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Review article

Glaucoma: Current treatment and impact of advanced drug delivery systems

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ABSTRACT

The human eye being a complex and a very sensitive organ makes the drug delivery task challenging. An increase in the intra-ocular pressure at the aqueous humour leads to glaucoma which is not only indecipherable but can also be the reason of blindness for many. The presently available marketed formulations using anti-glaucoma drugs have issues of either difficulty in crossing the blood- retinal barrier or lower systemic bioavailability. Hence, the drugs having lower therapeutic index would need to be administered frequently, which eventually lead to deposition of concentrated solutions at ocular site, producing toxic effects and cellular damage to the eye. To overcome these drawbacks the novel drug delivery systems like In-situ gels, liposomes, niosomes, hydrogel, dendrimers, nanoparticles, solid lipid nanoparticles, Microneedles or ocular inserts play an important role to enhance the therapeutic efficacy of the anti-glaucomic drugs. The present review briefs the current treatments in terms of drugs used and in detail the impact of utilizing the above mentioned novel drug delivery systems in the treatment of glaucoma.

1. Introduction

The human eye is one of the most complex and sensitive organs of the body. It is the most extensively used sensory organ and falls under the category of "human features with unusual anatomy and physiology". These factors along with a bunch of others make the ophthalmic drug delivery system the most interesting and challenging one. The internal structure of the human eye is divided into two distinct sections, namely the anterior and the posterior section. (Fig. 1) [1] The anterior section, in turn, comprises of the anterior and the posterior chamber. It is a pure division of the eyeball length into its composite halves. While the space from Cornea to the Iris make up the anterior chamber, which from the Iris to the Lens constitute the posterior chamber. Although both are fluid filled, the anterior chamber is filled with aqueous humour while the posterior chamber, because of its proximity to the optic nerves, is filled with vitreous humour. Aqueous humour, a transparent watery fluid secreted by the ciliary epithelium present in the anterior chamber, provides nutrition to the lens and cornea [2,3] Aqueous humour flows from posterior chamber to the anterior chamber through the trabecular meshwork, a spongy tissue located around the base of the cornea and then drains into canal of Schlemm. The clear fluid then finally drains into the venous system which constitutes intrascleral, episcleral and lastly conjunctival veins [4,5]. The whole process, thus, constitutes the drainage system of the eye and if this drainage system is completely or partially blocked, there is an increase in the pressure inside the eye.

This pressure inside the eye is termed as intraocular pressure (IOP). The increase in the IOP can lead to various disorders in the eye. The measurement of the eye pressure is called tonometry and the instrument used to measure is called tonometer [6]. The IOP of a healthy human eye ranges from 10 to 21 mm Hg [7]. In diseased state, the range varies from 5 to 40 mm Hg [8].

One of the major risk factors in glaucoma is an elevated IOP (above 22 mm Hg), although it is not the only indicator [9]. Approximately, 70 million people are suffering from glaucoma worldwide with 10% being bilaterally blind [10]. The main reason which contributes to blindness in the United States is glaucoma [11]. It is recorded that more than 2 million people currently suffer from glaucoma in the United States among which 80,000 have become completely or partially blind [12]. The statistics show that, by 2020 United States will have more than 3 million people suffering from glaucoma and it is reported that by the year 2040, it will increase to 111 million people [10,13].

Glaucoma is a group of slowly progressive eye diseases/disorders resulting from increased intraocular pressure (IOP). This increase in IOP cannot be tolerated by normal eyes and it eventually causes progressive injury to the optic nerve. This uninterrupted long term damage to optic nerve leads to failing of communication between retina and the brain and eventually to an irreversible vision loss [14]. Glaucoma

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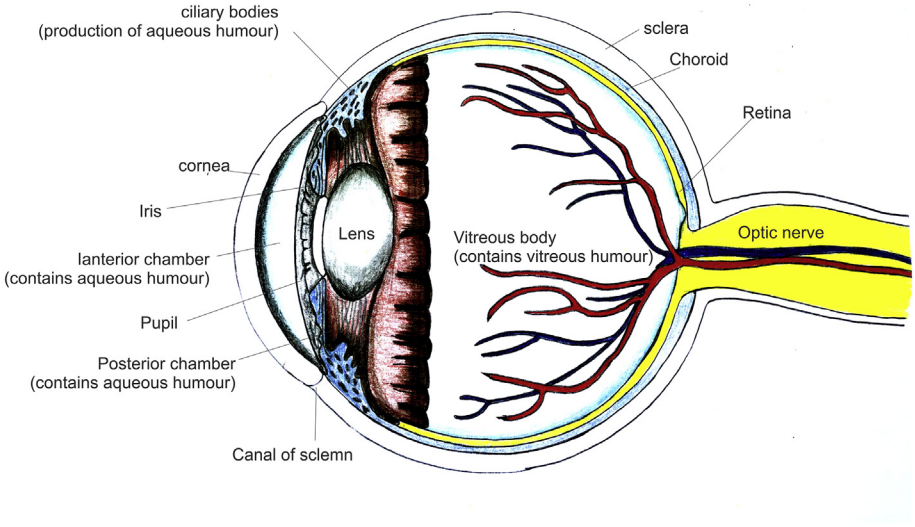

Fig. 1. Human eye.

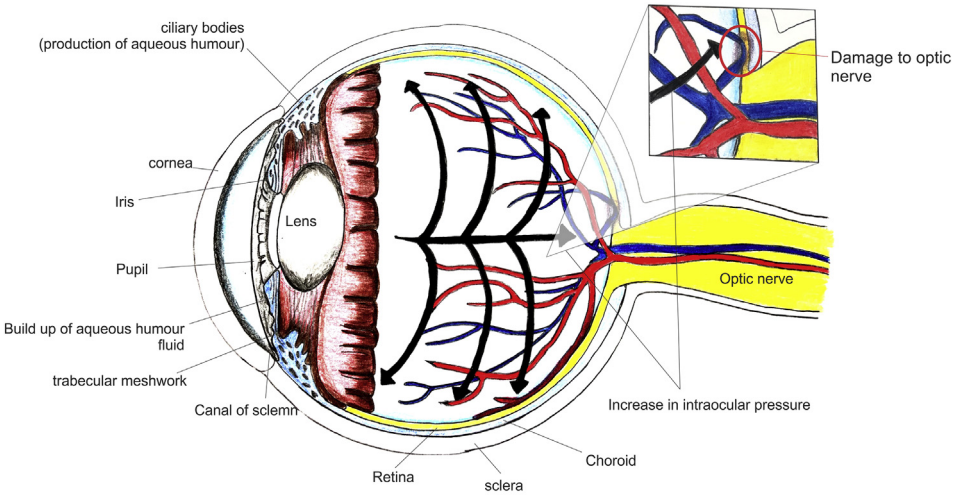

Fig. 2. Human glaucomic eye.

mainly affects the middle aged and elderly people and is the second main leading cause for vision loss after cataract. There are different types of glaucoma depending upon the severity and causes. Glaucoma can be referred as “the sneak thief of sight” as the open angle glaucoma fails to show any sign or symptoms. The patient is usually unaware of the signs and symptoms and is unaware of slight vision loss. If there is delay in the diagnosis, it could lead to the permanent damage of the optic nerve of the eye. Fig. 2 illustrates the glaucomic eye where an increase in the IOP leads to damage of the optic nerves.

The two main categories are open-angle glaucoma and angle-closure glaucoma. Open-angle glaucoma is the most common form of glaucoma which primarily develops slowly. Closed angle glaucoma occurs unexpectedly. The common signs and symptoms for closed angle glaucoma are pain and slight loss in vision. Permanent damage can be prevented if the patient promptly seeks medical help at the first sign of discomfort [15].

The other divisions include Normal tension glaucoma, Pigmentary glaucoma and Uveitic glaucoma. Normal tension glaucoma is rare and it leads to optic nerve damage absent any change in the IOP. The factor contributing to this type of glaucoma might be reduced supply of blood to the optic nerve. Pigmentary glaucoma is a type of an open angle glaucoma. It generally occurs during early adulthood and extends to middle adulthood. There is rise in the eye pressure due to pigment cells and pigment cells present in the iris get dispersed in the eye [16]. Uveitic glaucoma occurs due to variations in aqueous production and its outflow. The glaucoma arising from uvea leads to change in anatomy of the anterior chamber angle. Treating uveitis with corticosteroids leads to rise in IOP [17]. There is restriction in the outflow of aqueous fluid as trabecular meshwork fails to perform. Apart from primary glaucoma, there are a few other types of glaucoma called secondary glaucoma. The examples include Pseudoexfoliative glaucoma, Neovascular glaucoma and Traumatic glaucoma aka Blunt glaucoma. Secondary glaucoma can also occur by faulty surgeries [18].

The symptoms of glaucoma vary for primary open angle glaucoma and closed angle glaucoma. Primary open angle glaucoma generally arises with peripheral loss of vision in the initial stage and tunnel vision loss in the advance stage. The symptoms of closed angle glaucoma include blurred vision, eye pain, red eyes and other vision problems [19].

The main cause of primary glaucoma is unknown but secondary glaucoma can happen by advanced cataract, inflammation, tumour and diabetes. There are other risk factors which lead to glaucoma such as old age, ethnic background, corneal thickness along with other eye injuries and long term usage of corticosteroids. It also includes other illness conditions such as myopia, diabetes and hyperthyroidism [20]. The drug absorption can occur through two different pathways such as corneal and non-corneal pathways. Majority of the drug is transported and absorbed in the eye through corneal pathway while the rest is absorbed in the eye through nasolacrimal dust [21].

