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Micro-needles- Innovation and approach to Transdermal drug delivery system

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ABSTRACT

In addition to being non-invasive and practical, transdermal drug delivery has a variety of benefits for the patient, including avoiding first pass metabolism and preventing gastrointestinal degradation. The ability of microneedle arrays to penetrate the stratum corneum, the skin's protective barrier, and open a channel for drug penetration to the dermal tissue beneath has been shown to increase the number of substances susceptible to transdermal delivery. In recent years, there has been a lot of research done on microneedles for the delivery of drugs and vaccines as well as for minimally invasive patient monitoring and diagnostics. This review focuses on a variety of microneedle technology issues, including their varieties, uses, advantages, drawbacks, regulatory implications, and mechanical factors.

Key Words-Micro-needles, Need, classification, regulatory and mechanical considerations, TDDS, Clinical trials, benefits and limitations.

INTRODUCTION

The integrated strategy increased the success rate in research and development in the fields of pharmaceutical sciences and health care. Because they have advantages over oral and injectable drug administration, transdermal drug delivery systems (TDDS) are one of the most important areas of research in the field of drug delivery [1]. As a result, TDDS develops as a platform for the systemic and local administration of medicines, immunological biologicals, and macromolecules. Additionally, TDDS's main drawback is its poor permeability through stratum corneum (SC). This restriction might be overcome by adopting fresh, creative methods like microneedles (MNs). As a result, several researchers started using MNs to get around SC's barrier and other drawbacks related to TDDS. Regarding the use of MNs alone or in conjunction with TDDS, there is a lot of research and development going on.

The stratum corneum can be punctured by microneedles, which are three-dimensional (3D) microstructures with microscale length (typically 1000 m) and can create momentary microchannels via which exogenous molecules can passively permeate into the skin. The penetration depth of microneedles might be made shallow enough to avoid coming in contact with nerve receptors in the lower reticular dermis. As a result, administering medication is painless. This microneedle-based transdermal delivery method appears to offer a self-management, patient-friendly and effective drug delivery method [2].

NEED OF MICRONEEDLES

The traditional drug delivery methods, such as oral, parenteral, topical, and TDDS, have significant restrictions on the medication's permeability and rate of absorption. In terms of patient care, this has an impact on the drug's efficacy. As a result, several novel strategies have been researched and put into practise to get around these constraints. Among these cutting-edge methods, MNs are one of the greatest options. MNs are tiny, micron-sized structures with penetrating needles formed of a variety of fabrication materials, including silicon, polymers, metals, polysaccharides, and glass, among others. They can be used as a TDDS for more effective medication absorption across the various layers of skin. Via increasing the permeability of numerous pharmaceuticals through the skin, MNs have the enormous potential to enhance their therapeutic efficacy [3, 4].

Moreover, the MNs improve the patient compliance in different aspects, like it is less painful, easy to use; no skilled or trained personnel are required for application etc. The advancement in MNs development and their application may achieve a significant place in patient healthcare in coming future [5].

BENEFITS AND LIMITATIONS

The MNs have benefits some of which are listed in

1. Microneedles are less intrusive and have dimensions that prevent them from irritating the patient's nerves or stimulating nerves.
2. They are also appropriate for drugs with short biological half-lives and limited therapeutic indices.
3. Keeping first-pass metabolism to a minimum
4. Avoiding stomach-related compatibility
5. Improved patient compliance as a result of lower dose frequency
6. Few or no negative effects
7. Enhanced bioavailable
8. It is possible to provide large-sized molecules.
9. Microneedle devices, which come in the form of inexpensive disposable patches, have the potential to be applied without the assistance of a clinical professional or even by the patient themselves, improving the pharmacokinetic profile of therapeutic component delivery, removing the risk of needle stick injuries, and lowering the amount of "sharps" and other biohazardous waste.
10. Preservation of the drug level in plasma
11. Microneedle patch technology has already demonstrated promising results in delivering lyophilized or liquid formulation-based vaccines and macromolecules such as influenza vaccines and insulin, and has the potential to overcome the challenges involved in mass vaccination against COVID-19 throughout the world [6-8]. Studies have shown that microneedles can effectively administer solid-state influenza vaccine into mice skin [9] and that a minimally invasive method using microneedles and skin electroporation can deliver macromolecular medicines to deep skin tissues in rats [10].
12. Several microneedle designs allow for the skin-penetration of medications. Microneedles with hollow or side-openings enable pressure-driven or drug diffusion [11].
13. A variety of molecules have been transdermally delivered using microneedles of various designs, including the anthrax vaccine [12], aminolaevulinic acid [13], calcein [14], erythropoietin [15], bovine serum albumin [16,17], ovalbumin [18], insulin [19,20], and plasmid DNA [21]. However, issues with heating of carbohydrates and polymers, which can lead to drug breakdown during the moulding of microneedles at high temperatures, have arisen when therapeutic agents are delivered by dissolving or coated microneedles [22].
14. Accurately coating microneedles is a difficulty, but coated or degradable microneedles may be able to administer therapeutic drugs in lower regulated quantities than hollow microneedles, which are more likely to become blocked with minute debris during insertion [23].

