WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 23, 570-581. Review Article ISSN 2277–7105

A REVIEW ARTICLE ON: MICRONEEDLE PATCHES FOR TRANSDERMAL DRUG DELIVERY SYSTEM

Mr. Abhay Trimbak Athare*, Dr. Megha T. Salve, Mrs. Kalpana S. Kale

Shivajirao Pawar College of Pharmacy Pachegaon.

Article Received on
14 Oct. 2024,

Revised on 03 Nov. 2024,
Accepted on 24 Nov. 2024

DOI: 10.20959/wjpr202423-34765

***Corresponding Author**
Mr. Abhay Trimbak Athare
Shivajirao Pawar College of Pharmacy Pachegaon.

ABSTRACT

Transdermal patches have been used for a significant amount of time for drug delivery through the skin. The further development of transdermal technology demonstrated the significant effectiveness of transdermal patches designed for the passive diffusion of medication. The development of transdermal delivery systems continued with the introduction of iontophoresis and sonophoresis. The microneedle array is now gaining interest from researchers due to its great usefulness in transdermal delivery of very large molecules that are ionic and hydrophilic in nature. In this technical note, we discuss the present situation, uses, and latest developments in delivering important molecules through the skin using microneedle arrays. The use of microneedles has been extensively studied, with a focus on developing them for administering biotherapeutics, biomacromolecules, insulin, growth hormones, immunobiologics, proteins, siRNA, and peptides. The potential of microneedles to revolutionize the worldwide transdermal market is emphasized by the successful implementation of microneedle technologies in clinical trials leading to global market entry. The introduction of commercial microneedle products into the market is eagerly awaited due to their potential to have a significant impact on clinical medicine in the coming years.

KEYWORD: Transdermal Drug Delivery, Skin Permeation, Membrane moderated systems, Adhesive diffusion controlled system, Microreservoir system.

INTRODUCTION

Research on drug delivery has thoroughly examined ways to effectively and safely transport proteins, DNA, genes, antibodies, and vaccines into human bodies in recent times. Traditional methods of drug administration, like taking medication by mouth or injecting it

under the skin, have their drawbacks as a drug can become ineffective due to Phase I metabolism when taken orally.[1] Yet, transdermal technology is constrained by the fact that most drugs are unable to penetrate the skin at the necessary therapeutic levels, largely due to the thick and impermeable outer layer of the stratum corneum. The obstacle presented by the skin of humans restricts transdermal administration to only lipophilic, low molecular weight powerful medications.[2] In general, these techniques improve drug delivery through the outermost layer of skin either by creating pores or enhancing diffusion, and Zhang's research effectively explains the principles and mechanisms of these methods.[3]

Drug delivery systems (DDSs) enhance drug therapy by utilizing current formulations to minimize side effects, improve patient adherence, and maximize drug potency and efficiency through efficient drug administration. DDSs are created with the intent of enhancing bioavailability and efficacy of treatment, lowering negative reactions, and promoting greater patient adherence. DDSs are categorized by the method of administration, with options including oral intake, skin application, injection, inhaling through the lungs, and administration through mucous membranes. Transdermal administration is the most frequently used method due to its minimal discomfort for patients and simplicity of use. The effort to administer medication through the skin has a rich past, since the skin is the biggest organ on the human body. Initially, early TDD systems were developed to target specific areas of damage due to the perceived impermeability of the skin against harmful substances, microorganisms, or chemicals, in order to protect the body. Nevertheless, the advancement of TDD systems sped up when the FDA approved the Transderm-Scop patch for delivering scopolamine, a painkiller, in 1979. Later on, patches were created for administering small lipid-soluble medications like nitroglycerin, nicotine, and fentanyl.[4]

