

CHALLENGES AND OPPORTUNITIES IN OPHTHALMIC INSERT DEVELOPMENT: A PROMISING APPROACH TO OCULAR DRUG DELIVERY

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ABSTRACT

Ophthalmic inserts are new technologies that seek to improve medication uptake and management of some eye conditions by offering a constant therapeutic level. The anatomy of the eye has been integrated with the system, making the administration of drugs a much more challenging hurdle for the transducer to overcome. There is a barrier within the eye tissues known as the blood-retinal barrier, which limits contact to the area and makes medication poorly bioavailable. In addition, the cornea is most likely physiologically impermeable through the topical route. Therefore, to distribute drugs to the posterior segment involves retaining systems or employing special devices to hold the drug for an extended time. Devices such as microneedles or iontophoresis cause pain during delivery, so painless methods, which involve ophthalmic or ocular inserts, are preferable. Their residence time or contact time with the drug is long, and therefore, bioavailability is enhanced through steady or controlled release. The different ocular inserts, their composition, and the polymers that go into making them are all covered in this article. Types of ocular inserts, such as insoluble, soluble, and bio-erodible inserts, are explained briefly. Also, the general excipients used to prepare the inserts, and their description have been included. The regulatory landscape for ophthalmic inserts also presents hurdles, as they are classified as drug-device combination products, necessitating compliance with pharmaceutical and medical device regulations, which can extend approval timelines and increase development costs.

INTRODUCTION

The effectiveness of drug delivery through the ocular route is a challenging task because of the complex nature and physiology of the eye. For the anterior segment of the eye, conventional dosage forms like eye drops, suspensions, and

ointments have been popular in the market and are widely used. The delivery of the drug into the posterior segment of the eye requires novel systems like ocular implants, which are made of either biodegradable or non-biodegradable polymers. Also, the delivery to the

posterior part is difficult because of the complex physiology of the eye tissue¹. The use of eye drops and other conventional dosage forms gives low bioavailability of the drug, and the waste of the drug is higher. Later, high-viscosity formulations were used to increase the contact time with the corneal surface. So, ointments that have viscosity-enhancing agents and are water-insoluble to enhance the drug eye contact time came into the market. Later, the invention of ocular inserts made the delivery of the drug easier to the posterior parts of the eye. However, they need to be irritation-free, painless, and patient-compliant. The conventional formulations have rapid pre-corneal elimination, which the inserts have overcome.

Tear film generally contains 7 μ L of fluid, but on insertion of eye drops or solutions, it increases to 30 μ L. Moreover, because of the limited capacity of the eye to hold the fluid, a fraction of the drug solution, along with the tears, gets squeezed out and leads to the wastage of the drug. Drugs from the tear film diffuse into the cornea or the conjunctiva with comparatively high permeability and a larger area. So, the permeation of the drug through the conjunctiva is 20 times higher than from the cornea. Due to the tear film barrier, the bioavailability of the drug is a maximum of 1-2% in the case of ocular delivery². Hence, higher concentrations are required to obtain therapeutic action, which might also be toxic to the cornea. Also, a significant fraction of drugs enter systemic circulation by pre-corneal absorption, which may enhance the side effects and adverse reactions of the drug. The invention of the ocular inserts has overcome the drug's unwanted effects and increased its bioavailability. Further research on the ophthalmic inserts can be done for the delivery of two incompatible drugs and a sustained or controlled drug

release. These inserts are made of biocompatible polymers that have low toxicity and can release the drug in a sustained manner. The main action of the insert that leads to increased bioavailability is an increase in the residence time or contact time. These have overcome the painful way of drug delivery, such as microneedles and iontophoresis.

The globe of the eye, or the eyeball, is embedded in the orbit of the skull and is a slightly asymmetric sphere. The diameter of an adult's eyeball is about 2.5cm. Several parts of the eyeball include the cornea, iris, pupil, lens, sclera, retina, optical disc, etc. The outermost part of the eye consists of the cornea and sclera. The cornea refracts the light onto the lens, and the sclera is a connective tissue coat that protects the eye from external forces³. The conjunctiva is the visible part of the sclera. The choroid, ciliary body, and iris comprise the eye's central layer. Aqueous production occurs in the ciliary body and controls the lens's strength and form. The iris controls the pupil's size to control how much light reaches the retina. The outer retinal layers receive oxygen and nourishment from the choroid, a vascular layer. The retina is the inner layer of the eye, a complex, layered arrangement of neurons that process and capture light. The aqueous, the vitreous, and the lens are the three translucent organs encircled by the ocular layers⁴. The human eyeball comprises three layers: the outer fibrous layer, whose anterior part is the cornea, and the posterior part is the sclera; the middle vascular layer, consisting of the ciliary body and iris; and the third nervous layer, the retina. The sclera is white and contains the microcirculation for the nourishment of tissues. The cornea is 0.5 – 1 mm thick and contains corneal epithelium, stroma, and corneal

endothelium. Epithelium protects against bacterial invasions. A labelled diagram of the eye is given in Fig. 1.

