EVALUATION OF DESIGN AND INSERTION ANALYSIS OF A CONICAL SHAPED POLYMERIC BASED MICRONEEDLE FOR TRANSDERMAL DRUG DELIVERY APPLICATIONS

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Highlight
This article focuses on structural design of an eco-friendly, recyclable featured conical-shaped PMMA polymeric based microneedle for medical applications.

Abstract
Transportation of drug through parental routes are conventionally followed through hypodermic injection methods, where hypodermic injections are administered into the human skin for drug release. However, there are some issues observed when these hypodermic needles are being used, there are instances where the needle is being inserted leaves some needle fractures in the skin. To cater to the issue scientific researchers are voraciously working on designing and developing polymeric type of microneedle structures for various medical diagnostic applications for glucose monitoring, drug delivery, and other applications. This article presents the structural design of a conical-shaped polymeric microneedle and the insertion force while being pierced into the skin. Simulations at different insertion angles on microneedle are analyzed by arriving with total needle displacements in the process of insertion. The von mises stress is also analyzed with applied force at different insertion angles resulted in incremental change in stress exerted by the microneedle. The resultant stress is below the yield stress which makes the microneedle pierce into the skin without breakage.

Keywords
eco-friendly polymers; drug delivery; micro needle; transdermal drug delivery.

Introduction

Transdermal drug delivery method (TDD) generally refers to the delivery of therapeutics which are channelized across the skin's innermost layers. This method of drug being delivered into the skin's layers overcomes issues like routing the drug through oral passage which can lead to gastrointestinal tract irritability and poor compliance from the patient point of view [1]. However, this method of transdermal means of delivering the drug offers better release over a period of time when being compared with that of administering the drug through oral cavity [2,3]. Polymeric microneedles are receiving attention in medical and biological sciences especially drug delivery due to their prime advantages which are their biocompatibility properties when being compared with that of the other materials. Polymeric microneedles have improved method for transdermal transportation of drugs as they are routed into the skin's startum-corneum barrier with minimal invasiveness and with ease [1]. Pharmaceutical giants and biotechnology based companies are focusing on drug research and developmental of microneedles with loaded protein based drugs [4–6]. This will tend towards progress and extensive technological outburst in the production of microneedles which clinically important for the upcoming future [4]. As discussed with regards to the microneedles the mechanical properties and their biocompatibility of the material chosen plays a key role in manufacturing and and in their performance analysis. In general, for mass production manufacturers are keen on low production cost with exceptional mechanical stability towards their fabrication. To cater this, need an ideal and viable option is to choose a material from polymeric family with good mechanical stability which can be tailor-made for different mechanical strengths with appropriate functions [7]. To be able to successfully penetrate into the skin's surface, depends on various factors which are the length of the microneedle, density, tip and base diameters. Microneedles which tend to have higher value of

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Young's Modulus will aid in better mechanical stability and with good penetration capacity [8]. A higher Young's Modulus tends with better stability and when the tensile strength is considered the shape and size of the microneedle need to be considered [9]. The design of a microneedle is a prime factor for determining the effectiveness of a microneedle [10,11]. Microneedles are commonly designed as an array of structures either they resemble in a conical form or in a pyramidal shape which are used to pierce through the skin surface to transport the drugs [12]. The materials which are used in micro needle fabrication are considered to be the one of the utmost factors in the designing aspects, since this factor totally governs the mechanical strength and medicinal drug transportation viabilities for the micro needle. Consequently, other pivotal issues which need to be considered are the density of the material, the overall height from (base to tip), the diameter and also the width of the tip, [8]. Microneedles with either conical shapes or pyramidal-shaped structures are fabricated or formed with the application of various materials which typically range from 250mm and can even go up to 2000 mm in height which has the technique to travel across the human skin's internal layers to deliver the targeted drug molecules [12]. Scientific researchers and scientists have worked upon various microneedle lengths, widths, and thickness and on tip size portions towards optimized penetration [13].

Methods

Material selection:

