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Abstract

The transdermal route is employed as an alternate method in many therapeutic applications to get over the important drawbacks of oral medication delivery. Transdermal microneedle arrays have been used for drug administration via the skin for a very long time. Microneedles are devices with a reputation for being highly efficacious and flexible. Microneedles are devices with a reputation for being highly effective and flexible. Intellectual and industrial groups are interested in this technology because of its remarkable properties, which include painless penetration, low cost, excellent medicinal productivity, and relative protection. Microneedles exhibit remarkable properties for a range of biological applications, including

the transport of extremely large molecules exhibiting ionic and polar physical-chemical characteristics. In several biological fields, such as immunization delivery, diagnosis, and therapy, microneedles are helpful A new class of instruments with great promise for the biomedical industry is microneedles. In the years to come, transdermal microneedle innovations are expected to become a preferred method of administering medication as they are affordable, painless, and effective. We describe current breakthroughs in microneedles for therapeutic uses in this study. We investigate the constituent materials and manufacturing technologies that improve the administration of importantmedicinal compounds through the skin. We also examine the utility of improved microneedles asmedication delivery techniques.

Keywords:-Microneedle devices; transdermal penetration; drug delivery,stratum corneum,

Painless administrati

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Introduction

Topical creams and hypodermic needles are widely used to deliver medications via the transdermal route. Nonetheless, the limited bioavailability of topical creams, as well as the pain associated with hypodermic needles, pose significant problems in transdermal medication delivery. The limitations of these two conventional transdermal drug delivery techniques have been studied in an attempt to address microneedle arrays [1]. In recent decades, microneedle technologies have drawn a lot of interest as injection methods that minimally alter a person's biochemistry for interstitial fluid collection, medication administration, and diagnostic purposes. Microneedles cause little discomfort, tissue damage, and dermal layer irritation since they can only penetrate a small portion of skin at a restricted depth [2].Microneedle developments, in particular, have gained prominence in healthcare because they promise to eliminate needle phobiaproblems microneedles address various safety issues associated with the disposal of hypodermic needles. This article examines the many applications of microneedles for transdermal medication administration.. And vaccine delivery for a number of illness conditions, as well as their advantagesover alternative therapeutic administration methods. We also examine the variety of materials employed, as well as the unique ways used to create several types of microneedles for various therapeutic applications.Microneedles are designed to pierce the epidermis and deliver medicationdirectly to the sub epidermal vasculature [3]In 1976, the concept of microneedles first established. However, until the first use of microelectromechanical devices in 1998 and the simultaneous acquisition of an American patent for the microneedle for transdermal administration, they were not practical [4].The four most popular ways to administer medications are transdermal, intramuscular, intravenous, and oral [5].Because it is both easy and cost-effective, oral administration is the most often employed method for medication delivery. It is, however, linked to reduced medication absorption caused by drug breakdown in the gastrointestinal tract (GIT) microenvironment, which is impacted by low pH and food. Furthermore, the hepatic first-pass action of the cytochrome P450 (CYP450) enzyme system significantly reduces the bioavailabilityof orally taken medications [6,7]. Intravenous and intra-arterial drug delivery, on the other hand, arethe most dangerous modes of administration. This is because drugs may be administered to organs in enormous quantities and without control, leading to toxic effects that might include excruciating pain. [8] The cause of injection pain is mechanical Damage to nerve fibers brought induced by a needle incision [9] Pressure might also result in pain

from fluid building up inside the tissues, or sudden tissue dislodging due to rapid fluid flow [9]

Microneedle delivery is designed to penetrate only the maizeified layer of the epidermis and is not capable of reaching nerve endings or blood vessels. Therefore, patients are unlikely to experience massive pain during the procedure. [10].in Table 1.

Table 1. Comparative analysis and drug delivery applications of transdermal patches, hypodermic needles, and topical [11]

	Topical cream	**Transdermal Patch**	**Hypodermic Needle**	**Microneedle**
Description	Creams and Ointments	Cohesive patch placed on the skin	Sharp tip with a small opening at the end	Microneedles fixed on the surface of a small patch
Application	Steady	Steady	Rapid	Rapid
Pain	Pain-free	Pain-free	Sore	Pain-free
Bioavailability	Less	Less	Good	Good
Patient Compliance	Non-compliant	Compliant	Non-compliant	Compliant
Self administration	Yes	Yes	No	Yes

