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Microneedles: An efficient technique to enhance Transdermal Drug Delivery System

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Abstract

Microneedle technology has emerged as a promising tool for enhancing transdermal drug delivery. This technology involves the use of micron-sized needles to create microchannels in the skin, allowing for the delivery of drugs, vaccines, and other therapeutic agents. The skin's outermost layer, the stratum corneum, is the primary barrier to drug penetration, and microneedles have been shown to effectively bypass this barrier. Various types of microneedles have been developed, including solid, coated, dissolving, and hollow microneedles, each with its own advantages and disadvantages. Microneedles have been used to deliver a range of therapeutic agents, including insulin, vaccines, and cancer therapies. The technology has several benefits, including painless and minimally invasive delivery, improved drug penetration, and reduced side effects. Microneedles have also been shown to enhance the delivery of oligonucleotides, vaccines, and other biological agents. Overall, microneedle technology has the potential to revolutionize the field of transdermal drug delivery, offering new hope for the treatment of various diseases and disorders.

Keywords: Microneedle technology; Transdermal drug delivery; Minimally invasive; Therapeutic agents; Microneedle fabrication material

1. Introduction

A range of minimally or non-invasive methods for delivering drugs across the skin are included in transdermal drug delivery systems, which offer an appealing substitute for parenteral and oral drug administration systems [1]. A new kind of transdermal drug delivery method called a microneedle enhances drug penetration through the skin's strongest barrier. The process entails the development of a more extensive drug transport pathway by hypodermic needles of micron size, which can penetrate the stratum corneum and deliver the medication straight into the layer of the epidermis or dermis [2]. The concept of microneedles was first noticed in 1976. However, they remained ineffective until the first application of microelectromechanical systems in 1998, when the American patent on the microneedle for transdermal distribution was issued, simultaneously approving the idea of microneedles [3]. With an average thickness of 20 to 30 μm, the stratum corneum (SC), the primary layer of skin, is the hardest material to penetrate for drug delivery. It is made up of several keratinocyte layers [4]. Plant crude material standardization is growing essential in today's world. Items from main Blood veins, lymphatics, nerves, and the many skin appendages are all found in the dermis [5]. Intramuscular or hypodermic injections are the main methods used to deliver macromolecules over the skin. These two approaches have several drawbacks, including pain, needle anxiety, patient noncompliance, and unintentional needlestick injuries [6]. The system has been shown to be an effective method for delivering drug molecules with larger masses (above 500 Da) and different polarity. The medicinal elements include small chemicals, biomacromolecules (proteins, hormones, and peptides), vaccinations for SARS, MERS, and COVID-19, and genes [7].

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2. Skin anatomy and transdermal drug delivery system

About 15% of the total weight is made up of the skin, which is the biggest organ. Its entire surface area is around 20 square feet. We are protected from the harmful effects of UV rays by our skin. Along with allowing touch, heat, and cold sensations and aiding in body temperature regulation, it also acts as a barrier against mechanical, thermal, and physical as well as terrifying chemicals [8]. The epidermis, which is the outermost layer and contains the stratum corneum, the dermis, which is the intermediate layer, and the hypodermis, which is the innermost layer, are the three parts that comprise skin. The epidermis is composed of several layers. The top layer is composed of dead cells that periodically shed and are progressively replaced by cells from the base layer. Due to the presence of collagen and elastin fiber, it provides strength and elasticity in the dermis, which connects the epidermis and hypodermis [9]. With a thickness of a few millimeters (2.97-0.28mm), it serves as a barrier to prevent the transdermal absorption of various chemical and biological substances [10].

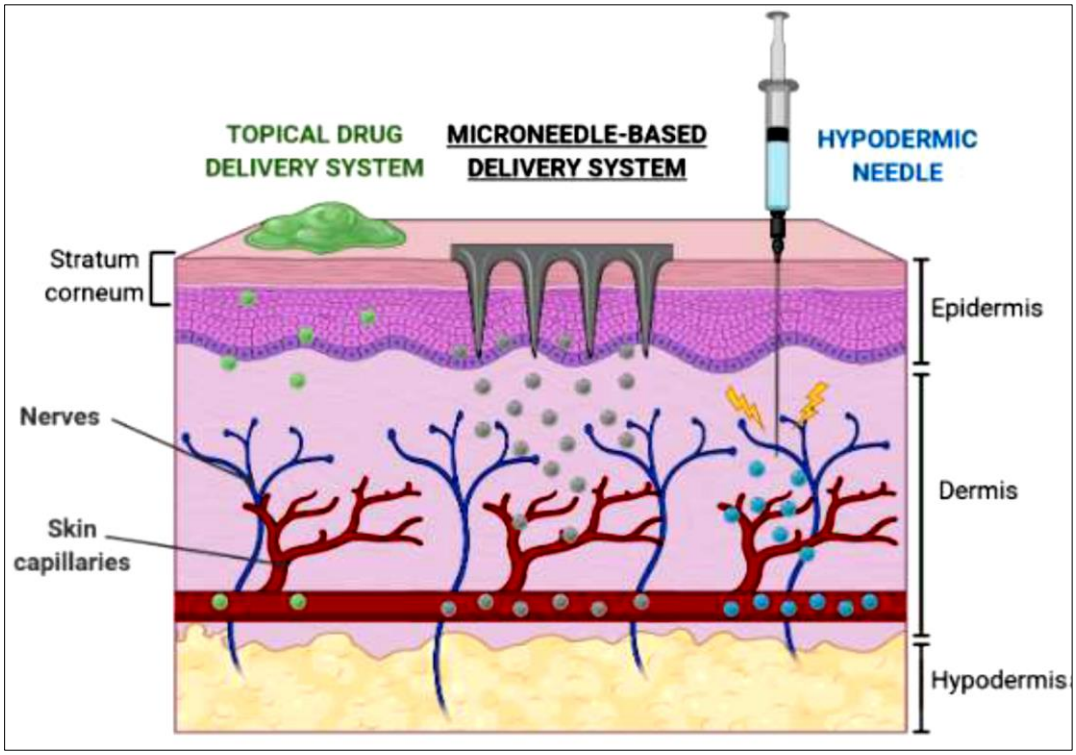

Figure 1 Type of skin anatomy [11]

