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Review Article

Advancements In Ocular Drug Delivery System: A Comprehensive Review

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ABSTRACT

The intricate anatomy of the eye presents formidable challenges to effective drug delivery. In response, pharmacosomes have emerged as a promising strategy to address these hurdles, offering targeted drug delivery with controlled release, a crucial requirement for successful treatment outcomes. By integrating a variety of technologies such as in-situ gel, nanoparticles, liposomes, nanosuspensions, microemulsions, iontophoresis, and visual implants, pharmacosomes provide a versatile platform for optimizing drug delivery to ocular tissues. Over the past three decades, significant advancements have been made in developing advanced pharmaceutical formulations tailored specifically for ocular applications. These innovations have substantially enhanced the bioavailability of drugs in ocular tissues, facilitating sustained and controlled release, thus improving therapeutic outcomes. However, the eye's unique anatomical and physiological barriers, including the cornea, sclera, and retina, continue to present significant challenges for drug delivery. While recent advancements in ocular drug administration hold promise for improved treatment outcomes, ongoing research is essential to refine these systems, minimize adverse effects, and tailor them to individual patient needs. Therefore, continuous exploration and refinement of ocular drug delivery technologies are paramount, promising to enhance therapeutic efficacy and elevate the standard of patient care in ophthalmic medicine.

INTRODUCTION

Eyes are one of the vital organs in a human body. As an organ of sense, it permits people to watch and associated with their environment. By and large, the eyeball is isolated into two parts, to be specific the front and the back fragments(1,3). The front portion of the eyeball contains the cornea, iris, focal point, conjunctiva, ciliary body and fluid

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funniness whereas the back section comprises of sclera, choroid, retinal color epithelium, neural retina, optic nerves and vitreous funniness.(1, 30) Novel strategy medicate may be mounted at the cull-de sac or conjunctival empty space of eye is called Chances.(19) These sorts of obstructions are profoundly influencing the bioavailability of ophthalmic drugs. In ophthalmic sedate conveyance framework, the quick and broad disposal is the most issue of routine eye drop from eye. This trouble comes about in colossal misfortune of medicate. As it were a less sum of sedate enters the corneal layer and passes to inner tissue of eye. The most division of medicate misfortune contain lachrymal waste and sedate weakening by tears. This fulfillment decreases the visual bioavailability and conduct to undesirable side effect and poisonous quality(2,31) Eye drops are the foremost commonly utilized routine topical ophthalmic dose shapes due to their ease of organization and tall persistent compliance(4,29)

Most commonly accessible ophthalmic arrangements are eye drops and treatments around 70% of the eye dose definitions in showcase. But these arrangements when ingraining into the cul-de-sac are quickly depleted absent from the visual depth due to tear stream and lachrymal nasal waste. As it were a little sum is accessible for its helpful impact coming about in visit dosing. So overcome to these issues more up to date pharmaceutical ophthalmic definition such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis and visual embeds have been created in final three decades increment the bioavailability of the sedate as a supported and controlled manner(5, 32) Visual medicate conveyance has been a major challenge for researchers due to its one of a kind life systems and physiology which contains different sorts of obstructions such as diverse layers of cornea, sclera and retina counting blood fluid and blood–retinal obstructions, choroidal and conjunctival blood stream etc. These boundaries cause a noteworthy challenge for conveyance of a medicate alone or in a dose shape, particularly to the back fragment of the eye.(6,32) Different methodologies for visual medicate conveyance are considered; from essential detailing techniques for moving forward accessibility of drugs. Chances can be primarily arranged as gels, treatments, microspheres, visual embeds and nanoparticles etc.(7)

The following features are necessary to optimize ocular drug delivery systems(10,35).

- Absorbs well into the cornea.
- Prolonged exposure of the drug to corneal tissue.
- Simple installation and disassembly for the patient.
- Non-irritating and comfortable formulation (viscous solution does not cause tearing and flashes of reflexes).
- Rheological properties and suitable viscosity concentration

ANATOMY AND PHYSIOLOGY OF EYE

Eyes are the organs of vision. It is found within the eye attachment and is innervated by the optic nerve (moment cranial nerve). It has a nearly circular shape and is around 2.5 cm in breadth. The space between the eye and the circle is possessed by greasy tissue. The hard lining of the eye attachment and fat offer assistance secure the eye from harm. The primary is the front portion, which incorporates the cornea, conjunctiva, fluid humor, iris, ciliary body, and focal point. The moment is the back portion which incorporates the retina, choroid, sclera and focal point. The blood-eye obstruction incorporates the blood-aqueous obstruction and the blood-retinal boundary. They are obvious obstructions between the blood and the eye, playing an imperative part within the entrance and annihilation of ophthalmic drugs as well as keeping up homeostatic control. The blood-retinal barrier could be a posterior

obstruction comprising of an deepest boundary within the endothelial layer of retinal vessels and an external obstruction within the retinal color epithelium. (8) The eyeball comprises of numerous layers with a particular structure and is separated into two portions. The primary is the anterior portion which incorporates the cornea, conjunctiva, fluid humor, iris, ciliary body and focal point. The moment is the back portion that includes the retina, choroid, sclera, and focal point. The eye is round, found within the circle and ensured by the eyelids. With a breadth of 24 mm and a volume of 6.5 cm3, it weighs almost 7.5 g. A few layers with a particular structure make up the eyeball and isolate it into two fragments. (8,9)

