REVIEW ARTICLE

Microneedles for Proteins and Peptides Delivery: Current Aspect and Future Perspective

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Abstract

More than half of the top 20 most famous drugs fall under biopharmaceuticals, with projections indicating a $388 billion value by 2024 that shows how effective protein, peptide, and antibody-based treatments are. However, the methods for effective medication delivery have been limited by the inherent characteristics of biopharmaceuticals. Although the intravenous route offers 100% bioavailability, patients frequently link it with discomfort and needle anxiety, which might result in resistance to receiving necessary therapy. Since then, several non-invasive techniques have been developed to get beyond these restrictions. One such tactic is microneedles (MNs), which can painlessly pierce the stratum corneum barrier and significantly improve transdermal medication delivery of various medicines. This review summarizes several studies that strive to enhance MN-based transdermal biopharmaceutical delivery. The ability to increase MN production at a lower cost and the application's long-term safety will be key factors in determining the full potential of MNs as a drug delivery technology for biopharmaceuticals. Thus, the existing obstacles to the clinical translation of MNs are also examined, along with potential solutions.

Key words: Bioavailability, medication delivery, microneedles, peptides, proteins

INTRODUCTION

By bypassing the skin's stratum corneum barrier with the help of a minimally invasive device called a microneedle (MN) array, it is possible to improve transdermal drug delivery. A MN typically consists of several tiny projections made of silicon, metal, or polymeric materials that are fastened to a support that limits how deeply the device can penetrate the skin.[1,2] The actual MNs can take the shape of sharp protrusions, microblades, or structures resembling needles. It can either be solid or have a hollow bore through the center. Compared to proteins, peptides are smaller. Proteins are made up of 50 amino acids or more, whereas traditionally, peptides are classified as molecules that include between 2 and 50 amino acids.[3,4]

Significant progress has been made in drug delivery in recent years to improve patient compliance and therapeutic efficacy. MNs technology has become one of these cutting-edge methods that shows promise in delivering medications based on proteins and peptides.[5,6] Because they avoid the drawbacks of typical injection techniques, MNs provide a painless and minimally intrusive way to administer drugs. This review paper presents an extensive overview of the state-of-the-art MNs-based drug delivery techniques now in use, as well as any potential applications in treating proteins and peptides.[7,8]

Shortly, peptides and proteins will increasingly be utilized to treat cancer, diabetes, and autoimmune diseases. However, bioavailability issues, unstable formulations, and frequent dosing prevent their remarkable efficacy. MNs can be applied from the micrometer to millimeter range by enhancing the delivery of high molecular weight drugs only to the outer skin layer, that is, the stratum corneum.[9]

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Advantages of MN-based delivery

In this section, we discuss the numerous benefits of utilizing MNs to deliver proteins and peptides in medicine. Moreover, the painless and less invasive nature of MNs enhances patients' comfort and compliance. These needles avoid undergoing a first-pass metabolism associated with administering drugs orally thereby enhancing drug bioavailability. Moreover, the ability to self-administer MNs,' eliminates the need for medical training and opens up the opportunity for the public to access them.[10] Some of the advantages of MN are shown in Figure 1.

HISTORY

MNs are a long-thought idea that has seen impacts and has been the result of advancements in numerous scientific domains. Here is the historical perspective of MNs.

Early concepts and applications

It was in the 70s that researchers first came up with the idea of utilizing MNs for drug delivery – consequently suggesting the need for thinner, smaller syringes to avoid invasive treatment. Initially, these needles were used to penetrate the natural skin barriers and lessen pain and tissue injury.[11]

Silicon MNs

Silicon MNs started to become popular as possible technological advances in the late nineties and the early 2000s. By making use of the identical microfabrication techniques that are used in designing semiconductor devices, we were in a position to control accurately the dimensions as well as the shape of silicon MNs. For drug delivery through the skin, the main purpose of these MNs is to release small molecules, vaccination, and even local anesthesia.[12]

Hollow MNs and intradermal drug delivery

Targeting the dense web of blood arteries and immune cells in the dermal layer of the skin, these MNs enabled accurate intradermal drug administration. Given that it may provide benefits including dose sparing and better immune responses, intradermal administration of vaccinations has become very important. Attention turned to hollow MNs that could administer more medicines, per unit area.[13]

