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Ocular Drug Delivery System: Review

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ABSTRACT

In this ocular drug delivery system (ODDS) is one of the most challenging talks by pharmaceutical researchers. For the prolonged duration by the major barrier in ocular medication is the ability to maintain a therapeutic level of drug to the site of action. In this management of the eye, ailments take off the effective concentration of the time. This ocular drug delivery system is hampered by the barriers protecting the eye. The bioavailability of the active drug substance is the major hurdle to overcome. Topical administration for the ocular therapeutics is ideal because the smaller dose is required compared to the systemic use of its rapid onset of action. In this topical absorption is reach the inner parts of the eye, this trans-corneal penetration is believed to the major route of the drug application. The ocular absorption is the much slower process the elimination. This conventional ocular dosage form, including eye drops, is no longer sufficient to combat ocular disease. Conventional drug therapy, an essential factor in ocular pharmacokinetics and explores various approaches like eye ointment, gels viscosity enhancer, prodrug, penetration enhancers, microparticles, liposomes, niosomes, ocular inserts, implants, intravitreal injection, nanoparticles, nanosuspension, microemulsion, iontophoresis, and periocular injection to improve the ocular bioavailability of the drug. They provide the continuous and controlled release of the drug to the anterior and posterior chamber.

INTRODUCTION:

Ocular drug delivery is the most attractive and interesting to the pharmaceutical segment. But there is an arduous struggle facing by pharmaceutical scientists. This ancient ophthalmic solution, ointment, and suspension dosage forms are no longer satisfied the therapeutic action as necessary to some current virulent diseases. This ocular drug delivery system (ODDS) is most of the challenging task faced by pharmaceutical researchers. These ophthalmic formulations are available in the buffered, isotonic, and sterile solution. For the ocular drug, the formulation is prepared in several types of dosage forms. In this ocular drug delivery system basis of the anatomy and physiology of the eye is a unique, complex, and incomparable structure.[1] This can be divided into two different types. 1. Anterior segment/ Types. 2.Posterior segment/ Types.

In this anterior segment are 1/3 portion of the eye is occupied. While this rest portion comes under the posterior segment. The cornea, conjunctiva, iris, capillary body, and lens make the anterior portion of the eye. In the posterior segment, some eyes include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve, and vitrom humor.

The most difficult challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. This barrier may affect the bioavailability of the drug. This type of problem results in extensive loss of drugs. The bioavailability of the ocular drug or ophthalmic drug is very poor due to the efficient protective mechanisms of the eye. That is the blinking, baseline, and reflex lachrymation and drainage remove rapidly foreign particles including the drug from the surface of the eyes. There are many elements are affected the eye and can also lose the eyesight. Therefore, many ophthalmic formulations are available in the market. There are classified into two different types one of the conventional and another is non-conventional and another is non-conventional drug delivery system. The most common ophthalmic preparation is available in the eye drops and ointments about 70% of the eye dosage formulation in the market.[2]

In this Ocular drug delivery system are following characteristics are required.

- A good corneal penetration.
- A continued contact time of drug with corneal tissue.
- Easiness I installation and removal.

– A nonirritative form.

– Good Rheological properties.

On this development of the sustained and controlled release drug delivery system, there is main attention made from the last two decades. The avoid dose frequency and improvement of the drug effect the aim of such system based on the localization on site of action. The main aim of pharmaco-therapeutics at the intended site of action is the achievement of an effective drug concentration of the desired period of the ocular disposition and elimination of the therapeutic agents is thee dependent upon it. Physicochemical properties as well as their relevant Ocular anatomy and physiology.[3] It requires an integrated knowledge of the drug molecule and constraints offered by this ocular route of administration. The various approaches have attempts to increases the bioavailability and their duration of the therapeutic action of ocular drugs. These ocular drug delivery systems can be divided into two categories. The first is based on the use of a sustained drug delivery system that provides controlled and continuous delivery of ophthalmic drugs. The second part is the maximum corneal drug absorption and minimum pre-corneal drug loss.[4]

Idea ophthalmic drug delivery must be able to sustain drug release and remain in the vicinity of the front of the eye for prolong period. Consequently, it is imperative to optimize ophthalmic drug delivery one of the ways to do so is by the addition of polymers of various grads, development of in situ gel or colloidal suspension, or using erodible or non-erodible inserts to prolong the precorneal drug retention.[5] The intraocular drug delivery and the system of this tissue can be improved with intraocular injection and implants, but they must be given by ophthalmologists and specialized nurses. Intravitreal delivery is the only clinical option for the treatment of the posterior segment disease (eg. Of the retina and choroid). This burden of the injections to patients and their healthcare system is enormous for example nearly 20 million anti-vascular endothelial growth factor(VEFG) injections are given intravitreally per year to treat wet age-related muscular degeneration(WAMD). This multifactorial approach allows us to generate a quantitative sample framework that will help in the choice of the doses their release rates and system without the need for expertise in pharmacokinetics or pharmacodynamic modeling.[6]

