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Research article

A systematic review of microneedles technology in drug delivery through a bibliometric and patent overview

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ABSTRACT

The transdermal drug delivery (TDD) route has gathered considerable attention for its potential to improve therapeutic efficacy while minimizing systemic side effects. Among transdermal technologies, microneedle (MN) devices have proven to be a promising approach that combines the advantages of traditional needle injections and non-invasive topical applications. This review provides a comprehensive analysis of progress in transdermal drug delivery systems (TDDS) via MN from 2000 to 2023, integrating bibliometric analysis and patent landscape to present a multifaceted perspective on the evolution of this technology. The study identifies key trends, challenges, and opportunities in the research, implementation, and commercialization of MN tools through a systematic examination of scientific literature and an extensive investigation of global patent databases. The study of bibliometric trends reveals the leading experts, organizations, companies, and countries contributing to this field, collaboration networks, and the thematic evolution of research topics. The patent analysis offers insights into innovative trajectories, key players, and geographical distribution of intellectual property. This review resumes the latest advancements in MN devices and provides a strategic outlook that can guide future research directions, promote partnerships, and inform stakeholders involved in the development of TDDS.

1. Introduction

TDDS represents a developmental frontier in pharmaceutical technology, which aims to transport medications across the skin in a regulated mode [1]. Despite the advantages of TDDS, including overcoming the first-pass metabolism and improving patient compliance, the stratum corneum (SC) remains a significant obstacle to the permeation of most medicines [2]. MN devices have been introduced as a novel approach to overcome this hindrance. Microneedles painlessly go through the SC, creating transient microchannels that assist with the pharmacological substances' release directly into the systemic circulation or to targeted skin layers. The current state of research in MN technologies for TDD is characterized by rapid growth and innovation [3–6]. Researchers and pharmaceutical companies have actively developed various types of MNs for clinical applications [7,8], including dissolving [9],

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hydrogel-forming [10], solid [11], hollow [12], and coated MNs [13]. All have shown the potential to administer drugs painlessly and easily, making them attractive for patients with chronic diseases and prolonged treatments [14]. MN technologies have gained popularity and attention in both academic and industry sectors [3]. Scientific research in MN technologies for TDD has progressed, with a significant increase in articles published in the last decades. It focused on various aspects, such as physicochemical properties [15], drug formulation [16], pharmacokinetics [17], vaccine development [18], drug administration [19], patient compliance [20], skin rejuvenation [21], ocular drug delivery [22], and controlled insulin delivery [23]. The interest in MN research has also extended to areas like fabrication technology, including the use of novel polymeric materials [24], 3D printing [25], and digital technology [26] for their manufacturing. In the same way, the retrieved patents concerning MN technologies in TDD cover a large range of applications. MN trends highlight the importance of innovative materials and engineering processes [27–29] to improve patient outcomes. Innovation in MN facilitates efficient administration of drugs [30–33] and vaccines, focusing on improving treatment effectiveness and patient compliance [34]. Moreover, integrating components suggests an effective transition to smart TDDS that can monitor and release in real-time and in a controlled way [35], enabling customized therapies and addressing global health challenges. However, in the case of MN technology, transitioning from laboratory testing to clinical trials involves overcoming numerous technical, biological, regulatory, and commercial obstacles, which are still hard. These complex keys are often interconnected. Biological and physiological factors play a significant role, as the human skin varies widely between individuals and among the various areas of the same individual, affecting the effectiveness and safety of MNs. Since MNs must meet stringent regulatory requirements, demanding precise statements about the active substance released to ensure safety and efficacy, regulatory issues further move this innovative technology away from the market. Technical difficulties are also an important barrier. The large-scale production of MNs with consistent size and characteristics is not standard, and even small production variations can affect therapeutic performances. Industrial scalability and commercialization are tough, also because MNs working well in the laboratory often require specific and unavailable machinery for mass production, thus significantly increasing the investment costs.

This study aims to examine recent progress and present knowledge on MN as a TDDS. The review offers an extensive analysis of materials and methods used in the manufacture of MN, as well as their specific fields of application, such as diabetes and vaccines. Furthermore, it emphasizes the advanced development in clinical studies through in vitro and in vivo trials and improved patient compliance, especially for prolonged treatments. In addition, patent analysis aims to identify key innovations and trends, map the competitive landscape, assess technological impact and value, and evaluate geographical distribution. This comprehensive approach addresses the issue of using emerging technologies for actual prospects through the analysis of patent applications over time.

2. Methods

Bibliometric and patent analysis were performed using Scopus and The Lens databases, respectively. Although the literature analysis was carried out with a broad and unbiased approach, this method has limitations stemming from relying on a single well of articles. Some manuscripts are not captured, even if SCOPUS is a well-established, reputable, and extensive database. However, its wide coverage ensures access to many relevant articles, making it suitable for good bibliometric analysis. Additionally, Scopus provides robust tools for citation analysis, enabling researchers to monitor the impact and interconnections of published works effectively.

Similarly, the patent analysis is limited to the documents sourced by LENS from its accessible database. However, it is a user-friendly retrieval tool that accesses extensive information from international patent databases.

According to PRISMA flow in FIGURE 1, in the identification phase, a first search in the Scopus database using keywords related to "transderm*", "drug*", "deliver*", "microneedle*", and "micro-needle*", led to 2,183 documents. At the same time, The Lens database

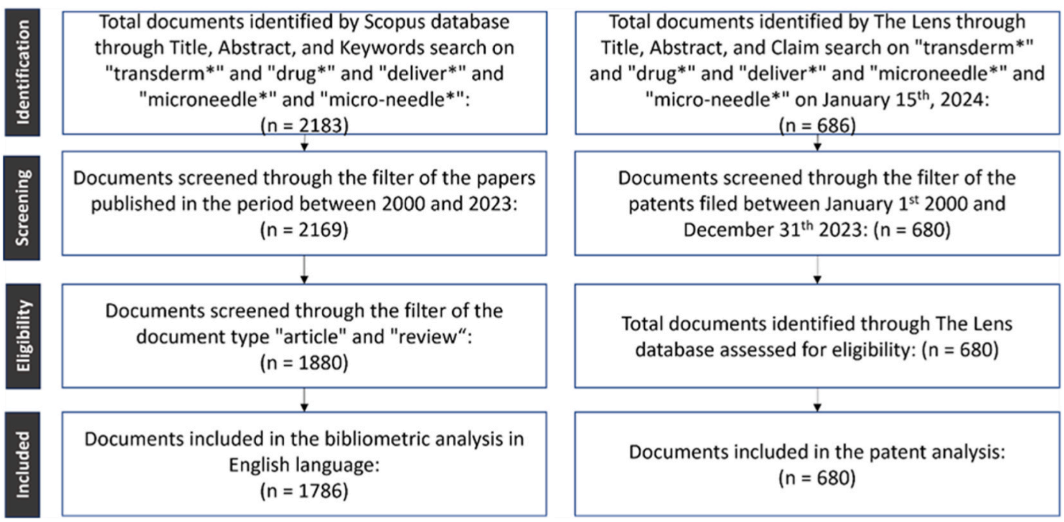

Fig. 1. PRISMA flow for the search of articles and patents on MN.

search, using titles, abstracts, and claims with the same set of keywords, produced 686 documents. In the screening phase, the Scopus documents were filtered by publication date, selecting papers published between 2000 and 2023, and reducing the documents to 2169. Similarly, in The Lens database, only patents filed between January 1, 2000, and December 31, 2023 were selected, retaining all 686 documents identified as matching the date criteria. In the eligibility phase, the further screening of Scopus documents by type, specifically selecting "article" and "review", reduced the number to 1880. For The Lens database, all 680 documents identified in the screening phase were assessed for eligibility. Finally, in the inclusion phase, the Scopus database documents were filtered by language, selecting only those available in English, resulting in 1786 documents included in the bibliometric analysis. The patent analysis retained all 680 documents previously identified by The Lens database.

