WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Ocular Drug Delivery Systems – An Overview

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ABSTRACT :

The objective of this review is to present an update on the current knowledge within this field of ocular drug delivery system (ODDS). The unique anatomy of the eye makes it is a protected organ and structure restrict entry of the drug into the site of action. There is a lots of route of choice for drug delivery but the ODDS becomes the most compelling and attractive attempt in frond of pharmaceutical science. Different technique in ODDS have been devloped to enhance the bioavailability and to increase the contact time of topically applied drugs to the eye. In an opthalmic dosage from the reduced bioavailability is due to different ocular barriers. The different Nano formulation have been introduced for anterior as well as posterior segment of ocular drug delivery. These novel devices or formulations are easy to formulae, to irritating, high peroneal residence time, and enhance ocular biovailability of therapeutic. In this review the various new drug delivery system applied in the eye such as nanoparticles, Nano suspention, liposomes, noisome and viscosity enhancers etc. are discussed.

Keywords:Ocular delivery, Bioavailability, opthalmic, nanoparticles, Liposomes.

1.0 Introduction:

The eye is a complex organ and unique both anatomically and physiologically. Novel approachdrug can be installed on the cull-de sac or conjunctival cavity of eye is known as ODDS (S Rawat,et al.,2020). The normal volume of tear fluid in the cul-de sac is about 7-8 micro liter. Ophthalmic formulation or preparation are specialized sterile preparation of dosage form. Drug can be installed on to the external surface i.e. topical, administered inside i.e. intraocular or adjacent i.e. periocular to the eye. the one of the most interesting and challenging task of ODDSis faced by the pharmaceuticals and researchers. the characteristics structure of the eye restricts the entry of the drug molecule at the specific site of action(KP Sampath kumar,et al.,2013)in ODDS most commonly used administered dosage form are suspension, solution & ointment. poor bioavailability of drug can occur due to peroneal loss factors which includes lacrimation, solution drainage, tear dilution, tear turnover, conjunctival absorption, transient residence time in the cull-de sac or conjunctival cavity, and the major challenges are relative impermeability of the corneal epithelial membrane. Various approaches that have been assaying to increase the bioavailability as well as duration of therapeutic action of Ocular drug i.e. ocular insert, Nano suspension, micro emulsion, liposomes, noisome, nanoparticles and dendrimers etc. this review will provide an overview on advantage and disadvantage of ODDS, various barrier to drug permeation, drug selection criteria for Ocular drug delivery and novel approach (A.Patel,et al.,2013)

- **Important factor has to be considered when attempting Drug delivery system to the eye:**

(1) How the blood- eye barrier (systemic to ocular) or cornea (external to ocular) is crossed by the drug to reach the site of action.
(2) How to prolong the duration of drug such as frequency of drug Administration can be reduced.
(3) How to localize the pharmacodynamics action at the eye and minimize drug action on other tissue(S.Palani et al.,2010).

The pharmaceutical scientist's most compulsive and demanding delivery mechanism is ocular drug delivery. The eye's particular shape, function, and biology make it highly impervious to outside chemicals. The formulator's main goal is to get beyond the eye's protective barriers without inflicting long-term tissue damage. These types of barriers have a significant impact on ophthalmic drug bioavailability. The quick and broad removal of conventional eye drops from the eye is the fundamental challenge in ophthalmic medication delivery systems. As a result of the difficulty, a significant amount of medicine is lost. Only a small amount of medication goes through the corneal layer and into the eye's inner tissue. Lachrymal drainage and medication dilution by tears are the two most common types of drug loss.

Ocular drug delivery is one of the most fascinating and challenging tasks that formulators face. As a result, effective ocular medication delivery has remained a difficulty to date. Because of the eye's unique physiology, anatomy, and biochemistry, it is resistant to some active molecules; thus, efficient eye medication delivery systems should be devised by technologists with the goal of overcoming ocular barriers with minimal tissue damage. Poor ocular bioavailability of standard eye formulations is caused by physiological barriers such as nasolacrimal drainage, tear dilution, and tear turnover. The human eye, in particular, is such a complex organ due to its anatomy, physiology, and biochemistry that it is almost impervious to external molecules, including drugs." The eye's unique anatomy and physiology contribute to its high level of protection, which prevents drugs from entering the

