Insertion Experiment and Resistance Tests of Solid Polymer Micro Needles Array

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Keywords: Polymer micro-needle, Hot embossing, Taguchi method.

Abstract. Microneedles have been made from silicon, glass, and metal. Nowadays, many promising technologies are focused on polymers since they are biodegradable, biocompatible, and easy to fabricate. They can penetrate safely in the body, providing a drug distribution method and eliminating the risk of the needles fracturing and buckling. The problem faced by most transdermal patches is the low permeability of skin. Microneedles have been shown to greatly increase the skin's permeability, allowing for an effective transfer of drugs. They however still face numerous challenges. This work addresses the challenge to effectively microneedle insertion into porcine skin, which is similar to human skin. A 7x7 solid polymer microneedle array made by hot embossing process was tested for insertion. Results show that the array is extremely resistant to insertion, it can withstand very high forces and even multiple insertions without blunting.

Introduction

With the development of micro-electro-mechanical systems (MEMS) and materials science, a more efficient and safer traditional transdermal drug delivery (TDD) like microneedle (MN) emerges. MN technology has received much attention in the medical community and the beauty industry. Microneedles (MNs) can eliminate the side effects of typical injection needle, such as skin damage, infection, and pain, and easy to use, in contrast to hypodermic needles [1]. Furthermore as an alternative, transdermal patches provide convenient, time-release delivery that avoids the gastrointestinal tract [2]. Appeared clearly for MNs technology development, it becomes possible for MNs array to strengthen the TDD, in addition to the increase of the skin permeability, therefore to deliver drugs into skin, such as insulin and vaccine, providing a new direction for drug delivery systems. MNs will play a decisive role in promoting micro-sample analysis, trace injection, blood fluid analysis, sampling and vaccines against influenza [3]. MNs have been demonstrated to be pain-free and potentially low-cost and easy-to use [4]. Generally, MNs should not break when bent slightly, and not rupture when pulled out after piercing the skin (except dissolvable MNs).

In this paper, solid polymer MNs manufactured by hot embossing method was discussed, a mechanical model of MN was established, and then an appropriate force equations was built. After the strength of a polymer MN was verified, the piercing situations of different shapes were simulated, the optimized structures of MNs were obtained. Based on the stress condition, three kinds of common polymers with different geometries were simulated using MATLAB and ANSYS. The results showed that all kinds could satisfy the strength requirements.

Based on that, PMMA, PC and PLA were chosen to fabricate MNs, details of MNs fabrication with hot embossing process were presented [5]. To minimize the cycle time while maintaining quality, non-isothermally of embossing step was used [6]. Through the experiments, the significant embossing factors were decided by Taguchi method, and quality of MNs are evaluated. Lastly, tests were made to verify the properties of MN.

Experimental procedure

This part presents an illustrative sequence of implementation of experimental work for process parameters optimization under three parameter settings and one-quality response. Taguchi orthogonal method is used for investigating the optimal performance characteristics from a set of factors through design of experiment (DOE). Hot embossing process has many potential factors, although all of these machine settings are acceptable factors, DOE aims to reduce the number of these factors thus reduce the cycles to be run. Based on Taguchi orthogonal method to design experiment, the array ***L16 (4***^{3}***)*** was selected in this paper. The control factors and their levels are shown in Table 1 below (eg.PMMA). There are 16 treatments for all combinations; tow replications are used for each setting to increase the sensitivity of statistical analysis.

