

Tiny Needles Offer a Potential Long-lasting Treatment for Retinal Disease

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Abstract

Glaucoma and corneal neovascularization which is the world leading eye disease could be given new treatment options by use of tiny microneedles which are small enough to an unaided eye. Microneedles range in length from 400 to 700 μm could provide a better medium of drug delivery into the eyes and thereby better disease management. The microneedle technology of drug delivery will be targeting specific to the eye and there by decrease the quantity of the drug and increase the effectiveness with minimal side effects. One of the leading causes of blindness is glaucoma, which happens when untreated and corneal neovascularization, causes an additional growth of blood vessels that damage the vision. Development of microneedle-based systems is being experimented with a way where the drug is precisely put into the part of the eye. Thus, coupling this delivery with a controlled release formulation may allow treating a condition for weeks or months. Thus, this review elucidates on the current research and the design which may act as a potential treatment for retinal disease.

Key words: Corneal neovascularization, eye, glaucoma, microneedle, ocular drug delivery

INTRODUCTION

Delivery of drug delivery using current methods into the eye is an extremely inefficient process by the topical or systemic administration. Intraocular injection is effective, but also alarms a safety concern as it is associated with the series of side effects. There is an increasing demand for better methods of ophthalmic drug delivery, which will be safe and effective. Topical application of the drug as an eye drop is the traditional and conventional route where the drug enters by diffusion into the cornea or sclera.^[1-3] Drug delivery to intraocular tissues across the eye, such as retina and choroid, has certain limitations. A limitation of the current methods of topical drug delivery is as follows: Loss of drug due to tear drain from per cornea, corneal epithelium, and conjunctiva creates a barrier to solute flux.^[4] Other drug delivery methods, such as intraocular injections or ocular implants confirmed improved delivery effectiveness; however, additional factors, including safety issues and patient compliance need to be considered. Some of the examples such as the poorly targeted nature of eye drops cause widespread, systematic exposure, where 8–53% of glaucoma patients suffer from side effects.^[5] Transscleral drug delivery is an ideal route of delivery across the eye, as it has a large

sclera surface area. Around 95% of the globe's surface area is covered by sclera tissue, which provides more space for drug delivery into the eye.

Transdermal administration of the drug through microneedle technology has been acknowledged over the past few decades. Studies have found that use of microneedle technology has enhanced the delivery of drugs into the skin. This review describes the future prospects of the microneedles that could be used for delivery of the drug to the eye. Ocular drug delivery through microneedle technology has advantages as follows: (1) Reduction in pain and trauma as compared to hypodermic injection; (2) well tolerated and increases patient compliance; and (3) provide target delivery of the drug across the eye.^[6-8] Different types of microneedles are involved in drug delivery such as solid metal and hollow glass microneedles. For solid microneedles, drug formulations are coated onto the shafts of the needles. The insertion of coated microneedles into

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the sclera or cornea should deposit drug directly into the ocular tissue area across the barrier of corneal epithelium and conjunctiva. The coated drug that dissolves off the needle shaft is stored in the sclera or corneal tissue and is delivered into the eye by diffusion. After insertion into the sclera, the drug is injected into the ocular tissue using pressure-driven flow. Coupling with an insertion device, the insertion depth of the needle into the tissue can be precisely controlled. Both methods may attain the following goals in delivery of the drug across the eye: (1) Increases the amount of drug delivery as compared to topically administered drug; (2) localized delivery of the drug as compared to systemic administration; (3) safer delivery approach relative to intraocular injection; and (4) prolonged drug release periods.

Ocular drug delivery

Nowadays, ophthalmologists face a big challenge in effectively delivering drugs to the back (retinal, choroid, and vitreous body) of the eye. The most conventional way of ocular delivery is using eye drops, but only a small amount of the drug can actually reach the targeted area.

The tear fluid on the surface of the eye is basically responsible for washing away most of the applied drugs. Intraocular injections and implantation are the alternative methods that offer better delivery efficiency; however, complications associated with safety and patient compliance must also be considered. The development of microneedles

showed excellent potential as a novel drug delivery tool for transdermal drug delivery.^[9-11] They could minimize tissue damage with their small size and also provide a better-targeted delivery. Microneedle technology can be also be used in the effective management of the treatment of diabetic retinopathy and macular degeneration like disorders.

