3D Printed Microneedle for Transdermal Drug Delivery Application

By
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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 (Honors)

Department of Pharmacy
Brac University
September 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.
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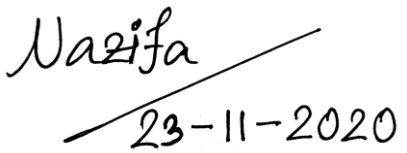

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Approval

The thesis titled “3D Printed Microneedle for Transdermal Drug Delivery Application” submitted by Nazifa Haque Rafa (16346006) of Summer 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors of Pharmacy (Honors)

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Ethics Statement

This study does not involve any human and animal trial.

Abstract

Microneedling is a relatively new treatment option in the drug delivery system as well as has been recognized for a broad range of applications like skin rejuvenation, acne scarring, rhytides, surgical scars, dyschromia, melasma, enlarged pores, and transdermal drug delivery. The role of three-dimensional printing as a fabrication technology for sophisticated transdermal drug delivery systems is explored in literature. 3D printing was proved to be an effective technology for the fabrication of biocompatible and scalable microneedle patches. Through this 3D printed microneedle device, injured or damage to tissue and organs are treated. As apparent from the continuous clinical preliminaries of a wide assortment of medications for different clinical conditions, there is an extraordinary future for the transdermal delivery of drugs. Therefore, this paper aims to explain an overview of the designing properties and methods for a 3D printed microneedle, and its uses and advantages in pharmaceutical applications. Future work will involve investigation of the use of 3D printed microneedle in the transdermal delivery of drugs among patients.

Keywords: Microneedle, 3D printed microneedle, transdermal drug delivery, Additive manufacture, Advantages.

Dedication

I want to dedicate this project to my respectable supervisor Dr. Md. Jasim Uddin, Assistant Professor in Department of Pharmacy, Brac University for his continuous guidance throughout my project.

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I would like to proceed by thanking the Almighty who is the source of our strength and knowledge which have enabled me to complete this project with full diligence.

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List of Acronyms

3DP	Three-dimensional printing
MN	Microneedle
TDDS	Transdermal drug delivery system
FDM	Fused deposition model
AM	Additive manufacture
CAD	Computer aided design
PDMS	Poly dimethyl siloxane
PVA	Poly vinyl alcohol
PVP	Poly vinyl pyrolidone
CMC	Carboxy methyl cellulose
SLA	Stereolithography

Chapter 1

Introduction

1.1Microneedle

Microneedles are microscopic applicators used to deliver vaccines or other drugs across various barriers. Microneedling, alsoknown as percutaneous collagen induction therapy as well as it is a relatively new treatment option in dermatology. Although laser skin resurfacing has long been considered the treatment of choice for photo-aged and scarred skin, microneedling has recently been recognized for a broad range of applications that are included with skin rejuvenation, acne scarring, rhytides, surgical scars, dyschromia, melasma, enlarged pores, and transdermal drug delivery(Alster and Graham 2018).Microneedling procedures are growing in popularity for a wide variety of skin conditions.The microneedle system consists of micron-sized needles arranged on a small patch.The microneedle drug delivery system has been developed and is believed to be the hybrid of both in view of the problems of the hypodermic needle and the transdermal patch. Depending on the type of microneedle and the material used, microneedles can be formulated into different sizes. Larger and thicker needles can go deep into the dermis, damage the nerves and cause pain. They are mainly 150-1500 microns long, 50-250 microns wide and have a tip thickness of 1-25 microns. A microneedle device is intended to create a transport path of a micron size and the needle diameter is kept between a few microns. In many other forms, microneedle tips can be cylindrical, triangular, pointed, pentagonal, and octagonal. (Waghule et al. 2019).Strong, coated, dissolving, hollow, and hydrogel microneedles are different types of microneedles manufactured and investigated for their use in drug delivery. Each microneedle type has its own way of delivering the medication into the epidermis. Some

are only used in the stratum of the corneum to create pores. In addition, some are precoated on their surface with the drug solution, some of them are dissolvable and some are pre-filled with the drug solution(Waghule et al. 2019).

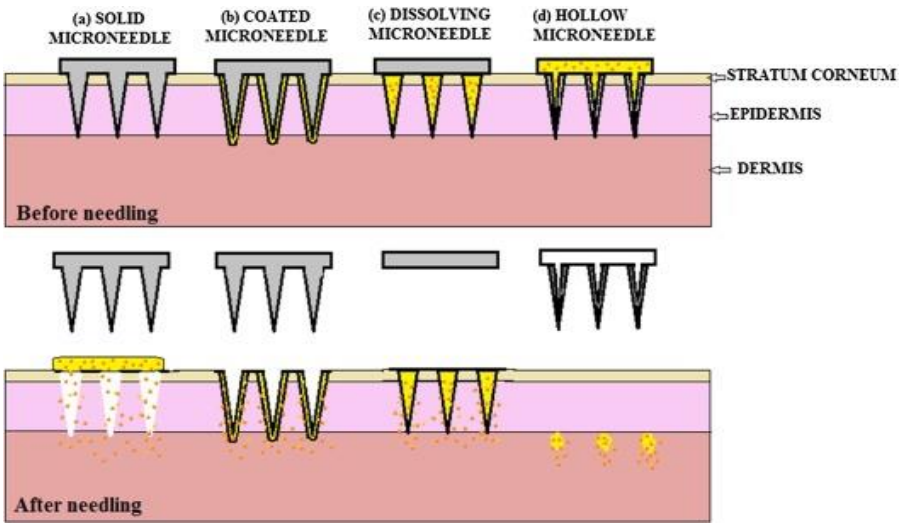


Figure 1: Different types of microneedles(Waghule et al. 2019).

Table 1: Microneedling at a glance(Tuan-Mahmood et al. 2013).

- Treatable conditions: scars (atrophic/burn/other), rhytides, skin laxity, striae
- Contraindications: active infection, acne, keloid predisposition, immune suppression
- Treatment preparation: mild cleanser, topical 30%lidocaine, hyaluronic acid gel
- Technique: Perpendicular device placement with manual skin traction for smooth delivery of microneedles Multidirectional placement (cross-hatching) of microneedle passes. Use pinpoint bleeding as guide to treatment endpoint. Manual pressure with ice water compresses for hemostasis
- Post-treatment care0–4 h: hyaluronic acid gel4–72 h: 1% hydrocortisone/nonallergic moisturizer/physical sunblock SPF 30+48 h: makeup application5–7 h: resume active product use
- Side effects: mild erythema, edema, skin flaking·48–72 h
- Repeat treatments: biweekly to monthly·3–6sessions; maintenance (variable)

1.2Importance of microneedle drug delivery

Microneedles were first conceptualized for drug delivery many decades ago. Microneedles have been utilized to convey a wide scope of various low atomic weight drugs, biotherapeutics, and immunizations, incorporating distributed human investigations with various little particle and protein medications and antibodies.Influenza vaccination utilizing an empty microneedle is in across the board clinical use and various strong microneedle items are sold for restorative purposes.Despite applications in the skin, bioactive delivery to the eye and cells has also been modified for microneedles. Most vaccines and biotherapeutics are injected via a hypodermic needle. Injection offers a cost-effective, simple and direct way to deliver virtually any form of molecule into the body. However, hypodermic needles cannot be effectivelyutilized by patients themselves and are subsequently utilized basicallywithin the clinic or at domestic by patients who have gottenuncommonpreparing on appropriate infusionstrategy, secure needle transfer, and other issues. Oral delivery to a great extent overcomes these, but numerous drugs cannot be given by this course due to poor retention and drug degradation within the gastrointestinal tract and liver. Other routes of administrations have moreover been explored, but none offer the wide viability of coordinateinfusionusing a needle(Kim, Park, and Prausnitz 2012).A few of the patients have to needle-phobia. Instead of maintaining a strategic distance from needles, researchers have proposed contracting the needle to micron dimensions in arrange to form utilize of its effective deliverycapabilities whereas movingforward understanding compliance and security. As a micron-scale unit, a microneedle should be sufficiently expansive to provide any medication or small particulate formulation early, but still is inadequate to prevent discomfort, fear and the need to administer expert training. A microneedle enables precise tissue localization

of distribution while growing, such as within the skin, the suprachoroidal region of the eye, and the nucleus of the cell.

1.3 3D printing and itspopularity

3D printing is gaining popularity by providing a tool for fast, cost-effective, and highly customizable fabrication. Even though additive manufacturing or "3D printing"wasfirstintroduced in 1983, the technology has become widespread only in the past few years. The value of the 3D printing market grew from $288 million in 2012 to $2.5 billion in 2013 and is projected to grow to $16.2 billion by 2018(Oskui et al. 2016). Much of this growth has occurred in the life sciences, where 3D printing has found applications in dentistry,prosthetics and implantabledevices,5,6surgical instruments,and even tissue and organreplacement.By providing businesses, researchers, physicians with custom objects and tools quickly and inexpensively, 3D printers are revolutionizing manufacturing, accelerating research, and changing how medicine is practiced.Therefore, the ability to 3D print microneedle masters quickly using commercially available equipment would be an improvement in the field.

1.4Development of 3D printed microneedle

The idea of 3DP has evolved from the early 70′ of the twentieth century when Pierre A. L. Giraud described the method of application of powdered material and subsequent solidification of each layer through the action of high energy beam. The microneedle (MN), a profoundly effective and flexible gadget, has pulled in broad logical and mechanical interests in the previous

decades because of noticeable properties including painless penetration, low cost, excellent therapeutic efficacy, and relative safety.An incredible exertion has been made, to sum up, the development of microneedles, their materials, the most recent manufacture strategy, for example, three-dimensional printing (3DP). Critically, an assortment of delegate biomedical utilizationof microneedles, for example, illness treatment, immune biological, infection analysis and restorative field, are featured.

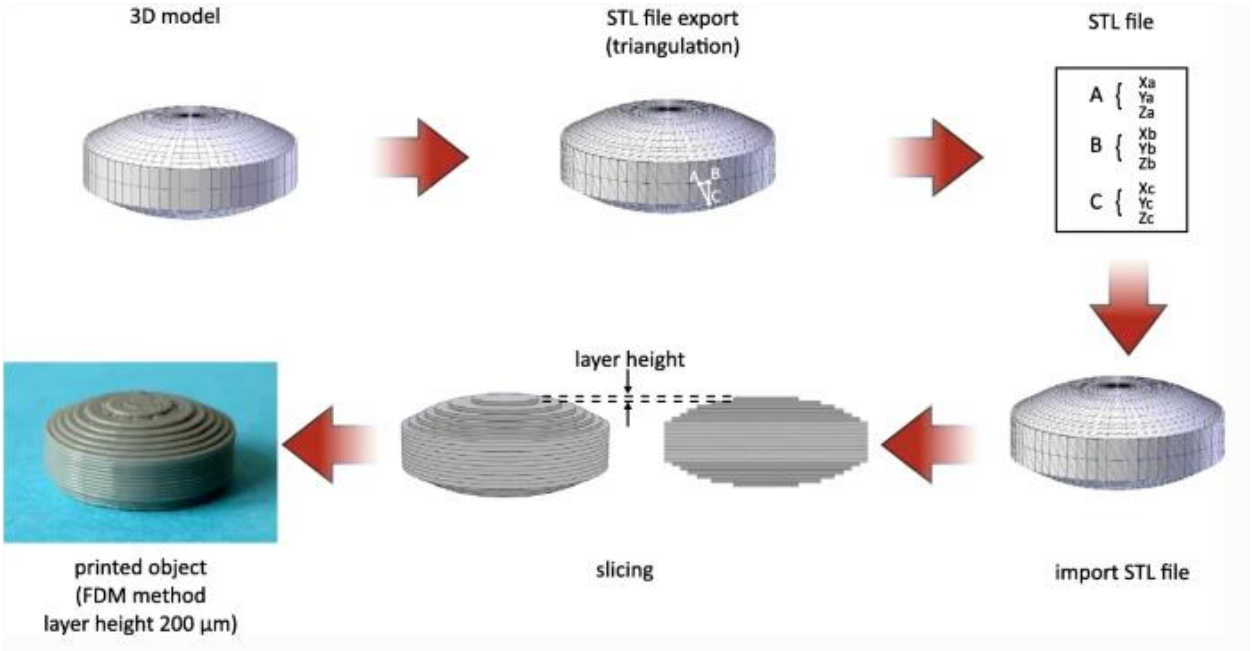


Figure 2: The development of 3D printed object.

1.5Motivation of 3D printed microneedle for the transdermal drug delivery system

Nowadays, three-dimensional printing is one of the fastest developing branches of technology, art and science, and still broadens the applications. The role of three-dimensional printing as a manufacturing innovation for modern transdermal drug delivery frameworks is investigated in

writing. A group of particular innovations that utilize a virtual model to create a physical item through numerically controlled devices is included in3D printing. The progresses within the field of TDD,however, are not very apparentbutpresently are being explored and the results are showing up to be empowering. There is a constant motivation towards new concepts in drug design, a better understanding of material properties, manufacturing technology and processes that assure high quality of dosage forms. Basically, the motivation of the work was to investigate the use of such printed materials as a potential release device in a transdermal patch.

