Brief Review on Novel Control Drug Delivery System of Ocular Inserts

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Abstract- *There are several eye illnesses that can affect the eye and cause vision loss. As a result, there are numerous ophthalmic drug delivery systems accessible. There are two types of medication delivery systems; conventional and non-conventional. About 70% of the eye dose formulations on the market are eye drops and ointments, which are the most regularly accessible ophthalmic medications. Significant guidelines have been directed toward newer drug delivery systems for ophthalmic administration to improve ocular drug bioavailability. To avoid frequent drug administration, the researcher has always used an ocular insert to deliver the drug at a controlled rate. The ocular insert is made up of numerous layers of controlled, delayed, or sustained release biodegradable implantable components. According to their solubility, inserts can be classified as insoluble, soluble, or biodegradable. The drug's release from the insert is determined by diffusion, osmosis, and bio-erosion.*

Keywords- ocular inserts, drug delivery system, controlled release, diffusion, osmosis, bio-erosion.

I. INTRODUCTION

Ocular drug delivery is one of the most challenging endeavors for pharmaceutical researchers. Ophthalmic preparation are specific dosage forms intended to infused on to the topical surface of eye, instilled inside the eye and used along with optical devices. In conventional eye drops, the intraocular bioavailability of the drug in anterior region is less than 5% and a bioavailability in the posterior region is less than 1%. This is due to naso-lachrymal,drainage, lacrimation and drug dilution with tear fluid, tear turnover and conjuctival absorption and various ocular barriers. So, in order to have a therapeutic impact, a high dose is needed, which in turn may cause toxicity (1,2).In suspension types of pharmaceutical dosage forms are made with comparatively water-insoluble pharmaceuticals, to prevent the intolerably high toxicity produced by saturated solutions of water-soluble medications However, the rate of drug release from the suspension depends on how quickly the drug particles in the medium dissolve.Due to the particles present in suspended medication, irritation potential is the drawback. In ointments, it produces film over the eye;therefore, it results in blurring of vision.

Attempts have been made over the past few years to increase ocular bioavailability using altering the formulation of a product, such as mucoadhesive viscosity and application polymers. So far, these methods for extending reduced corneal contact time have resulted in enhanced ocular bioavailability through the use of ionophores, ion-pairs, liposomes and prodrug. Some of the more modern, sensitive, and effective ocular administration systems are being developed, including collagen shields, biodegradable polymeric systems, and inserts.

II. ANATOMY AND PHYSIOLOGY OF EYE:(5,6,7)

Understanding the consequences of a drug in the eye requires knowledge of the anatomy of the eye. The ocular system has three layers: the outer, middle, and inner. The cornea and sclera are part of the outer region. The cornea serves as a physical barrier, while the sclera maintains the shape of the eye. The cornea has a vascular structure and sensory nerves that give it transparency. When compared to anionic drugs, the negative charge on a cornea favours permeation of hydrophilic cationic drugs. The cornea's permeability issues are also caused by its five layers, which include the epithelial layer, bowman's membrane, stroma, Descemet's membrane, and endothelium. The epithelial layer is a multilayer of stratified squamous epithelial cells connected by a tight junction that limits the penetration of hydrophilic drugs. The stroma is composed of charged and highly organised hydrophilic collagen, limiting hydrophobic drug penetration even further. The iris, ciliary body, and choroid comprise the ocular system's middle layer. The iris regulates pupil size and the amount of light that enters the pupil. The ciliary body secretes aqueous humour, a clear, slightly alkaline ocular fluid that nourishes the retina.Aqueous humor is formed through three mechanisms: diffusion, ultrafiltration, and active secretion. Active secretion is the primary source of aqueous humour formation. Around 70-90% of the aqueous humour exits via the conventional pathway (aqueous humour exits via the trabecular meshwork, across the inner wall of Schlemm's canal, into its lumen, and into draining collector channels, aqueous veins, and episcleral veins), whereas 10-30% exit via the non-conventional pathway, which includes the ciliary muscle and supraciliary

and suprachoroidal spaces. The conjunctiva, a thin, highly vascularized, semi-transparent connective tissue that covers the surface of the eyeball, is another important component of the eye.

