International Journal of Medical and Pharmaceutical Sciences
Open access peer-reviewed Journal
Volume 2, Issue 6, Page 210-219.
https://doi.org/10.5281/zenodo.20719279

Review Article

Advancements in Ophthalmic Drug Delivery: A Review on Ocular Inserts

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Sterile medications known as optical inserts are placed into the cul-de-sac or conjunctiva. They contain medications and are solid or circumfluous, thin, and multilayered. Usually, They consists of polymeric medium that incorporate medication. The distribution of ocular medications is one of the most sensitive and exciting duties for a pharmaceutical chemist. The challenge for the deviser is to breach the protective layer of the without causing irreversible damage to the eye tissue. Innovative optical drug delivery techniques are currently under exploration to ensure prolonged duration and regulated release. Some of the more modern, sensitive, and efficient optical delivery methods being developed to improve the optical absorption rate and long-term benefits of optical specificity are collagen securities, biodegradable polymeric systems, and inserts. The inserts can be categorized as insoluble or biodegradable based on their solubility. The release of medication from the insert is influenced by diffusion, osmosis, and bioerosion of the medication.

Keywords: Opthalmic drug delivery, Ocular inserts, Absorption rate.

INTRODUCTION

The human eye is an organ that enables us to perceive and interpret visual information. It works by detecting light and transferring signals to the brain, which processes these signals to form images. The eye pays a crucial role in the visual system and its intricate structure allows us to easily perceive our surroundings. The bioavailability of medication administered via conventional eye drops is significantly low due to factors such as nasolacrimal drainage, tear production and dilution of medication with tear fluid, as well as tear turnover and conjunctival absorption. Additionally, the binding of medications to proteins further contributes to the loss of drugs through the precorneal tear film elimination pathway. Consequently only a small percentage 1-3% of medication effectively penetrates the cornea and reaches the intraocular tissue, So to overcome these problem new medicine delivery systems similar as in-situ gels, optical inserts, nanoparticles, Nano-suspensions and micro-emulsions have been created to enhance the bioavailability of the medication in a sustained and controlled fashion.[1] The regular application of eye drops is essential to ensure a continuous therapeutic drug level, leading to a significant and variable treatment effect.[4] To achieve improved ocular bioavailability and prolonged drug action, optical inserts, biodegradable polymer systems, and collagen shields are currently under development.[2] Optical inserts are defined as sterile medictions that posses a thin, multilayered structure ,saturated with medicine, and exhibit either a solid thickness. These insert are designed to be placed into the cul-de-sac or sac of conjunctiva, with their dimensions and shape specifically customized for ophthalmic use.[3,4] Less frequently, these inserts are positioned on the cornea or within the upper fornix. They are widely used as topical remedies and are typically composed of a polymeric carrier that contains medication.[5,6] They are made up of a

polymeric support that may or may not include medication, with the final element being integrated as a result within the polymeric support.[7]

History of ocular inserts

The initial solid medication was utilized in the 19th century, composed of sections of dry sludge paper that had been infused with dry substances (similar to pilocarpine hydrochloride or atropine sulfate). Small pieces were cut and placed beneath the eyelid. Lamellae, which are the precursors to the modern accountable inserts, were subsequently developed. These included various ophthalmic agents in glycerinated gelatin. Until the early part of the 20th century, glycerinated gelatin "plates" were incorporated in approved publications. However, with the implementation of stricter regulations regarding the sterility of ophthalmic products, the use of plates was discontinued. The application of ophthalmic inserts is becoming increasingly popular in contemporary times.[8]

Ophthalmic insert as a mechanism for prolonged delivery of eye medications:

Sterile formulation distinguished by a thin,multilayered composition, which can be either solid or semisolid are infused with therapeutic agents and positioned within the conjunctival sac or cul de sac , known as ophthalmic inserts. These inserts are crafted with particular dimensions and configurations appropriate for ocular use. They are composed of a polymeric formulation that may incorporate one or more active pharmaceutical components.[10]