2.1. Literature data

The scientific bibliography's data was gathered in a single day (January 4, 2024) from Scopus, which is the widest peer-reviewed literature data bank in several scientific fields. Clustering and organization of Scopus outputs were performed using Excel. The data sample collection was carried out according to the PRISMA flow diagram reported in Fig. 1. The items of the search were defined by the query (TITLE-ABS-KEY (transderm*) AND TITLE-ABS-KEY (drug*) AND TITLE-ABS-KEY (deliver*) AND TITLE-ABS-KEY (microneedle*) OR TITLE-ABS-KEY (micro-needle*) OR TITLE-ABS-KEY (micro AND needle*)) AND PUBYEAR >1999 AND PUBYEAR <2024 AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re")) AND (LIMIT-TO (LANGUAGE, "English")). Restricting manuscripts published from 2000 to 2023 allowed data to be collected on various aspects, including articles, keywords, authors, institutions, countries, citation counts, sources of financing, and trade journals.

Software for bibliometric visualization analyzed the obtained information to generate knowledge maps [36]. Herein VOSviewer version 1.6.19 extracted bibliographic details, such as researchers, institutions, keywords, states, and citations, and got the related network maps. To unveil prominent issues and explore focal points in the scientific bibliography, studies on co-authorship and co-occurrence were carried out. The examination of co-authorship patterns shows international collaborative efforts [37]. The keyword coexistence analysis leverages word frequency to assess their relational closeness, providing insights into prevailing topics and emerging trends within the field. This review examines the most frequently occurring keywords in the found publications to discern the pivotal areas within MN research. The maps report nodes as tagged circles, whose size is directly proportional to the frequency in the co-occurrence analysis, while the color depends on the specific belonging cluster. Nodes are connected by links whose thickness and length reflect the intensity of the relationship between them. The 1000 lines, corresponding to the 1000 strong connections between nodes, are shown. VOSviewer can define clusters with the keywords belonging to them and the correlations between the different clusters through a colored map [38]. Decoding clusters aids scientists in recognizing tendencies within the scientific bibliography. Examining the clusters and their keywords enables scientists to uncover the most dynamic domains and explore opportunities for collaboration.

2.2. Filed and granted patents

According to PRISMA flow in Fig. 1, on January 4, 2024, a patent query was made, by The Lens database, defined by the text: (Title: (transderm*) OR (Abstract: (transderm*) OR Claims: (transderm*))) AND ((Title: (drug*) OR (Abstract: (drug*) OR Claims: (drug*))) AND ((Title: (deliver*) OR (Abstract: (deliver*) OR Claims: (deliver*))) AND (Title: (microneedle*) OR (Abstract: (microneedle*) OR Claims: (microneedle*))))).

Patents dated from January 1, 2000, to December 31, 2023, were selected through a search conducted on The Lens platform. An analysis of the growth and distribution in the timeframe 2000–2023 on patents about TDD via MN was carried out. The assessment

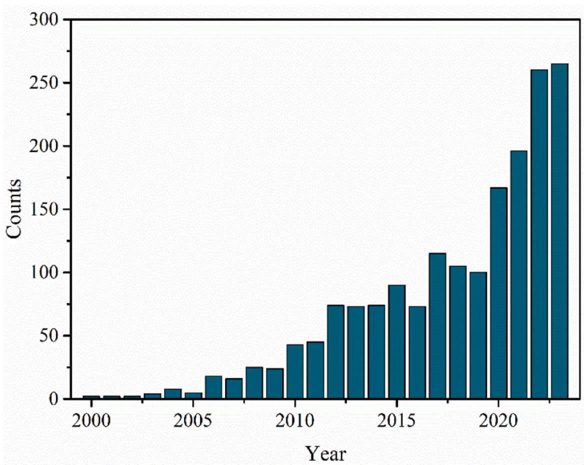

Fig. 2. Number of papers concerning MN for TDD per year according to Scopus.

included the identification of key factors, such as country of origin, primary owners, and classifications. Moreover, a connection analysis, which considers keyword presence, has been implemented. It presumes that documents sharing common keywords are interconnected, allowing the identification of innovative trends. An Excel data sheet was used for clustering and information outputs, while VOSviewer was used to develop the analysis of connections made through keyword occurrence.

3. Results and discussion

3.1. Publication on TDD via MNs

Scopus search produced 1785 manuscripts concerning research on MN from 2000 to 2023. As shown in Fig. 2, the number of articles on MN published annually grew from 2 in 2000 to 265 in 2023, following an increase rate of 34 % average per year. Moreover, notable spikes occurred in 2012 (+64 %), 2017 (+58 %), and 2020 (+67 %). Various factors were considered to provide a detailed interpretation of the boosts in the number of publications on MN in those years. From 2010 onward, the MN field has significantly developed since its inception. The initial research phases, which primarily focused on feasibility and proof of concept, had largely been concluded. Since 2010 researchers began exploring a broader range of applications. Noteworthy technological advancements in microfabrication techniques have emerged [39], enabling the development of more sophisticated designs [40], and overcoming the previous limitations in MN manufacturing [41,42]. The potential of MN for TDD gained increasing recognition, resulting in heightened funding and collaboration between academia and industry. Furthermore, the application of MN expanded to encompass vaccine delivery [43–45]. In May 2011, the Food and Drug Administration (FDA) approved the first MN-based vaccine, Sanofi Pasteur's Fluzone - a vaccine that is identical to Intanza [46]. In 2017, the use of MN extended to cosmetic applications [47–49], and biosensing [50,51]. A significant increase in clinical trials involving MN technologies was recorded, along with the growing commercial interest of pharmaceutical companies. In 2020, the unprecedented pandemic COVID-19 created an urgent need for innovative vaccine delivery methods [52–55]. MNs, being minimally invasive and potentially self-administrable, gained significant attention as a potential tool for mass vaccination campaigns [56]. The focus on vaccine delivery, including for COVID-19, probably stimulated further research and publications in the field of MN. So, these jumps in publication numbers can be attributed to field maturation, technological advancements, extended applications, increased commercial and clinical interest, and specific global health challenges that highlighted the potential of MN technology.

3.2. Leading Journals and most influential articles in MN research

The recovered manuscripts on MN for TDD were edited in 440 journals. Leading Journals in the publishing of papers on MN are reported in Table 1. The top 10 covers about 31 % of the articles on this topic. International Journal of Pharmaceutics was the most prolific one (105 articles), while Journal of Controlled Release was the most highly cited one (9425 citations).

"Transdermal drug delivery" by Prausnitz et al., published in Nature Biotechnology in 2008 [57] resulted as the more highly referred paper; second place was "Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies" by Mitragotri et al., published in Nature Reviews Drug Discovery [58]. Table 2 reports the most quoted manuscripts on MN.

These articles emphasize the relevant advances and several employments of MN technology in the TDD field, underlining its potential to revolutionize drug administration. Several studies focus on innovative manufacturing techniques and design improvements for MNs. Biodegradable and soluble MNs can reduce medical waste and improve patient compliance while eliminating needle disposal. Microfabrication techniques enhance precision in the creation of MNs for macromolecules and nanoparticles delivery, widening the field of therapeutic products. The applications of MN technology in drug administration are mainly dedicated to specific objectives. MN in vaccination offers a minimally invasive alternative to traditional injections, potentially increasing the efficacy, acceptance, and coverage of the vaccine. In the management of chronic diseases, they can be included in wearable devices for prolonged medicine administration and monitoring, improving patient management and adherence to treatment protocols.

Furthermore, the bibliographic analysis reveals the main scientific areas of interest in MN for TDD - namely Pharmacology, Material Science, Engineering, Biochemistry, Chemistry, and Medicine - emphasizing the importance of MN research in all these scientific fields.

Table 1
Leading journals in number of publications on MN for TDD, according to Scopus.

Place	Journal	IF (2023)	Publications (Percentage)	Citations
1	International Journal of Pharmaceutics	5.8	105 (5.9 %)	4,596
2	Journal of Controlled Release	10.8	89 (5.0 %)	9,425
3	Pharmaceutics	5.4	81 (4.5 %)	2,206
4	Journal of Drug Delivery Science and Technology	5	61 (3.4 %)	993
5	Drug Delivery and Translational Research	5.7	52 (2.9 %)	1,335
6	Pharmaceutical Research	4.6	44 (2.5 %)	3,994
7	Journal of Pharmaceutical Sciences	3.8	44 (2.5 %)	1,630
8	European Journal of Pharmaceutics and Biopharmaceutics	4.9	35 (2.0 %)	1,999
9	Expert Opinion on Drug Delivery	8.1	27 (1.5 %)	1,282
10	Advanced Drug Delivery Reviews	16.1	27 (1.5 %)	4,708

Table 2
The most quoted papers on MN according to Scopus.

