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Drug Delivery Through Microneedles for Improved Permeability and Efficacy: Fabrication, Methodology and Applications

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Abstract

Microneedles are categorized into solid, coating, dissolving, and hydrogel formulations, featuring materials such as silicon, metal, polymer, glass, and ceramic. Diverse manufacturing techniques are employed to impart distinct shapes, sizes, and properties. Ongoing clinical trials demonstrate the evolving nature of microneedles, incorporating a variety of drugs with consistently positive outcomes. The field of microneedles in transdermal drug delivery is rapidly expanding, promising improved patient access to medications by supplanting traditional administration methods. This innovative approach holds great promise for delivering therapeutic effects across a range of fields. This innovative technology exhibits remarkable flexibility, capable of administering several hundred milligrams of proteins directly into the systemic circulation. Researchers are exploring the combination of methods, for transdermal drug delivery and to enhance drug permeability further. Consequently, microneedles can be designed with various modifications to intelligently facilitate drug delivery through the skin, representing a ground breaking advancement in the realm of transdermal drug delivery systems. This review provides current approach, challenges and trend in microneedle applicability and fabrication.

Keywords: Drug delivery; Microneedles; Polymers; Absorption rate; Fabrication.
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1. Introduction

Traditional drug and vaccine delivery methods, including hypodermal injections, oral medications, topical creams, and sublingual approaches, are associated with numerous undesirable effects.[1-4] Hypodermal injections carry risks such as needle injuries, infectious diseases, and STDs. Administering drugs through hypodermal injections requires specialized skills, limiting self-administration by patients and necessitating the involvement of trained professionals like nurses or doctors. These injections can also cause pain, touch nerve endings, and induce anxiety, making administration challenging for non-cooperative patients.[1-2]

While oral drugs are easy to administer, they have their drawbacks. Variations in pH across different body parts may destabilize the drug. Enzyme activity and metabolism can also lead to drug destabilization in cellular environment.[3] The low availability is due to diffusion rate, slow drug metabolism, absorption rate.[4] Sublingual administration is influenced by external factors such as drug solubility in salivary secretion, diet, and the consumption of alcohol or smoking, affecting drug absorption.[5,6]

This review addresses the purpose of using microneedles to administer various substances, including peptides (insulin), genetic materials (oligonucleotides, plasmid DNA), and different types of vaccines (viral, bacterial, and DNA). Microneedles offer potential solutions to the challenges posed by traditional methods of drug and vaccine and vaccine administration, including hypodermal injections, oral delivery, topical applications, and sublingual approaches.

The primary goal of transdermal drug delivery is to achieve controlled drug release into the systemic circulation at a

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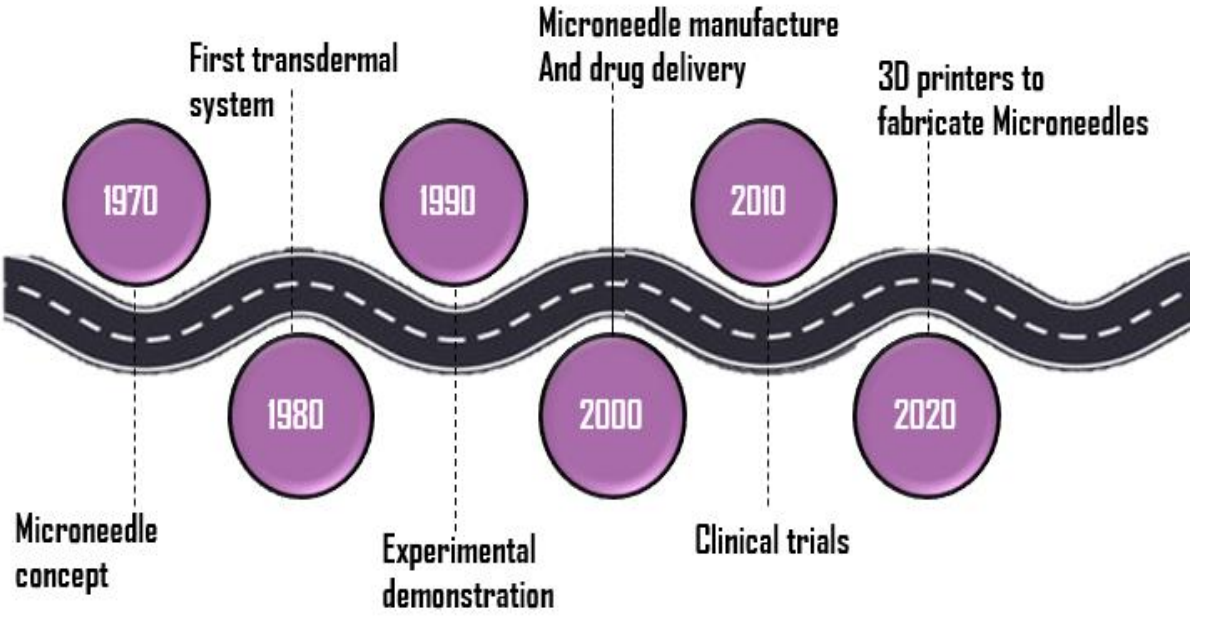

Fig. 1 History of microneedles.