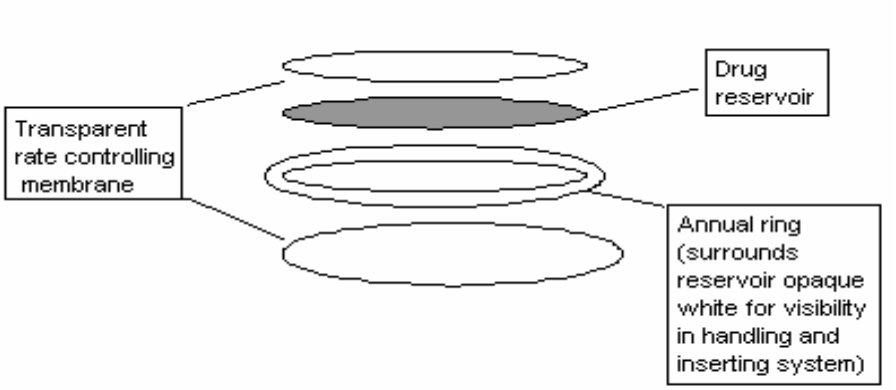

Fig. 1. Schemetic diagram of ophthalmic insert

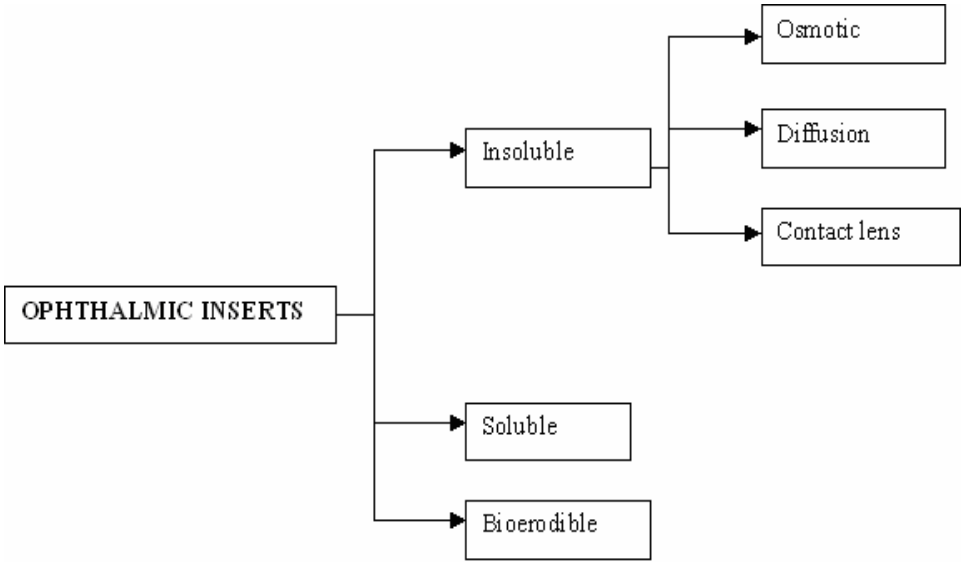

Fig 2. Classification of Ophthalmic inserts

The primary objective of ophthalmic inserts is to enhance the duration of contact between the medication and the conjunctival surface, ensuring a sustained release that is appropriate for either topical or systemic treatment. In contrast to traditional ophthalmic medications, such as eye drops, solid ophthalmic formulations offer several advantages, including:

- Increased contact time, which consequently improves bioavailability.
- The potential for extended drug release, leading to enhanced efficacy.
- A decrease in systemic side effects, resulting in fewer adverse reactions.
- A reduction in the frequency of administrations, thereby improving patient compliance.

