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A REVIEW ON NOVEL DRUG DELIVERY SYSTEM FOR EYE

Adarsh Kumar Verma*[1], Aman[1], Sneha Pandey[1], Mo Alkama[1], Monam[1], Mo Anas[1], Vasiullah[1], Priyanka Gupta[1], Yadav Pooja Ramesh[1], Dhiraj[1], Gaurav Verma[1], Deepak Kumar[1] and Akash Yadav[1]

[1]R. C. C. College of Pharmacy Basti Up.

***Corresponding Author: Adarsh Kumar Verma**

R. C. C. College of Pharmacy Basti Up.

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ABSTRACT

Sight, or vision, is crucial for human survival. Due to the unique architecture and physiology of the eye, drug delivery scientists and pharmacologists have faced significant difficulties. For the treatment of eye problems, topical administration of both traditional and cutting-edge medication formulations is available. Ophthalmic solutions, suspensions, ointments, gels, and inserts are examples of conventional dosage forms. Microemulsions, nanosuspensions, dendrimers, niosomes, liposomes, etc. are examples of novel dosage forms. Comparing novel drug delivery systems to traditional drug delivery systems, the bioavailability of the medicine is enhanced. The obstacles offered by numerous anterior and posterior segment disorders can be significantly improved, according to recent advancements in the field of ophthalmic drug administration. Here in this article, we are going to discuss the anatomy of the eye, and conventional and novel ophthalmic techniques.

KEYWORDS: Ophthalmic, Dosage forms, Novel, Drug delivery, Technology.

1. INTRODUCTION

The ocular drug delivery system is a dosage form. It is used again for disorders that will cause infections in the eyes. The prolonged contact of the drugs with the eye will increase the therapeutic efficacy and bioavailability of ocular drugs.[1] The development of newer, more sensitive diagnostic techniques and therapeutic agents gives urgency to the development of the most successful and advanced ocular drug delivery systems. The eye will be infected easily because it is sensitive and located on the surface of the body. The medication is to be repeated throughout the eye and is composed of a transparent cornea, lens, and vitreous body without blood. The main bulk of the eye (the cornea) is made up of crisscrossing layers of collagen and is bound by elastic lamina on both the front and back. The cornea is richly supplied with free nerve endings. The transparent is continued posteriorly into the opaque white sclera. It consists of tough fibrous tissue. Both the cornea and sclera withstand the tension constantly maintained in the eye. The eye is constantly cleansed and lubricated by the lacrimal apparatus, which consists of four structures, e.g., lachrymal glands, lachrymal canals, the lacrimal sac, and the nasolacrimal duct. The physiological barriers to diffusion and productive absorption of topically applied drugs exist in the precorneal and corneal spaces. The eye is a slightly asymmetrical globe, about an inch in diameter, which helps in viewing the world around the living being, hence the term "photoreceptors".[2] The eyes contain lachrymal glands which produce tears to lubricate the surface of the eyeball. Wash away dust particles falling on the surface of the eyeball. It helps in killing germs, thus preventing infection. Communicate emotions.[1]

The human eye faces many obstacles viz., Astigmatism, cataracts, cat eye syndrome, colour blindness, conjunctivitis, diabetic retinopathy, glaucoma, haemolacria, heterochromia, hyperopia, macular degeneration, myopia, optic neuritis, presbyopia, polycoria and so on goes the list of eye infections that start from harmless dry eyes and lead to loss of vision Although many potent drugs are available to treat most of ocular complaints, there are many ocular barriers such as tear film, corneal, conjunctival, and blood-ocular barriers that hinder their therapeutic efficacy. Conventional eye drops are wasted by blinking and tear flow. Therefore, their bioavailability is minimized to less than 5%.[1] Cornea is composed of epithelium, stroma, and endothelium. Epithelium allows only the passage of small and lipophilic drug. However, stroma allows the passage of hydrophilic drugs.[2] Endothelium conserves the transparency of the cornea and affords selective entry for hydrophilic drugs and macromolecules into the aqueous humor. The conjunctiva provides a minor impact to drug absorption compared to the cornea, though certain macromolecular nanomedicines, peptides, and oligonucleotides penetrate to the deep layers of the eye absolutely through these tissues. Blood-ocular barriers prevent the passage of xenobiotic compounds into the blood stream. They are classified into blood-aqueous barrier (BAB) in the anterior segment and blood-retinal barrier (BRB) in the posterior segment of the eye.[4] Ocular formulations are intended to be applied on the anterior surface (topical route) of the eye, delivered intraocularly (inside the eye), periocularly (subtenon or juxtascleral), or in combination with ocular devices. Ocular dosage forms could be liquid, semi-solid, solid, or mixed. Liquid dosage include drops, suspension, and emulsion. Eye drops represent more than 95% of the marketed ocular products.[5] They are used for delivering the medication into the anterior part of the eye but with short residence time.[6] Ocular suspensions and emulsions have the ability to deliver hydrophobic drugs, but may lead to blurred vision. Ocular gels and ointments (semi-solid) could significantly enhance residence time. Solid dosage forms could be used to deliver water-sensitive drugs (powder), provide zero order release model (insert), or sustain residence time (therapeutic contact lens).[7,8]