3. Microneedles

As its name implies, MNs are needles that are micron-sized and used for transdermal medication administration vaccines. These needles have been extensively studied as a potential replacement for conventional needle injections since MN can improve the penetration of tiny compounds, macromolecules, and vaccinations through the skin [6]. This innovative transdermal drug delivery system is gathering popularity for the purpose of distributing medications through needles. It incorporates a variety of needle types, such as solid micro needles and micro needle patches, each of which has a distinct mechanism of action. The production of dissolving/hydrogel microneedles is the primary application of this method [12]. It is made up of a variety of microstructure protrusion covered in a medication. It is possible to create microneedles inside a patch for transdermal drug delivery. As can be seen from the qualities of currently accessible medications, they are made from a variety of materials, including silicon, silicon dioxide, polymers, glass, and other materials [8]. In the past few decades, a lot of attention has been paid to several different types of microneedles. Each type of microneedle is put into a category based on how it delivers drugs, which are: microneedles that are (a) solid, (b) hollow, (c) covered, (d) hydrogel, and (e) that dissolve [13]. There is possible to create microneedles inside a patch for transdermal drug delivery. They are manufactured utilizing a variety of materials, including silicon, silicon dioxide, polymers, glass, and other materials. The necessity for a low-cost, repeatable method of delivering drugs to the epidermal layer without damaging nerve cells or increasing the likelihood of microbial penetration led to the development of microneedles [8].

3.1. Advantage of microneedle

- The active ingredient in the medication is administered painlessly.
- Local administration allows for the avoidance of first-pass metabolism [5].
- The injection site heals more quickly than with a hypodermic needle.
- It is feasible to distribute drugs in a targeted manner.
- A dose reduction may result from increased pharmacological efficacy [14].
- Individual cells could receive highly targeted drug delivery from minuscule microneedles [20].
- Needles that are used only once are readily disposed of and may biodegrade [15].
- It is possible to cure a sizable surface area. Drugs can be given for prolonged periods of time at a steady rate [15].

3.2. Disadvantages of microneedles

- Microneedles have the following drawbacks: their dosing accuracy may be lower than that of hypodermic needles [16].
- The delivery and bioavailability of drugs are impacted by the external environment.
- The veins may collapse if injections are given often and repeatedly.
- Hollow microneedles can be blocked by compressed cutaneous tissue.
- The medication will bounce off the skin's surface if it is not administered carefully [14].
- If the medication concentration is high beneath the skin, local inflammation may occur. Allergies or sensitive skin can cause skin irritation.
- The points of the microneedles can break off and be left beneath the skin since they are so tiny and considerably thinner than the diameter of hair [15].

4. Type of microneedles

Based on how they administer medications to the skin, microneedles can be categorized into the following kinds, as illustrated in figure-2 [17].

4.1. Solid microneedles

Since solid microneedles are introduced and removed to create pores on the skin's surface that are 55 microns in size, they can be utilized as a skin pretreatment [18]. These are frequently used to produce pores in the skin, allowing medications to penetrate more efficiently. These needles enter the skin and generate microscopic channels that allow the medicine to reach the deeper layers of the skin. This approach improves drug penetration and has both local and systemic effects [19]. Because of their precise geometry, solid microneedles can be used to puncture the stratum corneum, forming microchannels in the skin that let the medication disseminate [20]. Numerous researchers are also looking at stainless steel microneedles. Following the uske of stainless-steel MN arrays, improved distribution of captopril and metoprolol tartrate was investigated [21]. Since silicon is the most crucial material to utilize, several research groups have examined the effectiveness of solid microneedle therapy for the intradermal delivery of insulin (both in vitro and in vivo) and have shown a considerable reduction in blood glucose levels [22]. Before manufacture can begin, the Food and Drug Administration must approve these materials based on their safety and biocompatibility [23]. Various teams of researchers examined the effectiveness of solid microneedle therapy for intradermal insulin delivery (both in vitro and in vivo) and found that blood glucose levels were significantly lowered. Martanto and associates found that solid microneedle insertion reduced blood glucose levels in diabetic rats by 80%. Additionally, these microneedles enhanced insulin delivery to a similar level of 0.05–0.5 units of subcutaneous injection of insulin [22].