Classification of Ocular Insurts: (Based upon their solubility behaviour)

1) Insoluble inserts

a) Diffusion based
b) Osmotic based
c) Soft contact lenses

2) Soluble inserts

3) Bioerodible inserts[14]

The sensation of a foreign body results in discomfort, which in turn affects patient compliance negatively, excessive tearing that accompanies irritation, diminishes the effectiveness of the medication, and lowers its concentration. A properly designed optical insert will alleviate the sensation caused by its placement and offers

- Simple application and insertion.
- No expulsion while in use.
- Consistent release kinetics (Zero-order drug delivery).
- Suitable for a range of medications.
- No interference with vision and oxygen permeability.
- Sterility.
- Stability.
- Ease of production.

1. Insoluble Ophthalmic Inserts

i. The insoluable inserts are categorized into three groups- diffusion systems
ii. Bibulous systems/ Osmotic inserts
iii. Hydrophilic contact lenses.

The initial two categories encompass a force that interacts with the inner surface of the rate controller and supplies medication to it. The force can be composed of a liquid, gel, colloid, semisolid, solid matrix, or a carrier that contains the drug either uniformly or non-uniformly dispersed or dissolved within it.Carriers can be composed of hydrophobic, hydrophilic, organic, inorganic, naturally occurring, or synthetic materials. The third category includes contact lenses. The insolubility of these lenses represents their primary drawback, as they must be removed after use.

a) Diffusion inserts

A central drug reservoir surrounded by specially created semi-permeable or microporous membranes that allow the drug to diffuse from the reservoir at a meticulously regulated rate is used to compare diffusion systems.[21] The lachrymal fluid that seeps through the membrane of This system controls the drug's release until the internal pressure reaches a sufficient level to compel the drug out of the reservoir. The rate of drug delivery is regulated by diffusion through the membrane regulates the drug delivery rate, and this can be managed.[22]

Table 1: Components of diffusional inserts

Main reservoir	Glycerine, PG,water, methyl cellulose combined with water, sodium alginate, ethylele glycol.
Micropores membrane	Polycarbonates, polyvinyl chloride, polysulfones, cellulose esters, crosslinked poly (ethyl oxide), cross-linked polyvinylpyrrolidone, and cross-linked polyvinyl alcohol

b) Osmotic inserts:

The osmotic inserts consist of a central section surrounded by a peripheral section.[23] Two separate compartments or a single reservoir can make up the initial central section. In the first instance, The medication is surrounded by the polymer, forming separate small deposits, and it may or may not include an additional osmotic solution that is distributed throughout the polymeric matrix. In the alternative scenario, the osmotic solutes and the drug are divided into two separate compartments; a semi-permeable membrane encases the osmotic solute reservoir, while an elastic impermeable membrane surrounds the drug reservoir. The second peripheral component of these osmotic inserts is consistently a covering screen made of an insoluble semi-permeable polymer. [25,26] The semi-permeable polymeric membrane facilitates the flow of incision fluid into additional deposits, thereby moistening and dissolving them. The hydrostatic pressure generated by the solubilized deposits exerts force on the polymer matrix, leading to its rupture into perforations. Furthermore, this hydrostatic pressure also results in the release of the drug through these openings from the deposits located close to the device's surface that is in contact with the eye. This aligns with the zero-order drug release characteristic that defines the absorbent component.

Table 2: Components of osmotic inserts

Water permeable matrix	Ethylene - vinyl esters copolymers, Divers- plasticized polyvinyl chloride (PVC), polyethylene, cross-linked polyvinylpyrrolidone(PVP)
Semi permeable membrane	Cellulose acetate derivatives, Divers – Ethyl vinyl acetate (EVA), polyesters of acrylic and methacrylic acids (Eudragit ®).
Osmotic agents	Inorganic – magnesium sulfate, sodium chloride, potassium phosphate dibasic sodium carbonate and sodium sulfate. Organic- calcium lactate, magnesium succinate and tartaric acid. Carbohydrates – Sorbitol, mannitol, glucose and sucrose.