Article	PY	Journal	Citations	Ref
Transdermal drug delivery	2008	Nature Biotechnology	2,333	[57]
Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies	2014	Nature Reviews Drug Discovery	1,207	[58]
Microneedles for drug and vaccine delivery	2012	Advanced Drug Delivery Reviews	1,201	[59]
Microneedles for transdermal drug delivery	2004	Advanced Drug Delivery Reviews	1,161	[60]
Novel mechanisms and devices to enable successful transdermal drug delivery	2001	European Journal of Pharmaceutical Sciences	1,017	[61]
Wearable/disposable sweat-based glucose monitoring device with multistage transdermal drug delivery module	2017	Science Advances	797	[62]
Biodegradable polymer microneedles: Fabrication, mechanics and transdermal drug delivery	2005	Journal of Controlled Release	741	[63]
Dissolving microneedles for transdermal drug delivery	2008	Biomaterials	688	[64]
Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: Fabrication methods and transport studies	2003	Proceedings of the National Academy of Sciences of the United States of America	685	[65]
Insertion of microneedles into skin: Measurement and prediction of insertion force and needle fracture force	2004	Journal of Biomechanics	614	[66]

3.3. Scientific research on MN worldwide

Scientific productivity on MN for TDD is reported in Fig. 3. The countries that have contributed most actively to MN research are colored red, the medium-prolific countries are green, and those with low publication rates are painted in soft pink.

The results showed that 70 countries contributed to MN research. China - with 508 publications - is the most productive, followed by the USA (452), the UK (214), and India (205). The highest number of papers from these countries is probably due to their large public and private investments. Outlining the main funders, comprising government agencies or non-profit organizations, over time, the United States and China have made substantial contributions to the MN sector, through investments of public funds. In China, financial support comes from entities such as the National Natural Science Foundation of China (NSFC), the Fundamental Research Funds for the Central Universities, and the National Key Research and Development Program of China. Meanwhile, in the US, financial supporters include organisms such as the National Institutes of Health (NIH), the National Institute of Biomedical Imaging and Bioengineering, and the National Science Foundation (NSF).

3.4. International research collaborations on MN for TDD

Health research is globally acknowledged for its significance, with MN being one of its most appealing issues. This study employs VOSviewer to examine international cooperation in MN research through the analysis of co-authored papers (Fig. 4). The network, which includes 49 countries, as shown in Fig. 4a, is divided into four distinct clusters, represented by different colors, interconnected by co-authorship links. The blue cluster - constituted of 11 countries, with the US at its center - has the highest number of articles (750)

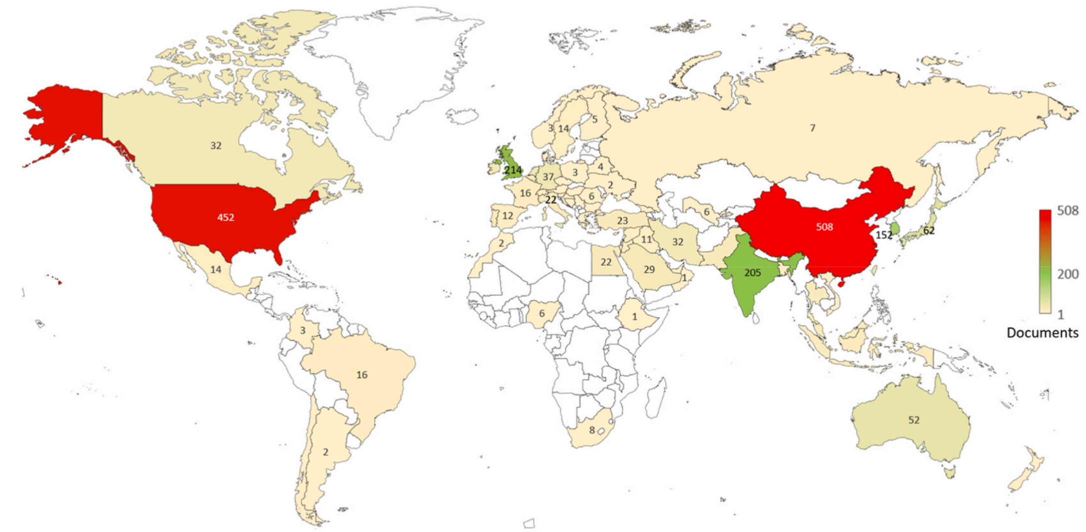

Fig. 3. Productivity of countries in publishing research papers on MN for TDD. Color-productivity match: red - high productivity; green - medium productivity; pink - low productivity. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and citations (50,691). In the network visualization, the circle size represents the total link strength of each country, defined as the capacity to generate co-authorship links with other countries. In the density visualization (Fig. 4b), the magnitude of the circle corresponds to the number of scientific papers co-authored – referring to international collaborations - for each country in the field of MN for TDD.

3.5. Co-occurrence analysis of the main keywords in research articles

The term co-occurrence refers to the frequency of a keyword in various documents. Keywords within research papers are pivotal in defining the research topic and enhancing the detectability of scientific articles. Here, VOSviewer was employed to extract and cluster the top 366 keywords (Fig. 5). These clusters reveal groups of keywords that frequently appear together in scientific literature, offering insights into the main research themes and trends within MN for the TDD field. Terms are related to the phases that are involved in technological development, such as design procedures, fabrication techniques, materials, applications, impact, and so on. The cluster

