https://africanjournalofbiomedicalresearch.com/index.php/AJBR
Afr. J. Biomed. Res. Vol. 27(4s) (December 2024); 5540 - 5557
Review Article

A Paradigm Shift In Ocular Drug Delivery System: Review On Ocular Inserts For Treatment Of Glaucoma

E. Ezhilarasan[1], L. Premalatha[2], Dr. S. Umadevi[3*], M. Nallamuthu[4]

[1]M. Pharm, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai-600 117, Tamil Nadu.
Email id: elumalaiezhil0318@gmail.com
[2]M. Pharm, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai-600 117, Tamil Nadu.
Email id: pav01reddi@gmail.com
[3*]Professor, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai-600 117, Tamil Nadu.
Email id: umadevi.sps@velsuniv.ac.in
[4]Research Scholar, Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies, Pallavaram, Chennai-600 117, Tamil Nadu, India.
Email id: nallamuthubpharm@gmail.com

***Corresponding Author:** Dr. S. Umadevi
*Professor, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai, Tamilnadu. Email id: umadevi.sps@vistas.ac.in. Mobile No: +918667469884,
ORCİD ID: Umadevi Sankararajan 0000-0003-0242-2461

ABSTRACT
Glaucoma is related to neurodegenerative disease associated with intraocular pressure within the eye. It leads to loss of vision and decreased contrast sensitivity gradually over time by damaging the optic nerve, which causes. Ocular inserts are sterile, thin, multi-layered delivering devices with biodegradable drug material, inserted into the lower eyelid which release the medication at sustained and increased contact time of medication into the eye may increase the bioavailability of medication. Eye drops require frequent medication administration and medication loss leads to less bioavailability but the ocular inserts improve the patient's convenience by preventing the frequent administration of reduced dose dumping into the eye. It releases the medication by process of osmosis, diffusion, bioerosion, and sustained release into the eye to increase the bioavailability. Ocular inserts are classified based on their solubility profile are soluble inserts, insoluble inserts, and bioerodible inserts. It is prepared by solvent casting, mold preparation, gel foam disc, hot melt extrusion, and glass substrate technique method. This article is an attempt to present a detailed review of ocular inserts as an advanced drug delivery for glaucoma.

Keywords: Ocular inserts, Intraocular pressure, Glaucoma, Sustained release.

***Author for correspondence: Email:** *umadevi.sps@vistas.ac.in.*

Received: 03 December 2024 Accepted: 05 December 2024

DOI: https://doi.org/10.53555/AJBR.v27i4S.4631

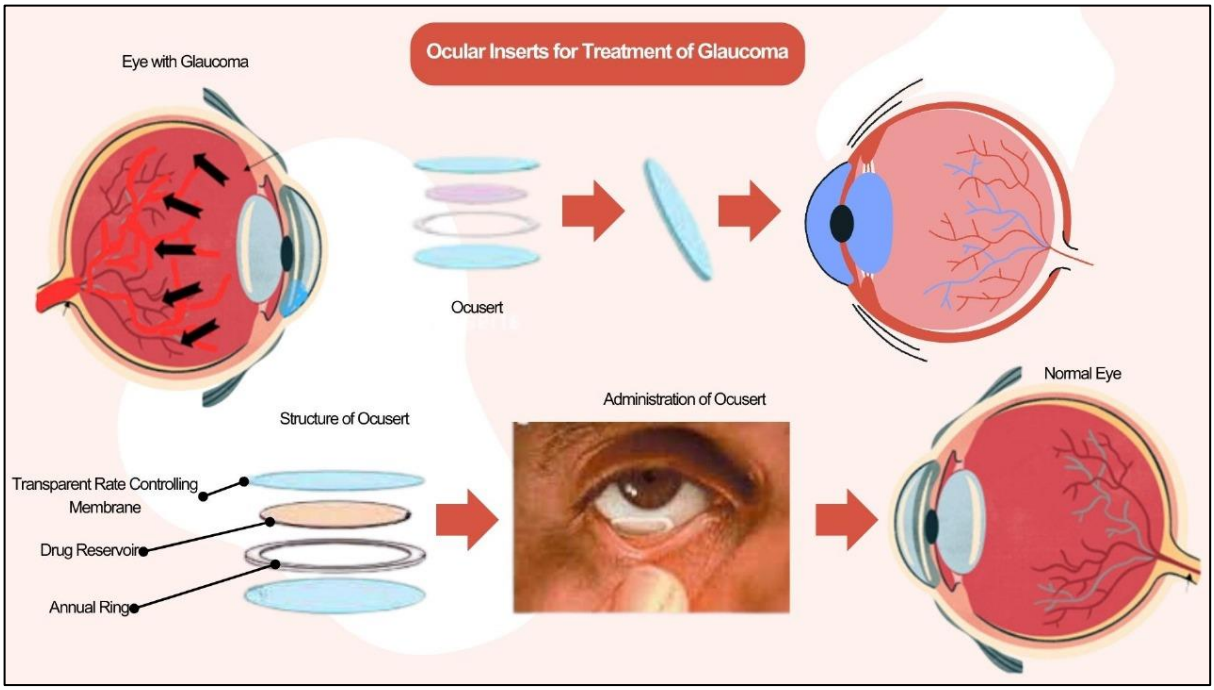

Fig.1 Graphical Abstract

INTRODUCTION

Ocular inserts are sterile drug-delivering devices with solid or semi-solid consistency formulations that are placed between the conjunctival sac surface of the eye and the lower eyelid. Polymeric systems fabricated the inserts and they usually contained drug or drug-free inserts. It can be manufactured in a variety of sizes and shapes but are usually thin multi-layered cylinders. Normally, the drug is loaded into the polymeric system either in solution or as a dispersion. Ocular inserts provided a sustained release of a drug, and prolonged retention in the precorneal as a result ocular absorption was increased. The mechanism of drug release from ocular inserts by diffusion, osmosis, and bioerosion.[1] The therapeutic efficacy for ocular delivery was enhanced by increased contact time with the corneal surface, while developing eye drops, or eye ointment viscosity enhancers were used for this purpose. Unfortunately, these dosage forms give marginal sustained release of medication as a result bioavailability of eye drops in ocular delivery was very poor, and frequent administration was required to obtain desired therapeutic effects. To overcome these problems, most of the studies recently on ocular inserts, to sustained release of medication with one or more active substances but it has some challenging tasks, preventing irritation to patients while inserting inserts into patients. These inserts are formulated with solid or semi-solid consistency and various shapes based on ophthalmic application.[2]

Glaucoma

Glaucoma contributes irreversible blindness to over 80 million people by 2020, it may increase to 111.8 million by 2040. It has a prevalence of 3.5% in 40-80 aged people.[3] This is also called the silent thief of sight because in the early stages, most patients do not experience any symptoms and are undiagnosed, only patients can experience symptoms at advanced levels of disease progress so additional care should be taken to treat glaucoma. It affects the transmission of images to the brain by damaging the optic nerve, which leads to irreversible vision loss over time. Although there is no permanent cure for glaucoma, only patients can manage their condition within levels, only regular checkups by doctors can treat glaucoma before causing irreversible vision loss because restoring the lost vision is not possible, and maintaining intraocular pressure within the condition is the only option to prevent optic nerve damage.[4] The main cause of glaucoma, aqueous humor usually follows outside by mesh-like structure in the eye. If the channels get blocked it build up fluid too much inside the eye which increases the intraocular pressure in that case most blockage is not known but more chances to get it from genetic reasons. The less common factors for glaucoma include chemical injury to the eye, infection, inflammatory condition in eye, and surgeries done for other conditions in the eye.[5]. Graphical illustration of normal and eye with glaucoma shown in Fig.2.

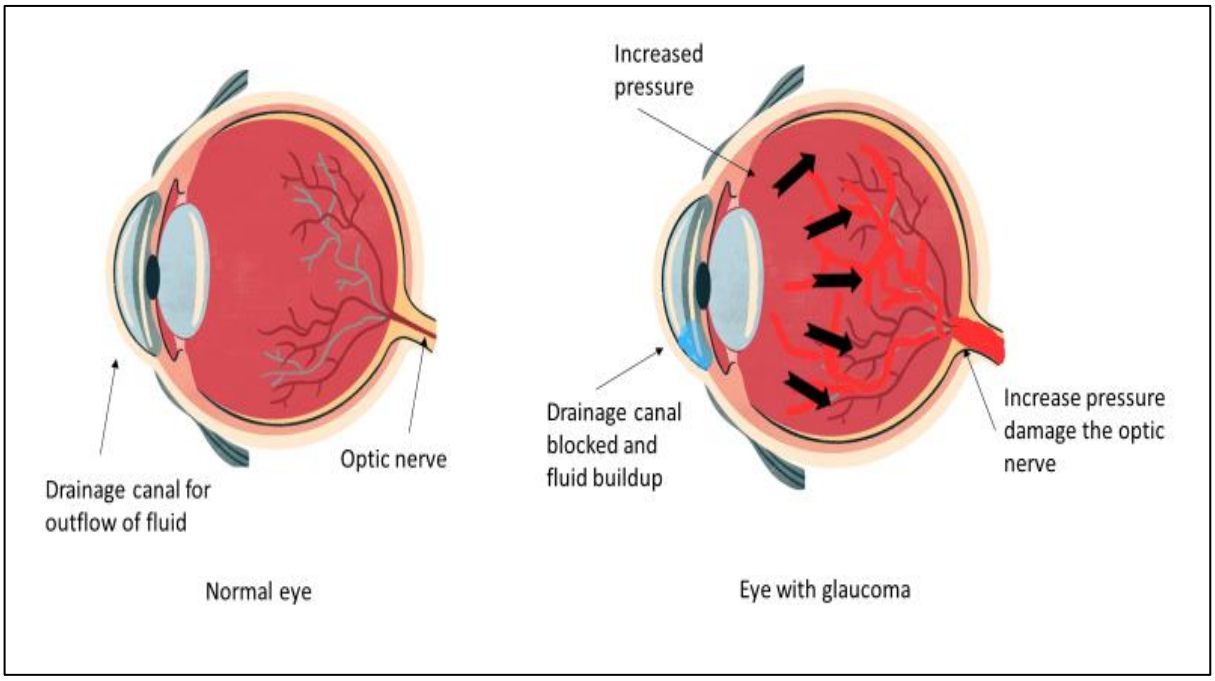

Fig.2 The difference between the normal eye and eye with glaucoma

VARIES GLAUCOMA CONDITIONS

Primary open angle glaucoma

This is also called as wide angles Glaucoma, trabecular meshwork looks good in shape and functioning normally however fluid doesn't exit from eyes which build the more fluid and increased intraocular pressure.[6]

Normal Tension glaucoma

Eye pressure is within the normal range but blind patches in vision damages the nerve responsible for vision transformation and leads to vision loss.[6]

Angle closure glaucoma

This Angle closure or narrow angle glaucoma, the drain between the iris and cornea becomes too small, prevents the tear fluid draining as normal. So intraocular pressure suddenly increased. It has been related to cataracts, farsightedness.[6]

Secondary angle closure glaucoma

This occurs due to a different condition, such as diabetes, cataracts, uveitis (inflammation on eye) and eyes might be bothered by bright lights (light sensitivity or photophobia).[6]

Pigmentary glaucoma

Drainage canals of eyes get clogged with minute particles of pigment from iris.[6]

Plan of glaucoma treatment

Intraocular pressure can be reduced and vision loss can be preserved by using medicine, laser therapy, and surgery, but each individual will respond to each kind of treatment based on their disease condition and severity.[3]

MEDICATIONS FOR GLAUCOMA TREATMENT

Eye is an organ with a blood ocular barrier which has challenges to pass pills or injections to the bloodstream, presence of blood ocular as barrier. To overcome this blood ocular barrier, medications are administered to the surface of the eye. Eye drops or eye ointments are medication absorbed into the eye by natural circulation. Most glaucoma medications are exclusively offered as eye drops. They are works based on the principle of reducing intraocular pressure within the eye by increasing fluid outflow from the eye. which was administered 1 to 4 times a day. Recently various treatment options are also available for glaucoma.[7]

Prostaglandin analogues

Prostaglandin analogs act as vasodilators which dilates the blood vessels and facilitates the tear fluid exit from the eye, later eliminated by the lymphatic system.[8] The mechanism of prostaglandin analogues illustrated in Fig.3 and analogues listed in Table 1.

