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A review on Microneedles: A Transdermal Drug Delivery System

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ABSTRACT
Microneedles (MN) possess the potential to emerge as a highly innovative tool for drug delivery and monitoring purposes. By penetrating the skin and piercing the stratum corneum barrier, they enable the delivery of drugs to the viable skin layers and the extraction of body fluids. MN, being an efficient and versatile device, has garnered significant scientific and industrial interest over the past few decades. This is primarily due to its notable attributes such as painless penetration, affordability, excellent therapeutic efficacy, and relative safety. The robust microneedle, which facilitates transdermal delivery, holds immense potential in creating advanced functional devices with superior characteristics for biomedical applications. In recent years, microneedle-based devices have demonstrated their efficiency in delivering both small and macro-molecules, including chemotherapeutics, proteins, genetic material, and nanoparticle-based anticancer therapies. This capability has prompted the utilization of microneedle devices in the development of new anticancer vaccines. These vaccines can permeate tumor tissue and simultaneously enhance the effectiveness of therapeutic agents. Based on the promising outcomes exhibited by microneedle systems in the local administration of anticancer therapeutics, this review provides a comprehensive summary of the various microneedle formulations developed thus far for application in cancer therapy.

I. INTRODUCTION

A novel approach to drug delivery, known as Microneedles (Mn), addresses the issue of poor adherence due to pain associated with conventional injections. While oral administration is convenient, the first-pass effect limits the efficiency of drug delivery. Microneedles physically penetrate the stratum corneum, creating micropores larger than macromolecular drugs, allowing for direct channels for drug diffusion. Additionally, drugs can be loaded in hollow microneedles for direct injection into the circulatory system, or mixed with a soluble substance to penetrate the skin and reach the circulatory system. Microneedles offer a solution for both transdermal and non-transdermal drug delivery.[1]. Microneedles, also known as MNs, are innovative tools made from a range of materials including polymers, ceramics, and metals. These devices are specifically engineered to facilitate the delivery of vaccines, bioactive molecules, or recreational agents into the epidermal and intradermal layers of the skin. Additionally, they can effectively collect substances and bio-signals

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from the body.[2],The term 'microneedle' was initially reported in 1921, with subsequent advancements aimed at reducing insertion pain and minimizing tissue damage.[3]In 1971, the utilization of MNs for drug delivery was reported as a method for micro-dissection of echinoderm eggs.[4].Both solid and hollow MNs were included in the study. Following that, the first MN coated with a drug was patented in [year]. The utilization of MNs for in vivo studies was first reported in 1998.[5],Subsequent to the delivery of genetic material.[6].In the year 2000, the delivery of vaccines through MNs took place.[7] ,Nano-particles delivery facilitated by MNs (2003).[8], dissolvable MNs(2005) [9],hollow MNs for sample extraction(2005) [10]cosmetic application of MNs (2005)[11] and MNs in diagnostic applications (2005)[12].