The eye is encompassed by three diverse layers: the external layer, the centre layer, and the inward layer. The external layer is made up of the cornea and sclera. These are stringy tissues that ensure the eyeball. The sclera, nonstop with the cornea, may be a white, versatile avascular tissue. It covers 80% of the eye tunic. The cornea, connected to the sclera at the limbus, may be a lean (0.5 mm), avascular, and straightforward layer that permits light to reach the eyeball. The front and back parts of the eye are anatomically divided by the sclera and cornea (8,11) The eye is one of the foremost complex organs within the human body. Within the human eye, three layers can be recognized. The external locale is made up of the cornea and sclera. The iris controls the estimate of the understudy and thus the sum of light coming to the retina; The ciliary body controls the strength and shape of the focal point and is where liquid is delivered; and the choroid may be a vascular layer that gives oxygen and supplements to the external layers of the retina.The inward layer of the eye is the retina, a complex structure made up of numerous layers of nerve cells that identify and process light.The three transparent structures surrounded by layers of the eye are called the aqueous layer, the crystalline layer, and the crystalline layer.(12) The eye could be a round structure with a divider comprising of three layers; the external portion of the sclera, the centre portion of the choroid layer, ciliary body and iris and the internal portion of the neural tissue layer of the retina .The eye is made up of a straightforward cornea, focal point, and avascular vitreous body .Oxygen and nutrients are transported to this avascular tissue by the aqueous humor, which incorporates a tall oxygen substance and an osmotic weight comparative to blood.(8)

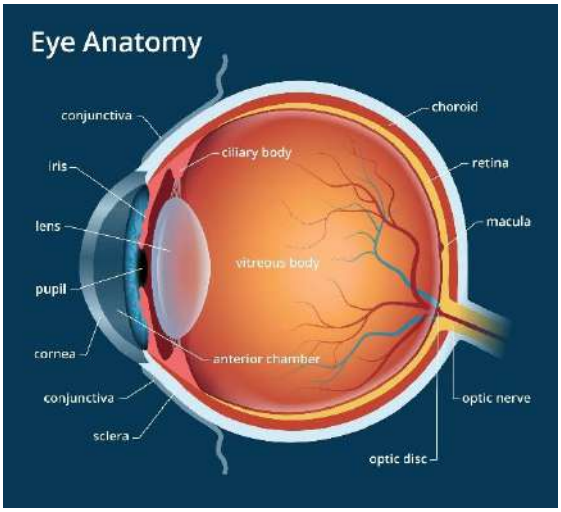

Fig No 1. Anatomy Of Eye

1. **Sclera (White part of eye): -**

The sclera is basically composed of collagen filaments and proteoglycans implanted in an extracellular network. Scleral porousness depends on atomic span and diminishes around exponentially with atomic span. The back sclera is composed of a looser tissue of collagen filaments than the front sclera, and the human sclera is generally thick close the limbus (0.53 + 0.14 mm) and more slender at the equator (0.39 + 0.17 mm), it gets to be indeed thicker close the optic nerve (0.9-1 mm). We discover that an increment in drugs with hydrophobic/lipophilic properties diminishes the penetrability of the sclera. Hydrophilic drugs can more effectively diffuse through the fluid medium of proteoglycans and into the pores of the stringy lattice than lipophilic drugs. The charge of sedate atoms can influence scleral penetrability. Emphatically charged drugs

tie to contrarily charged proteoglycan frameworks, which can decrease their porousness. (13) The whites of the eyes offer assistance interface the eyeballs and muscles. (34)

2. Cornea (clear lens in front of eye):-

The cornea comprises of three layers such as epithelium, stroma and endothelium and a mechanical boundary to repress transport of exogenous substances into the eye. Each layer has a diverse extremity and a rate restricting structure for sedate penetration. The corneal epithelium is lipophilic nature and tight intersections are shaped to confine paracellular sedate penetration from the tear film. The stroma is composed of collagen fibrils. The exceedingly hydrated structure of the stroma acts as a boundary to penetration of lipophilie medicate particles. Corneal endothelium is the deepest monolayer of hexagonal formed cells and acts as a isolating obstruction between the stroma and fluid humor. The endothelial intersections are cracked and encourage the section of macromolecules between watery humor and stroma. (14)

3. Conjuctiva: -

The conjunctiva ensures the eye additionally included within the arrangement and upkeep of the precorneal tear film. The conjunctiva may be a lean straightforward layer lies within the inward surface of the eyelids which is reflected onto the globe. The conjunctiva is made of an epithelium, a profoundly vascularised substantia propria, and a submucosa. (7) The bulbar epithelium contains 5 to 7 cell layers. The structure takes after a pallisadeand not a pavemente corneal epithelium cells are associated by tight intersections, which render the conjunctiva generally impermeable. The atoms up to 20,000 Da can cross the conjunctiva, whereas the cornea is limit to molecules larger than 5000 Da. The human conjunctiva is around 2 and 30 times more retention of drugs than the cornea conjointly proposed that misfortune of sedate by this course may be a major way for sedate clearance. The most noteworthy thickness of conjunctiva is due the nearness of 1.5 million goblet cell changing with age depended among the intersubject changeability and age. The vernal conjunctivitis and atopic kerato conjunctivitis happen due to the incredible variety in challis cell thickness comes about as it were in a little contrast in tear mucin concentration. (15,32)

4. Retina: -

The tactile retina covers the internal portion of the back 2/3 of the earth's divider. It could be a sensitive structure; in its living state it is straightforward and contains a purple-red colour due to the rod's purple colour when seen. The retina could be a multilayered sheet of neural tissue firmly connected to a layer of colour epithelial cells. (33) The retina is the tissue that lines the inward surface of the eye, encompassing the vitreous depth. During embryogenesis, the spinal retina creates from the optic glass. The last mentioned is shaped by the invagination of the optic vesicle, which could be a characteristic improvement of the embryonic forebrain. The inward divider of the optic glass (encompassing the vitreous depth) in the long run gets to be the neural retina; the external divider (encompassed by the choroid and sclera) gets to be the retinal colour epithelium (assault). The retina is secured and held in its legitimate position by the encompassing sclera and cornea. The neural retina comprises of six primary sorts of neurons: photoreceptors, bipolar cells, flat cells, amacrine cells, and ganglion cells, which sense and handle light signals, and muller glia, which act as the organizing spine of the neural retina. The cells of the neural retina are organized in a few parallel layers. (fig:2) (8,12)