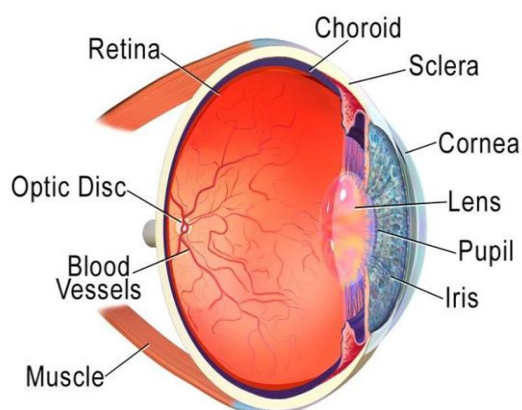


Fig. 1: Eye anatomy

OCULAR BARRIERS

Topical ocular medications, usually applied as eye drops, are the standard dosage forms for treating ocular illnesses. These drugs must first overcome the tear film because they rapidly remove injected materials from the eye and lower their bioavailability. The membranous barriers include the cornea, conjunctiva, iris-ciliary body, and retina. There are two routes of passage for the drugs in ocular delivery, which are the corneal route and the scleral route. The drug absorption route depends on the drug's physicochemical characteristics. Tight junctions in the corneal epithelium restrict the passage of hydrophilic drugs and macromolecules through the corneal route. Meanwhile, in the stroma, abundant hydrated collagen affects the diffusion of lipophilic drugs, and the leaky junctions in the endothelium ease the passage of hydrophilic and macromolecular drugs. The scleral route is less efficient but is helpful for hydrophilic and larger molecules. A large amount of the dose is wasted by systemic absorption before passing the corneal barrier. The remaining is passed into the anterior part of the eyeball by penetration through the

conjunctiva, sclera, and cornea. The permeability order is conjunctiva> sclera>cornea. There are three main ocular barriers, including the lacrimal fluid barrier, which constitutes a significant barrier. A stream of lachrymal liquid removes a portion of the drug from its surface at a discharge rate of approximately 1 l/min. The nasolacrimal conduit quickly and efficiently eliminates some portion of the drug. The normal tear volume is 7-9 μL with a turnover rate of 16% per minute. Significantly increased lacrimation dilutes the dose that was given. As a result, the drug concentration is reduced, which results in less medication absorption. Further, this reduces the time the tissue is in contact with drug molecules, resulting in rapid evacuation from the precorneal area by lacrimation, nasolacrimal drainage, and spillage. An inner and an outer barrier is the blood-retina barrier (BRB). The barrier created at the retinal pigment epithelial (RPE) cell layer is known as the outer BRB, and it partially controls the flow of nutrients and solutes from the choroid to the subretinal region. The inner BRB, in contrast, is found in the inner retinal microvasculature and is made up of the microvascular endothelium that lines these vessels. The barrier is crucial for preserving retinal homeostasis because the tight connections between these cells enable the highly selective transport of chemicals from the blood to the retina.

There are various physicochemical factors affecting drug absorption. One of the critical parameters is the drug's solubility. The pH of the environment and pka of the drug affect the solubility and ionization. Unionized drug molecules can easily penetrate through membranes when compared to ionized molecules. Studies show that unionized pilocarpine has greater permeability than the ionized form.

Another factor includes the charge of the molecule. For example, the corneal epithelium has a negative charge; cationic molecules penetrate faster than anionic molecules⁶. Lipophilicity is yet another essential factor to consider, as different layers of the cornea have different permeabilities toward lipophilic drugs. The cornea's inner layer, i.e., the stroma, is permeable to hydrophilic molecules, whereas the outer epithelial layers are permeable to lipophilic molecules. Hence, the optimum Log P value ranges from 2-4 for corneal permeation⁷. Molecular weight and size play essential roles in the paracellular route of absorption. The diameter of tight junctions in the epithelium is 2 nm, so molecules with a molecular weight of less than 500 Daltons can pass through it. Also, the conjunctiva has a larger pore diameter, allowing small to medium peptides of 5000 to 10000 Daltons to pass through⁸.

MECHANISMS FOR DRUG RELEASE INTO THE EYE

Ophthalmic inserts are designed to deliver therapeutic agents directly to the ocular surface, primarily through diffusion mechanisms. The core principle behind their operation involves the controlled release of drugs from a reservoir contained within a polymeric body. This body is typically formed from nonallergenic materials that are insoluble in tear fluid, thus ensuring sustained and localized drug delivery over an extended period⁹. The primary mechanism by which drugs are delivered from these inserts is paracellular or transcellular diffusion, dictated by concentration gradients across the ocular tissues. The drug is released into the tear fluid or the eye cavity through a rate-controlling membrane. In the case of inserts, a compact, non-erodible body with pores is rate-determining¹⁰. Also, in the

case of soluble devices, dissolution can be why the polymer's dissolution rate determines the release rate, as the drug is homogeneously dispersed in the polymer. Generally, the release of drugs in the case of devices follows the Fickian square root of time kinetics or zero order.

