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MICRONEEDLE VACCINES: A NEW ERA IN IMMUNIZATION TECHNOLOGY

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A B S T R A C T

Immunization is a key part of primary health care and global health security.Every year ,infectious diseases claim millions of lives,primarily in developing nations,and might be largely avoided with the use of vaccines.Vaccines work by stimulating the body's immune system to produce antibodies that fight diseases-causing germs. The development of vaccines involves careful consideration of antigen classes, formulation, and delivery routes. Vaccine administration can be mucosal (nasal, oral, buccal, sublingual, rectal, vaginal) or parenteral (intramuscular, subcutaneous, intravenous, intradermal), depending on the site of infection, transmission route, and desired immune response. Vaccination remains one of the most cost-effective medical interventions, continuously evolving to enhance efficacy and accessibility. Microneedles (MNs) are medical devices primarily used for drug delivery, disease diagnostics, and collagen induction therapy. Consisting of micro-sized needles (25–2000 μm), MNs offer precise and minimally invasive applications. Though first proposed in the 1970s, their popularity has grown due to advancements in materials and applications. Since the 2000s, MNs have been developed using materials such as silicon, metal, and polymers, and they exist in various forms, including solid, hollow, coated, and hydrogel types. MNs facilitate drug, vaccine, and therapeutic delivery through microneedle patches or microarray patches, with applications spanning ophthalmic, vaginal, transdermal, cardiac, vascular, and gastrointestinal drug administration. Among the most economical medical procedures, microneedle vaccination continues to evolve, improving its effectiveness and accessibility in disease prevention.

Keywords: Microneedles, Imminization, Transdermal drug delivery, Route of administration, Coated patches

INTRODUCTION

For centuries, infectious diseases have been common throughout human history. Building on this finding, English physician Edward Jenner inoculates 8-year-old James Phipps in May 1796 with substance extracted from a milkmaid's hand cowpox sore. Phipps recovered well even though he experienced a local reaction and felt ill for a few days. Jenner tests Phipps' resistance by inoculating him with material from a human smallpox sore two months later, in July 1796. Phipps is the first person to receive a smallpox vaccination and maintains excellent health. The word "vaccine" was later coined and was derived from the Latin word vacca, meaning cow. A biological preparation that offers active acquired immunity to a specific infectious or malignant disease is called a vaccine. Human health has profited immensely from the development and continued application of vaccines to prevent disease. Human life expectancy has increased as a result of the eradication, control, or dismissal of numerous illnesses, which has allowed numerous generations of children to live to adulthood. In order to create immunity against the invasive pathogen without giving in to the disease's pathophysiology, vaccines imitate illnesses and make use of the immune system. Historically, vaccinations have been divided into three categories: nucleic acid, subunit, and entire pathogen. First, there are more subtypes of whole pathogen vaccines. One such subtype is live attenuated vaccines, which use a weakened form of the pathogen to create immunity. while lacking the ability to spread the illness. Whole pathogen vaccines that use chemical or high-temperature methods to inactivate the pathogen are also known as inactivated vaccines. Second, in order to elicit protection, subunit vaccines concentrate on separating and purifying particular elements from the pathogen (or synthetic synthesis). Lastly, genetic

material that encodes for the antigens is introduced through messenger RNA or plasmid DNA in nucleic acid vaccinations. Vaccination is thought to be one of the most economical medical procedures ever developed. Throughout the vaccine's development, the targeted product profile is crucial. The choice of vaccination dose types is influenced by various factors, including vaccine antigen classes, including live attenuated, inactivated, subunit, and most recently, mRNA-based. Its efficacy is ultimately impacted by the formulation development that results. The formulation's planned mode of administration is a crucial issue throughout development. When choosing a vaccine delivery method, the crucial balance between mucosal and systemic immune responses has always been a key factor. The mucosal immune response requires tolerance, whereas systemic immunity requires the immune system to be ready.Vaccines are currently administered parenterally and mucosally. The nasal, oral, buccal, sublingual, rectal, and vaginal mucosal surfaces are among them. Additionally, the parenteral sites consist of intradermal, intramuscular, subcutaneous, and intravenous. The route of vaccination delivery is determined by a number of criteria, including the site of infection, the mode of transmission, the type of vaccine, and the anticipated immune response.

HISTORY

Although the idea of microneedles originated in the 1970s with the usage of giant hypodermic needles, it wasn't until the 1990s that microfabrication manufacturing technology gained attraction. When Orentreich found that applying tri-bevelled needles to the skin can potentially induce the release of a bristle strand, the idea of MNs was finally tested in 1994. Over time, public awareness of MNs increased as a result of research into their potential to enhance transdermal drug delivery. Since then, a great deal of research has been done on MNs, which has helped to produce a variety of MN kinds, materials, and fabrication techniques. Adverse effects and application are investigated. Clinical trials on the use of MNs in medication delivery started in the 2000s. The Georgia Institute of Technology research team led by Mark Prausnitz first discussed microneedles in a 1998 study that showed they could penetrate the stratum corneum, the topmost layer of the human skin, and were thus appropriate for the transdermal delivery of medicinal substances. Through its design, further studies on microneedle drug delivery have investigated the technology's potential uses in medicine and cosmetics. The goal of this early study was to investigate the potential of employing microneedles for immunisation in the future. Since then, scientists have investigated the delivery of insulin, vaccinations, anti-inflammatory drugs, and other medications via microneedles. In dermatology, skin rollers and microneedles are used to cure scarring. As previously mentioned, microneedles have also been investigated for local targeted drug delivery at other drug delivery sites, including the gastrointestinal tract, ocular, vascular, etc. As a more effective, localised drug delivery system without the disadvantages of systemic exposure or toxicity, the gastrointestinal tract, vaginal tract, and eyes have demonstrated increasingly compelling results. Any microneedle design's main objective is to pierce the stratum corneum, the skin's outermost layer (10–15 μm). Although microneedles are long enough to penetrate the stratum corneum, their length prevents them from stimulating deeper-lying nerves, which results in minimal or no pain. The kinds of medications that can be administered through intact skin are limited, according to research.