c) Soft contact lenses

These frameworks are systematically organized and consist of a covalently crosslinked hydrophilic or hydrophobic polymer, which forms a three-dimensional network or matrix that can retain both water and solid components.[29] When a hydrophilic contact lens is placed in a drug solution, it takes up the drug; however, the precision of delivery is not as high as that provided by other non-invasive ophthalmic systems. The release of the drug from such a system is generally very rapid at first and then decreases exponentially over time. The rate of release can be diminished by uniformly integrating the drug during the manufacturing phase or by incorporating a hydrophobic component. Contact lenses present considerable promise as systems for delivering drugs ophthalmically.[30]

2) Soluble Ophthalmic inserts

The initial category of ophthalmic inserts consists of soluble inserts. They offer a notable advantage, as they can be placed and do not require removal from their operational location.[31]

Types

a) Derived from natural polymers, like collagen.

b) On the base of semi-synthetic or synthetic polymers.

The method for absorbing the remedial agents involves immersing the insert in a drug containing solution, followed by drying and desiccating it prior to application to the eye. The concentration of the drug in the emulsion, the quantity of binding agent and the duration of soaking will all influence the extent to which the drug is loaded.[3] The soluble ophthalmic inserts that incorporate synthetic or semi-synthetic polymers provide the new benefits of a generally straightforward design. a) Based on

products that are well-suited for ophthalmic applications. b) Easily reused through traditional methods – slow sinking extrusion, contraction, or injection molding. The medication is released from such systems through the penetration of incisions into the insert, which triggers the release of the medication through diffusion and creates a gel layer around the core of the insert. This external gel formation further facilitates the release, yet it remains regulated by diffusion.The release rate J, is deduced from Fick's law provides the following equation33.

J = AdkCS\ L

When A represents the face area of the membrane.

K denotes the prolixity measure of the medicine.

L indicates the membrane consistency.

CS refers to the solubility of the medicine in water.

D signifies the prolixity measure of the Ocuserts membrane.

Since all the variables on the right side of the equation below are constant, the release rate of the device is also constant. The additional factors that influence the release of medicine from these Ocuserts include:

• Penetration of the addition.
• Clumping of the matrix.
• Dissolution of the medicine and the polymers.
• Relaxation of the polymeric chain.

The soluble insert composed of cellulose derivatives can be modified through exposure to gamma radiation without altering the cellulose components[34]. A reduced release rate is achieved by incorporating a polymer typically utilized for enteric coatings into the matrix or by introducing an appropriate amount of hydrophobic polymer that can decrease the penetration of the gastric fluid, thereby reducing the release of the medication without affecting the solubility of the insert when added in the correct proportions. [31]

A. Bio-erodible ocular inserts

These inserts are made of bio-erodible polymers that dissolve when chemical linkages are hydrolyzed, such as polyester derivatives and cross-linked gelatin derivatives. The ability to adjust the rate of erosion of these bio-erodible polymers by altering their final structure during synthesis and by adding cationic or anionic surfactants is a significant benefit. Attia et al.[22] increased the bioavailability of dexamethasone in the rabbit eye by using a cross-linked gelatin insert. When compared to a dexamethasone suspension, the levels of the drug in the aqueous humor were found to be four times higher. Nevertheless, depending on the physiology and lachrimation patterns of each patient, erodible systems can have widely differing rates of erosion, and inflammatory reactions might be brought on by breakdown products and leftover solvents from the polymer production process.

1. Lacrisert

Lacriserts are rod-shaped devices made of hydroxyl propyl cellulose, designed without preservatives, and are beneficial for individuals suffering from dry eye syndrome. Weighing 5 mg, each Lacrisert has a diameter of 12.7 mm and a length of 3.5 mm. These devices are particularly effective in treating keratitis, especially when symptoms are challenging to manage with artificial tears alone. Lacriserts are inserted into the cul-de-sac cavity, where they absorb moisture from the conjunctiva and cornea, creating a hydrophilic film that stabilizes the tear film, thereby providing hydration and lubrication to the cornea. The device dissolves within 24 hours.[34]

2. SODI

A bitsy round wafer called the Soluble Ocular Drug Insert (SODI) was created for space aviators who were unfit to use eye drops when in light circumstances. ABE is a sterile, round- shaped thin film composed of acrylamide, N- vinyl pyrrolidone, and ethylacrylate. It weights roughly 15 – 16 milligrams. It's used to treat trachoma and glaucoma. It gets wet and softens in ten to fifteen seconds after being placed in a unacceptable cul-de-sac. The film transforms into a thick polymer mass after 10 to 15 twinkles, also into polymer results after 30 to 60 twinkles, and it continues to deliver the drug for around 24 hours.