target site of action. The human eyeball is spherical in shape, with a diameter of nearly one inch. It is covered by a number of layers and interconnected complexes, each of which serves a different purpose while assisting vision. There are three main layers to the eye: The outer layer, known as the sclera, and the cornea; the middle layer, known as the vascular tunic, which consists of the iris, the choroid, and the ciliary body; and the inner layer, known as the nervous tunic, which consists of the retina and photoreceptors. The tear film's makeup is determined by the discharge of electrolytes, fluid, and mucins by the t- conjunctiva, which consists of the outer epithelium and its underlying stroma. The epithelium, Bowman's membrane, the lamellar stroma, Descemet's membrane, and the endothelium are the five layers that make up the cornea, which is the main channel for intraocular absorption. The surrounding sclera and cornea protect and hold the retina, the tissue that lines the inner eye surface and surrounds the vitreous chamber, in the proper position. Furthermore, the aqueous humour is a jelly-like liquid that fills the "anterior chamber of the eye," which is located behind the comea and in front of the lens, and is located in the outer chamber of the eye. The "eye colour" is determined by the iris, which is visible through the comea. The posterior layer of all irises is darkly pigmented, however the quantity of pigment in the anterior or stromal layer is responsible for a variety of colours. The iris' primary function is to control the pupil's size(N.U.Okur*et al*., 2020).

To optimize ophthalmic drug delivery systems the following characteristics are required:

- Sterility
- Isotonicity
- Minimum protein binding
- Less drainage tendency
- Buffer/ pH adjustment
- A continued contact time of drug with corneal tissue
- Easiness in installation and removal.
- A non-irritative form
- Good rheological properties
- **Advantages of Ocular drug delivery system:-**

1) It provides controlled drug delivery systems.
2) Better shelf life and no preservatives.
3) It increases the bioavailability of drug by increasing the corneal contact time.
4) it provides better patient compliance and reduced administration frequency.
5) increase in shelf life due to absence of water.
6) The make self- administration of drug is possible.
7) hey bypass the protective ophthalmic barriers, such as drainage, conjunctival absorption and lacrimation.
8) It provides targeting within the Ocular globe so as to prevent the loss to other ocular tissue.
9) It has less visual and systemic side effects.
1) **Limitation of Ocular drug delivery system:-**
1) Some devices are difficult to insert and remove.
2) It is difficult to handle.
3) It is expensive.
4) There is occasional loss while rubbing eyes.
5) In emergency dosage form cannot be terminated.
6) Feeling movement around the eye.
7) Instability for dissolved drug.
8) Feeling foreign body sensation.
9) A very short time solution stays at the surface of eye.
10)A very short time the solution stays at the surface of the eye.

2.0 Historical Development:

Today, there is a growing interest in innovative medication delivery systems, with increased research and funding. Despite the long history, numerous firms are collaborating on the development of long-lasting medication delivery systems for both the anterior and posterior segments. Despite the fact that glaucoma affects the optic nerve, it is nonetheless treated as an anterior segment illness. The anterior segment is used to administer pharmacological therapy for glaucoma. Sustained release technology for glaucoma treatment is being investigated by a number of businesses. Alza Corporation was the first company to introduce a medicine delivery system for the eyes in the 1970s. Ocusert was a one-week

pilocarpine delivery implant that was implanted in the conjunctival sac. It was deemed ineffective since it caused patient suffering, thus it was scrapped. It took another 20 years for Chiron Vision to introduce vitrasert, the world's first intraocular medicine delivery implant, in 1995. The orphan disease CMV retinitis, an opportunistic infection associated with HIV, was treated with vitrasert, which administered ganciclovir to the back of the eye. This was the first time surgeons were able to implant a drug-delivery device into the posterior portion of the eye over a period of 4 to 6 months, which was a huge step forward for patients. The product was launched at a price of $4,500, which was shocking at the time, but it was justified considering the device's ability to distribute medicine for such a long period of time for this unmet medical need. The next intraocular implant did not appear for another almost ten years. Bausch + Lomb was founded in the year 2005. Retisert employed the same technology as Vitrasert but was smaller because the business had bought Chiron Vision's technology. The FDA approved it for the treatment of noninfectious posterior uveitis, an orphan illness with a treatment time of more than 32 months. With the introduction of the anti-VEGF medication ranibizumab in 2006, the pharmacologic environment for the posterior region shifted substantially (Lucentis, Genentech). The treatment of neovascular age-related macular degeneration, DME, and macular edoema following retinal vein closure with this large-molecule biologic medication is suggested. Aflibercept (Eylea, Regeneron), a second new large-molecule anti-VEGF biologic, was released a few years later. Companies began to see the potential of creating implants as vehicles for medicine delivery to the back of the eye after the release of this second product. Allergan introduced Ozurdex (dexamethasone implant 0.7 mg) in 2009, which differed from previous implants in that it did not require a trip to the operating room. Another milestone was the first time a drug delivery implant could be injected in a clinic setting. Iluvien (fluocinolone acetonide implant 0.19 mg) was introduced by Alimera Sciences in 2011, and it contains the same steroid as Retisert but is smaller and can be injected rather than implanted. Iluvien is a drug that is used to treat DME. Dextenza (dexamethasone ophthalmic insert 0.4 mg) was approved by the FDA in 2018 to treat ocular pain after ophthalmic surgery, according to Ocular Therapeutic. For up to 30 days, the intracanalicular insert delivers medication to the ocular surface.

