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Review Article

MICRONEEDLES A POSSIBLE SUCCESSOR TECHNOLOGY FOR TDDS: A PATENT ANALYSIS

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ABSTRACT

The market size for transdermal drug delivery systems was assessed at USD 5.9 billion in 2020 and is expected to reach USD 8.4 billion by 2028, expanding at a compound annual growth rate (CAGR) of 4.5% from 2021 to 2028. Micro Jet injectors, iontophoresis, electroporation, sonophoresis, microneedles, powdered injection, surface ablation, jet injectors and stripping by tape are some of the methods that enhance the delivery and ease of administration of larger molecules which is the major hindrance in case of Transdermal drug delivery system (TDDS). This type of delivery offers immediate delivery and avoids lag time. Microneedles are hollow cannulas inserted into the skin at 50 µm to 500 µm. The micro needle drug delivery systems market is projected to register a CAGR of 7.8% during the forecast period of 2022-2027. The microneedle drug delivery systems market is segmented by product type (solid, hollow, coated, and dissolvable), application (drug delivery, vaccine delivery, dermatology, and other applications), and geography (North America, Europe, Asia-Pacific, Middle-East and Africa, and South America). This review summerizes the recent patents granted in the area of micro-needling in the year 2022 and also the commercial market of microneedles until now.

Keywords: TDDS, Microneedles, Patents, Skin, Commercial market

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INTRODUCTION

The ultimate objective of any sort of drug product delivery system is to deliver an adequate therapeutic dose of medication to the target site in the body for anticipated action while maintaining the desired drug concentration inside the body. The therapeutic effectiveness of a medicine is strongly affected by the route of delivery [1-3]. A topical drug delivery system is a local drug delivery system that delivers topical drugs via the skin to treat skin disorders [4,5]. If the drug substance is non-electrolyte and has a favourable lipid/water partition, the skin absorption of the drug is increased. FDA has proposed a topical drug categorization system (TCS) based on the effective Biopharmaceutics Classification System (BCS) for oral immediate-release solid dose formulations [6]. There are three evaluation criteria and four classes in all as shown in fig. 1. Qualitative (Q1), quantitative (Q2), and *in vitro* release (IVR) rate similarity are the three parameters (Q3) [7].

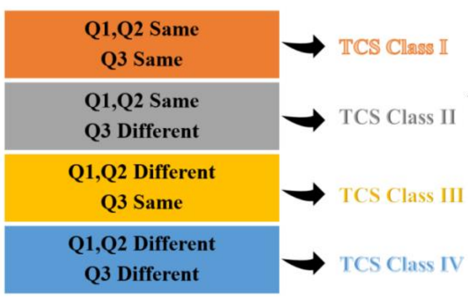

Fig. 1: TCS System for topical drug delivery system [7]

One of the most current topical routes being studied is transdermal drug delivery, which offers several potential benefits over traditional oral or parenteral administration, such as the elimination of pain, discomfort, and poor compliance associated with injections; the prevention of drug degradation in the stomach; the avoidance of first-pass liver metabolism; the possibility of increased bioavailability; the maintenance of relatively constant blood concentrations; and the elimination of drug degradation in the stomach [8] . Transdermal delivery is possible only with molecules less than 500 DA and adequate lipophilic balance [9]. In transdermal delivery, the drug is carried across the skin from applied patches by different mechanisms [10-15] . Technically the drug can pass the skin barrier actively or passively depending upon the various external permeation enhancers [16-22] . Based on their research, Prausnitz and Langer have divided the development of transdermal drug administration into four main eras [23]. By adopting patch-based technologies that rely on natural dispersion, the first generation aimed to provide modest drug loads. The second generation focused on activating medication delivery using chemical precursors [24-26]. The third generation includes electroporation, thermal ablation and microneedles which may precisely target the drug upon penetration into the stratum corneum. In the fourth generation sensing modalities are combined with microneedles for drug administration to precisely control the release of pharmacological substances [27]. More than 35 transdermal products have been authorised for sale in the United States, and roughly 16 active components have been authorised for usage globally [28-30]. From 2020s estimated USD 5.9 billion, the transdermal drug delivery systems market is predicted to grow to USD 8.4 billion by 2028, at a CAGR (compound annual growth rate) of 4.5 per cent as shown in fig. 2 [31].

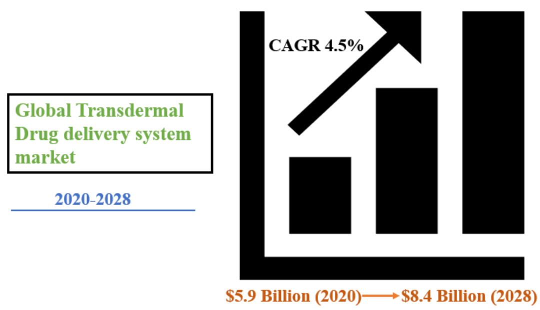

Fig. 2: The global market size of transdermal drug delivery system [31]

But fast transport is always the choice for researchers . Many such investigatory methods are under clinical trials. As Stratum corneum the primary barrier for drug absorption via the skin restricts the transdermal administration of drugs with high molecular weights and/or high water solubility [32-35]. Therapeutic peptides and proteins with a high molecular weight, such as anti-cancer drugs, hormones, growth factors, vaccines, analgesics, anti-hypertensives, thrombolytics, and many others present particular difficulties for transdermal distribution. Therefore, there has been a concentrated effort to explore and create novel ways for enhancing the Stratum corneum barrier's permeability [36, 37] Micro Jet injectors, iontophoresis, electroporation, sonophoresis, microneedles, powdered injection, surface ablation, jet injectors and stripping by tape are some of the methods that enhance the delivery and ease of administration of larger molecules . This type of delivery offers immediate delivery and avoids lag time [38-42]. The machine-related parameters can be adjusted as per individual needs. Numerous manuscripts have reviewed different types of transdermal drug delivery technologies so, the conclusion from most of those papers state the usage of microneedles as recent advancement in the area of topical drug delivery system [43]. Several review articles have also explored specific technologies, such as the various methods for fabricating microneedles or the devices that are presently being utilised in clinical trials or may be employed shortly [44]. It is safe to presume that the most important features of Microneedles research have been covered in reviews and research papers. Nonetheless, there are few attempts to assess the trend in the development of microneedle technology [45]. In other words, it is unclear from the literature how slowly or quickly the development of microneedle-based technologies is proceeding. Furthermore, it is unclear from the existing data what method could be used to quantify the trends and, if the trend could be quantified correctly, considering that microneedles-based research is still relatively new in comparison to other transdermal drug delivery systems [46]. Microneedles can be considered to be a micron scale hybrid between transdermal drug delivery system and hypodermic syringes to overcome limitations that are associated with the individual application. Microneedles are hollow cannulas inserted into the skin at an external length of 50 µm to 500 µm [47-50]. Microneedle patches are tested for the delivery of vaccines and larger peptides in the body [51]. The active response is observed while delivering drugs via microneedles. Microneedles deliver the drug into the body at a specific rate and painlessly [52-54]. They do not stimulate the underlying pain-stimulating needles and are adjusted as per the need of the drug molecule for their effective delivery. Microneedles utilize microscopic needles which protrude into the skin and then deliver the medicament for a prescribed period as shown in fig. 3 [55]. During the forecast period of 2022-2027, the market for microneedle drug delivery systems is expected to grow at a CAGR of 7.8 %. The microneedle drug delivery systems market is segmented by product type (solid, hollow, coated, and dissolvable), application (drug delivery, vaccine delivery, dermatology, and other applications), and geography (North America, Europe, Asia-Pacific, Middle-East and Africa, and South America) [56-62]. Henry and co-workers conducted the first trials for the microneedle and deliver calcein into the body at three different rates however the experiment was interrupted due to the leakage from the microneedle array [28]. After this, McAllister and co-workers administered insulin and other molecules by this method into the cadaver skin and determined the permeation [29]. Silicon wafers with reactive iontophoresis was used for the preparation of the microneedles [63, 64]. In June 2021, PharmaTher and TSRL entered a co-development agreement to develop microneedle patch delivery technology for psychedelics and antivirals. The alliance has committed to commercialize a patented hydrogel-forming microneedle patch delivery technology [65-69]. In August 2020, Zosana Pharma Corporation partnered with EVERSANA, a commercial service provider in the life science industry, to commercialize and distribute Qtrypta in the United States. Qtrypta is an intracutaneous patch coated with the drug Zolmitriptan for the acute treatment of migraine [70-76]. The materials that have been used to fabricate their range from metal, glass, silicon and biodegradable polymers (polydimethylsiloxane) and silk fibroin [77]. Under this review paper, we would be discussing the recent patents granted for different types of microneedles in 2022 and also the commercial market of microneedles.

