Journal of Electrical Engineering
The Institution of Engineers, Bangladesh
Vol. EE 36, No. II, December 2009

Solid Silicon Microneedles for Safe and Effective Drug Delivery to Human Eye

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***Abstract*— Guidelines on the fabrication of solid, out-of-plane Silicon (Si) microneedles for drug delivery to the posterior segment of human eye have been provided. The posterior and the anterior chambers of the human eye have been studied along with the major obstacles to drug delivery, and thereafter a minimally invasive route for systematic drug delivery to the back segment was selected. Microneedle parameters were chosen so that drugs can be delivered successfully through the selected route. The entire fabrication process was simulated and the resultant micro structures have been reported and analyzed. A mechanical strength analysis was subsequently carried out for solid out-of-plane Si microneedles by using column buckling and bending forces. The data obtained from the analysis indicated that the fabricated needles should be able to withstand the pressure exerted by a thin layer of fibrous human tissue.**

Index Terms*— Microneedle, posterior eye segment, ocular delivery, RIE, etch isotropy, tissue resistance, scleral route, cornea, ocular barrier.

I. Introduction

DRUG delivery to the anterior and the posterior segments of the human eye has been one of the major challenges for biomedical engineers. The existing drug delivery processes to the eye involve the use of micro-device implants, contact lenses, perfusion devices, multiple injections, ocuserts, iontophoresis, creation of artificial anterior fluid chambers etc [1]-[4], [6]-[8]. Over the past decade, researchers have identified several problems with some of these methods that are considered both inefficient and unfriendly to patients [3]. Apart from difficulty of insertion, local drug delivery by implants may not cover the contra lateral eye, which makes it a rather inefficient method. There is also a possibility of these implants causing toxic reactions if used over a long period of time. Excessive use may also lead to ocular complications and may interfere with systematic blood circulations and the nervous system. Another major obstacle is that devices implanted in the posterior treatment fail to recognize and treat extra-ocular diseases.

Topical administration of drugs fails to effectively treat posterior segment diseases of the eye including age-related macular degeneration or ARMD, diabetic retinopathy, posterior uveitis, retinitis due to glaucoma etc [6]. The major problem with multiple intraocular or periocular injections is that they are inconvenient for patient. Multiple injections also increase the possibility of ocular infections, both short and long terms. There is also some possibility of the patient getting endopthalmitis and retinal hemorrhage [7].

By using microneedles we can avoid the problems posed by conventional eye injections or implant devices. Microneedles can provide a constant flow of liquid over a long period of time to a particular area, maintaining a sustained concentration gradient. Greater control over drug release and sample intake can be achieved with microneedles. Microneedles penetrate only a few hundred micrometers into the sclera so they are painless and easy to use [1]. A distinct advantage is that microneedles can bypass the blood retinal barrier or BRB. Microneedles should provide a minimally invasive way of delivering drugs effectively without contact with the cornea. Other advantages include treating extraocular and intraocular infections, higher efficiency and treatment of intraocular diseases by direct supply of drugs to the posterior segment etc. [3].

Microneedles are an attractive innovation of modern biomedical engineering that finds numerous applications in drug and gene delivery, protein and DNA injection etc. Some common microneedles are shown in figure 1. Microneedle research involves searching for new biodegradable polymers, modification of existing micromachining techniques, and introducing easy and cheaper processes for the fabrication of microneedles suitable for biomedical applications. Previously, glass, steel, dissolvable, polymer microneedles were fabricated using existing fabrication processes and were used in the medical field. However, Silicon (Si) provides a number of advantages over other materials in terms of device integration, simple fabrication, and availability. Si has been proved to be non-toxic to humans when used in small amounts [5]. Therefore, Si can be used as a material for microneedles for drug delivery to the eye.