Dissolving MNs

The use of biodegradable, dissolving MNs for drug administration became more popular in the 2000s. These MNs were made to dissolve or disintegrate as soon as they were inserted into the skin, allowing the medicine they contained to be released gradually. Dissolving MNs made them safer and more suitable for self-administration by eliminating the requirement for needle removal and lowering the chance of needle-stick wounds.[14]

Coated MNs

Another variant in the MN landscape has been coated MNs. These MNs allowed for the controlled and sustained release of medications since they had a solid base with a drug-coated coating. Upon implantation of the MN, the drug-coating may disintegrate, release, or infiltrate into the skin. Coated MNs presented potential benefits for delivering proteins and peptides with controlled release kinetics and enabled flexibility in medication release patterns.[15]

Recent advancements

Recent developments in the field of MNs focus on new methods of fabrication, which permit innovations in 3-D printing, micro-molding, and laser ablation that can result in complex geometries and increased drug loads, extending their use to diagnostics, biosensors, and biomarker monitoring, besides drug delivery.[16]

MNs are designed to provide less invasive, patient-friendly delivery of medicines. Recently developed improvements increased their accuracy in delivering a drug in assorted therapeutic areas.[17] Some of the various types of MNs used for protein and peptide delivery systems are shown in Figure 2.

CHALLENGES

Challenges for MNs

This approach in drug delivery and biomedical applications is related to the use of MNs, which are rather promising. These tiny, typically tens to hundreds of micrometer-long structures

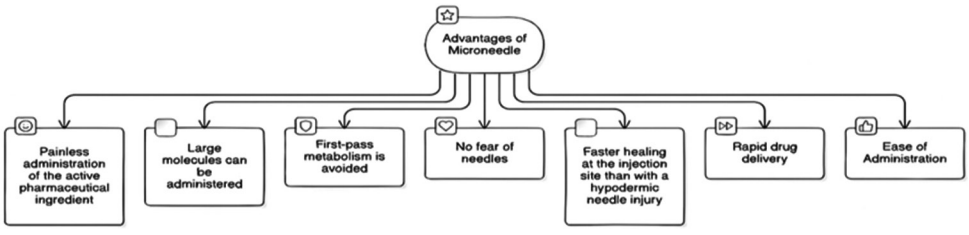

Figure 1: Advantages of microneedle

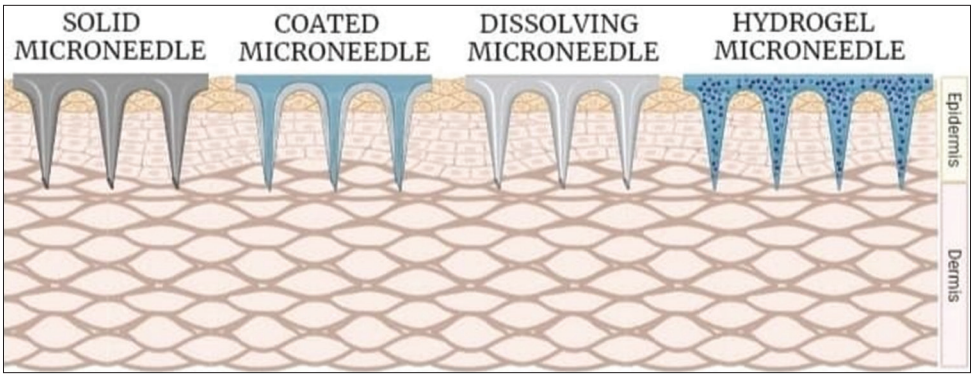

Figure 2: Various types of microneedles used in the protein and peptide delivery system

show great promise for the painless and effective delivery of therapeutic agents through the skin. MNs have numerous advantages, but there are obstacles to their development and use.[18] The goal of this article is to examine the problems with MN technology and discuss the potential

Fabrication methods

Probably, the development of cost-effective fabrication methods is one of the major challenges for MN technology. There are several techniques applied, such as lithography micro-molding, and laser ablation; however, reproducibility of quality and material compatibility results are still the object of investigation.[19]

