Review

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Advancements in vaccine delivery: harnessing 3D printing for microneedle patch technology

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Abstract

The development of 3D-printed microneedle (MN) technology is a significant step in vaccine delivery, providing a painless, effective, and adaptable substitute for conventional injection-based techniques. Direct transdermal vaccination distribution without the need for needles is made possible by microneedle patches, which employ a variety of tiny needles that dissolve when they penetrate the skin. By using 3D printing to precisely customise microneedles' size, shape, and density to meet particular vaccine requirements, administration control can be improved and vaccine efficiency may even be increased. Furthermore, rapid prototyping made possible by 3D printing speeds up the development process, enabling quicker testing and improvement of vaccines. Additionally, this scalable technology can greatly increase vaccine accessibility, particularly in environments with limited resources. Research indicates that by directly interacting with the skin's immune-rich layers, microneedle patches enhance antigen delivery and elicit a strong immune response. Because MN technology offers a useful, self-administrable vaccination approach with little waste, it has significant potential for use in public health applications, notably during pandemics. This study emphasises how 3D-printed microneedle patches have the potential to revolutionise vaccination procedures and increase vaccine accessibility globally.

Keywords: 3D printing, drug delivery systems, microneedle patches, transdermal immunization, Transdermal Immunization, vaccine delivery

Introduction

Transdermal medication delivery has promise as a more convenient and secure option than intravenous and oral drug administration[1]. Transdermal distribution's efficacy can be attributed to a better comprehension of the physicochemical and pharmacokinetic principles that underpin skin wall function[2]. In addition to performing vital physiological functions, the skin, an organ that covers the outside of the body, acts as a barrier to protect the body from the environment. Homeostatic regulation of body fluids, thermoregulation, nociception, and protection are all included in these roles[3]. To protect the human body from dangerous antigens, the immunization process is crucial, making vaccines an essential component of global healthcare systems. Preventive vaccinations have shown significant effectiveness in eliminating certain infectious diseases, including smallpox and measles. When these vaccinations are administered, they can help reduce the spread of other common infectious diseases, such as COVID-19 and Ebola, which are currently on the rise[4]. Vaccines are designed to introduce specific antigens into the immune system, resulting in strong and long-lasting immune responses that guard against infections and proactively delay the onset of disease. Vaccine success often depends on the efficient delivery of allergens and adjuvants to particular subsets of innate immune cells, such as dendritic cells and macrophages. This method aims to stimulate T cells, induce the creation of plasma cells that release antibodies, optimize antigen presentation, and promote memory T or B cell growth[5]. Immunizations are often administered by bolus injection into subcutaneous tissue or muscles, although the intradermal (ID) approach is becoming more and more popular. This effect is caused by antibodies found in human skin, specifically Langerhans cells and dermal dendritic cells[6].

HIGHLIGHTS

- Instead of using typical injections, microneedle patches provide immunisations via the skin in a painless manner.
- Microneedles may be precisely customised with 3D printing to deliver vaccines efficiently.
- The regulated delivery of vaccines made possible by microneedles may increase their effectiveness.
- Rapid prototyping made possible by 3D printing speeds up the creation and testing of vaccines.
- This method increases the accessibility of vaccines worldwide by providing scalable production.