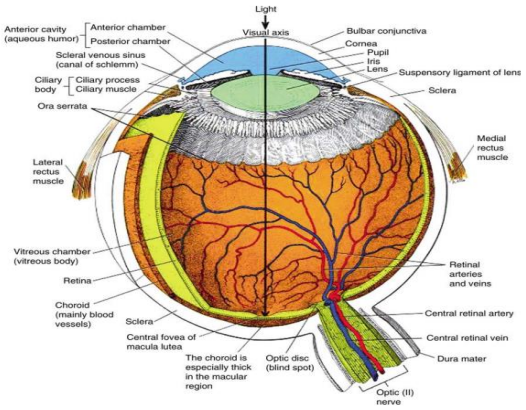


Figure 1: schematic diagram of human eye.

The currently existing patterns are in vogue: (8)

• Ocular inserts (biodegradable and non-biodegradable), for example, Ocuserts, Alza Corp.
• Mucoadhesive dosage forms (ocular films or sheath, ophthaCoil, polymer rods, HEMA hydrogel, Dispersion, polysulfone capillary fiber).
• Collagen shields, cyclodextrine-based system, ophthalmic rods (artificial tear inserts, e.g., Lacrisert).
•Filter paper strips (drug-impregnated filter paper strips for staining agent — sodium fluorescent, lissamine green, and rose Bengal.
• Soft contact lenses, implants, flexible coils, and cotton pledgets (Drug presoaked hydrogel type, polymeric gels).

History of ocular inserts: (9)

The first solid medications were squares of dry filter paper that had been previously impregnated with dry solutions; these were the forerunners of the modern insoluble inserts and were utilised in the nineteenth century (e.g., atropine sulphate, pilocarpine hydrochloride). Small pieces were cut and placed beneath the eyelid. Lamellae, the forerunners of the modern soluble inserts, were later created. They were made of glycerinated gelatin that included several ophthalmic medications. Up to the early part of the 20th century, official compendia contained glycerinated gelatin "lamellae." Lamellae were used, but their use was discontinued when stricter guidelines for the sterility of ophthalmic preparations were implemented. Ophthalmic inserts are currently generating more interest.

III. OCULAR INSERTS:(10)

Ocular inserts are preparations with a solid or semisolid consistency that are specifically designed for ophthalmic use in terms of size and shape (i.e., rods or shields). These inserts are usually placed in the lower fornix, but they can also be placed in the upper fornix or on the cornea. They are typically made up of a polymeric vehicle that contains the drug and are primarily used for topical therapy. The primary goal of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue in order to achieve a sustained release suitable for topical or systemic treatment.

A. Merits of ocular inserts:(11)

1. The use of an ocular insert can alleviate the side effects associated with conventional dosage form pulsed dosing.
2. Provides controlled and sustained drug delivery.
3. Improves drug ocular bioavailability by increasing corneal contact time.
4. Allows for targeting within the ocular globe to prevent loss of other ocular tissues.
5. Get around protective barriers such as drainage, lacrimation, and conjunctival absorption.
6. Provide patient comfort, improve patient compliance, and improve drug therapeutic performance.
7. Provide better delivery system housing.
8. Increased shelf life in comparison to aqueous solutions.

B. Demerits of ocular inserts:(12)

1. One significant disadvantage of ocular inserts is their ‘solidity,' or the fact that patients perceive them as an extraneous body in the eye. This might represent a major psychological and physical barrier to user acceptance and compliance.
2. Their movement around the eye; in rare cases, unwanted migration of the insert to the upper fornix complicates simple removal.
3. Inadvertent loss while sleeping or rubbing the eyes.
4. Interference with vision.
5. Difficult placement of the ocular inserts.

IV. MECHANISM OF DRUG RELEASE:(13, 14,15)

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

A. Diffusion:

The drug is continuously released at a controlled rate through the membrane into the tear fluid by the Diffusion mechanism. If the insert is made of a solid, non-erodible body with pores and drug dispersion. Drug release can occur via diffusion through the pores. Controlled release can be further regulated by gradual dissolution of solid dispersed drug within this matrix due to aqueous solution inward diffusion.

When the insert is inserted into the eye, water from the tear fluid begins to penetrate the matrix, causing swelling and, as a result, polymer chain relaxation and drug diffusion occurs. The dissolution of the matrix that occurs after swelling is determined by the polymer structure: linear amorphous polymers dissolve much faster than cross-linked or partially crystalline polymers. In general, release from these devices follows Fickian 'square root of time' kinetics; however, in some cases, known as case II transport, zero order kinetics has been observed.

