

Fabrication and Analysis of Three Dimensional Polymer Microneedle Array Potentially for Transdermal Drug Delivery

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Abstract

Fabrication of Microneedle has attracted the great importance recently to reduce needle insertion pain and furthermore tissue trauma. LIGA, two photon photopolymerization, bulk lithography etc. are the various fabrication methods used for the development of these microneedles. However, despite the number of advantages of these methods, the use of microneedle is still less due to lesser throughput. Further these methods also incurred higher fabrication cost.

This paper proposes a microfabrication method for polymer microneedles using sequential stereolithography and micromolding. The methodology includes preparing microneedle array using microstereolithography machine which is followed with preparing a micromold and then finally a microneedle array is made by using biocompatible, thermally curable polymer. Further, finite element analysis of microneedle array is carried out with an aim to verify the structural strength (to withstand resistance offered by skin during insertion) of the fabricated microneedle to withstand requirements for painless drug delivery.

Keywords - High Aspect Ratio, Microneedle, Microstereolithography, Micromolding, Polymethyl methacrylate (PMMA).

I. INTRODUCTION

Most of the drugs taken for medication purpose are usually in the form of pills or injections, but these methods are not always optimal [1, 2]. Drugs which cannot be taken as pills are usually administered through injections and this introduces the problems of pain, possible infection. Conventional needles used for transdermal drug delivery (TDD) as well as for transdermal blood extraction (TBE) but these type of needles not only causes pain to patients but these are difficult to integrate with medical devices involving small scale point of application. As microneedles are made in micron sizes they reduce pain to a greater extent during insertion into skin as compared to conventional needles.

Human skin is considered as a primary input for the design of microneedle. Human skin is

categorized into three layers from outer to inner depth are: Epidermis or Stratum Corneum (SC), Dermis and Hypodermis. While using TDD, the drugs are inserted into skin through outermost epidermis or SC layer and delivered to blood vessels through microneedle conduits. This does not cause any pain to patients as there are no nerves present in SC layer. During TBE the microneedle is inserted till lower part of epidermis for blood extraction. Here, although the microneedles comes in direct contact with blood vessels, the minimum invasive area of needle and optimum shank length causes very little pain. Considering the skin deformation, the shank length for microneedle is limited to 300 to 400 μm for TDD whereas 700 to 900 μm for TBE.

There are various factors to be considered while designing the microneedles, such as robust material and using acute tip angle so as to make penetration into skin easier and also controlling the shank length during insertion so as to prevent contact with nerve endings. At the same time it is important to prevent breaking of tip of needle into skin and minimum invasive area to reduce pain as discussed before. The microneedles should have enough length so as to reach the blood vessels in case of blood extraction application and also that the microneedles should be made in the form of array so that it will find the blood vessel easily [4].

This paper presents the alternative way of developing the microneedle array which includes sequential microstereolithography and micromolding process. Further towards the application for transdermal drug delivery the finite element analysis is performed on the microneedle to evaluate its structural strength.

II. FABRICATION OF MICRONEEDLE ARRAY USING MICROSTEREOLITHOGRAPHY

A. CAD Model of Proposed Microneedle Array

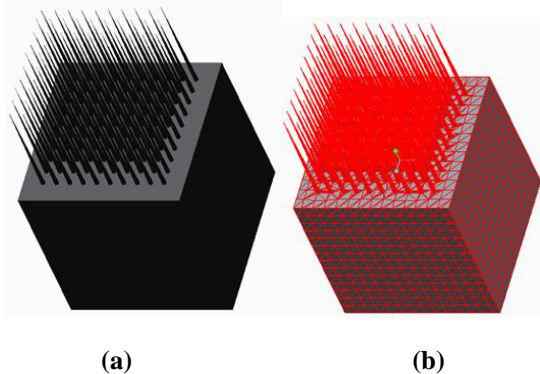


Fig. 1 A) CAD Model of Microneedle Array B) STL Format File of Microneedle Array

Figure 1 shows the CAD model of microneedle array prepared using PRO-ENGINEER (CREO 2.0) software. The model contains 10 x 10 array of solid microneedle. Each microneedle is having a base diameter of 100 μm and centre to centre spacing between each microneedle is 500 μm . The length of each microneedle is 500 μm . The prepared CAD model is then converted in STL (stereolithography) format file using the same PRO-E (CREO 2.0) software so as to be feed into Microstereolithography machine.