Eye structure and anatomy

The human eye is a spherical shell of tissues which also contains the lens and iris and is largely filled with water and has a diameter of 23–24 mm.^[12] The surface of the eye is made up of three layers, namely the outer sclera, the middle choroid, and the inner retina as mentioned in Figure 1.

On the human eye, 7% of the total surface area are cornea, which is the transparent region of the eye. The thickness in the middle region of the human cornea is about 0.52 mm; thickness is about 0.67 mm at the limbus.^[13] The cornea is the main route for delivery of the drug across the eyes. The cornea has a multilayered tissue, which contains epithelial cells along with stroma, Bowman's layer, and endothelial base.^[14] The sclera is a thin spherically shaped connective tissue that gives the eye its shape. The cornea supports and controls the eye as it is attached to the ocular muscle. The front portion of the sclera is the "white of the eye". The scleral tissue is connected by the conjunctiva, which is a transparent layer located on the anterior surface near the cornea. The remainder of the scleral tissue consists of a layer called a Tenon's capsule, a thin

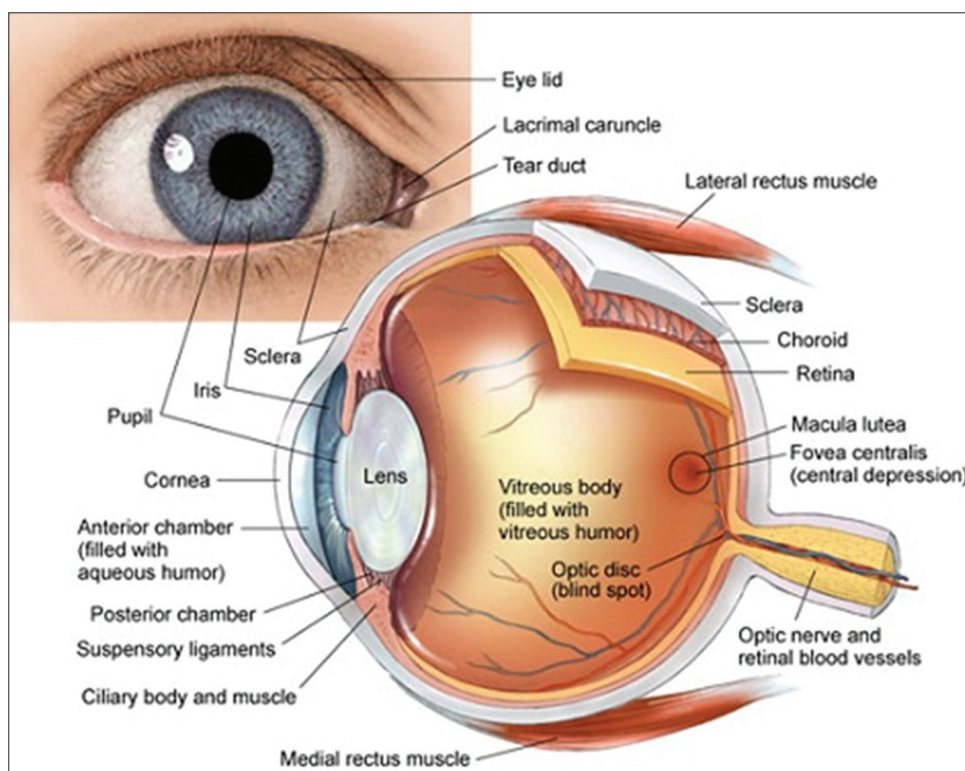


Figure 1: Physiology of eye

connective tissue layer overlying the episclera. The scleral tissue, which contains the nerve involved in vision is lined by the blood vessels, choroid, and retina. The thickness of the scleral tissue can sustain higher volumes of the drug as the permeability of the sclera is greater than cornea due to the larger surface area. The drug delivery to scleral tissue would be of interest in the future.

Common vision problems

Blindness and visual impairment extract a great price from individuals and society, estimated conservatively at \$4 billion annually.^[15] Around 95.2 million people, mainly 40 years and above are more prone to blindness and >3.4 million people are considered visually impaired.