MICRONEEDLES

Medical devices known as microneedles (MNs) are employed mainly in drug delivery, illness diagnostics, and collagen induction therapy. Arrays of micro-sized needles, ranging in size from 25 μm to 2000 μm, make up MNs, which are renowned for being precise and minimally invasive procedures. Despite being first proposed in the 1970s, microneedling has become increasingly popular because of its advantages for cosmetics and medicine delivery.New MN manufacturing materials, including silicon, metal, and polymers, have been discovered since the 2000s. In addition to materials, there are several types of MNs (solid, hollow, coated, and hydrogel). MNs are medical devices used for microneedling, mostly for medication administration, but they can also be designed to serve other purposes. Although the study on MNs has improved certain areas, such as tools and methods, users of MNs may experience negative outcomes. Medical devices with a micron scale that are used to deliver medications, vaccinations, and other therapeutic substances are called microneedle patches or microarray patches.Microneedles have been used for ophthalmic, vaginal, transungual, cardiac, vascular, gastrointestinal, and intracochlear drug administration, but their use was first investigated for transdermal drug delivery applications.Microneedles are made using a variety of techniques, most often micromolding or photolithographic procedures.In order to cast microneedles, these techniques entail etching small structures into silicon or resin. Numerous materials, including silicon, titanium, stainless steel, and polymers, are used to make microneedles.

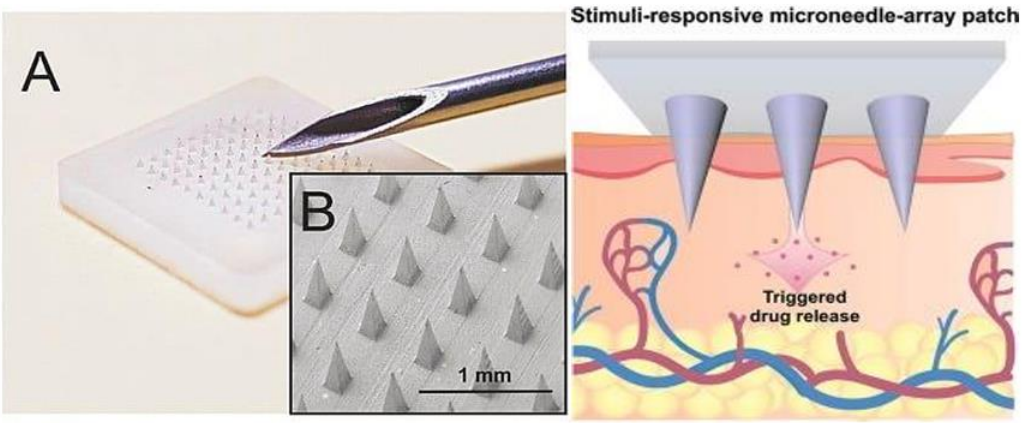

Figure 1. Side comparison of microneedle (350μm in depth) to standard hollowbore needle.

Some microneedles are designed like needles to pierce the skin, but they are made of a medicine that will be administered to the body. Despite their differences in size, form, and purpose, microneedles are all utilised as a substitute for other delivery systems, such as the traditional hypodermic needle or other injection tools. Advanced devices known as stimuli-responsive microneedles release medicinal drugs in response to environmental cues like light, pH, and temperature. Typically, microneedles are applied using tiny arrays or simply a single needle. In arrays, a number of microneedles—from a few to several hundred—are affixed to an applicator, which is occasionally a patch or another solid stamping tool. Patients' skin is treated with the arrays, which are administered. Patients are given time to allow for the efficient delivery of medications after the arrays are put on their skin. Since microneedles are less dangerous than other needles and require less training to use, doctors can administer medications to patients more safely and painlessly while avoiding some of the disadvantages of other drug delivery methods, such as infection risk, hazardous waste production, or expense.

TYPES OF MICRONEEDLES:

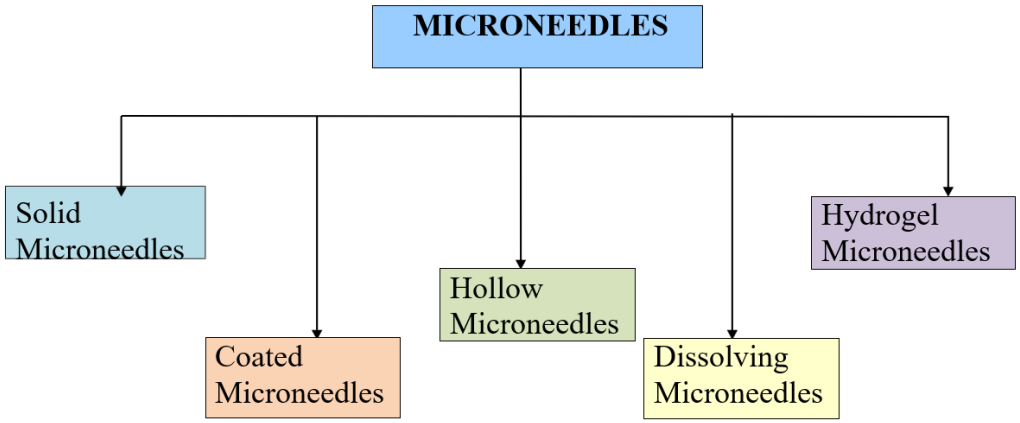

Figure 2. Types of microneedles

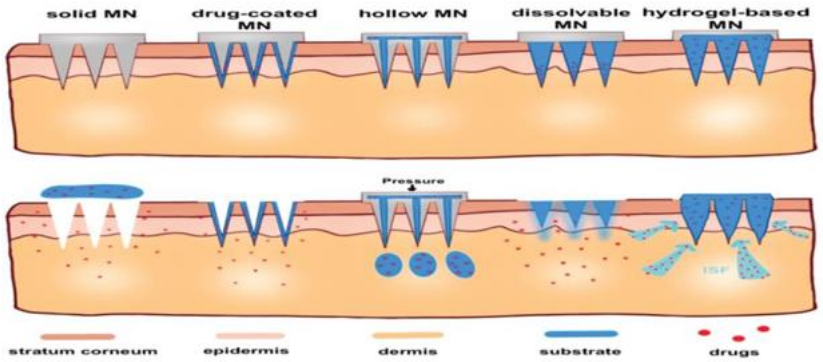

Figure 3. Microniddles mechanism

Solid Microneedles:

- Solid microneedles are sharp needles that make tiny holes in the skin to let medications penetrate the epidermis and develop pores on the stratum corneum. Solid MNs are the first type of MNs made and are the most widely utilised.
- Following application, the medication is passively and gradually absorbed through a large number of micropores.
- They are the most widely used kind of microneedle and are frequently used to get the skin ready for medication administration. SOLID microneedles are being used by dermatologists in collagen induction treatments, which entail repeatedly puncturing the skin with microneedles to induce the expression and deposition of collagen and elastin proteins.

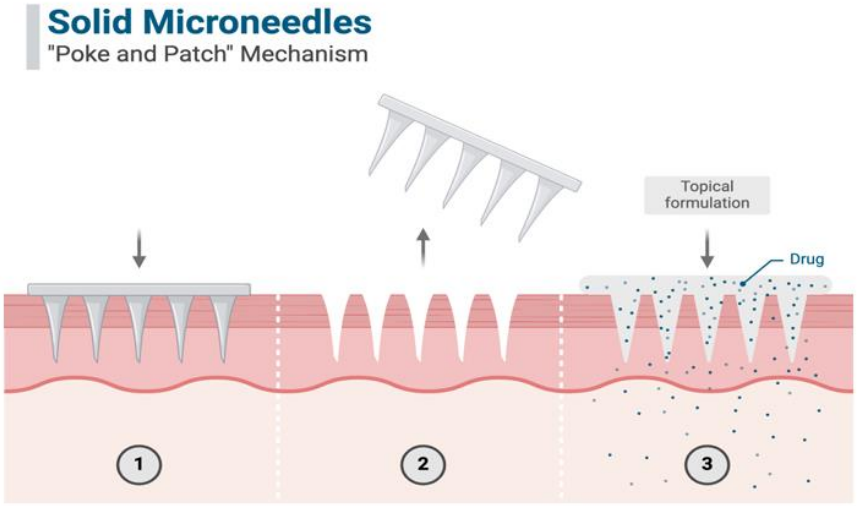

Figure 4. Solid Microneedles

Coated Microneedles:

- Numerous biomedical uses for coated microneedles exist, such as the treatment of Alzheimer's disease and psoriasis.
- Microneedles with a coating on their surface are known as coated microneedles.
- A medication, stabilising agent, and surfactant may be included in the coating.
- One advantage of coated MNs is that, in comparison to other drug administration routes, less medication is required. This is due to the fact that the drug coating will disintegrate rapidly and enter the bloodstream through the skin.
- Drugs can be delivered through the skin with microneedles without causing discomfort or invasiveness. Drug waste can be avoided, and dosage can be controlled by selectively coating the microneedle shafts.

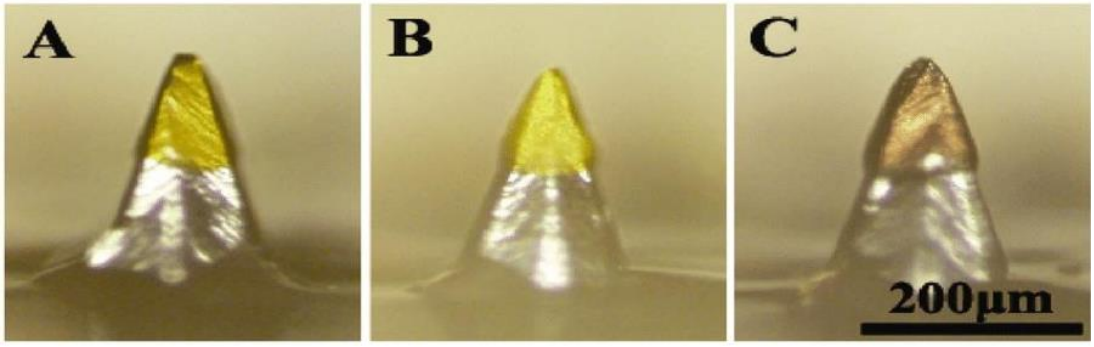

Figure 5. Microneedles Coated with different model-drugs

Hollow Microneedles:

- One medical tool that can be used to inject medications into the skin is a hollow microneedle (HMN).
- Body fluids can also be extracted using HMNs.

