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A Systematic Review On Novel Drug Delivery For The Treatment of Glaucoma

Aditi D. Jamankar[1], Yashkumar A. Meshram[2], Abhishek R. Kale[3], Abhijit K. Banait[4], Achyut R. Kandalkar[5]

Jagadambha Institute Of Pharmacy & Research, Kalamb, Maharastra 445401, India [1-5]

ABSTRACT:

Glaucoma is considered as one of the biggest health problem in world. It's main cause of blindness due to asymptomatic nature in early stages and also due to patient compliance. It's estimated that2.2 million people in the United States and 67 million people worldwide have glaucoma. The reduction of intraocular pressure(IOP) by medicinal or surgical means has been a tribune treatment for glaucoma. The number of medicines are effective in reducing IOP. These medicines are substantially applied as eye drops. Still, patient compliance can be poor and due to multitudinous disadvantages of conventional ophthalmic lozenge forms, several new delivery systems designed to address the issue of conventional dosage forms and to insure harmonious reduction of IOP. This delivery system includes In- situ gels, optical inserts, optical implants, microneedles, Nano system, contact lenses, etc. This review is about NDDS which are applicable in the treatment of Glaucoma along with their formulation, mechanism and other applications.

Keywords: IOP, Patient Compliance, Glaucoma, Novel Drug Delivery System, Aqueous Humor

1. INTRODUCTION

Glaucoma, a progressive optic neuropathy characterized by elevated intraocular pressure (IOP) and subsequent damage to the optic nerve, remains a leading cause of irreversible blindness worldwide. Despite advancements in therapeutic interventions, the challenge lies in achieving effective and sustained drug delivery to the ocular tissues. Traditional methods, such as eye drops, face limitations in terms of patient compliance, efficacy, and the ability to maintain optimal drug concentrations at the target site. In response to these challenges, novel drug delivery systems have emerged as promising alternatives, revolutionizing the landscape of glaucoma treatment. The quest for improved drug delivery systems stems from the need to address the shortcomings of conventional approaches and enhance the therapeutic outcomes for glaucoma patients. Novel drug delivery systems offer the potential to optimize drug bioavailability, extend the duration of action, and minimize systemic side effects. These advancements not only aim to enhance patient adherence but also seek to overcome anatomical and physiological barriers that impede effective drug penetration into the ocular tissues.[1]

This exploration into novel drug delivery for glaucoma treatment encompasses a diverse array of technologies, including sustained-release implants, nanoparticles, liposomes, and microneedle-based systems, among others. Each approach brings its unique set of advantages, whether it be prolonged drug release, improved bioavailability, or targeted delivery to specific ocular tissues. As researchers delve into the intricacies of these innovative strategies, the potential to transform glaucoma management becomes increasingly evident.

This comprehensive review delves into the current landscape of novel drug delivery systems for the treatment of glaucoma, highlighting the principles, advancements, and challenges associated with each approach. By understanding the nuances of these emerging technologies, clinicians, researchers, and pharmaceutical developers can contribute to the evolution of glaucoma therapeutics, offering new hope for improved patient outcomes and preserving visual health.

NDDS refers to approaches, phrasings, technologies, and systems for transporting a pharmaceutical emulsion in the body as demanded to safely achieve it's asked remedial effect. New medicine delivery system is a new approach to medicine delivery that addresses the limitations of the traditional medicine delivery systems.

Objectives of NDDS in treatment of Glaucoma;
The primary objective of exploring novel drug delivery systems for glaucoma treatment is to overcome limitations associated with conventional approaches, such as eye drops. The aim is to improve patient adherence, optimize drug bioavailability, and ensure sustained therapeutic concentrations at the target site. This seeks to enhance the overall efficacy of glaucoma management by effectively controlling intraocular pressure and preserving optic nerve function.

2. GLAUCOMA:

Glaucoma is a group of diseases in which the optic eye nerves is damaged leading to irreversible loss of vision, in the most cases this damage is due to increased pressure within the eye. Glaucoma is commonly caused by increased in intraocular pressure/ocular hypertension (high pressure of fluids "aqueous humor" within the eye), causing optic nerve damage.

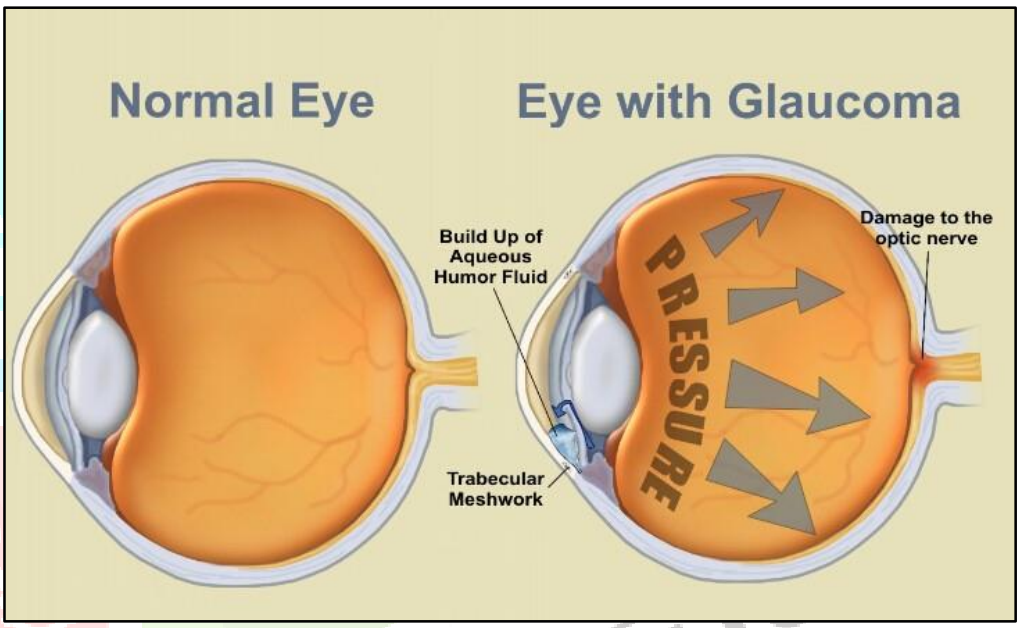

Fig No.1: Comparison of Normal Eye Vs Glaucoma [2]

2.1 Types of Glaucoma

Glaucoma is a group of eye conditions characterized by damage to the optic nerve, often associated with elevated intraocular pressure (IOP). There are several types of glaucoma, with the two main categories being primary open-angle glaucoma (POAG) and angle-closure glaucoma. [4]
Types of Glaucoma are;

1) Primary Open-Angle Glaucoma (POAG):

- POAG is the most common form of glaucoma. It develops gradually and painlessly, often with no noticeable symptoms in the early stages.
- Mechanism: The drainage angle of the eye remains open, but the trabecular meshwork becomes less efficient in draining aqueous humor, leading to a gradual increase in IOP.
- Risk Factors: Age, family history, and African, Hispanic, or Asian ancestry are common risk factors.

