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REVIEW ARTICLE

An Advancement in Microneedles: An Integrated Perspective

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ABSTRACT
Global biomedical science has recently seen a breakthrough with the development of microneedles (MNs) technology. Microneedles (MNs)-based drug delivery has the potential to solve the current constraints of drug delivery, including poor biodistribution, low bioavailability, insufficient skin penetration, and poor absorption. Nanotechnology has significantly altered the methods used to fabricate microneedles (MNs) and changed the design from traditional to innovative by combining different kinds of natural and synthetic materials. Nowadays, because of its many uses and wide range of applications, microneedles (MNs) technology has become more and more well-known in medication delivery and biomedical research around the globe. This review has covered the current state of microneedles (MNs) advancement in general as well as its applications and potential future developments.
Keywords: *Microneedles (MNs), Polyvinyl Pyrrolidone (PVP), Droplet-born air blowing (DAB), Osteoarthritis (OA), Poly (lactic-co-glycolic acid) (PLGA), Electromagnetic compatibility (EMC).*

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INTRODUCTION

In 1976, microneedles (MNs) were originally introduced, and concurrently, an American patent for its transdermal administration method was published [1]. Drug delivery was the primary focus of microneedles' early biomedical uses. The following delivery methods are generally be used to administer active pharmacological compositions of drugs: oral administration, parenteral route, transdermal distribution, and other penetration-enhancing techniques [2].

Transdermal delivery has emerged as a unique approach for subcutaneous medication release in recent years. It reduces the volatility of the drug's serum levels by avoiding the gastroenteric side effects and the liver's first-pass metabolism. Because of their limited invasiveness, painlessness, and ease of self-administration, microneedles (MNs), an emerging technique for transdermal drug delivery, have shown great promise in both fundamental research and clinical applications. Microneedles (MNs) are made up of several micro-projections of various forms, typically between 25 and 2000μm in height, that are affixed to a base support. Micron-sized transport channels can be produced by applying microneedles (MNs) arrays on biological membranes. Microneedles (MNs) have been demonstrated to pass through the stratum corneum (SC) and permeate the skin. Therefore, the principal benefit of using microneedles (MNs) is the promise of pain-free delivery of both small and large molecular weight active pharmaceutical ingredients (APIs) [2].

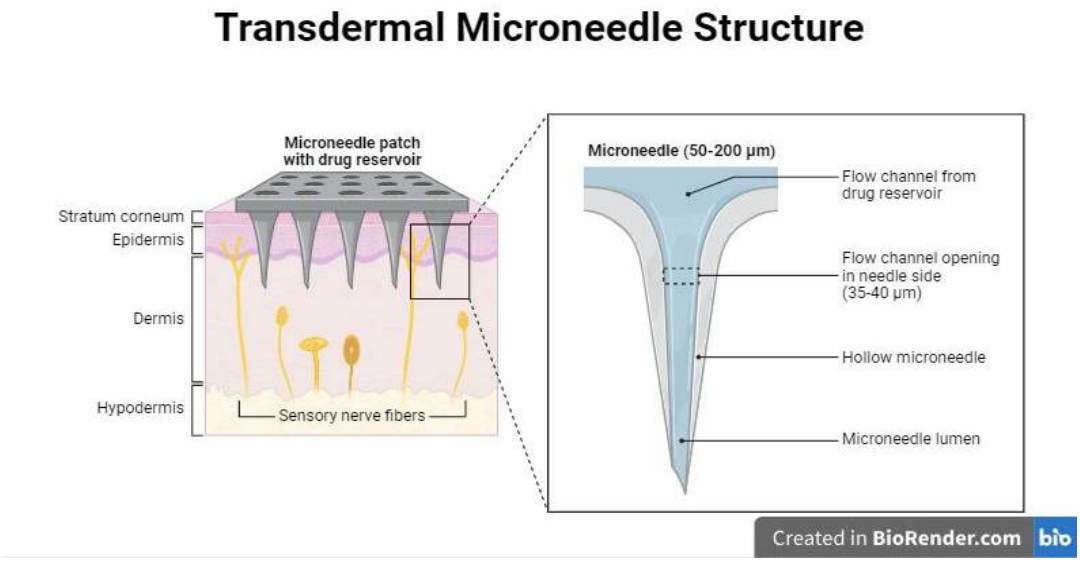

Figure 1: Microneedle structure

Microneedles (MNs) classification:

Based on variations in drug delivery Microneedles (MNs) may be classified as solid, hollow, dissolving, or coated microneedles (MNs)

1. Solid microneedles- Since solid microneedles are inserted and extracted to create pores with a size of microns on the skin's surface, they can be utilised as a pretreatment for the skin. They function according to the "poke and patch" theory as microchannels are formed. These microchannels facilitate direct diffusion of a formulation into the dermal layer, hence augmenting the drug's permeability. Research conducted on rat skin has demonstrated that, when held in occlusive conditions, the micropores created by the microneedles persisted for at least 72 hours following microneedle therapy [3].
2. Hollow microneedles- These systems of microneedles are a scaled-down version of traditional hypodermic needles. Hollow microneedle depiction at the microscopic level [4]. It is challenging to produce hollow microneedles (MNs) because of their structure and fragility. Further creating a range of hollow metal microneedles in one such investigation. In diabetic rats, the administration of insulin using these microneedles was investigated [5].
3. Dissolving microneedles- Dissolving microneedles function according to the "poke and release" theory. Compared to other microneedles, they are simple to make and utilize, which is why they have attracted a lot of interest lately [6]. After application, the microneedles (MNs) dissolve into the skin, releasing the medicinal substance that has been conjugated. Because of their simple construction and practical one-step application method, these microneedles (MNs) offer an advantage over conventional solid and hollow microneedles. artificial microarrays with hyaluronic acid microneedles that dissolve [7].
4. Coated microneedles- Coated microneedles are those that operate according to the "coat and poke" theory. These microneedles (MNs) are made of solid microneedles on a solid base covered in medication solutions or dispersions. Numerous techniques for coating microneedles have been investigated [8]. An alternate method for drug deposition on the microneedles is spray coating; however, this approach is not able to prevent drug loss due to spraying on the array's substrate, which is not available for drug permeation

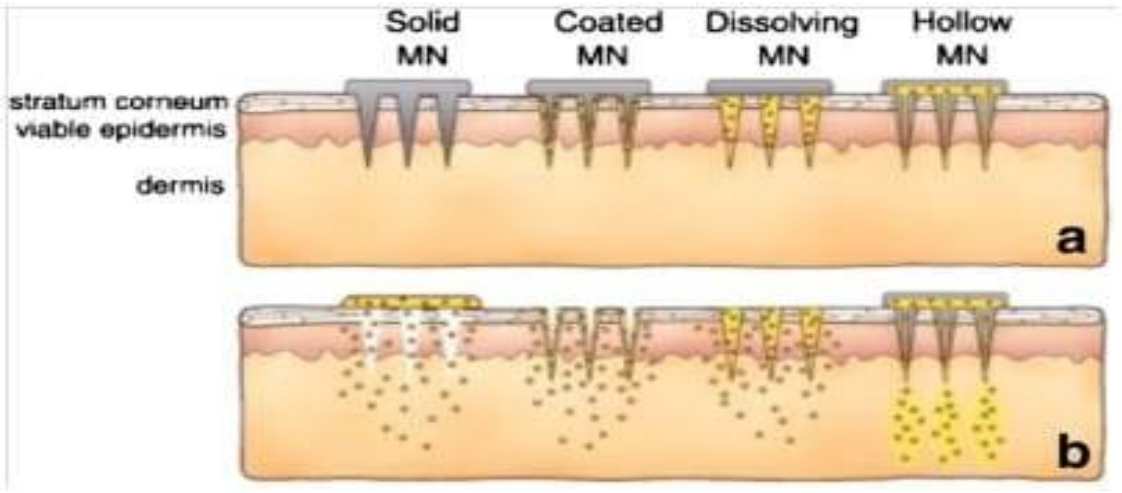

Figure 2: Classification of microneedle[9]

Fabrication techniques:

The skin is a highly elastic organ with a high tensile strength. Microneedles (MNs) need to be at their maximum strength to enter the body without breaking or cracking during insertion in order to work as intended. As a result, creating microneedles is difficult. The choice of material, microneedles (MNs) geometry, and required skin depth all influence the fabrication process. For example, metal microneedles are better designed using microelectromechanical systems, although polymeric microneedles may be suitable for solvent-casting. The technology employed for manufacturing has led to the classification of the fabrication procedures [10].