B. Microneedle Array Pattern

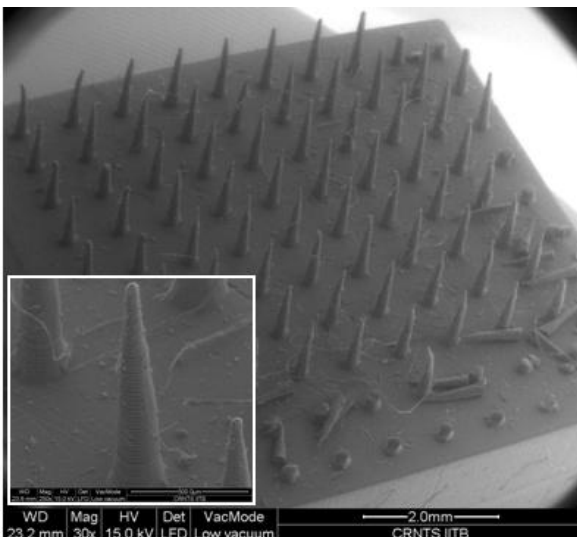


Fig. 2 SEM image of microneedle array pattern (Inset: Magnified image of one of the microneedle from the array).

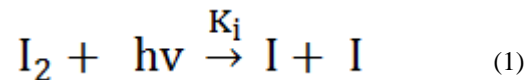
Microstereolithography machine ‘Envision Tec GmbH’ at Sarto Electronics, Andheri is used to make microneedle array pattern as per the information provided using STL format file. The material used to make this pattern was RCP-30.

Figure 2 shows the SEM images of the prepared microneedle array. Some of the microneedles are seen to be damaged in the SEM image. This is due to resolution limit of the stereolithography machine used for array. Inset in Figure 1 shows single microneedle. The needle can be seen as output of the stacked layer with stair-stepping effect on the lateral surface of the needle.

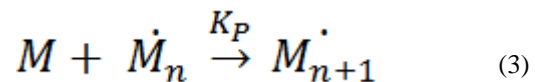
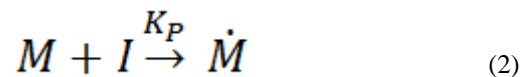
1) Curing Depth Control in Stereolithography Machine used

Microstereolithography machine works by photopolymerization of resin molecules. Some of the parameters that mostly affect the curing depth are: (a) Temperature (b) Concentration of absorber and initiator (c) light intensity.

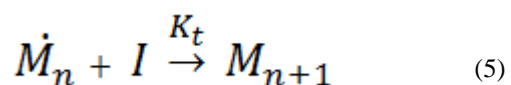
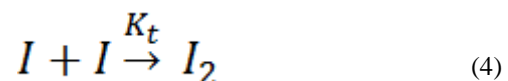
Typical reactants which are involved in photo polymerization reaction are initiator, and monomer molecule. The reaction works in 3 steps. The first step is initiation of free radical by photo radiation. The reaction takes place is as follow [16]:

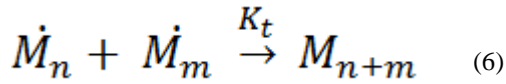


The initiator molecule splits and generates radicals when UV rays from source falls on it and it is denoted by I in reaction equation (1). These free radicals now combine with other monomer molecule present in resin and generate longer chain radicals which are also called as ‘Oligomers’. This step is called as propagation and the reactions that take place are as follows:



Last step is called as termination. Where generated free radicals combine with chain and the reaction is terminated. The reactions involved are:





The kinetic equation for photoinitiated polymerization is given by [17]

$$-\frac{d[M]}{dx} = R_i + R_p \quad (7)$$

where R_p is given by

$$R_p = K_p [M][I] \quad (8)$$

R_p is the rate of polymerization

R_i is the rate of initiation of free radical by UV light exposure.

