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Review article

Applications of microneedles in delivering drugs for various ocular diseases

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ABSTRACT

Treatment of majority of eye diseases involve the use of eye drops or eye ointments, which have major drawbacks of needing frequent administration, lower bioavailability and inability to cross the various eye barriers. This necessitates the use of novel delivery systems. Microneedles (MNs) as an alternate novel delivery system facilitate drug delivery to various ocular diseases with promising approaches in healthcare. Advances in pharmaceutical technology have made MNs provide localized, effective, less invasive and targeted drug delivery in the eye. The purpose of this review is to provide an insight to efficacious therapeutic applications the MNs can bring in various ocular diseases. Out of which, glaucoma, age-related macular degeneration, uveitis, retinal vascular occlusion and retinitis pigmentosa are majorly discussed. Among the various types of MNs; solid coated, hollow and dissolving polymeric MNs are specifically focused for their applications in ocular diseases. In addition, MNs shows improvement in the visual acuity and decreases the progression of the different ocular diseases.

1. Introduction

Formulation development of novel drug delivery systems in the area of eye are one of the most challenging because eye as an organ is most sensitive to work on. Human eye has a spherical shape with diameter of 23–24 mm and is divided into two major segments that is anterior and posterior segment [1]. The anterior part of the human eye has cornea, iris, aqueous humor, ciliary body, conjunctiva; while the sclera, retina, choroid, optic nerve forms the posterior part of the eye [2]. Anterior segment diseases include glaucoma, cataract, conjunctivitis, anterior uveitis while posterior segment diseases include age related macular dysfunction (AMD), retinitis pigmentosa (RP), diabetic retinopathy. In most of these disease there is a chance of partial vision loss or complete blindness. Presently the different approaches to treat ocular diseases include topical eye drops, oral therapy by tablets, intrascleral and intravitreal injection [3]. Topical and systemic route of administering drugs result in low therapeutic drug levels due to multiple ocular barriers, requiring administration of unnecessarily high concentrations of which leads to toxicity [4]. It was estimated that around 285 million people are suffering from vision problem, in which the population of totally blind affected individuals are around 39 million and approximately 246 million population have low vision [1]. The conventional drug delivery for eye suffers from drawbacks of needing repeated drug administration which leads to patient non-compliance. These issues arise the need to have novel drug delivery systems to provide not only the sustained drug action but also targeted delivery to overcome the drawbacks of the conventional therapy [4].

Among the various novel drug delivery systems, injectable formulations have the most impactful application as they can deliver the right amount of drug in the desired area of the eye. Conventional hypodermic needles are used for giving therapy through intraocular injections. There are various routes through which these intraocular injections are given namely, subconjuctivial, periocular, intravitreal (IVT), intracorneal etc. Considering this, some of the disadvantages associated with intraocular injections are invasive nature, frequent application of injections leads to non-compliance and also less bioavailability [4–6].

Microneedles (MNs) are devices made up of polymer or metal having dimensions in the range of few micrometres to 200 μm. MNs have micro sized projections which makes them minimal invasive in nature. These MNs are able to not only overcome the disadvantages associated with the presently used conventional delivery systems but also are able to cross the ocular barriers to specifically target the drugs at the needed site of action. MNs as a technique is efficient enough for expediting percutaneous drug delivery. Other than the promising role MNs have shown in eye treatment they are also useful in percutaneous delivery across the oral mucosal, GIT and even nail. These micron sized needle have easy insertion on to the eye for various types of applications. As compared to the traditional hypodermic needles these are less painful and may be formulated to release the drug over a period of

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Table 1
Different anterior segment barriers.

Anterior segment barriers		
1	Pre-corneal lacrimal fluid	The clearance and turnover rate of lacrimal fluid through nasolacrimal duct is around 1 µL/min [8]. Cornea, lacrimal fluid, aqueous humor and tear contain some amount of proteins and peptides. These proteins and peptides bind with the drug molecules and interfere with their release and permeation [9].
2	Cornea	The main function of cornea is to protect the ocular tissue and limit the entry of outside molecules [10]. Cornea is composed of five distinct layers which plays important role in the transport of molecule from anterior to posterior segment. These are epithelium, bowman's layer, Descemet's membrane, stroma and endothelium. Importantly lipophilic molecule easily crosses the barrier due to barrier lipoidal nature but hydrophilic and macromolecule are not able to cross [11,12].
3	Conjunctival membrane	Here, the presence of various blood capillaries results in loss of drug which leads to less ocular bioavailability. The drug lost enters into the systemic circulation causing systemic side effects [13].

extended time. Hence, would not be required to be administered repeatedly [7].

This review article reflects the therapeutic applications of MNs in several ocular diseases. There are various obstacles associated with the conventional ocular delivery system, the article provides an insight of how MNs overcome these obstacles and provide effective drug delivery. Among various types of ocular diseases some of them are glaucoma, age-related macular degeneration, uveitis, retinal vascular occlusion and retinitis pigmentosa are majorly discussed. The article gives brief explanation of various studies conducting on the use MNs in these ocular diseases, which is directed to give advantage to the researcher to work on in this area.

2. Different barriers associated with anterior and posterior segments of the eye

Barriers associated with ocular drug delivery which hamper the delivery of the correct amount of drug reaching the desired point of contact. These barriers are divided into anterior and posterior barriers and are elaborated in Table 1 and Table 2 respectively.