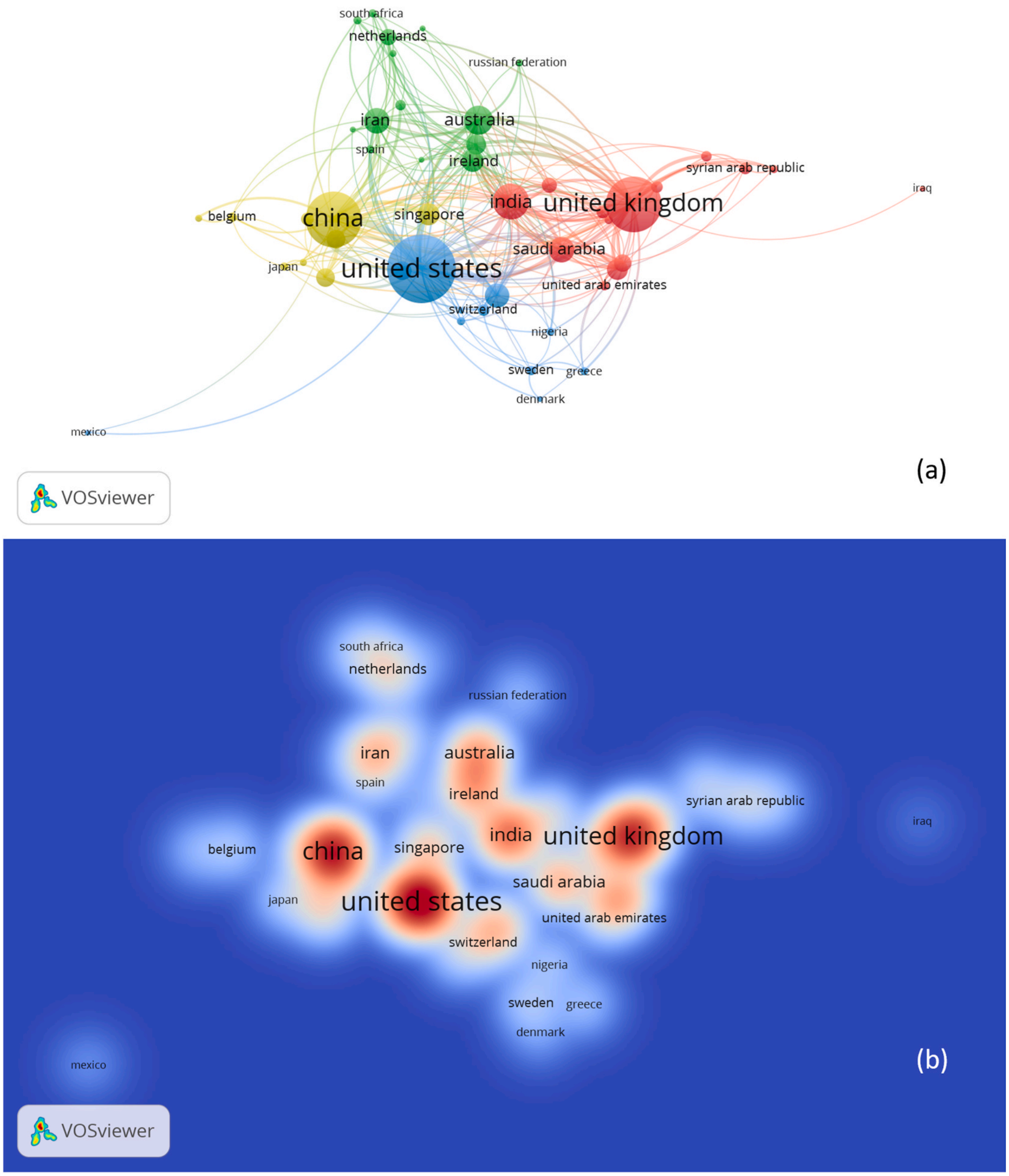

Fig. 4. World co-authorships on MN for TDD: (a) map of the international network; (b) density visualization of the co-authored scientific publications.

identification shows their interconnection, providing a comprehensive overview of the research landscape. Table 3 reports the top 20 keywords for each identified cluster. These keywords were determined by the total link strength, which indicates their significance and frequency of co-occurrence with other keywords in the dataset.

Fig. 5 provides a graphic representation of the relationships between frequently co-occurring keywords in scientific papers on MN, using VOSviewer. This cluster map highlights the main research areas and their interconnections within the field.

Cluster 1 - in red - reflects the intricacy of the drug's formulation and its interaction with the human skin. It emphasizes the complexities involved in drug delivery, particularly focusing on aspects such as "drug delivery system", "stratum corneum", "drug formulation", "drug penetration" and "skin absorption". These keywords highlight the challenges and strategies essential for effective medicine release through the skin obstacle, a key factor for the success of TDDS, including optimization of shape and dimension of MN for better penetration [67,68]. Glover et al. [69] focused on the use of MN systems in ocular drug delivery, addressing the limitations of traditional ocular therapies. The review reported the challenges faced with conventional methods, such as the poor bioavailability of topical eye drops and the invasive nature of intraocular injections. MN technologies were presented as a novel solution, offering localized, minimally invasive drug delivery to enhance medical treatment outcomes and patient comfort. The development of various MN solutions, including dissolving, coated, hollow, and bio-inspired MN, was extensively discussed in the context of ocular applications. These types were evaluated for their specific advantages and limitations in delivering drugs to the eye, highlighting their potential to revolutionize ocular treatments.

Cluster 2 - in green - is centered around the technology and materials involved in the design and realization of MN. It includes aspects like "3D printing," "biodegradable polymers," "chitosan," and "hyaluronic acid." These terms not only emphasize the methods and strategies of manufacturing but also underscore the importance of using biocompatible and environmentally sustainable materials, ensuring a patient-friendly approach. Azmana et al. [70] analyzed the crucial relevance of materials in the fabrication of MN for TDDS. Their research highlights how the choice of materials significantly influences functionality, efficiency, and patient compliance in drug administration via innovative routes. Diverse types of materials were considered, each with unique properties contributing to the performance of MN. Polymers emerged as a standout choice due to their biocompatibility, an essential factor for minimizing negative effects in patients. Moreover, the inherent flexibility of polymers minimizes the chance of breakage while penetrating the skin, ensuring a more consistent and reliable drug delivery. The beneficial properties of biodegradable polymers like polylactic acid (PLA), polyglycolic acid (PGA), Poly Lactic-co-Glycolic Acid (PLGA) are presented, as the ability to dissolve within the body, eliminating the need for removal and reducing potential skin irritation. Park et al. [63] confirmed the pivotal part of materials in the fabrication of MN in determining their effectiveness, safety, and manufacturability. Furthermore, biodegradable polymers (PLA, PGA, PLGA) provide the necessary strength to ensure skin penetration without breaking, though they are flexible enough to avoid causing injury. The use of chitosan derived from chitin is particularly noteworthy for its biocompatibility and non-toxicity, making it an ideal candidate for patient-safe applications [71]. Hyaluronic acid, naturally occurring in human skin, is another material of interest, appreciated for its

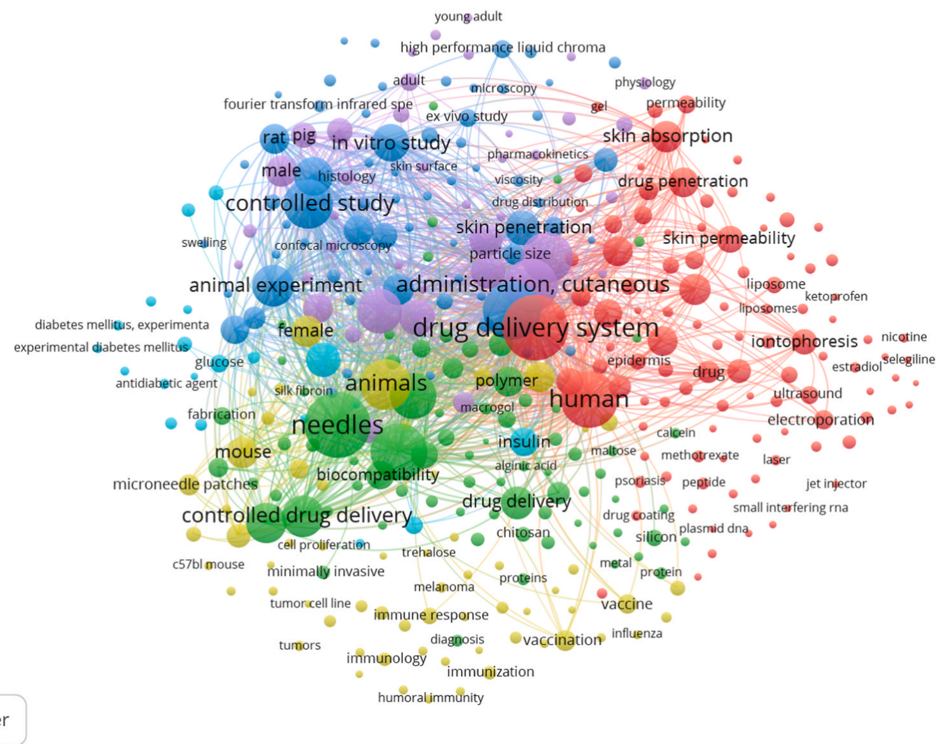

Fig. 5. Co-occurrence cluster map of the main keywords in scientific articles on MN for TDD.

Table 3
Top 20 Keywords per cluster of Scopus search.

Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
drug delivery system	microneedles	nonhuman	vaccination	administration, cutaneous	transdermal delivery
human	polymer	controlled study	animal cell	cutaneous drug administration	insulin
stratum corneum	hyaluronic acid	animal experiment	drug efficacy	microinjections	glucose
unclassified drug	controlled drug delivery	animal tissue	vaccine	procedures	diabetes mellitus
drug formulation	hydrogel	in vitro study	intradermal drug administration	metabolism	glucose blood level
drug penetration	3d printing	skin penetration	microneedle patches	equipment design	sprague dawley rat
skin absorption	alginic acid	drug release	immune response	drug effect	blood
transdermal drug administration	biocompatibility	rat	influenza vaccine	adult	diabetes mellitus, experimental
skin permeability	povidone	in vivo study	mammals	human tissue	hypoglycemic agents
pharmaceutical preparations	polyvinyl alcohol	animal model	human cell	diffusion	antidiabetic agent
drug	polymerization	drug solubility	immunology	drug liberation	biochemistry
nanoparticle	microtechnology	cytotoxicity	immunization	histology	diabetes
drug bioavailability	nanofabrication	dissolution	ovalbumin	skin water loss	blood glucose
iontophoresis	chitosan	particle size	mice, inbred balb/c	surface property	experimental diabetes mellitus
molecular weight	biodegradability	drug stability	pathology	erythema	antidiabetic activity
physical chemistry	controlled drug release	ex vivo study	immunogenicity	physiology	insulin dependent diabetes mellitus
skin irritation	polyglactin	high performance liquid chromatography	diseases	pharmacokinetics	metformin
drug delivery system	micromolding	sustained drug release	immunoglobulin g	drug compounding	antiinfective agent
drug safety	three dimensional printing	encapsulation	delayed-action preparations	porosity	hypoglycemia
epidermis	silicon	solubility	injections, intradermal	human experiment	

moisturizing properties and compatibility with skin tissue [72]. Regarding MN manufacturing, Polydimethylsiloxane (PDMS) used in micro-molding allows accurate replication of the MN designs, is suited for visual inspection during the process, does not react with the polymers used for the MN fabrication, and is flexible and durable, resulting in an ideal material for molds useable repeatedly, with enhanced efficiency of the production [73]. The advent of 3D printing technology has further revolutionized MN fabrication, allowing precise customization with a wide variety of materials, as outlined in Elahpour et al. [74].