The main reason contributing to low absorption and poor bioavailability of drug in the eye is pre-corneal loss factors. These factors are solution drainage, tear turnover, tear dynamics, lacrimation etc. Around 50–75 μl solution per drop is delivered by normal eye dropper. By the time eye reaches back to its normal resident volume i.e.7 μl, majority of the drug portion is quickly drained. There is about 70 to 80 percentage loss of drug on the anterior portion of the eye and very little drug is left to reach cornea and get absorbed in the inner tissue of the eye. The anatomy and physiology of the cornea becomes the barrier for absorption of the drug rapidly. It thus decreases the residence time which can be overcome by frequent instillation of eye drops which further leads to repetitive dosing of drug and poor patient compliance [22]. For systemic absorption of drugs, it is required to cross blood – retinal – barrier (BRB). The drug then reaches anterior ocular tissue through posterior ocular tissue. These barriers decrease the absorption of poorly lipid soluble drug. Drugs having low therapeutic index have to be repeatedly administered to maintain the therapeutic concentration. This Frequent repetitive administration of these concentrated solutions at ocular site produces toxic effects and cellular damage to the eye [23]. In order to increase the ophthalmic bio-availability and increase the residence time, various vehicles have come into knowledge such as ointments, inserts, suspensions and gels. These delivery systems, however, are not into much use because of the blurred vision and ocular irritation from ointments, gels and suspensions giving rise to low patient compliance [24].

It is very important to overcome the drawbacks of conventional eye drops, which is possible by altering and modifying the dosage form. The dosage form should be formulated in such a way that it should enhance the absorption and increase the corneal retention time of drug on the eye. Novel drug delivery systems have been developed with productive features such as good histocompatibility, no immunogenicity, no toxicity and can easily pass through cornea [25].

Novel drug delivery systems have ease the instillation of eye drops and have increased patient compliance by lowering the dose of the drug. It has also targeted the sustained and controlled release property which further exacerbates and increase the ocular bioavailability by increasing the absorption of the drug [26].

2. Drugs used in the treatment of glaucoma

The treatment for glaucoma depends on the causes, risk factors, severity and type of glaucoma. Every treatment which is available has some sort of adverse effects or disadvantages. Each glaucomic patient should be treated according to their susceptibility [15]. Glaucoma can be reduced by stopping the progression of intra ocular pressure in the eye. The reduction of intra ocular pressure can be done by various methods i.e. laser treatment, surgery and medicinal treatment. The laser treatment includes argon laser trabeculoplasty and selective laser trabeculoplasty whereas surgical treatment includes iris procedures, filtration procedures and non-penetrating filtration procedures [27]. The medicinal treatment of glaucoma includes drugs of various classes such as prostaglandin analogues, beta blockers, carbonic anhydrase inhibitors, adrenergic agonist, miotics and hyperosmotic agents. These classes of drugs either increase the flow of fluid from the eye or reduce the production of the fluid from eye [28]. However, glaucoma can never be completely cured. Eye drops, being effective are often used over surgeries for treating glaucoma. In spite of that some patients do not respond well to conventional eye drops because the medication gets absorbed on the surface layer of the eye into conjunctival blood vessels. Heart rate and breathing functions are also affected as active ingredient enters into the bloodstream. Premedical history cases of asthma may worsen by the use of eye drops. It has some disadvantages such as eye irritation, hypotension, cardiac and respiratory failure, slow heart rate, allergic conjunctivitis, worsening of asthma and impotence. Each class of the drugs have different type of mechanism to lower the IOP in the eye so understanding of the basic mechanism of these classes is necessary [29].

2.1. Prostaglandin analogues

In most of the countries the prostaglandin analogues are the first line treatment of glaucoma [30]. The prostaglandin analogues increase the drainage of the aqueous humour thus decreasing the intra ocular pressure in the eye. Prostaglandin analogues relaxes the muscles of the interior of the eye thus increasing the outflow of the fluid from the eye [31]. The prostaglandins are the hydrophobic prodrugs which mimic the prostaglandin in our body to increase the drainage of fluid through canal of Schlemm as described in Fig. 3. The prostaglandin family have minimal side effects as they are given in a very low concentration. This makes these drugs very much attractive to patients and physician [32]. However, prostaglandins have local ocular side effects like irritation, redness of eye and discoloration of iris and surrounding skin [33].

2.2. Beta blockers

Beta blockers are beta adrenergic receptor agonist which reduces IOP by decreasing the production of aqueous humour in eye. They are classified into two categories i.e. non selective beta blockers (timolol, levobunol, etc.) and selective beta blockers (betaxolol). After the approval of the first beta blocker for the treatment of intra ocular pressure reduction by US-FDA, timolol became the first choice of the treatment of glaucoma. They reduce the pressure by blocking the beta adrenoceptor in ciliary body which is further elucidated in Fig. 4. Thus it leads to lower production of aqueous humour and reduction in IOP [34,35]. Beta blockers have ability to decrease the heart rate and may cause adverse side effect to the patient having a medical history of cardiac disease, but these beta blockers are highly stable and highly hydrophilic in nature and requires dosing at least twice a day to maintain the intra ocular pressure [33].

2.3. Carbonic anhydrase inhibitor

Carbonic anhydrase inhibitors are mainly sulphonamide drugs acting on ciliary epithelium (illustrated in Fig. 5). They inhibit the carbonic anhydrase isoenzyme II catalyses, which is directly responsible for the conversion of CO_2 and H_2O to HCO_3. This inhibition of CO_2 and H_2O to HCO_3 leads to decrease in the production of aqueous humour in the eye [36]. Dorzolamide was the first carbonic anhydrase inhibitor launched as a topical eye drop for decreasing IOP. It reduces IOP by decreasing the aqueous humour production in the eye. When the effect of beta blocker is resisted or contradicted dorzolamide can be given to patients as the first line treatment of glaucoma. It is also observed timolol and dorzolamide combination works more efficiently compared to the single drug for reducing IOP [37].

2.4. Alpha adrenergic agonists

Alpha adrenergic drugs lower the ocular pressure through alpha adrenergic stimulation. The stimulation causes constriction in the blood vessels and thus decreases the aqueous humour production [38]. Alpha adrenergics are successful in producing result during the day rather than night [39].

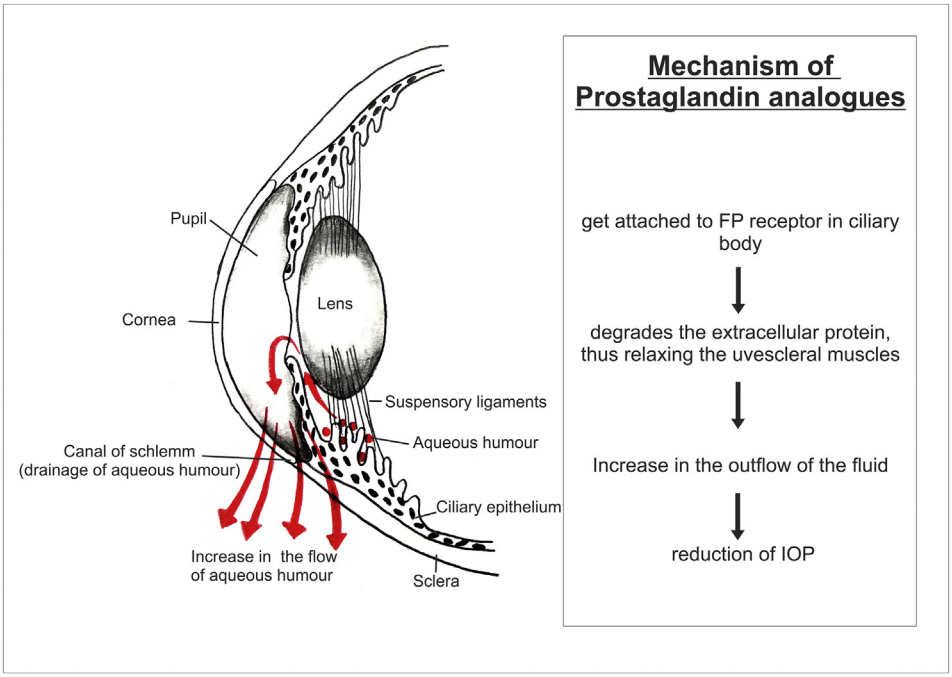

Fig. 3. Mechanism of prostaglandin analogues.

To treat glaucoma, selective a2 adrenergic agonists such as apraclonidine and brominidine, a derivative of clonidine is used. It was ascertained that Clonidine, a systemic antihypertensive drug decreased the IOP by decreasing the production of aqueous humour as illustrated in Fig. 6. Alas, it noticeably reduced the systemic blood pressure. Apraclonidine functions similar to that of clonidine except the fact that it does not cross blood brain barrier (BBB) and therefore systemic hypotension is not witnessed [40].

Originally, to prevent increasing IOP 1% apraclonidine stored in single use dispenser was accepted but this accompanied surgical procedures. In case of 0.5% apraclonidine, long term application was required in order to decrease IOP. It is deprived of cardiovascular side effects although many other common side effects were observed such as dry mouth and dry nose. Brimonidine is also similar to apraclonidine. Many patients have outlined that it causes dry mouth. In contrary to apraclonidine, it crosses BBB and chances of mild systemic hypotension may occur [41].