The barriers mentioned in Tables 1 and 2 reflect upon the need to develop an alternate delivery system for the eye which would allow the delivery of the drugs.

3. Different types of MNs

There are different types of MNs with varied therapeutic applications. However, the three types: solid coated, hollow and dissolving polymeric MNs have tremendous role in ocular drug delivery. Fig. 1 gives in detail the different anatomical features of the eye with placement of these three types of MNs. These three types are discussed in detail in further sections.

3.1. Solid coated microneedles

Solid coated MNs are the type of MNs which are designed to simply poke the tissue and the coating will immediately dissolve. After which they can be removed. The poking will create a micron sized channel which would allow effective or targeted delivery of the medication [7]. Solid MNs main function is to create pores within sclera or cornea of the eye. Material used for the fabrication of MNs includes metals like stainless steel, silicon probes. Using of these materials for ocular delivery has disadvantages of being non-biodegradable and difficulty in fabrication process [21]. In solid coated MNs, coating formulation are applied onto the surface of MNs so when it is poked in the ocular tissue, dissolution of coating formulation will take place and medicament will release as shown in Fig. 2 [22].

3.2. Hollow microneedles

Hollow MNs are micron dimension needles having formulation present inside the needles only. For the effective delivery of medication inside the ocular tissue. Different formulations like nanoparticles and micro particles are used to deliver the drug through hollow MNs. Apart from the delivery into the eye hollow MNs are also used to deliver the drugs to the skin like for insulin and for vaccine drug delivery [23]. Hollow MN's are manufactured from borosilicate micropipette tube, biodegradable polymers or in some cases stainless steel can also be used. Besides these materials, borosilicate micropipette tube is not considered as an ideal material for clinical application. The fabrication process includes micropipette puller technique wherein the material is pulled up using a machine to create hollow space as well as help to lengthen the needles. The strategy involve in delivery of medication is to prick the ocular tissue, medication will release from the hollow space of MNs and the patch will remove out as shown in Fig. 3 [24].

It provides targeted drug delivery in glaucoma treatment i.e. supracilliary delivery which require volume around 35 µL confirmed from various studies. The medication release from the hollow MNs follow diffusion release mechanism which allow the faster delivery of drug at a particular site within the eye [25].

3.3. Dissolving polymeric microneedles

To overcome the various disadvantages associated with hollow and solid coated MNs like fabrication, applicability, difficulty in infusion, accuracy etc. dissolving polymeric MNs come up as a strategy which shows their feasibility with the ocular tissue as compared to hollow and solid coated MNs [26]. They are fabricated with different types of polymers which are biodegradable, biocompatible, easy to insert within the ocular tissue The strategy associated with dissolving polymeric MNs

Table 2
Different posterior segment barriers.

Posterior segment barriers		
1	Sclera	Sclera, the white portion of the eye, has considerable aqueous content which allows hydrophilic molecule to diffuse into the tissue more readily that hydrophobic ones [14,15].
2	Choroid	The main function of choroid is to provide nutrition, oxygen to the retina and also it is highly vascularized part [16,17]. Delivery of drug to the retina decreases because of changes occur in choroidal thickness with age [18,19].
3	Blood- Retinal Barrier	Most important ocular barrier is blood- retinal barrier composed of retinal pigment epithelium and retinal capillaries of endothelial cells. Because of presence of various matrix proteins, entry of unwanted molecule is restricted [20].
4	Retina	As there are no barriers associated with retina but the inner membrane of retina consist of 10 different matrix proteins which restrict the entry of drug molecules [18].