B. Osmosis:(14)

The insert in the Osmosis mechanism consists of a transverse impermeable elastic membrane that divides the interior of the insert into two compartments; a semi-permeable membrane and the impermeable elastic membrane surrounds the first compartment, while the impermeable material elastic membrane surrounds the second compartment. The insert's impermeable wall contains a drug release aperture. The first compartment contains a solute that cannot pass through the semipermeable membrane, while the second compartment serves as a reservoir for the drug, which is either liquid or gel. When the inserts is placed in the eye, the first compartment expands and the second compartment contracts this is due to diffusion of water into the first compartment and stretches the elastic membrane.

C. Bio-erosion: (15)

The insert in the bio-erosion method is made out of a matrix of bio-erodible material in which the medicine is disseminated. When the insert comes into contact with tear fluid, bio-erosion of the matrix results in regulated continuous release of the medication. The medication is distributed uniformly throughout the matrix;however, it is claimed that if the drug is superficially concentrated in the matrix, a more controlled release is obtained. A chemical or enzymatic hydrolytic reaction that leads to polymer solubilization or degrades to smaller, water-soluble molecules controls drug release in fully erodible or E-type devices. These polymers can be hydrolysed in bulk or on the surface, resulting in zero-order release kinetics as long as the devicesretain a stable surface shape and the drug is poorlywater soluble.

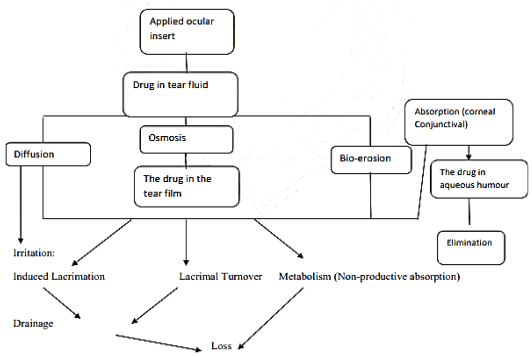
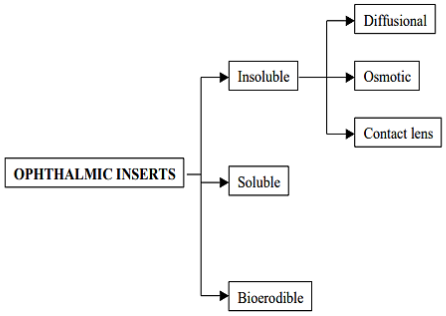


Figure:2Mechanism of action of drug release from ocular inserts (16)

V. CLASSIFICATION OF OCULAR INSERTS (based upon the solubility behaviour):

1) Insoluble
   a) Diffusion
   b) Osmotic
   c) Contact lens
2) Soluble
3) Bio-erodible



The desired criteria for a controlled release ocular insert are as follows; (17)

The foreign-body sensation produces discomfort, which leads to poor patient compliance and excessive lachrymation, which dilutes and decreases the concentration of the medicine. A well-designed ocular insert will reduce the feeling generated by its insertion and has a longer lifespan.

- Simple handling and insertion.
- Expulsion is not possible while wearing it.
- Release kinetics reproducibility (Zero-order drug delivery).
- It is applicable to a wide range of medications.
- No obstruction to eyesight or oxygen permeability.
- Sterility
- Consistency, Manufacturing simplicity.

1. Insoluble ophthalmic inserts:

Inserts made up of insoluble polymer can be classified into two categories:

A. Reservoir system:(18)

Each type of insert has a unique medication release profile. Drug can be released from reservoir systems by diffusion or osmotic mechanism. It contains a liquid, a gel, a colloid, a semisolid, a solid matrix, or a drug-containing carrier. Hydrophobic, hydrophilic, organic, natural, or synthetic polymers are used to make carriers.

It is further classified into two types:

1. Diffusional inserts/Ocuserts
2. Osmotic inserts

a) Diffusional inserts:(19)

The diffusional systems are made up of a core reservoir of drug surrounded by specially constructed semipermeable or microporous membranes that allow the drug to diffuse through the reservoir at a precise rate. The lacrimal fluid penetrating the membrane controls drug release from such a system until a significant internal pressure is reached to push the drug out of the reservoir. The rate of medication distribution is determined by diffusion through the membrane, which can be regulated.