Macular degeneration, glaucoma, corneal neovascularization, and diabetic retinopathy are the most important cause of peripheral and central vision loss which greatly affects the patient's lifestyle. Causes of corneal neovascularization may be due to infectious pathogens, inflammatory responses, physical trauma, or degenerative diseases. Mainly, conventional therapy involves the use of steroids such as hydrocortisone and dexamethasone. However, the use of steroids causes serious side effects such as cataract and glaucoma.^[16] In the case of glaucoma is a chronic disease, where both structural and functional damage takes place mainly to retinal ganglion cells (RGC) and their axons, causing irreversible blindness. There are many factors involved in causing retinal disease such as oxidative stress, inflammatory processes, metabolic abnormalities, and also blood flow disturbances.^[17]

In the case of glaucoma, current therapeutic options are not sufficient for curing this disease, novel therapies need to be implemented that can protect RGC from degeneration. New remedial strategies need to be implemented for avoiding side effects which may functional, repeatable, easy to utilize, and cost-effective. Furthermore, these models should mimic the condition during the course of the human retinal disease such as glaucoma and corneal neovascularization. However, the intrastromal injection of bevacizumab using hypodermic needle has been found to be promising in treating corneal neovascularization. Researchers earlier stated the use of the surgical introduction of catheters and conventional in hypodermic needles for suprachoroidal space, but presently, the use of microneedles is introduced due to its simplicity, reliability, and rapid method for suprachoroidal injection. The first drug named "bevacizumab" was demonstrated in humans using microneedle into the suprachoroidal space of four human eyes.^[18] The most widespread reason for the central loss of vision in geriatrics is age-related macular degeneration (ARMD); which damages the tissue that supports the light-sensitive retinal cells.^[19] The disease is categorized into two stages: Dry disease, which is the background disease, and wet disease, damaged blood vessels leads to complications of dry disease and loss of vision. Loss

of macular function which lies in the center of the retina can lead to impaired vision like loss of central visual tasks such as reading and face recognition. Recently, therapeutic drugs, such as macugen (Pegaptanib sodium injection) and lucentis (Ranibizumab injection), have been shown to help preserving vision in the patient with ARMD by slowing vision loss. The recommended dose of macugen is 0.3 mg/6 weeks of administration through intravitreal injection. Lucentis is injected intravitreally into the eye at a dose of 0.5 mg on a monthly basis; however, each dose costs close to \$2000^[20] where most ARMD patients could not afford.

AMRD is a disease caused by the formation of abnormal blood vessels leading to rapid vision loss. The second leading cause of adult blindness is glaucoma, which is known to increase pressure in the eye. The optic nerve can be damaged by increased pressure, which can further lead to visual impairment. The damage can lead to peripheral vision loss followed by central vision loss and blindness. Glaucoma is a disease that is caused by an elevation of intraocular pressure within the eye. The treatment of glaucoma primarily involves the use of eye drop solutions containing drugs such as prostaglandin analogs (improving fluid drainage), beta-blockers, alpha-adrenergic agonists, and carbonic anhydrase inhibitors.

Normally these drops need to be applied to the eye 3–5 times per day, which often leads to poor patient compliance, especially among elders. The blood vessel may leak fluid or become fragile forming scarred tissue when it is damaged in the retina. This can lead to retinopathy and can blur and distort the vision. Recent studies have shown that injection of steroids can reduce the progression of the disease.^[21]

Conventional ocular drug delivery methods

The eye, like every nervous organ of the body, is naturally well protected from the systemic circulation. The local drug administration into the back of the eye, particularly in the retina, at an effective concentration with reduced local or general side effects, is one of the main issues often faced by ophthalmologists today. Four approaches of drug delivery are suggested for treating posterior segment disease, namely - topical, systemic, intraocular injection, and periocular injection. Topical drug applicant through eye drop is the traditional therapy, which has limitations.