The Various Fabrication Techniques are as follows,

Fabrication of polymeric microneedles (MNs) using solvent:

a. Micromolding-
   A variety of polymers, including pectin (natural polymers) and Polyvinyl alcohol (PVA) and Polyvinyl Pyrrolidone (PVP) (synthetic or semisynthetic polymers), are made by micromolding [6] . The method makes use of several techniques to evenly pour a liquid polymeric solution into the mold, and then it removes any air spaces. Using a vacuum (or centrifuge, if preferred) to remove air spaces might be combined with oven drying and subsequent removal from the mold.
b. Droplet-born air blowing (DAB)
   With the help of air blowing, a polymer droplet is shaped as a microneedle (MNs) in this approach, which eliminates the requirement for severe external conditions like heat and ultra-violet (UV) irradiation. The solution is first dispensed onto the top and lower plates, respectively. The viscous solution is extended by gently pulling the two plates apart while they remain in contact. Next, under carefully monitored circumstances, the extended viscous solution is exposed to blowing air. This drying stage provides the desired form. Kim and colleagues proposed the fabrication method. To regulate the droplet's size, concentration, and regulated drug loading without causing drug loss, one polymer drop per millilitre is utilised. This process has been used in the fabrication of insulin loaded dissolving microneedles where a successful use of insulin loaded dissolving microneedles reduced blood glucose levels in diabetic mice [11].
c. Pulling pipettes: The pulling pipettes technique is limited to the creation of hollow glass microneedles. High temperatures are applied to the glass, and then microneedles (MNs) arrays are produced by using a micropipette puller to remove the heated glass. Programmable pullers can be used to increase the stability and consistency of this approach [12].

Mechanism of Drug Delivery Using Microneedles (MNs):

The medicine is administered topically in accordance with the diffusion mechanism. The skin becomes briefly disturbed in the microneedle medication delivery method. To create a microneedle device, hundreds of microneedles are arranged in arrays on a small patch, similar to a typical transdermal patch found in the market, with the goal of delivering enough medication to produce the necessary therapeutic response. It avoids the barrier layer by penetrating the stratum corneum. The medication is injected directly into the upper dermis or epidermis, where it enters the systemic circulation and, upon reaching the site of action, has a therapeutic effect [13].

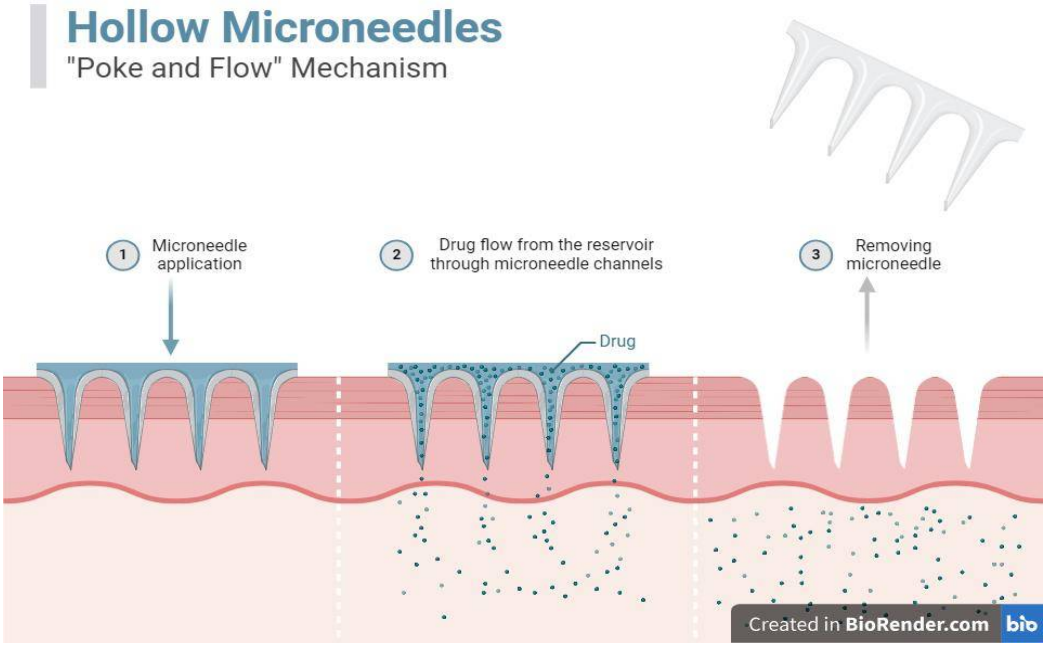

Figure 3: Hollow microneedle

Microneedles (MNs) insertion techniques:

Different strategies have been used to release the medications via microneedles. They are explained as follows:

1. Poke and patch: This method involves poking the skin with solid microneedles to generate microchannels, then applying a transdermal patch to release the medication by the mechanism of diffusion into the micron-sized pore channels [7,14].
2. Coat and poke/Dip and scrape: This method involves coating needles with medication so that it diffuses into the skin before inserting them to release the medication [14].
3. Poke and flow: This method is used with hollow microneedles, in which the medication flows through microchannels after the microneedles are injected into the skin
4. Poke and release: This process is used to dissolve and hydrogel-form microneedles, allowing for the release of medication as the microneedles dissolve [15].

Application of microneedles (MNs):

1) Osteoarthritis (OA):

As a non-invasive route of administration, microneedles (MNs) percutaneous administration is not as ideal as parenteral administration. Percutaneous administration can also stop the breakdown of enzymes caused by the liver and gastrointestinal tract. A few possible advantages of employing microneedles (MNs) in the treatment of Osteoarthritis (OA) include the avoidance of liver metabolism, the reduction of severe adverse drug reactions in the gastrointestinal tract, the achievement of long-term and sustained drug release, and the simplicity of stopping drug delivery in the event of toxicity [16].

Drugs can be sustainably and long-term administered to bodily areas with high flexibility thanks to multifunctional bionic microneedles (MNs).

Rats with osteoarthritis in their knee joints showed a significant reduction in edema and inflammation following the application of glucocorticoid-loaded microneedles (MNs) [16]. Chen et al. created quickly generated two-layer microneedles (MNs) that contained an insoluble substrate and a soluble needle body. Meloxicam was encapsulated at the tip of the MNs using a water-soluble polymer. The results showed the advantages of microneedles (MNs), such as their strong analgesic and anti-inflammatory effects, relatively good relative bioavailability (122.3%), rapid drug release (91.72% within 30 minutes), effective skin administration (79.18%), and lack of obvious skin irritation [17].

2)The Delivery of Vaccine: Microneedles (MNs) vaccine can be used to package or encapsulate DNA vaccines, subunit antigens, or live or inactivated virus vaccines. It can also be carried in solid form and maintained at room temperature [18]. It also reduces sharp medical waste and provides a painless, non-

invasive, easy way to handle and transfer reagents which does not require a cold chain for storing or transportation.

Furthermore, it can aid in reducing the effects and dissemination of infectious blood-borne illnesses in developing nations or in rural areas with little access to healthcare and management [19]. In a comprehensive preclinical immunogenicity study [20]. gave mice the MERS-CoV and SARS-CoV-2 vaccinations by either traditional subcutaneous needle injection or percutaneous delivery of dissolved microneedles arrays (MNA). The mice developed antibodies against SARS-CoV-2 in less than two weeks. Mice immunised with SARS-CoV-2 showed a similar pattern to those immunised with MERS-CoV, and both vaccinations produced antibody levels sufficient to neutralise the virus for at least a year in mice.

Moreover, it has been demonstrated that this type of delivery of these vaccinations results in a more robust immune response compared to conventional hypodermic needle injections. By lowering the necessary vaccine dose, microneedles arrays (MNA) delivery has the potential to expedite the process of vaccine production and save money dramatically. Additionally, it is anticipated that as microneedles (MNs) technology develops and evolves, faster responses to developing pandemics will be possible [19].

3) Cancers:

A) Skin cancer: Using the acanthocyte and basal cell layers, microneedles (MNs) can enter the stratum corneum (SC) and administer the medication to the dermis region. Given the biology of skin cancer, medication delivery by microneedles is the most effective way to treat skin cancer [21].

