Microneedle Mediated Approaches in Ocular Drug Delivery

By

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Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

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Ethics Statement

This study does not involve any kind of human or animal trial.

Abstract

The delivery of specific drugs to the desired site of action to the eye remain a major challenge in treating the chronic diseases of the eye. Due to inadequate quantity of drugs being delivered to the diseased site, the chronic eye disease management becomes a challenge and is a reason for vision impairment in a lot of patients worldwide. In current practice, the treatment is usually done by the conventional forms of treatment e.g., topical formulations which have a low bioavailability, permeation, diffusion rate and causes irritation, inflammation, toxicity etc. The chronic eye conditions such as macular degeneration, diabetic retinopathy, retinal vein occlusion needs a consistent form of treatment which is effective and have a high patient compliance. This reviews the feasibility of microneedles in the ocular drug delivery and discusses the possibilities and challenges of its application to the eye.

Keywords: Ocular drug delivery; Microneedles; Targeted delivery; Fabrication; Eye diseases.

Dedication

Dedicated to my parents and my elder sister.

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Introduction

The complex pathological conditions of the eye require precise treatment procedures which demands the exact concentration of the drugs to be present at the site of action at therapeutic levels (Bhanu et al., 2017; Jung et al., 2018). But the current treatment options available to us couldn't fulfil this requirement successfully (Farkouh et al., 2016; Gote et al., 2019; Shen et al., 2018). For example, the topical formulations have issues such as low bioavailability, systemic toxicity etc. & the intravitreal injections could deliver drugs with acceptable precision but it is extremely painful and have a very low patient compliance and causes severe complications such as retinal detachment, retinal vein occlusion, bleeding, tissue damage, chances of infections (H. Chen, 2015; Chiang et al., 2017; J. K. Patel et al., 2018). The diabetic patients who have retinopathy requires chronic care, thus none of the options prove to be a viable treatment (Jiang et al., 2018; Kang-Mieler et al., 2020). The use of microneedle could open doors to a more refined form of ocular drug delivery by allowing precise targeted drug delivery which could be sustained for prolonged period of time (Dugam et al., 2021; Kjar & Huang, 2019; Tekko & Raj Singh, 2018; Terashima, Tatsukawa, Takahashi, et al., 2020). The objective of this review to focus on the development of novel ocular drug delivery system for the better treatment and management of chronic eye diseases for both the anterior and the posterior segment. The use of microneedles is a potential device to be used to deliver drugs precisely to the targeted tissues of the eye and thereby releasing drugs at a controlled rate for a sustained period of time. Hereby, the recent literature was reviewed to put focus on the administration of microneedles to the ocular tissues and the existing fabrication techniques as well and the commercial, clinical & regulatory aspects of the translation of this technology in future.

1.1 General aspects of ocular drug delivery

1.1.1 Anatomical considerations of drug delivery to eyes

Drug delivery to the eye is presently one of the most testing regions in the current drug delivery field because of the one-of-a-kind structure and physiology of the eye and the presence of natural barriers in the eye. Therefore, novel drug delivery strategies have been examined to improve ocular drug permeation and increment of the intraocular bioavailability (Faheem & Abdelkader, 2019). The structure of the eye could be broadly classified into two parts, the anterior segment and the posterior segment. The anterior segment takes up one third of the eye and the posterior segment occupies the rest. The anterior portion consists of cornea, conjunctiva, aqueous humor, iris, ciliary body & lens. While the posterior segment is made up of retinal pigment epithelium, neural retina, sclera, choroid, vitreous humor, choroid & optic nerve. There are several diseases of the anterior and the posterior segment of the eye that acts as a threat to the vision (Patel, 2013). **Figure 1** shows the overview of the classification of the ocular drug delivery systems.

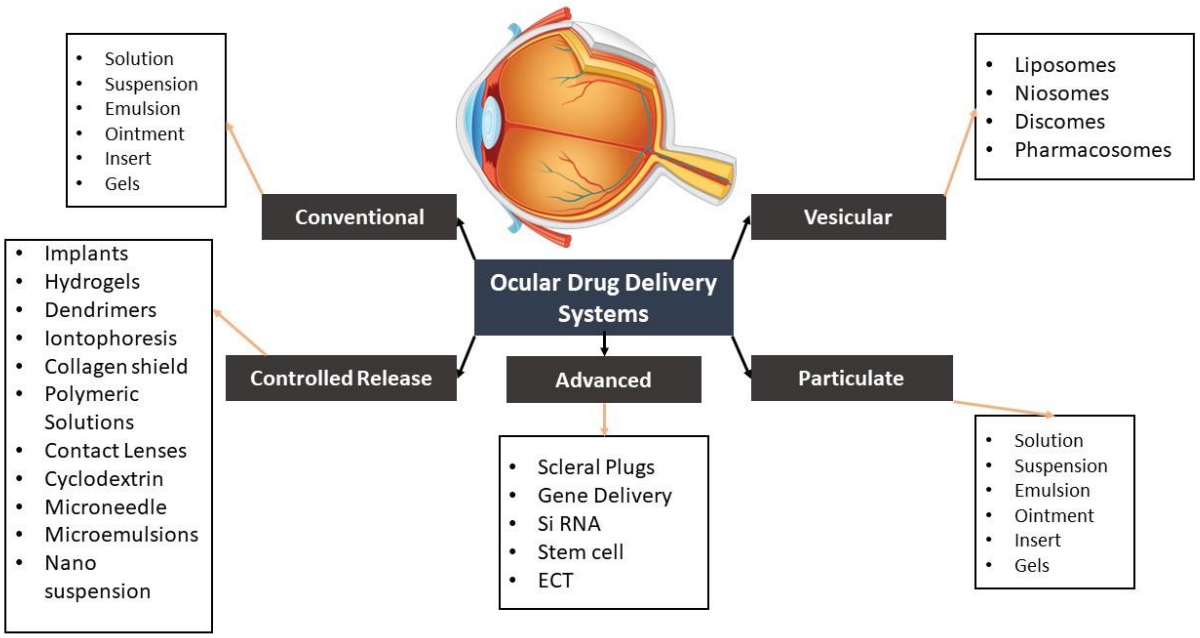

Figure 1: *Classification of the ocular drug delivery systems (Bhanu et al., 2017; Kang-Mieler et al., 2020). Different types of ocular drug delivery systems such as conventional, controlled release, advanced, particulate, vesicular has been classified further to show different sets of options available.*

1.1.2 Barriers to the delivery of the drugs to the ocular tissues

The barriers to the delivery of drugs to the eyes is a major concern in achieving the successful treatment of ocular diseases. Delivering medications to specific intraocular targets and achieving an optimal drug concentration is limited by a number of inherent anatomical and physiological ocular barriers (Huang et al., 2018). The scleral delivery poses barriers such as the static barrier, which is the pigmented epithelial cells of the sclera, choroid & retina (Suri et al., 2020). Other type of barriers includes the dynamic barriers such as the lymph flow in the conjunctiva, episcleral tissues & finally in the blood. The blood flow in the choroids, conjunctiva & the presence of constant tear flow & metabolic barriers such as pumps & enzymes also acts a significant barrier to the drug distribution and ultimately affects the bioavailability of the drug (Suri et al., 2020)(Huang et al., 2018). It has been discovered that only 5% of the drugs administered by topical formulations such eye drops reach the targeted deep tissues of the eye (Patel, 2013). For the drugs to reach the systemic circulation & to produce the desired therapeutic effect, high doses are required to overcome the low bioavailability. This poses a massive concern since the chances of toxicity increases as dose increases. Therefore, the long search of highly efficient drug delivery system remains.

Table 1 shows the major physical barriers of the eye for both the anterior and the posterior segment and describes how the barriers affect the entry of drugs to the ocular tissues.

Table 1: *Summarizing the major physical barriers of the eye (Patel, 2013; Yavuz & Kompella, 2017).*

The physical barriers of the anterior segment		
1.	Lacrimal Fluid (Pre- Corneal)	The rate at which the lacrimal fluid is being exchanged via the nasolacrimal duct is approximately 1 µl/min. The fluids present in the eye such as lacrimal fluid, aqueous humor and tears consist of a small amount proteins and peptide molecules. They bind with the drugs to make a complex and hampers the drug release and drug permeation in the deeper eye tissues.
2.	Cornea	Cornea prevents the entry of foreign particle into the eye and protects the sensitive tissues of the eye. It is usually made up of 5 layers which are distinguishable and have a massive impact in the process of transporting molecules from the anterior to the posterior tissues of the eye. The tissues are as follows: epithelium, stroma, bowman's layer, descemet's membrane and the epithelium. The lipophilic molecules are bole to surpass the barrier due to the lipophilic nature of the barrier but the large hydrophilic molecules are not capable to cross it.
3.	Conjunctival membrane	Different blood capillaries present in the membrane results in drug loss and thus ultimately leads to lower bioavailability. The drugs which are lost enters the systemic blood flow and thus causes toxicity.

Table 1 *continued…*

The physical barriers of the posterior segment		
1.	Sclera	The white portion of the eye is known as sclera which has a high aqueous content. This facilitates the diffusion of the hydrophilic molecules into the ocular tissues at a faster rate compared to the hydrophobic ones.
2.	Choroid	Choroid supplies the nutrients and oxygen to the retinal cells. It contains a very small number of blood vessels. The drug delivery to the retina becomes difficult with ageing since the thickness of the choroid decreases.
3.	Blood-retinal barrier	This is one of the prime barriers of the eye to the delivery of drug molecules to the eye. It consists of the retinal pigment epithelium and the capillaries of the retinal epithelial cells. The entry of foreign molecules is restricted due to the presence of matrix proteins.
4.	Retina	Barriers are absent in the retina but the presence of the proteins in the inner membrane limits the entrance of drug molecules.

1.1.3 Common eye diseases

Pathological conditions of the eye results in the impairment of vision in the long run. Some of the common eye diseases include: age related macular degeneration, glaucoma, cataract & diabetic retinopathy. The loss of vision is usually a result of the damage in the retinal layer of the eyes which takes place due to the diseases of the back of the eye i.e., the posterior segment. Macular degeneration is considered one of the leading causes of blindness in the elderly. It occurs due to the neovascular complications in the retinal or subretinal pigment epithelium exudation or hemorrhage (Singh et al., 2020). The chronic high glucose in diabetic patients makes harm the layers of retinal endothelium which brings about issues, for example, diabetic retinopathy (DR), diabetic macular edema (DME), and retinal vein occlusion (RVO). Elevated oxidative stress and ageing creates damaging changes in the epithelium of the retinal cells and brunch's membrane in the macular region which kills the photoreceptor cells. Overexpression of the vascular endothelial growth factors causes retinal and choroidal neovascularization which is the primary reason of most the posterior eye segment disorders. The preferred form of treatment of these complications before the discovery of anti VGEF agents were the phenomenon of the photocoagulation implication which descends the need of oxygen for the retinal cells. The retinal neovascularization was reduced by this therapy in the past. Other forms of treatment which is widely used nowadays are the intravitreal injections to access the posterior region of the eye (Gote et al., 2019). But this treatment has massive limitations such as retinal hemorrhage and is highly painful to the patients. Topical formulations such as eye drops and eye ointments has issues such as low bioavailability, high dosage requirement, chances of systemic toxicity. Hence, scientists are desperately searching new methods of drug delivery to the eyes. Multiple approaches such as developing novel drug delivery systems including nano formulations, implants allow sustained and controlled release of drugs and

will help in maintaining constant systemic concentration of the drug for the desired therapeutic effects (Gote et al., 2019).

