Microneedle: Recent Advancements In Transdermal Drug Delivery System

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Abstract

Due to its reduced invasiveness, low rejection rate, and remarkable ease of administration, transdermal drug delivery (TDD) has recently become a viable alternative to oral and injectable administration. The transdermal medication delivery method is a treatment strategy that is extraordinarily safe and well-tolerated and has enormous potential for delivering active ingredients against a variety of illnesses. However, because to the low skin permeability of the majority of active medicines in the formulation, its application is currently restricted in clinical settings. To get over this restriction, new strategies for skin permeation improvement techniques are offered. The drug delivery industry has undergone a revolution due to recent advances at the nano and microscale. A growing trend in drug delivery applications is the use of several kinds of microneedles (MNs), in particular because they are safe, compliant with patient preferences, and practical. Microneedles are a distinct, cutting-edge, and successful method created to administer medicinal chemicals and immunological components in a number of disorders. With appropriate examples and recent developments, various MN types—solid, hollow, coated, dissolving, and hydrogel forming—are described. We summarize recent developments in microneedles for therapeutic uses in this review.

Keywords: Transdermal Drug Delivery System, Microneedles, Recent Advancement, Microneedle patches, skin permeability.

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INTRODUCTION

The term "drug delivery system" (TDDS) refers to a group of physicochemical technologies that can regulate the distribution and release of pharmacologically active chemicals into cells, tissues, and organs so that they can exert their effects as effectively as possible. Different administration methods include oral administration, transdermal administration, lung inhalation, mucosal administration, and intravenous injection etc. Transdermal administration has the benefit of not causing pain or bleeding, being simple to administer oneself, requiring a low dosage, and having a high level of drug integrity, which significantly decreases the side effects associated with oral or injectable medications. TDDS administers the medication into the circulation slowly, avoiding the first-pass effect of the liver, improves the curative effect, and reduces the dosage frequency. TDDS is a painless method of systemic drug delivery that involves application of a drug formulation on to intact and healthy skin. To enhance the transdermal delivery of drug molecule using Microneedles have been widely used especially as a pre-treatment in which drug can diffuse through residual holes in skin from a topical formulation. Microneedles assist in faster healing at injection site as compared to that with a hypodermic needle with ease of administration. Advances in Microneedle research leads to the development of dissolvable/degradable and hollow Microneedles to deliver drugs at a higher dose and to engineer controlled drug release.

Continuous study is required to investigate various skin permeability-promoting methods in order to fully exploit the benefits of transdermal drug delivery systems (TDDS). To treat conditions including Obesity, Parkinson's disease, Diabetes6, analgesia7, Alzheimer's disease8, osteoporosis9, Hypertension10 and more. Phase III clinical studies for some microneedle-based medication delivery systems have begun. Microneedle based drug delivery systems are placed to the test because the clinical applicability of microneedles in immunization has not yet given promising results to gain acceptance as a potent substitute for hypodermic needles. Transdermal devices are used manage blood sugar levels for an extended period of time, improving patient compliance. Therefore, TDDS has been utilized to optimize diabetes management. Hormone replacement therapy (HRT), calcitonin, bisphosphonates (BPs), selective estrogen receptor modulators (SERMs), non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying antirheumatic drugs (DMARDs) are some of the treatments for skeletal disorders that are currently offered in clinics. Despite the fact that these treatments are known for their therapeutic benefit but also for their side effects. At the moment, drug delivery against many bone disorders also uses the TDDS. Patients are unlikely to experience intense
pain during the operation because microneedles formulated as TDDS are only intended to pierce the cornified layer and the viable epidermis, not nerve endings or blood vessels. New microneedle delivery devices have revolutionized medication administration methods and have a bright future in therapeutic settings. This review emphasizes on the need of transdermal drug delivery system, different methods for promotion of permeations, recent advancements and future anticipation.

