REVIEW ARTICLE

Microneedle Transdermal Patches- A Novel Painless Approach with Improved Bioavailability for the Treatment of Diseases with Special Prevalence to Neonatal Infections

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ABSTRACT

Microneedle transdermal drug delivery systems (TDDS) present a compelling substitute for parenteral and oral administration methods in the treatment of several illnesses. The past several decades have seen a revolution in technology that has changed the production of micro-structured devices, including the development of microneedles for transdermal patches. These devices are used to deliver drugs, proteins, insulin, antibiotics, vaccinations, and other therapies through the skin. They are proven to be beneficial for the prevention of newborn infections. Successful treatments for conditions like cancer, diabetes, rheumatoid arthritis, Alzheimer's disease, and migraines can be achieved with the use of transdermal microneedle patches. Microneedles have the potential to offer prolonged immunity, dosage sparing, and improved protection against viral challenges. The epidermis and dermis are immunologically rich layers, and because of the needles' micron-size structure, these devices have shown to be significantly more effective at targeting these layers, indicating their potential utility in the creation of next-generation vaccines. Within the framework of developing vaccines. Microneedle transdermal patches' main benefits are that they are easy to use, painless, and non-invasive. Here, we discuss the types of microneedle transdermal patches and how microneedle transdermal patches are now being used to treat infections in newborns and vaccination and as a more cost-effective self-administration approach. This also enhances the bioavailability when used in vaccination therapy. Next, we'll go over how microneedle transdermal patches are currently used to treat a variety of illnesses effectively, including those that affect newborns.

Keywords: Transdermal, Microneedles, Bioavailability, Rheumatoid arthritis.

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INTRODUCTION

The scientific term for medical devices that transfer medications into or throughout the body is a drug delivery system. These technologies include administration methods like oral tablets or injection-based vaccinations. The work of biomedical engineers, who have also contributed to the development of various innovative drug delivery techniques, has substantially advanced our understanding of the physiological barriers to efficient medicine administration.[1] Drug delivery systems (DDSs) are designed to successfully administer the necessary dosage of pharmaceuticals to the appropriate target locations while maintaining optimal drug levels. Current DDS research focuses on topics like liposomes, nanoparticles, implants, microencapsulation, microneedle transdermal drug delivery, and polymers.[2] This approach makes it possible to easily stop using the medication in cases of toxicity, guarantees continuous drug release, and may minimize side effects. Patients find microneedles transdermal patches a convenient way to administer medication because they are painless and can be used independently. Because of the physicochemical characteristics of the medicine, conventional drug administration routes, like oral and parenteral routes, frequently have restrictions. For example, oral administrations are linked to first-pass metabolism, which significantly lowers the medicines' bioavailability. Injections are intrusive, typically uncomfortable, and may cause needle anxiety in patients, particularly young ones. They also typically need to be administered by qualified individuals.[3,4]

Conversely, microneedles (MNs) are capable of penetrating the outermost layer of the skin (stratum corneum) to locally administer bioactive molecules into the epidermis and/ or superficial dermis.[5] Microneedle percutaneous administration

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is a non-invasive delivery method that is a preferable alternative to parenteral administration as shown in Figure 1. Furthermore, the percutaneous injection can stop the breakdown of enzymes connected to the liver and digestive system. Microneedle therapy may provide several advantages, such as preventing liver metabolism, lessening the detrimental effects of oral drugs on the digestive tract, achieving continuous and sustained drug release, and simplifying the process of stopping drug delivery in the event of toxicity.[6] The application of medication to extremely flexible bodily parts over an extended period is done with a multifunctional bionic microneedle.

A novel drug compound's development is time- and money-consuming. Through the application of several techniques, the ratio of "old" medications' safety to effectiveness has been increased. Another incredibly intriguing approach to targeted drug delivery is the ongoing study of delayed drug delivery and controlled medication distribution. Notably, a large body of work and several publications from the US and Europe have been created by Indian researchers.[7] Control drug delivery can also be obtained by microneedle transdermal patches.[8]

Transdermal Patches

Transdermal patches frequently contain many layers.

- The first and deepest sticky layer adheres to the skin.
- Rate-controlling micropore membrane – This membrane regulates the speed at which drugs are delivered to the skin's surface.
- The principal drug reservoir layer is where the active medication to be given is kept.
- The outer backing sheet, which acts as an occlusive supporting layer.