Cluster 3 – in blue - emphasizes preclinical research and testing with terms like "animal experiment", "in vitro study", "animal model", and "controlled study". The cluster focuses on assessing safety and efficacy before human clinical trials. Animal testing and in vitro trials are important for scientific research, providing valuable insights into disease mechanisms and treatment efficacy. They are essential for progress in the medical field and the development of new treatments. Hyaluronic acid (HA) MN has been assessed for the administration of Minoxidil (MXD) [75] - a common topical treatment for alopecia - whose effectiveness is hindered by a low absorption rate. The impact of HA on hair dermal papilla (HDP), which regulates hair follicle development, is examined. HA promotes cell adhesion and reduces cell substrate in mice with chemotherapy-induced alopecia. Dissolving HA-MN containing MXD demonstrates superior results in hair growth in comparison to topical MXD application. Likewise, a formulation of gelatin methacrylate crosslinked together with polyethylene glycol diacrylate (PEGDA) has been tested as a platform for drug delivery on mice and mini-pigs [76]. In this case, MoS2 nanosheets have been incorporated as photothermal components into MN hydrogels, featuring on-demand release properties. MoS2-MN patches, tested ex vivo and in vivo, have shown that – if subject to photothermal stimulus - load and release insulin, limiting blood glucose comparable to those achieved by subcutaneous injection.

Cluster 4 - in yellow - investigates the body's biological and immunological responses to TDD by MN, as indicated by keywords like "antibody response", "antigen," and "immune system." In 2019 Niu et al. compared the delivery of vaccine NPs through intravenous subcutaneous and intradermal routes [77]. Administering through hollow MN led to an initial rapid transit through the draining lymph nodes, with minimal overall systemic exposure. Ovalbumin (OVA) - embedded in poly(D,L -lactide-coglycolide) NPs and employed as a model of a vaccine formulation - showed a more rapid antibody affinity maturation compared to soluble OVA-based vaccine. This, as well as a substantially better antibody response, makes MN a promising approach to improve vaccine efficacy. In a recent review, for minor systemic exposure, together with the painless and minimally invasive treatment, the MN has been analyzed as a useful system for TDD in skin-related immune disorders [78]. Drug delivery, which is topically hindered by the SC and a limited permeation of APIs encapsulated in nanocarrier, is improved using MN. Several previous studies on the use of MN in treatment-immune system disorders related to the skin have already shown their advantages [79,80], in particular for polymer-based MN, whose dissolution is biocompatible [81]. MN therapy generally improves patient comfort, which is of great interest for prolonged treatments, such as skin-related immune diseases.

Cluster 5 – in purple - centers on the clinical applications and practical aspects of TDD, including "administration", "cutaneous", "skin", "clinical effectiveness", and "patient compliance". An important driving force for the development of MN technology is to alleviate patient discomfort, phobia, and anxiety in both adults and children [82,83] relating to the use of subcutaneous injections. PLGA based disposal MN patch ensures an effective administration of drugs with a low invasive method. It is achieved by placing the MN patch directly to the target site of the skin, thereby passing the initial metabolic step and avoiding gastrointestinal issues (pH, enzymatic degradation, hepatic metabolism) [84]. As early as 2009, Donnely and colleagues showed that MN significantly reduce microbial infiltration compared to hypodermic needle puncture [85]. They found no microorganism passed through the vital epidermis in skin punctured by MN, unlike skin perforated by conventional needle. In addition, improving patient safety involves aseptic or sterile manufacturing practices and the production of MN with self-disabling materials such as dissolving or biodegradable polymers to discourage improper or unintentional reuse.

Cluster 6 – in blue sky - focuses on specific therapeutic applications, especially in diabetes management, with words like "transdermal delivery," "insulin", "diabetes mellitus", "antidiabetic activity", and "blood glucose level", all strictly inherent the same theme. In this area, the aims are to improve glycemic control, minimize the probability of hypoglycemia, and guarantee simpler regimens. In 2023 MNs Insulin aspart (IAsp) and insulin degludec (IDeg) were analyzed to administrate postprandial and basal blood glucose levels, respectively [86]. PVA-based MNs covered by insulin solutions showed good stability of the insulin encapsulated. Studies in diabetic rats reported that dissolving MNs have a comparable impact to subcutaneous injections for hypoglycemic administration, with better compliance of the patients. More recently, a novel MN system has been designed for transcutaneous insulin delivery, with pH-sensitive insulin-loaded nanoparticles (SNP(I)) along with glucose oxidase (GOx) and catalase (CAT) loaded into pH-insensitive nanoparticles (iSNP(G + C)) [87]. It is a pH-driven platform [88,89], where SNP(I) respond to changes in glucose levels, rapidly disintegrating in mildly acidic conditions induced by GOx in iSNP(G + C) during hyperglycemic states and facilitating insulin release. In vivo trials on mice with type 1 diabete exhibited an efficient management of blood glucose levels over a prolonged time.

Table 4 provides detailed examples of published research articles, highlighting the drug or nanoparticle released, the method of preparation, the material used, and the main findings. Each example is associated with a specific cluster identified in Table 3.

3.6. Analysis of patents

The dataset comprises 682 retrieved patents, classified in 352 groups. A total of 101 distinct applicants are identified and 115 documents are granted. Within the retrieved database, 18 documents received citations exceeding 100 times (highly cited patents). World Intellectual Property Organization applications are linked to an undetermined geographical area, therefore related documents have been omitted. The number of citations serves as a metric for the patent's significance. Citation indexing is a crucial tool for assessing the patent's value and impact. Table 5 reports the most cited patents according to The Lens research. The document

Table 4
Cases of MN systems in scientific papers. Drug, fabrication method, material, inference, and belonging cluster are reported.

Drug/Prodrug/NPs Released	Method of preparation	Material	Inference	Cluster	Ref
Methotrexate-thymidine kinase-hyaluronic acid (MTX-TK-HA)	Nano precipitation of PLA-mPEG and MTX-TK-HA solutions	Poly(lactic Acid)-poly(ethylene glycol) methyl ether (PLA-mPEG)	MTX-TK-HA/PLA-mPEG nanoassemblies achieve CD44-targeting and Reactive Oxygen Species-sensitive delivery of MTX in psoriasis treatment	4	[81]
Insulin	Molding and drying of a mix of insulin, proline and silk fibroin	Silk fibroin	Insulin maintains its biological activity and achieves a sustained release effect	6	[90]
Alendronate sodium (ALS)	Centrifugation assisted micromolding of a mixture of ALS-loaded niosomes and polymer	PolyVinyl Pyrrolidone (PVP)/ poly (vinyl alcohol) (PVA)	Niosomes containing ALS TDD via MNs provides sustained release	3	[91]
Niacinamide/ascorbic acid	Molding of Niacinamide and ascorbic acid-based SH/AP MNs	Sodium Hyaluronate (SH) and AmyloPectin (AP)	Skin permeability of SH and AP using MNs improved	1	[92]
Meloxicam	Meloxicam loaded MNs prepared using micro-molding technique	PVA/PVP	Fast and complete drug release	5	[93]
Exendin-4 (Ex4)	Dual mineralized particles (m-GOx and m-Ex4) loaded together to alginate into the tips of a mold	Alginate	Responsive release and improvement of the therapeutic performance of Ex4	6	[94]
None (placebo)	Casting in the mold under vacuum	PVA/sucrose.	Proven feasibility of using dissolving MNs for (self)administration of drug and vaccine	5	[19]
Adenovirus-based Plasmodium falciparum malaria vaccine (AdHu5–PfRH5)	Molding of dissolving MNs	Trehalose	Enhancement of protective immune responses	4	[95]
Cisplatin (CPT)	Photopolymerization of consecutive layers of polymer using stereolithography (SLA)	Soluplus® (co-polymer of polyvinyl caprolactame-polyvinyl acetate-polyethyleneglycol)	Effective cancer treatment via CPT loaded cross-MNs	2	[96]
Doxorubicin (DOX)/ docetaxe (DTX)	Micromolding of encapsulated DOX/DTX in PVA	PVA	DOX and DTX loaded MNs led to a substantial decrease in tumor size	3	[47]
Vascular endothelial growth factor (VEGF)	Molding of chitosan (CS) e poly(N-isopropylacrylamide) (pNIPAM) hydrogel pre-gel.	CS/pNIPAM	Promotion of wound healing in a severely infected wound model	2	[97]
Polymyxin b	Molding of PVP/trehalose/glycerol	PVP/trehalose/glycerl	Ability to deliver the active peptide after the formulation process	1	[16]