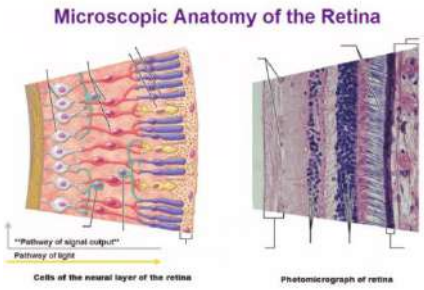

Fig No 2 Retina

5. Choroid/Bruch's membrane: -

Choroid is one of the foremost exceedingly vascularized tissues of the body to supply the blood to retina. The choroidal capillary endothelial cells are fenestrated and in people are moderately huge in breadth (20-40 um). Bruch's layer (BM) causes thickening with age. These changes cause expanded calcification of versatile filaments expanded cross linkage of collagen filaments and expanded turn over glycosaminoglycans. The progressed glycation conclusion items and lipofuscin gather in BM. Thickness changes of choroid and BM might influence medicate penetrability from sub conjunctiva space into the retina and vitreous (13)

6. Pupil: -

The pupil is sometimes referred to as the black "centre" of the eye, although it is more appropriately characterized as the circular opening in the center of the iris through which light travels. The pupillary reflex (also known as the "light reflex") regulates the size of the pupil and hence the quantity of light admitted into the eye. (16)

7. Iris: -

The iris is a thin, circular contractile curtain that sits in front of the lens but behind the cornea. The iris is a variable-size diaphragm that adjusts the size of the pupil to control how much light enters the eye. It is the coloured portion of the eye (shades might vary separately such as blue, green, brown, hazel, or Gray). (16)

8. Lens: -

The lens is a transparent structure contained within a tiny transparent capsule. It is placed behind the pupil of the eye and is surrounded by the ciliary muscles. It contributes to the refraction of light as it travels through the eye. The lens directs light into a picture on the retina. It can accomplish this because the curvature of the lens changes depending on the distance between the person's eye to the object(s) being viewed. Accommodation is the process by which the ciliary muscles contract and relax to change the curvature of the lens. (16)

9. Macula: -

The macula is the retina's central area. The macula includes a large number of photoreceptor cells, which turn light into nerve impulses. Because of the high concentration of photoreceptors, the macula allows humans to perceive minute details like newspaper. The fovea, located at the very center of the macula, is where we have our finest eyesight. (16)

ADVANTAGES OF OCULAR DRUG DELIVERY SYSTEMS (5,17)

1. More precise dosage. To counteract the negative effects of pulsed dosing created by traditional techniques.
2. To give a consistent and regulated medication distribution.
3. Increase the corneal contact time to improve medication ocular absorption. This can be accomplished by good adhesion to the corneal surface.
4. Provide targeting inside the ocular globe to avoid loss of other ocular tissues.
5. To get over protective barriers such drainage, lacrimation, and conjunctival absorption.
6. To promote comfort, enhance patient compliance, and improve the therapeutic performance of the medicine.
7. Provide better housing for the delivery system.

DISADVATAGES OF OCULAR DRUG DELIVERY SYSTEMS (18,19)

1. Certain devices are difficult to install and remove.
2. It is difficult to manage.
3. It's pricey.
4. Occasional loss occurs while rubbing eyes.
5. The emergency dose shape cannot be cancelled.
6. Sensing movements around the focus.
7. The dissolved medication is unstable.
8. Experiencing an international frame sense.
9. An extremely rapid response stays on the floor of the eye.
10. In a very short period, the response stays on the floor of the attention.

BARRIERS OF DRUG PERMEATION: (5,10,32)

1. DRUG LOSS FROM THE OCULAR SURFACE

After instillation, the stream of lacrimal liquid expels ingraining compounds from the surface of the eye. Indeed, in spite of the fact that the lacrimal turnover rate is as it were approximately 1 µl/min the overabundance volume of the ingraining liquid is flown to the nasolacrimal channel quickly in a handful of minutes. Another source of non-productive drug expulsion is its systemic retention rather than visual assimilation. Systemic retention may take put either specifically from the conjunctival sac through neighborhood blood capillaries or after the arrangement stream to the nasal depression. Besides, most of little atomic weight sedate measurements is ingested into systemic circulation quickly in few minutes. This contrasts the moo visual bioavailability of less than 5%. Medicate assimilation into the systemic circulation diminishes the sedate concentration in lacrimal liquid broadly. Subsequently, steady medicate discharge from strong conveyance framework to the tear liquid may lead as it were to visual bioavailability of approximately 10%, since most of the medicate is cleared by the neighbourhood systemic retention besides.

2. Lacrimal fluid-eye barriers: -

Corneal epithelium limits sedate assimilation from the lacrimal liquid into the eye. The corneal obstruction is shaped upon development of the epithelial cells. They relocate from the limbal locale towards the middle of the cornea and to the apical surface. The foremost apical corneal epithelial cells frame tight intersections that constrain the paracellular sedate saturation. In this manner, lipophilic drugs have ordinarily at slightest an arrange of magnitude higher porousness within the cornea than the hydrophilic drugs. In spite of the snugness of the corneal epithelial layer, transcorneal saturation is the most course of medicate entrance from the lacrimal liquid to the watery humour (Fig. 3). In common, the conjunctiva is more cracked epithelium than the cornea and its surface region is additionally about 20 times more noteworthy than that of the cornea. Sedate retention over the bulbar conjunctiva has picked up expanding consideration as of late, since conjunctiva is additionally decently penetrable to the hydrophilic and huge atoms. Hence, it may serve as a course of assimilation for bigger bio-organic compounds such as proteins and peptides. Clinically utilized drugs are for the most part little and reasonably lipophilic. Hence, the corneal course is as of now overwhelming. In both films, cornea and conjunctiva, standards of detached dissemination have been broadly examined, but the part of dynamic transporters is as it were inadequately examined.

