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A Review on Microneedles Patches Transdermal Drug Delivery System

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Abstract: *A revolutionary approach transdermal drug delivery has emerged as a viable alternative to traditional oral and injectable routes, offering improved patient compliance and reduces side effects. Microneedle patches have garnered significant attention in recent years as a primising technology for transdermal drug delivery. these microscopic needle arrays create micro- channels in the skin, enabling the delivery of therapeutics, including small molecules, peptides, proteins. Recent studies have demonstrated the efficacy of microneedle patches in delivering various therapeutics, including vaccines, hormones, and painkillers. The patches have shown improved bioavailability, reduced dosing frequency, and enhanced therapeutic outcomes. Additionally, microneedle patches have been found to be safe and well-tolerated, with minimal skin irritation and no significant adverse effects. Despite the promising results, challenges persist, including scalability, cost-effectiveness, and regulatory hurdles. Ongoing research aims to address these limitations, exploring new materials, designs, and manufacturing processes. The development of microneedle patches for transdermal drug delivery has the potential to transform the pharmaceutical industry, offering improved treatment outcomes, enhanced patient compliance, and reduced healthcare costs.*

Keywords: Microneedle patches, Transdermal drug delivery, Bioavailability , Targeted delivery, Patient compliance

I. INTRODUCTION

For a long time, oral administration has been considered as most popular route for drug delivery due to its convenience, lack of invasiveness and possibility of self-administration However, the drug administered orally can be extensively degraded in the liver or GI tract before reaching to systemic circulation. The transdermal route of drug delivery offers an attractive, non-invasive route of drug administration. Drugs administered through the transdermal route show high bioavailability avoiding gastrointestinal degradation and first-pass metabolism .Transdermal drug delivery using microneedles is increasingly gaining interest due to the issues associated with oral drug delivery routes. Gastrointestinal route exposes the drug to acid and enzymes present in the stomach, leading to denaturation of the compound and resulting in poor bioavailability. Microneedle transdermal drug delivery addresses the problems linked to oral delivery and to relieves the discomfort of patients associated with injections to increase patient compliance. The success of transdermal drug delivery has been severely limited by the inability of most drugs to enter the skin at therapeutically useful rates. Recently, the use of micron-scale needles in increasing skin permeability has been proposed and shown to dramatically increase transdermal delivery, especially for macromolecules. Using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials. Most drug delivery studies have emphasized solid microneedles, which have been shown to increase skin permeability to a broad range of molecules and nanoparticles in vitro. In vivo studies have demonstrated delivery of oligonucleotides, reduction of blood glucose level by insulin, and induction of immune responses from protein and DNA vaccines. For these studies, needle arrays have been used to pierce holes into skin to increase transport by diffusion or iontophoresis or as drug carriers that release drug into the skin from a microneedle surface coating. Hollow microneedles have also been developed and shown to microinject insulin to diabetic rats. To address practical applications of microneedles, the ratio of microneedle

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fracture force to skin insertion force (i.e. margin of safety) was found to be optimal for needles with small tip radius and large wall thickness. Microneedles inserted into the skin of human subjects were reported as painless. Together, these results suggest that microneedles represent a promising technology to deliver therapeutic compounds into the skin for a range of possible applications.

HISTOLOGY OF SKIN

The skin acts as a vital barrier, controlling the two-way movement of nutrients, water, and ions while shielding the body from harmful substances and physical harm. Structural details of human skin. The skin is composed of three distinct layers: the epidermis, dermis and hypodermis. The epidermis provides a barrier to pathogen invasion and regulates the amount of water released from the body. The dermis is tightly connected to the epidermis by the basement membrane; the dermis primarily consists of extracellular matrix, which is produced by fibroblasts. The dermis can be separated into two distinct layers, the superficial layer adjacent to the epidermis (papillary dermis) and a thicker layer below (reticular dermis). It also contains mechanoreceptors, thermoreceptors, hair follicles, sweat glands, sebaceous glands, lymphatic vessels, nerves and blood vessels. Those blood vessels provide nutrients and waste removal for both dermal and epidermal compartment

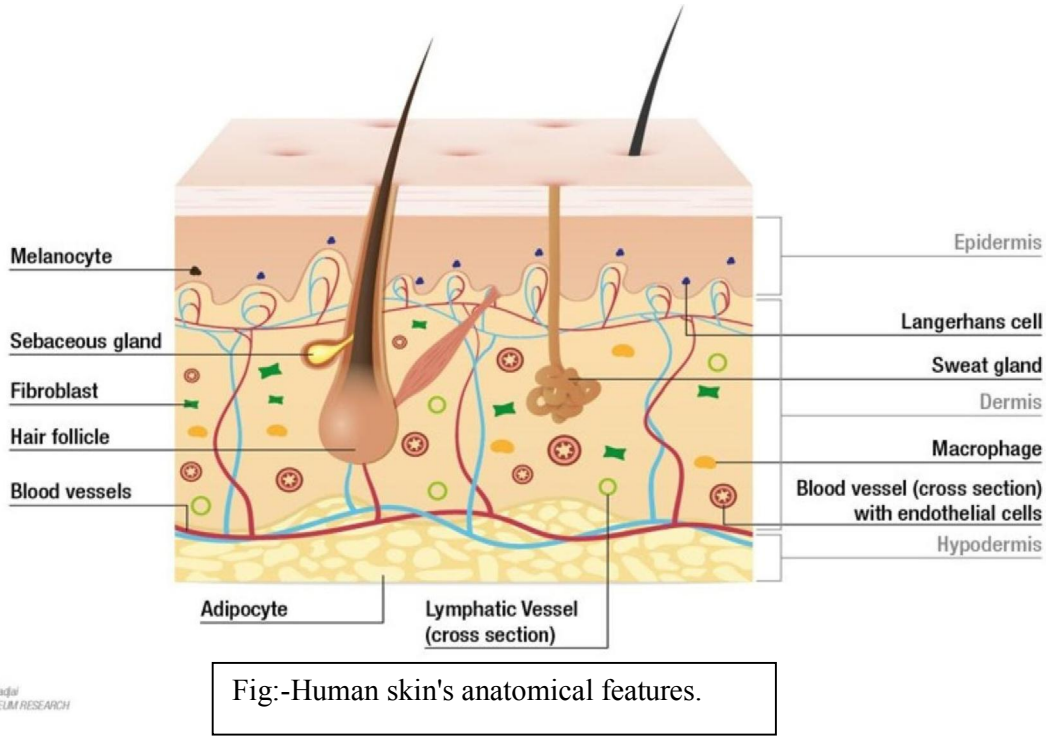

Fig:-Human skin's anatomical features.

