Emergence of Transdermal Drug Delivery Technologies: A Historical Synopsis and Systematic Review on Microneedles

Nonye Linda Ifekpolugo

ABSTRACT

Introduced as an appealing alternative to oral and parenteral drug delivery systems, the concept of transdermal drug delivery has undergone significant expansion from the first-generation transdermal patches and permeation-enhancement-driven second-generation agents to the stratum corneum bypassing techniques of third-generation transdermal delivery agents, including microneedles. Commonly referred to as a micron-scale conjugate of transdermal drug products and hypodermic needles, microneedles were introduced primarily to circumvent issues of patient compliance triggered by pain, inflammation, and, in severe cases, abscesses and lesions at the site of administration following the use of hypodermic needles. Since its inception, this concept has evolved majorly in terms of form, material, fabrication technique, and design, and this article thus aims to explore the historical background of microneedles, their modern-day clinical applications, and the challenges and regulatory considerations surrounding their use.

Keywords: Microneedles, Transdermal drug delivery, Drug delivery technologies

Pharmaceutical Scientist, Seoul, South Korea

Correspondence to:
Nonye Linda Ifekpolugo,
nonyeifekpolugo2@gmail.com

Additional material is published online only. To view please visit the journal online.

Cite this as: Ifekpolugo NL. Emergence of Transdermal Drug Delivery Technologies: A Historical Synopsis and Systematic Review on Microneedles. Premier Journal of Science 2024;1:100019

DOI: https://doi.org/10.70389/PJS.100019

Received: 31 July 2024

Revised: 30 September 2024

Accepted: 30 September 2024

Published: 15 October 2024

Ethical approval: N/a

Consent: N/a

Funding: No industry funding

Conflicts of interest: N/a

Author contribution:
Nonye Linda Ifekpolugo – Conceptualization, Writing – original draft, review and editing

Guarantor: Nonye Linda Ifekpolugo

Provenance and peer-review: Commissioned and externally peer-reviewed

Data availability statement: N/a

Introduction

Transdermal drug delivery encompasses techniques to facilitate drug movement via skin barriers and into the systemic circulation, and its inception was to deal with problems of stability, bioavailability, and first-pass metabolism associated with the oral route, as well as issues of skin trauma and ultimately compliance associated with the parenteral routes of drug administration.[1] Convenience and thus better compliance, a bypass of first-pass metabolism and improved stability, the potential of system modification to achieve tunable release characteristics, etc., are only some of the comparative advantages that have come to be associated with this route of drug delivery.[2,3]

Transdermal drug delivery systems (TDDS) exist in three broad generational categories (Figure 1).[1] First-generation TDDS operated on the principle of a diffusion-based uptake of majorly lipophilic therapeutic agents, with the 1972 FDA-approved scopolamine patch for motion sickness being one of the representative commercially available products of this generation.[4] However, certain requirements, including low molecular weight and sufficient lipophilicity, placed a limitation on the number of therapeutic agents that could be administered via this route, prompting increasing research into other transdermal delivery systems.[1] The next generation of TDDS enhanced skin permeability by employing chemical enhancers, including amphiphilic molecules, surfactants, esters, etc., to trigger a transient distortion of the stratum corneum, external energy sources to accelerate the delivery efficiency of drug compounds, and ultrasound, the frequency of which could alter the lipid structure of the stratum corneum.[5] The need for processes that ensure minimal skin trauma informed the introduction of third-generation TDDs, including high-energy power methods and microneedles.[4] While high-energy methods, including radiofrequency ablation, laser ablation, etc., are capable of expanding the scope of therapeutic agents that could be delivered transdermally, their adaptation is limited by expensive, specialized, and technical implementation protocols, a phenomenon that has prompted more intensive research into microneedles as an alternative system for transdermal drug delivery.[4] In addition, while the channels created by delivery techniques of the first, second, and third generations were nanometer-sized, facilitating the transdermal delivery of smaller molecules, the micron-sized channels created by microneedles hold the promise of the transdermal delivery of macromolecules and larger complexes.[6]

The concept of microneedles is one of several techniques that have been developed to facilitate drug diffusion across the epidermis and into systemic circulation and is a growing focus of pharmaceutical research. This delivery system typically consists of an array of micron-sized needles less than 1 mm in length, supported on a base, and capable of epidermal penetration and bypass of the stratum corneum to create microchannels that facilitate transdermal drug deposition while maintaining minimal interaction with nerve endings in the dermis.[7]

Following an intellectual property submission conceptualizing the application of microneedles to drug delivery to the US patent office in 1971, Martin S. Gerstel and Virgil A. Place are regarded as pioneers of this delivery system.[8,9] However, it was not until the 1990s, following advancements in the microelectronics industry, that the equipment needed to realize this concept became more readily available.[6] The rationale behind the inception of and increasing research into microneedles is inspired by their potential benefits in comparison to traditional parenteral systems, including a design that ensures minimal interaction with the pain and touch receptors in the dermis, thus guaranteeing minimum pain and discomfort; ease of application requiring no specialized training; convenience; and improved patient compliance, among others.[9] Microneedle technology is currently being largely investigated, particularly for the delivery of macromolecules including hormones, insulin, siRNA, and other peptides.[10] A 2021 literature analysis by Rohan et al.,[11] with an investigation scope utilizing data