3.0 Anatomy of Eye:

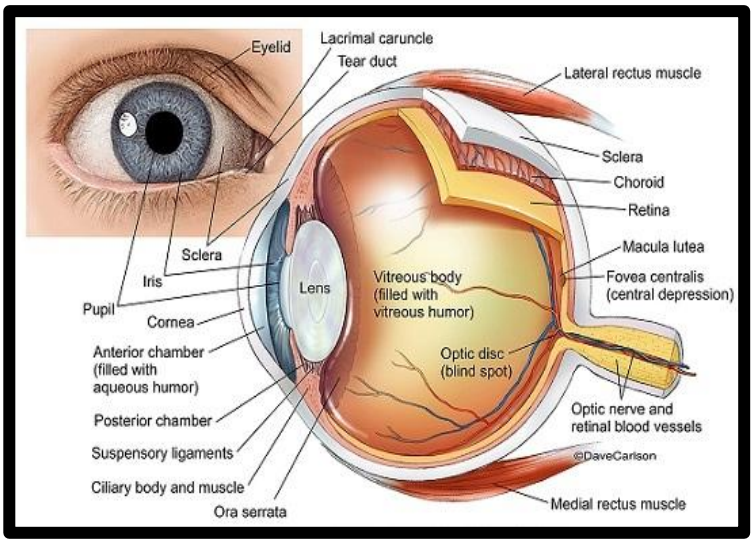

Fig 1: Anatomy of Eye

- **Sclera**

Collagen fibres and proteoglycans embedded in an extracellular matrix make up the majority of the sclera. Scleral permeability is proportional to molecule radius and decreases approximately exponentially. The posterior sclera has a looser weave than the anterior sclera, and the human selera is somewhat thick towards the limbus (0.53 + 0.14 mm), thin at the equator (0.39 + 0.17 mm), and substantially thicker near the optic nerve (0.9-1.0mm). Lower permeability in selera is associated with an increase in hydrophobic/lipophilic medicines. Hydrophilic medications are more likely than lipophilic pharmaceuticals to pass through the aqueous medium of proteoglycans in fibre matrix pores. The permeability of a medicinal molecule across the sclera can be affected by its charge. Because of their positive charge, positively charged medicines have a lower permeability.

- **conjunctiva**:

The conjunctiva serves to protect the eye while also forming and maintaining the precorneal tear film. The conjunctiva is a thin transparent membrane that covers the inside of the eyelids and reflects light onto the globe. An epithelium, a highly vascularized substantia propria, and a sub mucosa make up the conjunctiva. 7 The bulbar epithelium is made up of 5 to 7 layers of cells. The corneal epithelial cells are joined by tight connections, making the conjunctiva more impermeable, similar to a pallisade rather than a pavement. The conjunctiva allows molecules up to 20,000 Da to pass through,

however the cornea is limited to molecules larger than 5000 Da. The human conjunctiva absorbs between 2 and 30 times more medicines than the cornea. It suggested that drug loss via this mechanism is a primary avenue for medication clearance. The presence of 1.5 million globlet cells varies with age depending on intersuject variability and age, resulting in the greatest density of conjunctiva. Because of the large variance in goblet cell density, vernal conjunctivitis and atopic kerato conjunctivitis develops with only a slight differential in tear mucin content(N.V.Karbhari*et al*.2016).

- **Retina**

The retina is a layer of tissue that covers the back of the human eye. The retina can be thought of as a "screen" on which light that has travelled through the cornea, aqueous humour, pupil, lens, and ultimately the vitreous humour before reaching the retina forms a picture. Theretina's job isn't only to be a screen on which an image can be generated; it also collects the information contained in that image and sends it to the brain in a way that the body can understand. As a result, the retinal "screen" lining the interior of the eye is a light-sensitive structure. It is made up of photosensitive cells (called rods and cones) and nerve fibres that transform the light they perceive into electrical signals(R.Dhanpal,*et al*.,2012).

- **Choroid**

The choroid layer, which is located behind the retina, absorbs unneeded radiation and feeds the retina's outer layers. It is a thin, dark brown membrane that is highly vascular (i.e., it has blood vessels) and contains a pigment that absorbs excess light and so prevents impaired vision (due to too much light on the retina). One of the highest blood flows in the body is in the choroid. The lamina fusa is a thin layer of tissue that connects the choroid to the sclera's inner surface.

- **Optic nerve**

The optic nerve (a bundle of over one million nerve fibers) transmits nerve signals from the eye to the brain. These nerve transmissions carry picture information for the brain to process. The optic nerve refers to the visible front surface of the optic nerve on the retina. (R .Dhanapal,*et al*.,2012).