2. Eye Anatomy[9,10,11,12]

The eye sits in a protective bony socket called the orbit. Six extraocular muscles in the orbit are attached to the eye. These muscles move the eye up and down, side to side, and rotate the eye. The extraocular muscles are attached to the white part of the eye called the sclera. This is a strong layer of tissue that covers nearly the entire surface of the eyeball.

2.1 The Surface of the Eye: The surface of the eye and the inner surface of the eyelids are covered with a clear membrane called the conjunctiva.

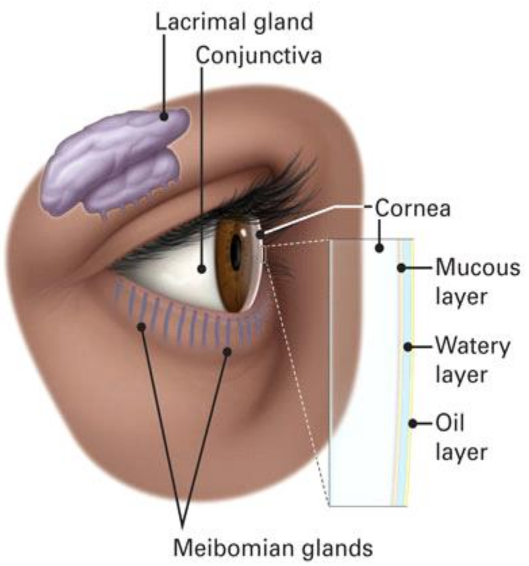

Fig. No 01. The layers of the tear film keep the front of the eye lubricated.

Tears lubricate the eye and are made up of three layers. These three layers together are called the tear film. The mucous layer is made by the conjunctiva. The watery part of the tears is made by the lacrimal gland. The eye's lacrimal gland sits under the outside edge of the eyebrow (away from the nose) in the orbit. The meibomian gland makes the oil that becomes another part of the tear film. Tears drain from the eye through the tear duct.

2.2. The Front of the Eye: Light is focused into the eye through the clear, dome-shaped front portion of the eye called the cornea. Behind the cornea is a fluid-filled space called the anterior chamber. The fluid is called aqueous humor. The eye is always producing aqueous humor. To maintain a constant eye pressure, aqueous humor also drains from the eye in an area called the drainage angle.

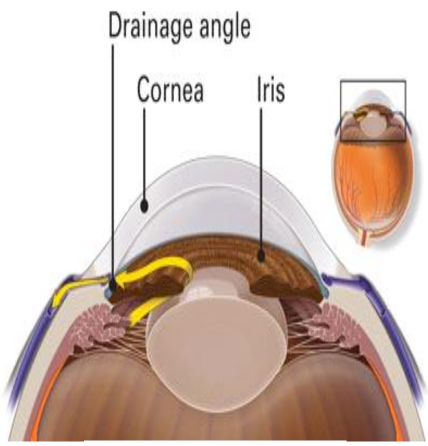

Fig. No. 2: front of eye.