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Microneedles are used to administer immunizations through the ID method. The human epidermis has a high degree of impermeability, and microneedles (MNs) are tiny devices that can penetrate it. This special property enables MNs to target the dermal microcirculation directly, facilitating the effective administration of a variety of active compounds, including drugs, ribonucleic acids, deoxyribonucleic acids, and vaccinations.[7-9]. The academic literature refers to microneedles, or MNs, as arrays of solid needle projections that are micrometers in size.These structures have the unusual capacity to pass through the stratum corneum, the skin's outermost layer of defense, without creating discomfort. Consequently, the application of pharmaceuticals to the skin's dermis, the underlying layer, and epidermis, the outermost layer, is facilitated by MNs. The materials that can be utilized to make microneedles include silicon, polymers, and solid metallic objects. Then, therapeutic compounds can be applied to these materials. As an alternative, biodegradable polymers can be used to encase medicinal compounds in MNs[10,11]. The devices that are intended to function in tandem with solid and drug-coated, dissolvable, hollow, or hydrogel-based microneedles can be used to categorize MNs into one of five types in this overview. Transdermal drug delivery offers unique advantages over oral and injection-mediated administration methods because of its potential for self-administration, painless delivery, and enhanced bioavailability. Through the use of microneedles, the skin's main limitation – its high impermeability – was addressed. These microscopic, sharp projections, known as microneedles, efficiently penetrate the epidermis' outermost layer and gain entry to the dermal microcirculation. Through the use of hollow, solid-coated, poke-and-patch, and dissolvable microneedles, macromolecules, DNA, proteins, and vaccines can now be administered more easily. Despite the high level of scientific interest in microneedles, it is important to remember that there are currently very few commercially available devices, the majority of which are employed for cosmetic purposes[12-16].

Traditional vaccine delivery methods

Oral route

Historically, vaccinations have been administered subcutaneously or intramuscularly. Oral administration is the preferred method of delivering vaccines due to its numerous advantages, such as easy administration and availability[17-19]. Not only can oral vaccines minimize the risks associated with needle systems, but they also can enhance mucosal and systemic immunity[20]. The majority of conventional parenteral vaccinations are designed to target solely systemic diseases Oral immunizations can effectively inhibit the majority of enteric and mucosal infections, including Giardia, N. meningitidis, and N. gonorrhea, by enhancing mucosal immunity and so preventing sickness[21,22]. Several vaccines can be administered orally; these include cholera, typhus, and live attenuated polio vaccines[23]. One significant factor contributing to the absence of success can be attributed to the limited efficacy of oral vaccinations in eliciting a robust immunological response. This is because they are unable to transfer the antigen intact to the specific location where it has to be sampled, known as the antigen sampling or "M" cells. Antigens have difficulties in preserving their immunogenicity inside the acidic milieu of the gastric environment and evading enzymatic degradation within the intestinal tract. In addition, the existence of a defensive mucus layer functions to diminish the concentration of the antigens and limit its capacity to reach the mucosal epithelium, hence reducing the probability of interaction between the antigens and the mucosal immune system. Consequently, to achieve successful oral vaccination, a greater amount of antigens is required compared to nasal or parenteral injection, making the oral route unsuitable for regular administration[19,21,24,25]. Different routes and traditional methods of vaccination are shown in Fig. 1.

Nasal route

The human nose is an intricate organ that is covered with highly vascularized mucosa. The body's first line of defense against airborne microbes is the mucosa, which is composed of specialized cells and well-organized lymphatic tissues[24]. The delivery of medication through the nasal route is a needle-free technique that effectively enhances both systemic and mucosal immune responses. Given the capacity of the nose to elicit mucosal immunity, it assumes the dual role of initiating and executing immune responses in remote mucosal regions through the dissemination of immune cells that execute their tasks within the mucosal immune system[25,26]. Nasal delivery methods are becoming more popular for administering systemic medications and vaccinations due to their ability to use lesser doses and distribute formulations directly to the desired location[27,28]. Nasal administration circumvents issues related to the first metabolism and systemic degradation of medicines, resulting in prompt absorption, quick onset of effects, and enhanced bioavailability. With the introduction of Flumist®, a live, weakened intranasal flu vaccine, a major step forward in nasal vaccination was made in June 2003[29]. Novel drug delivery methods must possess efficacy and safety, ensuring enhanced absorption, consistent bioavailability, accurate dosing, and strong patient adherence. Mucosal enzymes and antigen properties such as polarity, pH, lipophilicity, and particle size considerably limit the nasal route's absorption of certain compounds. These factors also have an impact on the bioavailability and clinical effects of the substances[30]. It is important to note that the nose is specifically built to expel any foreign substances that enter the body. Hence, enhancing lung deposition is highly intricate due to the predominant deposition of particles in the nasal mucosa[31].

