FABRICATION OF DISSOLVABLE MICRONEEDLE PATCHES

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Abstract

The purpose of the study is to fabricate a dissolvable microneedle patch considering the production cost, effort and effectiveness. Those patches have needles in micron scale. Those needles contain drug and they transfer the drug by dissolving under the layers of skin. Microneedle patch is a healthier and more effective drug delivery system. This study is about fabricating microneedle patches by using vacuum and heat. A new methodology is presented in this report. CMC, PLA, PCL, PLA & PCL combination and chitosan polymers are used to fabricate microneedle patches in this project. PLA and PCL mixed solution gave promising results for fabrication. The trials will continue.

Keywords: Microneedle patches, microneedle patches fabrication, local drug delivery, transdermal drug delivery

1.Introduction

For a long time, syringes, pills and topical creams are used as transdermal drug delivery systems and they are still in use. Those delivery systems have many disadvantages. Syringes necessitate trained personnel. They cause pain and tissue damage after the application also can cause needle stick injuries. According to WHO, almost 2 million people were infected with hepatitis B, 35 000 people with HIV and 315 000 with hepatitis C because of the needle stick injuries (Mandelbaum-Schmid, 2015)***[1].*** Vaccines have to maintain the cold chain for to be used with syringes, but it is challenging to maintain the cold chain while transporting especially in Third World countries since the vaccines spoil when it is colder or hotter than it is supposed to be. Pills can't be used as a local drug delivery system also dosage and the rate of drug delivery can't be controlled. Topical creams are not efficient enough. Since the molecules of cream are bigger than the pores of the skin, creams had to corrode the skin to pass under it. Even with the corrosion of the skin, the whole drug can't be delivered under the skin.

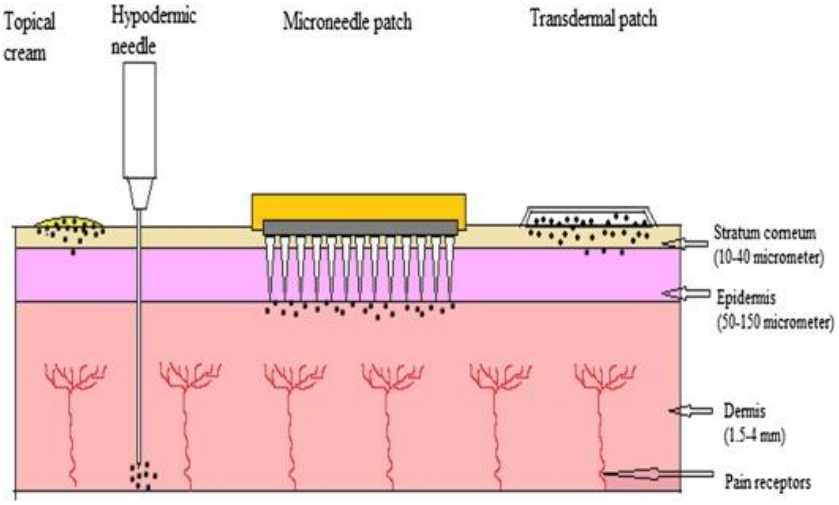

Figure 1: Drug Delivery Systems ***[2]***

This project is about a newer method for transdermal drug delivery called microneedle patches. Those patches have micron size dissolvable needles on it. Those microneedles penetrate the stratum corneum which is the first layer of the human skin and the physical barrier against drug delivery and reaches up to the desired level of the layer to deliver the drug. Since they are dissolvable in the human body, they are harmless and non-invasive when it is compared to other delivery systems. They can also provide dosage and rate for the drug delivery thanks to its dissolvable nature.

Transdermal drug delivery with microneedle patches is a new concept that is known for a few decades. Indeed, since late 1990, it has become a significant research area due to the development of microfabrication technology. In literature, there are 5 main design types of microneedles. These are solid, coated, dissolvable, hollow and hydrogel-forming microneedles*(Larrañeta et al., 2016*) ***[3].*** This study focuses on the production of hydrogel-forming microneedles.