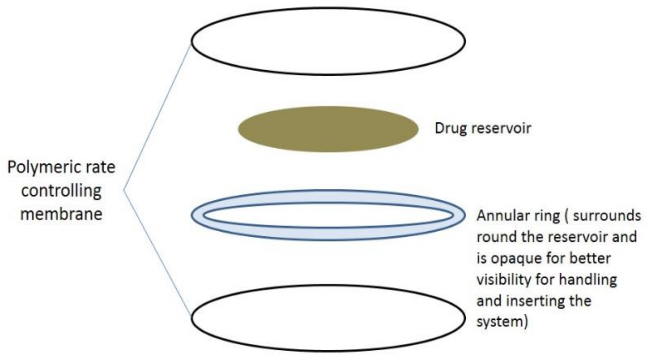


Figure: 3 diffusional inserts

Table 1: Components of diffusional inserts.

Central reservoir	Glycerin, ethylene glycol, propylene glycol, water, methyl cellulose mixed with water, sodium alginate, poly(vinyl pyrolidone), poly ox ethylene sterate.
Microspores membrane	Polycarbonate, polyvinyl chloride, polysulfones, cellulose ester, cross-linked poly (ethyl oxide), cross-linked polyvinyl pyrrolidone and cross-linked polyvinyl alcohol.

b) Osmotic inserts:(20,21)

The osmotic inserts are generally composed of a central part surrounded by a peripheral part and are of two types:

Type1:The central part is made up of a single reservoir of a drug, with or without an extra osmotic solution, which is spread throughout a polymeric matrix, so that the drug is surrounded by the polymer as discrete tiny deposits. The inserts' second peripheral component is a covering film consisting of an insoluble semi-permeable polymer. The osmotic pressure acting on the polymer matrix ruptures it in the form of apertures. The drug is subsequently released through these pores from deposits near the device's surface.

Type2: The central part is divided into two different divisions. The drug and osmotic solutes are separated into two compartments, with the drug reservoir bordered by an elastic impermeable membrane and the osmotic solute reservoir surrounded by a semipermeable membrane. The second peripheral portion is comparable to type 1. The tear diffuses into the osmotic compartment, creating an osmotic pressure that stretches the elastic membrane while contracting the compartment containing the drug, forcing the active component through the single drug release aperture.

Tablet 2: Components of osmotic inserts.

Water permeable matrix	Ethylene- vinyl ester copolymers, Divers- plasticized polyvinyl chloride, Polyethylene, cross linked polyvinyl pyrrolidone.
Semipermeable membrane	Cellulose acetate derivatives Divers- ethylene vinyl acetate, polyester of acrylic and methacrylic acids.
Osmotic agents	Inorganic – magnesium sulfate, sodium chloride, potassium phosphate dibasic, sodium carbonate and sodium sulfate and tartaric acid. Carbohydrates- sorbitol, mannitol, glucose.

B. Matrix system:(22)

This system belongs to the category of insoluble ophthalmic devices (contact lenses). They contain a 3D matrix of cross-linked hydrophilic/hydrophobic polymer. They are effective at retaining water, aqueous drug solution, or solid constituents. After absorbing water, the polymer (hydrophilic/hydrophobic) swells. Welling occurs as a result of the osmotic pressure of polymeric segments.

c) Contact lens:(23,24)

Contact lenses are formed devices that were originally used to correct vision. By pre-soaking them in medication solutions, their role as prospective drug delivery systems has been expanded. The key advantage of this method is the ability to improve vision while also releasing medication. Contact lens is categories into five types.

a) Rigid
b) Semi-rigid
c) Elastomeric
d) Soft hydrophilic
e) bio-polymeric

Rigid contact lenses have the disadvantage of being made of polymers that are impermeable to moisture and oxygen (e.g., poly methyl methacrylic acid), a problem that has been solved by employing gas permeable polymers such as cellulose acetate butyrate. These devices, however, are not appropriate for long-term medication administration to the eye, and their stiffness makes them highly painful to wear.As a result, soft hydrophilic contact lenses for sustained release of drugs such as pilocarpine, chloramphenicol, and tetracycline prednisolone sodium phosphate were produced. In the composition of these lenses, the most widely utilized polymer is hydroxy ethyl methyl metacrylic acid copolymerized with poly (vinyl pyrrolidone) or ethylene glycol dimethacrylic acid (EGDM). Poly (vinyl pyrrolidone) is used to increase hydration water, whereas EGDM is utilised to decrease hydration water. Because they are easier to fit and tolerate, soft hydrophilic contact lenses are quite popular. The integration of drugs into contact lenses is determined by whether their structure is hydrophilic or hydrophobic. When a contact lens (containing 35 to 80% water) is soaked in solution, the medication is absorbed.The amount of drug, the soaking period of the contact lens, and the drug concentration in the soaking solution all have a significant impact on drug release.