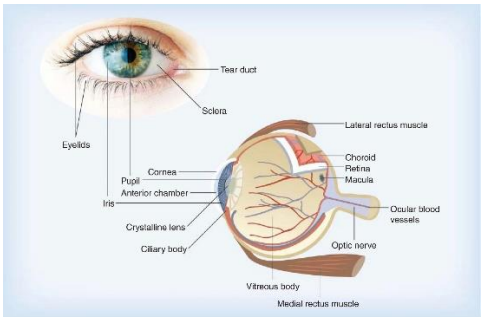

Figure No. 1: Ocular drug delivery system

Advantages of ocular drug delivery system:[7]

1. To increase the accurate dosing to overcome the side effects of pulsed dosing produce by the conventional system.

2. To provide sustained and controlled drug delivery.

3. To increase the ocular bioavailability of the drug by increasing corneal contact time. This can be achieved by increasing corneal contact time. This can be achieved by effective adherence to the corneal surface.

4. These ocular drug delivery systems (ODDS) provides targeting within the ocular globe to prevent the loss of other ocular tissues.

5. In this circumvent the protective barriers like drainage.

6. To provide comfort, better compliance with the patient, and to improve the therapeutic performance of the drug.

7. To provide a more effective and housing delivery system.

8. They have generally quick absorption and fewer visual and systemic side effects.

9. They can easily be administered by the patient himself.

10. In this ocular drug delivery system are has better patient compliance. [7]

Disadvantages of ocular drug delivery system:[8-9]

1. The drug solution is the stays a very small period on the eye surface.

2. They can interfere with the vision.

3. It can show the instability of the dissolved drug.

4. There is a need to use preservatives.

5. They should generally rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in the frequent dosing regimen.

6. The major portion of the dose administered drains into the lacrimal duct and causes unwanted systemic side effects.

7. The physiological restriction is the limited permeability of the cornea resulting in low absorption of ophthalmic drug formulation. [8, 9]

Ocular drug delivery routes:

Intra vitreal: In this intravitreal route of administration of the drug or other substance they are injected within vitreous humor of the eye in which this substance is delivered into the eye. In this intravitreal route of administration are used to treat the various condition.[10]

Intra cameral: In this intra cameral route of administration of the drug within the chamber, such as the anterior or posterior chamber of the eye.Example: Anesthesia injection of an anesthetic agent into the anterior chamber of the eye usually during surgery.

Peril ocular: In this peril ocular steroid injection they involve the placement of the steroid around the eye to treat intraocular inflammation or swelling of the eye.[11]

Supera choroidal: This suprachoroidal space they are space is a space lying between the sclera and the choroid. These are the administration of the drug in the suprachoroidal region of the eye.

Table No. 1: Ocular inserts devices[25]

Sr. No.	Name	Description
1.	Soluble ocular drug inserts	A small oval wafer, a compound of soluble copolymers consisting of acrylamide, ethyl acetate, soften on insertion.
2.	Collagen shields	The erodible disc consists of the cross-link porcine sclera collagen.
3.	Ocuserts	A flat, flexible, elliptical insoluble device consisting of two-layer, enclosing a reservoir, use commercially to deliver pilocarpine for 7 days.
4.	Minidisc or ocular therapeutic system	4-5mm diameter contoured either hydrophilic or hydrophobic disc.
5.	Lacrisert	Rose-shaped device made from hydroxyl propyl cellulose use for the eye syndrome as an alternative to tears.
6.	Dry drops	A preservative-free of hydrophilic polymer solution that is freeze-dried on the tip of a soft hydrophobic carrier strip immediately hydrate in a tear strip.
7.	Gel-foam	The slab of gel foam was impregnated with a mixture of drug and cetyl ester wax in chloroform.
8.	New ophthalmic drug delivery system	Medicated solid polyvinyl alcohol flag that is attached to paper covered with handle. This applicable the flag is detached and gradually dissolves, releasing the drug.
9.	Bio-adhesive ophthalmic eye inserts	Adhesive rods are based on a mixture of hydroxyl propyl cellulose, ethylcellulose, polyacrylic acid cellulose phthalate.

Sub conjunctiva: This sub conjunctiva route is the administration of the drug to the mucus membrane that is the exposed portion of the eyeball and inner surface of the eyelids.[12]

Topical: They are mostly in the form of eye drops, ointment, gels, or emulsions to treat the anterior segment diseases. It is the most preferred method due to the cause of administration and low cost.

Systemic: This generally blood-aqueous barrier and blood-retinal barrier are the major barriers for the anterior segment and posterior segment of the ocular drug delivery system.