Behind the anterior chamber is the eye's iris (the colored part of the eye) and the dark hole in the middle called the pupil. Muscles in the iris dilate (widen) or constrict (narrow) the pupil to control the amount of light reaching the back of the eye. Directly behind the pupil sits the lens. The lens focuses light toward the back of the eye. The lens changes shape to help the eye focus on objects up close. Small fibers called zonules are attached to the capsule holding the lens, suspending it from the eye wall. The lens is surrounded by the lens capsule, which is left in place when the lens is removed during cataract surgery. Some types of replacement intraocular lenses go inside the capsule, where the natural lens was. By helping to focus light as it enters the eye, the cornea and the lens both play important roles in giving us clear vision. In fact, 70% of the eye's focusing power comes from the cornea and 30% from the lens.

2.3. The Back of the Eye: The vitreous cavity lies between the lens and the back of the eye. A jellylike substance called vitreous humor fills the cavity.

Light that is focused into the eye by the cornea and lens passes through the vitreous onto the retina — the light-sensitive tissue lining the back of the eye. A tiny but very specialized area of the retina called the macula is responsible for giving us our detailed, central vision. The other part of the retina, the peripheral retina, provides us with our peripheral (side) vision.

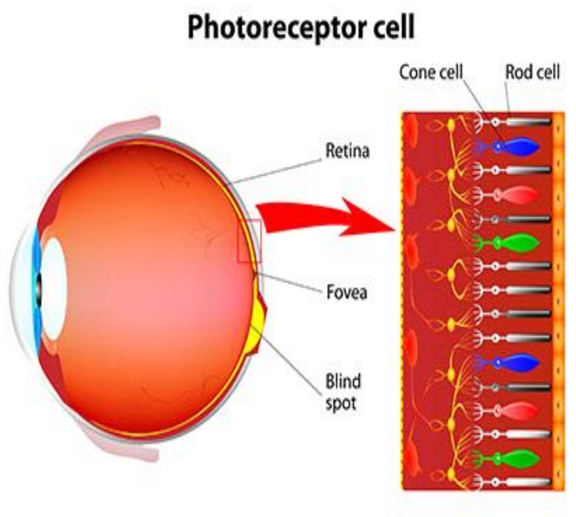

Fig. No.03: Photoreceptor cell.

The retina has special cells called photoreceptors. These cells change light into energy that is transmitted to the brain. There are two types of photoreceptors: rods and cones. Rods perceive black and white, and enable night vision. Cones perceive color, and provide central (detail) vision. The retina sends light as electrical impulses through the optic nerve to the brain. The optic nerve is made up of millions of nerve fibers that transmit these impulses to the visual cortex — the part of the brain responsible for our sight.

3. Ocular Diseases

3.1. Cataract

Cataract is chief cause of loss of vision worldwide. About 40–60% of blindness in the world is caused as a complication of cataract.[1] As said by the National Programme for Control of Blindness and Visual Impairment, the major reason of avoidable blindness in India is cataract (62.6%).[2] Cataract could be defined as the development of cloudiness/opacification in the eye lens. The risk factors include exposure to UV light, diabetes, bad nutrition, genetic determinism, and smoking. Cataract could be divided into three types: cortical, nuclear, or posterior subcapsular.

3.2. Glaucoma

Glaucoma is a famous optic neuropathy disease. Symptoms start with blurred vision that progresses into irreversible blindness in the late stage. It leads to blindness as a result of slow deterioration of optic nerve axon and fatality of retinal ganglion cells.[3] It is commonly connected with elevation in intraocular pressure (IOP) because of irregular formation or obstruction of the aqueous humor.[12] Risk factors include age, race, diabetes, genetics, nearsightedness, migraine, and retinal vascular caliber. Glaucoma is more common in women population as they represent 55% of open angle glaucoma, 70% of angle closure glaucoma, and 59% of all forms of glaucoma in 2010.[1] Worldwide incidence is estimated at 76 million at 2020 and is expected to elevate to 112 million by 2040.[13] There are two types of glaucoma: open angle and closed angle. Open angle glaucoma has no symptoms and is characterized by enlarging optic disc cupping and visual field that results in elevated prevention of drainage of aqueous humor through trabecular meshwork. However, closed angle is characterized by the elevated pressure resulted from the blockage of outflow pathways.[15] About 76 million people suffered from glaucoma and the number is expected to reach 112 million by 2040.[6] brimonidine tartrate.[12]