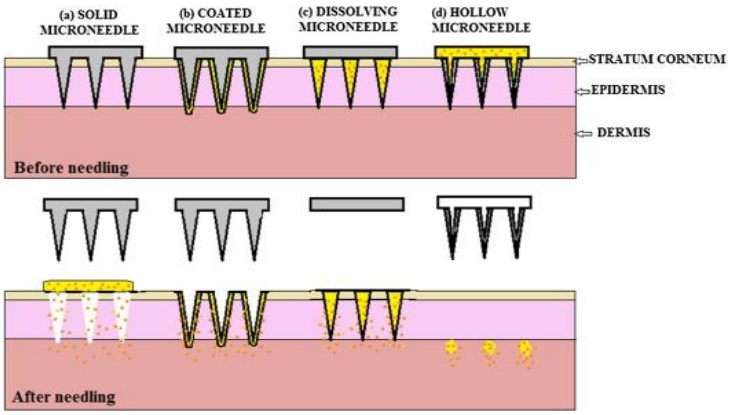

Figure 2: Microneedle types ***[2]***

The main focus is to find a new method to produce microneedle patches considering the issues: The cost of production, the effectiveness of the application and the applicability of the manufacturing method for industry. To pursue this goal, this project aspires to change the dimensions and the angles of the microneedles and use vacuum and heating to construct the PDMS production mold. Then, find a convenient polymer which is suitable to form the microneedle shape and to deliver the drug.

2.Materials & Methodology

The production process can be divided into 3 main subsections:

1. Micro milling the Master Mold
2. Micro molding the Production Mold
3. Fabricating Microneedle Patches

2.1 Design & Production of Master Mold

Master Mold is the first step to fabricate a microneedle patch. The master mold is the main mold due to its effect on producibility and shape of the production mold and of the microneedle patches.

The master mold is designed with SolidWorks as a microneedle array. There are 3x2 master molds despite only one master mold is enough to produce production molds. However, having more master mold fastened production. Microneedles are designed in obelisk shape with 44.5° apex angle since the obelisk-shaped needles minimize the insertion forces and can deliver more bioactive cargo to human skin than the pyramidal-shaped needles, also when apex angle is 30° needles shrink more*(Bediz et al., 2013*) ***[4]***. The targeted dimensions can be seen in Figure 3(B,C,D).

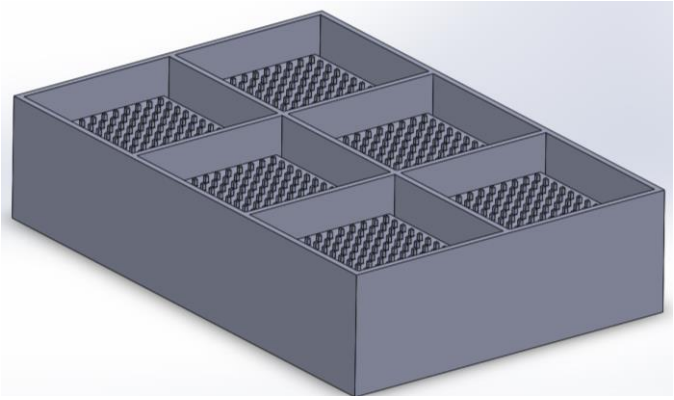

Figure 3.A: Master Mold design with micro needle arrays

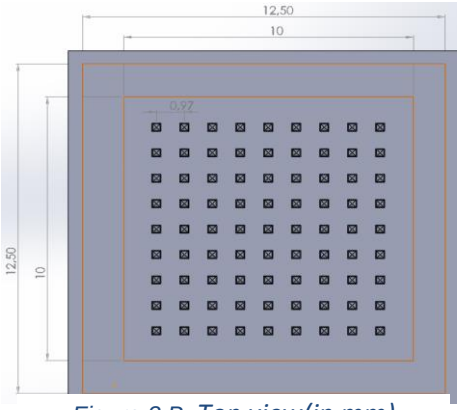

Figure 3.B: Top view(in mm)