- **Iris**

It's the colored portion of the eye that helps regulate how much light gets in. The iris is a thin circular contractile curtain that lies behind the cornea and in front of the lens. The iris' job is to control the quantity of light that enters the eye by adjusting the size of the pupil.

- **Ciliary Muscle:**

The ciliary muscle is a ring of striated smooth muscles in the central layer of the eye that regulates accommodation for viewing objects at different distances. The curvature of the lens changes as the ciliary muscle contracts and relaxes.

- **Pupil:**

The amount of light allowed into the eye is determined by a dark opening in the iris. The pupil appears to be the dark "centre" of the eye, but it is actually the circular aperture in the centre of the iris through which light travels into the eye."

- **Cornea:**

The clear, translucent bulging cornea at the front of the eye that transmits images to the nervous system's back end. The adult cornea has a radius of about 7-8mm and covers about one-sixth of the total surface area of the eye ball. It is a vascular tissue to which nutrients and oxygen are supplied via lachrymal fluid and aqueous humour, as well as blood vessels of the cornea-sclera junction in fig.1. The epithelium, bowman's layer, stroma, descemet's membrane, and endothelium are the five layers that make up the cornea, which is the principal conduit for drug absorption into the eye. 5 10 6 layers of cells make up the epithelium. The middle corneal thickness is 0.5-0.7 mm.The corneal epithelium is the principal barrier to drug absorption into the eye, in contrast to several other epithelial tissues (intestinal, nasal, bronchial, and tracheal) that are comparatively impervious. The epithelium is squamous stratified (5-6 layers of cells), with a thickness of 50-100 um and a daily cell layer turnover of roughly one. The basal cells have a tight connection that serves as a barrier against dust particles and most bacteria, as well as medicine absorption. The principal channel for drug penetration across the corneal epithelium is the transcellular or paracellular pathway. Lipophilic medications use the transcellular route to penetrate, whereas hydrophilic drugs use the paracellular route (passive or altered diffusion through intercellular spaces of the cells). The Bowman's membrane is an 8-14m thick cellular homogenous layer that lies between the epithelium's basement membrane and the stroma. The stroma, also known as the substaniapropria, makes up around 90% of the corneal thickness and contains about 85% water as well as 200-250 collagenous lamellae. The lamellae give physical strength while maintaining the membrane's visual transparency. The hydrophilic solutes diffuse through the open structure of the stroma. The endothelium secretes the descemet's membrane, which lies between the stroma and the endothelium(N .V .Karbhari *et al*., 2016).

- **Commonly caused Eye infection:**

Bacteria are the causative pathogens for a large number of eye infections. In addition virus, fungus and protozoans also cause eye infections. As such, eyes are prone to number of diseases but more commonly found are mentioned here.

- Conjunctivitis.
- Blepharitis.
- Keratitis.
- Cataract.
- Iritis (anterior uveitis).

- Glaucoma.(k.p.sampthKumar,*et al*.,2013).

4.ROUTES OF OCULAR DRUG DELIVERY:

1) Topical route

Eye drops are commonly used to administer topical ocular drugs, although they only have a short contact period on the eye surface. Formulation design can extend the length of contact, and thus the duration of medication effect (e.g. gels, gelifying formulations, ointments, and inserts).

2) Subconjunctival administration

Subconjunctival injections have traditionally been used to transfer medications to the uvea at higher concentrations. For a variety of reasons, this method of drug delivery is currently gaining traction. Progress in materials science and pharmaceutical formulation has opened up new doors for developing controlled release formulations to deliver medications to the posterior segment and direct the healing process following surgery.

3) Intravitreal administration

Direct medication administration into the vitreous has the specific benefit of allowing for easier access to the vitreous and retina. It should be emphasised, however, that due to the RPE (Retinal Pigment Epithelium) barrier, transport from the vitreous to the choroid is more difficult. Small molecules can move quickly through the vitreous, whereas big molecules, especially those that are positively charged, have limited mobility. (N.V.Karbhari*et al*.,2016).

4) Intracameral route

In this method of administration, a drug's site of action is the anterior or posterior chambers of the eye. It's proven by injecting anaesthesia into the anterior chamber of the eye, which is normally done after surgery.

5) Perilocular route

In this route of administration, the medication is given around the eye. Peril ocular steroid injection, which involves injecting steroids around the eye to alleviate intraocular inflammation or edoema, explains it.

6) Suprachoroidal route

In this method of administration, the supra choroid region of the eye is the target. Suprachoroidal space refers to the area between the sclera and the choroid.

7) Systemic route

The blood-aqueous barrier (BAB) and the blood-retinal barrier (BRB) for the anterior and posterior portions of the eye, respectively, are common barriers to the systemic administration of ophthalmic medicines.