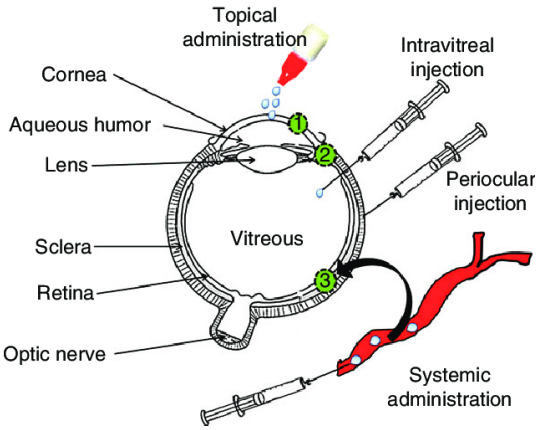

Figure No. 2: Route of ocular drug delivery system

Physical approaches conventional ophthalmic dosage form:

1. Viscosity enhancers:- In many ophthalmic drug formulations various polymers are used to increasing the viscosity. They also increase the precorneal residence time and hence the greater transcorneal penetration of the drug into the anterior chamber. In this viscosity, enhancers are improvement of the bioavailability it has been the minimal effects of humans. In this polymers used are polyvi66nyl alcohol (PVA), methylcellulose, polyvinylpyrrolidone (PVP), hydroxyethylcellulose, HPMC, and hydroxypropyl cellulose. Natural polymers such as veegum, HA, xanthum gum are also used as the viscosity enhancer.[14-16]

2. Eye ointments:- These are ointments that are mainly formulated by using a mixture of solid and semi-solid. This solid mixture is mainly included in the hydrocarbon (paraffin). The above mixture is melting or softening point close to body temperature and they are non-irritating to the eye. In this mainly micronized powder, the medicinal agents are added to the base. In this mixture is instillation in the eye their ointments break up into small drops. Therefore the increasing bioavailability to use the ointment is useful.[15-17]

3. Penetration enhancers:- There are generally increasing the permeability of the corneal epithelial membrane are transport characteristics across the cornea they can be minimized. They are ophthalmic drug bioavailability is increased than their approach used to which lies

in increasing transiently the permeability characteristics of the cornea with suitable substances is known as the permeability enhancer. These permeability enhancers are also known as absorption promoters.[18]

4. Prodrug: The main important principle of the prodrug is to enhance the drug permeability through the modification of their hydrophilicity or their lipophilicity of the drug. The ideal prodrug should not only have the increased lipophilicity and high partition coefficient but must also have high enzyme susceptibility.[19]

A barrier to ocular drug delivery system: The main disadvantage is systemic administration of ocular therapeutics it is low ocular bioavailability and only 1 to 2% of the administered dose reaches the anterior segment. Therefore, these clinical practices of ocular diseases related to the anterior segment of the eye that is the cornea, conjunctiva, sclera, anterior uvea, etc. the topical administration of the therapeutics has preferred the route of administration. In this to be an ideal route of administration it has to be overcome certain physicochemical, metabolic, and biological barriers to reach the intended site of action.[20]

The following barriers are involved in the ocular drug delivery system.

1. Physiological barriers of ocular drug delivery system

2. Drug loss from the ocular surface

3. Lacrimal fluid eye barriers

4. Blood ocular barriers

5. Ocular wall barriers

6. Retinal barriers

1. Physiological barriers of ODDS:-

These physiological barriers are generally the diffusion and productive absorption of the topically applied drug. They exist in the precorneal and corneal spaces. In this precorneal constraint such as the tear dilution, solution drainage, lacrimation, tear turnover, and conjunctival absorption they are responsible for the poor ocular bioavailability of conventional ophthalmic dosage form. In this drug solution drainage away from the precorneal area has shown to be the most significant factor in the reducing contact time of the drug with the cornea and consequently ocular bioavailability of the dosage forms. In the

instilled dose leaves is the precorneal area within the two minutes of the installation of the humans. This ophthalmic dropper delivers 50-70µl of the eye drops. If these patients are not blinked the eye can hold about 30 µl without spilling on to the cheek. [21]

2. Drug loss from the ocular surface:-

After the installation of the lacrimal fluid removes instilled compounds from the surface of the eye. In this, corneal and conjunctival superficial layers from of the ocular surface that is the contact of the tear film. This ocular surface is generally created to the defense barrier against the penetration from the undesired molecules. Even though their lacrimal turnover rate is only about 1 µl/min the excess volume of the instilled fluid is flown to a nasolacrimal duct that is rapidly in a couple of minutes. Another source of the non-productive drug the removal of its systemic adsorption instead of ocular absorption. This systemic absorption rate may take place either they are directly from the conjunctiva sac via the local blood capillaries and after the solution flow to the nasal cavity. In this ocular surface, they are creating the defense barrier against the penetration from undesired molecules. This corneal surface Is only 5% of the total ocular surface and there are remaining 95% is occupied by the conjunctiva. This contrasts with the low ocular bioavailability is less than 5%. Drug absorption in the systemic circulation decreases the drug concentration in lacrimal fluid extensively. Therefore, this constant drug release of the solid delivery system is to the tear fluid may lead only to the ocular bioavailability is about 10% since most of the drugs are cleared by the local systemic absorption anyway.[21]

3. Lacrimal fluid- eye barriers:-

These lacrimal fluid-eye barriers have involved the corneal epithelium limits of drug absorption from the lacrimal fluid into the eye. In this, the corneal epithelial cell from the drug have typically at least an order magnitude to higher permeability in the cornea than the hydrophilic drugs. This corneal barrier is formed upon the maturation of the epithelial cells. They generally migrate from the limbal region is towards the center of the cornea and to the apical surface. In these generally, the conjunctiva is the leakier epithelium than that of the cornea and its surface area is also nearly 20 times greater than that of the corneal epithelial layer, transcorneal permeation is the main and important route of the drug entrances from the lacrimal fluid to the aqueous humor. In this the drug absorption acrosses the bulbar conjunctiva has been gained increasing attending recently since this conjunctiva is also fairly the permeation to the hydrophilic molecules. It may also serve as the route of absorption is

larger bio-organic compounds such as proteins and peptides. These are clinically used drugs are generally fairly lipophilic.