The stratum corneum (SC) is a component of the epidermis and typically measures around 100 micrometers in thickness. The stratum corneum plays a significant role in both the skin's barrier function and its control of water. In certain immune skin conditions, the immune response attack is directed towards the skin as the target tissue. Additionally, the human skin has a "skin immune system" made up of various cells such as Langerhans cells, T lymphocytes, keratinocytes, macrophages, and dendritic cells. The absorption function of human skin relies heavily on the presence of the SC. The main way topical drugs are utilized to treat diseases in dermatologic conditions is through the absorption function of the skin. Nonetheless, the skin's absorption capability is restricted, hindering the absorption of topical

drugs through the skin. It should be noted that the skin also serves a function of aesthetic appreciation that is often overlooked. A claim that stands out is that people reflect their health through their skin.[5] Microstructures with microscale length, known as microneedles and often <1000 μm in size, puncture the stratum corneum and create temporary microchannels that allow external molecules to passively diffuse into the skin. Microneedles could be crafted so that they only penetrate superficially to avoid coming into contact with nerve receptors in the lower reticular dermis. This leads to a drug administration without pain. This microneedle-based transdermal delivery method shows great potential for providing a convenient, patient-oriented, and effective means of administering medication.[6] Various approaches, such as chemical and physical boosters, have demonstrated a restricted ability to address this issue in numerous instances. Recently, there has been a lot of focus on microneedles, which combine features of hypodermic needles and transdermal patches to address the limitations of both injections and patches. This transdermal patch consists of tiny needles at a micron scale that can puncture the skin to create tiny pores, allowing drugs to be delivered painlessly by passing through the stratum corneum, which is the main barrier to permeability on the skin. Microneedles are used in the pharmaceutical industry to make drug administration less invasive and to collect biological fluids. Several studies have discovered a notable rise in drug penetration through the skin by using microneedle arrays by themselves, along with other enhancers (such as iontophoresis or electroporation), or by incorporating more advanced devices like micropumps. Microneedles have proven to be highly effective in aiding the transport of large molecules, watery compounds, and various vehicles like lipid vesicles and nanoparticles.[7]

Advantages

1. It can prevent challenges in the absorption of drugs in the gastrointestinal tract caused by factors such as pH levels, enzymatic processes, and interactions with food, liquids, and other orally administered medications.
2. It can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.
3. To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.
4. Noninvasive, avoiding the inconvenience of parenteral therapy.
5. They offered prolonged treatment with just one dose, increasing adherence compared to other forms that need to be taken more often, such as the 7-day transdermal clonidine.

6. The activity of drugs having a start half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.[8]
8. Pain free & easy administration.
9. Large molecules can be administered.
10. First pass metabolism is avoided.
11. Faster healing at injection site than with a hypodermic needle.
12. Good tolerability without long term ocdema or erythema.
13. Rapid drug delivery.
14. Specific skin area can be targeted.[9]

Disadvantages

1. Skin irritation may result because of allergy or sensitive skin
2. Local inflammation may result if the concentration of drug is high under the skin
3. Using the device with care is necessary to prevent particles from bouncing off the skin or escaping if not held vertically, potentially penetrating the skin to various extents.
4. The thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too
5. External environment, like hydration of the skin, could affect delivery
6. Tip of the microneedle may break off and remain within the skin on removal of the patch
7. Compressed dermal tissue can block hollow microneedles.[10]
8. "Bouncing off" can be occur.
9. The thickness of the stratum corneum & other skin layers varies b/w individuals & penetration depth of particle could vary.
10. Environment condition may affect delivery. Chances of tip breaking on removal [9].

Mechanisam

Microneedles consist of two components: invasive and supporting components. The invasive part consists of numerous needles ranging in length from 25 to 2000 microns. The supporting element is a base plate that provides even mechanical support for the sharp needle tips to penetrate the SC effectively. Both components can either be made from the same material or from different materials before being securely joined together. One of the main functions of an MNP is to form a tiny channel within the skin and act as a way to transport substances.

