RESEARCH ARTICLE

Biocompatible Polymer Microneedle for Transdermal Drug Delivery: Classification, Recent Trends, and Application

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Received: 08th February, 2022; Revised: 05th March, 2022; Accepted: 12th March, 2022; Available Online: 25th March, 2022

ABSTRACT

Microneedle plays an efficient role in delivering drugs as a modernized technique. The research on microneedle is still a challenging role as it involves various factors like design, material, drug nature, drug delivery approach, and other environmental facts. Proportional with design, testing of microneedle also involves various methods like experimental, analytical, and numerical methods. The available testing methods for predicting the microneedle behavior under compression loading are discussed. In this review, the categorization of microneedle based on the fabrication, types, geometrical shape, drug delivery approach, and material so far used is elaborated. The drive of this paper is to deliver a detailed outline of polymer materials on microneedle. It is observed that in recent years polymer microneedle can endure the applied force and avoid a catastrophe during the puncture process for delivering drugs.

Keywords: Biocompatible, Microneedle, Polycarbonate, Skin structure, Transdermal Drug Delivery.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.1.39

How to cite this article: Radhika C, Gnanavel BK, Kamesh K. Biocompatible Polymer Microneedle for Transdermal Drug Delivery: Classification, Recent Trends, and Application. International Journal of Drug Delivery Technology. 2022;12(1):208-216.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Over the past decade, the conventional hypodermic syringe is being replaced with the microneedle to overcome the pain and injuries caused by the injection. The conventional hypodermic syringe is used for transporting the precise amount of the medicine from the syringe into human skin. During transportation, the hypodermic needle passes through different layers of human membrane consisting the Epidermis, Dermis, and Hypodermis. Such penetration when passes through beyond the dermis layer the nerve receptors get damaged causing severe pain. Considering the drawbacks of conventional hypodermic needles, microneedles are being developed for painless injection. The microneedles which are micron in size are designed, to travel up to the dermis layer thereby the needle doesn't damage the nerve receptor. This results in a painless injection. Thus designing a pain-free, nontoxic microneedle involves a challenging process to date.

CLASSIFICATION OF MICRONEEDLES

The microneedles are classified into different types. The microneedle types, fabrication methods, and their use in current technology is discussed.[1-4] The basic characteristics of the microneedle, the inserting behavior, and pain induced during the insertion of the microneedle is clarified.[5] In general, the classification of microneedles is based on the following process i) fabrication process, ii) types, iii) geometrical shape, iv) drug delivery approach, and v) materials.

Fabrication Process

The microneedles are fabricated as In-plane microneedle[6] and Out-of-plane microneedle as shown in Figure 1. In the in-plane microneedle, the needles are located equivalent to the base surface. The existence of a minor volume of microchannels permits the drug to permit through the membrane with a small distribution amount. In-plane silicon microneedle integrated with a poly dimethyl siloxane (PDMS) microfluid chip is fabricated for automatic protection. The design and dimension criteria required for fabricating the in-plane micro-needles is discussed.[7] The hollow in-plane microneedles is fabricated using Investment molding.[8] The in-plane microneedle with multiple recording sites is fabricated to record the neural signals.[9,10] The Invasive hollow in-plane microneedle is developed and fabricated using microfabrication technology.[11] The Out-of-plane microneedles has an increase in distribution rate as the needles are designed vertical to the surface. The Out-of-plane microneedles with hollow structure is fabricated for painless epidermal medicine distribution.[12]

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An array of hollow out-of-plane microneedle is fabricated using a micromachining technique.[13] A new fabrication procedure is done for procurement of out-of-plane microneedle designed for mass manufacture.[14]

Microneedle Types

The microneedles are classified based on the kinds as solid, coated, hollow, and dissolving microneedle as shown in Figure 2.