Need for transdermal drug delivery system: -
The function of the skin, which has multiple layers and is the body's outermost organ, is to protect us from the outside world by shielding us from poisons, heat, and chemicals. Each layer of skin has components that obstruct transdermal delivery, including the epidermis, which serves as a barrier, and the dermis, which houses blood vessels and generates skin cells. When it comes to the movement of compounds with high molecular weights, the barrier effect is crucial. It is widely acknowledged that in TDDS, the intracellular pathway is used for the delivery of drugs with tiny molecular weights. However, approaches and other mechanisms using the intracellular pathway in addition to the intercellular pathway are introduced and applied for compounds with a high molecular weight. Due to the way the skin is built, the portion known as lipid, which contains both cells and hydrophilic and hydrophobic chemicals, does not have a totally normal position but instead exists with some irregularity’s consistency. The concepts of physicochemical properties, which aim to improve medication administration through the skin, can explain these structural characteristics. The dermal layer's vascular system can next prevent transdermal delivery. A superficial arteriovenous plexus near the dermis has an endothelial layer on cell thick terminating in papillary loops. The interface between the tissues surrounding the skin and the human vasculature is represented by the epidermal junction in the upper dermis. In order to transfer the medicine to the skin tissue and pass through cellular and vascular tissue to reach the target tissue, the stratum corneum's barrier effect must be overcome. Only a tiny amount of the medicine can be given via the skin tissue, which is a difficulty. Novel TDDS solutions have been developed extensively to address this issue and have become popular administrative approaches. In terms of administered dose, cost-effectiveness, and therapeutic efficiency, such advancement could additionally provide a competitive edge over alternative drug administration strategies.

Techniques for the promotion of skin permeability of drugs: In order to increase the permeability of medications in the skin, transdermal drug delivery technology (TDDT) is the subject of research. Many studies on TDDS are now being conducted, and they employ various techniques to increase the skin's permeability and facilitate the delivery of medicines into the dermis. Passive enhancement and active augmentation make up the bulk of it.

1. Active delivery: -
   • Magnetophoresis: - It utilize magnetic field to promote entry of drug into the skin. The fundamental idea may be that the driving force's magnetic field can improve the distribution of molecules in the SC. The outcome demonstrated that the magnetic field may efficiently improve lidocaine hydrochloride's penetration into pig skin.
   • Iontophoresis: - Less than 0.5 mA/cm2 of externally applied potential difference causes it to encourage the passage of ions across the membrane, which has been shown to improve skin penetration and improve the rate of release of a number of medications with subpar absorption/permeation profiles. By using an electrochemical potential gradient, this method has been applied to the in vivo transport of ionic or non-ionic pharmaceuticals.
   • Electroporation: - It is a technique to immediately increase the permeability of the cell membrane by a strong electric field. The transient water pores on the cell membrane brought on by pulsed electric field may be the reason of the increased permeability. Proteins and nucleotides can be delivered by electroporation, which has also been utilized to deliver medications like fentanyl and insulin. The treatment of cancer, infectious disorders, and vaccinations all have a lot of potential for electroporation.
   • Ultrasound: - By using ultrasonography, drugs can be administered locally or systemically through the skin. The cavitation action creates holes in the skin, increasing tissue permeability, which is the primary mechanism of SC ultrasonic penetration. High frequency ultrasound (HFS) introduction and low frequency ultrasound (LFS) introduction are two current ultrasound applications and research areas (0.7–16 MHz). LFS can more effectively improve the penetration of medicinal molecules because it is discovered that the cavitation impact is inversely proportional to the ultrasonic frequency. The expansion of ultrasound's clinical applications depends heavily on the improvement of skin penetration effectiveness and the portability of ultrasound equipment.
   • Microneedles: - Drugs are given to the circulatory system by a needle in the innovative medication delivery technology known as the microneedle drug delivery system. This is among the most widely used strategies for transdermal medication delivery, and research is ongoing in this area. This technique uses micron-sized needles to puncture the epidermal layer of the skin with the goal of causing medication diffusion. Numerous studies have been conducted on the manufacture of microneedle systems while taking the goal, drug kind and dosage, and use targets into account. The prepared microneedles could be of various types, including solid microneedles that merely create a physical pathway through which drugs can be absorbed, drug-coated microneedles that facilitate delivery of drugs coated on the surfaces of the needles as they enter the skin.
dissolving microneedles made of drug formulations that dissolve in the body, and naturally delivered melting needles that involve drug storage in hollow needles followed by administration (such as those used in the delivery of insulin).14