Additional layers such as stabilizers, permeability enhancers, and packaging are also required for transdermal patches to be designed successfully. The adhesives in a transdermal patch, which serves as a carrier, allow the medicine to infiltrate the skin after holding it there until it is applied.[9]

Advantages Of Microneedle Transdermal Patches

- Drugs injected through the skin escape the first-pass hepatic metabolism and provide a steady plasma concentration of the medication. They also avoid the pH fluctuations associated with gastrointestinal transit.[10]
- It is feasible to self-administer the patch.
- Improved bioavailability, decreased systemic adverse effects, and fewer drug-to-drug interactions are all benefits of non-invasive, painless drug delivery.

Drawbacksofmicroneedle Transdermal Patches

- Expensive Treatment
- Possibilities of developing contact dermatitis, rashes, or localized irritation from wearing the patch.
- Because of the skin's small pore size and impermeability, only powerful medications can be selected as good candidates for transdermal patches.
- A maximum daily dose of 5 mg or less may be given. Only medications with a lipophilic character and good physicochemical qualities are suitable candidates for transdermal patches because they can effectively penetrate through the stratum corneum layer of skin.

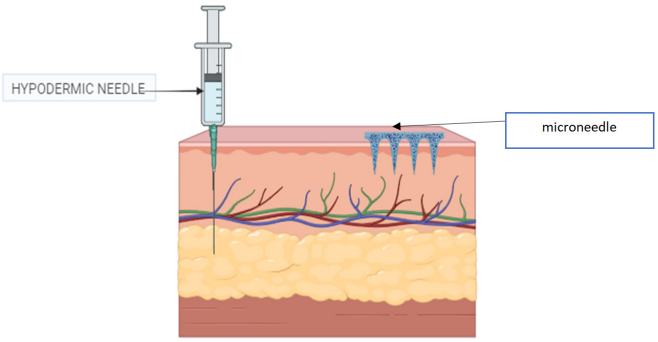

Figure 1: Comparison of drug delivery *via* microneedle and hypodermic needle

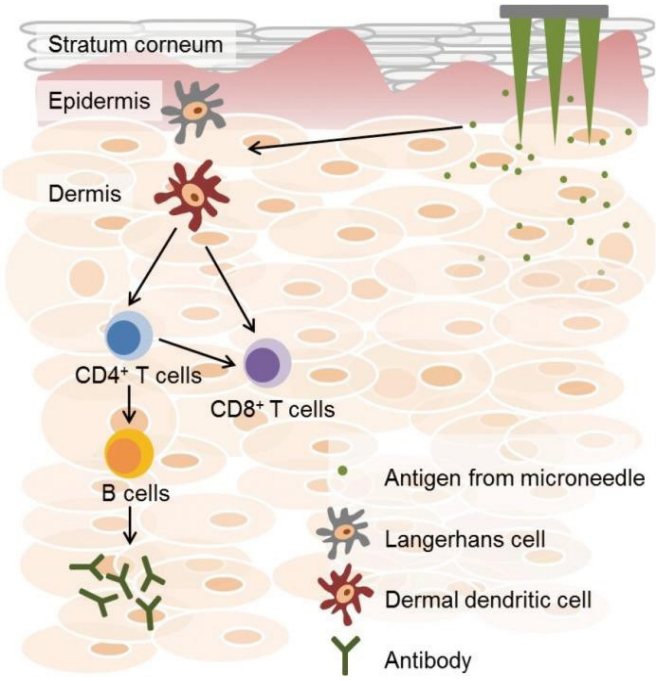

Figure 2: Working of microneedle

Recent Approaches In The Drug Delivery System

Microneedles (MNs) are a type of drug delivery device that only puncture the active cuticle and alive epidermis without injuring the nerve endings and blood vessels. MNs have a pointer size in the micron range and a needle length of 25 to 1000 m.

The patients don't feel terrible suffering during the operation because MNs are so tiny that they cannot harm blood vessels or stimulate dermal nerves. MNs might also assist patients with overcoming their fear of needles and avoiding the detrimental metabolic, gastrointestinal, and hepatic consequences of oral delivery,[11] still piercing the cuticle barrier without visibly hurting the patient. Additionally, it is capable of lasting results and extended release of pharmaceuticals under

particular circumstances by using unique material selection and design.[12]

Working of Microneedle

The activation of immune responses by the vaccine using microneedle as shown in Figure 2. When microneedles penetrate the skin layers dermis and epidermis, vaccine antigens are released into dermal tissue. Released antigens are processed by Langerhans cells and dermal dendritic cells (DCs). Dermal DCs contribute to trigger effector T cells, including CD4+and CD8+ T cells. Stimulated CD4+T cells activate B cells, which secrete antigen-specific antibodies.