The MNP function is impacted by the design of MNPs and needs adequate hardness, appropriate mechanical strength, and sufficient toughness. Indicators of malfunction in an MNP include needle tips that bend, deflect, or break. Selecting suitable materials and types of MNP is crucial due to these requirements.[11]

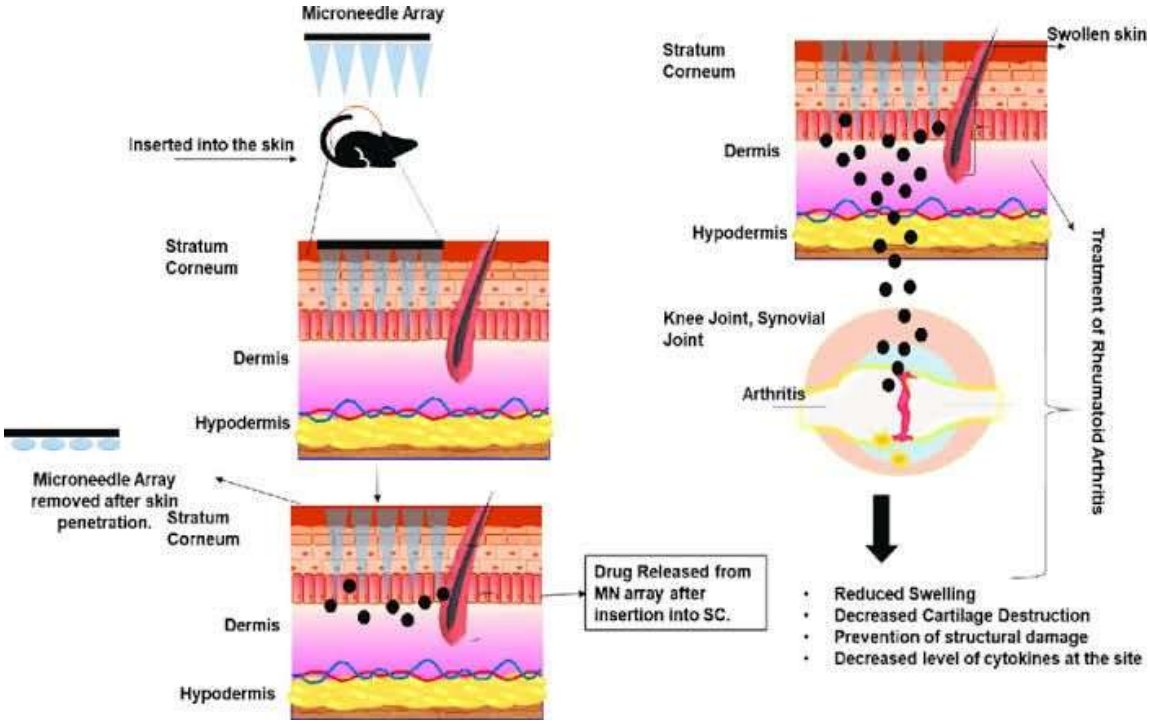

Fig. 1: Mechanism action of microneedle patches.[20]