2. Passive delivery: -
   - Transfersomes: - The edge activator makes transfersome have significant flexibility and deformability, which can be transmitted between cells. Notably, occlusive circumstances impede skin penetration of transfersomes.14
   - Liposomes: - They can simultaneously encapsulate hydrophilic and lipophilic compounds, are non-toxic, and have good biodegradability. Acne and other skin conditions have been successfully treated with liposomes.16
   - Niosomes: - Another new vesicle in recent years is the niosome, which is made of cholesterol and nonionic surfactants such polyoxyethylene alkyl ethers. Cholesterol and nonionic surfactants alter the structure of SC, making it more supple and permeable.17
   - Ethosomes: - Ethosomes have a larger amount of ethanol (20–50%) than regular liposome components. Alcohol can make cell membranes more fluid, kill SC, and enhance the function of drug delivery systems (DDS). Both hydrophilic and lipophilic medicines can be carried by ethosomes, and they can also be delivered in occlusive environments.14
   - Glycerosomes: - Glycerol has a similar effect as edge activator in that it makes the system more elastic and deformable and makes it easier for the system to penetrate the skin.14
   - Lipid nanoparticles: - Mechanism is still under study. The longevity of drug release, along with their excellent biodegradability, compatibility, low toxicity, and low cost of production, are what lipid nanoparticles are best known.
   - Polymeric nanoparticles: - It can create gradients in drug concentration to encourage drug penetration. Polymeric nanoparticles have also been demonstrated to gather in hair follicles and enter the epidermis through hair follicles. The most popular positively charged natural polymer, chitosan is well soluble in water and has strong bio adhesive qualities.18
   - Metal nanoparticles: - TDDS can also be created from nanoparticles made of metal oxides, titanium, silver, gold, and zinc. These tiny nanoparticles, which often contain drug compounds in their cores, have the capacity to passively permeate SC. As TDDS, you can also utilize nanoparticles made from metal oxides, titanium, silver, gold, and zinc. These tiny nanoparticles, whose centres are often coated with drug molecules, have the capacity to passively penetrate SC.19

Recent approaches in Transdermal drug delivery system and beyond: -
- Why microneedles over the other methods?
Then, somewhere in the 1970s, the concept of MNs was put forth and used for the first time as innovative drug delivery systems. Since then, other research has been conducted using outdated technical tools for analysing vaccines and medications for a range of viral illnesses and ailments such as cancer. MNs are straightforward, simple to use, non-invasive, and quicker healing effects that can be used in place of hypodermic microscopic needles for precise, localized, painless distribution in the layers of the dermis and subcutaneous fat of vaccine, medication, and gene. MNs, as their name suggests, are patches of micro-sized needles that are intended to deliver therapeutic drugs transcutaneously to the desired tumor site. In other words, it consists of a number of hypodermic needles combined with many smaller ones that can be applied trans dermally for self-administration.20

Types of microneedles: -
Wide range of materials, such as polymer, ceramics, stainless steel, silicon, metal, glass, titanium, and sugar, are used in the design of MNs.21 These are categorized as solid MNs, hollow MNs, dissolving MNs, coated MNs, and hydrogel-forming MNs based on the method of drug administration.22
- Solid microneedles: - The solid MNs work by entering the skin and forming channels that allow the formulation to penetrate the dermis, which contains dendritic or antigen-presenting cells, without passing through the stratum corneum layer (APC). Through the process of passive diffusion, these MNs can carry medication or vaccine formulation, which is then absorbed into the capillaries to provide systemic effects.23 Solid silicon microneedles with the following measurements were created for optimal transdermal drug delivery.24 A seminal study that sugar mix solutions in a vacuum at a low temperature might be used to manufacture sugar glass microneedles. The microneedles had a hard enough structural design to efficiently pierce human skin.25 Microneedles have been made for therapeutic applications from a range of materials, including metals, silicone, glass, non-biodegradable polymers, and biodegradable polymers.25.
- Coated microneedles: - As the name implies, coated MNs entail dosing the MNs with a medication suspension or vaccination solution. Drugs that can generate a significant immune response at low dosages are loaded for administration via coated MNs since the quantified amount of medication that can be loaded over the MNs is dependent on the coating solution’s thickness. Another study found that utilizing particular coating techniques to confine coatings to microneedle shafts only resulted in increased medication
delivery efficiency and decreased drug waste. Utilizing a hydrophobic covering material helps microneedles disengage from the skin when they are placed and come into contact with interstitial fluids. Coated microneedles are explored for delivery of multiple drugs through the same formulation. One research has done in which the microneedles has been coated with various formulations and agents does allowing co delivery of multiple drug with varied properties.

