants like sodium dodecyl sulphate, vitamin E tocopherol polyethylene glycol succinate (Vit E TPGS), octoxynol-40, and C8 lecithin are frequently used to formulate surfactant nanomicelles [Wang et al. (2018)]. Nanomicelles made from polymers like N-isopropyl acrylamide, vinyl pyrrolidone, acrylic acid, polyhydroxyethyl aspartamide, poly (ethylene glycol) - hexylsubstituted poly (lactides) [Cholkar et al. (2013b)]. Nanomiceller formulation is the potential carrier system for the poorly-water soluble drugs, apart from their nanosize (10-100), it enhances corneal permeation, increases solubility and stability of drugs, lowers adverse effects and better biocompatibility [Wang et al. (2018)]. Generally, these nanomicelles are made with amphiphilic molecules. These molecules may be surfactant or polymeric in nature. Currently, development of nanomiceller formulation-based technology for treatment of ocular disease is tremendously increased because of its high drug encapsulation capability, ease of preparation, small size, and hydrophilic nanomiceller corona generating aqueous solution and due to this properties it

enhances bioavailability of the therapeutic agent in ocular tissues results in better therapeutic outcomes [Cholkar et al. (2013a)]. In recent years, nanomicelles/ mixed nanomicelles loaded with active moiety such as dexamethasone, voclosporin and prodrugs have been find out to treat posterior related eye diseases. Nanomiceller with topical delivery have the potential to improve bioavailability in published studies. However, none has been proved to efficiently treat posterior ocular diseases in clinical studies [Wang et al. (2018)].

Polymeric nanoparticles

The polymeric nanoparticles consist of particles in the range of 1-1000nm in which the therapeutic agent is adsorbed, entrapped, conjugated, or encapsulated [Cholkar et al. (2013a)]. In order to deliver the drugs to the back side of eye i.e. posterior segment, by periocular and intraocular routes are alternative routes for drug delivery. Treatment by periocular or intraocular route is invasive approach and frequent administration is required which affects the patient safety and compliance. Due to the diversity and reliability of the polymer, the polymer-based nanoparticles representing the alternative solution for drug prolongation to the posterior segment of eye [Dubald et al. (2018)]. Polymeric nanoparticles can be made from natural or synthetic polymers, most frequently used natural polymers are polysaccharides such as chitosan, alginate, hyaluronic acid and dextran and polypeptides like gelatin and other collagen materials and synthetic polymers like poly(lactic-acid)(PLA), poly(lactic-co-glycolic-acid)(PLGA), polycaprolactone[Wang et al. (2018)], poly(2-hydroxyethylmethacrylate)(PHEMA) [Dubald et al. (2018)]. Now-a-days polymeric nanoparticles gained a lot of importance because they exhibit properties like biocompatibility, biodegradability and increases the pre-corneal retention time. Due to the unique anatomy and physiology of eye presents a great challenge for topical drug delivery of polymeric nanoparticles. The recent studies, proved that drug is delivered to the posterior segment of eye by topical instillation using polymeric nanoparticles [Wang et al. (2018)]. PLGA Nanoparticles: Poly lactic-co glycolic acid (PLGA), a copolymer of poly lactic acid (PLA) and poly glycolic acid (PGA). PLGA has been approved by US FDA as biodegradable material for use in medical applications such as surgical sutures, bone plate/ screws, tissue engineering scaffold and drug carrier system. PLGA is a biodegradable, biocompatible, controllable material with mechanical properties can be modified by changing PLA/PGA ratio and molecular weight. PLGA nanoparticles have high encapsulation efficiency for hydrosoluble or liposoluble drugs, even macromolecules, proteins, peptides, and nucleic acid. PLGA nanoparticles provides protection to encapsulated drugs from rapid inactivation, maintenance of slow drug release due to polymer degradation and targeting to specific region by surface modification [Wang et al. (2018)]. Study by Tahara et al. investigated the posterior ocular delivery of surface modified PLGA nanoparticles via topical instillation. For enhancing the mucoadhesive property, surface modification were performed with the chitosan, glycol chitosan, and polysorbate 80. After topical administration, it was found that surface modified PLGA nanoparticles could penetrate mouse retina. The in vivo fluorescence image analysis showed detectable fluorescence intensity of the coumarin-6 in the retina [Wang et al. (2018), Tsai et al. (2018), Tahara et al. (2017)].

