Design and Development of a Novel Medical Device Using Laser Molding Technology

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University
March 2020

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "Design and Development of a Novel Medical Device Using Laser Molding Technology" submitted by Julkernayen Ahmed (14346019) of Summer, 2014 has been accepted as satisfactory in partial fulfillment of the requirement for the degree Bachelor of Pharmacy (Hons.) on 2nd March 2020.

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Ethics Statement

This study involved no animal or human trials.

Abstract

Recently the outbreak of the novel coronavirus drew the attention of each corner of the world. Till now many countries are trying to develop many antiviral drugs or vaccine for the novel coronavirus. Recent news has been published (2020) that showed that this deadly virus has spread in the China. Transdermal delivery is an appropriate route for the delivery of antiviral drugs or vaccine by using the micro-needle as a tool. In this research, a laser-engineered microneedle mold was fabricated on a biocompatible acrylic sheet using a laser of CO_2. The optimized mold was tested for its characterization and efficiencies. Furthermore, the characterization tests were run on the fabricated microneedle using polymer and a breakthrough result has been achieved. An animal trial also being done already this gives a significant result about the skin penetration and delivery efficiency. Manufacturing a cost-effective delivery device will be great relief in this case. The laser engraved mold can be used to fabricate any desirable depth of microneedle which can be so useful for any antiviral drug or vaccine. Finally, this cost-effective molding technique can enable the delivery of transdermal drugs in a completely new role.

Keyword: transdermal delivery, micro-needle, molding technique, laser-engineered, acrylic sheet;

Dedication

I dedicate this project to my beloved Mother for the hardship she is doing for me

Acknowledgements

I would like to express my special thanks to the almighty for enabling me to carry out this research project in good health and frame-of –mind.

My earnest gratitude and appreciation go to my most venerable supervisor, Dr. Md. Jasim Uddin (Assistant Professor, Department of Pharmacy, Brac University) who gave me the golden opportunity to carry out my project that would not come to light without his undivided time, attention and guidance. His was of driving toward research and teaching was phenomenal.

I am also thankful to my honorable chairperson of Pharmacy Department, Professor Dr. Eva Rahman Kabir, who has been a continuous inspiration to me to develop and grow as a better person over the past years. I am grateful to Brac University, all the finest faculties, teaching assistants, laboratory officers and other working stuffs for creating a nice and professional environment while carrying out my project. I would like to use this opportunity to show my gratitude towards Dr. Hasina Yasmin (Professor, Department of Pharmacy, Brac University), who is a big milestone in both of my educational and career development.

Lastly, I would like to express a token of gratitude towards my parents without their support and prayers I would not have made as far as I have. I am cordially thankful to my friend Sanjida Amir for her dedication in this thesis project.

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List of Acronyms

MN	Microneedle
DDS	Drug delivery system
TDDS	Transdermal drug delivery system
3D	Three-dimensional
DNA	Deoxyribonucleic Acid
RNA	Ribonucleic Acid
PMMA	Polymethyl methacrylate

Chapter 1 Introduction

Delivery of drug is an essential step to get the most bioavailability of the specific drug. There is various conventional method of delivery drug. Among them parenteral promises the most bioavailability (Gulati & Gupta, 2011). Needles are one of the widely used medical device for parenteral drug delivery system. However, using needles requires trained individuals and greater skills (mentions other limitations). To overcome these complicacies in modern era, various technologies have been developed such as biodegradable implants, transdermal patches, intramuscular depot injections or microneedles and so on (Gulati & Gupta, 2011)

1.1 Drug delivery system

Drug delivery system (DDS) is a pharmaceutical formulation or device that has been engineered to achieve an ideal target delivery or controlled release of therapeutic agents in any diseased body. There is a various methods through which drug can be delivered. By National Institute of Biomedical Imaging and Bioengineering (NIBIB), there are four methods to deliver drug.

- By swallowing
- By inhalation
- By absorption through skin
- By intravenous injection

There are also various routes of drug administration, such as

- Buccal drug delivery
- Nasal drug delivery
- Ocular drug delivery
- Oral drug delivery

- Pulmonary drug delivery
- Sublingual drug delivery
- Vaginal/anal drug delivery
- Transdermal drug delivery

Each route has its own advantages and disadvantages.