- Hollow microneedles: Unlike the first two, hollow needles have a hollow core and a hole at the tip that allows the drug to be released. Although the two delivery methods are different, pre-existing vaccine formulation can be directly put into MNs in a smaller quantity without the need for additional processing since the action of drug release in MNs is relatively comparable to that of hypodermic needles. These needles can be used to provide hefty amounts of medication or substances with high molecular weights. Hollow microneedles give medications a precise pathway to travel through in order to reach the skin or other tissues. Similar to hypodermic needles, the hollow microneedles help with the pressurized, customizable delivery of medications in liquid form. Only hollow MNs have made it to the medical device market, despite years of development and a variety of MN forms. If the microneedle bore increases than the flow rate increases but at the same time it reduces the strength and sharpness. So, sometimes a metal coat is applied to increase the strength of microneedle but again this can make the needles sharp. The creation of porous ceramic microneedles that can administer medications under room temperature has advanced over the past few decades.

- Dissolvable and swellable microneedles: At the fabrication stage, the medicine that will be delivered is trapped inside the needle. The polymer used to create the needle's architecture degrades once it has pierced the stratum corneum, releasing the medicine it was holding. The advantage of making microneedles dissolve under the skin is that it significantly lowers the possibility of post-application needlestick injuries. The structure of swellable microneedle patches is based on a hydrogel, whose hydrophilic nature efficiently draws moisture from surrounding tissue, causing the microneedle core to enlarge and create pores into which the medicinal chemicals can diffuse. The key advantage of this method is the ability to convey the underlying micro circulation across the inflamed microneedle structure by using the base plate as a drug reservoir.

Material employed in microneedle for current technological applications: -

<table>
<thead>
<tr>
<th>Material used</th>
<th>Type of microneedle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronic acid</td>
<td>PH responsive</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>Swelling-shrinking</td>
</tr>
<tr>
<td>Alginate</td>
<td>Multi-round responsive</td>
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<tr>
<td>Dextrin</td>
<td>Water soluble</td>
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Brief information on microneedles: -

1. Properties of microneedle: Avoid first pass metabolism is one of the characteristics of microneedles. Customizable medication delivery and mechanically robust administration without pain.

2. Method of manufacturing of microneedles are: -
   - Solvent casting
   - Laser avlation
   - Wet etching
   - Photo lithography
   - Pulling pipettes
   - Laser cutting
   - Two photon polymerizations
   - Micro molding

3. Different techniques of coating: -
   - Gas jet drying
   - Spray coating
   - Deep coating
   - Electrohydro dynamic atomization
   - Inject printing – piezoelectric inject printing

Mechanism of microneedle for drug delivery: -

The main method of drug delivery using MNs relies on rupturing the skin barrier, which allows medicines to be released into the higher dermis layer for systemic absorption. In the poke and flow method, medication release from hollow needles is accomplished through passive or active diffusion (under any type of external pressure). Coated MNs that work via the coat-and-poke approach penetrate the skin's surface before releasing a coated medication formulation based on moisture. Last but not least, the poke and release method of dissolving MNs entails complete MN disintegration followed by medication release.
Applications of microneedle technology: -