predetermined rate.[7] Microneedles (Fig 1) facilitate drug penetration through the skin's layers, allowing for systemic circulation.[8] Additionally, microneedles have found applications in ocular drug delivery to the eye.[9] While the recent use of microneedles has demonstrated several advantages over existing drug delivery systems, some drawbacks have been identified. Nevertheless, the benefits of microneedles outweigh the drawbacks. Fabrication techniques for microneedles include lithography, casting, and molding, allowing for the creation of microneedles in various sizes, shapes, and densities based on the material properties.[1,10-12]

2. Transdermal drug delivery

The diagram (Fig. 2) above illustrates different modes of drug delivery through the skin. Topical creams and transdermal patches deliver drug molecules to the surface of the skin, specifically the stratum corneum. However, this method imposes limitations on the size of molecules that can be effectively delivered. Additionally, drug molecules must traverse the stratum corneum, affecting their bioavailability due to factors like pore size (ranging from 15 to 25 angstroms) and molecular polarity.[4] Another drawback is the extended onset time of the drug,[1] as delivery at the surface results in a longer diffusion time to reach systemic circulation compared to hypodermal injections or microneedles. Hypodermal injections, depicted in the image above, are a widely employed method for delivering various biological molecules. However, the needle's penetration beyond the pain receptor, as illustrated, results in a painful experience for the patient.[12] This frequently induces a fear of injections among patients, leading to suboptimal cooperation. Now, let's delve into the factors that advocate for the use of microneedles, aiming for a more effective and patient-friendly drug delivery process.

2.1 Microneedles

Microneedles, combining aspects of transdermal patches and hypodermal needles, are engineered to facilitate the entry of hydrophilic and large molecules through the skin. These microneedles aid the smooth passage of drugs through various skin layers—initially the stratum corneum, followed by the epidermis and, ultimately, the dermis.[8] The stratum corneum, selectively permeable, typically hinders the entry of hydrophilic molecules and those larger than 500 Daltons or 1 micrometer in diameter.[11,12,41] By creating disruptions in the skin, microneedles overcome these barriers, establishing pathways for the delivery of molecules to the dermis without accumulation in any dermal layers (Fig. 3). The transdermal drug delivery achieved through microneedles is designed to be minimally invasive, ensuring that the needles do not come into contact with nerve endings. Consequently, patients experience little to no pain during drug administration.[1,12]

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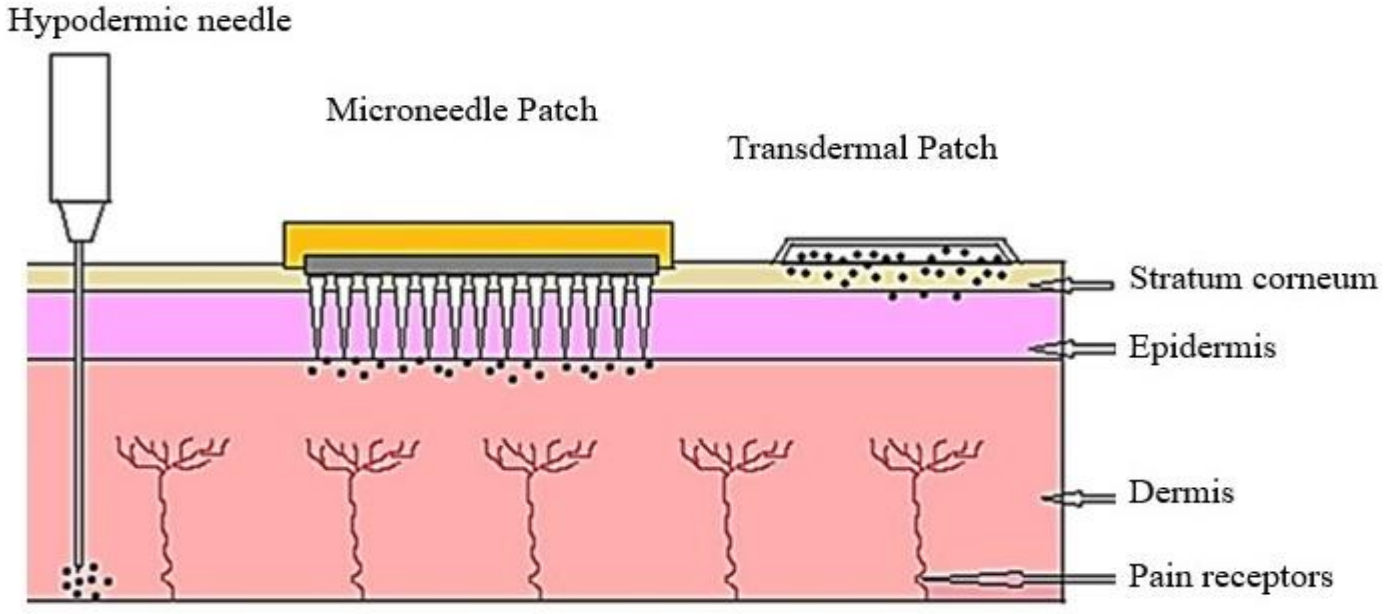

Fig. 2 Comparison of hypodermic needle, microneedle patch and transdermal patch. Reproduced with the permission form [1], Copyright 2018 Elsevier Masson SAS.