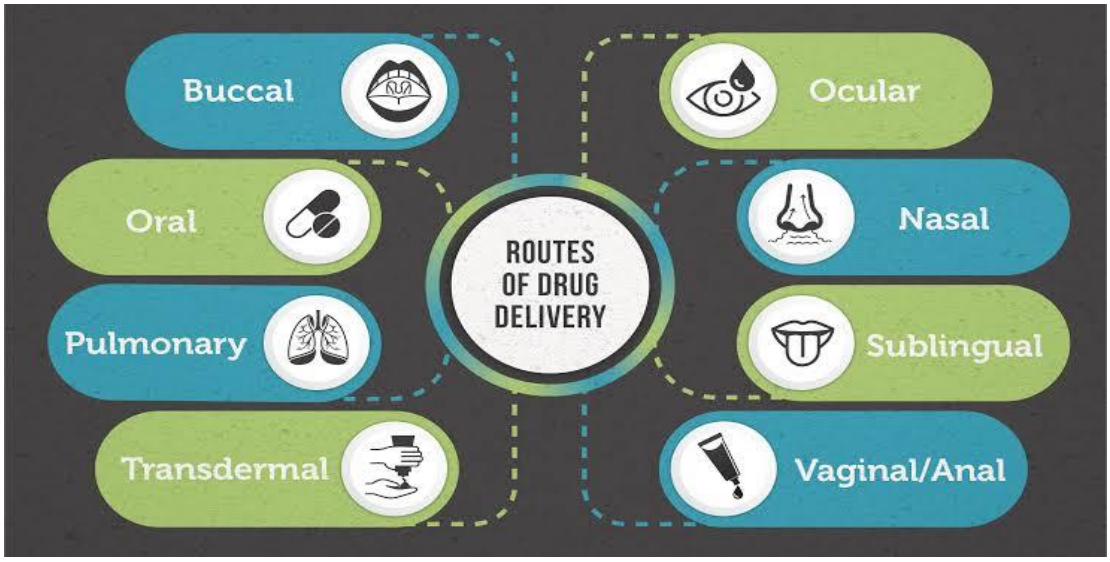

Figure 1 Different Drug Delivery Routes (Lansdowne, 2019)

1.1.1 Buccal delivery system

Drug delivered through buccal mucosa shows advantage of avoiding the first pass metabolism which cannot be ignored in case of oral drug delivery system (Shojaei, Chang, Guo, Burnside, & Couch, 2001). It also helps to ignore the presynaptic elimination in GI tract. However, as buccal mucosa is less permeable it does not provide rapid absorption and desirable bioavailability.

1.1.2 Nasal delivery system

Though the surface area of nasal delivery system is larger than other route of delivery however, the absorption of many drug are not adequate enough to reach the therapeutic

index. (Türker, Onur, & Özer, 2004). Although nasal route mimics the first pass metabolism the inadequate ability to absorb drug create complicacy.

1.1.3 Ocular delivery system

The major drawback of the ocular delivery system is poor bioavailability. Some drugs face complication to reach to the targeted site delivered from the ocular route (A. Patel, 2013). Another major disadvantage can be patient compliance as eye considered to a sensitive organ in human body.

1.1.4 Oral delivery system

Oral drug delivery system is the most widely used method in consideration of patient compliance, cost effectiveness, well-established method and noninvasiveness (Lee, Yun, & Park, 2016). However, for some instinct like for some mentally ill patient or geriatric patient it has a major drawback in the term of administration. Another disadvantage is low absorption

1.1.5 Pulmonary delivery system

Pulmonary route of drug delivery is widely known for the high bioavailability property because this route passes the first pass metabolism. So, the drug can directly enter into the blood stream to show its function. However, the main drawback of this route is it will create coughing if the particle size is big and also very low amount of drug can be tuned into this form (Rasenack, Steckel, & Müller, 2003; Shah, Shah, & Chivate, 2012).

1.1.6 Sublingual delivery system

The sublingual route of drug administration has some advantage such as, higher permeability and avoidance of first pass metabolism. Although, this route is incontinent while the patient is unresponsive and also this route lowers the therapeutic windows of some drug which has

been administered to a certain level(Hooda, Tripathi, & Kapoor, 2012; Narang & Sharma, 2011; Sheu, Hsieh, Chen, Chou, & Ho, 2016).

1.1.7 Vaginal delivery system

Vaginal route is intended to deliver drug to some local areas precisely. However, this route is not convenient for many drugs which cannot be converted to gel or topical formulation (das Neves & Bahia, 2006; Dobaria, Mashru, & Vadia, 2008; Johal, Garg, Rath, & Goyal, 2016; Vermani & Garg, 2000)

1.1.8 Transdermal delivery system

Transdermal drug delivery system is characterized as independent, discrete dose structures which, when applied to the unblemished skin, deliver the medication, through the skin at controlled rate to the blood system (Roberts, 1997). Transdermal drug delivery system (TDDS) had been recognized as a piece of novel medication delivery system (Murthy et al., 2006). There are many advantages compared to a very few disadvantage of this delivery system as like very few patients face dermatitis and the formulations has to be sterile which may increase the cost (Mitragotri, 2001). However, there are different advantages, such as, it can be given as an steady infusion for an extended period of time (Bagyalakshmi et al., 2006), as it does not pass gastrointestinal route it ignores the first pass metabolism which amplifies the efficacy of the drug at an significant level.

