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Original Article

PEGDA Microneedle Arrays Fabrication and Investigation of Mechanical Properties for Transdermal Vaccine Delivery

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Abstract *- Cone-shaped 6x6 microneedle arrays with a height of 600 µm and diameter of 300 µm for transdermal vaccine delivery were fabricated with Polyethylene glycol diacrylate (PEGDA) material by projection micro stereo-lithography (PµSL) method. Nano indenter was utilized to estimate the young's modulus and hardness of PEGDA materials. Nanoindentation was used to randomly perform compression tests on several different needles to calculate the largest forces that the PEGDA microneedles can sustain. It was identified that developed forces are quite more than the opposing forces offered by skin structure. The biocompatible features of PEGDA have made the microneedles suitable for advanced transdermal vaccine delivery applications, and they can be used as a solid or coated microneedles array for vaccine delivery.*

Keywords *- Array, cone, Fabrication, Microneedle, PEGDA, Vaccine.*

1. Introduction

The trademark highlights of this microneedle innovation are the quicker beginning of activity, better tolerant consistency, self-organization, further developed penetrability, bioavailability, biocompatibility, and viability [1]. Different technologists have contemplated microneedles (MNs) for conveying drugs through the transdermal course and surviving the restrictions of the ordinary methodologies [1, 2]. Microneedles were first conceptualized during the 1970s. However, it was not until the last part of the 1990s that they became critical research subjects because of headways in microfabrication innovation that empowered their fabrication [2]. Microneedles are injected over the skin structure to make watery pores through which medications diffuse to the dermal circulation [3]. Microneedles are sufficiently long to infiltrate the dermis yet are short and restricted to stay away from the feeling of dermal nerves or cut of dermal veins [4].

Microneedles of solid type are generally utilized for pre-treating the skin by framing pores [5]. Pointed tips of the needles infiltrate into the skin; make channels of micron size, through which the medication straightforwardly enters the skin layers on the utilization of a medication fix, in this way expanding the penetration [5]. Jab and fix strategy relates to microneedles of silicon type for transdermal medication conveyance applications [6]. The jab and fix duplicate jab the skin's initial layer up to the dermal, epidermal intersection with no aggravation [6]. Then, at that point, it delivers the medication stacked as a fix through micro-pores made on the skin [7]. Hence, the microneedles containing the medication plan are applied onto the site of microneedle application with the goal that the medication can diffuse to the shaped micro-channels [7]. Microneedles of solid types are reasonable for the conveyance of antibodies as it endures longer, have a stronger neutralizer reaction, are not difficult to make, have predominant mechanical properties, and have more honed tips when contrasted with other microneedles [8]. Also, the microneedle of solid type can be manufactured from various materials like silicon, metals, and polymer.

The coated microneedles are strong microneedles commonly covered with a medication arrangement. It conveys a more modest measure of the medication, relying upon the thickness of the covering layer [9]. A benefit of a microneedle of coated type is the fast conveyance of the medication to the skin. Microneedles coating can frequently be performed under surrounding conditions, and a coating under dry conditions might be steadier than a fluid plan [10]. A disadvantage of this approach is that microneedles of solid type can be covered with little amounts of medications as thick coatings lead to an exceptionally low skin conveyance proficiency and lesser sharpness at the tips [11]. Accordingly, microneedles of coated type for vaccine conveyance are just relevant for exceptionally powerful medications, like immunizations.

PEGDA is a biocompatible and FDA endorsed material for biomedical purposes, and its monomer can be polymerized into a strong massive design started by UV illumination [12]. Polyethylene glycol diacrylate (PEGDA) was chosen for building the needle shaft, exploiting its high mechanical strength and customizable crosslinking degree [13, 14]. PEGDA polymers are utilized in an assortment of biomedical applications as they can be effectively incorporated and display great biocompatibility, are non-poisonous, and is a biodegradable polymer [15]. Cone-shaped microneedles formed with polymers had forces of failure much greater than the forces of insertion [16].

The transdermal vaccination method utilizing biocompatible microneedles is a quickly improving area of exploration and applications. The terror of full pain hypodermic needles is sole of the basic reasons that many people keep away from acquiring vaccination [17]. Hence, producing a different pain-less way of vaccination utilizing microneedles is a remarkable research zone [18]. Microneedles contain arrays of miniature needles, which offer a painless way of conveying vaccines across the skin. Apart from being pain-free, microneedles give several benefits over general vaccination methods, such as being applied under the skin and administered into muscle [19].