Subcutaneous immunization

A novel approach to vaccine delivery is subcutaneous immunization (SCI), which involves applying vaccine antigens topically to the host's undamaged skin[32,33]. Systems for delivering medication without needles are now top of mind globally. Research into nasal and oral delivery devices is extensive. However, as was previously said, these routes may have certain drawbacks[34]. Cell-mediated immunity involves direct interaction between lymphocyte cells and antigens, resulting in an immune response. On the other hand, humoral immunity mostly relies on antibodies present in the blood plasma to impart

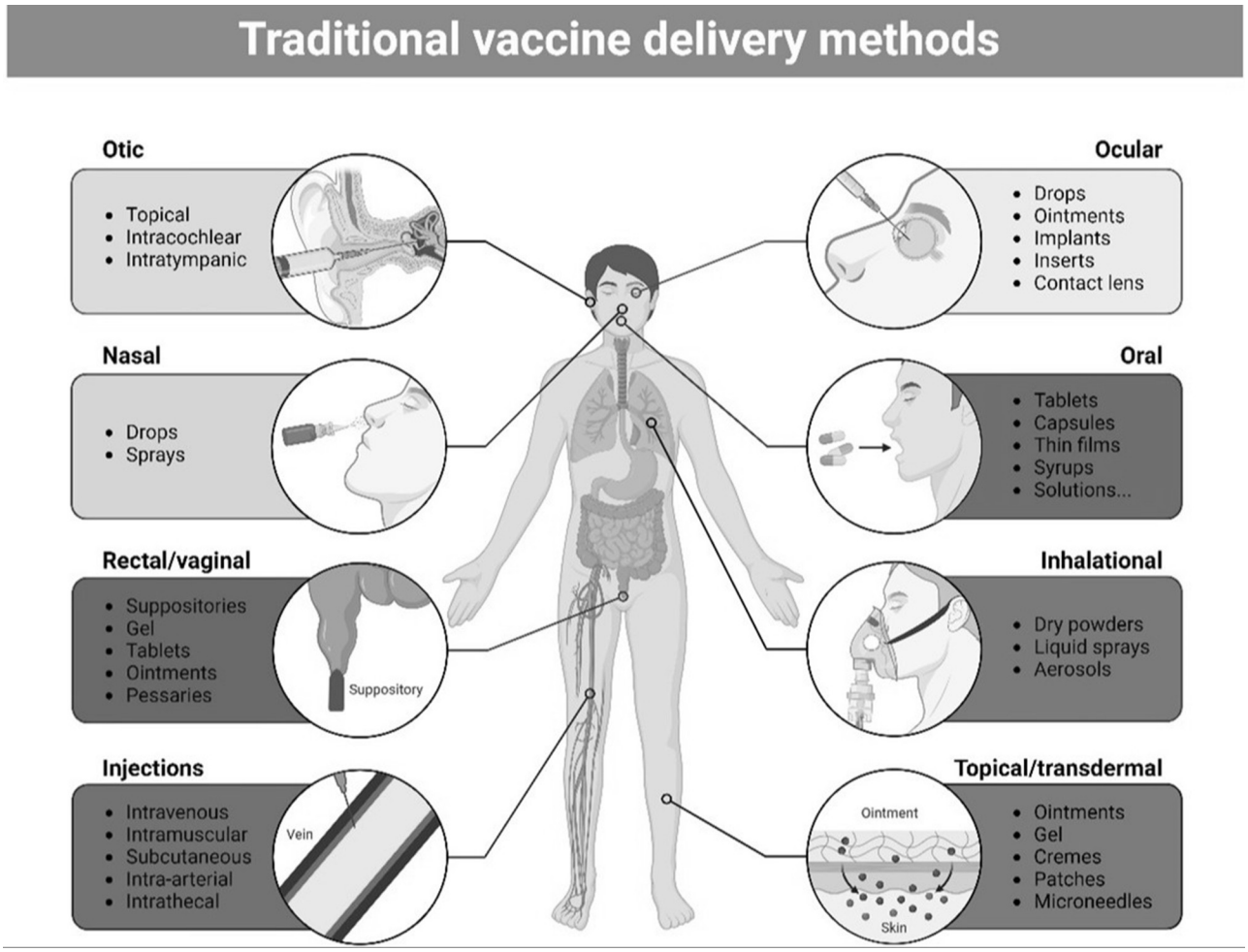

Figure 1. Traditional drug delivery route and vaccination method.