2. Soluble inserts:(25)

These soluble inserts have the benefit of being completely soluble, so they do not need to be withdrawn from their site of application, limiting the intervention to insertiononly. They are roughly classified into two types: natural polymers and synthetic or semi-synthetic polymers.

A. Natural polymers:

The first type soluble insert is made from natural polymer. Collagen is the most commonly used natural polymer in the production of soluble ophthalmic inserts. The therapeutic agent is absorbed preferably by soaking the insert in a drug-containing solution, drying, and rehydrating it before use on the eye. The amount of drug loaded is determined by the amount of binding agent present. The medication is progressively released from the interstices between the collagen molecules when the collagen degrades.

B. Semi-synthetic and synthetic polymers:

The second type of soluble insert is typically composed of semi-synthetic polymers (for example, cellulose derivatives) or synthetic polymers such as polyvinyl alcohol. The use of Eudragit, a polymer commonly used for enteric coating, as the insert's coating agent can reduce the release rate. However, the inherent issues with these soluble inserts are the rapid penetration of lachrymal fluid into the device, impaired vision caused by insert component solubilization, and the potential of ejection due to the device's initial dry and glassy quality.Ethyl cellulose, a hydrophobic polymer, can be utilised to reduce the deformation of the insert and thereby prevent impaired vision. The soluble inserts have the further benefit of having a generally basic design, being based on goods well suited for ophthalmic usage, and being simply processed using conventional processes. The major benefit is a lower release rate, which is still controlled by diffusion.

3. Bio-erodible inserts:

These inserts are made of bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) that dissolve due to chemical bond hydrolysis. The ability to modulate the erosion rate of these bio-erodible polymers by altering their final structure during synthesis and adding anionic or cationic surfactants is a significant advantage. However, erodible systems can have highly varying erosion rates dependent on individual patient physiology and lacrimation patterns, and degradation products and residual solvents used during polymer production might produce inflammatory reactions. The solid inserts absorb aqueous tear fluid and progressively dissolve or disintegrate. The drug is then gradually leached from the hydrophilic matrix. Bio-erodible ocular implants do not need to be removed once drug delivery is complete.The following sections address various major ocular inserts that are commercially available (SODI) or in advanced stages of development (collagen shields, Ocufit, NODS, and Minidisc).

Lacrisert:(26)

Lacrisert are non-preservative hydroxypropyl cellulose rod-shaped devices that are useful for dry eye

syndrome. It weighs 5 grams and has a diameter of 12.7 mm and a length of 3.5 mm. Lacrisert is effective in treating keratitis symptoms that are difficult to treat with artificial tears alone. It is placed into the cul-de-sac cavity and absorbs water from the conjunctiva and cornea, forming a hydrophilic coating that stabilizes the tear film for corneal hydration and lubrication. It disintegrates in 24 hours.

Soluble ophthalmic drug inserts:(27)

The Soluble Ocular Drug Insert (SODI) is a tiny oval wafer that was created for pilots who couldn't use eye drops in zero gravity. The ABE is an oval-shaped, sterile thin film consisting of acrylamide, N-vinyl pyrrolidone, and ethyl acrylate. It measures 15–16 milligrammes in weight. It is applied to the management of trachoma and glaucoma. It is placed into the lower cul-de-sac, where it soaks up water and softens within 10 to 15 seconds. Film releases medication for roughly 24 hours before transforming into a viscous polymer mass after 10-15 minutes and polymer solutions after 30–60 minutes.