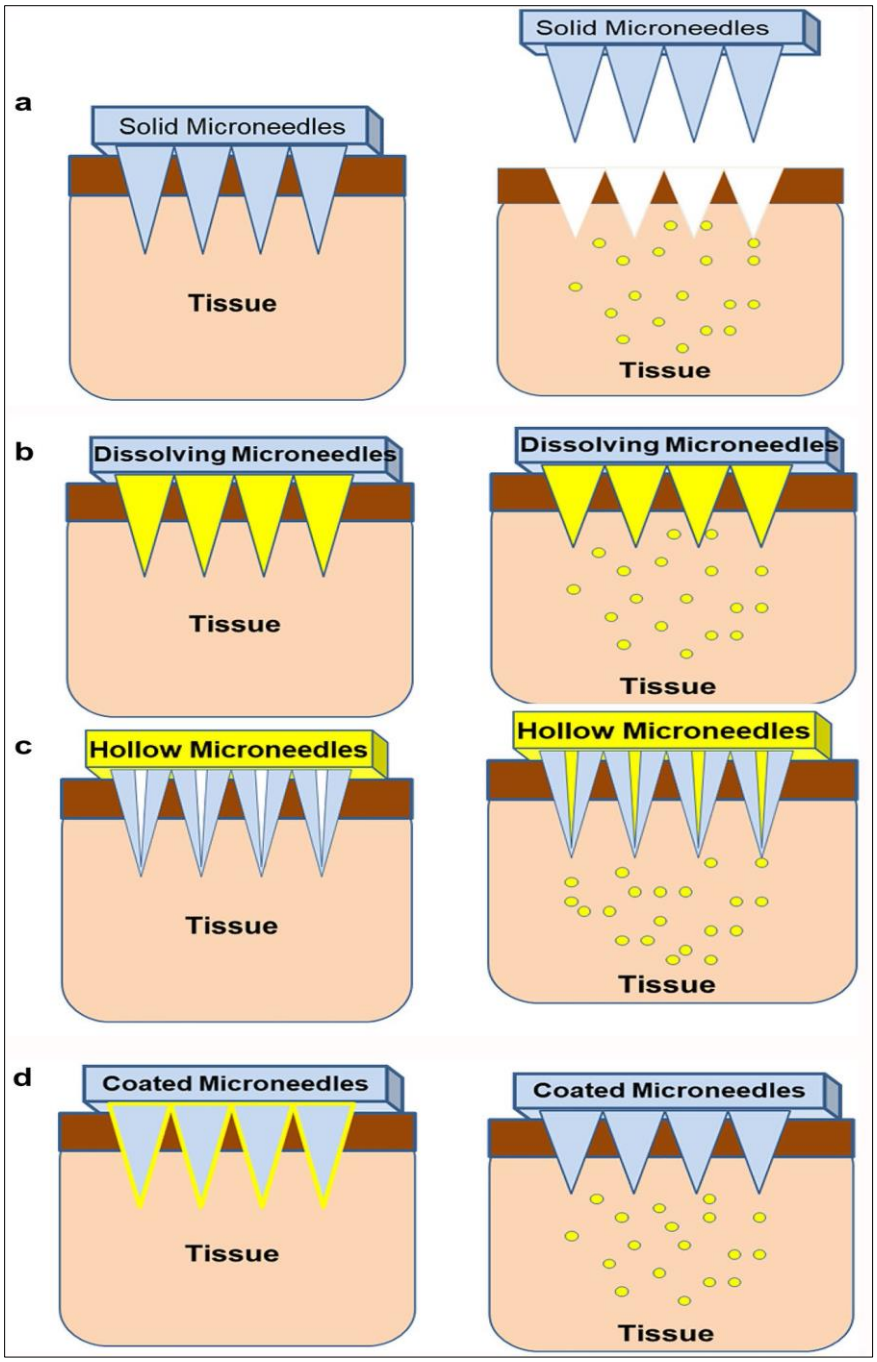

Figure 2 type of microneedle [24]

4.1.1. Coated Microneedle

The solid-type MN coated with a medicinal solution is the coated microneedle. Generally, the thickness of the coating layer determines how much of the medicine it contains [25]. Microneedles with a pharmacological coating on their surface are known as coated microneedles. Drug diffusion from the skin's surface to its deepest epidermal layer is made possible by this microneedle. However, because of the coating, the microneedle becomes thicker, and its penetration capacity may be affected. The coated microneedle proved to be quite useful for administering vaccines via the skin despite this drawback [26]. CMNs have been used to deliver small molecule medications such pilocarpine, lidocaine, and vitamin B more quickly [6].

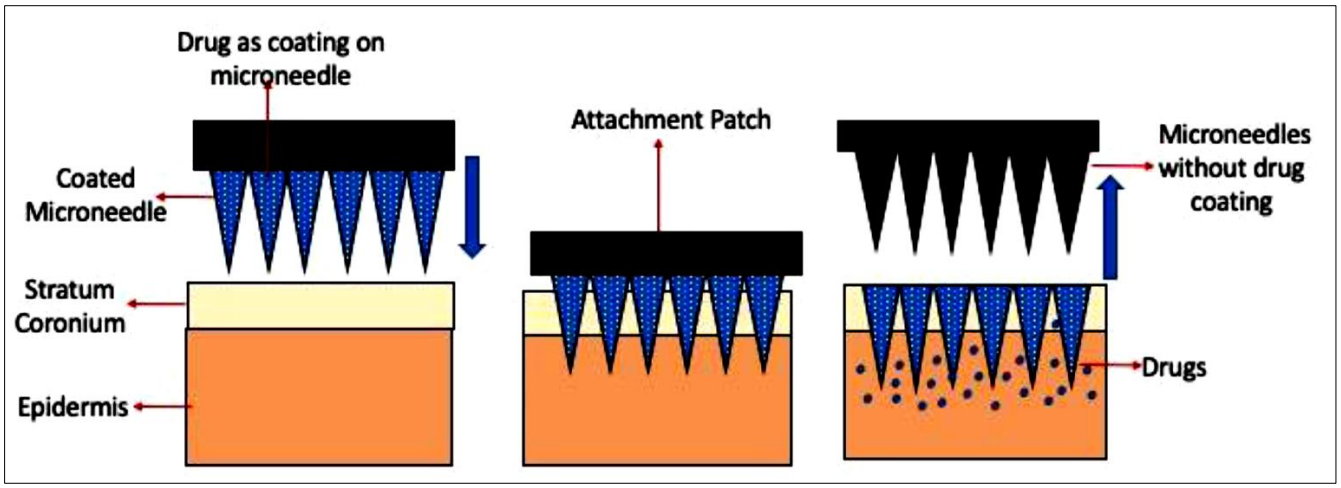

Figure 3 Drug delivery across the Stratum Corneum by drug coated microneedles [26]

