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Review Article

Microneedle Delivery of Protein and Peptides: Advances in Drug Delivery

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Abstract

Microneedles are the advances in the transdermal drug delivery system of proteins and peptide drugs which exerts its effect through the formation of the micro channels. Microneedles are of various types such as solid microneedles, dissolving microneedles, metallic microneedles, 3D printed microneedles; polymer based microneedles, Hydrogel microneedles and coated microneedles. Microneedle characterization is the most important part after the formulation. These dosage forms have both advantages and limitations. Stability enhancement, targeted drug delivery, low invasiveness, enhanced skin absorption etc. are some of the advantages associated with microneedles. Likewise shallow penetration, chances of skin irritation and injury, chances of degradation in different extreme temperature and pH etc. are some of the limitations. Needle integrity, uniform drug distribution, diffusion and degradation, sterility and contamination, immunogenicity and immune response, Activity preservation are the crucial parts that should be controlled during formulation. Improved stability of proteins, stabilization of inactive ingredients, utilization in the field of gene therapy and mRNA delivery, development of smart microneedles, development of multilayered microneedles, ligand targeting etc. are some of the advances in the microneedle delivery system. These delivery systems are widely recognized as the future of the drug delivery addressing the challenges associated with the patient compliance.

Keywords: Microneedles, Needle Integrity, Immunogenicity, Patient compliance

Background:

Therapeutic peptides and proteins like interferon's, insulin, monoclonal antibodies, and vasopressin are used to treat different disease conditions. Protein is extensively denaturated in the acidic environment of the stomach and also due to the degradative action of gastrointestinal enzymes, low bioavailability of them is encountered and as a result, these molecules are mostly administered via the parenteral route. In contrast, parenteral administration is invasive and medical supervision is important requirement. Because of the relatively short half-lives of these peptides and proteins, frequent dosing is required that can affect patient compliance. Transdermal delivery of peptides and proteins has multiple advantages over other routes of administration, such as avoiding degradation in the gastrointestinal tract in addition to a non-invasive, continuous delivery profile.[1, 2]

The skin possess the barrier property which prevent the free transdermal diffusion of different macromolecules which are hydrophilic in nature like peptides and proteins Hence, for the transportation of these macromolecules through the skin, certain physical or chemical enhancers are required.[3] Various physical techniques that facilitates for ease crossing of the dermal barrier are iontophoresis, sonophoresis, microporation and electroporation.[4] Similarly different chemicals facilitates for the chemical enhancement of the protein and peptide drugs for increasing the permeability of the skin such as surfactants, alcohols and sulfoxides.[5]

There is no feasibility of passive transdermal delivery; however, active transdermal delivery of peptides and proteins is another most prominent viable option. This approach can extensively overcome degradation in the gastrointestinal tract and thus helps for achieving the enhance patients compliance.[6]

Microneedle Delivery of Proteins/Peptide Drugs:

Microneedles are very small, micron-sized needles that penetrate the stratum corneum and produce microchannels in the skin upon administration, delivering the drug as in **Figure 1**. These are usually prepared by micro machining and other micro fabrication methods and can be built from a variety of components, including plastic, silicon, glass, metals, sugars, or biodegradable polymers.[7]

Microneedles are between 100 to 1500 µm long, and different types of geometrical designs of the needles for drug delivery have been investigated. Microneedle breaches the stratus corneum and parallelly the upper layer of the viable epidermis and it depends upon the length of the needle. The microchannels formed by

these needles enable drug passage with penetratration through the stratum corneum, which is regarded as principle barrier for the permeation of the desired drug. In addition to this, Microneedles don't reach the papillary dermis (the skin layer containing nerve endings), drug administration through this technology is both minimally invasive and painless.[8]

The microchannels which are formed by microneedles are much larger than drugs including macromolecules so that peptides and proteins drugs could permeate easily through the skin. Furthermore, the aqueous nature of the microchannels facilitates the delivery of hydrophilic peptides and proteins. Microneedles can be used for drug delivery adopting the various mechanisms such as initial insertion of solid microneedles into the skin to form microchannels and then applying the drug topically in such microchannels, insertion of the microneedles coated with the drugs, insertion of encapsulated drugs within the biodegradable microneedles and lastly using hollow microneedles to infuse drug into the skin.[9]

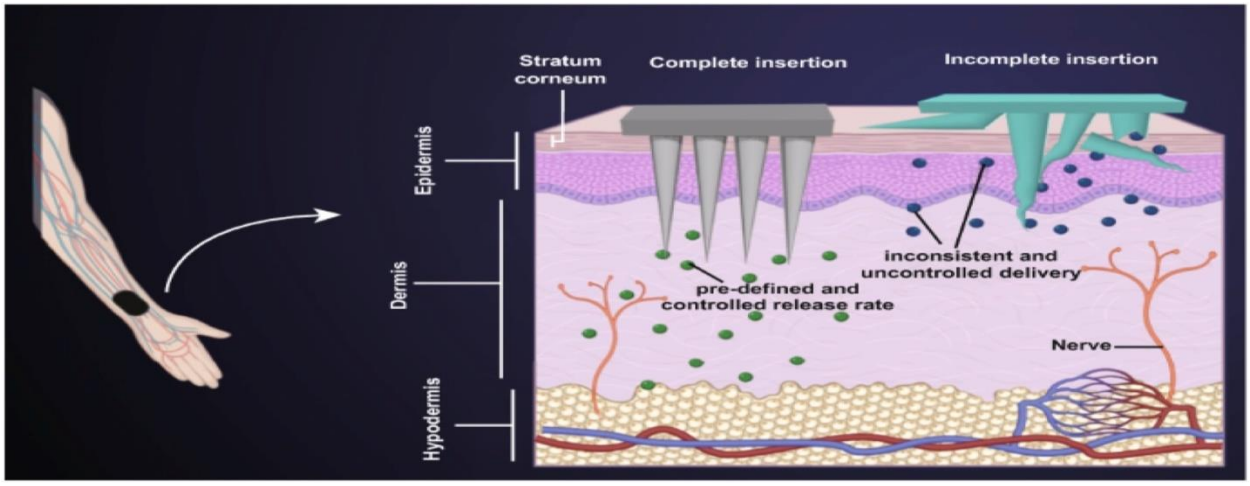

Figure 1: Administration of Microneedle Patch[10]

Types of Microneedles:

Microneedles of various types have been developed for protein and peptide delivery, with unique features aiming to optimize drug delivery depending on the needs of the biologics and the treatment.