3. Blood-ocular barriers: -

Blood-ocular barriers protect the eye from xenobiotics found in the bloodstream. These barriers consist of two parts: the blood-aqueous barrier and the blood-retina barrier. The endothelial cells of the uvea form the anterior blood-eye barrier. This barrier inhibits plasma albumin from entering the aqueous humor, as well as hydrophilic medicines from entering the

plasma. Inflammation may compromise the integrity of this barrier, allowing unfettered medication transport to the anterior chamber. In reality, the permeability of this barrier is poorly understood. The RPE and the tight walls of retinal capillaries form the posterior barrier between the bloodstream and the eye. Unlike retinal capillaries, the vasculature of the choroid contains significant blood flow. The choroid vasculature differs from retinal capillaries in that it has significant blood flow and permeable walls. Drugs can easily enter the choroidal extravascular space, but their distribution into the retina is restricted by the RPE and retinal endothelia. Despite its substantial blood flow, choroid blood flow accounts for just a small portion of the total blood flow in the body. Without appropriate targeting devices, only a small portion of the intravenous or oral medication dosage reaches the retina and choroid. Unlike the blood brain barrier, the blood-eye barrier has not been characterized in terms of drug transporter and metabolic enzyme expression. From the pharmacokinetic point of view bounty of fundamental inquire about is required some time recently the nature (29)

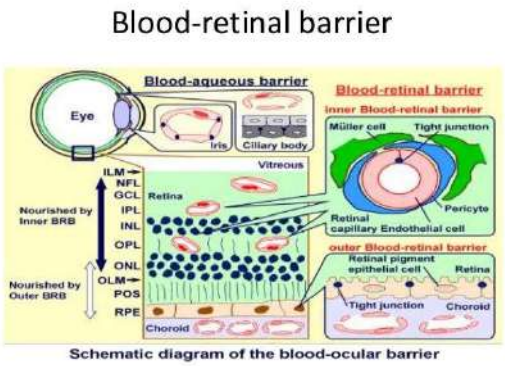

Fig No 3 Schematic diagram of the blood-ocular barrier

Methods to overcome barrier: (17)

I. Physical Methods

1. Iontophoresis
2. Sonophoresis
3. Microneedle

I. Physical methods

Physical force-based approaches, which were first used in transdermal drug administration, typically need a power-driven physical device to give energy to the barriers, improving transitory drug transport.

1. Iontophoresis:

It is the mechanism by which direct current transports ions into cells or tissues. Iontophoresis, the use of a low-intensity electrical current, improves medication transport across biological membranes by generating electro-repulsion and electro-osmosis of the drug molecule. Electro repulsion is typically used for the transportation of ionic medicines, although electro-osmosis can improve the transport of both neutral and charged molecules via convective solvent flow. The relative contribution of electro repulsion and electro-osmosis is determined by the drug's physicochemical qualities (e.g. size, charge, and charge-to-molecular-weight ratio) as well as the electrical properties of the biological membrane. Ocular iontophoresis is a drug delivery technology that is quick, painless, and safe, and in most circumstances results in the administration of a high concentration of medicine to a particular spot.

2. Sonophoresis /Ultrasound:

It includes the application of a sound field at frequencies higher than 20 kHz to move forward medicate transport over organic layers, counting visual obstructions. The instruments for ultrasound upgraded sedate conveyance take into consideration non-thermal (e.g. cavitation, acoustic spilling and mechanical push) and warm impacts with ultrasound parameters, co-administration of microbubbles and sedate characteristics, all having an impact on conveyance viability. Cavitation is by and large considered the transcendent figure for upgraded sedate conveyance and is characterized as the arrangement of microbubbles due to an acoustic weight angle inside the coupling medium. Corneal

penetrability improvement is for the most part a result of steady cavitation at moo ultrasound force, though both steady and inertial cavitation play vital parts at higher ultrasound qualities.

3. Microneedles:

Microneedles (MLs) are needles or arrays of needles that are sized at micrometers and are created using customizing microelectronics instruments. Drugs can pass through biological membranes when MLs are applied because they can form small transport channels. Numerous ML manufacturing techniques have been used to far, yielding a wide range of materials, combinations, sizes, and forms. Insertion of MLs across the corneal epithelium can result in enhanced medication delivery into the cornea and anterior portion of the eye. A wide range of polymeric MLs have proven particularly beneficial for intrascleral medication administration. Ocular MLs may be divided into four varieties based on how they are delivered: solid microneedles, drug-coated microneedles, dissolving microneedles, and hollow microneedles.

II. Chemical Approaches:

An established method in restorative sedate delivery is the chemical adjustment of pharmaceuticals to increase various physicochemical features such as dissolvability, steadiness, porousness, and avoidance of efflux pump, hence making significant progress toward restorative adequacy. Chemically modified medications with predictable metabolic bioconversion in the eye can be used thanks to the metabolic activity of the visual tissues.

The following are the key tactics in chemical techniques for ocular delivery:

- Creating ocular medications (prodrugs) that are inactive in locations other than the eyes
- Retro metabolic design: creating medications that go through a series of metabolic conversions before reaching their goal.
- Chemical alteration to recover the therapeutic action from a known inactive metabolite or analog, which reverts to its inactive state in a dependable one-step biotransformation (SD)

Ocular formulations

I. Drug delivery systems to anterior segment of the eye
II. Drug delivery systems to posterior segment of the eye
III. Advanced delivery system
IV. Vesicular drug delivery system

I. Drug delivery systems to anterior segment of the eye (9)

1. Eye-Drops

Drugs that operate on the surface of the eye or in the eye are frequently supplied as suspensions, emulsions, and solutions. Since this drug delivery mechanism does not reach acceptable drug concentrations in the posterior tissues, eye drops are often employed for anterior segment problems. Retention of a solution in the eye can be affected by a number of characteristics of the eye drop, including its viscosity, osmolality, concentration of hydrogen ions, and injected volume. To prolong the drug's effects for several hours, an eye drop creates a hydrogen bond with the negatively charged mucus, corneal, and conjunctival epithelium. Bacterial conjunctivitis can be treated using Inspire Pharmaceuticals Inc.'s Durasite-infused azithromycin ophthalmic solution.