3.3. Age-Related Macular Degeneration (AMD)

AMD is one of the main causes of loss of vision in developed countries. It is more frequent above the age of 50 years.[17] About 8.7% of worldwide blindness is initiated by AMD AMD.[8] Nearly 196 million people suffered from AMD at 2020 and the number is expected to reach 288 million by 2040.[18] It is a multifactorial degenerative complaint involving the posterior segment of the eye. Risk factors include aging, smoking, bad nutrition, high blood pressure, and immobility. There is no remedy for AMD till now, but its progression may be reduced by proper medications.[19] AMD could be divided into two types, dry (atropic or non-exudative) and wet (neovascular or emulative). Irregular angiogenesis (development of new blood vessels) in the retinal epithelium is the main character of AMD and results in drusen (yellow deposits under the retina), atropy, and separation of bruch's membrane.[20]

3.4. Conjunctivitis

Conjunctivitis is generally the most frequent ocular compliant. It is simply the inflammation of conjunctival tissue. It affects all ages, races, and genders.[20] According to the cause, it may classified into infectious or non-infectious. Infectious conjunctivitis results from microbial infection, while non-infectious conjunctivitis results from allergens and irritants [1 HYPERLINK "https://link.springer.com/article/10.1208/s12249-023-02516-9"5]. Symptoms of conjunctivitis include eye redness, eye discomfort, tears, and elevated eye secretions. Prevalence of allergic conjunctivitis is nearly 40% of global population.[21] Treatments of conjunctivitis include topical administration of antimicrobial (infectious) or anti-inflammatory agents (non-infectious).

3.5. Diabetic Retinopathy (DR)

Diabetic retinopathy is particular vascular complication related to both types of diabetes mellitus. About 60% of patients of type II and all patients of type I diabetes have a certain extent of retinopathy after 20 years of diabetes. Oxidative stress and inflammation result from the upregulation of proinflammatory mediators initiated by hyperglycemic disorders are the cause of development of DR. It is the third major trigger to blindness in the USA. After cataract and corneal blindness, the first and second triggers to blindness. types, proliferative and non-proliferative and both of them result eventually in progressive damage to the retina. Nowadays, diabetic retinopathy is managed through laser photocoagulation, vitrectomy, and pharmacological treatments. Laser photocoagulation works by closing the leaky blood vessels and possibly avoids blindness, but results in laser scar.

3.6-Retinoblastoma

Retinoblastoma is a malignant tumor distressing the retina and mainly prevails in children younger than 5 years old. Untreated retinoblastoma leads to blindness and finally mortality (99%). Its frequency is about 1 out of 20,000 live births.[29] Its occurrence rate is equal in both gender. It is caused due to mutation in tumor suppressor gene RB1 encoding for retinoblastoma protein. It could be unilateral (60%) or bilateral (40%).[1] The handling choices of retinoblastoma include radiotherapy, cryotherapy, systemic chemotherapy, and surgery. Latest studies propose that release of compensatory proangiogenic factors and angiogenic blood vessels development are the vital phases for treating retinoblastoma [2 HYPERLINK "https://link.springer.com/article/10.1208/s12249-023-02516-9"0].

3.7. Fungal Keratitis

Fungal keratitis occurs only in traumatic cornea, since healthy cornea would not allow any fungal infection. It is caused by different fungus like *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, and *Candida parapsilosis*.[31] Fungal keratitis represents 40% of the contagious keratitis in developing countries of third world.[1] Risk factors may be ocular (trauma, contact lens, prior corneal surgery, and topical corticosteroids) or systemic (diabetes, HIV positivity, and leprosy). Fungal keratitis leads to impaired wound healing, corneal ulceration, and stromal inflammatory infiltration. The corneal inflammation may alter miRNA expression [2 HYPERLINK "https://link.springer.com/article/10.1208/s12249-023-02516-9"2]. Oral or topical antifungal drugs are used to treat fungal keratitis. Corneal surgery approach could be required when the medicines are useless. In some situations, vision may not be restored even after surgery. Many papers consider the treatment of fungal keratitis. Younes *et al*. developed topical Sertaconazole nitrate loaded cubosomes and mixed micelles with enhanced safety and antifungal activity.[21,25] Figure 2 illustrates various ocular diseases