1.1.4 Current treatment methods & their limitations

The effective management of the chronic ocular diseases requires the localized delivery of drugs at a continuous basis. The treatment option for the posterior eye diseases such as diabetic retinopathy, macular degeneration requires the drug to reach the target tissues such as retina which is delivered using intravitreal injections. These injections require an invasive procedure and has a very low patient compliance and requires a set of skills possessed by trained healthcare professionals only. Thus, self-administration becomes almost impossible. A number of complications occur such as endophthalmitis, increment of intraocular pressure (IOP), cataract & retinal detachment. In a nutshell, it could be stated that the prolonged use of intravitreal injections could not be considered for chronic ocular conditions. Several advanced implants have been developed to reduce the drawbacks of the drug delivery to the eyes via the transscleral and the intraviral route which will allow a sustained and controlled release of drugs for a considerable period of time. Clinicians treat anterior segment disorders such as dry eye disease, cataract, and allergic conjunctivitis by topical eye drops. Upon topical instillation drugs are absorbed either by corneal route (cornea → aqueous humor → intraocular tissues) or non-corneal route (conjunctiva → sclera → choroid/RPE). The preferred route depends mainly on the corneal permeability of drug molecules (Gaudana et al., 2009). The bioavailability of the topical formulations for the eye is considerably low and needs to be addressed since a very high dose is required to reach the therapeutic level of the drug which results in the systemic toxicity. This occurs due to the low rate of diffusion, small retention time and a very high rate at which tears are being replaced. The topical formulations are usually administered to the anterior segment of the eye and a large portion of the

dose is lost when it is administered. To address this problem, different novel drug delivery systems are under development. (Achouri et al., 2013; Fangueiro et al., 2016). **Table 2** shows the advantages and disadvantages of each of the route of drug administration to the eyes along with the diseases treated via each of the routes.

Table 2: *Different routes of ocular drug administration (Gaudana, Aanthula et. al 2010).*

SL No.	Route of Administration	Advantages	Limitations	Treatment of Disease
1.	Topical	It has a high patient compliance since the self-administration is possible. It is non-invasive form of treatment thus there is very low risk of infection	The penetration of the drugs to the target tissues is difficult due to the presence of corneal barriers. The rate of drug diffusion is low and the drugs are likely to be diluted by the water content of tears.	• Conjunctivitis • Keratitis • Uveitis • Episcleritis • Scleritis • Blepharitis
2.	Intravitreal	The drugs are delivered directly to the retina and the vitreal structure and thus have a high bioavailability.	It has a low patient compliance. Several major risks exist such as retinal detachment, hemorrhage, occurrence of endophthalmitis and cataracts. It is a painful and invasive procedure	• Age related macular degeneration (AMD) • Branch retinal vein occlusion (BRVO) • Central Retinal Vein Occlusion (CRVO) • Diabetic macular edema (DME) • Cytomegalovirus (CMV) retinitis
3.	Subtenon	Non-invasive in nature. Lower risk of comorbidity in comparison to the delivery via intravitreal route. It maintains higher drug concentration in the vitreous tissues.	Chemiosmosis may occur along with subconjunctival hemorrhage. The retinal pigment epithelium acts a barrier.	• Diabetic macular edema (DME) • Age related macular degeneration (AMD) • Retinal vein occlusion (RVO) • Uveitis
4.	Posterior juxta scleral	Drugs can be deposited which is an advantage. It prevents the intraocular damage. The drug level in the macula could be	The barrier presented by the retinal pigment epithelium. The requirement of surgical procedures	• Age related macular degeneration (AMD) • The risk of endophthalmitis

		sustained for a period of 6 months.		
5.	Systemic/oral	The drug delivery system is non- invasive and have a high patient compliance.	The barriers present in the retinal blood and the blood aqueous layer. This leads to low bioavailability and causes systemic toxicity.	• Scleritis • Episcleritis • Cytomegalovirus (CMV) retinitis • Posterior uveitis
6.	Intra-corneal	The systemic and the corneal side effects are limited compared to the use of topical steroids. The drug concentration in the anterior part is higher.	The syndrome of endothelial cell destruction and also the anterior segment toxicity.	• Anesthesia • Treatment of endophthalmitis
7.	Subconjunctival	Depot formation is possible and it's used for the delivery of drugs to the anterior and the posterior drug delivery method.	The circulation of drugs in the choroidal and the conjunctival parts increase the chances of toxicity	• Glaucoma • Cytomegalovirus (CMV) retinitis • Age related macular degeneration (AMV)
8.	Retrobulbar		Respiratory arrest, retrobulbar hemorrhage, globe perforation	Anesthesia

*Note: **CMV** (Cytomegalovirus), **AMD** (Age related macular degeneration), **DME** (Diabetic macular edema), **RVO** (Retinal vein occlusion), **CRVO** (Central retinal vein occlusion, **BRVO** (Branched retinal vein occlusion)*

1.1.4.1 Topical Eye Drops

The topical eye drops are considered to be the most common, safe, convenient option for delivering drugs to the eyes for ages. It has a very high patient compliance, and could be self-administered by the patient themselves. But, the drug permeation and the concentration at the target site is not constant over time. At the time of administration, there is a high dose at the site which gradually declines as time progresses. The kinetics of the drug concentrations decreases via first order. The contact time of the drug is also a major concern because of the tear and lacrimal flow which results in very low bioavailability. Added agents known as additives are being added to the formulation

such as viscosity enhancers to increase the viscosity of the drug solution, permeation enhancers are used to increase the rate at which the drug enters the deep ocular tissues such as vitreous humor, retina etc. The permeation enhancers elevate the time at which the drug persists at the site of administration thus increasing the time of contact. The integrity of the corneal tissues is changed thus the permeation of the drugs are increased. The examples of the viscosity enhancers include the hydroxymethyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose etc. and the permeability enhancers such as Benzalkonium chloride, poly-oxy ethylene glycol ethers (lauryl, stearyl and oleyl) are mostly used. But, the use of these permeability enhancers has a major concern which is the precorneal loss. The thing that needs to be considered is the fact that the ocular tissues are highly selective in nature and will only allow specific molecules to surpass. The development of carrier systems which are inert is necessary to allow effective delivery of drugs to the specific target ocular tissue. Even if the field of nanotechnology and nano formulations are expanding at a drastic pace, the conventional formulations like these will still be able to occupy a larger portion of the market. However, there are several drawbacks that will require the attention and needs to be solved soon such as the instability of the formation, low rate of diffusion, the irritation at the site of administration, inflammation and thus hampering the vision of the individual. These conventional formulations are constantly being tried on to deliver the drug molecules to the back of the eye effectively but only a handful of success exist.

Although a considerable number of efforts in research are being made to improve the efficacy of the topical formulations, a lot of drawbacks still exist. The problems associated with these formulations includes the eyes becoming red after administration, thus triggering the inflammation of the site and also causing itching and discomfort to the eye. **Figure 2** traces the flowchart of the pharmacokinetics and the pharmacodynamics of the drugs administered to the eyes.

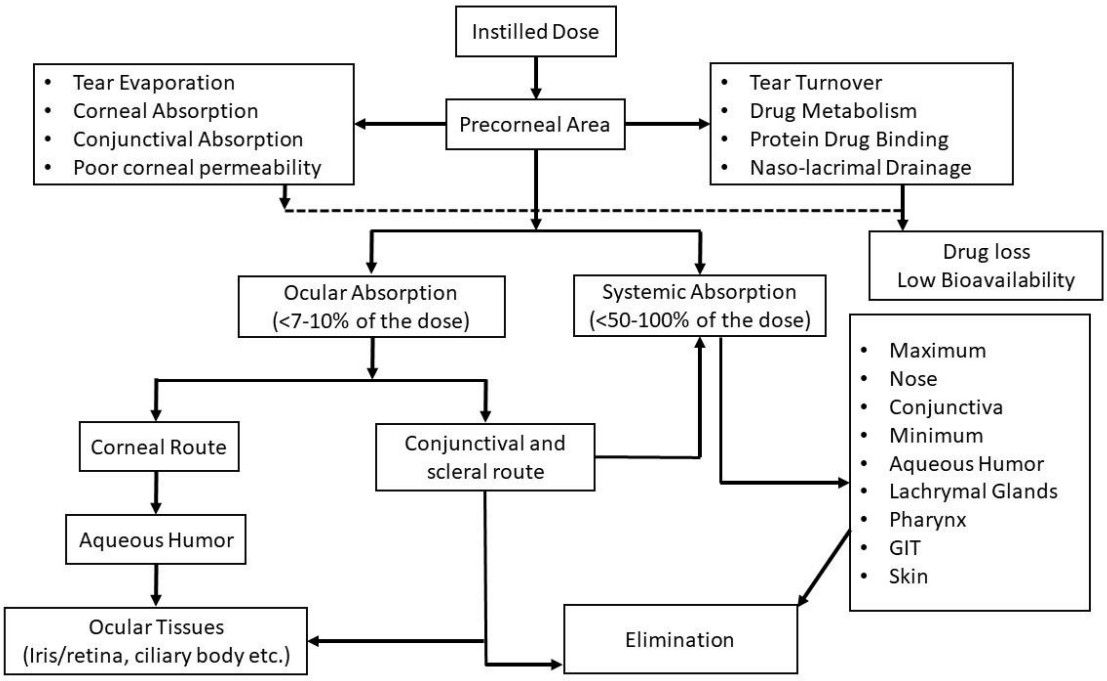

Figure 2: *Pharmacokinetics and Pharmacodynamics of Ocular Drug Delivery (del Amo & Urtti, 2015; Kang-Mieler et al., 2020). The route of absorption of the drugs inside the eyes is shown along with the route of absorption. The limiting factors of absorption along with the elimination route is also shown in the figure.*

1.1.5 Novel ocular drug delivery

1.1.5.1 Microneedle mediated ocular drug delivery

Microneedles can be used to deliver drugs to specific targeted ocular tissues with a minimal invasive method and will allow a greater accuracy and precision than the hypodermic injections. This will account for greater patient compliance and less complications which is involved with other treatments. The microneedles could be used for sustained delivery of drugs. It could be designed according to the patient requirements which could account for tailor made personalized medication via drug loading (Thakur Singh et al., 2017). The application of microneedles to deliver drugs to the eyes is a new concept and needs a lot of research in this field before it could be

commercially used by patients. But the advantages it offers are exciting and could drastically change the way drugs are delivered to the eyes today.

1.1.6 Nanotechnology and nanomedicine-based ocular drug delivery

Nanotechnology and nanomedicine-based drug delivery approach to the eyes is a rapidly changing area of research and is developing at a great pace. The use of nanotechnology in ophthalmic formulations is increasing for the treatment of both anterior and posterior eye diseases. These could result in developing formulations which has low irritation, higher bioavailability and improved ocular tissue compatibility.