1.2 Transdermal delivery device

There are various devices used to deliver drugs through transdermal route. Some of them are discussed below.

1.2.1 Transdermal Patch -Both topical and transdermal items are proposed for this transdermal patch application. Nonetheless, topical dermatological items are proposed for nearby activity while transdermal medication delivery system is utilized for fundamental medication delivery. Transdermal delivery system let the medication pass through the skin direct into the circulation system. The transdermal system of medication delivery is turning out to be well known in light of the fact that huge number of medications can be delivered by this course to treat different diseases. At present, transdermal patches are being used in a few remedial sector like treatment of coronary illness, hormone substitution and the board of movement disorder(Marwah, Garg, Goyal, & Rath, 2016)**.**

1.2.2 Microneedle - The second approach to transdermally deliver drugs is the use of microneedles, which is the focus of this current study and discussed in details below.

1.3 Microneedles

Microneedles, three-dimensional (3D) microstructures of microscale length (usually < 1000 μm), can penetrate the stratum corneum and generate short-term microchannels through which drug molecules can passively diffuse into the skin. Microneedles might be designed in such a way that the depth of penetration in the lower reticular dermis is shallow enough not to reach the pain receptors which results in the administration of drugs in painless manner. It is promising that this transdermal delivery approach based on microneedles will provide a self-management, patient-friendly and efficient drug delivery route(Donnelly, Raj Singh, & Woolfson, 2010). In figure 2 the mechanism of transdermal drug delivery system has been described.

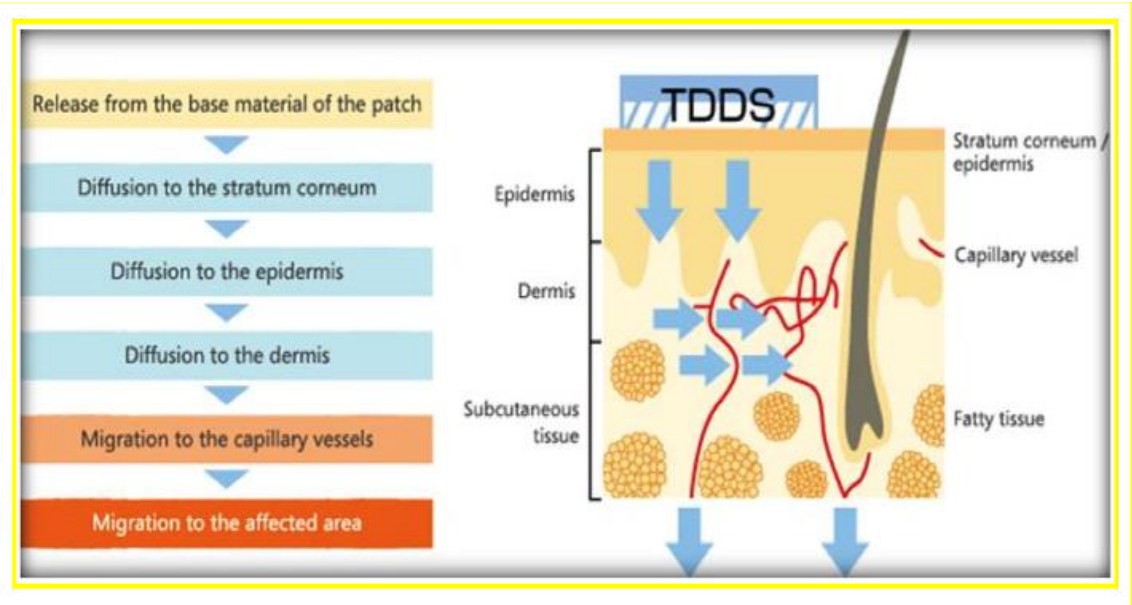

Figure 2 Mechanism of drug permeation through skin (Paresh A. Patil & Mali, 2017)

The concept of microneedles had been recognized by several decades ago. Furthermore, it had been coming to light in 1990's century when microfabrication came to light (Yeu-Chun, Jung-Hwan, & Mark R., 2012). Microneedles are described as a compact version conventional needle. By compacting the needles into micron dimension, increase the patience compliance such as pain, fear or need of an expert personal. However, this does not hold back the delivery of drug and particulate formulation (Yeu-Chun, Jung-Hwan, & Mark R., 2012) mainly drug and vaccines are delivered through microneedles. Microneedles base are usually less than 1mm in diameter. Microneedles create a pathway through epidermis layer by penetrating the outer layer of the skin. For this reason, microneedles do not cause pain like conventional hypodermic needles. According to fabrication process microneedles can be classified into two classes- in plane microneedles and out-of-plane microneedles.