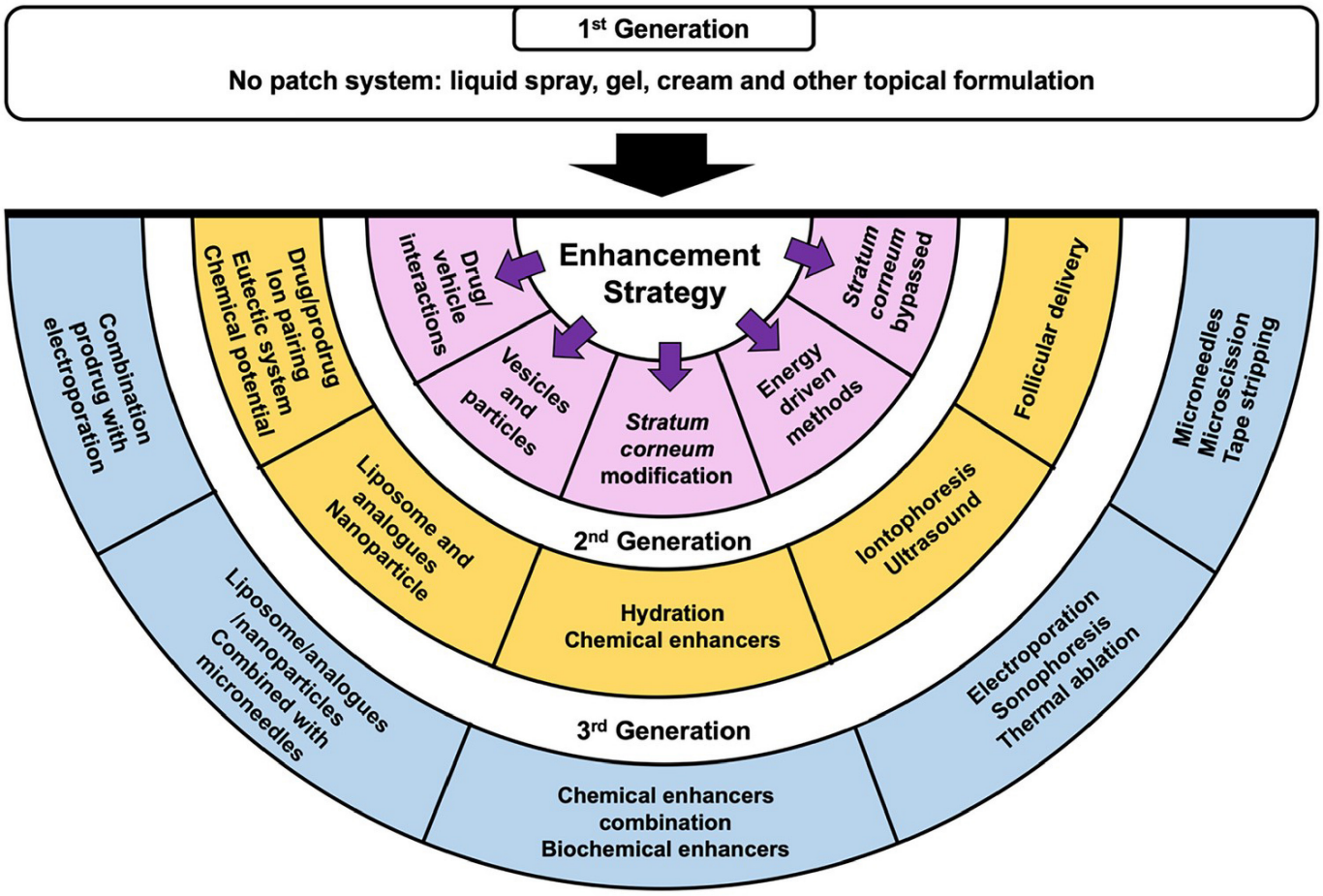

Fig 1 | Summary of the technologies utilized for enhancing transdermal drug delivery. Reproduced from Ramadon et al.[1] Creative Commons license: https://creativecommons.org/licenses/by/4.0/

from 1990 to 2018, revealed a publication count of 1,190, including research and review articles, thus underlining the increasing interest in and the growing impact of this technology.

This article focuses on the emergence of microneedles as a system for transdermal drug delivery, its evolution in terms of design and formulation material, as well as its clinical application and associated regulatory considerations.

Evolution of Microneedles

Microneedles have undergone comprehensive transformation encompassing formulation materials, fabrication techniques, and design. Solid, coated, hollow, dissolvable, and hydrogel-forming microneedles are now considered representative classes of microneedles, differing primarily in formulation material as well as the mechanism by which they initiate drug release (Figure 2).[12] Alongside these developments has been a corresponding evolution in terms of fabrication methods and design.

Type/Formulation Material:

Solid Microneedles:

These were the foremost class of microneedle systems to be developed, with metals such as nickel, stainless steel, and titanium being the primary fabrication materials.[13] They are typically manufactured via a variety of methods, including drawing lithography, micromolding, laser cutting, wet etching, metal electroplating, and so on.[14] This class of microneedles operates via a "poke and patch" mechanism generally involving pretreatment of the skin with the microneedles to create temporary microchannels that facilitate the transdermal permeation of subsequently applied topical agents, including gels, ointments, and creams.[15] Other variations of this mechanism exist, including the use of rolling microneedle devices to create miniscule skin perforations, as well as a "scrape and patch" mechanism in which microneedle devices create micropunctures on the skin, both followed by the introduction of therapeutic formulations.[16] Solid microneedles have found extensive application in the cosmetics industry, particularly as rollers and pens,[17] and are emerging systems for the delivery of vaccines due to their ability to trigger prolonged and heightened immunogenic responses compared to traditional parenteral systems.[18] A major drawback of this class of microneedles, however, is inaccurate dosing due to poor rheology, specifically after the administration of more viscous formulations.[13] Furthermore, issues of convenience due to a two-step application process,

DOI: https://doi.org/10.70389/PJS.100019 | Premier Journal of Science 2024;1:100019

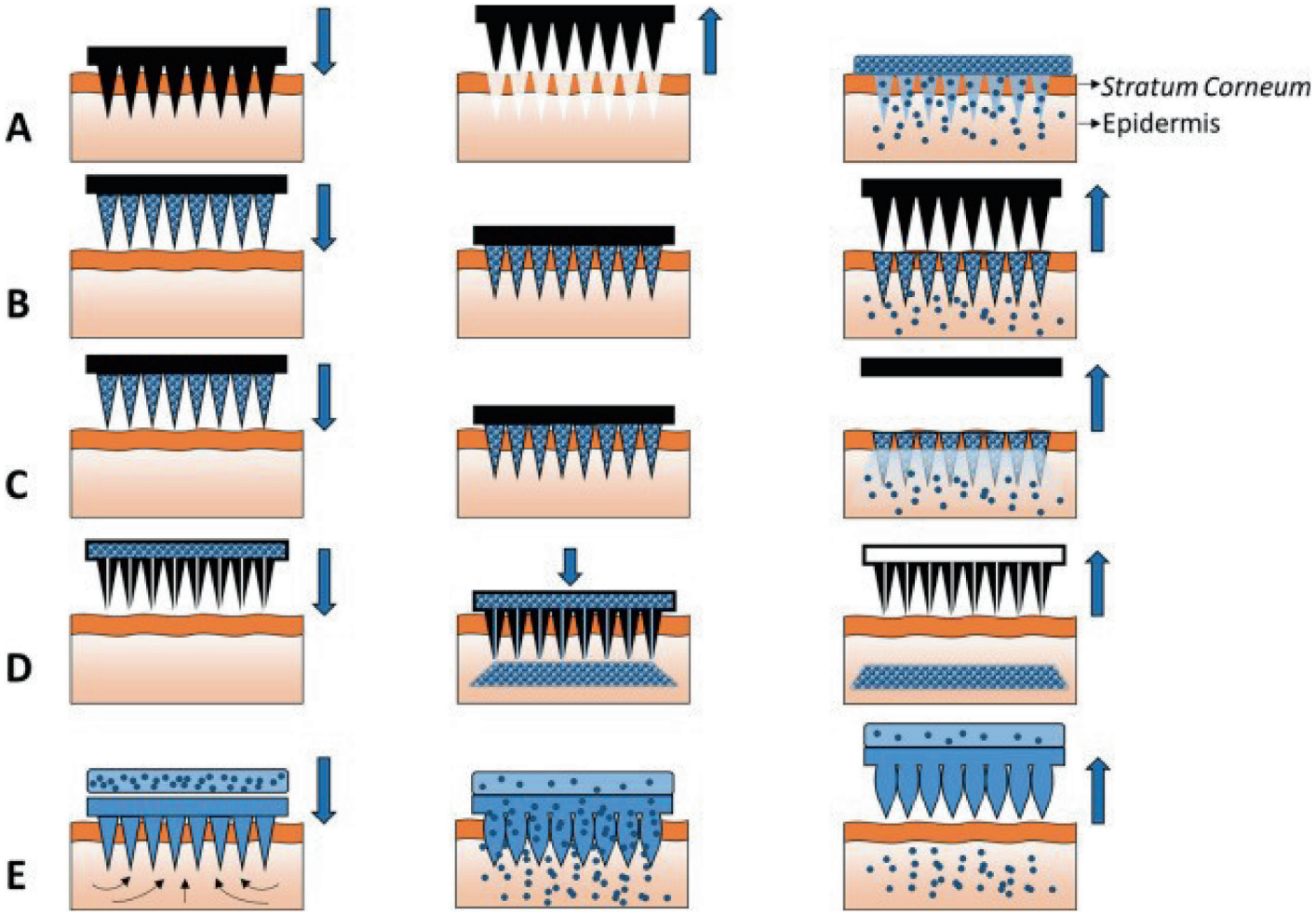

Fig 2 | A schematic representation of five different MN types used to facilitate drug delivery transdermally. (A) Solid MNs for increasing the permeability of a drug formulation by creating microholes across the skin. (B) Coated MNs for rapid dissolution of the coated drug into the skin. (C) Dissolvable MNs for rapid or controlled release of the drug incorporated within the microneedles. (D) Hollow MNs used to puncture the skin and enable the release of a liquid drug following active infusion or diffusion of the formulation through the needle bores. (E) Hydrogel-forming MNs take up interstitial fluids from the tissue, inducing diffusion of the drug located in a patch through the swollen microprojections. Reproduced from Larrañeta et al.[12] Creative Commons license: https://creativecommons.org/licenses/by/4.0/

increased risk of infection, and metal deposition in the skin have prompted increasing research into alternative microneedle-mediated delivery methods.[13]