1.1.6.1 Ocular implants

Ocular implants are usually designed to attain a localized delivery for a sustained period of time. The idea is to implement these implants to patients who has chronic eye conditions. Intravitreal injections for a chronic treatment accounts for massive discomfort for the patients and poses several complications. Thus, implants could act as a solution to this problem. But the implantation is an invasive procedure which requires incision in the posterior part of the eye (posterior to the lens and anterior to the retina). This surgery might be minor but requires extreme precision and skills. The development of implants could accommodate the limitations but factors such as acceptance of the patient, approval by the regulatory bodies remains a concern.

1.1.6.2 Contact lens

Contact lens are thin discs made of plastic which have a curved shape designed to attach to the cornea of the eye. When it is applied to the eye, it attaches to the corneal surface via surface tension. These lenses could be used to deliver drugs to the eyes when it is loaded with drugs. It was seen that the drugs delivered in this process had greater time of residence because of the slower tear flow through it. Thus, it will have greater bioavailability. Despite the advantages and efficiency of the lenses, limitations such as irritation, inflammation could result in the eyes and it is not a suitable mode of drug delivery for a sustained period of time for chronic eye conditions (Thakur Singh et al., 2017)(Faheem & Abdelkader, 2019). **Table 3** summarizes the advantages and disadvantages of the recent advancements in the field of ocular drug delivery system.

Table 3: *Discussing the advantages and disadvantages of the recent advancement in the ocular drug delivery system (Lee et al., 2020)*

SL No	Type of drug delivery system	Advantages	Disadvantages
1.	Ocular Implants	• The time of residence of the drugs increases • Allows controlled release of drugs • The frequency of administration is lowered • The delivery via the non-corneal route is possible	• It is difficult to insert into the eyes • The penetration enhancers used causes irritation
2.	Nanosuspensions	• The bioavailability is increased • The ease of commercialization • The physical activity is lengthened	• It is time consuming • The grinding ball undergoes abrasion
3.	Hydrogel Systems	• The polymers used are biodegradable • The drug release is extended and controlled • It does not cause toxicity	• The vision is blurred
4.	Liposomes	• The drug release is sustained for a long time • The bioavailability is high	• Costly • Non stable

		• It is biodegradable and biocompatible in nature • Usually doesn't trigger immune response	• the leakage fusion of drugs takes place
5.	Niosomes	• The ocular absorption is improved via trapping the hydrophilic drugs • The bioavailability is increased so is the drug penetration. • It is biocompatible and doesn't trigger an immune response	• Drug aggregation • Fusion • Hydrolysis • Smaller shelf life • Irritation in the eye
6.	Discomes	• The entrapment of the drug is higher compared to niosomes which results in improved bioavailability of the drugs which are hydrophilic.	• It is costly and causes irritation to the eye.
7.	Solid Lipid Nanoparticles (SLNs)	• The lipophilic and hydrophilic drug could be loaded with a higher capacity and could be sterilized by autoclaving which elevates the retention time and bioavailability of the drug	• Drug expulsion following polymeric transition during long storage
8.	Polymeric Nanoparticles	• It biodegradable and shows a greater penetration of the ocular tissues. • Doesn't initiate an immune response • Greater time of residence in the tissues and thus greater therapeutic effect	• Expensive and effect of burst
9.	Microspheres	• The delivery of the drug is controlled and have a higher bioavailability and have lower toxicity	• Expensive • Irritates the eye • Difficult to scale up • Shows burst effect
10.	Lipid Emulsions	• It is biodegradable and a longer release profile and a higher permeation of the ocular tissues and could be sterilized easily	• The drugs that are highly water soluble could not be used
11.	In-situ gelling system	• Higher retention time of the drugs in the tissues	• The vision is blurred and persists in the eyelids
12.	Contact lens	• The release of drugs could be sustained for a prolonged period of time	• The chronic use resulted in the decrease of the keratocytes in the cornea
13.	Cyclodextrin complexation	• The stability is higher and has a greater biological activity. The permeability of the cornea is higher and thus have a greater bioavailability • Limited side effects are seen	• If used in larger amounts, it leads to toxicity
14.	Dendrimer	• The efficacy and efficiency of the drug is higher and shows greater penetration	• The vision is blurred and leads to the loss of the eyesight.

Chapter: 2

Methodology

The resources were based on the available literature on the topic: “Microneedles for Ocular Drug Delivery”. The recent articles were searched from the databases like Pub Med, Science Direct, Google Scholar, SCOPUS using keywords such as, “Microneedle”, “Ocular drug delivery”, “Fabrication” etc. The idea was to collect the background information first on the topic to see the recent trends in this field. Then, the research gap was determined by going through the collected articles. There was an inclusion and exclusion criteria to filter out the articles and select those which is to be used in the writing process. Specific headings and subheadings were constructed to form the basic framework of the project. Under each of the headings and subheadings, research questions were formed. The answers to the research questions were collected via going through the articles from different sources mentioned above. The in-text citations and the bibliography were generated using the Mendeley Desktop version reference managing software. The purpose of the dissertation literature review is summarized in **Figure 3.** The entire review process is summarized in **Figure 4**

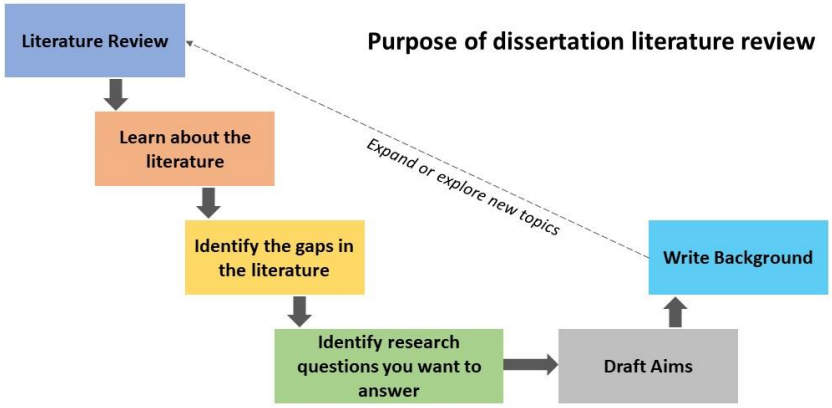

Figure 3: *Purpose of dissertation literature review (Kilubi, 2016)*

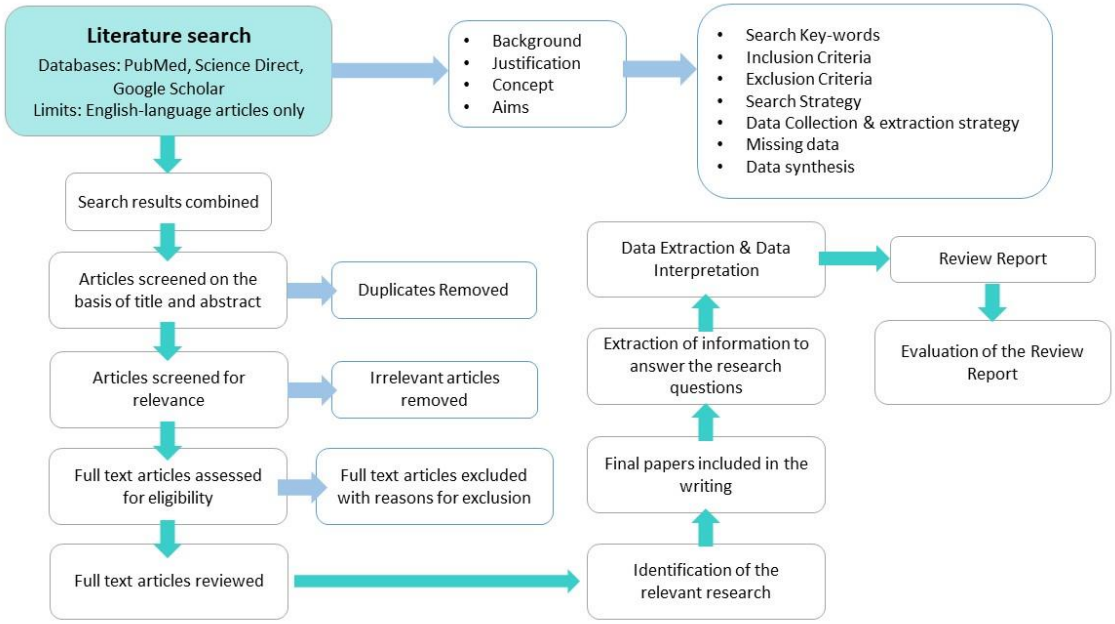

Figure 4: *The flowchart of the review process (Baldie et al., 2018; Levey et al., 2017)*

Chapter: 3

Microneedles in ocular drug delivery

Microneedles are devices that have dimensions ranging from few micrometers to 200 micrometers and are usually made from metals or polymers. The minute structure of microneedles allows them deliver drugs to the specific ocular tissues in a non-invasive and much more controlled manner than the conventional form of delivering drugs to the eyes. The potential of the application of microneedles are incredibly high. It was capable to address and combat the limitations associated with the conventional system of delivering the drugs to the eye and thereby attaining the delivery of the drugs to the targeted ocular tissue with considerable improvement in accuracy. (Gupta & Yadav, 2019). **Figure 5** shows the overview of the microneedles and its classifications

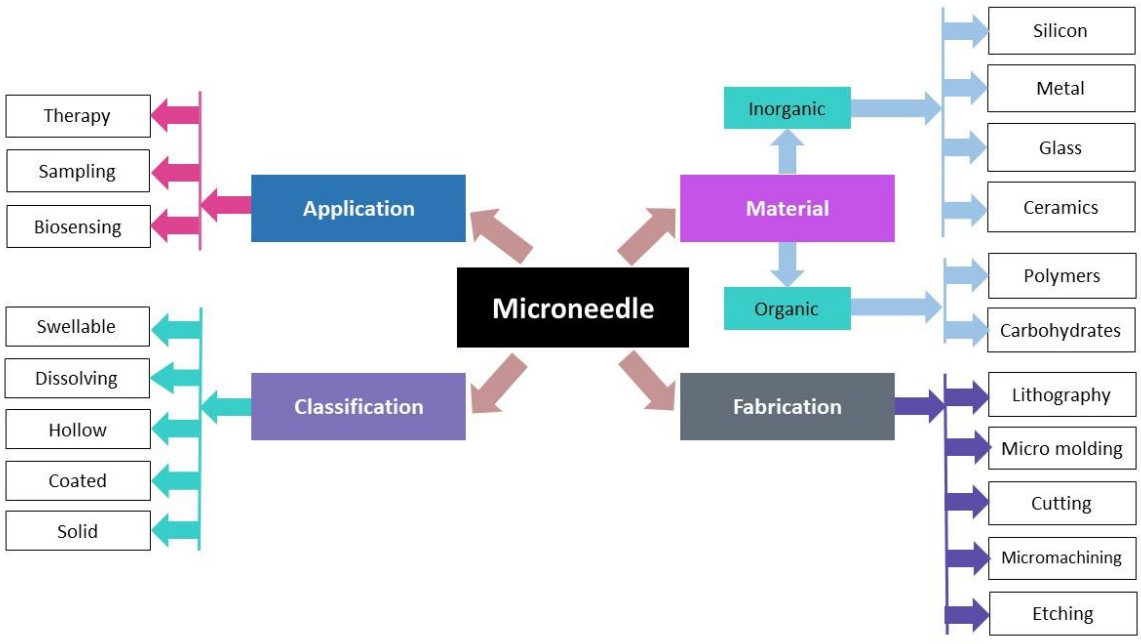

Figure 5: *Overview of Microneedles (Bhatnagar et al., 2017). Different aspects of microneedles are shown such as the classification, application, fabrication & material.*

3.1Types of microneedles

Various types of microneedles exist which have different therapeutic applications. However, four major types play crucial role in the targeted delivery of drugs to the eye. These are: solid coated, hollow & dissolving, polymeric microneedles.