2.5. Cholinergic or miotics

Miotics, cholinergic agonists or otherwise parasympathomimetics are preferred option as third line treatment. Frequent administered miotics are pilocarpine and carbacol [42]. It is administered locally in the form of drops. They are involved in increasing the rate of

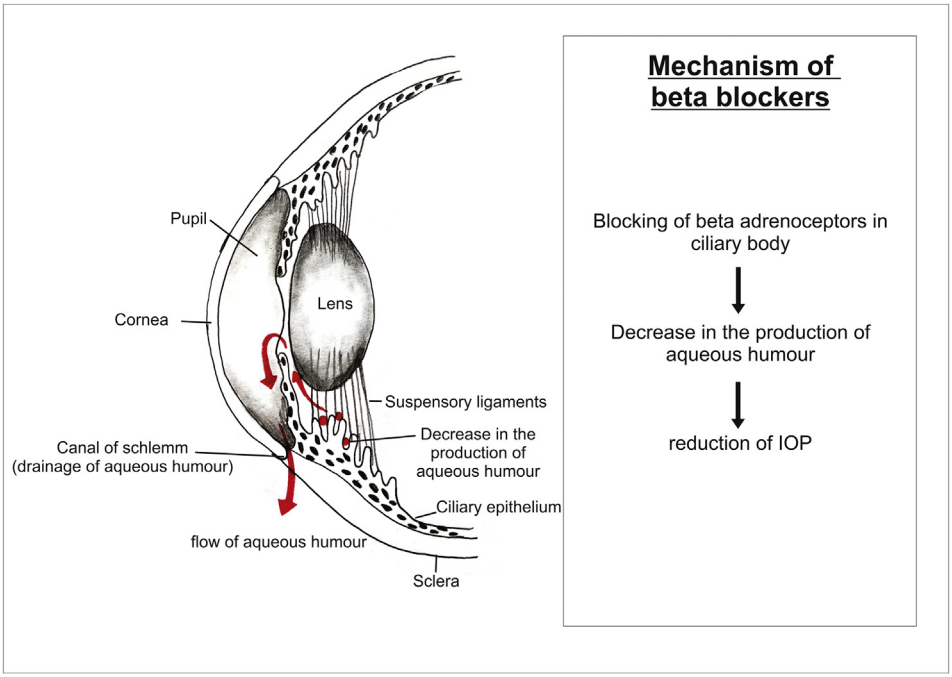

Fig. 4. Mechanism of beta blockers.

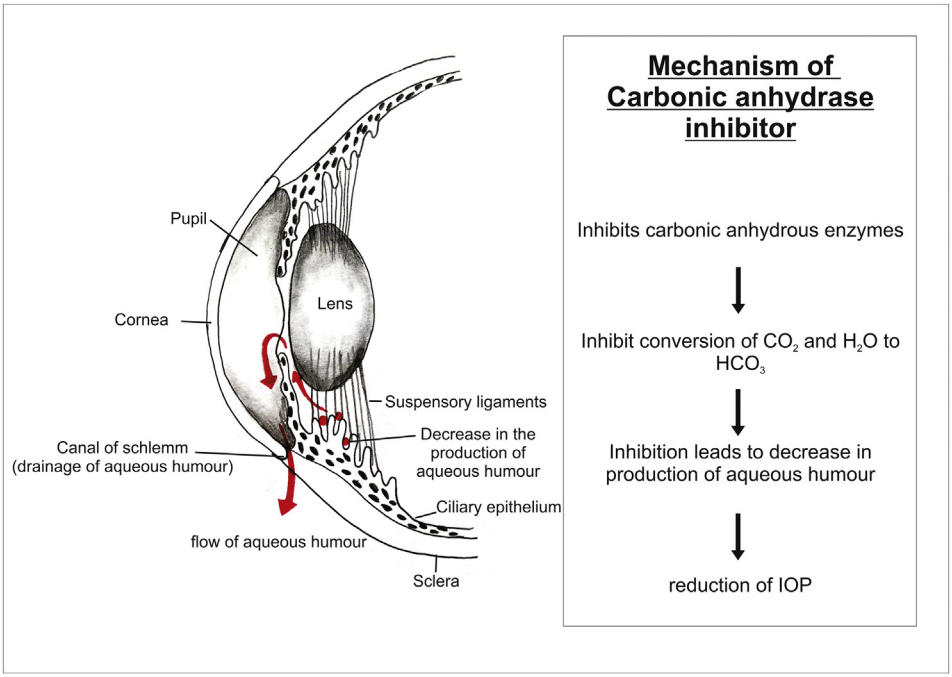

Fig. 5. Mechanism of carbonic anhydrase inhibitor.

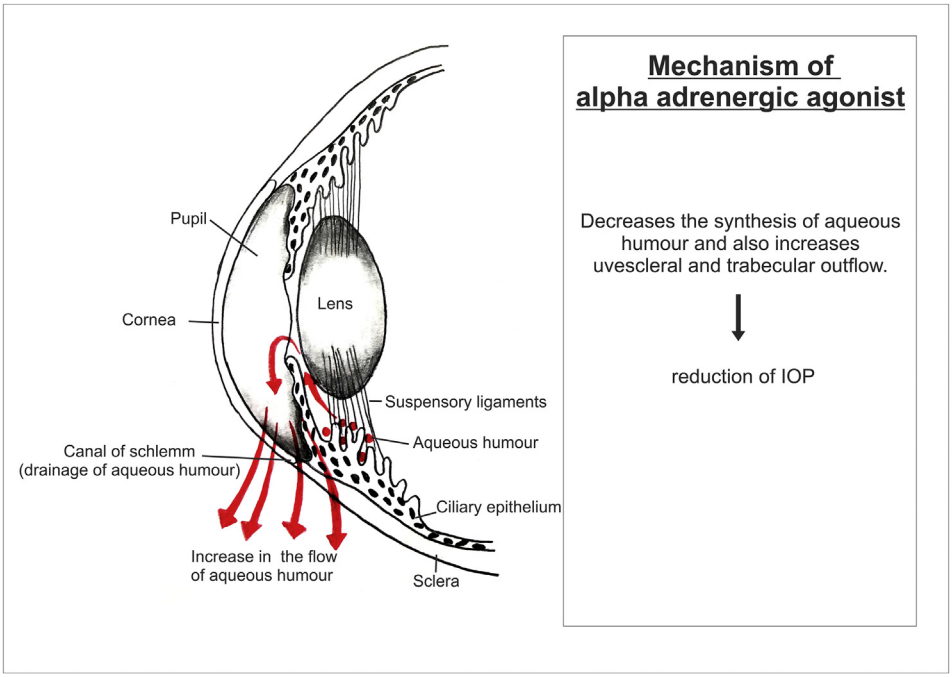

Fig. 6. Mechanism of alpha adrenergic agonist.

evacuation of aqueous humour from the eye by constricting the trabecular meshwork fibres (Fig. 7) [43]. Miotics are inexpensive when compared to other topical ocular medications. They have some disadvantages regardless of minimal side effects. Some of the drawbacks are frequent administration, blurred vision and spasm. The frequent administration of at least four times a day causes patient incompliance and cases of induced myopia. These challenges makes miotics restrained for patients who do respond much well to other topical ocular medications [44].

Combining two drugs in humans is found to be partially synergistic when associated with latanoprost, pilocarpine shows synergistic effect as it constricts the ciliary muscle and helps to decrease the outflow of uveosclera. Physostigmine when given in high doses was found to be effective in retaining the ocular hypotension caused due to latanoprost [45].

3. Impact of advanced drug delivery systems

Richard E Smalley, winner of 1996 Nobel prize in chemistry have stated that “we are about to be able to build things that work on the smallest possible length scales, atom by atom.” “There is a growing sense in the scientific and technical community that we are about to enter a golden new era” he added. This scientific golden new era he detailed was Nanotechnology. The term ‘Nanotechnology’ i.e.

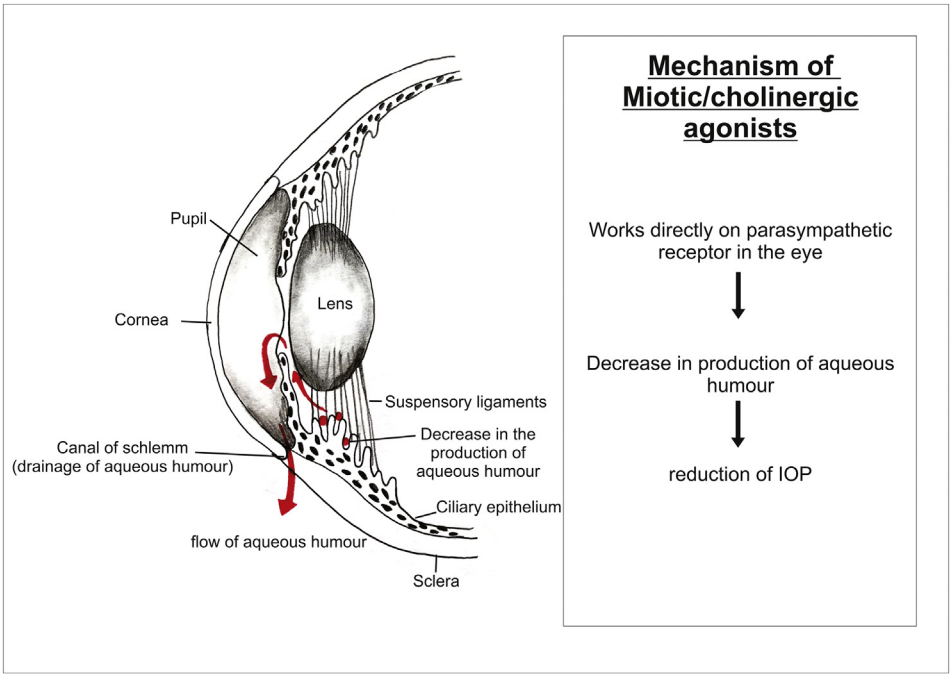

Fig. 7. Mechanism of cholinergic/miotics.

originated from Greek word 'nano' which means dwarf, can be defined as the technology that works on the principle of engineering and manufacturing at molecular level (nano size). Nanotechnology after that has taken a revolutionary dive in numerous fields such as robotics, medicines and communications. Nanotechnology in medicines and therapeutic are a topic of interest to many scientist and researchers. Nanotechnology in medicines involves the creation and use of the materials to produce intracellular structure and molecules [46].