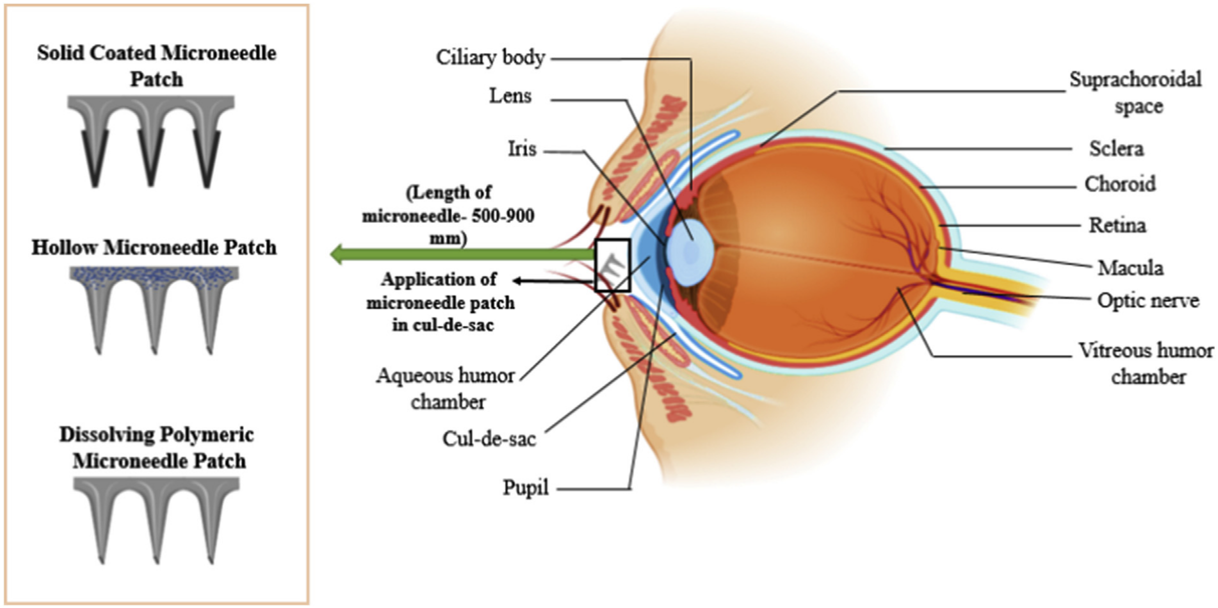

Fig 1. Human eye: Anatomical features with placement of three types of microneedles. The image depicts application of three types of microneedles (MNs) patch namely, solid coated MN patch, hollow MN patch and dissolving polymeric MN patch. These patches are applied in cul-de-sac region of the eye for effective delivery of medication.

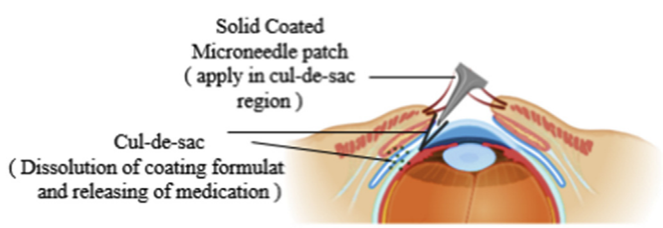

Fig 2. Mechanism of drug release from solid coated microneedles. The image depicts the mechanism of solid coated microneedles, which are applied in the cul-de-sac region of the eye and producing desirable action.

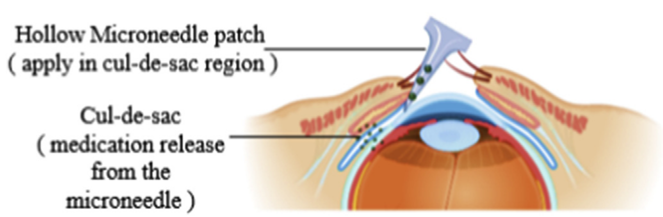

Fig 3. Mechanism of drug release from hollow microneedles. The image depicts the mechanism of hollow microneedles, which are applied in the cul-de-sac region of the eye and producing desirable action.

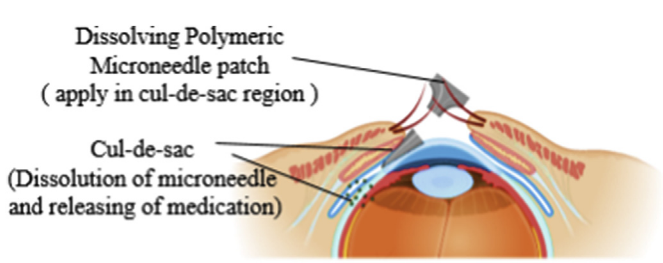

Fig 4. Mechanism of drug release from dissolving polymeric microneedles. The image depicts the mechanism of dissolving polymeric microneedles, which are applied in the cul-de-sac region of the eye and producing desirable action.

includes, firstly the Microneedle (MN) patch is applied to the ocular tissue and secondly the drug which already incorporated within the polymeric needle patch, will release inside the eye tissue [27] as shown in Fig. 4.

The fabrication process of dissolving polymeric MNs involve steps like-firstly, to prepare mold which is mostly made up from polydimethyl siloxane considered as biodegradable in nature [28]. Second step includes penetrating the mold with micron sized needle then afterwards drying of mold should be takes place and finally polymer drug formulation is introduced in the array of mold to get micron sized polymeric needles [29].

4. Application of microneedles in various ocular diseases

4.1. Glaucoma

Glaucoma is the leading cause of irreversible blindness, and it is estimated that it affects 70 million of population worldwide. It is a dysfunction of one or more peripheral nerves of the eye. Glaucoma is characterized by genetic as well as biological risk factors. It is a multifactorial disease which is characterized as degeneration of optic nerve and characteristic appearance of optic nerve called as cupping, death of retinal ganglionic cells, and ultimately visual field loss [30].

The major factor which is associated with glaucoma is increases in intraocular pressure (IOP). IOP is defined as balance between formation of aqueous humor by ciliary network and its removal through the internal outflow system [31,32]. Intra ocular pressure on the eye cause stress on the lamina cribrosa, which is a mesh like structure having nerve fibres and later on forming the optic nerve. Presence of stress on lamina cause disarrangement, distortion of lamina and result in damage of retinal ganglionic cells [33]. Secondary causes associate with glaucoma includes oxidative stress, impaired immunity, etc [34]. There are two internal outflow system trabecular meshwork system and uveal meshwork system. Trabecular meshwork system consists of connective tissues; it makes a bridge over scleral sulcus which is groove between sclera and cornea. Trabecular pathway is the primary pathway for the outflow of aqueous humor through the canal called as schlemm's canal. The pathway is called as conventional pathway where, aqueous humor drains into episcleral vein and aqueous vein [35]. While the other