Biocompatibility and safety

MNs must have very high biocompatibility with non-toxic, non-irritant, and non-allergenic materials. Sterility in the course of production and storage is highly important to avoid infections. Regulatory mechanical properties ensure strength during insertion. Extensive testing of biocompatibility by *in vitro*/*in vivo* will form experiments to be conducted for the safety and reliability of these devices.[19]

Skin penetration and insertion depth

The two most important things in the administration of medication via MNs are consistent and controlled penetration of the skin. Variations in thickness, elasticity, and moisture create problems. Whereas a good amount of progress has already been made in the design of MNs, getting uniform painless penetration that will not rise to tissue injury remains an active area of research adaptable to different skin conditions.[19]

Drug loading and release

MNs excel in simplicity and speed, but so far, controlled release and adequate drug load remain an eluded dream. The design of effective reservoir or dissolvable MNs relates to their loading efficacy, stability, and the *in vitro–in vivo* correlation of their drug release profiles, hence further proactive design research and more optimized drug composites.[20]

Regulatory consideration

This new medical technology, MNs, requires robust regulatory standards to be dealt with before clinical use. Companies need to ensure that the device passes pre-clinical and clinical evaluation for its safety, effectiveness, and quality. Collaboration that streamlines the regulatory path can help in the efficient development and approval of the same.[20]

Patient acceptance and usability

Looking at the adoption of the technology of MNs, sensitizing benefits for health practitioners, and reassuring patient concerns about ease, safety, and side effects can raise acceptance distinctly in clinical settings.[20]

Challenges for MNs in protein and peptide drug delivery (PPDD)

Although MNs represent a promising approach for the delivery of proteins/peptides, individual challenges bring down their full potential for medication delivery.

The stability of protein and peptide

Because proteins and peptides are such fine molecules, they are easily affected by denaturation, aggregation, and enzymatic destruction. The stability of these biomolecules may be affected by the manufacturing and storage procedures for MNs as well as the insertion and release of medications. Maintaining therapeutic efficacy during the MN administration method depends on ensuring the preservation of protein and peptide integrity.[21]

Formulation development

Developing suitable formulations for protein and peptide drugs that can be effectively delivered through MNs is a complex task. Formulation considerations include maintaining the stability of the drug, achieving the desired release kinetics, and ensuring compatibility with the MN material. In addition, formulating proteins and peptides that allow for efficient loading and release without compromising their activity is a significant challenge.[21]

Correction of needle design

Achieving effective and regulated medication delivery requires careful MN design. For efficient stratum corneum penetration, minimal discomfort and tissue injury, and maximum medication permeation, MN size, geometry, and mechanical qualities must be optimized. It can be difficult to balance these design elements for optimal performance, and doing so requires a thorough knowledge of the skin barrier and interactions with MNs on the skin.[22]

Scalability and manufacturing

Sustainable and cheap manufacturing procedures are required to achieve the clinical promise of MN-based medication delivery. Large-scale MN manufacture is difficult to achieve consistently and reproducibly because of issues with material choice, fine-tuning manufacturing processes, and quality verification. For MNs to be widely used in protein and peptide treatments, manufacturing procedures must be created that pharmaceutical businesses can simply adopt.[22]

Regulatory approval and clinical translation

Overcoming several regulatory and safety barriers is necessary for successfully transferring MN-based drug delivery devices from preclinical investigations to clinical applications. For regulatory approval, it is crucial to show that MNs are safe, effective, and stable, as well as to address issues with patient acceptance and compliance. Incorporating MN technologies into current medical practice presents important obstacles including meeting the demanding standards for clinical trials and dealing with the regulatory environment.[22]

Cost considerations

The cost-effectiveness of any MN-based medication delivery system is important in itself. The manufacturing costs should be worked out at par with the formulation development and production methods involved. The greater effort invested in collaborative working between researchers, physicians, engineers, and regulatory agencies will enhance cost-effectiveness, diffusing MN therapies widely to bring about a likely paradigm shift in disease management.[23]