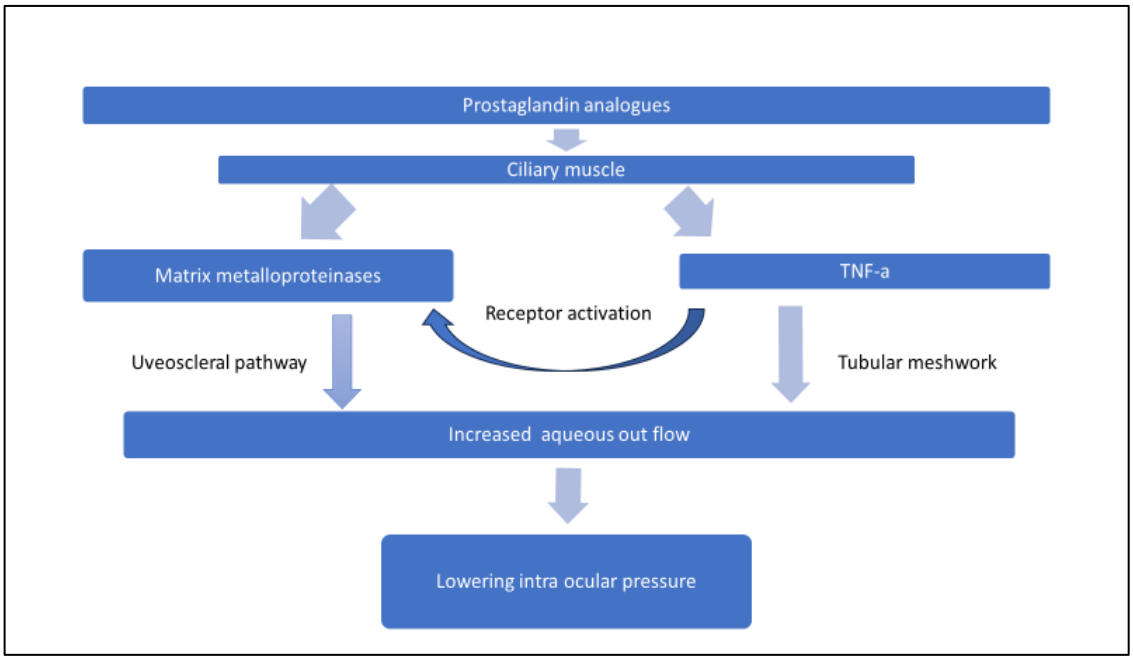

Fig.3 Prostaglandin analogues

Table 1 Prostaglandin analogues [8]

Medication	**Brand name (Eye drops)**
Latanoprost	Xalatan®
Unoprostone	Rescula®
Tafluprost	Zioptan®
Travoprost	Travatan®
Bimatoprost	Lumigan®

Beta adrenergic blockers

Beta blockers alter the nervous system response by binding with receptors as a result the body secretes less aqueous humor and lowers your IOP by an average of 20–27% in glaucoma.[9] Fig.4 shows an example of a beta adrenergic blocker.

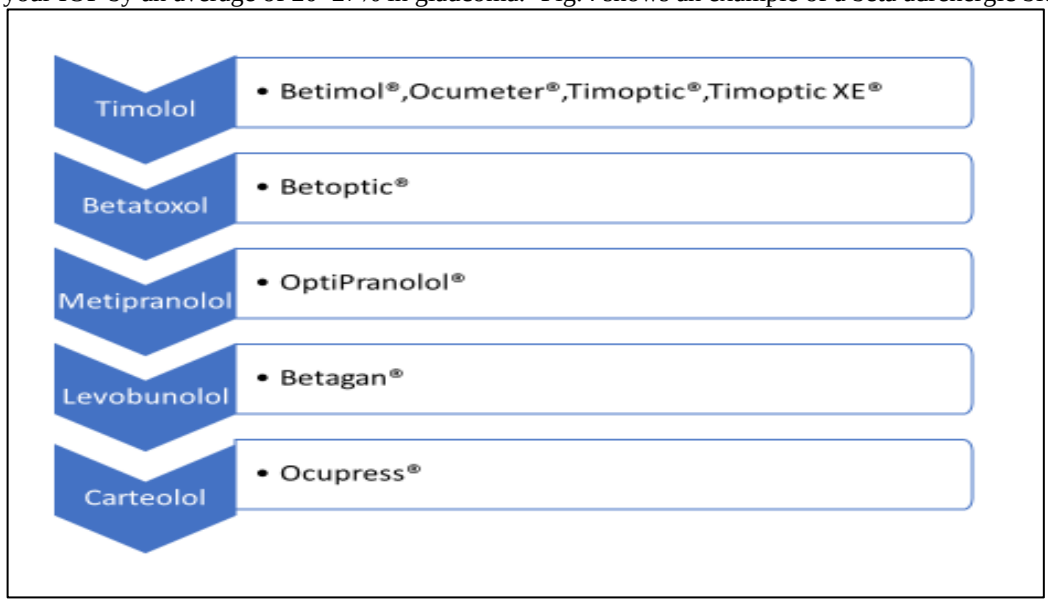

Fig.4 beta blockers

Alpha adrenergic agonist
This decreases the synthesis of aqueous fluid and improves aqueous humor exit through the uveoscleral route, resulting in a 13–29% drop in intraocular pressure.[10] Fig.5 displays an example of an alpha adrenergic agonist.

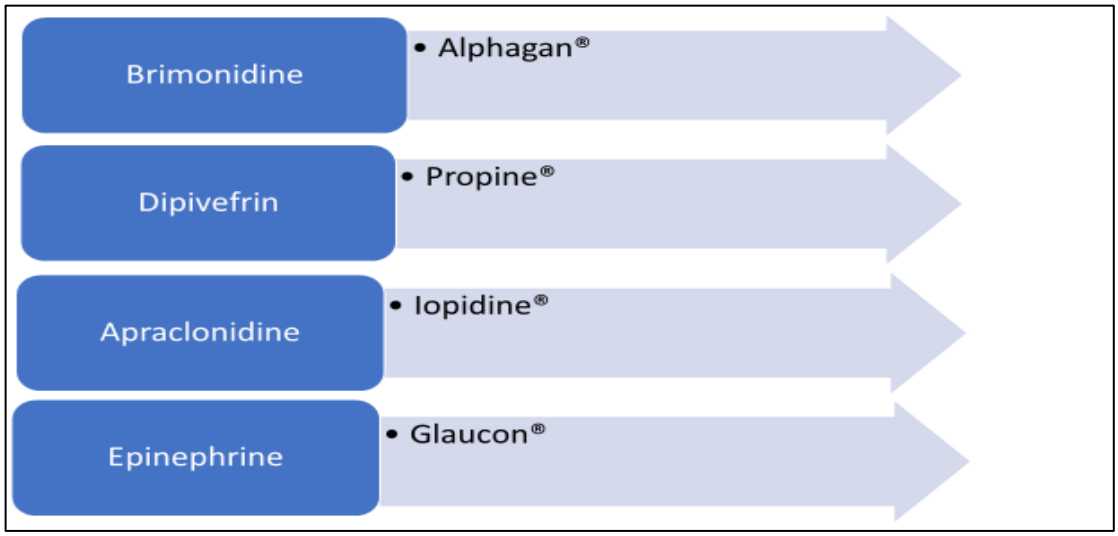

Fig.5 Alpha adrenergic agonist

Carbonic anhydrase inhibitors
Aqueous humor volume is decreased by blocking the enzymes that produce it. IOP may decrease about 15% to 20%. which also increases blood flow to the eye.[11] Fig.6 shows an illustration of an inhibitor of carbonic anhydrase.

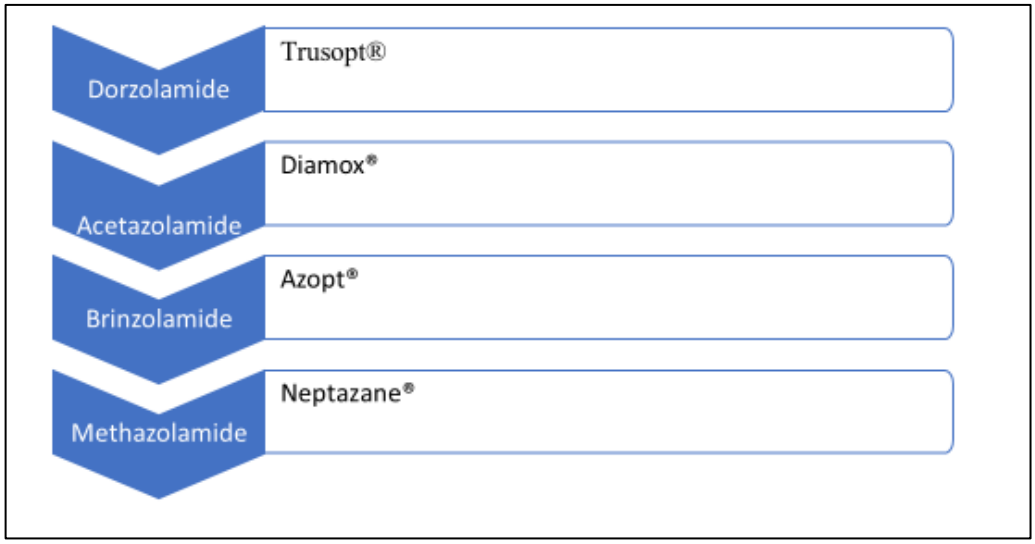

Fig.6 Carbonic anhydrase inhibitors

Cholinergic agents
These drugs open the drainage pathways and increase outflow to the glaucoma patient whose pupil size was much smaller, resulting in a 15–25% decrease in IOP.[12] An illustration of cholinergic agents can be found in Fig 7.