Solid Microneedle

Solid microneedles[15] is built as a complete single structure and is commonly designed for skin diagnosis. The process takes place with slow diffusion as inserting the needles into the membrane creates micropores continued by applying drug solution into the pores. A solid silicon microneedle array of 400 microneedles is fabricated with an area of 3X3 mm using microfabrication technology.[16] The super-short solid microneedle arrays (8X8, 10X10, and 12X12) is fabricated consisting of length 70–80 µm. The super-short microneedles are a harmless and effective technique for drug delivery.[17]

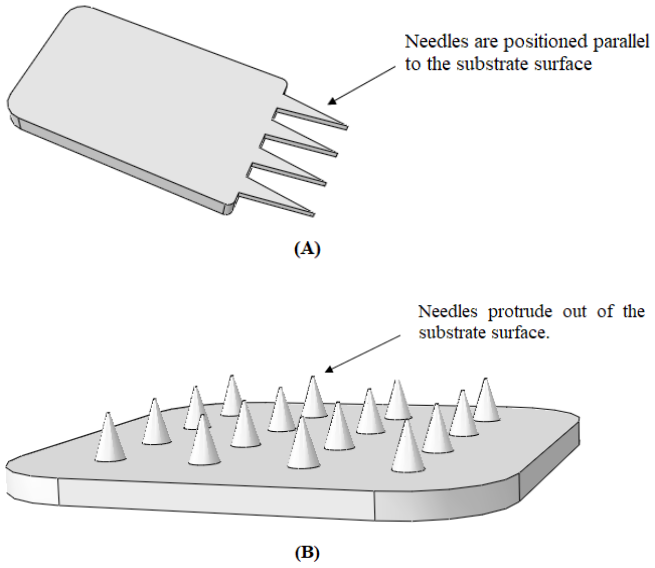

Figure 1: Microneedle based on the fabrication method A) In-plane microneedle and B) Out-of-plane microneedle.

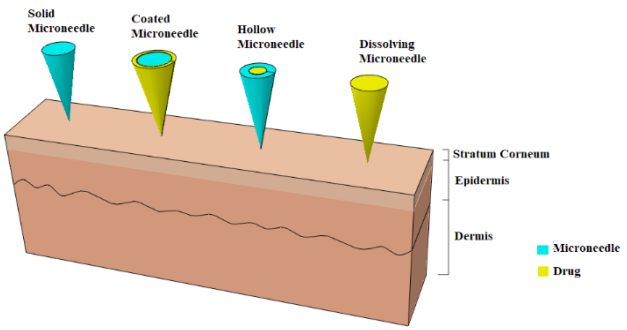

Figure 2: Schematic representation of various types (solid, coated, hollow, and dissolving) of microneedles.

Coated Microneedle

The coated microneedle is attained through covering the solid microneedles by means of a drug solution. When microneedle is injected into the membrane, the medicine resolution coated on the microneedle outer surface liquifies itself and settles beneath the skin.[18] A novel method for developing coated microneedle array is done using biocompatible polymers hydroxypropylmethylcellulose (HPMC) and carboxymethylcellulose (CMC) coating solution.[19] Coating of solid dispersions on microneedles is done using molten dip-coating solutions of water-insoluble drugs.[20] The solid microneedle is coated using the Piezoelectric inkjet coating technique.[21] The solid microneedle is coated with DNA vaccines for the vaccination of Alzheimer's disease.[22]

Hollow Microneedle

Hollow microneedles is designed with a hollow path created in the microneedle to store and deliver the drug into the membrane.[23-27] The first hollow out of plane microneedle with a side opening is presented.[28,29] A new fabrication method for developing hollow silicon dioxide (SiO_2) microneedle is discussed.[30] Besides having a single through-hole, microneedles with pores evolved for quick drawing of body liquid. The porous microneedles consist of numerous pores mainly designed for extracting body fluid by capillary action. The possibilities and constraints for developing porous microneedle technologies is discussed.[31] A new type of porous titanium (Ti) microneedles is fabricated grouping the mechanical cutting and wet etching process.[32] Later [33] fabricated the same material using a metal injection molding process. A porous microneedle array is fabricated by integrating the microneedle with a microfluidic system for interstitial fluid (ISF) collection.[34]