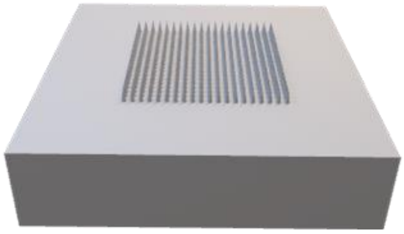

Fig. 3: 3D CAD diagram of microneedles [147]

Types of microneedles

Microneedles can form pores in the skin, allowing the drug to flow directly from the epidermis to the dermis [78]. Unlike conventional hypodermic needles, the microneedle does not irritate the patient's nerves, hence increasing patient compliance [79]. Microneedles are divided into four structural categories: solid microneedles, coated microneedles, dissolving microneedles, and hollow microneedles as shown in fig. 4 [80].

The drug delivery principle of these microneedles (respectively) are the "poke and patch" approach, the "coat and poke" approach, the "poke and release" approach, and the "poke and flow" approach [81].

Solid microneedles

Microneedles can create pores in the skin, allowing drugs to flow directly through the epidermis and into the dermis [82]. In contrast to conventional hypodermic needles, the microneedle enhances tolerating consistency because it does not irritate nerves [81].

Coated microneedles

Coated microneedles, which are coated with drug substances at their tips via dipping, gas-jet drying, ink-jet printing, or spraying, have solved the complex problem of solid microneedles [82]. The mechanism of coated microneedles for drug delivery is the "coat and poke" method. The microneedle patch is put into the skin, and the drug-coated microneedle tips subsequently release their contents into the skin.

Dissolving microneedles

Dissolving microneedles have several advantages over their solid and coated counterparts, including their ease of production, their usefulness, and their high drug loading [83]. Dissolving microneedles often work on the "coat and poke" principle, wherein the medication is contained in the microneedle tips and is released as the microneedle firmly penetrates the skin [84].

Hollow microneedles

Hollow microneedles, which offer the maximum degree of portion precision, are uncommon compared to other microneedle structures[85]. Otherwise empty microneedles can be used to securely inject drugs under the skin at weight-driven flow rates. Microneedles like these are typically produced using MEMS processes such as laser micromachining, lithographic patterning, microfabrication, and X-beam photolithography, on a metal or silicon substrate. Additionally, since the "poke and flow" delivery method of empty microneedles makes them ideal for blood extraction [86], they have been widely used for this purpose.

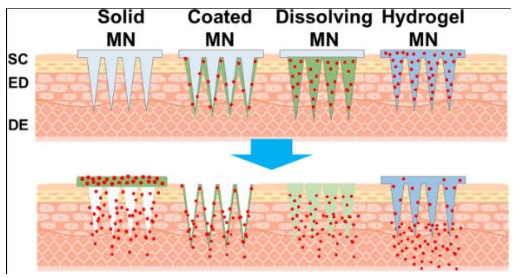

Fig. 4: Types of microneedles [145]

Methods

This analysis focuses on 2022 patent filings that are relevant to the topic at hand. To begin, we choose the keywords by consulting the MeSH (Medical Subject Headings) used to index papers in PubMed. Patents were searched by looking for the terms "microneedle" or "microneedle" and "drug delivery systems" anywhere in the title, abstract, or full text, as these terms were thought to be relevant to microneedle arrays that contain pharmaceutical compositions focused on potential clinical treatments. As a result, we removed any patents that were either not available, duplicates, or not published in English. From the European Patent Office (Espacenet) and the World Intellectual Property Organization databases, a grand total of 88 patents uncovered (WIPO). For this review, we focused on a subset of these patents-42 in total-that discuss various aspects of microneedles, including their categorization, materials, formulations, chemicals or medications, and stages of development. In addition to the United States and China, the patents came from a wide variety of other nations that are members of the Patent Cooperation Treaty (PCT) (CN).

Trends ın the development of mıcroneedles-based drug delıvery system

We looked at several forms of delivery microneedles to spot patterns. The transdermal route accounts for the vast majority of microneedle patents. It is important to consider both the target molecule and the targeted indication when deciding where to implant the microneedle. Injecting a molecule with a microneedle increases its permeability into the skin, allowing it to reach the living epidermis and/or dermis. Drugs and vaccinations against cancer, for example, can be delivered precisely where they are needed using microneedles, such as in the suprachoroidal area of the eye or under the tongue. The two most common types of microneedles used for delivery are solid (>30%) and hollow (>30%). Next came dissolvable and coated microneedles, each of which was mentioned in 18%-19% of delivery-related patents. Trends in the development of microneedles-based drug delivery system are shown in fig. 5 and 6.