There has always been a need for a novel drug delivery system which offers more biopharmaceutical properties and predictability of dosage [2]. Using microneedles for drug delivery to the eye is a fairly new concept since very little research was carried out in this field. Coated solid microneedles as well as hollow microneedles made from a variety of materials can be used to deliver drugs. Jason Jang et al. fabricated steel microneedles for drug delivery through intrascleral and intracorneal routes in vivo and in vitro [1]. They have measured the concentration of drugs in the posterior segment of the human eye. However, relatively little attention was paid to the selection of drug delivery routes or the

fabrication process of the needles. Therefore, in this paper we have provided guidelines on the fabrication of Si microneedles after selecting a suitable route for drug delivery to the back segment of the human eye. The fabricated needles show good force withstanding capability and should be able to penetrate the sclera without much damage. This process is minimally invasive, more effective than oral or topical administration of drugs and facilitates controlled delivery through the selected route.

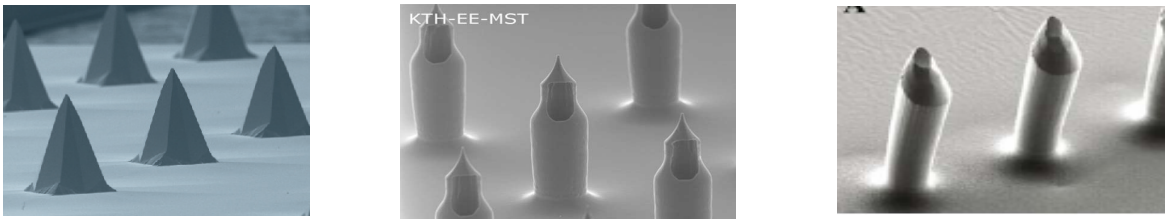


Fig. 1. Scanning Electron Microscopic (SEM) images of different types of microneedles.

II. Anterior and Posterior Segments of Human Eye: Barriers and Possible Routes

Figure 2 shows a cross sectional view of human eye with anterior and posterior segments indicated. The anterior segment is visible from outside and consists of a number of different tissues and cells. The major parts of the anterior segment are cornea, iris and ciliary body, anterior uvea, and aqueous humor. The posterior segment includes conjunctiva, sclera, choroid, retina, optic nerves and vitreous humor.

Drug delivery to the posterior segment is a formidable task [9] and has been a subject of research over the past couple of decades. Many diseases of the posterior segment require therapeutic levels of drugs. The major obstacle is that topical administration does not reach the posterior segment [8].

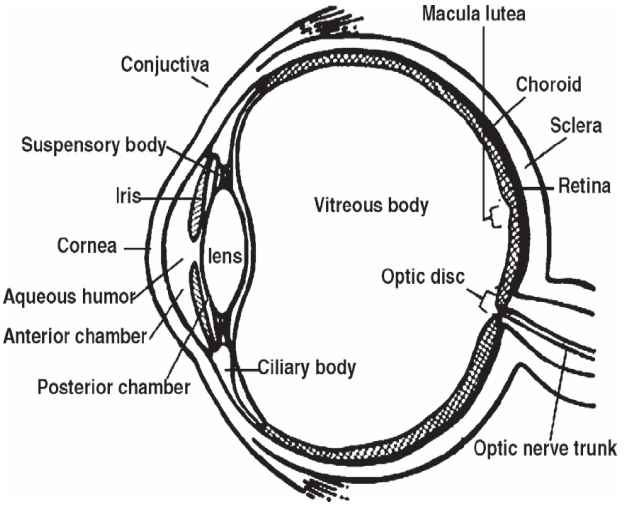


Fig. 2. Anatomy of human eye.

The general bioavailability of drugs is small, typically around 10% or less, which makes treatment of posterior segment eye diseases fairly difficult [9]-[10]. The anterior segment drug delivery has also been a subject of extensive research, since pre corneal factors like tear turnover, lachrymal drainage, nasal passage, aqueous humor act as ocular obstacles. Gunda et al. have shown that when a 50 μL volume is instilled topically, about 20 μL will be drained away [9].

Gunda et al, Rittenhouse et al, Ahmed et al, Hughes et al, Ambati et al, Urtti et al have done major research on transscleral, transconjunctival, and non-corneal absorption routes of drugs [9]-[14]. They have identified a number of possible routes for drugs to reach the posterior segment. The main drug delivery routes are given in figure 3.