The drug release profile from these inserts often follows zero-order kinetics, meaning that a constant amount of drug is released over time, independent of its concentration in the reservoir¹¹. The insert has a transverse impermeable elastic membrane separating the two compartments, where the first compartment is surrounded by a semi-permeable membrane and an impermeable elastic membrane containing a solute that cannot pass through a semi-permeable casing, and the subsequent partition is circumscribed by an elastic membrane and an impermeable membrane containing a drug reservoir¹². When the Ocular insert is positioned in an aqueous environment, it leads to an osmotic pressure difference due to water penetration into the first compartment, which causes the release of the drug through the aperture. Upon insertion between the sclera of the eyeball and the lower eyelid, the insert is held in place by the pressure of the eyelid. As the drug diffuses through the polymer matrix, it passes into the conjunctival sac and subsequently into the anterior segment of the eye. Notably, the unique physiological characteristics of the eye, including tear volume and turnover rates, play a crucial role in determining the effective concentration of the drug reaching its target tissues¹³. The insert is made of bio-erodible material, and the contact with tear fluid dissolves and releases the drug. The enzymatic hydrolytic reaction determines the release rate that leads to polymer solubilization or degradation to water-soluble molecules¹⁴.

OCULAR INSERTS

The eye is often used as a route for local drug delivery. In cases where systemic delivery is required, lifting the concentration of the drug to the required level can be harmful not only due to side effects but also to the eyes themselves. Due to their complex anatomy and physiology, achieving local drug delivery to the eyes isn't easy. Topical administration in the form of eye drops, suspensions, and gels poses significant limitations due to dilution of the medication in the tear film, lacrimal-nasal drainage pathways, and transconjunctival systemic absorption. Novel drug delivery systems modify these systems through ocular inserts, increasing the ocular residence time and controlled drug release. Ocular inserts are sterile preparations with semisolid or solid consistency and vary in size and shape to enable retention within the ophthalmic cavity. Depending on the formulation, the inserts can be positioned on the lower fornix of the eye, the upper fornix, or the cornea. The ocular inserts include the polymer and the drug as the main composition. The first ocular insert used was in the 19th century, and it was solid and insoluble, unlike the present soluble inserts. The dry filter paper was incorporated with a drug solution, cut into small square pieces, and placed under the eyelid. The following insert type was lamellae, which were glycerinated gelatin consisting of the drug. Later, they were not used due to a lack of sterility, and soluble inserts were developed. The different types of ocular inserts are given in Fig. 2.

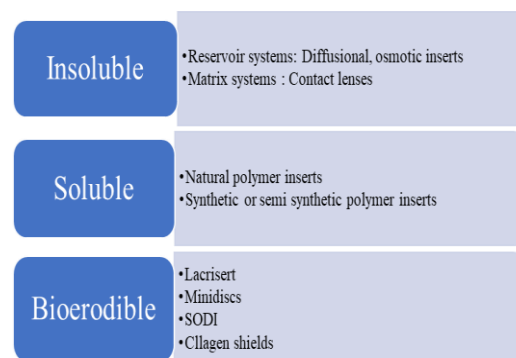


Fig. 2: Types of ocular inserts

Ophthalmic inserts offer several benefits for drug delivery in treating ocular conditions. One significant advantage is longer drug action and higher bioavailability than traditional vehicles due to increased ocular residency. Using ocular inserts overcomes the side effects of high dosing and frequent administration. Drug release is at a slow and pre-determined rate. There is reduced systemic absorption and pre-corneal elimination of the drug. Accurate dosing is possible, and better patient compliance is attained because of reduced frequent dosing. Ocular inserts can be used to deliver nanoparticulate drug formulations. There is a possibility of internal ocular tissues using ocular inserts, and because they are one-time-use devices, they are sterile and have no added preservatives. Furthermore, specific designs of inserts, such as those made with innovative polymers, can allow for controlled drug release tailored to meet therapeutic needs, potentially offering a more effective treatment option for patients with chronic conditions like glaucoma or dry eye disease. Innovations such as enzyme-triggered release mechanisms have been explored, which could allow for more efficient therapy by responding to specific physiological conditions¹⁵.

Despite their advantages, ophthalmic inserts have several drawbacks that may hinder their acceptance and use. One

notable disadvantage is comparably less patient compliance in the case of inserts, as patients feel the presence of the insert in the eye. It constitutes a physical and physiological barrier to user acceptance. An ophthalmic insert might be lost during sleep or the unconscious rubbing of the eye. In the case of insoluble inserts, removal should be done after the dose is released. The inserts do not stick to the eye, move around, and might get stuck where the removal is difficult (upper fornix). Medicated contact lenses may

interfere with the vision of the patient. Placement of the ocular inserts needs the assistance of an experienced person.

EXCIPIENTS USED IN OCULAR INSERTS

A summary of the common ocular insert excipients is given in Table 1. Notable among them is chitosan, a constituent made up of chitosan and linear polymer chains of N-acetyl-D-glucosamine and D-glucosamine monomers linked by β -(1-4).