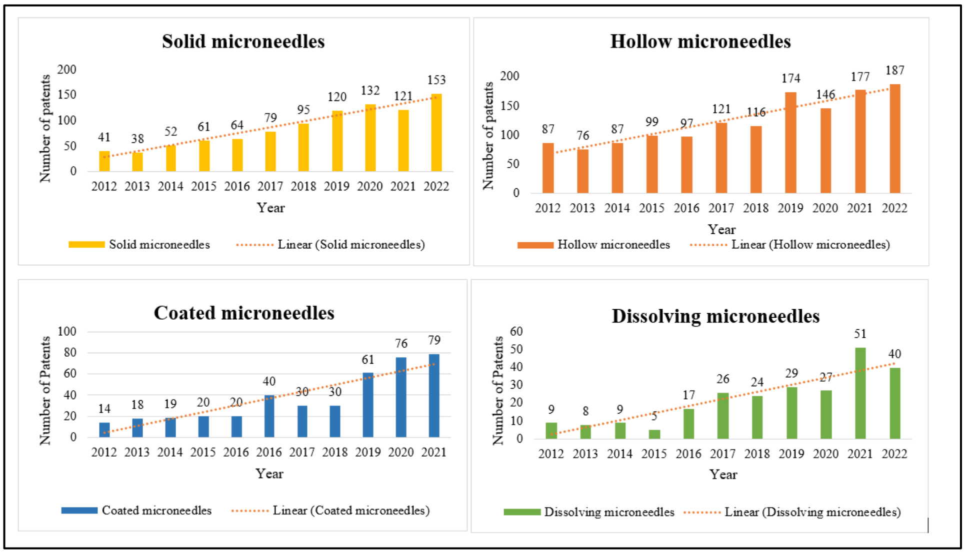

Fig. 5: Changing trend of patents related to types of microneedles from the year 2012-2022 [153]

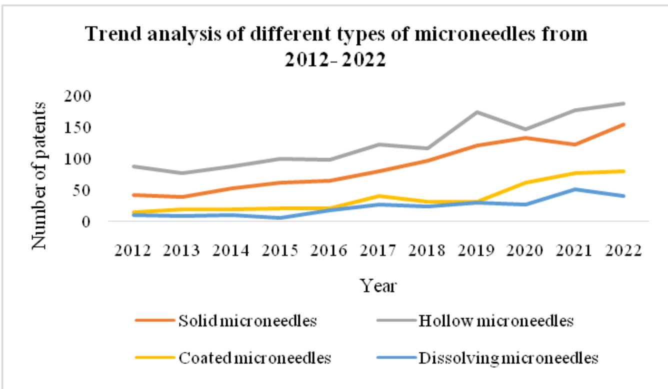

Fig. 6: Trend analysis of different types of microneedles from years 2012-2022 [153]