1.6 Purpose of the study

Since their introduction over 20 years ago, MN systems have attracted significant attention for their potential to replace traditional drug administration routes. Microneedles (MNs) are small devices that can pierce the outermost, most impermeable layer of the human skin and successfully deliver active substances such as drugs, Ribonucleic acid (RNA), Deoxyribonucleic acid (DNA), and vaccines straight into the dermal microcirculation. Due to their small size they leave skin nerves intact upon insertion, while they increase bioavailability since the medication doesn't go through any metabolic frameworks. MN-mediated drug delivery is realized through multiple strategies that employ solid, coated, hollow, hydrogel-forming and solubleMNs.Basically,the purpose of this study is to identify the latest type of MN design, challenges and strategies and to focus on recent and future developments for MN technology. Moreoverto illustrate the use of 3D printed MN in the transdermal drug delivery.

Chapter 2

Drug Delivery through MN

2.1Transdermal drug delivery

Transdermal drug delivery is defined as self-contained, discrete dosage forms when applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation. The transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems.The transdermal drug delivery system is the framework where the delivery of the active ingredients of the drug happens through the skin. Transdermal drug delivery can improve the therapeutic efficacy and safety of drugs because drugs are delivered through the skin at a predetermined and controlled rate(Saravanakumar et al. 2015).Transdermal drug delivery has made a significant commitment to clinical practice yet still can't seem to completely accomplish its potential as an option in contrast to oral delivery and hypodermic infusion. There are almost three generation on which transdermal drug delivery has been working. There are almost three generation through which transdermal drug delivery has continued its steady increase in clinical use for delivery of small, lipophilic, low-dose drugs.Second-generation delivery systems using chemical enhancers, nonconventional ultrasound and iontophoresis have also resulted in clinical products; the ability of iontophoresis to control delivery rates in real time provides added functionality. Third-generation delivery systems target their effects on skin's barrier layer of stratum corneum using microneedles, thermal ablation, microdermaabrasion, electroporation and conventional ultrasound(Prausnitz and Langer 2008).However, given the high costs in bringing new technologies to the market, as well as the technical issues of

delivering drugs past the stratum corneum, the transdermal field needs to overcome several obstacles before it can realize its true potential.

2.2Types of microneedle in drug delivery

A microneedle is a micron-sized needle with a height of 10–2000μm, a width of 10–50μm that is widely used in transdermal drug delivery systems with advantage of safe, painless, convenient, non-invasive, and efficient drug delivery.Microneedles are divided into four types: solid microneedles, coated microneedles, dissolving microneedles, and hollow microneedles. Different types of microneedles play different roles in different research fields. In recent years, microneedles have frequently been used to deliver drugs, genes, proteins, RNA, and vaccines, and have achieved an amazingly therapeutic effect. Unlike regular hypodermic needles, the microneedle has the ability to improve patient compliance as it does not hurt nerves. The drug delivery mechanisms of these microneedles (respectively) are the “poke and patch “approach, the “coat and poke” approach, the “poke and release” approach, and the “poke and flow” approach.

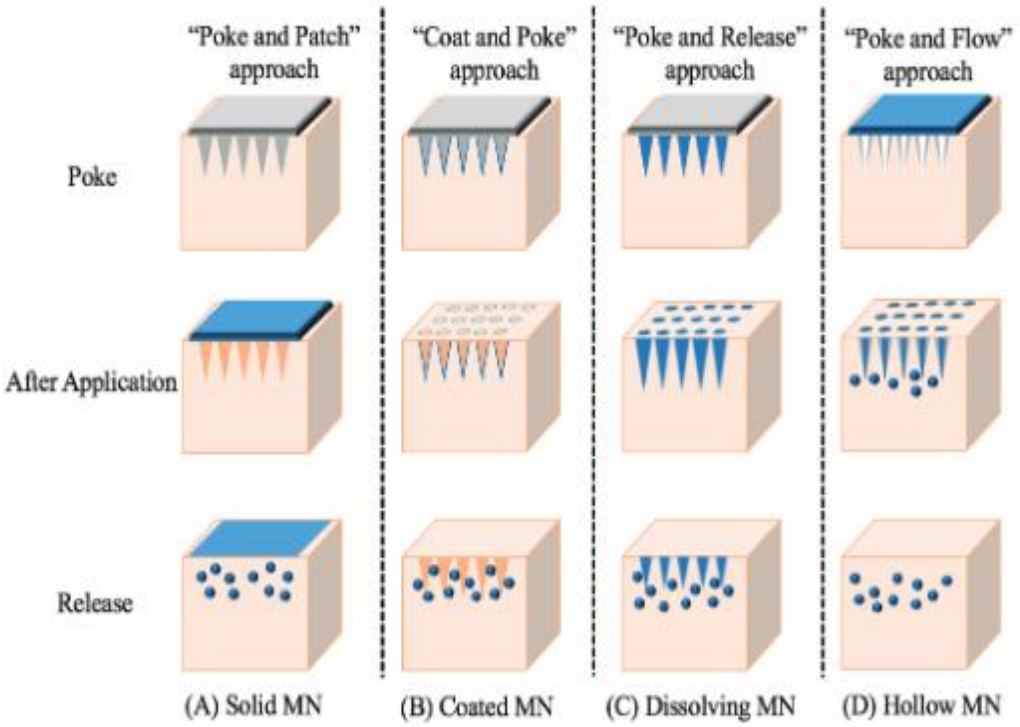


Figure 3: different types of microneedles(Hao et al. 2017).

(a) Solid microneedles use poke with patch approach, are used for pre-treatment of the skin; (b) Coated microneedles use a coat and poke approach, a coating of drug solution is applied on the needle surface; (c) Dissolving microneedles are made of biodegradable polymers; (d) Hollow microneedles are filled with the drug solution and deposit the drug in the dermis(Hao et al. 2017)

2.3Importance of transdermal drug delivery

The transdermal delivery system is fit for moving the medication through the skin into the blood circulation a fixed rate. The transdermal route gives an alternative to oral and IV delivery. Benefits of local delivery are properly documented includes targeted delivery, lower systemic

exposure, and lower toxicity than oral medications. This system is also helpful in the treatment of hair loss, neuropathic pain, acne, genital herpes, migraine, headaches, and sexual dysfunction. It has so many importances over conventional routes such as:

- Transdermal delivery avoids the stomach environment where the drug can be degraded
- Transdermal delivery avoids the first pass effect where active drug molecules can be converted to inactive molecules or even to molecules responsible for side effects.
- Provides steady plasma levels.
- Easy to use and non-invasive.
- Drug input can be stopped at any point after removal of the patch from the site
- Increases compliance and reduces medical costs.
- Improves bioavailability.
- Best route for pediatric patients.
- Suitable route for unconscious or vomiting patients.
- Lesser chances of overdose and easy detection of a drug.

2.4Precautions for using microneedle

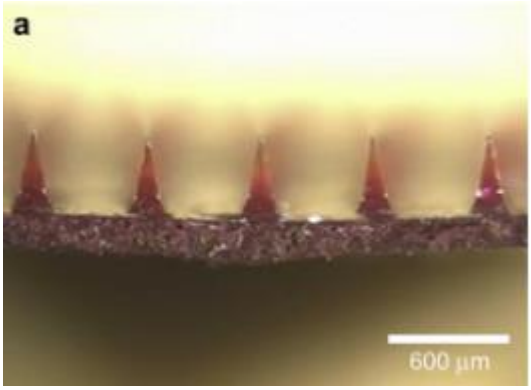
A wide range of materials from metal to polymers is used for manufacturing MNs.However,before precautions should be taken preciselybecause most materials introduce certain problems. For examples, the most common metals used for the production of MNs include stainless steel, titanium, palladium, nickel, platinum, alloys, and gold. Stainless steel is widely used for the production of MNs. However, it possesses higher corrosion rates compared to titanium alloys. Titanium alloys have stronger mechanical strength compared to stainless steel.

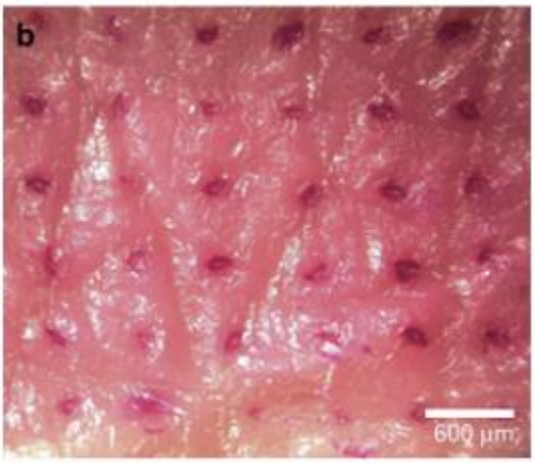
Platinum and palladium have been studied to a lesser extent in the production of MNs. Nickel has biocompatibility issues and should be used with precaution. Some other precautions shouldbe taken while using a microneedle. Such as: suspicious lesions- These must be diagnosed by a practitioner before beginning treatment.Discontinue autoimmune therapies and retinoid products 24 hours before to beginning treatment. It should not be treated over active acne, rosacea, or other inflammatory conditions. It should not be treated over open wounds. Do not use the device inside of the orbital rim, such as eyelids or inside the vermillion border of the lips. Consider prophylactic treatments for those clients prone to viral breakouts.

2.5Sustained drug release

Dissolving microneedles can be designed to gently encapsulate molecules, insert into the skin, and enable bolus or sustained release delivery. The microneedle system contained a concentration of 1 mg of sulforhodamine. Addition of microneedle imaging to pig cadaver skin. (a) A view of the back of the microneedle patch of the CMC added to the skin surface. (b) after injection into the skin for 3 s, CMC pyramidal microneedles. (c) Red tissue-marking dye stained skin to distinguish the sites of needle penetration after CMC pyramidal microneedle insertion. (d) Cross-sectional image of H&E-stained skin at a site of microneedle penetration of 10 wt% (on a dry basis). These microneedles designed for sustained release could be inserted into the skin as well as histological examinationshowed release of sulforhodamineall through the skin.Toevaluate sustained release properties in greater detail, microneedle patches into human cadaver skin is embedded and measured transdermal flux is measured. Sulforhodamine release fromCMC microneedle patches exhibited an initial lag time of a few hours, followed by a steady release for approximately 1day. Comparable behavior was seen for microneedle patches made of

amylopectin, but with slower energy. In this case, the lag time was longer, the release took place over a couple ofdays. The hypothesis that drug encapsulated inside the backing layer of a microneedle patch will spread out of the patch and into the skin is approved by this knowledge. In addition, it appears that changing the material of the microneedle patch matrix will alter the release kinetics. As distinctive drugs prescribed for distinctive signs require different release patterns, it is important to be able to discern release energy based on a defined schedule. The Release rate should also depend on sulforhodamine concentration in the patch. Consistent with this expectation, the drug release rate from a patch containing 30 wt% sulforhodaminewas approximately 3 times greater than a patch containing10 wt% sulforhodamine.





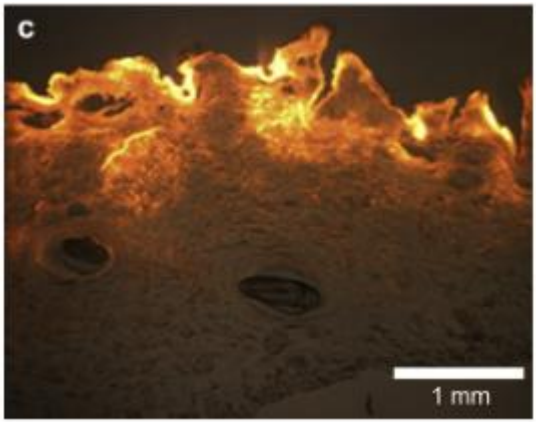


Figure 4: Dissolving microneedles for sustained release.