Table 1. The specific process parameters with their levels(PMMA)

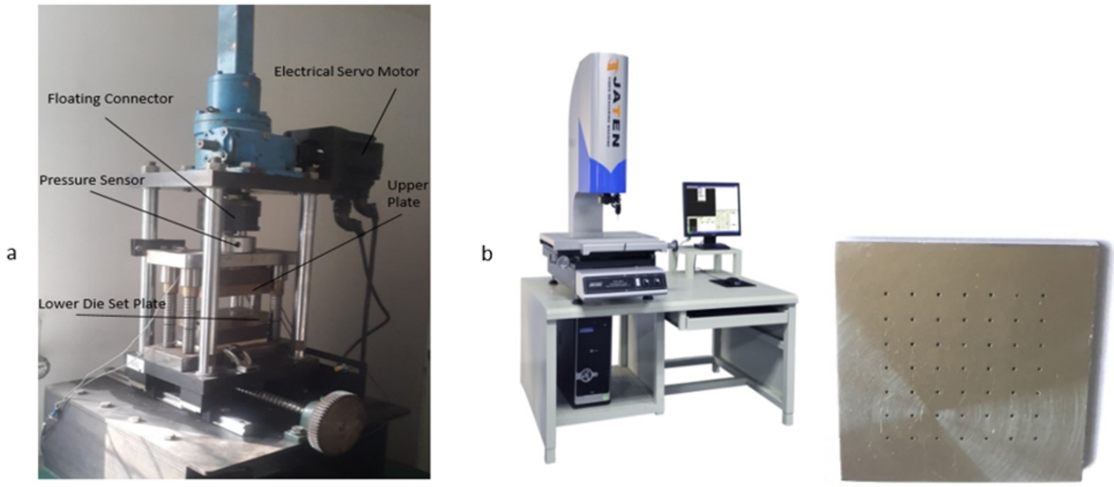
Parameters	Levels			
	1	2	3	4
Embossing temperature (ºC)	120	125	130	135
Embossing pressure (MPa)	5	7	9	11
Embossing time (s)	100	150	200	250

Experimental and Measurements machine used

The hot embossing apparatus is a flat-platen thermal embossing apparatus developed by the Institute of Plastics and Plastic Engineering of Beijing University of Chemical Technology as shown in Fig.1 (a). The effective area of embossing is 160 × 80 mm, a PLC controls the servomotor movement, the servo motor drives the screw lift to drive the upper and lower platen movement. The speed of the pressing upper mold platen could be set from 0.5 to 5.0 mm/s. The pressing force of embossing can be acquired up to 50 kN with a control accuracy of ±50N. A mold temperature controller from room temperature to 170 ºC can control the temperature of the mold with a control accuracy of ±1ºC.

The JTVMS-1510T 3D Image Measurement System Fig.1(b), product of China Dongguan Jaten Precision Instrument, carried on characterization of the microstructure of the embossed substrates.

The experimental mold was made of stainless steel with the size of 20×20 mm and a thickness of 2mm, and assumed isotropic and elastic because it involves little deformation as compared to the polymer. As shown in Fig.1(c), the mold is distributed with 7 × 7 MNs concave conical array, the distance between the adjacent cone hole is 2mm, the MN counterbore bottom diameter (cone Platform diameter) is 250µm, the top diameter (truncated cone) is 50 µm, and the depth is about 500µm.



(a) Hot embossing machine (b)Video measurement (c)Microneedle mold

Fig.1. Equipment for experiments

Materials and methods

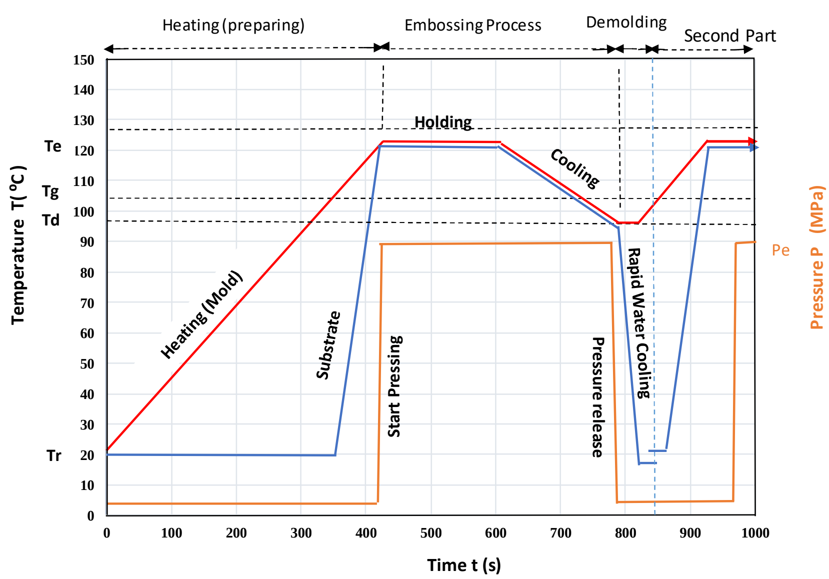
The polymer materials PMMA, PC, and PLA with the size of 24×24 and 1 mm in thickness were selected as the substrate material of the MNs. Main properties of the materials were listed in Table 2.