Dissolving Microneedle

The dissolving microneedle is self-dissolvable[35-37] is fabricated for delivering protein thereby withstanding the mechanical strength when inserted into the membrane.[38] The fast-dissolving fibroin microneedles is fabricated and described for the first time.[39] A dissolving microneedle array is developed consisting of 81 microneedles (9X9).[40] The dissolving microneedle is fabricated using hyaluronic acid to progress the transdermal distribution of medicines.[41,42]. For separation of dissolving microneedles into the skin[43] developed a method where the microneedle tips are encapsulated with hydrogel microparticles. The hydrogel microparticles when in contact with the body fluid, swells resulting in microneedle separation.

Drug Delivery Approach

The microneedles is classified consideration the drug distribution approach as 'poke with patch approach', 'coat and poke approach', 'poke and flow', and 'poke and release' as shown in Figure 3. The methods for delivering drug is classified and discussed.[44-46] The solid microneedles in flat, planar, and roller forms are introduced for cosmetic applications. This helps in treating scars, stretch marks, wrinkles, laxity in the skin, and for facial rejuvenation.[47-49] The 'poke with patch' approach, the solid microneedles is punctured into the

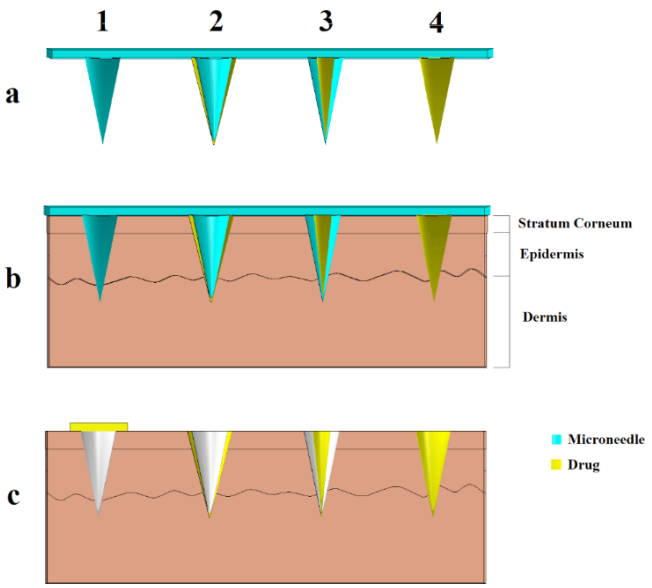

Figure 3: Representation of drug delivery approach of various types (Solid, coated, Hollow, and Dissolving) of microneedles (1) 'Poke with Patch' (2) 'Coat and poke' (3) 'Poke and flow' (4) 'Poke and release' and a) b) and c) represents Microneedles before, during and after insertion.

membrane surface forming micro holes. Then the microneedle is detached and the drug is applied on the membrane in the form of a ointment. In the 'coat and poke' method, the solid microneedles is glazed with the dissolvable drug solution. During insertion, the coated drug dissolves into the skin. This leads the microneedles to get detached from the drug solution and the microneedles are pulled off.[50] The 'poke and flow' method is attained via hollow microneedles. The hollow microneedles are inserted inside the membrane comparable to the poke with patch method. With the small bid of force, the medicine stored in the patch is released into the skin.[51] The 'poke and release' method is attained by means of dissolvable microneedles. The microneedles are made using biocompatible drugs. The dissolving microneedles is inserted inside the skin membrane and set free. After insertion, the microneedles self dissolves into the skin.

Geometrical Shape

The basic shape of microneedles includes cylindrical, conical, tapered, and pyramidal-shaped microneedles.[52] It is observed that the circular-shaped microneedles can withstand more amount of force than rectangular or square microneedles.[53] Using 3D printing technology microneedles can be manufactured in a varied choice of shapes. The classification of different shapes of the microneedle is listed in Table 1. The microneedle tips are available in plenty of shapes like cylindrical, triangular, pointed, pentagonal, and octagonal.[13,54,55] The super-short sharp tip and flat tip microneedles is designed and developed.[17] Microneedles with sharp tips are suitable for easy insertion to attain anticipated penetration.[56] Beveled tip microneedles are used for easy penetration and removal of the microneedles.[57,58] The in-plane

Table I: Classification of microneedles based on the geometrical shapes.