Recent Research on Microneedles Arrays

The very first drug to be licensed in the US using microneedle patch was scopolamine, which was introduced in 1979.[12] Transdermal medication administration is most typically accomplished with hypodermic needles, whereas topical creams transfer pharmaceuticals to the skin's surface with

minimum penetration. However, because to their pain, hypodermic needles are not routinely used.[12] Microneedles form transitory microspores through the stratum corneum to administer medications that are impermeable to the skin. Another crucial aspect to take into account when assessing microneedles is micro pore closure after drug delivery via microneedles, since this influences the pace of medication diffusion to the skin's the vascular system and interstitial fluid. [13].In a prior work, micro-projected holes were observed to shut around 25% of their diameter in the first 30 minutes and nearly completely after about 6 hours [14]. as stated by According to and Banga (2009),the period for which the microchannels remain open is a significant aspect that will influence medication delivery. They also noted that in a hairless rat model following microporation, epidermal barrier function recovers in 2-3 hours and pores shut in 15 hours [15].Bal et al. (2010) demonstrated that the pores do, in fact, shut extremely quickly within 15 minutes in most cases [16]

Classification and Fabrication

The primary goal of microneedles is to puncture the skin with micro-projections without inflicting nerve pain or injury, hence enhancing patient compliance and safety. Patches are also used to support microneedles, and they are built with a uniform, pressure-sensitive adhesive covering on one whole side of the patch meant for contact with the skin.. [17]Microneedles are classified into several types depending on a variety of factors such as drug or biomolecule delivery techniques, materials, and structural arrangement [18]. MN often produces the depth of 200 µm without reaching the dermis, resulting in there is no pain compared to other transdermal administration modalities. [19] Present. Since 1990, the microelectronics sector has made significant progress, which is extremely beneficial for microneedle micro-manufacturing [20]. Solid microneedles for skin preparation, dissolving and Swellable microneedles without remaining fragments, and coated microneedles are the four varieties of microneedles. Hollow MN for liquid medications and water-soluble drug formulations.

Microneedles-Based Transdermal Drug Delivery System

Different types of microneedles and their working

Solid Microneedles

Solid microneedles pierce the stratum corneum, forming microchannels and holes. Next, a patch with the formulation of a drug is put to the skin, enabling the medication to enter the skin through the transient tiny channels.. [21] Solid microneedles are intended to transfer drugs to the skin using the “poke-and-patch” method. An alternative method is called "encase and poke," when the MN are first coated with a medication and inserted into the stratum corneum. . Because there is no drug reservoiron the skin’s surface, all of the drug to be given is situated on the surface of the needle. A variationon the second method is "dip and scrape," in which the microneedles are submerged in a drug or therapeutic material solution and then scraped over the skin surface, leaving the drug or therapeuticsubstance behind within the microchannels created by the microneedles [22] Various types of solidmicroneedles are currently being developed. The following measurements were obtained by Narayanan and Raghavan (2017) for their solid silicon MN: a base width of 1 and a mean pitch of 156 µm 110.6µm; an aspect ratio of 1.43; a tip angle of 19.3 µm; and a tip diameter of 0.40 µm [23,24].Martin et al. (2012) shown in a seminal study that sugar mix concentrations in a state of vacuum at a low temperature may be used to manufacture sugar glass microneedles. The microneedles were physically robust enoughto penetrate human skin efficiently [25]. Cha et al. (2014) earlier suggested that a MN array of polylactic acid, (PDMS) molding were use to create polymer base microneedle [26]. Microneedles in height from 25 to 2000 mµ and are made of a varietyof materials and shapes.

Due of its outstanding qualities, silicon is a widely used material for the creation of microneedles. Micro-electromechanical systems (MEMS) are mostly made of silicon, which has outstanding mechanical strength and biocompatibility[27]. Glass-based microneedles are a viable choice for drug delivery applications due to their inertness, low cost, and speedy manufacture [28]Microneedles made of carbohydrates such as maltose, chitosan, trehalose, and starch can be created by micromolding. Micromolding and drawing lithography are routinely used to produce carbohydrate-based microneedles [29] in table 2

Materials	**Advantages**	**Disadvantages**	**Application**
Silicon	Biocompatible, hard, Mature fabrication technique	Sharp waste Brittle	Solid,Coated, Hollow Microneedles

Glass	Chemically inert, Transparent and cheap	Cumbersome Fabrication, Brittle	Hollow Microneedles
Ceramic materials	Natural porous	Long fabrication Time, significantly brittle	Hollow, Dissolving Microneedles
Metal	Biocompatibility High conductivity, have catalytic activity for some nonmetals	High cost for noble metals Allergic risk,	Solid,Coated, Hollow Microneedle
Polymers	Biodegradable (some)or Swellable, Easy fabrication	Low mechanical strength	Solid,Hollow, Coated, Dissolving, Swellable Microneedles

Table 2 .Materials for the fabrication of solid microneedles [23]