Table 2 Main properties of polymers

Material	Young's modulus(GPa)	Poisson's ratio	Tensile strength(MPa)	Density (g/cm^2)	Glass-transition temperature (ºC)
PC	2.0-2.4	0.37-0.39	55-75	1.2-1.22	145
PMMA	1.8-3.1	0.35-0.4	50-77	1.17-1.20	105
PLA	3-4	0.36	40-60	1.21-1.43	65

The hot embossing Cycle

The experiment cycle starts when the mold is placed on the lower set platen, and heated above its glass transition temperature (T_g)to the desired embossing temperature as illustrated in Fig.2. After reaching the embossing temperature, the polymer substrate was placed at the top of mold between the platens, the upper platen is then driven to the lower platen at ≈ 3 mm/s until a threshold force is detected, indicating that the upper platen is in contact with substrate and the mold. The upper platen then was driven down at ≈ 0.5 mm/s pressing the substrate until the desired embossing pressure is reached. The embossing pressure was maintained for the desired embossing time. Then the platens were cooled to the demolding temperature, while the pressure is still maintained, the platens are separated after the Demolding Temperature is reached. The mold with substrate are taken out from the machine, the part is separated from the mold using tweezer and quenched in water, then the mold placed again on the lower die set platen with the demolding temperature and start with the second test.



Tr: room temperature; ***Te***: embossing temperature; ***Td***: demolding temperature; ***Tg*** : glass transition temperature ; ***Pe***: embossing pressure

Fig. 2. Illustrative Diagram for Hot Embossing Process

Skin Penteration Experimental results and analysis of MNs

Porcine skin was cut to four pieces 50x50mm and marked as number 0, 1, 2, 3, 4. First, Measure the skin moisture for all parts before acupuncture and record it, then using the universal testing machine. For pressing the skin parts with MNs. No. 0 no pressing part, then pressing the parts 1,2, and 3 with

50,60,70,and(70N twice with different direction) respectively, with 3 minutes holding time. The moisturizer was applied on the four skin parts as shown in Fig.3, and rubbed for two minutes for all parts. Then stored in fresh keeping bags to prevent air-drying. After 10 minutes, the surface of the skin was cleaned with a paper towel to dry the surface moisture and oil content.

Then all parts were measured (ambient temperature 21°C, humidity 33% RH). Experimental data is shown in Table 3 and Fig.4 below.

Table 3 Test data of experiment

Category	Type	Test parts				
		untreated	1	2	3	4 Twice
Before test no moisturizer	Moisture	87.6	87.6	88.0	87.7	87.7
	Oil	27.3	28.0	28.1	27.7	27.6
After 15 min	Moisture	90.2	89.6	89.6	89.6	92.0
	Oil	28.8	28.6	28.6	28.8	28.9
After 30 min	Moisture	90.6	90.1	91.1	91.1	92.1
	Oil	28.8	28.8	29.1	29.1	29.3
After 60 min	Moisture	90.1	90.5	90.7	91.0	92.0
	Oil	28.8	28.9	29.0	29.1	29.5
After120 min	Moisture	90.0	91.0	90.4	91.7	92.3
	Oil	28.8	29.1	28.9	29.3	29.7
After 4 hours	Moisture	88.5	91.1	91.1	91.3	92.0
	Oil	28.3	29.3	29.1	29.2	29.9