Table 1: Key characteristics of excipients used in ocular insert

Excipients	Key characteristics	Advantages	Disadvantages
Chitosan	Deacetylation, Molecular weight, solubility, and polycationic in the H ⁺ environment	Interacting with negatively charged substances enhances mucosal penetration, is biocompatible and biodegradable, and limits the growth of cancer cells.	The final product of remarkable variability.
Hyaluronic acid	Anionic at physiological pH	Improves tissue hydration and tissue resistance, and removes free radicals.	Marginal side effects
Poloxamer	Non-ionic, amphiphilic flakes/paste/liquid	Thermo-reactive	Usable from 20-25 ^o °C, gelation concentration is high
PLGA	Nontoxic, soluble in various solvents	Biocompatible, highly crystalline, amorphous	
PVCL-PVA-PEG	Amphiphilic, soluble in both water and organic solvents	Increases the solubility of poorly soluble drugs by the formation of micelles	
Cetalkonium chloride	Positive charge, highly lipophilic, low toxicity	Antiseptic properties	
Gelatin	High dissolution in water	Gelling, emulsifying, and foaming properties.	None for long-term drug delivery and a Low rate of degradation.

Following the work on the glucocorticoid's structural analysis, the researchers prepared insoluble methyl- β -cyclodextrin-ammonium chitosan, which was found to be mucoadhesive and cytocompatible. Further enhancements, such as adding chitosan oligosaccharide with valyl valine and stearic acid, were used to improve biocompatibility and mucoadhesive properties of polymers. Hyaluronic acid consists of two sugars, N-acetyl-D-glucosamine and D-glucuronic acid, which are linked via β -1, 4-glycosidic bonds. This biopolymer is particularly important in accumulating polysaccharides and is termed glycosaminoglycans (GAGs). In the tissue, this polymer is essential for the skin cells to control the intercellular spaces. It is a cell scaffolding and skin volumetric regulator. Protective skin functions include safeguarding the underlying structures from external harmful factors. Additionally, it exists in synovial fluid and serves to lubricate joints. Skin cells serve as an ocular excipient.

Amphiphilic polypeptides known as Poloxamers, which have blocks of polyoxyethylene and polypropylene, are sold as Pluronics, Synperonics, and Tetronics in forms like fluids, glues, and pieces. Poloxamers are amphiphilic since they have a balance of hydrophilic and hydrophobic attributes. The preparation of these copolymers involves a stepwise addition of methyl oxide and epoxide blocks to propylene glycol, a low-weight organic compound soluble in water. Various poloxamers can be identified by their oligomeric composition and the size of the hydrophilic and hydrophobic segments. The most common are Poloxamer 407 and 188; their names indicate the molecular weights of the units of methyl oxide and epoxide, which constitute them. Together with

carboxymethylcellulose, these two types of poloxamers have been used to form in situ gels. In developing a nano-hydrogel, soy lecithin E200, glycerol, and polycarbophil were incorporated into the blend of the two polymers. Other researchers have incorporated chitosan gel with poloxamer 407 and 188. All these studies demonstrated evidence of the expected medication release¹⁶. Due to having linear chains of polylactic and polyglycolic acid monomers, PLGA is considered a biopolymer. It has two enantiomorphs: D-poly(lactic acid) (PDLA) and L-poly(lactic acid) (PLLA). Their best combination is in 50:50 blends. The four key stages of the depletion cycle are as follows: hydration, initial corrosion, continuous corrosion, and solubilization. The side products include lactic acid and glycolic acid. The physical factors influencing the corruption rate are sub-molecular polymer load, glass transition temperature, Brook criteria of drug molecular size, and hydrophilicity. PVCL-PVA-PEG is a copolymer of polyvinylcaprolactam, polyvinyl acetic acid derivative, and polyethylene glycol (PVCL-PVA-PEG). This amphiphilic polymer has a molecular weight of 90 to 140 kDa; thus, it is lipid- and water-soluble. Also, PVCL-PVA-PEG micelles with myricetin were synthesized. This product has an increased penetrative framework that enhances drug solubility and stability while non-toxically protecting tissue. Cetalkonium chloride is a quaternary ammonium compound from the alkylbenzyl dimethylammonium chloride germicide group. This is used for treating illnesses of the eyes and mouth, and the action works with a positive charge. CKC with 16 16-carbon chain is very lipophilic, which limits its water solubility. Research was conducted to evaluate the effect of CKC on focal points along with sterylamine. The cationic surfactants

influenced the quantity of the drug that was incorporated, and the system influenced the release. The crosslinks of the collagen polypeptide chain, which are replaced with peptide bonds, lead to the development of polypeptide gelatin. When collagen undergoes pretreatment with acidic solution, the positions of amino acids remain untouched and yield type A gelatin. Also, when collagen is pretreated with a basic solution, the asparagines and glutamate change to aspartame and glutamate due to hydrolysis and yield type B gelatin¹⁷.

whether soluble or insoluble. Both can release the drug at a pre-determined rate, and insoluble devices must be removed after emptying. Bio-erodible polymers dissolve in the eye due to enzymatic reactions and release the drug from the polymer mixture. The soluble and bio-erodible differ in the mechanism of polymer dissolution; soluble inserts dissolve due to swelling of the polymer, and chemical or enzymatic reactions form erodible ones. The basic description of the ocular inserts and formulations in research is outlined in Tables 2 and 3, respectively.