US6256533B1 "Apparatus and method for using an intracutaneous microneedle array" [98] is in the first place, with 621 citations. This Procter & Gamble Company's document of 1999 (priority date) describes a versatile MN array for minimally invasive drug delivery and body fluid sampling, utilizing silicon-based needles and iontophoresis for enhanced transdermal applications. It is essential to point out that pivotal innovations should be referenced more often. Furthermore, elder documents collected more citations primarily because they have been available longer, allowing more referencing opportunities. In contrast, newer patents may require additional time to gain visibility and be cited. Evaluating the influence and impact of a given document enables industrial and research sectors to make mindful choices about resource allocation and to address their efforts strategically.

Many patents focus on advances in the MN's conception and structure, including functionalized arrangements, to enhance drug delivery and accuracy. There is a growing trend towards integrating MN with healthcare platforms, patch systems, and multi-reservoir devices. The inclusion of complementary technologies such as integrated sensors and MN functionalization methods suggests a trend towards more sophisticated and personalized drug delivery approaches.

According to Table 6, which outlines the primary jurisdictions for patent filings or grants in MN-based technologies for TDD, the United States emerges as the leading country in terms of applications. The significant presence of biotech companies may be a key factor driving the focus of the applicants. China covers a considerable interest by patent applicants in MN, largely overcoming the European Patent Office.

3.7. Annual patent applications per year

Over time, the number of patent documents has steadily increased. Fig. 6 illustrates the trend in patent applications over the years, based on data from The Lens.

Between 2001 and 2007 there was only sporadic activity on MN for TDD with relatively low counts. A significant increase started around 2008, and a more pronounced rise began from 2016 onwards. Recent years, namely 2022 and 2023, show the highest counts, indicating a noticeable increase in patent-related activity. The upward trend in patent filings from 2008, especially from 2016 suggests a growing interest and development in MN technology. This could be due to advancements in the field, increased recognition of the technology's potential benefits, and a broader acceptance of transdermal delivery methods in medical and pharmaceutical practices. In the initial phases of technological progress, patent applications increase slowly, owing to the limited availability of new technologies and a constrained novelty landscape. Nevertheless, as singular and corporate efforts concentrate on pioneering new technologies, the volume of patent applications steadily rises, entering an acceleration phase. At this point, the growth in patent applications intensifies, driven by the necessity to safeguard the inventions. It is important to consider that, given the typical 18-month publication timeframe for patent application, the data for the last year and a half of the analyzed period (2022–2023) may not fully reflect the actual count.

Ranking among the most active patent applicants, U.S. companies are the leading participants in patenting MN technologies for TDD. The restrained participation of universities among them likely suggests that many MN technologies have reached a level of maturity that allows companies to explore in depth and in an autonomous way. Frequently, academic patents are pursued for scientific aims rather than for commercial ones. Kong et al. [108] undertook a comparative analysis of patents issued by universities and corporations, focusing on differences in the disclosure and clarity of the texts. This study emphasizes the different scopes and operational frameworks of universities and corporations, which affect the related approaches to patent composition. University patents typically prioritize advancing research and contributing to scientific knowledge, thereby enhancing accessibility and readability through comprehensive disclosure of technical information. In contrast, corporate patents primarily aim at the inventions' commercialization and protection to ensure profit, leading to less emphasis on full disclosure to preserve competitive advantage and proprietary information. Kimberly Clark Co (www.kimberly-clark.com/en-us), the main patent applicant, is primarily known to produce paper-based consumer products, such as tissues, diapers, and sanitary towels. MN technology represents a part of its broader strategy to diversify its product portfolio and venture into emerging markets, particularly in painless drug delivery and minimally

Table 5
Top 10 cited patents according to The Lens research.

Application Number	Application date	Title	Owner	Cited by	Ref
US6256533B1	1999-06-09	Apparatus and method for using an intracutaneous microneedle array	The Procter and Gamble Co	621	[98]
US6379324B1	1999-06-09	Intracutaneous microneedle array apparatus	The Procter and Gamble Co	507	[99]
US10303851B2	2014-03-14	Physician-centric health care delivery platform	Hana Patent Technology LLC	370	[100]
US20040106904A1	2003-10-07	Microneedle array patch	BIiovalve Technologies Inc. Valeritas Inc	318	[101]
US20060024358A1	2005-08-01	Multi-reservoir device for transdermal drug delivery and sensing	John T. Santini JR.	217	[102]
US20030083645A1	2002-09-09	Microneedle transport device	Massachusetts Institute of Technology	184	[103]
US20070078376A1	2006/09/12	Functionalized microneedles transdermal drug delivery systems, devices, and methods	Transcutaneous Tech Inc	174	[104]
US20090259176A1	2008-04-08	Transdermal patch system	Los Gatos Research Inc	170	[105]
US20100121307A1	2009-11-02	Microneedles, Microneedle Arrays, Methods for Making, and Transdermal and/or Intradermal Applications	Microfabrica Inc	168	[106]
US6835184B1	2004-12-28	Method and device for abrading skin	Becton Dickinson Co	153	[107]

Table 6
Main countries for number of filed and granted documents on MN for drug delivery.

Jurisdiction	Document counts
United States	227
China	182
European Patents	41
Canada	22
Australia	22
Korea, Republic of	14
Mexico	6
Japan	5
Germany	4
Russia	4

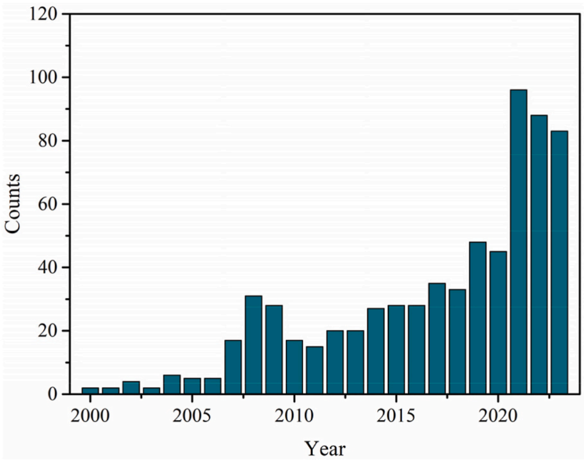

Fig. 6. Yearly evolution of MN patent applications according to The Lens.

invasive skin treatments. Kimberly Clark's involvement in this area likely involves research and development efforts toward MN-based product innovation. Thanks to its expertise in material sciences and large-scale production capabilities, Kimberly Clark could introduce pioneering e MN-based products to a wide consumer market.

3.8. Analysis of the main keyword in retrieved patents

The frequency of keywords appearing in titles and abstracts of patents was tracked to calculate their correlation. VOSviewer generated a co-occurrence network based on this analysis (Fig. 7a), according to which each keyword's total strength was assessed. In Fig. 7b, the color of each keyword reflects the date of its corresponding patent application. The color gradient transitions from blue, representing older patents, to green, and finally to yellow for the more recent ones. In this visualization, for instance, the newest documents, marked in yellow, pertain to fabrication technologies and treatment applications.