Microneedle patches deliver drugs directly to the dermis, eliminating concerns about loss in bioavailability due to diffusion. Importantly, the microneedles do not penetrate deep enough to reach pain receptors, rendering the process virtually pain-free. Studies, such as the one conducted by Gill *et al.*, have confirmed that microneedles cause significantly less pain compared to a twenty-six-gauge hypodermic needle.[13] The dimensions of microneedles can vary, typically ranging from 150 to 1500 micrometers in length, 50 to 250 micrometers in width, and 1 to 25 micrometers in thickness.[14,15]

2.2 Important aspects of microneedle

Two crucial aspects of microneedles that significantly impact drug delivery are the tip geometry and the overall structure of the microneedle. Microneedles can feature a variety of tip geometries, including cylindrical, triangular, pointed,

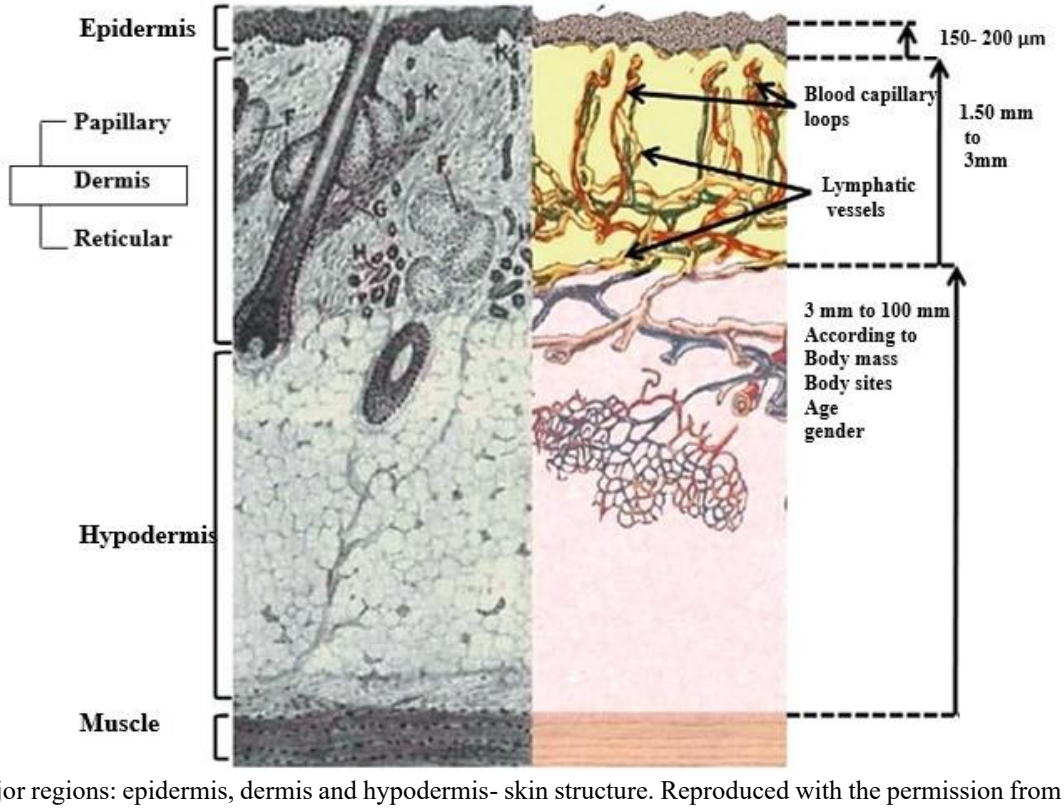

Fig. 3 Three major regions: epidermis, dermis and hypodermis- skin structure. Reproduced with the permission from [12], Copyright 2011 The Authors & Royal Pharmaceutical Society.

pentagonal, and octagonal shapes. These tip geometries play a crucial role in determining the penetration of the microneedle into the skin.[16] There are several types of microneedles based on their structure and functionality:

A. Solid microneedles: Primarily used for piercing the skin to create a pathway, after which a transdermal patch with the drug is applied. This method is known as the poke and patch technique, enhancing drug permeability.[17,18]

B. Coated microneedles: These microneedles are dipped into the desired drug just before administration to the patient. Coated microneedles facilitate the rapid dissolution of the coated drug.[17,19]

C. Dissolving microneedles: Typically used for the delivery of oligonucleotides or similar molecules, these needles are fabricated using polymers and sugars containing the active material (drug molecule). Dissolving microneedles allow for controlled drug delivery.[17,20]

D. Hollow microneedles: Fabricated to load the desired drug into the needle, which enters the dermis once the needle pierces through the skin. This method is also referred to as the poke and flow technique. [17,21]

E. Hydrogel microneedles: Cross-linked polymer microneedles without the drug are placed on a baseplate with a drug reservoir. Upon entering the skin, the polymer microneedles rapidly absorb interstitial fluids, causing the diffusion of the desired drug from the reservoir in the baseplate.[17]

2.3 Fabrication of microneedles

Microneedles are produced with meticulous precision through microfabrication techniques (Table 1), with casting and molding, along with lithography, emerging as commonly employed methods:

2.4 Casting and moulding

This method is versatile and applicable to the fabrication of various microneedle types. It is highly efficient, supporting mass production, and cost-effective due to the reusability of moulds. The process generates minimal bio-waste, contributing to its environmental friendliness. Resins are utilized to create moulds for microneedle preparation. Moulds can be manually crafted by making multiple piercings of desired dimensions in resin. Microneedle characterization is ensured using an electron microscope. This technique is commonly employed for producing biodegradable microneedles using polymers or carbohydrates. A slurry of the drug and desired material is poured into the mould, allowed to solidify, and then the mould is removed to obtain the microneedles. [22,23]

2.4.1 Lithography

Lithography, originally a printing process based on the immiscibility of oil and water,[24] has evolved to produce three-dimensional products like microneedles.