Equipped Nano-indentation is the usually utilized method for assessing the mechanical properties of microneedle materials at smaller scales [20]. One of the incredible benefits of the procedure is that numerous mechanical properties of materials may be resolved from the inspection of the indentation load-displacement curve only. This eliminates the necessity to estimate the indentation region by imaging and enables the computation of characteristics at the micron scale [21]. This method measures concerned material's hardness, young's modulus, and stiffness. Nano indenter was utilized to conduct compression tests on needles to evaluate the compression strength of microneedles and to check the capability of needles to penetrate the skin structure [22].

The microneedles were examined by field emission scanning electron microscopy (FESEM) and confocal microscopy images [23]. In SEM, a beam is checked, in a raster-filter design, over the outer layer of a specimen causing electrons to collaborate with atoms in the specimen and produce different signs. These signs contain data about the surface geography and structure of the specimen [24]. In confocal microscopy, intelligible light is discharged by a source and cantered onto a solitary point. Reflected fluorescence from the test goes back through the mirror and pinhole over the Detector. The specimen is examined across a central plane in two aspects to produce a picture [25].

This work here focused on fabricating a PEGDA solid microneedle array that can be used to create pores on the skin to apply vaccines across the skin. This developed microneedle array can be coated with vaccine particles for vaccine delivery, but a limited quantity of drugs can be delivered in this case. However, Nano indention tests were conducted to test the capability of microneedle arrays to penetrate the skin structure. This research proposed a unique projection micro stereolithographic method for developing microneedle arrays that can be utilized for transdermal vaccine delivery of microscale pharmacologic particles. Mainly, this work will represent a clear plan of action for every step that researchers need to follow to fabricate unique vaccine delivery systems that will be the future of healthcare devices.

2. Materials and Methods

The microneedle design is 3D solid cone-shaped with a keen tip **(Figure 2)**, giving the standard and intelligibility of skin penetration. The space from one tip of the needle to another tip needle of 6 x 6 microneedles array is 600 µm. The height of needles is restricted to 600 µm to avoid touching needles with one another. The base diameter of every needle is restricted to 300 µm. A rationalized image of the microneedle array with dimensions is shown in **Figure 1**. The cone-shaped PEGDA solid microneedles array (6 x 6) was developed with each needle height of 600 µm and diameter of 300 µm on the surface of the square block (6000 µm x 6000 µm x 500 µm), respectively.

to formulate the PEGDA polymer solution (Mn=700, Sigma Aldrich) was initially stirred with Ethanol (AR 98%) to the proportion of 3:4 (v/v) and was flustered on a stirrer of magnetic type at an ambient temperature of 240 C for one hour before the PEGDA melts completely. The trimethylbenzoyI diphenylphosphine oxide (TPO) initiator (Sigma Aldrich) was then mixed with a fixed composition of 0.30% (w/v), and after that mixing it for 1 hour to secure that it was entirely liquefied. Afterward, 0.05% (w/v) of the SUDAN-1 UV absorber was mixed to eliminate the additional drying, and the mixture was stirred up for the next 35 minutes up to the SUDAN-1 liquefied completely.