(a) CMC pyramidsamicroneedle encapsulating sulforhodamine only in the backing layer. (b)Skin surface showing sulforhodamine delivered into the skin by the insertion of the microneedles shown in part (a) for 12 h imaged by bright field microscopy. (c) Cross-sectional histological image of skin pierced by the microneedlesshown in part (a) for 12 h and imaged by an overlay of bright field and fluorescence microscopy. Pig cadaver skin was used(Lee, Park, and Prausnitz 2008)

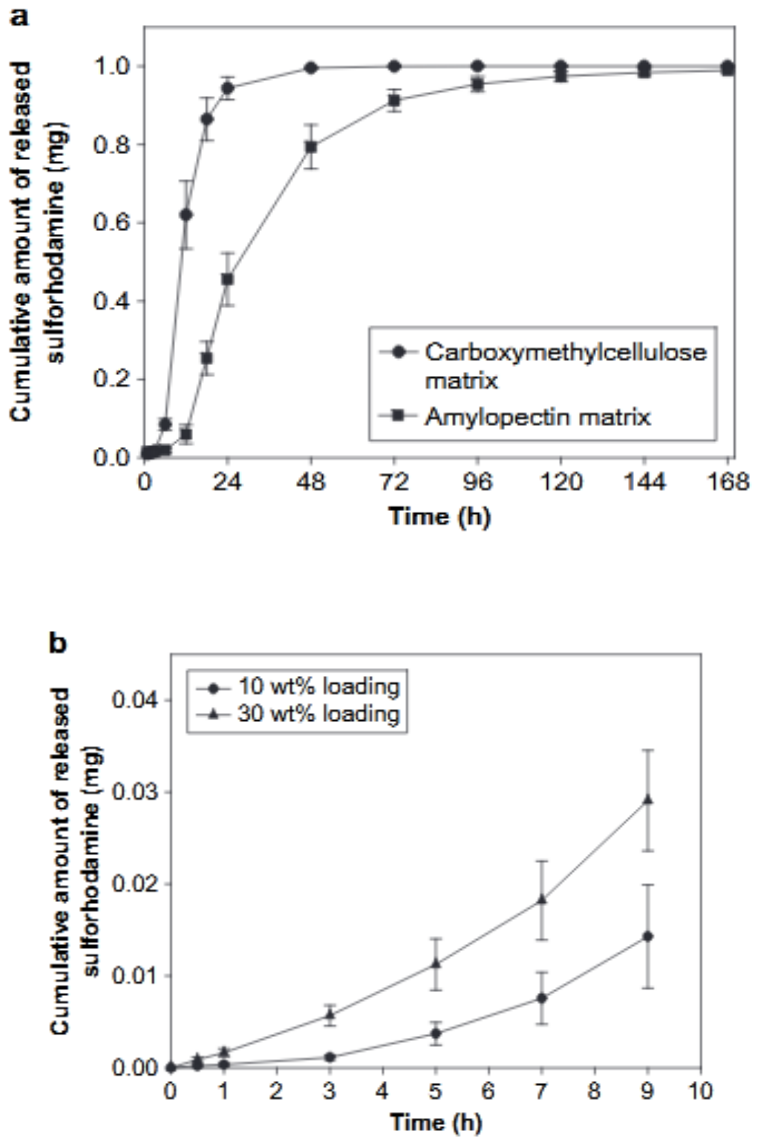


Figure 5: Transdermal release profile from dissolving microneedle patches.

(a)Cumulative release of sulforhodamine encapsulated at 10 wt% in thepyramidal microneedles and the backing layer of patches made of CMC andamylopectin. (b) Cumulative release during the initial release periodofsulforhodamine encapsulated at 10 wt% or 30 wt% only in the backing layer of CMC patches. Human cadaver epidermis was used. Average values are shown with standard error bars based on 3 replicate measurements(Lee et al. 2008)

2.6Drug materials for delivering through microneedle

Various materials, including poly (vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP), dextran carboxymethyl cellulose (CMC), chondroitin sulfate, and sugar have all been used to produce this type of MN array.The use of metal MNs for the delivery of different molecules, including macromolecules, such as BSA and insulin Photosensitizes [5-aminolevulinic acid, 5-aminolevulinic acid methyl ester and meso tetra (N-methyl-4-pyridyl)porphinetetratosylate] were also delivered after a pre-treatment with solid polymeric and silicon MN arrays. The transdermal permeation enhancement of non-steroidal anti-inflammatory drugs (diclofenac, ibuprofen, ketoprofen, paracetamol) was observed using a pre-treatment with MN roller devices. Small molecules delivered using dissolving MN include caffeine, lidocaine, metronidazole, ibuprofen sodium,sulforhodamineB and 5-aminolevulinic acid. Macromolecules delivered using dissolving MNs include insulin, low molecular weight heparin, ovalbumin, leuprolide acetate, erythropoietin and human growth hormone. Hydrogel-forming MN arrays have been used to deliver clinically relevant doses of low potency, high dose drug substance and also for rapid delivery of proteins. Studies carried out with hydrogel-forming MN arrays show their ability to enhance percutaneous delivery of a wide variety of molecules, such as small hydrophilic drugs (i.e. theophylline, caffeine, methylene blue, and metronidazole) and high molecular weight compounds (i.e. insulin and BSA)(Van Der Maaden, Jiskoot, and Bouwstra 2012).

2.7Application of MN

Fruitful utilization of microneedles relies upon device work that encourages microneedle inclusion and feasible infusion into skin, skin recuperation after microneedle expulsion, and

medication solidness during assembling, storage and delivery, and on persistent results, including an absence of agony, skin disturbance and skin disease, notwithstanding drug viability and wellbeing.When microneedles were first introduced for drug delivery applications, the primary objective was either to increase skin permeability through solid microneedle pretreatment or to create hollow microneedles with advanced practicality over conventional hypodermic needles.The applications of micro-needles have been extended to many fields, including transdermal,ocular, and intracellular delivery. However, the transdermal route is still the dominant area of application for microneedles, especially for vaccine delivery. In recent years, transdermal drug delivery systems have developed rapidly and became the third-largest drug delivery system after oral administration and injection.Infact, the microneedle delivery system not only could enhance drug delivery efficiency, but is also convenient, safe, painless, and improves patients' compliance. To date, the microneedle delivery system has been wildly used in cancer therapy, diagnosis, treatment fordiabetesand anti-inflammatory and analgesictreatment, among others. Reproducible insertion of microneedles to the desired depth, without breaking or bending, each time a patient will use a microneedle-based delivery system will be one of the most important requirements for efficient and accurate drug delivery. Skin isn't just a powerful boundary, yet besides supportive for delivering bioactive operators. Accordingly, it is very much applied in molecular discovery and treatment.Microneedles were generally presented for illness treatment by improving entrance and shipping drugs. At present, the utilization of microneedles is experiencing development in more fields including immune biological organization, infection determination, and restorative employments.

Disease treatment

A large portion of the biotherapeutic drugs, for example, peptides, proteins, hormone and characteristic operators neglect to be controlled effectively in light of first-pass digestion. However, the hypodermic infusion must be considered disregarding torment with the addition of a needle. The developing device, microneedle patches, is frequently viewed as a possible contender for hypodermic infusion, which is effortless, safe, and straightforward for patients to self-control. Transdermal drug delivery for infection treatment is as yet the problem area of utilization for microneedles(Yang et al. 2019).

Cancer

Conventional treatment regimens are included with a medical procedure, chemotherapy,and radiotherapy can prompt intense harmfulness and symptoms just as tumor repeat. An insignificantly intrusive malignancy treatment related to microneedle fixes consistently requests wide enthusiasm because of invaluable controllability, simple materialness and transcendent synergistic impact.

Diabetes

The danger of hypoglycemia inferable from visit supper time-related organization was fundamentally improved. To beat these difficulties, exhibited that a glucose responsive microneedle cluster patches managed the glucose adequately in blood by delivering insulin for

type 1 diabetes treatment. Glucose oxidase filled in as a powerful catalyst, which changed over glucose to gluconic corrosive with the utilization of oxygen.

Other diseases

Microneedle patches for transdermal drug delivery were likewise applied in the treatment of different sicknesses. Alzheimer's illness (AD), whose clinical manifestations are cognitive decline and language issues, is viewed as a ceaseless neuro-degenerative disorder. Anti-calcitonin gene-related peptides (A-CGRP) can specifically CGRP receptors, in this way repressing CGRP motioning to alleviate the pain. It was accounted for that the pain-relieving microneedle patches have a successful and straightforward choice to ease limited neuropathic torment by transdermally delivering the high explicitness of A-CGRP as contrasted and clinical medicines(Yang et al. 2019).

Chapter 3

3D printed MN

3D printed microneedle arrays were fabricated using a biocompatible resin through stereolithography (SLA) for transdermal insulin delivery. The optimization of the printing process resulted in superior skin penetration capacity of the 3D printed microneedles compared to metal arrays with minimum applied forces varying within the range of 2 to 5 N(Economidou et al. 2019).Microneedles (MNs) are playing aprogressivelyvitalpart in biomedical applications where negligiblyinvasivestrategies are being created that require intangible tissue penetration and drug delivery. To improve the integration of MNs in microelectromechanical devices, a high resolution 3D printing technique is executed. With the advent of methods to print beyond the optical diffraction limit, 3D printing, which is also known as additive manufacturing, has become a viable option for the fabrication of MNs. It has advanced through different technologies such as stereolithography (SLA), fused deposition modeling (FDM), and two photon polymerization (TPP). SLA has been used in various works to produce MNs for transdermal drug delivery, mainly to fabricate plain/solid MNs. The delivery method can be either by coating the MNs with the specified drug or can be preloaded in the case of biodegradable materials. To a lesser extent than SLA, the FDM 3D printing technique was used recently to fabricate biodegradable polymer MNs for transdermal drug delivery. Furthermore, 3D printing may facilitate simple customization of transdermal drug delivery systems to accommodate factors that influencedelivery contrasts in the skin thickness and hydration.To prove the appropriateness of the 3D printed MNs, they were used for a penetration test into both a skin-like material and mouse skin. Microneedles are being used today in drug delivery as they can assist in diagnosing

and delivering drugs to necessary areas. Numerous materials have been used to date including glass, silicon, glass, plastics, and metals(Moussi et al. 2020).

A microneedle is a three-dimensional (3D) micromechanical structure that breaches the stratum corneum of the skin to create micro-channels for passing active ingredients of the drug by transdermal drug delivery system. Typically grouped in a large number, microneedles are designed to be applied to the skin like a patch. When pressed onto the skin surface, the needles can cross the very outermost layer of the skin, which then creates microscopic pores, allowing the medicine to enter the body. Because the needles are tiny, the dermal nerves and blood vessels aren't affected, so there is no pain or bleeding when the patch is applied. Instead, patches covered with microneedles have been described as feeling similar to Velcro or a cat's tongue when touched. The needles are hard when they're dry as well as they can be easily applied to the skin. The medicine is held in a reservoir adjacent to the microneedles. When inserted, the microneedles draw in the fluid that bathes cells, and they then begin to swell. This opens up the structure of the material. When the fluid from the skin enters the patch, it dissolves the reservoir that holds the medicine, which is then able to move through the microneedles into the dermal layers of the skin that is rich in blood vessels. These blood vessels then transport the medicine to the rest of the body(Larrañeta et al. 2016).

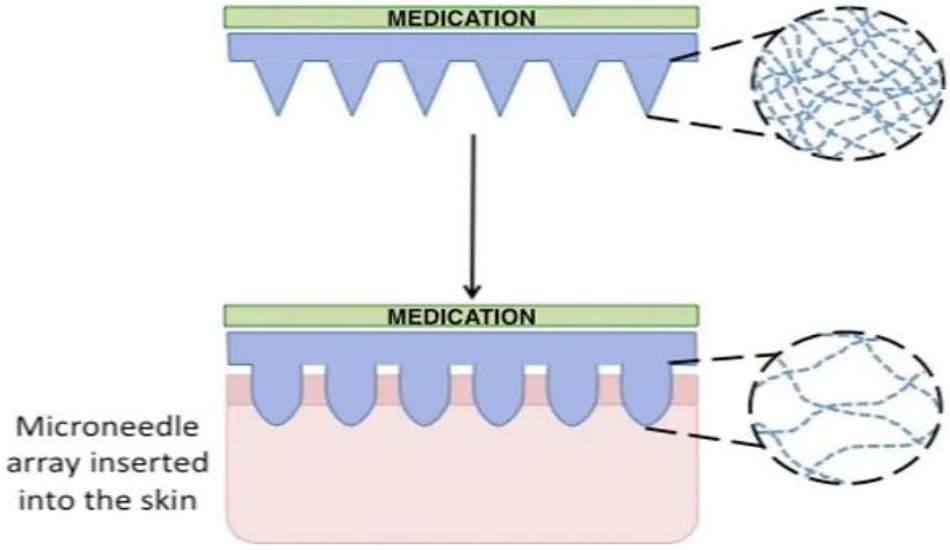


Figure 6: Microneedle application to the skin and swelling off the array.

The ability to develop and produce different shaped objects without the need for specific tooling offers businesses a higher level of flexibility when it comes to production as well as it helps to reduce costs. The strong point about 3Dprinting is that it improves innovation and is perfect for on-demand customization needs. Additive manufacturing (AM), 3D printing or Solid freeform Fabrication (SFF) may be aclusterof variedways that utilize a virtual computer-aided design (CAD) model to formanentity through the rear to back testimony of layers. Since its beginning in the1980s, it's upset most of the mechanical and scientific fields, empowering the fast and precise creation of structures and elements with levels of multifarious nature that are inaccessible through standard procedures. Clinical researchers imagined the distinctive prospects of 3D printing to on a really basic level modify however patients are treated, inform in taking present day medical specialty from the massively created to the redid. Soon after, inserts and medical specialty began to be 3D written with customized, quiet specific characteristics whereas, in tissue building, the attainableness of live tissue printing is as of currently explored(Ngo et al. 2018).

