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OCULAR DRUG DELIVERY SYSTEM- A NOVEL THERAPEUTIC APPROACH

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ABSTRACT
The purpose of this review is to give a recent update of the knowledge and challenges faced by today's formulation scientists in the field of ocular drug delivery. The ocular preparations are available as sterile, buffered, isotonic solution. Topical eye drop is the convenient and patient complaint route of drug administration. Also, it involves development of conventional topical formulations such as suspensions, emulsions and ointments. The major problem encountered by the conventional ocular dosage form include frequent dosing, the rapid precorneal drug loss due to its nasolacrimal drainage, tear turnover and drug dilution resulting in poor bioavailability. These lead to development of controlled and sustained release novel ocular drug delivery dosage forms such as nanoparticle, liposomes, ocuserts, in-situ gel, implants, contact lens, microneedles and mucoadhesive formulation over conventional dosage forms in terms of enhancing bioavailability, possess high precorneal residence time, feasibility of topical application, decreasing dosage frequency and reduce toxicity. This review briefly describes advantages, limitation of conventional ocular dosage form, an anatomical protective barrier in ocular drug delivery, and recent novel approaches of ocular drug delivery for various treatment.

KEYWORDS: Eye, ocular drug delivery, enhance bioavailability, novel approaches, sterile, precorneal residence time.

INTRODUCTION
Ocular drug delivery is one of the interesting and challenging tasks faced by pharmaceutical researcher.[1] The eye has been considered as a complex structure, mostly resistant to foreign substances including drug. The anterior and posterior segment of the eye is the two main different sections having anatomically and physiological function.[2] The anterior portion concerned about 1/3 of the eye such as cornea, conjunctiva, aqueous humour, iris, ciliary body, lens and the remaining second third occupied with a posterior portion made up of ocular tissue choroid, retinal pigment epithelial, optic nerve and vitreous humour.[3] The anterior and posterior segment of the eye is affected by numerous vision frightening diseases. Diseases affecting the anterior segment include glaucoma, allergic conjunctivitis, and cataract. While diabetic retinopathy and Age-related Macular Degeneration (AMD) are the most prevalent diseases affecting the posterior segment of the eye.[4] The most widely chosen non-invasive route is nothing but the topical instillation for drug administration to the anterior segment of the eye. Several drug delivery systems are available, of which 90% of marketed formulation for ophthalmic is conventional dosage form.[5] Nowadays, there are several types of ocular drug delivery systems in the market which includes ophthalmic eye drops as these are highly patient compliance. Others conventional formulation are emulsion, suspension, ointment and polymeric gel preparation.[6] The conventional topical formulation is applied predominantly to the anterior portion of the eye, which undergoes drug loss due to the defensive mechanism of the eye. This lead to the formulation of a novel ocular drug delivery system to increase the retention time on the eye surface to improve therapeutic efficacy.[7]

The novel ocular drug formulation has to reach the inner parts of the eye and trans-corneal penetration is believed to be the prime route for drug absorption. Ideal ophthalmic drug delivery must be able to remain in the vicinity of the eye for a prolonged period and to sustain the drug release.[8] However conventional formulations are associated with nasolacrimal drainage, tear dilution and tear turn-over of the eye are responsible for poor ocular bio-availability of eye formulation.[9]

These barriers create an important challenge for delivery of a drug alone or in a dosage form, more significantly to the posterior segment of the eye. Novel drug delivery system helps to sustain the concentration of drug within the therapeutic window to reduce the undesired effects and enhance the therapeutic benefits, with an ideal dose site or target specific delivery of drug can be done. The nanotechnology formed ophthalmic preparations are one

of the methods which is now being followed for anterior as well as posterior drug delivery. These nanotechnology-based systems with proper particle size are made to establish low irritation, appropriate bioavailability and ocular tissue compatibility.[10] Novel drug delivery system slows down the elimination of formulation from eye, increase the ease and enhance the corneal penetration of drug molecule to extent sustain delivery of drug.[11, 12, 13] Novel ocular formulation other than nanotechnology includes in-situ gel, liposome, noisome, micro emulsion, dendrites, iontophoresis and ocular inserts are developed to accelerate the bioavailability of the drug and to enhance penetration in the cornea and control the release of drug.[14] In ocular drug delivery maintaining a sufficient amount of drug at the targeted site for a prolong period of time is a challenging task.[15] The main aim behind this review article is to highlight the newer developments in the pharmaceutical ocular formulation.