Types of Microneedles

MN's research is primarily focused on the creation of a quick, efficient, safe, and practical drug delivery mechanism; solid MNs, coated MNs, hollow MNs, soluble or biodegradable MNs, swelling MNs, and porous MNs are some types of MNs. are some of the numerous types of MNs that can be used for drug administration.[13]

Solid microneedle

Solid MNs, which can be used for skin pretreatment, are constructed of metal or silicon and don't contain any medications. The MNs are taken out, and the medication Before it is absorbed into the body through the channels as shown in Figure 3, preparation is administered to the puncture site[14] once the punctured epidermis has developed microchannels. As the skin heals over many hours, the microchannels progressively close. This type of MN administration consists of two laborious stages, and it is impossible to determine exactly how many medications reach the body at any given time.[15] To find the ideal MN size in terms of efficient penetration and less intrusive drug administration, Howells et al. have described a straightforward single-step wet etch process for creating solid MNs of varied forms.

Coated microneedles

Coated MNs are MNs with surface drug loading. The medication is applied to the MNs' surface by coating, spraying, or dipping. The body absorbs the medication after dissolving when the needle is put into the skin as shown in Figure 4. This method is most appropriate for water-soluble medications since they have quick drug absorption, a high rate of usage, and simple dose control.[16] The application's reach is constrained to circumstances when the drug action is powerful and the amount of drug required is little, such as immunizations, and the amount of medication coated on the MNs is often microscopic. To increase MN arrays are covered with immunological polyelectrolyte multilayers to detect melanoma-specific T cells *in-vivo*.[17]

Hollow microneedle

The medication is already loaded into the hollow MN's body with a hole in the tip and pressurized using a syringe or micropump before being injected into the skin[18] as shown in Figure 5. Hollow MNs provide the biggest one-time infusion volume and most exact dosing of any type of MN, and the speed may be simple to modify (similar to injection). However, producing hollow MNs is expensive and has some drawbacks, such as the needle's pinhole being Skin tissue can readily prevent the needle wall's improper angle, and the needle's lack of physical strength, which causes the needle to shatter and stay in the skin after the inject.[19]