Microneedles have now found applications beyond their traditional use in the biomedical field, including long-term disease treatment, immunobiological therapy, disease diagnosis, and cosmetic procedures. Apart from delivering small molecule drugs, microneedles are also capable of administering a wide range of macromolecules in a precise manner, such as insulin, growth hormones, immunobiological vaccines, receptor agonists, proteins, and peptides. This targeted delivery directly into the epidermis significantly enhances the efficacy of these drugs for long-term disease treatment and immunobiological therapy. It is widely recognized that microneedles are categorized into four types based on their distinct mechanisms of drug delivery.[13,14,15,16,17] In regards to enhancing penetration effectiveness, dissolving microneedles exhibit a greater impact on disease therapeutic efficacy compared to the remaining three options. Nevertheless, the majority of the aforementioned microneedles can only be released in a single step, making long-term treatment challenging to achieve (18). Lately, significant emphasis has been placed on intelligent multifunction-responsive microneedles, which offer immense potential for transforming point-of-care (POC) disease diagnostics, disease prevention, and personalized long-term treatment.[19,20,21,22,23,24,25] A study has revealed the utilization of a patch with expandable microneedles to transfer skin interstitial fluid (SIF) containing glucose and cholesterol for point-of-care detection and personal healthcare monitoring. Furthermore, a flexible and wearable patch, combined with graphene doped with gold mesh, was employed to enhance electrochemical signals. This patch not only accurately measured the concentration of blood glucose and the pH of human sweat, along with temperature in the sweat-control module, but also delivered metformin transcutaneously using dissolving microneedles under hypoglycemic conditions for real-time therapy of diabetes. The results obtained from a wearable electrochemical analyzer were wirelessly transmitted to an application (APP) via Bluetooth technology, thus achieving the integration of diagnosis and personalized long-term therapy. Despite extensive efforts, cancer continues to be a major health issue affecting the global population. Recent data clearly indicate a rise in cancer incidence over the past few decades.[26,27].On the other hand, both the conventional (e.g. chemotherapy and radiotherapy) and novel (e.g. nanomedicines) anticancer therapeutics present sub-optimal efficacies [28,29]. Moreover, the clinical implementation of extremely encouraging nanoparticle-driven anticancer treatments has faced significant obstacles due to their limited ability to gather in the tumor tissue (specifically, less than 0.7% of the administered dosage reaches the tumor site).[30,31]Furthermore, the intricate nature of nanomedicines poses challenges in scaling up synthesis procedures and ensuring consistent therapeutic outcomes [29]. As a result, in recent years, scientists have begun to revisit the use of macroscale delivery devices such as microneedle systems and hydrogels. These devices offer the potential for localized and controlled delivery of therapeutic agents specifically to the tumor site.[32,33]Particularly, microneedle devices have demonstrated promising results supporting their potential application in anti-tumoral therapies. The concept of microneedle-based drug delivery systems was initially introduced over three decades ago, and in the last 15 years[34], there has been a significant increase in the pursuit of their practical clinical application[35,36]. Microneedles have since been manufactured using a variety of materials such as metals, polymers, glass, and ceramics, in various shapes and configurations to meet specific clinical requirements. Over the past decade, extensive preclinical evaluation studies have been conducted by the scientific community to validate the use of microneedles as drug delivery systems in the biomedical field. Microneedles have been utilized in both preclinical and clinical investigations to enhance passive transdermal delivery, assess vaccines' antigenicity, study altered protein pharmacokinetics and pharmacodynamics, evaluate pain and other sensations associated with

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microneedle delivery, and more recently, transport anticancer therapeutics[37,38]. In the realm of cancer therapy, microneedle devices have been investigated for their ability to stimulate anticancer immunologic responses (e.g., antigens, immune adjuvants, genetic material) or deliver anticancer compounds (e.g., drugs and nanoparticles).[39,40]

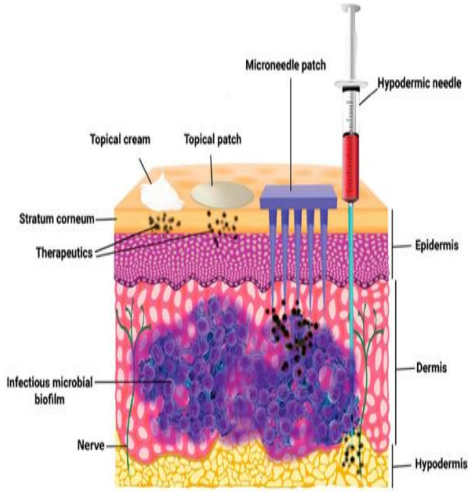
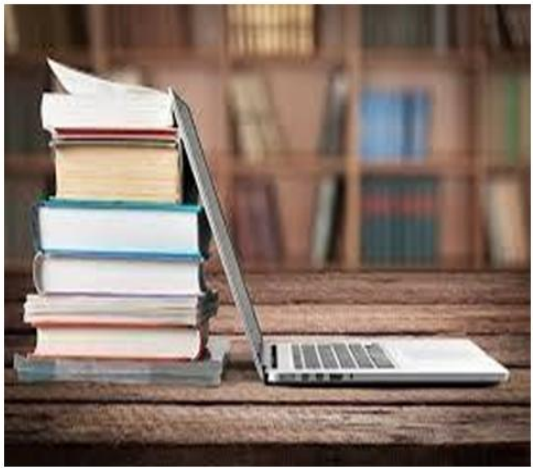