3.8. Ocular Drug Delivery Systems[23]

- Increased accurate dosing. To overcome the side Effects of pulsed dosing produced by conventional Systems.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by Increasing the corneal contact time. This can be achieved By effective adherence to corneal surface.
- To provide targeting within the ocular globe so as to Prevent the loss to other ocular tissues.
- To circumvent the protective barriers like drainage, Lacrimation and conjunctival absorption.
- To provide comfort, better compliance to the patient And to improve therapeutic performance of drug.
- To provide better housing of delivery system.
- They can easily administered by the patient himself.
- They have the quick absorption and less visual and Systemic side effects.
- Ocular drug delivery system has better patient Compliance.

3.8.1. Disadvantages Of Ocular Drug Delivery System[21]

- The drug solution stays very short time in the eye Surface.
- It shows poor bioavailability.
- Shows instability of the dissolved drug.
- There is a need to use preservatives.

3.8.2. Limitations Of Ocular Drug Delivery[21]

- Dosage form cannot be terminated during emergency.
- Interference with vision.
- Difficulty in placement and removal.
- Occasional loss during sleep or while rubbing eyes.

4. Approaches to improve ocular bioavailability

4.1. Use of viscosity enhancers

Viscosity-increasing polymers are highly preferred additive in the Ophthalmic formulations due to their properties of enhancing viscosity And thereby imparting benefit to the penetration of the drug into the Anterior chamber of the eye by lowering the elimination rate from the Preocular area, resulting in increase in precorneal residence time and Transcorneal penetration, but having very fewer effects for enhancing Bioavailability in human beings. Examples of polymers are polyvinyl Alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, Hydroxylethylcellulose, hydroxylpropyl methylcellulose (HPMC) and Hydroxypropyl cellulose.[21] As per Saettone et al. (1984), in their Study of tropicamide solution, by using PVA, HPMC, and PVP solution, At concentrations yielding the same viscosity of 20 cst, PVA has been Reported to be the most effective among all, probably due to the Adhesive property of PVA and its capability to enhance the thickness of The precorneal tear film.[21] Saettone et al. (1982) have stated in their Study that the retention of drug in the precorneal tear film does not Strictly belong to vehicle viscosity, but also with surface spreading Properties of the vehicle and to the capability of a polymer to use Water as the vehicle spreads over the ocular surface with each eye Blinking.[22]

4.2. Gel formulation

Gels are known to be significantly dilute cross-linked systems, which Show rigidity in the steady-state. Gels are generally liquid, but behave Like solids due to their three-dimensional cross-linked structure within The liquid.[23-25] On the other side, if the gels have extremely high Viscosity, they cannot improve bioavailability; instead, they will Control the release, which leads to reduced frequency of dosing to once A day. The highly viscous solution even leads to blurred vision and Matted eyelids, which substantially decrease patient's compliance. In Aqueous gel, viscosity building agents, such as PVA, polyacrylamide, Poloxamer, HPMC, Carbomer, polymethylvinylether, Maleic anhydride, And hydroxylpropylethylcellulose are incorporated, whereas hydrogel Or swellable water-insoluble polymers give rise to controlled drug Delivery systems.[26]

4.3. Prodrug formulation

By the development of prodrugs, many properties of the formulation Can be improved, which make it suitable for increasing drug Permeability through the cornea. It includes modification of the Chemical structure that imparts new characteristics to the active Moiety i.e. site-specificity and selectivity.[24] This can be explained Through examples; the formulations which have been developed as Prodrugs, are epinephrine, phenylephrine, timolol, and Pilocarpine. Other prodrugs are dipiverine, diester of pivalic acid and Epinephrine showing seventeen fold more permeability via cornea As compared to that of epinephrine, which is caused by its six Hundred folds more lipophilicity at pH 7.2. So a minor dose of the Drug solution (dipiverine), spreads over the entire eyeball and has a Therapeutic effect exactly the same as of epinephrine. When Compared with conventional eye drops consist of 2% epinephrine, Eye drops of dipiverine 0.1% show only mild activity by lowering the Intraocular pressure with a significant reduction of side effects.[28]

4.5. Penetration enhancers

Corneal epithelial membrane plays an important role in terms of Permeability. So, by increasing its permeability, the transport Property around cornea can be enhanced.[19,20] Agents showing Such properties are chelating agents, preservatives (like Benzalkonium chloride), surfactants and bile acid salts, but due to Local toxicity, they cannot be used in development ophthalmic Formulation.[21,22]

4.6. Approaches for controlled and continuous ocular drug delivery

The following ocular drug delivery systems have been reported for Controlled as well as continuous release of drugs.