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Epidermis:-

The topmost layer that communicates with the environment is the epidermis. It establishes a powerful defense against infections, poisons, and dehydration. The epidermal thickness varies from paper-thin (30 µm on the eyelids) to up to 600 µm in places that require extra resilience, such the palms and soles.

Basement Membrane:-

The exchange of oxygen, nutrients and waste molecules is controlled bi-directionally by a semipermeable sheet of extra cellular matrix proteins (ECM), the basement membrane. This basement membrane compartmentalizes the skin, yet holds epidermis and dermis together.

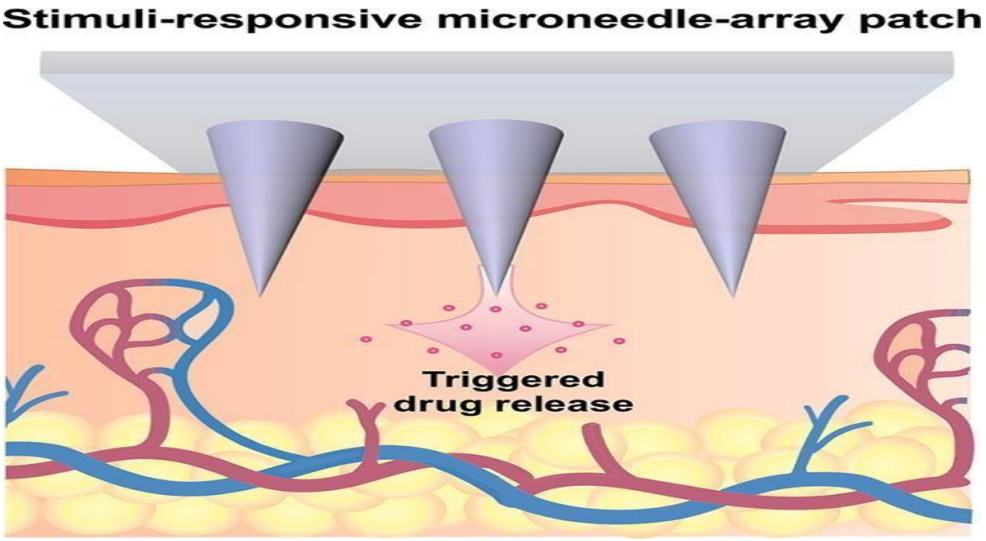
Dermis:-

The thickness of the dermis depends on its location and may vary between 2 mm and 6 mm Its primary role is thermoregulation through regulation of the blood supply and aspiration, to provide oxygen rich blood to the epidermis and to remove epidermal waste products

Hypodermis:-

The hypodermis, also known as the subcutis or subcutaneous layer, anchors the dermis to the underlying muscles and bones. It is a well-vascularized, loosely textured tissue that contains larger nerves and blood vessels, connective tissue and, most importantly, white adipose tissue [44]. Besides fibroblasts, the hypodermis harbors adipocytes and the so-called stromal-vascular cell fraction consisting of mesenchymal stem cells “preadipocytes”, endothelial cells, pericytes, T cells, and macrophages. The fat is stored in the form of large lipid droplets inside mature adipocytes and functions as an energy reserve for the body and provides insulation against cold or heat and physical protection.

MECHANISM OF MICRONEEDLES



The mechanism for MN delivery is based on the temporary disruption of the skin and the placement of MN in the epidermis or upper dermis layer by penetrating the stratum corneum barrier from where the drugs can reach its site of action . In the case of polymeric MN, biodegradable polymers are used to fabricate MN in which the drugs are encapsulated within the polymer matrix. When these MNs insert into the skin, the polymers are dissolved, degraded, or swelled to release the drugs.

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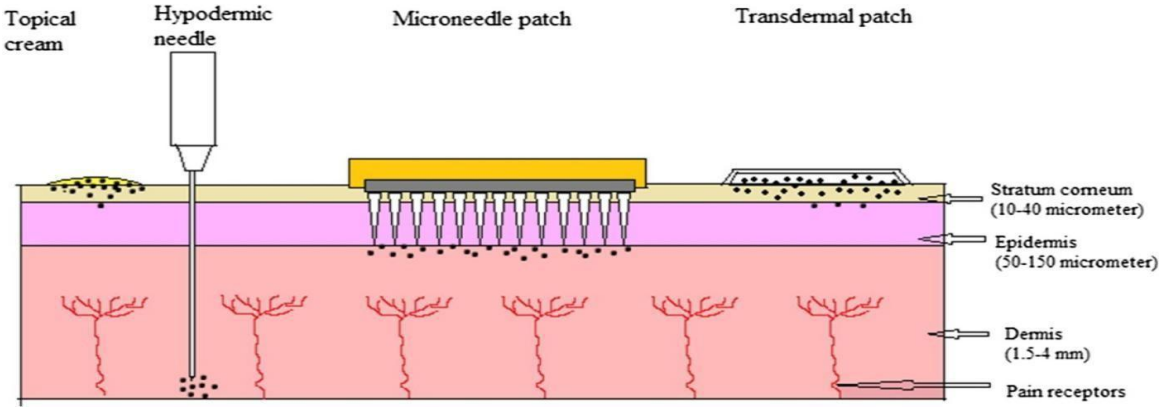

Fig: Mechanism of drug delivery by microneedle device: (1) Microneedle device with drug solution; (2) Device inserted into the skin; (3) Temporary mechanical disruption of the skin; (4) Releasing the drug in the epidermis; (5) Transport of drug to the site of action.