Geometrical shape	*References*
Cylinder	60, 61, 62
Cone	63, 64, 61, 65, 66, 67, 68
Pyramid	Square - 69, 67, 70, 52, 71
	Triangular - 72, 73
	Octahedral- 74
Tapered	75, 76, 77,78, 60
Spear	52, 15
Spherical pedestal	79
Candle-like	15, 80
Bullet-shaped	81, 82, 83
Spike	28, 84, 15
Lancet	61

Table 2: Classification of microneedles based on the tip shapes.

Tip shape	*References*
Circular	13
Pyramid	85, 86
Beveled	87, 58, 88, 89
Isosceles triangle	6
Knife-life edge	90
Pen pointed	91
Arrow-head	55
Snake fang, Volcano, micro-hypodermic	59

microneedle is fabricated with a tip shape consisting of an isosceles triangle.[6] The complex tip shape of volcano-like, a micro-hypodermic, and snake-fang design microneedle is discussed.[59] Based on the tip shape, the microneedles classification is listed as in Table 2.

Materials

Based on the materials, microneedles is made-up with silicon, metal, glass, composite, and polymer.[26,92]

Silicon

The procedure involved in fabricating silicon microneedle[16,29,91,93-95] via numerous fabrication process is conferred.[96,97] The microfabrication process to fabricate the silicon microneedle patch is discussed.[69] A novel ultrasharp silicon microneedle array is fabricated for biopotential monitoring.[98] The silicon microneedle arrays is developed using a low-cost hybrid etching technique for transdermal drug delivery.[74] The Silicon microneedle might easily break due to its brittle nature.

Metal

Metal microneedles possess good mechanical strength. The microneedles fabricated of metal materials include stainless steel, titanium, nickel, palladium, and palladium-cobalt arrays.[99-102] fabricated metal microneedles. The microneedle fabricated using Titanium materials possesses good resistance and bio-compactable.[32,33,103,104] The fabrication process of stainless-steel solid microneedles by electrochemical etching

and cutting technique is accessible.[105] Metals are convenient for the fabrication of microneedles than silicon material for their toughness.

Glass and Other Materials

An inexpensive device (needle puller) for pulling Glass Microneedles is developed.[106] The hollow glass microneedle is fabricated using micropipette puller.[107-111] The biocompatible pure titanium and titanium alloy microneedle is fabricated using the sputtering deposition method.[112] The microneedles is fabricated and developed using ceramic materials.[23,113-115] Hydrogels are formed with a three-dimensional (3D) network of polymer chains. The Hydrogel microneedles are fabricated in a wide range.[64,116-118] The fabrication process of sugar microneedles is discussed.[63,119,120]

Polymer

Polymers are widely used profitable materials in manufacturing applications. The choice of the suitable polymer material is based on principles like the type of disease, immune response, and route of administration.[121,122] The potential of biodegradable material, including synthetic and natural polymers for vaccine delivery is summarized.[123] The recent advancements in the synthesis of a variety of polymers is discussed.[124-130] The fabrication process of various types of polymer microneedles is elaborated.[124,125] The biodegradable polymer microneedles is fabricated using microfabrication techniques.[131] This polymer microneedle is used for delivering Tranexamic acid (TXA) treating patients for the whitening problem. The chitosan solid and hollow microneedles is fabricated using Cross-Over Lines (COL) laser engraving method.[132]