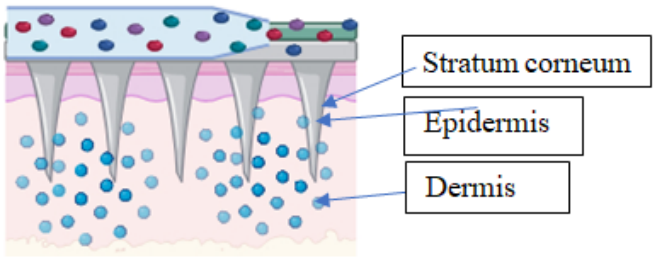

Figure 3: solid microneedle

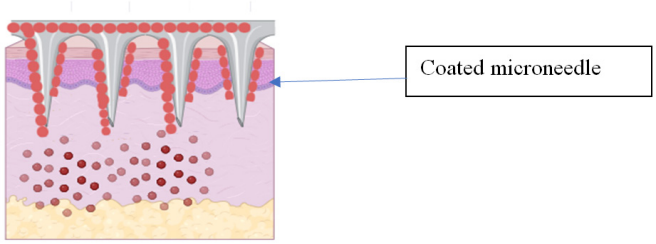

Figure 4: Coated microneedle

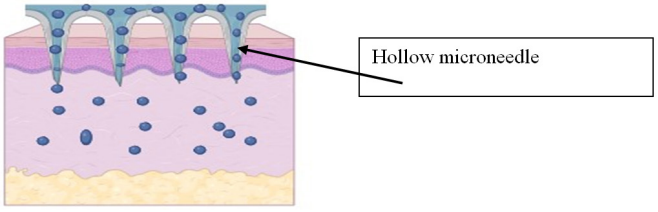

Figure 5: Hollow microneedle

Degradable and soluble microneedles

Currently, a lot of research is being done on soluble or biodegradable MNs. Biodegradable or water-soluble polymers can be used to create the MN body (Polylactide ethyl lactide, Polylactide, Polyglycolic Acid, Polycarbonate, etc.). Within minutes or hours of penetrating the skin, the needle body dissolves or disintegrates. The inside drug is subsequently released as the needle body separates from the substrate. Molecular nanoparticles (MNs) encase the molecules, as shown in Figure 6, may be either maintained or dissolved in the skin for bolus distribution without producing noxious, cutting medical waste.[20] By adopting the needle's body's material and form to the needs of the therapy, soluble MNs with various rates of degradation can be created. By modifying according to the necessary treatments, the material and form of the needle body, soluble MNs with various rates of degradation can be created. This procedure decreases the chance of cross-infection because they are not used frequently, and medical waste may be disposed of more readily because there is no sharps waste left over after usage.[21]

Swellable microneedle

A cross-linked hydrogel is used to create the relatively new form of MN known as swellable MNs, which may expand after absorbing interstitial fluid but do not break down (IF) as shown in Figure 7. The medicine can be pre-positioned at the base of this sort of hydrogel MNs or after the MNs have been pierced through the hydrogel's ability to absorb intercellular fluid and expand to form a gel channel on the skin.[22] The needle body and hydrogel MN substrate are both ready, which is the second—using a combination of pharmaceuticals and polymers. The fluid makes the needle enlarge after penetrating the skin, releasing the medication. Additionally, swellable MNs are used for more than simply medication delivery; they may also extract IF for more research.[23]

Porous microneedle

Due to their peculiar and special properties, porous MNs have recently received scientific attention. These MNs possess continuous nano- or micro-sized holes that allow capillary action to transport drugs or biofluids[24] as shown in Figure 8. Due to the abundance of pores, they are naturally brittle. Therefore, hard inorganic elements are needed to create porous MNs. Due to their difficult manufacturing method and simple fracture, porous MNs have thus gotten very little study in the past. In recent years, porous MNs have shown potential for drug and vaccine biosensing, administration, and ISF extraction.[25] The use of porous MNs for ISF analysis and medication distribution (penetration) has been effective because of their low-invasive partial stratum corneum cracking and associated micropores (extraction).[26]

MATERIALS USED IN MICRONEEDLE FORMULATION

Based on the patch's layout or components, different materials, such as metal or polymer, are employed in microneedles. In general, the materials used to make microneedles should be strong enough to penetrate the skin. Non-dissolving microneedles are powerful enough to be inserted beneath the skin without triggering an immune reaction because they are inert, biocompatible, and inert.[27] In contrast, the coating and dissolving microneedles' matrices ought to typically be both biocompatible and water-soluble. Moreover, it must dissolve or break down in the body without becoming poisonous. The adaptability of the matrices to medications is essential when creating, storing, and transporting microneedle patches.[28] The characteristics of many materials used to make microneedles are described below.

Metals used in microneedle formation

The characteristics of many materials are described in the paragraphs that follow in microneedles. Metal materials have a strong tensile and mechanical strength, which enables them to easily penetrate the skin. They are used to create solid, coated, and hollow microneedles. Generally speaking, titanium (Ti) and stainless steel are the two most common metals utilized in microneedles. Although stainless steel is the most popular metal for making microneedles, it corrodes more quickly than