There are **restrictions on the MNs**, some of which are listed in

1. Solid and hollow MNs may break at the tip and remain in the skin.
2. Repetitive injections increase the risk of vein collapse.
3. Skin penetration differs depending on the thickness of SC in each individual.
4. Delivery variation brought on by the skin's condition and the environment outside
5. The accuracy of dose is lower compared to hypodermic needles.
6. Hollow MNs may obstruct as a result of compacted cutaneous tissues.

CLASSIFICATION OF MNS

There are several different forms of microneedles. The sorts of microneedles, the fabrication processes, and their application in modern technology are reviewed [24 -27]. Clarified are the fundamental properties of the microneedle, the behaviour of inserting it, and the discomfort it causes throughout that process [28]. The following factors are generally used to categorise microneedles: I fabrication procedure; ii) type; iii) geometric shape; iv) drug delivery system; and v) materials.

MICRONEEDLE TYPES

Based on their types, the microneedles are divided into solid, coated, hollow, and dissolving microneedles.

1.Solid Microneedle

Solid microneedles [29] are frequently used for skin diagnostics and are constructed as a complete single structure. As the needles are inserted into the membrane, tiny pores are created, which are then filled with a medication solution to begin the diffusion process. Utilizing microfabrication technology, a 400-microneedle solid silicon microneedle array with a 3x3-mm area is created [30]. The fabrication of the ultra-short solid microneedle arrays (8X8, 10X10, and 12X12) results in their length being between 70 and 80 m. Super-short microneedles are a safe and efficient drug delivery method [31].

2.Coated Microneedle

The solid microneedles are covered with a medication solution to create the coated microneedle. The medication resolution coated on the microneedles outer surface liquefies as it is injected into the membrane and settles beneath the skin [32]. Utilizing biocompatible polymers hydroxy-propyl-methyl-cellulose (HPMC) and carboxymethylcellulose (CMC) coating solution, a novel technique for creating coated microneedle arrays has been developed [33]. Molten dip-coating solutions of water-insoluble medicines are used to coat solid dispersions on microneedles [34]. The Piezoelectric inkjet coating method is used to coat the solid microneedle [35]. DNA vaccines are coated on the solid microneedle for the prevention of Alzheimer's disease [36].

3. Hollow Microneedle

In order to store and distribute the medicine into the membrane, hollow microneedles are built with a hollow route established in the microneedle [37-41]. We show the first hollow out-of-plane microneedle with a side aperture [42, 43]. The development of hollow silicon dioxide (SiO2) microneedles using a new fabrication technique is addressed [44]. Microneedles with pores evolved in addition to having a single through-hole enabling rapid drawing of bodily fluid. The many pores that make up the porous microneedles are primarily intended for capillary action body fluid extraction.The potential and limitations of porous microneedle technology development are highlighted [45]. By combining the mechanical cutting and wet etching processes, a novel form of porous titanium (Ti) microneedles is created [46] Later [47] used a metal injection moulding technique to create the same material. By combining the microneedle with a microfluidic device for interstitial fluid (ISF) collection, a porous microneedle array is created [48].

4. Dissolving Microneedle

The fast-dissolving fibroin microneedles are created and described for the first time. The dissolving microneedle is self-dissolvable [49-51] and is made for delivering protein while withstanding mechanical strength when inserted into the membrane [52]. [53] A dissolving microneedle array of 81 microneedles (9X9)

is created [54]to further the transdermal delivery of medications; hyaluronic acid is used to create the dissolving microneedle [55, 56]. The microneedle tips are encased with hydrogel microparticles in a process that was devised [57] for the separation of dissolving microneedles into the skin. When the hydrogel microparticles come into touch with bodily fluid, they swell and separate the microneedles.

MICRONEEDLE MECHANICAL CHARACTERISATION

Mechanical characterization is an essential stage in the creation of successful MN devices. MNs regularly endure a variety of pressures, including as those incurred during insertion or removal. Therefore, in order to prevent failures, such devices must have intrinsic strength [58].

Table No.01- Characterization of MNs:

Sr. No.	Type	Description
1.	Axial force mechanical tests	A force is applied to the MNs in axial force mechanical tests that are perpendicular to the base plate [59]. Typically, a mechanical test station is required for this kind of test, which measures both displacement and force while the MNs are pushed against a hard surface at a predetermined rate [60]. The force-displacement curves produced when MN fracture takes place show a quick drop. The MN failure force is often determined as the maximum force applied just prior to this drop [61].
2.	Transverse force and shear strength mechanical tests	Incomplete insertion of MN arrays is usually caused by skin surface imperfections and its inherent flexibility, and transverse needle bending is frequently noticed. In order to investigate how MNs behave during application, a transverse fracture force test is required [61]. A transverse force (applied normal to the MN y-axis) is applied to a specific place on the MN shaft using a mechanical test station until the MN cracks. Once more, a sharp decline in the force-displacement curves denotes MN failure [59, 61].
3.	Base-plate strength and flexibility tests	The above-mentioned tests primarily examined the mechanical properties of the needles, but it was also crucial to evaluate the strength of the MN base-plate. It is obvious that it is unacceptable for the base-plate to fracture during patient application. Base-plates must therefore be adaptable enough to follow the topography of the skin without cracking. Three points bending test has been employed for this purpose [61].