2.4.2 Drawing Lithography

This technique utilizes the planar geometry of a two-dimensional substrate, such as a thermosetting polymer, to create a three-dimensional microstructure.[25] The frame comes into contact with the substrate, initiating microneedle mould fabrication. After solidification, the mould is separated.

Table 1. Microneedle materials and fabrication methods. Reproduced with the permission from [18].

Fabrication method	Material used for fabrication	Type of MN	Geometry
3D microlens mask Lithography	Glass	Solid	Pyramidal
Deep Ion reactive etching, wet or dry etching	Silicon	Solid, Hollow	Conical, Bevel
Laser ablation, etching, and micromolding	Polyhydroxyalkanoate, PMMA	Solid, Hollow	Conical
Sacrificial Micromolding and Selective Electrodeposition	PLA mold, Metal	Hollow	Conical, Pyramidal
Photolithography	PEGDA	Solid, Hollow, Dissolving	Cylindrical, conic, Pyramid
3D Printing (microstereolithography, Two-photon polymerization)	PEGDA, PVP, PEGDMA, PLA	Hollow, Solid, Coated	Square Pyramidal, Conical
Atomized spraying process	Polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate	Dissolvable, Hydrogel	Pyramidal
Pulling pipette	Glass	Solid, Hollow	Conical
Soft Lithography	Polycarbonate MN master mold, thermoplastic polyurethane (TPU), PDMS Solid, H	Solid, Hollow	Square Pyramid

2.4.3 Photo Lithography

Photolithography is a microfabrication technique that utilizes UV radiation to selectively define geometrical patterns on the substrate. In the case of a polymer substrate, the cross-linking process is facilitated by photocatalysts. By adjusting the position of the substrate, diverse shapes and sizes can be achieved, providing versatility in microneedle design.[26] Photolithography plays a crucial role in microneedle fabrication, ensuring precise control over pattern formation and allowing for the customization of microneedle shapes and sizes. Microneedles can be fabricated from various materials, and some of them are highlighted below:

2.4.4 Silicon

Biocompatibility*:* Silicon exhibits high biocompatibility, making it suitable for microneedle fabrication.

Mechanical Strength*:* Silicon possesses significant mechanical strength, enabling effective skin penetration.

Elasticity: The elastic properties of silicon allow for the fabrication of microneedles in diverse shapes, sizes, heights, and densities.[17,27,28]

2.4.5 Metals

Biocompatibility and Strength: Metals, such as stainless steel, titanium, palladium, palladium-cobalt alloys, and nickel, offer excellent biocompatibility and mechanical strength, making them suitable for microneedle construction.[17]

2.4.6 Ceramic

Ceramic, commonly sourced from materials like Alumina, can be produced using various methods. The process of pouring Alumina into a micro mould for microneedle production is cost-effective and scalable.[17,28]

2.4.7 Polymers

Polymers are widely preferred for their high biocompatibility, biodegradability, strength, low toxicity, and cost-effectiveness (Fig. 4). Some frequently utilized polymers include Poly methyl methylacrylate (PMMA), Polylactic acid (PLA), Polylactic-co-glycolic acid (PLGA), Poly glycolic acid (PGA), polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), cyclic-olefin copolymer, polycarbonate, and polystyrene (PS).[17]

2.4.8 Carbohydrates

Microneedles based on carbohydrates are typically fabricated by pouring a carbohydrate slurry mixed with the drug into a metal or silicon mould. These microneedles dissolve upon entering the skin, releasing their payload. Maltose is a frequently employed carbohydrate in this context. Carbohydrate-based microneedles are considered safe for human administration, and their fabrication is relatively inexpensive. The length of these microneedles varies from 150 micrometres to 2 millimetres.[17,30]

2.4.9 Encapsulation

The drug can be incorporated into microneedles in either a suspended or dispersed form, or in an encapsulated form using carriers such as liposomes, nanoparticles, or nanoliposomes.[18] Application methods include coating the drug with a polymer solution onto the microneedles or applying it as a patch. Physicochemical characterizations, including assessments of particle size, polydispersity index,viscosity, and zeta potential, are crucial and depend on the specific formulation employed in the microneedles.[1,18] Incorporating immiscible agents into a single heterogeneous vehicle, such as employing liposomes poses challenges due to the need for intricate formulations and issues related to loading efficiency and stability of these vehicles.