Hollow Microneedle

This device works identically to a conventional injectable syringe in numerous ways [30]. The tips of hollow microneedles have apertures that may be loaded with a medication. When the When medication is administered into the tissue, the top layer of the dermis, or epidermis, receives it first. Moreover, high molecular weight compounds including proteins, vaccines, and oligonucleotides may be transported via hollow microneedles [31]. The production of hollow microneedles is incredibly intricate, compared to those with a greater aspect ratio, which are similar to solid needles in that they don't have an internal support system, might fail if positioned incorrectly. Stress from improper handling of the patch assemblage or unit during insertion or removal may result in needle breakage and failure[32]. All things considered, microneedles have potential to develop into an incredibly sophisticated medical tool that can detect skin penetration and rupture of the stratum corneum barrier in the cornea, allowing for the administration of drugs into usable skin layers and the evacuation of bodilyfluids. Only hollow MNs have made it to the medical device market, despite years of developmentand a variety of MN forms [33]

Dissolvable/swellable microneedle

Utilizing swellable or dissolvent polymers is a new method of MN manufacturing. At the fabrication step, the medicine that will be delivered is placed inside the needle. After the needle

has pierced the stratum corneum, the polymer that forms the architecture of the needle breaks, releasing the medication that was imprisoned within The advantage of having microneedles that dissolve under the skin effectively lowers the of post-application damage from needle sticks [34]

Table 4. Dissolvable/swellable microneedle devices. Adapted with permission from[35]

Drugs	**Polymers**	**Types**
Dihydroergotamine mesylat	Polyvinylpyrrolidone.	Dissolving
Thymopentin	Polyvinylpyrrolidone.	Dissolving
Exendin-4	Carboxymethylcellulose	Dissolving
Fluorescent Model	HA/PVA.	Dissolving
Sumatriptan succinate	Polyvinylpyrrolidone	Dissolving
Adenosine	Hyaluronic acid	Dissolving
Vitamin K	succinate Poly	Dissolving
Curcumin	Gantrez® S-97 PEVE	Swellable

	MA and Tween 85	
Caffeine/Theophylline	Hydrolyzed PEVE-MA and PEG	Swellable extraction of fluid
FITC-dextran	Silk fibroin	Swellable

Coated Microneedles

A coated microneedle array consists of thin, water-soluble inactive excipients coated on the exteriors of tiny, sharp needle shafts attached to a supporting substrate by adhesive. [36]. A coated microneedle is made of a solid, sharp microneedle that is hydrophobic in water yet coated with inactive excipients [37].When aqueous interstitial fluids come into contact with the excipients within the microneedle coating, they dissolve [37]. The microneedle coatings are produced by immersing the microneedle array in a coating and carefully removing it at the proper rate. The study reports that the microneedles' removal rate from the coating solution was manually controlled at about 2 mm/s and 0.35 mm/s throughout film production and nook filling, respectively [38]. Fluorescence or bright-field microscopy was subsequently used to assess the homogeneity of the coating [17,38].In a different investigation, a thin drug formulation film with a solution layer of about200 µm was created by uniformly applying the coating fluid to the surface of a 10 mm diameter roller. The microneedle tips were 50 mm shorter in height than the device's top. The roller revolvedat a linear speed of 0.3 cm/s and was situated at the top of the apparatus.. As the microneedle tips rotated, the coating solution was stuck to their surface. The microneedles that were produced were vacuum-dried and frozen [39]. The paper also described a method of dip-coating using microneedle plates and fittings that were 3D printed. Before being 3D printed, the most suitable attachments and microneedle plate were created initially using the AutoCAD program). The fluid and the PL microneedles were to be kept apart using a polyformaldehyde plate. The components were assembled to create the coated microneedles device, and a computerized microscope was used to monitor and carefully guide the microneedle shafts as they were lowered into the reservoir. Throughout the production process, the portable holder dropped at a speed of 10 mm/min when it reached the coating mix from a reservoir. Following their immersion, microneedles were transferred at a steady 10 mm/min speed. The coated microneedles underwent disassembly, microscopic inspection, vacuum drying, and freezing [39].