Table 7 reports the main important clusters, revealing groups of keywords that frequently appear together in filed patents.

Cluster 1 – in red – focuses on MN's basic design features and material composition. Keywords such as "biodegradable polymer", "shape", "size", "length", "needle body", "base layer", "upper surface", and "micron" suggest a concentration on the physical characteristics and the innovation in the structure of MN. Patents in this cluster concern how MN are engineered to optimize penetration into the SC and effectively deliver active substances such as drugs or vaccines. In US11844920B2 a multicompartmental MN system was presented to diminish the skin's mechanical barrier by ensuring the vertical penetration of the MNs [109]. Similarly, arrays of polymeric hollow MNs connected to reservoirs to inject drugs by light pressure [110], arrays of metallic hollow MNs with sharp tips to facilitate puncturing [111], and MNs made via replica molding with microparticles containing active ingredients [112] were developed.

Patents in cluster 2 – in green – geared toward the systems that facilitate drug delivery using MN. Keywords such as "delivery system", "transdermal delivery", "agent", "composition", "formulation", and "absorption" focus on the therapeutic applications of MN technology, including the methods of drug administration, delivery, and their interactions with the organism. In US20230145564A1, gelatin microneedle patches for the release of curcumin – insoluble in water – were presented [113].

The third cluster – in blue – relates to the integration of MN with other components and systems that allows communication or control over the drug delivery process. Keywords such as "fluid communication", "housing", "reservoir", "user", "portion", "fluid",

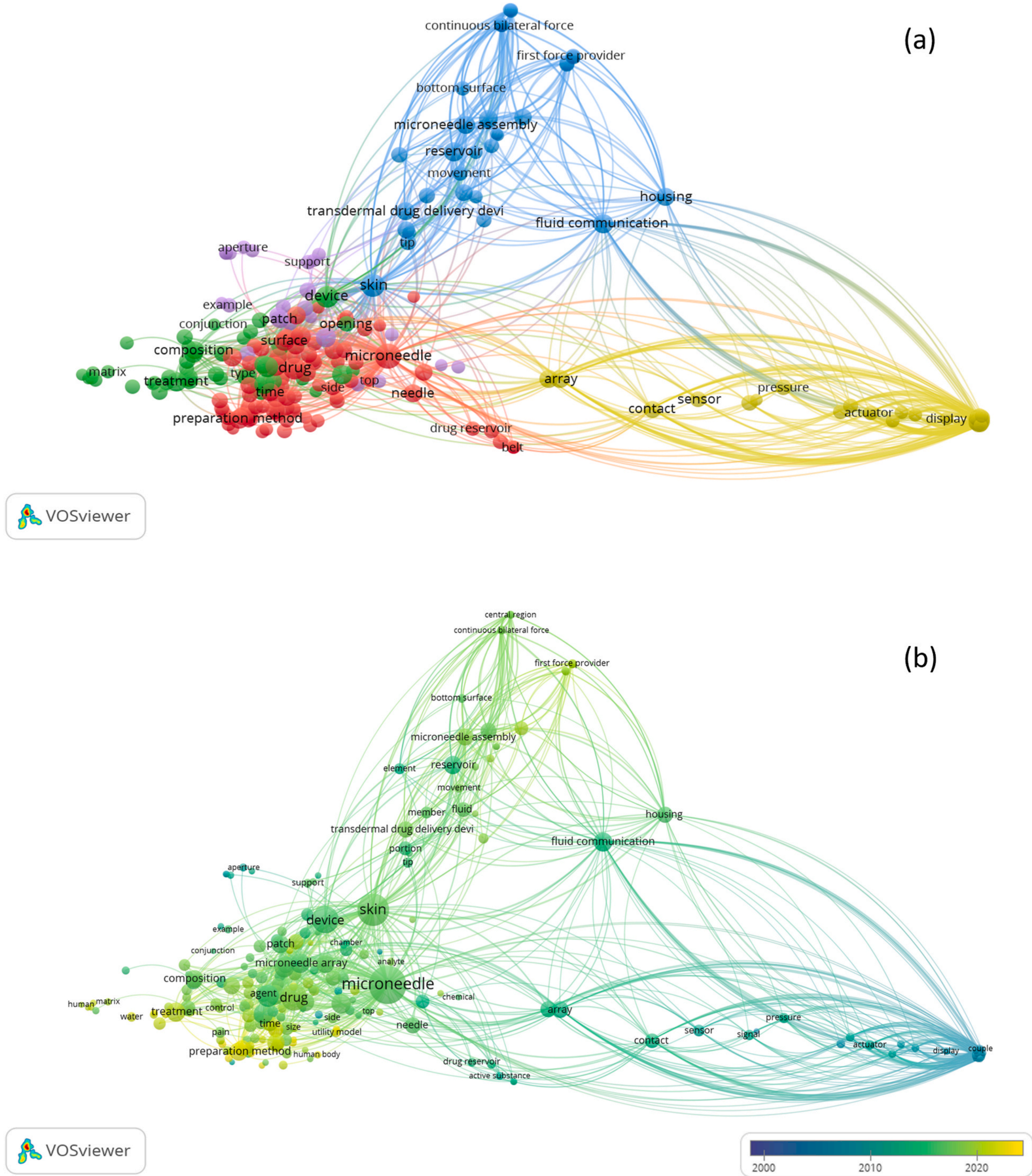

Fig. 7. (a) Total strength of the co-occurrence connections between keywords in MN patents; **(b)** evolution over the time of the co-occurrence clusters of the main MN patents keywords.

"component", "element", "interior", "bottom surface", and "apparatus" pone an emphasis on the user interface, reservoirs for holding medicinal fluids, and mechanical parts that make up the delivery device, potentially including the integration of smart technology. This represents an adaptable and easy-to-use approach for TDD with a mechanism controlled and adjustable by automatic devices wearable and operable remotely [114,115].

Keywords in cluster 4 – in yellow – refer to the diagnostic and monitoring capabilities that can be combined with MN technology. "Sensor", "signal", "pressure", "biological fluid", "sample", "infusion", "characteristic", "display", "diagnostic processing", and

Table 7
Top 20 Keywords per cluster according to The Lens.

Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
microneedle	device	skin	array	patient
array	delivery	fluid communication	patient	drug delivery
layer	transdermal delivery	housing	control	patch
preparation method	agent	reservoir	sensor	channel
substrate	composition	microneedle assembly	signal	compliance
needle body	formulation	user	pressure	barrier
device	transdermal patch	transdermal drug delivery device	actuator	concentration
component	amount	portion	biological fluid	manner
polymer	compound	fluid	sample	aperture
shape	therapeutic agent	element	infusion	support
area	delivery system	member	disposable cartridge	base portion
base	disease	tip	display	analyte
bottom	active agent	interior	diagnostic processing	aspect
hole	transdermal administration	bottom surface	distal end	body portion
size	pore	movement	handheld control unit	microneedle array device
biodegradable polymer	control	continuous bilateral force	handheld diagnostic unit	drug compound
permeability	matrix	component	invasive drug delivery system	flow
stratum corneum	absorption	skin attachment	keypad	example
mechanical property	cannabidiol	central region	medicinal fluid	vaccine
length	pharmaceutical composition	lower housing portion	medicinal fluid reservoir	chemical
raw material	prevention	upper housing portion	memory	wire
material	skin surface	first force provider	monitoring	skin patch
type	animal	second force provider	processor	detection
micron	pharmaceutical preparation	relative movement	signal indicative	presence
upper surface	mammal	apparatus	invasive	minimally invasive
		deformable component		
		cartridge		

"processor" point to patents that involve real-time monitoring of biomarkers or controlled delivery of drug in response to physiological signals, improving the functionality of MN in personalized medicine [116].

Cluster 5 – in purple – emphasizes advanced delivery methods and the interaction between the patient and the MN technology. Keywords such as "patient", "patch", "concentration", "analyte", "presence", "detection", "drug compound" and "vaccine" refer to designs to minimize discomfort, improve the efficiency of drug administration, and potentially strengthen vaccination efforts, as reported in Ref. [117].