2) Angle-Closure Glaucoma:

- Angle-closure glaucoma is less common but can be acute or chronic. It occurs when the drainage angle of the eye becomes blocked, causing a sudden or gradual increase in IOP.
- Mechanism: The angle formed by the cornea and iris narrows or closes, preventing the normal outflow of aqueous humor and leading to a rapid rise in IOP.
- Symptoms: Acute angle-closure glaucoma may present with severe eye pain, headache, blurred vision, and nausea.

3) Normal-Tension Glaucoma (NTG):

- In NTG, optic nerve damage occurs despite IOP being within the statistically normal range. The exact cause is not well understood.
- Mechanism: Factors other than IOP, such as vascular or blood flow abnormalities, may contribute to optic nerve damage.

4) Secondary Glaucoma:

- Secondary glaucoma is a result of other eye conditions or systemic diseases.
- Causes: Conditions such as uveitis, trauma, advanced cataracts, or systemic diseases like diabetes can lead to secondary glaucoma.

5) Congenital Glaucoma:

- Congenital glaucoma is present at birth and is often due to abnormal development of the eye's drainage system.
- Symptoms: Excessive tearing, light sensitivity, and enlargement of the eye may be observed in infants with congenital glaucoma.

2.2 Glaucoma Risk Factors:

Glaucoma is a complex eye condition influenced by various risk factors. Key risk factors for glaucoma include following:[5]

1) Elevated Intraocular Pressure (IOP):

Elevated IOP is a primary risk factor for glaucoma. While not all individuals with elevated IOP develop glaucoma, it is a significant contributing factor.

2) Age:

The risk of glaucoma increases with age, particularly after the age of 60. Individuals over 60 years old are more susceptible to developing glaucoma.

3) Family History:

A family history of glaucoma increases an individual's risk. Genetic factors may contribute to the development of the disease.

4) Ethnicity:

Certain ethnic groups, such as African-Americans, Hispanics, and Asians, have a higher risk of developing glaucoma compared to Caucasians.

5) Thin Corneas:

Thinner corneas have been associated with an increased risk of developing glaucoma.

6) Medical Conditions:

Certain medical conditions, including diabetes and hypertension, can increase the risk of glaucoma.

7) Previous Eye Injuries or Surgeries:

Individuals who have experienced previous eye injuries or surgeries may have an elevated risk of developing glaucoma.

8) Use of Corticosteroids:

Prolonged use of corticosteroid medications, whether in the form of eye drops, oral medications, or injections, may increase the risk of glaucoma.

2.3 Barriers for ocular drug delivery (for the treatment of Glaucoma)

Ocular drug delivery suffers from the following barrier effects:

1. Drug loss from the ocular surface

After using the lozenge form of the medicine in the optical system, inflow of lacrimal fluid wipes out a portion of the medicine from its face and its turnout rate is only about 1 µl/ min, whereas, a major portion of the medicine is wiped out through the nasolacrimal conduit snappily within twinkles. Other sources of medicine junking include the systemic immersion of the medicine, rather of being absorbed through the optical route. Systemic immersion is substantially directed through the conjunctival sac to the original blood capillaries or takes place after the result flows to the nasal depression. [12]

2. Lacrimal fluid-eye barriers

Immersion of the medicine from the lacrimal fluid can be limited by the corneal epithelium present in the eye. Tight junctions formed from corneal epithelial cells limit the saturation of the medicine paracellularly. Lipophilic medicines show advanced permeability in the cornea as compared to hydrophilic medicines. In other terms, we can say that conjunctiva has dense epithelium compared to that of the cornea and also has twenty times lesser face area than the cornea that supports rapid-fire systemic immersion. To ameliorate cases compliance and exclude the limitations of conventional glaucoma remedy ferocious work has been done regarding the development of new medicine delivery systems. new medicine delivery systems includes similar as expression of in situ gels, nanoparticles, liposomes, Nano suspense, micro conflation, optical inserts and so on, and their progress to overcome the problems associated with the being conventional lozenge forms and also to ameliorate the bioavailability as well as the sustained release of the medicine at the target position. [13]

2.4 Treatment for Glaucoma (By NDDS)

A major problem in glaucoma treatment, as in other habitual conditions, is cases 'non-adherence. Although blindness caused by glaucoma can be avoided if glaucoma is diagnosed and rightly treated in the early stages, multitudinous studies have shown the problem of intermittent remedy[7]. Another issue is the downsides of conventional ophthalmic lozenge forms. Although eye drops are easy to manufacture and regard for over 90 of all commercially available ophthalmic phrasings, their main excrescence is poor medicine bioavailability(BA)(up to 10)[8]. One of the reasons for poor medicine BA is the limited retention capacity of the cul-de-sac(generally 7 – 10 µL, maximum 50 µL)[9], followed by rapid-fire drainage caused by graveness or through the nasolacrimal conduit[10].

To ameliorate cases adherence and exclude the limitations of conventional glaucoma remedy, ferocious work has been done regarding the development of new medicine delivery systems. The development of new medicine delivery systems(NODDS) goes in two resemblant directions[11].

1. Extending a medicine's contact time with the eye face
2. Decelerating down its elimination.

Sustained release delivery systems, whether in the form of gel drops or implants, inserts, etc., are a promising approach.