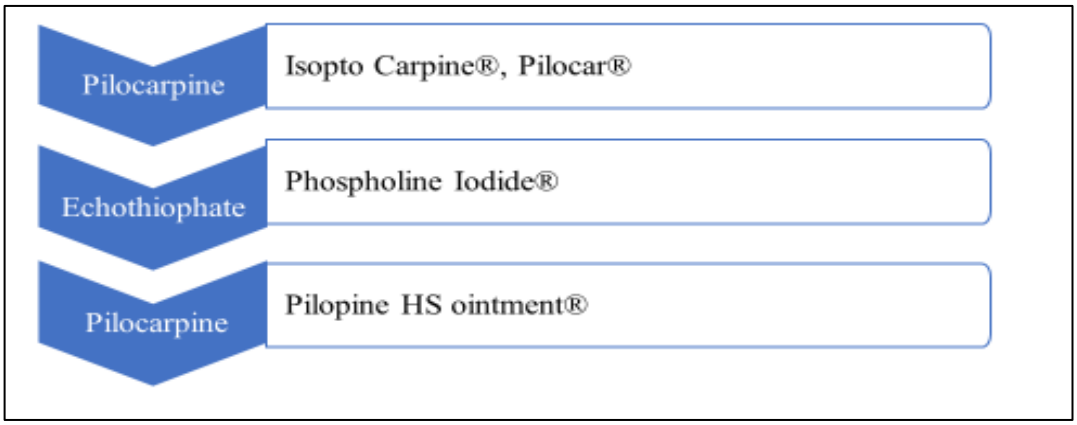

Fig.7 Cholinergic agents

Combination medication

Combination pharmaceuticals are made by two or more of the drugs that combine together in one formulation to produce superior results.[13] The glaucoma drug combination displayed in Table 2

Table 2 Combination medication [13]

Drug	Eye drops(Brand name)
Timolol and Dorzolamide	Cosopt®
Timolol and Latanoprost	Xalacom®
Timolol and Brimonidine	Combigan™
Brimonidine and Brinzolamide	Simbrinza™

SURGERY FOR GLAUCOMA

Surgery can reduce IOP effectively, in some situations, it will return pressure to normal level for a while without the need for any medication. Even Though surgery is chosen rarely for the initial course of treatment because it has some possible complications. Another reason while exceedingly bad outcomes of surgery often have more severe implications compared with medicine. That's why doctors will suggest surgery only when unable to use eye drops or other drugs, and don't reduce IOP. The majority of glaucoma surgical techniques reduce IOP by creating additional passageways to drain the aqueous humor and modify the tissues to reduce obstacles. surgically, the ciliary body reshaped lessen aqueous humor production. Surgery most likely to drop IOP sufficiently, minimizing or eliminating the need for other treatments to get medicine for glaucoma treatment. There is no assurance that any treatment selected will be effective for initially decreasing IOP or not. But in most circumstances, it could be feasible to try or repeat the process if the intended reduction in IOP is not achieved.[14]

Laser treatment

Compared with surgery, Laser operations have less pain, edema, and scarring because a laser focused light beam penetrates into the tissue more fast and precisely. Successful sealing off of blood vessels and nerve endings in the eye may be a quicker recovery time. IOP decrease by laser operations varies based on age of patient, type of glaucoma they have, any additional medical issues they may have. A laser process is generally quite safer than surgery, and can be safely repeated if more sessions are required.[15]

Trabeculoplasty

This laser treatment makes aqueous humor drainage process simpler. It can be done in a variety of ways.

- Selective laser trabeculoplasty (SLT) enlarges the channels for fluid drainage by selectively targeting cells in the trabecular meshwork with a low-level laser. The process can be repeated because it preserves some of the meshwor.[16]
- Argon laser trabeculoplasty directs trabecular meshwork by high energy laser beam. It enlarges the closed channels to new openings in blocked channels. To reduce the overcorrection, just half of the channels are typically treated at once, with the remaining channels being treated later, if necessary.[17]
- Micropulse Laser Trabeculoplasty uses microbursts of laser radiation. It reduces pressure similarly to SLT and ALT.[18]
- Laser peripheral iridotomy is used to treat fluid blocked by too small an angle between iris and cornea; lasers create some holes in the iris. [19]

Conventional glaucoma surgery

It is also called filtering surgery, which reduces IOP by a new pathway for aqueous humor drain. This method was frequently lifted and then reinstalled. It function as a filter, new openings increases outflow humor more gradually as a result, eye pressure is stabilized. [20]

Trabeculectomy

Trabecular meshwork is removed during this process to alternative drainage pathways. Incision made in the eye where the sclera meets the iris. Sclera is protected by the conjunctiva. Removing a little piece of the tissue at tubular meshwork makes a temporary flap-like opening through both layers. Through the openings aqueous humor flows and is absorbed by the blood vessels around the eye. The aqueous humor forms a bleb moves toward the surface of the eye.[21]

Trabectome®

A tiny incision is made in the co transparent layer that covers the cornea, after numbed. Part of trabecular meshwork cutted to increase fluid outflow. The eye does not have a permanent hole. It reduces IOP by about 30 %. [22]

Canaloplasty

A tiny incision is made to access the Schlemm's canal opening in trabecular meshwork. The canal, then cleared by inserting a microcatheter. [23]

Drainage Implant Devices

Implants placed into the eye to create an additional drainage channel. Implants may be used when other treatments haven't been successful. The plate of implants is situated at the back of the eye and the tube extends to the conjunctiva. The tube collects drains and is absorbed by capillaries.[24]

Drainage Implant Devices

Implants placed into the eye to create an additional drainage channel. Implants may be used when other treatments haven't been successful. The plate of implants is situated at the back of the eye and the tube extends to the conjunctiva. The tube collects drains and is absorbed by capillaries.[24]

OCULAR INSERTS

Ocular inserts are drug delivering sterile materials with solid or semisolid formulation, providing optimal suitability for ocular applications. Ocular inserts contain one or more drugs integrated in the form of a solution or dispersion. Enhancing the duration of the active drug form's retention in the eye is the primary goal of using ophthalmic inserts, as this guarantees a suitable sustained release. [25] Example of some of commercially available ocular inserts depicts in Table 3.

Benefits of using inserts as ocular delivery are following

1. Less doses administered, which results in higher patient compliance
2. It is possible to lessen harmful effects by reducing systemic side effects
3. Precise dose (as opposed to ocular drops, which the patient may inject incorrectly and partially miss)
4. Insert manufactured with specific dose, its entirely retained at administration
5. Preservative usage restrictions would lower the likelihood of hypersensitive reactions.

Table 3 Example of some of commercially available ocular inserts [48]

S.NO	NAME	COMPANY	COMPOSITION	INGREDIENTS	USES	AVANTAGES
1	Ocusert	Alza Corporation	Oval Shaped	Pilocarpine, Alginic Acid, copolymers	Treatment of Dry eye	Quick absorption an patients convenience
2	Soluble ocular drug inserts	Alza corporation	Oval shaped	Acrylamide, vinyl pyrrolidone	Treatment of glaucoma	Better patient compliances
3	Collagen shiels	Bausch and lomb pharmaceuticals	Ring shape	Silicon base prepolymer	Dry eye syndrome	Improve patience compliances
4	Lacrisert	Merck and co. INC	Rod shaped	Ethanol propylene glycol,dioxane,methanol	Dry eye syndrome	Increase ocular residence
5	Bio adhesive ophthalmic eye inserts	Sigma aldrich corporation	No specific shaped	Hydroxypropyl Cellulose, polyacrylic acid cellulose alate	Treatment of glaucoma	Reduction of systemic side effects

CLASSIFICATION OF OCULAR INSERT

Based on solubility and drug release properties, ocular inserts are classified into the three categories shown in Fig.8 that are Insoluble ocular inserts, Soluble ocular inserts, Bioerodible inserts.

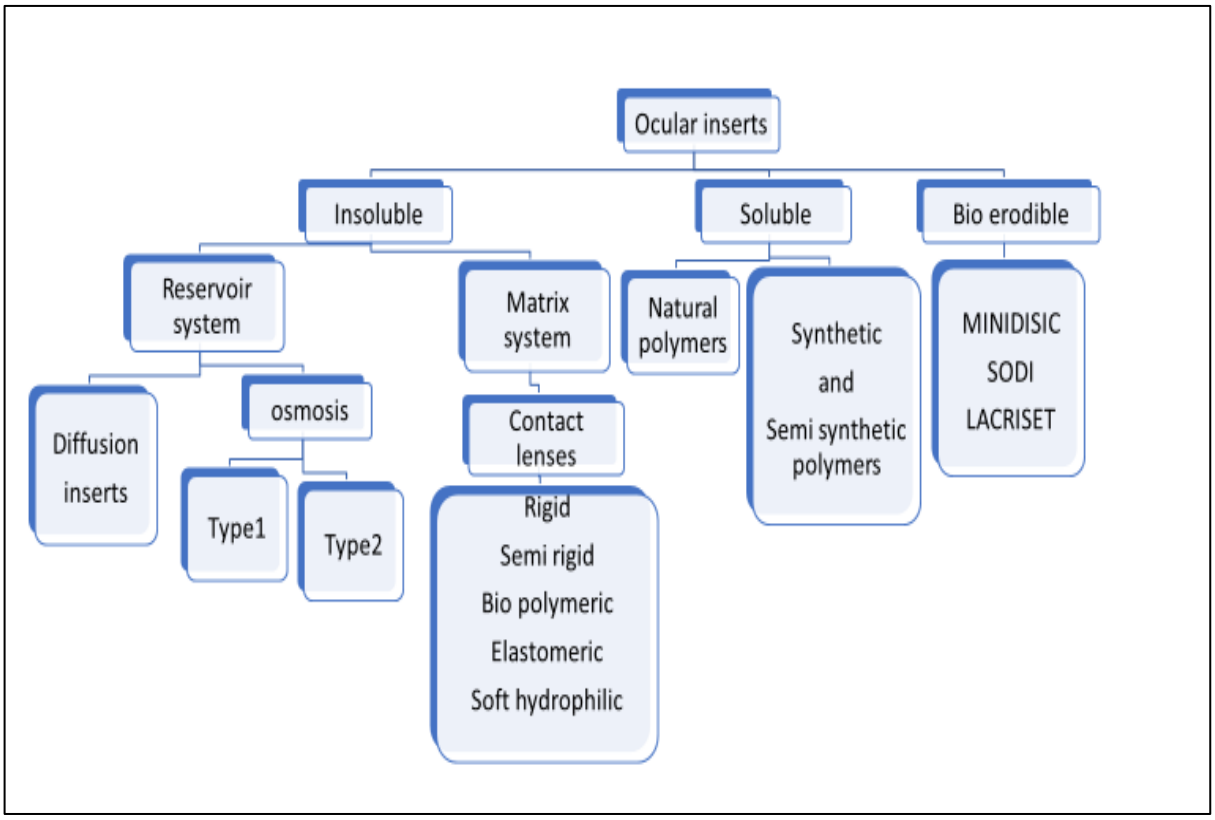

Fig.8 Classification of ocular inserts based on soluble, insoluble, bioerodible nature