Collagen shield:(28)

Collagen shield is made of cross-linked collagen and fetal calf skin tissue, and it is used as a corneal bandage to enhance wound healing. Tear fluid softens these devices and forms a thin malleable film with a disintegration rate of up to 10, 24, or 72 hours. Collagen film has been identified as a possible carrier for ophthalmic drug delivery systems because to its structural stability, high biocompatibility, and biological inertness. For medicine distribution to the eye, collagen ophthalmic inserts are available.

Minidisc:(29)

The minidisc is a contoured disc with a convex front and concave back surface that comes into contact with the eyeball. With a diameter of 4-5mm, it is similar to a small contact lens. The silicone-basedprepolymer—bis (4-methacryloxy) butyl polydimethyl siloxane is used to make the minidisc. Minidiscs can be hydrophilic or hydrophobic in order to allow for the prolonged release of both water soluble and insoluble medicines.

Table3: currently available ocular inserts(30)

Sr. No	Name	Company	Shape	Composition	Weight	Dimension	Uses	Advantages
1	Soluble ocular drug insert	Alza corporation	Oval shape	Acryl amids, vinyl pyrrolidone	15-16mg	Diameter-12.5mm, length-3.5mm	Glaucoma, dry eye treatment	Better patient compliance
2	Collagen shields	Bausch and Lomb pharmaceuticals	Ring shaped	Glycine, proline, hydroxyproline, and arginine	More than 25% of total body weight	Diameter-14.5mm	Treatment of dry eye	Reduce the corneal inflammation
3	Minidisc	Alza corporation	Rod shaped	Silicon based prepolymer	6.7-7.5gm	Diameter 4-5mm	Dry eye syndrome	Improve patient compliance
4	Lacrisert	Merck and co. INC	Rod shaped	Ethanol, propylene glycol, dioxane, methanol	5mg	Diameter-12.7mm, length-3.5mm	Dry eye syndromes	Increase ocular residence
5	Bio adhesive ophthalmic eye inserts	Sigma Aldrich corporation	No specific shape	Hydroxypropyl cellulose, polyacrylic acid cellulose-alate	20.5mg	Length-5mm, diameter-2mm	Treatment of glaucoma	Reduction of the systemic side effects
6	Ocuserts	Alza corporation	Oval shaped	Pilocarpine, alginic acid, ethylene-vinyl acetate copolymer	5.86-6.06mg	Length-3.5mm, diameter-12.5mm	Dry eye treatment	Quick absorption, easily administered by the patient himself

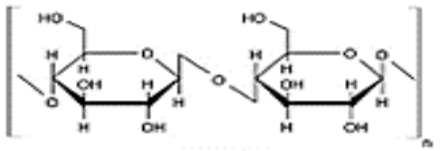
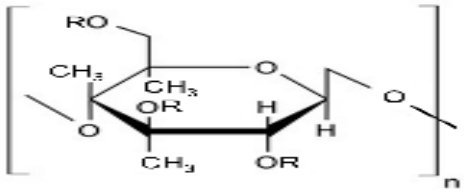
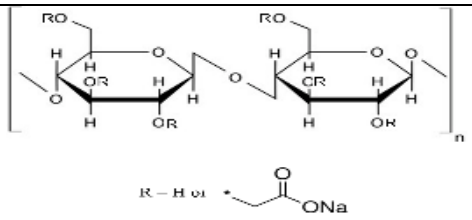
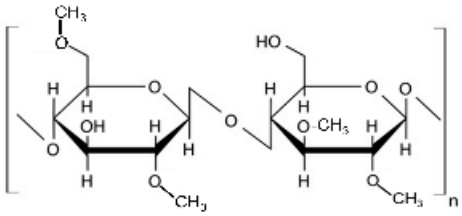
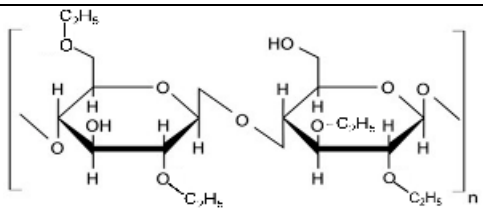
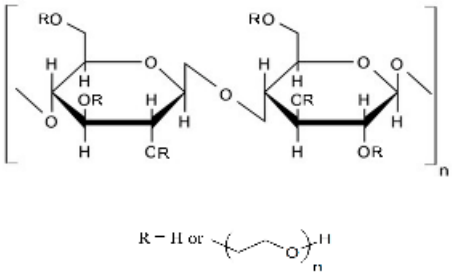
VI. POLYMER USED IN OCULAR INSERTS:(31)