immunity. According to information released by the Association of Reproductive Healthcare Professionals, the first transdermal patch used for an antiemetic drug was approved in 1981[35]. SCI is a straightforward method that entails the placement of a patch on the outermost layer of the skin. SCI harnesses the potent immune system present in the outermost layer of the skin, which is typically not targeted by vaccination methods that involve injecting substances directly into the body[36]. SCI systems employ an adjuvant that is included in a vaccination antigen. It is hypothesized that minor physical manipulation of the skin can augment the immune response by SCI, even with reduced amounts of adjuvants and antigens. While the exact mechanism of SCI remains unclear, it is hypothesized that skin moisture facilitates the penetration of the adjuvant into the outermost layer of the skin following the application of a vaccination patch containing both the adjuvant and the antigen[33].

3D printed microneedles

The biomedical area has witnessed a notable impact from the utilization of 3D printing technology. This impact is evident via the wide array of items now accessible in the market, as well as the diversified range of research endeavors. Prominent uses encompass the utilization of 3D printing technology for the development of models intended for surgical preparations and instructional purposes, particularly in the context of hard tissue repairs. Additionally, this technology has contributed to developments in the realm of tissue engineering. The application of the technology of 3D printing into the field of pharmaceutics is now restricted to a sole medication, namely Spritam, as authorized by the FDA. This particular drug, in the form of a tablet, is specifically designed to address the medical condition of epileptic seizures. Projections of significant growth in the market for 3D printed medicines, reaching a value of $522 million by 2030, have generated considerable attention in this field. Consequently, there is now a significant amount of research being conducted to investigate the appropriateness of different 3D printing technologies in the context of manufacturing tablets and medication delivery systems[37-39]. A multitude of materials, including metals, ceramics, and polymer compounds, can be manipulated using suitable physicochemical procedures thanks to the versatility of 3D printing technology. The many 3D printing methods exhibit a shared characteristic of constructing a tangible item by sequentially fabricating layers that are joined together. This process occurs within a singular apparatus known

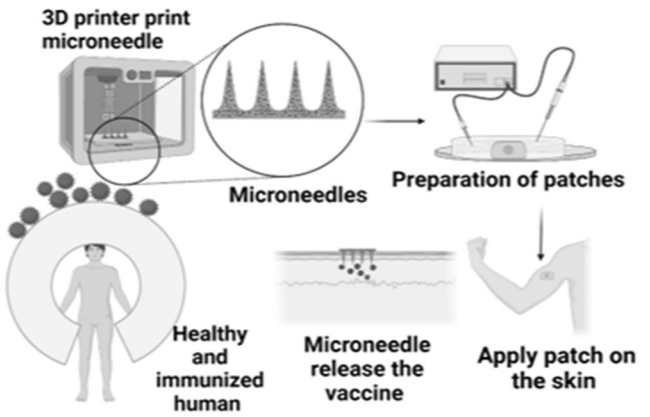

Figure 2. 3D printed microneedle technique.

as the 3D printer[40]. 3D printed microneedle technique is shown in Fig. 2.

Types of microneedles

Solid microneedles

Microneedles that are solid and are often constructed of metals, silicon, or polymer, are utilized to build the channels and prepare the tiny incisions for the drug delivery system. Imiquimod is one of the most successful therapies for basal cell carcinoma. Sabri *et al* found that solid microneedles enhanced the *ex vivo* transdermal absorption of the imiquimod and that the resultant intradermal depots persisted for up to 24 hours[41]. These channels act as conduits, allowing substances applied to the skin to pass through and penetrate deeper than the stratum corneum[42]. It is possible to penetrate the skin with solid-material microneedles both before and after a medication has been applied topically. Before implantation, a medication can also be applied to them. When they come into touch with bodily fluids, drug-coated microneedles will shed their drug coating, which will then allow the medication to be absorbed via the skin[43]. Solid microneedle vaccine delivery is shown in Fig. 3.