Insoluble ocular inserts

Insoluble inserts divided into two groups [26]

A. Reservoir systems

B. Matrix systems

A. Reservoir systems

The reservoir systems have diffusion and osmotic drug release mechanisms. It is made up of organic, natural, synthetic polymers.[27]

They have been divided into two subcategories:

Diffusion inserts

Osmotic inserts

1. Diffusion inserts

It is a drug delivery device by porous membranes. It is made up of a core reservoir carrying the medication that is surrounded by a semipermeable or micropores membrane that permits the drug to diffuse out at controlled rate by permitting lachrymal fluid until internal pressure is reached and details shown in Fig.9 and It is a predictable, time independent drug delivering device and increased concentrations of drug in the target tissues. Two types of Ocusert are available: pilo 20, pilo 40.[28]

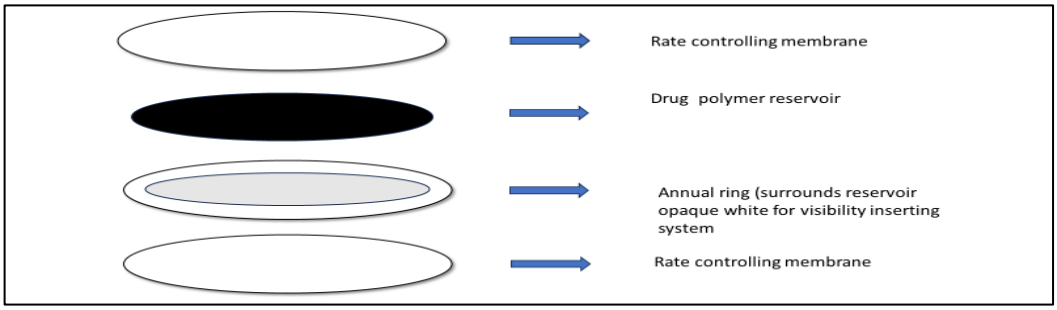

Fig.9 Ocuserts as diffusion mechanism

Osmotic insert

Osmotic inserts consist of two compartments sandwiched between rate controlling membranes, central compartment of drug reservoir and peripheral compartments of osmotic agent. Tears penetrate into the peripheral compartment, increasing osmotic pressure as a result of drugs released by diffusion. It came in two varieties[29]

Type 1: The peripheral compartment consists of insoluble, semi permeable polymer, and the center compartment consists of a single reservoir of a drug and osmotic solute. The polymer matrix ruptures in the form of apertures as a result of osmotic pressure. Drugs are released by the device's surface through these pores.[29]

.Type 2: Two different sections make up the core portion. Drug and the osmotic solutes in central compartments, osmotic solute reservoir being encircled

by a membrane that is semipermeable. The osmotic pressure increased by tear penetrates, its stretches the drug containing compartment to drug release at aperture.[30] The detail process displayed in Fig.10.

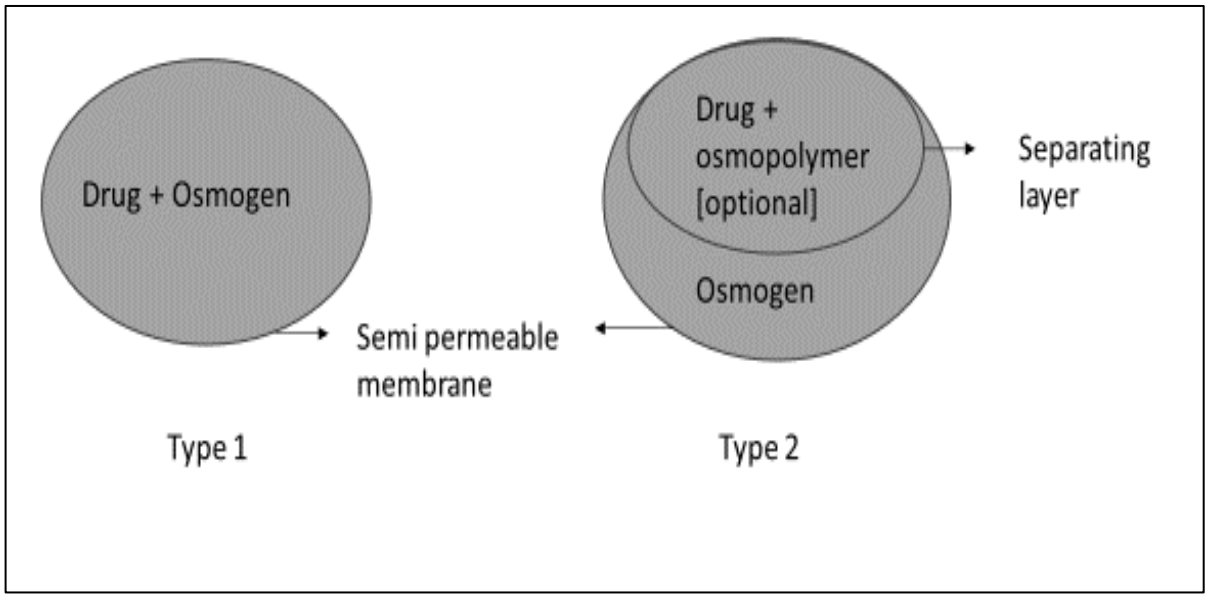

Fig.10 Osmotic agents with types

B. Matrix systems

It is made up of three-dimensional matrix made up of covalently bonded hydrophilic or hydrophobic polymers. While soaking the hydrophilic part in a drug solution which absorbs drugs.[31]

Contact lenses

Initially intended to correct vision, contact lenses are formed. By soaking them before hand in medication solutions, their utility has been expanded as possible drug delivery systems. The ability to concurrently correct vision and release medication is this system's key benefit. Contact lenses are divided into 5 groups, that's are Rigid, Semi rigid, Elastomeric, Soft hydrophilic, Bio polymeric.[32] Difference between medication release time profile of the eye drops and contact lenses demonstrated in Fig.11.

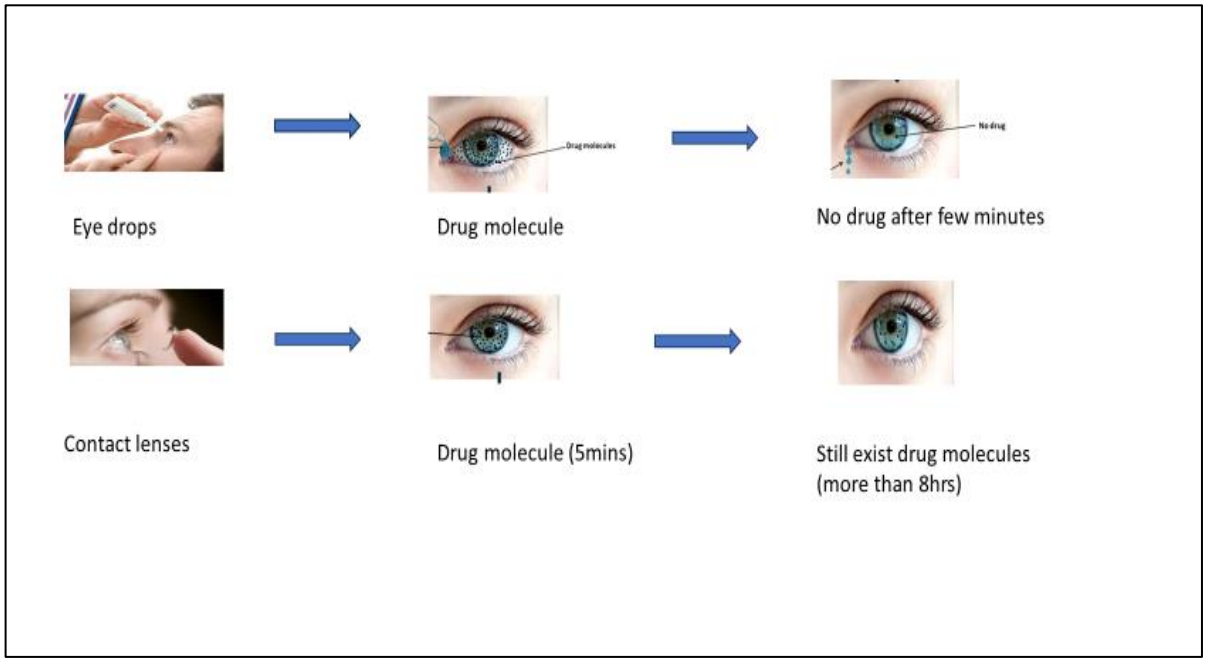

Fig.11 Difference between medication release time profile of the eye drops and contact lenses

Soluble ocular inserts

Soluble inserts have the benefit of being completely soluble, no necessary to withdraw from the applied site. Inserts are soaked in a drug then dried. By this process therapeutic agents are absorbed by inserts before being inserted into the eyes. Medication from this system is released by diffusion, penetrating tears into the inserts. They can be classified into two natural, synthetic or semi synthetic polymers.[33]

Natural polymers

This type of soluble inserts made of natural polymers. Collagen is the preferred natural polymer utilized soluble inserts. The insert is immersed in a mixture that contains the medication, dried before applying it to the eye. The quantity of drugs loaded is based on the concentration of binding agent, medication concentration, length of the soaking. When collagen disappears, medication is discharged gradually.[34]

Synthetic and semi synthetic polymers

This type of soluble insert is composed of synthetic, semi-synthetic polymer. The polyvinyl alcohol, cellulose and its derivatives are some of the examples. Hydrophobic polymer utilized to lessen the insert's distortion and hence avoid vision blur. Bio adhesive polymer, to reduce the danger of ejection.[35] Various synthetic polymers used are follow

Bio-erodible ocular inserts

These inserts are made of bioerodible polymers, which dissolve when chemical bonds are hydrolyzed. The ability to control the rate of erosion of these bioerodible polymers by altering their structural configuration by adding surfactants during the synthesis. It can have drastically different rates of erosion depending on lacrimation rate and physiological aspects of individual patients, degradation byproducts and leftover solvents from the polymer synthesis process can result in an inflammatory response. The discussion of some significant ocular inserts that are commercially available SODI, Minidisc, lacrisert .[36]

Soluble Ophthalmic Drug Inserts (SODI)

SODI was sterile thin films with oval shape. It is inserted into the upper conjunctival sac and adapts to the shape of the eye. Within 10 to 15 minutes, the film transforms into a viscous polymer that slowly dissolves within an hour and delivers the medication for 24hrs.[37]

The Minidisc ocular therapeutic system

It looks like a miniature contact lens shown in Fig.12 and It was made by silicone based prepolymers of hydrophilic and hydrophobic nature. To enhance the sustained release of soluble, insoluble drug molecules.[38]