• Immuno therapies: - Immune-based approaches frequently look at how vaccines are administered to the skin, the body's main immunological organ and a location where antigen-presenting cells (APCs) like dendritic cells, macrophages, and Langerhans cells are abundant. These APCs have the ability to trigger a systemic immune response against tumors by activating CD4+ and CD8+ T and B cells. In order to administer a combination of hyaluronic acid (HA) and antigenic peptides for preventative cancer immunotherapy, a biodegradable microneedle patch was created. To successfully deliver the antigen trans dermally, HA was coupled with the cytotoxic T-cell epitope peptide (SIINFEKL). This peptide was then added to a biodegradable HA microneedle patch. As a result, they found that exhibiting a long-term residence of more than 24 hours after delivery, that the HA-SIINFEKL conjugates placed into microneedles were located close to the site of administration of the microneedles. After only one transdermal microneedle patch immunization with HA-SIINFEKL conjugates, tumor formation in B16 melanoma model mice was dramatically reduced thanks to increased cytotoxic T-cell antigen-specific responses. The microneedles are made up of glucose oxidase (GOx), which converts blood glucose into gluconic acid, and biocompatible HA-containing aPD1-encapsulating dextran nanoparticles. The resulting low pH environment encourages nanoparticle self-dissociation and results in the large release of aPD1. Using dissolvable microneedles, DNA can be easily transferred to APCs in the skin. Distribution platforms that use DNA delivery vectors and microneedle systems function better, but the issue of increasing load capacity still exists. Another study investigated the transdermal administration of human IgG using in vitro microneedles as a model protein to deliver a monoclonal antibody. Studies using the immunohistochemical technique (IHC) have shown how IgG is transported across the skin. This study verified that when microneedle arrays, microneedle concentration, and microneedle length increased, so did the delivery of human IgG.

• Diabetes: - After being injected into the skin for around five minutes, microneedles totally disintegrate, quickly delivering their loaded contents into the skin. In one study, diabetic rats were given insulin-loaded microneedles to test the viability of dissolvable microneedles for the treatment of diabetes. Insulin's estimated 92% pharmacological availability and bioavailability demonstrates that it retains its pharmacological effectiveness even after being freed from the dissolving microneedles. The study showed that an increase in insulin permeability of the skin following the application of microneedle rollers was responsible for the quick fall in blood glucose levels in 1 h that was also directly associated with recovery. The study found that microneedle rollers 500 m or shorter are safe and efficient for in vivo transdermal insulin administration. For the transdermal administration of insulin to rats, authors developed novel hyaluronic acid (HA)-fabricated, insulin-loaded microneedle arrays. The self-dissolving, insulin-encapsulated HA microneedles stimulate a fast release of insulin upon cutaneous therapy. The insulin given by HA microneedles was efficiently absorbed from the skin into the bloodstream, according to pharmacokinetic and pharmacodynamic results. Additionally, the hypoglycemic effect brought on by the injection of subcutaneous insulin was nearly identical to that produced by the insulin-charged microneedles. The evidence points to the insulin-charged microneedles constructed of HA as a significant alternative method of delivering insulin to the blood circulation through the skin without running the risk of serious skin damage. Insulin penetration concentrations from these nanovesicles were powered by iontophoresis by skin-induced microchannels created by microneedles. A mechanism for delivering insulin that is both glucose- and hydrogen peroxide-responsive was created. PVs with transdermal microneedle patches shown outstanding biocompatibility ease of use in the administration. Effective drug release was achieved by the polymeric vesicles. Insulin and glucose oxidase (GOx) encapsulation in response to hyperglycemia. The quick response of the insulin release rate to elevated glucose levels may be further boosted exacerbated by GOx and produced hypoglycemia that was comparable to that caused by a subcutaneous injection or merely microneedles with an insulin charge. Therefore, transdermal insulin delivered by microneedles could be extremely beneficial for diabetic treatment. Using a double-layer, bullet-shaped microneedle array of water-swelling tips, novel method for the transdermal delivery of proteins medicines was developed. The swollen tips were treated with insulin using a gentle drop/dry procedure. In vivo, swellable microneedle patches' sustained release of insulin caused blood glucose levels to gradually drop.

• Occular microneedle delivery: - The majority of eye disorders are treated using eye drops or eye ointments, but these methods have a number of drawbacks, including frequent administration, low bioavailability, and inability to pass through different ocular barriers. Microneedles are an alternative new delivery technique that seeks to offer therapies with positive health outcomes for a range of eye ailments. Microneedles administer medications to the eye in a localized, efficient, less intrusive, and targeted manner thanks to advancements in pharmaceutical technology. For the treatment of numerous post-segment eye diseases, improved medication delivery targeting to the posterior part of the eye is essential. Microneedle iontophoresis in the suprachoroidal space (SCS) holds the potential to deliver eye medications specifically to the posterior pole of the eye. In a different investigation, experts used a method that involved fitting an eye patch with detachable
microneedle arrays that contained micro reservoirs for controlled ocular drug administration. The transmission of anti-angiogenic monoclonal antibody (DC101) to such an eye patch, according to the researchers, causes a reduction of almost 90% in the neovascular region in a corneal neovascularization disease model. Contrarily, a synergistic therapeutic benefit is provided by the fast release of the anti-inflammatory drug diclofenac followed by the extended release of DC101.