3.1.1 Solid coated microneedles

The structure of the solid microneedle is specially designed to penetrate the tissues and dissolve immediately. They could be then removed from the tissues. The result of the penetration is a microscopic hole through which the microneedle would be able to transfer drugs to the specific eye tissues. these microscopic holes create a channel which connects the interior of the eye tissue to the external environment and is created via the perforation created by the solid microneedles. Solid microneedles are usually fabricated with the materials such as stainless steel, silicon probes etc. the major concerns about the use of these materials are that they are non-biodegradable & the process of fabrication is complex. The drugs loaded in the coating of the microneedles dissolves to release the drugs to the ocular tissues (Gupta & Yadav, 2019).

3.1.2 Hollow Microneedles

Hollow microneedle, as the name suggests, have a hollow space inside the structure where the drugs are loaded. To make the delivery of the drugs more effective, nanoparticles are often used in formulation and is delivered via hollow microneedles. It has other massive applications such as insulin delivery, vaccine delivery etc. But the idea of the application of hollow microneedles in the eyes is a relatively new concept and has huge potential. The materials used for manufacturing the hollow microneedles are usually borosilicate micropipette and the biodegradable polymers. Stainless steel is also used occasionally. But the source of concern is that material borosilicate is

not ideal for clinical applications. The process of fabrication is difficult since the micropipettes are pulled to increase the length of the needles and to create a hollow space inside the needles in the process. The drug loaded hollow microneedles create an insertion in the ocular tissues to deliver the drugs from the hollow space. Therefore, this process of fabrication needs to be upgraded to manufacture the hollow microneedles in bulk quantities to supply according to the clinical demand (Gupta & Yadav, 2019).

3.1.3 Dissolving Polymeric Microneedles

Polymeric microneedles are manufactured using biodegradable polymers. They are thought to be more feasible than the solid microneedles because they are more biocompatible and easier to penetrate into the ocular tissues. the microneedle patch is to be applied onto the ocular tissues and then the drug present in the layer between the needle and the patch is released into the targeted tissues. The fabrication process of polymeric microneedles involves molding & the material used mostly is the biodegradable material poly-dimethyl siloxane. The method involves the penetration of the mold with needles which have the length of few microns and then the mold is to be dried. Afterwards, the formulation containing the polymers and the drugs are placed into the array of mold to finally complete the process of manufacturing the polymeric microneedles. The efficiency and personalization of this process requires the availability of the molds and customization of the process. Thus, personalized medication is difficult using this process of fabrication (Gupta & Yadav, 2019).

Table 4 shows the different types of microneedles, the materials used and the pros and cons of each type

Table 4: *Classification of microneedles (Sharma et al., 2019)*

SL No.	Microneedle classification	Fabrication Materials	Advantages	Restrictions
1.	Solid Microneedles	• Silicon • Stainless steel • Acrylic	• It shows a larger mechanical strength and thus can withstand higher forces	• The fabrication process consists of two steps • It has a low patient compliance
2.	Hollow Microneedles	• Silicon • Metal • Glass • Ceramic • Polymers	• Larger doses could be administered • Useful for molecules which have a higher mass	• Possibilities of blocking the needles • The fabrication process is complex • Expensive
3.	Coated Microneedles	• Stainless steel • Titanium • Polymer	• The process consists of a single step	• The amount of drug which could be coated on the surface of the needle is limited
4.	Dissolving or Biodegradable Microneedles	• Cellulose • Sugar (dextran) • Polyvinyl alcohol • Polyvinyl pyrrolidone • Carboxymethyl cellulose • Chitosan • Polyglycolic acid • Polylactide co glycolide (PLGA)	• The process consists of a single step • Doesn't need to be removed physically • The fabrication process is simple • Allows the delivery of drugs at a controlled rate • The patient compliance is high • Cheaper	• There are possibilities of the deposition of polymers in the skin • Larger temperature is needed for the biodegradable microneedles which have an effect on the amount of drug which could be loaded.
5.	Hydrogel forming	• Polyvinyl alcohol (PVA) • Polylactidide co glycolide (PGLA) • Chitosan • Ether co maleic acid	• Intact removal is possible • Don't leave any polymer residues • Less chances of infection	• Less mechanical strength • Difficult to maintain the shape geometrically

3.2 The use of microneedles in ocular drug delivery

3.2.1 Anterior segmental delivery of drugs

The drug formulations for the topical administration are viewed as the most helpful and reasonable methods of drug delivery to the front segment of the eye. The explanation behind this is the way that it doesn't include any intrusive strategies that could be conceivably unsafe and hazardous to the eyes. Yet, the significant worries of these conventional topical drugs are the low bioavailability, failure to arrive at the objective site of activity viably and the need of a very large amount of dose to achieve the level of the drug which could give the therapeutic effect which eventually prompts the poisonousness of the medications. The explanation behind low bioavailability could be the high pace of reflex squinting, high tear turnover rate, and the lacrimal emission of the eye. Every one of these elements decline the maintenance season of the medications to the visual tissues. Different factors, for example, the presence of metabolic catalysts like peptidases, amino ketone reductases, carbonic anhydrases, N-dealkylating specialists and so on present on the eye makes the visual medication conveyance a considerably more provoking assignment to achieve. The advancement of novel medication conveyance choices, for example, the utilization of microneedles is getting significantly more common to address those difficulties. One of the principal preliminaries of microneedles on the front eye fragment included the utilization of strong microneedles covered with DNA or protein as model particles. The microneedles were controlled into the scleral tissues of hares and human dead bodies ex vivo. The outcome got showed an intense improve in the bioavailability evaluated by a few orders in contrast with the customary eye drops. This had propelled the specialists to buckle down on its improvement in light of the variety of additional opportunities. To treat the corneal neovascularization, a comparable methodology was embraced where the microneedles were covered with bevacizumab and was embedded into the

cornea of rabbits. No antagonistic impact was noticed for this method of treatment upon microanatomical investigations. The drug loading limit of the solid microneedle is a region of concern if this strategy is to be applied in a huge scope clinical arrangement. To step up the limit of medication stacking, DRIE strategy for manufacture with complex fenestrations was utilized to create planar formed microneedles. Thus, the medication stacking limit was raised to 500% contrasted with the past application without fenestration. The productivity of the medication conveyance was assessed utilizing spectrophotometry and fluorescence microscopy on the test tissues of hare cornea. Other than the utilization of covered microneedles in visual medication conveyance, dissolvable microneedles are likewise being developed for the delivery of medications to the back portion of the eye. With respect to model, Raghu et al. manufactured a PVP based 3*3 microneedle exhibit which is formed like a cone having the accompanying measurements: tallness of 800 μm and a base of 300 μm. These were fabricated by the traditional trim interaction. The pace of medication arrival of these models relied upon the distinctive atomic loads of PVP (M/w =70 and 150kDa). Those dissolving microneedles contained 0.96-9.91 μg of medications while stacking and they delivered the medications inside 10-180s when applied. The penetrability test which was done ex vivo on the porcine eyes showed that the utilization of dissolving microneedles permitted the conveyance of medications at a higher porousness than the eye drops. A comparative report was finished with a similar dissolving microneedle to convey besifloxacin to the corneal tissues. 100 μg of besifloxacin was stacked in a 6*6 dissolvable microneedle cluster to convey into the human corneal tissues. The fixing of the microneedles for a time frame minutes fundamentally improved the penetration and dissemination in the cornea which showed an expanded antibacterial movement in the contaminated cornea in contrast with the free besifloxacin arrangement. A separable microneedle cluster was presented by Then et al.

as an eye fix. The microneedle could be embedded into the cornea of two unique materials (HA and methacrylated HA) which permitted the controlled arrival of medications and was created by means of trim. The restorative viability was upgraded by the energy of the biphasic discharge. This trial showed that the microneedle fix which is stacked with hostile to angiogenic monoclonal antibodies diminished 90% of the neovascular zone of the neo vascularized mouse models. The fundamental models of an effective corneal medication conveyance are the addition of the microneedle in the corneal tissue without entering the whole profundity of the tissue and not outperforming it to another tissue. This is a tremendous test since the cornea of the eye has a little profundity and is extremely flimsy and the fluid humor present at the rear of the cornea doesn't give sufficient steady ghastly power to encourage the inclusion of the microneedles. Consequently, the microneedles generally require the infusion helping instrument. One of the techniques that could be utilized is the utilization of a spring-stacked pen stage that infuses the microneedles momentarily with a spring created sway. In this interaction, the microneedles were collected at the tip of the pen and were applied to the mouse cornea. To play out this, the SU-8 microneedles were coordinated with an altered pen implement with the use of move shaping method with the PDMS form. The pen instrument utilized with microneedle had the option to convey rhodamine B into the stromal cornea without making a significant hole contrasted with the hole made when regular infusions are utilized. The adequacy of the organization of pen covered sunitinib malate was under close checking for the treating neovascularization in the corneal angiogenesis model. The treatment technique for the drug delivery of the foremost section of the eye could be adjusted for the supported medication conveyance for the treatment of irresistible sicknesses like keratitis. The eye drops for the treatment of keratitis has a low patient consistence due the prerequisite of rehashed measurement. The drug delivery through the contact focal point could permit supported

medication conveyance to the eyes yet has significant results like obstructing the oxygen supply and transportation of the cornea. For this very explanation, there is a prerequisite to build up a medication conveyance framework that could give supported arrival of medications subsequently decreasing the need of incessant organizations. The tip separable microneedle pens (d-MNPs) which contain the biodegradable tips stacked with drugs were created utilizing the exchange shaping interaction for the corneal stromal infusion. The boundaries for the effective corneal organization are as per the following: drug tip of 48 μm tallness, the abide season of 10s for the microneedle infusion, the microneedle spring load (k=2.29 N/mm), and the microneedle inclusion profundity of 86 μm which was improved by the association of mechanical pressure and was tried in vivo. After application, the tip is withdrawn and remains inside the tissue and starts delivering drugs continuously, and keeps doing as such for as long as 7 days. The remedial viability of the medication was additionally checked utilizing the mouse acanthamoeba keratitis model. There were no deterioration or results that were seen for the d-MNP infusion in the sick cornea after a time span of one day after the infusion. Following four days the treated cornea showed diminished mistiness because of the infusion. This impact was seen to be proceeded for two additional days (Lee et al.2020)