B) Breast cancer: As the medication becomes localised to the tumour location, researchers found that localised drug administration via the breast papilla dramatically inhibits the proliferation of cancer cells [22]. The way medications are supplied to the tumour site is expected to be disrupted by localised drug administration employing microneedles (MNs) [23]. Zein, a corn-derived prolamine protein, has been reported by Bhatnagar et al. to be employed as a delivery system for the drugs gemcitabine and tamoxifen, which are used to treat breast cancer. Zein microneedles (MNs) contained both gemcitabine and tamoxifen. Alternatively, rhodamine was used as a dye to coat both anti-breast cancer medications on zein microneedles (MNs) and assess coating quality.

In a different study, Bhatnagar and associates described dissolving microneedles (MNs) made using polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) to co-deliver docetaxel and doxorubicin for the treatment of breast cancer. After being inserted into the skin, the prepared microneedles (MNs) disintegrated in less than an hour. According to toxicity trials conducted on animals, administering both medications via microneedles (MNs) resulted in a higher survival percentage than injecting them intramuscularly. When these two medications were given together, the tumor's growth was more controlled than when they were given separately [24].

4) The Treatment of Diabetes:

When taking insulin, diabetics must continuously check their blood sugar levels [25]. One of the most significant and cutting edge uses of microneedles (MNs) is the delivery of insulin. The "Smart Insulin Patch" concept and prototype were originally disclosed in 2015, and Zhen Gu's research group established Zenomics to progress the clinical transformation of the product, combining an MN array made of a polymer substance (HA) is the basic idea, with a preparation that releases insulin in response to blood sugar. Utilizing micro needles (MNs) smaller than 1 mm can lessen injection-related pain and enhance patients' quality of life [12].

5) Usage in the Contraception Field:

Use in the contraceptive Sector: The microneedles (MNs) patch application has been expanded to include the contraceptive sector. Enough contraception is crucial for the health of women. They developed an easy-to-use, long-acting microneedles (MNs) patch for contraception which doesn't generate hazardous sharp waste, in order to increase long-term contraception. Levonorgestrel, (LNG), was injected into the biodegradable polymer Poly (lactic-co-glycolic acid) (PLGA) to create a microneedle body that releases Levonorgestrel, (LNG) gradually over the course of a month as a result of Poly (lactic-co-glycolic acid) (PLGA) slow breakdown in the body. Effervescent microneedle patches have been shown in these investigations to increase the effectiveness of long-acting contraception [26].

6) Disease diagnosis:

Using vacuum or capillary force, hollow microneedles can pierce the skin into the epidermis to remove SIF. Numerous diseases, including diabetes, atherosclerosis, thrombosis, cancer, and cardiovascular problems, were diagnosed using the isolated SIF metabolites [27].

7) Cosmetic applications:

Microneedles (MNs) are frequently utilised in cosmetic applications, including as hair growth and skin care. A dissolvable microneedle patch based on hyaluronic acid was created by Kim et al. to provide ascorbic acid and retinyl retinoate intradermally [28]. Using a solid microneedle, Kumar et al.

demonstrated improved local delivery of eflornithine, a medication used to treat facial hirsutism, both in vitro and in vivo.

Moreover, two alopecia areata patients were successfully treated with microneedle technology [29]. Following treatment, hair growth was observed in these patients. Utilizing a microneedle, successful clinical trials have been carried out in the areas of hypertrophic burn scar, atrophic acne scar, and atrophic face scarring. In terms of cosmetic uses, microneedles (MNs) are thought to be an effective treatment for wrinkles, skin lesions, ageing, and vulgaris. The market for cosmetics is growing, and this means that microneedles—rollers and patches—have a lot of potential