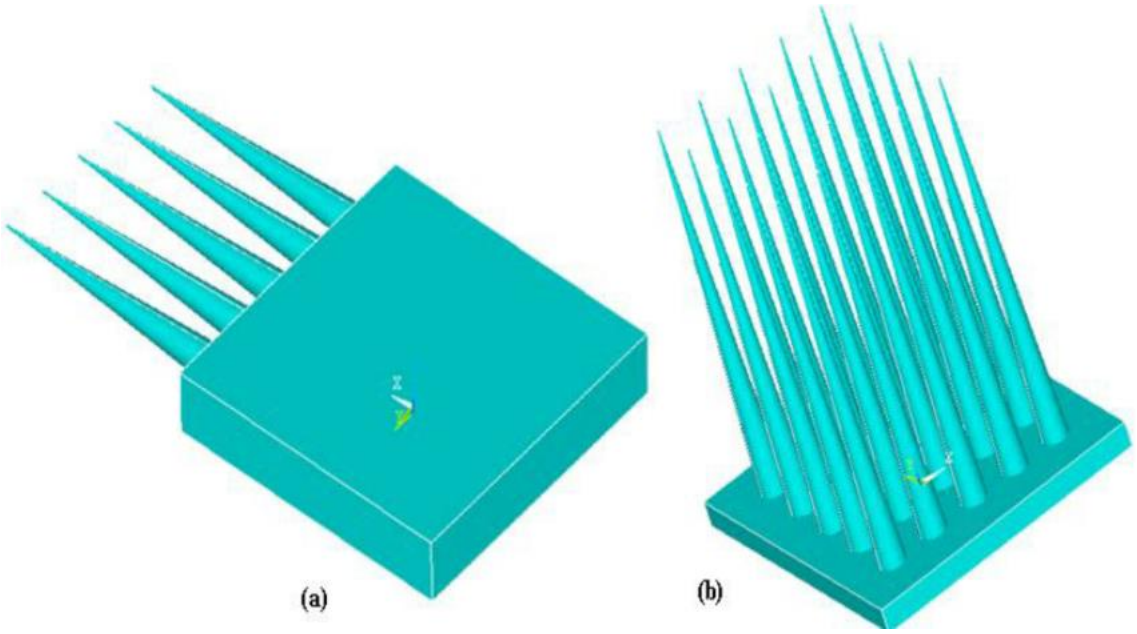

Figure 3 (a) In plane and (b) Out-of-plane microneedles (Ashraf, Tayyaba, & Afzulpurkar,

(a) It is a in plane microneedles which shaft is parallel to the subtract surface

(b) It is a out-of plane microneedles which shafts are out of the surface and it has

1.3.1 Types of Drug delivered through microneedle

There are some types of drugs which can be delivered through microneedles. Among them low molecular weight drug, biotherapeutics and vaccines are the utmost.

1.3.1.1 Low molecular weight drug

Skin pretreatment is emphasized for low atomic weight drugs delivered by the help of microneedle to accelerate the skin permeability. The reason for this is that the dose for systemic indication for a large number of drug are too huge to be in any way coated or condensed in microneedles. Bigger dosages can be delivered by pretreating the skin with microneedles and afterward controlling the medication from a broaden amount of time by dissemination through the skin pores that had been generated. On the other side, drug that have significant amount of molecular weight have higher diffusion coefficients in compared

with macromolecular drug and in this manner infuse into the skin more swiftly. In this way, a number of small particle drugs molecule have been delivered through microneedle and most microneedle pretreatment of the skin has been used to deliver lower molecular weight drug (Y. C. Kim, Park, & Prausnitz, 2012).

1.3.1.2 Biotherapeutics

Biotherapeutic drugs, for example, peptides, proteins, DNA and RNA, are large particles that can only with significant effort be delivered through oral route or through dermal route and in this manner are customarily given solely by hypodermic injection. Deliver with a microneedle ease this issue with a more secure way and more straightforward for patients who prefer self-administration. Since the part of biotherapeutics are significantly low (i.e., microgram dosages), a large number of biotherapeutics can be directed either coated onto microneedles or encapsulated inside dissolving microneedles. As a result of the little size of microneedles, drugs given on or inside the microneedles themselves are typically constrained to microgram portions, however low milligram dosages might be conceivable.

1.3.1.3 Vaccines

Microneedle use for vaccine delivery is advantageous not only for the ease of distribution and patient comfortability but also it creates a channel for vaccine to target the akin. It is as of now realized that the skin offers immunologic focal points over traditional intramuscular injection, yet as of not long ago there have not been basic, dependable strategies to inoculate in the skin (Y. C. Kim & Prausnitz, 2011; Mikszta & Laurent, 2008).Microneedles – both solid microneedle patch and hollow microneedles for intradermal infusion – address this drawbacks and can make skin vaccination down to earth a clinical possibility. Inspired by

these chances, antibody conveyance has been the most broadly examined utilization of microneedles**.**

1.3.2 Possible application in corona virus vaccines delivery

COVID-19 also known as the novel coronavirus is the deadliest virus in this world now a day. This virus is originated from Wuhan city in Hubei province in People's Republic of China. WHO has declared this virus deadlier than recent SARS and MERS outbreak till now 70000 affected people and closely to 2000 death cases. This is a unknown virus which affect the respiratory system and eventually induce pneumonia which lead to damage of one or more organ in the body and steers to death (Shindo & David L Heymann, 2020). As many companies are spending a lot of resource like Sanofi is trying to develope a vaccine for this virus (Kopecki, 2020). The microneedle can be used as a painless and patient compliance delivery device in this case (Prausnitz, Avenue, & View, 2009). As we also know this virus is hideously contagious (Shindo & David L Heymann, 2020) patient can themselves apply the vaccine without helping of other medical stuff.