3. IN SITU GEL SYSTEM (IGS):

Ophthalmic in- situ gelling is comprising of environmentally sensitive polymers that will be altered structurally with the small changes in specific conditions like pH, temperature and ionic strength in the terrain. In- situ forming gels are liquids during instillation into the eye and also undergoes rapid-fire gelation in the cul-de-sac of the eye to form viscoelastic gels in response to environmental changes(Fig. 3); incipiently release the medicine sluggishly under physiological conditions[14]. Accordingly, the hearthstone time of the gel formed in- situ will be extended and the medicine is released in a sustained manner which leads to enhanced bioavailability, minimized systemic immersion and reduced frequent dosing authority performing to bettered patient compliance[15]. likewise, some other implicit advantages similar as simple manufacturing process, ease of administration, and deliverance of accurate cure have been displayed by in-situ gelling systems[16].

Mechanisms of gelatinizing system

In- situ gel conformation may be achieved by a number of mechanisms including temperature, pH, and ion-actuated systems. Temperature touched off in- situ gel system which utilizes the temperature sensitive polymers that live as a liquid form below its low critical result temperature(LCST) and undergoes gelation when the environmental temperature rung or is above the LCST[17]. The pH convinced in- situ gel contains polymers which retain acidic or alkaline functional groups within the chain patch and undergoes a sol- gel phase transition on change from a low pH to high pH terrain[18]. Ion- actuated systems are also known as osmotically touched off in- situ gel systems wherein the polymer undergoes a sol- gel transition due to changes of ionic attention, which is generally touched off by mono or divalent cations in gash fluid particularly Na, Mg2 and Ca2[19]. In addition, sol- gel phase transition has known to be convinced by enzymatic cross linking and photon polymerization[20].

3.1 Temperature-triggered in-situ gel systems:

The temperature sensitive in- situ gel is the oldest, the most considerably studied and common type of stimulants- responsive gel. It can be fluently and precisely introduced into the eye in liquid form without producing vexation or blurred vision. The gel is formed at the precorneal temperature(35 °C) to endure the lachrymal fluid dilution without rapid-fire precorneal elimination of inseminated medicine after administration[21]. It has been recommended that a good thermo- responsive optical in- situ gel should retain the gelation temperature above the room temperature and suffer gel- sol transition at apre-corneal temperature in order to avoid storing in a refrigerator before instillation, which may occasionally affect in eye vexation due to cold nature[22]. Polymers used in temperature touched off in- situ gel systems

Ex. Poloxamers (Pluronic):

Due to their hydrophilic ethylene oxide and hydrophobic propylene oxide disciplines, poloxamers are a triblock copolymer poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)(PEO-PPO-PEO) that exhibit amphiphilic nature[23]. Pluronics, also known as Poloxamers, are a triple block of copolymers that gel at body temperature as the temperature rises over 15(w/w)[24]. The slow desolvation of the polymer, greater micellar aggregation, and increased trapping of the polymeric network are the main hypothesised mechanisms to explain the sol-gel phase transition at elevated temperatures. There are several grades of pluronic triblock copolymers available, each with a unique molecular weight and physical structure. The grades are assigned as L for liquid, P for paste, and F for flakes based on the physical description. The poloxamers 188(F-68), 237(F-87), 338(F-108), and 407(F-127)[25] are the ones that are most frequently utilised. The hydrophilic feature of Pluronic F-127(F-127) or Poloxamer 407(P407) (copolymer PEO106-PPO70- PEO106) is attributed to the presence of ethylene oxide (70). The copolymer F-127 has a molecular weight of 12,000 Da, a PEO/PPO rate of 21, is nontoxic, has a low viscosity below 4 °C, and above body temperature, forms a semisolid gel. Similarly, because to hydrogen liaison at low temperatures, F-127 is more soluble in cold water than in hot water [26].

3.2 pH triggered in-situ gelling systems:

All pH-sensitive polymers correspond of an acidic or a introductory group that can either accept or releases a proton in response to changes in environmental pH values. Polymers with numerous ionizable groups are called polyelectrolytes[27]. The most generally used pH- responsive polymers in ophthalmic phrasings are PAA, polycarbophil, CS, and cellulose acetate phthalate(CAP). In ophthalmic phrasings with high attention of PAA(Carbopol ®, Carbomer ®), the low pH value of the PAA result could beget damage to the eye face before being annulled by the lacrimal fluid. This handicap was answered by incompletely combining PAA with HPMC or other inert, density- enhancing polymers, without affecting the general rheological parcels of the expression[28]

Ex. Carbopol (Polyacrylic acid):

Carbopol is a polyacrylic acid(PAA) polymer, that displays a sol- gel phase transition in waterless result as a result of raising the pH above its pK of about5.5[29]. The carboxylic groups of PAA accept and release protons at low pH values and high pH values, independently. thus, at high pH, the PAA swells due to the electrostatic aversion of the negatively charged groups, releasing the medicine motes to the terrain[30]. It's considerably exploited in optical expression with the end of perfectingpre-corneal retention time of medicines. Carbopol provides the benefit of flaunting superior mucoadhesive parcels as compared to other polymers. Mucoadhesive parcels of carbopol is attributed to the commerce of poly(acrylic acid) with mucin that occurs by four mechanismsviz. electrostatic commerce, hydrogen cling, hydrophobic commerce and inter prolixity[31]. Despite carbopol displays excellent mucoadhesive parcels, the acidic nature of the gel is a

major debit which leads to vexation and damage to the eye apkins. thus, combinations of carbopol with other polymers including chitosan and HPMC were latterly developed to overwhelmed this problem[32].

3.3 Ion-activated in-situ gel system:

Ion-activated in-situ gelling systems form a crosslink with cations exists in the tear fluid (Na+, Ca2+ and Mg2+), thus forming a gel on the ocular surface, which give rise to an extended corneal contact time[30].The most commonly used ion-activated polymers in ocular formulations are gellan gum (Gelrite), hyaluronic acid and sodium alginates ,pectin.

Ex. Gellan gum:

Gellan gum are polysaccharides that can be used to induce ion-sensitive hydrogels. It's a direct anionic heteropolysaccharide made up of a tetrasaccharide repeating unit of glucose, glucuronic acid and rhamnose in the rate of 211[33]. Gellan comprises hydroxyl and carboxylic functional groups, which may interact with other polymers via hydrogen cling and/ or electrostatic lodestones[34]. A low- acetyl gellan goo is generally available in the request as Gelrite ®, which undergoes gelation in the presence of mono- or divalent cations. The electrolytes of the gash fluid especially Na, Mg2 and Ca2 cations are particularly known to induce gel conformation of the polymer upon instillation as a liquid result into the cul-de-sac[35].