Drug-coated microneedles

It is usual practice to use a solid microneedle in a transdermal delivery system for drugs to increase the transdermal permeation effectiveness of medications that are delivered through an implanted channel. Nevertheless, one drawback of the solid microneedle lies in its complex administration pathway, which often necessitates a two-step process for medication delivery to the skin. The problem has been effectively addressed by the use of coated microneedles, whereby pharmacological substances are put to their tips using diverse techniques like gas-jet the drying process, ink-jet the printing process, and spraying. The medicine administration strategy includes the use of coated microneedles which is colloquially known as the "coat and poke" technique. Comprehensively, the microneedle patches are inserted into the dermis, enabling the regulated release of medication that is applied on the surfaces of the microneedles. DeMuth *et al* developed a rapid-release microneedle coating capable of delivering DNA vaccines. The DNA and adjuvants demonstrated the capacity to remain in the skin for extended periods ranging from days to weeks following the administration of the DNA-coated microneedles. In addition, it was noted that the group that had DNA vaccination exhibited a rise in the production of memory T-cells, gene expression, and stimulation of immunological responses in comparison to the group that got the intradermal DNA injection[44-47].

Hollow microneedle

Hollow microneedles are characterized by an interior void that is occupied by a drug dispersed or solution. The artifacts display perforations at their points. The administration of the drug occurs via direct injection into the epidermis or dermal layers of the skin. The application of this technology is mostly observed in the context of macromolecules with high molecular weights, such as proteins, vaccines, and oligonucleotides[48-51]. If the medication is designed for prompt administration by a bolus

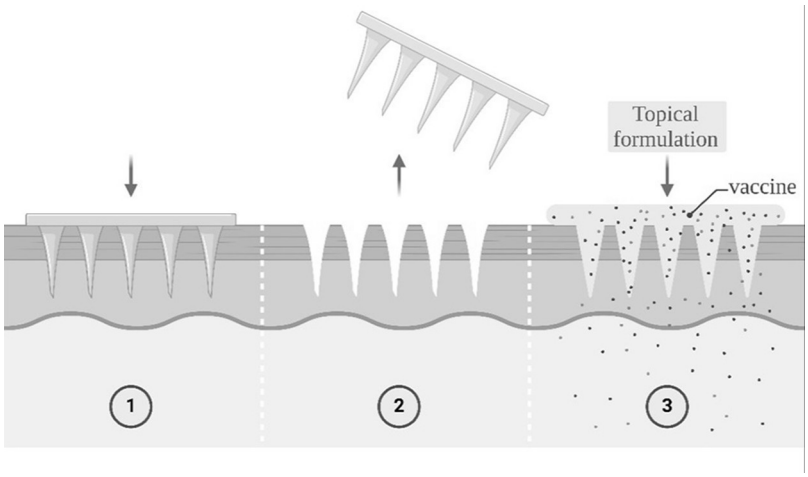

Figure 3. Solid microneedle delivers vaccine.

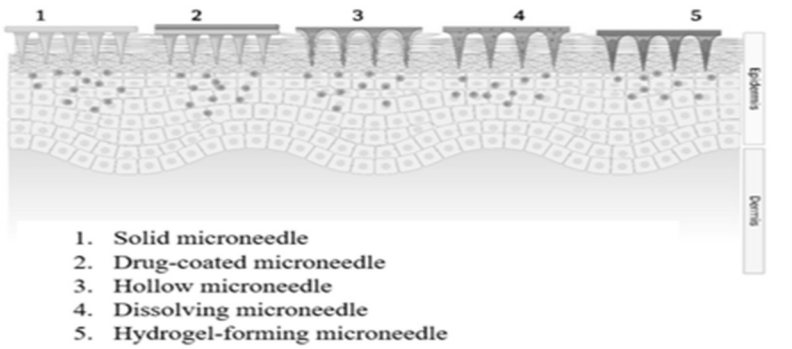

Figure 4. Different types of microneedles.