Coated Microneedles:

Unlike solid microneedles, coated microneedles typically allow for a one-step administration process.[19] Coated microneedles typically consist of a solid microneedle platform coated with solutions or suspensions of the therapeutic agent.[16] In recent times, these platforms have been fabricated from a variety of materials, majorly including metals [20–22] and polymers.[23–25] Dipping, gasjet drying, inkjet printing, spraying methods, etc., are some of the most commonly employed methods for coating microneedles.[15] These methods have now evolved to include excipients introduced into the coating formulation for diverse purposes, including viscosity and surface tension regulation as well as protection of labile therapeutic agents from degradation.[26] The use of coated microneedles for the simultaneous administration of multiple drugs by coating the needles with different therapeutic compounds is a concept that is increasingly being explored.[19] A major drawback associated with coated microneedles is a maximum drug loading capacity of 1 mg that is heavily influenced by factors such as the size of the microneedle array, coating technique, and density of the coating layer.[13]

Dissolving Microneedles:

Dissolving microneedles, employing biocompatible and lipophilic polymers as primary matrix material, were developed to address issues of biohazard and sharp waste residue associated with silicon and metal employed in the fabrication of solid and coated microneedles.[27] Polyvinylpyrolide, hyaluronic acid, and poly (methyl vinyl ether-co-maleic anhydride) are reportedly the most commonly employed polymers in the fabrication of drug-loaded dissolving microneedles, while polyvinyl acetate, trehalose,

chitosan, carboxymethylcellulose, and hyaluronic acid are frequently used in the development of vaccine-loaded dissolving microneedles.[28] This class of microneedles is fabricated primarily via a micromolding technique using prefabricated molds.[28] Dissolving microneedles operate via a poke and release mechanism characterized by the breakdown of the polymer matrix and release of the encapsulated therapeutic agent following needle insertion.[29] There is increasing research into the application of hyaluronic acid-based dissolving microneedles to the cosmetics industry primarily because of their natural occurrence in the body and, thus, biocompatibility.[28] Furthermore, the possibility of modification of polymer characteristics enables the potential fabrication of dissolving microneedles with tunable drug release properties.[30] Problems of hygroscopicity and inadequate needle strength, ineffective dose control, and drug loss following insufficient insertion have raised concerns surrounding the clinical applicability of dissolving microneedles.[27]

Hollow Microneedles:

Hollow microneedles were conceptualized primarily to address issues of limited drug loading capacity associated with previous microneedle models.[31] With similar morphology to conventional needles, this class of microneedles is able to facilitate delivery of drug solutions via a passive diffusion process or an active pressure-induced flow down the needle shaft.[32] Hollow microneedles are fabricated out of metal, silicon, ceramics, etc., primarily via manufacturing techniques such as microelectromechanical systems, etching, micromolding, and more recently, 3D printing.[31] Microneedle tip occlusion by skin and the need for extremely precise fabrication techniques have been reported as some of the major limitations associated with its development and use.[31]

Hydrogel Forming Microneedles:

Being the most recent class of microneedles, hydrogel-forming microneedles operate via a novel mechanism involving expansion of the microneedle matrix layer on contact with interstitial fluid (ISF), resulting in microchannels and thus enabling drug delivery.[33] Their capacity for extensive ISF uptake, which is a major source of biological markers, is a phenomenon that informs their current application to diagnosis and biosensing.[34] Polymers employed as microneedle matrix thus have to be capable of extensive water absorption and structural expansion following insertion, and cellulosic derivatives continue to be some of the most commonly applied matrix materials to the fabrication of hydrogel-forming microneedles.[13] While an improved drug loading capacity, adjustable release properties, lessened issues of biohazard, and safety are some associated advantages, limitations to the rate and extent of drug delivery, issues of potential toxicity, and tissue damage are some associated problems that continue to prompt intensive research into this class of microneedles.[34]

Fabrication Technology

Evolution in the form and design material of microneedles has brought about corresponding changes in fabrication technology. Some of the first methods for the manufacture of microneedles employed standard microfabrication techniques to etch micron-sized needles into silicon. These methods now also apply to materials like ceramic, metal, and PDMS (polydimethoxysilane).[35] 3D laser cutting and laser ablation techniques involving the application of infrared laser to the incision of steel or titanium plates to define MN structure and the use of photon pulses to sculpt desired geometries, respectively, have primarily been applied to the development of metal microneedles.[36] A relatively straightforward and budget-friendly centrifuge and vacuum-based micromolding process involving molds developed via lithography has found common application in the fabrication of sugar, polymer, and in some cases ceramic microneedles.[37] The atomized spraying method involving the deposition of drug formulation onto PDMS molds via high-pressure atomization and the droplet-born air blowing method, a drawing lithography technique that allows for the deposition of polymer droplets onto mold contour via gentle air injection, have been developed to address issues of geometric constraints and UV/heat-induced loss of activity, respectively, associated particularly with the fabrication and application of dissolving microneedles.[36] 3D printing involving the use of computer-aided design models and addressing issues of limited geometry and application is another budding specialization within the microneedle fabrication industry.[38] Antonara et al.[39] report a fused deposition modeling 3D negative mold printing technique to simplify the microneedle fabrication process. Following issues of unfavorable manufacturing conditions that have come to be associated with additive manufacturing techniques, including 3D printing, a 2023 paper reports the premier application of aerosol jet printing to the fabrication of dissolving microneedles.[40]

As the concept of microneedles for transdermal delivery continues to gain traction, the pharmaceutical industry continues to pursue research to develop more cost-effective and optimized fabrication methods that address current limitations to the development and clinical application of microneedles.

Design

Alongside formulation material and fabrication process, microneedles have also experienced significant design improvements to address limitations to effective drug delivery. Makvandi et al.[41] in a paper centered around the fabrication and application of microneedles that mimic biological systems detail a novel class of microneedles. Mosquito proboscis-inspired microneedles for blood sampling, bee stinger, eagle claw-inspired microneedles for improved tissue adhesion, etc., have raised questions surrounding the applicability of designs found in nature to the improvement of the transdermal drug delivery efficiency of conventional microneedle

DOI: https://doi.org/10.70389/PJS.100019 | Premier Journal of Science 2024;1:100019