Dimensions of microneedles-

Microneedles can be formulated in varying sizes depending on the type of microneedle and the material used. Since the epidermis is up to 1500 µm thick so the needle length of up to 1500 µm is sufficient to release the drug into the epidermis. Needles larger in length and thicker in diameter can go deep into the dermis, damage the nerves and cause pain . Mostly they are 150– 1500 microns long, 50–250 microns wide, and have 1–25 microns tip thickness. As discussed earlier the need for microneedle device is to create micron size transport pathway, the diameter of needles is kept between few microns. Microneedle tips can be cylindrical, triangular, pointed, pentagonal, octagonal and are available in many more shapes.

Fabrication of Microneedle Patches:-

The introduced microneedles are silicon microneedles which are first prepared at the year 1990. When micro fabrication technology had advanced to the point that making microneedle-like structures was relatively straightforward. Many additional methods have been developed to meet the needs of pharmaceutical manufacturing. Microneedle structures and molds fabrication Fabrication of the microneedles is the main part in the MNP fabrication. Microneedle structures are often fabricated using metal, silicon, or non-dissolving polymer and by poke and patch, as well as coat and poke devices. Microneedle structures are also used as masters to make molds that are used to fabricate poke and dissolve as well as poke and release MNPs. Silicon microneedles are often made using (deep) reactive ion etching. In this method, photolithographic methods are typically employed to define the microneedle spacing and base size, and plasma chemistry can be adjusted to alter the profile of the microneedle as it tapers to a sharp tip. It provides good control over microneedle shape but also requires significant method optimization. Reactive ion etching is being used to make extremely short (e.g., 100 µm) and sharp microneedle arrays for vaccine delivery targeted to the skin's epidermis. Wet etching of silicon is also used (e.g., in a bath of potassium hydroxide), where photolithographic methods, as well as silicon crystal planes, define the microneedle shapes

The microneedle drug delivery technology may include either of the five design types of microneedles such as solids,coated, hollow, dissolving, and hyrogel /swellable microneedle.

- Solid microneedles
- Coated microneedles
- Dissolving microneedles
- Hollow microneedles
- Swellable/Hydrogel forming microneedles

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Solid microneedles:-

Solid microneedles are typically in the range of 150-300 um in length tapered at a tip angle 15-20.

The microneedle can be made up of silicone,glass,and,metal.Metal and Glass are relatively non-biodegradable and there are saftey concerns in their use in the situation where they break under the skin.

Metals used in the fabrication of microneedles are stainless steel, iron, and nickel.

Method of Preparation of Microneedle:-

Method 1:- These microneedles can be prepared either by coating with the drug and then inserted into the skin or inserting the uncoated needle into the skin and creating microchannels and subsequently applying drug formulations such as cream, gel or spray (two step processes). In the former, after removal of the microneedle containing the device, the drug will remain deposited within the skin membranes.

Method 2:- drug present in the formulations to access and move through the pores created by microneedles to the underlying layer of skin. The main problem in the coated solid microneedle is that only small amount of drug formulation can be applied, otherwise an application of a thick layer of drug formulation reduces the sharpness of microneedles and therefore making insertion more difficult and painful. Likewise, the twostep process is tedious and can be inefficient and less viable economically in case of delivery of vaccines or gene

Advantage:-

low cost and number of mass production technologies and having sufficient mechanical strength making it not to break under the skin

Disadvantages:-

solid microneedles is the generation of biohazardous sharp waste which can lead to an effect on public health if it is not properly disposed.

The delay in restoration of pores created, typically restored within 2 h but can be extended up to 7 days in case of diclofenac and fluvastatin

Coated microneedles:

As the name denotes, these microneedles are first coated with the drug before administration of the latter. This method is an attempt to propel the previous approach forward to single application systems. As a result of this, the particular amount of drug can be delivered upon insertion of microneedles into the skin. The coating is achieved either by dipping or spraying process; either of the process uses a water-soluble formulation of the drug. In such a way, after puncturing the skin with the coated microneedle, the drug gets dissolved into the surrounding tissue and diffuse into microcirculation. Subsequently, the microneedle can be removed from the application site One approach of coating microneedles is through the use of electrohydrodynamic atomization (EHDA) . In this method, stainless steel microneedles with a height range between 600-900 µm in height were coupled with a ground electrode with a varying system of ethanol: methanol ratio of 50:50. Generally, this technique was reportedly used in making of nano and micrometerscaled coatings of pharmaceutical products.

Advantage:-

This method is the one-step application of its usage compared to the uncoated solid microneedles which is two-step technique.

Disadvantages:-

The desired dose of a drug can be only coated onto the tip and shaft of microneedles.

This may restrict the use of coated microneedle to deliver potent molecules.

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Dissolving microneedles:

The dissolving microneedles intended to release the incorporated drug after dissolving itself in the skin within minutes without generating sharp waste. These are made up of sugars such as dextrin, galactose, trehalose and maltose. which release the encapsulated drug within minute. When water soluble polymers such as methyl cellulose, PVP , polyvinyl alcohol, sodium alginate, HPMC or co-polymer e.g., poly (methyl vinyl ether co-maleic acid) etc. and for controlled release using PLGA over hrs to months are used to develop microneedles is generally termed as dissolving polymeric microneedles. Dissolving microneedles are basically designed to create channels for drugs, break in the skin, thereby dissolve and release other compounds to pass into the skin. It can also be molded into the intended shape before insertion. Maltose has been first reported for use and it is generally recognized as the safe substance for fabrication of microneedles. However, there is the disadvantage with the use of maltose microneedles; it absorbs water under high humidity condition and therefore it leads to bending and insertion of microneedles gets difficult . Dissolved microneedle arrays have been used to deliver a wide range of compounds, from hydrophilic, low molecular weight drugs to larger biopharmaceutical molecules, demonstrating the ability of such a platform to enhance the TDD. Micro-molding is the most preferred fabrication method for preparation of dissolving microneedles. The fabrication process of dissolving microneedles can be carried out by placing polymer solution into female molds and filling the microcavities of the mold under ambient conditions. These dissolving microneedles can appear to provide improved immunity to influenza when compared to vaccination with hypodermic needles.

Advantage:-

These microneedles is having the biodegradable property of material upon contact with the skin's interstitial fluid.
It includes the one-step process which is convenient for patients.