Novel Applications of Excipients

Use of Cyclodextrin

Cyclodextrin (CDs) are a family of natural cyclic oligosaccharides that are formed by bacterial digestion of starch which are usually comprise of α-D-glucopyranose units via covalent conjugation of α-1, 4-glycosidic linkages. CDs are cyclic structure, with hydrophilic outer surface and is enclosed by

the lipophilic internal cavity [Loftsson et al. (2008), Wang et al. (2018), Loftsson and Stefansson; 2017)]. The natural α-, β-, γ-, cyclodextrin comprises of six, seven and eight glucopyranose units, respectively. Aqueous solubility of natural cyclodextrin is somewhat limited thus several water soluble derivatives have been synthesized such as HPβCD, HPγCD [Loftsson et al. (2008)]. A key benefit of CDs over conventional penetration enhancers (for e.g. benzalkonium chloride, EDTA) is that they increases the ocular drug bioavailability by increasing drug solubility. Drug cyclodextrin complex is a useful way to increase the solubility of poorly water- soluble drugs without changing their molecular properties [Kompella et al. (2010)]. A luminous feature is that the saccharide nature of cyclodextrin has no toxicity for human beings. The use of CDs in ocular preparations results in enhanced permeability, biocompatibility, and decreased irritation. In addition, CDs are able to improve the aqueous solubility, stability, activity and the dispersion of ophthalmic drugs. The derivatives like hydroxypropyl-beta-cyclodextrin (HP-β-CD), and randomly methylated-beta-cyclodextrin (RM-β-CD) are currently used to formulate cyclodextrin- based eye drops with the aim to treat the ocular diseases [Wang et al. (2018)]. Nanoparticulate formulation of γCD-drug conjugates were able to deliver drug molecules to the back side of the eye, in contrast RM-β-CD drug solution causes localization of more drug into anterior chamber of the eye [Cholkar et al. (2013b)]. Loftsson et al. have examined the effects of various CDs [HP-β-CD and RM-β-CD] on ophthalmic delivery of dexamethasone [Loftsson and Stefansson; 2017].

Use of Penetration Enhancers

Penetration enhancers or absorption promoters is the best approach to improve the bioavailability and therapeutic response of the topically applied drugs [Furrer et al. (2002)]. The transport process across the corneal tissue is the rate determining step in ophthalmic drug absorption. By the use of the penetration enhancers permeability of the corneal epithelium is enhanced and it is the best approach to increase the drug transport across the corneal tissues and therefore improves the ocular bioavailability of the drug. There are two possible ways by which penetration enhancer's act either by increasing the permeability of the corneal cell membrane or loosing the tight junction between the epithelial cells, which primarily restricts the entry of the drug molecules via paracellular pathway [Manish and Kulkarni; 2012]. The entry of drug molecules through the paracellular pathway is primarily restricted by the tight junctions. Surface active penetration enhancers are believed to increase the permeability of the cell membrane, calcium chelators mainly act on the tight junction and most enhancers affects the cell membrane as well as tight junction [Kaur and Smitha;2002].

Types of penetration enhancers:

A. **Calcium chelators** such as EDTA act by loosing the tight junctions between the superficial epithelial cells and thus facilitating paracellular transport. EDTA acts on tight junctions producing ultra-structural changes in corneal epithelium resulting in water influx and decrease of the overall lipophilic characteristic.
B. **Surfactant** enhances the drug and peptide permeability through the cell membrane or via the transcellular pathway. Non- ionic surfactant such as brij 35, brij 78, brij 98, sodium deoxycholate, polyoxyethylene-9-lauryl ether, L-α-lysophosphatidylocholine. Polyoxyethylene-9-lauryl ether was found to be most effective surfactant among these. Bile acids and salts are amphipathic molecules that are self –active and self-associate to form the micelles in aqueous solution (e.g. deoxycholate, taurocholate, glycocholate). Lysophosphatidilo lipids are

amphiphilic surfactant as like other surfactant they can affect the intracellular proteins and polar groups of phospholipids in intercellular spaces.