The cornea is the outermost layer of the anterior segment and poses unique challenge to drug delivery [9], [12]. Both drugs that exhibit lipophilicity and drugs that exhibit hydrophilicity are barred by the cornea. This is because corneal epithelium shows lipophilicity while stroma acts as a reservoir for hydrophilic substances.

The conjunctiva is divided into two main parts: palpebral and bulbar, which show similar drug permeation characteristics. The conjunctival epithelium contains leaky blood vessels and consists of layers of soft human tissues that provide easy pathway to drug particles. Molecular size does not affect the drug particle flow through the conjunctiva [9]. The sclera is the opaque, white substance that is visible from outside. The sclera has variable thickness and variable drug permeation coefficient. Gunda et al. contended that the penetration of drugs through sclera is half as fast as that through the conjunctiva [9]. Both the sclera and the conjunctiva exhibit much higher drug permeation than cornea because of their soft tissues and porous blood vessels.

Inside the eye the retina and optic nerves are closely packed. Like the cornea, the retina is a sensitive part of the eye. The blood retinal barrier or BRB is the major obstacle to drug permeation posed by the retina; almost all drugs fail to penetrate this barrier [7]. Gunda et al have shown that the retina obstructs all drugs, regardless of their atomic size [9]. Intravenous injection is the most common way to deliver drugs to this segment. However, repeated dosage may cause retinal puncture and nervous damage, which may lead to long term ocular infections [15].

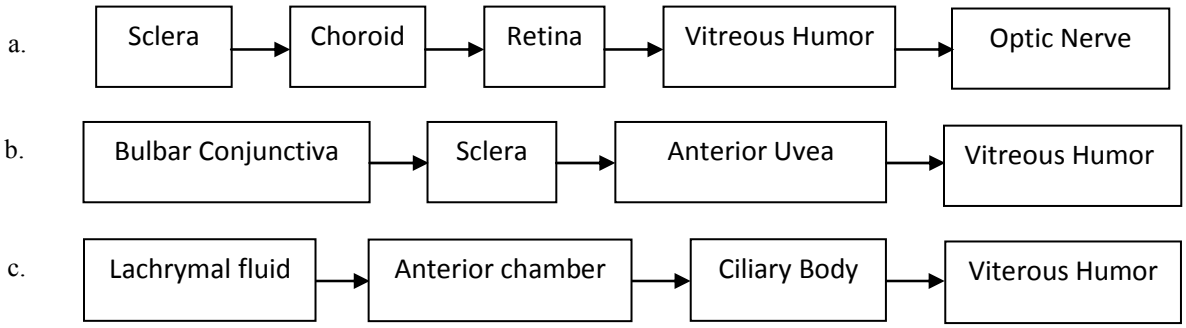


Fig. 3. Possible drug delivery routes to the posterior segment of human eye.

III. Selection of a Suitable Drug Delivery Route and Silicon Microneedle Entities

The corneal route of drug delivery poses several challenges in terms of poor permeability, sensitivity and small surface area [2]. The cornea consists of three layers namely corneal epithelium, stroma and endothelium, and it prevents the absorption and flow of both hydrophilic and lipophilic drugs. Therefore, this route should be avoided to increase efficiency of the process.

Both the sclera and the conjunctiva provide greater permeability to both hydrophilic and lipophilic drugs than the cornea; they also provide more surface area [7]-[12]. Although drug delivery via the bulbar conjunctiva and sclera has sometimes been termed "inefficient", a continuous dosage system through them can provide sufficient level of drugs. The scleral permeability is 20 times larger than that of the cornea and the conjunctival permeability is twice that of the sclera. The choroid consists of leaky vessels and porous walls that allow easy penetration of drugs. However, the sensitive retina poses major problems with its blood retinal barrier or BRB. The major problem with the route described in figure 3 c. is extremely poor bioavailability of drug. Lachrymal drainage is the major cause of poor availability of drugs. Usually tear turnover, conjunctival absorption and nasal drainage wash away a large portion of applied drugs. The route described in figure 3 a. should also be avoided because of the presence of the retina. Therefore, the only suitable path for microneedle is the one shown in figure 3 b., which avoids both the cornea and the retina. This route employs anterior uvea as drug depot, providing a steady flow of fluidic drugs to the vitreous humor.

