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MICRONEEDLES DRUG DELIVERY SYSTEM: INSIGHTS ON ITS FABRICATION TECHNIQUES AND CHALLENGES

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ABSTRACT

In recent years, there has been significant interest in an innovative transdermal delivery technology. This technology has the ability to distribute therapeutics and cosmeceuticals for various applications, such as vaccines, drugs, and biomolecules for skin-related issues. The advantages of microneedle patch technology have been thoroughly assessed in recent literature, resulting in a substantial increase in academic publications on the topic. However, like any new technology, the application of microneedle patches has potential limitations. In this review, we will discuss these limitations and emphasize the areas that require improvement. Emphasising these concerns early on should help scientists and technologists to address the matters in a timely fashion and to use their resources wisely.

Keywords: Microneedles, Transdermal drug delivery; Fabrication, Challenges.

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INTRODUCTION

Around 20% or less of total loaded drug is permeated across the skin from creams **[1]**. To resolve this hurdle, dermatologists are gradually turning their attention to latest transdermal drug delivery systems (TDDSs). Among TDDSs microneedles (MN) drug delivery systems are emerging swiftly in recent decades. The microneedle (MN) delivery system has attracted interest, among the available transdermal drug delivery, for many research institutes and companies. MN could be visualized as merge of hypodermic needle and transdermal patch **[2]**. MN system comprises a base plate with microneedles arrays upright to it.

MN is defined as the non-invasive, pain-free delivery of active drug molecules through the surface of skin. The MN delivery system composed of a series of array of sub millimeter-sized projecting needles (length up to 1500 µm) attached to a base support and it is able to penetrate into the outmost skin layer - stratum corneum. In this fashion, the pain-free delivery of active biomolecules is possible, as the MN system rescue interfering with skin nerve fibers and blood vessels which are located deep in the skin. The MN system has been demonstrated as a suitable method in delivering therapeutic ingredients with low to higher masses (over 500 Da) including small molecules, vaccines (COVID-19, SARS, MERS), bio-macromolecules (proteins, peptides, hormones) and genes **[3]**. MN application bypasses the main obstacle in a "smart" way and makes the delivery of drugs much easier.

MN technology was initially conceptualized and patented in 1950s, that times it took lag period for the potential of MN to be broadly recognized **[4]**. In 1998 a study was investigated that triggered the commanding use of MN for the delivery of vaccines **[5]**. Till to date large number of research studies on MN has conducted noticeably including over 4000 patents and active research papers have been published. There has been significant growth in recent few decades, including latest technologies of MN formulation and the characterization of MN in practicable setting.

MICRONEEDLES DELIVERY TECHNIQUES

The large surface and position of human skin make it an appropriate and non-invasive area for delivering active pharmaceutical agents and for collecting interstitial fluid sampling for biomarker detection too. Fundamentally, microneedles drug delivery systems are, non-invasive, self-administered and pain-free techniques that assist. They provide enhanced patient compliance and offer an alternative way to hypodermic needles. As researchers are taking keen interest in this field and sharp increase in publications is observed in the last three decades. MN are formed using several constitutional ingredients with numerous shapes and designs including metals, glass, polymers and hydrogels for various delivery approaches. Among the approaches, five are common and

well developed **[6, 7]**.

Coat and Poke (CP) or Coated MN

In "coat and poke" approach coating of active pharmaceutical agents on the external face of MN (silica, polymeric or metallic) is likely to produce coated MN. The stable and uniformly layered formulations allow the MN for effective drug delivery. The water-soluble drugs are of choice for such formulation and should allow multi-layer coating of them. Choice of a suitable coating method is crucial for acceptable formulation of coated MN. The incorporation and delivery of macromolecules along with hormones, vaccines and insulin has been testified for the coated MN **[8]**.

Poke and Patch (PP) or Solid MN

The "poke and patch" category involves the piercing of a solid MN to form small holes on skin surface, and then drug application upon skin in conventional way. The first fabrication of solid MN to deliver fluorexon (calcein) was reported on silicon using in vitro through human excised dermis **[9]**. Biocompatibility, cost and fragility and the complex fabricating method have piloted scientists to utilize other materials such as metals, polymers and ceramics for achieving improved conclusions. Although the fabrication of solid MN is technically easy as no coating or loading is required. The main limitations of solid MN are the two-step administration protocol, safety matters and no precise dosing with active drug formulations requirement. The potential of solid MN for the administration of vaccines, proteins and hormones, have also been investigated **[10]**.