Disadvantages:-

The main issue with these types of microneedles is pertaining to compatibility of sugars or polymers with active ingredients and the processing conditions such as extreme pH, high temperature, and solvents can influence the stability of incorporated proteins, vaccines and other drugs.
The ratio of drug to polymer or sugar as it significantly influences the mechanical strength of microneedles

Hollow microneedles*:*

Hollow microneedles consist of a drug reservoir (typically allowing up to 200 mL of drug formulation or drug alone) with a hollow bore in the center of the needle and principally indented to administer a large dose of drug solution to avoid the limitation of coated microneedles . When inserted into the skin, the hollow bore can bypass the SC layer of skin and produces a direct channel into the other lower layers of the epidermis. These can be fabricated from a commercially available 30-gauge hypodermic needles. These were fabricated by using isotropic etching followed by anisotropic etching to obtain a tapered tip. These needles are of 300 µm in height, with 130 µm outer diameter and 110 µm inner diameter at the tip followed by 80 µm inner diameter and 160 µm outer diameter at the base were fabricated using this technique. These microneedles can also be fabricated using another system like micro-electro-mechanical system technologies such as laser micromachining, deep reactive etching, an integrated lithographic molding technique, Xray photolithography.

Advantage:-

The delivery of high molecular weight compounds such as proteins, vaccines, oligonucleotides.

Disadvantages:-

These are very expensive to prepare and require expensive fabrication techniques.

Swellable/Hydrogel forming microneedles:

These are composed of hydrophilic hydrogel framework that absorbs surrounding tissue fluid and swells to generate microchannels or pathways within the needle through which therapeutic agents can diffuse into microcirculation. These

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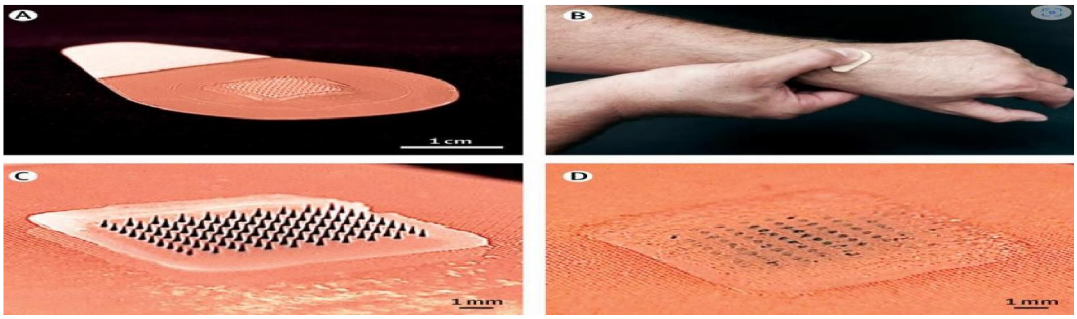
microneedles can be elaborated as an integrated system which consists of cross-linked needles projecting from a solid base plate to which an adhesive drug reservoir is attached. These are typically fabricated from aqueous blends of poly (methyl vinyl ether/maleic acid) and poly (ethylene glycol) via a micro molding process using silicone molds or by using laser engineering technology. When microneedle array is applied to skin, diffusion of the drug from patch occurs through the swollen micro-projections. The first two microneedle-based products, Soluvia and Micronjet are based on metal and silicon, respectively. These are typically suitable for the delivery of small hydrophilic drugs such as caffeine, methylene blue and high molecular weight compounds like (bovine serum albumin and insulin). Hydrogel microneedles offer better control of the delivery of compounds in the particular amount of dose and they are not blocked by the dermal tissue in contrast to the use of hollow microneedles

Advantage:-

The hydrogel-forming microneedles is they can be fabricated in the wide range of patch sizes and geometries
It can be sterilized. Compared to dissolving microneedle systems, the drug

MICRONEEDLE PATCHES SKIN APPLICATION

The complete success of the MNP's can be achieved by the reliable drug delivery with high patient acceptance with less pain. By the slow insertion by hand, the skin is highly elastic, which results in significant stretch/deformation of the skin before penetration. The various ways to overcome this limitation include using longer microneedles (i.e., approaching 1 mm in length. This approach may, therefore, be coupled with having drug only near the microneedle tip, so drug toward the base of the microneedle is not wasted because it does not enter the skin. A significant advantage is low-velocity insertion that it enables hand application of the MNP, which thereby avoids the cost, size, and complexity of a high-velocity applicator. Using shorter microneedles (e.g., 100–300 μm in length) and/or more completely penetrating microneedles into the skin requires dynamic insertion of the microneedles at high velocity (e.g., 3 m/s) such that the higher strain rate of application increases the skin's instantaneous stiffness. Microneedle geometry must also be optimized to allow for plastic engagement of the shorter microneedles with the skin, which also mitigates the bed of nails effect. A drawback of this approach, however, is the necessity of a high-velocity applicator to achieve this engagement with the skin consistently. Yet, despite the various microneedle designs and insertion devices that have been studied, complete microneedle skin insertion is not usually achieved



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TRANSPORT OF MOLECULES IN THE SKIN AFTER MICRONEEDLE PATCHES DELIVERY