Fig.3. Porcine skin treatment with moisturizer

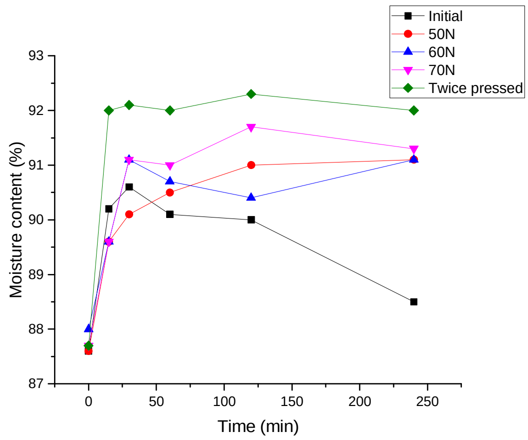


Fig. 4. Resultant curves of porcine skin moisture

Mechanical Strength and Rupture of MNs

In this test, Polyethylene (PE) film of a thickness 60μm folded into 7 layers pressed against the MNs. The MNs are inserted into the PE film layers supported by 2mm thickness Styrene Ethylene butylene Styrene (SEBS) plate, with a force of 10N, 20N, 25N, 30N, 50N and held for 15s, observation made after each insertion shows that the maximum depth value reached by forces above 25N based on the 6 layers pierced as shown in Fig.5. Moreover, the stratum corneoum (SC) is the main obstacle with around 40μm thickness therefore, once the microneedles have penetrated the SC, the resistive force falls drastically. In addition, no remarkable damage observed after repeatable insertion of MNs.

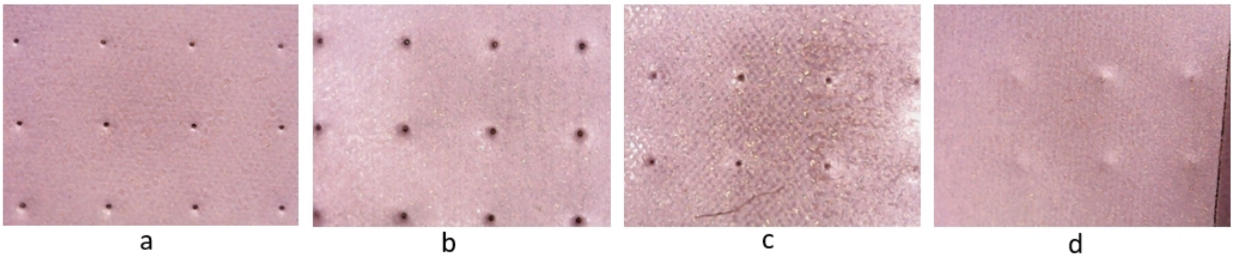


Figure 5. PE film layers after MNs pressing
with F=30N (a) 1st Layer, (b) 2nd Layer, (c) 6th Layer, (d) 7th Layer

Conclusion

The optimized solid polymer MN for cosmetic purpose was fabricated with low cost because of its innovative fabrication method that implies hot embossing. The biocompatible polymeric materials not only insure excellent biocompatibility for the patients but also extremely resistant considering insertion into the skin. It can withstand very high forces and does not break but crushes making the MN very safe for the patients as they cannot be broken and stay into the skin. Different insertion tests were performed on the porcine skin and PE film (which shows excellent resemblance to porcine skin). Results demonstrate that the insertion force is the most important parameter but can be compensated by optimising insertion speed and holding time. While the insertion force for our MN is already largely acceptable regarding patient comfort. All polymer materials tested assure good penetration, and no buckling and damage, and can be used safely.

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