Poke and Dissolve (PD) or Dissolving MN

The "poke and dissolve" approach uses typically biocompatible, biodegradable and affordable polymers and MN delivers water-soluble active therapeutic drugs into skin. Chitosan, hyaluronic acid, polylactic/glycolic acid and sucrose are those polymers frequently used for the fabrication of dissolvable MN. Polysaccharides have also been often utilized to prepare dissolvable MN because of their physico-chemical features, which permits fabrication and optimization with variable and adjustable functions and characteristics. This resulted emergence of carbohydrate-based MN with incredible benefits for serving as an appreciable uplift in biomolecules detection, biological response along with administration **[11]**. This "poke and dissolve" approach, contrary to silicon or metal, is based on the erosion of MN by interstitial fluid upon exposure into skin. Depending upon the properties of the composite, the dissolving step of MN material liberates the loaded moiety from the matrix for its local or further systemic absorption. Presently, the soluble MN are formed by utilizing simple sugars and polymers by commissioning either micromoulding or casting methods. The active therapeutic drugs are capsulated, stocked, and protected in the matrix and carried into the targeted site. After MN insertion into the skin the polymer degradation step takes place without leaving the hazardous leftover. The carbohydrate (sucrose) and fish gelatin-based MN have also been tried for vaccine delivery and a successful administration of MN in vaccine administration has been investigated **[12]**. The influenza virus vaccines application by MN were found to be safe with immunogenicity. The advantages include the avoidance of limitations of other techniques, for instance, sharp wastes and pump requirement for solid MN, the poor pharmacoeconomic of hollow MN, and a highly precise layering practice with coated MN. However, MN have their own drawbacks say low doses, compromised mechanical strength, and uncertain piercingabilities.

Poke and Flow (PH) or Hollow MN

Another applications of "coat and poke" MN approach has been described recently for the sensitive determination of protein biomarkers in an immunized mouse model **[13]**. MN of polystyrene loaded with a primary antibody were prepared, with an enhanced limit of detection, to determine inflammatory response in interstitial fluid. The key distinguishing attribute of coated MN is their capability to ensure bioactivity by avoiding the degradation of therapeutic molecules during the MN production process. Additionally, coating is one of most controlled and the easiest methods of getting MN functional. It makes possible the sampling and isolation for MN with precise detection ability. Nonetheless, some common restrictions are the low doses and coated payload may decrease the strength of MN, which causes MN with low strength and penetration ability.

The "poke and flow" technique by using hollow MN permit the supply of relatively large doses of active therapeutic drugs into the skin with could potentially at least sideline the dose constrain linked with solid MN **[14]**. For hollow MN, their structure allows to get control over the dosing and flow by pressure or diffusion or electronically and the integration into lab-on-chip devices. The hollow MN can be utilized to deliver macromolecules, including proteins, mRNA, vaccines, and diagnostic agents. MN can also be utilized for ECG measurements and the isolation and identification of glucose. However, the framework of hollow MN is comparatively sophisticated and suffers from clogging, structural fragility, drug leakage, requirement of a more tip size and poor insertion **[15-17]**.

Poke and Release (PR) or Hydrogel-forming MN

For hydrogel-forming MN soft materials have recently been used including swellable polymers (PEG-crosslinked poly(methyl vinyl ether-co-maleic