Applications of Microneedles Technologies: Biomedical Applications

Anticancer Therapeutic Drugs

To combat it, several treatment approaches, such as the use of microneedle arrays, have been created. Stereolithography(SLA) was used to create the microneedle arrays, which were then coated with a cisplatin formulation. The excellent 80% penetration depth of the 3D printed microneedles was shown by optical accuracy tomography analysis. Franz's cell diffusion experiments showed that cisplatin released at rates as fast as 80–90% in 1 hour. Furthermore, cisplatin was effectively able to penetrate Balb/c nude mice in vivo, Which resulted in improved anticancer activity and tumor regression. [40]In a different research, doxorubicin (DOX), an anticancer medication, was loaded onto gelatin methacryloyl (GelMA) microneedles, demonstrating prolonged drug release and effective transdermal therapeutic administration [41] lipid-coated cisplatin nanoparticles (LCCNPs)may be given transdermally utilizing dissolvable microneedles for efficient and secure anticancertreatment. A towering rate of 80% encapsulation of cisplatin into Neoplasm -targeting, pH- responsive lipid nanoparticles was observed. The high encapsulation rate significantly enhanced the solubility of cisplatin and its in vitro antitumor cytotoxic impact.[42]A light activating microneedle therapeutic device was developed by Chen et al. (2016a). As a result, they were able to produce cytotoxic anti-cancer effects that were synergistic on small tumors. A dissolvable poly(vinyl alcohol)/polyvinylpyrrolidone protective collecting patch, doxorubicin (DOX),lanthanum hexaboride, and polycaprolactone microneedles were used to make this device. The embedded microneedle array dissolves at 50 C when exposed to near-infrared radiation, releasing DOX across a wide region and eliminating malignancies, according to the study. This is accomplished by uniformly burning the target tissue to produce a considerable thermal ablation.region.[43]

Diabetes

The transdermal intake of insulin from microneedles happens after full microneedle breakdown after 60 minutes of contact to the skin of rats in vivo, according to studies employing diabetic rats. In one investigation, streptozotocin-induced diabetic rats were given insulin-filled microneedles fabricated from stainless steel sheets to implant under their skin in order to reduce blood sugar levels. This was done by transdermal insulin intake. The solid metal microneedles enhanced transdermal insulin distribution and reduced blood glucose levels in diabetic rats by 80%, as demonstrated by radioimmunoassay [44]. In a different investigation, a dissolving microneedle patch for efficient transdermal insulin administration was created utilizing gelatin and starch [45]In more studies, Forthe transdermal administration of insulin to rats, scientists 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 circulation, according to pharmacokinetic and pharmacodynamics results. Additionally, the hypoglycemic effect brought onby the injection of subcutaneous insulin was nearly identical to that produced by the insulin charged microneedles. The evidence points to the HA-made, insulin-charged microneedles as a significantalternative method for delivering insulin through the skin. The blood circulation without risking significant skin injury [46]In a different research, a novel microneedle drug delivery system that used mesoporous silica nanoparticles filled with insulin and sensitive to hydrogen peroxide demonstrated rapid and painless administration [47]

Bacterial Disease

According to a different research, a patch with the ability to stop bacterial infections and promote tissue remodeling is very helpful for wound healing [48]. Chitosan, a material widely used to treat injury, has many good qualities, one of which is a natural antibacterial trait. . The investigators create a patch with a clever, thermo sensitive drug delivery mechanism to expedite healing of wounds using chitosan microneedle array (CSMNA). One of the many helpful features of chitosan, a material widely used to treat wounds, is that it naturally has an antibacterial effect. Additionally, the architecture of microneedles promotes efficient loading of compounds to this particular region and prevents overly tight skin adhesion to the patch. Additionally, endothelial vascular growth

factor (VEGF) is incorporated into the CSMNA microspores, and VEGF is present in the thermosensitive hydrogel. Inflammation at the site of the wound causes a increase in temperature, which can be used to control the intelligent release of medication.[48].Another study examined the effectiveness of using antibacterial microneedles made of hyaluronic acid (HA) and green tea extract (GT) to administer green tea (GT) [49].

Ocular Microneedle Delivery

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 [50]. An eye patch was adhere with removable microneedle arrays griping micro reservoirs for controlled ocular medication administration in a various investigation [51 As per the doctor, in a corneal neovascularization illness model, the administration of Angiogenesis antibody (DC101) results in over 90% neovascular region depletion. Contrarily, a synergistic therapeutic benefit is given by the amalgamation of a sustained release of DC101 with an anti-inflammatory drug (diclofenac) [51].

Conclusions and Future Perspectives

Many different types and designs of transdermal administration of a wide spectrum of molecules have been accomplished. With today's technology, the range of drugs that may be successfully delivered transdermally has been greatly expanded. This will significantly boost the market for transdermal delivery, which will become increasingly significant as the number of innovative medications keeps growing. The appealing qualities of microneedle-based devices, such as low pain, little invasiveness, minor inflammation, if any, and complete skin regeneration within a few hours, have been emphasized in small-scale clinical trials. Closure delivery mechanisms have a great deal of promise for application in the tracking of therapeutic medications or analytes without intrusive procedures. Further development may potentially make advantage of microneedle technology. Focus group studies specify The Microneedles Ideology must investigate key areas for the development of technology. This guarantees that reproducible microneedles are used by all patientsand that successful insertion is confirmed. Clinical studies for a significant number of small and large industrial participants' respective microneedle-based devices are now being conducted. The

methods proposed 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 contemporary knowledge feed sector 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 to enhance illness detection, diagnosis, and management. thus also enhancing the general wellness of life of the individual receiving treatment.

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