REGULATORY CONSIDERATION

Because MN array-based products are so novel, there are currently no regulatory requirements established for them. As businesses plan to commercialise MN patches, they will need to address this issue when they request marketing authorization in the upcoming years. The skin's surface is all that is covered by traditional transdermal patch systems. However, MN passes the stratum corneum barrier and frequently reaches the dermis and viable epidermis. A number of fresh scientific and regulatory problems are sparked by the skin's outermost protective layer being breached. Since MN has a completely different mode of action than existing transdermal patch systems, it is likely that it will be classified as a new dosage form under regulatory consideration.Specifications for these new products should also be established. Guidelines were provided by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use to aid in the development of international standards for novel drug substances and drug products that have not yet been approved for use in the United States, the European Union, or Japan. These rules are referred to as Q6A. The following definitions apply to specifications in accordance with these rules: A list of tests, references to analytical techniques, and the necessary acceptance criteria, which are limits, ranges, or other specifications for the tests mentioned.It lays forth the set of requirements that a drug substance or drug

product must meet in order to be accepted for usage as intended. To ensure the consistent manufacture of high-quality drug substances and drug products, specifications are an essential component of the quality assurance system [62].

CLINICAL TRIALS APPLICATION TO MICRO-NEEDLE [63]

Table No. 02: MNs in clinical Trials:

Year	Title	Condition	Phase	Status
2007	A study to assess the safety and efficacy of a microneedle device for local anaesthesia	Local anaesthesia Intradermal Injections (MicronJet)	-	Completed
2007	pilot study to assess the safety, PK and PD of insulin injected via MicronJet or conventional needle	Intradermal injection	Phase 0	Completed
2010	Pharmacokinetics/dynamics of basal (continuous) insulin infusion administered either intradermally or subcutaneously	Diabetes mellitus, type 1 Diabetes mellitus, type 2	Phase 1 Phase 2	Completed
2012	Intradermal versus intramuscular polio vaccine booster in HIVinfected subjects (idipv)	Polio immunity	Phase 2	Completed
2013	Immunogenicity of inactivated and live polio vaccines	Poliomyelitis	Phase 3	Completed
2011	Comparison of 4 influenza vaccines in seniors (PCIRNRT09)	Influenza vaccine	Phase 4	Completed

When compared to conventional subcutaneous injections, the delivery of insulin utilising MN may be related with higher patient compliance. The delivery of a 10-IU standardised insulin lispro utilising stainless steel MNs of three different lengths—1.25, 1.50, and 1.75 mm—was evaluated in people (10 healthy adults) [64,65].

Several clinical experiments have looked at the distribution of lidocaine and other local anaesthetics utilising solid and hollow MNs. The effectiveness of lidocaine administered via hollow 500 mm MNs against Mantoux injection with 26-Ga hypodermic needles was compared in a randomised single blind research with 15 volunteers [66]. MNs were rated as less uncomfortable than hypodermic needles by volunteers. For both injection techniques, lidocaine had an equal anaesthetic effect. 25 healthy participants participated in a different trial to assess the efficiency of MN arrays in facilitating topical anaesthesia using a dyclonine cream [67]. By a factor of 3, MN use decreased the amount of time it took for a pain stimulus to result in a substantial pain reduction.

It is apparent that over the past five years, the number of MN clinical trials has significantly expanded. The growing interest in MN technology is the key factor that may be used to explain this. Notably, only a few circumstances have been investigated in these trials, and most of these use MN injection devices rather than MN array-based patches. Therefore, further clinical research will be needed over the course of the next ten years to demonstrate the effectiveness and advantages of MN delivery systems over conventional distribution systems.

v CONCLUSION

Only substances with the necessary physicochemical qualities, which permit passage across the SC and into the viable epidermis, have been used for transdermal medication delivery in the past. Transdermal therapeutic drug administration is constantly improving thanks to research of MN delivery mechanisms, which would never passively traverse the SC otherwise. Beyond the straightforward, solid MN design, the original MN concept has evolved into second- and third-generation technologies made from a variety of materials, with various shapes and delivery briefs.Researchers in this field now place a high priority on MN product development and regulation due to the trend toward improving transdermal administration of bigger peptide, protein, and vaccine components as well as conventional molecules. Numerous research institutes throughout the world are still debating clinical trials, and with the introduction of MicronJet®, it is eagerly awaited for MN goods to become commercially available.

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