1.4 Molding Material

Various molding materials are used for molding the microneedles such as silicon, silicon dioxide, silicon nitride, glass, semiconductor, metal, alloys, and polymers. Each material has its own advantage and disadvantage.

Table 1 Performance comparison in term of peak and average value(Ashraf, Tayyaba, Afzulpurkar, et al., 2011)

Material	Overall shape	Tip shape	Structure

Silicon	Cylindrical	Volcano	Solid
Silicon dioxide	Pyramid	Snake fang	Hollow
Silicon Nitride	Candle	Micro-	In-plane
Glass	Spike	hypodermis	Out-of-plane

In this table describes about various materials used for molding and the probable shape these materials can turn into.

1.4.1 Silicon

Silicon forms MNs with substantial mechanical strength that empowers the MNs to successfully pierce the skin(Wilke, Mulcahy, Ye, & Morrissey, 2005). Silicon may be used for the assembly of solid (Mikszta et al., 2002; O'Mahony, 2014) hollow(McGrath et al., 2011; Sivamani et al., 2005; Smart & Subramanian, 2000; Van Damme et al., 2009) and coated (McGrath et al., 2011) MNs. It may be used for fabricating MNs with varied shapes and heights (Wei-Ze et al., 2010; Wilke et al., 2005). The limitations of are silicon is expensive , complex formation necessities, fabrication times is higher and sophisticated multi-step fabrication process (Banga, 2009). Risk involving silicon MNs includes practicable fracture within the skin inflicting issues of safety. However, silicon has been vastly used for amplifying and easing percutaneous drug delivery system (Aoyagi, Izumi, Isono, Fukuda, & Ogawa, 2007; Bodhale, Nisar, & Afzulpurkar, 2010)

1.4.2 Metal

Usual metals utilized for the generation of MNs are stainless steel(Gupta, Gill, Andrews, & Prausnitz, 2011; Jiang et al., 2007; S. R. Patel et al., 2012), titanium(Cormier et al., 2004; McCarthy, Otto, & Rao, 2011), palladium(Chandrasekaran & Frazier, 2002), nickel(Chandrasekaran & Frazier, 2002; Norman et al., 2013), platinum(Invernale et al., 2014), mix compounds(Bhattacharya, Kam, Song, & Mazumder, 2012; Chandrasekaran &

Frazier, 2002) and gold(Chandrasekaran & Frazier, 2002). Metals are used for the generation of solid, hollow and as the foundation of the coated MNs. Favorable position of utilizing solid metals is their attractive mechanical properties and high elasticity which empowers simple infiltration through stratum corneum.

Satinless steel is broadly utilized for the generation of MNs. However, it has higher erosion rates contrasted with titanium compounds (Amalraju & Dawood, 2012). Titanium material have more grounded mechanical quality contrasted with stainless steel(Amalraju & Dawood, 2012). Platinum and palladium have been concentrated to a lesser degree for formation of MNs. Nickel has an issues with biologically compitable, and might be utilized with safety measure (Assad, Lemieux, Rivard, & Yahia, 1999)

1.4.3 Ceramics

Ceramics incorporate alumina (Bystrova & Luttge, 2011), calcium phosphate and calcium sulfate(Theiss et al., 2005). These materials are being used to create solid, hollow or coated sort of MNs. Silicon alkoxide alongside monomers has been altered to formulate a half material called Ormocer®(Doraiswamy et al., 2010; S. D. Gittard et al., 2009). Alumina is biologically compatible(Theiss et al., 2005). However, it has appeared to break certainly on being exposed to manual pressure power(Bystrova & Luttge, 2011). Calcium phosphate and calcium sulfate then again are biologically compatible(Christel, 1992) as well as have likewise demonstrated the capacity to withstand break when penetrate skin(Cai, Xia, Bredenberg, & Engqvist, 2014). Ormocer® is more preferable and shows great biocompatibility (Ovsianikov et al., 2007).