2. Opthalmic Inserts

Sterile preparations having a solid or semisolid consistency, specifically formulated for ocular use, are called ophthalmic inserts. The lower fornix is where the inserts are inserted, whereas the upper fornix or cornea are used less frequently.

Classification of ocular inserts

Based upon their solubility behaviour

I. Insoluble inserts
II. Soluble inserts
III. Bioerodible inserts

I. Insoluble ocuserts (21)

Reservoir systems and matrix systems are two classifications for insoluble ocuserts.

a. Reservoir system

The medication is released in this system either by an osmotic mechanism or by diffusion. It comprises liquid, gel, colloid, semisolid, solid matrix, or drug-containing carrier, in that order.

Diffusional insert or ocuserts

This innovative ocular medicine delivery device is based on porous membrane occuserts. Diffusional release mechanisms underpin the drug release from occusert implants. The medicine is allowed to diffuse through the core reservoir of the diffusional systems at a carefully controlled pace thanks to specially engineered semipermeable or microporous membranes around it. The lacrimal fluid that passes through the membrane in such a device regulates the release of the medication until an internal pressure is achieved that forces the drug out of the reservoir. Diffusion through the membrane, which one may regulate, governs the pace of medication delivery. For instance, pilocarpine, an ocular hypotensive medication, has a uniform regulated release (20 or 40µg/hr) for seven days with the ocusert device.It includes two outside layers made of ethylene vinyl acetate co polymer (EVA) sandwiched between two inside layers composed of pilocarpine in alginate gel, with di(ethylhexyl) phthalate serving as a release enhancer. Ocusert has a few drawbacks, including a challenging insertion process, ejecting the device from the eye, and causing discomfort during insertion.

Osmotic inserts

Osmotic inserts are typically formed of a center section bordered by a peripheral part and are classified into two types:

Type 1

The center component is made up of a single drug reservoir surrounded by a polymer in the form of discrete tiny deposits, with or without an extra osmotic solution scattered throughout the matrix. The inserts' second peripheral element was made up of an insoluble semipermeable polymer sheet. The osmotic pressure on the polymer matrix leads it to break, resulting in apertures. Near the device's surface, drug is released from the deposits through these pores.

Type 2

The middle section is divided into two divisions. The drug and osmotic solutes are separated into two compartments, with an elastic impermeable membrane around the drug reservoir and a semi-permeable membrane surrounding the osmotic solute reservoir. The second peripheral portion of this kind is comparable to type 1. Tear fluid diffuses into the peripheral deposits via the semipermeable polymeric barrier, wetting and causing them to dissolve. The solubilized deposits produce hydrostatic pressure against the polymer matrix, causing it to break in the form of apertures. The drug is then delivered through these pores from deposits at the device's surface that is in contact with the eye, using just hydrostatic pressure.

b. Matrix systems

Contact lenses and a subset of insoluble ophthalmic devices make up the second category of matrix systems. It is a three-dimensional network or matrix made up of covalently cross-linked hydrophilic or hydrophobic polymers that may hold water, aqueous drug solution, or solid components.

Contact lenses

Initially, contact lenses were employed to correct eyesight. These are structured structures composed of a covalently cross-linked hydrophilic or hydrophobic polymer that creates a three-dimensional network or matrix capable of holding water, aqueous solutions, or solid components. When a hydrophilic contact lens is immersed in a drug solution, it absorbs the medicine but does not provide the same level of precision as other non-

soluble ophthalmic systems. Drug release from such a device is often quite quick at first and then decreases significantly over time. The release rate can be reduced by introducing a homogeneous drug combination during the manufacturing process or by using a hydrophobic component. Contact lenses are split into five types: rigid, semi-rigid, elastomeric, soft hydrophilic, and biopolymeric.

II. Soluble Ophthalmic inserts

Soluble inserts are the earliest type of ophthalmic inserts. Soluble inserts are often classified as erodible, monolithic polymeric devices that release the medicine and do not require removal as they gradually dissolve. True dissolution is primarily achieved by polymer swelling, whereas erosion is caused by a chemical or enzymatic hydrolytic process. The active substance is disseminated uniformly in swelling-controlled devices made of glassy polymers. When the insert is inserted in the eye, water from the tear fluid penetrates the matrix, causing swelling and polymer chain relaxation, as well as medication diffusion.

Types of soluble ophthalmic inserts

a. Based on natural polymers e.g. collagen.
b. Based on synthetic or semi synthetic polymers

a. Natural polymers

b. The natural polymer utilized to make soluble ophthalmic inserts is ideally collagen. The therapeutic agent is best absorbed by soaking the insert in a drug-containing solution, drying it, then rehydrating it before applying it to the eye. The amount of drug loaded is determined by the amount of binding agent present, the concentration of the drug solution in which the composite is soaked, and the soaking time. As the collagen degrades, the medication gradually emerges from the spaces between the collagen molecules.

c. Synthetic and semi-synthetic polymer

This is based on the usage of polymers, namely semi-synthetic polymers (e.g., cellulose derivatives) and synthetic polymers, such as polyvinyl alcohol. Eudragit, a polymer commonly used for enteric coating or as an insert coating agent, can be employed to achieve a lower release rate. Ethyl cellulose, a hydrophobic polymer, can be utilized to reduce the deformation of the insert, preventing blurred vision.

III.Bio-erodible ocular inserts

These inserts are made of bio-erodible polymers (for example, cross-linked gelatin derivatives and polyester derivatives), which dissolve due to chemical bond hydrolysis. The ability to modulate the erosion rate of these bio-erodible polymers by synthesis modifications and the addition of anionic or cationic surfactants is a significant benefit. Some significant ocular implants that are commercially available (SODI) or in advanced development (collagen shields, Ocufit, and Minidisc).