Fig no 1 comparison of skin penetration depths across different drug delivery systems.



II. LITERATURE REVIEW

Jie Xu ,Danfeng Xu , Xuan Xuan and Huacheng HeA The microneedle (MN) is a drug delivery device that was initially developed in 1976. It is designed to be painless and minimally invasive. Over time, microneedle technology has advanced, leading to the development of microneedles with various shapes (cone and pyramid) and forms (solid, drug-coated, hollow, dissolvable, and hydrogel-based microneedles). This review focuses on the applications of microneedles in biomedical areas. To begin with, the review provides a brief introduction to the classifications and manufacturing of microneedles. This allows us to understand the advantages and fabrication methods of different types of microneedles. Next, the review presents an overview of the research conducted on microneedles in biomedical therapy. This includes their use in drug delivery systems, disease diagnosis, wound repair, and cancer therapy. Finally, the review discusses the safety of microneedles and explores the future prospects of this technology.

Andre F. Moreira, Carolina F. Rodrigues, Telma A. Jacinto, S ´ onia P. ´Miguel, Elisabete C. Costa, Il´ıdio J. Correia In recent years, researchers have been focusing on macroscale delivery systems that can be implanted directly on tumor tissue, eliminating the complications associated with systemic delivery of therapeutics. Among these systems, microneedle-based devices have gained significant attention. These devices have the ability to efficiently deliver both small and macro-molecules, including chemotherapeutics, proteins, genetic material, and nanoparticle-based anticancer therapies. This unique capability has led to the exploration of microneedle devices for the development of novel anticancer vaccines. These vaccines aim to penetrate the tumor tissue and enhance the effectiveness of therapeutic agents simultaneously.

Jian Yang , Xinli Liu , Yunzhi Fu , Yujun Song The microneedle, a device that is highly efficient and versatile, has garnered significant attention from both the scientific and industrial communities in recent decades. This is due to its notable properties, which include painless penetration, low cost, excellent therapeutic efficacy, and relative safety. The robust microneedle, which enables transdermal delivery, holds immense potential for the development of advanced functional devices for biomedical applications. This review aims to provide a comprehensive overview of the advancements in microneedles, including their materials and the latest fabrication method, such as three-dimensional printing (3DP). Furthermore, it highlights a range of representative biomedical applications of microneedles, such as disease treatment, immunobiological administration, disease diagnosis, and the cosmetic field.

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2)General properties of microneedles

Microneedle devices consist of tiny needles, measuring in microns, which can be organized individually or grouped together in small arrays to facilitate the targeted administration of therapeutic molecules.[41,42] .The micro-projections typically have widths ranging from 50 to 250 µm and lengths that vary from a few micrometers to as much as 1500 µm.[42,43]. The primary goal of microneedles application is to establish a route for the transportation of therapeutic molecules, circumventing the external obstacles that hinder the penetration of therapeutics into the desired tissue.

As illustrated in Figure 2, these microneedle configurations facilitate the administration of therapeutics through various mechanisms, offering potential for regulating the timing of therapeutic effects.