CATEGORY OF MNS

MNs were studied and employed for this purpose to deliver a variety of drugs and therapeutic substances. While the specific pharmaceuticals used with MNs may differ depending on the stage of research and development, the following ten examples of the medicines that have been explored or proven for administration using MNs are provided:

Insulin

MNs have been researched as a potential replacement for traditional insulin injections in the treatment of diabetes. They offer a less intrusive technique that might improve patient compliance.[24]

Vaccines

A cutting-edge, painless method of giving vaccines using MNs has been investigated. Numerous vaccinations, including those that protect against influenza, measles hepatitis B, HIV, or the human papillomavirus, have been administered using them.[24]

Growth factors

For purposes including regeneration of tissues and wound healing, growth hormones such as platelet-derived growth factor, or PDGF, and converting beta growth factor (TGF-) have been injected using MNs.[25]

Anticoagulants

To treat conditions such as deep vein thrombosis, or DVT, or to prevent thrombosis during surgical procedures, the precise delivery of anticoagulant drugs utilizing MNs, such as heparin, has been studied.[25]

Analgesics

MNs have been examined for the administration of regional anesthesia, which includes lidocaine or a drug called for pain relief and anesthesia.[25]

Anti-inflammatory drugs

These drugs, along with others, especially those administered through MNs, have been successfully used to treat skin conditions such as psoriasis, eczema, and dermatitis.[26]

Anticancer drugs

MN-based targeted administration of anticancer drugs such as paclitaxel or doxorubicin has been researched to target specific tumor areas and lessen systemic side effects.[26]

Antibiotics

The use of MNs for the precise administration of medications to treat skin infections, notably MRSA or methicillin-resistant Staphylococcus infections, has been examined.

Hormones

MNs have been used in studies on the transdermal delivery of hormonal such as estrogen or androgen for replacement therapy for hormones and contraception.[26]

Peptide-based drugs

MNs have been used to deliver peptide-based drugs for the treatment of pain, skin rejuvenation, and other therapeutic applications. It is important to keep in mind that the study on the application of MNs for administering medications is ongoing, and even while certain drugs have been tested using MNs, there might be variations in their clinical accessibility and regulatory approval. Depending on the intended use and level of research, the precise drug compositions and MN designs may change.[26]

LIMITATION OF MNS FOR PPDD

Size and complexity of the medication

Because MNs have a limited capacity for drug loading, they are not always able to deliver large and complicated protein and peptide medicines. Some medications could be too big to be given efficiently using MNs.[27]

Needle length and infiltration depth

MNs have a limited length and may not be able to deliver. Protein and peptide medications to the skin deeply enough. This may lead to insufficient treatment effects and subpar drug absorption.[27]

Manufacturing complexity

It can be expensive and technically difficult to fabricate MNs with the necessary size, structural integrity, and drug-loading capabilities for protein and peptide medicines. For mass production, the manufacturing technique could not be scalable.

Patient acceptability and compliance

Not all patients may be suited for MN-based medication administration, particularly those who have skin problems that prevent MN application or needle phobia. Limiting considerations may include patient acceptability and compliance with this delivery strategy.[27]

Infection or tissue damage risk

Using MNs incorrectly or repeatedly increases the risk of infection or tissue damage. This is, especially concerning for protein and peptide medications that need a sterile setting to be administered.[27]

MECHANISM MNS FOR PPDD

There are many important processes in the MN method for protein and peptide medication delivery:

Skin penetration

MNs are intended to pierce the stratum corneum, the skin's outermost layer. Large molecules such as proteins and peptides are prevented from penetrating through this layer, which serves as a barrier. By piercing the skin to the size of micrometers, MNs remove this obstacle and provide the medications with direct access to the underlying tissue.[28]

Drug loading

There are two types of MNs: hollow and solid. When it comes to solid MNs, the medications might be encapsulated or coated on the outside of the MNs structure. For hollow MNs, the drugs can be loaded into a reservoir or a dissolvable matrix inside the needle.[28]