4.1.2. Dissolving Microneedles

According to its features, the dissolving microneedle, first debuted in 2005, is a technology that shows promise. The biodegradable and biocompatible materials used to make the dissolving microneedles tend to break down and dissolve in bodily fluids. Drugs can be released into the skin quickly after dissolving microneedles [27]. The release of medications or vaccines embedded in polymers can be regulated by dissolving microneedles made of safe materials like natural and biodegradable polymers. In other words, when used for disease diagnosis and treatment, dissolving microneedles that regulate the release of encapsulated medicinal substances are safe and painless [28]. The development of dissolvable microneedles for influenza immunization has proven successful. The tips of the microneedles are composed of antigens combined with sodium carboxymethyl cellulose and trehalose [29].

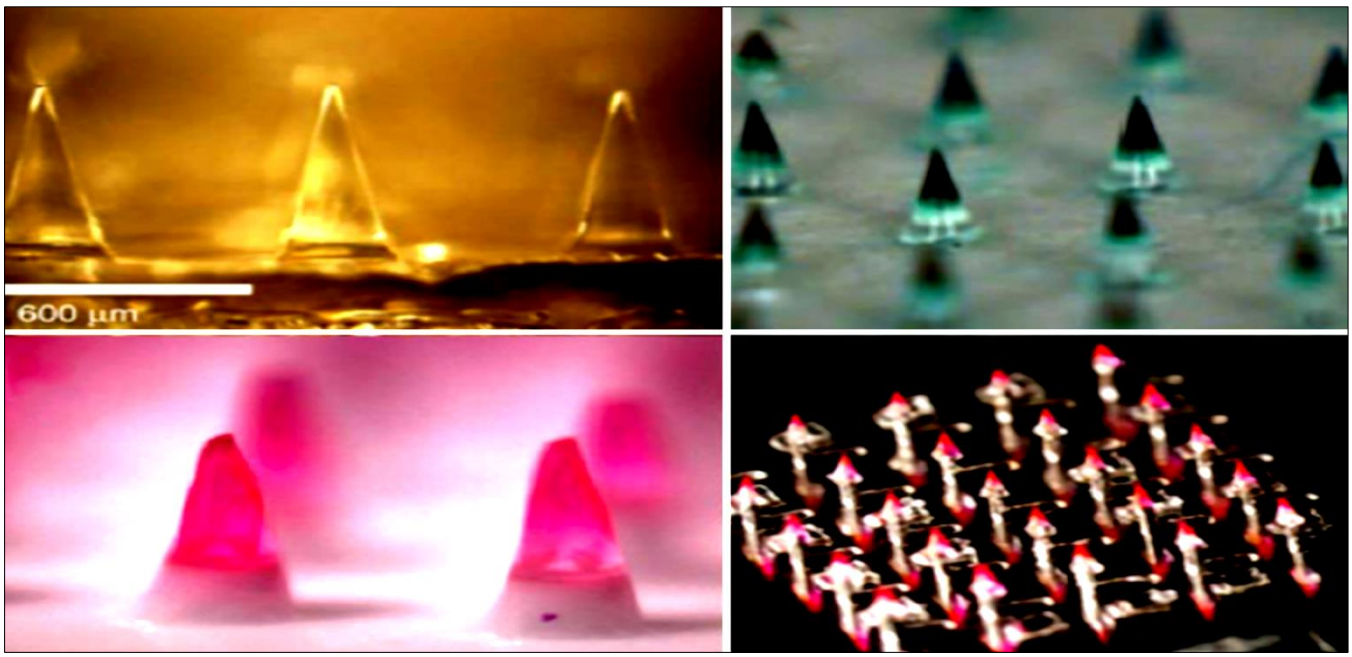

Figure 4 Dissolving microneedles [20]

4.1.3. Hollow Microneedles

One characteristic that sets hollow microneedles (MNs) apart from hypodermic injections is their micron range size. In the middle of each protrusion is a conduit [30]. Other systems, such as micro-electro-mechanical systems, can also be used to create these microneedles. These technologies include X-Ray photolithography, deep reactive etching, laser

micromachining, and integrated lithographic molding (Kim, 2012b). For therapeutic drug monitoring and the testing of biomarkers from interstitial fluid, like in the case of glucose monitoring, they can be utilized as an alternate method for patient fluid collection that doesn't involve discomfort or bleeding [31]. In contrast, modest doses of hollow microneedles cannot be contained, which may lead to poor clinical results [32]. Compared to subcutaneous injection, liquid formulation allows for faster administration and covers a larger region. To create hollow microneedles made of polymers for flexible devices [33]. A hollow bore is in the middle of hollow microneedles [34]. Ceramics, metal, silicon, and glass have been used to make hollow microneedles [35]. Many microneedle fabrication techniques aim to reduce microneedle height and offer a better safety margin [3]. To effectively distribute medications and minimally penetrate the stratum corneum of the skin, hollow MN is made using microfabrication technology similar to that of hypodermic needles. Hollow MN can be used to extract bodily fluids for analysis, such as glucose testing, and to provide medications at predetermined timings [36].