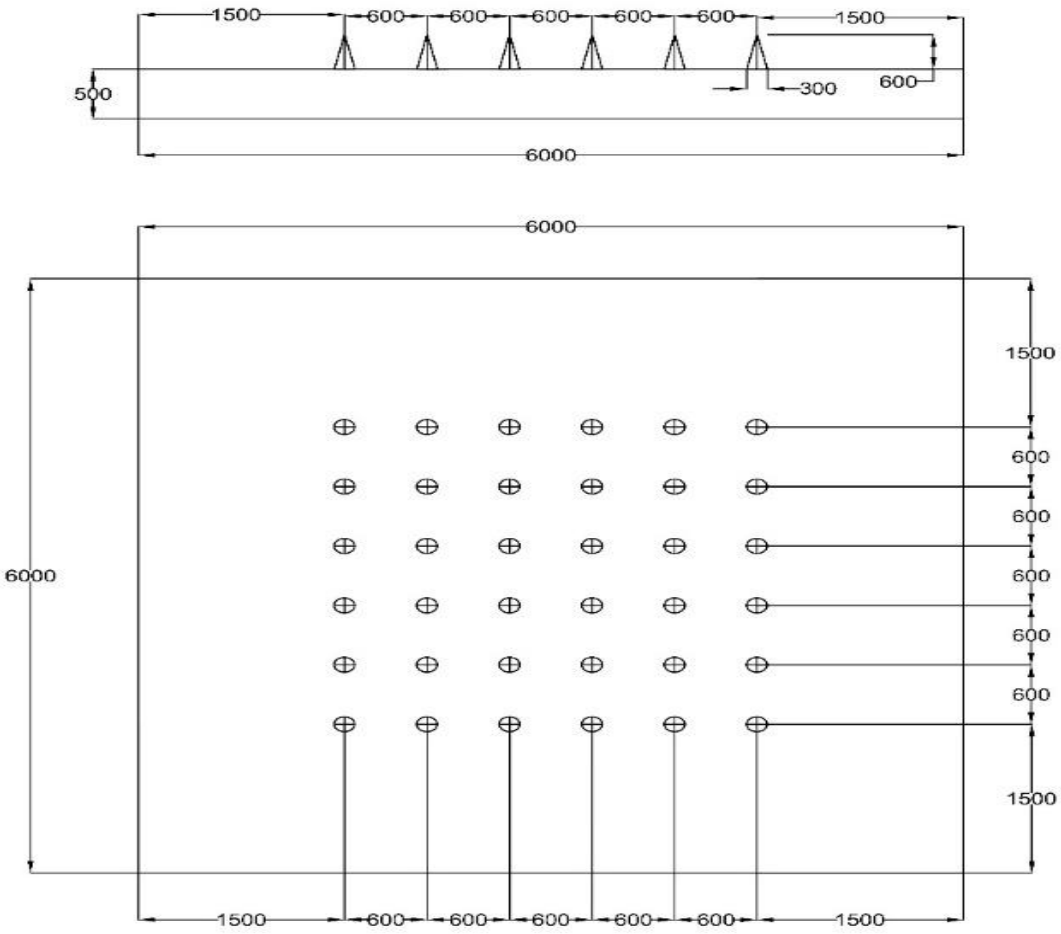

Fig. 1 Elevation and Plan Views of Microneedle Array

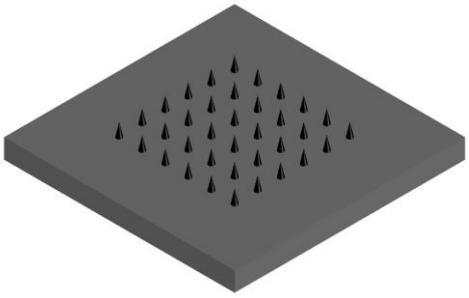

Fig. 2 Three dimensional Structure of Cone-Shaped Microneedle Array

3. Results and Discussion

3.1 Fabrication of Microneedles Array with Projection Micro Stereo-Lithography (PμSL)

This process produces the critical 3D micron cone-shaped microneedle array structures (Figure 5), where these geometries are developed in the form of layer-by-layer formation, which is derived from STL files. That layers are converted into binary images over a computer-generated array with mirrors in micron-sized digital format on the DMD device. Then rays of light are reflected on the mirrors of microarrays over the DMD device as per the input binary images, and this light is transmitted through an objective lens. Therefore, an accurately developed pattern is constituted on a polymer PEGDA resin surface with the required size and geometry. This projected layer is hardened at the identical time overexposed for the photopolymerization method. When the initial layer's drying is completed, the wafer is dipped into the UV drying resin according to the predetermined measurement of the STL file, and the next layer is developed over the existing layer. A critical microneedle array will be developed by drying all the layers from the lower portion to the top. During process flow

(Figure 3), CAD files are initially converted into STL and then bitmap image files. LabVIEW-based control software for automatic process controller has been utilized to give input process parameters such as the thickness of the layer, dwell and curing time, Z-axis motion control, DMD, and control lamp. Fabrication hardware (Figure 4) contains UV LED where intensity, power, and projection parameters are controlled; also, in DMD number of image files and projection parameters are controlled, and finally, layer thickness and z-axis speed parameters are controlled [26-27].