4. Blood-ocular barrier:- The eye is mainly protected from the xenobiotics in blood steam by the blood-ocular barriers. They mainly this blood ocular barrier are divided into two parts:

- Blood aqueous barrier- anterior blood barriers.
- Blood retina barrier- posterior blood eye barriers.

These anterior blood eye barriers are generally composed of the endothelial cells in the uvea. In these blood ocular barriers are prevents the access of the plasma albumin into the aqueous humor and its limit also the access of hydrophilic drug from the plasma into the aqueous humor. There is the posterior barrier between the bloodstream and the eye is comprised of the retinal pigments epithelium (RPM) and their tight wall of retinal capillaries. Unlike the retinal capillaries is vasculature of the choroid has been the extensive blood flow and leaky walls. The main drugs are easily gain access to the choroidal extravascular space but their distribution into the retina is limited by the RPE and retinal endothelial. In their plasma aqueous humor are generally inflammation may disrupt the integrity of this barrier. Therefore, without the specific targeting the systems only a minute fraction of the intravenous or oral drug dose gain to the retina and choroid. In this blood-ocular barrier, the blood eye barriers have not characterized the terms of the drug their transporter and metabolic enzymes expression. From this pharmacokinetic perspective, plenty of basic research is needed before the nature of the blood eye barrier.

5. Ocular wall barriers:-

In these generally, the ocular wall barriers are the skeleton of the eye globe consists of the rigid scleral collagenous shell. That is generally lined internally by the uveal tract. This sclera is covered by the posterior wall is 80%of the eye globe except for the small posterior opening occupied by the optic nerve head. The rest of the globe is generally covered anteriorly by the cornea. This scleral stroma is composed of bundles of collagen, fibroblasts, and a moderate amount of ground substance. This is generally the issue is essentially avascular but lines superficially vascular episclera. These large channels penetrate by the sclera to allow the passage of the vessels and their nerves to the choroid side.[22]

6. Retinal Barriers:-

It generally consists of 10 layers.

1.1 The retinal pigment epithelium.

1.2 Photoreceptor outer segments.

1.3 External limiting membrane.

1.4 Outer nuclear layer.

1.5 Inner nuclear layer.

1.6 Inner plexiform layer

1.7 Outer plexiform layer.

1.8 Ganglion cell layer.

1.9 Nerve fiber layer.

1.10 Internal limiting membrane.

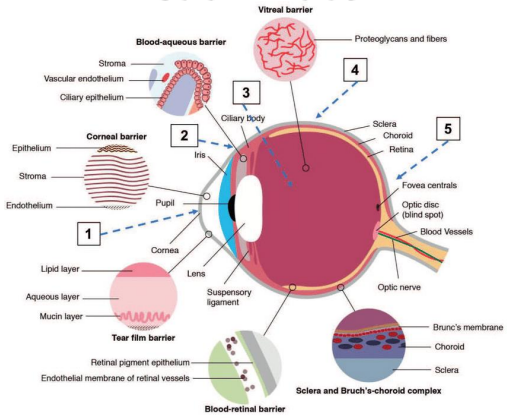

Figure No. 3: Barriers of ocular drug delivery system

Mechanism of Drug release of ocular drug delivery system:[5] The mechanism of controlled drug release into the eye is as follows.

1. Diffusion: In this diffusion mechanism are generally the drug released is continuously at a controlled rate through the membrane into tear fluid. The release of the drug takes place the diffusion through the process to diffuse from a region to higher drug concentration across the concentration grade. If their inserts they are formed the solid nonerodible body with pores and dispersed drug. This release of the drug generally takes place via diffusion through the

pores. This controlled release can be further regulated through the gradual dissolution of the solid dispersed drug with this matrix as their result of the inward diffusion of the aqueous solution. In this soluble device, they are true dissolution occurs mainly through the polymer swelling since these glassy polymers are essentially drug-impermeable, no diffusion through the dry matrix occurs.

1. Osmosis: In this osmosis mechanism are generally the inserts can be transverse impermeable elastic membrane in their interior of the inserts into the first compartments to second compartments. The first compartments are bounded by the semi-permeable membrane to the impermeable elastic membrane and the compartment is bounded by the impermeable material and their elastic membrane. This is a drug aperture in the impermeable wall of inserts. There is the first compartment contains a solute that cannot pass through the semi-permeable membrane. The second compartment provides the reservoir for the drug they which again is in the liquid or gel form.in these inserts is placed in the aqueous environment of the eye. The diffuse water into the first compartment and stretches the elastic membrane expand to the first compartment and contract to the second compartment so that the drug is forced through the drug release aperture.