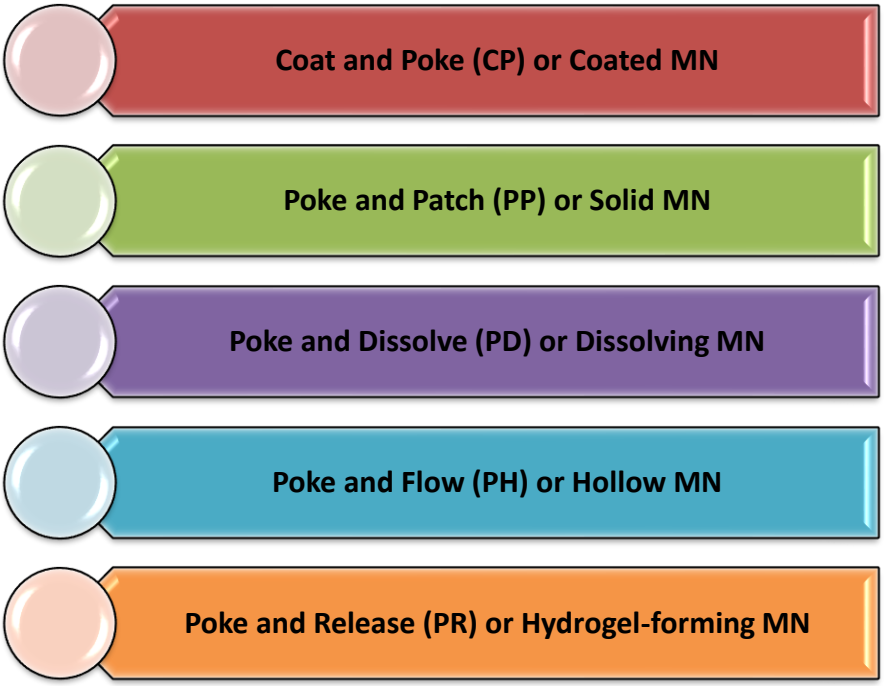

Figure 1: Microneedle-based delivery approaches.

acid and poloxamer,), and silk fibroin with phenylboronic acid/acrylamide **[18, 19]**. Upon insertion into the skin, the polymers absorb the interstitial fluid into their 3D matrix, facilitating in the transfer of active drugs through created mini ducts. The response-triggered delivery of active biomolecules applications, for instance insulin, is notable research as it overcomes the necessity for persistent glucose nursing and delivers medicine on reception of physiological response. The diagnostic utilization of hydrogel-forming MN include lithium monitoring and detection of glucose **[20, 21]**. By regulating the polymer proportion and degradation from minutes to days a refined delivery time is quite possible. The poor strength and therapeutic drug doses are the main drawbacks of hydrogel-forming MN. This type of MN needs much perfections to be used for any practicable commercial delivery in up next decade.

CHALLENGES OF THE MICRONEEDLE DELIVERY SYSTEM

Commercialization of MN from laboratories to a pharma industry is a desirous but challenging task for execution. To translate MN technology from the research lab to industry, some key questions and challenges should be addressed and considered into consideration. The main challenges for the successful launch of a MN delivery system are discussed.

Lack of Existing Infrastructure

The fabrication of MN is generally more sophisticated than conventional dosage forms such as orals, topicals, inhalers or injectables. It is directly associated with the unique features of MN products, but the precise structural requirements, necessary for successful drug delivery, encounter a risk to industry trying to pilot production to commercial-size batches. The use of MN based product in cosmetics is probable the principal contributor to scientific developments and infrastructure development in any region. Otherwise, the industry must depend on angel stockholders to develop MN for pharmaceutical drugs and vaccines **[22]**.

Cost Challenges

An economic evaluation, of MN technology and its comparison to existing delivery system, has not been carried out extensively. A study indicated an estimated to be 1.5 million dollars for MN-based delivery compared with 2.5 million dollars for SC application as a total cost for a vaccination program **[23]**. The economical cost of MN is based on several factors including the effectiveness and approval rates of the MN compared to the conventional subcutaneous delivery of vaccines. A model, where healthcare team was assigned to manage the MN-based system, estimated an economical or dominant MN application about 10 dollars price point in majority of reviewed circumstances.

Biocompatibility and Stability Challenges

To ensure the safety aspects of MN for human exposure biocompatibility in main parameter for which numerous tests are essential based on contact periods. The common recommended tests are irritation, cytotoxicity, sensitization and intracutaneous reactivity for short term contact **[24]**. For more than 30 hours genotoxicity and subacute/subchronic systematic toxicity examinations are suggested additionally.

The use of aqueous polymeric substance to fabricate MN without the use to elevated fabrication temperature during heating stage may be more significant useful in avoiding the degradation of active biomolecules particularly heat sensitive proteins and peptides. However, the stability of MN loaded drug has to be appraised to protect breakage during storage by storing MN at various temperatures usually 4 to 60 °C. Th stability of MN can be further prolonged by the addition of stabilizers (trehalose and sucrose) and keeping the storage conditions cool and dry **[25]**.