Novel ocular formulation includes some common excipients to improve drug contact time and bioavailability various tonicity adjuster like magnesium chloride, calcium dihydrochloride and sodium chloride. Lubricant like Carboxy methyl cellulose (CMC), viscosity enhancer like Glycerine, Carboxymethylcellulose sodium and hydroxy methyl cellulose. Surfactants such as polysorbate 20, 40, 60 and 80 and pH adjuster such as hydrochloric acid, sodium citrate dihydrate and sodium hydroxide, Preservative like polyethylene glycol 400, sodium hyaluronate and a sodium chlorite and additives to topical eye drops is cyclodextrins which is acting as complex former.[16,17] Benzalkonium chloride, ethylene diamine tetra acetic acid-sodium salt use as a permeation enhancer for improving ocular delivery as well as preservative.[18,19] Boric acid is commonly used as a buffer and antimicrobial in ocular formulations. Several researchers have introduced mucoadhesive polymers such as chitosan and hydroxymethyl cellulose ether and other cellulose derivatives.[20] This review briefly describes advantages, limitation of conventional ocular dosage form, an anatomical protective barrier in ocular drug delivery, and recent novel approaches of ocular drug delivery for various treatment.

ANATOMY AND PHYSIOLOGY OF THE EYE

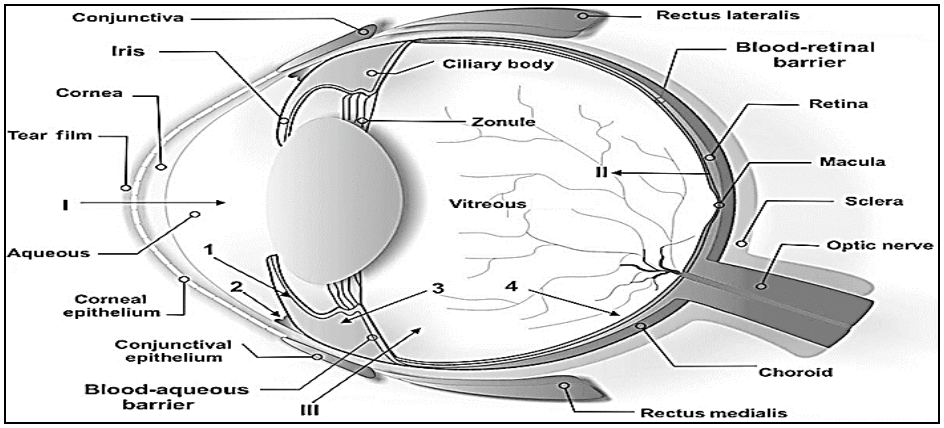
The eye is most complex organ of the human body. The human eye consists of three layers. The outer layer comprises the cornea and the sclera.[21] The cornea refracts and transmits the light to the lens and protects the eye against infection and structural damage to the deeper parts. The sclera forms a connective tissue coat that maintains its shape and secures the eye from internal and external forces. The conjunctiva is a transparent mucosal membrane that covers the visible part of the sclera. The middle layer of the eye is comprised of the iris, the ciliary body and the choroid. The iris controls the size of the pupil, and the amount of light reaching the retina; the ciliary body regulates the power and shape of the lens and the choroid is a vascular layer that provides nutrients and oxygen to the outer retinal layers. The inner layer of the eye is the retina, a complex layered structure of neurons that process and capture light. The three transparent structures surrounded by the ocular layers are called the aqueous, the vitreous and the lens.[22,23]

The adnexal structure of the eye includes the eyelids, conjunctiva, caruncle and lachrymal glands. The eyelids are the fold of the skin that protects and cover the eye. They also contain gland that produce oily secretion.[24]

The conjunctiva is thin moist layer of tissue that lines some organ and body cavities. It also secretes mucus that lubricate the eyeball and it keeps it moist.[25,26] The caruncle is small, pinkish portion on the innermost corner of eye. The Lacrimal gland also known as tear glands is located at the upper, outermost corner of the eye. This tear gland secrets tears to keep the surface of the eye moist and lubricated.[27]

Aqueous humor is an optically clear, slightly alkaline ocular fluid that is formed by epithelial cells of ciliary body from plasma aqueous humor are responsible to supply nutrients and oxygen to avascular tissue, cornea and lens and also help to remove waste product, macrophage and other debris from posterior of the cornea and anterior of the lens. It also plays a major role in maintaining the shape and internal ailments of eye ball along with production of intraocular pressure. Vitreous humor is a hydrogel Matrix consisting of hyaluronic acid, proteoglycans and collagen fibrils.[28]