2. Bio-erosion: In this bio-erosion mechanism is the body of the insert is constituted from a bio-erodible material in which is the drug contact of the insert with the tear fluid result is controlled sustained release of the drug or a drug by bio-erosion of the matrix. This drug may be dispersed uniformly throughout the matrix but it is generally believed a more controlled release is obtained the drug id the superficially concentrated in the drug matrix.

1. Insoluble Ocuserts:- This is the only insoluble types can usually deliver drugs by the variety of method of sat controlled predetermined rate but need the removal the eye when empty.[23]

In their insoluble inserts are generally classified into two categories.

a. Reservoir System: In this reservoir system generally the drug is released either by diffusion or by an osmotic process. It contains respectively a liquid, gels, colloid, semisolids, or a carrier containing drugs.

i. Diffusion inserts or ocuserts:- These diffusion inserts are the subsystems of the reservoir system. This is based on the porous membrane ocuserts system is a novel ocular

drug delivery system. This diffusion inserts/ concerts drug release is based on a diffusional release mechanism.

ii. Osmotic Inserts: In this, osmotic inserts are also subtypes of the reservoir system. These are used composed of a central part bounded by a peripheral part and there are two different types are included.

- **Type 1:-** The central part of composed a single reservoir of a drug surrounded by the polymer as discrete small deposits, with or without additional osmotic solute dispersed throughout the polymeric matrix. These insoluble semipermeable polymer films comprised the second peripheral part of these inserts. In these forms of apertures, the osmotic pressure against the polymer matrix causes the rupture.

- **Type 2:-** These are the central part of the two different compartments. In these two separate compartments the drug and osmotic solute are placed, the drug reservoir is surrounded by the elastic impermeable membrane, and by the semi-permeable membrane the osmotic solute reservoir. The second peripheral part of this type is similar to type 1.

b. Matrix system:- These are the second category of insoluble ophthalmic inserts. They are mainly represented by contact lenses and a particular group of insoluble ophthalmic devices. It can be forming a three-dimensional network or matrix capable of retaining the water, aqueous drug solution, or solid compartment and consist of covalent cross-linked hydrophilic or hydrophobic polymers.

– **Contact lenses**: These contact lenses are initially used for vision correction. The possibility of correcting vision and releasing drugs simultaneously is the main advantage of this system. In this contact lenses are divided into 5 parts. Rigid, Semi-rigid, Elastomeric, Soft hydrophilic, Bio-polymeric.

2. Soluble concerts: These soluble inserts are normally they can be defined as the erodible, monolithic polymeric devices that are releasing the drug and they do not need removal while undergoing gradual dissolution. These polymers swelling true dissolution occurs mainly, while to a chemical or their enzymatic hydrolytic process erosion corresponds. This swelling controlled device can be in glassy polymers, the active agents are homogeneously dispersed. The water from tear fluid begins to penetrate the matrix when the inserts are placed in the eye, then releasing the drug content, swelling, and consequently polymer chain relaxation.

The drug diffusion they do not need to be removed the site of the application is their main advantage of this system. These soluble inserts are generally divided into two categories:

a. Natural polymers

b. Synthetic and semi-synthetic polymers

a. Natural polymers: These natural polymers are produced soluble ophthalmic inserts that can be used for preferable collagen. The therapeutic agents have preferably absorbed the soaking inserts. This solution containing drug drying and re-hydrating before use on the eye. The concentration of the drug solution which can the composite is soaked as well as the duration of the soaking and their amount of the binding agents present the amount of the drug-loaded well depend. These natural polymers as they collagen dissolve the drug is gradually released from the interstices between the collagen molecules.[23]

b. **Synthetic and semi-synthetic polymer:** These synthetic and semi-synthetic polymers are the second subtype of the soluble inserts. These are generally based on the use of polymer i.e semi-synthetic polymer (Ex. cellulose derivatives). The synthetic polymer (Ex. Polyvinyl alcohol) by using the eudragit, a polymeric this can usually use for the enteric coating or as a coating agent of the insert, decreased the release rate of the obtained.

3. Bio-erodible ocular inserts:[24] These bio-erodible ocular inserts are formed by cross-linked gelatin derivatives and polyester derivatives. If these undergo hydrolysis of the chemical bonds and dissolution. The main advantage of the bio-erodible ocular insert polymer is the possibilities of modulating the erosion they can rate by modifying their final structure during synthesis. These can be the addition of the anionic or cationic surfactant. They're some of the important ocular inserts that are available commercially soluble ophthalmic development for collagen shields.

In this, bio-erodible ocular inserts are divided into two subtypes:

a. Soluble ophthalmic drug inserts.

b. Collagen shields.

a. Soluble ophthalmic drug inserts: This SODI is generally a small oval wafer, which was then developed by the Soviet scientists for cosmonauts who could not use eye drops in weightless conditions.

b. Collagen shields: In this are a structural portion of bones, tendons, ligaments, and skin and comprise more than 25% of the total body protein in mammals. If this body protein has to be several biomedical applications they which is derived from intestinal collagen. The main application of which is probably catgut suture.