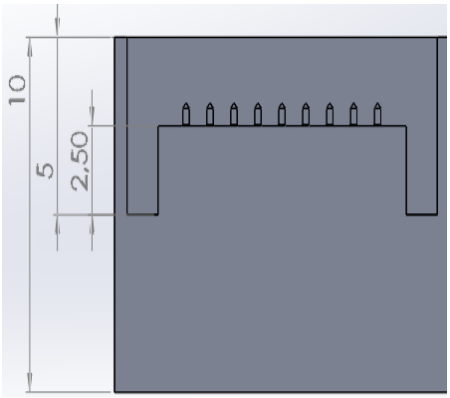

Figure 3.C: Cross Section(in mm)

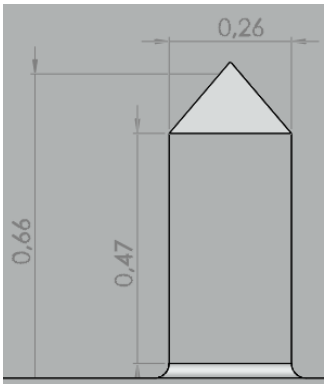

Figure 3.D: Needles(in mm)

Then, KERN EVO CNC Micro milling machine is used to create the master mold using plexiglass that has 2 cm thickness.

*Figure 4: KERN EVO CNC Machine**[5]***

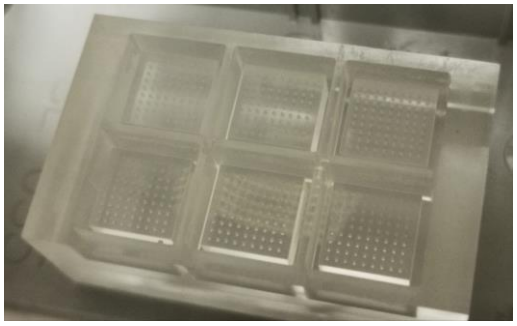

Figure 5: Manufactured Plexiglass Master Mold

After the manufacturing process of the master mold is finished, the mold is examined via Stereo Microscope. Imprecise measurement is made with microscope to understand the difference between target mold and the manufactured mold. In Figure 6.A, it can be seen that manufactured mold's dimensions are close to the target mold. Moreover, obelisk shape of the microneedles is well manufactured and can be seen in Figure 6.B.