METHODOLOGY

Ophthalmic inserts have been classified based on their physiological behavior,

Name	Description	Year	Reference
Ocusert	Flat, flexible, elliptical insoluble device consisting of two layers enclosing a reservoir.	1975, 1980	Quigley et al. and Urquhart et al.
SODI	A small oval wafer, composed of a soluble copolymer consisting of acrylamide, N-vinyl pyrrolidone, and ethyl acrylate, softens upon insertion.	1976	Khromow et al.
Collagen shields	Used as tear substitutes and as a delivery system.	1977, 1978	Bloomfield et al.
Lacrisert	A rod-shaped device made from hydroxypropyl cellulose is used to treat dry eye.	1978	Lamberts et al.
NODS	Medicated solid polyvinyl alcohol flag that is attached to a paper handle. After the application, the drug is released after the paper gets detached	1985	Lloyd et al.
Minidisk	4-5 mm diameter contoured either hydrophilic or hydrophobic drug.	1985	Karthikeyan, Deivasigamani, et al. 2008
BODI	Adhesive rods based on a mixture of hydroxypropyl cellulose, ethyl cellulose, polyacrylic acid, and cellulose acetate phthalate.	1995	Khromow et al.

Table 2: Description of different types of ocular insert devices

Drug delivery system	Carrier	Drug	Effect	Reference
Soluble insert	HPC/ D-lactose/eudragit	Pilocarpine	Increased bioavailability	Saettone et al. 1992
Bio-erodible insert	PVMMMA	Pilocarpine	Delayed and decreased peak concentration of the drug	Urtti et al. 1989
Insoluble insert	Ethylene vinyl acetate; alginate	Pilocarpine	Sustained release for over 7 days	Sendelbeck et al. 1975
Soluble insert	HPC/eudragit	Timolol	Sustained release of the drug and decreased systemic peak concentration	Yamamoto et al. 1992
Soluble insert	Collagen	Gentamicin	The highest tissue concentration was found after 3 hours of insertion.	Bloomfield et al. 1978
Bio-erodible insert	Polypeptide	Idoxuridine	Better therapeutic action compared to drops.	Pavan-Langston et al. 1975

Table 3: Ocular inserts in research

Insoluble ocular inserts are further divided into two categories: reservoir and matrix systems. Reservoir systems comprise hydrophilic, hydrophobic, organic, inorganic, natural, or synthetic carriers. The main demerit of the insoluble inserts is the removal of the insert after emptying. Fig. 3 shows the image of an insoluble ocular insert in the eye¹⁸.

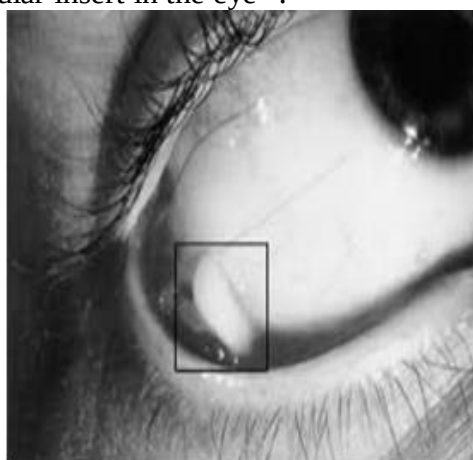


Fig. 3. Ocular insert

- a. Reservoir systems: Diffusional inserts are also known as ocuserts. This system possesses a reservoir of drugs covered with a semi-permeable or microporous membrane, which regulates the drug release rate. Furthermore, the rate at which the lacrimal fluid permeates through the membrane creates internal pressure that propels the drug out of the reservoir. According to Urquhart, pilocarpine Ocusert, which Alza Corporation developed, is known for several notable advantages. Ocusert's release profile was predetermined and controlled; also, its use avoided the side effects of miosis and myopia. An osmotic insert consists of a core and a shell. Two subclasses of osmotic inserts can be defined based on the structure of the central compartment. The components of the osmotic insert are presented in Table 4.

Water-permeable matrix	Ethylene: Vinyl ester copolymers Divers: Plasticized polyvinyl chloride, polyethylene.
Semi-permeable membrane	Cellulose acetate derivatives, Eudragit.
Osmotic agents	Inorganic: Sodium chloride, magnesium sulfate. Organic: Calcium lactate, tartaric acid. Carbohydrates: Sorbitol, mannitol, glucose.

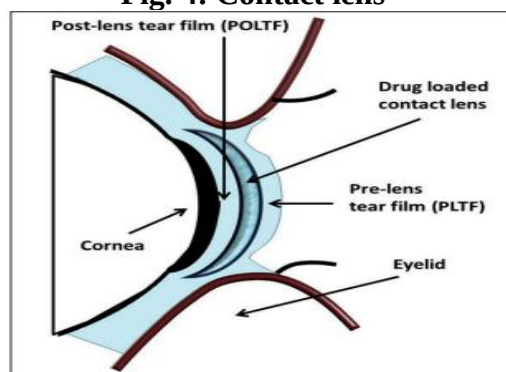
Table 4: Components of osmotic inserts

Type 1: The central part contains a drug reservoir in a polymer matrix, with or without an osmotic solute. The peripheral part contains a covering film made of an insoluble semi-permeable polymer. Drug release will occur because of a difference in osmotic pressures, causing breakage of the film. Type 2: Type 2 inserts contain two separate, distinct compartments. In this case, the osmotic solute has its distinct compartment. An elastic impermeable membrane encloses the drug compartment, while a semi-permeable membrane encloses the reservoir of osmotic solute. The peripheral second compartment is like the type 1 insert, where the osmotic pressure is induced due to tear diffusion and causes the drug release²⁰.