The objectification of optimal amounts of calcium gluconate to gellan phrasings lead to the conformation of gellan calcium gluconate- dissembled gash fluid(STF) gels with a significantly advanced strength than when gellan alone was mixed with STF. It undergoes gelation by both temperature sensitive or cations convinced medium. The possible medium of gelation includes the conformation of double spiral junction zones followed by aggregation of the double spiral parts to form a three- dimensional network by hydrogen relating with water and complexation with cations[36].

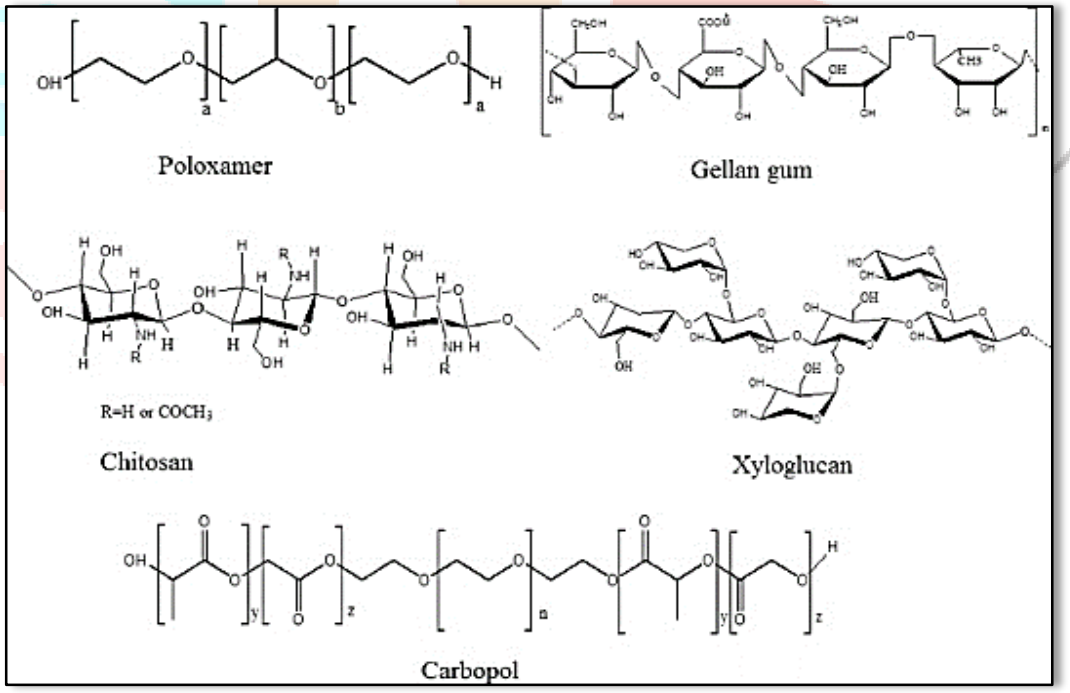

Fig. No.2: The chemical structure of some in-situ gel polymers [37]

4. OCULER INSERTS:

Optical inserts are sterile solid and circumfluous phrasings that are placed in the conjunctival sac between the face of the eye and the lower eyelid. They're fabricated from polymeric systems, and generally contain a medicine(although medicine-free inserts are also used) and can be manufactured in a variety of sizes and shapes but are generally thinmulti-layered cylinders. typically, the medicine is loaded into the polymeric system either in result or as a dissipation. optical inserts are frequently handed a sustained medicine release, dragged precorneal retention leading to increased optical immersion. optical inserts may release a drug by prolixity, osmosis, or memoir corrosion. After placing the insert into the gash fluid, water diffuses into the first cube, leading to stretching of the elastic membrane. The performing expansion of the first cube leads to a compression of the alternate cube, expelling the medicine via a release perforation. With memoir

corrosion, intraocular inserts made frombio-erodible polymers absorb the waterless gashes also suffer corrosion, releasing the medicine at a controlled rate[38].

Ocufit SR System :

The Ocufit SR ® system is a medicine- eluting, rod- shaped optical device that can be fitted into the lower and upper conjunctival fornix[39]. The spherical rod, shaped and dimensioned to fit into the mortal fornix, was manufactured from a silicone elastomer and loaded with timolol. The study showed that the positioning of this system in the upper conjunctival sac leads to increased optical medicine immersion. [40]

4.1 Topical Ophthalmic Drug Delivery Device:

The Topical Ophthalmic Drug Delivery Device(TODDD ™), developed by Amorphex cures(Andover, MA, USA), is a soft, flexible, topical optic device made of clear elastomeric material, worn under the upper eyelid in contact with the conjunctiva(Figure 3C). Pre-clinical trials of TODDD ™ containing timolol, prostaglandins, or their combination have been reported, which can deliver multiple specifics and ensure continuous delivery for over to 90 days. Leahy etal. estimated the effectiveness of TODDD ™ with timolol in normotensive rabbits. They set up that a maximum IOP reduction was maintained throughout the entire three- month trial period[41]. Anotherpre- clinical study in eight Beagle hounds using TODDD ™ with latanoprost showed IOP reduction analogous to that of timolol. still, retention rates were low and at the end of the study period of 16 days, only three bias were in place, which could still be due to the third eyelid(nictitating) membrane of the brutes. It can't be said with certainty that the same would be the case in humans. Both studies showed no systemic drug attention[42].