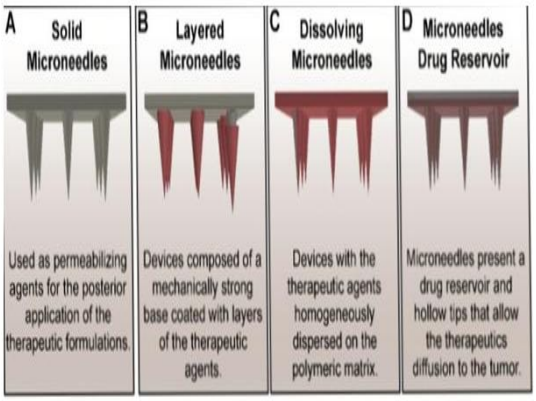

Fig no.2Representation of the main microneedle designs explored for drug delivery applications, (A) Solid microneedles, (B) Layered microneedles, (C) Dissolving microneedles, and (D) Microneedles drug reservoir.

Classification of microneedles

Based on variations in drug delivery

Microneedles may be classified as solid, hollow, dissolving, or coated microneedles

Solid microneedles

Solid microneedles can serve as a skin pre-treatment by creating micron-scaled pores on the skin surface upon insertion and removal. This 'poke and patch' method involves the formation of microchannels, which improve drug permeability by enabling direct diffusion from a formulation into the dermal layer. Research conducted on rat skin has demonstrated that the micropores produced by microneedles persisted for a minimum of 72 hours following treatment, especially when kept under occlusive conditions. [44]

The 'scrape and patch' technique is a modified version of the conventional solid microneedle method. In this approach, micro-abrasions are created on the skin by scraping microneedles, microprojections, or microblades over it.[45]

Hollow microneedles

The microneedle systems are a smaller iteration of the traditional hypodermic needles. Drug administration is accomplished by utilizing a pressure-driven liquid flow of the formulation[46]. Significant amounts of medication can be administered into the dermal layer using this method[47]. The fabrication of hollow MNs poses challenges due to their delicate structure. In a particular research project, a set of hollow metal microneedles was created.

Microneedles effectively regulate drug dosage and release timing, although the manufacturing process posed challenges such as needle breakage and lumen blockage.

Dissolving microneedles

Dissolving microneedles function based on a 'poke and release' mechanism. They are simple to produce and use in comparison to other microneedles, making them a subject of significant interest in recent times[47] Dissolving MNs are crafted from biodegradable materials like sugars or biodegradable polymers and can be filled with therapeutic substances. Once administered, these microneedles dissolve in the skin, releasing the therapeutic agent they contain[48]. This type of microneedle offers an advantage over traditional solid and hollow microneedles due to their easy manufacturing process and convenient single-step application approach. Liu et al. developed microarrays comprising dissolving hyaluronic acid microneedles.[49]

Coated microneedles

Coated microneedles, also known as Mns, are microneedles that operate on the 'coat and poke' principle. These microneedles consist of a solid base with a coating of drug solutions or dispersions. Various methods have been researched for coating microneedles[50,51]. The most commonly used technique is dip coating, which can be challenging due to the requirement for precise control to ensure accurate insertion of the microneedles into the dipping solution[52]. An

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alternative method is spray coating, which allows for drug deposition on the microneedles but may result in drug loss through spraying on the substrate of the microneedles array, limiting drug permeation.[53]

Table 1: A detailed list of advantages, disadvantages, and method of delivery of various MNs.

Mns classification	Advantages	Disadvantages	Method of drug delivery	Reference
Solid	Can be made from a range of materials	Microneedle fracture under skin Limited surface area available for drug absorption	Createmicroconduits in skin to which drug is applied	55,56
Hollow	High drug load can be injected	Must be fabricated with strong materials to withstandto flow pressure	Pressure driven flow through needle	47,46
Dissolving	Easy manufacturing	Only biodegradable materials can be used	Dissolve under skin to release drug payload	40,49
Coated	Used for potent Drugs requiring low doses	Associated with drug loss while manufacturing, temperature limitations	Coating drug release	54,

Based on material selection

MNs can be made from metals, silicone, ceramic, or polymers. For the purpose of this analysis, the construction material has been divided into two categories: non-degradable and degradable. Non-degradable materials encompass metals, silicone, and ceramics, whereas degradable materials consist of polysaccharides and biodegradable polymers.