Soluble ophthalmic drug insert

Soviet scientists created the soluble ophthalmic drug insert (SODI), a tiny oval wafer, for cosmonauts who were unable to utilize eye drops while in weightlessness. A soluble copolymer of ethyl acrylate, acrylamide, and N-vinyl pyrrolidone is called a SODI. It comes in the shape of oval-shaped, sterile thin film or wafers that weigh between 15 and 16 mg. next its insertion into the upper conjunctival sac, the SODI softens in 10 to 15 seconds, taking on the shape of the eyeball; the film then transforms into a polymeric clot in the next 10 to 15 minutes, which eventually dissolves in 1 hour while releasing the medication.

Collagen shields

Over twenty-five percent of the protein in animals' bodies is made up of collagen, which is the structural protein of skin, tendons, ligaments, and bones. Nowadays, collagen shields made of bovine corium (dermis) or porcine scleral tissue are used in collagen shield manufacturing. Type I

and some type III collagen are present in these materials. They have a contact lens-like shape and are delivered dried, so you have to rehydrate them before inserting them. The amount of time a lens takes to dissolve is determined by variations in the collagen crosslinking caused by ultraviolet radiation (UV) during production. There are now three types of collagen shields that dissolve in 12, 24, and 72 hours. The dimensions of corneal collagen shields are 14.5–16.0 mm in diameter, 9 mm for the base curve, and 0.15–0.19 mm in the center.

Ocufit

The 1992-patent Ocufit is a silicone elastomer sustained release rod device being developed by Escalon Ophthalmics Inc. (Skillman, NJ). Its dimensions and form were intended to match those of the human conjunctival fornix. As a result, its diameter and length are limited to 1.9 mm and 25–30 mm, respectively; nevertheless, lesser versions are intended for toddlers and newborns.

The Minidisc ocular therapeutic system

The Minidisc ocular therapeutic system (OTS), a monolytic polymeric device first reported by Bawa et al. (Bausch and Lomb, Rochester, New York), is shaped like a tiny (4-5 mm) contact lens, with a convex and a concave face, the latter of which roughly conforms to the sclera of the eye. According to reports, the device's specific dimensions and form make it simple to position beneath either the top or lower lid without sacrificing comfort, visibility, or oxygen permeability. Table 1 lists the ocular insert devices.

Table 1: Ocular inserts devices

Name	Description
Ocular soluble medication	Place in little oval wafer; it will soften upon insertion. The wafer is made of soluble copolymers that include actylamide, N-venyl pyrrolidone, and ethyl acetate.
New method for delivering drugs to the eyes	Medicated solid polyvinyl alcohol flag with a handle made of paper attached. Upon application, the drug-releasing flag separates and slowly dissolves.
Collagen barriers	Porcine scleral collagen cross-links make up the erodible disc.
Ocusert	Commercially available, flat, flexible, elliptical insoluble device with two layers encircling a reservoir that delivers pilocarpine for seven days
Small-disk or eye therapy	structure hydrophilic or hydrophobic disk with a shape and a diameter of 4-5 mm
Lacrisert	Hydroxy propyl cellulose rose-shaped device used as a replacement to tears for eye syndrome
Gelfoam	Gelfoam slabs impregnated in chloroform with a medicine and cetyl ester wax combination
Dry drops	On the tip of a soft, hydrophobic carrier strip, a preservative-free hydrophilic polymer solution is freeze dried; the strip then instantly hydrates in the tear strip.

3.Punctal Plugs

A well-established method for extending the retention period and boosting absorption and effectiveness following the application of eye drops is to block drainage through the nasolacrimal system by inserting a punctual plug into the puncta.

The effectiveness of ocular hyposensitive agents in eye drops in conjunction with punctual plug occlusion is documented.

4. Subconjunctival/Episcleral Implants

Biodegradable polymers and medications can be used to create a scleral plug, which can be inserted into the pars plana area of the eye and delivers

medication dosages gradually over several months as it breaks down. The kind of polymers utilized, their molecular weights, and the amount of medication in the plug all affect the release profiles. The silicone matrix episcleral implant LX201 (Lux Biosciences, USA) is intended to provide cyclosporine A to the surface of the eye for a duration of one year. The implant has a flat bottom in contact with the episclera and a rounded top in contact with the anterior surface.

5. Ointment and Gels

With ophthalmic ointments and gels, the duration of medication interaction with the external eye surface can be extended. Gels and ointments can thereby increase the duration of effect and improve the ocular bioavailability of medications. The ointment fragments into tiny droplets and stays in the cul de sac for a long time as a drug depot. However, matting of the eyelids and blurring of vision can restrict their uses.

II. Drug delivery systems to posterior segment of the eye (22)

1. Intravitreal Implants

Durasert™ Technology System

The DurasertTM technology system (pSivida Crop.,US) distributes medications for predefined durations ranging from days to years by utilizing a drug core surrounded by one or more polymer layers.The polymer layers' permeability regulates the drug's release.Cytomegalovirus retinitis can be treated with ganciclovir-loaded implants using the DurasertTM technology system.This implant, which is composed of PVA and ethylene vinyl acetate copolymer (EVA), releases ganciclovir over the course of six to eight months by passive diffusion through a tiny hole in the EVA at the base of the device.

Novadur™ Technology

The FDA has authorized Ozurdex® (Allergan Inc., US), an intravitreal implant made of PLGA (6.5 mm in length and 0.45 mm in diameter) and contains 0.7 mg of dexamethasone.It is used to treat macular edema brought on by central and branch retinal vein occlusions (BRVO and CRVO). Ozurdex® is injected into the vitreous cavity using a specialized injector equipped with a 22-gauge needle.

I-vation™ TA

The vitreous of the eye is treated with triamcinolone acetonide (TA) administered by I-vationTM technology (Sur Modics Inc., US). The titanium helical coil (0.5 mm in length and 0.21 mm in width) used in the I-vationTM intravitral implant is covered with TA (925µg), EVA, and non-biodegradable polymers such poly(methylmethacrylate).This implant has a minimum two-year in vivo lifespan.