Cornea is the main route for transportation of drug to anterior chamber, for systemic administration of drugs retinal pigment epithelium and the retinal capillary endothelium are the main barriers. Intravitreal injection is an incursive approach to reach the vitreous. The administration of drugs can be carried out from the anterior chamber either by venous blood flow after moving across the iris surface or by the aqueous outflow. Drugs are removed from the vitreous through diffusion in to the anterior chamber or at the blood retinal barrier.[29] A significant challenge to the formulator is to circumvent the protective barriers of the eye like drainage, lacrimation and conjunctive absorption without causing permanent tissue damage.[30] The main region of drug loss includes lachrymal drainage and drug dilution by tears. The corneal epithelium forms the primary obstacle to drug absorption via topical administration.[31] The pores of the corneal epithelium are negatively charged at physiological pH, therefore negatively charged molecules permeate slowly as compared to positively charged molecules.[32] Various researches have shown that molecular weight up to 70 kDa can readily penetrate the sclera, whereas through the cornea it is less than 1 kDa.[33] The large surface area (~95% of the total ocular surface area of the eye) offers the possibility of delivering active agents to specific locations of the retina via transcleral absorption.[34]



Fi g. No. 01: Anatomy and Physiology of eye.

ADVANTAGES OF NOVEL OCULAR DRUG DELIVERY SYSTEMS OVER CONVENTIONAL DRUG DELIVERY SYSTEM[35,36, 37]

1. Increased accurate dosing of novel ocular drug delivery system
2. To reduce the side effects of pulsed dosing induced by conventional systems.
3. To supply sustained and controlled drug delivery.
4. To extend the ocular bioavailability of drug by increasing the corneal contact time. This can be attained by effective adherence to corneal surface.
5. To supply targeting within the ocular globe so as prevent the loss to other ocular tissues.
6. It improves patient compliance and even offer comfort and enhance therapeutic drug performance.
7. The systemic effects as well as visual side effects are lower and absorption is faster.
8. They are easily managed by patients himself.
9. Absence of preservative in some single and multiple dosage form reduce the risk of sensitive reactions in comparison to aqueous solutions.
10. Combinational therapeutic approaches are also possible.
11. Novel drug delivery system eliminates the limitations of conventional drug delivery system.

SOME DISADVANTAGES OF NOVEL OCULAR DRUG DELIVERY SYSTEM[38, 39, 40]

1. The occasional unintentional loss during sleep or while rubbing of eyes.
2. Drug delivery to ocular posterior segment through topical application still remains a challenge, only 1-5% or less of a topically instilled dose was delivered into inner ocular tissues.
3. Poor bioavailability and instability for dissolved drugs.
4. Interference with vision and difficulty in placement and removal.
5. Dosage termination is not possible.

FORMULATION CONSIDERATION

The ocular

ACTIVE PHARMACEUTCAL INGREDIENTS (API)

Table 1: List of API in ocular formulation.

Sr. No	API	Disease	Formulation	Reference
1.	Moxifloxacin	Bacterial Infection	Eye Drops	Smith A, Penne father PM, Kaye SB, Hart CA.[41]
2.	Flurbiprofen sodium	Cataract Removal	Emulsion	Karasawa F, Ehata T, Okuda T, Satoh T.[42]
3.	Ketorolac amide Derivative	Inflammation of ocular mucosa	Solution	Graff G.H., Hellberg M.R., Yanni J.M.[43]
4.	Tacrolimus	Allergic Conjunctivitis	Ointment	Chen J.Q, Liu Y.[44]
5.	Chloramphenicol	Trachoma and Keratitis	Ointment	Lv F.F, Zheng, L.Q, and Tung, C.H.[45]
6.	Pilocarpine Hydrochloride	Glaucoma	Solution	Lin H., Sung K.C.[46]

Excipient

The excipient used here are chelating agent, tonicity agent, preservative, antioxidant, buffer, demulcent etc. along with ingredients. These excipients will improve the solubility, permeability and bioavailability of poorly soluble drugs.[47] Some excipients are listed below:

1. **Demulcent:** The substances which have effects that include hydrophilic polymers which are semisolid formulation and also increases viscosity whereas hyaluronic acid is used as a polymer that forms biodegradable and biocompatible matrix. Some other examples are polyvinyl alcohol, glycerin,

povidone, carboxymethyl cellulose, hydroxyethyl cellulose.[48]