- A portion of the drug may leak or become blocked, which could impair the overall administration of the medication; however, MNs insertion, stored drug, is immediately injected into the dermis, effectively facilitating the absorption of either large-molecular or large-dosage drugs.
- HMNs can be used to precisely administer medications and are less intrusive and painful for patients.

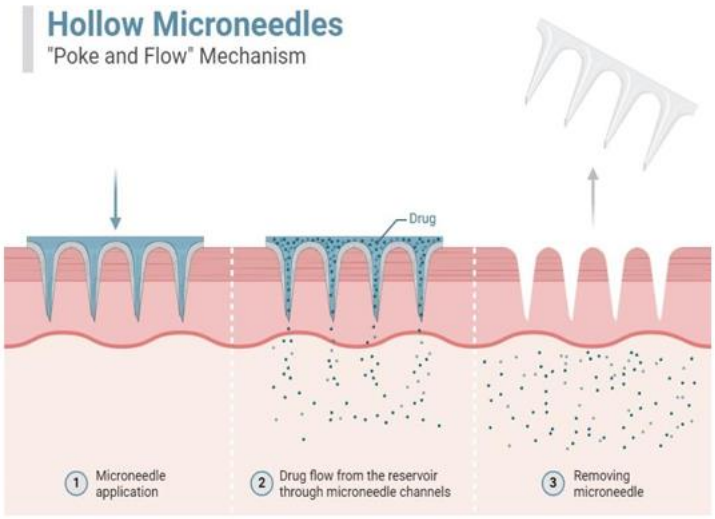

Figure 6. Hollow Microneedles

Dissolving Microneedles:

- Dissolving microneedles are tiny needles formed of biodegradable polymers that dissolve and release medications into the skin. They are primarily built of water-soluble medications.
- The medications and polymers are absorbed by the body once the microneedles are placed into the skin and the polymer needles break down, releasing the drugs into the skin. Drugs, vaccines, peptides, and other biotherapeutics are delivered via them.

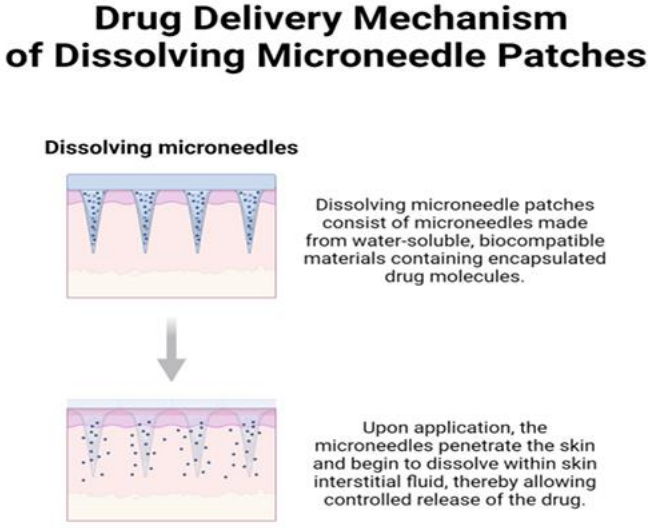

Figure 7. Dissolving microneedles

Hydogel Microneedles:

- When inserted into the skin, hydrogel microneedles (HMNs) swell to administer medications, vaccinations, or other treatments.
- They are a minimally invasive drug delivery method that has several uses, such as transdermal drug delivery, dentistry, and wound healing.
- Hydrophilic compounds are used to make HMNs swell when they come into touch with the skin.
- After implantation, they are intended to dissolve or disintegrate. Drugs, vaccinations, and other therapies can be administered via HMNs.

- Additionally, they can be utilised to remove relevant drug molecules from the skin for further examination.