Table 1: Microneedle based products as transdermal delivery

Brand Name	Active Ingredient	Description	Manufacturer	Application	References
AdminPen™	–	Microneedle array-based pen-injector device	AdminMed, California, USA	Used for painless delivery of pharmaceutical drugs or cosmetic actives.	[30]
Corplex™	Donepezil & Corplex Memantine	Dissolvable microneedle patch	Corium International Inc., USA	Treatment of Alzheimer's disease.	[31]
Darmaroller®	–	Metallic microneedle array	Derma spark, Canada	Treatment of acne, stretch mark, hair loss by enhancing drug absorption.	[32]
IDflu®/Intanza®	Trivalent inactivated split-virion influenza vaccine	Intradermal microneedle injection	Sanofi Pasteur, Lyon, France	Prefilled with influenza vaccine for intradermal influenza vaccination.	[32]
MicroCor® PTH	Teriparatide [rDNA origin]	Dissolvable peptide microneedle patch	Corium International Inc., USA	Treatment of Osteoporosis.	[31]
MicroHyala®	Hyaluronic acid	Dissolvable microneedle patch	CosMED Pharmaceutical Co. Ltd., Japan	Treatment of skin wrinkle.	[32]
Micro-Trans®	–	Microneedle patch	Valeritas Inc., USA	Used to deliver the drug into the dermis without limitations of drug size, structure, charge, or the patient's skin characteristics.	[32]
Nanoject®	–	Microneedle array-based device	Debiotech, Switzerland	Used for intradermal and hypodermic drug delivery and for interstitial fluid diagnostics.	[32]
Qtrypta®	Zolmitriptan	Adhesive Dermally Applied Microarray (ADAM)	Zosano Pharma, USA	Treatment of acute migraine.	[31]
Soluvia®	–	Hollow microneedle array	Becton Dickinson, USA	Prefillable microinjection system for accurate intradermal delivery of drugs and vaccines.	[32]

Regulatory guidelines for Microneedles (MNs):

In November, the U.S. Food and Drug Administration (FDA) published final guidelines that define "microneedles" and specify when a product utilising microneedling may have to abide by device restrictions. A microneedling product's classification as a device depends on its intended use, which includes but is not limited to the diagnosis, cure, mitigation, treatment, or prevention of disease, as well as

its intention to change the structure or function of any bodily part, according to the Regulatory Considerations for Microneedling Products guidance document.

Devices with similar technological features, such as a range of needles and "micro-protrusion" tips or pins, which can be dull or sharp and come in various lengths, are classified as "microneedling products" by the Food and Drug Administration (FDA). Other broad terms that might be used to describe microneedling goods include microneedling or needling devices, needlers, dermal rollers, microneedle rollers, microneedle stamps, dermal stamps, and variations. These instruments include dermabrasion devices, needle probes that emit or transfer energy of any type to a patient (such as radio-frequency needles), tattoo machine needles, hypodermic needles or other injection needles, and acupuncture needles [33].

According to section 201(h) of the FD&C Act, microneedling goods are not devices if they are not meant to be used in the diagnosis of diseases or other conditions, or in the cure, mitigation, treatment, or prevention of disease, and if they are not meant to alter the structure or any function of the body.

For instance, microneedling products that simply make the following claims and do not really penetrate living skin (such as the epidermal and dermal layers of the skin) would often not be considered devices: help exfoliate the skin (i.e., disrupt or remove the stratum corneum); enhance the skin's appearance; smooth out the texture and appearance of the skin; and give the skin a radiant appearance.

Generally speaking, these microneedling goods wouldn't be considered devices, but they might still be governed by additional FD&C Act requirements or other federal legislation or regulations that are handled by different federal authorities[33].

In order for a device containing microneedles to be classified as Class I and qualify for an exemption, the Food and Drug Administration (FDA) mandated that the needle length must be 0.3 mm or less. This ensures that the needles are small enough to pierce only the outermost layer of skin, which is the dead layer, and do not penetrate deeper into the skin to alter its structure or function. Furthermore, there is no therapeutic advantage that these gadgets may claim. Food and Drug Administration (FDA) oversight of Class I devices is not applicable, and the label, design, functions, and marketing must all adhere to tight requirements. The Food and Drug Administration (FDA) website contains the requirements for exempt devices. The Food and Drug Administration (FDA) publishes a monthly list of 510(k)s that have been approved. Any device that uses microneedles, whether it be motorized or manual, and has needles longer than 0.3 mm has the potential to change the structure and function of skin; therefore, it must be controlled. These consist of those designed to improve the absorption of pharmaceuticals or serve as a delivery method for topical cosmeceuticals. Either Class II or Class III applies to these devices. When general controls are not sufficient to provide a reasonable assurance of a device's safety and effectiveness but particular controls can be created, the Food and Drug Administration (FDA) classifies the device as class II. These unique controls are often available on the Food and Drug Administration (FDA) website and are device-specific. Devices in this class must submit a Premarket Notification 510(k), and the manufacturer cannot distribute the device commercially until it obtains an Food and Drug Administration (FDA) letter of significant equivalency permitting its use. The websites of the Food and Drug Administration (FDA) provide a list of the requirements for Premarket Notification 510(k)

Device component information, a technical description of the device and its parts (including needle length, needle geometry, maximum penetration depth, and puncture rate), a suggested treatment plan, disposal guidelines, reprocessing guidelines for reusable parts, and shelf life must all be included on the labelling for these kinds of devices. Patient-facing device labels must contain information on how to use the device, a recommended course of treatment, potential risks and benefits, and post-operative care guidelines [33].