Lately in the recent times, polymeric based micro needles are gaining a tremendous interest in the field of medical and biological sciences. Most of the polymers in polymeric family exhibit good rate of rigidity with an added biocompatibility compliance, which enables the polymeric-based micro needles which evades the fractures and side effects when they are administered into the skin. Some polymers in the polymeric family are also soluble in water as its medium. Thus, drugs can be encapsulated in dissolving kind of micro needles. As these polymeric micro needles also have property of relatively low melting point of temperature, fabrication techniques like microinjection molding can be used in the preparation of polymer micro needles. A common widely used molding technique which injection molding technique wherein the process the materials are melt widely used are polymeric based materials, they are allowed to flow with high force by maintaining high pressure through a plunger based setup which enters into a mold cavity, after passing, opens up to a phase of solidification and thereafter gets ejected thereby produces an exact replicate structure on the surface. Thus, mold based fabrication technique could further reduce the manufacturing cost and still remains to be the most viable option for mass production [14]. Solid truncated conical shaped micro needles which are made with poly methyl methacrylate (PMMA) material, measuring the tip radius of 20 µm and with a diameter of 40µm and 650 µm in height with a bottom dimensional radius of 100µm and 200µm diameters is chosen for the model. Polymeric micro needles are ideally considered as they tend to show exhibit excellent properties of biocompatibility, added to that their property of rigidity and their built quality, makes them capable enough for transportation of wide range of drugs without any hindrance to in their dimensional mechanical properties [15]. Hence there is a dire need to contribute to the overall development of polymeric-based microneedles. More importantly considering the type of polymer used, an efficient and intricate design of the micro needle tip, length and width of the needle, and the manufacturing modality are the prime parameters in the overall development of the micro needle [16]. One of the prime challenges being linked with polymeric type of micro needles are their penetrating capacity through the skin's layers. In many cases, the mechanical strength tends to be weaker in polymers that are soluble in water compared to that of the materials which do not dissolve like silicon or in metals, and encapsulation of the drug to be introduced will be a factor of compromising on the rigidity and strength of the Microneedles [16,17].When polymeric microneedles are taken into consideration, their uniqueness pertains to their mechanical stability and in their strength, add to that their modulus of elasticity and fracture rigidity, they are the pivotal factors. Mechanically stronger based polymeric microneedles are sufficiently capable enough to withstand the forces without deformations i.e., their bending and breakage limits [18]. Apart from this, the tissue under target for MN's is it the application through the transdermal means or the non-transdermal method must be taken into consideration with the right kind of polymeric microneedles. However, the method of application for non- transdermal means for the target areas like the tissue of an eye, vascular linked tissues, and of the digestive tract system polymeric microneedles are the viable option which can bend and they are simple to use through surgical means, with an ideal balance of their strength and flexibility options, only when targeting soft type of tissues which require comparatively less pressure in terms of their insertion strength [19].

Design Parameters

The fundamental characteristic of micro needles is that they should meet some pivotal requirements for achieving the desired need of penetrating into the skin layers with ease subjective to pain free when being administered. To achieve the objective, the micro needles which are designed are to made sharp enough meeting a rigidity to handle the requirement. Simultaneously when they are administered there should not be any mechanical damage or fracture pertaining to the material. The micro needles which are designed and manufactured should not compromise on the length of the micro needle and in diameter, to avoid contacts with other organs. The authors clearly illustrated in [20], after taking into consideration the skin deformation allied issues and concluded that length of the micro needle can be further restricted to 300µm-400µm range. Further it can be assumed by considering the flexibility issue of the skin, the assumed length will not be sufficient to penetrate into the skin layers effectively. Thus, the micro needle length in this work is considered to be 650 µm. Figure 1 shows the schematic diagram and dimensions of the designed microneedle.

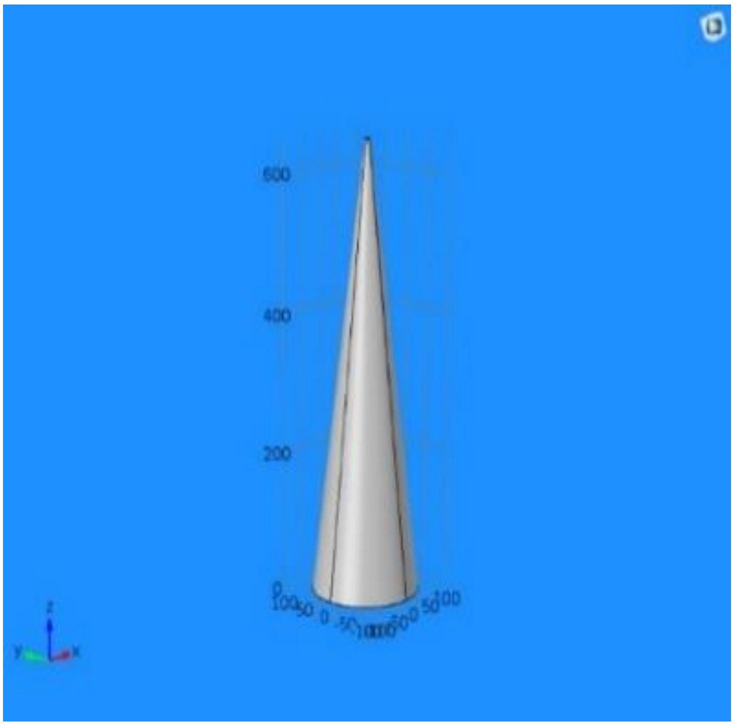

Figure 1. Geometrical shape of a micro needle (MN) in Longitudinal view. *Source: Author.*