Commercıal microneedles ın the market by 2022

Different categories of microneedles are present in the market which serve different roles and are formulated to deliver different therapeutic and cosmaceutical responses. Clinical findings showing that a Trivalent Influenza Vaccine based using Zosano Pharma's transdermal microneedle technique is as immunogenic as a higher-dose intramuscular injection were published by the company in 2022. The findings also showed that the vaccine was successfully delivered via their microneedle method, resulting in antibody levels that matched all three of the EMEA's recommendations for influenza vaccination efficacy. Researchers at Pharma Ther released promising findings on their LSD microneedle patch in 2021. These findings may encourage the business to move on with phase 2 clinical studies of LSD in 2022. TSRL and PharmaTher announced their partnership to create microneedle patches in June 2021. The new cooperation and collaboration would be used to collect and pool resources and intelligence to create intradermal delivery systems for medicinal applications. Both firms contributed to the creation of the microneedle delivery method. In the year 2020, PharmaTher had licenced microneedle technology from the University of California, and TSRL had begun developing microneedle prototype patches with assistance from the prestigious National Institute of Allergy and Infectious Diseases. The Austrian Institute of Technology announced in June 2021 a partnership with In-Vision and DirectSens to launch the NUMBAT research project, which utilised high-resolution DLP 3D printing to create an array and group of polymeric microneedles for minimally invasive and less painful glucose monitoring. Monitoring glucose levels is critical for persons with diabetes. In the next years, this event is anticipated to have a favourable effect on the market. Aesthetics Biomedical, a leading producer of aesthetics products, said in June 2021 that it had acquired FDA permission for its Vivace RF Micro-needling device, which will be used at both 1MHz and 2MHz frequencies. The innovative micro-needling method was designed and created to provide patients with more luminous skin. Influenza in healthy adults of working age contributes greatly to this disease's socioeconomic burden. Intanza® 9 g (Sanofi Pasteur) is a microneedle-delivered intradermal trivalent inactivated influenza vaccine approved in 2009 for the prevention of seasonal influenza in individuals aged 18 to 59. The microneedle method reliably and reproducibly distributes the vaccine to the dermis. According to clinical studies, Intanza 9 g is similarly immunogenic and well tolerated in individuals of working age as a typical intramuscular inactivated trivalent vaccination. Local responses to Intanza 9 mg, primarily erythema, are transient, typically mild or moderate, and have no effect on acceptance. At least 95% of both vaccine recipients and prescribers believe Intanza 9 g to be satisfactory, especially because of its short needle and speedy administration. Because Intanza® 9 g provides an alternative to intramuscular vaccines, it may contribute to an increase in influenza vaccination rates [87]. The MicroCor system from Corium employs dissolving microstructures (microneedles) for needle-free delivery of biologics through the skin. When a quick beginning of action is desired, this technology can potentially be used with small molecules. MicroCor PTH(1-34) product candidate contains the authorised osteoporosis medicine Forteo® (teriparatide [rDNA origin] injectable) manufactured by Eli Lilly. Forteo requires a daily self-administered injection, the disposal of sharps (needles), and refrigeration. MicroCor PTH(1-34) has passed Phase 2a clinical study with success. We have also demonstrated the capability to include a wide variety of compounds, including small molecules, peptides, proteins, monoclonal antibodies, and vaccines, into the MicroCor system. The MicroCor drug-in-tip technology, combined active therapeutic medicines with patented polymer and excipient combinations to produce arrays of solid-state biodegradable microstructures. These arrays are created specifically to maximise the local or systemic distribution of medicinal or preventative substances. Upon application, MicroCor arrays penetrate the surface layers of the skin and dissolve or biodegrade. MicroCor can lessen or eliminate the bleeding and discomfort associated with conventional injections. In addition, by delivering vaccines to the higher layers of skin, which are rich in antigen-presenting cells, MicroCor has the potential to generate a more strong and more persistent immune response. In certain instances, this may allow us to develop a vaccine that permits dosage sparing and/or the omission of adjuvants. Corium has created GMP manufacturing facilities, quality systems for scale-up, and cost-effective production procedures to support preclinical and clinical research projects [88]. The skin provides the biggest immunological barrier against infection and is an easily accessible place for immunisation, notwithstanding the difficulty of intradermal (ID) injection. MicronJetTM is a microneedle that consistently injects antigens extremely close to the dendritic cells of the skin. Trivalent virosomal-adjuvanted influenza vaccine was used in a dose-sparing intradermal injection research with 280 healthy adult volunteers. ID injection of 3 µg using the MicronJetTM was well tolerated and demonstrated a statistically larger geometric mean fold rise than the same dose ID injection using a conventional needle (Mantoux technique) for the H1N1 and B strains or a 15 µg intramuscular (IM) injection for the H3N2 strain. Thus, the immune response appears to rely partially on the injection device and route. The MicronJetTM may permit dose-sparing while providing a greater response to influenza immunisation; more clinical evaluation is warranted [89]. Valeritas, Inc., a medical technology company focused on the development and commercialization of new drug delivery solutions, gained CE Mark certification and ISO 13485: 2003 Quality Management System Certification for its V-GoTM Disposable Insulin Delivery Device. The V-Go is intended to provide uncomplicated basal-bolus therapy for insulin-dependent individuals [90]. A High-Density Microarray Patch is the foundation of Vaxxas's technological platform (HD-MAP). The HD-MAP material from Vaxxas is easily manufactured by injection moulding to make small patches with thousands of extremely short (0.25 mm) micro projections. Vaxxas has created innovative methods that allow vaccines to be applied to micro projections sterile conditions. The HD-MAP efficiently distributes the vaccine through its microprojections to the dense populations of immune cells just beneath the skin's surface. Microprojections also activate natural immuno-cellular alarms, resulting in fast vaccine component transport to lymph nodes and a robust immune response. [91] Zosano Pharma Corporation (NASDAQ: ZSAN), a clinical-stage speciality pharmaceutical business, today reported favourable Phase 2 clinical trial results for its patented, quick onset, transdermal ZP-Glucagon patch for severe hypoglycemia. The purpose of Phase 2 clinical study was to compare the safety and efficacy of the ZP-Glucagon patch to the current standard of care in treating insulin-induced hypoglycemia in Type 1 diabetic adults [92]. The eDermaStamp® by Dermaroller® creates micro-injuries of the epidermis and dermis that are minimally invasive and do not result in open wounds or ablative damage. After a short time, the puncturing channels shut, and these micro-injuries initiate the body's wound-healing, resulting in an increase in collagen formation in the treated skin. The eDermaStamp® by Dermaroller® induces the formation of new tissue by encouraging the regeneration of healthy cells in precisely targeted locations exhibiting indications of age. It minimises wrinkles effectively, tightens and thickens the skin, and-probably most impressively-fills and smoothes scars [93]. CosMED Pharmaceutical Co. Ltd. (CosMED) is an RandD-driven company that specialises in the creation of transdermal therapeutic systems, such as transdermal medicine, cosmetics, medical adhesives, and laboratory equipment for transdermal investigations. MicroHyala® is an innovative and one-of-a-kind microneedle product. Since November 2008, CosMED has created microneedle cosmetics, which are the first microneedle products to be commercially successful. Using MicroHyala® technology, CosMED competes in the transdermal vaccination and protein drug markets [94]. As an alternative method for the delivery of vaccines, microneedle patches are attracting growing attention. Using TheraJect's microneedle technology, an approved seasonal influenza vaccine from 2007 to 2008 was produced into dissolvable microneedles in this study (VaxMat). The microneedles' tips were composed of antigens combined with trehalose and sodium carboxymethyl cellulose [95]. Pain-free, blood-free, minimally invasive transdermal drug delivery systems for large molecules to the Epidermis, Syringe Delivery is Obsolete for Numerous Pharmaceuticals and Vaccines DrugMAT is more effective than existing transdermal Patches since it reliably transports even the largest molecules of drug amenable to Proteins, Vaccines, etc. Generally, cosmetics, genetic materials, and other applications employ dissolving microneedles. DEBIOTECH creates cutting-edge medical devices utilising micro and nanotechnology, microelectronics, and novel materials. DEBIOTECH focuses specifically on implantable and non-implantable drug delivery and diagnostic devices. DEBIOTECH's main competency is the identification of innovative technologies and the creation of new devices in this field. Then, these gadgets are licenced by multinational pharmaceutical and medical device corporations [96]. DEBIOTECH is a world-renowned leader in the field of MEMS (MicroElectroMechanical Systems)-based drug delivery. In addition to Nanoject Microneedles for intradermal injection (CTI Medtech Award 2008), the company is developing a patch pump for continuous subcutaneous infusion of insulin (Swiss Technology Award 2006) [97]. The BD SoluviaTM pre-fillable microinjection system is an integrated glass pre-fillable syringe system with a 1.5 mm x 30-G BD microneedle. This design enables intradermal administration of the vaccination. The Macroflux® technology utilises a tiny patch and applicator to provide a needle-free method for tranthe sdermal delivery of therapeutic proteins, peptides, and vaccinations. It combines painless and easy drug administration with quick drug delivery and good bioavailability. The patch consists of a thin titanium screen with drug-coated microprojections that, when applied to the skin, form superficial routes through the skin's outer layer to facilitate the movement of molecules. Prior to its spin-off, Macrofluy completed early clinical trials with five different medicines in over 300 participants [98]. Micro-injuries to the epidermis (outer layer of skin) and dermis (middle layer of skin) are created by the Dermapen microneedling pen's segmented microneedle delivery system (the inner layer of skin). Consequently, the micro traumas stimulate the body's intrinsic capacity for repair. Each Dermapen tip is equipped with 12 needles and our exclusive SureSpaceTM and SafLok technologies. Consequently, these safety measures are present in each Dermapen needle tip and pen. In addition, by utilising SureSpaceTM and SafLokTM microneedling pen technologies, practitioners can provide their patients with the safest possible microneedling therapy while achieving the best microneedling results [99, 100]. The 3MTM Hollow Microstructured Transdermal System is compatible with a broad range of drug quantities (up to 2 ml) and molecular types, so long as liquid stability is maintained. This technique combines passive, patient-friendly transdermal distribution with the versatility of parenteral injections. In addition to tiny molecules, the 3M Hollow Microstructured Transdermal System is designed for intradermal delivery of liquid formulations, such as proteins and peptides. Microneedles that are hollow are capable of delivering up to 2 ml of high-value biological compositions [101]. Seventh Sense Biosystems, Inc. (7SBio), creators of the world's first push-button blood collection device, announced today that it's TAP® II blood collection equipment has obtained CE mark clearance from the European Commission. This authorization enables consumers and patients in the European Union to access quick, convenient, and more comfortable home blood collection at the touch of a button [102, 148]. Microneedle patches are garnering significant attention as an alternate strategy for the delivery of vaccines. Using TheraJect's microneedle technology, an approved seasonal influenza vaccine from 2007 to 2008 was produced into dissolvable microneedles in this study (VaxMat). The tips of the microneedles were constructed of antigens combined with trehalose and sodium carboxymethyl cellulose. The patches comprising 15 µg per strain of influenza antigen were carefully characterised to ensure the antigen's stability after fabrication into microneedles. The Symphony continuous glucose monitoring system might be the first "noninvasive" glucose monitor to successfully reach the market, according to the report. According to the report, there is a high demand on the market for patients and medical experts to employ in their practises and surgical procedures. As the number of diabetic patients rises, the usage of a needle to test blood glucose is becoming obsolete, and an effective continuous monitoring device is becoming increasingly needed [102]. Details of commercial microneedles in the market are given in table 1, fig. 7.