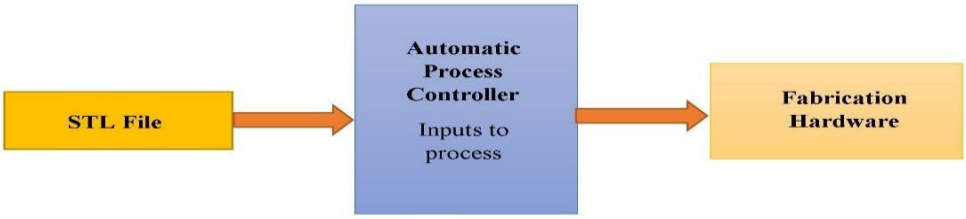

Fig. 3 Process Flow of Entire Fabrication Process

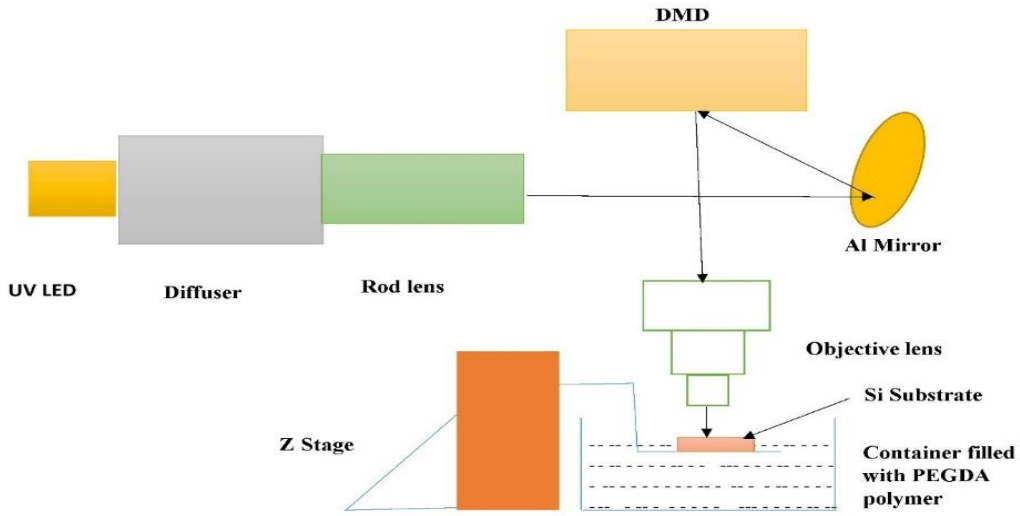

Fig. 4 Process Flow of Entire Fabrication Process

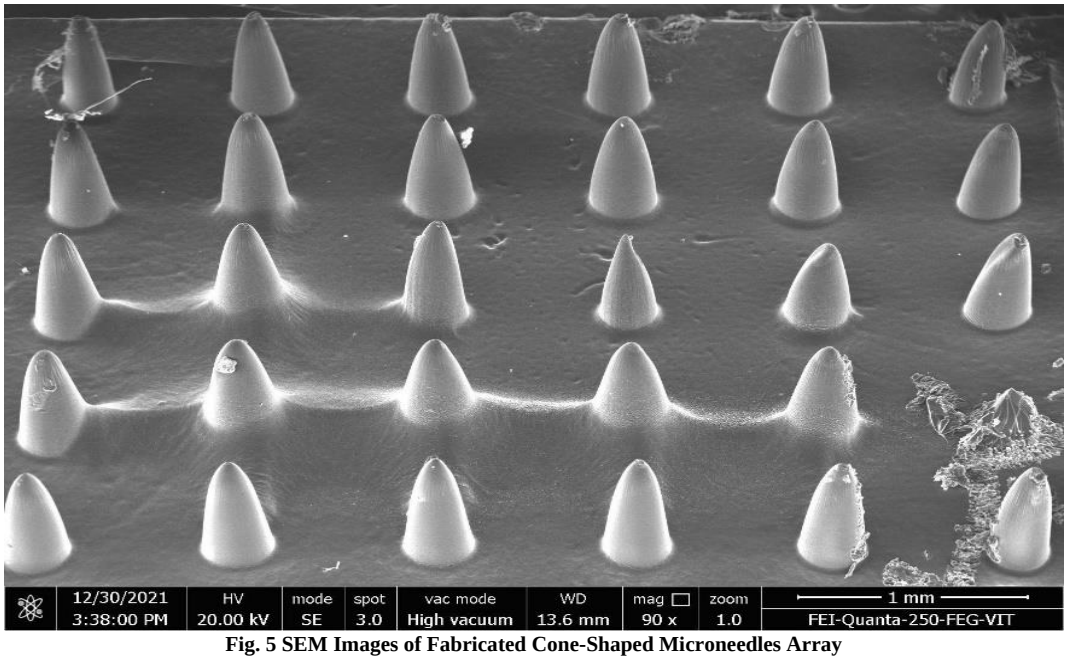

Fig. 5 SEM Images of Fabricated Cone-Shaped Microneedles Array

3.2. Confocal Imaging and Measurements of Microneedles Array

The microneedle array was carefully viewed, and the dimensions of the microneedle were taken by utilizing confocal microscopy (Olympus LEXT 4000, Japan) to investigate the regularity of the microneedles. The microneedle's dimensions were measured with a field of view of 600 µm × 300 µm and a needle tip thickness of 20 µm. The microneedles' height, base diameter, and tip sharpness were estimated, and all needles are almost uniform. Some needles available at the edges of the array are damaged (Figure 5) in some samples. By randomly considering 10 needles, the mean height was measured as approximately 580 µm (Figure 6), and the base diameter (Figure 7) was 330 µm with a tip diameter of 25 µm.