b. Matrix systems: The matrix systems mainly include contact lenses. They are made of polymers that form a matrix and can retain the aqueous drug solution or solid drug. By absorbing water, swelling occurs. Contact lenses are the devices used for vision correction; later, they have been advanced as medicated contact lenses where the lens is pre-soaked in the drug solution before use²¹. Refojo has suggested a subdivision of contact lenses into five types: rigid (disadvantage of oxygen and moisture low permeability), semi-rigid, elastomeric, soft hydrophilic (for prolonged release of drugs like tetracycline), and biopolymeric. The most widely used polymer composition

for soft hydrophilic lenses is hydroxyethyl methyl methacrylic acid copolymerized with polyvinyl pyrrolidone (PVP) or ethylene glycol methacrylic acid (EGDM). PVP has been used to increase water hydration, and EGDM has been used to decrease water hydration. Drug release from contact lenses is based on the concentration of the soaking solution, which is faster initially and slows down with time²². Furthermore, further innovations included the incorporation of nanoparticles into contact lenses, which resulted in an effective extended drug release. The image of the contact lens is given in Fig. 4.

Fig. 4: Contact lens



There were no drawbacks, such as loss of transparency and other aggregation problems, from the use of nanoparticles. However, there might be a burst of drug release on more extended storage periods. The recent innovations in contact lenses and polymers are given in Table 5.

Table 5: Recent molecular imprinting techniques used in contact lens

DEAA- N, N-diethyl acrylamide, DMAA- N, N-dimethyl acrylamide, MAA- methacrylic acid, MMA- methyl methacrylate, HEMA- hydroxyethyl methacrylate, and EGDMA ethylene glycol dimethacrylate.

make the ocular inserts of drugs for a

Backbone monomers	Functional monomers	Cross-linker	Drug	Reference
HEMA	MAA, MMA	EGDMA	Timolol	(Gulsen and Chauhan 2005)
DEAA	MAA	EDGMA	Timolol	(Danion et al 2007)
DEAA, HEMA, DMAA	MAA	EDGMA	Timolol	(Kapoor and Chauhan 2008)

Soluble ocular inserts are ophthalmic inserts that get entirely solubilized in the eye along with drug release, so they do not need to be removed from the application site. Soluble inserts are categorized into two types based on the polymer used: natural polymer and synthetic or semi-synthetic polymer²³. These soluble inserts are made of a natural polymer like collagen. Inserts are incorporated with the drug by soaking in the drug solution. They are in a dry state and rehydrated before use. Collagen gets dissolved in the tear solution, and drug release occurs. The amount of drug loaded into the insert depends on the concentration of the drug solution and the binding agent used. Synthetic polymers are polyvinyl alcohol and ethylene vinyl acetate copolymer, and semi-synthetic polymers are cellulose derivatives²⁴. On the use of eudragit, the polymer generally used for the enteric coating of tablets, a decrease in the drug release rate from the insert has been observed. So, this effect has been used to

longer duration of action. Also, the demerit of contact lenses is blurred vision, which is caused by the penetration of lachrymal fluids for solubilization. Initially, the insert is dry and glassy and does not interrupt the patient's vision, but that glassy state has a risk of breakage and expulsion. A polymer like ethyl cellulose decreases the deformation to overcome the blurred vision caused by the insert. A carbomer, a bio-adhesive polymer, is used for the glassy state. The basic components used in soluble inserts are mentioned in Table 6.

Polymers	Cellulose derivatives: Methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose Synthetics: Polyvinyl alcohol, ethylene vinyl acetate copolymer
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Additives	Plasticizer: Polyethylene glycol, glycerine. Enteric coating polymer: Cellulose acetate phthalate, HPMC phthalate. Complexing agent: Polyvinyl pyrrolidone Bio-adhesives: Polyacrylic acids, carbomer
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Table 6: Components of soluble inserts containing synthetic polymers

Bioerodible ocular inserts are crafted from materials that undergo degradation in the body, thus releasing their drug payload gradually. Common materials used for bio-erodible inserts include poly(orthoesters) and poly(orthocarbonates), which provide controlled drug-release mechanisms while minimizing the need for surgical removal after their therapeutic function is fulfilled. This approach not only simplifies treatment regimens but also improves patient compliance by reducing the frequency of insert replacement. Bio-erodible polymers like crosslinked gelatin and polyester derivatives prepare these ocular inserts. Dissolution of the polymer occurs due to the hydrolysis of the chemical bonds or an enzymatic reaction²⁵. The dissolution rate can be modified by modulating their chemical structure by adding an anionic or cationic surfactant. When Attia used a crosslinked gelatin insert, a four-fold greater dexamethasone level was observed in the rabbit eye's aqueous humor²⁶. The demerit of the bio-erodible polymer is that the degradation products can cause an inflammatory reaction.