- Viral infection: - Patches of microneedles are becoming a more and more viable alternative delivery mechanism for vaccines. Using TheraJect microneedles, a seasonal influenza vaccine was created between 2007 and 2008. (VaxMat). The tips of the microneedles had antigens imbedded in them that were combined with trehalose and sodium carboxymethyl cellulose. To confirm the stability of the generated antigen in microneedles, the patches containing 15 g of each flu antigen strain were routinely analysed. Due to excipient presence and very low vaccine concentration on the microneedle plates, standard radial immuno-diffusion study could no longer be used to identify the samples. Additionally, innovative approaches like the capture of antigens in microneedle-patches, enzyme-linked tests, and enzyme digestion combined with mass testing were used. Monovalent H1N1 vaccine immunogenicity in mice at doses of 0.1 and 1 g. After microneedle treatment the preliminary findings from the mice studies are promising and show that the delivery of influenza vaccinations using microneedle technology is possible.

- Bacterial infection: - Dissolvable polymeric microneedles (DPMNs) are innovative transdermal drug delivery systems that are less invasive and have higher patient compliance. In order to fabricate microneedles, a little amount of graphene oxide (GO) is included into biocompatible polymers, which produces significant new DPMN characteristics. Significantly improved mechanical strength, better moisture tolerance, anti-inflammatory and antibacterial qualities, self-sterilization, and controllers activated by near-infrared light are a few of these qualities. These new characteristics improve the efficacy and simplicity of transdermal products, improve drug release monitoring, broaden the range of polymers that can be used in the production of DPMN, prevent microbial contamination during storage and transport, and reduce the risk of infection in clinical applications. Chitosan, a substance frequently used for wound healing, was shown to have numerous beneficial properties, including an innate antibacterial characteristic. The authors created a patch with a clever, thermo responsive drug delivery system using chitosan microneedle biomass (CSMA) to speed up wound healing suggested using bacteria-sensitive nanoparticles (NPs) made from poly(lactic-co-glycolic acid), poly(caprolactone), and chitosan to create dissolvable DOX microneedles in order to improve biofilm penetration and, more specifically, the distribution of DOX to the injection site. The dermatokinetic profiles of DOX were dramatically improved by increased retention periods when these NPs were integrated into microneedles as compared to needle-free patches.

- Microneedles for cancer therapy:
  - For breast cancer: - It starts in the breast tissues and spreads to the mammary gland ducts or the lobules that supply the ducts. If found early enough, it is a treatable kind of cancer, but if not treated, the tumor spreads to other organs and becomes fatal. Drug/vaccine laden microneedles can be used to deliver treatments into the skin for tumor-targeted activity in the treatment of cancer.
  - For prostate cancer: - The most frequent non-skin malignant cancer kind and the second most prevalent cancer in men, behind lung cancer, is prostate cancer. Genetic, environmental, and hormonal abnormalities that lead to chronic inflammation are the primary causes of tumours.

In a different study, Cole and colleagues developed a twotier delivery system that delivers DNA vaccines for the treatment of prostate cancer using cationic RALA/pDNA nanoparticles packaged in a dissolvable MNs patch. This study is the first to describe the utilization of a RALA/pPSCA combination to immunise mice with encoded prostate stem cell antigen (mPSCA). The prostate stem cell antigen (PSCA) and NP-MN conjugate were put to the test for their capacity to complex. A tumor-specific immune response was also displayed by this conjugate structure, and it suppressed the growth of TRAMP C-1 prostate tumours ex vivo, demonstrating the value of the MN delivery method for the treatment of prostate cancer.
For cervical cancer: - Recently, researchers have suggested using the lyophilization approach to increase the RALA/pDNA nanoparticles' loading capacity in the patch made of soluble polyvinyl pyrrolidine. Studies conducted in vivo showed that MNs permitted the delivery of over 50 g of pDNA per patch, which is a considerable increase above previously administered amount. Importantly, this study found that altering the manufacturing process did not significantly alter the mechanical characteristics or functionality of MNs. Additionally, in vivo testing employing female mice to assess the effectiveness of MNs revealed good tumour suppression, an improved humoral response, and improved anti-cancer activity. In general, the study suggested an unique construction method to boost delivery rate via MNs, which also demonstrated to be a better method than the conventional i.m. injection.46