3.2.2 Posterior segmental delivery of drugs

A portion of the normal infections of the posterior fragment of the eye require the medication to arrive at the assigned objective tissues, for example, the macular or fringe retina. Regular types of treatment include intravitreal infusions which are straightforwardly infused through both sclera and glassy humor to convey the medications straightforwardly to the focused-on tissues in the back fragment. In spite of the dependability of this technique for delivery, it includes obtrusive strategies and has a great deal of disadvantages (e.g. Dying, intraocular diseases, and so on) Empty

microneedles could be utilized to stack drugs in the empty space between the sclera and the choroid which is known as the suprachoroidal space (SCS) and is a possible option for the intravitreal infusions. An investigation was done where microneedles were embedded into the human scleral tissues of thickness 5-7 mm from the limbus. The empty microneedle was incorporated with the pen-like infusion gadget, the microneedles had the length in the middle of 700-1000 µm. This cycle empowered the supported arrival of medications from the SCS and brought down the dosing recurrence. The medication conveyance by means of the SCS course expanded the medication fixation to the back section by 10 creases subsequently the medications arrived at the site of activity more viably than the intravitreal infusions. Because of the expandible idea of the SCS, the obstruction of stream was lower contrasted with the encompassing incompressible tissues, thus, the microneedles don't have to enter genuinely into the SCS or to open it by means of gruff analyzation. The liquid which was infused by the empty microneedles streamed effectively into the SCS in practically no time and extended it anatomically. In another investigation, the improvement of a plan was done where the medication model entered the SCS layer and the medication arrived at the back portion when the medication was conveyed by means of empty microneedles. The portrayal of the microneedles was finished utilizing the bunny eyes where the impacts of definition creation, the volume of the infusion, and the medication dissemination time was being checked and investigated. This utilization of microneedle to the SCS was approved by the unmistakable side biomedical, GA. This association had played out various clinical preliminaries for the commercialization of the medication conveyance by means of SCS course with microneedles (US clinical preliminary NCT02952001). As referenced already, the microneedle pen was received to convey medications to the back fragment of the eye. In the later examination, Park et al, built up a system to convey drugs that was simple and permitted sway

addition. The speed of inclusion could be constrained by the utilization of this gadget. It had been assumed that the model medication or the little atoms could be conveyed through the sclera by controlling the profundity of the injury in the tissue. Consequently, to control the profundity of inclusion dependent on the speed of the addition of microneedles, three sorts of springs having distinctive spring constants were utilized. The spring constants of the accompanying springs are as per the following: 73.5 +/ - 5.1, 360.2 +/ - 10.3, and 1561.4 +/ - 10.4 N/m and the addition profundities were. 58, 219 and 312 μm separately. The dissemination of the model medication rhodamine across the sclera was looked at and investigated between the three unique gatherings: 1. Effective organization; 2. Physically embedded microneedles; 3. Microneedle pen addition. The tests that were done ex vivo uncovered that the sclera had the best convergence of rhodamine and is circulated over the biggest surface territory. Afterward, the in vivo results did on the beagle eyes showed that the medication diffused all through the sclera from the site of addition in the limbus to arrive at the back fragment of the eye. The empty microneedles which are slim in nature could be utilized for the general intravitreal infusion yet the length ought to be adequately long to arrive at the profundity of addition to bridge the external hindrance of the eye. To make this potential, techniques, for example, super high AR and empty microneedles (otherwise called the pinnacle microneedles) have been manufactured utilizing reverse drawing lithography on the dull customary needles. The microneedle tip that was sloped at a 15-degree point to the pinnacle microneedle was manufactured by the utilization of a laser shaper to achieve the elective technique for intravitreal infusion with least obtrusiveness (Lee et al., 2020)

3.3 Opportunities of the application of the microneedles in ocular drug delivery

The microneedles are an appealing innovation that offers a negligibly intrusive drug delivery framework. It has been widely utilized throughout the most recent 15 years to improve transdermal medication conveyance and its advancement had prompted a gigantic move from the customary needle-based insulin infusions. The microneedles are normally 25-2000 μm and they are created by the utilization of an assortment of materials and are of various shapes. The materials which are generally utilized for creation are silicon, glass, or polymers to produce both of the strong or empty kinds of microneedles. The easy idea of organization of the microneedles raised the exploration interest among researchers to expand its applications to effortless and non-intrusive medication conveyance strategies in various territories. The commercialization of those wide scopes of uses stays a test. The advantages of the microneedle application to the eye over the intrusive intraocular infusions which utilize long hypodermic needles make it a reasonable possibility to supplant the regular types of eye medicines. The length of the microneedles is sufficiently long to outperform the visual obstructions with potential preferences, for example, bypassing the visual boundary work (epithelium and sclera), permitting the limited drug delivery of the focused-on tissues (intrascleral and intrastromal conveyance), the torment is minimizable, diminishing the odds of tissue harm and contamination, expanding the patient consistence. Another examination led by Gliger et. al showed the effective conveyance of triamcinolone acetonide to the SCS which was done in vivo utilizing the 33 G empty microneedles having 850 mm stature. There were no clear unfavorable impacts of the investigation, for example, expanded intraocular pressure, drug harmfulness, or discharge of any kind. Intrascleral delivery was finished with the empty microneedles where the embed framing thermo-responsive poloxamer-based gels were utilized in

situ. The components of the empty microneedles were: 400, 500, 600 mm in tallness and were manufactured from the hypodermic needles (for example 27, 29 and 30 G) and the infiltration profundity was tried on the rabbit sclera. The supported medication conveyance of the fluorescein sodium was noticed for 24 hours. The rate fluctuated with the profundity of gel delivery. The intrascleral and intracorneal drug conveyance of the model medications were likewise researched. The model medications utilized were fluorescein sodium and fluorescein isothiocyanate dextrans (Atomic load of 70 kDa and 150 kDa individually) and quickly dissolving polyvinylpyrrolidone based microneedles were utilized. The dissolving microneedle varieties of 800 mm tallness and 300 mm width showed an uncommon expansion in the restriction of the intraocular drug contrasted with the periocular skin organization. In this way, it very well may be expressed that the microneedles could be utilized for the restricted medication conveyance of both the front and back portions of the eye. The utilization of microneedles for ocular drug delivery could change the manner by which the medication definitions are conveyed to the eyes. Be that as it may, the ebb and flow impediments and difficulties in the visual microneedle application require further examination to empower its far-reaching clinical application. **Figure 6** show the process of drug delivery at the site of insertion via hollow microneedles

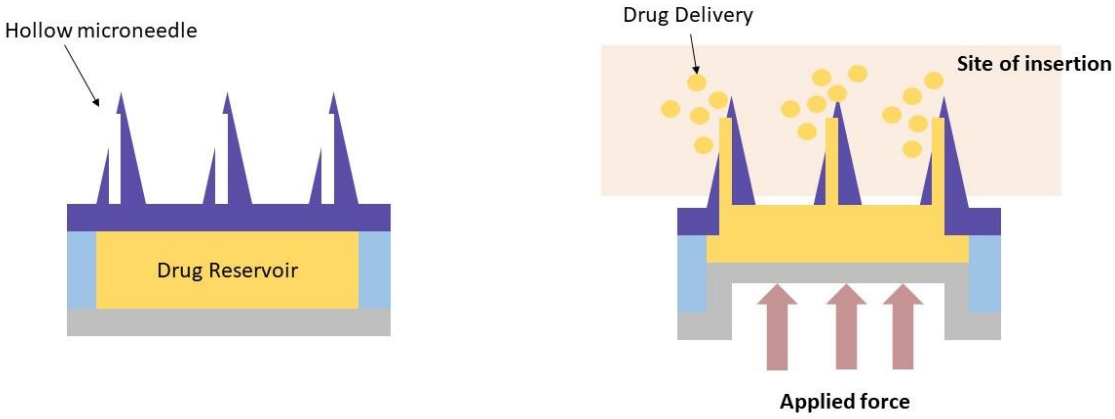

Figure 6: *Targeted drug delivery via hollow microneedle (Juhnke & Mühlbacher, 2013). The hollow microneedle contains a drug reservoir which contains the drugs stored in the hollow space of the microneedle. During insertion, the applied force allows the drugs to be released at the site of insertion*

Table 5 shows the comparative animal studies to determine the pharmacokinetic and pharmacodynamic properties in the eye tissues of rabbits and humans

Table 5: *Comparative studies of the pharmacokinetically relevant anatomical and physiological parameters in the eyes of rabbits and humans (del Amo & Urtti, 2015)*

				Rabbit	**Human**	**References**
Physiological values affecting CL_{ivt}	Blood flow mediated CL_{ivt}	Barrier Surface Area	Surface Area of RPE	520[a] mm^2	1204 ± 184[b] mm^2	(Raechenbach et al. 1994) Panda-Jonas et al. 1994)
		Barrier Permeability	TEER OF RPE layer	179 ± 6 ohm.cm^2	79 ± 48 ohm.cm^2	(Koyano et al. 1993) (Quinn and Miller 1992)
		Blood Flows	Choroidal Blood Flow	62 ml/h	43 ml/h	(Nilsson and Alm. 2012) (Sebag et al. 1994)
			Retinal Blood Flow	0.66 ml/h	0.26 ml/h	(Nilsson and Alm. 2012) (Feke et al. 1989)
			Ciliary body blood flow	4.91 ml/h	5.34[c] ml/h	(Nilsson and Alm. 2012) (Alm and Bill. 1973)
			Iridial Blood Flow	3.72 ml/h	1.02[c] ml/h	(Nilsson and Alm. 2012) (Alm and Bill. 1973)
	Aqueous humor flow mediated CL_{ivt}	Aqueous humor flow		0.18 ml/h	0.14 ml/h	(Barany and Kinsey. 1949) (Brubaker. 1982)
		Barrier between vitreous and anterior chamber		Unidentified	Unidentified	
Physiological values affecting $V_{ss.ivt}$ of all drugs		Ocular volumes	Vitreous volume	1.15 ml	4 ml	(del Amo et al. 2015) (Ruby et.al 2006)
			Lens Weight	0.33-0.53 g	0.15-0.26 g	(Zamudio and Candia. 2011) (Hemenger et al. 1995)
			Uveal tract & retina weight	0.16 g		(Wiederholt et al. 1986)
			Choroid weight	0.059 g		(Wu et al. 1970)
			Iris Weight	0.057 g		(Wu et al. 1970)
			Ciliary body weight	0.050 g		(Wu et al. 1970)
		Tissue affinities	$K_{p\ ocular\ tissues}$	No data	No data	

Chapter: 4

Fabrication of microneedles

As of now, four primary kinds of microneedles are normally utilized for the delivery of drugs: solid, hollow, coated, dissolvable or biodegradable microneedles. The solid microneedles are generally utilized in dermatology as they structure miniature cuts in the pretreatment to permit the drug plan to be delivered into the targeted tissues with high permeability across the hindrance of the tissues. The medications are blended in with polymer covering plans and are covered into the outside of the microneedles for the confined drug delivery. Different cycles including the dissolvable microneedles are utilized for the supported drug delivery since the bio functional materials are saddled to keep up the medication strength in the microneedle patches. Likewise, the hollow microneedles are utilized to give characterized channels to the focused-on drug delivery to the particular tissues. microfabrication and micromachining procedures had been used to create various kinds of microneedles. As of late, other manufacture strategies, for example, drawing lithography and progressed forming innovation have been utilized to make microneedle of different shapes and sizes (aspect ratio = 0.7-100) and size (height 200-2000 μm). The **figure 7** illustrates the process of the microneedle fabrication starting from the drug solution to the formation of microneedle patches/arrays