systems.[41] In order to circumvent issues associated with long application time and waning patient compliance following the application of long-acting MNs to achieve extended release of the embedded therapeutic agent, the concept of rapidly separable microneedles is slowly gaining traction.[42] This novel microneedle design, encompassing patches with a rapidly dissolving backing layer, patches with a more delicate hinge between the backings and needle tips, as well as hydrogel-based microneedles, holds the promise of a significantly reduced administration time.[42] The conceptualization of stimuli-responsive microneedles was primarily to address issues of toxicity caused by inadvertent drug discharge by restricting the release of the embedded therapeutic agent only in response to stimuli indicative of the associated physiological stress.[43] Following this, microneedles have been fabricated capable of drug release in response to endogenous stimuli, including pH, glucose, and reactive oxygen species, and exogenous stimuli, including light, temperature, ultrasound, mechanical tension, etc.[44] Following increasing research into "nano-in-micro" systems consisting of drug nanoparticles entrapped within microneedle tips to facilitate improved drug delivery, Li et al.[45] attempted the fabrication of diclofenac nanoparticle-loaded microneedles, which exhibited enhanced *ex vivo* skin penetration, rapid drug uptake, and a sustained release profile following *in vivo* studies. Compartmental microneedle systems consisting of multiple chambers per needle array to allow for the simultaneous administration of different therapeutic agents, particularly vaccines, are another example of a microneedle design strategy that is slowly gaining popularity.[46] In a 2024 paper aimed at visualizing the possibility of a system capable of the concurrent delivery of protein molecules, Wright et al.[47] attempted the fabrication and characterization of a multilayered microneedle system for the triphasic delivery of small molecules and proteins, with results highlighting the need for a more in-depth research into techniques that could be implemented to effect distinct drug release between phases. Furthermore, in a bid to regulate drug release kinetics, Park et al.[48] attempted the development of a biphasic microneedle system consisting of poly(lactic-co-glycolic acid) (PLGA) and polyvinylpyrrolidone (PVP) as matrix material, the *in vitro* characterization studies of which revealed a sustained release of the embedded therapeutic, Bovine Serum Albumin (BSA), from the PLGA layer over the 7-day experimental period and an almost immediate release from the PVP layer within 30 minutes of insertion, thus highlighting the potential of application of multilayered microneedle designs to diseases requiring a rapid initial dose followed by a prolonged release of the therapeutic agent.

Increased research into microneedles propelled by its potential to revolutionize health care has triggered a corresponding evolution in terms of form, fabrication material, technology, and design, and the coming years hold the promise of a more widespread and extensive integration of microneedles into potentially every sector of the healthcare industry.

Application of Microneedles

The concept of microneedles is finding growing applications in the healthcare industry. Its application has been broadly categorized into cosmetic, therapeutic, and diagnostic.[49] The application of microneedles to the cosmetics industry has been divided into two general categories: stimulation of the skin's natural rejuvenative process and augmented delivery of therapeutics to the skin for purposes including skin brightening, hydration, scar and hyperpigmentation management, and wrinkle erasure.[50] A 2023 study attempted the fabrication of hydrolyzed collagen-based microneedles for the transdermal delivery of collagen, the *in vivo* evaluation of which highlighted its ability to positively impact dermal collagen levels.[51] Following its extensive application to skin care as a humectant, several authors have attempted the fabrication of hyaluronic acid or hyaluronic acid derivative-based microneedles for managing hydration and wrinkling.[52–54]

The therapeutic application of microneedles is primarily due to the convenience of use in cases of chronic diseases requiring long-term therapy, the potential for lower dosing and reduced incidence of side effects, enhanced drug delivery efficiency, particularly in conditions characterized by a direct mechanical or pathological trauma to the skin, etc. Following this, microneedles have been developed and characterized for the delivery of therapeutic agents for a variety of disease conditions, including diabetes mellitus,[55,56] cancer,[57,58] psoriasis,[59,60] chronic and neuropathic pain,[61,62] hypertension,[63,64] etc.

Furthermore, the abundance of antigen-presenting cells in the dermis translating to a more efficient immune response activation has informed increasing research into the application of microneedles to the delivery of vaccines,[65] but despite the widespread excitement fueled by the potential of this application to revolutionize the process of immunization, particularly in developing countries, due to issues of excessive fabrication cost and limited funding, Intanza, Fluzone, and MicronJet600 remain the only commercially available microneedle-based systems for vaccine delivery.[66]

The convenience of self-administration, improved delivery, and prolonged efficacy associated with microneedles have also prompted their application to the delivery of contraceptive agents.[67] Rajput et al. [68] attempted the fabrication of a levonorgestrel liposome-loaded microneedle array patch (MAP) that exhibited sustained release of this contraceptive agent over a 28-day period. Another recent study achieved an approximately 6-month sustained release of levonorgestrel via a novel core-shell design system fabricated by a sequential casting method employing PLGA, poly(l-lactide), and poly(D,L-lactide) as polymer materials.[69] Burgeoning research into this field highlights the potential of microneedle systems

to replace conventional oral, ring, intrauterine, and implantable contraception methods.

Furthermore, the discovery of ISF as another source of biomarkers in addition to urine, sweat, saliva, etc. has informed the application of microneedles as a painless extraction method for obtaining ISF samples for disease diagnosis and monitoring.[70] These systems typically function by employing microneedle-linked reservoirs or highly swellable microneedles for ISF collection followed by ISF retrieval and external analysis or by the incorporation of detection protocols within the microneedle array itself, enabling immediate detection and, in more sophisticated devices, quantification of biomarker concentration.[71]

The application of solid microneedles to vaccine administration has been informed by their ability to induce a prolonged and enhanced antibody response in comparison to traditional intramuscular vaccine administration.[18] Hollow microneedles have been adopted for the administration of rapid bolus injections as well as infusions due to their ability to influence medication flow rate by adjustment of time and volume of drug delivery.[19] The delivery of the influenza vaccine using coated microneedles has been extensively researched, and despite the potential of application of coated microneedles to the enhanced transdermal delivery of a wide variety of therapeutic agents, including viruses, nucleic acids, etc., certain factors including hydrophilicity and stability of therapeutic agents are factors that require thorough consideration before their use.[26] Due to their biocompatibility and scalability, dissolving microneedles have found major application in the delivery of vaccines.[72] The swellability of hydrogel microneedles, on the other hand, coupled with their biocompatibility and zero polymer residue, has informed their principal adaptability to passive ISF uptake and extraction[34] (Figure 3)[28] further provides a graphical overview of current trends in reported clinical applications of microneedles.