The development in nanoscale technologies have changed the scientific landscape in healthcare industry and have given rise to many new developments in terms of medicines and delivery of drugs. Many type of new drug delivery discovered including targeted and controlled release drug delivery. When nanotechnology is applied in ophthalmology, it has led to development of various novel drug delivery systems such as nanoparticles for the treatment of various ocular diseases such as glaucoma, cataract, conjunctivitis and other eye infections. Nanoparticles are particles of size ranging from 10 to 1000 nm. These nanoparticles are used as vehicles for the drug to get delivered. The loading of drugs in nanoparticle is easy and they are capable of loading any type of drug [47]. Their ability of loading both the hydrophilic and lipophilic drugs helps in increasing the permeation through the ocular barrier in the eye. These drug loaded nanoparticles constituent of an ideal drug delivery system which can penetrate through the ocular physiological barriers. They direct the drugs to target specific ocular intracellular components by passive diffusion or by ligand targeting mechanism.

3.1. In-situ gelling system

The ocular barrier and the defence mechanism of the human eye prevent the passage and retention of drug solutions. These ocular barriers lead to low ocular permeability of drugs and also their absorption in the eye. So to counteract these barriers, there is a need for a drug delivery system that facilitates retention on the surface of the eye for a longer duration after installation. Novel drug delivery system such as in-situ gel systems, owing to their property of good adherence and viscosity, are known to achieve the objective of retention. The enhanced permeation and absorption will eventually lead to a better bioavailability of the drug in the eye.

The ocular in-situ gelling system is defined as the system in which liquid formulation upon installation into the eye gets converted into a thin layered gel. In-situ gels are in a solution form but when exposed to the physiological changes in the eye, the stimuli get activated and the drug solution gets converted into a gel. This transition of the solution into a gel is called phase transition and is shown in Fig. 8.

In order to obtain such phase transitions various types of polymers are used to prepare in-situ gels. Polymers which respond to stimuli are emerging as a great curiosity for ocular delivery. These polymers are macromolecules which on subjection to environment undergo physicochemical changes. The stimulus provokes chemical changes and leads to structural changes in the polymers. These polymers get activated to different stimuli such as physical, chemical or biological changes. The physical changes could be the effects of temperature, stress or light. The chemical changes include alterations in pH and ionic strength while the biological change is the change which occurs due to enzymatic reaction or hormones. The stimulus can also be triggered by electric and magnetic field and can occur naturally by a feedback mechanism [48]. pH-triggered polymers are the polymers which upon a change in pH gets converted from solution to gel. pH-triggered polymers consist of weak acids such as carboxylic acid or weak bases like ammonium salts with pKa values ranging from 3 to 10. These polymers are capable of accepting or donating protons as a cause of change in pH in the surrounding and can be termed as polyelectrolytes [49]. These polymers are often used in ophthalmic drug delivery. The commonly used polymers to formulate in-situ gels are carbopols and polycarbophils [50].

The carbopols are categorized under anionic polymers. Kumar and Himmelstein tried preparing the in-situ gel using polyacrylic acid which converts to gel when it comes in contact with pH 7.4. They found that the concentration of polymer was very high to obtain the gelation. The high amount of polymer with low pH of 4 will neutralise the lacrimal fluid causing damage to the surface of the eye. However, they later used HPMC (a viscosity enhancing polymer) in combination with polyacrylic acid which eventually resulted in a pH-responsive polymer solution (pH −4) to achieve gelation upon delivery in the eye (pH 7.4) [51].

Before Kumar and Himmelstein, various researchers had worked on developing a better pH-responsive in-situ gel to obtain a sustained release with minimum side and adverse effects. Polymers like carbopol have been still one of the favourite pH responsive polymer and used

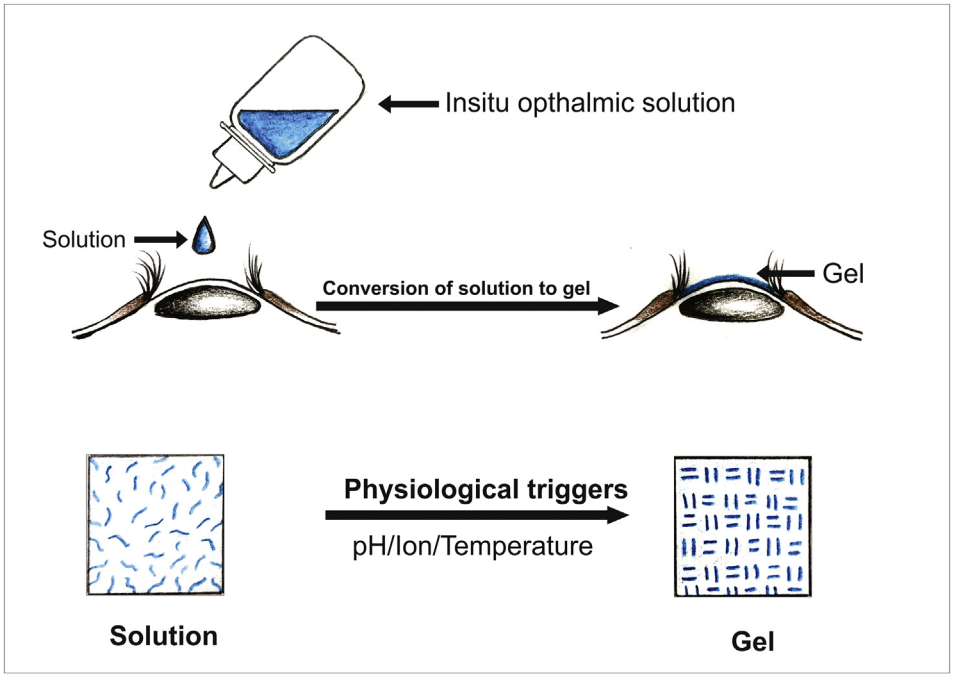

Fig. 8. In-situ gel.

from decades with different types of viscosity enhancing polymers. The in-situ gelling system showed better adherence to the surface of eye and also gave the controlled release of drug over the period of 24 h [52]. Gupta and Vyas in 2010 prepared a timolol maleate loaded in-situ gelling system to treat glaucoma using carbopol combined with chitosan, which acted as the viscosity increasing agent [53]. In 2018 Pang and his research group confirmed that the ocular in-situ gel reduces the absorption of drug systemically as compared to marketed conventional eye drops. This decrease in absorption reduces the possibility of systemic toxicity and other side effects of drugs. They prepared in-situ gel of brimonidine tartrate using carbopol and HPMC to compare the in vivo pharmacodynamics and pharmacokinetics studies of the formulation. The pharmacodynamics result data confirmed that in-situ gel was better in decreasing IOP as compared to the conventional eye drops. Moreover, the in vivo pharmacokinetics data revealed that the plasma AUC of the in-situ gel was lower than that of a conventional eye drop thus proving the lower systemic absorption of an eye drop over the in-situ gel [54].

Thermoresponsive polymers are the type of polymers which undergo structural transformation when subjected to various degrees of temperature [55]. This thermo-sensitive in-situ solution does not produce any irritation and blurred vision to eye. The gel conversion of the solution happens at the temperature of 35 degree when it comes in contact with the precorneal surface. A good thermosensitive in-situ gel should be in a solution form at room temperature and convert to gel when in contact with precorneal temperature in order to avoid the cooling of the solution which, sometimes, could cause irritation to the eye [56].

Many researchers used polymers with a viscosity enhancer or mucoadhesive agent to increase the retention time of the gel on the surface of the eye. The in-situ gel of nimodipine using thermosensitive polymer HPMC was formulated and it was found that *in-situ* gel prepared using nimodipine and HPMC was able to adhere on the surface of the eye as opposed to the conventional eye drops [57]. Gratieri et al. prepared an in-situ gel using poloxamer and chitosan to increase the retention time of drug to treat ocular disease. The research group demonstrated that the addition of mucoadhesive agent in the formulation have increased the mechanical strength and texture properties of poloxamer formulation and increased the retention period of gel as compared to conventional eye drops [58]. Whereas, Ion sensitive or ion activated in-situ gels are the polymers which, when in contact with certain ions, gets converted to gel form. The various types of ions could be mono or divalent cations such as $K+$, $Na+$, $Ca2+$, $Mg2+$. These ions help naturally occurring anionic polymers such as gellan gum and sodium alginate to get converted into gel [59]. The most commonly used ion-sensitive polymers are gellan gum, alginate and alginic acid, pectins [60].

Kesarla et al. prepared a nanoparticle loaded in-situ gel using ion-sensitive polymer gellan gum. Gellan gum was used as a gelling agent who got converted to gel upon contact with the tear fluid and ions present in them. The nanoparticle loaded gel remained for an extended period on the surface of the eye. Confocal data proved and demonstrated corneal permeation of nanoparticles and the formulation was stable which improved precorneal retention time and adhesion [61].

J Sun developed a novel in-situ gel of brinzolamide using gellan gum to give sustained release of the drug. The gellan gum in formulation, seen as safe and bioadhesive in nature, thus led to a sustained release of the drug [62].