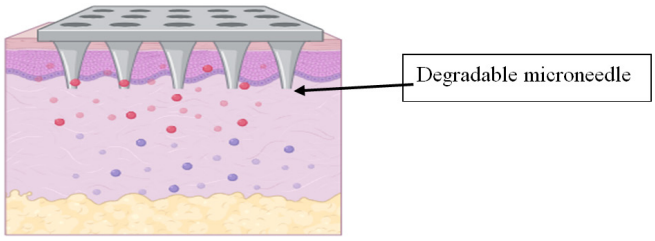

Figure 6: Degradable microneedle

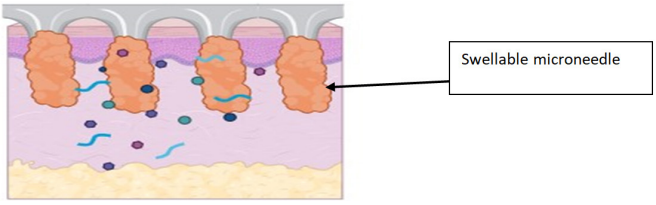

Figure 7: Swellable microneedle

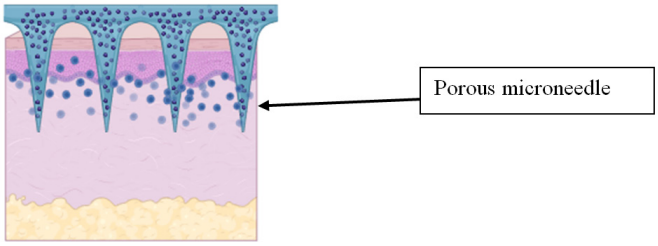

Figure 8: Porous microneedle

Ti alloy. While Ti alloys cost more than stainless steel, they offer stronger mechanical strength.[29] Silicon is frequently utilized to make solid and coated microneedles because it possesses the mechanical strength necessary for skin implantation. Using deep reactive ion etching and photolithography, silicon microneedles with small, sharp points and lengths of 100 m or less can be precisely made. However, the manufacturing speed is sluggish, the process is expensive, and the equipment required is expensive. When the silicon microneedle separates from the skin and pieces are left in the tissue, safety issues may arise. Recently, silicon has replaced solid microneedles in reverse master molds.[30]

Polymers used in Microneedles

Water-soluble, biocompatible, and mechanically sturdy polymers should be used to make microneedles that can be inserted into the skin. The most popular method for creating polymer microneedles is solvent casting. An inverse mold is created using the microneedle structure, which is then coated with a polymer formulation, allowed to cure, and peeled off.[31] The solvent-casting procedure produces dissolving or hydrogel microneedles using a variety of polymers, including hydroxypropyl methylcellulose, hyaluronic acid, polyvinyl pyrrolidone, and poly lactic-co-glycolic acid (PLGA).[32]

Ceramic in microneedle

Studies have looked into the use of ceramic materials for creating microneedles since they are biocompatible and offer enough mechanical strength. These materials include alumina, calcium phosphate, and calcium sulfate.[33]

Applications of Microneedle Transdermal Patches

The results are depicted in Figure 9.

Treatment of Diseases by Microneedle Transdermal Patches

Microneedle patches, an emerging device, are frequently considered good candidates for hypodermic injection, which is easy for patients to self-administer, painless, and safe. The main area of application for microneedles is still transdermal medication delivery for the treatment of diseases.

Skin functions as a robust barrier and a practical delivery system for bioactive compounds. It functions effectively in molecular diagnosis and therapy as a result. To enhance drug delivery and penetration, microneedles were frequently developed for medical purposes. Currently, microneedles are being utilized in several other fields, including immunological administration, disease diagnosis, and cosmetic applications.[34]

Diabetes

The patient's compliance is likely to decline with the complex and numerous daily injections. Additionally, there was a notable improvement in the risk of hypoglycemia due to frequent mealtime administration. To address these issues, insulin was delivered via glucose-responsive microneedle array patches, which effectively controlled blood glucose levels in type 1 diabetic patients. Using self-assembled artificial vesicles, the smart insulin patch provided a different way to treat diabetes quickly, painlessly, and safely. A type 2 diabetes treatment pH-responsive microneedle patch made of alginate. This dual mineralized peptide/protein nanoparticle-loaded patch was created to prevent fast loss without requiring numerous daily injections. For patients with type 2 diabetes, an alginate-based microneedle patch would be a good option to achieve easy administration.[35]

Cancer

Conventional treatment plans, such as radiotherapy, chemotherapy, and surgery, might cause acute toxicity, adverse effects, and tumor recurrence. Microneedle patches as a minimally invasive cancer treatment have always piqued curiosity due to their favorable controllability, ease of application, and strong synergistic effect. The potential approach allows for significantly lower volumes than intradermal injections, which further improves the immunogenicity and efficacy of tumor vaccine formulations' interference have emerged as a cutting-edge therapeutic strategy to target particular genes in the treatment of cancer. The microneedle array's effectiveness in delivering siRNA to the tumor site and preventing the activity that advances the tumor. The E6/E7 plasmid DNA in the dissolving microneedle patch is encapsulated by RALA peptide. In a therapeutic model, the microneedle platform can postpone tumor beginning and reduce tumor progression.