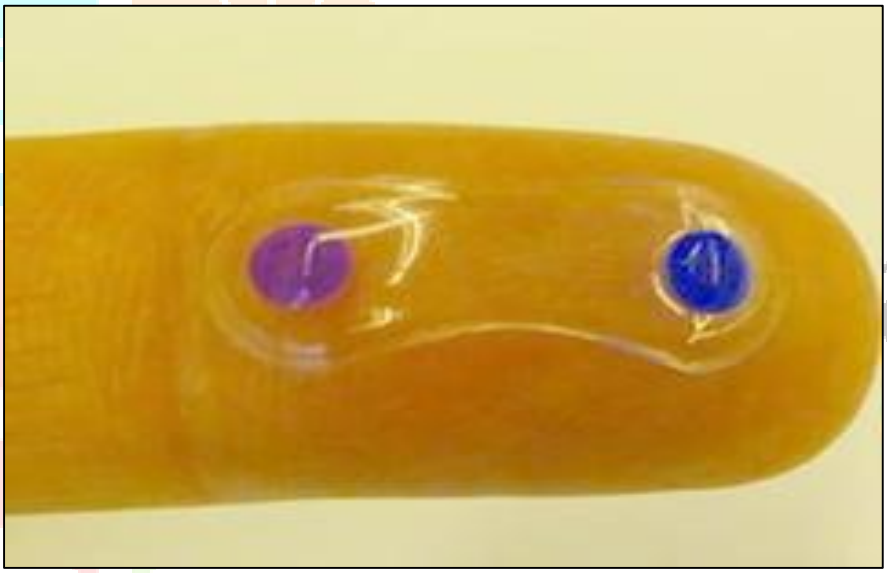

Fig. No.3: Topical Ophthalmic drug delivery device[43]

4.2 Topical Ocular Ring:

The topical optical ring is an interesting kind of optical insert. This expression is free of preservatives and comes in compasses that range in size from 24 to 29 mm. It contains 13 mg of bimatoprost mixed within a silicone matrix that is layered on an inner polypropylene carrier structure. The physical silicone parcels, the silicone-medicine matrix face area, and the concentration of bimatoprost within the silicone-medicine matrix all influence how quickly bimatoprost releases into the gash film. Bimatoprost inserts delivered a decreasing amount of medication over a six-month period, from about 35 mg on day 0 to 6 mg on day 180. Expression studies have been carried out to investigate the possibility of including latanoprost or travoprost in the silicone matrix. Given its relatively large capacity for a sustained-release system, the ring is capable of delivering two medications, such as timolol and bimatoprost. Additionally, six months of IOP decrease following application of this ring has been confirmed by clinical investigations. Its safety and tolerability have been established. It has good main retention rates and is available in a variety of vibrant sizes to help cases select the best one[44].

Fig No.4: Ocular Ring for ocular drug delivery[45]

4.3 Punctal Plugs:

Punctal entrapments are bitsy bias that are placed in the eye's gash tubes(called puncta). Puncta are the bitsy openings in your eyelids that drain gashes from your eyes. The draw is about the size of a grain of rice, and it blocks gashes from draining from the eye.

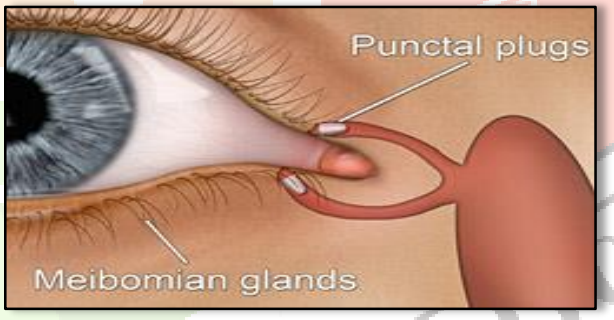

Fig. No.5: Illustration of Punctal Plug[47]

This helps keep the eye's face wettish and comfortable, relieving itchy, burning and red eyes. Punctal entrapments are also called punctum entrapments, lacrimal entrapments or occluders. Generally they're fitted in the puncta of the upper or lower eyelids, or in both. Another type of draw is placed in a deeper part of the tear conduit(the canaliculus).

There are about two types of Punctal Plugs:

4.3.1 Temporary/dissolving plugs:

These are made of a material (similar as collagen) that gradationally breaks down and is absorbed by the body. These entrapments can last in the eye from a many days to months. Temporary entrapments are frequently used to keep the eye wettish after having refractive surgery, similar as LASIK. They're also used when you want to try out punctal entrapments to see if they help relieve your dry eye.

4.3.2 Semi-permanent plugs:

These are composed of a medical plastic that lasts longer, like silicone or tempera. These entrapments are meant to remain in the eyelid for a longtime. However, your ophthalmologist can remove them, If necessary. A different kind of semi-permanent punctal draw is fitted into the canaliculus, a deeper section of the tear conduit. The eye is fully eyeless to these entrapments[46].

4.3 Insertion:

Utmost punctal and canalicular entrapments are fitted exercising an inserter which help guide and release the draw when both sides of the inserter are squeezed. Some entrapments come preloaded in the inserter while others bear homemade lading into the inserter using forceps. Unlike other canalicular entrapments, the Smart draw is fitted into the canaliculus exercising technical forceps with one- third left pooching from the punctum.

4.4 Removel:

Utmost people find punctal entrapments don't beget any problems. Still, side goods canhappen.However, scratchiness or if you suppose you have an eye infection, If you feel any eyepain.tell your eye croaker right down. They may choose to remove the entrapments. How the entrapments are removed depends on which type you have. To remove silicone entrapments, your eye croaker will use forceps to gently pull the entrapments from the tear conduit. Another way to remove these entrapments is by flushing them out with a swab water result. This system forces the entrapments out of the gash tubes into the nose or throat. Entrapments that are deeper in the tear conduit(in the canaliculus) are removed with surgery.

4 Drug Delivery Implants

Medication may be delivered by optical implants into the eye for a very long time. Long-term steroid administration implants were previously available. Polymers, pure sword, or other essence can be used to create optical implants, which can be biodegradable or non-biodegradable as drug delivery methods. PLA, silicon, or PLGA can be used to create biodegradable implants. They eventually break down and are absorbed in the eye. However, non-biodegradable implants require surgical removal, which may result in difficulties. They can be composed of vinyl alcohol or essence, which are polymers related to PVA and ethylene[48].

5.1 Case study of Bimatoprost:

The biodegradable implant Bimatoprost SR, created by Allergan plc (Dublin, Ireland), distributes bimatoprost continuously for more than six months. The biodegradable NOVADURTM medication delivery system includes bimatoprost. The foundation of the NOVADURTM technology is polyglactin PLGA, which has undergone minor modifications to provide an invariant release of bimatoprost for up to six months.[49]

Pharmacology: The bimatoprost implant is composed of biodegradable polymers designed to release bimatoprost in a non- pulsatile, steady- state manner over a 90- day period. In an beast study involving treatment of tykes with the bimatoprost implant(15ug),80.5 of the bimatoprost cargo was set up to be released by day 51 and99.8 had been released by day 80. Compared to topical dosing, attention of active medicine were 4,400-fold advanced at the iris- ciliary body with the bimatoprost implant.[50]

Mode of Action: Bimatoprost belongs to the prostaglandin analog(PGA) medicine class and has been shown to lower IOP by adding waterless humor exodus via both the conventional trabecular route as well as the uveoscleral route[51]. Results from a study of normotensive beagle tykes that entered the bimatoprost implant(30ug) suggest that the agent may also increase waterless humor exodus by dwindling episcleral venous pressure. [52]

Administration: The bimatoprost implant is preloaded within a sterile applicator with a 28- hand needle tip. Under aseptic conditions, the guru inserts the needle into clear cornea, enters the anterior chamber, and also depresses an selector button to release the implant. Following release of the implant, the needle is removed and the case is instructed to sit upright for at least one hour.