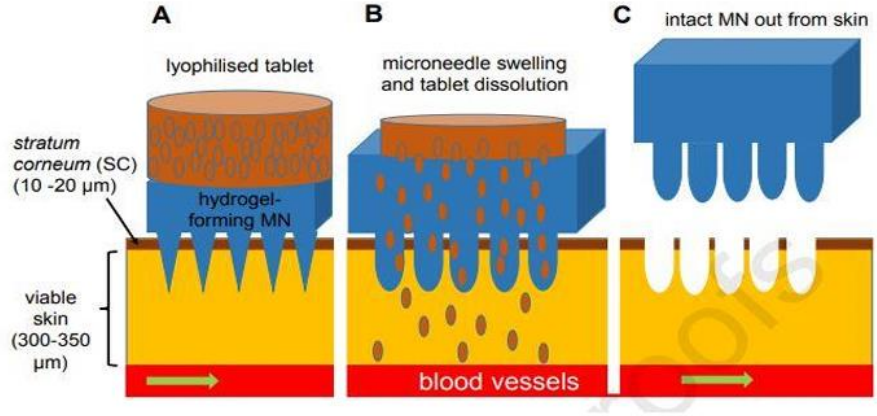

Figure 8. Hydrogel microneedles

Various conventional routes of vaccination

Mucosal Route

Delivering the vaccine through mucosal locations such as the nasal, oral, buccal, sublingual, rectal, and vaginal is known as mucosal vaccination. Mucosal tissues encompass an important section of the body, which is accessible to a variety of pathogenic pathogens. Sexually transmitted infections like gonorrhoea and other genital tract infections, respiratory tract infections including COVID-19, influenza, and respiratory syncytial virus, and digestive tract infections like rotavirus are examples of mucosal infections. Developing ways to neutralize these infectious agents at their site of entry is crucial because many illnesses arise at mucosal locations. Mucosal immunisation would therefore be a desirable path for a localised immune response since it would replicate the natural infection. Immune responses are also induced systemically and/or at other mucosal locations by mucosal immunization.Moreover, mucosa associated lymphoid tissue (MALT), a well-organised lymphatic tissue, is present in the mucosal interface. The immune system's innate and adaptive components are both included in MALT. Compared to the parenteral approach, mucosal vaccination offers a number of benefits, including patient compatibility, lack of sharp waste generation, and no need for a medical professional. Mucosal immunisation has previously only addressed the oral route. Sublingual, vaginal, and rectal routes have, however, recently been investigated using experimental animal models. However, the only licensed vaccines on the market at the moment are oral and nasal.

Nasal Route

The process of delivering vaccinations via the nose, usually as a nasal spray, is known as the nasal route of vaccination. In order to trigger an immune response, this technique makes use of the mucosal immune system, which is present in the nasal passages and other mucosal regions of the body. This is how it operates: Typically, the vaccine is sprayed or misted into the nostrils, where the mucosal surfaces absorb it. After identifying the vaccine's ingredients, the immune system launches systemic and local (mucosal) immunological reactions to aid the body in identifying and preventing particular infections in the future. The only approved nasal spray flu vaccine available for purchase is FluMist Quadrivalent® (live attenuated influenza vaccination), which offers defence against influenza A (H1N1, H3N2) and influenza B.

Oral Route

The immune system in the gut wall's mucosa-associated lymphoid tissue (MALT) and Peyer's patch is stimulated by oral vaccination. It activates both systemic and mucosal immune sites. The oral route doesn't need a medical expert and is safe, patient-compatible, and simple to administer. However, there are difficulties in developing oral vaccines. Mucosal enzymes in the hostile gut environment would degrade a number of antigens, which are proteins by nature. As a result, oral vaccination antigens are unstable. Large amounts of antigen would be needed for the oral approach. Tolerance is the outcome of the oral mucosal vaccination, though. Among the oral vaccinations now on the market are the Rotavirus Vaccine Live Oral RotarixTM (GlaxoSmithKline Biologicals), the Typhoid Vaccine Live Oral Ty21a VivotifTM (Berna Biotech, Ltd.), the Cholera Vaccine Live Oral VaxchoraTM (PaxVax Bermuda Ltd.), and others.These have been demonstrated to be successful in immune system stimulation and illness prevention. Among the leading producers of oral vaccines worldwide are Aventis (Sanofi S.A.), Serum Institute of India Pvt. Ltd., and GlaxoSmithKline Plc. Compared to soluble antigens, particulate vaccinations offer a number of benefits. As of yet, no approved oral particle vaccination exists. Nonetheless, the benefits of particle vaccinations are currently well understood.

Buccal and Sublingual Route

Both buccal and sublingual routes are mucosal vaccination techniques that make use of the oral cavity's abundant vascular supply to produce both localised and systemic immune responses. The Buccal Route Location is Buccal mucosa,

inside the cheek. Works on a mechanism in which vaccine antigens enter the buccal mucosa through either transcellular (endocytosis) or paracellular (tight junctions) pathways. Dendritic cells (DCs) and Langerhans cells interact with antigens to cause systemic and mucosal immune reactions. Due to keratinised epithelium, absorption is slower.The sublingual path has the location of sublingual mucosa, beneath the tongue. Works by Rapid absorption of vaccination antigens is made possible by a thin, non keratinised mucosa. Antigens avoid first-pass metabolism and enter the capillary blood supply directly. The immune response is started by antigen-presenting cells (APCs) and mucosal dendritic cells (DCs).

Rectal Route

The vaccine is administered via the rectum, where antigens penetrate the rectal mucosa.Antigens bypass the liver (via inferior and middle rectal veins) and enter systemic circulation.Antigens interact with gut-associated lymphoid tissue (GALT), stimulating dendritic cells (DCs) and mucosal immunity.Triggers IgA (mucosal) and IgG (systemic) antibodies, protecting against infections.Vaccines against polio, rotavirus, and HIV are being explored via this route.

Vaginal Route

The vaginal route of vaccine administration for genital infections and malignancies, including cervical infections and the human papillomavirus (HPV), was the subject of recent studies. For a localised immune response in genital infections, topical vaccination might be practical. Following vaccination with inactivated and live-attenuated vaccines, the genital mucosa produces particular immune responses. Another study shows that adjuvants and an interleukin-12 intravaginal vaccination strategy against gonorrhoea are driven by outer membrane vesicles (OMV) with T-helper cells. These investigations are effective when conducted on experimental animal models that have not yet been used on humans. However, patient incompatibility with the vaginal mode of vaccine delivery is expected to be an issue. Parenteral Route The parenteral method is used to provide the majority of the vaccinations on the market. The parenteral method is also used to administer newly improved COVID-19 vaccinations. This route provides a number of methods, including intradermal (targeting antigen-presenting cells in the dermal region), subcutaneous (SC) (slow sustained release), and intramuscular (IM) slow sustained release. The vaccine can be administered to the dermis, muscle, SC area, or veins, depending on the kind of immunological response that is intended. Antigen burst release may be useful in eliciting an innate immune response. Nonetheless, contemporary studies concentrate on needle-free delivery methods that offer more priming to the innate immune system and a longer duration of slow, sustained release of antigens, resulting in the best possible adaptive immunological response.