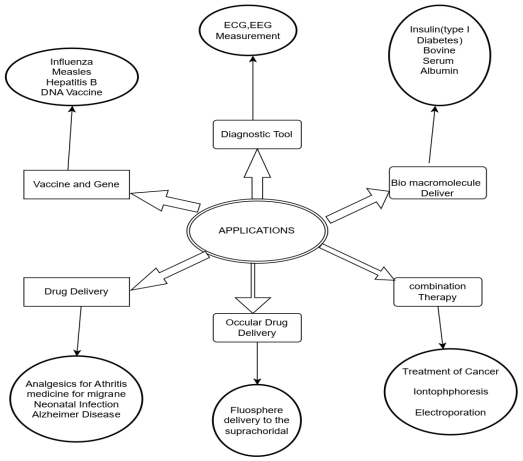

Figure 9: Applications of microneedle

Obesity

Adipose tissue comes in two varieties: white adipose tissue (WAT) and brown adipose tissue (BAT). BAT is essential for generating heat, which raises the body's energy consumption. Although the excess energy stored in WAT led to weight increase, the presence of free fatty acids and reactive oxygen species may worsen the illness. It has been observed that caffeine from tea or coffee has anti-obesity properties without being detrimental to people. Mice fed a high-fat diet and made obese can significantly lose weight when the microneedle-loading caffeine is dissolved. Caffeine has remarkable anti-obesity therapeutic effects by increasing the effectiveness of its transdermal administration.[36]

Alzheimer's disease

Despite having a low oral bioavailability, huperzine A (Hup A) is used to treat Alzheimer's disease (AD). The Hup A will be transdermal delivered using a dissolving microneedle patch (DMNP). Along with its *in-vitro* drug release patterns, its pharmacodynamics and *in-vivo* pharmacokinetics will be investigated. Skin penetration and intradermal dissolving test experiments showed that the blank DMNP could dissolve quickly in five minutes and penetrate the skin to an appropriate depth.[37]

Migraine

Migraine is a frequent neurological illness that reduces the quality of life and productivity. An ergot derivative called dihydroergotamine mesylate (DHE) is especially helpful in treating moderate-to-severe acute migraine episodes in patients who do not react to triptan derivatives. The disadvantages of the current DHE formulations in subcutaneous injection and nasal spray, such as discomfort, undesirable side effects, and low bioavailability, must be addressed with a novel approach to DHE delivery that enables painless self-administration, a quick start of action, and high bioavailability.[38]

Analgesic

The lidocaine-encapsulated microneedle integrated transdermal patch is a useful alternative to injections and passive transdermal systems for the treatment of both acute and chronic pain. The skin absorbs the lidocaine more quickly within 5 minutes after MITP application.[39]

Table 1: Available marketed formulations of microneedle transdermal patches

Brand Name	*Manufacturer*	*Description*	*Application*	*References*
Vaxmat	There jet Inc USA	Dissolved microneedle patch	It's used to deliver macromolecules, proteins, peptides, and vaccines.	[48]
Micro trans	Valeritas Inc USA	Dissolved microneedle patch	It delivers hundreds of micrograms of drug rapidly through the stratum corneum into the epidermal tissue	[49]
Drag Mat	There jet Inc USA	Dissolved microneedle patch	It delivers hundreds of micrograms of drug rapidly through the stratum corneum into the epidermal tissue.	[50]
Microinject	Nanopass Inc Israel	Intradermal microneedle patch	It's used with any standard syringe for the painless delivery of drugs, proteins, and vaccines.	[51]
Macro flux	Zosano Pharma Inc USA	Metallic microneedle arrays	Delivery of peptides and vaccine.	[52]
Microcore	Corium International Inc USA	Dissolved peptide microneedle patch	Deliver small as well as large molecules like protein and peptides and vaccines.	[53]

Neonatal infections

Severe infections in newborns are a major cause of mortality among young people in low- and middle-income countries, accounting for an estimated 26 to 36% of neonatal deaths globally. Safe, water-soluble, biodegradable, or biocompatible polymers are used to make dissolving microneedles, which act as a matrix to hold the medicament to be delivered. The encapsulated medication is released by microneedles when they break down after being inserted into the skin and coming into touch with the interstitial fluid of the skin. Numerous compounds, including low molecular weight (MW) medications, macromolecules, and vaccines, have been effectively administered via this MN system.[40]