2. **Tonicity Agent:** They are used for adjusting the tonicity of the ophthalmic liquid. Some examples are sodium chloride, potassium chloride, magnesium chloride, calcium dihydrochloride.
3. **Chelating agent/ Preservatives/ Surfactants:** They are the penetration increasing substances in ophthalmic solution that will enhance their corneal absorption. Some examples are Benzalkonium chloride, surfactants like polysorbate 80 and bile acid salts.[49]
4. **Prodrugs:** These Prodrugs will enhance corneal drug permeability. The drugs which increase the permeability through prodrug formulation are epinephrine, timolol and pilocarpine.[50]
5. **Antioxidant:** They are used in reducing oxidation of any compound. Some examples are sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxy anisole.
6. **Buffer:** They include any weak conjugate acid-base pair for maintaining a desirable pH range. Some examples are Acetate buffers, citrate buffers, phosphate buffers, borate buffers.

CONVENTIONAL TOPICAL OCULAR DRUG DELIVERY SYSTEM

There are various types of ocular drug delivery system in the market including ophthalmic eye drops which are commonly used by patients and Others are emulsion, suspension, ointment and polymeric gel preparation.

Eye Drops

Eye drops are the most suitable, non-invasive and patient compliant among topical eye preparations. These forms are isotonic and sterile. The optimum pH for eye drops equals of tear fluid is about 7.4. In deciding whether to buffer the drug in this form, one should take into account the tissue tolerance to the preparation and the stability of active ingredient. If the pH value gets beyond the range of 4–8, there may be irritation, the patient may feel discomfort, and the drug bioavailability can decrease because of increased tearing. Besides, the tear drainage that increases with the volume of eye drops can led to the dilution and loss of the solution. Other than that, the amount of the drug absorbed into the ocular tissue cannot be estimated due to the limited holding capacity of the eye pocket.[51]

Emulsion

The interest in using emulsion in the past has been resuscitated by submicron emulsion (ranged between 0.1μm and 0.3μm) with non-ionic surfactant to increase its stability.[52] An ophthalmic lipid emulsion improves the ocular bioavailability of lipophilic or poorly soluble drugs by increasing drug solubility in the oil droplet and by accelerating drug penetration into intraocular tissues. Ophthalmic lipid emulsion is also promising with respect to its good tolerance, high stability, and ease of manufacturing.[53] Although, ophthalmic emulsions come with their own limitations. They have low stability and are prone to several types of instability phenomena such as creaming, coalescence and flocculation. Coalescence is a process by which the dispersed droplets in the suspension are constantly combined to form larger droplets. Flocculation is other instability process in which the dispersed phase comes out from the suspension and forms flakes. Other than that, one phase in the emulsion can migrate either to the bottom or the top depending on their relative densities, forming a separated layer between the two phases known as creaming. Thus, the study suggested the use of surfactants to improve the kinetic stability of the emulsion products.[54]

Suspensions

Suspension can be defined as a dispersion of finely insoluble active pharmaceutical ingredients in a solvent. To put it another way, it is a concentrated solution of active pharmaceutical ingredients. This type of ocular drug delivery system has many benefits over ophthalmic drops. The main benefit is that it can improves drug contact time and duration of action because of the insoluble suspension that remains in the precorneal pocket instead of being washed away or diluted by the tear. The strengthening of the duration of the drug action is due to the different particle sizes of the suspended particles. The small particles will replenish the absorbed drug while the large particles will be retained in the precorneal pocket and undergo slow dissolution.[55] Despite all the benefits, suspension also has several drawbacks. For example, it needs to be shaken to reach the required dosage level. This will decrease patient compliance and differ the dosage of the drug delivered to the eye. With low patient compliance, the efficacy of the suspension might also be affected.[56]

Ointment

The ointment is a mixture of semisolid, which is non-irritating to the eye and melts at the body's physiological temperature. Generally, there are two types of ointment, a simple-based ointment which is made up of one continuous phase of ointment, and a compound-based ointment which consists of a two-phase system like emulsion. When applied to the eye, the ointment will break into small drops that will remain in the conjunctival sac for an extended period of time. This action leads to the major advantage of ointment, such that it serves as a drug depot in the conjunctival sac which enhances and prolongs its absorption. The desirable attributes of ointment development should include several factors such that it needs to be non-irritating to the eye, uniform, easily manufactured, and does not cause excessive blurred vision. Although it can enhance and prolong drug absorption. Ophthalmic ointment faces a significant drawback that can reduce its efficacy. The application of ointment can lead to occasional irritation and blurring of vision, resulting in low patient compliance. Due to this, it is generally being applied at night before sleep.[57]