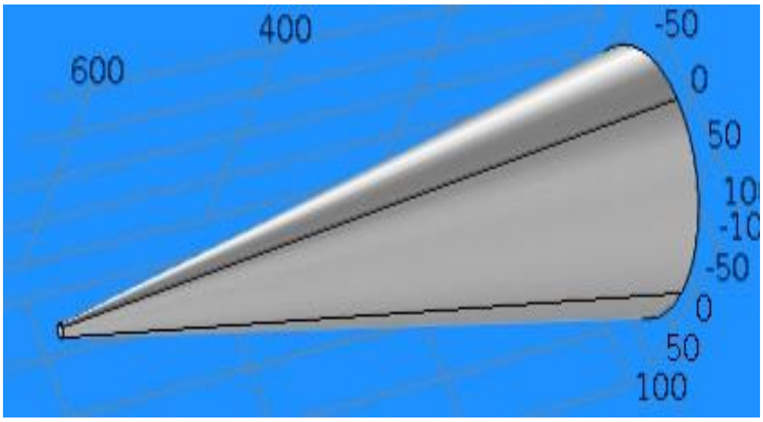

Figure 2. Geometrical shape of a microneedle (MN) in Lateral view. *Source: Author.*

The designed micro needle in this study is considered to be a solid truncated cone like structure, the base being with broader and narrows like a tip as it goes to the tip which is illustrated in Figure 1. The shape is designed in such a manner, to minimize the effects of bending stress on the micro needle when exerted and also the deformities failure of buckling, during the process of insertion of micro needle into the skin when being compared with other high aspect ratios or column-like structures [21]. Evidently by sharpening the tip of the micro needle and reducing the tip diameter (L) by simultaneously increasing the angle of bevel i.e. (ɵ), will lessen the impact of the insertion force on the micro needle. In spite of working to lessening the effect of insertion force, leads in resulting in tip fractures when the micro needle is in the process of penetration and also a trade-off between the sharpness and mechanical strength of the tip which should be considered. The material properties are given

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below in Table 1.

Table 1. Properties of PMMA Material. *Source: Author.*

Elastic modulus	3 GPa
Poisson's Ratio	0.400
Shear Modulus	3.202 GPa
Density	1900 kg/m^3
Tensile Strength Factor	1.434 GPa
Yield Strength Factor	1.394 GPa

The mechanical properties of micro needles pertaining to their (elasticity modulus values and the value of fracture forces) need to be analyzed in order to make sure that micro needles will not undergo any sort of deformity in their structure or breakage issues also called as fracture issues during the process of skin insertion tests. Mechanical testing is quite common practice when the necessity arises to measure the maximum for exerted axially, which is the common cause for micro needle failure. However even if the Young's modulus of the material and the base of the diameter dimensions are strengthened will give rise to an increase in the yield force exerted of the micro needles. On the contrary if a condition arises wherein force of failure of the micro needle is increased by simultaneously decreasing the overall length of the micro needle, which leads to a condition of critical buckling (lateral way of deflection) load of a column decreases by increasing column's length [5,22].

These explanations are proved analytically by referring to Euler's formula, the equation for critical buckling load [23].

(1) $$P_{cr} = \pi^2 EI / (KL)^2$$

where:
P_{cr} is the critical load;
E is considered as the Young's modulus
I is the cross sectional area of the micro needle;
L being the total length of the needle
K to be considered as the effective length factor.

K is related to the boundary conditions of the column. All the above conditions are applied considering the micro needle as a fixed-free column or fixed-pinned column, the corresponding effective length factor is K is considered to be value of 2 or nearly K = 0.699, respectively [24,25]

Design Criteria of Interest
Insertion angle and counting on the Von misses stress on the polymeric microneedle was the interest of this paper. In this simulation model a parametric sweep analysis different angle of deflection was performed for various angles of (Θ) and the stress is analyzed. Thus, the range of insertion angle was considered to be from 0 radians to 0.26 radians (i.e., from 0 degree to 15 degree of deflections. A coarse meshing type is selected for analysis. The surface stress exerted on the needle tip is very low at 0 radians and stands out to be 1.91MPa and surface stress is radiated throughout the needle and stands out to be 6.28 MPa. The microneedle reflects their typical angle of insertion criteria at the two extremity values. The material applied to the microneedle stands out to be Poly-methyl-methacrylate (PMMA).

The applied force on the microneedle was subjected to be kept at a constant value of 0.058N. The computations of the model were generated by using the governing equations of motion and strain displacement equations. The base of the microneedle was set as a fixed constraint, and the tip of the microneedle was chosen as the boundary load location. A parametric sweep was used to sweep the insertion angle from 0 rad to 0.26 rad in steps of 0.010 rad. The resultant Von Mises Stress from this simulation is analyzed and discussed.