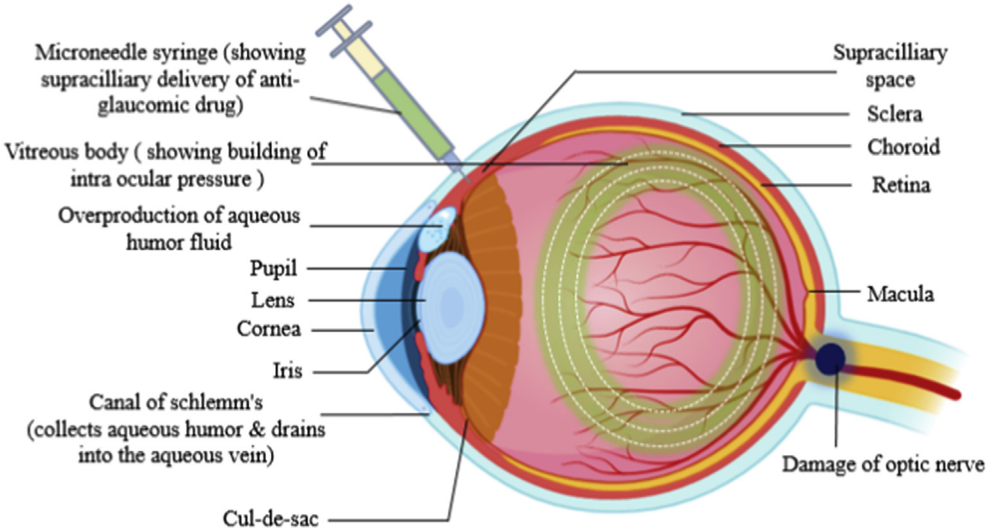

Fig 5. Human Glaucomic Eye. The image illustrates human glaucomic eye that depicts development of intraocular pressure and also leads to damage of the optic nerve. Image also shows delivery of medication in glaucomic eye through syringe onto which hollow MN is attached and it is given in the supracilliary space for effective and targeted delivery.

pathway is named as unconventional pathway or uveal meshwork system, here aqueous humor out through the sclera and drains into episcleral vein and aqueous vein [36,37]. There are various diagnostic features associated with the glaucoma as depicted in Fig. 5.

There are two main types of glaucoma, primary open angle glaucoma and closed angle glaucoma. In primary-open angle glaucoma, conditions arise like increase resistance in aqueous humor outflow and obstruction in trabecular meshwork pathway [38]. While in closed angle glaucoma obstruction in aqueous flow occur due to iris and this lead to increase in intraocular pressure and damage of optic nerve [39]. The treatment for glaucoma includes use of topical agents, different class of drugs are used in glaucoma like beta blocker, alpha adrenergic agonist, carbonic anhydrase, prostaglandin analogues, cholinergics, etc. while in severe cases surgeries are performed like trabeculectomy in case of open angle glaucoma and iridotomy in case of closed angle glaucoma [40]. Emerging therapy also takeover these conventional therapies for glaucoma which include use of MNs and specifically given into the supracilliary area for effective delivery of drug and some medications and routes for glaucoma are still in research process.

Jiang et al., demonstrated the use of coated stainless steel MNs for the drug delivery in the anterior part of the eye for the treatment of glaucoma. They use pilocarpine which is given through intrascleral route and increase the absorption rate of drug around 45 fold [7]. It was also demonstrated that there was an increase in the delivery of fluorescein by 60-fold when it was compared with topical delivery. The size of MNs was 500–750 µm in length. They also illustrated the use hollow MNs for delivery of sulforhodamine through intrascleral route. The fabrication of hollow MNs was done using borosilicate micropipette tube which allow delivery of drug at a particular concentration i.e. 10–35 µL from each MN present in the array [7,41,42].

Patel et al. studied the use of hollow MNs for the delivery of drug into the suprachoroidal space. In this study, they demonstrate the slow delivery of drug incorporated in nanoparticle and micro particle formulation into the posterior segment of the eye [43].

4.2. Age related macular degeneration (AMD)

AMD is a condition occur in elder people which is characterized by loss of vision due to degradation or degeneration of macula portion of retina, which functions as for central vision [44]. So as macula is affected, the outer layer of retina, retinal pigment epithelium membrane is also degraded [45]. It causes loss of cones and rods photoreceptor cells which ultimately die afterwards and leads to severe symptoms such as vision loss completely [46]. It is acquired condition which affects millions of people around the world [47]. There are several risk factors linked with AMD like family history, age, sun exposure, ocular factors, oxidative stress and smoking [48]. Classification of AMD includes-dry AMD and wet AMD. Dry AMD is defined as formation and deposition of drusen i.e. accumulation of white coloured material near retinal pigment epithelium. while wet AMD is new vessels establishment which is weak and leaky in nature. Wet AMD is considered more severe form of AMD are described in Fig. 6 [49,50]. Pathogenesis of AMD can be categorized into three different categories depicted in Table 3.