3.1Applications of 3D printed microneedle for transdermal drug delivery

The capability to viably pass away drug molecules to bring down skin layers wherever the medication can head to the circulation through the rich capillary vasculature of the stratum, has been investigated for an assortment of materials(e.g. polymeric frameworks, metallic microneedles) and techniques (e.g.transdermal patches, iontophoretic frameworks, synthetic penetration enhancers). The first TDD frameworks went regarding as precursor of the trendywaysand that they highlight the employment of the medication containing formulation legitimately onto the skin, taking into consideration the retention of drug molecules and their entanglement within the layer corneum. The latter then works as a tank, step by step guiding the medication into the epidermis. In the early frameworks, the whole drug quantity was managed in one single menstruation, through the topical application of ointments, gels and splashes, a method applied basically for treating vascular sicknesses and hormone substitution. Microneedles are created in ever-changing measurements; their height (25–2000 μm) consoles that the needles can reach the profundity of the skin's capillary framework, whereas their breadth (50–250 μm in base and1–25 μm in the tip) discovers that nerves contained within the dermis layer canstayclean upon application. This absence of pain in combination with the ability of self-application makes micro-needle systems highly patient-compliant. Microneedle structures permit the belief of a couple of drug delivery approaches. Microneedles were used in the initial study as a permeability enhancer prior to a drug-loaded patch software framework. The performance of the microneedle system is closely linked to its manufacturing technique, since the latter must guarantee the manufacture at the micro level of a delicate and reproducible geometry, bearing all the characteristics which guarantee the patient's pain-free application and the efficient transport of the drug to the systemic circulation. Modern technology provides a wide range of techniques,

such as lithography, electrochemical and photochemical etching, laser cutting, electroplating, laser micromachining and micro moulding, used for the manufacture of microneedles (A. Konta, García-Piña, and Serrano 2017).

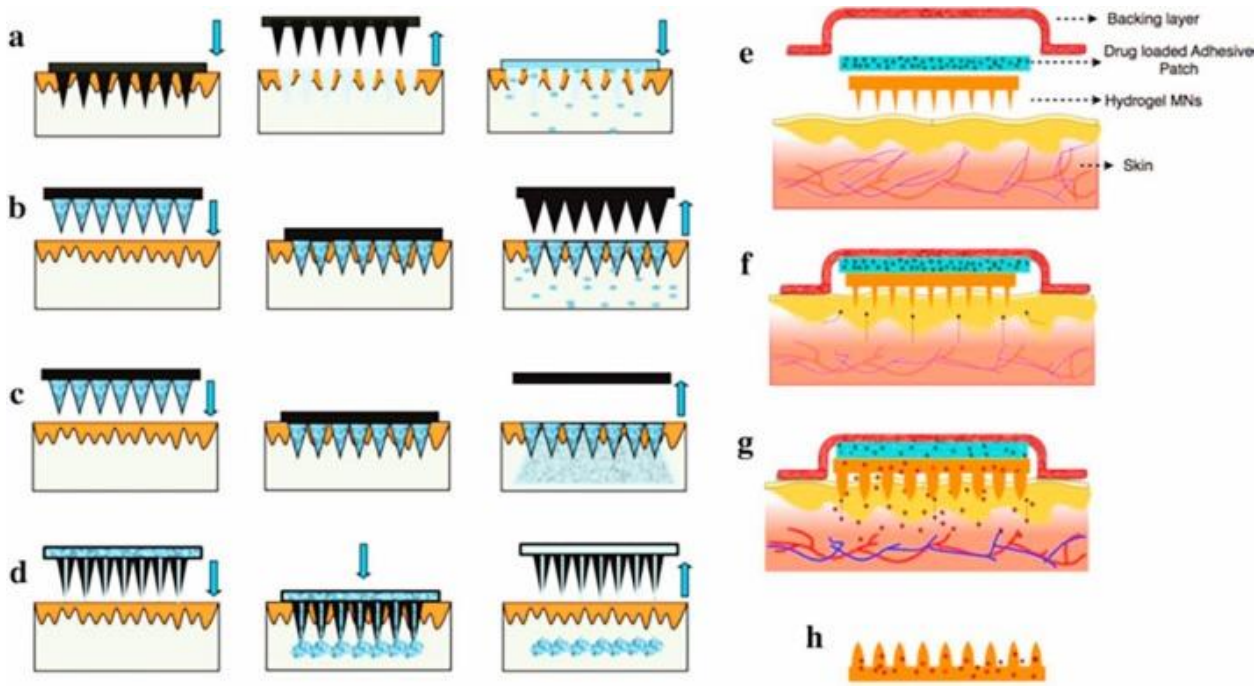


Figure 7: Schematic illustration of techniques of microneedle software to the pores and skin to achieve stronger transdermal drug delivery.

(a–d) Traditional techniques of microneedle mediated drug deliverythroughoutpore and skin. (a) Solid microneedles that are implemented and eliminated to create briefmicropores, observed with the aid of usingsoftwareofaconventional transdermal patch. (b) Solid microneedles arecovered with a drug for immediately delivery thatiseliminated after coating material dissolves. (c)Soluble polymeric/carbohydrate microneedles containing a drug that dissolves in skin interstitial fluid over time, thereby handing over the drug. (d) Hollow microneedles for delivery of fluids containing the drug. (e–h) Novel hydrogel-forming polymeric microneedles for controlled transdermal drug delivery. (e) Exploded view of the incorporated hydrogel microneedle patch,

(f)software of the incorporated hydrogel microneedle patch to the pores and skin surface, (g)diffusion of water, which reasons managed swelling of the microneedle arrays, forming an in-situ hydrogel conduit. Besides these outcomes in liberation and diffusion of drug molecules from the adhesive patch via the hydrogel microneedle into the pores and skin. (h) The hydrogel microneedle arrays stay intact,even after elimination from the pores and skin, thereby leaving no polymeric material in the pores and skin following drug delivery(Donnelly et al. 2012).

Microneedles facilitate transdermal drug delivery through piercing micro-scale pores via the stratumcorneum. They usually penetrate the most effective idea the stratumcorneuminto the nociceptors of the pores as well as skin will now no longer be stimulated. Therefore, as an opportunity approach, microneedles offer a minimally invasive approach for drug delivery. Additive manufacturing is known as three-dimensional (3D) printing revolutionized the sphere of pharmaceutical and biomedical sciences because of their abilities for immediate and cost-effective prototyping of complicated structures. Transdermal drug delivery has been used since 1981 as an alternative route of oral and parenteral administration of drugs to minimize and avoid limitations associated with them. Transdermal systems are often a desirable form of drug delivery because this route avoids the degradation of drugs in the GI tract and first-pass metabolism, which in the end reduces the frequent administration of drugs and the plasma level “peaks and valleys “often caused by oral dosing and therefore the risk of side effects. This process is, however, limited by the outer layer of the skin, the stratum corneum, to small (<400–500 Da), lipophilic(logP1–3) and potent molecules with elimination half-life<10 h and low oral bioavailability. Microneedles (MNs) are micrometer-sized needles (solid or hollow) with a length of 50–900lm, and a diameter of much less than 300lm which create microchannels and penetrate up to70–200lm via most effective outermost layers of skin, superficial sufficient now

no longer to reach the nerve receptors in the reticular dermis. Therefore, as an alternative approach,microneedlesoffer a minimally invasive method for forming micro-scale channels into the pores and skin for delivering numerous additives in secure, painless and cost-effective manners. These micro-channels help topically carried outdrugmolecules to skip the SC, which is the most important drawback for transdermal permeation, and makes them a higher candidate for drug delivery compared to conventional transdermal patches or hypodermic needles that are frequently painful. They have some benefits included thedecreased risk of infection, ease of disposal, minimal invasiveness, and the capacity to increase the Transcutaneous flux of drugs. 3-D printers for printing plastic substances include fused deposition modeling (FDM), selective laser sintering (SLS) and stereolithography (SLA). In FDM, through a high-temperature nozzle that solidifies on a construction sheet, a molten thermoplastic polymer filament is extruded through rollers. FDM techniques are flexible, safe and cost-effective and can be used by the Food and Drug Administration (FDA) to print reusable, biodegradable thermoplastic material with an extremely low melting point that contains polylactic acid (PLA) and polyvinyl alcohol that is allowed to be used in dissolvable stitches. However, the biggest challenge is low resolution in terms of manufacturing fine structures like microneedles(Camović et al. 2020).

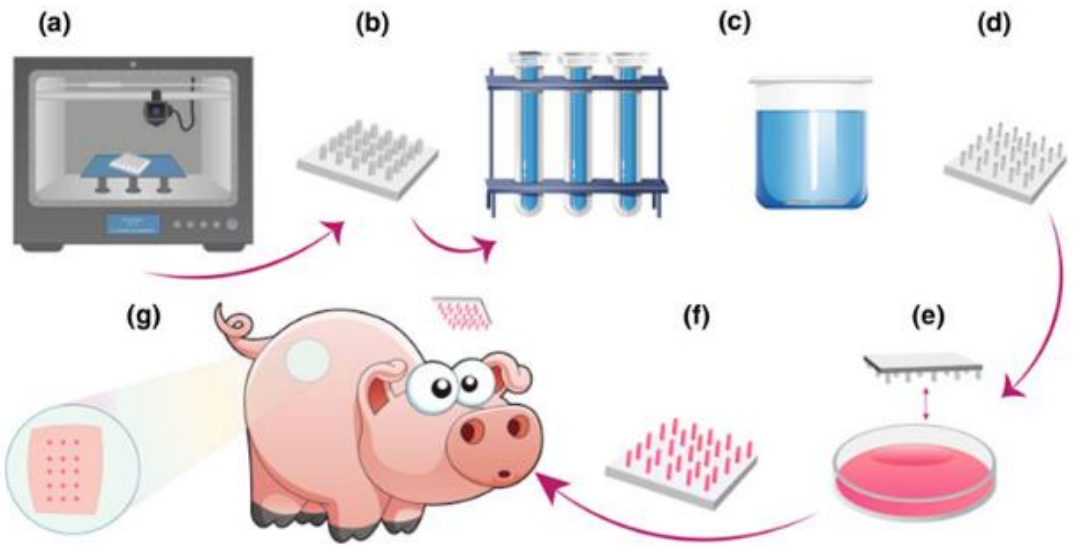


Figure 8: Schematic illustration ofa)3-D printing of microneedles via way of means of the use of FDM, b)3-D printed microneedles as fabricated,c) chemically etched microneedles the use of 5M KOH,d) detached microneedles after washing with water,e)loadingdrugthe use of "dippingmethod", f) coated microneedles, g) fracturetestofmicroneedles in porcine skin.

3.2Printing techniques of 3D printed microneedle fabrication and design

Microneedles,arrays of micron-sized needles that painlessly puncture the pores and skin, changetransdermal delivery of medicinal drugswhicharetough to supplythe usage of a lot of standard routes. Many vital design parameters, besides microneedle size, shape, spacing, and composition, are recognized to influenceeffectively. Microneedles were made of lots of different substances along with metal, silicon, and natural and artificial polymers. Although numeroussubstanceswere utilized, microneedles manufactured from biocompatible substances are taken into consideration the gold preferred for affected person safety due to the fact they keep away from immunological dangersrelatedtounintended microneedle fragmentation inside the pores and skin. Recently, a need for improved manipulation over microneedle design parameters, which include composition, height, sharpness, issue ratio, inter-needle spacing, and microneedle shape, has been demonstrated. Such design parameters are recognized to persuade microneedle efficacy. Forexampleplenty of work has been accomplished to identify suitable substances for

microneedle fabrication. While metals aregenerallystrong enough, biocompatible polymers have to be compelled to be cautiously decided on to ownadequatemechanical energy.Because an effectivemicroneedle has to be compelled to insert into the pores and skin without breaking, every pressure needed for insertion and also the failure energy of the materialisimportant.Microneedle form, element ratio, and composition dictate energy, whereas microneedle sharpness is the variety of needles in an array that affect insertion pressure (Johnson et al. 2016).