3.1.1. Dual and multi stimuli response gelling system

Recently the combination of polymers with different gelling mechanism is used to formulate the ocular in-situ gels. While all the polymers have some weakness or drawbacks, a combination of polymers could help in removing these drawbacks. This use of combination of polymer leads to assured gelling leading to better therapeutic effect and better patient compliance. Recently various researchers used the combination of polymers to improve drug delivery [63]. Gupta et al. used a pH and temperature sensitive polymer to prepare the timolol maleate loaded in-situ gel. Both the polymers have ensured the gelation of the solution on the surface of the eye. The ophthalmic solution of timolol maleate gave better gel retention, improved drug permeation and was non-irritant [64]. Again in 2010 Gupta et al. prepared a timolol maleate loaded in-situ gel of ion and pH sensitive polymers and ensured gelation by using two different types of polymers. The results obtained were remarkable and the formulation was non-irritant and well tolerable. This recent advancement of combining polymers of different mechanisms of gelling have improved potential for the future and can be used in the drug therapy of glaucoma and various other eye disorders

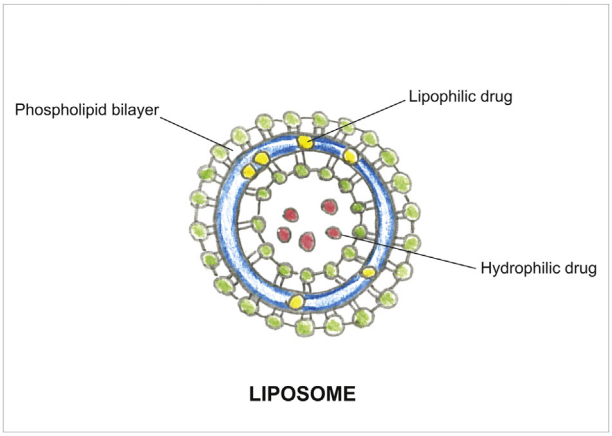

Fig. 9. Liposomes.

[65].

3.2. Liposomes

Liposomes are the vesicles made up of natural or synthetic lipid materials comprising of phospholipid bilayers containing inner core and outer lipid layer [66]. Liposomes were first introduced by Alec Bangham in 1965. After few decades the research on liposomes took pace and it became one of the preferred choice of drug carriers as few liposomal formulation (e.g. Doxil liposomes) got approval from US-FDA. In last 10 years there are about more than 10,000 papers related to liposomes got published.

Liposomes are classified on basis of size, structure and the method by which they are prepared. Structurally they are divided in two types' unilamellar vesicles and multilamellar vesicles. On the basis of size they are divided as small unilamellar vesicles (SUV), large unilamellar vesicles (LUV) and giant unilamellar vesicles (GUV). Liposomes contains aqueous core and outer lipid layer (Fig. 9) which makes them unique as they can deliver both hydrophilic and hydrophobic drug to the eye. They are highly biocompatible, biodegradable and harmless [67,68].

Biodegradable nature of the liposomes is due to the lipids present on the outer core of liposomes. Liposomes are prepared using various types of the natural and synthetic lipids. Surface charge on the liposomes depends on the lipid used to prepare or formulate them. It is observed that positively charged liposomes shows better permeability compared to neutral and negatively charged liposomes.

For ophthalmic delivery of drug liposomes have represented as a perfect delivery because of good biocompatibility, cell membrane like structure and capacity to encapsulate both hydrophobic [69] and hydrophilic [70] medications. Liposomes have demonstrated great effectiveness in the delivery of drug to anterior or posterior portion of eye.

Huang [71] formed liposomes using betaxolol hydrochloride which on evaluation showed increased pre-corneal retention time in rabbits and decreased precorneal loss. Natarajan et al. [72] developed a liposomal formulation of latanoprost using egg-phosphotidylcholine. The liposomes then evaluated in vitro and found that the nano sized liposomes gave a very slow and sustained release of drug (60%) in 14 days. For in vivo experiments, a single egg-phosphotidylcholine loaded lanatoprost injection dose was injected in the subconjuctivial portion of eye of rabbit. The in vivo experimental data showed that the single egg phosphotidylecholine loaded liposomes was able provide sustained release to lower IOP for more than 90 days and also showed better release compared to that of daily marketed eye drop.

Fahmy et al. prepared liposomes of latanoprost/thymoquinone (Lt/Ty) loaded in DPPC (1, 2-dipalmitoyl-Sn-glycero-3-phosphocholine) for subconjunctivial route. It was found that the Lt/Ty loaded liposomes showed high drug encapsulation and was able to reduce IOP for significantly more than 84 h. The sustained effect of liposomes was compared to the conventional ophthalmic solution of latanoprost and it was found that liposomes were able to release drug for a very long period of time in glaucomateous rabbits [73].

Kouchak et al. recently developed a phosphotidyl choline loaded dorzolamide HCl nanoliposomes and compared it with the conventional marketed dorzolamide HCl ophthalmic solution in 20 glaucomic patients with increased ocular hypertension. The clinical trials showed a substantial reduction on IOP of patient treated with dorzolamide HCl nanoliposomes compared to marketed formulation. The liposomes due to similarity between lipid bilayer with positive charge makes them more adherent to corneal layers which eventually lead to better bioavailability of drug [74].

3.3. Niosomes

The human eye is protected by many defence mechanisms such as epithelial layer which hinder the penetration, tear flow and the blinking reflexes of eye. All the three mechanisms are responsible for forbidding the penetration of the drug to cornea and aqueous humour. So there is a need of a novel drug delivery which could increase the penetration of the drug to the deeper layers of eye and thus overcoming the drawbacks of conventional drug deliveries [75]. Niosomes are bilayered vesicles same as liposomes, consisting of amphiphilic non-ionic surfactants (Fig. 10). They are composed of two essential components like cholesterol and non-ionic surfactants. Niosomes are non-immunogenic, biocompatible and biodegradable in nature. Due to lower toxicity levels while using non-ionic surfactants, niosomes are preferred over other drug delivery system like liposomes. Niosomes are proven to be advantageous as they provide better physicochemical stability as well as improve the drug permeation. They are found to be stable chemically within range of 10–1000 nm. Hence, in between 10 and 1000 nm they are efficient enough to incorporate both hydrophilic and lipophilic drugs appropriately [76]. The size of niosomes solely depends on the method of preparation used to formulate. The niosomes can be formulated by using various types of techniques. The properties of the niosomes differ extensively because of the method used for their production and the composition of the bilayer. Many researchers from decades used different ways to formulate niosomes.

Thin layer evaporation (TLE) is the common and easy technique used to prepare niosomes. Soni and Saini evaporated organic solvent from the lipid and surfactant solution with timolol maleate which eventually lead to the formation of a thin layer lipid-surfactant film. The obtained film is then hydrated using an aqueous solution to produce multilamellar vesicles of timolol maleate i.e. niosomes. Niosomes formed using TLE method shown better sustained release of the drug in

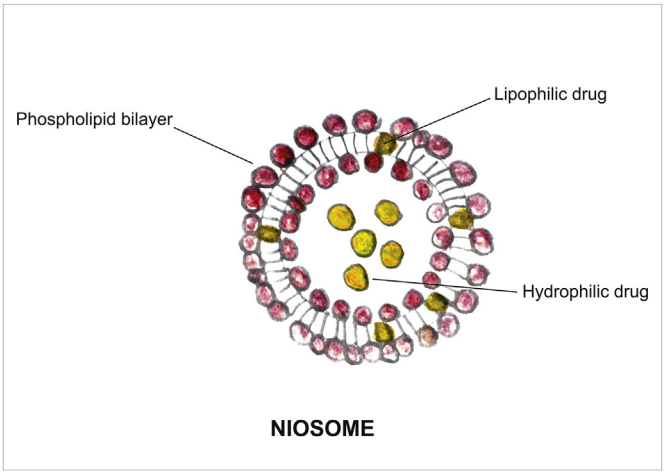

Fig. 10. Niosome.

the eye. It increased the permeation of the drug through ocular barrier to 65.90% in the time period of 8 h which is approximately 150% more than the permeation of conventional dose. TLE is an easy method for the laboratory researchers and the only disadvantage of the method is that organic solvents are used in the formulation [77]. Dehaghi et al., recently developed dorzolamide loaded niosome vesicle using two different methods; thin film hydration and phosphate gradient method. The formulations were evaluated for encapsulation efficacy, lipid to drug ratio, cholesterol percentage, pH to suit the best outcome in terms of release. The study found that increase in cholesterol level with lipid lead to increase in encapsulation efficiency. This formulated niosomal formulation could provide a much better release of the drug for a long period of time [78].

3.4. Hydrogel

Networks of macromolecular 3-D crosslinked polymer either by covalent or non-covalent bonds are termed hydrogels. Various interactions such as van der Waals interactions, covalent bond formation, hydrogen bonding or physical attractions lead to crosslinking in the polymer. These cross linked polymers are beneficial for carrying molecules and drugs in view of the fact of their porous and entangled network structure. The crosslink structure of hydrogel helps in retaining its structure [79]. The covalent cross-linked structure is prepared by a technique of polymerization. Nano sized gels are dispersions which due to their entangled network retain more water as well as the structure gives possibility of adding diverse functional group vectors for targeting [80]. Hydrogel is capable of controlling the aqueous humour flow through the anterior chamber by limiting the IOP. Restricted outflow through aqueous humour is the result of behaviour of hydrogel. These behaviours can be subcategorized as the weight of the polymer, density of the cross linked polymers, water linkage etc.