Treatment for AMD includes, anti-VEGF (Vascular Endothelial Growth Factor) VEGF is a type of glycoprotein and take part in the formation and maturation of new blood vessels and maintain the vascular permeability by binding with its receptor which is present on endothelial cells [55]. Overexpression of VEGF in case of AMD patients causes formation of new leaky blood vessels which on further progression cause haemorrhage [58]. To prevent the formation of new blood vessels anti-VEGF therapy Pegaptanib, Ranibizumab, Bevacizumab is given as an intravitreal injection [59–61].

Photodynamic treatment (PDT) which includes using of photosensitizing drug, verteporfin (Visudyne) which is given by intravenous route for 10 min along with shining of cold laser at 689 nm wavelength for 15 min into the eye that will function as to excite or activate the drug [50,53]. The activated drug damage the endothelial cells, or it directly damage the abnormal blood vessels in CNV. Latest literature suggests that, PDT in some cases increase the expression of VEGF that will create dreadful condition and allow to use anti-VEGF therapy along with PDT [62]. Another treatment described as laser photocoagulation wherein, argon and krypton laser is used. Laser produces the rays having enough energy to cause thermal reaction and because of thermal reaction abnormal blood vessels coagulate and blocked [63].

In this section three current studies related to use of MNs in the treatment of AMD are described in detail to understand the role of MNs in AMD.

Kadonosono et al. studied the use of tissue plasminogen activator (tPA) and air using MN to treat sub-macular haemorrhage which occur in case of secondary age-related macular degeneration. Sub-macular haemorrhage is a condition in which blood is being present between the retinal pigment epithelium and retina. Presence of blood arise due to choroidal neovascularization or wet AMD [64,65]. The tPA is used to dissolve the clot and air is used to displace the clot. In this study, first they performed vitrectomy which is the removal of vitreous humor from the eye. Afterwards MN was connected with syringe and the whole instrument was installed in vitrectomy machine [65,66]. The tPA was given at a pressure of 15 mmHg while the air was given with the same MN at a pressure of 4 to 6 mmHg. The result of the study has shown that

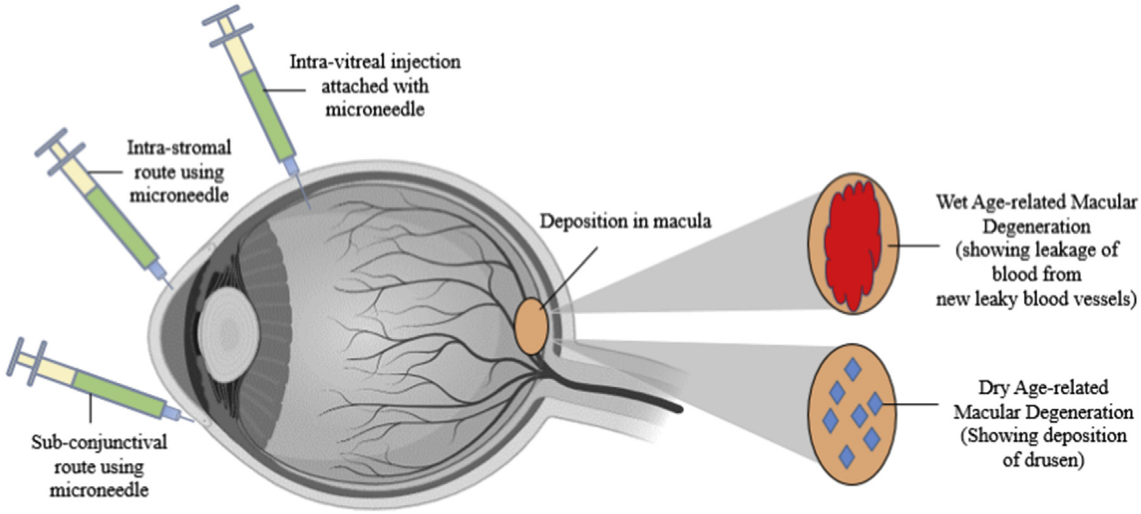

Fig 6. Different routes of medication through microneedle in Age-related Macular Degeneration (AMD). The image showing AMD disease in the eye wherein drusen deposition occur in dry AMD and in wet AMD leaky new blood vessels are formed. It shows various routes through which injection (attached with microneedle) is given like sub-conjunctival, intrastromal and intravitreal route.

Table 3
Pathogenesis of AMD.

Drusen genesis/non-exudative form/non-neovascular form	Lipofuscin genesis	Angiogenesis/exudative form/neovascular form
(A) Deposition of small yellow coloured fatty substances called drusen, which collect between Retinal Pigment Epithelium (RPE) and Bruch's membrane in retina of an eye [51]. (B) Drusen contain substances which lead to inflammation further like lipoproteins, lipids, amyloid beta or (Aβ) and complement factors (mainly cause inflammation) [52]. Drusen can be categorized as hard and soft drusen. Soft is considered as more severe form as compared to hard which on progression of disease leads to advanced or exudative form of AMD [53].	(A) Lipofuscin genesis is the main characteristic feature of stargardt disease. The disease is described as mutation in *ABCA4* gene (ATP Binding cassette subfamily A and member 4). Because of mutation, it causes deposition of lipid materials which is termed as lipofuscin genesis. This process is also observed in retinal degenerative disease like AMD [54].	(A) Neovascular form of AMD is define as emergence of new blood vessels from existing one. (B) These new blood vessels are fragile or leaky in nature which makes it different from normal blood vessels [55]. (C) If leakage occur on further progression of disease leads to haemorrhage between RPE membrane and the choroid [56]. (D) Several factors associated with this specifically VEGF (vascular endothelial growth factor) which function as to activate the G_0 stage of cell and cause multiplication of cells or growth of cells, relocation of cells cause neovascularization [57].