Non degradable materials

Metals

Soluvia® represents one of the initial MN-based products crafted from metal to enter the market. In addition to Soluvia®, another product that successfully made its way to the market is the silicone-based Micronjet®. Stainless steel and titanium stand out as the most frequently utilized metals in the production of MNs. These metal MNs can be manufactured in various forms such as solid, hollow, or coated microneedles[57].

Silicone

Silicone is a widely used material for microneedle devices and has been studied for more than two decades. Silicone MN arrays can serve as primary molds in micromoulding (see figure no. 3). The use of silicone enables the fabrication of microneedles with different geometries. Narayanan et al utilized an etching technique to create silicone microneedles. They experimented with etching factors such as the use of Tetramethylammonium Hydroxide (TMAH) in varying concentrations, time and rate of etching, and temperature to produce sharper microneedles with a higher aspect ratio.[58,59]

Ceramic

Alumina is a widely used material for MN production due to its porosity, which allows for a defined volume of active to be held. Gypsum and Brushite are alternative materials used for MN fabrication. Ormocer®, a novel material composed of organically modified silicone alkoxides and organic monomers, has also been utilized for MN

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production. This material forms a 3D network that enhances the absorption area for drug solutions. A study conducted involved the fabrication of Ormocer® MNs with varying aspect ratios using laser two-photon polymerization..[60]

Synthetic polymers

Various artificial polymers have been studied for their potential application in MNs, including polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVA). Poly (methyl methacrylate) (PMMA) is a biocompatible polymer commonly utilized in MN arrays.[61]

Degradable materials:

Natural

Carbohydrates present a viable option for creating microneedles due to their affordability and safety. In addition to their excellent biocompatibility, carbohydrates also exhibit low toxicity and some types are known for their strength and toughness. These materials are not only cost-effective but also easily biodegradable[66]. Furthermore, carbohydrates can be easily shaped into microneedles using master templates[67]. They can also be combined with active ingredients to form an active-carbohydrate mixture, which can then be cast into molds that dissolve upon skin insertion to release the drug payload[62]. Maltose is one of the most commonly used sugars for preparing microneedle arrays[49].

Synthetic

Various synthetic macromolecular materials have been utilized in the production of MNs. Examples of these materials are polylactic acid (PLA), polyglycolic acid (PGA), and polylactic-co-glycolic acid (PLGA). The drug release from MNs is controlled by these materials, with the composition of the MN materials playing a crucial role in this process.[63]

Manufacturing of microneedles

Microneedles are composed of silicon, metals, and polymers. Silicon is easily moldable but prone to breakage, requiring a sterile environment and high manufacturing costs. Metals, on the other hand, are more cost-effective but generate waste and biohazardousbyproducts. Polymers, being highly viscous and fracture-resistant, are largely biocompatible and suitable for economical mass production, making them a popular choice for creating microneedles in biomedical fields. Various biocompatible materials like carboxymethyl cellulose (CMC), PVA, PVP, PLGA, hyaluronic acid (HA), and methacrylated hyaluronic acid (MeHA) have been developed for microneedle fabrication. For instance, Mao et al. successfully loaded poorly water-soluble rapamycin into PVP microneedles, leveraging PVP's ability to enhance rapamycin's solubility in the body. Additionally, when PVP microneedles were tested with human umbilical vein endothelial cells for 48 hours, the cells exhibited a survival rate exceeding 90%, indicating exceptional biocompatibility. Yao and colleagues observed the degradation of MeHAmicroneedles in a simulated in vivo setting, revealing that a 3% MeHA concentration provided optimal mechanical strength and gradual degradation over an 8-day period. Moreover, the MeHA microneedle group displayed significantly higher cell activity (NIH-3T3 cells) compared to the control group.[64,65,66,]