Solid Microneedles: These are the simplest type of microneedles which are used mainly to form microchannels in the skin to promote permeability and allow for protein or peptide delivery from a different route (e.g., topical application, diffusion). The proteins or PEGs are administered topically subsequent to the generation of microchannels from the needles, or they can be supplied via topical patches or some other drug delivery system. Design of such microneedles is simple and easy to manufacture. They either create micro channels without putting the drug in the skin, and therefore cause minimal discomfort. However controlled or sustained drug release is not possible through these microneedles.[11]

Dissolving Microneedles: These microneedles are composed of biocompatible water-soluble polysaccharides, peptides or polymers. The microneedles dissolve upon insertion into the skin to release the encapsulated drug (e.g., proteins or peptides) directly to the skin. The biologics are stored in the microneedles in the dry or lyophilized form. As the microneedles dissolve in moisture in the skin, they release the biologic directly into the dermis. These types of microneedles do not require the removal of the needle after application and can control the release of proteins and peptides. They are applicable for big and small biologics. However they are constrained to lower doses and also they may not dissolve as evenly or completely.

Liraglutide which is the popular protein drugs has been prepared for the diabetes control and obesity control. Encapsulation technique was used for this molecule for the preparation of the dissolving microneedle patch.[12]

Polymer-Based Microneedles: These are formed from biodegradable polymers like poly lactic-co-glycolic acid (PLGA), polyvinyl alcohol (PVA) or hyaluronic acid. By controlling the composition and structure of the polymers, sustained release of proteins and peptides can be obtained. Depending on the application, the release profile can be sustained or delayed. These types of microneedle facilitate the controlled release and thus enables sustained/fixed time-delayed drug delivery. They are also considered to be biodegradable and biocompatible materials. However formulation and manufacturing processes of these types is complex and they are not suitable for all protein and peptide drugs.[13]

Coated Microneedles: Coated microneedles have a layer of a drug (e.g., protein or peptide) coated on them. The coating is formed to elute the biologic once the microneedles are inserted into the skin via either mechanical penetration or dissolution. The protein or peptide is coated onto microneedle surface. As the coating dissolves or is mechanically chipped away, the drug is released in the skin. These offer a high precision and controlled delivery of proteins and peptides. Release is comparatively faster than that of dissolving microneedles and they can be customized to achieve varying release rates. Stability of the protein/peptide

can be improved through such microneedles.[14] However it is difficult to apply a coat evenly in such types of microneedles. Some peptides or proteins lose their activity during coating or release.

Coated microneedle of the desmopressin, a synthetic peptide hormone was developed and tested. Safety and the efficient delivery of such microneedle has been ensured.[15]

Hydrogel Microneedles: These microneedles are fabricated from hydrophilic materials, such as hydrogels, which swell upon contact with water (e.g., moisture from the skin). This swelling may facilitate the distribution of proteins and peptides. Either the biologics are encapsulated in the hydrogels or acts as a carrier system that releases the drug as the hydrogel absorbs moisture from the skin. This allows for a controlled and sustained release of the biologic. They are considered to be ideal for proteins and peptides that need a controlled, extended release. Hydrogels are protective to sensitive biologics against degradation. However these types of microneedle**s** are potentially less effective for large biologics that need deeper diffusion into tissue and dangers of swelling and ageing is another concern.[16, 17]

Metallic Microneedles: These micronized needles, consists of metals (stainless steel, titanium, gold). Metallic microneedles are mostly applied where robust and durable needles where penetration of tough skin layers are required. They are not as widely used for protein and peptide delivery, but they can be used to deliver biologics in tandem with other materials. The microneedles work under the principle that they can pierce the skin to form microchannels within the skin layers and later drug release into the skin either through topical application or through other systems (for instance, encapsulated drug delivery in combination with the microneedles). It is thick and can penetrate tough epidermal layers. Microneedles are very stable, which allows higher doses of biologics to be delivered. However it is challenging to manufacture metal microneedles on a large scale and to do so cost-effectively. They may create greater pain than other types of microneedles and there is high dependence on the systems for drug release using metallic microneedles.[18]

Hollow Metalic Microneedles of the insulin was developed and tested successfully in the rats in which the diabetes is induced.[19]

Solid Microneedles with reservoirs: These are solid microneedles containing small reservoirs or pockets within the needle structure that can hold and release proteins and peptides. The drug is usually released by diffusion or by an external stimulus (e.g., electrical, thermal).: The drug contained in the microreservoirs of the microneedles is released over time due to skin moisture or other release triggering mechanisms. These enables controlled as well as sustained release of biologics. In addition, they can carry both small and large molecules and they are considered ideal for use with critical precision and continuous delivery. However, manufacturing process is complex and storage of excessive amount of biologics is not possible in the microneedles.[11]

3D-Printed Microneedles: These are the microneedles with complex drug delivery systems and geometries, produced using 3D printing as in **Figure 2**. 3D-printed microneedles can be designed to contain encapsulated proteins or peptides in the microneedles themselves or in microreservoirs for a desired release profile. In such microneedles**,** shape and dosage delivery can be highly tailored as per our requirement with various layers or chambers so as to allow for multi-drug delivery. It provides the pain free delivery of the biologics.[20]