The variable thickness of the human sclera is an important factor in ocular drug delivery. Olsen et al. have shown that the permeability of the sclera is inversely proportional to its thickness [8]. Therefore, microneedles should be inserted closer to the equator and away from optic nerves for minimal invasion.

Since Si microneedles penetrate the sclera which is the first barrier to the posterior segment, understanding the surface characteristics and surface area of the sclera is of utmost importance. Scleral thickness of the human eye varies significantly from the corneoscleral limbus to the equator to the optic nerve [4], with a minimum thickness of around 400 μm near the equator and a maximum thickness of 900 μm around the optic nerve. The mean scleral thickness is around 600 μm [1]. According to these findings, Si microneedles for therapeutic drug delivery should be longer than 400 μm so that they can safely penetrate both the conjunctiva and sclera, but their length should not exceed 900μm, in order to prevent any possible damage to the nerves.

For enhanced penetration capability, the needles should be tapered; the tip should be beveled and should have thickness in the nanometer range. The fabricated microneedles should be circular in order to optimize the design process [16]. The needle diameter is selected based on two important aspects: mechanical viability and minimal invasion. We propose varying needle base widths ranging from 10 μm to 15 μm. Taller needle should have thicker base for greater mechanical stability. The effectiveness of the base and length dimensions is proved in the mechanical analysis section.

IV. Fabrication of Solid Silicon Microneedles by Reactive Ion Etch

Numerous techniques have evolved over the course of time for fabrication of Si microneedles. Researchers have employed ultraviolet (UV) LIGA process, vapor-liquid-solid growth technique, wet etch, plasma etch, and reactive ion etch (RIE) techniques in the past [17]-[21]. Islam et al. have provided a comprehensive study on these processes [17]. They have compared the popular etch techniques and contended that RIE is the most suitable way to fabricate very high aspect ratio, tapered tip Si needles. Here we have used isotropic RIE technique with $SF_6/0_2$ as etchant for microneedle fabrication.

The entire fabrication process was simulated by a process simulator called ATHENA®. ATHENA® is a simulation module provided by Silvaco® International that provides a good platform for micro and nanostructure fabrication [17]. The ELITE module of ATHENA® allows the use of sophisticated models for etch process. This process is modeled by defining a machine and invoking the machine to perform etch. ELITE uses a string algorithm to describe topographical changes that occur during etching process. As micro/nanofabrication technology becomes more complex, modeling each step of the manufacturing process is increasingly important for predicting the performance of the technology. The microneedle structures obtained from

simulation have been analyzed and their properties have been investigated in a later section.

Si microneedles were fabricated on a 500 µm p-type (Boron doped) Si substrate. The front side of the [100] oriented wafer was cleaned for processing. After deposition of a layer of thickness 20 µm of silicon di-oxide (SiO_2) by chemical vapor deposition or CVD, the wafer was coated with a positive photoresist having a thickness of 15 µm. The wafer was then exposed to UV ray and a window was created for sidewall etching. Afterwards, the wafer was baked. Excess photoresist and SiO_2 layer was removed. The etch mask employed is circular, so that the needles have a round shape with a sharp tip. The wafer was then inserted into the RIE chamber. The SF_6 gas flow rate and O_2 gas flow rate were controlled simultaneously for proper etch isotropy. The etch rate for 450 µm tall and 10 µm base width needles was 2.2 µm/ minute with an etch isotropy of 0.0232. Etch rates and etch isotropy coefficients have been varied to obtain optimum structure in each case. The etch rates and isotropy coefficients for microneedles 550 µm, 600 µm and 700 µm tall needles are given in table-I below. The gas flow rate and etch time can also be found in table I. Using inductively coupled plasma etch (ICP) technique, the tip of the sidewall was sharpened, which resulted in a beveled shape. After the sidewall etching process was complete, the needles were coated with biodegradable materials and drug molecules. This method of drug delivery is called the "coat and poke" approach [23]. The fabricated needles are shown in figure 4.