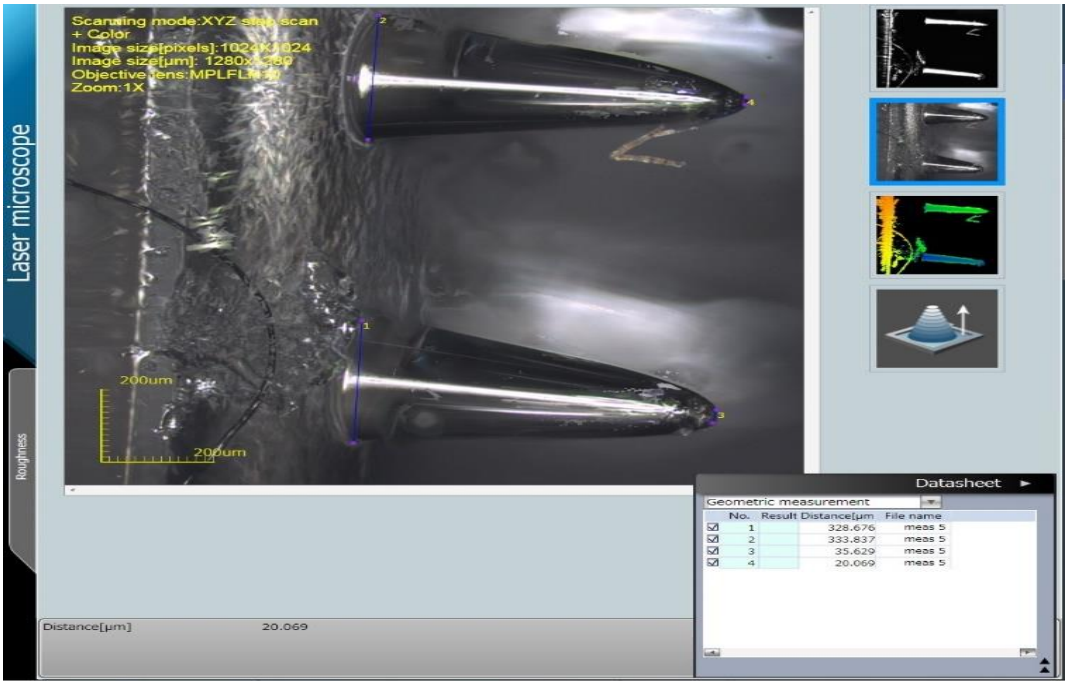

Fig. 6 Base and a Tip Diameter of Cone-Shaped Microneedles

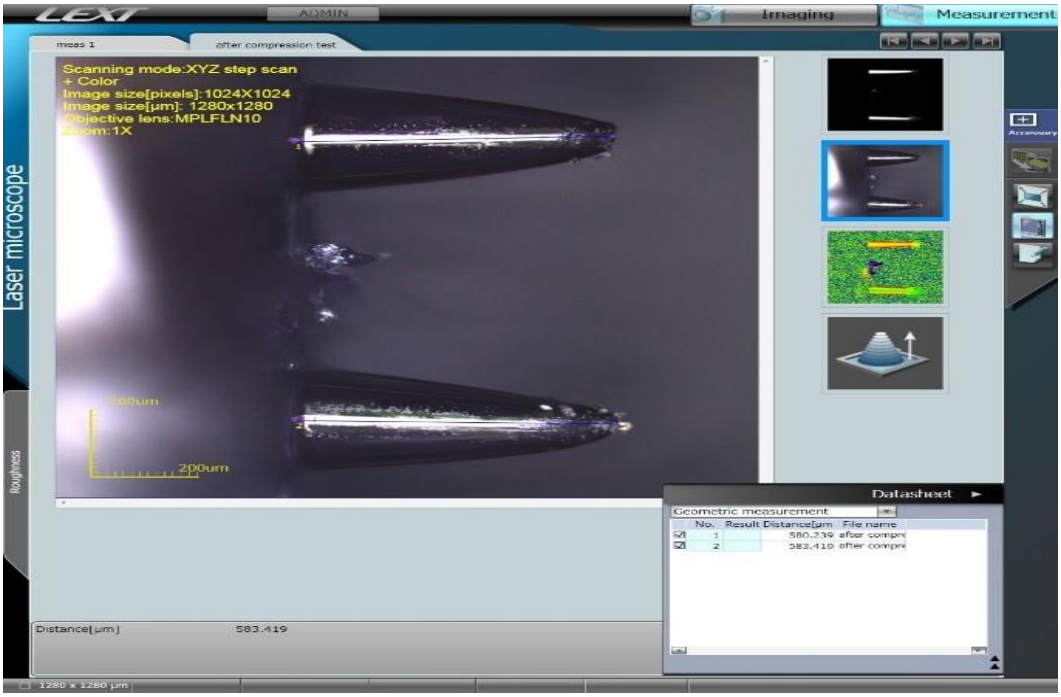

Fig. 7 Height of Cone-Shaped Microneedles

3.3. Material Properties with Nano Indentation

A Nano Indenter equipment (KLA Tencor, G200) was utilized to evaluate young's modulus (E) and hardness (H) values for Polyethylene glycol diacrylate (PEGDA), M_n=700. Hardness, the force offered by material against the insertion of the needle, and young's modulus, stiffness are crucial parameters for all substances utilized in microneedles and other transdermal medication conveyance gadgets. Depending on the highest load applied, the depth of indenter and slope of loading and unloading curve, the young's modulus, and hardness values are estimated. Before testing, PEGDA material is cured and cleaned at ambient temperature. Tests are conducted with a diamond tip called Berkovich tip on one sample, and the indentations are applied at two locations of microneedles. The indentation test contains the maximum load application, 1.4 mN during test1 and 0.7 mN during test 2. PEGDA developed the hardness and Young's modulus values, with a maximum hardness value of ~30 MPa (Figure 8) and a maximum modulus value of ~200 MPa (Figure 9) during two loading cycles. Anand et al. suggest that high young's modulus values provide a larger needle failure force than the insertion forces [24]. Anand et al. tested PEGDA, M_n=600, where the young's modulus is ~607 MPa with the same hardness value that leads to a larger failure force, which indicates the material has less strength.

3.4. Compression Test with Nano Indenter on Microneedles

Generally, microneedles undergo resistance forces while penetrating the skin where the force applied must be greater than the skin's antagonistic forces. to envisage the capability of microneedles to resist forces without failure during penetration into skin structure, a compression test was conducted with a nanoindenter Table 1. The loading curve is shown in Figure 11, which indicates the load applied on microneedle 2x1 for 15 seconds with a diamond-shaped indenter, where the load varied gradually. The maximum load applied on the tip is 300 mN. The holding curve indicates the holding of the applied load on the microneedle for 10 seconds.