Challenges in ophthalmic drug delivery system:[26]

There are specific challenges of designing a therapeutic system is achieve an optimal concentration of the drug active site of appropriate duration to provide the ocular delivery system with high therapeutic efficacy. These anatomy, physiology, and barrier function of the cornea compromise rapid drug absorption. This frequent instillation of eye drops they are necessary to maintain the therapeutic drug level in the tear film or at the site of action. But their frequent use of highly concentrated solution may induce toxic side effects and cellular damage at the ocular surface.

It is mainly the poor drug bioavailability of the ocular dosage form is mainly precorneal loss factor which includes solution drainage, lacrimation, tear dynamics, tear dilution, tear turnover, conjunctiva absorption, non-productive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane. The following challenges are involved in the ophthalmic drug delivery system.

1. Anterior segment delivery challenges
2. Posterior segment delivery challenges

1. Anterior segment delivery challenges: In these anterior segments they are ailment of the eye, topical administration of the usually preferred over systemic administration, because of the reaching the anatomical barrier of the cornea any drug molecules administrated by this ocular route. It has to be cross the precorneal barriers, this first barrier that slows the penetration of an active ingredient into the eye, and its consists of the tear film and their conjunctiva. Their poor drug bioavailability of the drugs from the ocular dosage form is mainly due to the precorneal loss factors. There frequent instillation of eye drops they are necessary to maintain the therapeutic drug level.

2. Posterior segment delivery challenges: The mainly topical ocular medication they do not reach the posterior segment. The drug targets the high efficiency of the blood-retinal barrier (BRB). This delivery of the drug to the posterior segment of the ocular tissue is prevented by

the same factor these are responsible for the poor ocular drug bioavailability. This addition of the blood-retinal barrier (BRB) limits the effectiveness of the intravenous route in the posterior drug delivery.

The tight junction of BRB restricts the entry of systemically administered drugs into the retina. Are high concentration is required for the treatment of posterior segment diseases.

Novel approaches of ocular drug delivery systems:

1. Polymeric gels: In these they generally a common method of the prolonged ocular residence time of the drug. These drugs are increasing intraocular diffusion to increase the solution viscosity. In there are two groups of polymeric gels they can be distinguished by classically performed gels and the second is the in-situ forming gels. And their in-situ forming gels are viscous liquids, which undergo a sol-gel phase by the transition after exposure to the physiological condition in the cul-de-sac forming a viscoelastic gel.[27]

2. Bio-adhesive hydrogels: They can be generally defined as the maintenance of contact for an extended period of two materials, one of which when they're biological. In this, bio-adhesive hydrogels are commonly used excipients are the hydrophilic polymers belonging to different classes including the cellulose derivatives of polyacrylic such as carbomer, povidone, polyvinyl alcohol, sodium hyaluronate or sodium alginate, etc. The carbomer they have bio-adhesive properties which can be increasing the viscosity and residence time, they are capable of forming strong non-covalent bonds, with the musing coating biological membranes. In this generally, several performed gels are marketed to relieve the symptoms of dry eyes. These films increasing the contact time. They stimulate the continuous delivery of the tear due to high water retaining capacity and they allow installation frequency to be decreased compared to the eye drops.

In their dry eye syndrome to treat the hydrogels based on the hyaluronic acid (HA), they are increasingly used. HA is a high molecular weight biological polymer consisting of linear polysaccharides present in the extracellular matrix. The antibiotic gentamicin was formulated within the 0.25% HA it increases the precorneal drug residence time in the volunteers. It's shown the offer long-lasting antibiotic efficiency in 340 patients and preferred chloramphenicol eye drops.[27]

3. *In-situ* forming hydrogels: In this ocular drug delivery system is expected to deliver an accurate concentration of the drug over a predetermined period using an easy handle device.

In this new drug dosage form approach, they attempt to combine the advantages of both the solution and gels. In their in-situ gels, they are dropped as a solution into their conjunctival sac where they undergo a transition into the gel induced by a change in either temperature ion concentration or Ph. There are several polymers with such properties.

4. Temperature-induced gelation: In this temperature-induced gelation they are generally the sustained drug delivery system they can be achieved by using polymer changes from solution to the gel at eye temperature, eg. poloxamers. In these poloxamers, they are nonionic triblock copolymers composed of the central hydrophobic chain of polypropylene oxide combined by two hydrophilic chains of polyethylene oxide. Because of the length of polymer blocks their many different poloxamers with slightly differing properties. They are also known as the under the trade name of Pluronic^{R}, F-127. This yields colorless and transparent gels are the most commonly used polymer in pharmaceutical technology. In this low concentration (10.4-10.5%) pluronic gels form the monomolecular micelles.

5. Osmotically induced gelation: Gellan gum is a natural polymer extracted from the cultures of pseudomonas elodea. These are marketed under the brand name of Gelrite^{R} for human medical applications. In this generally, polymers are a low acetyl gellan gum that forms a clear gel in the presence of mono or divalent cations. The sodium salt from its dissolved in the aqueous solution of active ingredients. In this generally enhancing viscosity, the in-situ gelling interaction of the alginate with mucus they are responsible for the prolonged therapeutic effect. They are good adhesive behavior was due to the low surface tension (31.5mN/m) of the alginate formulation. They are lower than the critical surface tension of the mucin-coated cornea (38mN/m).