Table 1: Commercial microneedles in the market

S. No.	Company	Product	Mechanism	Use
1.	Becton Dickinson/Sanofi Pasteur	Intanza®	Pre-filled injection system	Ready-to-use influenza vaccine intradermal injectors
2.	Corium International, Inc.	MicroCor®	Dissolvable microneedle Device	Transport big molecules like proteins, peptides, and vaccinations, as well as smaller ones.
3.	NanoPass Technologies, Ltd.	MicronJet™	Hollow microneedle Device	It can be attached to a conventional syringe and used to inject medication, protein, or immunizations without causing any discomfort.
4.	Valeritas, Inc.	Micro-Trans™	Microneedle device	It is effective for dermal medication delivery regardless of drug size, drug structure, drug charge, or patient skin features.
5.	Vaxxas, Inc.	Nanopatch™	Vaccine-coated microneedle device	Used in vaccine delivery
6.	Zosano Pharma	ZP Patch	Drug-coated microneedle Patch	Used in glucagon delivery
7.	Derma spark, Canada	Dermaroller®	Metallic microneedle array	Used for the treatment of acne, stretch marks, and alopecia. enhanced medication absorption (minoxidil, hyaluronic acid, etc.).
8.	CosMED Pharmaceutical Co. Ltd., Japan	MicroHyala®	Dissolvable microneedle patch	Its anti-wrinkle properties are due to the hyaluronic acid it contains, which is absorbed by the skin.
9.	TheraJect Inc., USA	VaxMat®	Dissolvable microneedle patch	Macromolecules such as proteins, peptides, and vaccines can be transported with this method.
10.	TheraJect Inc., USA	Drugmat®	Dissolvable microneedle patch	It rapidly penetrates the stratum corneum and releases hundreds of milligrammes of medication into the epidermal layer.
11.	Debiotech, Switzerland	Nanoject®	Microneedle array-based device	Interstitial fluid diagnostics and drug delivery via intradermal and hypodermic routes
12.	Becton Dickinson, USA	Soluvia®	Hollow microneedle array	For precise intradermal delivery of medications and vaccines, use this prefillable microinjection device.
13.	Zosano Pharma Inc., USA	Macroflux®	Metallic microneedle array	Delivery of peptides and vaccines
14.	Dermapen	Dermapen®	Microneedle array-based device	Used to treat a variety of skin problems, including acne, stretch marks, and hair loss; it improves medicine absorption.
15.	3M Corp., USA	Microstructured transdermal patch	Hollow microneedle arrays	It can transfer liquid formulations with varying thicknesses.
16.	Seventh Sense Biosystems, Inc.	TAP 2 C™	Microneedle penetration/blood sampling	Blood sampling unit
17.	TheraJect	TheraJect™ Patch	Dissolvable microneedle device	For those acquainted, TheraJect, Inc. is a biopharmaceutical company in the preclinical organisation devoted to the distribution of pharmaceuticals and vaccinations in an innovative transdermal method that doesn't require the use of needles
18.	Echo. Therapeutics, Inc.	Symphony® Continuous Glucose Monitor	Glucose monitoring	The Symphony ® CGM System is a wireless, non-invasive (needle-free), continuous glucose monitoring system.

Fig. 7: Commercial microneedles in the market [146]

Patents in mıcro needlıng technology in the year 2022

The inventors, firms, countries of protection, materials, formulations, chemicals or pharmaceuticals, and development status of the selected patents for the fabrication of microneedles arrays are listed in table 2.

Patents in microneedles technology depending upon the application of microneedles in disease targeting and treatment

Yu Yun Long and colleagues identified a composition that would enhance wound healing via micro needling. The composition was formulated using 0.01-0.1 parts tannic acid, 0.001-0.002 parts $AgNO_3$, and 4–10 parts *Rhizoma bletillae* polysaccharide [103]. *Chen Kuen Ren et al.*, researched microneedle arrays that provided a minimally invasive platform for the administration of ocular medications [104]. A composition for a microneedle patch capable of delivering therapeutically active substances to a perilesional region for the treatment of a skin disease was disclosed by *Waldman Reid et al.* [105] who further revealed a method for the treatment of a skin ailment that involves the perilesional application of a dissolvable microneedle patch including microneedles, a therapeutically active drug, and a biodegradable polymer. *Natalie Artzi et al.* described techniques for treating a skin disorder as well as methods for locally reducing an immune response in the tissues of such patients. Methods included contacting a microneedle array composed of a degradable hyaluronic acid polymer with a disulfide bond, a therapeutic agent and applying pressure on the microneedle array that penetrated the skin surface, thereby releasing the therapeutic agent beneath the skin surface while simultaneously capturing it for subsequent analysis [108]. *Rhee Yun Seok et al.* devised a microneedle patch device for providing a significant quantity of drugs continuously to the skin. A microneedle patch provided by one aspect of the present invention increased drug content per unit area (1 cm^2) to a maximum of 100 mg compared to existing microneedles and therefore had a higher drug content per unit area than an existing transdermal absorption agent that was capable of delivering the drug into the body for a short time (within 24 h) and other for a long time (approximately three days or more) via micropores formed by microneedles [112]. The method of administering a dual therapeutic and cosmetic agent discovered by *Xu Bai et al.* allows for the transdermal application of a single agent with both therapeutic and cosmetic applications. Transdermal delivery was accomplished by administering a dual therapeutic and cosmetic substance to the recipient's skin in conjunction with a microneedle array [113]. *Yan Qinying et al.*, the invention pertains to pharmaceutical preparations and, more specifically to a microneedle for treating psoriasis via percutaneous delivery of lipidosome, as well as a method for preparing the microneedle [119]. *Su Jian Yu et al.*, present a plum slice and borneol soluble micro-needle eyed patch and its preparation technique for eliminating under-eye puffiness. The eyed pad made by the innovation was simple to prepare, effective at removing the pouch, user-friendly, and highly portable [124]. *Yingli et al.*, the invention describes a device for administering medication to the meibomian glands. The device includes a handle, a treatment head, and a meibomian gland drug delivery patch [136]. *Tamayol Ali et al.*, the invention relates to wound healing formulations and method which consists of microneedle arrays and devices for treating wounds and bacterial infections [144].