$[M]$ is the concentration of monomer

$[I]$ is the concentration of radical chain.

K_p is the reaction rate constant of propagation.

C. Preparation of Mold

To prepare a mold following requirements are to be fulfilled:

1) Suitable Material to Make Mold

Proposed material for mold is mixture of Alumina Powder having a grain size 0.014 mm and Polydimethylsiloxane (PDMS). PDMS used is Sylgard 184, a two-part heat curable system. PDMS is made in the ratio of 10 parts of polymer: 1 part of hardener (w/w) (as instructed by manufacturer) and mixture for mold in turn will be made in proportion of 6 parts of alumina powder: 5 parts of PDMS by weight. (Optimality decided after mixture made in various proportions).

2) Degasification Chamber

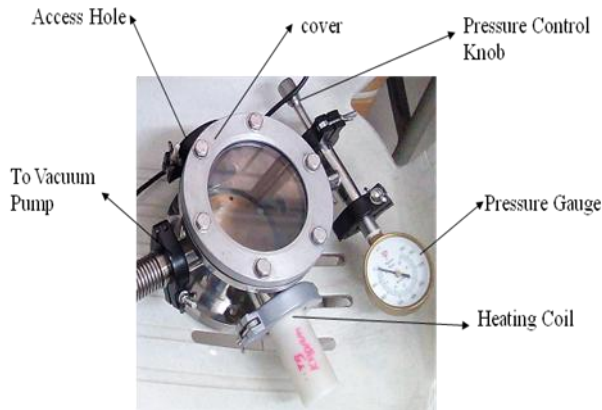


Fig. 3 Degasification Chamber

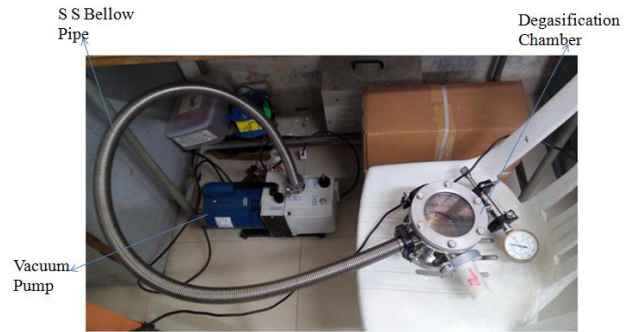


Fig. 4 Set up for Degasification Chamber

As the mixture prepared will contain air bubbles due to vigorous mixing Degasification chamber will be required to remove it.

To prepare degasification chamber, an airtight container is used. It is made up of Steel and Glass while the inside plate is made up of Copper. Container has four openings viz., one for connection to vacuum pump through Bellow pipe, second port is connected to vacuum gauge, third for heating coil and fourth opening is fitted with toughened glass flanges to observe the air bubbles.

3) Vacuum Pump

Vacuum Pump is required to create vacuum pressure in Degasification chamber.

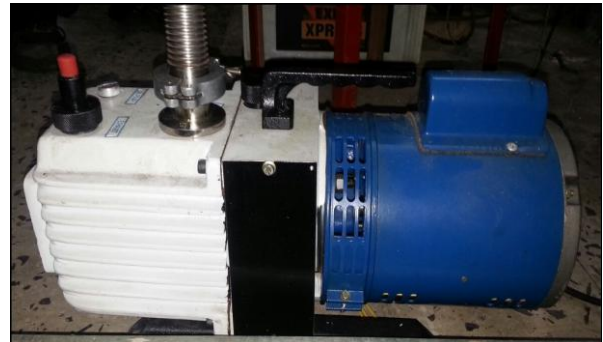


Fig. 5 Vacuum Pump

Specification of vacuum pump used:

Power: 370 W,
Voltage: 225 V, 1Ph, 50 Hz, 4.2A,
RPM: 1425.