This mode of delivery can be easily accessed; however, it requires often-repeated applications (up to 5 times per day). In general, the treatment with drops is ineffective in disease treatment across the eye due to various barriers. Tears from the eye rapidly wash away the applied drug and hence could not reach the vitreous body, the retina, and the choroid at sufficient levels. In addition, the ineffectiveness is due to the long diffusion path length, the impermeability of cornea, and counter-direction of intraocular convection to large molecules.^[22] Although a systemic drug delivery approach

option is available, it has a poor reach to the tissue in the back of the eye due to two barriers: Blood-aqueous and blood-retinal barriers. The blood-aqueous barrier limits the entry of drugs into the humor of the eye and thereby prevents the exchange of material between the eye chamber and blood. The drug entry is also prevented by the blood-retinal barrier into the vitreous tissue through the extravascular space. The retinal pigmented epithelium also has tight junctions that form an effective barrier. This leads to higher systemic doses and thereby adds to the toxicity and side effects. The traditional therapies of administering the drugs across the eye that are more effective are intravitreal (into the eye) injections. The concentration of the drug in the systemic circulation decreases exponentially after injection in the tissue with due course of time, is the main problem of both the methods. This indicates that for maintaining the concentration of the drug; the timely injection of the drug needs to be administered into the eye. In addition, the injections can potentially induce complications, such as retinal detachments, cataracts, infections, and pain.^[23] There is an attention to drug delivery through the periocular route where the drug is interfaced with the scleral tissue in recent years. Periocular route delivery of drug reaches the posterior segment by three main ways: Systemic circulation, transscleral route, and the anterior route through cornea, humor, and the vitreous body.^[24] Subconjunctival route lowers the systemic absorption of drugs and thereby low side effects in providing the localized effect of the drug.^[25]

Sclera permeability

The sclera tissue primarily is made up of proteoglycan which mainly contains collagen and 70% water. The sclera tissue is microporous and elastic in nature.^[26,27] Large surface area of scleral tissue which is 16 cm² makes a large volume of drug delivery easier than into the cornea (1 cm² surface area).

The sclera is permeable to a variety of drug range that has been observed in various studies. Sclera tissue offers minimal resistance to the diffused drug than cornea as reported by Maurice and Polgar in the study.^[28] Dextran (40 kDa) and serum albumin (69 kDa) can easily penetrate the sclera whereas cornea is impermeable to drug with a higher molecular weight (>1kDa).^[29] However, the lower molecular weight drug was found to have higher permeability into scleral tissue as exhibited inverse relationship. Both sclera and corneal stroma exhibited similar permeability to carbonic anhydrase inhibitor.^[30] Adrenergic blocking drug and hydrocortisone permeability are higher in scleral tissue than cornea.^[31,32] To predict the permeability of a broad spectrum of drugs, the theoretical model was developed. This model was validated without the need of any parameters and exhibited a steady state of transport data from different compounds such as drug and macromolecules. The transient transport behavior of the molecule was further validated on carboxy fluorescein flux on experimental bases which predicts the complementary model. Further, the permeability of sclera tissue can widen

by hydrating tissue and increased temperature. Cryotherapy, age, or diode laser have no effect contributing permeability of scleral tissue. Studies have shown that prostaglandins can improve scleral permeability by increasing expression of matrix metalloproteases. Prostaglandin can further enhance transscleral drug delivery across the eye.^[33-35]

Transscleral delivery

Transdermal route of drug delivery is a better means of administration into the posterior segment of the eye where the larger scleral surface area is present. Transscleral delivery of the drug could also be optimized based on the difference in sclera thickness and greater permeability. Transscleral delivery of the drug through ocular implants, periocular injection, and biodegradable polymers has also shown potential.

The ideal method of administration of the drug to the posterior segments is through periocular injection which has been found as a promising route for the delivery of the drug using the range of formulations.^[36] This method of drug delivery offers the sustained release of drug with minimal invasive compared to intravitreal injection. Weijtens *et al.* found that periocular injection is more effective than orally administered drug for delivering dexamethasone into the back of the human eye.^[37] Lee *et al.* injected radiolabelled mannitol subconjunctivally in rabbits and observed direct penetration through sclera was the major route of the delivery of the drug into the posterior segment.^[38] A transscleral implant made out of either a gel formulation or biodegradable polymers can also be used the safe method with minimal invasiveness for delivery of the drug.

Human eye has a high tolerance of foreign bodies on the sclera tissue. Dexamethasone drug exhibited sustained release across the sclera as shown in the preliminary study.^[39] Yasukawa *et al.* investigated using biodegradable implants, composed of hydrophilic or hydrophobic polymers, in the shape of rods, plugs, discs or sheets, and an implantable rod is being applied in the Phase II trial in the management of macular edema along and diabetic retinopathy.^[40] Transscleral delivery of the different classes of drugs such as fluorescein, antibiotics, and steroids was increased with the help of iontophoresis.^[41] However, this method may cause further complications such as retinal edema, damage of the normal retina, and retinal pigment epithelial hyperplasia.^[42] Further improvements may be needed with this approach.