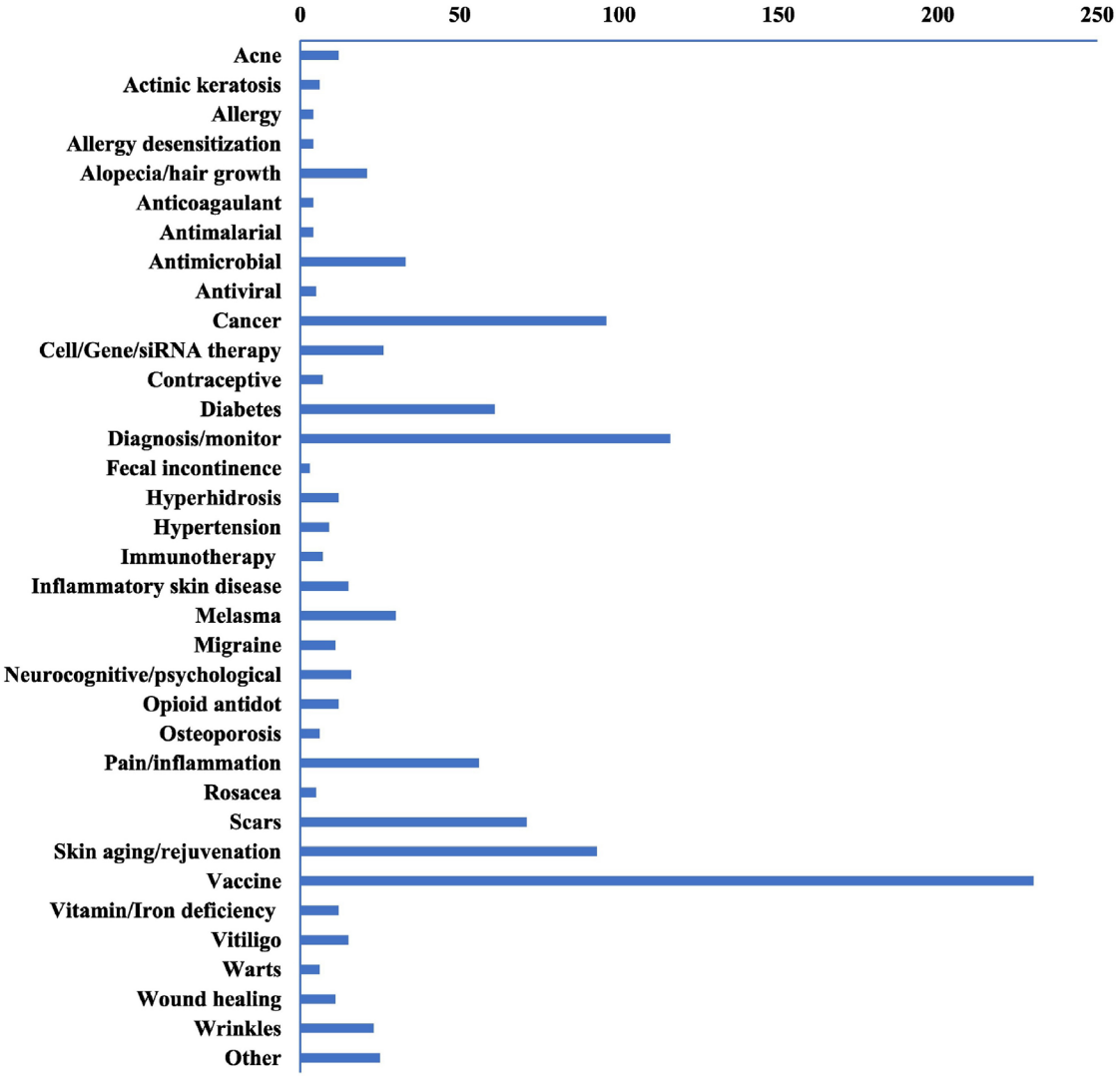

Fig 3 | Recent trends in the therapeutic applications of microneedles reported in the literature, 2000–2021 (n = 1067). Derived from www.ncbi.nlm.nih.gov/pubmed/. Search query: '(microneedle) OR (microneedling) OR (micro-needle) OR (microarray patch) AND (skin). Reproduced from Sartawi et al.[28] Creative Commons license: https://creativecommons.org/licenses/by/4.0/

DOI: https://doi.org/10.70389/PJS.100019 | Premier Journal of Science 2024;1:100019

Challenges/Economic Feasibility, Regulatory Considerations, Future Prospects, Conclusion

Challenges/Economic Feasibility

The rapid evolution of the concept of microneedles has led to a corresponding increase in application challenges and regulatory issues, visually summarized in Figure 4.[7] A major associated challenge continues to be the difference in skin thickness across various anatomical sites, age groups, gender, ethnicities, etc., which could potentially impact the extent and range of microneedle insertion and subsequently, dosing accuracy.[73] Uncontrollable drug delivery efficiency and a limited loading capacity are concerns primarily associated with solid and coated microneedle forms, respectively.[7] Issues of biohazard traceable to the potential risk of accumulated deposition of polymeric material under the skin pose a limitation to the long-term use of dissolving microneedles.[74] Concerns have been raised regarding the class of drugs that can be incorporated into microneedles, as only highly soluble drugs can be effectively integrated into these delivery systems.[75]

Furthermore, factors including aseptic fabrication processes and environment, scale-up, quality control protocols and regulations, packaging, and transport have grossly impacted the manufacture, widespread commercialization, and clinical adaptation of microneedles.[12]

The novelty of microneedle manufacturing processes, particularly micro-production techniques, would thus require considerable capital investment, translating to raised production costs.[76] From a study centered around manufacturing readiness within the microneedle industry, developer interviews report elevated MAP manufacturing costs triggered by a dearth of contract manufacturing organizations able and willing to embark upon quality-controlled development processes due to issues of a shortage of development partners, minimal return on investment, a lack of standardization, and regulation within the microneedle industry with regards to high-priority and high-application microneedle design categories.[77] Following this, in order to ensure optimal production processes that are budget-conscious, it is imperative to standardize fabrication methods and employ materials that, while being economical, also maintain the stability and viability of the encapsulated therapeutic agent.

A study involving the comparative evaluation of the cost efficiency of microneedles in a measles vaccination program highlighted a projected cost of $1.66 (microneedle patch) in contrast to $2.64 (conventional subcutaneous vaccination) per case prevention, a phenomenon the authors point to the potential cost effectiveness of microneedles, albeit its dependence on consumer acceptance/approval of this novel system.[78] Another study aimed at exploring the economic impact of microneedle patch introduction into the influenza vaccination market reported profitability at all price levels ($9.50–$30) and market shares (10–60%), specifically under the management of a healthcare professional.[79]

Another economic concern that has been reported to have the potential to threaten continuous microneedle innovation and widespread commercialization is the perceived dearth of any substantial profit margin for investment industries when new technology is rapidly made open source or public domain, thus diminishing its economic strength and leaving these investment companies at a loss.[80]

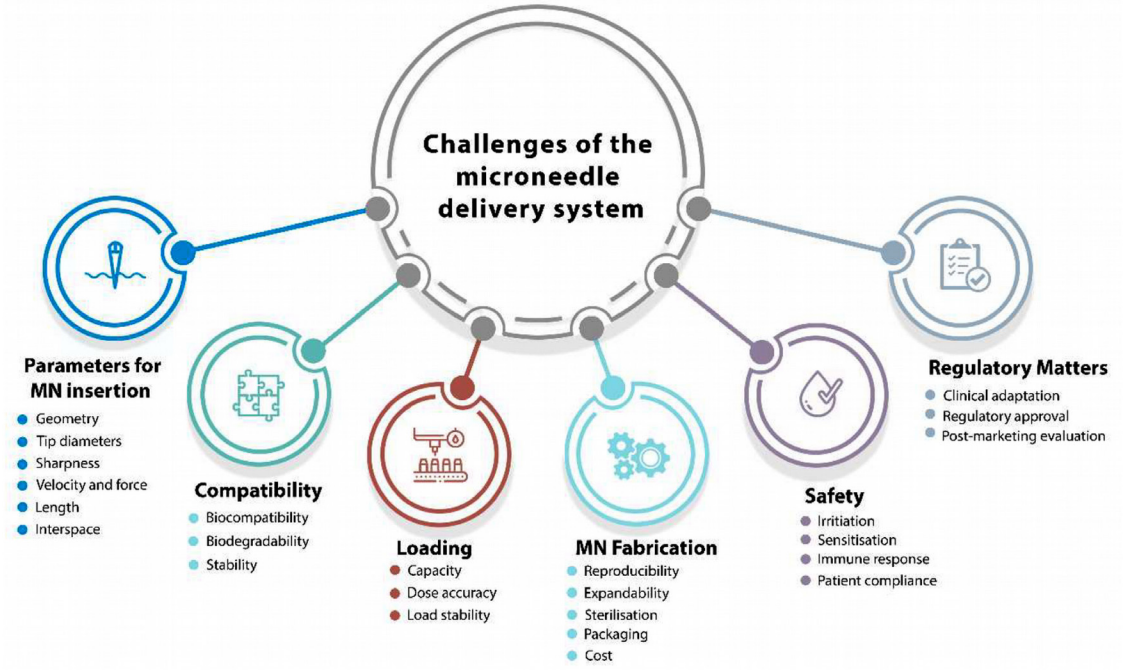

Fig 4 | Factors affecting the development of the microneedle-based delivery system. Reproduced from Avcil and Çelik[7] Creative Commons license: https://creativecommons.org/licenses/by/4.0/

Addressing these outlined issues of elevated production costs, non-standardized production and evaluation protocols, rapid public access, etc., among others, will be crucial for the effective commercialization and integration into the clinical use of microneedles.

Regulatory Considerations

Owing to the relative novelty of microneedles as a system for drug delivery, standardized techniques and processes regarding their scale-up and manufacture, sterilization, packaging, storage and transportation, disposal, etc., are still yet to be properly outlined and established.