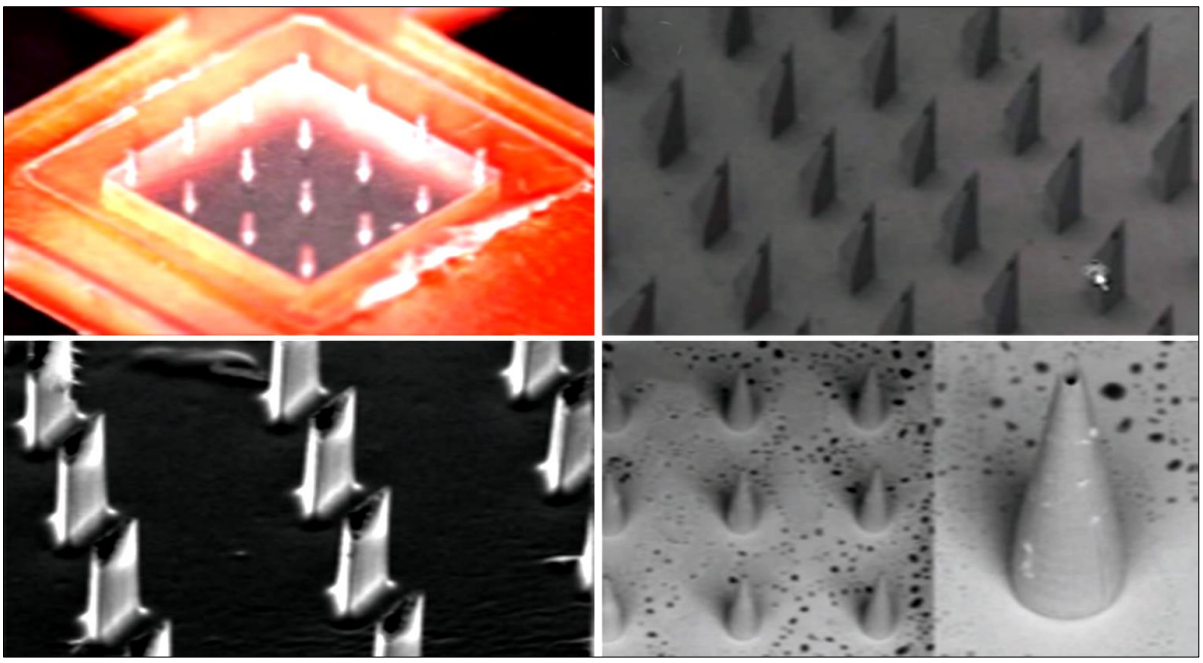

Figure 5 Hollow microneedles [20]

4.1.4. Hydrogel Microneedles

Hydrogel polymer hydrophilic shape allows them to absorb a lot of water into their three-dimensional network of polymers [37]. Channels are eventually formed as a result, enabling the transport of medication from the reservoir into the microcirculation. The swelling feature of the polymer functions as a rate-regulating membrane [38]. Additional benefits of hydrogel-forming microneedles are their ability to be manufactured in a variety of patch sizes and geometries, their ease of sterilization, their ability to with stand hole closure while in use, and their ability to be extracted from the skin entirely undamaged [49].

4.2. Microneedle fabrication material and its properties

4.2.1. Silicon

In the 1990s, silicon was used to create the first microneedle. Silicon is a crystalline material that is anisotropic. Its characteristics are determined by the crystal lattice alignment, which exhibits varying elastic moduli (50 to 180 GPa) [21]. The primary drawbacks of silicon microneedles are their lengthy, multi-step creation process and high manufacturing costs [38]. When the silicon microneedle breaks off from the skin and pieces are left in the tissue, it may provide a safety risk. Instead of solid microneedles, silicon is now utilized in reverse master molds [40].

4.2.2. Ceramic

One of the most popular types of materials used to make MN is alumina (Al2O3). Because of its porosity, alumina can contain a specific volume of active material. MNs have also been made from brushite and gypsum. MNs have been created using a unique material called Ormocer®, which is composed of organically modified silicon alkoxides and organic monomers. It creates a three-dimensional network that expands the region where medication solutions can be

absorbed. In a work by Ovsianikov et al. (2007), laser two-photon polymerization was used to produce Ormocer® MN at various aspect ratios. Without breaking, the artificial MNs pierced the fat tissue of the pigs [18].

4.2.3. Polymers

Several biodegradable and biocompatible polymers, such as polymethyl methacrylate, polylactic acid, polyglycolic acid, polylactic glycolic acid, polycarbonate, polyvinylpyrrolidone, polyvinyl acetate, styrene, and others, are used to make microneedles. Their primary application is in the manufacturing of hydrogel-forming and dissolving microneedle arrays. Improved resistance and plasticity for skin penetration were demonstrated by microneedles made using Gantrez AN-1391, a copolymer of polymethyl vinyl ether comaleic anhydride [2].

4.2.4. Metals

Titanium and stainless steel are the two primary metals used in the microneedling technique. Palladium-cobalt alloys are also excellent substitutes. For metal, a high level of in-vivo biocompatibility is matched with robust mechanical properties. This resin is better suitable for making microneedles than silicon since it is more difficult to break. The first stainless steel was used in the production of microneedles [4].