6. Combination of polymers: Some of the polymers are used drawbacks and combining the various polymers holds greater compliance and improved the therapeutic efficiency. The ophthalmic delivery system of the ofloxacin they are using polyacrylic acid (carbapol 940) in combination with HPMC acting as a viscosity-enhancing agent. In a US patent, Lin and sung developed the ophthalmic drug formulation of the pilocarpine containing carbapol or pluronic or a combination of the carbapol and pluronic. This is preferred the formulation that containing the combination of 0.3% of carbapol and 14% of pluronic. The result is it led to better drug retention than the individual polymer solution. There is a pharmacological response that showed a 1.85 fold increasing the retention as compared to the aqueous pilocarpine solution.[29]

7. Liposomes: Liposomes are microscopic vesicles composed of one or more concentric lipid bilayers. They are separated by the water or aqueous buffer compartments. Which increases the probability of ocular drug absorption. Their ability to especially desired a drug that is poorly absorbed. The drug is a low partition coefficient with poor solubility or those with medium to high molecular weights. These liposomes as an ocular drug delivery system have been observed to be the in parts, due to their surface charge. Liposomes are the phospholipids in this lipids viscosity are used in the target in drug for the specific site of action. These mainly provide controlled and sustained drug release and also improves drug bioavailability. The liposome they are completely biodegradation and they are relatively toxic but they are less stable than polymeric drug delivery system.[30]

8. Artificial tear inserts: LACRISERT In this type of insert they are rod-shaped pellet of hydroxyl propyl cellulose without preservative is commercially available. This artificial tear insert device is designed by the sustained release artificial tear for the treatment of eye problems.

9. Filter Paper Strips: In these filter paper strips they are generally used by the sodium fluorescein and rose Bengal dyes. These dyes are mainly used for diagnostic purposes in corneal injuries and infections.

10. Microemulsion: Microemulsion is generally the most important and useful dosage form. In this microemulsion are the natural defense of the eye, they due to their intrinsic properties and specific structure. The microemulsion is prepared b inexpensive processes through auto emulsification and they supply the energy. These can be easily sterilized, so there is a stable and high capacity for dissolving the drug. These generally in vivo results and preliminary studies on healthy volunteers have shown a delayed effect and an increase in the bioavailability of the drug. Microemulsion they have generally stable dispersion of water and their co-surfactant in the manner or reduce interfacial tension. It improves ocular bioavailability. They have higher thermodynamic stability in small droplet size (~ 100nm) and clear appearance. These oil in water systems generally consisting of the Pilocarpine using the lecithin propylene glycol, PEG200 as a surfactant/ co-surfactant, and isopropyl myristate as the oil phase has been designed.[28]

11. Ocular inserts: In these ocular inserts are generally the solid dosage forms. They can overcome the disadvantage and problems reported by traditional ophthalmic preparations such as aqueous solutions, suspension, and ointments. These ocular inserts are mainly were

prepared by using different techniques to make soluble erodible, non-erodible, and hydrogel inserts.

12. Collagen Shields: These on of the most important and most useful biomaterials used in the ocular drug delivery system. This due to being outstanding biocompatibility and safety due to thee its biological characteristics such as biodegradability and weak antigenicity by made collagen the primary resource in medical application. These collagen shields are hydrated before they are placed on the eye. They mainly had stored in a dehydrated place.

13. Niosomes: They are generally chemically more stable compared to liposomes. These are the bilayer structural vesicles mode by the nonionic surfactant. They are capable of encapsulating both lipophilic and hydrophilic compounds. Niosomes reduce the systemic drainage and improve the residence time which leads to the increases the ocular bioavailability. These are generally nontoxic and do not require special handling techniques. These niosomes are generally non-biodegradable and non-biocompatible. In these recent approaches to deliver the cyclopentolate, niosomal formulation was developed. Niosomal formulation coated the (chitosan or carbopol) timolol maleate exhibited significant IOP lowering the effect in rabbits as compared with the timolol solution.[31]

14. Nanoparticles/ Nonospheres: In these generally the polymeric drug delivery includes the micro and nanoparticles. In this, nanoparticles are ranging from 10mm to 1mm in which the drug is dissolved or absorbed. Their encapsulation of the drug leads to the stabilization of the drug. They represent the most important drug carrier for ophthalmic application. They are also classified into two categories first is the Nanospheres and another is the Nano capsule. In this Nanospheres are the small capsule with a central cavity is surrounded by a polymeric membrane. And the Nano capsule is the solid material sphere. Nanocapsules is more bioadhesive properties.[31]

15. Nano suspension: There is Nano suspension is defined as the sub-micron colloidal system which consists of the poorly water-soluble drug, suspended inappropriate dispersion medium they stabilized by the surfactant. These Nano suspensions, usually consist of colloidal carriers like a polymeric resin which are inert. Nano suspension is also increasing ocular bioavailability are also increasing ocular bioavailability. They have prolonged contact time of the ocular dosage form.