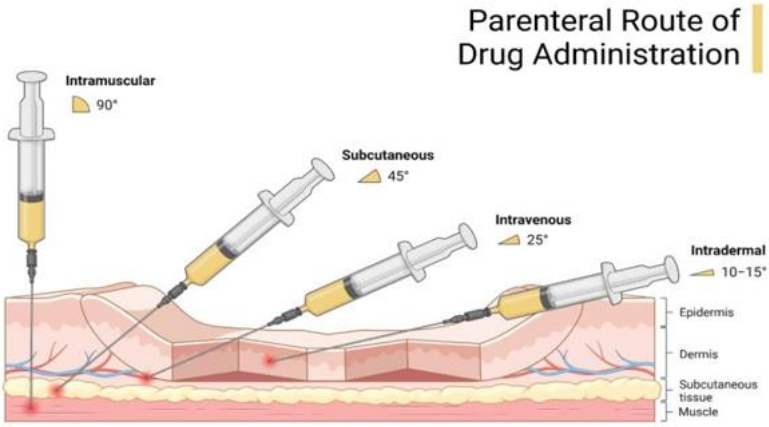

Figure 9. Parenteral Route of drug administration

Intramuscular Route

Intramuscular vaccinations are injected into the deltoid (upper arm) and vastuslateralis (anterolateral thigh, advised in babies). The intramuscular method is typically used to give inactivated vaccinations. The intramuscular method is used to administer the newly created Pfizer-BioNTech and Moderna COVID-19 vaccines. An excellent systemic immune response involving IgM, IgG, and IgA antibodies is usually induced by these innovative mRNA-based vaccines. Very strong mucosal immunity in the form of IgA is not induced by IM immunisation. However, when it comes to intramuscular injection, the vaccine dose is more effective.

Subcutaneous Route

Subcutaneous vaccines are administered under the skin. Between the muscle and the skin, the vaccine is injected. The SC routes are used to administer live-attenuated vaccines, such as MMR and yellow fever.

Intravenous Route
The quickest way to administer a vaccine is intravenously. The vaccine is immediately injected into the veins. Recently, this approach has been investigated for the development of a TB vaccine. Researchers have previously looked into this approach in an effort to create a vaccine to prevent malaria. The fact that the vaccination antigen is quickly removed from circulation and that it must be delivered by a qualified specialist is a significant disadvantage of this approach.

Intradermal Route
Antigen-presenting cells, such as dermal dendritic cells and Langerhans cells in the epidermis, are abundant in the intradermal region. There are efforts underway to develop alternative vaccination delivery technologies. Needlestick injuries can be decreased with needle-free disposable syringe injectors. Research is being done on microneedles, which are tiny needle patches loaded with vaccine that don't require cold chain storage. Because microneedles are smaller than traditional syringe needles, they may be delivered precisely into the dermal layers. Patients get a painless injection and less needle fear because the insertion depth is shallow enough to prevent impinging on innervated tissue.

Vaccination using Microneedles
In order to prevent disease, a vaccine must be administered to the body in order to stimulate an immunological response. Vaccines contain antigens, which are weak or inactive components of a pathogen.The body's immune system produces antibodies in response to the antigen.Immunisation is the process of developing resistance to an infectious disease, typically by the use of a vaccination, and each antibody is trained to recognise a single antigen.A micrometre-sized needle called a microneedle is used to create microscopic pores in biological membranes to increase permeability. Hundreds of microneedles are arranged in an array or tiny patch to create the device. Additionally, they enable ISF biomarker monitoring and synchronised drug delivery. In addition to being painless, microneedles provide a number of benefits over traditional immunisation methods, including intramuscular and subcutaneous. The traditional microfabrication techniques of adding, deleting, and copying microstructures using photolithographic processes, silicon etching, laser cutting, metal electroplating, and micromolding provide the basis of the majority of micro neddle fabrication techniques. The immune system can be stimulated to combat viral infections via microneedle vaccination. For instance, a hepatitis B vaccine can be administered via microarrays.

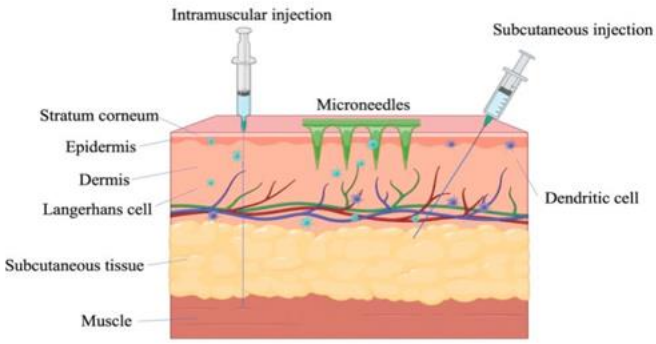

Figure 10. Microneedle Vaccination

Applications
Microneedles offer a fresh approach to community-based and at-home healthcare. The reduced rates of microbial invasion into delivery sites are an additional advantage of microneedles. Both adults and children can suffer from needle phobia, which can occasionally result in fainting. Microneedle arrays offer the advantage of lowering patients' anxiety levels when they are exposed to hypodermic needles. Compared to traditional injections, microneedles have been demonstrated to be significantly less painful while also enhancing psychological and emotional comfort.