1.4.4 Glass

Glass MNs of different shapes have been made which effectively penetrate through stratum corneum (Martanto et al., 2006; Wang, Cornwell, Hill, & Prausnitz, 2006). The hollow

microneedle (Amin & Ahmed, 2013; Gupta, Felner, & Prausnitz, 2009) is regularly created by the glass. Primary weakness including silica glass is its fragile property and has a probable reason of breakage of needle tips in skin which can cause irritation and granulomas (Finley & Knabb, 1982). On the other hand, borosilicate glass has indicated great biocompatibility

1.4.5 Polymers

Polymers have been mainly used for the manufacturing of dissolving/biodegradable or hydrogel shaping MNs. Usually hydroxypropyl methylcellulose (HPMC) (J. Y. Kim et al., 2016), hyaluronic acid (Katsumi et al., 2012), carboxymethycellulose, alginates or manufactured polymers like poly (methylvinylether/maleic anhydride) (Caffarel-Salvador et al., 2015)i.e. Gantrez® (Caffarel-Salvador et al., 2015), polystyrene(Luangveera et al., 2015) polyvinyl alcohol, PVP (polyvinylpyrrolidone) (Caffarel-Salvador et al., 2015), polylactic corrosive (PLA), polyglycolic corrosive (PGA) and their co-polymers (PLGA) (Park, Allen, & Prausnitz, 2005) can be recognized as polymer. Polymers offer significant amount of positivity of their biologically degradable property and biocompatibility (Dhar, Akhlaghi, & Tam, 2012; Donnelly et al., 2013; Grayson et al., 2004).

1.5 Microneedles fabrication techniques

There are many conventional methods of fabricating microneedles such as photolithography or laser cutting. For laser cutting a CO2 laser is required. It engraves a silicon mold or an acrylic sheet by the desire diameter(Prausnitz, 2004). There is another technology using silicon glass. Silicon glass is engraved by laser cut based on desire length and diameter for specific drug(Martin, Allender, Brain, Morrissey, & Birchall, 2012). Ceramic micro molding is a process by which ceramic slurry is being micro molded and it is advantageous from one side because it is less cost effective than the others are(Bystrova & Luttge, 2011; Gal et al., 2019). Another technique can be separable arrowhead. The associated disadvantages with

biodegradable microneedle are overcome by the increased mechanical strength associated with metal microneedles. In addition, the issue of bio hazardous sharp waste disposal is overcome by the microneedles' dissolving component. Some other new technologies have been introduced recently. Among them photolithography, deep lithography, deep reactive ion etching (DRIN), micro-molding, bi-mask technique, LIGA, hot embossing, UV excimer laser etc. (Aoyagi et al., 2007; Ashraf et al., 2010; Bodhale et al., 2010; Chu, Choi, & Prausnitz, 2010; Nejad, Sadeqi, Kiaee, & Sonkusale, 2018).

1.5.1 Laser engraving technology

This technique is followed for fabricating metallic MNs. Stainless steel is the most used material for this fabrication. In this process, sheets are being fabricated into micron size needles using infrared laser whereby the shape and direction of the design are drafted in a product for example AutoCAD. The laser beam follows the design of the needle, removes the metal sheet and makes the needles in the plane of the sheet. The subsequent stage is cleaning of these sheets and brings out the MNs out of sheet at a 90° angle. Last structure is then electropolished which sharpen the tips (Cormier et al., 2004; Gill & Prausnitz, 2007)

1.5.2 Laser Ablation

Alongside laser cutting, laser ablation is additionally being used for manufacturing strong metallic figure. Alongside stainless steel, metals such as tantalum are likewise manufactured. Here, light beam is centered on a metallic plate. The procedure depends on the standard of “twisted light with spin." Following a laser beam shot this light, a projection shows up at the focal point of the surface which has been treated. The basic projection can be achieved with a reasonable shape by laminating by light pulse. After three light pulse, the projection turns into a needle with a structure of around 10μm. The MNs can be shrank by using some more light impulse, bringing about a tip measurement of under 0.3μm (Omatsu et al., 2010).

1.5.3 Photolithography

Photolithography is can be applied to create MNs from ceramic and polymers for example poly (ethylene glycol) diacrylate. This process has the ability to fabricate both, solid and hollow MN. The process starts with covering the substrate with a Photosensitive Polymer using Twist Covering system. Silicon wafer used as a substrate and the Polymer is known as Photoresist which is solidified thermally. The photoresist is then bring to bright radiation through a veil. UV light controls "cross-connect" obligations of the polymer for example it either starts or restrains crosslinking. Along these lines, the dissolvability of the polymer substrate presented to U.V varies definitely from that in the shade of cover. The bit of the Photoresist uncovered is dispensed with by dunking the treated substrate in the creating arrangement. In the last advance, otherwise called carving step, the drawing made of photoresist is then repeated on the substrate with wet or dry synthetic assault(Dardano et al., 2015).