Skin insertion and dissolution

These are typically applied to the skin using a patch or a device. The MNs painlessly pierce the stratum corneum, reaching the viable epidermis or the dermis where the drug can be effectively delivered. In the case of dissolvable MNs, they gradually dissolve or disintegrate within the skin, releasing the drug.[28]

Enhanced drug delivery

MNs not only provide a pathway for drug delivery but also enhance the absorption and permeation of proteins and peptides. The MNs insertion creates transient nanopores or microchannels in the skin, increasing the surface area available for drug absorption and facilitating the diffusion of drugs into the tissue.[28]

Drug release and diffusion

After the MNs are inserted into the skin, the loaded drugs can be released in a controllable manner. In the case of solid MNs, the drugs could dissolve or disperse from the surface of the MNs; then, diffusion may drive them to move into the tissue. Hollow MNs can be directly injected through the skin or linger from the reservoir because of osmotic pressure or mechanical forces.

DIMENSIONS OF MNS

Length

MNs can measure a length range anywhere from 100 to 2000 mm. The skin thickness required for dosage or any other type of therapeutic is used to determine the length. The short form is suitable for transdermal drug delivery whereas the longer form accesses deep-seated tissues or specific body parts.[29]

Diameter

MNs measurements can vary remarkably depending on their manufacturing processes Since hollow 1 MNs have a hollow lumen for drug administration, their diameters are usually bigger than those of solid MNs, which typically range in diameter from 10 to 200 mm. Tens to hundreds of micrometers can be the diameter of a hollow MNs.[29]

Tip geometry

MNs have tip shapes such as conical, pyramidal, or cylindrical, depending on what is to be done. Thereafter, the tips of a conical kind show better skin penetration, while cylindrical tips were found to control the release of drugs. Fabrication techniques, resulting in high accuracy, such as photolithography or molding, ensure that tips are rendered for purposes of optimal therapy results and subject comfort.[29]

MATERIAL USED FOR MANUFACTURING MNS

In making MNs, people use various materials depending on the purpose of use and desired characteristics. These are some of the materials that are frequently used in MNs production:

Inorganic non-metallic materials

Silicon

Despite their established production processes and compatibility with semiconductor processing methods, silicon MNs are broadly used. They can be formed using microfabrication techniques such as photolithography and etching.[30]

With the properties of high strength, chemical stability, and heat resistance, silicon is undoubtedly a perfect material for medical instruments, in particular, systems used for replacing joints or microfluidic systems. The new techniques to configure complex silicon geometries open the way for them to be adopted in extremely different applications, from infusion tubes to contact eye lenses.[30,31]

Ceramics

Ceramic materials such as alumina (Al2O3) or silicon nitride (SiN) can be utilized in producing MNs. MNs composed of these ceramics are famous for having great resistance against chemicals, high thermal stability, and mechanical strength.

Metal

Metal alloys

Commonly, MNs, which are largely used, contain different metal compounds such as stainless steel, titanium, and nickel. These materials can be produced via micromachining or electroforming techniques and have good mechanical strength. For applications that call for increased endurance or where accurate penetration is required, metal MNs are acceptable.[31] For hollow, coated, solid-state, and other types of MNs, metal is an appropriate material. Titanium, aluminum, and nickel are among the metals used in MNs. Metal MNs, however, have the drawbacks of being rigid and non-degradable.[32]

Stainless steel

It offers excellent mechanical strength, corrosion resistance, and biocompatibility, which makes stainless steel best for surgical implants and metal MNs in general, with AISI316L and AISI317L grades.[33]

Titanium

Titanium is a silver-white transition metal broadly applied in medical fields due to its low density, high strength, stable chemical properties, good temperature, and acid resistance. Li JY developed a titanium porous MN array using an enhanced MIM technique that effectively penetrated human forearm skin without fracture.[33]

Aluminum

The most affordable and practical medicinal substance is aluminum, a silver-white light metal that has great qualities such as ductility, lightweight, and corrosion resistance. The addition of a dense network of needle-like nanotube thin film channels that cover a substantial surface area to aluminum MNs improves their mechanical properties and allows for the transport of more medicines.[33]