Polymeric gels

The ocular gel is another dosage form for delivering drugs to the eye topically. Gels are made up of various materials such as mucoadhesive polymers which are important for the localized delivery of active ingredients. Mucoadhesive polymers have been used in ophthalmic gels to increase their efficacy. This polymer provides an attachment for the drug carrier to a biological tissue resulting in an extended contact time and an improved ocular bioavailability.[58] There are two types of ophthalmic gels, namely performed gel and in-situ forming gel. The ophthalmic preformed gel is less preferable as a dosage form because it is present as a gel substance at room temperature. This property has limited use in ophthalmic drug delivery because of low accuracy and reproducibility administration of drugs, often producing blurry vision, crusty eyelids, and lachrymation. Due to this, in situ gels become a focus in the gelling system as it provides both advantages of solution and gel. In situ forming gel is a viscous liquid preparation that will change to a gel phase using either one of these three mechanisms which are pH triggered, temperature triggered, or ion activated. It is preferred over the preformed gel as it is more comfortable, easily administered as a drop, and causes less to no problem to the vision.[59] It is difficult to administer an accurate dose with preformed gel due to the variation of the amount of drug delivered during administration. However, with in situ gel-forming formulation, it is possible to administer accurate and reproducible quantities of dose. Moreover, the relatively prolonged action duration of in situ forming gel reduces the administration frequency and thus increases patient compliance.[60]

NOVEL APPROACHES

There are various types of novel inventions have been made in pharmaceutical industry in terms to improve efficacy and therapeutic effect of medications. Some of the novel ocular approaches are:

Liposomes

Liposomes are membrane like vesicles, consisting of phospholipid bi-layers surrounding an aqueous compartment.[61] Created when matrix of phospholipids is agitated in aqueous medium to disperse two phases. Phospholipids used are Phosphatidylcholine, Phophotidicacid, Sphingomyelin, Phosphatidylserine, Cardiolipin.[62] Drugs encapsulated in liposomes are expected to be transported without rapid poly (lactide-co-glycolide) degradation and minimum side effects to the recipients. It has been used locally and systemically for targeting of drugs to specific organs or for prolonging drug effect.[63] Liposomes has an affinity to bind to, ocular surfaces, and release contents at optimal rates.[64] Positively charged liposomes have a more affinity, to increase both precorneal drug retention and drug bioavailability. The corneal epithelium is thinly coated with negatively charged mucin to which the positive surface charge of the liposome may imbibe more strongly. Ciprofloxin was also formulated in liposomal environmental which lowered tear-driven dilution in the conjunctival sac, Multilamellar vesicles from lecithin and alpha-l-dipalmithoyl-phosphatidylcholine were used to prepare liposome containing ciprofloxacin.[65] It provides controlled, selective drug delivery, enhance bioavailability and their potential in ocular drug delivery appears greater for lipophilic than hydrophilic compounds. Liposomes offer the advantage of being completely biodegradable and relatively innocuous but are less stable than particulate polymeric drug delivery systems. Liposomes were found to be a potential delivery system for administration of a number of drugs to the eye.[66-67] A method has been developed to target drugs locally in the eye via a light-based mechanism. The method is called as laser-targeted delivery, which causes the liposomes to release their contents in the blood in less than 0.1 second.[68-69] The potential of liposomes as topical ophthalmic drug delivery system is restricted by their stability and limited drug-loading capability. Large scale manufacturing of liposomes is expensive and challenging.[70]

Nanoparticles

Nanoparticles are defined as particles with a diameter of less than 1μm, comprising of various biodegradable or non-biodegradable polymers, lipids, phospholipids or metals.[71] They are classified as nanospheres or nano capsules depending upon whether the drug has been uniformly dispersed or coated with in polymeric material. Nanoparticle provide sustained release and prolonged therapeutic activity when retained in cul-de-sac after topical administration and the entrapped drug must be liberated from the particles at an appropriate rate.[72] Enhanced permeation across the cornea was also observed when poly nanoparticles were coated with polyethylene glycol.[73] This system resulted in burst release during the first hour followed by sustained release for 24 hours. This approach helps in reducing the dosing frequency of the antibiotic because of the sustained action observed after single administration.[74] Nanosuspensions are sub-micron colloidal systems made with inert polymeric resins and usually have a poorly water-soluble drug suspended in an appropriate dispersion mode.[75,76]