4) Hot Air Oven

Hot air oven is first set to 100⁰ c. It usually takes 5 minutes to attain a temperature of 100⁰ c. Microneedle array pattern is then kept in inverted position in PDMS-ceramic mixture which together kept in Hot air oven for curing of polymer mixture at 100⁰ c for about 35 min.

The Mixture solidifies at 100⁰ c which is then allowed to cool at room temperature.



Fig. 6 Hot Air Oven

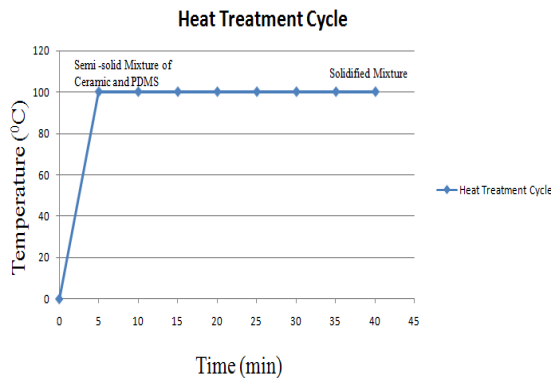


Fig. 7 Heat Treatment Cycle

D. Fabrication of Polymer Microneedle Array

- Material selected for Microneedle Array is Polymethyl methacrylate (PMMA).
- PMMA is a transparent thermoplastic polymer having melting point 160⁰ [15].
- After micromold is made, molten PMMA is poured into mold and allowed to cool at room temperature. After separating the mold, the solidified part will be in the form of microneedle array.

E. Analysis of Fabricated Microneedle Array

During skin insertion, the possible failure of the microneedle may occur due to bending or buckling. An axial force acts on the microneedle tip during insertion into skin. This axial force is compressive in nature and it causes buckling of the microneedle. The microneedle experiences resistive force exerted by skin during insertion, hence for piercing the microneedle into skin; the applied axial force has to be greater than skin resistance force. The axial force (compressive force), which the microneedle can withstand without breaking is given by:

$$F_{\text{compressive}} = \sigma_y \cdot A \quad (1)$$

Where, σ_y is the yield strength of the material and A is cross-sectional area of the microneedle tip.

As microneedle penetrates into human skin, it experiences the resistive forces exerted by the human skin. To penetrate the human skin, the outside force or pressure must be greater than the resistance of skin. The skin resistance offered before it is punctured is given by the following equation:

$$F_{\text{resistance}} = P_{\text{pierce}} \cdot A \quad (2)$$

Where, P_{pierce} is the required pressure to pierce the microneedle into skin [18].

1) Simulation of Microneedle Model on Ansys

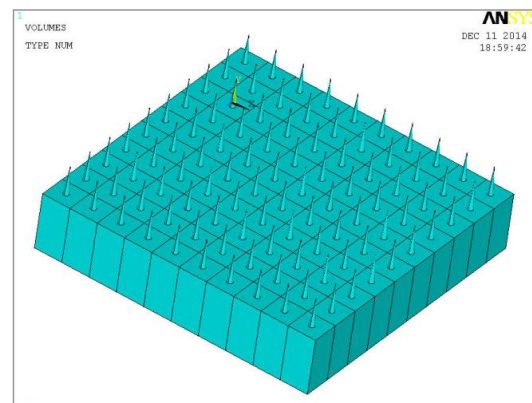


Fig. 8 Microneedle Model on Ansys

The analysis of microneedle model was performed on Ansys 12.1 in which the material for microneedle is taken as PMMA which is having young's modulus of 1.18 GPa and Poisson's ratio of 0.37. The length of the needle is 500 microns and diameter of 100 microns.