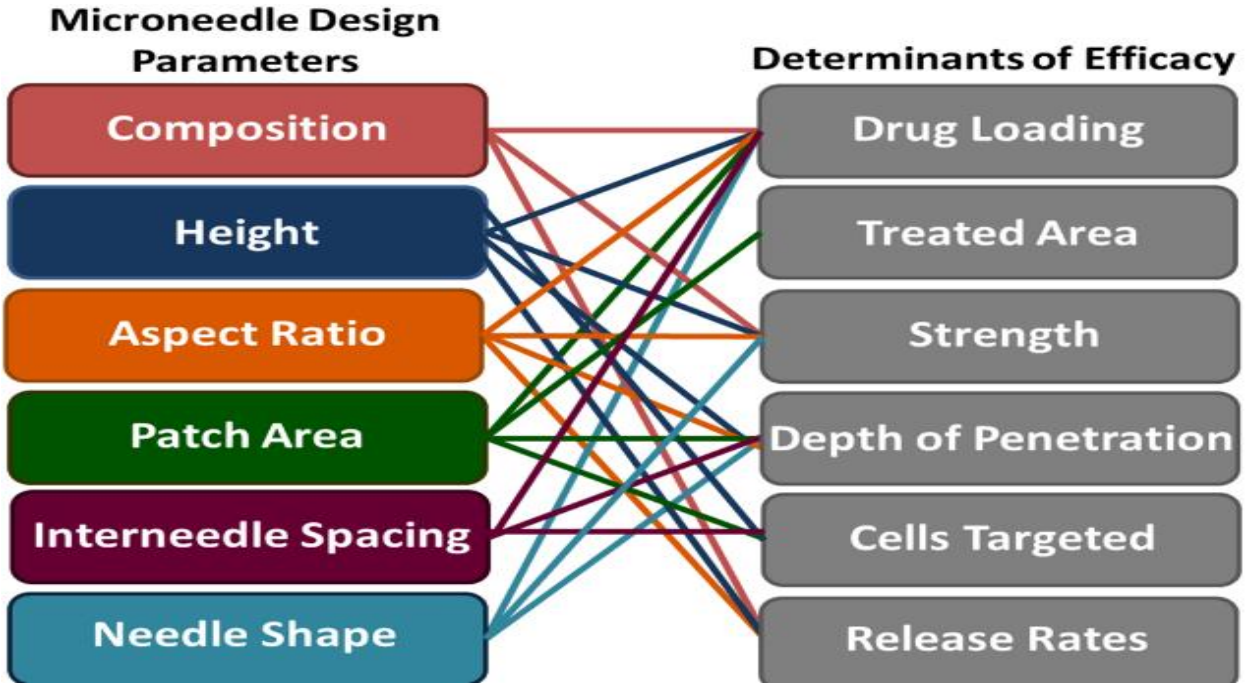


Figure 9: Relationship among microneedle design parameters and therapeutic efficacy(Johnson et al**.** 2016)

Further, microneedledesign parameters affect theoverallquantity ofhealingthat may beefficientlydelivered to the body. Because of their little size, the encapsulation and delivery of therapeutically applicable parts of medication aretough for somethingbutthe mosteffective therapeutics. Ideally, new microneedle designscould also be unexpectedly prototyped to consistentlyexploreeach layout parameter to optimizeefficaciousness. However, because of the

complex nature of contemporary microneedle fabrication strategies (which include silicon etching, titled (ultraviolet) photolithography, and laser ablation mixed with micro molding), lead instances for brand new designs are at the order of months. Further, many of those strategies have technical barriers that preventcertainkinds of microneedles (which include tall, sharp, and/or excessive component ratio structures) from being produced. For this reason, microneedle height, component ratio, and spacing are normally dictated with the aid of using the feasibility of fabrication instead ofperfectdesign.Awide varietyof latest microneedle fabrication strategies, which include drawing lithography, photon polymerization and electro drawing, were developed to deal with the restrictions of conventional approaches, however aren't widely adopted(Johnson et al. 2016).

With a 3D modeling software program, numerous MN shapes had been designed and published unexpectedly with custom needle density, length, and shape. Scanning electron microscopy showed that our technique resulted in needle tip sizes in the variety of 1–55μm,that could effectively penetrate and damage off into porcine skin. Additive manufacturing, more typically referred to as3-D printing, is a way of fabricating physical components from a virtual version generated bythe usage of computer aided design software program via way of means ofincludingsubstances layer with the aid of using layer. For instance, the photo-initiators required

in theSLA printingmethodarepoisonous and are incompatible with transdermal drug delivery.

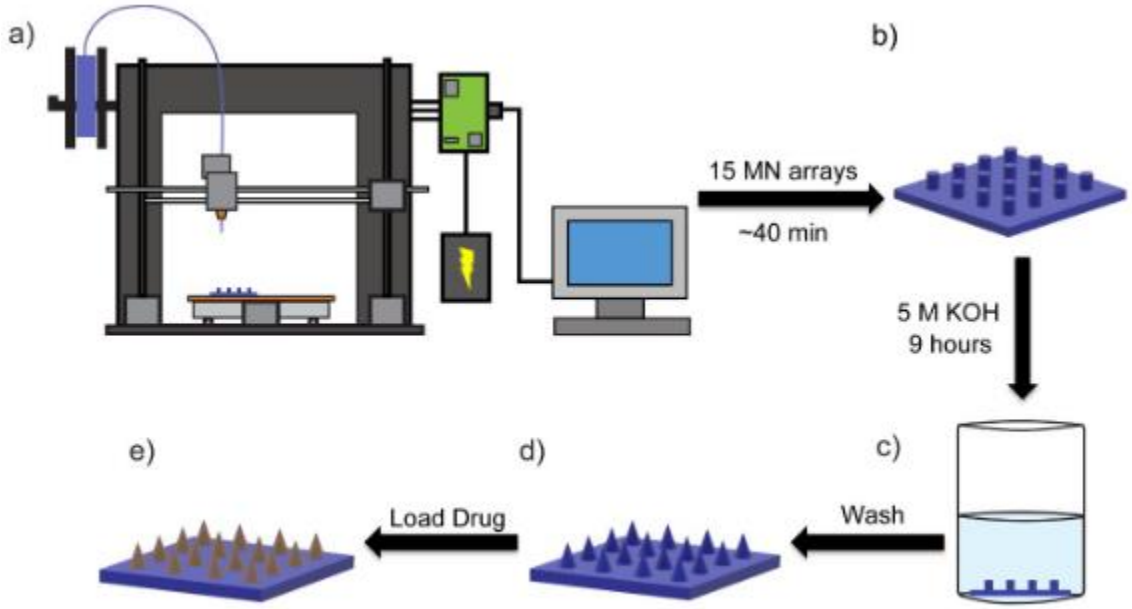


Figure 10: Schematic illustrationofa) FDM3D printer used for microneedle production b) 3Dpublished microneedles as fabricated c) chemically etched microneedles the use of an alkaline solution d) etched microneedles after washing with water e) microneedles after drug loading(Luzuriaga et al. 2018)

At a minimum, the 3Dpublished MN array has to be compelled to be expected to successfully penetrate the skin, which could be enough to permit drug delivery with the help of coatinga healing onto the surface of the needles. Thus, it's far narrowed the choice of a thermoplastic compound to PLA, a typical filament want for FDM printing. With the filament need in hand, over the direction of our investigation, we have a tendency to test seven MN shapesthat are schematically illustrated on the following table, to print an array that meets the above criteria(Krieger et al. 2019).

Table 2: Microneedle designs tested with the 3D printer

Array	Shape	Printer	Etch	Parafilm	Skin
Type 1		×	×	×	×
Type 2		×	×	×	×
Type 3		×	×	×	×
Type 4		×	×	×	×
Type 5		✓	✓	✓	×
Type 6		✓	✓	✓	×
Type 7		✓	✓	✓	✓

Type1 and Type 2 have been examined to gain sharp tips.However this sharp feature surpassed the decision of even small diameter warm end (350 μm) and these designs have been poorly replicated through the 3D printer. Even extra slowchanges, illustrated as Type 3 and 4, have been malformed after printing, as a result of the filament deposition process. Overall, Types 1-4confirmed that slow changes could now no longer be finished due to poor adhesion among extruded layers, common trouble that takes place in FDM printing of small structures. Owing to this limitation, we changed our method in needle Types 5–7 through the usage of terraced layers instead of slow sloping, which proved to be successful(Krieger et al. 2019).

3.3Advantages of transdermal drug delivery

Transdermal delivery has a variety of advantages compared with the oral route. In particular, it is used when there is a significant first-pass effect of the liver that can prematurely metabolize

drugs. Transdermal delivery also has advantages over hypodermic injections, which are painful, generate dangerous medical waste and pose the risk of disease transmission by needle re-use, especially in developing countries. Besides, transdermal systems are noninvasive and can be self-administered. They can provide a release for long periods of time (up to one week). They also improve patient compliance as the systems are generally inexpensive.Even the delivery of a therapeutic level of the medication is painless, the patient does not have to inject himself, there are no heavy delivery systems to handle or harmful needles to dispose of and the drug itself has little to no gastrointestinal effects. The benefits of transdermal delivery are evident. The drug's peak plasma levels are lowered, leading to reduced side effects. In addition, transdermal delivery is useful for drugs that have a high liver first pass effect, have low oral absorption, require repeated administration, or interact with stomach acid. The first passing effect results in a large quantity of the medication being lost. It absorbs drugs through the skin. By avoiding the liver, however, enter the general circulation directly, with less overall drug absorption occurring(Saravanakumar et al. 2015).

- A painless, non-invasive way to inject drugs directly into the body is by topical patches.
- Topical patches are a safer way of delivering drugs that are broken down by the acids of the stomach, not well absorbed by the intestine or badly degraded by the liver.
- Topical patches over long periods of time over a regulated, steady distribution of medication.
- Topical patches have fewer side effects than supplements or oral drugs.
- It is easier to use and identify topical patches.
- Topical patches are a choice for individuals who do not or choose not to take oral drugs or supplements.

- Topical patches are cost-effective.
- People prefer topical patches(Patel et al. 2012).

Certainly, each dosage form has its unique place in medicine, but some attributes of the transdermal delivery system provide distinct advantages over the traditional methods of attaining systemic levels of drugs. Cleary has listed important advantages and of the transdermal delivery systems. The advantages are that the system 1) avoids chemically hostile GI environment, 2) does not have GI distress or other physiologic contraindications of the oral route, 3) provides adequate absorption of drugs with some oral absorption promptly, 4) increases patient compliance, 5) avoids first-pass effect, 6) allows effective use of drugs with short biological half-lives, 7) allows administration of drugs with narrow therapeutic window, 8) provides controlled plasma levels of potent drugs, and 9) interrupts drug input promptly when toxicities occur(Tiwari et al. 2013).

3.4Development of microneedle fabrication and application in industry

The pharmaceutical industry is ready to register for the fourth business revolution with the 3D printing of medicines. The industrial revolution in its starting converted drug remedy with large-scale production in the meetingline, symbolized with the help of using the production of tablets in 1834(Araújo et al. 2019a). In spite of the modernization of commercial facilities and advances in great issues, the bases of the pharmaceutical production methodology are not changed. 3Dprinting has revolutionized varied sectors of human activity over aprevious couple of decades, being one of the pillars of the fourth industrial revolution. In recent years, using this era of

medication guidance has established immense potential. This is why specialists around the world show that the pharmaceutical discipline has later on been given, after two centuries, the chance tocreate an excellent technological jump. Diversified drug delivery devices the usage of3D FDM technologies is being advanced at a fast pace by dozens of researches organizations in exclusive parts of the world. Nevertheless to allow the economic viability of this period, another step has to be taken. A collaboration between pharmaceutical companies and the combination of pharmacies in a very complementary supply chain looks like the most attainable opportunity to form a fresh route to the market in the delicate of previous works and considering the extrusion technique already used with the aid of the pharmaceutical industry.

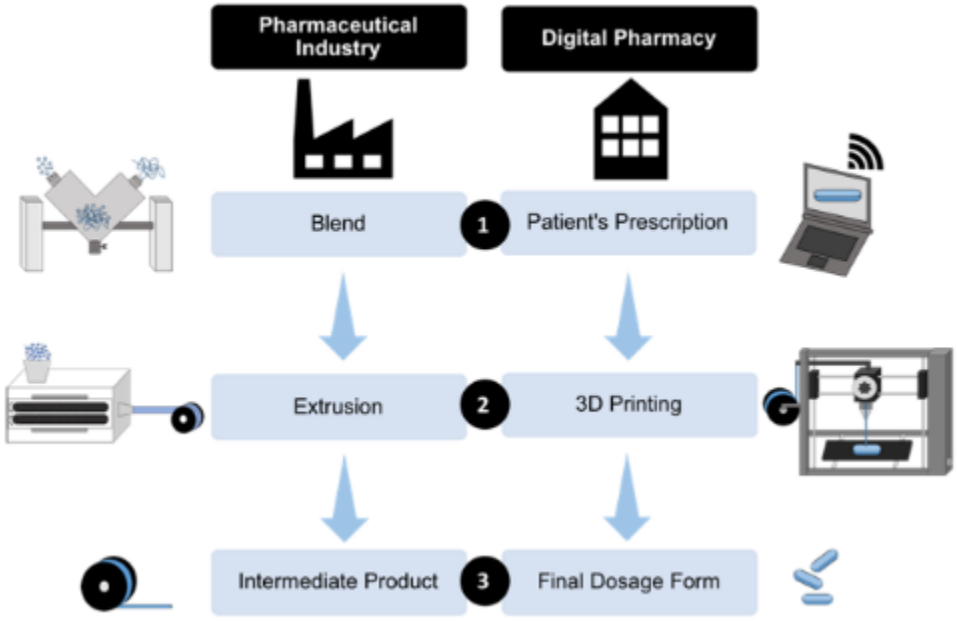


Figure 11: Schematic steps required for the industrial manufacturing of filaments and the elaboration of customized drug delivery tool in digital pharmacies(Araújo et al. 2019a)

A familiar technique with industrial production profiles is the manufacture of drug-loaded filaments used to feed FDM 3D printers(Araújo et al. 2019b). In the preliminary section, the industry dedicated to generating the filaments ought to conduct analysis and improvement for each product, primarily based} totally on the chosen drug and most popular drug release profile many 3D printing technologies have misplaced their patents over the past decade, that became a decisive aspect in creating these machines more accessible to the general public and to the pharmaceutical industry. 3D printing on an industrial scale provides advantages, as a result of the layout of advanced geometries, whereas as compared to acompletely different technology, like tableting, is not as competitive. 3D printing in an industrial scale provides advantages, as a result of the layout of complicated geometries, whereas compared to totally different technology, like tableting, is not as competitive(Araújo et al. 2019b). Many 3D printing technologies have misplaced their patents over the past decade, which became a decisive side in creating these machines bigger accessible to the general public and to the pharmaceutical industry.