Types of Microneedle

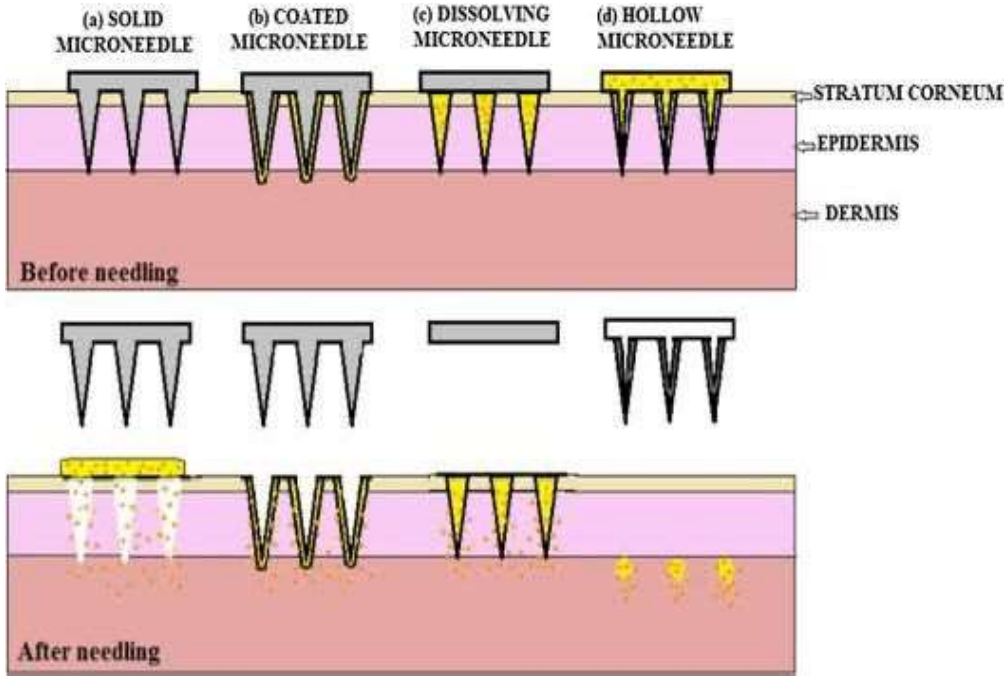

Fig. 2: Types of Microneedle.[19]

1. Solid Microneedle
2. Coated Microneedle
3. Dissolvable Microneedle
4. Hollow Microneedle

1. Solid Microneedle

Sharp geometric microneedles are structured to penetrate the stratum corneum, creating microchannels on the skin for drug diffusion. The medication is typically placed on a pliable surface beneath the micro-needle formation. When the skin patch is applied to the skin, the microneedles enter the skin and the drugs are absorbed by the capillaries for systemic treatment to take place.[12] Solid micro needles are arrays of projections used to create holes in the stratum corneum before applying a drug and then they are removed. These can essentially form tiny holes in the skin that allow drug molecules to easily penetrate.[13]

2. Coated Microneedle

This type Microneedle coated with the drug reservoir solution. In this type of Microneedle drug delivery drug release is very quickly from needle and spread lower epidermis and upper dermis region. The amount of drug that can be loaded depends on the thickness of the "coating layer" and the "size of the needle" which is usually very less. Coated microneedles use coat and poke approach.[14] In these two designs, the compounds have close contact with the body of the needle. In CMNs, a coating of drug solution is applied to the surface of the needle, while a biodegradable polymer with drugs dissolved in it is used in DMNs. Neither of them need a subsequent procedure for transdermal drug delivery. Generally speaking, the coated drug layer stays water soluble so that the drug can be released from the outer layer after the insertion of CMNs into the surface of the skin and with sufficient exposure to the watery environment of the tissue. In the research of Lee et al., bleomycin-coated microneedles were developed to complete the delivery of bleomycin into the subepidermal skin layer, providing an effective treatment for warts without causing pain or fear in patients.[15]

3. Disssolvable Microneedle

In contrast to coated microneedles, dissolving microneedles dissolve entirely in the skin and do not leave any bio hazardous waste after use. The microneedles are usually made of safe and inert water-soluble materials like polymers and sugars that dissolve in the skin once

inserted. Although dissolving microneedles can enhance skin permeability as a pretreatment, drugs are frequently enclosed within the microneedle for delivery into the skin.[16]

4. Hollow Microneedle

TDD is utilized in two different methods with hollow microneedles. The primary purpose is to substitute traditional needles, primarily for reducing pain and fear. The second purpose is to prolong the drug injection duration by integrating a hollow microneedle with a drug reservoir. As mentioned before, hollow microneedles have a more intricate manufacturing process compared to solid ones. Both types can be made from ceramics, metals, or polymers.[17] The design and mechanical concepts of HMNs resemble hypodermic needles with a channel, as both have hollow centers and holes at the tips of the needles. The substances move into the needle's cavity, driven by the pressure equipment. Specially designed devices can now fully control the rate at which compounds stored in the needle enter the body, enhancing personalized drug delivery options for various needs. According to prior studies, HMNs are employed for substances with a high molecular weight like proteins, vaccines, and oligonucleotides.[18]

Evaluation of Microneedle

1. Characteristic Method

- Drug: Various physicochemical characterizations including particle size, polydispersity index, viscosity, and zeta potential.
- Patch: Drug release, adhesion, permeation tests.