Extrusion based 3D printing of the microneedle patch of glucose responsive releasing insulin was developed using the sodium alginate and hydroxyapatite for 3D printing for the purpose of glucose control in diabetes and concluded as a potential method.[21]

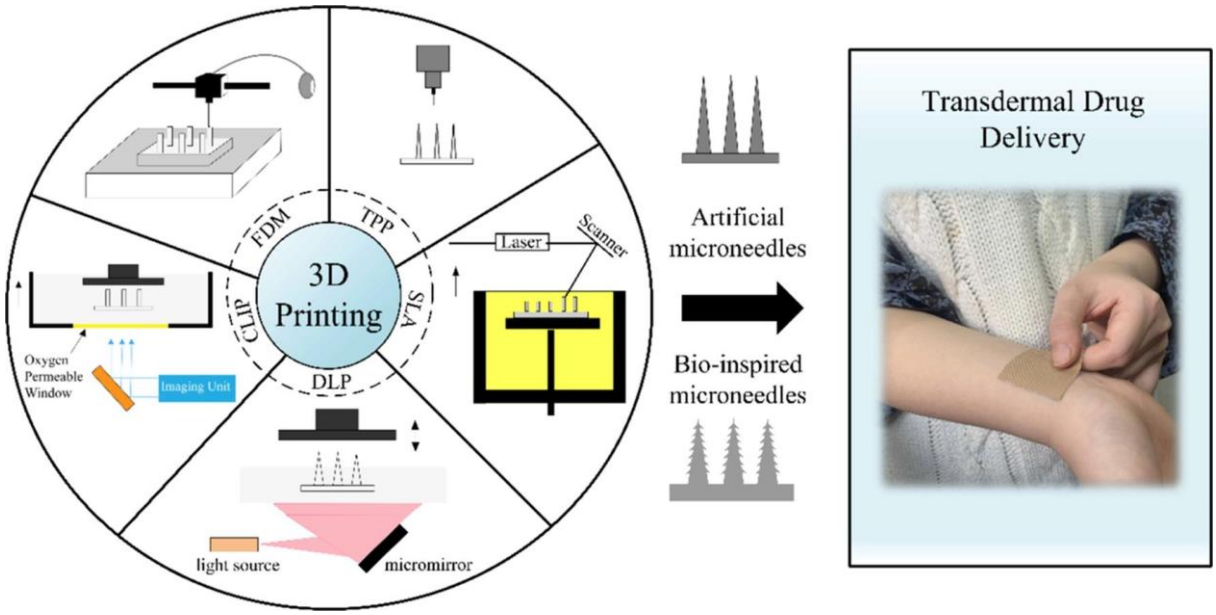

Figure 2: 3D printing Microneedle delivery[22]

Evaluation of Microneedle System of Proteins and Peptides [23-25]

Analytical assessment of microneedles (MNs) for protein/peptide delivery requires varieties of techniques to establish the quality, efficiency, and activity of the microneedle systems. These assessments confirm that the microneedles adhere to or exceed the necessary benchmarks encompassing safety, efficacy, and stability, especially concerning delicate biologics such as protein and peptide delivery.

Microneedle Geometry and Size: The geometry, length, diameter, and the surface structure of microneedles need to be characterized to ensure the capability of microneedles in breaking the skin and administering drugs. These properties can be evaluated by techniques such as scanning electron microscopy (SEM), optical microscopy and confocal microscopy. SEM shows a fine morphology of microneedle tips, edges, and the overall structure, which is beneficial to defect identification (e.g., fractures or shape irregularities). The use of optical microscopy is helpful for assessing the basic microneedle array architecture, while confocal microscopy may be employed to assess microneedle penetration into skin model or tissue samples.

Microneedle Mechanical Properties: The mechanical strength of the microneedles must be sufficient to puncture the skin without breaking. This can be assessed using methods like, measuring the force required to penetrate the skin, measuring the tensile strength of the microneedles to assess their flexibility and breakage force, force-displacement testing for the rotating deformation and rupture behaviour due to applied forces.

Surface Roughness and Texture: Microneedles should have a smooth surface texture to facilitate penetration without irritating the skin, therefore atomic force microscopy (AFM) or profilometry can be used to measure surface roughness.

Drug Loading and Encapsulation Efficiency: The proportion of protein or peptide that is successfully encapsulated in the microneedles relative to the total amount employed in the formulation needs to be evaluated. This is important for the delivery of the specified dose. The encapsulated proteins or peptides can be quantified by high-performance liquid chromatography (HPLC) or liquid chromatography-mass spectrometry (LC-MS). While UV-Vis spectrophotometry or fluorescence spectroscopy are useful for measuring protein loading using the absorbance or fluorescence properties of the biologics.[26]

Drug Distribution Uniformity: Uniform distribution of the protein or peptide with respect to the microneedle array is essential for uniform delivery. The distribution of the fluorescently tagged proteins or peptides inside microneedles can be assessed by such techniques like laser scanning or fluorescent imaging.[23]

In Vitro Release Testing: In vitro release experiments using dialysis or Franz diffusion cells are commonly conducted to assess the protein or peptide release profile from the microneedles. These techniques help to replicate the release profile of biologics from microneedles into a skin model or a buffer solution over time. The concentration of released protein or peptide can be quantified at different time points using ELISA (Enzyme-Linked Immunosorbent Assay) or HPLC. Cumulative release studies determine how much drug is released over time and the rate of release (sustained release or burst release).[27]

Burst Release: It is also referred to as fast release; Burst release is the release of proteins and peptides within few hours in large quantities when microneedle is used. This is crucial to consider for ensuring controlled delivery, particularly with dissolving or coated microneedles.[28]

Microneedle Skin Penetration Studies: Microneedles must penetrate the skin appropriately with minimal hypertrophic damage. Real-time monitoring of microneedle insertion and drug diffusion across skin layers can be achieved through penetration tests on human skin models (e.g., ex vivo pig skin or porcine skin) using optical coherence tomography (OCT) or confocal microscopy. Microneedle treatment was followed by histological analysis (e.g., haematoxylin and eosin (H&E) staining), which help assess skin integrity and identify potential damage that microneedles may cause (e.g., inflammation, tissue destruction).[29]