Hydrogels have potential of imbibing water up to thousand times and swell without undergoing change in its physical structure (Fig. 11). Hydrophilic groups like amide, hydroxyl and sulfonic acid in polymers owe to property of absorbing water. The presence of these groups has the capacity to hydrate the polymer to various degrees which is influenced by nature of the environment and composition of the polymer [81].

There are various polymeric hydrogels which can be incorporated into contact lens and aid in releasing the drug by subsequently absorbing them. Contact lens have calibre of soaking many drugs and deliver them into lacrimal fluid when the lens is initially immersed in solution. The investigated polymer for the delivery of ophthalmic drugs is Poly-hydro xyethylmethacrylate (pHEMA). It was found that the aptitude of pHEMA hydrogels was augmented when it was incorporated

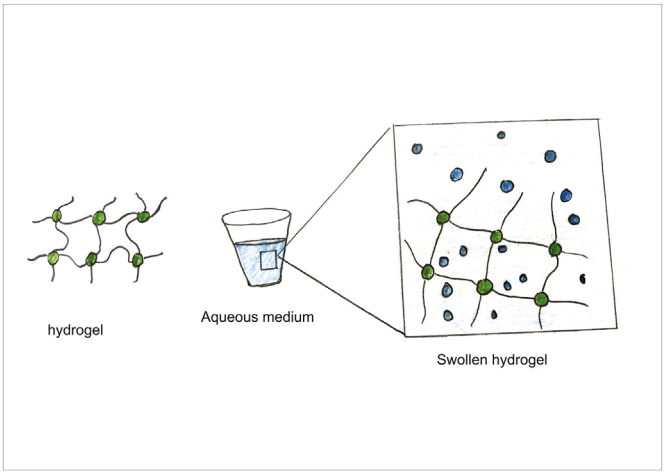

Fig. 11. Hydrogel.

with the combination of N-(3-aminopropyl) methacrylamide (APMA) and 4-vinylpyridine (VP) in the network for proper distribution of ocular drugs. The incorporated monomers reserved the properties of both the ocular lens and the water in the ocular lens. It maintained the viscoelastic properties although an exceptional increase was observed when ibuprofen was loaded as a monomer. When the polymers pHEMA–VP and pHEMA–APMA were dried and filled, it was examined that water swelled to several folds promptly; however, the ionic interactions restrained the drug release below 10% [82].

Cheng et al. formulated thermosensitive hydrogel of latanoprost and curcumin loaded nanoparticles to evaluate the side effect due to repetitive dosing of prostaglandin analogues i.e. latanoprost. The study demonstrated the sustained release of the latanoprost and curcumin was observed in the hydrogel formulation. The adherence on the precorneal surface was increased and the developed hydrogel was able to reduce IOP for seven days [83].

Although many studies have been done on anti-glaucomic drug to get sustained release of those drugs but still more further research is required to attain more sustained release to lower IOP for more period of time. Scientists recently developed a timolol maleate combination of hydrogels i.e. thermosensitive elastin and silk elastin to overcome the problem of conventional ophthalmic eye drop. The study found that the combination hydrogel played a potential role in increasing the retention of drug on cornea and reducing the IOP for a longer period of time [84].

3.5. Dendrimers

The name dendrimer is derived from combination of two Greek words, dendron and meros. Dendrons means ‘tree’ while meros meaning ‘part’. Dendrimer is also known as ‘cascade molecules’. Dendrimers were first described by Vögtle in the year 1978 [85].

Dendrimers are macromolecular 3D shaped structure made of polymeric material and is extensively branched with enormous surface function. The exclusive properties of dendrimers are high intensity of branching, solubility in water, regular size, determinate molecular weight and presence of internal cavities to trap drug for drug delivery. Dendrimers are globular or ellipsoidal in shape generally. They are composed of three components namely, central core, branches and functional groups present on the surface from which two functional groups which are reactive are present in the central core. The branches comprise radically concentric layers. These concentric layers are known as ‘generations’. The functional groups present on the surface are useful for determination of physical properties [86].

The corneal epithelium of eyes are quasi impermeable. Hence, for increased bioavailability and efficacy, long residence time is required. The corneal epithelium is liable to be harmed by bacteria, virus and fungus. It is also vulnerable to mechanical injuries. To treat certain disorders like glaucoma or diabetic retinopathy, lachrymal drainage in the eye faces difficulty in order to get better therapeutic drug concentration. Henceforth, it is much needed to improve the bioavailability [87]. This can be achieved by using water soluble polymers as it increases the viscosity and thereby aids in bioadhesion of the drug which is instilled.

Initially, the results of the studies which were carried out were much appreciable for lipophilic drugs than hydrophilic drugs. In such cases, to overcome the issues, dendrimers are acknowledged [88].

One of the most commonly used polymers in the preparation of dendrimers is poly(amidoamine) (PAMAM). The PAMAM dendrimers can be elucidated as polymers which can be either liquid or semi-solid and consists of number of groups such as carboxylic, amine and hydroxyl groups. The PAMAM dendrimers have characteristics of solubilizing even poor water-soluble drugs in their zones which contain cascade tiers in the inner zone and terminal moieties on surface region [89,90] PAMAM dendrimers have showed their potential in ocular drug delivery many times [91].

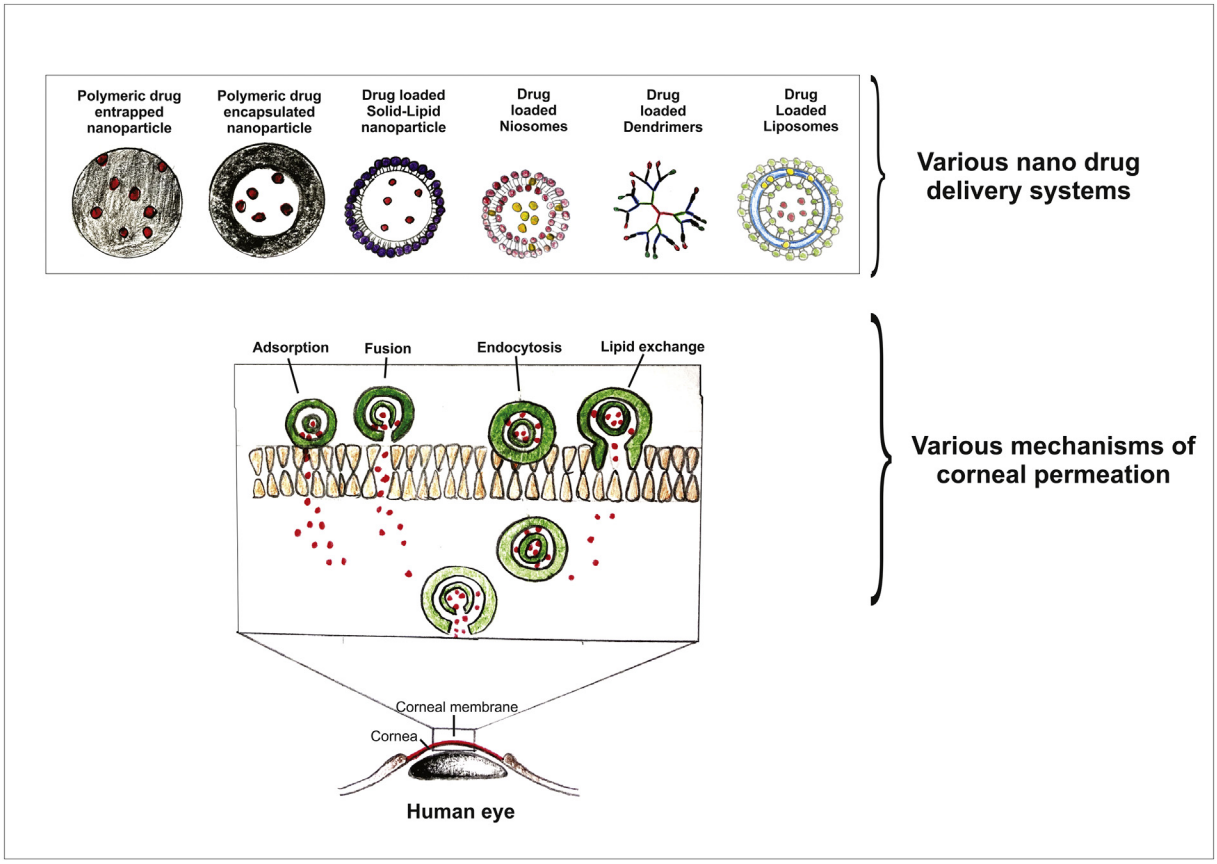

Fig. 12. Mechanism of various nano-drug delivery systems for corneal permeation.

Recently Lancina et al., investigated brimonidine tartrate loaded PAMAM Dendrimers for the ocular therapy of glaucoma. The prepared brimonidine tartrate loaded dedrimers were incorporated to nanofibers using electrospinning to form nanomat. The drug-dendrimer loaded nanomat was studied in vivo in normal tension rabbits and compared with the normal eye drop and it was reported that drug-dendrimer loaded nanomat was non-irritant and tolerated well by animals. The study data also suggested that dendrimer loaded nanofibres were able to lower IOP for a day in just one single dose [92].

3.6. Nanoparticles

Nanoparticles have the ability to increase the permeation of drugs across the ocular barrier in the eye [93,94]. Nanoparticles can deliver drug to both the anterior and posterior chamber of the eye through drug transport mechanism surpassing the blood-aqueous barrier and blood-retina barrier. For the management of ocular disease such as glaucoma the drug retention and penetration of the drug into eye is a major area of concern. Drugs in nanoparticles can either be entrapped (nanospheres) or encapsulated (nanocapsules). Nanoparticles can be made up by various types of polymers, lipids, etc. [95]. Fig. 12 shows mechanism of various nano-drug delivery systems for corneal permeation.