4.2.5. Glass

Hollow glass microneedles can be etched or pulled with a micropipette. Strong enough for skin implantation, it allows for a simple tapered shape procedure. Biocompatible fabric is resilient under temperature and pressure, making it easier to sanitize. Microneedles are readily broken, and if the point stays in the skin tissue, it can induce inflammation or granulomas [41].

4.2.6. Carbohydrate

Maltose, a carbohydrate, is one of the most widely used sugars. Polysaccharides and other sugars such as galactose, mannitol, trehalose, sucrose, xylitol, and others can be used. Carbohydrate slurries are made with silicon or metal templates. To create the microneedles, the drug-loaded carbohydrate mixture is poured into the molds. The distribution of medications into the skin is regulated by the controlled breakdown of carbohydrates. Although they are inexpensive and safe to consume, carbohydrates degrade at very high temperatures, which makes the production process challenging [14].

4.2.7. Encapsulation

Liposomes, nanoparticles, or nanoliposomes are examples of carriers that can be used to encapsulate the medicine or combine it into microneedles in a suspended or dispersed form. It is difficult to incorporate immiscible compounds into a single heterogeneous vehicle, such liposomes, because complex formulations are required, and there are problems with loading efficiency and stability of these vehicles [42].

4.2.8. Sugars

MNs that can penetrate SC are produced by sugars such maltose, trehalose, raffinose, mannitol, xylitol, and galactose. They have additional disadvantages, too, such as instability, the requirement for high processing temperatures, and quick pore resealing [30].

4.2.9. Fabrication technology

To fabricate the small microneedle tips, which have a scale of several tens of micrometers and are highly accurate and reliable, microneedle master molds are mostly manufactured in factories using deep reactive particle etching. Due to the high cost of the equipment and maintenance, entry into the field of microneedle analysis is difficult, and only a few companies have access to the production technology [41].

4.3. Applications of microneedle

4.3.1. Oligonucleotides delivery

Oligonucleotides are short segments of RNA or DNA. Oligonucleotides are challenging to deliver to their intracellular destination. The microneedle method can used to disperse 20-mer phosphorothioated oligodeoxy nucleotides. When skin is broken, more medication reaches the place of action [32].

4.3.2. Vaccine Delivery:

A dissolvable MN is a form of MN that is often utilized in vaccine delivery. The dissolvable MNs replaced the usual hypodermic injection needles used to give immunizations. Unlike other types of MN, soluble MNs are biocompatible, robust, scalable, and do not generate biohazardous waste. Malaria, diphtheria, influenza, Hepatitis B, HIV, and polio vaccines were administered using soluble [43].

4.3.3. Cancer immunotherapy

Biodegradable Microneedle Patch: In a B16 melanoma model in mice, a biodegradable microneedle patch that delivered hyaluronate-antigenic peptide (cytotoxic T-cell epitope) as a preventative cancer immunotherapy showed a notable suppression of tumor growth [42].

4.3.4. Treatment for diabetes

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high blood glucose levels due to impairments in insulin production, insulin action resistance, or a combination of both [44]. Giving insulin with the practical and aesthetically pleasing microneedle drug delivery system is easy. To allow transdermal delivery of exendin-4 in Type 2 diabetic GK/Slc rats, Liu et al. developed a microneedle array including tips filled with hyaluronic acid. In terms of hypoglycemic action and improved transdermal absorption of Exendin-4 without causing skin injury, tip-loaded microneedle arrays proved better than subcutaneous injection [45].

Some Benefits Using a CGM for Regular Diabetes Care, A lot of research shows that continuously glucose monitoring (CGM) can improve a diabetic's health and quality of life. Using CGM devices has been linked to a lower HbA1c in people with type 2 diabetes mellitus (T2DM) who are on insulin or a non-insulin therapy, as well as in children and adults with type 1 diabetes mellitus (T1DM), compared to using SMBG. This is a big change in how diabetes patients are treated, moving from reactive measures to proactive measures to keep blood sugar levels from getting too high or too low [46].

4.3.5. Mucosa therapy

Human growth hormone (HGH) and human insulin are administered to the buccal mucosa via soluble microneedles. People who used the visual analog pain scale say they feel a lot less pain after getting microneedles. Furthermore, doxorubicin was first applied to Poly D, L-lactic-co-glycolic acid (PLGA) nanoparticles, as previously reported in a study. Microneedles can then use to transport these nanoparticles to the oral phantom tumor site. These coated microneedles have the advantage of preserving the doxorubicin (DOX) and causing less side effects than traditional injections [11].

5. Conclusion

Microneedle technology has shown significant potential in enhancing transdermal drug delivery. With its ability to create microchannels in the skin, microneedles offer a minimally invasive and painless approach to delivering drugs, vaccines, and other therapeutic agents. The technology has several benefits, including improved drug penetration and reduced side effects, making it an exciting area of study. Further research is needed to fully realize the potential of microneedle technology and to overcome the challenges associated with its development and commercialization.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Kaur M, Sharma S, Saggar S. Microneedles: Novel and Futuristic Approach in Transdermal Drug Delivery System – A Review, Pharmaceutical Sciences. 2022;2(1):9-24.

[2] Bhattacharyya S, Kotresh KH. Microneedles- A new paradigm in transdermal delivery of therapeutic agents, Pharm Sci Asia. 2022;49(5):435-445. DOI:10.29090/psa.2022.05.22.230.

[3] Mdanda S, Ubanako P, Kondiah PPD, Kumar P and Choonara YE. Recent Advances in Microneedle Platforms for Transdermal Drug Delivery Technologies, Polymer. 2021;13(15):1-24. https://doi.org/10.3390/polym13152405

[4] Salih OS, Al-akkam EJ. Microneedles as A Magical Technology to facilitate Transdermal Drug Delivery: A Review Article, International Journal of Drug Delivery Technology. 2022;12(2):896-901. DOI:10.25258/ijddt.12.2.76.