LIMITATIONS: -

- The bacterium that penetrates through microchannels created during MNs' "poke and patch" method causes infections or skin response.47
- MNs are typically constructed of non-irritating materials, although MNs made of ceramic or glass have been linked to irritation-related contact dermatitis, erythema, hyperpigmentation, and inflammation at the site of application.48 Similar to this, MNs manufactured of silicon or any metallic material frequently exhibit problems with biocompatibility and toxicity.49
- MNs continue to struggle with a low dosage carrying capacity. MNs should only be used for chemotherapy when the drug is particularly effective at low doses. However, changes are being used to transport small/large therapeutic molecules (drug/protein) directly into the systemic circulation, such as hydrogel-forming MNs and hollow or dissolving MNs.49
- The application of multiple patches of microneedle within a given area may leads to the skin infection, rashes, lesions, irritation and many more.
- The requirement of good biocompatible material is the must. Hence, it could be the limitation for the microneedle drug delivery.
- The limited amount of drug is only loaded via microneedle drug delivery system.
- There is a major task to allow the penetration of hydrophilic drug via skin.
- The use of the microneedle device should be done with ultimate care to avoid the bouncing off the skin surface.
- As the thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too accordingly.
- The external environment such as hydration of the skin could also affect the delivery of the drug.
- The repetitive injection may results to the collapsing of the veins.
- The tip of the microneedle may break off and remain within the skin on removal of the patch.
- Through the Transdermal Drug Delivery System drug cannot achieve the high concentration in the blood.

FUTURE ANTICIPATION: -

Drugs can be administered through the skin to the systemic circulation using a variety of devices and TDDSs. Through TDDS, medications are typically reliably and safely supplied, and they remain secure from biochemical alterations until they reach the intended tissue. As evidenced by a surge in research papers, patent applications, and commercially accessible products from numerous companies and research institutes in recent years, TDDS has grown in scope both domestically and internationally.50 The limits of the current easy application type and patch type needles are supplemented by the advantages of microneedles, which combine to produce higher treatment efficacy and effects. In addition, microneedles are gaining significant interest even among TDDS modalities. To do this, production and commercialization techniques are being created with the careful application of cutting-edge technology like 3D & 4D bioprinting. The advancement in various formulation and micro fabrication techniques are currently being focused to aid the delivery of protein drugs via Microneedles. Microneedle-based micro devices promise to expand the scope for delivery of vaccines and therapeutic agents through the skin and withdrawing bio fluids for point of care diagnostics so called Theranostics. Further development may also make advantage of microneedle technologies. Scientists are developing numerous technologies to deliver the drug through the skin. There are various alterations and modifications has been investigated in the conventional microneedles. Focus group assessments identify key areas that the Microneedles Ideology must research in order to advance the technology. This guarantees that reproducible microneedles are used by all patients and that successful insertion is confirmed. Clinical trials for a significant number of small and large industrial participants' respective microneedle-based devices are now being conducted. The methods planned and developed to assure low-cost, dependable means of mass-producing microneedles will be examined in future research along with potential regulatory difficulties involving the employment of microneedle devices. With the essential modern knowledge feed industry growing quickly, the market for microneedles overall appears to have a very bright future. In due course, it is envisaged that technological advancements based on microneedles would help improve disease detection, diagnosis, and management while also raising the standard of living for patients around the world in terms of their health. The emerging technology is flexible enough and can be used to administer some
hundreds of milligrams of protein, which go directly into the systemic circulation.49 Transdermal Drug Delivery System along with ultrasound is also studied in order to further elevate the drug permeability. Therefore, microneedles can be fabricated with a variety of modifications in order to smartly deliver the drug via the skin which provides a novel direction and revolution the field of TDDS.

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