Efficacy: The efficacy of the bimatoprost implant was delved in two 20- month phase III trials involving 1,122 subjects that were randomized to treatment with the implant versus topical timolol eye drops. Cases that were randomized to the bimatoprost implant had the medicine administered in the study eye on day 1, week 16, and week 32. Cases randomized to topical timolol were treated with doubly diurnal dosing. By week 12, cases randomized to the bimatoprost implant achieved an IOP reduction from24.6 to17.7 mmHg, representing roughly 30 reduction from birth. The bimatoprost implant metpre-defined criteria fornon-inferiority compared to timolol. This system has proven to be effective, safe, and well- permitted with the limitation of delivering only minimum medicine attention into anterior chamber, and may have implicit complications similar as elevated IOP and retinal detachment as well as keratitis as a result of herpes simplex contagion reactivation after implant injection. [51]

5 Microneedles:

It's possible to develop a long- term release(eg. 3 – 4 months) expression of a glaucoma drug that can be fitted in an office setting. Subconjunctival administration of glaucoma specifics in extended- release phrasings can avoid the case adherence issue. Unlike MEMS bias, they're unresistant delivery systems, able of sustained, long- term delivery of specifics. Injection of being medicines into the subconjunctival space can lead to prolonged delivery compared with simple topical operation, in the order of hours or days[53].
Microneedles had shown prominent in vitro penetration into sclera and rapid-fire dissolution of coating result after insertion while in vivo medicine position was set up to be significantly advanced than the position observed following topical medicine administration like pilocarpine[54].
Microneedles are medicine delivery bias manufactured using essence or polymers with confines between 10 and 200 μm. The ultradimensions of these bias make the medicine delivery less invasive and more targeted to the spots of medicine action. Jiang and associates used 500- to 750- μm-long carpeted pristine sword microneedles delivering pilocarpine into the anterior chamber via the intrascleral route. The authors reported a45-fold increase in medicine immersion compared with conventional eye drops[55].

The MN's ocular application is focused primarily on only:

- Carpeted MNs – that punch the optical towel and also, the medicine expression is dissolved within twinkles of insertion, followed shortly later by device junking,
- Concave MNs – that enable the effective administration of medicines within the optical towel through unresistant prolixity or pressure, from external force, and
- Dissolving polymer MNs – composed of a answerable matrix that fully dissolves when administered

There are three types of MNs enable rapid-fire medicine delivery and reclamation of either the MNs or their baseplates, therefore imitating the operation of conventional hypodermic needles. Solid and concave MNs can be used to administer a wide range of remedial agents including nano-, microparticles, depot forming gels, or medicine results Solid MNs form flash microchannels to ameliorate the permeability of active substances or deliver free or encapsulated medicines, peptides, or vaccines. still, solid MNs are made of pristine sword and silicone, which arenon-biodegradable. thus, farther preclinical studies are demanded to determine their safety and efficacity for intraocular medicine delivery. The success of injectable delivery depends on their capability to target the specific anatomic point of action for those active substances allowing sustained delivery in lower boluses. In short, interest is growing in this area, as MNs can be used in a minimally invasive way for the administration of colorful medicine motes, not just antiglaucoma medicines, both for rapid-fire and possible controlled medicine release. Although towel trauma after MN operation is significantly lower than the hole made by intravitreal injections, it's necessary to conduct farther studies so as to gain fresh information on the medium and duration of recovery.[56]

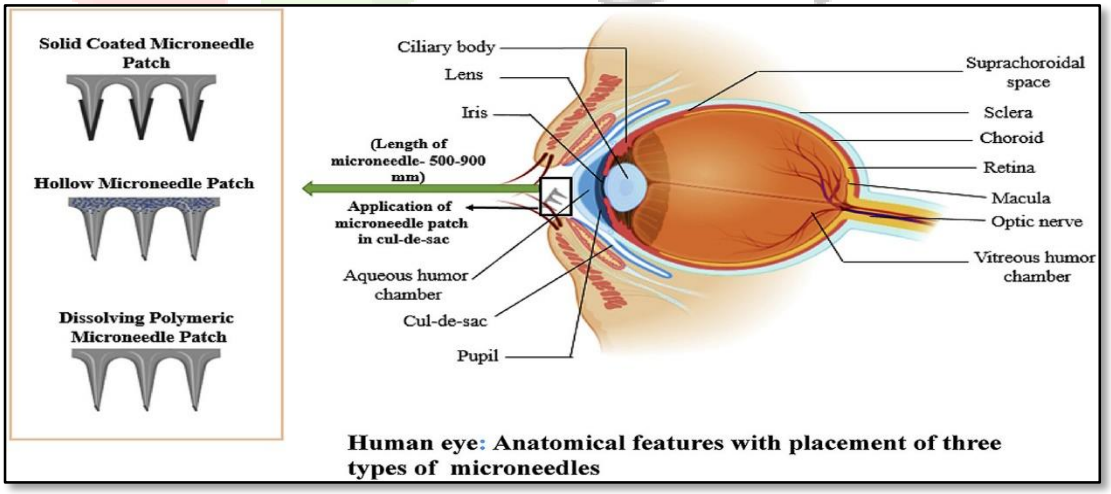

Fig. No.6: Microneedle for Glaucoma [57]

7. NANOSYSTEMS:

"Knowledge applied at the nanoscale" refers to the field of nanotechnology (1 – 100 nm). numerous nanomaterials have intriguing parcels, similar as toxin, biocompatibility, and biodegradability, in addition to electrical conductivity and swank packages. The selection of a nanomaterial depends on the drug(including its hydrophobicity, size, and stability), the intended use, and the mode of administration. Systems for delivering specifics that are grounded on nanotechnology may ameliorate patient adherence, lower adverse goods, boost efficacity, and save vision in glaucoma cases. The drug release and side goods situation are affected by the face, size, and form of nanosystem packets. Incorporating natural, synthetic, orsemi-synthetic polymers into nanoformulations for glaucoma treatment is possible. Natural polymers have the capability to be neutral, amphipathic, cationic, or anionic. Although they all act the extracellular matrix, they can differ from batch to batch, produce immunogenicity, and come polluted fluently. Again, synthetic polymers warrant immunogenicity, have a well defined structure, and easily regulated gobbets. It's simple to exercise them in colorful ways. Combinations of natural and synthetic, as well as synthetic and natural, have been developed due to the lower mechanical parcels of natural polymers and the moderate biocompatibility of synthetic polymers. exemplifications of these combinations are collagen and acrylate and alginate and acrylate.