DISCUSSION

With technological advancement, many novel ocuserts are available commercially in the market. Soluble ophthalmic drug inserts (SODI) are small, wafer-like structures that are oval. These were developed for ocular medication for cosmonauts, where the eyedrops cannot be used. They are made of gelatin and later developed by using collagen. The first development of SODI was by chemists

and ophthalmologists from Russia. Later, a soluble copolymer of acrylamide, N-vinylpyrrolidone, and ethyl acrylate was developed to formulate SODI. These were the soluble ocular inserts in thin films weighing 15 to 16mg. They get softened within 15 seconds and release the drug for up to 1 hour²⁷. Collagen is the human body protein obtained from bones, ligaments, and tendons. The first use of collagen was by Bloomfield in 1977 to deliver gentamicin. Compared with other formulations like ointment and drops, collagen insert gave the highest drug concentration in the eye tissue²⁸. However, the major drawback of the collagen shields is that the cornea must be anesthetized, and the physicians use blunt forceps to insert the shield. This highlights the need for further research to develop more patient-friendly drug delivery methods. Ocufit is a rod-shaped device made of silicone elastomer used for the sustained release of the drug²⁹. Ocufit was patented in 1992 and is presently developed by Escalon ophthalmic. It is designed to fit in the fornix, and sizes vary from children to adults. Insoluble ocufit had both features of sustained drug release and long retention time. It has no obstruction with eye diseases like conjunctivitis, trachoma, etc.³⁰. Minidisc is a monolithic polymeric device, which is also referred to as a minidisc ocular therapeutic system, first developed by Bawa et al. Minidisc is shaped like a miniature concave lens with a 4-5mm diameter to fit in the sclera. Also, in comparison with lacrisert, minidisc requires less time for insertion. Various mini discs are non-erodible hydrophilic, non-erodible hydrophobic, and erodible³¹.

The potential incorporation of new technologies like nanotechnology into ophthalmic inserts has a promise of greater targeted drug delivery with lower waste and cost of treatment, especially regarding invasive procedures concerning penetrating ocular barriers³². Biodegradable and biocompatible polymers comprise several microparticles, including polylactide and poly(lactic co-glycolic acid). The injectable microparticles provide sustained release of the drug over time, under intravenous administration. Some benefits of using microparticles include high in vivo biocompatible durability and precision-controlled release. These formulations can incorporate both micro and macro hydrophilic and lipophilic drugs³³. A class of nanoparticles synthesized from

biodegradable polymers such as PLA and chitosan includes lipids, phospholipids, and even certain metals. Nanoparticles are defined to have a size smaller than 1 μ m. Drug molecules can be encapsulated or attached to the nanoparticle surface. Dendrimers, a type of nanoparticle, have an inner core with branches covering it, meaning they can carry multiple copies of surface groups. Also, acrylic acid is used in the formulation to enhance the bioadhesive properties, leading to longer residence times. Some recent nanoparticulate formulations and their regulatory status are outlined in Table 7.

Product	Nanoformulation	Indication	FDA approval status
Restasis	Nanoemulsion	Dry eye	Approved
Ozurdex	Dexamethasone biodegradable implant	Macular edema	Approved
visudyne	liposome	AMD	Approved
TLC399(prodex)	Lipid-based nanoparticles	Macular edema	Phase 2
POLAT-001	Liposome	Glaucoma	Phase2

Table 7: Regulatory status of ocular inserts

CLINICAL APPLICATIONS

Ophthalmic inserts have gained attention for their versatility in treating various ocular conditions. Applications include glaucoma, infections, and inflammation treatments, benefiting from prolonged contact time and consistent drug release. EGP-437 delivered through the ocular drug delivery system (EGDS) has been explored in clinical trials for conditions such as dry eye and postsurgical inflammation, demonstrating promising

results in reducing patient treatment burdens³⁴. Glaucoma is one of the leading causes of vision loss worldwide, primarily managed through topical anti-glaucoma medications. However, the bioavailability of these treatments is typically below 5% due to high precorneal loss and low corneal penetration. Frequent administration often leads to poor patient compliance, exacerbating the disease. Sustained-release systems, such as ophthalmic inserts, are being developed to

address these issues by improving bioavailability and maintaining therapeutic efficacy, thereby enhancing patient adherence to treatment regimens³⁵. Dry eye disease (DED) is a condition that leads to significant ocular surface damage and instability of the tear film. Treatment strategies are insufficient because of the need for frequent dosing, which often leads to poor adherence. New sustained-release ophthalmic inserts may be able to provide palliative care by alleviating symptoms through continuous delivery. Both diabetic retinopathy (DR) and age-related macular degeneration (AMD) are essential and critical diseases necessitating appropriate therapeutic interventions to avert vision loss. Oftentimes, traditional methods of care, such as intravitreal injections, pose a threat to ocular health and are frequently associated with low patient adherence due to the constant need for in-office provider visits³⁶. This emphasizes the need for sustained-release formats to enhance patient comfort and optimize drug delivery while minimizing traditional method risks.