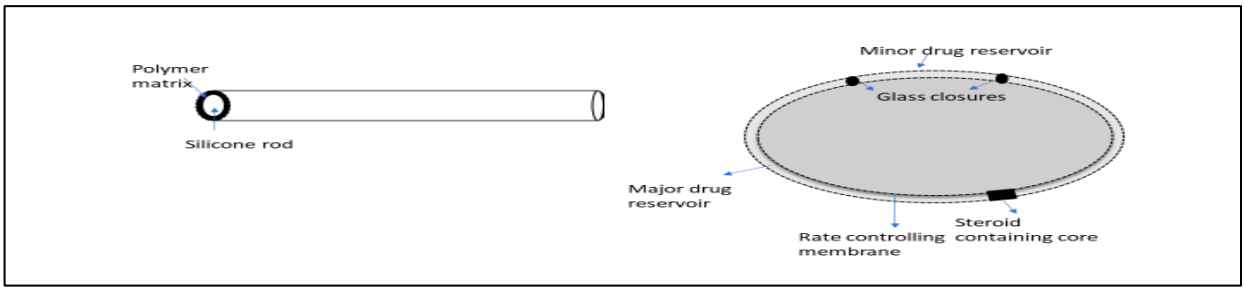

Fig.12 Minidisc ocular inserts

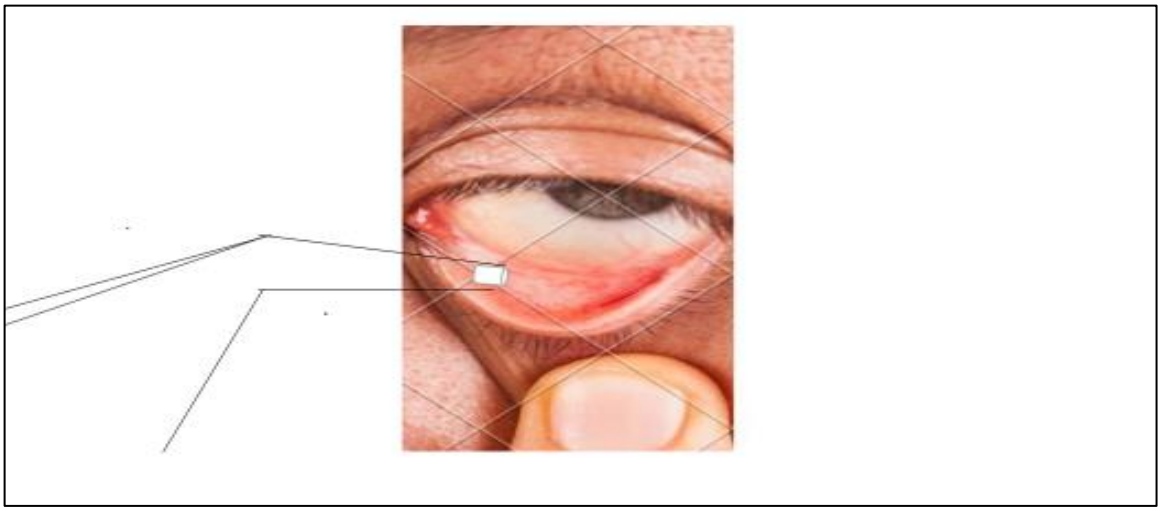

Fig.13 Lacriserts

Lacrisert

It is a rod-shaped and sterilized device demonstrated in Fig.13 & It was made up of hydroxypropyl cellulose without any preservatives. It is inserted into an inferior fornix, from the conjunctiva and cornea it imbibes the water and forms the hydrophilic film. This film hydrates the cornea. It weighs about 5 mg, diameter 12.7mm, length 3.5 mm. It dissolves within 24 hrs. [39]

FORMULATION METHOD OF OCULAR INSERTS

Solvent casting method

In this method, polymer was dissolved in a suitable solvent and then a plasticizer was added into the above mixture after constant stirring, and then precisely weighed amounts of the medication are added to create

a uniform dispersion. Once the proper mixture has been created and cast to the petri dish using inverted funnels. As a result, the film can evaporate gradually and consistently at ambient temperature until it is cured. The dry film was cutted with desired size and shape, kept in an airtight container.[40] The comprehensive procedure depicted in Fig.14.

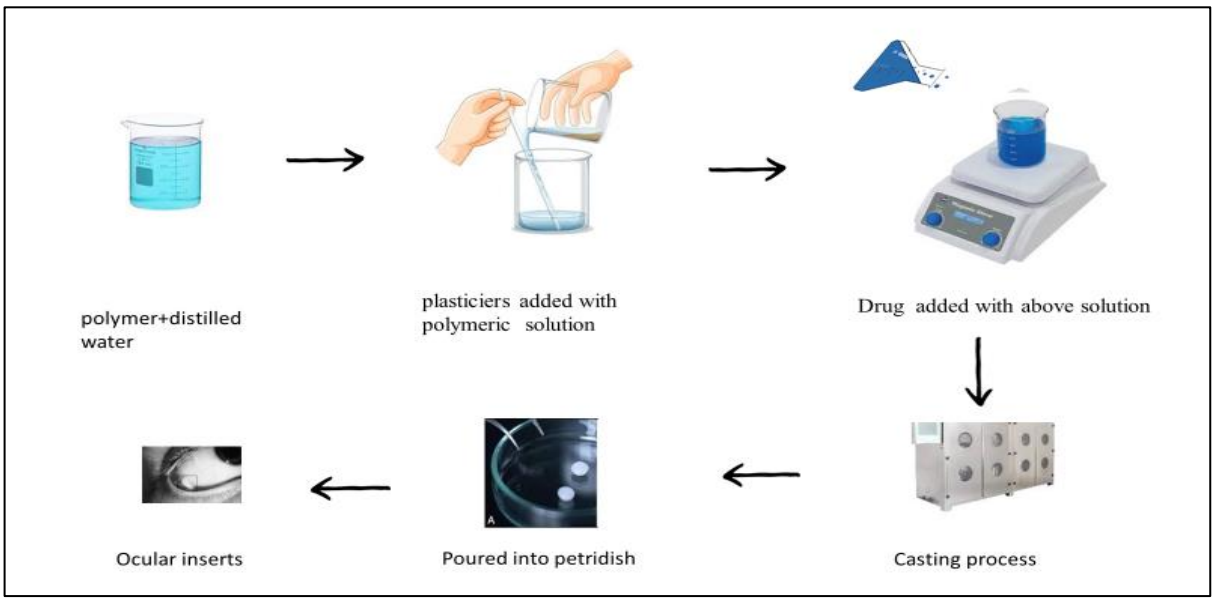

Fig.14 Solvent casting method

Glass substrate technique

In this process soaking the polymer in 1% acetic acid solution at one day for producing transparent liquid. The remedy has been filtered. To dissolve the complex in the polymer solution, the necessary amount of medication is added and vortexed for 15 minutes. The solution described above receives plasticizer. Once the viscous solution is prepared, it is set aside for 30 minutes to remove air bubbles. Films that control rate are created.[40] The entire process illustrated in Fig.15.

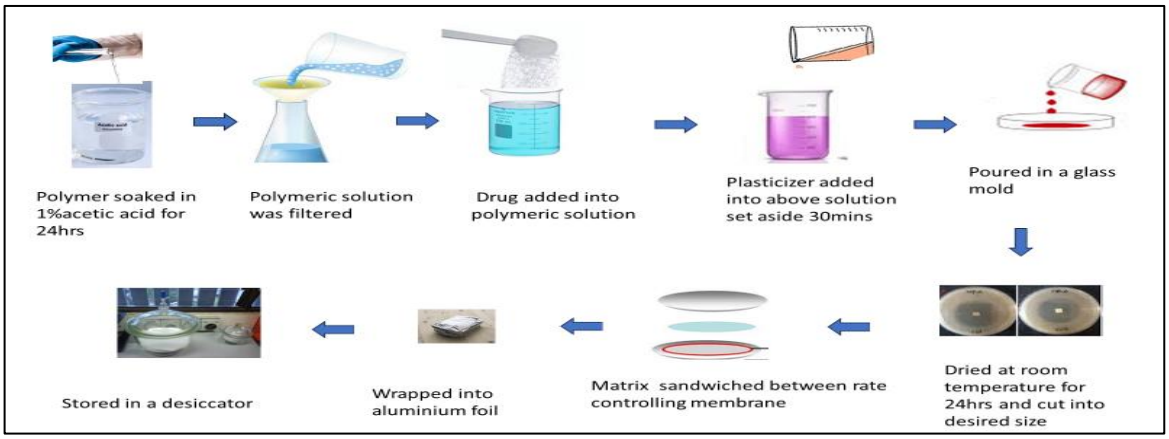

Fig.15 Glass substrate method

Melt extrusion method

The drug and polymer was filtered through a sieve with a mesh size of 60# then it was mixed. Above the mixture plasticizer was added. The mixture is poured into the in Fig.16.

equipment to melt flow rate. Inserts was extrudate and sized properly, packed with polyethylene aluminum by heat-sealed and gamma-sterilized.[41] The complete procedure is shown

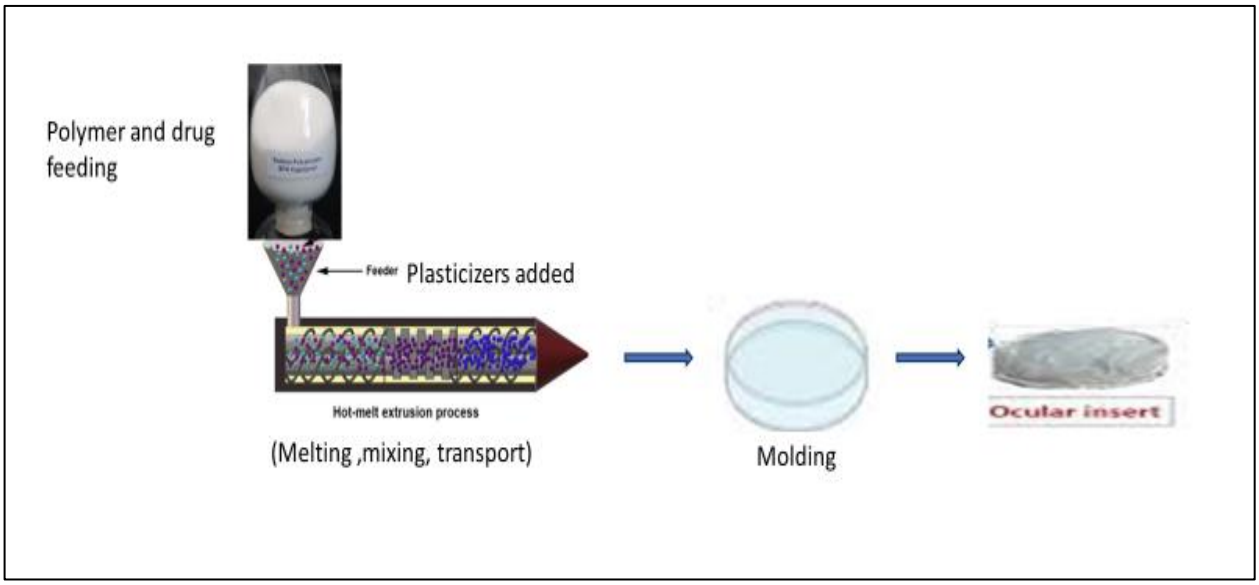

Fig.16 Hot melt extrusion method

Gel foam disc method

Using a standard hole punch, a gelfoam disc with a 4 mm diameter and 0.5 mm thickness was created. Drug and polymer dissolved 50% (v/v) ethanol in a volume of 25L water. On the gelfoam disk, the solution was applied. The matrices were dried in a vacuum. By using this technique, placebo devices devoid of medication were also created.[42]

Mold preparation method

Molds are prepared by various materials and various shapes based on type of inserts (silicone inserts are made of polymethylsiloxane in the form of rods). Properly weighed ratios of polymer, medicament, and excipients were taken and mixed into homogeneously. The mixes were poured into the molds, and they were then left to cure for 24 hours at 45 °C. The resulting rubbery cylinders were correctly sliced to provide a precise amount of medication content. Depending on the type of insert, the range of 4–12 mm of length 2.7–8.0 mg of weight. The mold inserts were dipped into a polymeric solution for coating and air dried. Hydration testing is performed after coating. [43] The full procedure is shown in Fig.17.