injection, it is feasible to adjust both the drug rate of flow and the release pressure. The microneedles possess the capacity to deliver a substantial quantity of medicine due to their ability to contain a greater volume of the drug within the needle's internal area. Ensuring a consistent rate of flow is crucial in this context. An augmentation in the diameter of the microneedle can result in an escalation in the rate of fluid flow, albeit at the expense of diminished structural integrity and acuity. In certain instances, a metallic coating is utilized on microneedles to enhance their structural integrity. Nevertheless, it is crucial to acknowledge that the use of this coating could perhaps lead to an augmented level of needle sharpness. Mishra and colleagues fabricated hollow microneedles that were arranged in alignment on a silicon substrate. The microneedles had a length that varied between 500 and 600 micrometers, accompanied by a diameter outside of Hundred micrometers. A flow rate of 0.93 microliters per second ($\mu l\ s^{-1}$) was achieved by applying a pressure difference of 2 kilopascals[52-54]. Different type of microneedles is shown in Fig. 4.

Dissolving microneedle

The drug is often enclosed in biodegradable polymers during the manufacturing process of dissolving microneedles. The polymer that makes up the needle shape dissolves after penetrating the stratum corneum, releasing the drug that was previously enclosed and is indicated by the letter (e). Since a microneedle is not removed after delivery, using dissolving microneedles requires a unique procedural method. The mechanism in question can be characterized as a "poke and release" kind. The utilization of dissolving microneedles addresses many challenges associated with solid microneedles due to their inherent mechanism, which eliminates the need for any further manipulation after insertion. The utilization of dissolving microneedles within the dermis offers a significant advantage by effectively mitigating the potential hazards associated with needle-stick injuries after their administration[55-57]. Moreover, new studies have been conducted on bioresponsive microneedles. In their study, Wang *et al* present a description of microneedles that are constructed using hyaluronic acid and incorporate pH-sensitive dextran nanoparticles. These nanoparticles act as carriers for the enzyme glucose oxidase, which speeds up the transformation of blood sugar into gluconic acid, and for aPD1. The resulting acidic environment aids in the nanoparticles' ability to self-dissociate, releasing aPD1 for the treatment of melanoma[58-61].

Hydrogel-forming microneedle

This particular microneedle variant has been newly created. Fabricated from super-swelling polymers are microneedles. Due to their hydrophilic properties, polymers can effectively absorb a significant quantity of water within their three-dimensional polymeric structure. The phenomenon of polymer expansion occurs when these polymers are introduced into the dermal layer, facilitated by the presence of interstitial fluid. As a result, conduits are created between the capillary circulation and the medicine patch. Microneedles are employed exclusively before needling to disrupt the integrity of the skin barriers. Swelling is distinguished by its function as a membrane that regulates rate. The objects possess the characteristic of being adaptable in terms of their dimensions and configuration. The microneedles possess notable attributes in terms of their convenient sterilization process and their ability to be removed from the skin without damage. The objective of this approach was to mitigate the gastrointestinal adverse effects commonly observed with oral delivery of the drug. The findings of the study revealed that the medicine exhibited enhanced penetration and bioavailability when administered using the microneedles that were specifically created for this purpose. Cross-linked polymers are commonly employed in the fabrication of swellable microneedles for medication delivery[62].

Manufacturing technique

Microneedles may be made using several different 3D printing methods. Some examples of these techniques include stereolithography, or "3-D printing with light," and selective laser sintering[63].

Selective laser sintering

Selective laser sintering is a process that was initially developed by a group of researchers affiliated with the University of Texas at Austin. These researchers included Gong H, Rafi K, Gu H, and Starr B. The technique involves the fusion of powder beds. The fact that this technique was the first powder bed additive manufacturing technology to be made available for commercial use is a significant accomplishment.