3.6.1. Chitosan based NPs

Polymeric nanoparticles have attracted the interest of many researchers by increasing the retention time of the drug precorneally. Chitosan (CS) is one of the natural polysaccharide and is composed of the 2-amino-2-doexy-beta-D-glucan with some glycosidic linkages [96]. CS is more suitable for the drug delivery as it is nontoxic, biodegradable and biocompatible with good mucoadhesive properties. The potential of CS is resisted by only its limited solubility in water and they are soluble only in acidic solutions [97]. Betaxolol hydrochloride (BH) is a selective beta-adrenergic blocking agent used for lowering IOP. However, BH like other ophthalmic solution is drained out of the eye rapidly. To overcome this problem Li J and group have recently developed a BH loaded chitosan/montmorillonite (CS/MT) nanoparticles [98]. Pharmacokinetics data of BH-CS/MT nanoparticles showed that AUC0-t (Area under curve) and MRT0-t (Mean residence time) was 1.99 and 1.75 times higher than that of the convention BH solution. The research paper data displayed that CS/MT played a major role in increasing the absorption of drug in eye thus increasing the bioavailability of drug i.e. BH. Chitosan polymer is used by many scientist and researchers for developing nanoparticle. As previously discussed the solubility of chitosan in aqueous solution is limited and they are soluble in only acidic solutions which eventually limits is ocular application and cause severe irritation to eye. Zhao and group for the first time used a derivative of chitosan, Galactosylated chitosan (GC) to develop nanoparticle of timolol maleate for ophthalmic delivery [99]. This GC is water soluble at neutral pH, have better mucoadhesion and good cell compatibility compared to that of CS. The study found that nanoparticle of GC was more lipid soluble than normal chitosan loaded nanoparticles with better transcorneal penetration. The in-vivo pharmacodynamics data suggested that timolol maleate loaded GC nanoparticles provided sustained release of timolol maleate compared to that on marketed timolol maleate eye drop.

3.6.2. PLGA based NPs

Poor encapsulation capacity of hydrophilic drugs in nanoparticles made of polymers is still a major disadvantage or challenge faced by formulation scientists. Warsi et al. formulated PLGA nanoparticles of Dorzolamide using emulsifying agents (PVA and Vitamin E TPGS) for increasing the encapsulation efficiency of drug in polymeric nanoparticles [100]. The study found that emulsifiers used for preparing nanoparticles have increased the encapsulation efficiency of drug and

also increased the transcorneal permeation up to 2.5 times than that of a conventional drug solution. The PLGA coated both type of nanoparticles have shown better adherence and reduced IOP in just a single instillation. Topical instillation of drug in eye is the most common and easy method to deliver anti-glaucomic drugs but it also comes with disadvantages such poor patient compliance due to repetitive dosing. So to target high concentration of the drug in eye with an aim to prolong the retention of time of nanoparticles and they can be given through subconjunctival route. Salama et al., formulated subconjunctival injection of Brinzolamide loaded nanoparticle of PLGA using various types of surfactants [101]. The polymeric nanoparticles made of PLGA showed release of drug up to 10 days in one single injection. The in-vivo study on rabbits showed that the nanoparticles of PLGA were a convenient nanocarrier system for the subconjunctival injection of brimonidine tartrate.

Poor aqueous solubility of the drugs leads to poor bioavailability of drugs in eye. Forskolin, an ocular hypotensive agent is a lipophilic drug and have poor solubility. Encapsulation of these lipophilic drugs could help in overcoming this problem. N Khan and group in 2018 prepared CS coated PLGA nanoparticle of Forskolin [102]. The use of both the PLGA (synthetic) and chitosan (natural) polymers helped in achieving better permeation and mucoadhesiveness on the surface of cornea and sclera. The drug release data showed that the release of Forskolin nanoparticles was slow with 90% of release in 72 h compared to conventional drug suspension was 96.6% in 12 h both the polymers helped nanoparticle in sustaining the release of the drug and decreasing the IOP for a longer period of time.

3.6.3. Gelatin based nanoparticles

Polymer like gelatin is gaining appreciation in ocular drug delivery and because of its biocompatibility and safety profile. Gelatin is economical and easily available from plenty of resources naturally. It has been reported that timolol maleate loaded gelatin nanoparticles show better mucoadhesion and permeability because of its positive charge physiological properties which is attracted to negatively charged lipid layers in corneal endothelium [103]. The in vivo data of nanoparticle of timolol maleate loaded gelatin have showed sustained release of the drug which eventually leads to decrease in IOP for a longer duration of time compared to marketed eye drop of timolol maleate. Recently Liao and group prepared mesoporous silica nanoparticles to attend sustained release of pilocarpine with coating of gelatin [104]. Mesopouros silica is a mesoporous (a material having pores size from 2 to 50 nm) of silica is a recent advancement in the field of nanotechnology. The intracameral administration of pilocarpine loaded gelatin coated mesoporous silica nanoparticles (P-G/MS) showed high release profile lasting till 36 days in vitro. The in vivo data in male albino rabbits showed that the P-G/MS was able to reduce the IOP for about 21 days.

3.7. Solid lipid nanoparticles

To successfully deliver the drug through nanoparticles depends on the type of polymer used to formulate nanoparticles. The polymers used are often costly and the availability of safe polymers is less which is an issue that cannot be ignored while scaling up of nanoparticles. To solve these limitations of polymeric nanoparticles lipids are an alternate that can be used to formulate the nanoparticles. Lipids are easily available from natural sources and nanoparticles formulated using lipids is known as solid lipid nanoparticles (SLNs). Rui et al. worked on solid lipid nanoparticles of methazolamide, a carbonic anhydrase inhibitor. The Draize test study found that the SLN of methazolamide was non-irritant due to use of the phospholipid carrier. The final data also stated that the SLN of drugs were able to reduce IOP for long period of time compared to marketed formulation thus providing sustained release of drug [105]. The negative charge on the SLNs is a major problem which hinders the penetration and absorption of the drug on cornea surface. So to overcome this problems the latest approach was to coat the SLNs with cationic polymers to increase the corneal absorption of drug in to eye. Wang and group have developed a chitosan (cationic/water soluble/low molecular weight) loaded SLNs of methazolamide to increase the corneal adherence. The prepared chitosan coated SLNs of methazolamide were compared with uncoated SLNs and marketed eye drop of drug. The in vivo data indicated that chitosan loaded SLNs were much better and prolonged compared to both uncoated SLNs and marketed formulation. The coated SLNs did not show any irritation in eye while performing the Draize test for ocular irritancy.

The other approach for increasing the ocular penetration and absorption of drug through SLNs is the use of cationic lipids for formulating SLNs. Leonardi et al., have prepared cationic SLNs of melatonin to enhance its hypotensive effect to treat glaucoma [106]. The formulation was prepared using cationic lipid so that it will increase the electrostatic interaction of cationic SLNs to negatively charged mucin on the epithelial portion of eye. This positive-negative charged interaction increased SLNs mucoadhessivness that lead to enhance in penetration and absorption of drug. In vivo data showed decrease in IOP in albino rabbits for more than 24 h. The study data suggested SLNs as one of the best novel carriers for drug delivery of anti-glaucomic drugs.

3.8. Microneedles

Microneedles are solid and hollow needles of micron measurements that were first developed for the transdermal delivery of drug. Recently, microneedles are also suggested for transscleral drug delivery to eye. Microneedles can be used for the targeted delivery of the drug in to ocular tissues with very minimum invasion into eye. The microneedles are able to inject free drug as well as encapsulated nanosized particles too. The hollow type of microneedles are often used for the delivery of various types of vaccines and used in transdermal delivery. The solid type of microneedles (Fig. 13) have been utilized either to frame smaller scale gaps in the skin to enhance porousness or to deliver drugs that are coated onto the needles [107].

Jiang and group of researchers have prepared microneedles for the ocular delivery and tested the hypothesis that hollow type of microneedles are able to infuse various types of solutions into eye including nanoparticles and microparticles. Hence, they prepared hollow microneedles and from the evaluation it was observed that the individual needle could deliver 10–35 μl of liquid into the sclera, thus forming an intrascleral drug terminal [108]. This type of microneedles can be loaded with antiglaucomic drugs to treat glaucoma.

Jiang and Gill have investigated the potential of pilocarpine coated microneedles and their applications. Both in-vito and in-vivo evaluation of coated solid microneedles was done on dead human eye. The evaluation study of microneedles showed brilliant penetration into sclera and rapid dissolution of coated drug sample in to eye after insertion. They compared the conventional eye drop and analysed that microneedles were able to deliver more amount of drug in the eye compared to conventional eye drop [109].

3.9. Ocular inserts

Ocular inserts are the solid and semisolid polymeric mass that is placed under the conjunctival portion of the eye i.e. between the lower eyelid and surface of eye (Fig. 14). The conventional eye drops have low corneal contact time and poor bioavailability due to the rapid elimination of the drug because of the washout or drainage and lachrymation. Ocular inserts are used to overcome the problems related to the conventional eye drops. It will provide drug through eye for a long period of time and decrease the number of doses. It will increase the precorneal contact time to give better absorption of the drug [110].