Insertion Challenges

Various parameters including base and tip diameters, geometry and length alter the ability of MN to effectively pierce the skin for drug delivery. The geometry is evident that the penetration characteristics and mechanical strength of MN are governed by the geometric configuration of MN arrays on base **[26-28]**. The cone-shaped MN exhibits the perfect geometry then hexagonal triangular and square with greater needle insertion for the delivery of immunization and ovalbumin **[29].**

Tip diameter and Sharpness play a vital role for MN insertion into dermis. A blunt tip (60–160 µm diameters) depends on the tip frontal area and need a comparatively high insertion force for a controlled drug applications **[30]**. The fabrication of sharp tips MN is crucial to accomplish a drug delivery to the desired level. It has been studied that MN with <15 µm tip diameters enter into dermis more efficiently than MN of tip with larger diameter for the effective delivery of biomolecules. The sharpness of MN tips can facilitate and control the puncture force but at the same time an increased tip sharpness decreases the mechanical strength of MN leading to a high probabilityof bending and breakage.

Length of MN should be kept into consideration if the intentions are to achieve access to the blood, it may be desirable to create pores that deliver deep into skin. This may be one logic for variable microneedle lengths (up to 1000 µm) that have been reported in the literature **[31]**..

Dosing Challenges

The inability to monitor dose delivery and low drug loading capacity remain among the main hurdle to establish MN technology for clinical administration particularly challenging for vaccination. A coated MN can only enable the delivery of bolus dose (upto 1 mg) of the loaded drug. However hollow MN allow a continuous infusion or "as- needed/on-demand" dose after insertion into skin.

The dosage accuracy of MN in accurate and continuous fashion drug release is another subject that involves keen consideration **[32, 33]**. As proteinous drugs (say insulin, parathyroid hormones, erythropoietin, growth hormones, glucagon) are prone to rapid inactivation and degradation during storage their dose accuracy is more challenging tasks. These issues could be adequately fingered out by the incorporation of stabilizers, proper storage conditions, dry/cool storages, suitable packaging and polymer concentration **[34,35]**.

Skin Irritation Challenges

The immunogenic behavior of human skin makes it an extremely responsive site for drug delivery through MN administration of active agents. A common effect side includes mild and temporary erythema apparency depending on the size, fabricating substances, and active molecules. Before any human clinical trials, these safety testing (immune responses) must be determined using animal models. Contrary to this excessive immune responsiveness of human dermis could offer an ideal chance for MN to deliver vaccines **[36]**.

Sterilization Challenges

Sterilization of MN to meet pharmaceutical standards may be mandatory by the regulatory agencies to safeguard the consumers. The method of sterilization including microwave radiation, moist heat, gamma rays, and ethylene oxide may be misfit for MN themselves and for sensitive loaded ingredients such as biomolecules, vaccines, peptides. The substance and ingredients used for MN formulation governs the selection of sterilization method. For solid MN of silicon, metals, and glass, dry heat sterilization, ethylene oxide, electron beam, gamma radiation and moist heat sterilization are the most common techniques used. The gamma irradiation at a sterility assurance level of 10^{-6} can be employed for sterilization without deleterious effect on structures or drug delivery capabilities of HMN **[37-39].** In a study of silver nanoparticles, researchers found that the pores created MN were free from microbes until the dermis is restored completely **[40]**, it is what they called self-sterilization of MN.

Regulatory and Commercial Challenges

The regulatory body critically analyzes the clinical application, repeatability, efficacy of MN animal testing, cell investigations and clinical trials. The cases of MN products for therapeutic efficacy are growing exponentially. An approval submission necessitates satisfactory information about MN product manufacturing and analysis validations including content uniformity, stability testing, risk analysis, manufacturing, sterility validation. If all requirements can be appropriately addressed to cater the requirements of regulators, then the dream of MN commercialization will soon be converted into reality exponentially. The first new drug application of titanium MN with a coated zolmitriptan (Qtrypta by Zosano Pharma), for

acute migraine treatment, was submitted to FDA in 2020.

CONCLUSIONS

The future looks promising for the development of microneedle-based drug delivery products that can be sold on the market. Researchers are conducting extensive studies on microneedles to find efficient ways of delivering therapeutic drugs. This is crucial because we urgently need new methods to expand the transdermal market for hydrophilic molecules, macromolecules, proteins, and conventional medicines for new therapeutic indications. The microneedle industry is expected to flourish as new information is discovered, leading to advancements in the field. While several clinical trials have proven the effectiveness of microneedles, there is still a need for more preclinical studies. Additionally, the use of novel manufacturing methods is expected to reduce costs and simplify fabrication procedures in the near future.

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