In November 2020, the US FDA issued a document, "Regulatory Considerations for Microneedling Products," detailing the agency's recommendations on the scope and definition of microneedle products/devices. A major limitation to the establishment of appropriate quality control measures for microneedles, however, has been reported to stem from a dearth of appropriate distinction guidelines regarding microneedle classification, either as a medical device for those products that are to be applied primarily to diagnosis or as a drug product for those developed primarily for the delivery of therapeutic substances.[7,81] Furthermore, the cumbersome nature of the product catalog with the US FDA necessitating microneedle submission as a combination product stipulating exhaustive analysis and review information complicates and draws out product approval, a phenomenon severely impeding its entry into the market.[7]

In addition, accurate assessment and maintenance of drug content among individual needles and whole patches, particularly for dissolving, coated, and hydrogel-forming needles, is another reported regulatory concern with regard to content homogeneity associated with this class of transdermal delivery agents.[82] Erythema and dermal irritation, an elevated risk of cross-contamination and pathogen transmission associated majorly with solid and hollow microneedles, potential problems of usability and convenience alongside appropriate disposal measures, and the hazard of reuse are only some other key regulatory considerations associated with microneedles.[81,83]

As the microneedle landscape continues to evolve, continued collaboration between researchers, investors, industry stakeholders, and regulatory bodies will remain pivotal to the resolution of currently presenting concerns, the streamlining of associated approval protocols, and a seamless transition of this drug delivery system from bench to bedside.

Future Prospects

Several healthcare intelligence/market analysis firms catalog a microneedle market value of USD 549.15 million as of 2022, a figure that is projected to leap by a CAGR of 7.5% to an estimated USD 979.39 million by 2030.

Microneedle application to the management of a variety of disease conditions has gone a long way in terms of fabrication technology and design, a phenomenon that, going forward, is projected to be on par with rapid advancements in technology and innovation.

The concept of application of microneedles to the management of diabetes mellitus is evolving to encompass chemically and electronically regulated systems that facilitate self- regulation and automatic release of insulin in response to blood glucose levels; systems that hold the promise of better glycemic control and ultimately, an improved quality of life for patients.[84] Prospective application of microneedle systems to oncotherapy has been detailed to potentially be based on a patient-specific precision-medicine model incorporating closed-loop devices fitted with biosensors sensitive to specific tumor-associated stimuli, metabolites, and even targets, allowing for seamless detection of physiological anomalies, data monitoring, collection and analysis, therapy, and overall patient care.[85] Microneedle application to vaccine delivery has perhaps witnessed the most growth in terms of approval and translation to clinical practice, with approximately a quarter of published scholarly articles on microneedles as of 2015 being centered around vaccine delivery.[86] For efficient translation of this system into immunization programs, microneedles for vaccine delivery would have to evolve in a direction that could ensure product stability even in the absence of cold chain, dose actuation and regulated immunogenicity, effective post-administration surveillance, etc.[87]

Microneedles for diagnostic purposes are evolving to accommodate wearable systems incorporating biosensors and units for data measurement, processing, and transmission, with even much lower detection limits, a phenomenon that could consolidate the concept of remote healthcare services allowing for off-site patient diagnosisandmedicalmanagement.[88,89]Nanotechnology-mediated microneedle transdermal delivery of drugs is another concept slowly gaining popularity, particularly for the delivery of genes, vaccines, and immune mediators and the management of skin disorders due to the associated benefits of these combined systems, including an augmented dermal permeability of nanoparticles, tunable drug release properties, and the possibility of new adjunctive therapies.[90]

While these projected technological innovations might lead to raised production costs, there is also the possibility of novel development approaches that could trigger a swift and widespread approval and acceptance of these products by regulatory agencies, clinicians, and consumers, a phenomenon that could positively influence the long-term affordability of microneedles.

Conclusion

The plethora of benefits associated with microneedles as a system for transdermal drug delivery continues to prompt increasing research into its development with the hopes of standardized and approved models that could support an extensive and absolute translation into clinical practice.

This paper thus summarizes the evolution of microneedles in terms of type/formulation material,

DOI: https://doi.org/10.70389/PJS.100019 | Premier Journal of Science 2024;1:100019

fabrication method, design, and application, as well as challenges and regulatory considerations surrounding its development and implementation.

The establishment of systematic manufacturing protocols, testing modalities, including clinical trials, and a methodic and transparent route toward regulatory approval are critical to the attainment of the objective of effective adoption and commercialization of this delivery system.