7.1 Nanoparticles:

The medicine is known as a dissolved, trapped, reprised, or nanoparticle- attached nanoparticle matrix as a particulate disturbance or a solid particulate with sizes between 10 and 1000NM. Nanoparticles are in solid form and are either unformed or crystalline4- 7 like nanospheres and nanocapsules of the size 10- 200 nm. Nanoparticles, nanospheres or nanocapsules may be attained according to the medication system. Nanocapsules are systems in which the medicinal product is confined to a depression with a unique polymeric membrane, while the nanosphere is a matrix system that physically and constantly disperses the pharmaceutical product. Nanoparticles have been completely studied as a targeted medicine delivery system9. Active targeting or unresistant targeting can achieve targeted medicine delivery. Active medicine targeting may do through either the conjugation of the medicine patch with a cell or towel-specific ligand 10. While unresistant medicine targeting by incorporating a medicine patch intomicro-particles or nanoparticles can be achieved. The Colloidal Framework for Drug Delivery Nanoparticles(NP) correspond of natural, synthetic andsemi-synthetic polymers. NP flyspeck size varies with periphery between 10 nm to 1,000 nm11.

The different inner structure of this colloidal medicine delivery system.

- Matrix- type nanospheres
- Reservoir- type nanocapsules

Nano -particles benefits:

1. They're point-specific, biodegradable,non-toxic and store for at least a time.
2. You may target a medicine to a particular position in the body by adding targeted ligands to flyspeck shells or by using glamorous guidance.
3. They give regulated medicine release rates and characteristics for flyspeck declination that can fluently be modulated using matrix element selection.
4. The lading of the drug is high and without a chemical response medicines can be introduced into the systems; this is an essential factor to guard medicine operation.
5. They've better remedial efficacity and overall response unit cure.
6. The system can be used on different routes similar as oral, nasal, motherly, intraocular,etc.
7. Nanoparticles can fluently be manipulated to achieve both unresistant and active medicine targets following parenteral administration, flyspeck size and face characteristics[58].

7.1.1 Liposomes:

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25-10000 nm in periphery. They're having an intimate contact with the corneal and cojuctival shells which is desirable for medicines that are inadequately absorbed, the medicines with low partition measure poor solubility or those with medium to high molecular weights and increases the probability of optical medicine immersion.

7.1.2 Niosomes:

The major limitations of liposomes are chemical insecurity, oxidative declination of Phospholipids cost and chastity of natural phospholipids. To avoid this niosomes are developed as they're chemically stable as compared to liposomes and can entrap both hydrophobic and amphiphilic medicines. Niosomes are bitsy lamellar structures, which are formed on the amalgamation of non ionic surfactant of the alkyl Or dialkyl polyglycerol ether class and cholesterol with posterior hydration in waterless media. Structurally, niosomes are analogous to liposomes, in that they ’re also made up of bilayer. still, the bilayer in the case of niosomes is made up ofnon-ionic face active agents rather than phospholipids as seen in the case of liposomes[54]

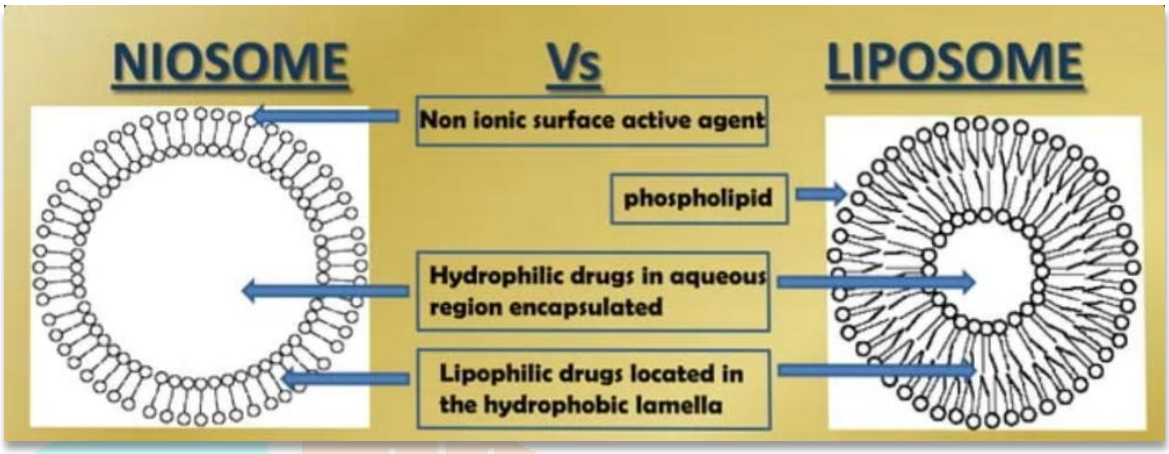

Fig. No.7: Niosomes Vs Liposomes[54]

8. Lens Therapy for Glaucoma:

Hydrophilic polymer networks joined chemically form the structure of soft contact lenses. Although their primary application is in the field of vision correction, they may also find utility in the administration of hydrophilic medications, such as dorzolamide and timolol, which elute transiently from the heavily doped polymer network. Since contact lenses are widely accepted in situations where those used for medicine administration are marketed as "smart" contact lenses, they are recognised as a potential method of delivering medication. 2-hydroxyethylmethacrylate is used to make soft contact lenses (HEMA). Medicine delivery can be regulated and sustained with the use of medicated contact lenses. The main channel for prolonged medication release and extended medicinal hearthstone duration is passive prolixity. Medicine delivery can be regulated and sustained with the use of medicated contact lenses. The main channel for prolonged medication release and extended medicinal hearthstone duration is passive prolixity. Soak and release lenses, vitamin E-loaded lenses, enzyme-touched off release lenses, film impregnation in contact lenses, coloured contact lenses, and topical ophthalmic drug delivery bias are some of the medicated contact lenses that have been used to treat glaucoma.