History of microneedles

Microneedles created for transdermal delivery of the drug seeks to combine the benefits of both conventional hypodermic needle injection and transdermal patches, which minimizes the limitations associated with each technique. The benefits of microneedle technology are that the drug can be delivered

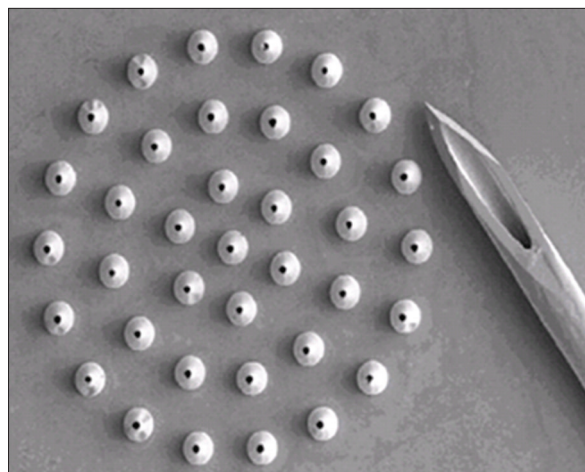


Figure 2: Microscopic image shows a hollow metallic microneedle array (500 μm tall) next to a conventional hypodermic syringe needle used for drug delivery

transdermally by minimally invasive means. Over the past decade, several designs of microneedles have been explored using tools from the microelectronics industry. Microneedles can be made of varying micro size, shapes, and materials as mentioned in Figure 2. From solid metal to hollow spikes and further microneedle can be made of biodegradable polymer. Depending on the microneedle type, it can have its unique functionality. Typically, these microneedles are hundreds of microns in length, on the order of 100 μm at the base and having a sharp tip that is ones to tens of microns in diameter. The microneedle fabrication cost would be inexpensive when produced in bulk quantities.

Solid microneedles

Transdermal drug delivery into the skin is attained by creating micron-sized holes into the tissue. This achieves by solid microneedle technology. Solid microneedles have a strong, sharp mechanical tip, which is cost effective and can be produced in bulk.

Silicon microneedles

Solid spikes are the simplest form of microneedles. Besides being solid, their unifying characteristics include fairly simple fabrication scheme and also being very sharp. Using a deep-reactive ion etching (RIE) method, silicon microneedles were fabricated. Silicon microneedle is fabricated by depositing chromium mask layer over the silicon wafer; the further pattern is using the photolithography method into dots of the desired needle size base. Silicon microneedle of high aspect ratio is created by etching the wafer with oxygen/fluorine plasma mixture. Microneedles transport the drug transdermally into the skin by creating micro-scaled holes. The study performed by Henry *et al.* exhibited that transdermal delivery of the drug through silicon microneedle technology.^[43] The penetration of microneedles

through the upper layer of skin (stratum corneum) created direct pathways for molecules that would not normally be able to diffuse through the skin barrier due to size or water soluble. In addition, Kaushik *et al.* *in vivo* tested the pain level associated by means of the insertion of silicon microneedle arrays into human skin.^[44] The study showed that the microneedles caused an insignificant amount of pain compared to conventional hypodermic needle insertion, and no subjects reported any adverse reactions.

Metal microneedles

For microneedle fabrication; metal is considered as a good alternative material due to its mechanical strength, relatively inexpensive than other materials and ease in fabrication. Solid, stainless steel microneedles can be made by a laser-cutting technique. The resulting needle structures are bent out of the sheet, and electropolished. The needles can be in either single microneedles or multi-needle array form. Recently, a new delivery method associated with metal microneedles was developed. Different sized molecular compounds like proteins, nucleic acid can coat onto the shafts of single metal micro needles or multi-arrays of microneedles. After insertion into the tissue, the naturally hydrophilic-coating instantly dissolves off the microneedle shafts and creates drug depots within the tissue to provide sustained release.

Hollow microneedles

Solid microneedle creates a miniature hole after insertion and thereby makes the skin permeable for controlled drug delivery into the tissue. Hollow microneedle was fabricated in such a way which will transport the drug through the hollow shaft into the tissue. Microneedle structure with hollow lumen expands a horizon have various benefits such as delivery of large macromolecules; convective transport delivery of the drug as a replacement for passive diffusion; and limit cross-contamination during delivery. Hollow microneedle technology has exhibited better transdermal drug delivery.