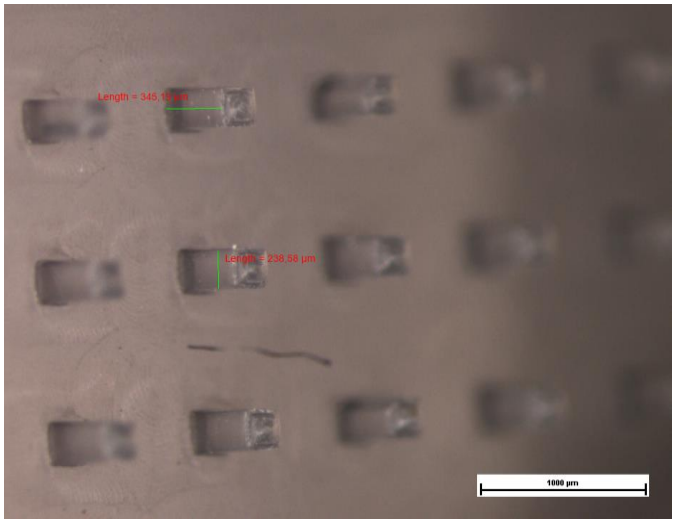

Figure 6.A: Stereo Microscope View & Dimensions of Master Mold

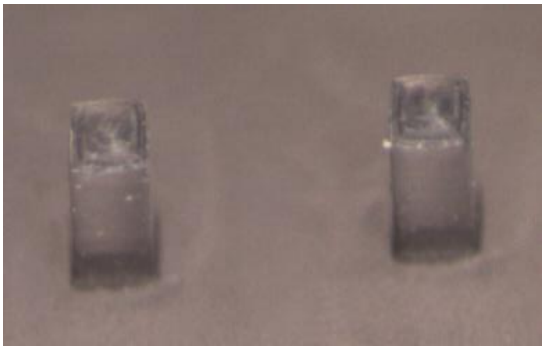

Figure 6.B: Stereo Microscope View of Obelisk-Shaped Needles on Master Mold

2.2 Fabrication of Production mold

Molding PDMS Production Mold

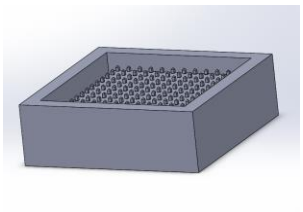

Figure 7.A: Master Mold

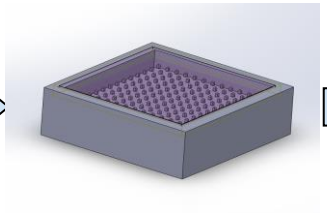

Figure 7. B: Curing PDMS Mold in Master Mold

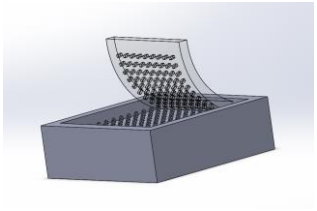

Figure 7. C: Pulling out PDMS Production Mold

The production mold is made of polydimethylsiloxane which will be named as PDMS in this article. PDMS is mixed with curing agent in 10:1 ratio. Then, the mixture is vacuumed by using desiccator for 5 minutes, during this process vacuum is broken multiple times to eliminate the bubbles which are produced during the blending process. Accordingly, the bubble-free PDMS-Curing agent mixture became ready for molding. The mixture is casted in the production mold and it is vacuumed in the desiccator for another 5 minutes. This process could be continued till there is no bubble remains. Then, the mold is heated at 60°C for 4 hours. When the small scratches are seen in the surface of the production mold(*Figure 8.A*), it became ready for cooling in room temperature. After cooling for 1 hour, PDMS production molds are separated from the master mold with the help of scalpel and tweezers.

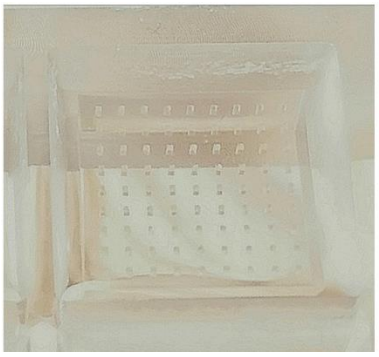

Figure 8.A: Cured PDMS in Master Mold

Figure 8.B: PDMS Production Mold

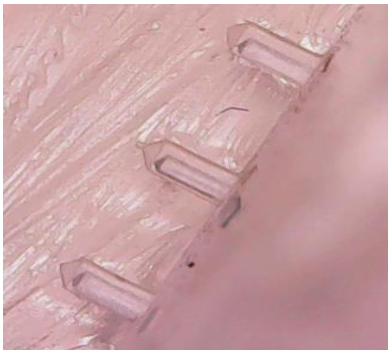

Figure 8.C: Cross Section of PDMS Production Mold

2.3 Fabrication of the Microneedle Patch

The third and the final step for this project is the fabrication of the microneedle patches. To fabricate the patches, a hydrogel solution and the production mold is needed. Patches have to be dissolvable in human body, indeed, the material used in this process has to be dissolvable. In this project, CMC, PLA, PCL, PLA & PCL combination and chitosan are used as hydrogel.

The first polymer was low molecular weight chitosan($C_{56}H_{103}H_9O_{39}$) as hydrogel which is dissolved in HCL. The solution is casted in the production mold and cured in a vacuum oven under 26.5 °C and 100 mbar. After this process the microneedle patch was extremely dry (Figure 9.A), and the needles were unformed(Figure 9.B). Thus, the trial was unsuccessful.