Table 4
Two types of retinal ocular occlusion.

S.No		Retinal vein occlusion	Retinal artery occlusion [100]
1	Cause	Blockage of retinal veins which lead thrombosis	Blockage of retinal arteries which lead thrombosis
2	Category	Central Retinal Vein Occlusion (CRVO) and Branched Retinal Vein Occlusion (BRVO) [91,92] CRVO is more devastating as compared to the BRVO but BRVO is more common than CRVO [93].	Central Retinal Artery Occlusion (CRAO) and Branched Retinal Artery Occlusion (BRAO)
3	Risk Factors	High blood pressure, high cholesterol, smoking, haemodynamic and haematogenic changes, diabetes Other risk factors include, compression, generated by central artery. Central vein and central artery in retina run together so, when there are any changes occurred in the central artery it causes impact on the central vein. Due to compression, flow of blood in veins are affected and thrombosis occur [94,95]. Further complications related with retinal vein occlusion are neovascularization, vitreous haemorrhage and edema in the macula [91].	Diabetes mellitus, hypertension, vascular spasm, atherosclerotic plaques (fat deposition), carotid artery disease and angigitis. Sometimes severe glaucoma and ophthalmic surgeries which cause compression on arterial vessel also leads to the development of disease.
4	Treatment	There is no proven treatment develop till now for the disease, medications are only useful to avoid future complications [91]. It includes tissue plasminogen activator which work as thrombolysis through intra-vitreal route; anti-VEGF therapy is given also from intra-vitreal route via injection; corticosteroids are used to avoid complications associated with the components that take part in the development of retinal vein occlusion and laser treatment also gaining importance nowadays [96–99].	Here also, there is no clinically approved treatment available. Therapy for the disease to increase the perfusion pressure of retinal circulation are used to reduce the intra-ocular pressure which includes, carbonic anhydrase inhibitors, dilatation of vessels through vasodilators, thrombolytic agents, antiplatelet therapy and fibrinolytic agents. It was reported that ocular massage also helps to dilatation of vessels and disintegrate clots.

the procedure helps to avoid surgical complications and able to achieve improved visual acuity using MNs [65].

The use of tower MNs via intravitreal injection to deliver anti-vascular endothelial growth factor antibody to treat exudative form of AMD or neovascularization as depicted in Fig. 6 [67]. In this study the effect of IVT injection through hypodermic needle and tower needle was studied. Hypodermic needles are 27–30 gauge needles, most commonly used in the treatment of neovascular AMD. It is having large outer diameter due to which leads to surgical complications like haemorrhage, retinal detachment, flow of drug in opposite direction,

Table 5
Different forms of non-syndromic RP.

S.No.	Autosomal Dominant RP [105]	Autosomal Recessive RP [106]	X-linked RP [106]
1	RHO (Rhodopsin)	RPE65 (retinoid isomerohydrolase 65)	RPGR (RP GTPase regulator)
2	PRPF 31 (Pre-mRNA processing factor)	PDE6A & PDE6B (Rod cGMP- specific 3′, 5′ cyclic phosphodiesterase)	
3	PRPH2 (Peripherin 2/RDS- Retinal degenerative slow gene).		
4	RP1(Retinitis pigmentosa 1)		

cataract, etc. [67,68]. To avoid these complications associated with hypodermic needles, new type of needle named as tower needle have been developed. Tower MNs are the type of hollow MN with less outer diameter and long enough to penetrate sclera. In this study, they induced neovascularization in a mouse using laser to generate AMD mouse model and delivered anti-VEGF antibody therapy via tower MN. Later to confirm the size of bleb in both the cases, they inject sodium fluorescein through IVT and measure the size [69,70]. On comparing both these needles it was found that, hypodermic MNs cause bleb formation, meaning, during needle penetration a small hole is formed called as scleral hole which leads to formation of channel through which vitreous humor flow from vitreous chamber to subconjuctivial space [70]. The accumulation of fluid in the subconjuctivial space called as bleb. While with tower MN there is no or less bleb formation as the outer diameter of tower MN is less. Also there is no surgical complications associated with tower MNs [71].

Y.C. Kim et al. studied the hypothesis of intrastromal delivery of bevacizumab using coated MN and compared with topical and subconjuctivial delivery for the treatment of corneal neovascularization [72]. They induce corneal neovascularization in the healthy New Zealand rabbits with silk suture and later they monitored the formation of neovascularization. First, dose is given through topical route show less effectiveness because of various barrier properties, loss of drug and side effects [73,74]. Second, delivery of drug through subconjuctivial route via hypodermic needle cause side effects like thinning of conjunctiva, changes occur in sclera, etc. [75–77]. Third, dose is given through intrastromal route with coated MN [77–79]. Later they compared the result obtained from all these studies and found drug delivery through coated MN show promising effect with reduced side effects and provide targeted drug delivery to the corneal stroma to treat corneal neovascularization. Yet intrastromal route is considered same as subconjuctivial route but usage of drug is less in intrastromal route and also it is considered as superior to topical route [72].