NT-501

Via an implanted device in the vitreous, encapsulated cell technology (Neurotech Pharmaceuticals Inc., US) delivers ciliary neutropic factor (CNTF) extracellularly through long-term, sustained intraocular release at consistent levels. It contains human RPE cells that have undergone genetic modification to produce human CNTF recombinant. The device is made up of six strands of cell-loaded polyethylene terephthalate yarn encased in a sealed, semi-permeable membrane capsule. A small sclera incision is used to surgically implant the device into the vitreous, and one end of the device is secured with a single stitch through a titanium loop.The semipermeable barrier shields the contents from host cells immunologic assault while permitting the outward diffusion of CNTF and other cellular metabolites and the inward diffusion of nutrients required to ensure the cell survival in the vitreous cavity.

2. Injectable particulate systems

IBI-20089

Icon Bioscience Inc.'s VerisomeTM drug delivery platform technology is used in IBI-20089 to administer triamcinolone acetonide (TA).In contact with saltwater, the IBI-20089 solution

takes on a milky, somewhat opaque hue and gels.IBI-20089 is a biodegradable benzyl benzoate solution containing TA. It is intended to administer medication with a single intravitreal injection for up to a year.

RETAAC

Patients with diabetic macular edema (DME) may benefit from intravitreal injections of RETAAC, which have been shown to be more effective than injections of bare TA. For a year, eyes treated with RETAAC demonstrated reduced retinal thickness and enhanced visual acuity.The retina can take it without any problems.

Cortiject®

Target tissue activated corticosteroid prodrug is encapsulated in an oily carrier and phospholipid surfactant in Cortiject® (Novagali Pharma S.A.), a preservative-free emulsion.

Visudyne®

Photosensitizer is a component of the intravenous liposomal formulation Visudyne® (QLT Ophthalmics Inc., USA). Verteporfin in photodynamic treatment for pathologic myopia, suspected ocular histoplasmosis, or AMD-related subfoveal choroidal neovascularization. Low-density lipoprotein (LDL), a kind of plasma lipoprotein, has been demonstrated to increase the number of LDL receptors in tumor cells, which enhances the administration of hydrophobic verteporfin to malignant tissue. Since phosphatidyl glycerol makes up a significant portion of the Visudyne® formulation, undissociated verteporfin that is still encapsulated in liposomes is accumulated in vascular endothelial cells via LDL receptor-mediated endocytosis. Verteporfin released in blood from liposomes is associated with LDL and uptakes in neovascular tissues.

III. Advanced delivery system (23)

1. Cell encapsulation

Encapsulated cell technology (ECT) is the process of entrapping immunologically separated cells with hollow fibers or microcapsules prior to their delivery into the eye. It makes it possible to deliver therapeutic proteins to the posterior areas of the eye in a regulated, continuous, and long-term manner. The patient's vitreous humour secretes ciliary neurotrophic factor due to the polymer implant that contains genetically engineered human RPE cells. Chronic ocular disorders such as neuroprotection in glaucoma, antiangiogenesis in choroidal neovascularization, and anti-inflammatory factors in uveitis are treated with ECT using a delivery system.

2. Gene therapy

Gene therapy techniques are employed in conjunction with tissue engineering to cure blindness caused by corneal disorders, cataracts, glaucoma, etc. Gene transfer and gene therapy applications include the manipulation of many viruses, such as adenovirus, retrovirus, adenoassociated virus, and herpes simplex virus. Ocular gene transfer by topical application is the fastest method. Because of their great effectiveness, retroviral vectors are utilized, which limits their clinical usage. By extending the duration of the vector's interaction with the ocular surface, the sophisticated delivery methods could improve transgenic expression and enable non-invasive administration.

3. Stem cell Therapy:

The cornea and retina, which are essential for visual function, can be restored with cell therapy. Currently, treating eye diseases involves either getting rid of the harmful substance or trying to lessen its effects. The most effective ocular use for limbal stem cells is their transplantation from a source other than the patient to regenerate the corneal epithelium. Limbal cells can be obtained from donors, autografts, cadaver eyes, and cultured cells.

4. Protein and peptide therapy

A key component of medication administration is the transportation of therapeutic proteins and peptides to the eye. However, a number of

constraints, including solubility, metabolism, size, and membrane permeability, limit how effectively they may be delivered. Hydrophilic peptides with low membrane permeability can have their permeability increased by structurally altering the molecule. The recommended method for systemic distribution of such big molecules is not the ocular route. Transscleral delivery of immunoglobulin G to the retina is an efficient method with negligible systemic absorption.

5. Scleral plug therapy

Made of biodegradable polymers and medications, scleral plugs can be placed at the pars plana area of the eye by a straightforward operation. When it biodegrades, effective dosages of medications are released for several months. The kind of polymers utilized, their molecular weight, and the amount of medication in the plug all affect the release profiles. The plugs are useful in the treatment of vitreoretinal illnesses that need vitrectomy, such as proliferative vitreoretinopathy and viral retinitis that reacts to recurrent intravitreal injections.

6. siRNA therapy

The choroidal neovascularization is treated with siRNA therapy. These strategies are applied in clinical studies, where the siRNA is targeted against either VEGF or VEGF receptor 1 (VEGFR1). Topical use of siRNA is intended to inhibit corneal neovascularization by targeting VEGF or its receptors. Gene delivery in ocular disease processes also occurs via siRNA treatment. According to reports, siRNA may be used in the pathophysiology and creation of novel therapeutics for ocular illnesses, drawing on both in vitro and in vivo research. Using polymer vesicles or liposomes linked with antibodies, new encapsulated siRNA is created.

7. Oligonucliotide therapy

Oligonucleotide (ON) treatment works by interfering with the transcription of DNA to mRNA or the translation of mRNA to proteins, hence preventing the creation of cellular proteins. The antisense molecules obstruct protein synthesis and interfere with gene expression.

The effectiveness of antisense oligonucleotides is shown to be influenced by several variables. The length of the ON species is taken into account first. According to reports, ONs with a length of 17–25 bases are ideal because they may partially hybridize with non-target RNA species. When transferring DNA and RNA oligonucleotides to cells, the main obstacle to take into account is biological stability. It is possible to prevent nuclease activity by altering bases, sugar moieties, and phosphate backbones.