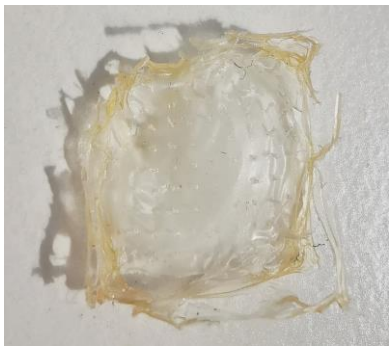

Figure 9.A: Chitosan Microneedle Patch

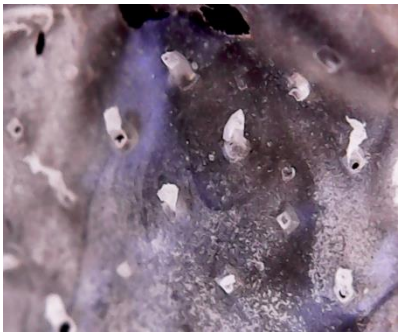

Figure 9.B: Microscope View of Chitosan Microneedles

The second polymer was Polylactic acid(PLA, $C_3H_4O_2$) dissolved in chloroform. After the inefficient trials with chitosan, PLA was a prospering material to be the base of microneedle arrays. It is vacuumed via desiccator and dried in room temperature due to its sensibility of temperature. After 12 hours of curing period the microneedles were formed. However, the backing layer of the patch was still too thin.

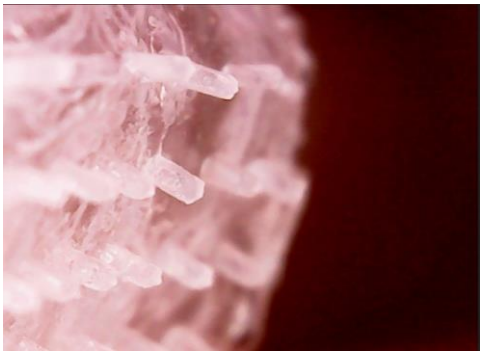

Figure 4: Microscope View of PLA Microneedles

The third polymer was Polycaprolactone(PCL, $C_6H_{10}O_2$) dissolved in chloroform. The solution is casted in the mold and vacuumed via desiccator and dried at room temperature for 5 hours. The upper layer of the patch was dry but the inner, needle, part of the patch wasn't totally dried. Consequently, the needles were not totally formed(*Figure 11*). Thus, this trial was unsuccessful.

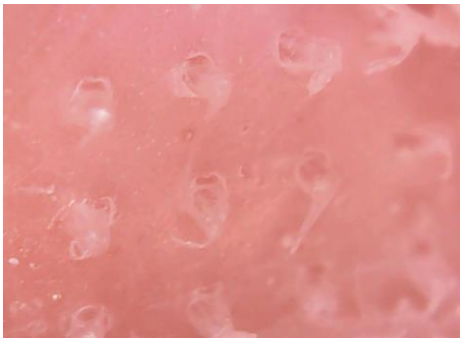

Figure 5: Microscope View of Failed PLC Microneedles

The fourth polymer was Sodium Carboxymethyl Cellulose(CMC) which is dissolved in distilled water. The solution is casten in the production mold and vacuumed and heated in a vacuum oven at room temperature. Unfortunately, because of the viscosity of the solution, it did not interpenetrate into the needle hallows. Thus, the structure was not fully formed. This trial should be retested with a less viscous solution to get a better result.

The fifth and the last solution was a mixture of Polylactic acid(PLA) and Polycaprolactone(PCL). According to the previous research, the best results are reached when the PLA and PCL is used together. Again, the solution is casted in the production mold, vacuumed via desiccator and exsiccated at room temperature. After 1 day of curing, the result was satisfactory. The needles were formed accurately, and the tissue of the microneedle patch was tough enough to pierce the skin.