Silicon hollow microneedles

The most logical technique for the inclusion of a lumen in the silicon spikes presented is the addition of an etching step to form a fluidic channel using standard photolithography and isotropic-anisotropic etching combination.^[45] Silicon dioxide is coated onto the silicon wafer which prevents the upper oxide layer to define the needle lumen. The large circular mask was patterned on the front side after depositing silicon nitride which tapered the microneedle. Symmetrical needle structures were achieved by adjusting the isotropic relative positioning after removing both silicon dioxide and silicon nitride. The hollow silicon structures have been created in three-dimensional arrays out of the substrate plane.

Metal hollow microneedles

Hollow metal microneedles can be created using laser micromachining. Microneedles with straight walls are made of cylindrical holes by use of molds which are created by RIE through silicon wafers or lithographically. This fabrication of microneedle had defined holes in SU-8 photoresist polymer. As the contact area between the microneedle and the skin was reduced, less pressure was needed for inserting microneedle into the skin tissue. The metal content in the microneedle exhibited strong and solid stability to its structure. In a study Martanto *et al.*, insulin was administered into hairless diabetic rats *in vivo* using these hollow microneedle arrays. After 4 h of delivery, the glycemic levels of the rats were reduced to 47% of their original value, which indicated the successful transdermal delivery.

Glass hollow microneedles

Glass microneedles which are hollow in nature can be swiftly fabricated for small-scale usage by singing various geometric parameters. These glass hollow microneedles have large drug loading dose and can be inserted into the tissue with breakage for the treatment. Mc-Allister *et al.* inserted a microneedle made of glass for delivery of insulin into the diabetic hairless rat's skin for a 30 min infusion period. The microneedle was inserted at a depth of 500–800 μm inside the tissue with the tip radius of 60 μm for effective drug delivery. A 70% reduction of glycemic levels was found during 5 h after insulin was administered.

Variation in microneedles

A variety of microneedles are being fabricated in addition to hollow and solid microneedles such as the biodegradable polymer, and sugar with a variety of functions. Biodegradable polymers were formed as they are biocompatible with tissue.^[46] With the help of lithography-based methods; biodegradable microneedles were fabricated. From the master structure, a replica of microneedle was created by melting biodegradable into the molds.

Polymer microneedles serve as a drug implant when injected into the tissue as compared to traditional solid and hollow microneedles. Park *et al.* inserted microneedle into human cadaver skin which was loaded with calcein/bovine serum albumin (BSA). Depending on the formulation, the release of calcein/BSA from the microneedle ranged from hours to months as observed in the *in vitro* studies. Microneedles made out of maltose mixed with ascorbate were developed for transdermal delivery of drugs.^[47] The tests showed the sugar-based microneedles spontaneously dissolved and released ascorbate into the epidermis and dermis of human skin. No dermatological problems were reported. Aside from being a drug delivery tool, microneedles can also be used

as a biosensor. Attaching large molecular weight molecules onto the sensor affects the sensor signal stability, which is one of the main reasons for the loss of biosensor activity. Fabrication of microdialysis onto microneedle can exclude large molecular weight molecules.^[48]

CONCLUSION

Intraocular injection, topical, and systemic administration are the traditional methods which have limitations effectively deliver the drug into the eyes. Hence, this necessitates for developing the better ocular delivery of the drug with less threat of eye complication; which is essential improving posterior segment ocular disease treatment. Transdermal drug delivery through microneedle technology has a huge prospect of drug delivery. Microneedle technology exhibits minimal invasive methods of drug delivery across the ocular tissue. This review provides current approaches toward highlighting the present benefits of using microneedles technology as a novel drug delivery method. This microneedle technology exhibits minimal invasive methods to deliver the drug across the ocular tissue for treatment of the disease. The majority of patients still struggle to in curing both glaucoma and corneal neovascularization; even with the using sophisticated intraocular injection and systemic administration.

The microneedles may be recommended as a more convenient and superior mode of eye drug delivery. This device that can be implanted, which would be safe, easy, pain-free, and reasonable method in the management of retinal disease caused during diabetes in the near future.

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