2. Dimensional Evaluation

- Needle Geometry: Height, Width & radius of the tip.
- Use Optical & Electrical microscope & for 3D study SEM and Confocal laser microscope.

3. Mechanical properties and insertion force

- To check structural integrity and the insertion force.[21]

4. In-vitro evaluation

- Microneedles are accomplished by using various mediums like agarose gel and methanol to insert the microneedles.
- Optimization of the microneedles.

- To find out penetration force and bending force of microneedles.
- To evaluate strength of microneedle.
- To determine the dissolution rate of coating material.
- Estimate the efficiency of drug delivery.

5. In-vivo preclinical evaluation

- Generally mice, rabbits, guinea pigs, mouse and are used.
- To perform skin toxicity test.
- To determine penetration force in different skin.
- To determine mechanical stability of microneedle.
- To determine bending breakage force.
- To perform various non-clinical safety study and pharmacological study.
- To assess different factors such as immune response, DNA damage potential, skin irritation and allergic reactions, impact on fetal development, short-term and long-term skin toxicity, and potential for causing cancer.[22]

Application

Psoriasis is a long-lasting inflammatory skin condition caused by multiple genes. It is characterized by immunity involvement and relapses frequently occur. It is estimated that around 2% of the global population is affected by psoriasis, which has a detrimental impact on the quality of life for those who suffer from it. The precise reason behind psoriasis remains uncertain. Even after extensive research and some progress, there is still no definitive understanding of the cause and development of this illness. The immune system plays a role in the development of psoriasis, with key factors such as TNF-a, IL-17A, and IL-23 being recognized. Psoriasis patches usually show redness, scale, raised red bumps, and thickened skin. Itching, flaking, and noticeable patches are the primary common indicators of psoriasis and can greatly affect one's quality of life; the absence of a cure for psoriasis is unfortunate. Local and systemic medications have been commonly utilized for an extended period in the treatment of dermatological conditions. To prevent further harm to health, psoriasis is treated with topical medications, physical therapy, and systemic therapy. Nevertheless, applying a topical treatment can be messy and time-consuming, often causing issues with oiliness and stickiness. Physical therapy, which is an important aspect of psoriasis treatment, has fairly strict guidelines regarding how often and for how long it should be administered. Side effects are frequently linked with systemic therapy.[23]