The initial development of this technique was focused on plastic samples and utilized pointwise laser scanning technology. However, later developments have increased its application by utilizing other heat sources to encompass metal and ceramic materials. The feed cartridges are used to inject the polymer- or ceramic-containing powder material into the powder bed. The powder material undergoes preheating by the utilization of infrared heaters. This process is employed to sustain the desired temperatures of the components intended for formation, while simultaneously minimizing the demand for the CO_2 laser[64,65].

Stereolithography

The initial advancement in stereolithography occurred throughout the 1970s. This technique involves the incremental construction of three-dimensional structures through the process of selectively solidifying photosensitive materials using UV light. Over time, several methodologies have been devised for stereolithography systems, and these methodologies may be categorized into four distinct generations. Hull invented the first version of the procedure, which involved scanning a liquid material with a laser beam. This method produced three-dimensional structures, although it wasn't quite as effective as it may have been. To tackle the problem of inadequate efficiency, scholars developed an enhanced version of stereolithography, referred to as projection stereolithography. The utilization of photomasks facilitated the concurrent curing of individual layers, hence enabling this technological progress. The year 2015 witnessed a notable advancement in the field of stereolithography, with the introduction of the third generation. This iteration demonstrated a substantial enhancement in printing velocity when compared to its preceding iterations[52,66-67].

Continuous liquid interface production

The continuous liquid interface production (CLIP) method is a photopolymerization technology that displays much-improved build rates in comparison to the traditional layer-by-layer stereolithography approach. There is a significant difference between the two. The approach was created by Tumbleston *et al* to efficiently fabricate three-dimensional objects from a liquid bath. This technique enables the production of seamless components without layers, resulting in higher printing speeds. Additionally, it is possible to fabricate structures with resolutions that are less than 100 microns[68]. Furthermore, due to the continuous nature of CLIP, the rate at which the projected pictures are refreshed does not have an impact on the pace at which printing occurs. Consequently, this enables the creation of seamless 3D objects without the requirement for model slicing[69,70].

Delivery of drugs and vaccines

Microneedle devices offer distinct benefits compared to conventional hypodermic needles when it comes to administering drugs and vaccines. Microneedles are minimally intrusive, as their size is specifically engineered to prevent nerve stimulation and minimize patient discomfort. Experiments on human skin have shown that microneedle penetration causes less pain compared to conventional hypodermic needles. This reduction in pain has been measured using the visual analog scale, which indicates a roughly 90% decrease in pain when a microneedle penetrates 480 μm into the skin, as opposed to a hypodermic needle that goes several millimeters deep[71,72]. Conventional hypodermic needles have poor pharmacokinetic profiles for medication and vaccine administration, and needle injuries and misuse are prevalent. Microneedle devices, such as cheap disposable patches, can be self-applied or administered without clinical expertise to improve therapeutic component delivery pharmacokinetics, reduce needle stick injury, and reduce "sharps" and other biohazardous waste. Disposable microneedle patches could prevent HIV transmission by encouraging self-administration of testing and medicines in transitional and developing nations. Oral drug delivery may solve some of these issues, but many drugs degrade in the liver and gastrointestinal tract[73], so intravenous, intramuscular, or subcutaneous injections are still common in all healthcare settings. Microneedle patch distribution, in contrast to conventional immunization, employs a markedly reduced vaccination dose. This approach specifically targets the robust immune system of the skin, resulting in a heightened immunological response and a more effective utilization of the antigen[74].

The utilization of microneedle patch technology holds promise in addressing the obstacles associated with widespread COVID-19 vaccination efforts globally. This technology has already demonstrated successful outcomes in administering lyophilized or liquid-based vaccines, as well as large molecules such as influenza vaccines and insulin[52,75,76].

Supporting microneedle efficacy

Microneedles signify a notable improvement in vaccine delivery systems, possessing the potential to markedly improve vaccine efficacy. Here are key concepts concerning how microneedles may enhance vaccine efficacy:

Augmented immune reaction

Microneedles administer vaccinations directly into the skin, which is abundant in immune cells such as Langerhans and dendritic cells. This tailored delivery can provoke a more robust immune response than conventional intramuscular injections. Research indicates that microneedle immunization can enhance memory cellular immune responses and elevate the number of antibody-secreting cells, both essential for efficient virus clearance[77,78].