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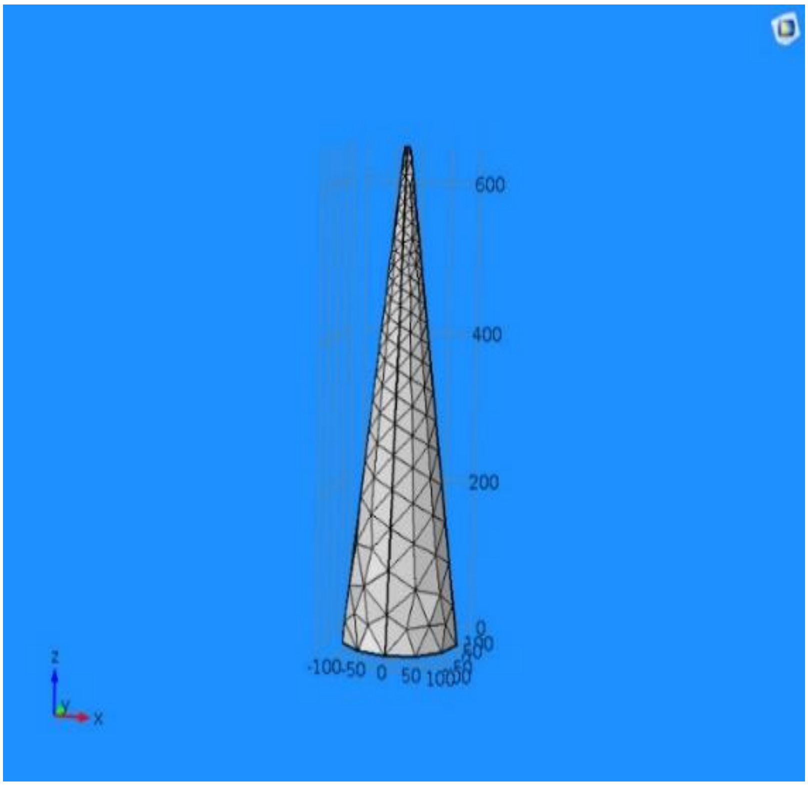


Figure 3. Mesh Analysis of the PMMA Polymeric Microneedle. *Source: Author.*

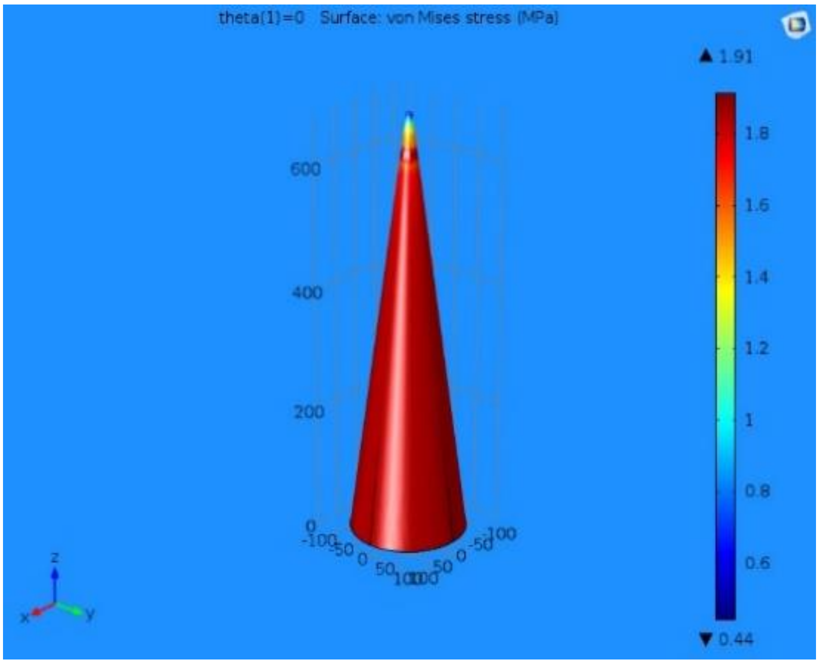


Figure 4. Surface stress on a PMMA Polymeric Microneedle at 0 radians. *Source: Author.*

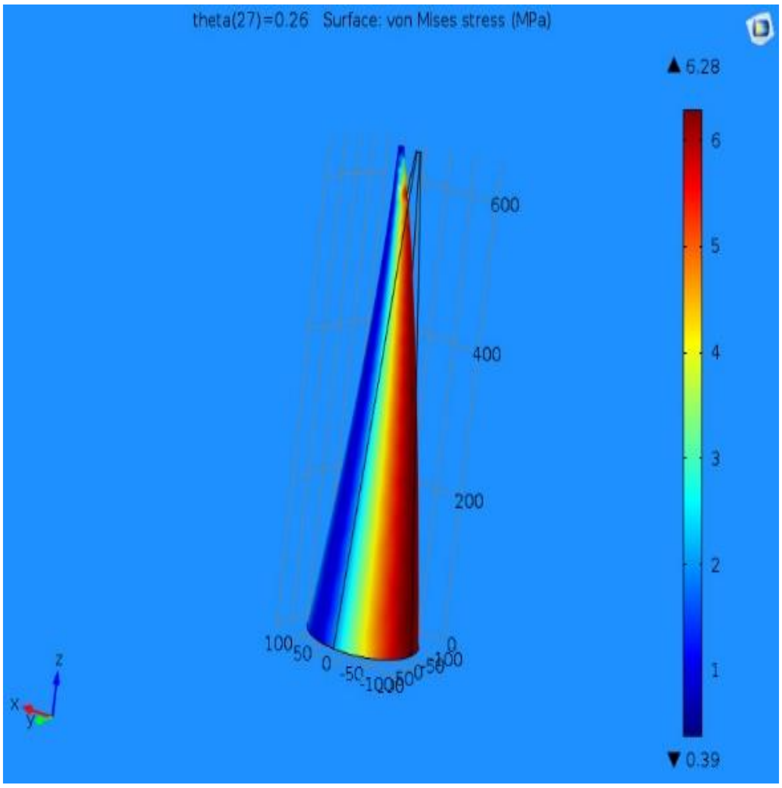


Figure 5. Surface Stress on a PMMA Polymeric Microneedle at 0.26rad. *Source: Author.*