Future perspectives of microneedle technology:

One of the most crucial elements in obtaining microneedle applications is effective and consistent skin penetration. However, because of the suppleness of human skin, this may result in partial or total microneedle penetration. Because human skin varies in thickness, the microneedle sensor's monitoring area may change based on the user's age, gender, race, Body mass index (BMI), and skin area. This can cause irregular signals for monitoring. In this way, selecting the appropriate components, such silicon and polymers, can improve the microneedle's strength and stiffness.

Concurrently, the microneedle's permeability can be improved through the optimization of many parameters, such as needle density, spacing, height, tip radius, and base diameter. It can also be used in conjunction with skin preparation methods including exfoliation, scrubbing, and localised heating to improve the permeability of the skin. to control the insertion force and ensure that the skin is entered at the right depth and angle, it can be used in conjunction with an appropriate applicator [14]. By adding

permeation enhancers, surfactants, acidifiers and other chemicals to the drug-delivery microneedle's chemical structure, drug absorption can also be enhanced.
In addition to the potential for tissue damage and inflammation, nonspecific binding during microneedle insertion may cause proteins, cells or macromolecules to accumulate on the microneedle sensor's surface. The target analyte won't be able to diffuse to the microneedle sensor's surface as a result of this quick adsorption, which will cause the sensing signal to gradually drop over time. The microneedle sensor's service life can be increased by modifying the surface, coating it, using biomass molecules, or using several subarrays with varying coating kinds and thicknesses to activate each sensor array in turn. These enhancements will encourage the use of microneedles in real-world applications. The advancement of microneedle technology is necessary to cater to the individual demands of patients as personalised and precision medicine grow.
Research has the potential to modify the medication release rate of microneedles through modifications to their design, material and drug carrier, tailored to the individual needs of patients. Additionally, intelligent microneedle systems that are capable of real-time treatment plan adjustments are being investigated. Electrochemically controlled multiple drug delivery actuators can be constructed to be used with drug delivery microneedles to give more precise control over the release of various therapeutic drugs on a single microneedle patch. To create compact, painless and convenient disease management devices, a tightly integrated, closed-loop module capability can also exist in a microneedle patch thanks to a system architecture that links drug delivery with microneedle array detection.
The Microneedle method is a viable option in the fight against the COVID-19 pandemic, as its effects are being felt globally. A microneedles (MNs)-based oropharyngeal swab was introduced by Chen et al. to help lower false negative results in COVID-19 testing. This idea enables the physicians to distinguish between positive and negative samples by effectively trapping the virus. Since the COVID-19 vaccination is currently accessible, those who are capable of self-administering the shot may receive it from microneedles (MNs) [33].

CONCLUSION

Microneedles (MNs) technology has revolutionised the field of drug delivery and biomedical research, offering a minimally invasive and painless method for administering therapeutics. Microneedles (MNs) can be classified into solid, hollow, dissolving and coated types, each with unique characteristics and applications. Fabrication techniques, such as micromolding, droplet-born air blowing, and pulling pipettes, have been developed to create microneedles (MNs) with precise control over their geometry and material properties. Microneedles (MNs)-based drug delivery systems have shown promise in treating various diseases, including osteoarthritis, diabetes, cancer, and infectious diseases. They offer improved bioavailability, reduced side effects and enhanced patient compliance. Additionally, Microneedles (MNs) have been explored for cosmetic apaplications, such as skin rejuvenation and hair growth. Regulatory guidelines for microneedle products have been established by the Food and Drug Administration (FDA), categorizing them into Class I, II, or III devices based on their intended use and risk profile. Future perspectives for microneedle technology include enhancing skin penetration, improving drug absorption, and developing personalised and precision medicine approaches. Overall, microneedle technology has the potential to transform the field of drug delivery and biomedical research, offering a versatile and innovative platform for addressing various medical needs

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