Figure 4 shows the solid Si microneedles after complete fabrication process. The needle height ranges from 450 µm to 700 µm and their base width varies from 10 to 15 µm. The out-of-plane solid needles are prismatic and circular shaped with beveled tips. The beveled tip provides greater force withstanding ability and allows easy penetration into soft human tissues [19]. The circular shape of these needles allows them to withstand greater puncture pressure [24].

V. Analysis of Mechanical Properties of Silicon Microneedles

Si microneedle, when inserted into the eye act as a solid beam on which force is applied as the resistance of human tissues. Hence, it is necessary to understand the concepts and theories for mechanical viability of fabricated microneedle. A principal concern in microneedle design is needle failure which is essentially material failure. To overcome these issues researchers have explored numerous needle designs and types [24] - [26]. Availability of data is a major problem when it comes to the eye, since no research has been carried out in this area to date. The human eye is a complex structure, composed of a number of layers, each with its own unique tissues and tissue thickness. Eye resistance force cannot be estimated unless research is done to illustrate the mechanical strength of each of the eye segments. Therefore, extensive research is required before the mechanical stability of these fabricated needles can be tested against human eye tissues in vivo.

Aggarwal et al. have provided important data in terms of mechanical characterization of hollow and solid Si microneedles [24]. When the microneedle is inserted into the skin, it experiences a skin resistance of 3.183 MPa. However, once inside the skin, the tissue resistance is smaller, around 1.6 MPa since human tissues are much softer with leaky blood vessels [27]. We have used the tissue resistance value provided by Aggarwal et al. in order to test the mechanical strength of the fabricated microneedles. We need to know the moment of inertia of the microneedles to carry out necessary calculation. For a solid circular Si microneedle, the moment of inertia, I is given by - [24], [25]

$$I = (\pi / 64) \times D^4 \tag{1}$$

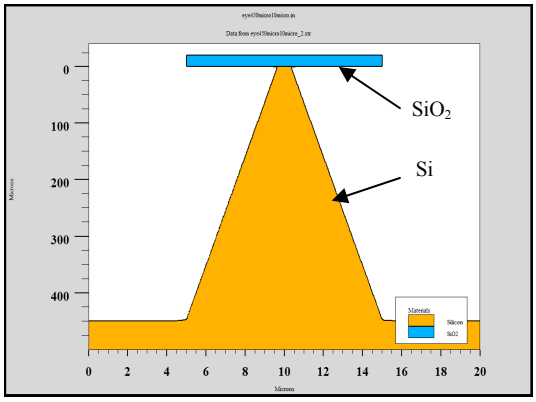
where D = Diameter of the circular Si microneedle. The maximum bending force for a circular microneedle is

$$F_{bend} = \frac{\sigma_y \times I}{c \times L} \tag{2}$$

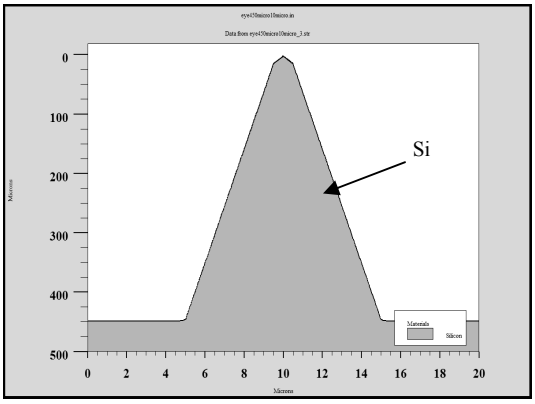
TABLE I. Solid Si Microneedle Fabrication