Mathematical modeling & Governing equations

Equation of Motion can be written as:

(2)
$$\nabla \cdot \sigma + F.v = \rho \frac{\partial^2 U}{\partial t^2}$$

General Strain Displacement Equation can be written as

(3)
$$\varepsilon = \frac{1}{2}[\nabla u + (\nabla u).T]$$

Equation of motion can be written as

(4)
$$-\Delta\, \sigma = Fv$$

Simulations

Conical shaped polymeric microneedle at different eigen frequencies and the relative stress surface displacement distributions are carried out with simultaneously observing the deformations in the microneedle structure. The polymeric microneedle is designed to withstand the breakage failure while being inserted into the skin's surface. However, when the microneedle is inserted into the skin's surface the microneedle exerts some reaction forces onto it. When the reactive forces are more than the incidental forces the microneedle exerts a state deformation leading to breakage called the fracture. These anomalies need to be taken into consideration while designing the microneedle and while loading the microneedle into the skin. In the above simulation it is observed that the needle retains its shape without any deformation and the entire stress is equally distributed from the tip of the base needle to the base of the needle. The stress being concentrated maximum at the tip of the needle and minimum at of the needle. The stress factor changes in accordance with the change in the Eigen frequency. Total surface displacement to the corresponding frequency are being simulated in the above figure.

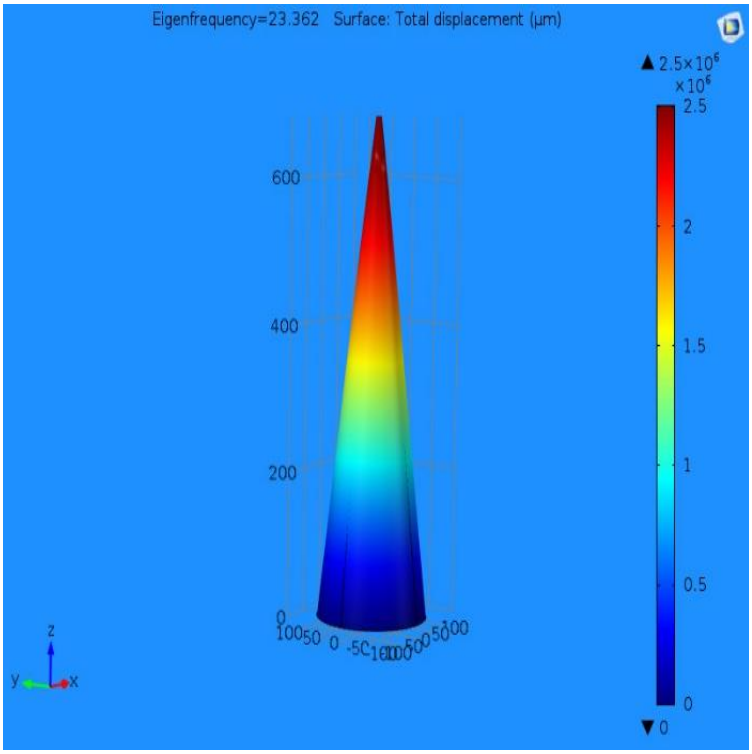


Figure 6. Total Displacement without deformation of the needle structure (Longitudinal View). *Source: Author.*