Patents in micro needling depending upon the technology innovation

Ahn Jun Young et al., reported a microneedle biosensor and a method for its fabrication [106]. *Praharaj Seemit et al.*, developed a technique for additive manufacturing that was used to create a support layer with microneedle protrusions [107]. *Dean Kamen et al.*, developed a microneedle containing delivery device for providing a therapeutic drug to a patient, having a base comprising a first side with a skin-adhering faced and a second side with a reservoir section [109]. The floating microneedle assembly created by *Mccaffrey et al.*, was detached from the device and protected by a pump housing [110]. The microneedle assembly would administer liquid medication to the user. *Matthew Hopcroft et al.*, [111] created a sensor for aiding the study of biological specimens *in vivo* employing a stiff needle with a protruding initial end for skin penetration. The invention of *Chang Sobin et al.*, provides microneedle delivery adapter devices and methods of administering drugs using the devices, including methods for inducing an immune response in a subject by administering an immunising composition containing a Sars-Cov-2 pathogen to the subject's skin [114]. *Shimizu Hiroko et al.*, created a needle applicator for feeding a liquid through a plurality of microneedles or adjacent to them onto a surface [115]. *Kim Seong Ok* and colleagues created the microneedle assembly [116]. *Kwak Min Kyu et al.*, intended to invent a composition for the treatment of atopic dermatitis comprising a nanosized bee pollen extract as the active ingredient and a microneedle patch used the same, and more specifically, a composition for the treatment of atopic dermatitis comprising a nanosized bee pollen extract as the active ingredient [117]. *Qian Hongliang et al.*, innovation revealed a double-response double-layer cross-linked insulin-controlled delivery microneedle and a technique for its fabrication. The microneedle comprises a backing layer part and a needle tip part, wherein the backing layer part was made from a soluble polymer solution and an insulin drug delivery system was arranged in the needle tip part [129]. *Pei Haifeng et al.*, the invention relates to the field of medical equipment more specifically to a revolutionary double-layer medicine balloon [139]. *Alary Marc et al.*, a precise array of distinct microneedles may be produced using a film with first and second, externally facing main surfaces [142]. *Aksit Aykut et al.*, the subject matter disclosed relates to a system and technique for the transmembrane administration of therapeutic drugs to the inner ear. The system comprises several microneedles that could be given to the rounded window membrane by a delivery device, such as a catheter which was capable of penetrating the rounded window membrane in a controlled manner to form temporary and self-closing perforations [143].

Table 2: Patents in microneedling technology in the year 2022

S. No.	Key invention	Patent no.	Applicant	Date	Inventor	Reference
1.	Microneedle for promoting wound healing	CN114668778A	Southwest National University	19-04-2022	Yu Yunlong; Zeng Rui, Qu Yan, Yang Xiao	[103]
2.	Microneedle array with an interlocking feature	WO2022197452A2	University Washington State [US]	22-09-2022	Chen Kuen Ren, Amer Maher	[104]
3.	Perilesional treatment of skin conditions	WO2022204255A1	Veradermics	29-09-2022	Waldman Reid	[105]
4.	Microneedle biosensor and manufacturing method for the same	WO2022149754A1	Albiti Inc [KR]	14-07-2022	Ahn Jun Young, Jang Eun Hee	[106]
5.	System and method for manufacturing microneedle assemblies with medicaments	US2022305736A1	Xerox Corp [US]	29-09-2022	Praharaj Seemit, Liu Chu-Heng, Herrmann Douglas K, Lefevre Jason M, Mcconville Paul J	[107]
6.	Microneedles and methods for treating the skin	WO2022183126A1	Brigham and Womens Hospital Inc [US], Massachusetts Inst Technology [US]	29-09-2022	Artzi Natalie, Dosta Pere, Puigmal Nuria, Solhjou Zhabiz, Yatim Karim, Azzi Jamil	[108]
7.	Medical agent dispensing systems, methods, and apparatuses	US2022273924A1	Deka Products Lp [US]	01-09-2022	Kamen Dean, Lanigan Richard	[109]
8.	Drug delivery device including pump with floating microneedle assembly	US2022273927A1	Insulet Corp [US]	01-09-2022	Mccaffrey Maureen, Cardinali Steven, O'connor Jason	[110]
9.	Needle sensor and method of manufacturing the same	US2022273240A1	Laxmi Therapeutic Devices Inc [US]	01-09-2022	Hopcroft Matthew	[111]
10.	Microneedle patch system for transdermal drug delivery	WO2022177205A1	Nat University Gyeongsang Iacf [KR]	25-08-2022	Rhee Yun Seok, Song Sangbyeong, Lee Jaemin, Song Chanwoo, Noh Inhwan	[112]
11.	Method of administering a dual therapeutic and cosmetic agent	US2022265589A1	Nanomed Skincare Inc [US]	25-08-2022	Xu Bai	[113]
12.	Systems and methods for administering vaccine composition using modular multi-vial microchannel delivery adapter devices	WO2022173863A1	Aquavit Pharmaceuticals Inc [US]	18-08-2022	Chang Sobin, Nevrivy Daniel,Sankaranarayan Saiprasad	[114]
13.	Needle applicator and puncture injection kit	WO2022168713A1	Shiseido Co Ltd [JP]	11-08-2022	Shimizu Hiroko, Obana Takakazu, Yoshimura Mika, Ogai Noriyuki, Toda Yasuhiro	[115]
14.	Microneedle assembly	KR102425556B1	Daewoong Therapeutics [KR]	29-07-2022	Kim Seong Ok, Youn Young Sook, Kim Jae Heon	[116]
15.	Composition for treating atopy comprising nanosized bee pollen extract as an active ingredient and a microneedle patch using the same	KR20220104429A	Eulji University Industry Academy Coopera	26-07-2022	Kwak Min Kyu, Lee Yun Kyung	[117]
16.	Polyglycerol, complex gel composition containing said polyglycerol, drug delivery microneedle including said complex gel composition, and methods for producing same	WO2022154055A1	Kanagawa Institute Of Industrial Science And Tech [JP], University Nat Corp Tokyo Medical and Dental [JP]	21-07-22	Matsumoto Akira, Miyazaki Takuya	[118]
17.	Microneedle for treating psoriasis through percutaneous delivery of lipidosome and preparation method of microneedle	CN114432230A	Zhejiang Industrial University	06-05-2022	Yan Qinying, Fang Min, Yang Gensheng, Weng Jiaqi; Shen Shulin, Wang Yan	[119]
18.	Slow-release microneedle patch and preparation method thereof	CN114668712A	Shenzhen College	24-03-2022	Gao Yunhua, He Meilin, Yang Guozhong, Zhang Suohui	[120]
19.	Preparation method of a hollow microneedle patch, hollow microneedle patch and injection device	CN114344699A	University Sichuan	11-01-2022	Gou Maling, Li Rong	[121]
20.	Degradable slow-release composite microneedle for treating food allergy and preparation method thereof	CN114668709A	University Chinese Agricultural	28-06-2022	Che Huilian, Zhang Erkang, Zeng Binghui, Liu Guirong, Yao Lu, Wang Qi	[122]
21.	Soluble Superoxide Dismutase microneedle patch with anti-ageing effect	CN114259458A	Shanghai Hu Yang Biotechnology Co Ltd	04-01-2022	Dong Liang, Chen Yongli, Zhang Shan, Zhang Yanyan, Gan Miao	[123]
22.	Plum slice and Borneol soluble micro-needle eye patch for removing eye puffiness and preparation method thereof	CN114366700A	Xinxiang Shenzhen Science and Tech Co Ltd	19-04-2022	Su Jianyu, Fan Penghui, Lyu Manxia, Hou Yuchao, Wang Yanjiao	[124]
23.	Soluble microneedle and manufacturing method thereof	CN114558242A	Youmicro Pearl Ha Biotechnology Co Ltd	31-05-2022	Leng Gang, Lee Sung Guk, Ma Yonghao	[125]
24.	Polydopamine photothermal conversion effect microneedles and preparation method thereof	CN114504727A (B)	Guangzhou Nali Biotechnology Co Ltd	17-05-2022	Chen Yanbiao, Chen Jiali, Tang Cong,Li Sidong	[126]
25.	Glucagon-loaded wearable device for treating hypoglycemia	CN114376569A	University Zhejiang	19-01-2022	Zheng Chao, Yu Xiang, Tanie; Zhang Yikai, Wang Shengyao, Ye Shu, Hu Yepeng	[127]
26.	Silicon-based ice microneedle and preparation method thereof	CN114588527A	University Suzhou	7-06-2022	Su Xiaodong, Cheng Wei, Zou Shuai, Ni Mengfei, Dai Longfei	[128]