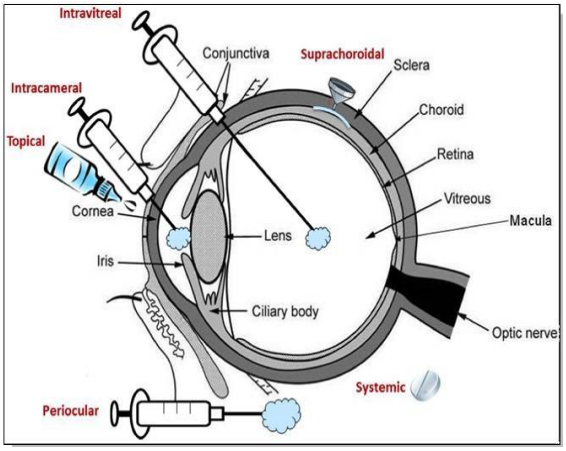

Fig. 2. Route Of Ocular Drug Delivery

5.0 Barriers for ocular drug delivery :

1)Drug loss from the ocular surface:

After using the dosage form of the drug in the ocular system, flow of lacrimal fluid wipes out a portion of the drug from its surface and its turnout rate is only about 1 ul/min, whereas, a major portion of the drug is wiped out through the nasolacrimal duct quickly within minutes. Other sources of drug removal include the systemic absorption of the drug, instead of being absorbed through the ocular route. Systemic absorption is mostly directed through

the conjunctival sac to the local blood capillaries or takes place after the solution flows to the nasal cavity .

2)Lacrimal fluid-eye barriers:

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

3)Blood-ocular barriers:

Blood-ocular barriers are present in the bloodstream, which protect the eye from xenobiotics. It comprises of two parts, namely blood aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of endothelial cells in the uvea, i.e., the middle layer of the eye below sclera, iris, ciliary body and choroid. This barrier works to prevent the entry of hydrophilic drugs present in plasma to the aqueous humor and also limits the entrance of plasma albumin in aqueous humor. The posterior barrier which resides in between the eye and stream of plasma consists of retinal pigment epithelium (RPE) and retinal capillaries, resulting in tight wall junction. Choroid vasculature comprises of extensive blood flow and leaky walls, due to which easy access of drugs occurs in the choroidal extravascular spchoroida but again their distribution in the retina is limited due to the presence of RPE and retinal endothelium.(V.K. Raj, *et al.*,2020).

6.0 Drug selection criteria for Ocular drug delivery:

- **Solutions**

Solutions are commonly used to give drugs that have an effect on the eye or the eye surface. Ophthalmic solutions are sterile and do not contain any foreign particles. For topical delivery of medicines to the eye, solutions are a common dose form. Solubility, ocular toxicity, pka, ph effect, tonicity, buffer capacity, viscosity, compatibility with other chemicals in the formulation, preservatives to be utilized, and comfort when administered into the eye are the key factors that determine formulations in an ocular drug delivery system.

Advantages

1) Simplicity of large scale manufacture
2) convenience
3) Usually do not interfere with vision of patient

Disadvantages

1) Solution having very short time interval so rapid precorneal elimination from the eye.
2) The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration and the instilled volume.
3) 75% is lost via nasolacrimal drainage so having poor bioavailability.
4) Occular drug delivery having non sustained action.
5) To be administered at frequent intervals.

- **Suspensions**

Suspension is the dispersion of finely split insoluble API in an aqueous solvent containing a suspending and dispersing agent. Another type of non-invasive medication carrier system is an eye topical drop. Because it is retained in the precomeal pocket, ophthalmic suspension improves medication contact time and duration of action when compared to drug solution. When compared to eye drops, these are more complicated.

Suspending agents, wetting agents, buffers, and preservatives are all included in an ophthalmic suspension. Suspending agents are used to prevent sedimentation and improve a suspension's rheological properties. Suspending agents commonly employed in ophthalmic suspensions include cellulosic derivatives such as methyl cellulose, caboxy methyl cellulose, and hydroxyl propyl methyl cellulose, as well as synthetic polymers such as polyethylene glycol.Wetting agents are used to reduce the contact angle between the wetting liquid and the solid surface. Benzalkonium chloride, Benzethonium chloride, Cetylpyridinium chloride, Nonoxynol 10, Octoxynol 9, Poloxamer, Polyoxyl 50 stearate, Polyoxyl 20 cetostearyl ether, Polyoxyl 40 stearate are some of the most commonly used wetting and solubilizing agents.

- **Emulsion**

There should be no indication of breaking or coalescence in ophthalmic emulsions, which are mainly dispersions of oily droplets in an aqueous phase. An emulsion-based formulation offers the benefit of improving medication solubility and bioavailability. There are two types of emulsion systems that are commercially employed as carriers for active pharmaceuticals: water in water (o/w) and water in oil (w/o). For ophthalmic medication delivery, o/w emulsion is commonly used and highly favoured over w/o system due to reduced irritation and improved ocular tolerance. The advantage of this sort of formulation is that the medicine is released from the vehicle for a longer period of time. The disadvantages of emulsion are patient noncompliance.