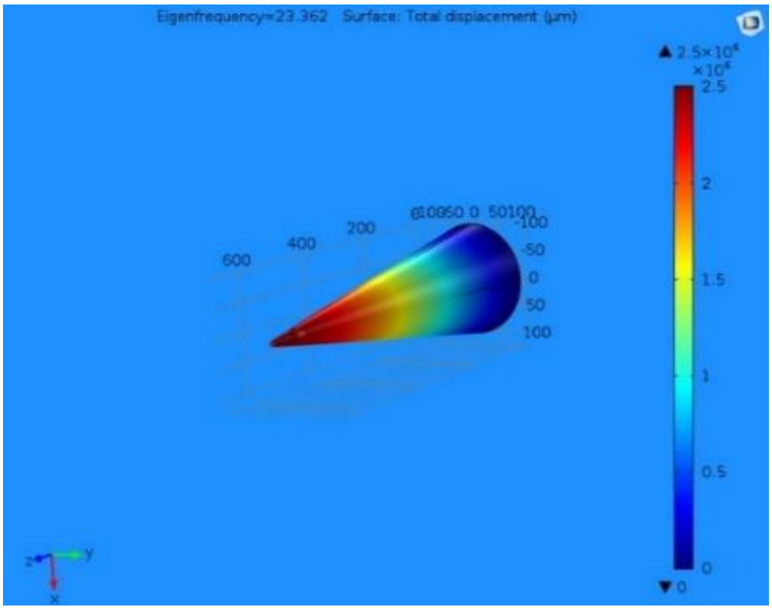
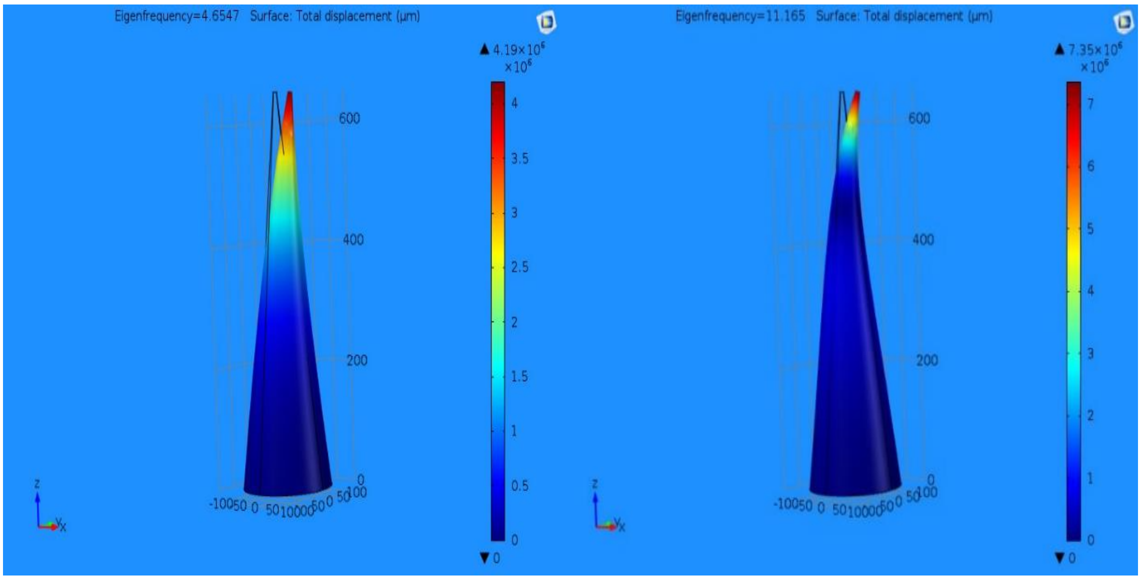


Figure 7. Total Displacement without deformation of needle structure (Lateral View). *Source: Author.*

Total surface displacement of the polymeric microneedle is shown in a lateral view where the stress distribution is evident from the tip of the microneedle to the base of the microneedle. The stress distribution is equally spread along the whole length of the microneedle. It exerts a maximum at the tip of the microneedle and a minimum at the base diameter of the microneedle. The importance of maintaining a sharp tip for the microneedle is that the insertion will be smooth and effective on the skin surface. Sharp tips and corrugated tips, slant tips of different designs are used for microneedle.

Here in the above simulation, it is observed that by varying the frequency there also observed that there is a change in the structure of the needle, a bulge is observed at 200μm to 400μm and also slightly on the above heights. The maximum stress tends to shift to the middle portion of the needle.



Figures 8 and 9. Total Displacement with initial stages of deformation. *Source: Author.*

Figures 8, 9 depicts the displacements exerted by the microneedle at different eigen frequencies, structural deformations on the microneedle. In the initial stages of the deformation, the stress is shifted towards the tip and distributed throughout the microneedle. It is analyzed that after an eigenfrequency of 4.567, with a minimum stress is distributed from the lower half of the microneedle to its base. It is evident from the literature that the minimum stress required for a microneedle to pierce into the skin is found to be as 3.18MPa and as it surpassed the value the needle can pierce into the skin at this particular frequency with a total displacement of 4.19MPa. Further, there is an increase in the stress component concerning the structural deformation of the microneedle. It is evident from the simulations that as there is an increase in the eigenfrequency.