Dendrimers

Dendrimers are macro molecular compounds which is made up of a series of branches surrounding a central core. Their nanosized, ease of preparation, functionalization and possibility to attach multiple surface groups render them suitable alternative vehicle for ophthalmic drug delivery.[77] Dendrimers are globular, nanostructured polymers(3-20nm) with a well-defined shape, narrow polydispersity. Some dendrimers possess antimicrobial properties, and can be used as surface coating agents and drugs carriers.[78] These hydro-gel are being explored in wide range of applications from drug delivery to wound healing. One of the advantages of using these dendrimers in a hydro-gel is that they offer numerous surface groups that enable

high cross-linking densities at very low polymer concentration.[79,80,81]

Niosomes

In order to circumvent the limitations of liposomes, such as chemical instability, oxidative degradation of phospholipids, can entrap both hydrophilic and hydrophobic drugs. They are non-toxic and do not require special handling techniques.[82] Noisome are non-ionic surfactant vesicles are considered to have potential applications in the delivery of amphiphilic drugs. An increased ocular bioavailability of water soluble, entrapped in niosomes, may be due to the fact that surfactants also act as penetration enhancers as they can remove the mucus layer and break functional complexes.[83] Both noisome and discomes of water-soluble drug timolol maleate and found that discomes entrapped comparatively a higher amount of drug (25% as compared to 14% in case of niosomes).[84] Moreover, a rise in ocular bioavailability was found to be approximately 3.07-fold correlated to 2.48-fold in case of niosomes with regards to timolol maleate. It is feasible to use non-ionic surfactant vesicles as carriers for the ophthalmic controlled delivery of a water-soluble local antibiotic, Gentamicin sulphate.[85]

Implants

Sustained release ocular implants are the drug delivery devices for sustained release of molecules for either biodegradable or non-biodegradable polymeric matrices over several months to years. The intraocular implants were developed in order to achieve controlled and sustained drug delivery to treat long term ophthalmic disorders. These devices can be implanted in sub-conjunctival, episcleral, intravitreal, intracameral regions. Biodegradable solid implants are fabricated using Polylactic Acid (PLA), Polyglycolic Acid (PGA), and Polylactic-co-Glycolic Acid (PLGA) Polycaprolactones (PCL) polyanhydrides which does not need post treatment surgical removal unlike non-biodegradable implants, but can cause erratic drug release profile. The implants can be inserted into various sites of the eye depending upon the ailment and condition to be treated.[86,87] Non-biodegradable implants are made up of polyvinyl-alcohol (PVA) Ethylene vinyl acetate (EVA), Polysulfide Capillary Fibre (PCF). Intravitreal implants of fluocinolone acetonide were developed for the treatment of posterior segment and reported to control the ocular inflammation of retina.[88]

In-situ

There is high scope for research work on in-situ gel system in order to provide advanced techniques in drug delivery systems. For local ophthalmic delivery system different compounds such as autonomic drugs, anti-inflammatory agent & antimicrobial agent are used to release intra-ocular tension in glaucoma. To overcome the bioavailability problem ophthalmic in-situ gel were developed. To enhance the bioavailability various viscosity enhancers have been used to improve the viscosity of formulation in order to prolong the precorneal residence time & increases the bioavailability, easy to manufacture. Penetration enhancer such as preservatives, chelating agent, surfactants are used to develop corneal drug penetration.[89] In situ ocular gel is considered to be one of the novel ocular drug delivery systems. In situ gel system comprise delivery vehicle composed of polymers (natural, semi synthetic or synthetic) which has a special property of sol-gel conversion when influenced by some biological stimulus and more residence time.[90]

CONCLUSION

We conclude that a novel approaches on ocular drug delivery system shows that the development of ophthalmic solutions is found to be safe as targeting the eye to treat ocular diseases with wide variety of novel approaches become easy. Novel approach diminish the major issue of least bootability that is associated with conventional dosage for ocular delivery and provide enhanced retention of dose in the eye, as the residence time of ophthalmic formulation are increased on the corneal surface dose frequency is reduced. maximum efficacy of drug is obtained when the size is in nano range hence no ocular irritation. These novel formulations generally give extended or controlled release in the ocular tissues. Novel formulations provide better patient compliance, therapeutic activity and least toxicity.

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CONFLICT OF INTERESTS

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