C. **Preservatives** such as benzalkonium chloride, cetylpyridinium chloride shows the highest promoting effect on corneal drug penetration from amongst currently used preservatives.
D. **Glycosides** some of the glycosides with the surface activity have been used successfully as penetration enhancers for e.g. saponin, digitonin, fatty acid etc.
E. **Miscellaneous group** of substances includes azone, cytochalasins, ionophores etc.
[Penetration enhancers like Azone (laurocapram), hexamethylene lauramide, hexamethylene octanamide, and decylmethyl sulfoxide are used as corneal penetration enhancers] [Kaur and Smitha; 2002, Manish and Kulkarni; 2012, Saini and Kumar; 2012, Malhotra and Majumdar; 2001].

Prodrug Approach

It is a chemical approach to deliver the drug moiety in order to enhance the drug absorption [Barot et al. (2012)]. Significant benefits in various properties like solubility, stability, permeability and evasion of efflux pump have been gained [Gaudana et al. (2009)]. Many prodrugs have been utilized to overcome the efflux of drug molecules and target the desired tissue like polymeric prodrug system, lipid prodrugs, co-drug systems, transporter- targeted systems, pro-prodrugs, Retrometabolic drug design and hydrophilic prodrug strategies. Now-a-days prodrug design coupled with formulation development approaches is an emerging method for the drug delivery to the posterior segment of the eye [Wang et al. (2018)]. Chemical modification such as prodrug targeting to the various nutrient transporters like amino acid, peptide, and vitamins has evolved a great interest in improving ocular drug delivery. The most commonly utilized functional groups in ophthalmic prodrug design are carboxylic, hydroxyl, amine and carbonyl groups. Modification of these functional groups which includes esters, carbamates, phosphates and oxime results in ocular prodrugs [Barot et al. (2012)].

Novel Ocular Devices

Ocular Implants

Ocular implants are specifically designed to provide the sustained release of the drug molecule from either biodegradable or non-biodegradable polymeric matrix over the several months to years [Thrimawithana et al. (2011)]. These ocular implants helps to prevent multiple intraocular injections and associated complications [Cholkar et al. (2013a)]. Implants provides direct drug delivery to the target site with the minimal side effects [Peptu et al. (2015)]. Based on the biodegradation nature of the polymer used, implants are classified as nonbiodegradable and biodegradable implants. Long lasting drug release can be achieved by nonbiodegradable implants [Kompella et al. (2010)]. From the biodegradable implants more erratic drug release occurs due to the changes in the properties of the system with polymer degradation. While biodegradable system offers the advantage of the physiological clearance of the all system components over time, nonbiodegradable system remain permanently in the body until it is surgically removed [Peptu et al. (2015), Thrimawithana et al, (2011)].

Usually for the drug delivery to the back side of the eye tissues, implants are placed intravitreally by making the incision through the minor surgery at pars plana of the eye which is located posterior to the lens and anterior to the retina [Cholkar et al. (2013a), Peptu et al. (2015)].

IMPLANT TYPE	POLYMERS MOST COMMONLY USED	MARKETED EXAMPLES	REFs
Biodegradable implants	• Polylactic acid • (PLA) • Polyglycolic acid • (PGA) • Poly(lactic-co-glycolic acid) (PLGA) • Polycaprolactone (PCL) • Polyanhydrides • Poly(orthoester)(POE)	Ozurdex Surodex Verisome	[Cholkar et al. (2013a)] [Kompella et al. (2010)] [Thrimawithana et al. (2011)]
Non-biodegradable implants	• Polyvinyl alcohol(PVA) • Ethylene vinyl acetate (EVA) • Polysulfone capillary fiber (PCF)	Vitrasert Retisert Iluvien Renexux NT-503	[Cholkar et al. (2013a)] [Kompella et al. (2010)] [Thrimawithana et al. (2011)]