- **Eye drops:**

Eye drops are saline-based drops that are administered through the eyes. Because the ocular medication delivery system does not reach sufficient drug

concentrations in the posterior tissues, eye drops are primarily employed for anterior segment eye problems. Some properties that affect retention of a solution in the eye include hydrogen ion concentration, osmolality, viscosity, and instilled volume. After delivery of the drug into the eye, only about 5% of the drug is absorbed; the majority of the drug is washed away with the lachrymal fluid or absorbed systemically in the nasolacrimal duct and pharyngeal sites.Antihistamines, steroids (which are widely used in glaucoma patients), beta receptor blockers, prostaglandins, topical anaesthetics, and other ingredients may be present. Some eye drops are available on the market.

- **Recent work done in eye drops**

New Eye Drops Can Dissolve Cataracts with No Need for Surgery Zhang and his research team went on to develop eye drops that contained lanosterol as a drug treatment for cataracts.

- **Ointment**

Ophthalmic ointments are a semisolid dosage form that is typically made from a combination of semisolid and solid hydrocarbons such as paraffin, which have a melting point or softening point that is close to body temperature and are non-irritating to the eye. It is possible to increase contact duration with the external ocular surface by using an ophthalmic ointment carrier, although various drawbacks, such as vision blurring, may limit its use. To ensure sustained effect over a 24-hour period, a pilopine HS gel containing pilocarpine was employed. Various researchers have observed that ointment vehicles can improve the corneal contact time of many medications taken via the topical ocular route, extending the duration of action and increasing drug ocular bioavailability. Externally, ophthalmic ointments are applied to the surface of the eye.

- **Sprays**

Pupil dilation or cycloplegics (paralysis of the cilliary muscle of the eye) examinations are the most common uses for eye spray. Even ophthalmic sprays are not often utilized, but some patients with mydriatics or cycloplegics use eye spray alone or in combination.

- **Viscous Solution**

These solutions are made in the laboratory by adding polymer and increasing the viscosity of eye preparations so that the residence time in the precorneal area can be enhanced, resulting in more transcorneal penetration of the medication into the anterior chamber. It has modest impact on humans in terms of improving bioavailability. Some viscosifying agents, such as cellulose and polyacrylic acid, are used to make the viscous solution. Carbomer and Xanthan gum both have a role in raising the viscosity of these agents. Methylcellulose, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), hydroxyethylcellulose, hydroxypropyl methylcellulose (HPMC), and hydroxyl-propylcellulose are some of the other polymers used. As viscosity enhancers, natural polymers such as HA, veegum, alginates, xanthan gum, gelatin, acacia, and tragacanth can be employed. These, on the other hand, are afflicted.

- **Gels**

Ophthalmic gels are made up of mucoadhesive polymers that deliver an active component to the eye in a targeted manner. These polymers boost ocular bioavailability by extending the drug's contact time with biological tissues. Gellan gum, alginic acid, xyloglucan, pectin, chitosan, poloxamer, gellan gum, sodium alginate are the most commonly used polymers in ocular gels.

Advantages

1) Increase contact time.
2) Greater storage stability.

Disadvantages

1) Blurred vision but less then ointment.
2) Poor patient complianc

7. Novel approaches for ocular drug delivery :

Nanoparticles:

Nanoparticles range in size from 10 to 1000 nanometers. For the delivery of opthalmic drugs. Lipids, protein, and natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA), and polycaprolactone make up nanoparticles. Nanoparticles can be found in the form of nanocapsules or nanospheres in drugs. The medicine is contained within the polymer shell of a nanocapsule. The medication is consistently dispersed throughout the polymeric matrix in nanospheres. Nanoparticles have been gaining attention for Ocular drug delivery in recent days, and a few researchers have loaded nanoparticles for distribution to both the anterior and posterior segments of occular tissue. The most commonly studied nanoparticle for enhancing precorneal residency is chitosan coating. Because chitosan is positively charged, it attaches to the cornea's negatively charged surface.As a result, precorneal residence improves and clearance decreases. When compared to commercial solution, kanamycin-loaded chitosan nanoparticles showed high ocular absorption at a lower dose frequency in rabbit eyes. Nanoparticles have also been chosen as an alternative technique for long-term medication delivery to ocular tissue in the posterior segment. The deposition of nanoparticles for posterior segment delivery is determined by their size and surface properties. A commercialised prolonged drug release in the aqueous humour was achieved using PLA nanospheres colloidal suspension containing acyclovir. Acyclovir concentration is significantly higher than in the free medication

formulation.