S. No.	Key invention	Patent no.	Applicant	Date	Inventor	Reference
27.	Double response double layer cross-linked insulin controllable delivery microneedle and preparation method thereof	CN114569706A	Chinese Pharmacology University	03-06-2022	Qian Hongliang, He Mujiao, Li Qihang, Ma Yuhong, Chen Wei, Huang Dechun	[129]
28.	Rapid separation type liposome composite sustained-release microneedle and preparation method thereof	CN114569583A	Medium Mountain University	08-03-2022	Zeng Xiaowei, Yang Yao, Hu Jingwen, Huang Ping, Yang Li, Hou Ailin, Lin Jiachan	[130]
29.	Microneedle array enzyme composite electrode and preparation method thereof	CN114569124A	Southern Hospital of Southern Medical University	08-03-2022	Zhou Cuiping, Li Xu, Liu Zhaobin	[131]
30.	A method for manufacturing a microneedle	KR102427901B1	Daewoong Therapeutics [KR]	02-08-2022	Kang Yoonsik, Im Jiyeon, Eum Jaehong, Lee Booyong, Kim Donghwan, Kang Bokki	[132]
31.	Macromolecular soluble microneedle patch and preparation method thereof	CN114515267A	University Wuhan Tech	20-05-2022	Hu Ping, Liu Yang, Fan Lihong, Zhang Xingui, Chen Tiantian, Tong Zexin	[133]
32.	Composite microneedle balloon and preparation method thereof	CN114470341A	Nanjing Tympanic Building Hospital	02-03-2022	Zhao Yuanjin, Zhang Xiaoxuan, Cheng Yi, Zhang Dagan, Shang Yixuan	[134]
33.	Microneedle female die, the preparation process of microneedle female die, microneedle patch and preparation process of microneedle patch	CN114454392A	Youmicro Pearl Ha Biotechnology Co Ltd	28-01-2022	Lee Sung Guk, Leng Gang, Ma Yonghao, Yang Jian	[135]
34.	Device for delivery of drug to meibomian glands	CN114081716A	Shenzhen Hospital of Southern Medical University	22-01-2022	Li Yingli, Liao Sizhao, Su Wenhua, Zhao Pengyue, Li Xue, Yang Meiqing, Gao Na, Zhou Lili	[136]
35.	Bacteria-responsive microneedle patch as well as preparation method and application thereof	CN114432276A	University Changzhou	27-01-22	Wang Jianhao, Lei Xiaoling, Zhou Xinpei, Li Mengjin, Qiu Lin, Zhou Shuwen, Cui Pengfei, Wang Cheng, Gao Zihan	[137]
36.	Dissoluble microneedle containing active microalgae, microneedle patch, preparation method and application	CN114557954A	Australia University	03-03-2022	Wang Ruibing, Zhang Qingwen, Wang Zeyu	[138]
37.	Novel double-layer medicine balloon	CN114569868A	Military And Western War Area General Hospital For Chinese People Liberation	03-06-22	Pei Haifeng, Mou Dong, Peng Ke, Wang Zhen, Wang Xiong, Wang Peng, Li Jing	[139]
38.	Microneedle immunotherapeutic multi-component system and a method for vaccination	US2022023605A1	Microneedles Inc [US]	27-01-2022	Zvezdin Vasilii, Pavlov Andrei	[140]
39.	Methods and compositions for microflillng the skin with hyaluronic acid using microchannel technology	US2022257494A1	Aquavit Pharmaceuticals Inc [US]	18-08-2022	Chang Sobin	[141]
40.	Microneedle arrays and methods for making and using	US2022111189A1	Johnson and Johnson Consumer Inc [US]	14-04-2022	Alary Marc, Hopson Peyton, Liu Jan-Joo, Lunde Erik, Patel Bharat, Morano Emanuel	[142]
41.	Microneedles to deliver therapeutic agent across membranes	US2022176096A1	University Columbia [US]	09-06-2022	Aksit Aykut, Lalwani Anil K, Kysar Jeffrey W, West Alan	[143]
42.	Drug delivery using microneedle arrays	US2022273926A1	University Nebraska [US]	01-09-2022	Tamayol Ali, Derakhshandeh Hossein, Mostafalu Pooria	[144]

Patents in microneedles technology according to the nature of the chemical constituents

Che Huilian et al., created bacteriostatic sprays and disclosed a degradable slow-release composite microneedle and method for its manufacture for treating food allergy. The composite microneedle consists of a base and a needle tip with anti-allergic drugs included in the needle tip material [122]. A superoxide dismutase-soluble microneedle patch with an anti-ageing effect was disclosed by *Dong Liang et al.* who worked on anti-ageing superoxide dismutase soluble microneedle patch which consisted of a backing layer and a needle tip layer consisting of soluble microneedles arrayed on the backing layer. Compared to other procedures for making soluble microneedles, freeze-drying was utilised [123]. *Chen Yanbiao et al.,* described a polydopamine microneedle with a photothermal conversion action and its preparation process. The microneedle had a shell and a cavity when the shell was formed by crosslinking a temperature-sensitive polymer, the cavity was prepared in a laser pore-forming mode and the cavity was used for loading polydopamine nanoparticles and an active drug [126]. *Zheng Chao et al.,* the invention provides a glucagon-loaded wearable device for treating hypoglycemia which comprised of housing which comprised of an upper cover, a bottom shell and watchbands arranged on two sides used for fixing the wearable device on the surface of human skin, the controlled module, the lifting module and the drug delivery module [127*]. Su Xiaodong et al.,* disclosed a silicon-based ice microneedle and a method for its preparation. The silicon-based ice microneedle comprises a silicon wafer and a number of micron needle-shaped structures formed on the silicon wafer and distributed in an array, hollow structures penetrating through the tops of the micron needle-shaped structures to the bottom of the silicon wafer, and ice soluble needle tips [128]. *Zeng Xiaowei et al.,* the invention pertains to microneedle drug delivery systems and more specifically to a quick separation typed liposome composite sustained-release microneedle and its manufacturing process [130]. *Hu Ping et al.'s* current invention relates to a polymer-soluble microneedle patch and a method for its preparation, when mass ratio of polyvinyl alcohol to the tannic acid in the polyvinyl alcohol-tannic acid composite material was 12: 2 [133, 151]. *Lee Sung Guk et al.,* invention pertains to the field of microneedles The microneedle consists of a PDMS forming groove and a defoaming film, with several microneedle protrusions arrayed in the PDMS forming groove. In addition, the defoaming film adhered to the upper PDMS forming groove [135, 152]. *Wang Jianhao et al.,* invented microneedle patches, bacterial responsive drug-loaded nanoparticles, and a polymer matrix [137]. *Chang Sobin et al.,* provided an effective amount of hyaluronic acid in solid form forming the hyaluronic acid in an aqueous solution and delivering the solution comprising hyaluronic acid to the subject's skin [141].