3. Minidisc

The convex front and concave back faces of the minidisc's curved slice make contact with the eyeball. It resembles an atomic contact lens with a 4- to 5-mm radius. The minidisc is composed of butyl polydimethyl siloxane and silicone grounded pre-polymer-α-bis(4-methacryloxy). To allow for the prolonged release of both water-soluble and non-soluble medications, minidiscs can be hydrophilic or hydrophobic.

4. Collagen shields

The collagen guard primarily consists of cross-linked collagen, created using fetal skin tissue and designed as a corneal thickness to facilitate the healing of cracks. Tear fluid renders these materials soft and creates a thin, flexible film with a dissolution rate of up to 10, 24, or 72 hours. Due to its structural integrity, excellent biocompatibility, and natural inertness, collagen film has been demonstrated to serve as an effective carrier for ophthalmic drug delivery systems. Collagen ophthalmic inserts are available for the administration of medication to the eye.[35]

B. **Non-Erodible Ocular Insert**

The Non-erodible ocular inserts include Ocusert, and Contact lens

1.Ocusert

An irreversible delicate sandwich technology was employed in this. A tiny piece of medication complex is squashed between two clear discs of micropervious membrane made of ethylene-vinyl acetate copolymer to create an ocusert medicine force. Tear fluid can enter the medicinal force cube through the micropervious membranes, which dissolve the medication from the complex. Figures 3. 26 and 27 illustrate the sandwich technology utilized in optical inserts.

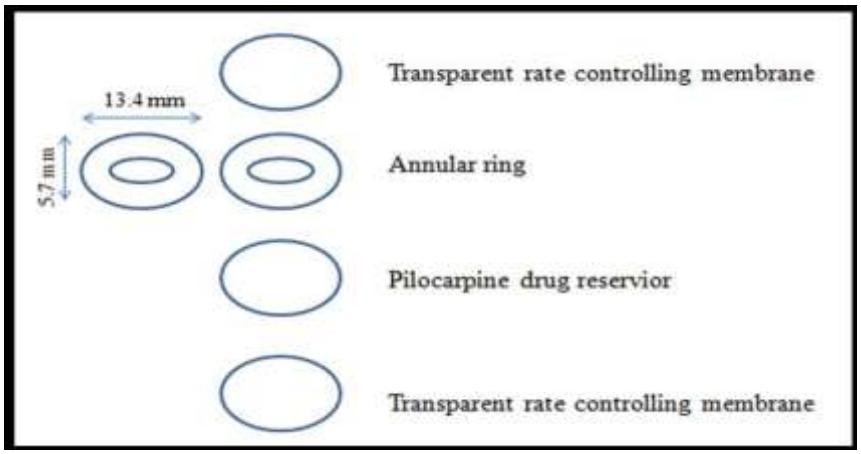

Figure 3: Ocusert

2. Contact lenses

Soaking contact lenses in medicinal solutions allows them to absorb water-soluble medications. Long-term drug release is achieved by placing these drug-saturated contact lenses in the eye. The medications' ocular residence time can be extended by using hydrophilic contact lenses.[20, 28,29]