1. Transdermal Drug Delivery – Painless and efficient drug administration.
2. Vaccination – Enhances immune response with minimal invasiveness.
3. Insulin Delivery – Helps in diabetes management.
4. Cancer Therapy – Targeted drug delivery for tumors.
5. Cosmetic Applications – Skin rejuvenation, anti-aging, and scar treatment.
6. Biosensing – Real-time monitoring of biomarkers.
7. Gene Delivery – DNA and RNA-based therapies.
8. Neurological Disorders – Delivers drugs for conditions like Parkinson’s and Alzheimer’s.
9. Cardiovascular Drug Delivery – Administers blood thinners and heart medications.

10. Ophthalmic Applications – Delivers drugs to the cornea or retina without injections.

Safety Profile

Among the frequent adverse effects (AEs) of MNs following therapy are oedema, erythema (redness of the skin), and transient pain. Certain cases may also result in pinpoint bleeding, itching, discomfort, and bruises. However, MNs are a rather safe tool because the majority of the negative side effects are transient and may go away on their own within 24 hours of the treatment. Low exposure to chemical irritants and photoprotection are frequently recommended for a speedy recovery and reduced risk of skin inflammation. Furthermore, contact dermatitis may occur if the patient has an allergy to the medication or the MNs' substanceitional hypodermic needle or other injection tools.

CONCLUSIONS

The slow, continuous release of vaccine antigens from microneedles makes them an extremely effective drug delivery method for vaccination. They do away with the requirement for a trained individual to deliver the vaccination. They have the potential to be an appealing approach for mass vaccinations during pandemics because they can basically be self-administered. Microneedles have been shown to be highly effective in boosting a strong immune response against a range of bacterial and viral infections as well as cancer immunotherapy, in addition to being patient-compliant. The skin's large supply of dermal dendritic cells, Langerhans cells, and other immune components is responsible for this strong immunological response. Biodegradable polymers and creative polymer modifications are used in microneedles to create devices with adjustable characteristics. underdeveloped nations, better vaccinations could save many lives. By increasing vaccine effectiveness, lowering the demand for qualified healthcare professionals, streamlining the supply chain, lowering the risk of sharp objects, decreasing vaccine waste, eliminating the need for vaccine reconstitution, and lowering the cost of immunisation, MNPs provide benefits that potentially enhance vaccination.

REFERENCE

1. Stern, A.M.; Markel, H. The History of Vaccines and Immunization: Familiar Patterns, New Challenges. Health Aff. 2005, 24, 611–621.
2. Ipshita Menon , Priyal Bagwe , Keegan Braz Gomes , Lotika Bajaj , Rikhav Gala , Mohammad N. Uddin , Martin J. D'Souza and Susu M. Zughaier . Microneedles: A New Generation Vaccine Delivery System. Micromachines 2021, 12.
3. Tucak, Amina; Sirbubalo, Merima; Hindija, Lamija; Rahić, Ognjenka; Hadžiabdić, Jasmina; Muhamedagić, Kenan; Čekić, Ahmet; Vranić, Edina (2020-10-27). "Microneedles: Characteristics, Materials, Production Methods and Commercial Development" . Micromachines. 11 (11): 961.
4. Singh, Aashim; Yadav, Savita (2016). "Microneedling: Advances and widening horizons" . Indian Dermatology Online Journal. 7(4): 244–254.
5. Aldawood, Faisal Khaled; Andar, Abhay; Desai, Salil (2021). "A Comprehensive Review of Microneedles: Types, Materials, Processes, Characterizations and Applications". Polymers. 13 (16): 2815.
6. Henry S, McAllister DV, Allen MG, Prausnitz MR (August 1998). "Microfabricated microneedles: a novel approach to transdermal drug delivery". Journal of Pharmaceutical Sciences. 87 (8): 922–925.
7. McConville A, Hegarty C, Davis J (June 2018). "Mini-Review: Assessing the Potential Impact of Microneedle Technologies on Home Healthcare Applications". Medicines. 5 (2): 50
8. Dharadhar S, Majumdar A, Dhoble S, Patravale V (February 2019). "Microneedles for transdermal drug delivery: a systematic review". Drug Development and Industrial Pharmacy. 45 (2): 188–201.
9. Panda A, Matadh VA, Suresh S, Shivakumar HN, Murthy SN (January 2022). "Non dermal applications of microneedle drug delivery systems". Drug Delivery and Translational Research. 12 (1): 67–78.
10. Peppi M, Marie A, Belline C, Borenstein JT (April 2018) "Intracochlear drug delivery systems: a novel approach whose time has come" . Expert Opinion on Drug Delivery. 15 (4): 319–324.
11. Park JH, Allen MG, Prausnitz MR (May 2005). "Biodegradable polymer microneedles: fabrication, mechanics and transdermal drug delivery". Journal of Controlled Release. 104 (1): 51–66.
12. Waghule, Tejashree; Singhvi, Gautam; Dubey, Sunil Kumar; Pandey, Murali Monohar; Gupta, Gaurav; Singh, Mahaveer; Dua, Kamal (2019-01-01). "Microneedles: A smart approach and increasing potential for transdermal drug delivery system" . Biomedicine & Pharmacotherapy. 109: 1249–1258.
13. Aldawood, Faisal Khaled; Andar, Abhay; Desai, Salil (2021). "A Comprehensive Review of Microneedles: Types, Materials, Processes, Characterizations and Applications" . Polymers. 13 (16): 2815.
14. Jeong HR, Lee HS, Choi IJ, Park JH (January 2017). "Considerations in the use of microneedles: pain, convenience, anxiety and safety". Journal of Drug Targeting. 25 (1): 29–40.
15. Kwon, Ki Mun; Lim, Su-Min; Choi, Seulgi; Kim, Da-Hee; Jin, Hee-Eun; Jee, Grace; Hong, Kee-Jong; Kim, Joo Young (2017-07-01). "Microneedles: quick and easy delivery methods of vaccines" . Clinical and Experimental Vaccine Research. 6 (2): 156–159.