Drawing Lithography

Lithography drawing involves the use of a viscous polymer in the glass transition process to achieve the manufacturing performance of a 3D microstructure. In the thermal drawing of microneedles, the biodegradable thermoplastic poly(lactic-co glycolic acid) (PLGA) is vertically stretched by a metal pillar while controlling the speed. The top is broken by fast drawing to form a microneedle structure, and the shape of the microneedle can be adjusted by changing the temperature and fracture speed after cooling. It is essential to ensure that the material properties remain unchanged after heat treatment (Figure 3A). For instance, Chen et al. proposed a magnetorheological drawing lithography method to form a flexible microneedle array. This method only requires one step, which involves forming the compressed droplets of curable magnetorheological fluid on a flexible substrate. Subsequently, the microneedle was solidified in an oven for 1 hour at a temperature of 90 ◦C, resulting in increased penetration of calcium protein through rabbit skin after application.[67,68,]

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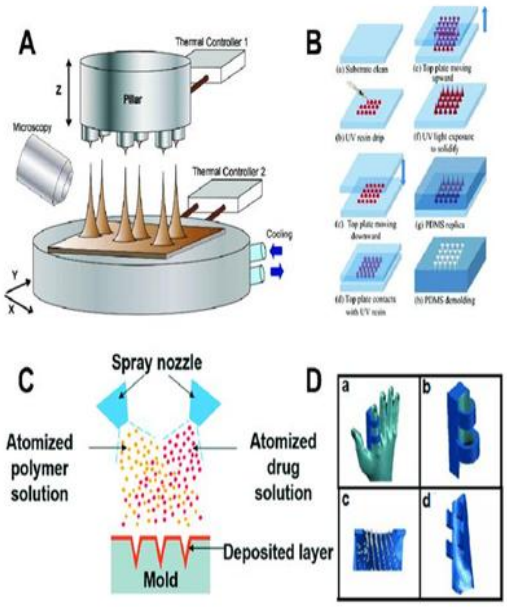

Fig no 3Illustration of methods for making microneedles under different conditions. (A) Theshape of the microneedle is fixed by heating–cooling thermal controller. (B) Fabrication process ofthe microneedle mold by UV. (C) Scheme of dual-nozzle spray depositionprocess. D) Scheme ofproducing a personabyzedmicroneedl by 3d printing

Micromolding

In micro-molding, a mold with specific specifications is essential, typically made of resin. The resin is solidified through exposure to UV light for 30-40 seconds at varying power levels. The solidified structures are then replicated using polydimethylsiloxane (PDMS) to create a mold for a microneedle array, which can be filled with water-soluble or biodegradable materials. The microneedles are produced through casting and coating processes. Amifostine-loaded MN patches are obtained, filled in the mold, and subjected to vacuum at room temperature for 2 minutes to dry. Subsequently, the MN surface is immersed in a solution containing UV light-irradiated 1% trimethylbenzoyl phosphine oxide. However, solutions with high viscosity tend to produce bubbles after filling the mold, while low-viscosity solutions may result in microneedles that are too thin, reducing their physical properties. The appropriate viscosity was determined by observing the flow condition of different concentrations of CMC in test tubes. After selecting 3% CMC, the solutions were centrifuged, poured into molds, and placed in a vacuum at 65°C for 24 hours. Vacuum or centrifugation was applied after filling the mold to overcome the constraints of surface tension and viscosity of the solution, necessitating additional steps in the micro-molding process[69]. An atomized spray process was utilized to minimize the effects of liquid surface tension and viscosity during mold filling. MN patches were fabricated using a dual-nozzle spray deposition process to enhance drug stability by eliminating emulsification and reducing adverse interactions with solvents[70]