Nanosuspension:

Nano suspension is a colloidal dispersion of submicron medication particles stabilized by polymer or surfactant. It has proven to be an effective method for delivering hydrophobic drugs. It has a number of advantages in ocular drug administration systems, including sterilisation, reduced eye irritation, increased precorneal residence time, and increased ocular bioavailability of drugs that are insoluble in tear fluid. Various research studies have established the effectiveness of nanosuspension in enhancing glucocorticoid bioavailability in the eye. Inert polymeric resins are utilised to make the polymeric nanosuspension, which can be used as an important drug delivery vehicle with the ability to improve drug release and bioavailability. Because such carriers have such properties, they can be employed as inert carriers in ophthalmic drugs. Nanosuspension can also change pharmacokinetics parameters, improving the safety and efficacy of medication formulations such as poloxamers, lecithins, Pondoes, and polylobate. Water soluble solvents such as butyl acetate, benzyl alcohol, and other pharmaceutical solvents are used in nanosuspension. Wetting agents are surfactants. ethanol, glycofurol, isopropanol, and other alcohols It has the ability to operate as a co-surfactant. In nanosuspension preparations, buffer salt and osmogene are utilised as additions N gulati.

liposomes:

Liposomes are lipid vesicles with one or more phospholipid bilayers enclosing an aqueous core that are biodegradable and harmless in nature. Liposomes range in size from 0.08 to 10.00 micrometres in diameter. Small unilamellar vesicle (10-100 nm), large unilamellar vesicle (100-300 nm), and multilamellar vesicle are the three forms of liposomes (contain more than one bilayer) Because of their superior biocompatibility, cell-like structure, and capacity to encapsulate both hydrophilic and hydrophobic medicines, liposomes are a suitable technology for ocular formulation. Several research studies have shown that liposomes are efficient for both the anterior and posterior segments of ocular administration. The sonication of phospholipid dispersion, reverse phase evaporation, solvent injection, and calcium induced fusion methods can all be used to make liposomes. These compositions are made up of phosphatidylcholine, as well as additional components such as cholesterol and lipid attached hydrophilic polymer Phospholipids such as phosphatidylcholine, phosphatidic acid, and sphingomyelin are used in the body. Liposomes can cling to the eye's surface for longer periods of time, increasing bioavailability.

Niosomes:

Chemically stable, bilayerd Nano carriers made of nonionic surfactant are obnoxious. Both hydrophilic and hydrophobic drugs are carried by it. Niosomes have a number of advantages, including the fact that they are biocompatible, biodegradable, and nonimmunogenic, allowing them to extend the time the drug is in contact with the cornea, enhancing the drug's bioavailability. Because they chemically entrap both hydrophilic and hydrophobic drugs, niosomes were designed to overcome the limitations of liposomes. Discosomes are a modified type of niosomes. Ophthalmic drugs are also carried by discosomes. This has the advantage of not allowing it to enter the systemic circulation, as well as a better fit in the conjunctival cavity due to its disc form. The benefits of niosomes include improved patient compatibility and a lower cost. Chemically stable, bilayerd Nano carriers made of nonionic surfactant are obnoxious. Both hydrophilic and hydrophobic drugs are carried by it. Niosomes have a number of advantages, including the fact that they are biocompatible, biodegradable, and nonimmunogenic, allowing them to extend the time the drug is in contact with the cornea, enhancing the drug's bioavailability. Because they chemically entrap both hydrophilic and hydrophobic drugs, niosomes were designed to overcome the limitations of liposomes. Discosomes are a modified type of niosomes. Ophthalmic drugs are also carried by discosomes. This has the advantage of not allowing it to enter the systemic circulation, as well as a better fit in the conjunctival cavity due to its disc form. The benefits of niosomes include improved patient compatibility and a lower cost.

Dendrimers:

Dendrimers are a star-shaped polymeric structure that is nanosized and extremely branching. This system comes in a variety of molecular weights with amine, hydroxyl, or carboxyl functional groups at the terminal end. the functional group at the end of a targeted molecule that is used to conjugate it to another molecule. Dendrimers are utilised in medicine delivery as a carrier system. To deliver a medicine, the molecular weight, surface charge, molecule shape, and functional group must all be chosen carefully. Dendrimers' highly branching structure allows for the inclusion of a wide spectrum of drugs, both hydrophilic and hydrophobic.

Use of viscosity inhancers:

Increased viscosity Polymers are a popular ingredient in ophthalmic preparations because of their ability to increase viscosity, allowing for better medication penetration into the anterior chamber of the eye. By lowering the rate of removal from the preocular area, more precorneal residence time and transcrenial penetration are achieved, but the effect on bioavailability in humans is minimal. Polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), hydroxymethylcellulose, hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose are examples of polymers.