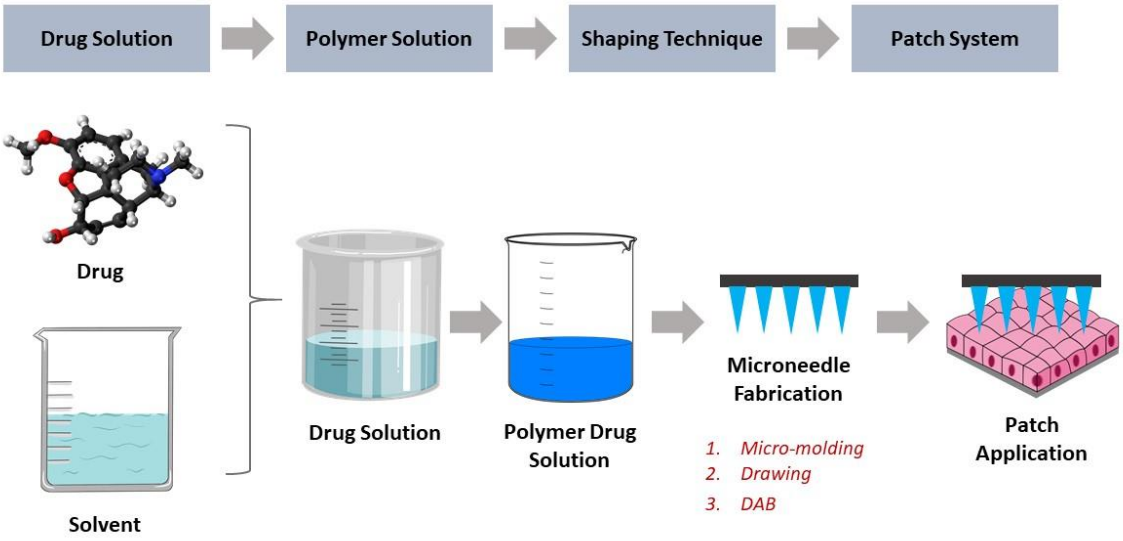

Figure 7: *Schematic Process of microneedle fabrication (Tucak et al., 2020; Waghule et al., 2019). The solvent and the drug solution are combined and then polymer is added to form the polymer drug solution. Different fabrication techniques were used until a microneedle patch is formed which is administered to the site of insertion*

4.1 Microfabrication

The microfabrication innovations which are adjusted from the assembling of incorporated circuits were demonstrated to be appropriate for the enormous scope creation of microneedles with high reproducibility. the absolute first microneedle was constructed utilizing this microfabrication strategy with silicon. the ordinary microfabrication procedures incorporate photolithography, meager film statement, and scratching which were utilized for manufacture. the last state of the microneedles essentially relies upon the last advance of creation which is either a wet engraving or a dry engraving measure. the diverse cluster of shapes is conceivable to create because of the adaptability of the dry drawing measure. it permits the client to control the boundaries including the gas stream rate, carve pressure, temperature, force, predisposition, and the sort of veiling layer. the microneedles could be modified by changing these boundaries appropriately. then again, the

wet carving measure has a few restrictions with regards to the state of the microneedles. the principal silicon microneedle created for the medication conveyance was manufactured utilizing the profound receptive particle drawing measure (DRIE) of silicon wafers. a 20*20 microneedle cluster with the needles of tallness 150 µm and 150 µm dividing and was created on a 2cm * 2cm chip. the ordinary silicon dry etchants, for example, SF6 and O2 were utilized to carve the silicon the vertical way, though the CF4 was utilized to forestall the horizontal undermining (Bosch Cycle) bringing about a higher perspective proportion (AR) microneedle. the length of the microneedles was characterized by utilizing the bosch interaction. the underlying passivation step guaranteed additional assurance to the tip of the microneedles. with respect to model, a microneedle tip having a stature of 40 µm and an angle proportion of 1 was shaped by means of under scratching utilizing O2 AND SF6. thusly, the bosch cycle was likewise used to make an opening in the tightened empty microneedles. anisotropic wet engraving measure was likewise used to deliver the silicon empty microneedles. the engraving rate relies upon the silicon plane direction during the methodology which is not normal for the dry scratching measure where the engraving rate is autonomous of the gem planes. wafers with a square designed veil could be scratched by KOH answer for make the pyramid-molded holes, tightened at 54.22 degrees. The microneedles which are decorated could be made into various shapes by changing the compound etchant, shower temperature, or cover plan. The microneedles which have an angle proportion of 1-1.15 and tallness of 70-80 µm were formed from a solitary silicon wafer and were utilized for the infusion of DNA into the plant or creature tissues. the thickness of the microneedles in a cluster could be expanded up to % by changing the veil shape into a square, circle, or jewel. The expansion of carving pays constructions, for example, the square with fingers can likewise change the shape and thickness of the microneedles; a mix of KOH scratching and dicing is embraced to make more mind-boggling

microneedles structure and to improve the addition capacity. In **figure 8** the process of the fabrication of silicon hollow microneedle has been illustrated. The process of wet etching used to fabricate the silicon microneedle is shown in **figure 9**

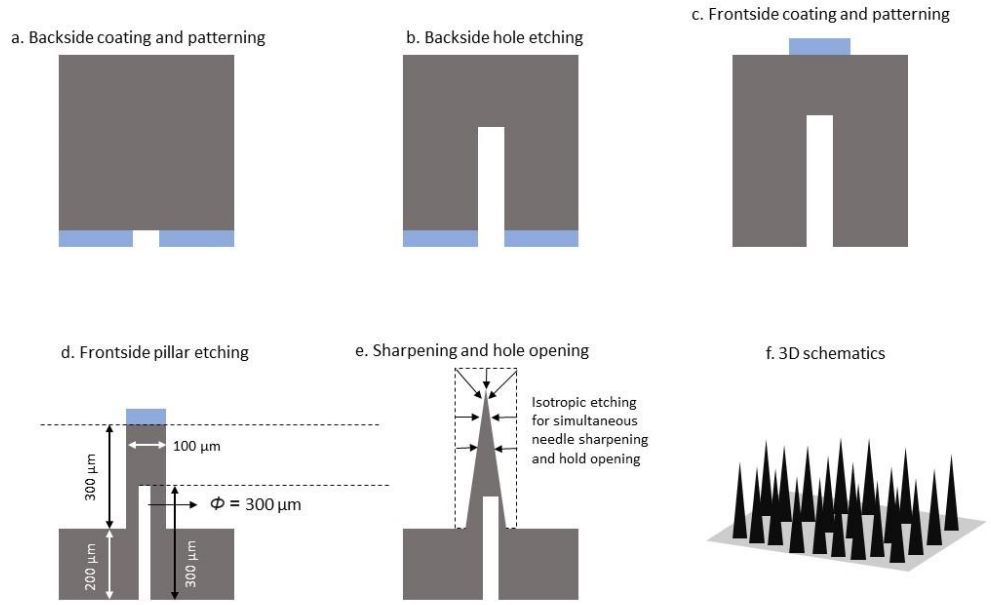

Figure 8: *Fabrication of Silicon Hollow Microneedle (Li et al., 2019). The formation of 3D schematics of microneedle arrays of hollow microneedles via etching*

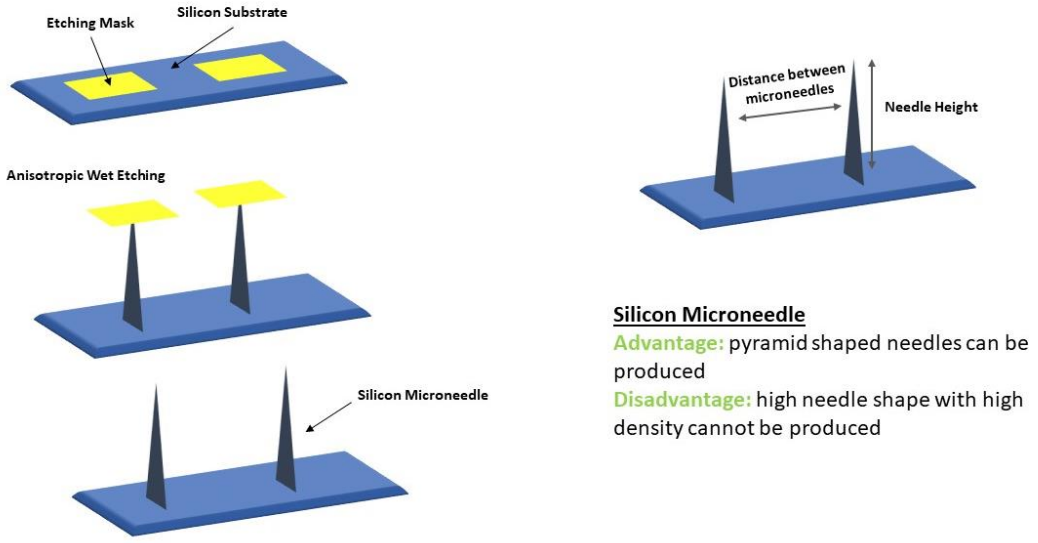

Figure 9: *The fabrication process of silicon microneedles via wet etching process (Pradeep Narayanan & Raghavan, 2017). The process of anisotropic wet etching is used to fabricate the silicon microneedles where the needle height and the distance between the microneedles are controlled.*

4.2 Other techniques

Different approach to the process of the fabrication of the microneedles has been used that involved the application of the lasers in the cutting process of the microneedles to definite shapes. The microneedles were made into a pyramid shape using the metal in the ablation process using laser cutting; thus, the obtained resolution of the microneedles was micron sized. Those microneedles which were of the height of 40 micrometers were made by allowing different settings in the laser emitting device such as, how many shots needed? Or customizing the aspect ratio in the mask in the manufacturing process. The process involved the use of a sheet of metal. Those with height of 40 micrometers and 0.3 as the diameter of the tip to form the arrays of 5*6. The two-dimensional microneedles were fabricated using the IR laser in the process of cutting the metal sheet, and thus, it was done at the plane of the stainless steel which used the device which was bent at right angles opposite of the plane. Two layers were formed in the process of the development of the microneedles involving the solution of the SU-8 material spread over the Pyrex glass and those were exposed to the ultraviolet light and was made to direct at two-degree range of angles from 3-5. This led to the formation of the pillars of those material. Several adjustments need to be made eg: the aspect ratio being at the range of 4-6 and the length being 400-500 micrometers. The entire process was accomplished in a single step. Another technique with groundbreaking potential in this field is the use of 3d printing process in the fabrication procedures of the microneedle. But this process is quite complex compared to the other processes used currently. It could dramatically elevate the resolution of the microneedles and it would have sharp edges which would allow

greater penetration. In **figure 10**, the process of fabrication of SU-8 hollow microneedle has been outlined