3.5Materials' composition of microneedle

Microneedles (MN) are micron-sized needles, starting from 25 to 2000 μm in height, made of lots of substances and shapes. The substancesinclude ceramic, glass, polydimethylsiloxane (PDMS), dextrin and polymers, in addition tometalsincludingstainless-steel and titanium. In order to utilize those MNs for drug delivery, a lot ofsubstanceshad been used for manufacture, such as metals, silicon, glass, non-biodegradable polymers and biodegradable polymers. The maximumcommonsubstances are mentioned below:

Silicon MN

The dimensions of needles have beenabout80 μ m on the base, 150 μ m in duration,andabout 1 μ m radius of curvature on the tip. These needles have been able to increase pores and skin permeability of calcein, insulin, and bovine serum albumin.Fabricated silicon MN through a dry etching technique, the use of a trendy wafer of 525μ m thickness, and a conical-formed stable MN with an aspect ratio of 4.5:1.Another sort of solid silicon MNs, referred to as micro enhancer arrays, have been etched from silicon wafers the use of lithography and potassium hydroxide etching, have beenabletosupplybare plasmid DNA into mice pores and skin. These needles measured 50–200μ m in duration over a 1cm 2 location and had a blunt tip. The importance of this study became the feasibleness of the employment of blunt-tipped MNs to scrape the pores and skin for elevated the delivery of DNAvaccineto getare a sponge. Fabricated sharp hole silicon MN tips with side-openings. Additionally, the ideasare sealed with a layer of gold coating to yield a closed-package system(Larrañeta et al. 2016).

Table 3: Lists of the most common materials used for fabrication of MN

Metals	Synthetic polymer		Natural polymer
	Biodegradable	Non-biodegradable	
Silicon	Poly lactic acid (PLA)	Poly vinyl acetate	Carboxy methyl cellulose (CMC)
Stainless steel	Poly glycolic acid (PGA)	Alginic acid	Amylopectin
Titanium	Polycarbonate	Gantrez AN139	Dextran
Palladium	Poly vinyl pyrrolidone (PVP)	Carbopol 971 P-NF	Galactose
Nickel	Polylactide-co-glycolic acid (PLGA)	Polyetherimide	Maltose

Metal MNs

Metal MN have proper mechanical strength, are easy to fabricate, rather inexpensive, and the metals used, which include stainless steel, titanium, and nickel, have establishedprotectiondata in FDA medical accepted devices. They were fabricated with the aid of using laser cutting (e.g. stainless steel), moist etching (e.g. titanium), laser ablation, and steel electroplating methods. The smallest used hypodermic needles (30/31 G) have been translated into arrays of MNs. This technique forms a metal MN by deposition of a few laser pulses onto a metal target, significantly improving the time and cost of fabrication of two-dimensional metal MN arrays(Larrañeta et al. 2016).

Ceramic MN

The use of ceramic substances raised the opportunity to manufacture solid and porous MNs, which might be loaded with liquid for drug delivery or diagnostic sampling. Solid ceramic MNs were fabricated by micro-molding alumina slurry using a (PDMS) MN mold and ceramic sintering. Ceramic MNs have also been lithographically fabricated using a two-pho-ton-induced polymerization approach. Using a Galvano scanner and a micro positioning system to induce polymerization locally in the form of the MN, an intense laser was scanned within a photosensitive polymer-ceramic hybrid resin(Ali et al. 2020).

Coated MNs

The micron lengths of needles enforce special coating formulation to obtain uniform coatings and spatial control over the region of the MN to be coated, because the effects of surface tension,

capillarity and viscous forces become more prominent at these small length scales. Therefore, for coating drug formulation, solid MNs should be composed of surfactants to facilitate wetting and spreading of the drug solution on the MN surface during the coating process, viscosity enhancers to increase coating thickness, and stabilizing agent to protect and stabilize biomolecules during drying and storage. In addition, coating solution excipients and solvent have to be secure for human use, and the coating technology has to be compatible with production strategies and now no longerharmcoated drugs(Ali et al. 2020).

Chapter 4

Current situation of 3D MN

4.1Drug products already as 3D printed MN

Individual variability is an increasing worldwide trouble while treating patients from exceptional backgrounds with various customs, metabolism, and necessities. Dose adjustment is often primarily based totally on empirical methods, and therefore, the risk of undesirable aspect consequences to arise is high. Three-dimensional (3D) Printed drugs are revolution sing the pharmaceutical market as potential equipment to gain personalized remedies adapted to the precisenecessitiesof every patient, taking into account their age, weight, comorbidities, pharmacogenetic, and pharmacokinetic characteristics.In accordance with the most abundant and representative therapeutic response profile, the aforementioned science pretends to elude the natural ability of the pharmaceutical industry to produce medicine. Drug mass production impedes the growth of drugs before all the specifics of each person are taken into account. This is especially important for pediatric and geriatric populations, contributing to insufficient doses of therapy and a high risk of adverse effects. Adjustment of the dosage according to pharmacogenetic and pharmacokinetic characteristics, weight, and age is important in order to realize the therapeutic impact needed and to improve the balance of efficacy/toxicity. Similarly, a variation in colors, flavors, and even the shape of solid dosage formulations will greatly improve medication adherence in both children and the elderly. In 2015, the FDA approved the primary3Dpublished drug, Spritam, containing levetiracetam, an antiepileptic API(A. A. Konta, García-Piña, and Serrano 2017). The pharmacological efficacy was discovered to be equalto respect to standardtablets;however, with the great development that the solubilization time

changed intosubstantiallydecreased because of its porous and soluble matrix composition. The 3D printing revolution is also possible in the manufacture of custom, drug-ladendevicetailored in form and length for every patient. Nose-shaped masks, loaded with salicylic acid, intended for anti-pimplesremedieshad beenadvanced in a rapidly and green man.Currently, the manufacturing of patches loaded with 5-fluorouracil, poly (lactic-co-glycolic) acid,and PCL had been efficaciously revealed and implanted immediately into pancreatic cancer. The geometry of the patch and the release kinetics had been manipulated, keeping the drug release for a complete of four weeks. After that period, the patch turned biodegraded in the body. The concept of "polypill" refers to a single tablet that consists of amixture of numerous drugs. Therefore, it affordshugeadvantages in polymedicated patients,consisting of the elderly. Different polypillsusing 3D extrusion printing had been effectively created. As an example, captopril, nifedipine, and glipizide, to deal with high blood pressure and type 2 diabetes, had been manufactured in a single pill by the use of3D printing. The era has moved ahead and currently,prototypes together with five different varieties of APIs with exclusive release profiles had been produced. Three APIs (pravastatin, atenolol, and ramipril) were contained in the extended-release compartment, in which the drug was physically isolated with the aid of a hydrophobic cellulose acetate permeable membrane. On top of the above compartment, an immediate release compartment containing aspirin and hydrochlorothiazide transformed into deposited (A. A. Konta et al. 2017).

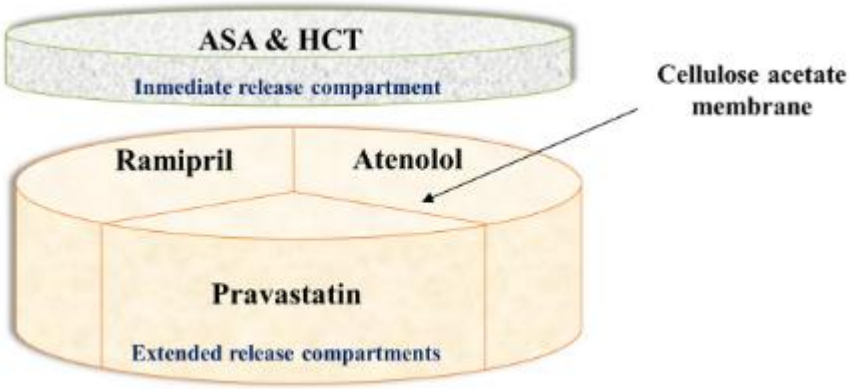


Figure 12: 3D printed polypill(A. A. Konta et al. 2017).

4.2 Price range

Three-dimensional (3D) printing for preoperative planning has been intensively developed in recent years. However, the implementation of these solutions in hospitals is still difficult due to high costs, very much expensive industrial-grade printers, and software that is difficult to obtain and learn with a lack of a defined process. It's far less expensive and takes far less time to create prototypes, jigs, tools, and fixtures using 3Dprinting. But once the setup and tooling costs are paid for, traditional manufacturing techniques like injection molding can produce objects in volume more quickly and at a lower cost. While most low-cost 3D-printed microneedles to date display low aspect ratios and poor tip sharpness, we show that by introducing a two-step “Print & Fill” mold fabrication method, it is possible to obtain high-aspect-ratio sharp needles that are capable of penetrating tissue(Witowski et al. 2017).

4.3Applications of microneedle available in the present marketed product

The improvement of a microneedle array has received momentum and now emerges as the area of top research. These technologies are being advanced for handing over biotherapeutics, biomacromolecules, like insulin, increase hormones,immune biological, proteins, and peptides. Insulin-loaded dissolvable microneedle of starch and gelatin and bovine serum albumin microneedles are a several very specific examples. Vaccine delivery with the aid of using the microneedle erais supposed to update hypodermic needle for heading off site-specific pain. Very new research has been made currently that the recombinant coronavirus vaccine transportsviapores and skin with the assist of microneedle era for the remedy of COVID-19. This technology helped deliver SARS-CoV-2 S1 sub-unit vaccines that elicited effective antigen-precise antibody responses that were obvious starting 2 weeks after immunization, and their research supported the medicalimprovement of MN-primarily based totally recombinant protein subunit vaccines towards SARS, MERS, COVID-19, and different rising infectious diseases. For ocular drug delivery, the microneedle-basedtechniques were morepowerful than topical application. Moreover, using microneedles was recommended in pain-free and rapid local anesthesia. They advanced lidocaine coated microneedle that confirmed in vitro pores and skin penetration and greater delivery of the drug in a totally quick duration, i.e., in 2 min. For painmanagement, meloxicam-loaded polymeric microneedles have additionally been organized using polydimethylsiloxane molds. The in vitro releasersearchconfirmed approximately100% drug release in 60 min. The drug deposition was determined to be 63.37%, and transdermal flux was determined to be 1.60 $\mu g/cm^2/h$.Improvement in the pores and skin permeation was discovered to be expanded as much as 2.58-folds in comparison to that of the free drug solution. The delivery of chemotherapeutic agents has additionally been successfully investigated. It was

mentioned that a microneedle patch-mediated treatment of bacterial biofilms, that's a patch microneedle treatment for the successful elimination of biofilms with the aid of using penetrating the biofilm and delivering antibiotics without delay to areas of activegrowth.Neuropathic pain as a result ofnerveharm is tough to deal with due to the fact modern systemic pharmacological treatments producerestrictedpaincomfort and have unwantedaspecteffects;even asmodernlocal anesthetics have tendto blockeach sensory and motor function nonspecifically. Neuropathic pain treatment analgesic microneedle patch (AMN) and AMN patches painlessly transdermal calcitonin gene-associated peptide (CGRP) antagonist peptide, providing efficient and healthy analgesia on neuropathic pain models consisting of spared nerve damage (SNI), diabetic neuropathy, and neurogenic inflammatory pain in rats caused by UV radiation. It has additionally been utilized in mixture with electroporation, iontophoresis, and differenttechniquesto present synergistic effects. This figure shows thediverse applications of microneedles.