4.3. Uveitis

Uveitis is a broad term covering the inflammatory and infectious conditions related with the eye. It is considered as major form of ocular disease which leads to blindness. Uvea is the inner lining within the eye consisting of iris, choroid, ciliary body and also associated structures like retina, sclera and optic nerve [80,81]. Uveitis can be categorized into four categories namely, anterior, intermediate, posterior and panuveitis. The primary site for anterior uveitis is anterior chamber; for intermediate uveitis, vitreous; for posterior uveitis, retina or choroid and for panuveitis all three sites are involved anterior chamber, vitreous and retina or choroid [82]. The most common cause of infectious uveitis includes toxoplasmosis, leptospirosis, onchocerciasis, cysticecosis, etc. while the cause associated with non-infectious uveitis is heterochromic iridocyclitis, chorioretinopathy, etc. [83,84]. Management of disease require treatment which includes medications like immunosuppressive agents that includes corticosteroids; cytotoxic drugs like chlorambucil, cyclophosphamide; biological agents like TNF-α like etanercept, infliximab, adalimumab; non-corticosteroids therapy include Anti-VEGF therapy (Bevacizumab) [84–88].

Study related with the treatment of posterior uveitis using MN described under as:

Gilger et al. demonstrated the use of MN for the treatment of acute posterior uveitis by administering triamcinolone acetonide (TA). As there are several complications associated with delivery of medication in the posterior segment of the eye. So they develop a method in which medication is given through hollow MN in the suprachoroidal space (SCS) (potential space between choroid and sclera adjacent to the posterior segment of the eye). In this study they use porcine model to evaluate the effect of TA in acute posterior uveitis. Result of the study shows that 2 mg of TA was able to reduce posterior inflammation as far as for 3 days. Also there was no sign of retinal toxicity or elevated IOP after SCS injection [89].

4.4. Retinal vascular occlusion

Retinal vascular occlusion is the retinal disease characterized by loss of vision. For the efficient working of retina, it requires constant supply of blood, oxygen, nutrients and also removal of waste. The vascular system which is present in the retina includes several arteries and veins. When these arteries and vein gets blocked or clots developed it leads to a condition called as occlusion. Retinal vascular occlusion is divided into two types: retinal vein occlusion and retinal artery occlusion as depicted in Table 4 [90].

Study related with the use of MNs to treat retinal vein occlusion depicted as: Kadonosono et al. illustrated the use of MN for retinal endovascular cannulation to treat central retinal vein occlusion. Earlier, cannulas made up of glass are used to treat the disease but because of frangibility and other complications, they develop a novel method of using MNs to dilate the retinal vein occlusion [101]. In this study, they fabricated a stainless steel 50 μm MN having 20 μm inner diameter. The MN is attached to the syringe having 10 μl of saline solution and design to pierce the occulated central retinal vein in order to remove thrombus which is present inside the vein. Here, they enrolled 12 patients having this disease to perform their study. The result shows that there were no or few complications occurred, the surgical treatment with MN shows effective result and able to improve visual acuity [101].

In one of the recent study, it was reported that the endovascular cannulation can be performed with the help of MNs to treat retinal artery occlusion [102]. In this study 13 CRAO patients were enrolled and surgery was performed with tPA to treat embolism within the artery. For this they use 47-gauge MN fabricated with stainless steel and attached with the syringe. First vitrectomy was performed a then tPA solution was successfully injection using MN attached with the syringe. Around 85% patients showed improvement in the visual acuity after cannulation. There was only single complication occurred in one of the treated eye which shows vitreous haemorrhage. The result of the study describes as endovascular cannulation using MN to treat CRAO proves to be successful if it is performed as soon as after the onset of CRAO symptoms [102].

4.5. Retinitis pigmentosa (RP)

Retinitis pigmentosa is an inherited form of ocular disease consist of different heterogeneous conditions that occur because of damage in rod and cone cells, especially rod cells and in later course of disease cone cells are also affected and therefore this condition is also known as rod-cone dystrophy. The characteristic feature of RP is change in the

Table 6
Different forms of syndromic RP [107].

Frequent syndromes	Less frequent syndromes	Dysmorphic syndromes	Metabolic disease	Neurological disease
Usher syndrome	Senior Loken syndrome (SLS)	Cohen syndrome	Abetalipoproteinemia (Bassen Korntzweig disease)	Neuronal ceroid lipofuscinosis (also called Batten disease or amaurotic idiocies),
Bardet Biedl syndrome (BBS)	Alport syndrome	Jeune syndrome	Bietti's disease	Joubert syndrome (JBTS)
		Cockayne syndrome	Refsum disease	Hallervorden-Spatz syndrome

pigment of photoreceptor cells that will lead to pigmentation which occurred in bone-spicules form in early stages of disease. The symptoms related to RP is night blindness in primary stage because of rod cell impairment, as disease progresses, it affects the peripheral vision also because of impairment of macula and fovea which leads to cone cell dysfunctioning [103]. Retinitis pigmentosa broadly categorized as syndromic form and non-syndromic form of disease. Non-syndromic form includes conditions which may occur due to mutation in several types of genes while syndromic form includes ocular along with systemic disease [104]. On the basis of types of genes non-syndromic forms categorized as; Autosomal Dominant RP, Autosomal Recessive RP and X-linked RP [105]. The genes which is most commonly responsible for causing non-syndromic RP is given under Table 5 while syndromic forms of RP are describe under Table 6.