Fig.: Summary of types of implants

Contact Lenses

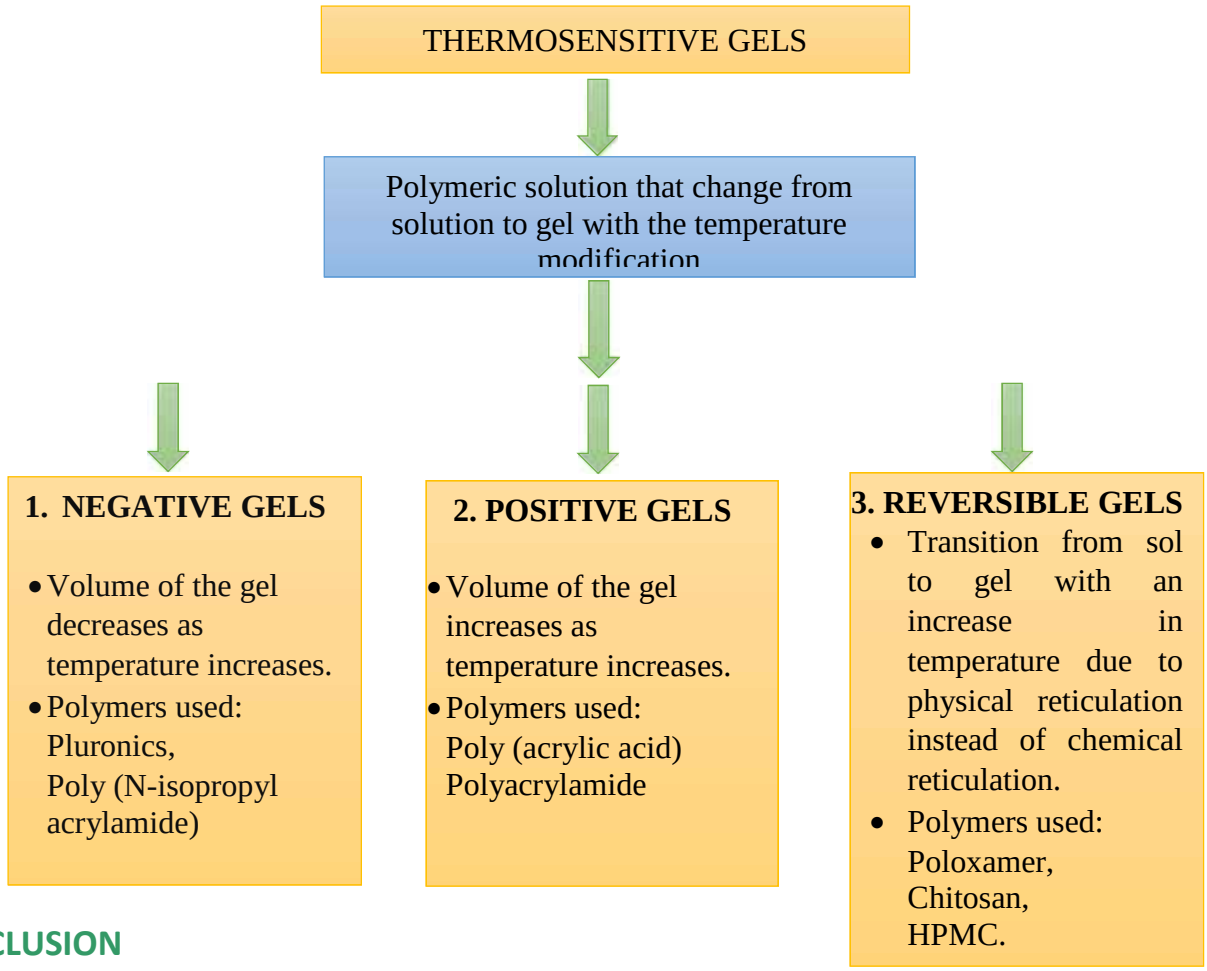
Contact lens are designed to provide the extended release of the drug molecule into the eye [Shende and Godbole; 2016]. These are thin, curve, round piece of the plastic placed directly on the surface of the eye, which are designed to cover the cornea [Cholkar et al. (2013a), Dubald et al. (2018)]. The current challenges in developing the contact lenses as ocular drug delivery system are to sustain the drug release for longer periods, incorporation of sufficient amounts of the drug into the lens matrix, good optical clarity, and patient comfort during prolonged wear and biocompatibility [Kompella et al. (2010), Dubald et al. (2018)]. Prolonged wear of the contact lens is associated with the risk of infection such as microbial keratitis and dry eye syndrome. Contact lenses are contraindicated in various inflammatory conditions such as anterior uveitis, vernal conjunctivitis, microbial keratitis and dry eye syndrome, limiting the applicability of this delivery system [Kompella et al. (2010)]. Loading of the drug is achieved with the methods like imprinting, simple soaking, colloidal nanoparticles. Most important focus during the lenses development are the preservation of the oxygen permeability and transparency of it. Even though contact lenses are the alternative and promising ocular drug delivery system, they are an expensive form which needs cleaning and handling. There are two types of the therapeutic contact lenses: scleral rigid gas permeable (RGP) lenses and soft lenses. Scleral lenses are large, thin and used in treatment of the various eye conditions like glaucoma, chronic dry eye, allergies and infections [Dubald et al. (2018)].