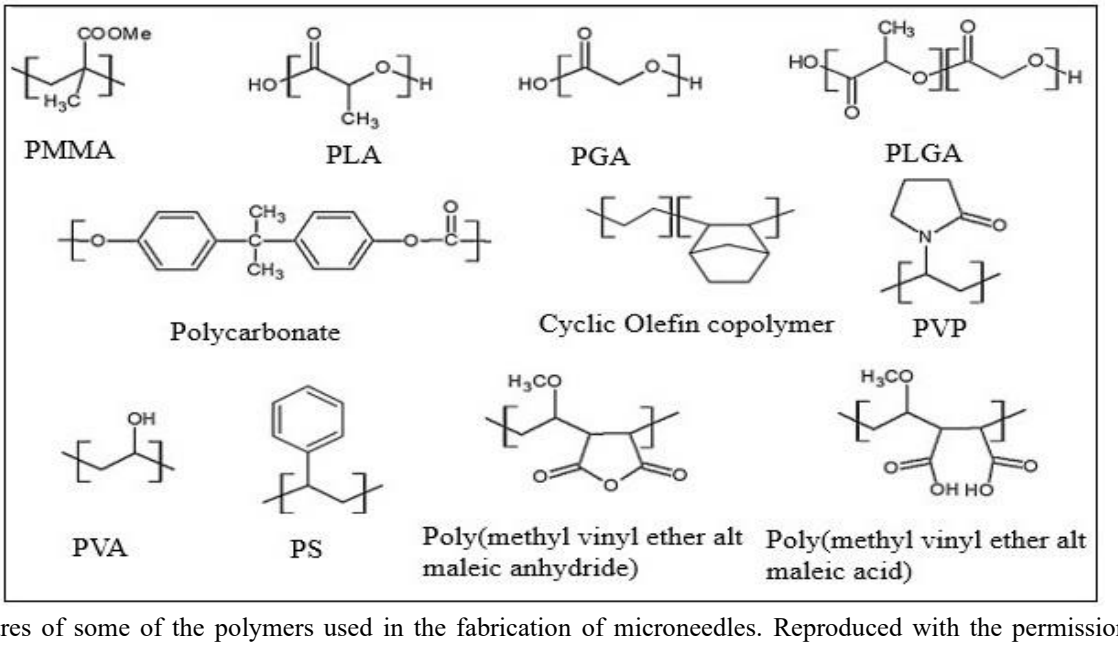

Fig. 4 Structures of some of the polymers used in the fabrication of microneedles. Reproduced with the permission from [17],

3. Applications of microneedles

3.1 Peptide delivery

3.1.1 Insulin delivery

Solid Microneedles: An array of 105 solid microneedles, laser-cut from stainless steel with a base width of 50 by 200 micrometres along a length of 1000 micrometres and tips angled at 20 degrees, demonstrated increased skin permeability to insulin when administered to diabetic rats. This led to a rapid and steady reduction in blood glucose levels.[31]

Hollow Microneedles*:* Transdermal administration of insulin to type 1 diabetes patients using hollow microneedles showed increased onset and offset times compared to subcutaneous administration. Significantly, the pain during administration was lower with the hollow microneedle.[32]

3.2 Cancer immunotherapy

Biodegradable Microneedle Patch: A biodegradable microneedle patch delivering hyaluronate-antigenic peptide (cytotoxic T-cell epitope) as a prophylactic cancer immunotherapy demonstrated significant inhibition of tumour growth in a B16 melanoma model in mice.[33]

3.3 Hormone delivery

3.3.1 Parathyroid hormones

Coated microneedles for parathyroid hormone delivery showed shorter tmax and t1/2 compared to commercially available treatment. Increased spine bone density was observed with very little variability, and there was an additional increase in hip bone density not seen with the commercial treatment.[34]

3.3.2 Human growth hormone (HGH) - titanium solid microneedles

Titanium solid microneedles delivering human growth hormone demonstrated biocompatibility comparable to conventional subcutaneous injections, with no skin irritabilities, indicating that microneedle patches are more user-friendly.[35]

3.3.3 HGH - dissolving microneedles

Human growth hormone delivered using dissolving microneedles showed pharmacokinetics comparable to conventional hormone delivery methods (Table 2). Upon patch removal, the microneedles were almost completely dissolved.[36] Microneedles offer a promising avenue for self-administering hormones with minimal side effects and the generation of biohazardous waste.

3.4 Oligonucleotide delivery

Oligonucleotides, with the potential to cure various diseases, are traditionally delivered through invasive methods like intravitreal injections.[37] Transdermal delivery of oligodeoxynucleotides using solid microneedles made from stainless steel or titanium has shown faster absorption compared to intact skin approaches.[38]

3.5 Plasmid delivery

Gene Therapy: Plasmid DNA is commonly used in gene therapy for treating genetic disorders, posing a challenge for transdermal delivery due to the stratum corneum acting as a barrier.[39]

Solid Microneedles*:* Delivery of macromolecules like beta-galactosidase and charged fluorescent molecules to the epidermis of skin treated with solid microneedles has been observed using fluorescent microscopy. This suggests that plasmid DNA may be transdermally delivered using microneedles, supported by preliminary gene expression studies.[39]

Coated Microneedles: Plasmid DNA can also be delivered using coated microneedles. Factors such as the amount of DNA loaded, the rate of dissolution at the application site, and proper administration to create similar punctures are critical for the rate of gene expression.[40,41]

3.6 Vaccine delivery

Background: The skin, being the largest organ and easily accessible, accounts for one-third of the body's blood circulation, making it an ideal site for vaccination.[42]

3.7 Viral vaccines

3.7.1 Live attenuated vaccines

These vaccines use live viruses with reduced viral properties or debilitated pathogenicity factors. When administered, they induce an immune response that is remembered by memory cells, allowing rapid multiplication in response to the

Table 2. Exploring the differences among drug delivery methods, such as topical creams, transdermal patches, hypodermic needles, and microneedles.