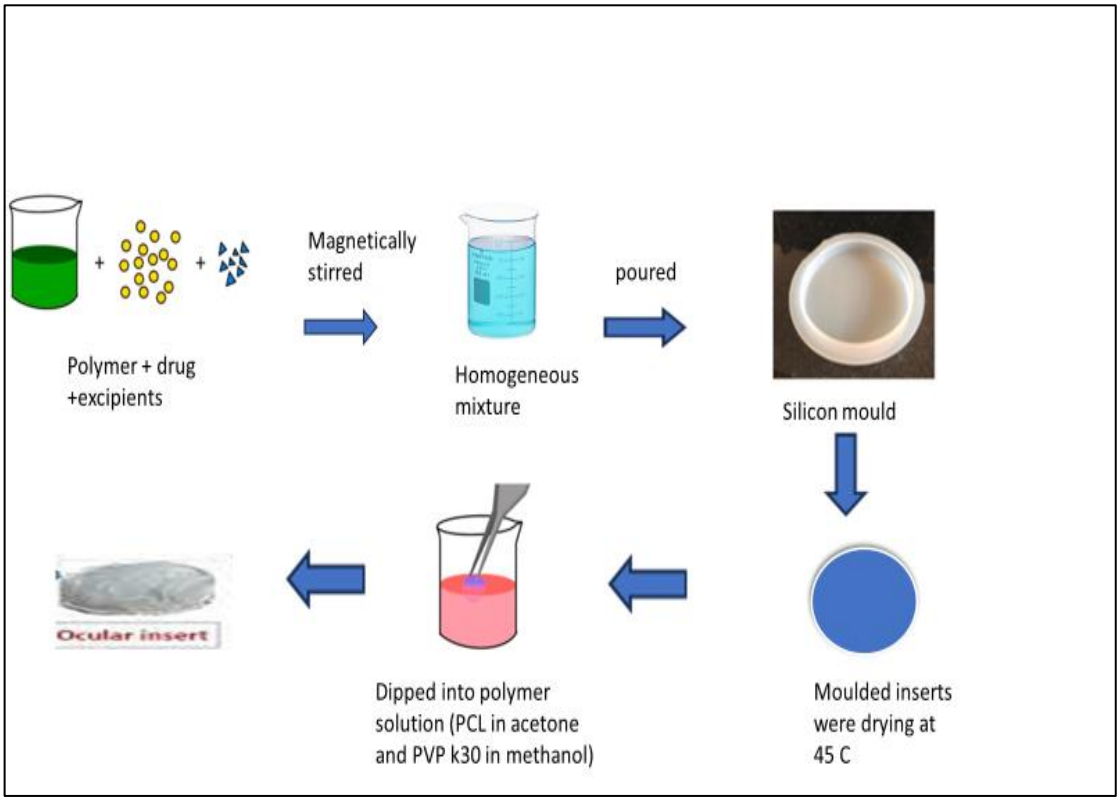

Fig.17 Molding method

EVALUATION PARAMETERS OF OCULAR INSERTS

Evaluation parameters are listed in Fig.18.

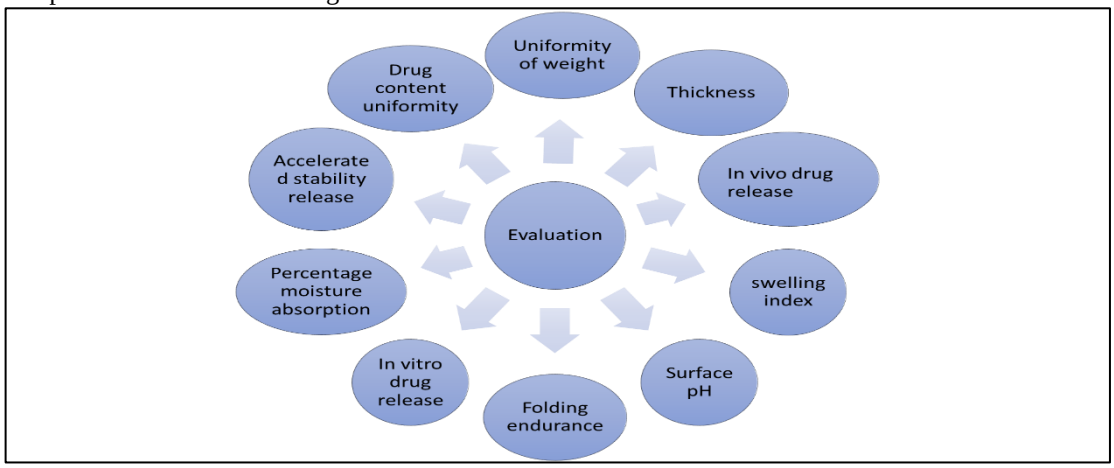

Fig.18 Evaluation parameters for ocular insert

Drug content Uniformity

The film was cutted in different places, placed each film in a 7.4 phosphate buffer, then drug extracted from inserts by shaking. From this extracted solution one milliliter was taken and diluted and analyzed by spectrophotometer.[44]

Percentage moisture absorption

Initially weights Ocular inserts were taken and placed in desiccators with saturated aluminum chloride 100ml to calculate the percentage moisture absorption. After three days, ocular inserts was again weighed;[45]

$$percentage\ moisture\ absorption = (final\ weight - initial\ weight)/initial\ weight * 100$$

Thickness

Utilizing a DIAL caliper, film thickness was measured, and average of film thickness of all films was computed.[40]

Swelling index

Film is cut and weighed and it is soaked in tear fluid for 1 hour. After 1 hour, the film is reweighed.[46]

$$swelling\ index = final\ weight - initial\ weight/initial\ weight$$

Uniformity of weight

Ocular inserts are cutted into three films and weighed by weighing balance. From weights Mean value and standard deviation was determined.[44]

Surface pH determination

pH meter was used to determine the surface pH. The film swells by soaking for 1hr in distilled water. The electrode of the pH meter dipped into the beaker containing the film until reading obtained.[44]

Folding endurance

It was determine by ocular inserts folded repeatedly until the damage occurs or until sign of damage, count the number of folding before damage occurs was determined.[47]

In vitro diffusion studies

Franz diffusion cell was used to carry out this study. It was used to determine the permeability of the medication. It has two compartments in this device. First one a donor compartment for dosage formulations like ocular inserts, another one is a receptor compartment for tear fluid, which stimulates tears. Membrane with semi-permeable or egg membrane was used to separate two sides of the compartment. The machinery was turned on and temperature, RPM for study parameters were setted and dosage formulation placed first in the donor compartment and tear fluid placed in the reservoir compartment. After sample was taken and diluted at desired solvent and analyzed by spectroscopy.[37]

In vivo drug release rate study

Before the in vivo investigation, the inserts are disinfected using ultraviolet (UV) radiation. A thin layer of 100 mg of the pure medication is put over the inserts in a Petri dish. Forceps, plastic bags, and this Petri dish are all put inside the UV sterilization chamber for one hour. Using a sterilization chamber, the inserts are moved into a polyethylene bag after being sterilized. After appropriately diluted at 7.4 buffer of phosphate and sterilization of pure medications and inserts, the UV spectrophotometer is used to determine their potency. For the experiment, albino rabbits only male at weight of 2.5 to 3.0 kg are needed. Seven albino rabbits are used, with one serving as the control and the other receiving the inserts simultaneously into one eye. At 2 to 24 hours evenly, inserts are removed and their medication content is examined. The initial drug content of insert is decreased by remaining medication. This will reveal how much medication was injected into the animal eyes. The experiment is done twice as previously after a one-week wash interval.[48]

Stability studies

It used to determine the loss of medication while storing inserts for a long period at normal conditions. This

testing triple separate petri dishes were taken and the films of the insert was kept inside and then it was kept in various temperatures. Time taken to degrade each insert film was noted.[42]

Mechanism of drug release

Diffusion, Osmosis, Bio-erosion are the mechanism of drug release by the ocular inserts [37]. The whole mechanism shown in Fig.19**.**