In low-resource countries, neonatal infections are a major cause of childhood death. Guidelines from the World Health Organization (WHO) for the outpatient management of potentially severe bacterial infections (PSBIs) in neonates and early infants in cases when hospitalization is not a viable option. Intramuscular gentamicin (GEN) and oral amoxicillin are supplied in vials or ampoules and Health care professionals must have access to safe injectable supplies and know how to properly dispose of sharps. They must also be trained in dose calculation or choosing a suitable amount based on the patient's weight band. A streamlined solution that dissolves polymeric microneedle (MN) arrays to administer GEN transdermally for the outpatient treatment of serious infections in newborns.[41]

Vaccination

Transdermal immunization with biodegradable microneedles is a rapidly emerging field of study and application. The majority of people's main justification for not being vaccinated is that they are terrified of uncomfortable needles. Therefore, it has been essential to do research into developing an alternative, painless immunization method using microneedles. Microneedles, a collection of tiny needles, offer a painless method of dispersing active chemicals all over the skin. In addition to being painless, microneedles have several advantages over conventional immunization techniques, such as intramuscular and subcutaneous injections. Table 1 shows some of the marketed formulations of microneedle transdermal patches of vaccines.[42]

Hepatitis B

Vaccine stability and antigen persistence are somewhat limited in their shelf lives at high temperatures. Recombination of these formulations is a recently developed alternative vaccine administration method that can be used to extend life by needle injection for hepatitis B94.[43]

Cholera vaccine

Vaccine molecules can be transported more widely by using microneedle arrays as temporary conduits. The clinical response is better when cholera toxin is administered via microneedle rather than traditional intramuscular injection.[44]

Hormones and organic compounds

Complete penetration and dissolving duration are important factors to consider when using dissolving microneedles. Maltose microneedles may deliver monoclonal antibodies in one minute as opposed to a whole day when utilizing solid microneedles. Hormones and chemical compounds could also be administered in small doses *via* dissolving microneedles.[45]

Influenza virus

Inactivated influenza virus vaccine combined with biocompatible polymer microneedles improved vaccine immunogenicity; under the same circumstances, this was better than intramuscular injection. The above-mentioned techniques were 1000 times less successful than dissolving microneedles at the same dose for lung viral clearance.[46]

Diphtheria toxoid and tetanus toxoid

Using hollow microneedles to regulate the immune response, protein antigen nanoparticle vaccines were used to enhance vaccine efficacy. The findings indicated that intradermal injection of nanoparticle vaccines, in combination with hollow microneedle administration, is a highly effective way to boost cellular immune responses. The ability of the ceramic nonporous microneedle arrays to transfer tetanus and diphtheria toxoids is improved.[47]

RESULT AND DISCUSSION

Microneedle transdermal patches have been developed and deployed for delivering small or macromolecules during the

last few decades. As emphasized in this thorough review, recent research has shown that temporarily disrupting the skin microchannel lifespan improves the transdermal transport efficiency of tiny molecular medicines. Transdermal delivery of macromolecules, including therapeutic peptides and proteins, vaccines, and synergistic effect of combined enhancement in addition to microneedle treatment, were briefed. Moreover, MN mechanical tests and their characterization are explored in the literature. Since they were developed in the 1970s, microneedles have undergone continuous development. Glass and stainless steel are examples of well-established materials that have been used in the MN mechanism of drug administration to a variety of polysaccharides. A comprehensive comprehension and advancement in the microelectronics sector has rendered the fabrication procedure facile and economically viable. MNs have been produced using a variety of polymers. In this review, a framework for reviewing and debating the types, compositions, and configurations of microneedles—a novel and exciting technique to improve skin permeability for the treatment of diseases like diabetes, cancer, neonatal infections, and vaccination has been described. This study describes a framework for analyzing and discussing the many kinds, materials, and arrangements of microneedles—a cutting-edge and intriguing method of enhancing skin permeability.

CONCLUSION

Microneedle transdermal patches have been successfully used in the treatment of many diseases like cancer, diabetes, Alzheimer's disease, migraine and rheumatoid arthritis. The microneedle transdermal patches have the potential to offer prolonged immunity, dosage sparing, and improved protection against viral challenges. The epidermis and dermis are immunologically rich layers, and because of the needles' micron-size structure, these devices have shown to be significantly more effective at targeting these layers, indicating their potential utility in the creation of next-generation vaccines.. The microneedle patches are easy to use, painless, and non-invasive to treat infections in newborns and vaccination. It also enhances the bioavailability and is used for controlled release effects.

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