Administration	Onset of action	Pain	Bioavailability	Self-administration	Mechanism
Topical cream	Slow	Painless	Poor	Possible	Through pores on the skin
Transdermal	Slow	Painless	Insufficient	Possible	Poor diffusion of large molecules through the stratum corneum
Hypodermic	Fast	Painful	Sufficient	Not Possible	Drugs placed directly in the dermis
Microneedle	Fast	Painless	Sufficient	Possible	Enhanced permeability due to direct placement of drug into epidermis or dermis

pathogenic virus. However, they may pose a risk for infectious states in individuals with weakened immunity (Table 3). Storage conditions for live attenuated vaccines are critical, requiring temperatures below 8 °C.[43]

Microneedle Patch Development: Microneedle patches have been created for measles and rubella (Table 4). In Rhesus macaques, measles neutralizing antibodies were observed in 100% of the sample population, compared to 75% in the subcutaneously treated group. Rubella neutralizing antibody titres were higher than 10 IU/mL in both groups.[44] Trials for other live attenuated vaccines, including zoster and Flavivirus, have also been conducted.[43]

Table 3. Types of vaccines.

Type of Vaccine	Examples
Live attenuated	Measles and Rubella
	Flavivirus
	Zoster
Inactivated	Influenza- H1N1, H3N2
	Polio
	Retrovirus
	Rabies
subunit	Zika
	Influenza-H1N1
Virus like particle	Influenza-H1N1, H3N2, H5N1

3.7.2 Inactivated virus

In this type of vaccine, viruses are cultivated in specific cell lines, tissues, or embryonic cells. These cultures are then inactivated using chemicals like formalin or physical methods such as pH alteration, heat, or irradiation with UV or electron beams. Although they exhibit lower immunogenicity compared to live attenuated virus vaccines, inactivated virus vaccines are safer as the viruses cannot revert to their virulent form, making them suitable for disease eradication processes.[43,45] The influenza virus vaccine, when delivered to mice using coated microneedle patches (5 needles with 10 micrograms of the vaccine), demonstrated complete delivery within minutes, eliciting strong antibody responses.[46] Microneedles have also been employed for delivering vaccines against polio, rotavirus, rabies, H1N1, H3N2, hepatitis A, *etc*.[43,45]

3.7.2 Subunit vaccines

Subunit vaccines involve extracting the antigenic part of a virus and injecting it into the body to induce an immune response. Alternatively, the gene encoding the antigen can be inserted into bacteria, and the produced antigen can be purified and administered as a vaccine. This method is safe with no risk of infection. Administration of a recombinant Zika virus vaccine using dissolvable microneedles in mice resulted in significant antibody levels four weeks after immunization. Offspring born to immunized mice also exhibited partial resistance to the infection. Subunit vaccines for Influenza H1N1 have been tested, showing positive H1N1 antibody results.[43]

3.7.3 Virus-Like particles

Virus-like particles (VLPs) represent a stable form of viral vaccines, making them highly suitable for vaccine delivery. These particles structurally resemble actual viruses but lack the genetic material, rendering them non-virulent. However, they still induce an immune response similar to actual viral particles. Microneedle testing of Influenza H1N1, H3N2, H5N1 VLP vaccines showed no adverse side effects in healthy volunteers.[43]

3.7.4 DNA vaccines

DNA vaccines involve administering weakened infectious components of a virus to elicit an immune response without causing the actual infection.[47] These vaccines consist of antigen-coded plasmid vectors containing the gene of interest. DNA vaccines are more thermostable than viral or bacterial vaccines, easier to produce at a large scale, cost-effective, and safe, as they cannot revert to virulent forms. Dissolving microneedles have been employed to test EBOLA DNA and rabies DNA vaccines. Solid microneedles have also delivered penetrating peptides targeting dendritic cells and facilitating gene transformation to prevent malignant melanoma.[43,45]

3.7.5 Bacterial vaccine

Bacterial vaccines, categorized as toxoids, subunit vaccines, killed whole cell vaccines, and live attenuated vaccines, are being tested using microneedle patches. Trials include a tetanus vaccine, showing significant tetanus-specific IgG antibodies in pups of pregnant mice after administration. Diphtheria toxoid and cholera toxin have also undergone testing with microneedles.[43,48]

3.8 Drug delivery to the eye

Microneedles enable minimally invasive drug delivery to the eyes, demonstrated by their ability to penetrate a human cadaver's sclera with sufficient mechanical strength. Coated microneedles dissolved drugs within 30 seconds in the tissue, while hollow microneedles successfully delivered aqueous solutions into the sclera, highlighting their potential for eye drug delivery.[9]

3.9 Advantages of using microneedles for drug delivery

Self-administration*:* Microneedles, available as patches, offer the convenience of self-administration by patients following their physician's instructions.[1]

Accurate Reproducible Results: Microneedle-based drug administration exhibits minimal variation in drug bioavailability across different patients.[1,43]

Improved Permeability and Efficacy: Penetrating the stratum corneum, microneedles enhance drug permeability and efficacy.[43]

Table 4. Vaccines, MNs and outcome. Reproduced with the permission from [54], Copyright 2017 American Association of Pharmaceutical Scientists.