References

1. Ramadon D, McCrudden MTC, Courtenay AJ, Donnelly RF. Enhancement strategies for transdermal drug delivery systems: current trends and applications. Drug Deliv Transl Res. 2022;12(4):758–91.
2. Phatale V, Vaiphei KK, Jha S, Patil D, Agrawal M, Alexander A. Overcoming skin barriers through advanced transdermal drug delivery approaches. J Controlled Release. 2022;351:361–80.
3. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: a review. Biomater Res. 2021;25(1):24.
4. Lee H, Song C, Baik S, Kim D, Hyeon T, Kim DH. Device-assisted transdermal drug delivery. Adv Drug Delivery Rev. 2018;127:35–45.
5. Joshi N, Azizi Machekposhti S, Narayan RJ. Evolution of transdermal drug delivery devices and novel microneedle technologies: a historical perspective and review. JID Innovations. 2023;3(6):100225.
6. Prausnitz MR. Microneedles for transdermal drug delivery. Adv Drug Deliv Rev. 2004;56(5):581–7.
7. Avcil M, Çelik A. Microneedles in drug delivery: progress and challenges. Micromachines. 2021;12(11):1321.
8. Lev-Tov H. How microneedles can change cutaneous drug delivery – small needles make a big difference. JAMA Dermatol. 2017;153(7):631–2.
9. Gowda BHJ, Ahmed MG, Sanjana A. Can microneedles replace hypodermic needles? Reson. 2022;27:63–85.
10. Halder J, Gupta S, Kumari R, Gupta G Das, Rai VK. Microneedle array: applications, recent advances, and clinical pertinence in transdermal drug delivery. J Pharm Innovation. 2020;16:558–65.
11. Ingrole RSJ, Azizoglu E, Dul M, Birchall JC, Gill HS, Prausnitz MR. Trends of microneedle technology in the scientific literature, patents, clinical trials and internet activity. Biomaterials. 2021;267:120491.
12. Larrañeta E, Lutton REM, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: materials science, manufacture and commercial development. Mater Sci Eng: R: Rep. 2016;104:1–32.
13. Oliveira C, Teixeira JA, Oliveira N, Ferreira S, Botelho CM. Microneedles' device: design, fabrication, and applications. Macromolecules. 2024;4(2):320–55.
14. Mdanda S, Ubanako P, Kondiah PPD, Kumar P, Choonara YE. Recent advances in microneedle platforms for transdermal drug delivery technologies. Polymers. 2021;13(15):2405.
15. Hao Y, Li W, Zhou XL, Yang F, Qian ZY. Microneedles-based transdermal drug delivery systems: a review. J Biomed Nanotechnol. 2017;13(12):1581–97.
16. Nagarkar R, Singh M, Nguyen HX, Jonnalagadda S. A review of recent advances in microneedle technology for transdermal drug delivery. J Drug Delivery Sci Technol. 2020;59:101923.
17. Rzhevskiy AS, Singh TRR, Donnelly RF, Anissimov YG. Microneedles as the technique of drug delivery enhancement in diverse organs and tissues. J Controlled Release. 2018;270:184–202.
18. Ita K. Transdermal delivery of drugs with microneedles—potential and challenges. Pharmaceutics. 2015;7(3):90–105.
19. Waghule T, Singhvi G, Dubey SK, Pandey MM, Gupta G, Singh M, et al. Microneedles: a smart approach and increasing potential for transdermal drug delivery system. Biomed Pharmacother. 2019;109:249–58.
20. Zhao X, Coulman SA, Hanna SJ, Wong FS, Dayan CM, Birchall JC. Formulation of hydrophobic peptides for skin delivery via coated microneedles. J Controlled Release. 2017;265:2–13.
21. Zhao X, Birchall JC, Coulman SA, Tatovic D, Singh RK, Wen L, et al. Microneedle delivery of autoantigen for immunotherapy in type 1 diabetes. J Controlled Release. 2016;223:178–87.
22. Ma Y, Tao W, Krebs SJ, Sutton WF, Haigwood NL, Gill HS. Vaccine delivery to the oral cavity using coated microneedles induces systemic and mucosal immunity. Pharm Res. 2014;31:2393–403.
23. Chen Y, Chen BZ, Wang QL, Jin X, Guo XD. Fabrication of coated polymer microneedles for transdermal drug delivery. J Controlled Release. 2017;265:14–21.
24. Jeong HR, Jun H, Cha HR, Lee JM, Park JH. Safe coated microneedles with reduced puncture occurrence after administration. Micromachines. 2020;11(8):710.
25. Choi JE, Cha HR, Kim S, Kim JS, Kim MJ, Chung HW, et al. Preparation of particle- attached microneedles using a dry coating process. J Controlled Release. 2022;351:1003–16.
26. Ingrole RSJ, Gill HS. Microneedle coating methods: a review with a perspective. J Pharmacol Exp Ther. 2019;370(3):555–69.
27. Ita K. Dissolving microneedles for transdermal drug delivery: advances and challenges. Biomed Pharmacother. 2017;93:1116–27.
28. Sartawi Z, Blackshields C, Faisal W. Dissolving microneedles: applications and growing therapeutic potential. J Controlled Release. 2022;348:186–205.
29. Dalvi M, Kharat P, Thakor P, Bhavana V, Singh SB, Mehra NK. Panorama of dissolving microneedles for transdermal drug delivery. Life Sci. 2021;284:119877.
30. Ali M, Namjoshi S, Benson HAE, Mohammed Y, Kumeria T. Dissolvable polymer microneedles for drug delivery and diagnostics. J Controlled Release. 2022;347:561–89.
31. Cárcamo-Martínez Á, Mallon B, Domínguez-Robles J, Vora LK, Anjani QK, Donnelly RF. Hollow microneedles: a perspective in biomedical applications. Int J Pharm. 2021;599:120455.
32. Ita K. Ceramic microneedles and hollow microneedles for transdermal drug delivery: two decades of research. J Drug Delivery Sci Technol. 2018;44:314–22.
33. Li Y, Bi D, Hu Z, Yang Y, Liu Y, Leung WK. Hydrogel-forming microneedles with applications in oral diseases management. Materials. 2023;16(13):4805.
34. Turner JG, White LR, Estrela P, Leese HS. Hydrogel-forming microneedles: current advancements and future trends. Macromol Biosci. 2020;21(2):2000307.
35. Singh TRR, McMillan H, Mooney K, Alkilani AZ, Donnelly RF. Fabrication of microneedles. In: Dragicevic N, Maibach HI, editors. Percutaneous Penetration Enhancers Physical Methods in Penetration Enhancement. 2017;(p). Springer Berlin Heidelberg.
36. Tucak A, Sirbubalo M, Hindija L, Rahić O, Hadžiabdić J, Muhamedagić K, et al. Microneedles: characteristics, materials, production methods and commercial development. Micromachines. 2020;11(11):961.
37. Gupta J, Gupta R, Vanshita. Microneedle technology: an insight into recent advancements and future trends in drug and vaccine delivery. ASSAY Drug Dev Technol. 2021;19(2):97–114.
38. Zhang W, Zhang W, Li C, Zhang J, Qin L, Lai Y. Recent advances of microneedles and their application in disease treatment. Int J Mol Sci. 2022;23(5):2401.
39. Antonara L, Dallas PP, Rekkas DM. A novel 3D printing enabled method for fast and reliable construction of polymeric microneedles using experimental design. J Drug Deliv Sci Technol. 2022;68:102888.
40. Ako H, O'Mahony J, Hughes H, McLoughlin P, O'Reilly NJ. A novel approach to the manufacture of dissolving microneedles arrays using aerosol jet printing. Appl Mater Today. 2023;35:101958.
41. Makvandi P, Maleki A, Shabani M, Hutton ARJ, Kirkby M, Jamaledin R, et al. Bioinspired microneedle patches: biomimetic designs, fabrication, and biomedical applications. Matter. 2022;5(2):390–429.
42. Wang C, Jiang X, Zeng Y, Terry RN, Li W. Rapidly separable microneedle patches for controlled release of therapeutics for long-acting therapies. Med Drug Discovery. 2022;13:100118.
43. Gowda BHJ, Ahmed MG, Sahebkar A, Riadi Y, Shukla R, Kesharwani P. Stimuli- Responsive microneedles as a transdermal drug delivery system: a demand-supply strategy. Biomacromolecules. 2022;23(4):1519–44.
44. Liu R, Li A, Lang Y, Cai H, Tang X, Li D, et al. Stimuli-responsive polymer microneedles: a rising transdermal drug delivery system and Its applications in biomedical. J Drug Delivery Sci Technol. 2023;88:104922.