8. Aptamer

Oligonucleotide ligands known as aptamers are employed to bind molecules with a high degree of affinity. Through an iterative process of adsorption, recovery, and reamplification, it is separated from synthesized nucleic acid. It exhibits great selectivity and extremely low binding with the target compounds. The RNA aptamer pegaptanib sodium (Pfizer) targets the VEGF isoform that is mainly in charge of vascular permeability and pathological eye neovascularization.

9. Ribozyme therapy

RNA enzymes, also known as ribozymes, are single-stranded RNA molecules with the ability to adopt three-dimensional conformations and catalyze the cleavage, ligation, and polymerization of nucleotides involving DNA or RNA at particular sites. By cleaving the phosphodiester backbone at a particular cutting location, it attaches itself to the target RNA molecule and renders it inactive. In cases with autosomal dominant retinitis pigmentosa (ADRP), ribozyme administration appears to be beneficial for managing the condition. Gene mutations causing altered proteins that cause photoreceptor cells to undergo apoptosis are the cause of ADRP.

IV. Vesicular system (24)

1. Liposomes

Liposomes are lipid-based vesicles that have an aqueous volume inside of them. Liposomal drug delivery systems are capable of delivering lipophilic medications to the ocular system. They are in close proximity to the surfaces of the cornea and conjunctiva, which is advantageous for poorly absorbed, low-partition-coefficient, and poorly soluble medicines. Thus, it improves the absorption of drugs into the eyes.

2. Niosomes

Nonionic surfactant vesicles known as niosomes may be used to transport hydrophobic or amphiphilic medications. Compared to liposomes, they are more stable.As a result, they may readily target the medication to the eye.

3. Pharmacosomes

Pharmacosomes are a useful technique for achieving targeted medication delivery and controlled release, among other desirable therapeutic objectives. Any medication containing an active hydrogen atom (-COOH, -OH, -NH2, etc.) can be esterified to a lipid with or without a spacer chain, producing a molecule that is highly amphiphilic and that will help the organism transfer its membranes, tissues, or cell walls. These are described as colloidal dispersions of pharmaceuticals that are covalently bonded to lipids. Depending on the chemical nature of the drug-lipid combination, these can exist as ultrafine vesicular, micellar, or hexagonal aggregates. The pharmacosomes exhibit improved stability, easier corneal transport, and a regulated release profile.

MECHANISM OF DRUG RELEASE

The following describes the mechanism of controlled drug delivery into the eye:

a. Diffusion
b. Osmosis
c. Bio-erosion.

A. Diffusion:

Through the membrane and into the tear fluid, the medicine is continually delivered at a predetermined pace in the Diffusion mechanism. if the insert is made of a non-erodible, solid body with pores and a distributed medication. Diffusion through the pores may cause the medication to discharge. Due to inward diffusion of aqueous solutions, the solid medication placed inside this matrix can gradually dissolve, further regulating controlled release (28). True dissolving in a soluble device mostly happens as a result of polymer swelling. The active ingredient in swelling-controlled devices is uniformly distributed throughout a glassy polymer. Glassy polymers do not allow drug diffusion through the dry matrix since they are basically drug-impermeable. Water from the tear fluid starts to seep into the matrix when the insert is inserted into the eye. This causes swelling, which in turn causes polymer chain relaxation and drug diffusion. Following the swelling process, the matrix dissolves, and this process is influenced by the polymer structure. Polymers that are linear and amorphous dissolve considerably more quickly than those that are cross-linked or partly crystalline. In general, release from these devices follows Fickian kinetics, or the "square root of time." In rare cases, however, it is referred to as zero order or case II transport. (5,24,25)

B. Osmosis

The insert in the Osmosis mechanism is made up of a transverse impermeable elastic membrane that divides the interior into two compartments: the first compartment is enclosed by the impermeable elastic membrane and a semi-permeable membrane, and the second compartment is enclosed by both the impermeable material and the elastic membrane. The insert's impermeable wall has a medication release hole. The medicine, which is once more in liquid or gel form, is stored in the second compartment, which also has a solute that is unable to flow through the semipermeable barrier. Water diffuses into the first compartment of the insert when it is put in the aqueous environment of the eye, stretching the elastic

membrane to cause the first compartment to expand and the second compartment to contract, forcing the drug through the drug release aperture. (5, 26)

C. Bio-Erosion (5,25,26) :

The drug is placed within a matrix of bioerodible material that makes up the insert's body structure in the bioerosion process. By use of matrix bioerosion, the insert's contact with tear fluid causes a regulated, prolonged release of the medication. The medication can be evenly distributed throughout the matrix, but it's thought that if the medication is surface-concentrated, a more regulated release will occur. The rate of drug release in fully erodible or E-type devices is regulated by a hydrolytic process, either chemical or enzymatic, which results in the breakdown of the polymer into smaller, watersoluble molecules. According to Heller's specifications (27) these polymers can hydrolyze in bulk or on the surface.

CONCLUSION:

To sum up, the complex architecture of the eye presents significant challenges for the administration of medications. Conventional techniques, including ocular drops, have problems with limited bioavailability and quick elimination. Novel formulations such as in-situ gels and nanoparticles have been developed to improve medication penetration and retention in response to these difficulties. Overcoming obstacles like the cornea and blood-eye barrier, which limit access to the inside of the eye, is essential for the successful delivery of drugs into the eyes. Furthermore, it is critical to guarantee patient comfort and compliance, which calls for formulations with appropriate rheological characteristics and low irritation. Even while developments in ocular drug administration present encouraging opportunities for better treatment outcomes, further research is necessary to increase the effectiveness of these systems, minimize any negative effects, and modify them. Future advancements might transform ocular therapeutics and provide patients with safer and more effective treatment choices for a range of eye disorders by utilizing a greater understanding of ocular anatomy and physiology.

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