[5] Jagtap SV, Kshirsagar PK, Kore VU, Deshmukh MT, Shete RV. A Review: Transdermal Microneedle, Curr. Pharm. Res. 2018;8(2):2357-2367.

[6] Mahato R. Microneedles in Drug Delivery. Emerging Nanotechnologies for Diagnostics, Drug Delivery, and Medical Devices. United States;2017. P. 231-349. ISBN 978-0-323-42978-8

[7] Avcil M, Celik A. Review Microneedles in Drug Delivery: Progress and Challenges, Micromachines. 2021;12(11):1-15. https://doi.org/10.3390/mi12111321.

[8] Sekar L, Seenivasan R, Reddy MV, Varma KD, Ahmed SS, Pachiyappan JK, GNK ganesh. advancements in microneedle technology: comprehensive insights into versatile drug delivery mechanisms, International Journal of Applied Pharmaceutics. 2024; 16(2): 1-11. DOI:https://dx.doi.org/10.22159/ijap.2024v16i2.49564.

[9] Sohail A, Bandyopadhyay R, Jana K, Gayen B, Khan A, Debnath B, Bishal A. Exploring Microneedle Systems for Transdermal Drug Administration, JCHR. 2024 14(2): 2115-2127.

[10] Deulkar DA, Kubde JA, Hatwar PR and Bakal RL. A review on transdermal drug delivery system, GSC Advanced Research and Reviews. 2024;18(02):347–361. DOI: https://doi.org/10.30574/gscarr.2024.18.2.0052

[11] Kaur R, Arora V. Advancements in microneedle-based drug Delivery systems: A painless revolution in Transdermal medicine, EDP science. 2024;509: 1-23. DOI: https://doi.org/10.1051/e3sconf/202450902002

[12] Rotake SB, Hatwar PR, Bakal RL and Kohale NB. Transdermal drug delivery system recent advancements: A comprehensive review. GSC Biological and Pharmaceutical Sciences. 2024; 28(02): 059–072

[13] Sartawi Z, Blackshields C, Faisal W. Dissolving microneedles: Applications and growing therapeutic potential. J Control Release. 2022; 348:186-205. doi: 10.1016/j.jconrel.2022.05.045. Epub 2022 Jun 7. PMID: 35662577.

[14] Mahajan S, Choudhary S, Gayakwad D, Dr. Koka S, Dr. Sharma P, Dr. Darwhekar GN. Review On Microneedle Drug Delivery System, World Journal of Pharmaceutical Research. 2021; 10(1):847-858. DOI: 10.20959/wjpr202111-21488

[15] Ogundele MI, Okafor HK. Microneedles: A Potent Modern Tool in Enhancing Transdermal Drug Delivery, Curr Trends Biomedical Eng & Biosci. 2017;10(1):1-9. DOI: 10.19080/CTBEB.2017.10.555776

[16] Bariya SH, Gohel MC, Mehta TA, Sharma OP. Microneedles: an emerging transdermal drug Delivery system, Journal of pharmacy and pharmacology. 2011;64:11-29. doi:10.1111/j.20427158.2011.01369.x

[17] Sabeeh AA, Hussain AM. The Growing Role of Hydrogel Microneedles in Transdermal Drug Delivery, International Journal of Drug Delivery Technology. 2021;11(2):611-616. DOI: 10.25258/ijddt.11.2.67

[18] Nagarkar R, Singh M, Nguyen HX, Jonnalagadda S. A review of recent advances in Microneedle technology for Transdermal drug delivery, Journal of Drug Delivery Science and Technology. 2020;1-18. https://doi.org/10.1016/j.jddst.2020.101923.

[19] Haider I, Ameer N, Akhtar CS. Use of Microneedle Technique In TDDS: A Review Article, Mdsric. 2023;1-18.

[20] Manoj VR, Manoj H. Review on Transdermal Microneedle-Based Drug Delivery, Asian J Pharm Clin Res. 2019;12(1);18-29. DOI:http://dx.doi.org/10.22159/ajpcr.2019.v12i1.27434

[21] Waghule T, Singhvi G, Dubey SK, Pandey MM, Gupta G, Singh M, Dua K. Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomed Pharmacother. 2019;109:1249-1258. doi: 10.1016/j.biopha.2018.10.078. Epub 2018 Nov 9. PMID: 30551375.

[22] Nguyen HX, Nguyen CN. Microneedle-Mediated Transdermal Delivery of Biopharmaceuticals. Pharmaceutics. 2023 Jan 13;15(1):277. doi: 10.3390/pharmaceutics15010277. PMID: 36678906; PMCID: PMC9864466

[23] Agrawal S, Gandhi SN, Gurjar P, Saraswathy N. Microneedles: An advancement to transdermal drug delivery system Approach, Journal of Applied Pharmaceutical Science. 2020;10(03): 149-159. DOI: 10.7324/JAPS.2020.103019

[24] Panda A, Matadh VA, Suresh S, Shivakumar HN, Murthy SN. Non-dermal applications of microneedle drug delivery systems, Drug Delivery and Translational Research.2021;12(11):1-13. https://DOI: 10.1007/s13346-021-00922-9

[25] Aldawood FK, Andar A, Desai S. A Comprehensive Review of Microneedles: Types, Materials, Processes, Characterizations and Applications, MDPI. 2021;13(16): 1-34. https://doi.org/10.3390/polym13162815

[26] Gulati P, Pannu S, Kumar M, Bhatia A, Mandal UK, & Chopra S. Microneedles based Drug delivery systems: an updated review, International Journal of Health Sciences. 2022; 6(7):209–242. https://doi.org/10.53730/ijhs.v6n7.10813

[27] Teja MR, Glory CH, Morise JS, Naik BV, Kumar JNS. Transdermal delivery of drugs with microneedle: current trends and fabrication, IJRAR. 2022;9(4):372-380.