Microneedle Type	Fabrication Process							
	Etch Type	Isotropy and Etch Rate	Etchant	SF_6 Gas Flow Rate [a]	Pressure (mTorr)	Etch Time	Needle Height	Base Width
Solid, Prismatic, Circular Si Microneedle	Isotropic RIE	0.0232, 2.2 µm/minute	SF_6/O_2	220 sccm	12	3 hours and 22 minutes	450 µm	10 µm
Solid, Prismatic, Circular Si Microneedle	Isotropic RIE	0.0186, 1.8 µm/minute	SF_6/O_2	175 sccm	10	5 hours and 4 minutes	550 µm	12 µm
Solid, Prismatic, Circular Si Microneedle	Isotropic RIE	0.0221, 1.9 µm/minute	SF_6/O_2	200 sccm	12	5 hours and 16 minutes	600 µm	15 µm
Solid, Prismatic, Circular Si Microneedle	Isotropic RIE	0.024, 2.5 µm/minute	SF_6/O_2	350 sccm	18	4 hours and 40 minutes	700 µm	15 µm

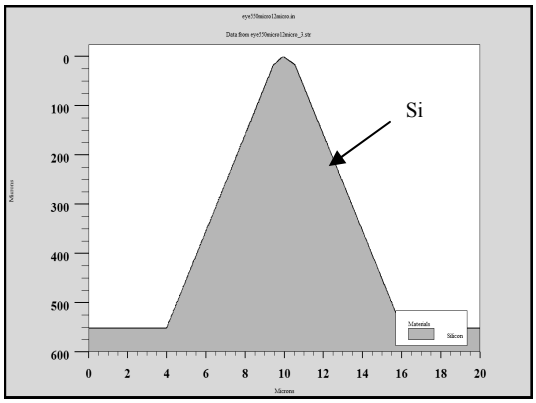
a. Reference [22]



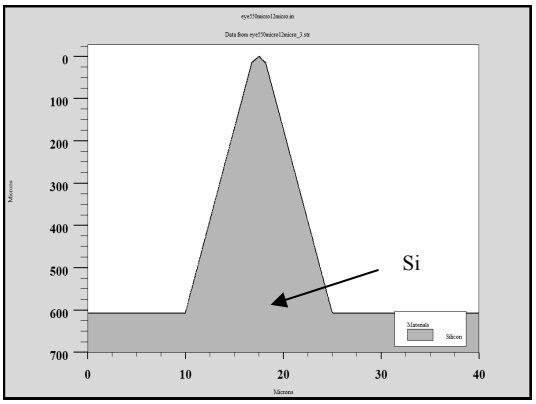
a. Si microneedle with etch mask (SiO_2) shown after a complete RIE process



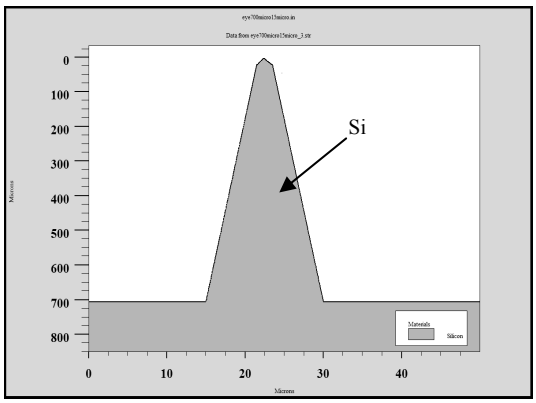
b. 450 µm tall beveled Si microneedle, aspect ratio is approximately 50:1



c. 550 µm tall beveled Si microneedle, aspect ratio is 55:1



d. 600 µm tall beveled Si microneedle, aspect ratio is 40:1



e. 700 µm tall beveled Si microneedle, aspect ratio is approximately 46:1

Fig. 4. Solid Si Microneedles.

where c is the distance of the neutral axis (z axis, in this case) to the outermost edge of the microneedle. For a circular microneedle, c is D/2 where D is the outer diameter while for rectangular microneedle c is H/2, H being the outer height. For square shaped microneedles, c is H/2 where H is the outer dimension. σ_y in the equation is the yield strength of the microneedle made of Si that is, 7 GPa [24], [25]. F_{bend} is essentially the limit of bending that the microneedle can tolerate without getting fractured.