Polymers

The polymer's easy formability, quick processing cycle, low cost, and broad range of material options make it simple to achieve large-scale manufacturing, and the needle has a decent amount of toughness. Polymer material molding has grown in importance as a study topic in the field of medical MN preparation because it may be both biocompatible as well as biodegradable at the same time.[34]

Polycarbonate

The molecular chains of high molecular weight polymers, such as polycarbonate, include carbonate groups. This long-lasting thermoplastic resin has exceptional electrical properties, high strength and elasticity, dimensional stability, and fatigue resistance. In addition, it can withstand weak acids and alkalis. Polycarbonate MNs can be manufactured by hot embossing because of the thermodynamic characteristics of polycarbonate.[35]

Polyvinylpyrrolidone (PVP)

The thermoplastic resin PVP is created by polymerizing ethylene. It benefits from not being poisonous, resilience

to the majority of acids and alkalis, and strong electrical insulation.

The mechanical strength of CaCO3-doped PVP MNs is higher than that of pure PVP MNs. In addition, by altering its geometry, its mechanical stability can be improved.[35]

Acrylate

Thus, acrylic polymers are valued due to their transparency, low toxicity, ease of production, adhesion, resistance to water, and durability, hence making the acrylic resin useful in many medical fields, including making acrylate MNs through melt extrusion and molding techniques.

Dextran

The former one gives good mechanical and material permeability. However, its mechanical strength could have potential implications for penetrating the skin in the dry state. Upon immersion in tissue fluid, it will swell to a structure that could have material transport capability. Swollen MNs are usually prepared with cross-linked hydrogel through soft lithography.

The addition of hydrogel gives the MNs the ability to administer medications continuously, allowing them to be employed in a variety of situations where a sustained release of medication over several days is necessary.[36]

Polyvinyl alcohol (PVA)

PVA, which can be employed as the primary component of the dissolving MNs, has good thermal degradation properties.

3D printing can be used to create PVA MNs. The hydrogel's high pore microstructure was first used to extract interstitial fluid, which was then used to heat and dissolve the PVA in a water bath. The target biomarker was quickly and effectively removed from the MNs patch, and its concentration in the solution was calculated.[36]

Carboxymethylcellulose

CMC is a cellulose-derived anionic polymer. The mechanical strength of the dissolving MNs, which enables the delivery of the drug, is enhanced. The mold-formed CMC MNs are biodegradable and biocompatible. They deliver human growth hormone and lidocaine efficiently and demonstrate improved permeability in a few minutes.[37]

Cellulose acetate phthalate (CAP)

pH-sensitive and water-permeable, CAP is derived from cellulose acetate by esterification with acetic acid. While CAP is safe for use in contact with skin, its decomposition may be caused by alkaline or oxidizing environments. Electrochemically induced changes in pH on the application of an electrical current would, therefore, make drug release-controlled CAP MNs well up or disintegrate, thereby enhancing accuracy in medication delivery.[37]

Glass

Glass MNs are fabricated using techniques such as thermal drawing, where a heated glass fiber is pulled to form a long, thin needle. Glass MNs offer high precision, transparency for visualization, and excellent biocompatibility.

Dissolving materials

For applications where the MNs need to dissolve or degrade after use, materials such as sugar, hydrogels, or water-soluble polymers such as PVA can be employed. Dissolvable MNs eliminate the need for needle disposal and offer a convenient way for drug delivery or painless blood sampling.[37]

It is important to note that the material selection depends on factors such as the intended application, mechanical requirements, biocompatibility, drug compatibility, and manufacturing capabilities.

METHODS USED FOR FABRICATION OF MNS

There are several methods used for MN fabrication each with its advantage and suitability for different materials and applications here are some commonly used methods

Micromolding

This method involves using a mold to fabricate an MN. A liquid or molten material such as polymer or metal is injected or cast into the mold and allowed to solidify once Solidified the MN array is de-molded micro molding technique includes hot embossing injection molding and soft lithography.[38]

Lithography-based technique

Lithography methods such as photolithography or deep reactive ion etching are commonly used for fabricating silicon or glass MNs. Photolithography involves using light-sensitive material (photoresist) and pattern masks to transfer the desired MN pattern onto a substrate DIRE uses a combination of plasma etching and masking techniques to etch precise features into silicon or glass of substrates.