45. Li M, Vora LK, Peng K, Sabri AHB, Qin N, Abbate M, et al. Novel nano-in-micro fabrication technique of diclofenac nanoparticles loaded microneedle patches for localised and systemic drug delivery. Biomater Adv. 2024;161:213889.
46. Parhi R. Recent advances in microneedle designs and their applications in drug and cosmeceutical delivery. J Drug Delivery Sci Technol. 2022;75:103639.
47. Wright N, Wu T, Wang Y. Multilayered microneedles for triphasic controlled delivery of small molecules and proteins. Macromol Biosci. 2023;24(4):2300431.
48. Park SC, Kim MJ, Baek SK, Park JH, Choi SO. Spray-formed layered polymer microneedles for controlled biphasic drug delivery. Polymers. 2019;11(2):369.
49. Bhatnagar S, Dave K, Venuganti VVK. Microneedles in the clinic. J Controlled Release. 2017;260:164–82.
50. Huang Y, Yu H, Wang L, Shen D, Ni Z, Ren S, et al. Research progress on cosmetic microneedle systems: preparation, property and application. Eur Polym J. 2022;163:110942.
51. Lv H, Gao N, Zhou Q, Wang Y, Ling G, Zhang P. Collagen-based dissolving microneedles with flexible pedestals: a transdermal delivery system for both anti- aging and skin diseases. Adv Healthcare Mater. 2023;12(21):2203295.
52. Jang M, Baek S, Kang G, Yang H, Kim S, Jung H. Dissolving microneedle with high molecular weight hyaluronic acid to improve skin wrinkles, dermal density and elasticity. Int J Cosmet Sci. 2020;42(3):302–9.
53. Zhang JN, Chen BZ, Ashfaq M, Zhang XP, Guo XD. Development of a BDDE-crosslinked hyaluronic acid based microneedles patch as a dermal filler for anti-ageing treatment. J Ind Eng Chem. 2018;65:363–9.
54. Fonseca DFS, Vilela C, Pinto RJB, Bastos V, Oliveira H, Catarino J, et al. Bacterial nanocellulose-hyaluronic acid microneedle patches for skin applications: in vitro and in vivo evaluation. Mater Sci Eng C. 2021;118:111350.
55. Tatovic D, Mcateer MA, Barry J, Barrientos A, Rodríguez Terradillos K, et al. Safety of the use of gold nanoparticles conjugated with proinsulin peptide and administered by hollow microneedles as an immunotherapy in type 1 diabetes. Immunother Adv. 2022;2(1):1–10.
56. Syafika N, Azis SBA, Enggi CK, Qonita HA, Mahmud TRA, Abizart A, et al. Glucose-responsive microparticle-loaded dissolving microneedles for selective delivery of metformin: a proof-of-concept study. Mol Pharmaceutics. 2023;20(2):1269–84.
57. Alafnan A, Seetharam AA, Hussain T, Gupta MS, Rizvi SMD, Moin A, et al. Development and characterization of PEGDA microneedles for localized drug delivery of gemcitabine to treat inflammatory breast cancer. Materials. 2022;15(21):7693.
58. Dosta P, Puigmal N, Cryer AM, Rodríguez AL, Scott E, Weissleder R, et al. Polymeric microneedles enable simultaneous delivery of cancer immunomodulatory drugs and detection of skin biomarkers. Theranostics. 2023;13(1):1–15.
59. Ren Y, Li J, Chen Y, Wang J, Chen Y, Wang Z, et al. Customized flexible hollow microneedles for psoriasis treatment with reduced-dose drug. Bioeng Transl Med. 2023;8(4):e10530.
60. Wu D, Shou X, Yu Y, Wang X, Chen G, Zhao Y, et al. Biologics-loaded photothermally dissolvable hyaluronic acid microneedle patch for psoriasis treatment. Adv Funct Mater. 2022;32(47):2205847.
61. Han H, Li B, Yang R, Guo HL, Li Q, Wang H, et al. NIR-remote selectively triggered buprenorphine hydrochloride release from microneedle patches for the treatment of neuropathic pain. ACS Biomater Sci Eng. 2024;10:5001–13.
62. Song K, Hao Y, Tan X, Huang H, Wang L, Zheng W. Microneedle-mediated delivery of ziconotide-loaded liposomes fused with exosomes for analgesia. J Controlled Release. 2023;356:448–62.
63. Chen Z, Lai Y, Xu S, Zhu M, Sun Y, Cheng Y, et al. A self-powered controllable microneedle drug delivery system for rapid blood pressure reduction. Nano Energy. 2024;123:109344.
64. Deshpande A, Mer V, Patel D, Thakkar H. Microneedle-assisted transdermal delivery of carvedilol nanosuspension for the treatment of hypertension. RSC Pharm. 2024;1:472–83.
65. Mansoor I, Eassa HA, Mohammed KHA, Abd El-Fattah MA, Abdo MH, Rashad E, et al. Microneedle-based vaccine delivery: review of an emerging technology. AAPS PharmSciTech. 2022;23:103.
66. Hossain MK, Ahmed T, Bhusal P, Subedi RK, Salahshoori I, Soltani M, et al. Microneedle systems for vaccine delivery: the story so far. Expert Rev Vaccines. 2021;19(12):1153–66.
67. Jiang X, Zeng Y, Zhang W, Wang C, Li W. Advances in microneedle patches for long- acting contraception. Acta Mater Med. 2023 5;2(1):1–8.
68. Rajput A, Osmani RAM, Khire A, Jaiswal S, Banerjee R. Levonorgestrel microneedle array patch for sustained release contraception: formulation, optimization and in vivo characterization. Molecules. 2022;27(7):2349.
69. Li W, Chen JY, Terry RN, Tang J, Romanyuk A, Schwendeman SP, et al. Core-shell microneedle patch for six-month controlled-release contraceptive delivery. Controlled Rel. 2022;347:489–99.
70. Amarnani R, Shende P. Microneedles in diagnostic, treatment and theranostics: an advancement in minimally-invasive delivery system. Biomed Microdevices. 2021;24:4.
71. Zhang X, Wang Y, Chi J, Zhao Y. Smart microneedles for therapy and diagnosis. Research. 2020;2020:7462915.
72. Aldawood FK, Andar A, Desai S. A comprehensive review of microneedles: types, materials, processes, characterizations and applications. Polymers. 2021;13(16):2815.
73. Donnelly RF, Raj Singh TR, Woolfson AD. Microneedle-based drug delivery systems: microfabrication, drug delivery, and safety. Drug Deliv. 2010;17(4):187–207.
74. Chandran R, Tohit ERM, Stanslas J, Tuan Mahmood TM. Recent advances and challenges in microneedle-mediated transdermal protein and peptide drug delivery. Biomater Bionanotechnol. 2019;495–525.
75. Jung JH, Jin SG. Microneedle for transdermal drug delivery: current trends and fabrication. J Pharm Invest. 2021;51:503–17.
76. Richter-Johnson J, Kumar P, Choonara YE, du Toit LC, Pillay V. Therapeutic applications and pharmacoeconomics of microneedle technology. Expert Rev Pharm Out. 2018;18(4):359–69.
77. Creelman B, Frivold C, Jessup S, Saxon G, Jarrahian C. Manufacturing readiness assessment for evaluation of the microneedle array patch industry: an exploration of barriers to full-scale manufacturing. Drug Deliv Transl Re 2022;12:368–75.
78. Adhikari BB, Goodson JL, Chu SY, Rota PA, Meltzer MI. Assessing the potential cost-effectiveness of microneedle patches in childhood measles vaccination programs: the case for further research and development. Drugs R&D. 2016;16:327–38.
79. Lee BY, Bartsch SM, Mvundura M, Jarrahian C, Zapf KM, Marinan K, et al. An economic model assessing the value of microneedle patch delivery of the seasonal influenza vaccine. Vaccine 2015;33(37):4727–36.
80. Ahmad NFN, Ghazali NNN, Wong YH. Concept design of transdermal microneedles for diagnosis and drug delivery: a review. Adv Eng Mater. 2021;23(12):2100503.
81. Nguyen HX, Nguyen CN. Microneedle-mediated transdermal delivery of biopharmaceuticals. Pharmaceutics. 2023;15(1):277.
82. Lee KJ, Jeong SS, Roh DH, Kim DY, Choi HK, Lee EH. A practical guide to the development of microneedle systems – in clinical trials or on the market. Int J Pharm. 2020;573:118778.
83. Donnelly RF, editor. Clinical Translation and Industrial Development of Microneedle-based Products. John Wiley & Sons, Ltd. 2018.
84. Martínez-Navarrete M, Pérez-López A, Guillot AJ, Cordeiro AS, Melero A, Aparicio-Blanco J. Latest advances in glucose-responsive microneedle-based systems for transdermal insulin delivery. Int J Biol Macromol. 2024;263(4):130301.
85. Ganeson K, Alias AH, Murugaiyah V, Amirul AAA, Ramakrishna S, Vigneswari S. Microneedles for efficient and precise drug delivery in cancer therapy. Pharmaceutics. 2023;15(3):744.
86. Shin CI, Jeong SD, Rejinold NS, Kim YC. Microneedles for vaccine delivery: challenges and future perspectives. Ther Deliv. 2017;8(6):447–60.
87. Sheng T, Luo B, Zhang W, Ge X, Yu J, Zhang Y, et al. Microneedle-mediated vaccination: innovation and translation. Adv Drug Delivery Rev. 2019;179:113919.
88. Liu GS, Kong Y, Wang Y, Luo Y, Fan X, Xie X, et al. Microneedles for transdermal diagnostics: recent advances and new horizons. Biomaterials. 2020;232:119740.
89. Yang J, Yang J, Gong X, Zheng Y, Yi S, Cheng Y, et al. Recent progress in microneedles-mediated diagnosis, therapy, and theranostic systems. Adv Healthcare Mater. 2022;11(10):2102547.
90. Alimardani V, Abolmaali SS, Yousefi G, Rahiminezhad Z, Abedi M, Tamaddon A, et al. Microneedle arrays combined with nanomedicine approaches for transdermal delivery of therapeutics. J Clin Med. 2021;10(2):181.