16. Mottaghitalab F, Farokhi M, Shokrgozar MA, Atyabi F, Hosseinkhani H (May 2015). "Silk fibroin nanoparticle as a novel drug delivery system". Journal of Controlled Release. 206: 161–176.
17. Turner, Joseph G.; White, Leah R.; Estrela, Pedro; Leese, Hannah S. (2021). "Hydrogel Forming Microneedles: Current Advancements and Future Trends" . Macromolecular Bioscience. 21 (2): e2000307.
18. Jaya Arya and Mark R. Prausnitz." Microneedle patches for vaccination in developing countrie". J Control Release. 2016 October 28; 240: 135–141.
19. Ogra, P.L.; Faden, H.; Welliver, R.C. Vaccination Strategies for Mucosal Immune Responses. Clin. Microbiol. Rev. 2001, 14, 430–445.
20. Li, M.; Wang, Y.; Sun, Y.; Cui, H.; Zhu, S.J.; Qiu, H.-J. Mucosal vaccines: Strategies and challenges. Immunol. Lett. 2020, 217, 116–125.
21. De Swart, R.L.; De Vries, R.D.; Rennick, L.J.; Van Amerongen, G.; McQuaid, S.; Verburgh, R.J.; Yüksel, S.; De Jong, A.; Lemon, K.; Nguyen, D.T.; et al. Needle-free delivery of measles virus vaccine to the lower respiratory tract of non-human primates elicits optimal immunity and protection. NPJ Vaccines 2017, 2, 1–11
22. Miquel-Clopés, A.; Bentley, E.G.; Stewart, J.P.; Carding, S.R. Mucosal vaccines and technology. Clin. Exp. Immunol. 2019, 196, 205–214.
23. Kraan, H.; Vrieling, H.; Czerkinsky, C.; Jiskoot, W.; Kersten, G.; Amorij, J.-P. Buccal and sublingual vaccine delivery. J. Control. Release 2014, 190, 580–592.
24. Fujihashi, K.; Koga, T.; Van Ginkel, F.W.; Hagiwara, Y.; McGhee, J.R. A dilemma for mucosal vaccination: Efficacy versus toxicity using enterotoxin-based adjuvants. Vaccine 2002, 20, 2431–2438.
25. Echchannaoui, H.; Bianchi, M.; Baud, D.; Bobst, M.; Stehle, J.-C.; Nardelli-Haefliger, D. Intravaginal Immunization of Mice with Recombinant Salmonella enterica Serovar Typhimurium Expressing Human Papillomavirus Type 16 Antigens as a Potential Route of Vaccination against Cervical Cancer. Infect. Immun. 2008, 76, 1940–1951.
26. Darrah, P.A.; Zeppa, J.J.; Maiello, P.; Hackney, J.A.; Ii, M.H.W.; Hughes, T.K.; Pokkali, S.; Ii, P.A.S.; Grant, N.L.; Rodgers, M.A.; et al. Prevention of tuberculosis in macaques after intravenous BCG immunization. Nature 2020, 577, 95–102.
27. Polack, F.P.; Thomas, S.J.; Kitchin, N.; Absalon, J.; Gurtman, A.; Lockhart, S.; Perez, J.L.; Marc, G.P.; Moreira, E.D.; Zerbini, C.; et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N. Engl. J. Med. 2020, 383, 2603–2615.
28. Hickling, J.K.; Jones, K.R.; Friede, M.; Zehrung, D.; Chen, D.; Kristensen, D. Intradermal delivery of vaccines: Potential benefits and current challenges. Bull. World Health Organ. 2011, 89, 221–226.
29. Gala, R.P.; Zaman, R.U.; D'Souza, M.J.; Zughaier, S.M. Novel Whole-Cell Inactivated Neisseria Gonorrhoeae Microparticles as Vaccine Formulation in Microneedle-Based Transdermal Immunization. Vaccines 2018, 6, 60
30. Rodgers, A.M.; Cordeiro, A.S.; Kissenpfennig, A.; Donnelly, R.F. Microneedle arrays for vaccine delivery: The possibilities, challenges and use of nanoparticles as a combinatorial approach for enhanced vaccine immunogenicity. Expert Opin. Drug Deliv. 2018, 15, 851–867.
31. Hickling, J.K.; Jones, K.R.; Friede, M.; Zehrung, D.; Chen, D.; Kristensen, D. Intradermal delivery of vaccines: Potential benefits and current challenges. Bull. World Health Organ. 2011, 89, 221–226.