Mechanism of Drug Release from Ocular Inserts

Diffusion

The drug is continuously delivered through the membrane at a controlled rate in this manner. The permeability through the pores enables the drug to be released if the insert consists of a solid, non-erodible body with pores and the medication is circulated. The gradual breakdown of the solid medication circulating in the matrix, due to the inward permeability of anhydrous results, can facilitate the controlled release of the medication. True dissolution in a responsive device primarily occurs due to polymer aggregation. The active ingredient in swelling-controlled devices is evenly distributed throughout a glassy polymer. Given that glassy polymers are nearly impermeable to

medications, there is no permeability through the dry matrix. Immersing contact lenses in medicinal solutions allows them to absorb water-soluble drugs. Prolonged drug release is accomplished by placing these drug-saturated contact lenses in the eye. The ocular residence time of the medications can be prolonged by utilizing hydrophilic contact lenses. [20,28,29]

Osmosis

In the Osmosis medium, the insert consists of a transverse impermeable elastic membrane that separates the internal components of the insert into two distinct chambers, referred to as the first and second chambers; the first cube is surrounded by a semi-permeable membrane and the impermeable elastic membrane, while the alternate cube is encased by an impermeable material and the elastic membrane. A perforation for medicine release is present in the impermeable membrane of the insert. The first cube houses a solute that cannot traverse the semi-permeable membrane, whereas the alternate cube generates a force for the medicine, which is available in either liquid or gel form. Upon placing the insert in the arid environment of the eye, water diffuses into the first cube, causing the elastic membrane to stretch, thereby expanding the first cube and compressing the alternate cube, which results in the medicine being expelled through the medicine release perforation.

Bioerosion

The medication is distributed within a matrix composed of bioerodible material that constitutes the insert in the bioerosion mechanism. Through the process of matrix bioerosion, the insert's interaction with the tear fluid facilitates a controlled and prolonged release of the medication. While the drug is uniformly distributed throughout the matrix, it is believed that a more regulated release can be accomplished by concentrating the drug superficially within the matrix. A chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or the breakdown into smaller, water-soluble molecules, governs the drug release in truly erodible or E-type devices. In cases where the medication exhibits poor solubility in water and the devices maintain a stable surface shape, these polymers may experience bulk or surface hydrolysis, which demonstrates zero-order release kinetics.

Evaluation test for ocular inserts:

1. Thickness
2. Folding Endurance Test
3. Surface pH
4. Weight uniformity
5. Drug content uniformity
6. Tensile strength
7. In vitro drug release study
8. Ex vivo transcorneal permeability study
9. Drug releasr kinetics
10. Accelerated stability study.

A. Film thickness -At various stages of the formulation, the film thickness is measured with a dial caliper, and the mean value is computed.10.

B. Folding Endurance Test -The film was folded repeatedly in the same spot until it broke or showed the first signs of breaking in order to measure folding endurance. The folding endurance value is the number of times the film could be folded in the same spot without breaking.[32]

C. pH of the surface- For 30 minutes, the inserts were left to swell in a closed petridish filled with 1 milliliter of distilled water at room temperature. To find the surface pH, the swelled device was taken out and the solution was put under a digital pH meter.[33]

D. Weight uniformity -Inserts were removed from each batch (n = 3) and weighed separately on a digital balance. The average insert weights were noted.[32]

E. Drug content uniformity -Each insert was put in a glass vial with 10 milliliters of artificial gash fluid to test the medicine's unity. Using a glamorous stirrer, the insert was dissolved. The result was also filtered, and 1 milliliter of the filtrate was taken out and adulterated with 10 milliliters of distilled water. A UV-visible spectrophotometer was used to measure absorbance.[32]

F. Tensile strength -Tensile Strength is Using the following formula, the produced flicks' tensile strength was determined.34, 35 Tensile strength N, is

equal to N/ mm2. The sample's cross-sectional area in millimeters

G. In vitro drug release study -Drug release exploration in vitro Franz prolixity cells and dialysis membranes were used to study the in vitro medicine release from the colorful optical implants. The corneal epithelium is mimicked by the dialysis membrane. lately made artificial gash fluid was poured into the receptor cube. While the receptor fluid was kept at 37 ± 0.5 ºC with nonstop shifting using a glamorous stirrer, a 1.5 cm2 area of optical film was placed on the dialysis membrane and the patron cube orifice was sealed with a glass cover slip. At different times up to six hours, a 1 ml sample was taken out of the receptor cube and subordinated to spectrophotometric analysis. An original volume of artificial gash fluid was used to replace each sample that was removed.[37]