Novel Ophthalmic Dosage Form

Hydrogels

Hydrogels are the three-dimensional, hydrophilic, polymeric network that have the ability to swell in water or aqueous solvent system and hold the solvents in a swollen cross-linked gel system for the drug delivery [Peptu et al. (2015), Shende and Godbole; 2016]. In ocular drug delivery, hydrogels are used to increase the residence time of the drug molecule on the surface of the eye, which ultimately results in increase in bioavailability of the drug molecule to the target site [Peptu et al. (2015)]. There are two types of hydrogels: Preformed gels and In-*situ* gels. The preformed gels are simple viscous solutions administered on the surface of the eye. This type of polymeric gel is commonly used Bioadhesive hydrogel to improve residence time on the eye and reduce the dosing frequency. Various mucoadhesive polymers used in formulation of Bioadhesive hydrogel such as methyl cellulose, hydroxyethyl cellulose, sodium hyaluronate, sodium alginate, povidone, polyvinyl alcohol, sodium

hyaluronate etc. In *situ* hydrogels are polymeric solutions which undergo sol-gel phase transition to form viscoelastic gel in response to the environmental stimuli. Phase transition can be achieved by changes in temperature, pH, and ionic composition or by UV irradiation [Peptu et al. (2015)]. Polymers are composed of basic and acidic groups that either accept or donate the proton in response to the changes in environmental pH [Laddha and Mahajan; 2017, Peptu et al. (2015)]. When polymers are comprise of acidic groups the solution turned to gel by increasing the pH. In contrast, polymers with basic groups are converted to a gel by decrease in pH. Polymers used in pH dependant system such as cellulose acetate, carbomer, magrogol, pseudo latex, polymethacrylic acid etc. [Peptu et al. (2015)]. Ion activated system is based on change in ionic strength of external environment. Ion induced gelation is triggered by cations present in tear fluid like Na^+, Mg^{2+}, Ca^{2+} . Generally anionic polymers are used in the formation of the ion sensitive drug delivery system [6]. Polymers used in ion activated system like sodium alginate, gellan gum, tamarind gum etc. [Laddha and Mahajan; 2017, Peptu et al. (2015)]



CONCLUSION

Effective treatment of the ocular diseases is a major challenge for researchers because of the nature of disease and presence of ocular barriers especially in posterior ocular segments. Drug delivery system via topical administration to target posterior segment of the eye should: 1) prolong the retention on the surface of eye, 2) enhance the drug permeability in ocular tissues, 3) efficiently deliver the drug to the targeted site. Several novel ocular drug delivery systems based on nanotechnology such as nanoparticles, nanosuspension, nanoemulsion, liposomes, polymeric nanoparticles, cyclodextrin nanoparticles, penetration enhancers, prodrug approach, implants, contact lenses etc. are being used to improve the fate of the drug in ocular tissues. These nanoparticles- based drug delivery systems improve patient compliance, minimizes side effects, and reduces frequency of administration.

Cyclodextrin nanoparticles, polymeric nanoparticles, penetration enhancers are promising alternative for treatment of back side of eye over conventional ophthalmic formulations.

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