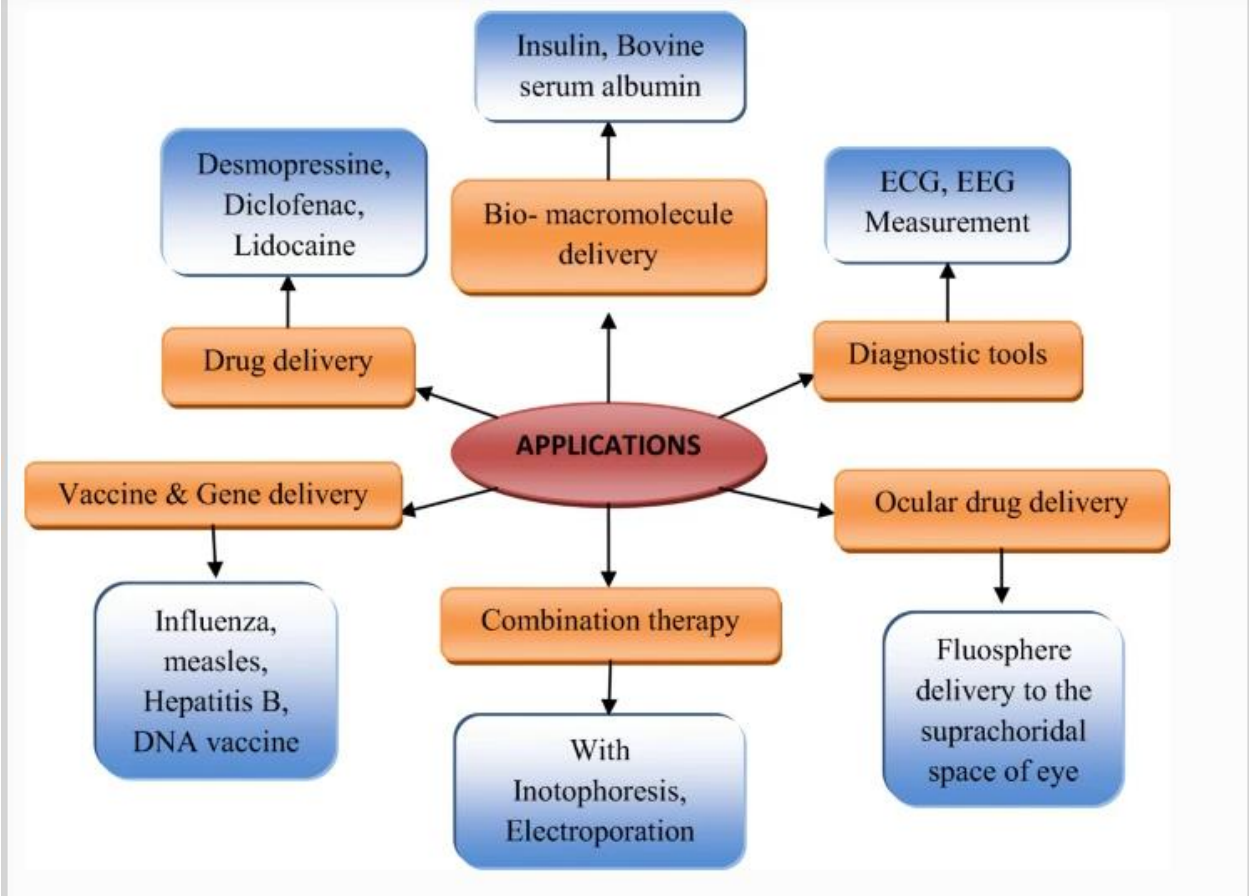


Figure 13: Applications of microneedle array in transdermal drug delivery(Halder et al. 2020)

As a subsequent step, diverse MN-based pharmaceutical products with different therapeutic advantages are available in the market. MNs have emerged as extra prominent in the past decade.As it overcomes many drawbacks of hypodermic needles, transdermal patches, and other traditional dosage types, the use of MNs as a way to administer medication needs to emerge as a more appealing strategy. Therefore, it's far important to examine patents that have been filed in the final decade to correlate the developments of MNs(Halder et al. 2020).

Table 4: Marketed microneedle-based transdermal products

Brand name	Manufacturer	Description	Application
Darmaroller®	Derma spark, Canada	Metallic microneedle array	Used to treat acne, stretch mark, hair loss. Able to enhance drug absorption (minoxidil, hyaluronic acid, etc.).
MicroHyala®	CosMED Pharmaceutical Co. Ltd., Japan	Dissolvable microneedle patch	It contains hyaluronic acid that is released in the skin to treat wrinkle.
VaxMat®	TheraJect Inc., USA	Dissolvable microneedle patch	It is used to deliver macromolecules, like proteins, peptides, and vaccines.
Micro-Trans®	Valeritas Inc., USA	Microneedle patch	It delivers the drug into the dermis without limitations of drug size, structure, charge, or the patient's skin characteristics.
Drugmat®	TheraJect Inc., USA	Dissolvable microneedle patch	It delivers hundreds of micrograms of drug rapidly through the stratum corneum into the epidermal tissue.
Nanoject®	Debiotech, Switzerland	Microneedle array-based device	Useful for intradermal and hypodermic drug delivery and for interstitial fluid diagnostics
Soluvia®	Becton Dickinson, USA	Hollow microneedle array	It is a prefillable microinjection system for accurate intradermal delivery of drugs and vaccines.
IDflu®/Intanza®	Sanofi Pasteur, Lyon, France	Intradermal microneedle injection	Prefilled with influenza vaccine for intradermal influenza vaccination.
Micronjet®	NanoPass Inc., Israel	Intradermal microneedle injection	It is used with any standard syringe for painless delivery of drugs, protein, and vaccines.
Macroflux®	Zosano Pharma Inc., USA	Metallic microneedle array	Delivery of peptides and vaccines
Microcore®	Corium International Inc., USA	Dissolvable peptide microneedle patch	Deliver small as well as large molecules, like proteins, peptides, and vaccines.
Dermapen®		Microneedle array-based device	Used for treating various conditions of skin, ranging from acne, stretch mark, and hair loss, and can enhance drug absorption.
Microstructured transdermal patch	3M Corp., USA	Hollow microneedle array	It delivers liquid formulations over a range of viscosities.

4.4Current trends of 3D printed microneedles

Three-dimensional (3D) printing is unexpectedly emerging within the pharmaceutical industry and new trends in drug enhancement include 3D printing of oral dosage types, implants, hydrogels, and existing drug delivery systems. Currently, 3D printing is based on oral dosage forms in drug production. (Russell 2018).Orphan drug tablets can be developed at low cost and on-demand as small batches. 3Dprinted hydrogels may be used as scaffolds in tissue engineering to increase cells or inserted into the body to provide controlled release of API. Currently, a huge share of 3Dprinted implants additionally provide controlled API release, that's beneficial for the promotion of bone recovery and the prevention of contamination after orthopedic surgical operation Implants have additionally been 3Dprintedthat release hormones for contraceptive

functions consequently their utility in medicine is increasing. Some studies inside the separate regions of oral dosage forms, hydrogels, implants and topical drug delivery have been completed. This has delivered3D printing to drug improvement and manufacturing; however, the data available may be very much unique to certain printers, APIs and processes. Consequently, it’s far important to supply a scientificassessment of the use of PRISMAguidelinesthat groups all available research into set areas so thatmoderndevelopments may be established. Currently best one certified3Dprinted product exists referred to asSpritam, containing the drug levetiracetam. It is an ODT and is produced through the Drop-on-Powder (DOP) method that’s a binder jetting technique that prints liquid binder onto skinny layers of powder. Consequently, it is hard to supplycontrolledreleasearrangements in this way and not all APIs are appropriate for use. Therefore, it's far important to understand the modern boundariesin the area of 3D printing and drug development.

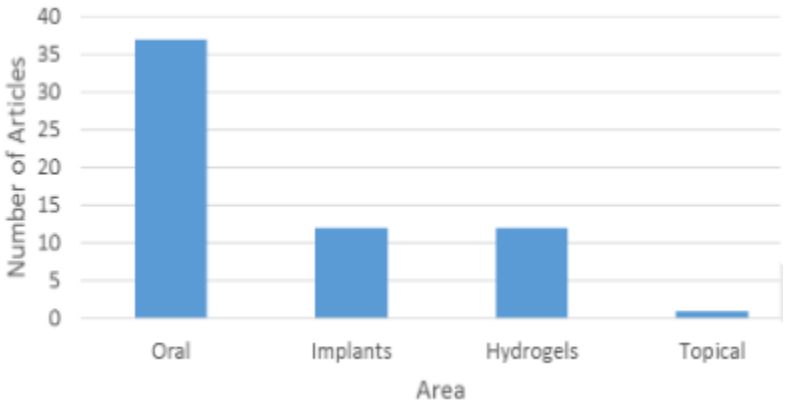


Figure 14: Distribution of dosage form focus detailed in articles examined.

Initial dosage form identification and route of administration developed that oral dosage forms, hydrogels, implants and topical dosage forms are the new critical trends within 3D printing and drug enhancement. Most current studies concentrate on oral dosage types .This is

mostpossiblyduetothe benefit of manufacture, a huge quantity of published records and information and preferential choice as a dosage form as oral dosage forms are most widely accepted and utilized by patients as they're small, discreet and easy to take(Liaw and Guvendiren 2017).

Chapter 5

Challenges to overcome

5.1Challenges and Method for Overcoming

Although 3D printing is staggeringly promising for the production of customized dosage forms, various technical and restrictive challenges require being overcome before its extensive usein pharmaceutical.Several 3D printing technologies (EXT, FDM, and PB) rely on nozzle mechanism were provided to construct sequenced layers throughout the formation of the printed object. This creates a significant challenge of retentive are producible and constant flow on demands the print head stops and re-starts throughout printing a single or more than one object. 3D printing technology improvements have introduced the prospect of personalized dose a step closer. The difference between compounded and manufactured medicine is a vitalquestionapproximately the policies of3Dprinted medicine. Moreover, vitalproblemsregarding3Dprinted medicines like tort liability and intellectual rights need to be addressed to defend manufactures and quit users. 3D printing and its capability in reshaping pharmaceutical product improvement and production have now no longer escaped the attention of regulatory bodies. However, meeting the modern regulatory requirements of the FDA might also additionally pose a significant hurdle thatcould obstruct their introduction to the market.For those problems to be resolved, FDA might also additionally need to give short-termguidance files and investigateto enhance its traditional rules to follow up with this rapidly-evolving technology. FDA identified that new problems implicating this technologywill rise up and the method for alternative is already underway. It is working on growing valid information on3D printing via its own research. To date, all registered medical devices and implantable produced

exploitation of this technology have been approved by the Premarket Notification, also known as the PMN or 510(k) pathway, by showing that a legally advertised device is signed up for 3D printed product. Such regulatory technique also can be applied for pharmaceutical products by approving a 3Dprinted dosage form as a bioequivalent product to accepted ones.Besides the traditional clearance routes, the FDA can also offer approval of 3Dmedicaldevicesvia abbreviated pathways. These pathways include pathways for emergency use, pathways for exemption for compassionate use. In August 2015, the FDA approved the primary 3Dprinted pill, Spritam (levetiracetam), despite all regulatory obstacles associated with 3D printing medicines (Paudel et al. 2010). In this situation the product is taken into consideration as approving new mass manufacturingfor an equivalent product. On the other hand, overcoming skin's impermeability remains a challenging task as well as several strategies that have been proposed to overcome the skin barrier namely; use of penetration, sonophoresis and iontophoresis(Paudel et al. 2010).Among the others, a promising approach is the use of microneedle arrays as a means to enhance the transport of actives across the skin. Microneedle arrays or simply microneedles (MNs) are miniature devices capable of piercing human skin painlessly.

5.2Limitations of 3D printed microneedle

There are several important design criteria to consider when designing and fabricating microneedles. Limiting the height of a needle to the sub-millimeter range allows for microneedle insertion to remain largely painless. Needle height also controls the depth to which a drug/vaccine may be delivered, or the depth from which a compound/signal is extracted in sensing applications. The aspect ratio of the needle influences ease of insertion and mechanical

integrity. While higher aspect ratio needles are easier to insert, a lower aspect ratio results in mechanically stronger needles. In drug delivery applications, both height and aspect ratio governsindividual microneedle volume as well as therefore control dosage. The tip radius is also a key parameter for ensuring microneedle skin insertion. Control of these dimensional parameters of microneedles is important, as this allows for tailoring of microneedle functionality(Moussi et al. 2020). These are some limitations:

- The surface texture is usually too rough.
- Materials have low heat deflection temperatures.
- Materials generally have low strengths.
- Material costs are far too high to restrict the growth of the market.
- Parts are generally not as dense as parts made by CNC and other processes.
- Color is only possible with Mcor and Zcorp and these do not provide for functional parts.
- It is too difficult to design for 3D printing.
- The software tool-chain is too complex.
- It is too difficult to 3D model.
- Manufacturing complex parts or organic parts need a lot of 3D modeling training.
- 3D scanners are not good enough and create holes in final files.
- Re-meshing software is not good enough.
- Printers are not large enough.
- Printers are not fast enough.
- Build quality and up-time on desktop systems is terrible.
- Industrial AM machines are too expensive.
- Machines are generally too slow.

- Very little R&D is done in 3D printing.
- The AMF file format has not been widely adopted by software tools that leaving us stuck with STL.
- Many desktop people are over-promising and using claims to sell their products.
- The media is saying “with a 3D printer you can make anything on the desktop” which is untrue.
- There is a reality distortion field whereby individuals accept that all the creations done by numerous organizations over numerous decades are all the while happening now.