Vaccines	MN type	Outcome
Diphtheria toxoid	Dissolving hollow MNs	Enhance the immune response more than a single full-dose administration delivery.
Anthrax rPa	MicroCor solid-state biodegradable MNs	Transdermal delivery of macromolecules can be conveniently and effectively accomplished using the MicroCor technology.
Recombinant Botulinum neurotoxin serotype A-binding domain BoNT/A[Hc] vaccine	Stainless steel MNs	Prevent chemical and physical incompatibilities found by adding several vaccines together.
Bovine Serum Albumin	Coated stainless steel MNs	Highly successful as a basic vaccine delivery tool for inducing defensive immune responses against viral infections.
Inactivated whole chikungunya virus	Nanopatch having antigen-coated miniaturized arrays	Highly efficient method for distributing vaccines, which are inexpensive and convenient to use
Chimeric Flavivirus Vaccine (ChimeriVax)9	Stainless steel MNs	Effective and safe
Hepatitis B surface antigen	Coated titanium MNs	Boost immune responses and give better shelf life.
Hepatitis C DNA Vaccine	Coated stainless steel MNs	Minimally invasive MNs were as efficient in priming cytotoxic T lymphocytes and offer a promising technology for DNA vaccination.
Influenza subunit vaccine (H3N2)	Metal MN in arrays	MN arrays form transient conduits and increase the transmission of vaccine molecules through skin barrier without sensation of pain.
Inactivated influenza virus (H3N2)	Coated stainless steel MN having linear array	Convenient delivery and potential for self-administration, provide a novel and highly effective immunization method.
Inactivated influenza virus	Dissolving MNs in array with encapsulated antigen	Give a new technology for easy and secure vaccination with enhanced immunogenicity, which may encourage expanded vaccine coverage.
Influenza vaccine	MN array connected to plastic adapter tip	Adjuvant increases cellular immunogenicity, protection and improves shelf life.
Seasonal flu vaccine (Fluvax)	Nanopatch with antigen-coated miniaturized arrays	Successful vaccination is achieved by far lower dose of antigens
Inactivated rabies virus suspension	Onvax (MN injection system)	Intradermal delivery using MN technology is safe and efficient resulting in protective seroconversion rate.
4pox DNA vaccine	Stainless steel electrical coated MN	Protective immune response, efficient delivery
Recombinant staphylococcal enterotoxin B vaccine (STEBVax)	Stainless steel MNs attached to 1-mL syringe	Prevent chemical and physical incompatibilities found by adding several vaccines together
Tetanus toxoid	MN coated with antigen	Improved immunogenicity will reduce the dose by 4 times
DNA delivered attenuated West Nile Virus	Nanopatch coated with antigen	Highly efficient method for delivering vaccines, which is inexpensive and convenient to use.
Recombinant F1-V fusion protein of Yersinia Pestis	Stainless steel MN	Protective immunity against plague, substantial health and economic benefits
Ovalbumin	Microprojection array system	Rapid reproducible intracutaneous administration of dry coated antigen, improved efficacy, and convenient to use. Antigenicity was also increased.
Human IgG	Maltose MNs	Transportation of macromolecules through skin was enhanced.

Fast Onset Action: Delivery in the dermis allows for faster drug entry into the systemic circulation compared to (Table 5) conventional methods like oral administration, transdermal patches, and topical creams.[43]

3.10 Disadvantages of using microneedles for drug delivery

1. Needle Fracture: Microneedles, due to their small size, may risk fracturing during poor storage or transport conditions. Breakage inside the skin, depending on the force applied, can lead to infections.[49]
2. Skin Infections: Multiple puncture wounds from microneedle patch application may result in infections if not closely monitored until the wounds are healed.

3.11 Immunological responses

Through MNs, the antigens enter the body and set off a generalized response that stimulates the immune cells, killing cancer cells.[50] The report also suggests method to cure cancer by developing a dissolving MN patch for the transdermal delivery of cisplatin to kill cancer cells.[18] The local effects of influenza immunization through coated metal microneedles on the skin have recently been examined. The results reveal a correlation between the immunization process and a localized surge of cells, such as neutrophils, monocytes, and dendritic cells, at the site of immunization.[51] Peanut protein administered via microneedles into the dermal layer of skin causes an immune response leading to production of peanut-specific immunoglobulins. Administration of a DNA vaccine by a microneedle array can effectively enhance the expression of the encoded antigen and greatly improve immunogenicity.[52]

4. In vitro and in vivo studies

The Franz diffusion cell apparatus is a frequently used tool in studies focusing on transdermal drug delivery to determine drug penetration into the skin (Fig. 5). In this experimental setup, pig ear skin is utilized and placed between the donor and receptor compartments. The cumulative drug release over time is graphed, generating drug penetration profiles for both untreated and microneedle (MN) treated skin. Reconstructed skin models find application in in vivo studies, often utilizing hairless rat animal models. Transepidermal water loss is a crucial parameter measured in these studies, and the Delfin VapoMeter is utilised as a tool for this purpose.[54,55]

Transdermal delivery may lead to several side effects, including mild or severe erythema at the application site. To gauge the extent of skin irritation, the Draize method was employed. Dermatological changes were carefully observed both before and after the application of the patch at the targeted site of action.[54]

Table 5. Advantages and disadvantages. Reproduced with the permission from [54], Copyright 2017 American Association of Pharmaceutical Scientists.

Approach	Description	Advantages	Disadvantages
Poke and patch	It involves MN piercing into skin and then drug patch is applied at the site to be treated.	Simple technique. Encapsulation. Is not required. Provide extended release	No precise dosing. Two step administration process. Reformulation of drug is needed. Low fraction of drug may be delivered.
Coat and poke	This approach involves coating of needles with the drug followed by insertion through the skin for release of drug.	Strength of MN. Is retained after coating. Pump or patch is not required. Dosing is precise.	Efficient coating procedure is required. Small dose. Drug reformulation is needed. Sharpness of MN is reduced thereby reducing penetration ability.
Dip and scrape	Approach in which, first, the MNs are to be dipped into a drug solution followed by scraping beyond the surface to leave behind the drug within the microabrasions that are formed by the needles.	Precise dosing. Extended release.	More complex approach.
Poke and flow	It is based on diffusion of vaccines through conduits of solid MNs.	Delivery of high volumes. Drug reformulation is not needed. Rate of delivery can be regulated. Precise dosing.	More complex device. Increased risk of arrays leakage. Risk of clogging impaired MNs.
Poke and release	Approach of MN delivery that consist of polymers or sugar, where after application and dissolution in the skin, release the active compounds.	No sharp waste (dissolving MNs). Pump or patch is not required. Dosing is precise.	Reformulation of drug needed. Small dose. Often fewer sharp MNs.