The maximum buckling force that a microneedle can withstand is given by –

$$F_{buck} = \frac{C \times \pi^2 \times E \times I}{L^2} \quad (3)$$

where E =169 GPa represents the Young's Modulus of Si, I is the moment of inertia for microneedle as described before and L is the effective length of the microneedle [24]. The value of the constant, C depends on the structural properties of the microneedle. Generally, for a solid circular microneedle, the value of C is 0.25 [24].

The theoretical pressure required to pierce human tissue has been given as 1.6 $X10^6$ Pa. This pressure is a major factor in determining the overall geometry of the solid microneedle. The resistance offered by human tissue is given by the following equation [24]

$$F_{tissue} = P_{tissue} \times A_{cc} \quad (4)$$

where A_{cc} is the cross sectional area of the microneedle. P_{tissue} is the pressure exerted by human tissue. F_{tissue} is the cross sectional area times the tissue resistance, which gives us resistance force value. We have used use this equation to calculate eye tissue resistance. For values of A_{cc}, we assumed a uniform circular shaped needle. The equation for A_{cc} is: A_{cc}= (1/4)×(π/D2) – where D is the diameter of the solid Si microneedle. The cross sectional area was measured using a uniform circular cross section for all the microneedles.

Using the mathematical equations (1)-(4), we calculated the tissue resistance, maximum bending and buckling forces of our Si microneedles and compared the resultant values. Details of mechanical calculations are given in table II. For a microneedle to be effective, human tissue resistance must be smaller than both maximum bending force and maximum buckling force.

From the analysis above, it is obvious that the maximum bending and buckling force values are much greater than tissue puncture pressure for all the microneedles that we have fabricated. We can safely state that the fabricated microneedles should be able to withstand the pressure exerted by human cells and tissues and should be able to deliver drugs to eye without tip breakage or any other deformation to their structures.

VI. CONLCUSION

Fabrication of solid out-of-plane Si microneedles was carried out extensively, with needle heights ranging from 450 µm to 700 µm, and base widths ranging from 10 µm to 15 µm. Microneedle entities were chosen based on the selected route of drug delivery to the posterior segment of the human eye. The mechanical properties of the fabricated microneedles have been tested by using column bending and buckling analyses which are the most widely used techniques for force resistance test. The results indicate that the microneedles should be able to penetrate soft ocular tissue and be able to deliver drugs successfully through the selected drug delivery route. However, human in vivo studies should be carried out in order to test the needles and measure their strength accurately. Extensive research is also required for proper understanding of the nature of ocular tissues and cell layers. Future work includes integration of the fabricated microneedles with on-chip devices and application of these lab-on-chip devices to the treatment of ocular diseases [28].

TABLE II. MECHANICAL CHARACTERIZATION OF SOLID SI MICRONEEDLES

Microneedle Type	**Force and Tissue Resistance Values** [b]			
	Maximum Bending Force (F_{bend})	**Maximum Buckling Force (F_{buck})**	**Tissue (Puncture) Pressure (F_{tissue})**	**Applicability**
450 µm tall, 10 µm width,tip tapered, circular, solid	1.53 mN	1.01 mN	0.12 mN	Should be applicable
550 µm tall, 12 µm width, tip tapered, circular, solid	2.16 mN	1.41 mN	0.18 mN	Should be applicable
600 µm tall, 15 µm width, tip tapered, circular, solid	3.87 mN	2.88 mN	0.28 mN	Should be applicable
700 µm tall, 15 µm width, tip tapered, circular, solid	3.32 mN	2.12 mN	0.283 mN	Should be applicable

b. Reference [27]

ACKNOWLEDGMENT

The author would like to thank the Department of Electrical and Electronic Engineering, Bangladesh University of Engineering and Technology profusely for continuous assistance and encouragement throughout the work. The author is also grateful to Md. Gaffar, Lecturer, Prime Asia University, Dhaka, Bangladesh for his help with the simulation software ATHENA®.

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