5.3Regulatory aspects

Despite the numerous applications of MNs mentioned in the literature in animal studies and human assessments (generallyconcerningprotection or pain), no reviews ofcontaminationhad been found. The pores and skin have been proven to get better barrier properties conveniently after MN treatment and to be much lessproneto*Escherichiacoli* penetration than pores and skin that was pierced via way of means of 26- and23-gauge hypodermic needles. But because MNs puncture the SC, which serves as the most barriers for pores and skin protectionis far paramount to investigatethe potential threat of contaminationprovidedthrough microbial loadsintroduced in theproductionsystem. Based on danger assessment, regulatory companies can also additionally stipulate stringent microbial limits or sterility testing, relying on whether sterility is required. Whether MNs are manufactured under aseptic situations or sterilized terminally may also rely on (lack of) compatibility among terminal sterilization strategies and strong MN products, because of the excessive costs related to sterile processing. The standardproductionsystemought to be

designed to utilize in-technique cleaning, filtration, or sterilization steps thatassist forattaining or keeping low bioburdens for theMNs in downstream processes,consisting of sterile filtering inkjet printer ink and photopolymer solutions before use or steam sterilizing base MNs before coating. Additionally, the manufacture ofMNs from materials proven to have antibacterial properties may also justify not desiring sterilization for MN products (Tarbox,Watts,Cui and Williams,2018).

5.4Microneedle modeling tools

Several computer-based tools are developed for MN modeling using each in-house programming and commercial softwarepackage. These tools are typically developed for specific modeling functions.For example, once the parameters such as the ratio (a) were needed to be checked for the squared MNs patch optimization, an in-house java programming tool was created to realize the objective. An optimum was then calculated so that the data was also used to refine the physical measurements of MNs with greater precision.In addition, based on the optimized parameters acquired from the software, the permeability of different drug molecules through the skin treated with MNs is predicted by using diffusion coefficient relationships. For example, the correlations between the diffusion coefficient and the permeability of certain sample molecules to the skin (Calcein, insulin, bovine serum albumin, nanosphere particles with radii of 25 and 50 nm respectively) deduced from theoretical relationships are given in the figure.A relatively recent research used an image process method based on MATLAB to accumulate skin pore profiles from histological images that illustrate cross-sectional views of the skin treated with MNs. During this analysis, the computational domain was directly derived from histological images of MN treated skin and used for computer drug delivery simulations.Researchers have also developed a method based on MATLAB that was used to modeltrajectories and penetration

depth of the delivery of micro-particles into MN-pierced skin by gene gun. The purpose of the analysis was to perform a computerized examination. However, like those found in gene arms, MNs may decrease the skin resistance to particulate delivery in the skin.

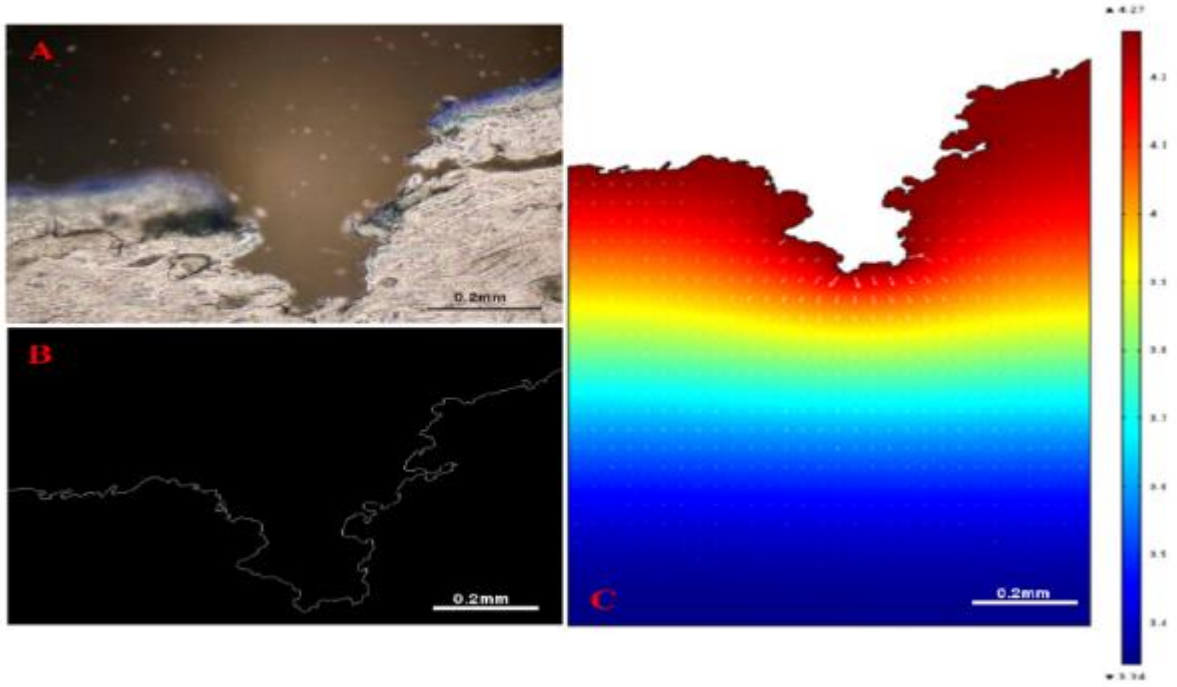


Figure 15: The histological image of sliced skin is processed by a MATLAB-based image processing tool.

(A) The original image of skin histology; (B) the outline of the skin captured by the image processing tool and (C) simulated diffusion profile of insulin in MN-pierced skin.

5.5 Optimize the effect of MN drug delivery

The technology of fabricating microneedle arrays to supply excessive molecular weight drugs throughout pores and skin in a minimally invasive way is receiving increasing attention. Microneedle arrays with different geometries weremanufacturedwith the usage ofsubstancessuch as glass, polymer, metal, etc. However, a framework that can perceive the most desirabledesigns

of these arrays appears to be lacking. This is essential due to the fact through optimizing the microneedles dimensions (e.g., the surface area of the patch, microneedle radius, etc.)(Al-Qallaf and Das 2009a). The permeability of medicine in pores and skin may be increased. Some common effects of the advanced optimization version for the enter parameters (Table 5) for each solid and hollowmicroneedles are listed in Table 5. As stated before, the method of optimization includesgrowing a way to maximize the pores and skin permeability to gain optimum microneedle design ofvariouspatterns with different geometries for solid and hollow microneedles.Therefore, the reason for those simulations is to discover each the optimum sample and distribution of the microneedles to enhance the overall performance of microneedles array. The effects supplied in Table 6 show that during the case of solid and hollow microneedles, the maximum values the optimization function (g) are about 0.081and 0.13, respectively. As mentioned below,various microneedlepatterns and their geometries (e.g., number of themicroneedles according to row, microneedle radius,etc.) had been optimized and analyzed to address their impacts in phrases of the optimization function (g), and thereby, the layout of microneedle. The outcome of the simulations lets us discovertheoptimum dimensions of microneedles via way of means ofreaching the maximum values of the optimization function (g). These optimum dimensions are then utilized in Equationtodecide the optimums pores and skin permeability. This isaccomplished via way of means ofbothvarious thecategory of pores and skin thickness in case of solid microneedles ormicroneedle length in case of hollow microneedles. Moreover, the optimum dimensions of both solid and hollow microneedles are correlated with the diffusion coefficient to be expecting numerous correlations for different microneedlesshapes and patterns(Al-Qallaf and Das 2009a).

Table 5: The input geometrical parameters used in this work for optimizing solid and hollow microneedles arrays

Parameters	Rectangular Pattern		Square/Diamond/Triangular Pattern		Scaling Parameters
	Solid	Hollow	Solid	Hollow	
N	$10^{\star} < n < 20^{\dagger}$	$4^{\ddagger} < n < 20^{\P}$	$3^{\S} < n < 10^{\|}$	$4^{\#} < n < 10^{\star\star}$	1
M	–	–	$4^{\S} < n < 20^{\|}$	$8^{\#} < n < 20^{\star\star}$	1
R	$0.0025^{\dagger\dagger} < R < 0.0075^{\star}$	$0.004^{\P} < R < 0.015^{\ddagger\ddagger}$	$0.005^{\P\P} < R < 0.01^{\S\S}$	$0.005^{\#} < R < 0.0125^{\star\star}$	0.0005
A	$0.04^{\star} < A < 0.81^{\|}$	$0.04^{\star} < A < 0.56^{\|\|}$	$0.03^{\S\S} < A < 1.6^{\#\#}$	$0.02^{\#} < A < 0.64^{\star\star}$	0.01
A	$2.7^{\star} < \alpha < 12^{\|}$	$3.1^{\P} < \alpha < 25^{\|\|}$	$3.5^{\S\S} < \alpha < 40^{\P\P}$	$3.2^{\star\star} < \alpha < 16^{\star\star}$	–
P_{tx}	–	–	$0.035^{\S\S} < P_{tx} < 0.2^{\P\P}$	$0.03^{\#} < P_{tx} < 0.04^{\star\star}$	0.001
P_{ty}	–	–	$0.035^{\S\S} < P_{ty} < 0.2^{\P\P}$	$0.03^{\#} < P_{ty} < 0.08^{\star\star}$	0.001

Table 6: The optimum parameters found using the developed framework for both solid and hollow microneedles for various patterns

Pattern	Solid microneedles				Hollow microneedles			
	Array	R	A	g	Array	R	A	g
Square	17 × 17	0.0065	0.15	0.081	15 × 15	0.0135	0.42	0.098
Diamond	16 × 16	0.0055	0.19	0.41	11 × 11	0.011	0.3	0.049
Triangular	12 × 12	0.006	0.11	0.047	9 × 9	0.0115	0.19	0.056
Rectangular	20 × 20	0.01	0.49	0.081	10 × 15	0.0125	0.18	0.130

Chapter 6

Conclusion

Microneedles are a promising, possibly powerful technology for the administration of therapeutics (e.g. vaccines or drugs) into the skin. MNs have transformed the field of transdermal drug delivery from simple skin patches to point-of-care devices. The evolution of MNs as a drug delivery technique has been exponentially rapid with two MNdevices already in the market for clinical use and a large number in clinical trials. This review comments on the biocompatibility of various materials available for MN fabrication. MN fabrication techniques have become more precise and robust with lithographic and molding as the most common choices of fabrication(Bhatnagar et al. 2019).

In the field of vaccination, microneedles extended the ability of TDD systems. Needle-freesystemscould have great effect in the third world countries in which terrible sanitation, scarce clinical sources and needle re-use cause infections or transmittable disease outbreaks. While conventional jet injectors have been utilized in mass vaccinations, the technology no longer guarantees that pathogens will not be spread since, in the third world, the costs of single-use disposable nozzles are prohibitive in the future to minimize costs through the introduction of additional cost-effective 3D printing technology. Nevertheless the future of 3D printing is predicated on some difficult circumstances and challenges that want to be overcome and invalidated in becoming a dominant development approach for TDD structures. The awful listing of acceptable biomaterials that simultaneously combine biocompatibility with various physical or chemical characteristics that could make them 3D printable (e.g. specific viscosities at a range of temperatures, photo-sensitivity) is one of the fundamental limitations. This listing is equally narrowed down within the case of dissolvable microneedles, within which the applicants areeven

fewer.In addition, the material must show excellent overall mechanical efficiency and belong-lasting enough to pierce the skin effectively without bending, cracking or failure.The restriction of the dosing quantity, which occurs in thecase of dissolvable and solid coated microneedles, is another important drawback(Lim et al. 2018a). It is also possible that the advancement of the prevailing 3D printing technologies and the implementation of new ones would improve the evolution of TDD systems.

Chapter 7

The future aspect of this study

There is a tremendous amount of research being carried out to study the influence of MN on transdermal drug delivery. There is immense potential for the use of these micron-sized needles for transdermal drug delivery enhancement. Despite thegreat successes of the MNs within thetransdermal drug and vaccine delivery, there still exist some challenges for the long-run use of MNs. One of the challenges of MNs is that though doses and delivering a rate of drug is often controlled well by MNs through some devices, and a few MNs are often used to monitor the situation of patients, most current MNs are unable to vary the delivery parameters in time upon the ever-changing condition of patients. Hence, it's urgent to develop the super-MNs within the future, that is consisted of MNs, biosensor, bioelectronics, automation, and so on, and are ready to monitor patient conditions, speedily modification the delivery parameters (such as ph, temperature, and dose) in response to the knowledge of the patient, understand the diagnostic and treatment purpose at the same time, and increase the compliance of the patient with the minimal side effects. Despite those issues, because of the distinctive properties of MNs, a lot of efficient and advanced MN systems are going to be developed for the market within the close to future. Definitely, MNs system for transdermal drug and vaccine delivery can have an excellent impact on the longer term medication(He et al. 2019)

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