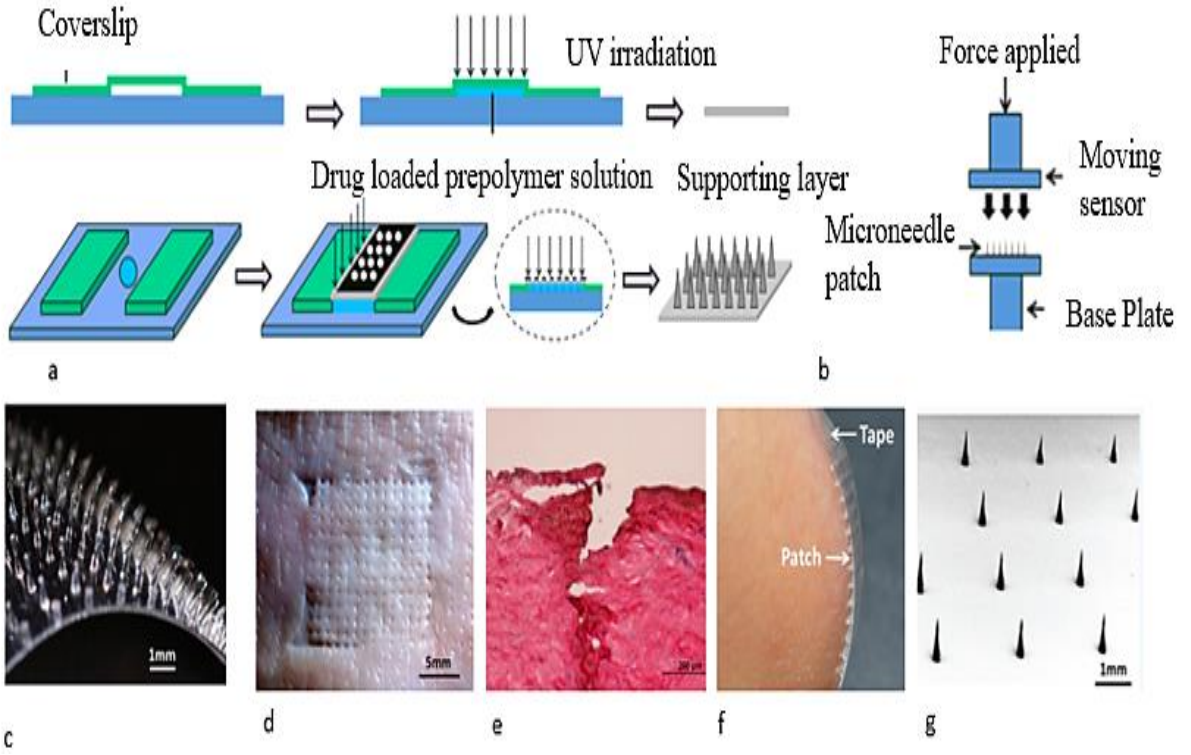

Fig. 5 Fabrication and characterization of the microneedle device. a) Fabrication procedure of the loaded microneedles. b) Mechanical compression test for the microneedles c) Image of a microneedle patch d) A piece of fresh porcine skin after being treated with the microneedle patch e) Histological assay of the pierced porcine skin f) The microneedle patch is able to bend flexibly when applied to the skin at the elbow joint g) A scanning electron microscopy image of the microneedles. Reproduced with the permission from [53], Copyright 2019 Elsevier B.V.

5. Conclusion

Since their inception in the early 1990s, microneedles have exhibited promising potential as an alternative to hypodermal and intramuscular injections. They prove to be efficient, if not superior, and simpler to administer than many conventional drug delivery techniques. Various fabrication methods, including lithography and casting and molding, have been employed to produce microneedles in diverse materials such as silicon, carbohydrates, polymers, and metals. The cost-effective fabrication and biodegradable nature of microneedles have positioned them as a notable player in the drug delivery market.

Microneedles offer several advantages over traditional drug delivery methods: painless application compared to injections, the potential for self-administration, and higher drug bioavailability compared to topical creams. Microneedles have successfully delivered drugs and vaccines, and their application extends to the cosmetic industry. Recently, microneedles have been utilized for drug delivery to the eye, reaching the suprachoroidal space to spread drugs across the eye. These factors make microneedles highly sought after in drug delivery. In regions like India, where access to medical facilities is limited, microneedles, combined with telemedicine, have the potential to transform vaccination processes, addressing issues related to needle injuries, pain, and the lack of medical practitioners in rural areas.

Microneedles, by reducing onset and offset times of drugs and improving drug efficacy, have the potential to revolutionize drug delivery. They mitigate issues related to hepatic first-pass metabolism, pH variations, and enzyme activity, providing faster relief to patients. As a revolutionary development in drug delivery, microneedles hold significant promise for widespread use in the pharmaceutical industry, aiming to enhance the overall quality of life.

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Conflict of Interest

There is no conflict of interest.

Supporting Information

Not applicable.

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