1.5.4 Two photon Polymerization

This technique requires refined apparatus and is utilized for polymers and ceramic production. It can likewise be utilized to deliver hollow kind of MNs. Two-Photon Polymerization (2PP) uses the rule of Photograph Excitation of initiator atoms. It starts polymerization of a pitch through multi-photon ingestion. The 2PP arrangement contains femtosecond or picosecond laser for example titanium: sapphire oscillator. It is balanced and centered with the end goal that at can move in three measurements around the polymer gum. The three-dimensional plan is incorporated with spatial directions utilizing PC helped structure. Two-photon assimilation brings about retention of vitality in a non-straight design, which incites breaking of concoction obligations of photo initiator atoms, situated in a little region of the polymer tar where the laser is engaged. The substrate turned polymerized along the hint of the laser as it is made to look over the pitch. After culmination of manufacture of

the MN, the non-illuminated tar is cleaned proper solvent and is restored utilizing ultraviolet light (Shaun D. Gittard et al., 2011, 2009).

1.6 Proposed material for molding

We will develop the molding by using silicon, wax and acrylic sheet. These materials are very cost effective. Industrial grade silicon rubber glue is easily accessible and can find by a very low price. And acrylics sheets are easily accrued by a low price.

1.6.1 Silicon

Silicon rubber glue is very chemical stable it has an ability to resist acid, base, solvent and many other chemical materials. It is not also flammable and toxic to solvent. So pouring a formulation on the mold to take out the microneedles of the formulation will not hamper the quality of the formulation (Emelyanenko, Boinovich, Bezdomnikov, Chulkova, & Emelyanenko, 2017; Sanchez-Hidalgo, Blanco, Menendez, Verdejo, & Lopez-Manchado, 2019).

1.6.2 Acrylic sheet

Poly (methyl methacrylate) PMMA otherwise called acrylic is a straightforward thermoplastic. It is frequently utilized in sheet structure because of its properties, for example, lightweight and break opposition as a choice to glass. It regularly fills in as a prudent option to polycarbonate at whatever point outrageous quality isn't wanted. It is frequently perceived in terms of professional career names, for example, Plexiglass, Lucite, Acrylite and Perspex. It doesn't contain any hints of bisphenol-A which is possibly destructive compound found in polycarbonate. Because of headways in innovation endeavors have been had to build the effect opposition and scratch obstruction of this material. PMMA or acrylic is a solid and lightweight material. The thickness of acrylic went between 1.17-1.20

g/cm3 which is half not as much as that of glass. The effect quality of PMMA is more prominent than that of glass and polysterene. Acrylic can transmit upto 92% of obvious light with only 3mm of thickness. With refractive record of 1.4905 at 589.3 nm it can reflect upto 4% light from its surface. Because of the ecological dependability of acrylic is better when contrasted with polystyrene and polyethylene it is considered for the greater part of the outside applications in the plastics business (Negim, Khatib, & Inkarbekov, 2013; Palm, Dupaix, & Castro, 2006).

1.7 Proposed technique for molding

Previously we have discussed about the various technique for molding. We are using laser cutting fabrication for the fabricating the mold for the microneedle as this is most cost-effective way than the other method described.

1.8 Purpose of study

1. Cost effective way of microneedle mold fabrication
2. Reduce the cost of microneedles manufacturing
3. Availability of microneedles to a greater number of people

Chapter 2 Materials and Method

2.1 Materials

We have started this experiment by fabricating a prototype of microneedle using industrial grade biodegradable plastic by laser cutting using a CO2 laser machine. We have developed the engraving design by AutoCAD. At the beginning we perform some trial and error method by using industrial grade silicon rubber glue and commercially available wax. After getting a distinctive success we had been shifted to biodegradable acrylic sheet which had engraved by the same CO2 laser cutting machine. We had developed a mold for the fabrication of polymer microneedle. We also had run through an animal trial by the fabricated polymer microneedle and an OCT test.

2.2 Essential software

AutoCAD 2017 had been used for the designing purpose for both for the prototype and mold. The structure work of the modern hardware industry depends on the drawing programming of the significant business. The most generally accepted software in the drawing programming is the AutoCAD programming(Hao, Yu, & Xue, 2002). It not just blessed the clients with an easy to understand interface, amazing scientific capacities and incredible pre-preparing and post-handling capacities, the activity is straightforward and simple to learn for the client's plan illustrations. These days, progressed industrialized profitability has become a significant marker of the plan level of a nation. The advancement of CAD innovation toward significantdata innovation is the inescapable pattern of customization, specialization and mix of assembling industry.

2.3 Formation of microneedle prototype

A microneedle prototype had been developed for the initial trial and error method. The conventional 3D method for microneedle to generate the prototype had been used here. Industrial grade plastic had been to generate the microneedle by the laser technology available in Bangladesh. The base height was .2mm and our needle formation was 8x6. Industrial grade plastic had been used as in case the polymer was not that heat label as the industrial grade plastic. The tip height was 1 mm.