H. Ex vivo transcorneal permeability study - Transcorneal permeation investigation in vivo Within an hour of the goat being killed, the entire eyeball was brought from the nearby butcher shop to the lab in cold (4ºC) normal saline. After gently removing the cornea and 2-4 mm of surrounding scleral tissue, the area was cleaned with cold normal saline until no proteins remained. An all-glass modified Franz diffusion cell was used to mount the isolated cornea by sandwiching the surrounding scleral tissue between the clamped donor and receptor compartments so that the donor compartment's epithelial surface faced the cell. Freshly made artificial tear fluid was poured into the receptor compartment. A glass cover slip was used to seal the donor compartment opening after a 1.5 cm2 patch of ocular film was applied to the cornea. A magnetic stirrer was used to continuously mix the receptor fluid, which was kept at 37 ± 0.5ºC. At different times up to six hours, a 1 ml sample was taken out of the receptor compartment and subjected to spectrophotometric analysis. An equivalent volume of artificial tear fluid was used to replace each sample that was removed.[38]

I. Drug release kinetics -When characterizing a drug dissolution profile, two crucial features of a drug delivery system are drug release mechanisms and kinetics. Mathematical models including zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models were utilized to explain the kinetics of the drug release from the optimized ocular insert. The goodness or fit test was used to determine the criterion for choosing the best model.

J. Sterility testing as per I.P. 2014

The direct inoculation method was used to test the sterility of the sterilized ocular implant.

Media culture

The fungus (C. albicans) and bacteria (S. aureus) were cultured in soyabean casein digest medium and alternative thioglycolate medium, respectively. 20 ml of media were made in accordance with I.P.2014, placed in a boiling test tube, securely sealed with cotton, and autoclaved for 20 minutes at 121ºC and 15 lb/inch gauge pressure to sterilize it.

Incubation and vaccination

The formulation was aseptically applied to the test tube with the appropriate media, and a positive and negative control were made for each media at the same time. For at least 14 days, the infected culture media for bacteria and fungus were kept in an incubator at 30 to 35 degrees Celsius and 20 to 25 degrees Celsius, respectively.

K. In agreement with ICH Guidelines, -expedited stability studies Accelerated stability studies are conducted in order to read the declination that takes place under typical storehouse settings over extended ages of time. The insert's flicks are placed in a different Petri dish and maintained at three distinct moisture situations and temperatures.[39]

CONCLUSION

By providing a controlled and sustained delivery of medication, along with enhanced bioavailability and increased corneal contact time, optical inserts have been established as beneficial since they eliminate the adverse effects associated with the rapid dosing of traditional forms. This advancement enhances the efficacy of the medication by preventing loss and encouraging improved patient compliance. Biodegradable and non-biodegradable optical inserts represent various categories of optical inserts that

have been developed thus far. These categories are further classified based on the materials utilized and the mechanisms by which the inserts facilitate medication delivery. For example, optical inserts can be composed of natural, synthetic, or semi-synthetic polymers, while non-biodegradable optical inserts encompass prolonged-release inserts, absorbent inserts, and soft contact lenses. Biodegradable optical inserts include collagen shields, Lacrisert, SODI, and Minidisc. Contact lenses and ocular inserts serve as examples of non-biodegradable materials.Future innovations could revolutionize ocular therapeutics, offering patients safer and more effective treatment options for various eye conditions by leveraging a deeper understanding of ocular anatomy and physiology.

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Cite: Ashvini Shinde*, Sushila Kaura, Advancements in Ophthalmic Drug Delivery: A Review on Ocular Inserts, Int. J. Med. Pharm. Sci., 2026, 2 (6), 210-219. https://doi.org/10.5281/zenodo.20719279