Three Dimensional (3D) Printing Technology

Three-dimensional printing is a cutting-edge manufacturing method that relies on 3D model data stored in computers. It involves the gradual accumulation of materials layer by layer, offering benefits such as exceptional accuracy, precision, flexibility, reduced manufacturing steps, and minimal waste. Various 3D printing techniques are currently utilized for producing microneedles for transdermal drug delivery, including 3D projection inkjet (3DPI), fused deposition modeling (FDM)[71], photopolymerization-based methods like stereolithography (SLA) and two/multi-photon polymerization (2PP/MPP), digital light processing (DLP), and laser-assisted bioprinting (LAB). While MPP boasts the highest resolution, it is constrained by speed and material limitations. On the other hand, SLA offers superior resolution but is more susceptible to oxygen inhibition compared to DLP[72]. The integration of three-dimensional printing into microneedle fabrication through photopolymerization has shown promising results. For instance, DLP-based 3D printing has been employed to create microneedles using a lower concentration of molecules in an aqueous solution through photo-crosslinking, combining silk fibroin with riboflavin to produce a flexible microneedle. By leveraging the low drug load of microneedles and the versatility of 3D printing, a dual-function microneedle array was developed on personalized curved surfaces for drug delivery and splint applications to treat a finger injury using DLP technology. These microneedles exhibit remarkable strength, capable of withstanding twice the average thumb force without breaking, leading to a significant increase in drug penetration through the skin.[73]

Applications

Numerous researches have showcased the utilization of microneedles ever since the first report in 1976. Broadly speaking, the use of microneedles in the field of biomedicine can be

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categorized into two main areas: treatment and diagnosis. Certain medications can be administered through the skin by employing microneedles. Various studies have indicated that microneedles are effective in transdermal delivery of metformin, lidocaine, insulin, vaccines, and human growth hormone (hGH).[74]

Wound Repair

Acne is a prevalent dermatological condition characterized by an excess of collagenase in response to local skin inflammation. The wound-healing process can lead to a reduction in collagen from the underlying lesions, resulting in atrophic (depressed) scars. Along with laser treatment and subcutaneous incision, disposable microneedle tips with adjustable depth and speed can be utilized to create uniform bleeding points on the skin, generating multiple micro-bruises in the dermis. These micro-bruises can initiate a series of growth factors that ultimately stimulate collagen production. Through tissue remodeling and vascular maturation, collagen is transformed into type I collagen, leading to skin tightening and repair.[75]

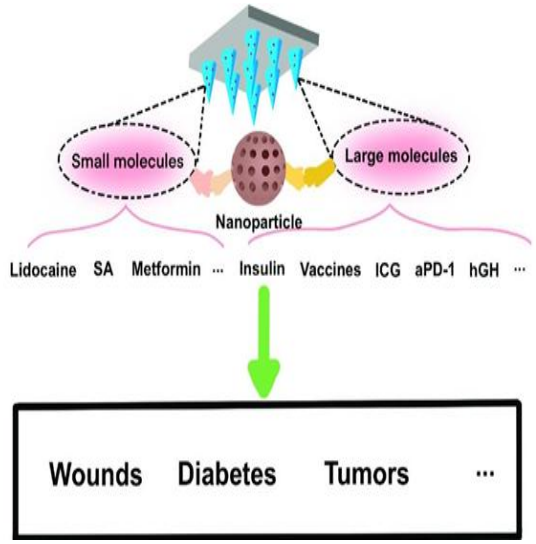

Fig no 4 Schematic representation of MNs with small and large molecules in the application of wounds repair, diabetesand tumor therapy.