FUTURE PERSPECTIVES

The development of ophthalmic inserts has seen significant progress, with various studies focusing on their safety and efficacy. A recent phase III clinical trial investigated cyclosporine A-loaded pH-sensitive Carbomer gel for treating moderate to severe dry eye disease (DED). This study demonstrated drastic improvements in tear secretion and DED symptoms among 312 test subjects, highlighting the gel's advantages, including a convenient once-a-day treatment regimen and a fast onset time of 2 weeks, as compared to traditional cyclosporine A emulsions. However, limitations such as the short follow-up period of 84 days necessitate further

research to establish the long-term safety profile of this novel formulation. Research has also revealed a challenging landscape for developing new ocular therapies, as many small molecular-weight drugs have been evaluated in clinical trials but failed to reach the market. Notable examples include brimonidine, squalamine lactate, and various tyrosine kinase inhibitors, all of which have either been discontinued or terminated in the testing phases. The lack of standardized reporting and missing negative trial results complicate the translation of preclinical findings into clinical applications, creating barriers to future advancements in ocular therapies. Moreover, developing ocular inserts involves innovative molding and extrusion processes for preparing polymer-based inserts. These processes ensure the inserts maintain a solid form while compatible with the eye's lacrimal fluids. Plasticizers, buffering agents, and preservatives can be incorporated into the formulations to enhance their efficacy and safety. The current state of research indicates a growing interest in identifying effective and safe vision therapy techniques. Emerging studies have explored alternative approaches, including interactive video games and dichoptic training, which could improve treatment outcomes for conditions such as strabismus³⁷. As the field of ocular therapeutics continues to evolve, ongoing research will play a crucial role in refining and advancing the use of ophthalmic inserts for patient care. The global market for ophthalmic drug delivery devices has grown significantly, driven primarily by the increasing prevalence of ocular disorders such as glaucoma, age-related macular degeneration (AMD), and cataracts. The market for ophthalmic drug delivery devices is bifurcated into direct and indirect sales, with the direct sales

segment commanding the largest market share. This segment is anticipated to grow at a CAGR of 6.15%, primarily involving sales to pharmaceutical companies through partnerships and contracts. However, regulatory compliance and compatibility between drugs and devices must be met before commercialization, per Food and Drug Administration (FDA) guidelines. The product segment continues to dominate the market share due to its various advantages, supported by key players and emerging start-ups. Noteworthy companies in this sector include Congruence Medical Solutions LLC, Becton, Dickinson and Company, and Schott AG. Developing innovative devices, such as pre-filled syringes, contributes to the sector's growth and increases product offerings³⁸.

CHALLENGES IN OCULAR INSERTS

Stringent regulatory requirements heavily influence the development and approval of ophthalmic inserts. The U.S. Food and Drug Administration (FDA) classifies ophthalmic formulations intended for administration as eye drops as drug-device combination products, significantly complicating the regulatory compliance landscape compared to standard drug approvals. This complexity arises from the need to meet pharmaceutical and medical device regulations, necessitating a comprehensive understanding of the specific requirements for each category³⁹. The lengthy regulatory process poses a significant barrier to market entry for new ophthalmic products, leading to increased developer expenses. Prolonged approval timelines hinder advancements in the ophthalmic drug delivery devices market and limit growth opportunities⁴⁰. The regulatory scrutiny on preservative usage in ophthalmic products, for instance,

requires a thorough assessment of excipients, as their quality and impurity profiles directly affect the critical quality attributes of the final product, such as stability and preservative efficacy. Moreover, manufacturers must ensure that the final sterilization requirements are adhered to, as any bioburden present can compromise the effectiveness of the sterilization process⁴¹. To meet these stringent regulations, the pharmaceutical industry is exploring innovative delivery systems, such as osmotic ophthalmic inserts, which can enhance drug compliance by reducing the frequency of administration compared to traditional eye drops⁴². These inserts prolong contact time with conjunctival tissues, facilitating sustained drug release and improving patient outcomes⁴³. However, introducing novel packaging solutions and environmentally sustainable materials must also align with regulatory expectations regarding safety and sterility⁴⁴. As the ophthalmic market evolves, ongoing collaboration between manufacturers and regulatory bodies is essential to ensure that new products can address unmet patient needs while complying with complex regulatory frameworks⁴⁵.

CONCLUSION

Ophthalmic inserts, as defined, are systems aimed at treating different diseases and are meant to enable direct delivery of drugs to the eyes so that their release is gradual and adequately controlled. There are considerable and essential complications with drug administration to the eye. Due to its very poor pH-dependent solubility, conventional dosage forms require frequent administration every four hours and can cause crystalline deposits to accumulate on the cornea. As more patients require less invasive treatments,

ocular implants are being developed to meet their needs. Ocuserts improve patient compliance by requiring fewer doses to be given. It extends the period of contact, which boosts bioavailability. It is possible to lessen harmful effects by minimizing systemic side effects. Not utilizing preservatives permits lower chances of allergic responses. Ocular inserts can be made using different techniques and evaluated through various criteria. Innovative and compliant approaches to delivering medications to the eye include Ocuserts. A soluble, insoluble, or biodegradable ocular insert category can all be classified as different types. The variety of materials used and their behavior during drug delivery further add to their sub-classification. The ocular inserts, such as diffusion, osmotic, and soft contact lenses, are insoluble with unique

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