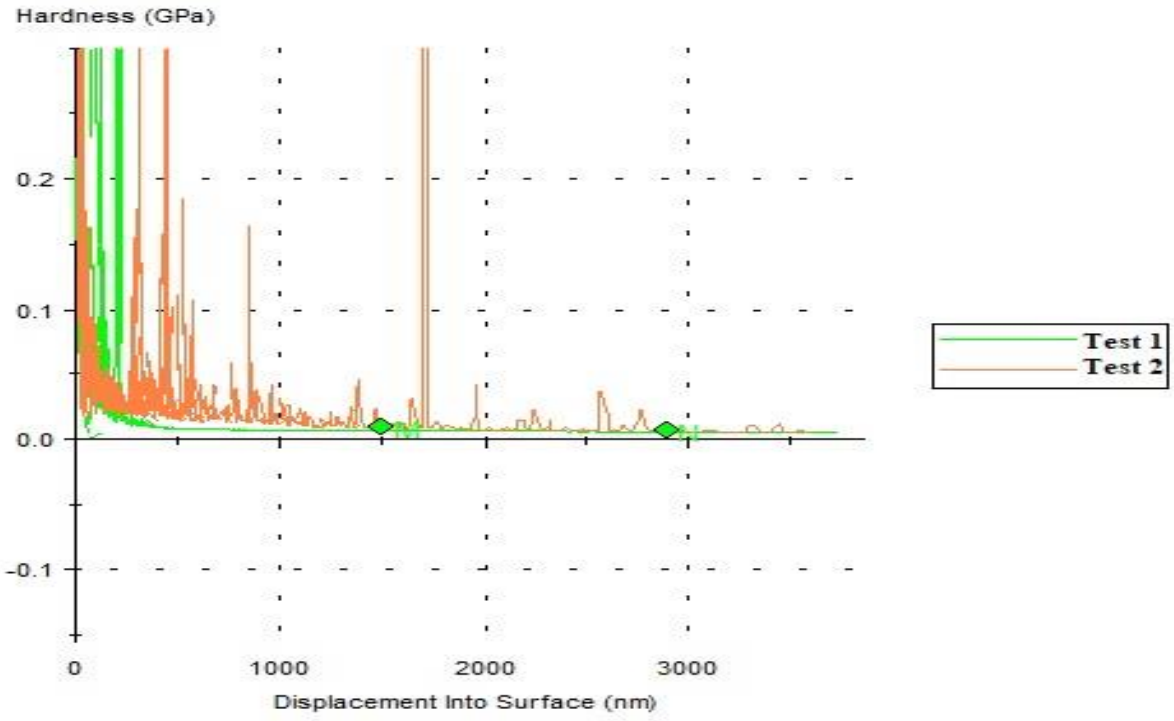

Fig. 8 Hardness of PEGDA microneedles

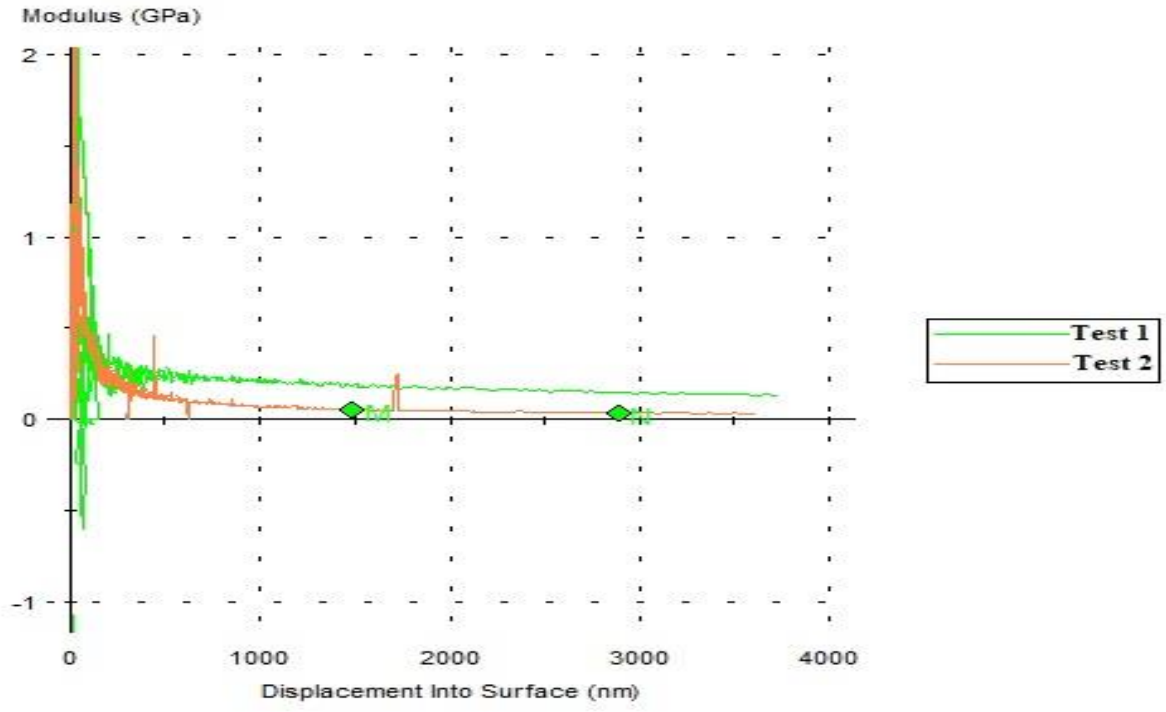

Fig. 9 Modulus of PEGDA microneedles

The unloading curve represents the removal of load gradually for 25 seconds. The microneedles are broken at 300 mN loads, as shown in Figure 10, and the compression test results are tabulated for different loads on four different needles are shown in Figure 9. Previous studies [21-25] proved that the force required to pierce human skin was 10mN. Jian et al. experimentally stated that the various dissolving microneedles are sustained only 50mN force. This nanoindentation compression test has proved that the needles made with PEGDA material will be sustained skin piercing.