Microneedle penetration into the skin, a substantial length of the microneedles is suddenly immersed in a wet cellular environment within the skin where the dry-formulated drug needs to become wet and dissolve. The ideal dissolution characteristics are dependent on the desired pharmacokinetics of the drug and its desired mode of action within the skin. For coated or dissolving microneedles, minimizing the amount of time the patch remains on the skin is desirable to improve patient acceptance and reduce the likelihood of premature patch removal. Between 2 and 20 min are often required, although rapid mechanical separation of a drug-loaded "arrowhead" from a microneedle shaft has yielded 1-s patch removal times. Faster drug dissolution times, which correspond to shorter patch wear times, may be limited in part by the dissolution characteristics of the drug, but can be modulated by the dissolution characteristics of the formulation matrix the drug is in. In fact, the drug and formulation matrix does not need to be fully dissolved before patch removal; they just need to be sufficiently dissolved or hydrated, so the microneedle coating or dissolving microneedle matrix remains in the skin when the patch is removed. This observation has also enabled formulations for extended drug release (even after short patch wear times) because formulations deposited in the skin by the microneedles could form a depot for slow drug release. Another approach to achieve short patch wear times is to minimize the amount of material to be dissolved and gives it a large surface-to-volume ratio. This can be achieved by thinner microneedles or microneedle coatings but often needs to be balanced with delivering a given dose, which may call for larger masses of drug and excipient . Once the drug has dissolved in the skin, it diffuses away from the site of delivery. For systemic uptake in the bloodstream, the drug should most likely diffuse to capillaries. Since capillaries are in high abundance in the superficial dermis, rates of uptake for various drugs after MNP administration are faster compared with rates after subcutaneous injection. In contrast, vaccine delivery is often targeted to the skin's abundant resident immunological cells, so rapid diffusion away from the site of administration may not be desirable. This type of skin vaccination has enabled improved immune responses (compared with standard needle and syringe injection into a muscle), as shown by vaccine dose sparing, greater longevity of immunity, and greater breadth of immunity. The ideal deposition site and duration of vaccine residence in the skin are not fully understood and remain subjects of investigation.

Microneddle Patches Application:-

The microneedle drug delivery system can be used to treat a variety of genetic skin diseases, as well as malignancies and infectious diseases. It can also be used for immunization. Because numerous cells may be treated at once, the microneedle medication delivery method of gene is superior than the microinjection technique. As a result, microneedles can distribute bioactive substances both systemically and locally. Antiviral, anti-diabetic, genetic, oncological, anti-osteoporosis, dermatological, and other forms of action should be the focus of future research and studies.

Disposal of Microneddle Patches:-

In some cases, when the drug delivery is not 100% efficient the safe disposal of microneedle patches important which is coming into the category of residual drug, biohazards, and sharp waste. However, in that cases, there may be dangers of residual drug exposure to others, including children, animals, and the environment, or there may be illicit use of the residual drug if, for example, it is a drug of addiction. Used MNPs are likely considered biohazardous waste because they contact bodily fluids like interstitial fluid of the skin. However, the amount of bodily fluid is probably small which is even less than the blood found on a used adhesive bandage. Used MNPs are considered sharps waste. Dissolving MNPs are likely not considered sharps waste because they contain no microneedles after use. Non dissolving such as coated microneedles may be considered sharps waste, although the hazard they pose is different from that of used hypodermic needles or scalpel blades and may, therefore, be handled differently. In all these cases, safe disposal may be facilitated through suitable waste streams such as placement in sharps containers or biohazard bags and/or through suitable packaging after use.

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Drug and vaccine stability in or on microneedles

MNPs need to be stored under conditions that maintain drug activity, microneedle integrity (e.g., sharp, strong, and not bent with coating intact), and cleanliness (e.g., sterility). This is accomplished not only through MNP design but also through packaging that provides physical protection from mechanical damage and environmental contamination. Storage at appropriate temperature and humidity (e.g., using desiccant) also contributes. Drugs have also been studied for their stability when formulated into MNPs. Human growth hormone retained most of its activity after storage for 15 months at room temperature using a CMC/trehalose formulation. Parathyroid hormone formulated in sucrose, EDTA, HCl, and polysorbate 20 on coated MNPs was stable for 2 years without refrigeration, but sterilization by gamma irradiation before storage was associated with reduced Drug Stability Over Time.

CHALLENGES IN MICRONEEDLE DRUG DELIVERY:

Endorsing the translation of MNs from research laboratories to the relevant industries is an exciting but demanding task for the near future. To translate this innovative technology from the lab bench to feasible products in the relevant markets, some crucial questions and challenges should be considered promptly. We hereafter discuss these challenges and active strategies to address these difficulties, which could determine the future of the field and its commercial applications. The main issues/concerns for the development of a microneedle-based delivery system is summarised in and discussed in the following sections.

Parameters Affecting Microneedle Insertion

The capability of MN patches to adequately puncture the skin is a vital requirement. When addressing this matter, the skin's characteristics, which might vary across the body and vary from person to person, should also be taken into account. The insertion and penetration behaviour of MNs to overcome the skin's elasticity is strongly dependent on several parameters, such as geometry, base and tip diameters, length, and interspace (centre-to-centre spacing) . An approach of "one-size-fits-all" cannot be envisaged in any design and development stages for any MN application. Infiltration and active delivery performance of MNs are strongly related to the geometry of individual MNs and the array, MN materials, the MN management method, and the characteristics of skin tissue. Depending on the target medicines and applications, the microneedle mechanical strength, insertion depth, and drug release profile could be finely tuned by modifying the microneedle shape and composition.

The geometry: The geometry of MNs is a parameter that should be taken into consideration early on when developing MNs for clinical applications. A recent study indicated that the mechanical strength and penetration characteristics of

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MNs are affected by the geometric structure of microneedle arrays. Simulations have shown a linear relationship between the mechanical strength and the number of vertices in the polygon base (e.g., triangular, square, and hexagonal microneedle bases), showing better insertion depths for the triangular and square-built microneedles. Superior capacity to insert into the skin was observed for the sharper edges of the triangular and square MNs compared to the hexagonal MNs. In a recent study, cone-shaped MNs were discovered to possess the ideal geometry for the delivery of ovalbumin and transcutaneous immunisation, with both greater needle insertion and a fast dismantling time for a more potent immune response obtained. A further improvement has been proposed recently to reduce the risk of insufficient drug delivery, wherein an array of hemispherical convexities was positioned in the lower half of the cone-shaped dissolving MNs to increase drug flux

Tip diameter and Sharpness: Tip diameter is another parameter for MN insertion. Relatively blunt MNs (tip diameters of 60–160 µm) require a relatively high insertion force (0.08–3.04 N) for controlled applications of MNs and are linearly reliant on the tip frontal area. To achieve a well-controlled manner to the desired depth, the fabrication of MNs with sharp tips is essential. For the successful delivery of therapeutics, it has been reported that MNs with smaller tip diameters (<15 µm) access the skin more smoothly than MNs with a tip diameter of larger magnitude. This is particularly important in vaccine delivery to achieve appropriate control over the penetration depth of MNs, not only for delivering the antigens but also for specifically targeting Langerhans cells residing in the epidermal layer or dendritic cells dwelling in the dermal layer of the skin for a robust adaptive response. The sharpness of the tips of microneedles can aid and control the puncture force. An increased tip sharpness, however, not only reduces the puncture force but also reduces the structural strength of the microneedles, leading to a high risk of breakage.