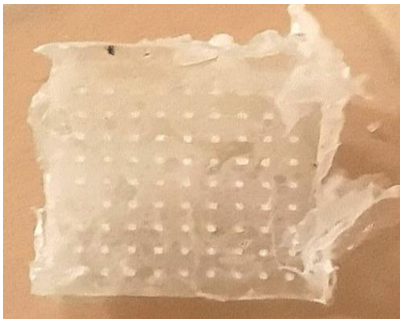

Figure 6.A: PLA&PCL Microneedle Patch

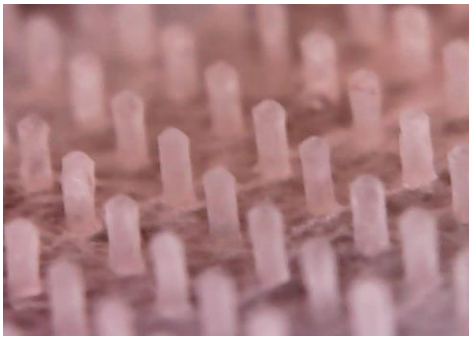

Figure 7.B: Microscope View of PLA&PCL Microneedles

3. Discussion and Conclusion

This project was about fabricating microneedle patches with less cost, less effort but with more effectiveness. The mold was designed by those criteria, but it has some problems which couldn't be forecast. Manufacturing larger master molds by micro milling takes more time thus, the master mold designed with small gaps. Due to its small and insufficient gaps, pulling out the PDMS production mold was hard and caused damages on the production mold. Now, the production molds don't have walls to hold hydrogel in. Larger gapped master mold was needed therefore, new master mold was designed. It is in the manufacturing process.

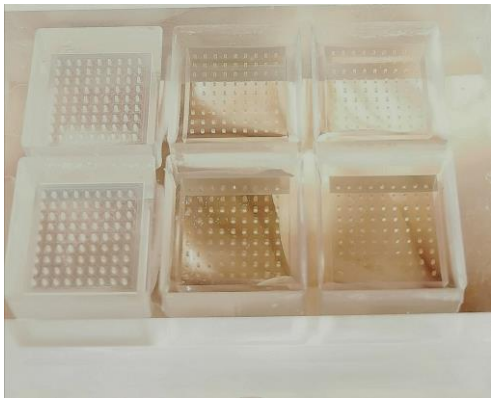

Figure 93.A: Old Master Mold

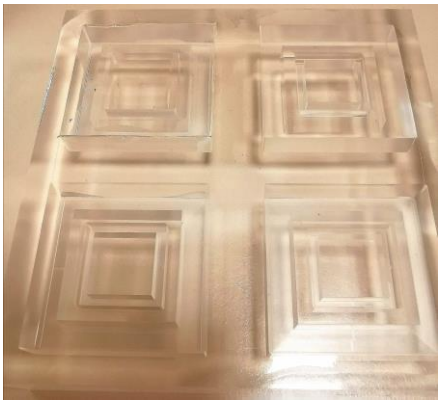

Figure 83.B: New Master Mold Trial

While waiting for the new master mold, a mold holder designed to be able to hold hydrogel in for fabrication of the microneedle patches. After the trials with first mold holder, it was seen that mold holder is too short, mold holder doesn't have enough capacity for hydrogel. Since hydrogels are preparing with solvents, when the solvents gone the cured materials formed very thin layers like paper. The wanted layer was thicker therefore new longer mold holder was needed. Second mold holder was longer, and it has a hole under it. It is designed with a hole because it is hard to pull the fabricated material and the production mold from a deeper molder. Then, the trials are made for the second mold holder. The hole was letting air in all the time thus, the vacuum couldn't be made properly. Parafilm was used to restrain the air entrance to mold holder from below.

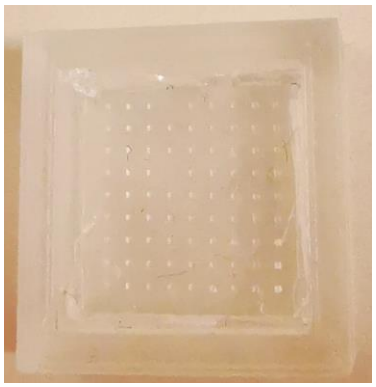

Figure 114.A: Old Mold Holder (1.5mm x1.5mm x0.6 mm)

Figure 104.B: New Mold Holder (1.5mm x1.5mm

When all the design problems are dealt, the trials for the fabrication of the microneedle began. Curing time for the materials was unknown, sometimes pulling out the material made before the curing therefore the needles wasn't fabricated properly. Also, solutions have some problems. For example, chitosan solution had a good viscosity for the application but for this, molecular weight should change. CMC solution was too viscous for the application, new solution should be prepared with more water. This project still has some flaws, but they can be solved with more trials and with some design changes. From the beginning of the project, first master mold is designed and manufactured from Plexiglas. Then, PDMS production mold is produced via micro molding by using vacuum and heat for the curing process of PDMS. Fabrication of microneedle patches from PDMS mold are started by using different hydrogel. Future work will be done with pharmaceutical companies' and with their drugs. Clinical trials will be done after all the problems were solved.

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