They are sterile solid devices made either of thin discs or cylinders of variable size and shape composed of polymer which may contain drug or may be devoid of it. The drug can be later included into the polymeric material as a solution or dispersion. Inserts are intended to

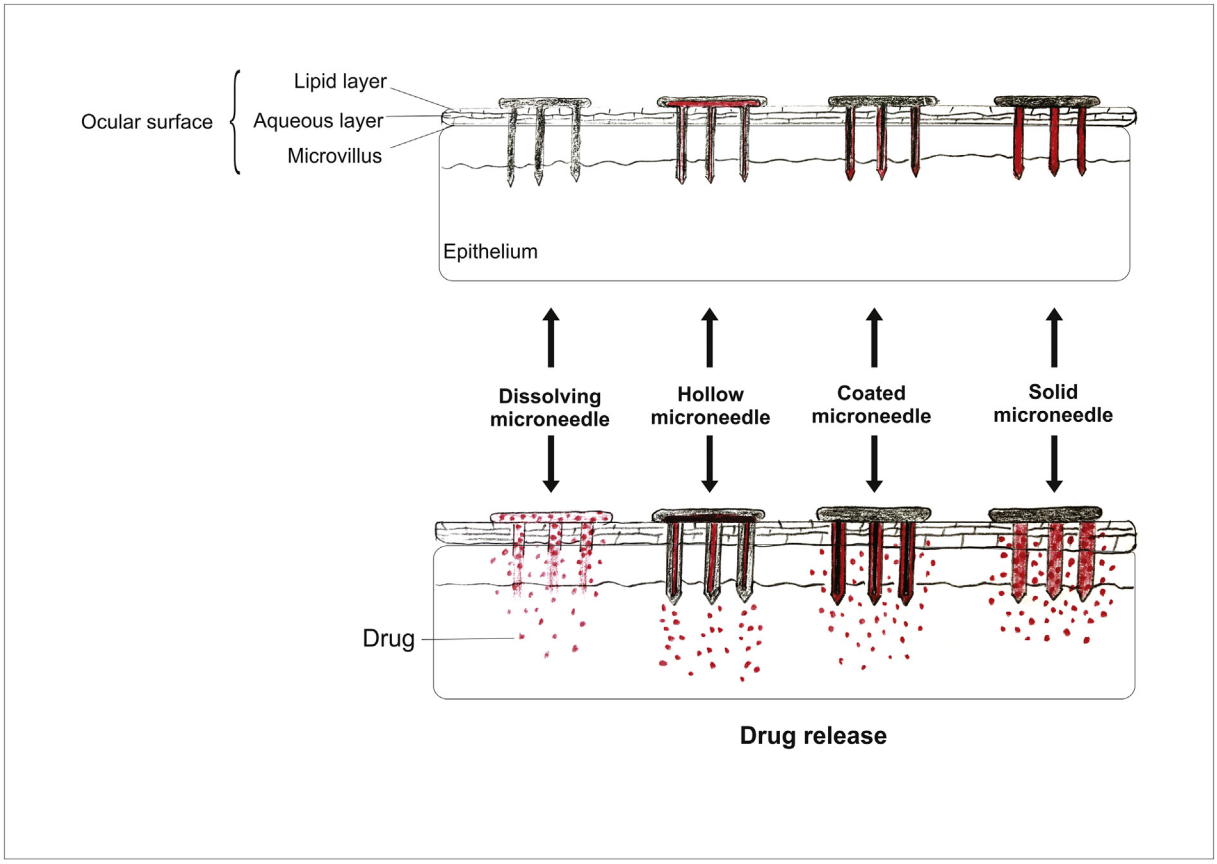

Fig. 13. Microneedles.

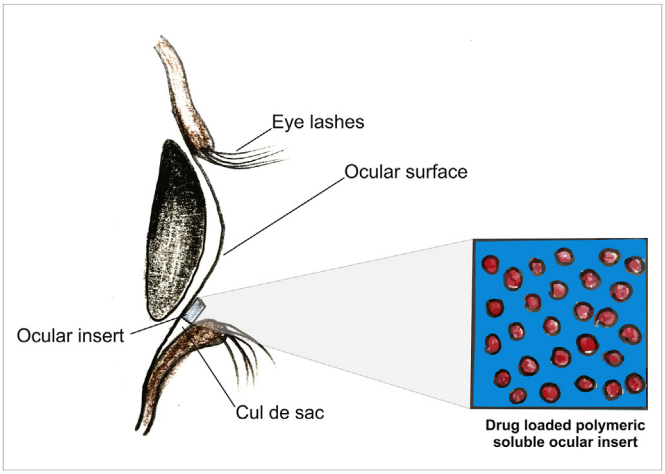

Fig. 14. Ocular insert.

deliver drugs in anterior region of the eye particularly, upper and lower conjunctiva [111].

Based on the physicochemical property of solubility, the inserts are classified as insoluble, soluble and bioerodible. The insoluble ocular inserts can further be divided into groups such as diffusion system, osmosis system and contact lenses. Soluble inserts are classified based on the type of polymer. Bioerodible inserts can be categorized as insoluble ocular inserts or soluble ocular inserts [112,113].

De Souza et al. recently have developed a mucoadhesive insert of chitosan polymer for the sustained release treatment of glaucoma by incorporating Brimonidine tartrate. The chitosan polymer was able to adhere on to the conjunctival area and it was mucoadhesive in nature. The cell study showed that insert had no burst release of the drug and was biocompatible in nature. Inserts showed remarkable in-vivo results in lowering IOP by providing sustained release of drug up to 30 days [114].

Franca et al. have prepared bimatoprost loaded chitosan polymer ocular insert for sustained delivery to treat glaucoma. The ocular insert was then evaluated and it was found that positively charged chitosan was mucoadhesive at negatively charged corneal surface of the eye thus increasing the corneal retention. The in-vivo studies demonstrated sustained release of drug up to 15 days [115].

A randomized phase II clinical trial for 6 month was done on selected glaucomic patients. The selected patients was given a bimatoprost loaded ocular insert and eye drop of timolol maleate twice daily. From the above study it was concluded that ocular insert of bimatoprost was safe and well tolerated [116].

3.10. Summary of advanced drug delivery systems

Having discussed the different novel drug delivery systems used in advanced treatment of glaucoma it is important to summarize them to have a clearer demonstration. The most common features or advantages linked to all delivery systems listed above include the ability to sustain the release of the entrapped anti-glaucomic drug from hours (more than 24 h) to days (7 days) by use of a single dose/application. To understand the distinctive feature of each delivery system Table 1 provides a summary of individual advanced delivery system in glaucoma.

4. Conclusion

Glaucoma is a disease in which there is an increase in the intra oc7ular pressure (IOP) in the eye leading to irreversible damage of the ocular nerves. If left untreated glaucoma may be responsible for the

Table 1
Summary of Distinctive features of the advanced drug delivery systems used in glaucoma.

Sr. no.	NDDS	Drugs used	Routes	Distinctive features[a] Outcome of the delivery system	Reference
1.	In-situ gel	Brimonidine tartrate	Topical eye drop	The in-situ gel system shows more adherence to the surface of the eye because of their mucus and bio adhesiveness. It is also able to sustain the release of the drug up to 24 h.	[54]
2.	Liposomes	Latanoprost	Subconjunctivial injection	The liposomal formulation is able to encapsulate both hydrophobic and hydrophilic drugs in their lipid bilayer and polar space respectively. They are able to sustain the release of the drug up to 90 days in one single liposomal dose.	[72]
3.	Niosomes	Dorzolamide HCl	Topical eye drops	The Niosomal formulation shows many advantages over liposomes like more stable, inexpensive, better entrapment efficiency compared to liposomes. Niosomes have better corneal penetration of drugs with release of the drug up to 24 h in single dose.	[79]
4.	Hydrogels	Timolol maleate	Topical eye drop	Hydrogels provide increased adherence and retention of the formulation on the surface of eye thus increasing the absorption leading to more bioavailability of the drug.	[84]
5.	Dendrimers	Brimonidine tartrate	Nano-mat	Dendrimers are easy to be functionalized and can be controlled in term of size and molecular weight. They can be encapsulated and delivered through other deliveries such as nano-mats, in-situ gel, hydrogel or ocular insert.	[92]
6.	Nanoparticles	Timolol maleate	Topical eye drop	Nanoparticles shows high encapsulation, high ocular permeation, prevent ocular toxicity of drugs, good stability and biocompatibility compared to that of other ocular deliveries. They can be delivered through various routes such as topical, transcorneal or subconjunctival routes.	[99]
7.	Microneedles	Pilocarpine	Microneedle patch	The delivery system itself penetrates through the ocular surface and releases the drug to obtain the highest of absorption. They do not need any surgery or major incision to place the microneedle patch.	[109]
8.	Ocular inserts	Bimatoprost	Soluble ocular dissolving insert	Ocular inserts are the most convenient of delivery systems they are simply placed in the cul-de-sac portion of the eye.	[115]

[a] Common Features (Advantages) linked to all delivery systems listed above include the ability to sustain the release of the entrapped anti-glaucomic drug from hours (more than 24 h) to days (7 days) by use of a single dose.

permanent loss of vision. The currently used drugs are available in the form of eye drops which have major drawbacks of repetitive dosing and lower precorneal retention time. The present review has presented the pharmacological aspects of different conventional drugs used to treat glaucoma and how these drugs can have improved efficacy by formulating as different advanced drug delivery systems. Over the years various attempts have been made to achieve the sustained or the controlled release of the drug to eye. These advanced drug delivery systems have potential to improve patient compliance, increase efficacy and effectiveness of drug, decrease side effects and at last preserving the vision of glaucomic patients.

Conflict of interest form

The authors declare no conflict of interest.

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