Application velocity and force: In close relationship with the tip diameters, the application velocity and force are other parameters in the MN delivery system that should be considered in detail. Several studies have reported that the penetration depth of MN arrays varies (from 10% up to 80%) and increases with the application velocity and force. A variety of patch configurations have been used, with similar outcomes of the penetration force per microneedle obtained. A 25-microneedle array with a tip radius of <100 nm requires an insertion force of 10 mN per microneedle for effective penetration into the skin. Two independent studies have also acknowledged these findings and reported that insertion forces of 15–20 mN and 15–30 mN per microneedle were required for operational insertion. These forces represent arrays of 10–100 microneedles, which give a total applicator force of 0.1–3 N. Although these forces are low, the need for consistent application may necessitate a controlled application approach or a device.

Length: Because the thickness of the SC and other skin layers differs across individuals, the particle insertion depth may also vary. The transport capability of the skin, once a MN patch has been applied, will depend on the perforation depth of the tissue. If a drug is relatively small and has high diffusion capacity, creating surface pores by microneedle application should be sufficient for therapeutic function. However, if rapid delivery to the bloodstream is the goal, it may be preferable to create pores that reach the dermis, where capillaries are located. This may be one reason for assorted microneedle lengths that have been reported to date. In addition to the shorter microneedles, there have been many studies that used long microneedles (up to 1000 µm long) to increase insulin permeability into the skin.

Interspace *(centre-to-centre spacing):* The skin is a topographically diverse surface capable of withstanding significant deformations prior to penetration. A significant number of distinct punctures must be generated when there is a high-density array of microneedles (e.g., more than 500/cm^2). This takes a lot of energy. Naturally, as the density and number of microneedles grow, so does the necessary force for skin puncture. This can result in increased feeling for the patient and may require the use of a larger/stronger device for certain applications. Needles with increasing width, length, and density can result in larger, longer, and more crowded holes, through which a higher amount of medication may diffuse. However, more tightly placed needles may cause the “bed-of-nails” effect too

Biocompatibility, Biodegradability, and Stability

One of the safety aspects of MN systems in clinical use is biocompatibility. To ensure that MN products are acceptable for human exposure, several tests are required to evaluate their biocompatibility based on contact periods of less than 24 h, between 24 h and 30 h, and more than 30 h. For the former two periods, the corresponding tests are cytotoxicity, sensitisation, irritation, and intracutaneous reactivity tests. Genotoxicity and subacute/subchronic systematic toxicity tests are additionally recommended for the latter period of use. The use of biodegradable materials is desirable for

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microneedles because these materials can be degraded and removed from the body safely. Therefore, using biodegradable polymeric systems for MN fabrication has been pursued in recent years. The primary benefit of polymeric microneedle systems is their ability to load medication into the microneedle matrix for discharge in the skin via biodegradation or dissolution in the body fluid of the skin.

The ability to manufacture microneedle structures from aqueous polymeric mixtures at room temperature without the requirement of a heating step might be a significant benefit in retaining the stability of an integrated medication, particularly in the case of therapies in which proteins and peptides are involved. Nonetheless, the stability of MN cargo has to be evaluated to ensure that fragile and easily degradable therapeutics are protected during storage. This is usually done by storing MNs and their cargo at various temperatures, including −25 °C, 4 °C, 20 °C, 40 °C and 60 °C, followed by analytical assessments. Generally, the protein cargo of MNs has better storage stability and longer shelf-life due to the rigid glassy microneedle matrices restraining the molecular mobility and limiting access to atmospheric oxygen. This can be further extended by the incorporation of stabilisers, including trehalose and sucrose. Attention to water is particularly critical when non-vacuum storage conditions are present, as they can not only destroy the stability of laden cargo but also the mechanical properties of the MNs themselves [75].

Dissolvable MNs are very susceptible to the surrounding humidity; therefore, the storage environment should be dry and cool for prolonged stability and extended shelf-life.

Loading Capacity and Dosage Accuracy

Loading capacity: A coated microneedle device can only deliver a bolus dose of around 1 mg of medicine. Although hollow microneedles allow for continuous infusion or "as-needed/on- demand" dosing, central exits may be obstructed by compressed skin tissue after microneedle insertion. Even though MNs have the potential to overcome the skin's barrier properties, their success is very much dependent on passive diffusion of the biological formulation into the skin. This can make it difficult to administer large dosages, and much of the dose can be lost on the skin's surface. As a result, the time of application and the inability to monitor dose delivery have caused reluctance to use this technology for certain clinical applications. One example is the distribution of vaccines for which dosage constancy is critical. Recent work has shown that administering vaccines directly to the epidermis and dermis of the skin has the potential to induce immunological responses with considerably less vaccine than standard intramuscular injection. These advantages, however, might be lost if just a tiny fraction of the administered dosage reaches the skin. While this is not an insurmountable obstacle to this technology, vaccines, in particular, require a threshold dosage to induce immunity, which might be more difficult to achieve when depending on passive diffusion.