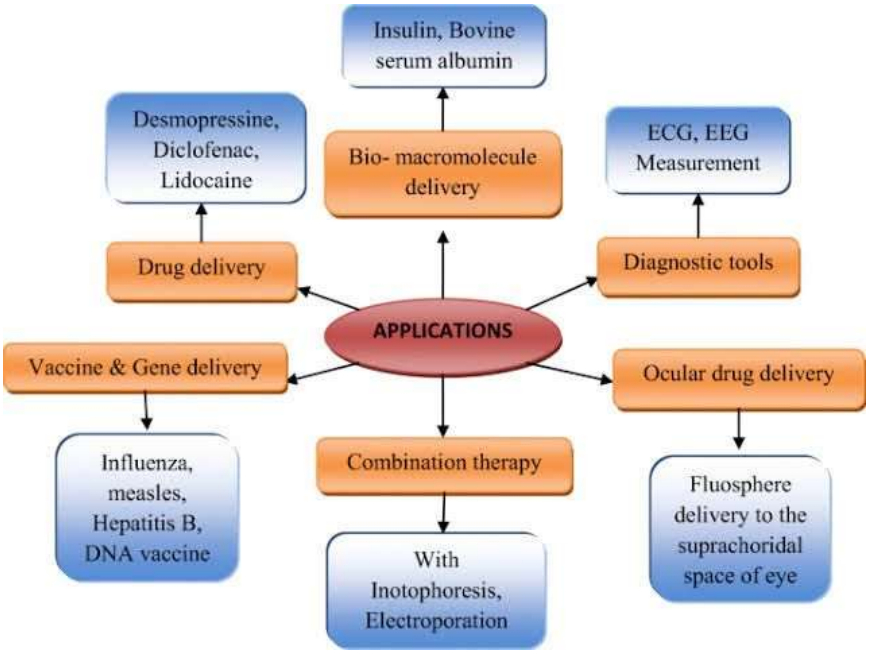

Fig. 3: Application of Microneedle.[25]

Microneedles have been investigated for a variety of uses and have been expanded into multiple industries. Due to the advantage of piercing in a less invasive way, in addition to serving as a substitute for traditional hypodermic treatment, they have also been used for delivering medication to the eyes, body as a whole, and inside cells. Microneedles have the capability to transport large molecular weight substances such as proteins and peptides, immunobiologicals such as vaccines and antibodies. They have also become popular in the cosmetic industry for treating acne, pigmentation, scars, wrinkles, and toning the skin.[24]

A recent study conducted by Kim and colleagues introduces a novel approach utilizing microneedle technology for delivering a recombinant coronavirus vaccine through the skin to treat COVID-19. This technology facilitated the production of SARS-CoV-2 S1 subunit vaccines that triggered strong antibody responses specific to the antigen, starting 2 weeks after vaccination. Their research backed the clinical advancement of MN-based recombinant protein subunit vaccines for SARS, MERS, COVID-19, and other new infectious diseases.[26] Treating neuropathic pain from nerve injuries is challenging due to the limited pain relief and unwanted side effects of current systemic medication, as well as the non-specific blocking of sensory and motor functions by current local anesthetics. Xie et al. created an analgesic microneedle patch (AMN) to treat neuropathic pain by delivering a CGRP antagonist peptide through the skin, providing effective and safe pain relief in various rat models of neuropathic pain.[27]

CONCLUSION

Numerous research investigations on microneedles have shown enough evidence to confirm that microneedles are effective and promising transdermal delivery systems. Their significant advantages have led to their increasing importance compared to traditional delivery methods as they are safe, convenient, and painless. Microneedles have been shown as the answer to the challenge presented by the stratum corneum, expanding the range of drugs and molecules that can be delivered through this pathway. Much effort has been exerted to make progress and examine the broad uses of microneedles. In addition to transporting many types of drug molecules, such as those that do not penetrate well, macromolecules, and biopharmaceuticals, microneedles have also been used for procedures like phlebotomy, diagnosis, and cosmeceuticals. Many studies have explored and documented the synergistic impact of combining microneedles with various methods like sonophoresis, electroporation, iontophoresis, vibratory actuation, etc. This has proven to be advantageous for effectively transporting drugs and macromolecules through the skin. Combining microneedles with carriers like vesicles, nanoparticles, microparticles, etc. enables the controlled release of drug molecules. Combining microneedles with micro pumps enables precise drug delivery, while loading drugs into pocketed and grooved microneedles allows for a larger amount of drug to be delivered. Therefore, it was determined that microneedles are more effective than hypodermic needles and other traditional delivery methods.

REFERENCES

1. Singh R, Singh S, Lillard JW Jr. Past, present, and future technologies for oral delivery of therapeutic proteins. J Pharm Sci., 2008; 97: 2497‑523.
2. Bora P, Kumar L, Arvind K, Bansal AK, Microneedle technology for advanced drug delivery: Evolving vistas, Current Research & Information on Pharmaceutical Sciences (CRIPS), 2008; 9(1): 7-10.
3. Zhang Y, Yu J, Kahkoska AR, Wang J, Buse JB, Gu Z. Advances in transdermal insulin delivery. Adv Drug Deliv Rev., 2019; 139: 51-70. doi:10.1016/j.addr.2018.1012.1006.
4. Ochoa M, Mousoulis C, Ziaie B. Polymeric microdevices for transdermal and subcutaneous drug delivery. Adv Drug Del Rev., 2012.
5. L. Gravitz, Nature, 2018; 563(7732): S83.
6. Donnelly RF, Raj Singh TR, Woolfson AD. Microneedle‑based drug delivery systems: Microfabrication, drug delivery, and safety. Drug Deliv, 2010; 17: 187‑207.