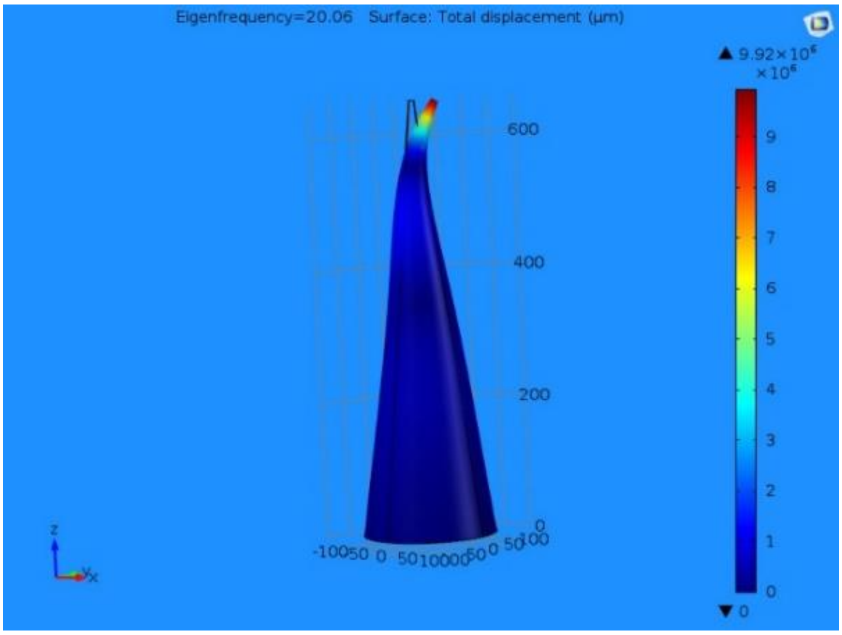


Figure 10. Displacement at mediocre stages of deformation. *Source: Author.*

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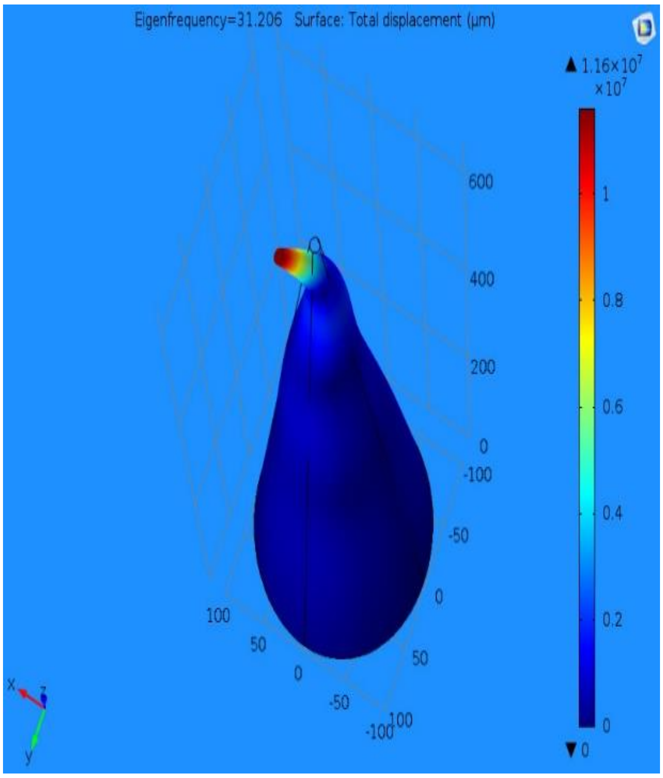

Figure 11. Total Displacement with deformation of needle structure. *Source: Author.*

At this point of eigenfrequency 31.206, the polymeric microneedle gets deformed exhibiting a maximum deformation stress-based Surface displacement of 0.116 µm.