2.4 Silicon rubber glue prototype

Silicon rubber glue had been used for the initial step. It had purchased this material form 'X' with a label 'DOWSIL RTV Sealant – 732 Multi-purpose sealant'. An incentive test had been run through to monitor the stability of this material by designing a prototype of a bottle tip (fig 4-5) form the silicon. After getting distinctive success we have designed a dice around the microneedle prototype where we pour the silicon sealant to bring out a mold of the prototype microneedle, we formulated by 3D painting.

Figure 5 bottle tip

Figure 4 Designed prorotype by silicon sealent

2.5 Wax prototype

After getting a major success from the silicon fabrication for further step commercial grade wax had been used. Wax was collected from a local general store. The process followed by placing the 3D printed plastic microneedle in a dice fabricated by hard paper. The wax had been heated up and then pours into dice. The wax had been completely crystalized like the microneedle prototype.

2.6 Procedure for designing for laser engraving

1. After opening the interface click new drawing.
2. Command unit and change the unit into mm
3. Click polyline and start drawing the plan of mold by inputting length and width measurements
4. Designing mold and section of needless in same procedures
5. To print it has to be in PDF in real scale
6. For that command Ctrl+p
7. Click print/plotter option and change it to DWG to PDF (fig-6)
8. Change paper size to A4
9. Untick fit to paper option and the scale should be 1:1
10. Select windows and make .pdf from model space
11. Open the PDF file in illustrator and engrave it from laser

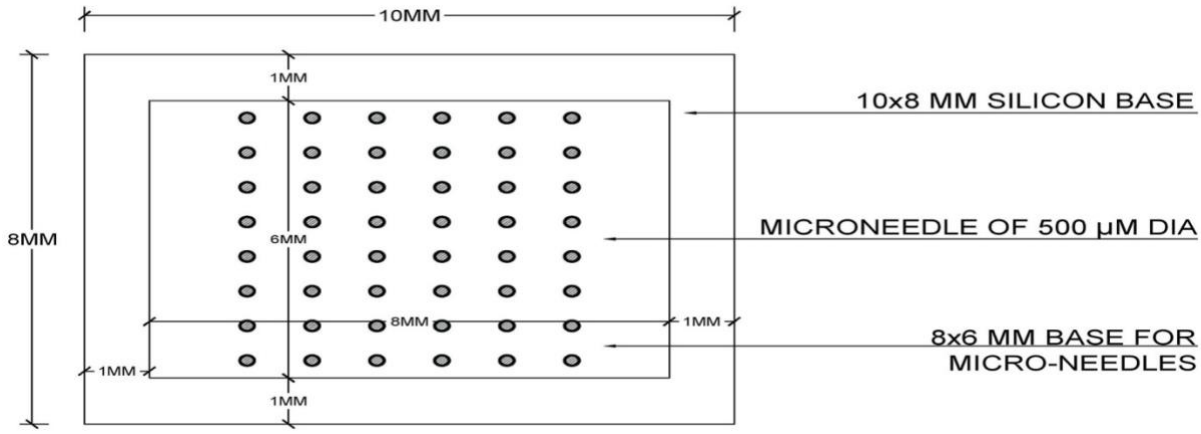

Figure 6 Design of mold for leaser engraving

This figure describes the formation of the hole for microneedle mold which has been used in the laser engraving

Chapter 3 Results

3.1 Silicon rubber glue mold prototype

Figure of the silicon rubber glue mold prototype which had been fabricated for the trial and error method has been shown in the figure 7.

Figure 7 Silicon rubber glue prototype

3.2 Wax mold prototype

The wax mold prototype which has been fabricated showed in the figure 8.

Figure 8 Wax fabricated mold prototype

3.3 Laser engraved mold for microneedle

The final laser engraved mold has been shown in figure 9 the microscopic view has been shown of the engraved microneedle.

Figure 9 Laser engraved mold for microneedle

Chapter 4 Discussion and Conclusion

4.1 Discussion

There is a various fabrication method for microneedle fabrication. However, fabricated microneedle mold by laser engraving is a very cost-effective way to formulate a microneedle. In this study, a very cost-effective molding method has been developed using acrylic sheet and CO_2laser engraving machine. From the figure 9 it has been ensured that the needle width and depth had been ensure perfectly. Figure 8 deliberately explain any desirable depth needle can be designed by AutoCAD software which can be used by the CO_2 laser engraving machine.

4.2 Conclusion

This experiment has explained a cost-effective way to fabricate microneedle. This can be helpful to deliver various types of drug also. The recent COVID-19 virus outbreak is alarming the world's health sector. As microneedle can deliver vaccines, a breakthrough discovery of a vaccine for COVID-19 can be delivered through microneedle. This low cost microneedle can play as a significant role in term of delivery device.

4.3 Future Aspect

In future, polymer drug loaded microneedle will be fabricated from this mold, which pharmacological efficacy will be tested.

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