Biologics cytotoxicity: These tests assess whether the microneedles are toxic to skin cells and any underlying tissues.[30]

Sensitization and Irritation: Skin irritation in vitro as well as in vivo tests can be conducted to identify any adverse reaction of the microneedles. Dermal irritation test is done in animal models to examine for redness, swelling or other signs of skin irritation.[31]

Immunogenicity: The risk of eliciting immune responses needs to be evaluated, especially when delivering proteins or peptides. Any immune responses to the delivered biologics can be monitored by cytokine assays or antibody assays.[32]

Stability of Protein: Proteins and peptides are affected by the environmental conditions. The stability of the biologics is evaluated through storing the microneedle patches at multiple temperatures (e.g., 4°C, 25°C, 40°C) and relative humidities and characterizing protein integrity with HPLC, SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis), or mass spectrometry. To estimate storage conditions of microneedles loaded with proteins or peptides for a longer period of time, stability studies at elevated temperatures and humidity conditions are conducted to predict their shelf-life.[33]

Freeze-Thaw Stability: Lyophilized state is commonly used by which proteins and peptides are loaded into microneedles in the powdered form. Freeze-thaw stability should be evaluated to understand stability against degradation/ inactivity after freeze-thaw processes.[34, 35]

Pharmacokinetics: The pharmacokinetics of proteins or peptides are essential in order to assess therapeutic activity, which includes evaluating how rapidly the proteins or peptides are absorbed into the blood stream and how they are distributed through the body.[36]

Sterility Testing: Since microneedles are commonly employed for both clinical and therapeutic purposes, it is important to verify sterility. To control the quality of microneedles, microbial contamination tests (bioburden tests or sterility tests) should be carried out.[37]

Testing for Endotoxins: The Limulus amebocyte lysate (LAL) assay is employed to check for endotoxins in the microneedles, which if present might lead to inflammation or other tasks during insertion[37]

Compliance and Acceptance by Patients: An important part of the evaluation process is assessing microneedle patches via self-administration, including the application process, adhesion, and comfort of patches. Microneedle delivery systems can be assessed in terms of patient acceptability and ease of use by collecting additional surveys and patient-reported outcomes in real-world-settings.

Advantages of Microneedle Patch of Protein and Peptides:[10]

Microneedle patches have several advantages for the delivery of proteins and peptides across the skin. Here are some key advantages:

Enhanced Skin Absorption: Microneedles form tiny passages within the skin facilitating the passage of macromolecules such as proteins and peptides, which would otherwise be unable to cross the skin barrier[38].

Low Invasiveness: Traditional injections or infusions, though being effective, can be painful and require to be administered by a professional; microneedle patches are very low-invasive and therefore a more comfortable.[39]

Controlled and Sustained Release: Microneedle patches can be engineered to enable controlled release of proteins and peptides, allowing for sustained delivery over time. These may enhance therapeutic efficacy and are potentially dosed less frequently[40].

Easy to Use: Patches are simple, allowing self-administration in patients, which can lead to higher compliance, especially in chronic therapies or aesthetic use.[41]

Reduced Side Effects: Microneedles can decrease systemic exposure of proteins and peptides by targeting them to the skin or underlying tissues, and thereby potentially limiting side effects that may occur with oral or IV delivery methods.

Facilitating Targeted Delivery: Microneedle patches enable targeted delivery with penetration of specific layers of the skin or tissues, which is especially advantageous in treating dermatological conditions or delivering biologics at the tissues directly.[42]

A painless and non-invasive procedure: Microneedle patches cause less discomfort when compared to conventional hypodermic needles, especially for sensitive people or patients who suffer from needle phobia.

Enhanced Stability: The patch stabilizes the proteins and peptides that would otherwise degrade in solution. These microneedles can be prefilled with dried-out proteins or peptides, making them easier to store and handle.[43]

Limitations of Proteins/Peptide Loaded Microneedle Patch:[44]

Despite of having several advantages, there are some limitation and disadvantages with associated with delivery of proteins and peptides:

Shallow Penetration: Microneedles are generally designed to pierce the topmost layer of skin (epidermis) as well as the upper dermis but do not penetrate deep tissues. This may restrict the administration of bigger proteins or peptides that need deeper tissue infiltration or systemic impacts.

Skin Differences: The efficacy of microneedles can vary depending on skin type, thickness, and hydration. In fact, people with thick skin may not get as much of the drugs out of their skin as people with thin, sensitive skin.

Potential for Skin Irritation or Injury: Microneedles are typically engineered to be as painless as possible, yet there remains a chance of irritation, redness, or even damage to the skin at the application site due to improper use or skin sensitivity. In some rare conditions more serious side effects such as infections could occur, if microneedles are not properly sterilized.

Stability and formulation issues: Proteins and peptides are known to be sensitive to the environmental conditions such as temperature, pH, and humidity. Biologics used in microneedle patches must be carefully formulated so that degradation or loss of activity does not occur during manufacture or application. The patch must be able to keep its active ingredients stable over time.

Cost and Production Complexity: The production and manufacture of microneedle patches, particularly for biologic drugs, may be more expensive and technically challenging than conventional drug delivery techniques. That could restrict broad access, or raise prices for patients.

Patient Acceptance: Although microneedles are less invasive than injections, some patients may be hesitant at the thought of having a patch with needles (even if they are small) placed on their skin. This barrier in the mind can be a hurdle to widespread adoption.

Challenges in Formulation[45]

Protein and peptide delivery in microneedles will require addressing several unique aspects that relate to the sensitive nature of these types of biologic molecules.