Laser ablation

Laser ablation involves using a higher energy laser to selectively remove material and create an MNs structure this

matter is used for fabricating metal MNs where the laser is directed into a metal sheet or file to create a desired needle shape.[38]

Drawing and pulling

Drawing and pulling methods are used for fabricating glass MNs. This technique involves heating a glass fiber and then drawing it to create a long thin needle-like structure thermal drawing or fiber pulling technique can achieve precise control over this dimension.

3D printing

Adaptive manufacturing techniques such as 3D printing are increasingly being used for MN fabrication. Using 3D printing can be directly fabricated layer by layer allowing for complex design and customisation. Different 3D printing technologies such as stereolithography and digital light processing can be employed for mechanical fabrication.[38]

EVOLUTION TRENDS IN MN FOR PROTEIN AND PEPTIDE DELIVERY SYSTEM

With improvements in design, components, and uses, MNs evolved significantly using time. Here is a summary of the major junctures in the development of MNs:

First generation MNs

The early MNs had solid, straightforward construction and pointed points. They were created mainly to get under the skin and establish temporary drug delivery routes. The primary components used for manufacturing these MNs were silicon or metal.[39]

The second generation of MNs

Had hollow channels between the needles. These tiny needles made it possible to deliver medicines, vaccinations, or other substances straight into the skin. Hollow MNs were created to get around the drawbacks of conventional hypodermic needles and offer minimally invasive and painless drug delivery.

Dissolving or biodegradable MNs

Although much has evolved with dissolvable MNs for the most part, sugar-based materials or biocompatible polymers that normally dissolve in the skin painless delivery of drugs or vaccines is done, and then the subsequent problems associated with needle disposal are removed.[39]

Patch systems and MN arrays

On a single platform, an MN array is an assortment of MNs. They come in solid, hollow, and dissolving varieties. When MNs are pre-mounted on a patch that may be placed on the skin, patch systems with MN arrays are frequently employed. Controlled drug release, prolonged shipment, and accessibility are made possible by this design.

MN-based sensors and diagnostics

MNs were developed as well to sense and treat. Small volumes of interstitial fluid can be extracted from the skin with these MNs, and the fluid can then be tested against various biomarkers or analytes. Applications such as glucose monitoring for the treatment of diabetes or monitoring of other physiological indicators have demonstrated promise for MN-based sensors.[40]

MNs for transdermal delivery

In addition to the delivery of substances, macromolecules such as proteins and peptides, which are generally unable to be shipped efficiently across the skin's barrier, are also being studied for transdermal delivery using MNs. People have created MNs that coat or are hollow to help these bigger molecules move across our skin.

APPLICATIONS OF MNS FOR PROTEIN AND PEPTIDE DELIVERY SYSTEM

MNs offer multiple benefits for the administration of peptide and protein medicines, particularly in addressing the challenges associated with transdermal dispersion. Here are some uses for MNs in the administration of peptide and protein drugs:

Diabetes management

MNs have been investigated for the minimally invasive and painless delivery of the protein hormone insulin. Insulin can be given in a regulated manner by developing MNs that can pierce the skin and reach the deeper tissue layers, potentially decreasing the need for repeated injections.[41]

Vaccination

The administration of vaccines, especially protein-based vaccines, has shown potential when using MNs. They can be utilized to directly transfer antigens into the skin, which is a rich source of cells that show antigens. The immune response may be increased and vaccine effectiveness may increase as a result of this focused delivery.

Peptide therapeutics

Therapeutic peptides often have limited oral bioavailability and may degrade in the gastrointestinal tract. These peptides can be delivered without harm using MNs. By skipping the stomach, MNs enable the direct administration of peptides into the epidermal layers, increasing their absorption and efficiency.[42]

Dermatology

The MNs may deliver protein and peptide medicines directly to skin diseases enhance therapies of cytokines, growth factors, and anti-inflammatory peptides, and minimize systemic side effects. Some of the applications of MNs for protein and peptide delivery systems are shown in Figure 3.