8.0 MECHANISM OF OCULAR DRUG DELIVERY SYSTEM:

A. Diffusion

B. Osmosis

C.Bioerosion

A. Diffusion

The medicine is continually released at a controlled pace across the membrane into the tear fluid in the Diffusion mechanism. If the insert is made up of a solid, non-erodible body with pores and a medication that has been disseminated. Diffusion through the pores can be used to release the medicine. The slow disintegration of solid distributed medication within this matrix as a result of inward diffusion of aqueous solutions can further govern controlled release. True dissolving in a soluble device occurs primarily as a result of polymer swelling. The active drug is homogeneously distributed in a glassy polymer in swelling-controlled devices. There is no drug diffusion through the dry matrix because glassy polymers are basically drug impermeable. When the insert is inserted in the eye, tear fluid begins to leak out. The rate at which the matrix dissolves after swelling is determined by the polymer structure: linear amorphous polymers dissolve much more quickly than cross-linked partly crystalline polymers. In general, Fickian'square root of time' kinetics govern release from these devices; but, in some cases, known as case II transport, zero order kinetics have been reported.

B. Osmosis

A transverse impermeable elastic membrane divides the interior of the insert into a first and a second compartment in the Osmosis mechanism; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, while the second compartment is bounded by an impermeable material and the elastic membrane. The impermeable wall of the insert has a medication release hole. The first compartment contains a solute that is unable to pass through the semi-permeable membrane, while the second compartment serves as a reservoir for the medicine, which is either liquid or gel. Water diffuses into the first compartment when the insert is placed in the aqueous environment of the eye, stretching the elastic membrane to expand the first compartment.

C. Bioerosion

The body of the insert is constructed from a matrix of bioerodible material in which the medicine is disseminated in the Bioerosion mechanism. When the insert comes into contact with tear fluid, bioerosion of the matrix results in a regulated, long-term release of the medicine. Although the drug can be disseminated uniformly throughout the matrix, it is thought that if the drug is superficially concentrated in the matrix, a more controlled release can be achieved. A chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or degradation to smaller, water-soluble molecules, controls the pace of drug release in fully erodible or E-type devices. Heller 1341 specifies that these polymers can be hydrolyzed in bulk or on the surface. Surface hydrolysis can cause erodible inserts to show signs of wear.

9.0 Marketed products of ocular drug delivery system:

Table 1:marketed product of ocular drug delivery system

S.No.	Product Name	Manufacturer	Dosage Form
1	Acivir	Cipla Limited	Ointment
2	Besivance	Bausch	Suspension
3	Cyclovir	Zydus Cadila Healthcare Ltd.	Ointment
4	Herperax	Gratia (Micro labs)	Ointment
5	Ocuvir	FDC Limited	Ointment
6	Ophtrhovir	Sunways India Pvt. Ltd.	Ointment
7	Optiviral	Entod Pharmaceuticals Ltd.	Ointment
8	Pilopini	Alcon	Gel
9	Restatis	Allergan	Emulsion
10	Timoptic	Allergan	*Insitu* Gel
11	Vira	Pharmtak Opthalmic Pvt. Ltd.	Ointment
12	Viroderm	Emcure Pharmaceuticals Ltd.	Ointment
13	Virucid	Klar Sehem Pvt. Ltd.	Ointment
14	Zirgan	Alliance	Gel
15	Zovirax	GSK Pharmaceuticals Ltd.	Ointment

10.0 Challenges and future perspectives:

Due to flaws in the current ocular drug delivery system, such as decreased drug bioavailability for topical medications and the invasive nature of posterior implants, novel technologies with superior and effective treatment for ocular illnesses are emerging. The prevalence of ocular diseases such as cataracts, dry eye disease, wet and dry AMD, glaucoma, DR, and DME is expected to rise during the next two decades. Eye drops are considered the safest and most convenient dosing option for the majority of anterior segment problems. Low medication bioavailability at the target tissue is a problem for eye drops. Controlled drug delivery using nano formulations such as nanomicelles, nanoparticles, liposomes, dendrimers, Nano wafers, and microneedles can result in increased drug bioavailability in anterior tissues. such as the conjunctiva and cornea Currently, all therapies for abnormalities of the rear of the eye are intrusive. Patients who receive frequent intravitreal injections may experience retinal detachment, bleeding, and pain. Ocular

drug delivery scientists face a difficult task in developing a noninvasive sustained drug delivery method for the posterior portion. As a result, novel noninvasive drug delivery systems that can overcome ocular barriers, sustain drug release, and maintain effective drug levels at the back of the eye are urgently needed.

11.0 Conclusion:

This review provides the brief knowledge about the ocular drug delivery system by disscusing briefly the anatomy of eye, routes of ocular drug delivery, barriers for ocular drug delivery, novel approches for ocular drug delivery, mechanism of ocular drug delivery system. Among this drug delivery system. Only few products have been, commercialized Recent technological advancement has changed the field of ocular drug delivery from conventional drop to sustained released and targeted ocular delivery system.

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