Dosage accuracy: The dosage accuracy of MN delivery systems in continuous drug delivery is an issue that requires close attention. Several methods using separable microneedles have been proposed for minimising the patch-wearing time and quickly removing the formulation from the MNs. Storing and delivering protein drugs, including insulin, erythropoietin, glucagon, growth hormones, and parathyroid hormones, are challenging tasks, as bio-macromolecules are prone to quick degradation and inactivation. These matters could be best handled by not only the incorporation of stabilisers but also by considering the whole process of MN manufacturing parameters, such as manufacturing and storage temperatures and drying conditions, polymer concentration, sterilisation, and packaging. As discussed earlier, MNs can be manufactured in various types and materials. The drug delivery efficiency when using solid MNs is rather difficult to control accurately. Coated MNs can efficiently deliver precise amounts of a drug but have limited drug loading capacity due to their small surface area for coating. Encapsulating drugs in the matrices of MNs is possible if dissolvable microneedles are fabricated primarily from hydrophilic, biocompatible, and biodegradable materials, and if the cargo can be discharged entirely within the skin's interstitial fluid without leading to unwanted debris. Relatively large doses and the controlled release (slow or fast delivery) of various drugs can be transferred without issues of reservoir leakage. Dissolvable microneedles might be an efficient approach to preserve and stabilise nano-sized compositions while improving nanoparticle penetration through the stratum corneum barrier. Various approaches have been thoroughly studied, and several analytical techniques for tracing and tracking the journey of nanomaterials with their valuable payloads, both in vitro and in vivo, have been developed.

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Skin Irritation and Recovery

The immunogenic nature of the skin makes it a highly responsive organ towards the MN delivery of any therapeutic agent. Mild and temporary erythema may develop as a side effect depending on the size, substance, and type of the given medication. Skin irritation, sensitisation, and immune response must also be evaluated as part of the safety assessments of MN products during clinical trials. This safety concern must be evaluated using animal testing before any human clinical trials. On the other hand, great immune responsiveness of the skin may present an opportunity for MN-based vaccine delivery if other obstacles have been addressed properly, as discussed.

Sterilisation of the Microneedle Patches

MN patch sterilisation is another challenge that should be taken into account early on when MN-based products are aimed for commercial application. If sterilisation is necessary, then the method of choice will be critical, because the most widely used methods, such as moist heat, gamma or microwave radiation, and ethylene oxide may deleteriously affect any cargoes with sensitive ingredients, including biomolecules, vaccines, peptides, and/or even the microneedles themselves. Although the risk of introducing bioburden into the sterile area of the body (e.g., epidermis and dermis) by MNs is significantly smaller than a single puncture by a hypodermic needle, complete sterilisation of MNs-based products may be obligatory by the regulatory bodies to safeguard the users. The material used for MN fabrication determines the method of choice for sterilisation. For solid MNs of metals, silicon, and glass, the sterilisation is straightforward; dry heat sterilisation, moist heat sterilisation, and gamma radiation are the most common methods employed. However, when delivering fragile biological active ingredients is in demand (e.g., using coated MNs), the method of choice should be carefully evaluated in terms of maintaining stability and activity of the coated ingredients. MNs constructed by carbohydrates and polymers (e.g., dissolving MNs) present the biggest challenge when choosing the sterilisation method, since the sterilisation not only affects the fragile loads but also the morphological, physicochemical, and mechanical properties of MNs themselves. The effects of various sterilisation methods, such as moist and dry heat sterilisation and gamma radiation, on dissolving and hydrogel-forming MNs have been studied, with ibuprofen and ovalbumin as model drugs. It was found that no measurable bioburden was detected, and levels of endotoxin were under the FDA limits if aseptic preparation was followed. However, moist and dry heat sterilisation damaged all formulations, whereas the gamma irradiation at a sterility assurance level (SAL) of 10^{-6} (according to the British Pharmacopeia) can be used for sterilisation without causing structural damages or affecting delivery capabilities of hydrogel-forming MNs. The radiation, however, destroyed ovalbumin and changed the appearance of ibuprofen. Alternative methods for delicate MNs have been proposed. Ethylene oxide and electron beam sterilisation were shown to be effective but less destructive methods for MN sterilisation. In another study, a self- sterilisation of MNs was proposed, in which silver nanoparticles were embedded in CMC MNs. The authors implied that the pores produced by MNs were free from microorganisms until the skin is healed completely.

It is clear that the information available in the literature is rather limited, and therefore, the sterilisation of MN-based products requires extensive research before going into commercial production and approval; this presents one of the most important challenges in MN-based delivery systems. In particular, endpoint sterilization for MN products requires a great deal of attention, as MN manufacturing under an aseptic condition could be both complicated and costly.

EVALUATION PARAMETERS

In vitro evaluation microneedles

In vitro evaluation microneedles are accomplished by using various mediums like agarose gel and methanol to insert the microneedles. In vitro tests are used to determine the characteristics of new test device or compound. The main key objectives of the in vitro testing of microneedles involves optimization of the microneedles, finding out the penetration force and bending force, evaluation of strength of microneedles, determination of the dissolution rate of coating material and the estimation of the efficiency of drug delivery. Various methods employed for conducting in vitro studies are as follows:

Method 1

In vitro methods tested the delivery efficacy of the microneedles. In this test, the microneedles are integrated with Paradimethylsiloxane biochip and black ink is injected by the microneedles into the petridish, contains methanol widely

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used. The right triangular microneedles with 8.5 and 15 tip taper angles and isosceles triangular microneedles with 9.5 and 30 tip taper angles have been used for this purpose.

Method 2

In this method, the diluted form of Rhodamine B dye is injected through the microneedles into the 1% agarose gel to evaluate the penetration and flow of the solution after penetrating into the 1% agarose gel.

Method 3

Inserting microneedles into the porcine cadaver skin and pig cadaver skin for 10s to 20 s and 5 minutes respectively are evaluated by this method. This method is used to test the delivery efficacy, dissolution rate of the coated material, which is coated on the microneedle tip, coated with vitamin B, calcein or sulforhodamine.

In Vivo Testing of microneedles

To conduct the in vivo preclinical study, generally mice, rabbits, guinea pigs, mouse and monkey etc are used. The main motive of the in vivo testing is the determination of safety as well toxicity of the tested compound. The key objectives behind in vivo testing of the microneedles includes to perform skin toxicity test, determination of penetration force in different skin, mechanical stability, bending breakage force, to perform various non-clinical safety study and pharmacological study, determination of various parameters like immunogenicity, genotoxicity, skin sensitization and allerginisation, study, developmental toxicity, acute and chronic dermal toxicity, carcinogenicity.

Method 1

This in vivo method involves testing of microneedles by pricking the microneedles into vein of the tail of hairless mice. It is used for the determination of the penetration force of the microneedles into the skin.