16. Microparticles: In these generally they are drugs containing the micron-sized polymeric particles suspended in a liquid medium. The drugs can be physically dispersed in the polymer

matrix or covalently bonded to the polymer backbone, microparticles have improves the precorneal residence time which leads to the continuous and sustained release o the drug. The microparticles are mainly biodegradation, bio adhesion, and biocompatible they are desired properties for the ocular drug delivery system. Some examples of microparticles are as follows.

- Microspheres of methylprednisolone are chemically linked to hydrogenate esters.
- Pilocarpine-loaded albumin or gelatin microspheres.
- Acyclovir- loaded chitosan microsphere.[30]

17. Implants: In these implants are the main goal of the intraocular implant design is to provide prolonged activity. Therewith the controlled drug release from the polymeric implant material. This intraocular administration of the implants always requires minor surgery. The ocular implants are generally classified into two categories i.e. the biodegradable device and the non-biodegradable device. In this, ocular implants are generally a form of the solid, semi-solid, or particulate-based delivery system.

18. Intravitreal injection: In this intravitreal injection is a drug solution directly into the vitreous via pars plana using a 30G needle which improves drug absorption over the systemically and topically delivered agents. It is mainly a drug that directly targets sites of the eyes. Intravitreal administration of the high concentration of the drug in the retina, it is associated with the various short term complication such as their retinal detachment, endophthalmitis, and intravitreal hemorrhages, therefore, patients need to be more carefully monitored in intravitreal injection. They have some disadvantages like may cause difficulties with toxicity they have a short half-life and should be administered repeatedly, side effects which include pain caused by the repeated injection, discomfort, poor acceptance by patients.[26]

19. Iontophoresis: In this, ocular iontophoresis has been gained significant interest recently due to their noninvasive nature of delivery to both anterior and posterior segments. This iontophoresis is classified as the trans corneal iontophoresis, the sclera is a larger surface area than the cornea (about 17cm^2 v/s 1.3cm^2) high degree of hydration, low number of cells and it is permeable to large molecular weight compounds.[26]

20. Eye ointments: Ointments are generally formulating by using a mixture of semi-solid and solid hydrocarbons like paraffin. They have a melting or softening point close to the body

temperature and monitoring to the eye. The ointment has a two-phasic system. The medicinal agents are added to the base either a solution or a finely micronized powder. By their instillation of the eye, ointment breaks up into small droplets and remains as a drug in a cul-de-sac for extended periods. Ointments are more useful in improving drug bioavailability.

Factors limiting ocular bioavailability of drugs: [15]

1. Tears:

– These tears are generally secreted from the lachrymal gland.

– Tears play a major role in maintaining normal eye function.

– In healthy people, tears are composed of water, electrolytes, lipids, proteins, glucose, and mucins.

– In some disease conditions, additional components can be found such as inflammatory mediators, antigens, and cytokines.

– The consequently minimizing the period during which drug can penetrate the ocular tissues.

2. Conjunctiva:

– Conjunctiva is generally constituted of mucus tissue.

– The conjunctiva contributes to the lubrication and protection of the eye by producing mucus and antimicrobial peptides.

– These conjunctivae are highly vascularized.

– They play an important role as a protective barrier on the ocular surface.

– The systemic absorption represents an obstacle to the posterior segment's application.

– For this reason, drug administration via the sub-conjunctiva route is an increased way to enhance the efficacy of topical drug application.

3. Cornea:

– The cornea is the anterior layer of the eye.

– In this addition to the protective effect on ocular tissue, the cornea refracts light.

– It characterized by the high water content that makes this corneal layer is impermeable to the lipophilic molecules.

– They are generally the corneal epithelium and its greater extent; stroma represents the barrier to the permeation of macromolecules.

– It should appear that is to penetration through the three layers molecules should have an amphiphilic nature by the presence of hydrophilic and lipophilic properties.

4. Sclera:

– The sclera maintains the shape of the eye globe resistance to an internal and external force to provide support for extraocular muscle.

– These sclerae are generally collagen fibrils and glycoproteins.

– The molecular radius and geometry and charge of the drug molecules are reported to affect their permeation through the sclera layer.

– This sclera is reported to the more permeable both small molecules are difficult to trap of negatively charged glycoproteins.

CONCLUSION:

Effective treatment of ocular diseases is a formidable challenge for scientists in the field. A new ophthalmic delivery system they include inserts collagen shields, disposable contact lenses, ocular films, and other formulation. In these ocular delivery systems are involved the newer trend is a combination of the drug delivery technologies for improving the therapeutic effect or therapeutic response of an efficacious drug. These ideal systems should have effective drug concentration at the target tissue. This tended period within a minimum systemic effect. Patient acceptance is very improvement in the design of any comfortable ophthalmic drug delivery system. Major improvements are required in the sustained drug release, larger-scale manufacturing, and stability. In these, ocular drug delivery system of ocserts provides many advantages such as improve patient compliance by reducing the frequency of dosing. They provide sustained and controlled drug delivery and reduce the dose and reduce adverse effects of the drug. These combinations of the drug delivery system could open the new directive for improving the therapeutic response of a non-efficacious system. They can overcome limitations and combine the advantages of a different system.

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