Major hurdles to the microneedle patches formulation of proteins and peptides are summarized below:

Stability of Proteins and Peptides: Protein and peptide are susceptible towards degradation including oxidation, hydrolysis and denaturation. Biologics can lose their structure and activity during the microneedle fabrication process itself, or when exposed to the environment (e.g., heat, light, moisture). The challenge is ensuring stability through the manufacturing and storage process.

Formulation for Proteins and Peptides: First of all, the protein in an unstable form and resistant to the processes (such as drying or heating) required for microneedle patch production. Lyophilization (freeze-drying) and other approaches can help but protein stability during rehydration and release plays a critical role.

Needle and Patch Design/Needle Integrity: Microneedles must be sharp enough to form microchannels in the skin but also strong enough not to break or deform during application. It is challenging to maintain the structural integrity of microneedles and to encapsulate the proteins or peptides properly.

Uniform Distribution: One of the challenges is to create a uniform distribution of peptides or proteins in microneedles. If the biologics are not uniformly delivered to the skin, it can result in ineffective or non-existent delivery in some areas of the skin and, subsequently, different therapeutic effects.

Release Profile/Controlled Release: Microneedles could offer a controlled or sustained release of biologics, one of its most significant advantages. Reaching the required release kinetics of proteins and peptides, however, is not straightforward. The formulation must enable a controlled release to prevent fast degradation.

Diffusion and Degradation: Proteins and peptides may diffuse out too quickly or degrade before reaching into the skin. It is, thus, essential to modify the composition such that the diffusion rates and stability at delivery site remain appropriate.

Skin Penetration and Absorption/Molecular Size: Proteins and peptides are typically large molecules that naturally have poor transdermal permeability. Obtaining effective penetration into the skin and an optimal absorption profile is challenging.

Co-Formulation for Penetration: Additional components, such as penetration enhancers or surfactants, may be necessary to promote movement of proteins and peptides through the skin. These additives should not affect the stability of the biologics.

Manufacturing Challenges: Production at Large Scale, Microneedle production requires careful monitoring of the fabrication step, and scaling up this method for high-throughput manufacturing can be difficult. Product quality must be addressed by issues related to consistent needle size and shape and uniform distribution of biologics.

Sterility and Contamination: Proteins and peptides are used in many therapeutic applications; hence, it is critical to maintain sterility during the microneedle fabrication process and storage. One of the big hurdles is engineering the microneedles to be used without compromising sterility prior to use.

Shelf-Life and Storage: It is difficult to store microneedle patches containing the proteins and peptides for long time. These biologics usually need certain temperature and humidity conditions to be stable. Making sure that the microneedle patches are resistant to degradation during long-term storage is crucial for practical utilization.

Packaging: The microneedles need to be packaged in a manner where the biologics are protected against environmental factors like temp fluctuations, moisture and light and that can cause lead to degradation.

Immunogenicity & bioactivity/ Immune Response: Depending on how derived, the proteins and peptides can induce an immune response in some people, which can then lead to unwanted side effects or reduced efficacy.

Activity Preservation: Once the protein or peptide is incorporated into the microneedle and delivered to the skin, it must maintain its therapeutic activity. Sufficiently protection of the biologic in delivery may take sophisticated efforts.

Patient-specific factors/Diversity of Patients: Patients differ in skin properties like thickness, hydration, and permeability. What works for one patient, may not work for another, so the formulation may need to be customized or optimized for different patient groups.

Advances in Microneedle Delivery of Protein and Peptide Drugs[46]

Improved Stability of Proteins and Peptides: New methods have been designed to encapsulate proteins and peptides in microneedles that are in a lyophilized (freeze-dried) state. Lyophilization protects the biologics from degradation during storage and transportation due to temperature, moisture, and oxidative stress. The proteins or peptides become active upon rehydration when applied.

Enhanced skin penetration and delivery: Advances in microneedle design such as sharper, longer and more flexible microneedles have enhanced skin penetration. To improve the delivery efficiency of proteins and peptides into the skin, researchers have also fabricated microneedles with different tip geometries (i.e. conical, pyramid-shaped).

Polymer-Based Microneedles: New progress in biocompatible polymers has enabled more robust microneedles capable of delivering larger doses of biologics. These polymers can also be designed to modulate the rate of biologic release for sustained or controlled delivery.[47]

Controlled Release Systems/Microreservoirs and Encapsulation: The introduction of microreservoirs or

encapsulation techniques into microneedles has facilitated the sustained and controlled release of proteins and peptides. This gives an effective biologic release for a long time without an intense effect, allowing the therapeutic effect to be reached while reducing the likelihood of the risk associated with high initial doses.

Layered microneedles: Microneedles are designed in multiple layers having different biologic or release profile. Such a layered design can be utilized for combination therapies since multiple proteins or peptides can be incorporated and released at different rates.[48]

Specificity and Targeted Delivery: Microneedles technology has improved to be able to deliver proteins and peptides more accurately to specific skin layers (or down into deeper tissues). However, microneedles can also be engineered to reach only the epidermis or shallow dermis, allowing this approach to be used in the treatment of superficial skin diseases, such as psoriasis or localized cosmetic procedures, for instance, the local delivery of growth factors for skin rejuvenation.

Targeting Ligands Loaded in Biologics Microneedles: Ligands (antibodies or peptides) are engineered and loaded in the microneedles to target some specific or desired cells. This allows for very localized delivery of proteins or peptides, enhancing efficacy and minimizing off-target effects.[49]

Combination Therapies: This has facilitated the co-delivery of proteins, peptides, and small molecules in a one-patch application. This has particular positive implications for combination therapies in oncology, autoimmune diseases, and chronic diseases that may require multiple agents to act synergistically.

Microneedle Patches for Gene Therapy and mRNA Delivery: The emergence of microneedle patches for the non-invasive delivery of genetic materials, including DNA and mRNA, as a potential means of delivering genetic-based therapies and enabling drug dosage without the need for injection. This has possible applications in vaccine delivery and genetic therapy, especially proteins and peptides that are produced within the body.[50]

Non-invasive Delivery: The main innovation offered by microneedle technology is the reduced invasiveness when compared to common infusion with hypodermic needles. Microneedles are relatively small and less invasive, resulting in less pain and not requiring a trained professional to inject the drug.