Table 8 reports some examples of patents belonging to the various clusters identified.

4. Conclusion

The MN-based TDDS are innovative technological platforms that have reported remarkable growth in the last decades, as evidenced by our bibliometric and patent analyses. This review shows how synergic efforts in research, development, and commercialization strongly drive rapid advances in MN technologies. The bibliometric analysis reveals a significant increase in scientific publications, reflecting the growing interest and collaborative cooperation at global level, particularly in China, the US, the UK, and India. The patent analysis corroborates these findings, pointing to an increase in patent filings, especially after the pandemic emergency, which is indicative of burgeoning innovation and the potential for new MN-based therapeutic solutions. The development and refinement of MN technologies have focused on overcoming the limitations of traditional transdermal delivery methods, offering a promising way for painless, and efficient drug administration directly into systemic circulation or targeted skin layers. In the last years, new solutions in the fabrication of different MN kinds, including dissolvable, hydrogel-forming, solid, hollow, and coated MNs, have expanded the possibilities for drug delivery and patient care, catering to chronic diseases and enabling self-administration. Emerging technologies and smart TDDS are set to revolutionize patient-specific therapies, further enhanced by digital and 3D printing techniques. Strategic partnerships among academia, industry, and public funding bodies have been pivotal in advancing MN research and development, as evidenced by the prolific funding from national and international agencies. The collaborative landscape, as depicted by co-authorship networks, underscores the global commitment to advancing MN technologies for healthcare improvement. The healthcare relevance of MN technologies is further confirmed by the results of clinical studies, reporting their efficacy in enhancing patient compliance, particularly for prolonged treatments. The integration of novel materials and engineering processes in MN fabrication has been instrumental in improving treatment outcomes and patient experiences.

What can we foresee for the future of MNs? The continuous exploration and development of biocompatible and biodegradable materials are pivotal for the advancement of MN-based TDDS. Utilizing cutting-edge fabrication methods, such as 3D printing, more efficient, safe, and patient-friendly drug delivery systems will be soon available. These innovations could lead to MN devices that are not only more effective in administering drugs but also significantly reduce the environmental impact, thanks to their biodegradability. Furthermore, the precision of additive manufacturing enables the production of MN tailored to specific drug administration needs, enhancing the overall efficacy and safety of treatments. Moreover, responsive MN systems represent a frontier in personalized

Table 8
Examples of patents related to the different clusters.

Application Number	Application date	Title	Owner	Note	Cluster	Ref
CN110115707A	2018-02-07	A kind of method and its application preparing porous polymer micropin based on phase detachment technique	Huazhong University of Science and Technology	Porous polymer MNs produced by replica molding, where the porosity is generated using phase separation technologies	1	[118]
CN114225210A	2021-12-31	Novel transdermal drug delivery micro-nano structure and preparation method thereof	Hangzhou Spectro Crystal Semiconductor Technology Co ltd	A new type of micro-nano structure for TDD. The multilayer structure of the needle tip obtained improves the adhesion capacity to tissues	1	[119]
CA2450367A1	2002-05-22	Microneedles for minimally invasive drug delivery	Abbott Laboratories	Hollow conical MN fabrication using semiconductor techniques. MNs have a larger base than height to reduce the possibility of breakage	1	[120]
US20160310417A1	2014-12-19	Formulations and Methods For Targeted Ocular Delivery of Therapeutic Agents	Emory University, Georgia Tech Research Corp	A fluid formulation administered by inserting a MN into the eye, and infusing the fluid formulation into the suprachoroidal space	2	[121]
US20230210762A1	2021-05-03	Transdermal drug delivery devices having psilocybin, lysergic acid diethylamide or 3,4-methylenedioxyme-thamphetamine coated microprotrusions	Emergex USA Corp	Titanium MNs covered with a biocompatible coating, that includes Psilocybin, Lysergic Acid Diethylamide, or 3,4-Methylenedioxyme-thamphetamine used to treat depression, anxiety, post-traumatic stress disorder, migraines, and cluster headaches	2	[122]
US20110052694A1	2010-08-31	Use of cannabidiol prodrugs in topical and transdermal administration with microneedles	Alltranz Inc	MNs used for delivering drugs comprising cannabinoids or cannabinoid prodrugs in the treatment of sicknesses, such as pancreatic cancer	2	[123]
US20120220980A1	2011-02-28	Transdermal Patch Containing Microneedles	Kimberly Clark Worldwide Inc	A patch for drug administration. including MNs, a drug reservoir, a rate control diaphragm, and a release member	3	[124]
US9649483B2	2009-10-15	Microneedle transdermal delivery device	Dewan Fazlul Hoque Chowdhury	A series of hollow MNs connected to a transport mechanism (belt or track around rollers) for controlled drug administration. The system can be manual or automatic	3	[125]
US20070161964A1	2006-01-10	Microneedle array, patch, and applicator for transdermal drug delivery	Vadim Yuzhakov	An applicator device composed of steel MNs and a reservoir of the active ingredient, placed on parallel planes	3	[126]
US6256533B1	1999-06-09	Apparatus and method for using an intracutaneous microneedle array	Procter and Gamble Co	An array of MNs as part of a closed-loop system to control drug delivery, based on information obtained from real-time analysis of body fluids	3–4	[98]
EP1695734A1	2002-05-22	Microneedles for minimally invasive drug delivery or for diagnostic sampling	Hospira Inc	A minimally invasive diagnostic system for sampling and analyzing a patient's biological fluid. An array of hollow silicon MNs is used as a biological fluid collection system	4	[34]
US20090187167A1	2008-12-17	Integrated intra-dermal delivery, diagnostic and communication system	New world pharmaceutics LLC	An Intra-Dermal Delivery, Diagnostic, and Communication (IDDC) MN-based system that utilizes an intelligent therapeutic agent delivery system with cells containing therapeutic and diagnostic agents	4–5	[117]
US10303851B2	2014-03-14	Physician-centric health care delivery platform	MD24 Patent Technology LLC	A system for diagnosing and treating patients, through remote monitoring. A computing device retrieves patient health data and generates patient diagnoses or treatment recommendations	5	[100]

medicine. By integrating sensors and delivery mechanisms, these systems can monitor patient conditions in real-time and adjust drug release accordingly. This ensures that the therapeutic agents are delivered at the optimal time and dose, tailored to the individual's needs. Such advancements could revolutionize the management of chronic diseases, where continuous monitoring and precise medication adjustments are crucial for effective treatment. Current and future studies are expanding clinical trials for MN-based TDDS across a variety of therapeutic areas to validate their efficacy and safety. By focusing on a broad spectrum of employments, from chronic diseases to vaccines and personalized medicine, MN technologies can be thoroughly assessed in diverse clinical settings. This will not only demonstrate their potential in treating various conditions but also build robust evidence to support their broader adoption in healthcare.

What advice can we take from this analysis? Fostering multidisciplinary collaborations is essential to unlock the full potential of TDDS assisted by MN. By bringing together experts from academia, industry, and healthcare, innovative solutions can be developed at the crossroads of material science, pharmaceuticals, and bioengineering. These collaborations can accelerate the translation of research findings into practical applications, driving forward the goal of drug administration. Moreover, prioritizing the development of user-friendly and minimally invasive MN systems is crucial for improving patient adherence to treatment regimens. Designing devices that are easy to use and cause minimal discomfort can significantly enhance the patient experience, leading to better treatment outcomes. Patient-centric designs also allow the accessibility of MN-based TDDS benefits to a wider population, including those who may be apprehensive about traditional drug delivery methods.

CRediT authorship contribution statement

Aniello Cammarano: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Stefania Dello Iacono:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Mario Battisti:** Writing – review & editing, Software, Formal analysis. **Luca De Stefano:** Writing – review & editing, Validation, Supervision, Data curation. **Caterina Meglio:** Writing – review & editing, Visualization, Project administration, Funding acquisition, Conceptualization. **Luigi Nicolais:** Writing – review & editing, Visualization, Project administration, Funding acquisition, Conceptualization.

Ethics statement

This study does not require review or approval by an ethics committee or informed consent, as no patient data was generated for this review article.

Data availability statement

data is available on request.

Availability of data

Data are available from the corresponding author on request.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Nothing to declare If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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