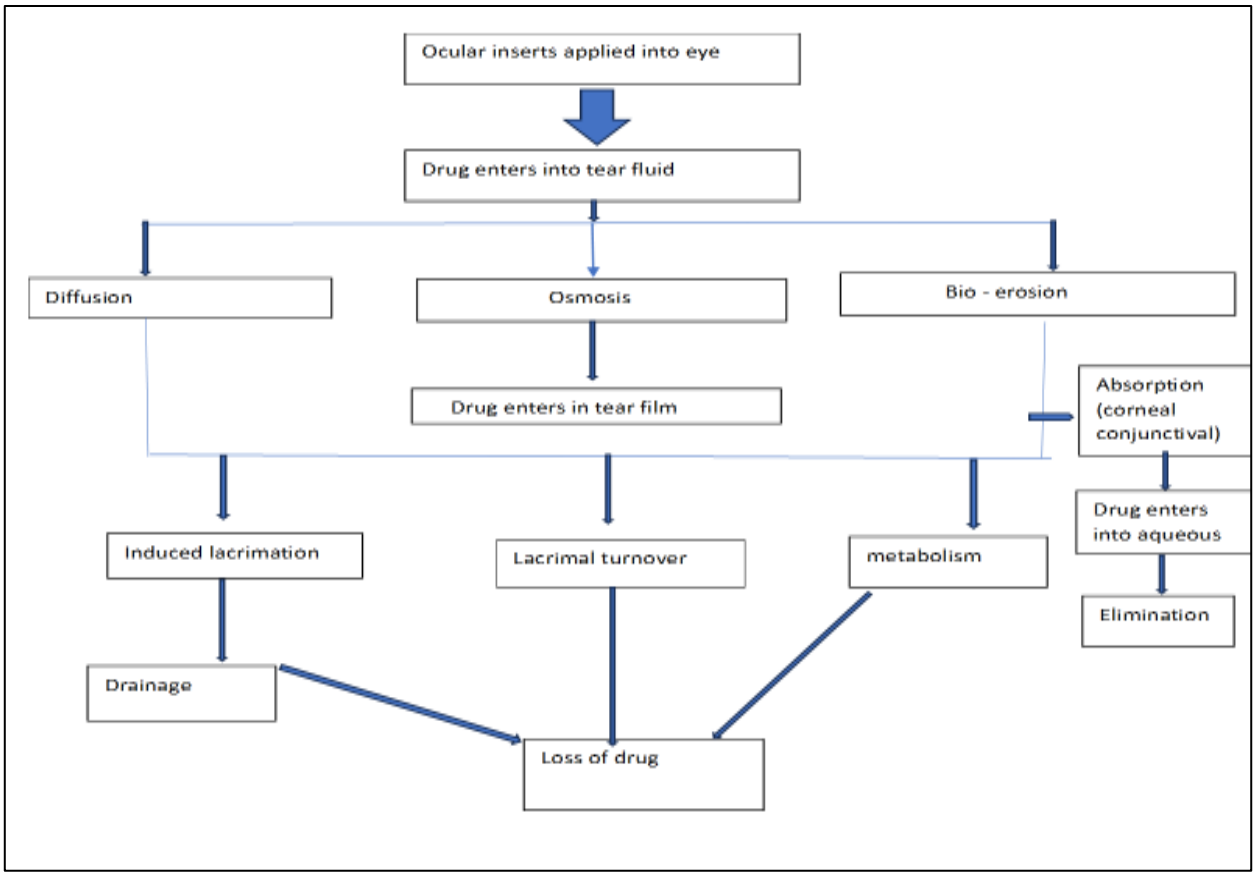

Fig.19 Mechanism of drug release

Diffusion

Diffusion system consists of a middle storage reservoir that was enclosed within a microporous membrane. Once inserts are placed in eyes its aqueous humor starts to seep into the matrix, as a result diffusion mechanism occurs by swelling process or polymer chain relaxation. In swelling process, insert matrix dissolves (how quickly it dissolves depends on the polymer's structure) and cross-the medication is continuously and at a set rate supplied into the tear fluid by the membrane in the Diffusion mechanism shown in Fig.20. If the insert is composed of a dense, impenetrable substance that has pores and contains a drug that has spread.[49] The medication might be released by diffusion action by porous membrane. Sustained release may also govern slow breakdown of a medication that has been distributed within the matrix which leads to inward diffusion of solutions. In the inserts with soluble, swelling of polymers is the primary cause of true dissolving. The active component of devices that control swelling is uniformly distributed in a glassy polymer. Drug diffusion cannot occur via a dry matrix because glassy polymers are almost drug-impervious. Polymers with s-links or crystal structure dissolve more slowly.[41]

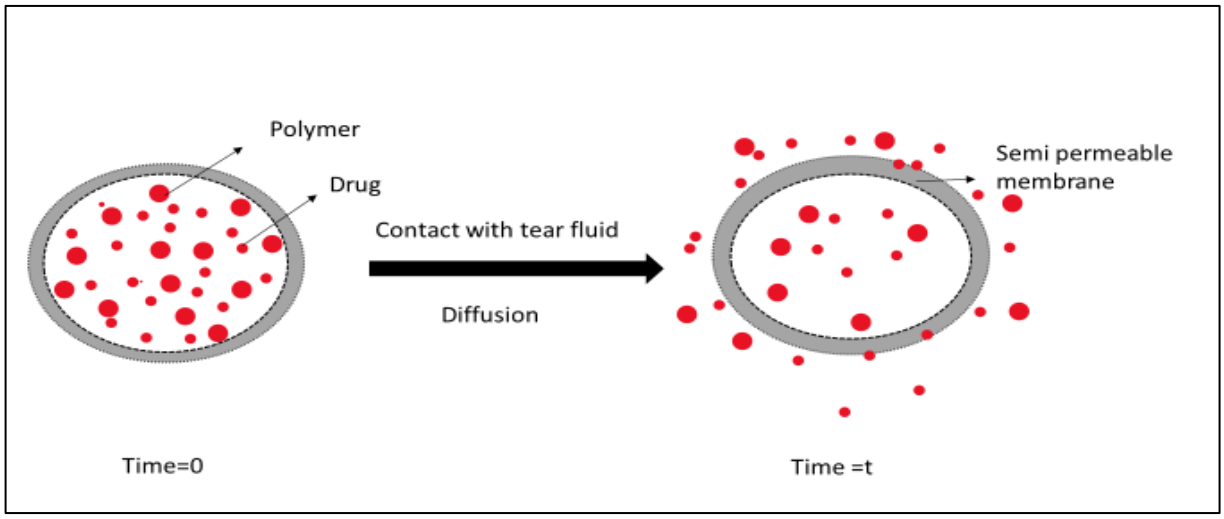

Fig.20 Diffusion mechanism

Osmosis

A transverse impenetrable flexible membrane that divides the insert's interior into a primary compartment and a separate other compartment serves as the insert for the Osmosis mechanism displayed in Fig.21 the primary compartment was surrounded by an elastic membrane and a semi-permeable membrane and the second compartment was an impenetrable and elastic membrane. Hole is located at the impenetrable wall of inserts to discharge the medication. The second portion of inserts acts as storage reservoir for the medication, Semi-permeable barrier prevents a solute from flowing through the primary compartment, as a results flexible membrane was stretched and expand the both compartment so the drug is release by force.[48]

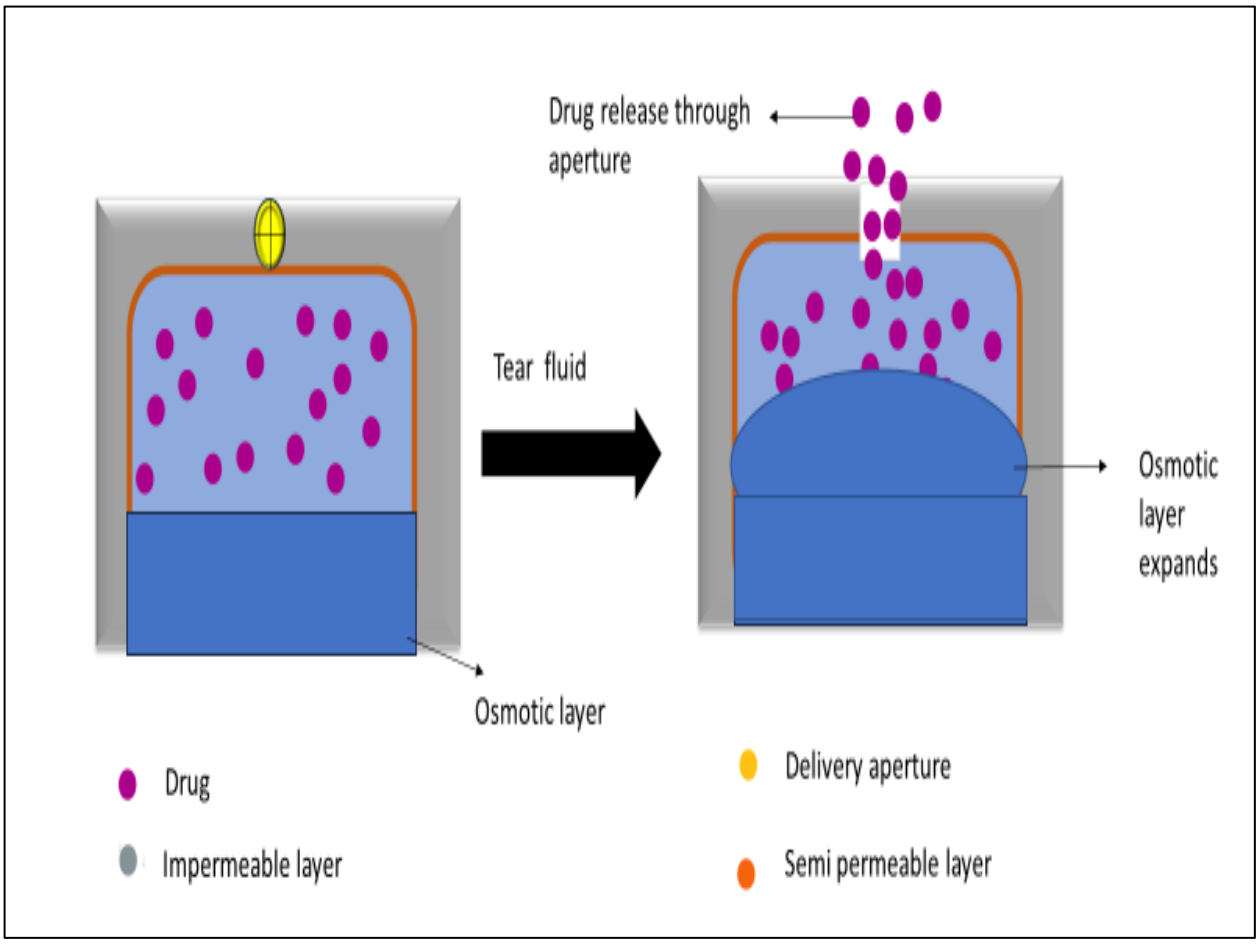

Fig.21 Osmosis mechanism

Bioerosion

Bioerosion mechanism where the medication is distributed into biodegradable material of matrix to build the insert's body and entire mechanism depicted in Fig.22. In the matrix drug may be uniformly dispersed because of hypothesized condition, controlled release will occur. Controlled discharge of the medication caused by inserts contact with tear fluids results in the matrix becoming biodegradable. In an erodible process, polymers break down into smaller particles by chemical and enzymatic reaction and water-soluble components present in the inserts govern the rate of drug release. These polymers undergo surface hydrolysis or bulk hydrolysis in erodible inserts following the kinetics of zero order.[50]

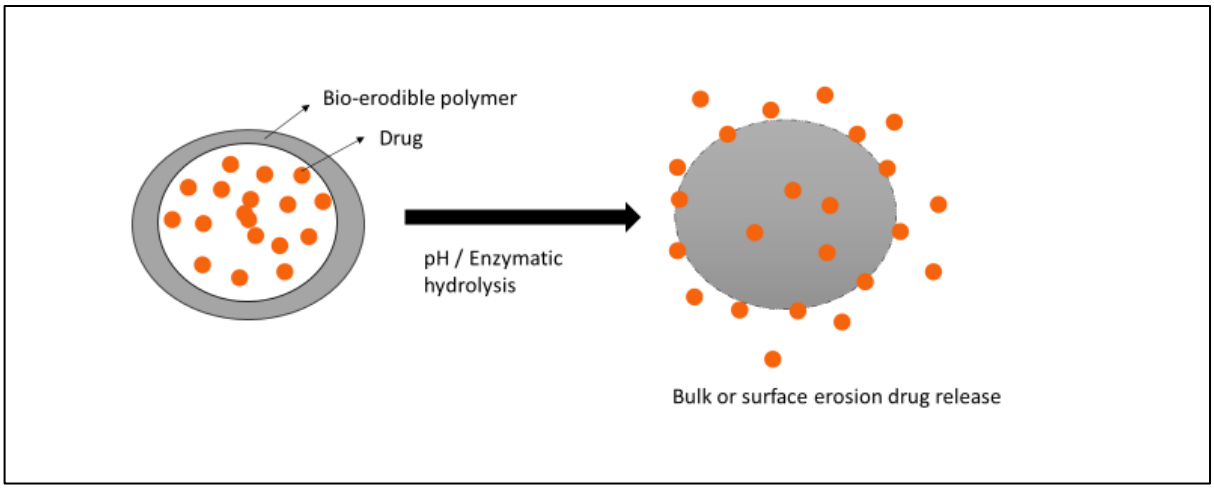

Fig.22 Bioerosion mechanism

CONCLUSION

For an ophthalmic formulation, a longer residence time on the ocular surface leads to a higher drug bioavailability and a lower administration frequency. Eye drops continue to be the most popular formulations despite recent advancements in ocular pharmaceutical delivery technologies because they are the least expensive, the simplest to administer, and do not obstruct vision. However, frequent administration is necessary. The effective and safe delivery of medicinal chemicals to the ocular tissues, particularly the tissues of the posterior segment, is a major challenge faced by formulation scientists due to a multitude of physiological barriers. Several techniques have been studied to obtain drug concentrations in the ocular tissues that are therapeutically effective. Thanks to recent technological developments, the field of ocular drug delivery has progressed from conventional drops to sustained release and customized ocular delivery devices. In the current technological era, combinatorial techniques seem to be the main area of research for developing safe and efficient ocular medicine delivery systems.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ACKNOWLEDGEMENT

We acknowledge the use of the digital library by Vels Institute of Science, Technology and Advanced Studies.