8.1 Soak and release:

A convenient, affordable, and easy method of loading medications into contact lenses is the soaking technique. Soaking the contact lens in the medication is the process. Comparable contact lenses might have interior tubes or depressions to hold medication motes. The soaking approach has been employed by many researchers to create corrective contact lenses that contain timolol, brimonidine, and pilocarpine—anti-glaucoma medications. The absorption and release of timolol maleate and brimonidine tartrate from contact lenses were investigated by Schultz et al. When used for 30 minutes a day for two weeks, in-vitro release of medication showed burst release with a table after one hour. However, in glaucoma cases, the results showed a comparable drop in IOP to eye drops obtained with a one-tenth(1/10) of the cure. The soaking method has drawbacks despite being rapid and affordable. Contact lenses have a poor affinity for the majority of ocular medications. The medication is briefly removed (burst release) from the contact lens due to insufficient retention, which causes a sharp decline in medication attentiveness. For corrective contact lens wearers with chronic eye diseases, such as those treated for glaucoma, burst release is ineffective since prolonged medication delivery is required.

8.2 Vitamin E – loaded lenses:

Objectification of vitamin E(tocopherol) into contact lenses can significantly protract the release of hydrophilic medicines. Theanti-oxidant parcels of vitamin E can cover the cornea from UV radiation as well as susceptible medicines from oxidation. This system is promising for hydrophilic medicines that don't dissolve in vitamin E, with tocopherol acting as a lipophilic hedge to medicine release, dragging prolixity time into the cornea. Contact lenses loaded with vitamin E were loaded with timolol and dorzolamide, to extend their contemporaneous release. The results showed that the objectification of vitamin E dragged the release duration for both medicines to around two days, perfecting IOP reduction compared with an eye drop.

8.2Film impregnation in contact lenses

Ciolino etal. reported on latanoprost – poly(lactic-co-glycolic acid) flicks of varying consistence in Methafilcon A lenses. Results revealed an early burst medicine followed by sustained release of latanoprost for one month. Contact lenses with thicker(40 – 45 mm in consistence) flicks released more medicine after the original burst medicine release. The contact lenses were manufactured in two lozenge variations high(149 g) and low(97 g) latanoprost. The IOP- lowering effectiveness of high- cure and low- cure latanoprost-eluting contact lenses was compared to latanoprost eye drops in adult glaucoma monkeys with a 3- week flop time between the two treatments. Topical latanoprost reduced IOP by2.91.0 to6.61.3 mmHg, 97- g contact lenses by4.01.1 to7.83.8 mmHg, and 149- g contact lenses by6.04.4 to10.22.5 mmHg. In vivo results demonstrated that the lenses handed sustained release of latanoprost for one month with waterless humor medicine attention similar to those attained with latanoprost eye drops[38].

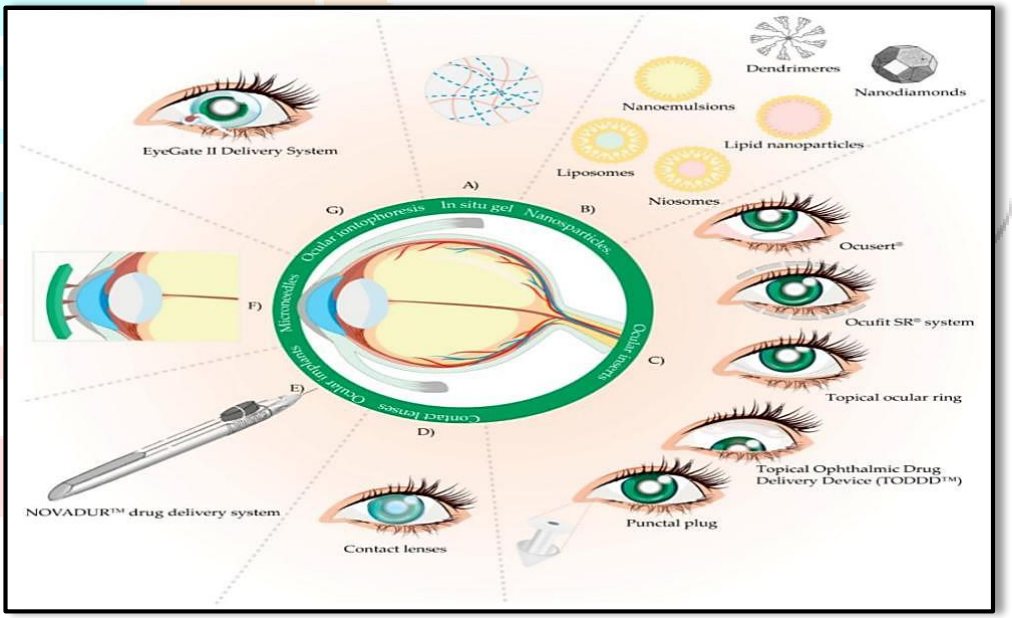

Fig No.8: drug delivery devices for glaucoma treatment [56]

Conclusion:

There are numerous effective topical specifics presently available for treating glaucoma. Still their clinical efficacy is limited by hamstrung delivery system, performing in poor target bioavailability, increased systemic immersion/ side goods and patient compliance. Compliance to remedial authority remains a critical issue for cases and rehearsing eye care professionals likewise. Novel, more effective delivery systems are on the horizon with implicit to ameliorate patient care by barring patient adherence factor and reducing side goods. Eventually, these new delivery systems for both IOP- lowering and implicit neuroprotective medicines can lead to lesser treatment options and preservation of vision in glaucoma. New platforms for furnishing sustained medicine delivery in glaucoma continue to evolve. The capability to incorporate effective commercially available medicines into more stable composites is an important element. Although further exploration is demanded to establish their clinical efficacy, new delivery systems will allow for further targeted medical remedy and for the occasion to further explore neuroprotective and gene- grounded curatives.

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