Patents in microneedles technology according to the modification of the category of microneedling

Matsumoto Akira et al., examined mechanical strength for puncturing the skin and strong drug-releasing capabilities after puncturing the skin with a micro-needle patch. The needle included a complex gel composition including polyglycerol and a copolymer comprising a Phenyl Boronate based monomer unit which was capable of retaining a drug and had drug-permeable properties [118]**.** *Gao Yunhua et al.,* the invention disclosed an implanted microneedle patch and a technique for its production. Initially, the invention disclosed an implantable slow-release microneedle comprising a needle pointed, a needle body, and a base when the needle pointed comprised a needle-pointed centre layer and a needle-pointed outer layer [120]. *Gou Maling et al.,* invention proposed a method for preparing a hollow microneedle patch and an injection device. The hollow microneedle array diagram and the bottom plate diagram were loaded into a digital light processing (DLP) system, the hollow microneedles were then generated according to the hollow microneedle array diagram, followed by the formation of the bottom plate. According to the method, a microneedle patch of large size and good quality could be manufactured swiftly, and the patch's structure could be precisely regulated and controlled [121]. *Leng Gang et al.,* the invention relates to a soluble microneedle and its method of manufacture [125]. *Zhou Cuiping et al.,* the invention offers a microneedle array enzyme composite electrode and a technique for its manufacture; it is related to the biomedical engineering sector [131]. *Kang Yoonsik et al.,* invented a mould in which one or more microneedle engraved parts were formed, including a tip engraved part and a reservoir engraved part communicating with the tip engraved part, and a raw material containing a pharmacological component in the microneedle engraved part which was the embodiment of the present invention [132]. *Zhao Yuanjin et al.,* the invention includes a composite microneedle balloon together with a technique for its preparation. The composite microneedle balloon comprises a medical balloon, a primary coating, and a secondary coating, wherein the surface of the medical balloon was coated with the primary coating and the secondary coating was uniformly distributed on the surface of the primary coating [134, 150]. *Wang Ruibing et al.,* invention discloses a dissolvable microneedle containing active microalgae, a microneedle patch, a preparation technique, and an application which related to microneedle technology and microalgae preparations. The dissolving microneedle patch based on the active microalgae produced oxygen in the deep layer of the skin via photosynthesis by delivering the active microalgae in order to achieve local treatment, and it was biocompatible, painless, minimally invasive, and adaptable [138]. *Zvezdin Vasilii et al.,* formed a dissolvable microneedle drug delivery system includes a fixation component with an opening window area and at least two replaceable and/or dissolvable inner matrices that fit successively into the window area. The fixation component consisted of an array of microneedles attached to its base, to secure the delivery system to the skin [140].

Current and future developments

It has been established that microneedles are potent devices that can considerably improve the efficacy of transdermal medication administration. The primary advantages of Microneedles systems are their painless method of drug delivery for a vast array of compounds, their high patient compliance, and their possibility for self-administration. Even though numerous Microneedle designs have been found to improve drug administration, there is still a need for Microneedles that can form micro-conduits/micro-pores with greater accuracy and reproducibility, to accommodate the difference in individual skin types and skin elasticity. Therefore, the various patents presented in this article have the potential to be utilised by patients for constant and reliable penetration into biological tissue throughout the device's lifetime with minimal inter-individual variability. Because ease of use is one of the primary selling advantages of conventional transdermal patches. Microneedles should ideally be reasonably inexpensive, reusable, portable, and simple to use by all patients, regardless of age or level of expertise. Lastly, it should be mentioned that few Microneedles are currently commercially accessible. Therefore, engineering, pharmaceutics, and the healthcare professions are faced with the difficult task of transforming patented innovations into clinically approved devices before widespread usage of Microneedles.

CONCLUSION

Our largest organ, the skin, serves as an intriguing and distinctive interface between the outside world and us. Since several years ago, it had been possible to administer drugs via intact skin. The fact that microneedle research in the US is one of the most successful novel research areas in drug delivery today is proof of the success of the microneedle drug delivery technology. Drugs like protein, peptides, vaccines, glucagon, minoxidil, and hyaluronic acid are already commercialised as microneedles. The US market for microneedles is currently rising at a rate of more than 7% CAGR yearly, and it is continuing to increase. The natural skin barrier's restriction on the penetration of foreign substances has inspired pharmaceutical scientists to develop a variety of strategies to modify the cutaneous membrane's permeability in order to obtain therapeutic levels of the active chemicals in the systemic circulation. The simplest and most extensively researched method among these is to employ microneedles to reversibly reduce the skin's barrier resistance. Numerous micro-needling procedures that have been used to facilitate the passage of active ingredients across skin have been documented in a plethora of research reports and patents in the scientific literature. Pharmaceutical companies examine several types of micro-needling technologies and their applications, but these are never published in scientific journals since they are patented by the investigators. Consequently, a thorough examination of patents is always required as part of any literature search on a specific subject. The current article has made an effort to cover the most recent micro-needling patents issued in 2022. Even though the information might not be complete, it might be helpful to point other researchers who are interested in transdermal skin treatments in the right direction. The patents have been awarded in a variety of areas, such as those pertaining to inventors, enterprises, nations offering protection, materials, procedures, chemicals, or pharmaceuticals, the stage of development of the chosen patents for the creation of microneedle arrays, and so forth. According to the use of microneedles in the targeting and treatment of diseases, the majority of patents for microneedle technology have been issued. The readers are also urged to do a thorough analysis of the microneedling patent landscape in light of technological advancements, chemical composition, and technological modifications.

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AUTHORS CONTRIBUTIONS

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CONFLICT OF INTERESTS

The authors declared no conflict of interest

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