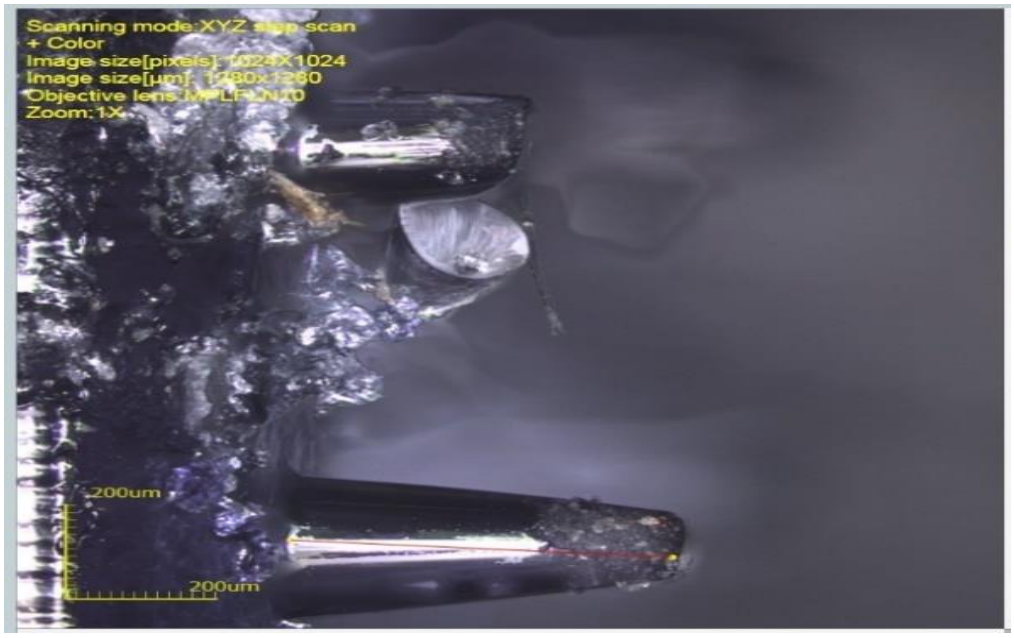

Fig. 10 Failure of the needle at 300 mN force

Table 1. Compression test results

Microneedle (MN) selected	The load applied (mN)							
	10	30	50	70	100	110	200	300
MN 2x3	Y	Y	Y	Y	Y	Y	Y	X
MN 2x4	Y	Y	Y	Y	Y	Y	Y	X
MN 2x5	Y	Y	Y	Y	Y	Y	Y	X
MN 3x3	Y	Y	Y	Y	Y	Y	Y	X
Y- Needle sustained X- Needle failed								

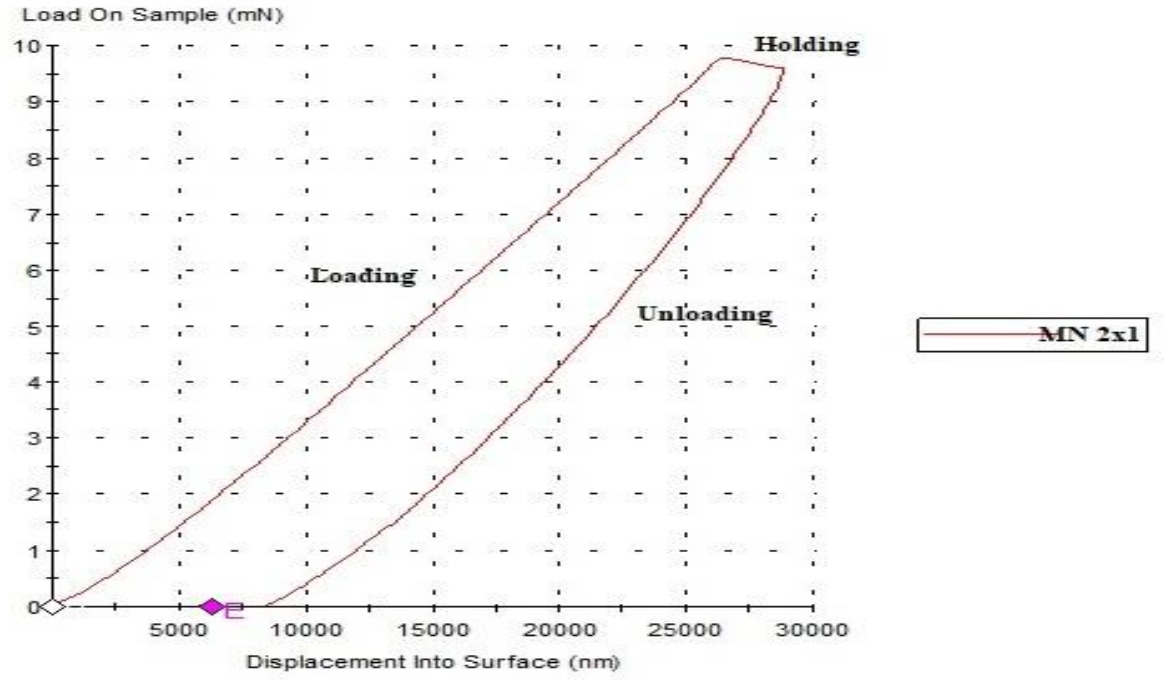

Fig. 11 Load vs. displacement curve of 2x1 microneedle at 10 mN

4. Conclusion

Initially, a 6x6 cone-shaped solid microneedle array was developed with PEGDA material of height of 600 µm, and a base diameter of 300 µm was performed. The presentation of microneedles, which could be 3D printed (PµSL) with an exceptionally high goal and exactness, flags another time for nano-medicine. Mechanical properties such as hardness 30 MPa and modulus 200 MPa were evaluated by the Nano indenter, which is sufficient for the skin penetration of the microneedle array. Microneedles are failed at 300 mN loads which are 96% higher enough and enable the microneedle arrays to pierce the skin. The results proved that microneedle arrays are a new method to enhance the efficiency of the distribution of vaccines across the skin layers.

Conflicts of Interest

"The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper."

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