Method 2

This method of in vivo testing of the microneedles, Rhodamine B is injected into tail of laboratory mouse-tail and anaesthetized for the determination of penetration force and bending breakage force.

Method 3

This method has been performed for the evaluation of vaccine delivery via microneedles. Ovalbumin is used in this method, as a model protein antigen and administered into hairless guinea pig by using solid metal microneedles at the rate of 20 µg ovalbumin in 5s up to 80 µg.

Method 4

In this method rabbits have been used to evaluate the vaccine delivery. The anthrax vaccine containing recombinant protective antigen (rPA) of Bacillus anthracis has been administered in the rabbits via solid and hollow microneedles.

DRUG/VACCINE MNP DELIVEY OUTCOMES IN TERMS OF PHARMAKOKINETICS AND PHARMACODYNAMICS

MNPs have been developed for delivery of dozens of different drugs in preclinical studies, and a few of them have been evaluated in clinical trials. Most studies have compared that the pharmacokinetics and pharmacodynamics of drug delivery to the skin are using MNPs to drug delivery to the muscle or subcutaneous space by hypodermic injection. The objective of either has been to show the similarity between the two routes of administration or improvements such as faster uptake of drug into the bloodstream, increased vaccine immunogenicity which is enabled by the MNP.

Vaccines

In addition to logistical and delivery advantages, MNP vaccination also offers improved immunogenicity [75-77]. Skin vaccination using MNP targets resident immune cells, such as epidermal Langerhans cells and dermal dendritic cells, and can be enhanced by circulating immune cells recruited to the site. There is also extensive fluid transport from the skin to the draining lymph nodes. Slow release of vaccines also increases immunogenicity.

The studies are going on in MNP vaccines such as diphtheria, chikungunya, and anthrax. These vaccines have also been immunogenic in animal models, including mice, rats, guinea pigs, rabbits, pigs, and macaques. The immune responses from both human and cellular have been measured which are often show a proof, of which is superior to hypodermic injection. Some vaccination literature has emphasized the use of extremely dense arrays of microneedles (e.g., 10,000/cm2) designed to kill cells in the epidermis at the site of each microneedle penetration. This approach deposits the vaccine in a local milieu of immunogenic signals released from dying and dead cells which can further enable significant vaccine dose control over the body by the MNP's.

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Drugs

Although vaccines have received more attention in the literature, small-molecule and peptide drugs have progressed further into clinical translation. Drugs have also been administered for local effects. These include drugs for photodynamic therapy and local skin anesthesia and also phenylephrine to treat fecal incontinence through local delivery near the anal sphincter.

Biotherapeutics have been administered using MNPs. Insulin has received considerable attention for bolus, basal, and glucoseresponsive delivery to the skin. Other peptide and protein drugs include erythropoietin, heparin, leuprolide acetate, desmopressin, and human growth hormone . Additional studies have administered plasmid DNA and small interfering RNA using MNPs.

Pharmaceuticals:-

MNP's playing a major role in the field of the medical field but it also has applications in the cosmetic types also. The first microneedle is cylindrical. The original purpose of these devices was to promote collagen production in the skin in response to the micro-injuries caused by the microneedles and thereby improve skin. They can be marketed in combination with topical formulations, for example, for microneedle pre-treatment that facilitates entry of materials applied to the skin. Dissolving microneedles made of hyaluronic acid have also been marketed for cosmetic purposes. On the basis of the success of intradermal hyaluronic acid injections used as fillers to combat the effects of aging on the skin. These products entered the marketplace more than 10 years ago and are gaining popularity. Such pharmaceutical products can eventually be integrated into the digitalization and automation processes involved in drug discovery and manufacture.

Safety

The development of MNP's is mainly occurred for the increased safety purposes. However, from the safety profiles from clinical trials and other human studies typically show only mild, transient erythema at the site of patch application as the most common side effect. Numerous studies have shown that microneedles cause little or no pain in human subjects. The possibility of infections occurring at the site of MNP application has received only limited attention, but infections have not been reported in human studies. Cosmetic microneedle roller devices are used repeatedly by the same person and are not sterilized between uses; this practice does not appear to cause infection, although no studies have been performed to look specifically at this question. Even when MNP's generate sharp waste; they may be less hazardous than hypodermic needles

II. CONCLUSION

Microneedles either in the form of patch or an array have been observed as a potential carrier for the effective transdermal delivery for the delivery of numerous macromolecular drugs. Various research reports studied confirmed that microneedles are ought to be the prominent carriers for enhancing the permeation deep into the systemic circulation and providing a painless, effective and safe route for the drug delivery. In future microneedles plays important role in innovation and design of controlled drug delivery for various drugs. These painless systems are slowly gaining importance and would qualify to be one of the important devices for controlled drug release in future. Thus, it was concluded that, these systems represented it to be an efficient and superior carriers as compared to other needle based formulation for the transdermal delivery.

Development of marketable microneedle-based drug delivery products is highly likely in near future. Extensive research in MNs is being conducted for the efficient delivery of therapeutics, as innovative transdermal drug delivery methods are urgently required to expand the transdermal market for hydrophilic molecules, macromolecules, proteins, and conventional medicines for new therapeutic indications. The future of the microneedle industry seems to be quite bright, with the rapid realisation of new information fuelling industrial progress. The effectiveness of MNs has been demonstrated in several clinical trials, but there have still been far more preclinical studies. Experts from academia, industry, and regulatory organisations are collaborating to help MNs to advance into safe and effective clinical usage provided that the shortcomings associated with these systems are promptly and rationally addressed. It is believed that, in time, microneedle-based technology will lead to improved illness prevention, diagnosis, and control, as well as an

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increase in the health-related quality of life of patients globally. Nonetheless, the complicated and expensive production of MNs, together with several application-related difficulties, could delay their clinical translation. This is evident from the clinical translation of microneedle applications in the pharmaceutical industry. For instance, the lack of clinical data on "www.clinicaltrials.gov" using "microneedle vaccine" indicates that the scale-up production of MNs is still a challenge. What is more, novel manufacturing methods, micromachining and 3D printing technologies in particular, are envisaged to lower the costs and simplify fabrication procedures in the near future.

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