Smart Microneedles: The development of smart microneedles is progressing such that they are designed to deliver proteins and peptides in response to environmental stimuli such as temperature, pH and skin hydration. These intelligent microneedles may improve the specificity of drug delivery, while allowing for better control of the timing and dosage of the therapy.[51]

Customizable Release Profiles: The use of microneedles that are made of biodegradable materials provide increased control of release kinetics. The degradation of microneedles in the skin can release in a controlled manner, which is beneficial for the delivery of proteins and peptides that need prolonged therapeutic effects.

Dual-functional Microneedles: Some microneedle patches are being designed to perform dual functions like drug delivery and diagnostics. For instance, they would be able to not only deliver therapeutic proteins, but also monitor the skin's biomarkers while the treatment is going on to assess its efficacy.

Nanotechnology: The implementation of nanotechnology in microneedles has leveraged enhanced delivery of proteins and peptides, for example, by loading the microneedle matrix with nanoparticles. Such nanoparticles protect the biologics, impart stability and encourage penetration into deeper layers of tissue.[52]

Antigen Delivery: Microneedles have been explored for delivery of protein-based vaccines, including for influenza and COVID-19 vaccines. Microneedles can deliver antigens more effectively than conventional injections, often inducing a faster immune response and potentially more efficacious vaccines.[53]

Personalized Medicine: Recent advancements in personalized medicine are enabling the design of microneedle patches with the dose suited to the unique therapeutic requirement of an individual. These patches would be tailored to administer customized proteins or peptides at an optimal concentration and release profile for each patient according to their genetic, or clinical profiles.[54]

Conclusion:

Microneedle delivery system of protein and peptide is one of the best approaches from the points of patient compliance. Researchers are extensively involved in the development of the microneedle-based dosage form design of various molecules in order to achieve the targeted and controlled delivery of the therapeutics. In conclusion, this approach can be considered as the future of drug delivery.

References

1. Banga AK. Therapeutic peptides and proteins: formulation, processing, and delivery systems: CRC press; 2005.

https://doi.org/10.1201/9781420039832

2. Herwadkar A, Banga AK. Transdermal delivery of peptides and proteins. Peptide and protein delivery: Elsevier; 2011. p. 69-86. https://doi.org/10.1016/B978-0-12-384935-9.10004-5

3. Adhikari D, Pokhrel S. An Overview on Protein and Peptide Drug Delivery System: Advancesand Strategies. Journal of Drug Discovery and Health Sciences. 2024;1(04):239-43.

4. Banga AK. Transdermal and intradermal delivery of therapeutic agents: application of physical technologies: CRC press; 2011. https://doi.org/10.1201/b10906

5. Magnusson B, Runn P. Effect of penetration enhancers on the permeation of the thyrotropin releasing hormone analogue pGlu-3-methyl-His-Pro amide through human epidermis. International journal of pharmaceutics. 1999;178(2):149-59. https://doi.org/10.1016/S0378-5173(98)00316-0 PMid:10205635

6. Herwadkar A, Banga AK. Peptide and protein transdermal drug delivery. Drug Discovery Today: Technologies. 2012;9(2):e147-e54. https://doi.org/10.1016/j.ddtec.2011.11.007 PMid:24064275

7. Sivamani RK, Liepmann D, Maibach HI. Microneedles and transdermal applications. Expert opinion on drug delivery. 2007;4(1):19-25. https://doi.org/10.1517/17425247.4.1.19 PMid:17184159

8. Sachdeva V, K. Banga A. Microneedles and their applications. Recent patents on drug delivery & formulation. 2011;5(2):95-132. https://doi.org/10.2174/187221111795471445 PMid:21453248

9. Banga AK. Microporation applications for enhancing drug delivery. Expert opinion on drug delivery. 2009;6(4):343-54. https://doi.org/10.1517/17425240902841935 PMid:19348604

10. Reinke A, Whiteside EJ, Windus L, Desai D, Stehr E, Rad ZF. The advantages of microneedle patches compared to conventional needle-based drug delivery and biopsy devices in medicine. Biomedical Engineering Advances. 2024:100127. https://doi.org/10.1016/j.bea.2024.100127

11. Tariq N, Ashraf MW, Tayyaba S. A review on solid microneedles for biomedical applications. Journal of Pharmaceutical Innovation. 2022;17(4):1464-83. https://doi.org/10.1007/s12247-021-09586-x

12. Rabiei M, Kashanian S, Bahrami G, Derakhshankhah H, Barzegari E, Samavati SS, et al. Dissolving microneedle-assisted long-acting Liraglutide delivery to control type 2 diabetes and obesity. European Journal of Pharmaceutical Sciences. 2021;167:106040. https://doi.org/10.1016/j.ejps.2021.106040 PMid:34655736

13. Singh P, Carrier A, Chen Y, Lin S, Wang J, Cui S, et al. Polymeric microneedles for controlled transdermal drug delivery. Journal of controlled release. 2019;315:97-113. https://doi.org/10.1016/j.jconrel.2019.10.022 PMid:31644938

14. Kapoor Y, Milewski M, Dick L, Zhang J, Bothe JR, Gehrt M, et al. Coated microneedles for transdermal delivery of a potent pharmaceutical peptide. Biomedical microdevices. 2020;22:1-10. https://doi.org/10.1007/s10544-019-0462-1 PMid:31845070

15. Cormier M, Johnson B, Ameri M, Nyam K, Libiran L, Zhang DD, et al. Transdermal delivery of desmopressin using a coated microneedle array patch system. Journal of controlled release. 2004;97(3):503-11. https://doi.org/10.1016/S0168-3659(04)00171-3 PMid:15212882