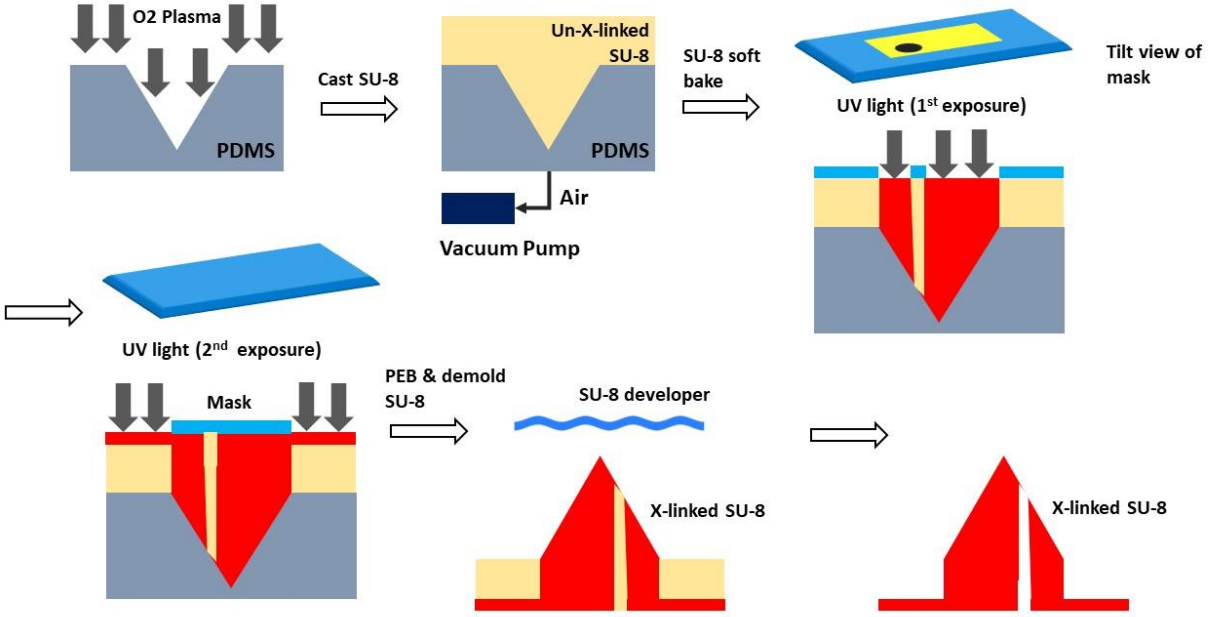

Figure 10: *Fabrication of SU-8 hollow microneedle (Wang et al., 2009)*

Recently, the fabrication of the microneedles introduced the use of the technology 3d printing to integrate with the manufacturing process and to add a more efficient and effective dimension to the large scale customizable microneedles. Notwithstanding the way that it is an expensive and muddled interaction, the extra cycle to hoist the printing goal is normally embraced to get the microneedles with sharp tips. Luzuriaga et al. created the microneedles by the utilization of combined testimony demonstrating (FDM) 3D printing of polylactic corrosive (PLA). For the ideal exactness of the microneedle tip, from the outset, a variety of 200-2500 µm in tallness and 400-600 µm in distance across was printed, and afterward it was carved in the 5M arrangement of KOH

for 9 hours. The carved microneedle cluster kept up the first length while the measurement and tip size were decreased (200-300 µm and 1-55 µm individually). The technique for stereolithography (STL) has a higher goal than the combined testimony demonstrating (FDM) and is utilized for printing the polymeric microneedle patches for transdermal insulin conveyance. The stature and measurement of the printed microneedles were around 1000 µm and the goal of the microneedles was lower than the microneedles delivered through traditional strategies. Hydrogels that are shrinkable could be a reasonable choice to improve the goal by utilizing them to make the miniature form. The hydrogel microneedle holes were made with the STL-printed microneedles. Subsequently, the shape made has a decreased size by 40% as a result of its drying out. **Figure 11** shows the schematic illustration of the fabrication process of polymeric microneedle via micro molding

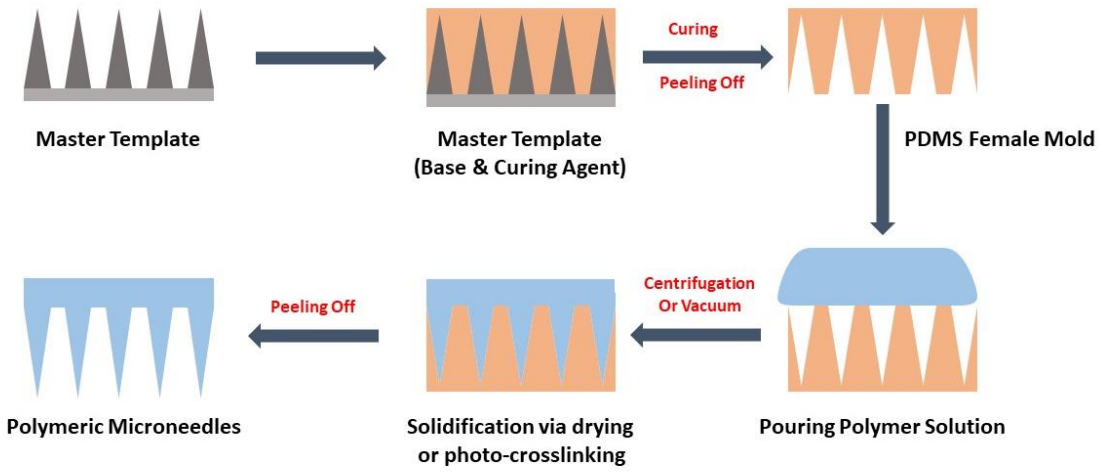

Figure 11: *Schematic Illustration of Polymeric Microneedle fabrication by micro molding (Wang et al., 2017). The master template is used to form the PDMS female mold in which the polymeric solution is poured and solidified to form the microneedles.*

4.3 Drawing Lithography

Despite the fact that etching has been the overwhelming strategy for the manufacture of microneedles, the method faces some basic difficulties and is restricted by the crucial subtractive nature. Drawing lithography had arisen as an elective that could be utilized to build up the 3d designs made of polymers straightforwardly from a two-dimensional surface. This interaction has a quicker strategy and is savvy and claims to can adjust the model of the microneedles for different biomedical applications contrasted with other creation strategies The shape of the scaffold was polymeric and was created by the elongation via drawing substrate of the SU-8 material. Furthermore, it couldn't handle the body of the microneedle clusters. that is the reason a comparable methodology was embraced to control the shape and make the clusters spatially discrete warm drawing. In this manner, explicit body profiles for the microneedles are accomplished. This attracting technique prompted the manufacture of biodegradable microneedles with super sharp tips which gave authority over the state of the microneedles. The process of drawing lithography for the fabrication of microneedles has been illustrated in **figure 12.** The **figure 13** shows the process of photolithography used for the fabrication of microneedles. **Table 6** summarizes the fabrication methods for different classes of microneedles

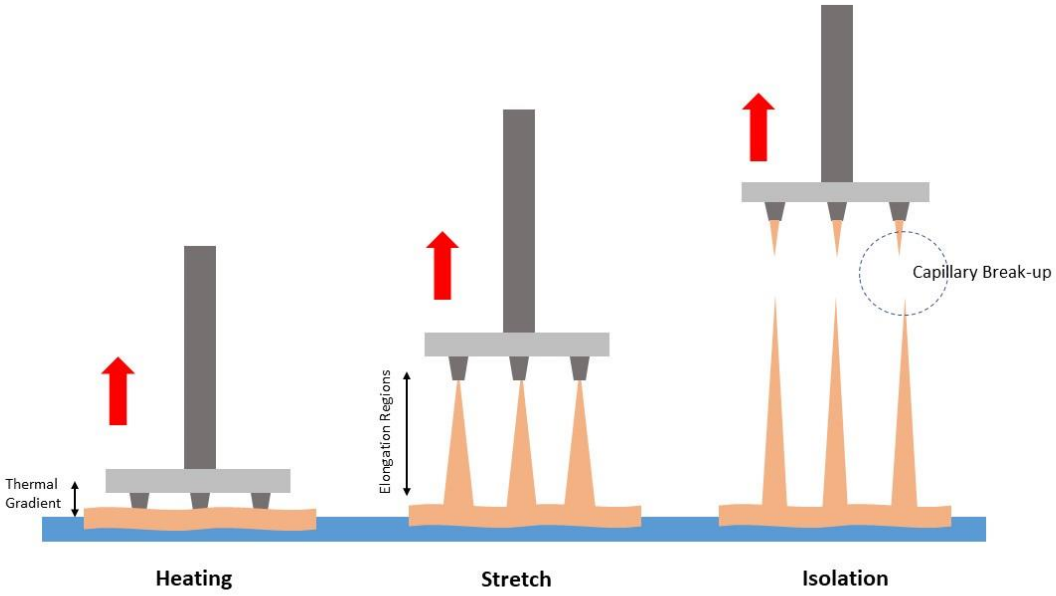

Figure 12: *Fabrication of microneedle by drawing lithography (Terashima, Tatsukawa, Suzuki, et al., 2020). It is carried out in three steps: heating, stretching & isolation.*

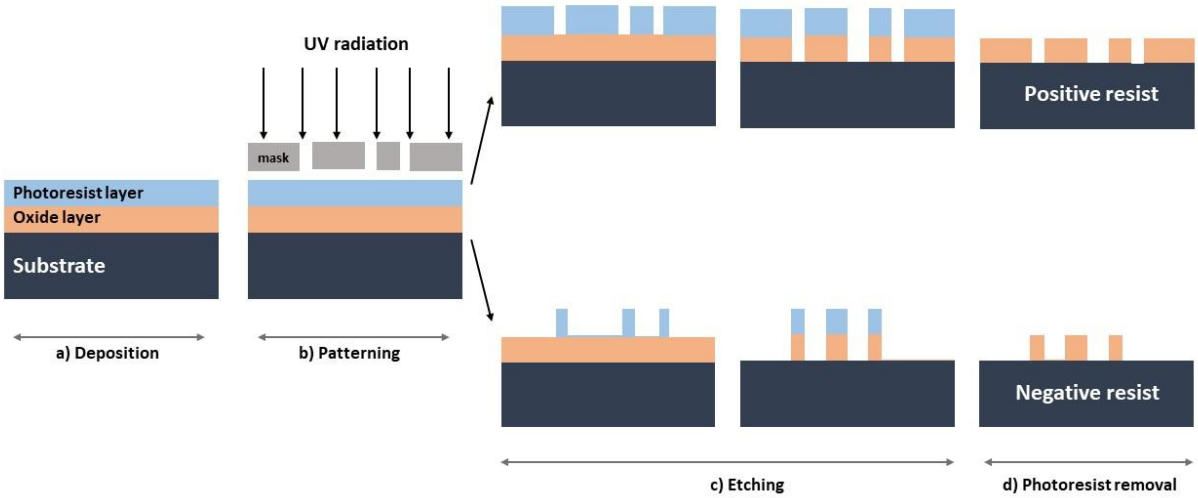

Figure 13: *The manufacturing process of microneedles via photolithography (Larrañeta et al., 2016). The process is divided into 4 steps: (a) deposition, (b) patterning, (c) etching, (d) photoresist material*