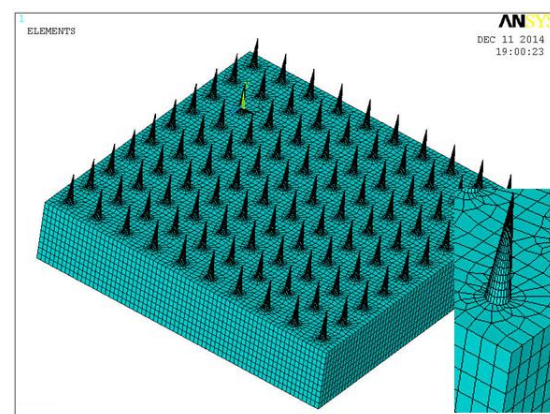


Fig. 9 Meshing of Microneedle Model

The array of 100 x 100 was initially made by using the element of SOLID 95 which is then subsequently meshed as shown above. Human skin offers a resistance of 3.18 MPa during microneedle insertion; hence fabricated microneedle should withstand the pressure greater than this value [18].

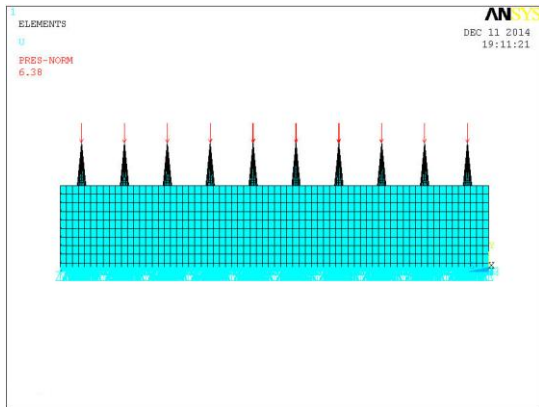


Fig. 10 Applying Pressure on Microneedle Array

For analyzing the stress effect on microneedle array the pressure of 6.38 MPa was applied on microneedle tip.

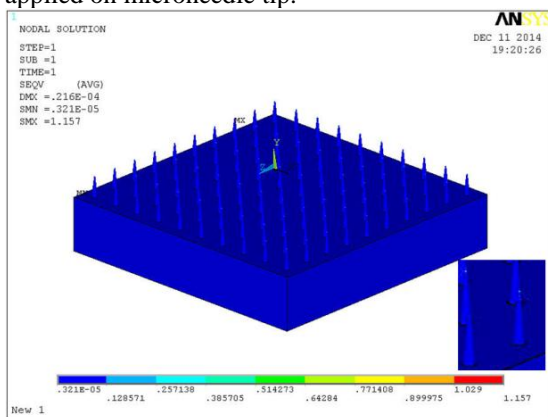


Fig. 11 Stress Analysis of Microneedle Array

As can be seen from the analysis that a deflection of 0.216×10^{-04} mm occurs at microneedle tip. Whereas minimum and maximum stress value of 0.321×10^{-05} and 1.157 N/mm^2 occurs at microneedle tip.

III. CONCLUSION AND FUTURE SCOPE

A. Conclusion

1. A microneedle array can be made of suitable biocompatible material using micromolding process.
2. Microneedle manufactured will fulfill the structural requirements for painless drug delivery that consists of High Aspect Ratio (HAR) shanks, 3D sharp tapered tip, and small invasive surface area.
3. PDMS microneedle seeded with biocompatible nanoparticles of the titanium may withstand the force required to pierce into the skin without tip breaking.
4. PDMS microneedle array seeded with biocompatible nanoparticles can be successfully used for nano/ micro scale drug delivery into skin.

B. Future Scope

Fabricated solid microneedles can be used to create micron scale holes in the skin thereby increasing the skin permeability due to which drug molecules can more easily transport through skin by diffusion.

Fabricated microneedle will provide minimal invasive means of painless drug delivery through skin.

Application of Microneedle will involve

i) Insulin and Oligonucleotide (short, single-stranded DNA or RNA molecules) delivery using “poke with patch” approach. It involves piercing solid microneedles into skin followed by application of patch at the treated site.

ii) Protein vaccine delivery using “coat and poke” approach that involves coating of drug onto microneedles and the inserted into the skin for drug release by dissolution.

iii) DNA vaccine delivery using “dip and scrape” approach where microneedles are first dipped into a drug solution and then scraped across the skin surface to leave behind the drug within the microabrasions created by the needles.

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