16. Hong X, Wu Z, Chen L, Wu F, Wei L, Yuan W. Hydrogel microneedle arrays for transdermal drug delivery. Nano-Micro Letters. 2014;6:191-9. https://doi.org/10.1007/BF03353783

17. Kim M, Jung B, Park J-H. Hydrogel swelling as a trigger to release biodegradable polymer microneedles in skin. Biomaterials. 2012;33(2):668-78. https://doi.org/10.1016/j.biomaterials.2011.09.074 PMid:22000788

18. Sargioti N, Levingstone TJ, O'Cearbhaill ED, McCarthy HO, Dunne NJ. Metallic microneedles for transdermal drug delivery: Applications, fabrication techniques and the effect of geometrical characteristics. Bioengineering. 2022;10(1):24. https://doi.org/10.3390/bioengineering10010024 PMid:36671595 PMCid:PMC9855189

19. Davis SP, Martanto W, Allen MG, Prausnitz MR. Hollow metal microneedles for insulin delivery to diabetic rats. IEEE Transactions on Biomedical Engineering. 2005;52(5):909-15. https://doi.org/10.1109/TBME.2005.845240 PMid:15887540

20. Dabbagh SR, Sarabi MR, Rahbarghazi R, Sokullu E, Yetisen AK, Tasoglu S. 3D-printed microneedles in biomedical applications. Iscience. 2021;24(1). https://doi.org/10.1016/j.isci.2020.102012 PMid:33506186 PMCid:PMC7814162

21. Wu M, Zhang Y, Huang H, Li J, Liu H, Guo Z, et al. Assisted 3D printing of microneedle patches for minimally invasive glucose control in diabetes. Materials Science and Engineering: C. 2020;117:111299. https://doi.org/10.1016/j.msec.2020.111299 PMid:32919660

22. Yang Q, Zhong W, Xu L, Li H, Yan Q, She Y, et al. Recent progress of 3D-printed microneedles for transdermal drug delivery. International journal of pharmaceutics. 2021;593:120106. https://doi.org/10.1016/j.ijpharm.2020.120106 PMid:33232756

23. Puri A, Nguyen HX, Tijani AO, Banga AK. Characterization of microneedles and microchannels for enhanced transdermal drug delivery. Therapeutic Delivery. 2021;12(1):77-103. https://doi.org/10.4155/tde-2020-0096 PMid:33410340

24. Lutton RE, Moore J, Larrañeta E, Ligett S, Woolfson AD, Donnelly RF. Microneedle characterisation: the need for universal acceptance criteria and GMP specifications when moving towards commercialisation. Drug delivery and translational research. 2015;5:313-31. https://doi.org/10.1007/s13346-015-0237-z PMid:26022578

25. Avcil M, Çelik A. Microneedles in drug delivery: progress and challenges. Micromachines. 2021;12(11):1321. https://doi.org/10.3390/mi12111321 PMid:34832733 PMCid:PMC8623547

26. Dillon C, Hughes H, O'Reilly NJ, Allender CJ, Barrow DA, McLoughlin P. Dissolving microneedle based transdermal delivery of therapeutic peptide analogues. International Journal of Pharmaceutics. 2019;565:9-19. https://doi.org/10.1016/j.ijpharm.2019.04.075 PMid:31047995

27. Dillon C, Hughes H, O'Reilly NJ, McLoughlin P. Formulation and characterisation of dissolving microneedles for the transdermal delivery of therapeutic peptides. International Journal of Pharmaceutics. 2017;526(1-2):125-36. https://doi.org/10.1016/j.ijpharm.2017.04.066 PMid:28461268

28. Wu Y, Vora LK, Wang Y, Adrianto MF, Tekko IA, Waite D, et al. Long-acting nanoparticle-loaded bilayer microneedles for protein delivery to the posterior segment of the eye. European Journal of Pharmaceutics and Biopharmaceutics. 2021;165:306-18. https://doi.org/10.1016/j.ejpb.2021.05.022 PMid:34048879

29. Liu S, Zhang S, Duan Y, Niu Y, Gu H, Zhao Z, et al. Transcutaneous immunization of recombinant Staphylococcal enterotoxin B protein using a dissolving microneedle provides potent protection against lethal enterotoxin challenge. Vaccine. 2019;37(29):3810-9. https://doi.org/10.1016/j.vaccine.2019.05.055 PMid:31147275

30. Kochhar JS, Zou S, Chan SY, Kang L. Protein encapsulation in polymeric microneedles by photolithography. International journal of nanomedicine. 2012:3143-54. https://doi.org/10.2147/IJN.S32000 PMid:22787403 PMCid:PMC3392142

31. Bisgaard SI. Evaluation of In-plane Silicon Microneedles for Allergy Diagnostics. 2023.

32. Zhao B, Jin Z, Yu Y, Li Y, Wang J, Wan W, et al. A Thermostable Dissolving Microneedle Vaccine with Recombinant Protein of Botulinum Neurotoxin Serotype A. Toxins. 2022;14(12):881. https://doi.org/10.3390/toxins14120881 PMid:36548778 PMCid:PMC9781108

33. Mönkäre J, Nejadnik MR, Baccouche K, Romeijn S, Jiskoot W, Bouwstra JA. IgG-loaded hyaluronan-based dissolving microneedles for intradermal protein delivery. Journal of controlled release. 2015;218:53-62. https://doi.org/10.1016/j.jconrel.2015.10.002 PMid:26437262

34. Shi M, McHugh KJ. Strategies for overcoming protein and peptide instability in biodegradable drug delivery systems. Advanced Drug Delivery Reviews. 2023;199:114904. https://doi.org/10.1016/j.addr.2023.114904 PMid:37263542 PMCid:PMC10526705

35. Courtenay AJ, McCrudden MT, McAvoy KJ, McCarthy HO, Donnelly RF. Microneedle-mediated transdermal delivery of bevacizumab. Molecular pharmaceutics. 2018;15(8):3545-56. https://doi.org/10.1021/acs.molpharmaceut.8b00544 PMid:29996645

36. Fukushima K, Ise A, Morita H, Hasegawa R, Ito Y, Sugioka N, et al. Two-layered dissolving microneedles for percutaneous delivery of peptide/protein drugs in rats. Pharmaceutical research.