7. Henry S, McAllister D, Allen MG, Prausnitz MR, Microfabricated microneedles, Journal of Pharmaceutical Sciences, 1998; 87(8): 922–925.
8. Mahato RA. Pharmaceutical dosage forms & drug delivery'' Published by CRS press, Taylor & Froncrs Group, 6000 Broken Sound Parkway, Sute 300, Boca Raton, 2002; 196-197.
9. https://www.slideshare.net/slideshow/microneedle-in-transdermal-drug-delivery-system/230783598.
10. Bonilla MD, Molina TE, Microneedle: A valuable physical enhancer to increase transdermal drug delivery, Journal of Clinical Pharmacology, 2011; 51(7): 964-977.
11. R. F. Donnelly, T. R. Raj Singh and A. D. Woolfson, Drug Deliv, 2010; 17: 187–207.
12. Choi CK, Kim JB, Jang EH, Youn YN, Ryu WH. Curved biodegradable microneedles for vascular drug delivery. Small, 2012; 8: 2483‑8.
13. Kumar SL, Singh V, Nanoemulsification-a novel targeted drug delivery tool, Journal of Drug Delivery and Therapeutics', 2012; 2(4): 40-45.
14. https://www.slideshare.net/slideshow/microneedle-a-smart-approch-for-transdermal-drug-delivery-system/249338237.
15. A. K. Shakya, R. S. J. Ingrole, G. Joshi, M. J. Uddin, S. Anvari, C. M. Davis and H. S. Gill, J. Controlled Release, 2019; 314: 38–47.
16. Kumar V, Kulkarni P, Raut R, Microneedle: Promising technique for transdermal drug delivery, International Journal of Pharma and Biosciences, 2011; 2(1): 684-708.
17. Chun K, Hashiguchi G, Toshiyoshi H, Le Pioufle B, Ishikawa J, editors. DNA injection into plant cell conglomerates by micromachined hollow microcapillary arrays. Proc. IEEE Micro Electro Mech. Syst. Workshop, 12th, Orlando, Piscataway, NJ: IEEE, 1999.
18. K. Ita, Pharmaceutics, 2015; 7: 90–105.
19. https://www.researchgate.net/figure/Different-types-of-microneedles-a-Solid-microneedles-with-a-poke-with-patch-approach_fig4_354069442.
20. https://www.researchgate.net/figure/Mechanism-of-action-of-microneedles-in-rheumatoid-arthritis_fig2_359264286.
21. https://www.slideshare.net/slideshow/microneedle/244905865.
22. https://www.slideshare.net/slideshow/microneedle-in-transdermal-drug-delivery-system/230783598.
23. H. L. Richards, D. G. Fortune, T. M. O'Sullivan, C. J. Main and C. E. M. Griffiths, J. Am. Acad. Dermatol., 1999; 41: 581–583.

24. Jagannathan S, Dawood CS, Rajesh K, Ayyappan SR, A novel approach in delivering immunobiologicals : a glimpse, Advanced Biotech, 2009; 5: 22–31.
25. https://link.springer.com/article/10.1007/s12247-020-09460-2.
26. Eun Kim GE, Huang S, Kenniston TW, Balmert SC, Carey CD. Microneedle array delivered recombinant coronavirus vaccines: immunogenicity and rapid translational development. Lancet, 2020; 2020.
27. Xie X, Pascual C, Lieu C, Oh S, Wang J, Zou B, et al. Analgesic microneedle patch for neuropathic pain therapy, 2017; 11(1): 395– 406.