[28] Borey VS, Ingle SB, Kotwal PV, Jadhao AG, Sheikh TR, Nagrik SU, Sanap JB. Recent Advanced of Fabrication Techniques and Application of Micro-Needle, Asian Journal of Pharmaceutical Research and Development. 2023; 11(3):59-66. DOI: http://dx.doi.org/10.22270/ajprd.v11i3.1254

[29] Nandagopal Giri MS, Antony R, Rangabhashiyam S, Sreekumar N, Selvaraju N. Overview of microneedle system: A third-generation transdermal drug delivery approach, Microsystem Technologies. 2014;1-25. DOI: 10.1007/s00542-014-2233-5

[30] Dharadhar S, Majumdar A, Dhoble S, Patravale V. Microneedles for transdermal drug delivery: a systematic review. Drug Dev Ind Pharm. 2019 Feb;45(2):188-201. doi: 10.1080/03639045.2018.1539497. Epub 2018 Nov 27. PMID: 30348022.

[31] Parhi R, Supriya ND. Review of Microneedle based Transdermal Drug Delivery Systems, International Journal of Pharmaceutical Sciences and Nanotechnology. 2019;12(11): 4511-4523.DOI: 10.37285/ijpsn.2019.12.3.1

[32] Jirole UD, Jirole DU, Shaikh SM, Shelake YP, Kadam SS, Hajare SS, Kulkarni AS. Microneedles: A Smart Approach for Transdermal Drug Delivery System, International Journal of Scientific Research in Science and Technology. 2023;10(1):612-623. doi : https://doi.org/10.32628/IJSRST2310165

[33] Valsa RM, Manoj H. Review on Transdermal Microneedle-Based Drug Delivery, Asian J Pharm Clin Res. 2019; 12(1):18-29. DOI: http://dx.doi.org/10.22159/ajpcr.2019.v12i1.27434

[34] Rathor S, Ram A. Advancement In Transdermal Drug Delivery System: Microneedles, Asian Journal of Pharmaceutical Research and Development.2017; 5(5):1-07.

[35] 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 Apr 15;599:120455. doi: 10.1016/j.ijpharm.2021.120455. Epub 2021 Mar 4. PMID: 33676993.

[36] Ogundele M, Okafor HK. Transdermal Drug Delivery: Microneedles, Their Fabrication and Current Trends in Delivery Methods, JPRI. 2017; 18(185): 1-14. DOI: 10.9734/JPRI/2017/36164

[37] Arora M, Laskar TT. Microneedles: Recent advances and development in the field of transdermal drug delivery technology, Journal of Drug Delivery and Therapeutics. 2023;13(3):155-163. DOI:http://dx.doi.org/10.22270/jddt.v13i3.5967

[38] Diwe IV, Mgbemere HE, Adeleye OA, Ekpe IC. Polymeric Microneedle Arrays for Transdermal Rapid Diagnostic Tests and Drug Delivery: A Review, Nigerian Journal of Technology. 2024; 43(2), 279 – 293. https://doi.org/10.4314/njt.v43i2.11

[39] Sharma D. Microneedles: an approach in transdermal drug delivery: a Review, PharmaTutor. 2018; 6(1); 7-15. http://dx.doi.org/10.29161/PT.v6.i1.2017.7

[40] Jung JH, Jin SG. Microneedle for transdermal drug delivery: current trends and fabrication, Journal of Pharmaceutical Investigation. 2021; 51(5):503–517. https://doi.org/10.1007/s40005-021-00512-4

[41] Mounika K, Dr. Swetha M. A Review on Micro Needle Based Transdermal Drug Delivery System, World Journal of Pharmaceutical Science and Research. 2023; 2(2): 11-17.

[42] Eshwar N, Naik N, Adeyanju O, Samrot AV, Bhat P, Salmataj S. Drug Delivery Through Microneedles for Improved Permeability and Efficacy: Fabrication, Methodology and Applications, Engineered Science.2023; 26: 1065(1-13). DOI: https://dx.doi.org/10.30919/es1065

[43] Shivani S, Babu PV. Microneedles: A Novel Approach in Transdermal Drug Delivery: Review Paper, 2023;03(11):652-661. DOI: https://doi.org/10.47191/ijpbms/v3-i11-12

[44] Dafe VN, Hatwar PR, Bakal RL and Kubde JA. Transdermal insulin delivery via microneedle technology, patches, and pumps offers a promising alternative to traditional subcutaneous injections for diabetes management. GSC Biological and Pharmaceutical Sciences, 2024, 29(01), 233–242.

[45] Butola K. A Review Article on Transdermal Drug Delivery System Based On-Microneedles, JRASB. 2022;1(3): 65-76. DOI: https://doi.org/10.55544/jrasb.1.3.9

[46] Karule VG, Kubde JA, Hatwar PR, Bakal RL and Kathole KS. Innovations in transdermal delivery: Exploring nicotine patches, microneedles and glucose monitoring technologies. GSC Biological and Pharmaceutical Sciences, 2024, 29(02), 341–355.