Applications in cosmetics and esthetics

MNs have been studied for the transdermal delivery of peptides in cosmetics and esthetics, such as collagen-stimulating peptides or skin-rejuvenating peptides. When administered directly to the dermal layer, these peptides may increase the production of collagen, improve skin texture, and minimize wrinkles.[43]

Drug delivery

MNs can offer pain-free delivery of drugs through the skin and reduce the risk of infection. This increases patient compliance, and the gamma-controlled release of a lot of types of drugs – from small chemicals to vaccines, proteins, peptides, and gene-based therapies – through skin layers becomes possible.[43]

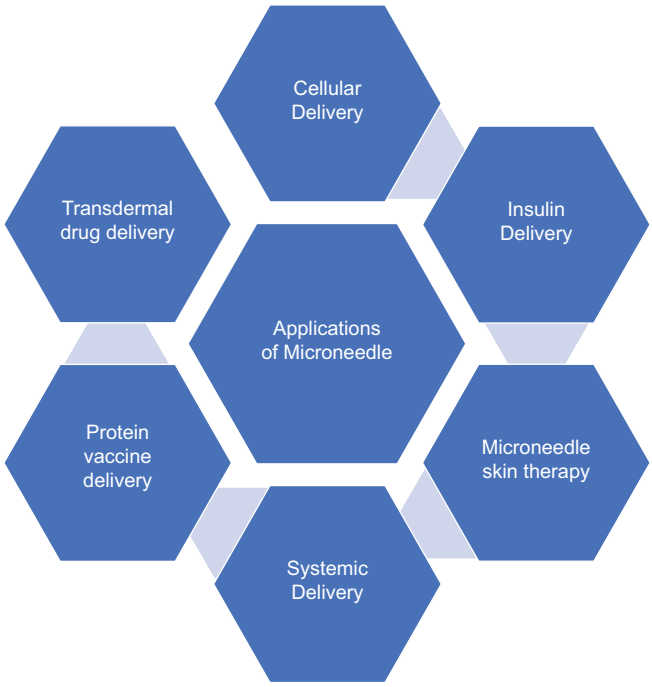

Figure 3: Applications of microneedle for protein and peptide delivery system

Diagnostics

MNs can be used non-invasively for diagnostics and sensing, for instance, monitoring lactate during sports events and glucose levels in diabetes. They extract interstitial fluid efficiently and promise hassle-free continuous monitoring for a myriad of substances.

Biomedical research

MNs are employed in numerous biomedical research applications including controlled micro-injury application on the skin for wound healing study or treatment efficiency evaluation, and tissue engineering involving dispersion of growth factors or cells in supporting tissue repair and regeneration.[43]

Sampling and analysis

A tiny sample of sweat or sebum can be collected for examination by MNs during drug testing and they may also be used to monitor health by collecting blood or interstitial fluid without invasive procedures.[43]

CONCLUSION

Drug delivery using MNs is a promising drug delivery method, especially concerning protein and peptide drugs. Such transport of drugs into subcutaneous tissues will neither pain nor degradation in the gastrointestinal tract. This method is highly effective in treatment with enhanced patient compliance since MNs can pass through the epidermal barrier to release stuff such as insulin, growth hormones, vaccines, and biologics. MNs Compared with traditional hypodermic needles, MNs are smaller and less invasive. Thus, more acceptability toward them occurs among patients. The use of these is also self-administration. Patients and thus the healthcare costs are reduced, whereas convenience increases for patients.[44]

However, in the handling, storage, and delivery of proteins and peptides, there are problems encountered. Sometimes, temperature, pH, and mechanical stress degrade these substances, indicating a big role in the proper choice of material and optimization of the formulation process. Even drug release in a controlled and sustained fashion is challenging; however, there are various means developed to overcome such challenges, so it is no longer a problem.

Although tremendous obstacles still exist in the manufacturing of scale-up, scalable, and cost-effective MNs, the technology does hold vast promise for the better improvement of drug

delivery of proteins and peptides. Probably, the most important advantages of the use of MNs include the localized distribution of the drug, increased stability, and enhanced comfort level in patients, and such developments are bound to be stepped up by further research and innovation in this area.[45]

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