Various therapies are available for treating retinitis pigmentosa which includes gene therapy, anti-apoptic agents, neurotrophic factors and retinal prostheses. Gene therapy is considered as one of the promising treatment in case of ocular disease as it reduces the systemic side effects along with it showed effective result in preclinical and clinical studies. It is performing by using viral as well as non-viral vectors. Viral vectors like AAV (Adeno associated virus, lentivirus and adenovirus) and non - viral vectors include liposomes, nanoparticles in compact form, various polymers and also polypeptides [108]. Viral vectors are generally injected through subretinal route provide easy transduction while non-viral vectors are injected through intravitreal route and its transduction is not efficient as with viral vectors. New advancement in non-viral treatment includes using of coated nanoparticle which is made up of polyactide and the coating formulation is made up of two components, human albumin serum and hyaluronic acid [109].

Treatment with use of neurotrophic factors, these factors are responsible for the development, survival and growth of neurons and maintain the maturation process of neurons. There are several number of neurotrophic factors present in a system, in case of an eye it is likely to be present in retina and in muller cells which function as a growth factor for neurons [110]. These are small protein secreted inside the body and act as a safeguard for photoreceptor cells. Some of them are ciliary neurotrophic factor (CNTF), glial cell derived neurotrophic factors (GDNF), fibroblast growth factor (FGF), brain derived neurotrophic factor (BDNF), etc [109]. Among all these factors, clinical trial is conducted on CNTF implants which contain RPE cells. On implantation these cells release CNTF through the membrane. Phase I data explain improvement in vision after one year of implantation without any adverse effect and phase II studies is going on [109].

Anti-apoptic agents are used to inhibit the mechanism of apoptosis of photoreceptor cells like myriocin, norgestrel, tauroursodeoxycholic acid (TUDCA) and rasagiline. TUDCA originate from bile of bears and act as a neuroprotective and inhibit the programme cell death mechanism [111]. Rasagiline main function is to inhibit the enzyme monoamine-oxidase and used as medication for Parkinson and have neuroprotective function [112]. Also norgestrel act as neuroprotective which is a progesterone derivate also increases the cell survival by doing anti-apoptic action [113]. Likewise, myriocin also increases the cell survival by destroying ceramide which act as an important factor in cell death pathway [114].

Retinal prostheses, these are the implanted devices for an eye which is use to regulate or increase the neuronal signal in photoreceptor cells to improve the vision with the help of power supply into those implanted devices. Argus II and Argus IMS are two approved devices for retinal therapy, their components include outer wireless part which supply power, inner part containing array of electrodes placed inside retina, receiving coil, external and internal coils, camera [115]. Other effective therapeutic approaches are vitamin therapy as an antioxidant, cell transplantation which includes retinal cell transplantation and stem cell transplantation are also considered as one of the novel techniques [115]. Study related with use of MN for gene delivery in the RP affected eye are described as below:

The study shows delivery of RNAi (interference) delivery through AAV based vector to treat mutated RHO (rhodopsin) autosomal dominant gene in the case retinitis pigmentosa. Principal emphasis of study is on suppression and replacement of mutated gene. Transgenic mouse model which mimic the human RHO autosomal dominant gene was used in the study [116,117]. AAV based vector carrying RNAi to supress the mutated gene along with replacing gene from the endogenous mouse. The vector was injected with the help of 34-gauge MN attached with the syringe in the subretinal space for efficient delivery. The current study shows the suppression and replacement of mutated gene in a mouse model provide effective improvement in the evaluation process during electroretinography (ERG), a machine which, measures the electrical signal of retina, inner retinal cells and photoreceptor cell. The result of the study described that, it is an efficient method to decrease the progression of disease or retinal degeneration and can be useful in many other leading genetic conditions [117].

5. Conclusion

Delivery of medication in the eye is a challenging aspect due to various ocular barriers and low therapeutic profile of conventional delivery. Lower drug penetration into the ocular tissue in conventional dosage forms lead to usage of intraocular injections. These conventional hypodermic needles are used to deliver drugs through various routes depending on the types of disease which includes intracorneal, intravitreal, periocular, supracilliary delivery etc., On the contrary, these conventional hypodermic needles have drawbacks like frequent administration, invasive nature and less bioavailability. These drawbacks are successfully overcome by micron sized MNs, which is the growing technology for effective drug delivery in the various ocular diseases. MNs not only decrease the progression of disease but also reduces the retinal degeneration. Mostly, three types of MNs are used for ocular drug delivery, solid coated MNs, hollow MNs and dissolving polymeric MNs. Numerous studies recently have shown application of MNs in ocular diseases like glaucoma, age related macular degeneration, uveitis, retinal vascular occlusion, retinitis pigmentosa and many more. In these studies, ocular therapy using MNs have indicated decrease in the progression of eye diseases and proves to be an upcoming emerging therapy. In conclusion, the MNs can be effectively used for most of the eye diseases even in cases which are genetically linked.

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