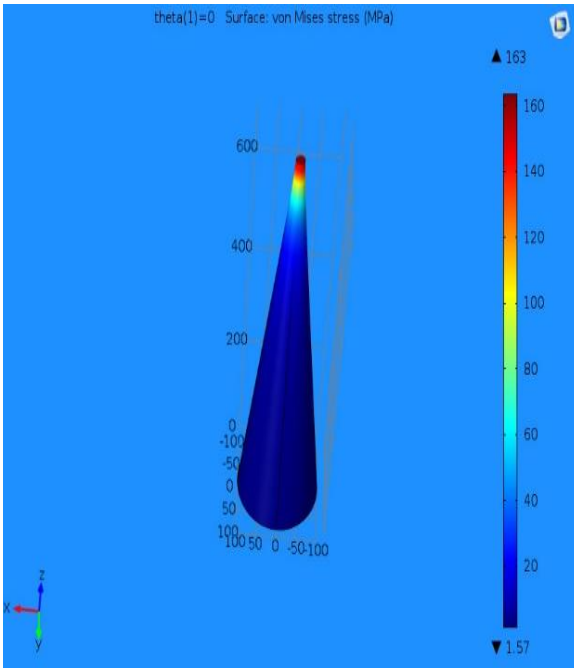

Figure 12. Stress observation at 0 degree. *Source: Author.*

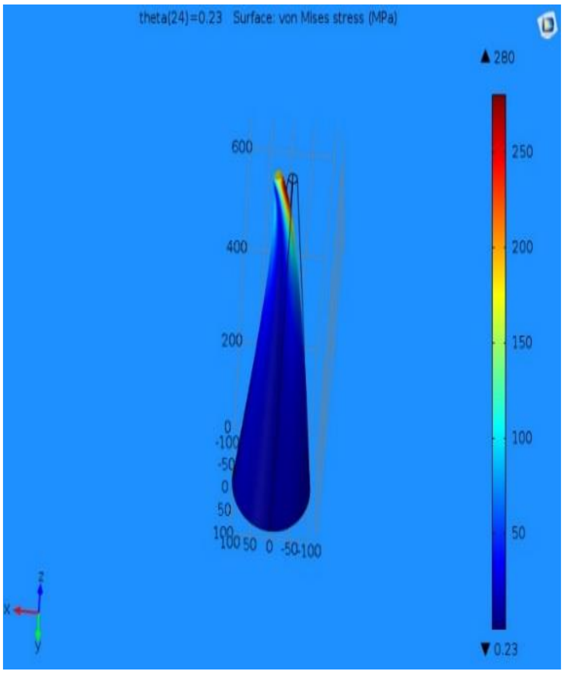

Figure 13. Stress observed at 0.21 degree. *Source: Author.*

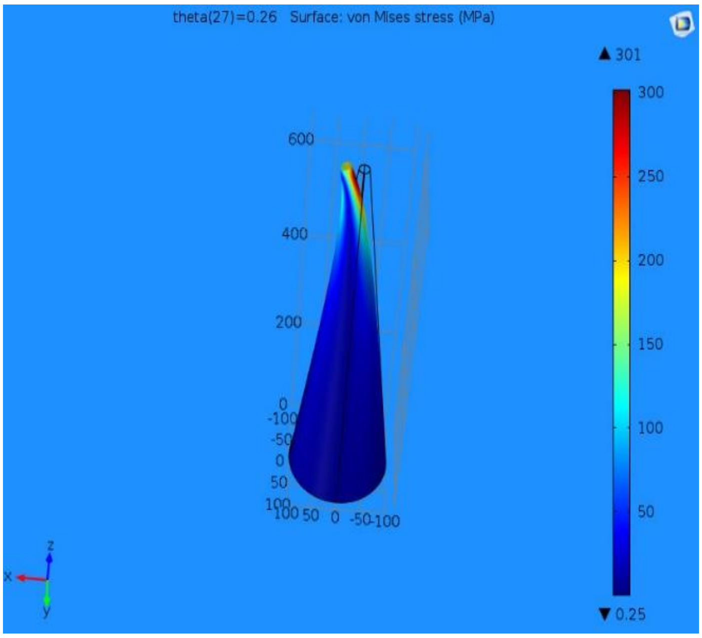

Figure 14. Stress observed at 0.25 degree. *Source: Author.*

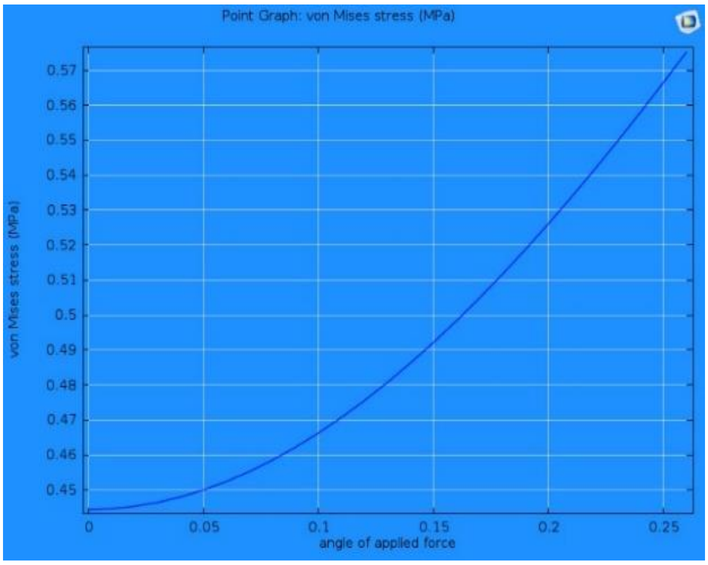

Figure 15. Angle of Applied Force Vs von Mises Stress. *Source: Author.*

The angle of applied force concerning the von Mises stress is depicted. It is evident that as the angle of applied force is changing there is an incremental change in the von Mises stress factor. The angle of applied force is directly proportional to the von Mises stress on the microneedle structure.

Impact

In the past few decades, there has been a substantial increase towards the materials which are reusable especially in the areas of agriculture cultivation, medicine and other allied areas. Polymers and their families are standing as the big head for the current plastics, and they are expanded into versatile areas. Research communities are steadfastly working out in these areas of polymeric materials to make them more and more user-friendly and there on to design and fabricate a new composite type of materials [26]. In the days to come these kinds of biodegradable polymeric materials will significantly reduce the need for polymeric materials which are synthetic in nature by reducing the fabrication costs, which in turn have progressive effects in the environment and an economically feasible option.

Conclusion

This model was designed to study the relationship between a single conical shaped polymeric PMMA micro needle’s insertion angle with that of the resultant Von Mises stresses. The results of this simulation study depict that the resultant von Mises stresses tend to be increased when there is an incremental change in the insertion angle; the minimum Von Mises stress of 163 MPa occurred at an angle of 0 rad and the maximum Von Mises stress of 301.00 MPa occurred at angle = 0.26 rad. To penetrate the skin, the micro needle's Von Mises stress needed to exceed the skin's resistive pressure of 3.18MPa, and to prevent yielding, the microneedle's Von Mises needed to remain below 400 MPa. As was determined from the Von Mises stress range of 163 to 301 MPa, all angles of insertion were below this yield stress of 400 MPa. The results clearly show that the microneedle is sufficient can be able to penetrate the skin layers and be capable enough to resist the needle breakage for all possible angles of insertion.

Conflict of interest
The authors declares that there is no conflict of interest.

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