2011;28:7-21. https://doi.org/10.1007/s11095-010-0097-7 PMid:20300802

37. Sartawi Z, Blackshields C, Faisal W. Dissolving microneedles: Applications and growing therapeutic potential. Journal of Controlled Release. 2022;348:186-205. https://doi.org/10.1016/j.jconrel.2022.05.045 PMid:35662577

38. Chen J, Bian J, Hantash BM, Albakr L, Hibbs DE, Xiang X, et al. Enhanced skin retention and permeation of a novel peptide via structural modification, chemical enhancement, and microneedles. International Journal of Pharmaceutics. 2021;606:120868. https://doi.org/10.1016/j.ijpharm.2021.120868 PMid:34242628

39. Asfour MH. Advanced trends in protein and peptide drug delivery: a special emphasis on aquasomes and microneedles techniques. Drug delivery and translational research. 2021;11:1-23. https://doi.org/10.1007/s13346-020-00746-z PMid:32337668

40. Yang L, Yang Y, Chen H, Mei L, Zeng X. Polymeric microneedle-mediated sustained release systems: Design strategies and promising applications for drug delivery. Asian Journal of Pharmaceutical Sciences. 2022;17(1):70-86. https://doi.org/10.1016/j.ajps.2021.07.002 PMid:35261645 PMCid:PMC8888142

41. Yadav AR, Mohite SK. Recent advances in protein and peptide drug delivery. Research journal of pharmaceutical dosage forms and technology. 2020;12(3):205-12. https://doi.org/10.5958/0975-4377.2020.00035.X

42. Schuetz YB, Naik A, Guy RH, Kalia YN. Emerging strategies for the transdermal delivery of peptide and protein drugs. Expert opinion on drug delivery. 2005;2(3):533-48. https://doi.org/10.1517/17425247.2.3.533 PMid:16296773

43. Koenitz L, Crean A, Vucen S. Stress factors affecting protein stability during the fabrication and storage of dissolvable microneedles. RPS Pharmacy and Pharmacology Reports. 2024;3(3):rqae018. https://doi.org/10.1093/rpsppr/rqae018

44. Long L-y, Zhang J, Yang Z, Guo Y, Hu X, Wang Y. Transdermal delivery of peptide and protein drugs: Strategies, advantages and disadvantages. Journal of Drug Delivery Science and Technology. 2020;60:102007. https://doi.org/10.1016/j.jddst.2020.102007

45. Lewis AL, Richard J. Challenges in the delivery of peptide drugs: an industry perspective. Therapeutic Delivery. 2015;6(2):149-63. https://doi.org/10.4155/tde.14.111 PMid:25690084

46. Liu T, Chen M, Fu J, Sun Y, Lu C, Quan G, et al. Recent advances in microneedles-mediated transdermal delivery of protein and peptide drugs. Acta Pharmaceutica Sinica B. 2021;11(8):2326-43. https://doi.org/10.1016/j.apsb.2021.03.003 PMid:34522590 PMCid:PMC8424228

47. Babity S, Laszlo E, Brambilla D. Polymer-based microneedles for decentralized diagnostics and monitoring: concepts, potentials, and challenges. Chemistry of Materials. 2021;33(18):7148-59. https://doi.org/10.1021/acs.chemmater.1c01866

48. Ito Y, Hirono M, Fukushima K, Sugioka N, Takada K. Two-layered dissolving microneedles formulated with intermediate-acting insulin. International journal of pharmaceutics. 2012;436(1-2):387-93. https://doi.org/10.1016/j.ijpharm.2012.06.047 PMid:22750407

49. Korkmaz E, Friedrich EE, Ramadan MH, Erdos G, Mathers AR, Ozdoganlar OB, et al. Therapeutic intradermal delivery of tumor necrosis factor-alpha antibodies using tip-loaded dissolvable microneedle arrays. Acta biomaterialia. 2015;24:96-105. https://doi.org/10.1016/j.actbio.2015.05.036 PMid:26093066 PMCid:PMC8266287

50. Koh KJ, Liu Y, Lim SH, Loh XJ, Kang L, Lim CY, et al. Formulation, characterization and evaluation of mRNA-loaded dissolvable polymeric microneedles (RNApatch). Scientific reports. 2018;8(1):11842. https://doi.org/10.1038/s41598-018-30290-3 PMid:30087399 PMCid:PMC6081392

51. Abbas AA, Hanif W, Steer I, Hasan E, Teenan O, Akhavani M, et al. ProT-Patch: A Smart Coated Polymeric Microneedle Enables Noninvasive Protein Delivery and Reprogramming of Epidermal Skin Identity. ACS Materials Letters. 2024;6(11):4997-5005. https://doi.org/10.1021/acsmaterialslett.4c01609

52. Larrañeta E, McCrudden MT, Courtenay AJ, Donnelly RF. Microneedles: a new frontier in nanomedicine delivery. Pharmaceutical research. 2016;33:1055-73. https://doi.org/10.1007/s11095-016-1885-5 PMid:26908048 PMCid:PMC4820498

53. Kim H, Seong K-Y, Lee JH, Park W, Yang SY, Hahn SK. Biodegradable microneedle patch delivering antigenic peptide-hyaluronate conjugate for cancer immunotherapy. ACS Biomaterials Science & Engineering. 2019;5(10):5150-8. https://doi.org/10.1021/acsbiomaterials.9b00961 PMid:33455221

54. Lamprou DA. Emerging Technologies in the Delivery of Proteins and Peptides. Bioprocess Online. 2021