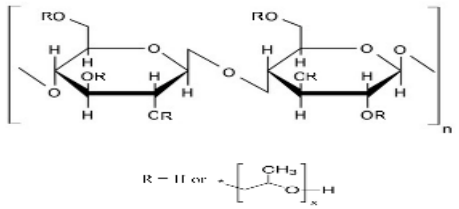
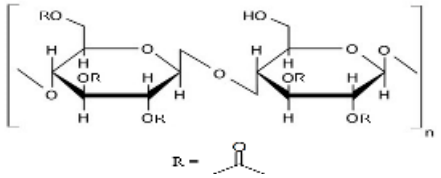
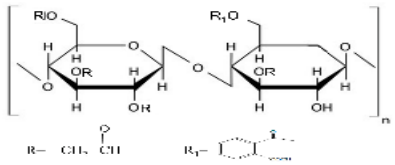
Cellulose derivatives in ocular drug delivery system:

Cellulose is one of the most common polymers used in ophthalmic preparations. In the 1940s, methylcellulose (MC) was originally employed as a viscosity enhancer in ocular formulations. Cellulosic polymers have since been extensively researched for ocular delivery in both animals and humans. Because pure cellulose is insoluble in water, cellulosic derivatives are widely used in ocular treatments. Methylcellulose (MC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), and carboxymethylcellulose (CMC) are the most often utilised cellulosic derivatives in ocular formulations. Cellulosic derivatives have valuable viscosity raising qualities that can be used to improve bioavailability in polymer-based ophthalmic formulations. These macromolecules also have obvious potential as medication carriers in the eye.However, the swelling properties, chemical properties, and structural morphology of these derivatives all have a significant impact on the release mechanism of the medicines loaded in these systems.

1. Cellulose
2. Methylcellulose (MC)
3. Hydroxyl propyl methylcellulose(HPMC)
4. Carboxymethyl cellulose(CMC)
5. Ethyl cellulose(EC)
6. Hydroxyethyl cellulose(HEC)
7. Hydroxypropyl cellulose(HPC)
8. Cellulose acetate(CA)
9. Cellulose acetate phthalate(CAP)
10. Polyvinyl pyrrolidone(PVP)
11. Polyvinyl alcohol(PVA)

Table4: Cellulose polymer structure, properties and application

Cellulose polymer	Structure/ modification	properties	Application
Cellulose		Sustainable natural polymer, good mechanical properties	Viscosity enhancer, water binding ability, adhesiveness
HPMC		Biodegradable, Bio-compatible material, transparency, and rheological properties.	Improve bioavailability and efficacy, prolonged retention.
CMC		Biocompatible, biodegradable, non- toxic and water-soluble.	Synergistic effects for dry eye with less blur vision and stickiness when blinking.
MC		Water-soluble, non-toxic, tasteless, and odorless, LCST polymer.	Prolonged residence time, bio adhesion.
EC		Linear, non-toxic, non-swellable polysaccharide, insoluble in water.	Enhanced corneal resistance time, extended or control release, retard drug release.
HEC		Biocompatible, biodegradable, hydrophilic, low toxic, and non-immunogenic	Sustained release and improve ocular performance

HPC		Highly plastic and hydrophobic compare to other cellulose ether derivative	Increases the ocular drug residence time of drug
CA		Non-toxic, non-irritant and biodegradable polymer, its heat resistant and less hygroscopic	Sustain the release, prolong the residence time of the drug
CAP		Hygroscopic to moisture and dissolve in GI fluid	Prolong residence time and control permeation of drug

VII. CONCLUSION

The study of ocular drug delivery has led to the commercialization of a few novel pharmaceuticals. However, these new technologies' performance is still far from ideal. An ideal system should be able to minimise systemic exposure. Thus, ocular insets have been found to be advantageous because they prevent drug loss and improve patient compliance while removing the adverse effects of pulsed dosing of conventional dosage forms. They also provide controlled and sustained drug delivery with increased bioavailability and corneal contact time.Different classes of ocular inserts, including soluble, insoluble, and biodegradable ocular inserts, have been developed yet.It has several benefits for treating eye related issues, however few of these are

accepted by the market. This is due to the expensive nature and the patient's unwillingness to employ unproven ophthalmic drug kinds.

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