REFERENCES

1. Rathore KS, Nema RK. An insight into ophthalmic drug delivery system. Int. J. Pharm Sci Drug Res. 2009;1;01-05.
2. Thakur R, Swami G. Promising implication of ocuserts in ocular disease. J Drug Deliv Ther. 2012;2;18-25.
3. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. J Am Med Assoc. 2014; 311(18):1901-11
4. Tham YC, Li X., and Wong TY. 2014. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. J Ophthalmol. 2014; 121(11):2081-90.
5. Kang JM, Tanna AP. Glaucoma. Med Clin North Am. 2021;12;493-510.
6. Rhee DJ. Primary Open-Angle Glaucoma. MSD Manual Professional version. 2023. Primary Open-Angle Glaucoma - Eye Disorders - MSD Manual Professional Edition (msdmanuals.com). Accessed 15 Dec 2023.
7. Parikh RS, Parikh SR, Navin S, Arun E, Thomas R. Practical approach to medical management of glaucoma. Indian J Ophthalmol. 2008;(3):223-30.
8. Camras CB, Alm A, Watson P, Stjernschantz J. Latanoprost, a prostaglandin analog, for glaucoma therapy. Efficacy and safety after 1 year of treatment in 198 patients. Latanoprost Study Groups. J Ophthalmol. 1996;103(11):1916-24.
9. Sena DF, Lindsley K. Neuroprotection for treatment of glaucoma in adults. Cochrane Database Syst Rev. 2013; 2(2):CD006539.
10. Apatachioae I, Chiselita D. Alpha-2 adrenergic agonists in the treatment of glaucoma. Oftalmologia. 1999;47(2):35-40.
11. Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol.

International Dorzolamide Study Group. Arch Ophthalmol. 1995;113(8):1009-16.
12. Merative, Micromedex. Antiglaucoma agent, Cholinergic, long acting (ophthalmic-route). Mayoclinic.2024. https://www.mayoclinic.org/drugs-supplements/antiglaucoma-agent-cholinergic-long-acting-ophthalmic-route/proper-use/drg-20070564?p=1. Accessed 2 Nov 2024.
13. Higginbotham EJ. Considerations in glaucoma therapy: fixed combinations versus their component medications. Clin Ophthalmol. 2010;4:1-9.
14. European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition. British Journal of Ophthalmology 2021;105:1-169.
15. Glaucoma: Treatment Options. National glaucoma research. 2022. https://www.brightfocus.org/glaucoma/publication/glaucoma-treatment-options#:~:text=Lowering%20eye%20pressure%20through%20medication,glaucoma%20with%20high%20eye%20pressure. Accessed 4 Jan 2023.
16. Jha B, Bhartiya S, Sharma R, Arora T, Dada T. Selective Laser Trabeculoplasty: An Overview. J Curr Glaucoma Pract. 2012;6(2):79-90.
17. Giacon JAA. Laser Trabeculoplasty: ALT vs SLT. Eye Wiki. 2023.https://eyewiki.aao.org/Laser_Trabeculoplasty:_ALT_vs_SLT. Accessed 6 Jan 2024.
18. Lee JWY, Yau GSK, Yick DWF, Yuen CYF. Micro Pulse Laser Trabeculoplasty for the Treatment of Open-Angle Glaucoma. Medicine (Baltimore). 2015;94(49);e2075.
19. Wen JC, Rezaei KA, Lam DL. Laser Peripheral Iridotomy Curriculum: Lecture and Simulation Practical. MedEdPORTAL. 2020;16;10903.
20. Tanuj D, Amit S, Saptorshi M. Combined subconjunctival and subscleral ologen implant insertion in trabeculectomy. Eye; 27(7);889.
21. Cillino S, Casuccio A, Di Pace F, Cagini C, Ferraro LL, Cillino G. Biodegradable collagen matrix implant versus mitomycin-C in trabeculectomy: five-year follow-up. BMC Ophthalmol. 2016;16:24.
22. Loewen N. Trabectome Surgery: A Minimally-Invasive Glaucoma Procedure. Glaucoma research foundation.2022. Trabectome Surgery: A Minimally-Invasive Glaucoma Procedure - Glaucoma Research Foundation. Accessed Aug 2023.
23. Shingleton B, Tetz M, Korber N. Circumferential viscodilation and tensioning of Schlemm canal (canaloplasty) with temporal clear corneal phacoemulsification cataract surgery for open-angle glaucoma and visually significant cataract: one-year results. J Cataract Refract Surg. 2008;34(3):433-40.
24. Kierstan What Is a Glaucoma Drainage Implant?. American academy of ophthalmology. 2023.What Is a Glaucoma Drainage Implant? - American Academy of Ophthalmology (aao.org). Accessed 24 Jan 2024.
25. Deivasigamani K, Mithun B, and Pandey VP. The concept of ocular inserts as drug delivery systems-An overview. Asian J Pharm Sci. 2008; 2:192-199.
26. Khokhar P, Shukla V. Ocular Drug Delivery System-A Review Based on Ocuserts. Int J Pharm Sci Res Rew. 2014;3(8):29-41.
27. Dabhi V, Yogi J, Bhimani B, Patel G. Ocular inserts as controlled drug delivery system. Int J Pharm Res Bio-Sci..2024;3(5);468-480.
28. Gurtler F, Gurny R. Patent literature review of ophthalmic inserts. Drug Dev Ind Pharm. 1995;21(1);01-18.
29. Bloomfield SE, Miyata T, Dunn MW, Bueser N, Stenzel KH, Rubin AL. Soluble gentamicin ophthalmic inserts as a drug delivery system. Arch Ophthalmol. 1978;96(5):885-7.
30. Ahmed I, Gokhale RD, Shah MV, Patton TF. Physicochemical determinants of drug diffusion across the conjunctiva, sclera, and cornea. J Pharm Sci. 1987;76(8):583-86.
31. Grass GM, Robinson JR. Mechanisms of corneal drug penetration. I: In vivo and in vitro kinetics. J Pharm Sci. 1988;77(1):3-14.
32. Alvarez-Lorenzo C, Hiratani H, Gómez-Amoza JL, Martínez-Pacheco R, Souto C, Concheiro A. Soft contact lenses capable of sustained delivery of timolol. J Pharm Sci. 2002;91(10):2182-92.
33. Kumar SKP, and Bhowmik D. 2013. Ocular inserts: A Novel Controlled Drug Delivery System. The Pharma Innovation Journal. 2013; 1: 1-16.
34. Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: An overview. World J Pharmacol. 2013;2(2):47-64.
35. Himmelstein KJ, Guvenir I., and Palton TP. Preliminary Pharmacokinetics model of pilocarpine uptake and distribution in the eye. J Pharm Sci. 1978;5;603-606.
36. Kriti D, Yashika U. Ocular inserts: Novel approach for drug delivery into eyes. GSC biol pharm sci. 2019;07(03);001–007.
37. Jain MK, Manque SA, and Deshpande SG. Controlled and Novel Drug Delivery. CBS Publisher; New Delhi. 2005. pp.82-96.
38. Brahmankar, D.M. and Jaiswal, S.B. (2009) Biopharmaceutics and Pharmacokinetics. 2nd Edition, Vallabh Prakashan, Delhi.2209. pp. 399-401;
39. Donald M, Aversa GD, Perry HD, Wittpenn JR, Donnenfeld ED, Nelinson DS. Hydroxypropyl cellulose ophthalmic inserts (lacrisert) reduce the signs and symptoms of dry eye syndrome and improve patient quality of life. Trans Am Ophthalmol Soc. 2009; 107:214-21.
40. Sahane NK, Banerjee SK, Gaikwad DD, and Jadhav SL. Ocular Inserts-A Review. Drug Inven Tod. 2010; 2:57-64.
41. Pandey P, Panwar AS, and Dwivedi P. Design and Evaluation of Ocular Inserts For Controlled Drug Delivery of Acyclovir. Int j pharm biol sci arch. 2011;2(4);1106-1110.

42. Lee YC, Millard J, Negvesky GJ, Butrus SI, Yalkowsky SH. Formulation and in vivo evaluation of ocular insert containing phenylephrine and tropicamide. Int J Pharm. 1999;182(1):121-6.
43. Chetoni P, Di Colo G, Grandi M, Morelli M, Saettone MF, Darougar S. Silicone rubber/hydrogel composite ophthalmic inserts: preparation and preliminary in vitro/in vivo evaluation. Eur J Pharm Biopharm. 1998;46(1):125-32.
44. Patel UL, Chotai NP, Nagda CD. Design and evaluation of ocular drug delivery system for controlled delivery of gatifloxacin sesquehydrate: In vitro and in vivo evaluation. Pharm Dev Technol. 2012;17(1):15-22.
45. Brogden RN, Heel RC, Pakes GE, Speight TM, Avery GS. Diclofenac sodium: a review of its pharmacological properties and therapeutic use in rheumatic diseases and pain of varying origin. Drugs. 1980;20(1):24-48.
46. Banker GS, Gore AY, Swarbrick J. Water vapour transmission properties of free polymer films. J Pharm Pharmacol. 1966;18(7);457-66.
47. Ubaidulla U, Reddy MVS, Ruckmani K, Ahmad FJ, Khar RK. Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on in vitro and in vivo characteristics. AAPS PharmSciTech. 2007; 8(1):E13–20.
48. Kumari A, Sharma PK, Garg VK, Garg G. Ocular inserts - Advancement in therapy of eye diseases. J Adv Pharm Technol Res. 2010;1(3):291-6.
49. Lonsdale HK. Controlled Release Delivery Systems: T.J. Roseman and S.Z. Mansdorf (Eds.), Marcel Dekker, New York, 1983, 402 + xv pp., $57.50. J Membr Sci.1983;15;115-16.
50. Heller J. Controlled release of biologically active compounds from bioerodible polymers. Biomaterials. 1980;1(1):51-7.