4.6.1-Liposomes

Liposomes are defined as microscopic vesicles which consist of one or More concentric lipid bilayers, divided via water or aqueous buffer Compartments. Liposomes are widely used in ocular formulations due to Their property of having intimate contact with eye surfaces, mainly Corneal and conjunctival area, thus drug absorption through ocular route Can be increased.[33] Formulation of liposomes can be developed by Using phosphatidylcholine, stearylamine and various amounts of Cholesterol or lecithin and L-dipalmitoyl-phosphatidylcholine.[24-27] Major advantages of this type of delivery system are due to their Properties, i.e., biocompatibility, biodegradability, amphiphilic property, Relative toxicity.

4.6.2-Niosomes

Niosomes are chemically stable, bi-layered nanocarriers made up of Nonionic surfactants and used as carriers for both hydrophilic and Hydrophobic drugs. They do not have drawbacks like liposomes that Are chemical instable, susceptible to oxidative degradation and made Up of phospholipids that are very much unstable as well as Expensive.[21] Thus, niosomes have lots of advantages Including that they are biodegradable, biocompatible and Nonimmunogenic, which make them increase the contact time Between drug and cornea, thereby increasing the bioavailability of Drugs. A modified form of niosomes is desmosomes that also acts as Carrier for ophthalmic drugs. The size of desmosomes lies between 12 To 16 .This gives it a benefit of not allowing it to enter in the General circulation and its disc shape provides better fit into the Conjunctival sac.[21] The size of desmosomes makes it different from Niosomes, as the former consists of nonionic surfactants and SolulanC[24], a derivative of lanolin and a mixture of ethoxylated.

4.6.3-Nanoparticles/nanospheres

These are polymeric colloidal particles, size varying from 10 nm to 1 nm, Where the drug is being dissolved, entrapped, encapsulated, or adsorbed.[23] 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 polylactics (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.

4.6.4. Nanosuspension and nanodispersions

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.

4.6.5. Microemulsion

A stable dispersion of water in oil, facilitated by adding surfactant and Co-surfactant in combination in a way to decrease interfacial tension, is Termed as a microemulsions. Microemulsion leads to decrease in Administration frequency and enhancing ocular drug bioavailability. Major advantages of this dosage form are its high thermodynamic Stability, smaller droplet size, i.e., 100 nm (approx.) and clear Appearance. Ansari et al. (2008) have reported a microemulsions Formulation, which is an oil in water system consisting of pilocarpine as a Drug, lecithin, propylene glycol, PEG 200 as surfactant/co-surfactants And isopropyl myristate forming the oil phase.[19]

4.6.6. Ocular inserts

Ophthalmic inserts are solid patches, which, when placed in the Conjunctival sac of the eye, slow down the rate of drug release. Ocular inserts also overcome the problem of frequent dosing by Maintaining drug concentration in an effective manner and give rise To controlled, sustained and continuous drug delivery. Ocular Inserts Also have various advantages like enhanced drug absorption due to Increased contact time and minimized.

4.6.7. 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. Implants can be categorized into two types Based on the characteristics of the polymer(s) used.

5. CONCLUSION

The effective management of ophthalmic diseases remains a difficult mission as a result of existence of many ocular obstacles in the anterior and posterior sections of the eye. There are many ocular routes of administration that are used in order to deliver the medication into the targeted site of action such as topical, intraocular, periocular, or in conjugation with ocular devices. Several approaches and technologies have been adopted in order to minimize dosing interval, administrated dose, and unwanted effects and to enhance ocular retention time, drug permeation efficacy, and ocular bioavailability via controlled and sustained drug delivery systems.

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