TESTING METHODS

To predict the needle behavior and skin response different testing methods are carried out using the physical test, experimental test, numerical simulation, analytical approach. The insertion of microneedles is tested on humans or animals in either *in-vivo* or *in-vitro* methods. Most physical tests are conducted on various models like the mouse, rat, guinea pig, rabbit, pig, macaque, and human volunteers.[133] A preliminary test was done in human subjects and confirmed that the microneedle could penetrate the skin without causing pain.[16] inserted the solid microneedles on human forearm skin which resulted in a painless insertion with no redness or swelling. The behavior of the hollow microneedle is tried on potatoes extracting the juice by capillary forces. The same test was then repeated on the human skin withdrawing blood without damaging the needle in a painless puncture.[134] Some researchers[115] evaluated the delivery of compounds in an eggplant and *ex vivo* human skin. Human volunteers successfully self-applied microneedle patches into their skin.[135]

The simulation to predict the mechanical behavior of microneedle is achieved.[7] The finite element analysis using ANSYS software is done to predict the von Mises stress.[136] The finite element analysis (FEA) using ANSYS 8.0 is performed to examine the effect of buckling and shear stress on the microneedle.[137] The FEA analysis is performed to forecast the bending performance and tensile stress distribution.[13,110,138] A nonlinear finite element technique to analyze and evaluate microneedle insertion force is formed.[139] The numerical simulation is done to estimate stress and buckling load.[140-142] The critical buckling load for CMC/MAL was 15N which is comparatively higher than the CMC/TRD CMC/SUC microneedle. The microneedle penetration using finite element analysis is accomplished for various geometries.[143] The simulations is executed using software to predict the structural behavior of microneedle and flow characteristics.[144,145]

APPLICATION

Various aids of microneedles like ailment handling, oligonucleotide delivery, immunobiological supervision, ailment analysis, and cosmetic field is discussed.[146] The design and benefits of microneedle technique is been permitted and in research is provided in detail.[147] The challenges and the potential of manufacturing and fabricating biomaterials is discussed.[148] The candle-like microneedle array is fabricated for ECG measurement on the hairy scalp.[149] A single-use nominally invasive self-calibrating glucose monitor of microneedles consisting hollow structure is developed.[150] The usage of a microneedle array intended for incessant monitoring the glucose level is deliberated.[151,152] The development of a glucose sensor for microneedle measuring the intradermal glucose sensing is conferred.[153] Some researchers[154] fabricated PLGA porous microneedle array for blood glucose monitoring.

RECENT RESEARCH

To promote research in the area[155] discussed the recent advances in the development of microneedles**.** It has been discussed[156] about the recent technical advances in wearable micro/nanodevices with unique capabilities or potential for single-cell sensing and transfection.[157] summarized the advance of microneedles including their materials and latest fabrication method, such as 3D printing. A fabricated array of gold microneedles (AuMNs) via the casting of conductive gold ink is used for urea sensing.[71] Some researchers[67] fabricated polymeric microneedle using 3D printing stereolithography technique for the transdermal delivery of insulin,[158] discussed the basic principles, printing mechanism, and most relevant polymer additive manufacturing (AM) technologies. For rapid administration of multiple therapeutic agents[72] used a multiplexed drug delivery actuator to release fluid in a controlled and switchable fashion.

CONCLUSION AND FUTURE WORK

Microneedles are available in plenty of shapes, sizes, and materials. Designing appropriate microneedles involves a challenging process. The insertion of microneedle into human skin without pain and needle fracture leads to a suitable design. Overall this review summarizes the potential usage of polymer materials in microneedle. The Classification of microneedle based on the fabrication process, types, geometrical shape, drug delivery approach, and material so far used is discussed.

The Schematic illustration defining the types of microneedle and drug delivery method is represented. The focus on biocompatible polymer materials in microneedle is given priority for its achievements in producing safe insertion without casuing serious issue. The testing process for predicting the microneedle behavior and skin response is discussed in detail. In this paper, a detailed study of the biocompatible polymer-based microneedle is performed. This study is used for the plan and advancement of microneedle for medicine distribution.

ACKNOWLEDGMENT

The authors would like to thank our institution Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences, SIMATS for their continuous support and valuable guidance.

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