Diabetes Therapy

Diabetes is a persistent medical condition, with diabetes-related issues impacting over 425 million individuals globally. The current approach to managing diabetes involves frequent injections of insulin from an external source to maintain stable blood sugar levels. However, the regular administration of insulin injections can result in long-term complications and low patient adherence, with the potential for insulin overdose leading to severe consequences, including shock or fatality. Hence, there is an urgent requirement for a convenient, non-invasive, and self-administered method that can be utilized repeatedly. It is crucial that the dosage can be tailored to individual needs. Additionally, microneedles, as a transdermal drug delivery system, offer advantages such as bypassing gastrointestinal irritation and first-pass effects associated with oral delivery.[76]

Cancer therapy

He and his team conducted additional research on a new microneedle (MN) after presenting MNs containing pH-responsive tumor-targeted lipid-coated cisplatin nanoparticles. This new MN was aimed at achieving a synergistic immuno-chemotherapy by combining it with anti-programmed cell death protein 1/cisplatindiammineplatinum@NPs (aPD-1/CDDP@NPs) antibodies. The results showed that MNs significantly improved response rates in squamous-cell carcinoma mice models that did not respond to a single aPD1 treatment. Therefore, MNs demonstrated potential for cancer treatment.[77]

Vaccines

Certain vaccines undergo lyophilization, dilution, and multiple injections, leading to increased expenses, wastage, and higher risk of contamination during handling and storage. The adoption of microneedles could lower costs and enhance immune response by providing sustained delivery. In a study using dissolvable microneedles for influenza vaccination in mice, researchers observed improved lung IgA levels, cellular immune responses, and antibody-secreting cells, resulting in more effective virus clearance. The study authors suggested that dissolvable microneedle patches offer practical benefits over traditional intramuscular injections and provide superior protective immunity.[80]

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Table No 2

Drug Coated Micro needles	Dissolvable Micro needles	Hollow Micro needles
Adenovirus Bacillus Calmette Guérin Chikungunya virus Hepatitis B Hepatitis C Herpes simplex virus Human papilloma virus Influenza	Adenovirus Amyloid beta peptide Diphtheria HIV Influenza Malaria Measles Poliovirus	Anthrax Clostridiumbotulinum Influenza Japanese encephalitis Poliovirus Rabies virus Staphylococcus

Biosensor

Microneedles are utilized in sensors for dual purposes: as active components of biosensors and for the collection and delivery of biological fluids to biosensors. In comparison to other continuous monitoring devices(78)microneedle biosensors offer several advantages(79)

1. Microneedles are less invasive to the skin due to their small size.
2. They exhibit fewer biofouling effects because of their replaceable nature.
3. Microneedles provide larger electrode surface areas for increased currents.
4. Microneedles are cost-effective yet accurate devices, capable of measuring glucose concentrations in dermal ISF, similar to blood.
5. The wound left by the microneedle sensor post-removal can heal within 24 hours.

Pain therapy

Lidocaine, a commonly used local anesthetic, is typically administered on its own or in conjunction with other medications to manage preoperative and postoperative procedural pain. A study showcased a microneedle containing lidocaine that offers rapid and sustained release, aiding in the relief of both acute and chronic injection pain. Additionally, researchers utilized dissolvable microneedles containing calcitonin-gene-related peptide receptor antagonist (anti-CGRP) peptides to alleviate chronic nerve pain stemming from inflammation post-trauma. These microneedles were then tested on rats experiencing neuropathic pain due to nerve injury, diabetic neuropathy, and neurogenic inflammation. Thermal and mechanical assessments demonstrated that microneedles loaded with anti-CGRP peptide could deliver safe and efficient analgesic effects.[81]

III. CONCLUSION

Over the past four decades since the creation of microneedles, a variety of techniques and materials have been employed to manufacture microneedles in order to enhance transdermal drug delivery efficacy. The materials utilized in the production of microneedles have progressed from metals to silicon and subsequently to polymers. The fabrication methods for microneedles have been refined and enhanced to become more adaptable and productive, transitioning from lithography to micromolds and 3D printing. Despite the fact that 3D printing has the capability to generate customized microneedles with a high drug-carrying capacity, this approach has not yet been widely adopted in clinical settings due to its expensive nature and intricate manufacturing process. Furthermore, it has been determined that different types of microneedles are suitable for specific drugs. Through further exploration, it has been discovered that microneedles can also serve as a means to identify biomarkers, such as blood glucose levels.

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