Table 6: *the methods available for the fabrication of microneedles (Sharma et al., 2019) (Waghule et al., 2019)*

SL No	Microneedle Type	Materials Used in Fabrication	The process of fabrication
1.	Solid Microneedles	Silicon	-Etching Process • Dry etching • Isotropic etching • Anisotropic wet etching -Dicing of the silicon substrate and then acid etching -3D laser ablation
		Metal	• Electroplating • Laser cutting • Wet etching
		Polymer Ceramic	Photolithography • Sintering Lithography • Micro molding
2.	Coated Microneedles	The microneedles are either dipped or sprayed with an aqueous solution which have a high viscosity thus it could retain greater amount of formulation when it is done with drying. it contains a surfactant which acts as an active agent and also as a stabilizing agent. The microneedles are dipped several times in the coating solution containing the drugs or a film could be used which is already formed from the drug solution and a roller is used.	
3.	Dissolving Microneedles	Micro molding techniques	
4.	Hollow Microneedles	• Laser micro matching • Microelectromechanical systems (MEMS) • Deep reactive ion etching • Deep x ray photolithography • Wet chemical etching • Micro fabrication	

Chapter 5:

The application devices & the safety concerns of microneedle

5.1 Devices used for the application of microneedle

It poses a huge challenge for the administration of the drugs to reach the tissues of the eye in an in vivo setting when the microneedles are used as a form of drug delivery mechanism. The advancement of the technology of microneedles allowed the process to be much more efficient since the first attempt on the eye. The challenges remain since the strength of the tissues of the eyes such as the sclera or the cornea doesn't possess or unable to provide the mechanical support to facilitate the insertion of the microneedles compared to the support from the skin tissues because of its toughness. The eye tissues are much more delicate than the skin tissues thus to deliver the desired drugs effectively via microneedles, the ocular system requires a delivery device for the microneedle application. A unique design was presented by Melody et al. which consists a device resembling like a pen for the application of the microneedles on a very small surface area of the ocular tissue and thus showed massive improvements in the penetration and permissibility of the microneedles. A large-scale pen type device was connected to a SU-8 microneedle in the form of patch and that covered an area of 200*200 squared micrometers and had a height of 140 micrometers. The model molecules used in the experiment was the rhodamine B, evans blue or the sunitinib malate. The microneedle pen device used for its administration was seen to have a considerable increase in the effectivity of the administration process and had led the drugs reach the targeted tissues at an efficient manner. The procedures of the infusion methods of the conventional microneedles were compared and analyzed with the use of the microneedle application devices by Matthaei et al and efforts to improve the manufacturing process was done. Considering the use of different infusion volumes and the use of needles of different lengths in

each case, it was observed that the process involving the use of the applicator device; the microneedle pen had more efficient and effective drug application to the eye and those reached the target tissues at a higher rate than the microneedles used without this device.

Table 7: *Physicochemical characteristics of Microneedles on target tissues (Lee et al., 2020). Different instances of animal & clinical studies of the microneedle application to the eyes*

SL No.	Site of insertion	Specifications	Type & Material	Model drug	Fabrication	Administration
1.	Cornea of rabbits	L: 400-700 μm AR: 2.6-3.0	Metal Coated	• DNA • Bevacizumab Instant Delivery of the drugs	2-dimensional laser cutting	Manual Patching
2.	Cornea of humans	L: 961 ± 27 μm AR: 2.4-2.8	PVA/PVP Dissolving	• Besifloxacin Sustained drug release which persists for almost 24 hours	Conventional Molding	Manual Patching
3.	Cornea of mouse	L: 500 μm AR: 2.0	MeHA/HA double layered	Immunoglobins which sustained for more than a day	Multiple Molding process	Manual Patching
4.	Cornea of mouse	L: 140 μm AR:0.7	SU-8 Coated	• Sunitinib Instant Delivery of the drugs	Transfer Molding process	Pen type injector
5.	Cornea of mouse	L: 150 μm AR: 1.5	SU-8/PGLA Hybrid	The sustained delivery of polyhexanide (PHMB) for greater than 4 days	Transfer Molding process	Pen type injector
6.	Choroid of pig	L: 750-1000 μm AR: 2.5-3.5	Glass or metal Hollow	• Bevacizumab Instant Injection	Conventional Machining process	Syringe
7.	Sclera of beagle	L: 400 μm AR: 1.5	SU-8 Coated	Instant delivery of rhodamine B	Transfer Molding process	Pen type injector
8.	Sclera of rabbit	L: 5-10 mm AR: ultra high	Nickel Hollow	Instant injection of phenylephrine	Drawing Lithography process	Syringe

Note: ***HA*** *(hyaluronic acid),* ***PGLA*** *(poly lactic co glycolic acid),* ***PVA*** *(polyvinyl alcohol),* ***PVP*** *(polyvinyl pyrrolidone),* ***PHMB*** *(polyhexanide),* ***SU-8*** *(epoxy based negative photoresist),* ***L*** *(length),* ***AR*** *(aspect ratio)*

5.2 The safety concerns of microneedles

The concerns of the safety factor of the use of microneedles on the eyes is somewhat debatable since it's a relatively new concept and is an unconventional form drug delivery to the eye. As mentioned before, the potential of this form of delivery is massive and thus the safety becomes an issue to look at via expert views. Before commercializing any form of microneedle use in the eye, absolute certainty must be attained regarding its safety. Though only a limited studies and research was carried out on this field, not a huge database could be found as references. Kim et al. studied the effectiveness of the use of the microneedle on the ocular tissues via in vivo procedures. They used the cornea collected from the rabbits to compare the effect a model drug delivered with microneedle and without a microneedle and determined the safety parameters of the application. The safety of the microneedle was determined via the histological approach of the tissues of the cornea. Only a small incision was found the surface of the cornea having a dimension of 200 micrometers. It disappeared within 24 hours leaving no issues or infection of any sort. Even if the experiment was repeated with different parameter changed and different variables being altered for a period 18 days, the corneal tissues recovered from the incision created by the microneedles thus ensuring that conditions such the darkening of the cornea was seen. No anatomical abnormalities or changes were seen the corneas treated by microneedles, also, there was no presence of any inflammation or the occurrence of immune response Therefore it validated the safety profile of the use of microneedles on the eyes. Further research in future will reveal more reliability regarding this matter.

Table 8: *List of clinical trials at present (Ingrole et al., 2021)*

SL No.	Clinical Trials/ govt. identifier	Title	Clinical trial phase	Conditions	Interventions	Sponsor	Locations	Number of participants
1.	NCT03203447	Suprachoroidal injection of triamcinolone Acetonide with IVT anti-VEGF in subjects with macular edema following RVO	3	Macular Edema	Drug: Suprachoroidal CLS-TA + IVT anti-VEGF agent	Clearside Biomedical, Inc.	Multiple	460
2.	NCT03126786	Suprachoroidal CLS-TA with intravitreal aflibercept versus aflibercept alone in subject with diabetic macular edema	2	Diabetic Macular Edema	Drug: IVT aflibercept Drug: Sham SC Drug: SC CLS-TA	Clearside Biomedical, Inc.	Multiple	71
3.	NCT03097315	Suprachoroidal injection of CLS-TA in subjects Non-infectious Uvetitis	3	Uveitis, Posterior Uveitis, Anterior Uveitis, Intermediate Panuveitis	Combination product: 4mg CLS-TA Suprachoroidal Injection	Clearside Biomedical, Inc.	Multiple	38
4.	NCT02952001	Extension study of patients with non-infectious uveitis who participated in CLS1001-301	3	Uveitis, Posterior Uveitis, Anterior Uveitis, Intermediate Panuveitis	Drug: 4mg CLS-TA Suprachoroidal Injection.	Clearside Biomedical, Inc.	Multiple	33
5.	NCT02949024	Suprachoroidal injection of CLS-TA alone with aflobercept in subjects with diabetic	1 & 2	Diabetic Macular Edema	Drug: IVT Aflibercept Drug: SC CLS-TA	Clearside Biomedical, Inc	Multiple	20

		macular edema						
6.	NCT02747030	Phase I RVC with ocriplasmin for CRVO	1	Central retinal vein occulsion	Drug: Ocriplasmin Intravenously	Universitaire Ziekenhuizen Leuven	UZ Leuven, Leuven, Viaams Brabant, Belgium	4
7.	NCT02595398	Suprachoroidal injection of CLS-TA in subjects with Macular Edema associated with non-infectious Uveitis	3	Uveitis Uveitis, Posterior Uveitis, Anterior Uveitis, Intermediate Panuveitis	Drug: 4mg CLS-TA Suprachoroidal injection Drug: Sham Procedure	Clearside Biomedical, Inc	Multiple	160
8.	NCT02255032	Suprachoroidal injection of triamcinolone acetonide in subjects with macular edema following non infectious uveitis	2	Uveitis Macular Edema Uveitis, Posterior Uveitis, Anterior Panuveitis Uveitis, Intermediate	Drug: 4mg CLS-TA Drug: 0.8mg CLS-TA	Clearside Biomedical, Inc	Multiple	22
9.	NCT01789320	Safety study of suprachoroidal triamcinolone acetonide via microneedle to treat uveitis	1 and 2	Uveitis Intermediate Uveitis Posterior Uveitis Panuveitis Noninfectious Uveitis	Drug: triamcinolone	Clearside biomedical, Inc	multiple	11

Chapter 6:

Discussion

Microneedle application on the eyes is a relatively new concept compared to the conventional forms of treatment of the eye which is there for ages. It is a massive upgrade to the efficiency and effectiveness of the chronic eye care and is believed to be more patient friendly. In this paper, the prospects of microneedle in the ocular drug delivery field have been discussed. The animal studies and some clinical trials which has taken place so far is showing promising results and a hope for the patients with complex eye conditions. The fabrication processes for the manufacture od microneedles are improving at a sheering pace ensuring the efficiency of the process.

Chapter: 7

Conclusion

The use of microneedles in the ocular drug delivery has massive potential and it is a work in progress. The opportunities and the applications of this novel drug delivery system are widespread and will be revealed even more in the coming years due to increased amount of research going on this filed. The microneedles will eventually limit the conventional forms of treatment that is available to treat the diseases of the eye. It will soon be able to treat those diseases much more efficiently and effectively. Even though it is a far-fetched idea to make it commercially available, but the pace at which it is developing and improving via the vigorous research in this field, it is not very far from the day that the conventional needle use in the eye would be completely eradicated.

Chapter: 8

Future Aspects

Within the end of this current decade, we could see a massive shift in the treatment process of the eye diseases. The use of microneedles will allow the patients to have personalized medication at a more accessible fashion than it is today. It will allow the self-administration, painless, safe and a more efficacious form of treatment at a higher accuracy. The treatment of acute and chronic blindness that is caused by macular degeneration, diabetic retinopathy, retinal vein occlusion will be have a more patient compliance and effective. The integration of methods such as 3D and 4D printing of microneedles could make the fabrication process of microneedles much more efficient and customizable according to the need of the patient.

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