Dose-sparing effects

Microneedles may facilitate dose-sparing, indicating that reduced vaccination doses could elicit comparable or superior immunogenicity compared to bigger doses delivered through conventional means. This is especially critical during pandemic scenarios where swift and extensive immunization is essential. Research suggests that microneedle patches have dose-sparing effects in clinical tests, facilitating efficient immunization with diminished antigen quantities[79,80].

Enhanced vaccine stability and distribution

Dissolvable microneedles enhance vaccine durability, obviating the necessity for cold-chain storage, a frequent logistical impediment in vaccine distribution, particularly in resource-limited environments.

The capacity to maintain vaccines at ambient temperature without compromising efficacy could enhance worldwide access and distribution of immunizations[81].

Decreased discomfort and enhanced acceptance

The painless characteristics of microneedle delivery improve patient acceptance and adherence, potentially elevating vaccination rates. Conventional needle injections may dissuade patients due to apprehension regarding discomfort or needles, but microneedles are frequently characterized as imparting merely a mild pressure on the skin. This augmented acceptance may result in enhanced vaccination coverage[82,83].

Programmable release mechanisms

The innovative design of microneedles facilitates the programmable release of antigens, effectively simulating many doses of conventional vaccines in a single application. This approach may improve the immune response by prolonging antigen presence, therefore fostering a more vigorous and enduring immunological reaction[84,85].

Future perspective

Future developments in 3D-printed microneedle technology for vaccination administration possess significant potential. These patches have the potential to revolutionize global vaccination initiatives by improving accessibility, particularly in resource-limited regions. Innovations like hydrogel-forming microneedles may provide continuous monitoring and medicine delivery, promoting personalized healthcare solutions[86,87]. Furthermore, integrating artificial intelligence and machine learning into the design and manufacturing processes may enhance microneedle efficacy, minimize errors, and forecast personalized treatment results. These patterns indicate that microneedles could transform transdermal drug delivery, better aligning healthcare with individual requirements and global desires[8,88].

Conclusion

The development of microneedle patch technology signifies a significant progression in vaccination administration, providing a minimally invasive and painless substitute for conventional injection techniques. The method utilises 3D-printed microneedles that dissolve upon application, administering vaccines directly through the skin's stratum corneum to the underlying immune-rich layers, so dramatically augmenting the immunogenic response. This transdermal approach eliminates the need for needle-based injections, which pose dangers like needle-stick injuries and discomfort. It also enables self-administration, rendering it suitable for extensive immunisation initiatives, particularly in resource-constrained environments. 3D printing enables the customization of microneedle patches in shape, size, and density, facilitating accurate dosage control and scalability, which is crucial for rapid responses to new infectious illnesses. Moreover, 3D printing technology has transformed the efficiency and affordability of prototyping and manufacturing, rendering microneedle patches more universally accessible. Although the potential of 3D-printed microneedles is significant, additional research is required to enhance their efficacy, optimize antigen administration, and guarantee safety across various populations. The incorporation of artificial intelligence in the manufacturing process may enhance quality control, forecast performance results, and aid in the creation of more sophisticated, patient-centric vaccination administration systems, microneedle patches signify a revolutionary advancement in vaccination, possessing the capacity to enhance healthcare accessibility and efficacy in both standard and emergency immunization initiatives.

Ethical approval

Ethics approval was not required for this review.

Consent

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Author's contribution

Conceptualisation: Shikha Yadav and Namrata Bhadouria. Methodology and investigation: Shikha Yadav, Namrata Bhadouria, and Sarad Pawar Naik Bukke. Analysis, interpreted the data and writing – original draft preparation: Shikha Yadav, Namrata Bhadouria, Sarad Pawar Naik Bukke, and Bayapa Reddy Narapureddy. Writing – review and editing: Shikha Yadav, Namrata Bhadouria, Sarad Pawar Naik Bukke, and Bayapa Reddy Narapureddy. All the authors read and approved the final manuscript.

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Data availability is not applicable to this article as no new data were created or analyzed in this study.

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