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A REVIEW ON MICRONEEDLE-ASSISTED TRANSDERMAL DRUG DELIVERY: REVOLUTIONIZING NON-INVASIVE THERAPY

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ABSTRACT

Transdermal drug delivery mediated by microneedles represents an innovative method for the delivery of therapeutic agents through the skin. The use of microneedles creates microscopic and temporary pathways through the stratum corneum and overcomes the primary hurdle of transdermal drug delivery, thereby enhancing the delivery of drugs to the systemic circulation. Microneedles provide a non-invasive, pain-free and convenient mode of drug delivery compared to hypodermic needles. Several categories of microneedles such as solid microneedles, coated microneedles, hollow microneedles, dissolving microneedles, hydrogel-forming microneedles, and bio-responsive microneedles have been designed for addressing various pharmaceutical and clinical objectives. The development in fabrication technologies, materials used, and drug delivery strategies has led to a wide range of applications of microneedles in delivering vaccines, insulin, hormones, proteins, peptides, nucleic acids, and anti-cancer agents. Significant advantages have been achieved using microneedle-mediated systems in infectious disease therapy, diabetic management, dermatological conditions, cancer treatments, and cosmetic applications. In spite of issues involving manufacturing scale-up, loading capacity, stability, and approval by health authorities, continuous advancements like smart microneedles, wearable devices, incorporation of nanotechnology, and AI-based designs have kept the field evolving. Microneedle technology overall is a promising delivery platform for the future of minimally invasive treatments and personalized medicine.

KEYWORDS: Microneedles, Transdermal Drug Delivery, Non-Invasive Therapy, Drug Delivery Systems, Vaccine Delivery, Dissolving Microneedles, Controlled Drug Release, Personalized Medicine.

INTRODUCTION

The concept of drug delivery plays an important role in medicine as the efficiency of the drugs is mainly influenced by the efficiency at which they reach their target site in the body. Traditional drug delivery techniques including oral administration of tablets, capsules, and injections have been used for years in treatment of different diseases. Unfortunately, this technique faces numerous challenges. Some of the oral drugs can undergo metabolism in the GI tract leading to decreased efficiency of the drugs while the other drugs can experience first-pass effect in the liver, thus making them less effective. On the other hand, injections offer faster results than other drug administration techniques but are painful and invasive. Consequently, there has been a need for new drug delivery approaches and techniques which are patient friendly and more effective. One of such techniques includes transdermal drug delivery system.[1]

The use of transdermal drug delivery systems is characterized by a wide range of benefits compared to other traditional techniques for drug administration. Transdermal systems allow for the delivery of controlled and sustained release, increasing patient adherence to the treatment, decreasing dosing frequency, and bypassing first-pass effects of drug metabolization. Nonetheless, the skin represents one of the largest barriers for drug permeation. Specifically, the outer layer of the skin known as the stratum corneum acts as an efficient skin barrier preventing the penetration of potentially harmful substances as well as pharmaceuticals. As a result, only some pharmaceuticals with unique physical and chemical properties can be delivered across the skin via transdermal patches. In order to increase the efficiency of transdermal drug delivery, several different enhancement techniques were invented, including chemical permeation enhancers, iontophoresis, sonophoresis, and microneedles.[2]

Microneedles refer to tiny needle-shaped devices that range between a few micrometers to several millimeters in length and help form microscopic holes in the skin. Unlike regular hypodermic needles, which penetrate deeper skin layers and cause activation of deep pain receptors in the process, microneedles do not go beyond the top layer of the skin, which helps reduce pain associated with treatment. Microneedles are responsible for facilitating delivery of various active substances that include small molecules, peptides, proteins, vaccines, insulin, genes, among others. Depending on their design and function, microneedles can be classified as solid, coated, hollow, dissolving, and hydrogel-forming. In addition to the effectiveness associated with the use of injections and convenience of patches, microneedles have proven to be a unique device for delivery of modern medicines.[3]

The development of novel microfabrication processes, advanced biomaterial science, and pharmaceutical technologies has increased the application scope of microneedles. Next generation microneedle technologies are now in development for use as means for controlled drug delivery, disease surveillance, and patient-specific therapies. The use of microneedles has been shown to be successful in the treatment and prevention of diseases such as diabetes, infectious diseases, cancer, skin disorders, and chronic diseases. Moreover, the simple application process of microneedles makes them more accessible and can even allow self-administration, thus ensuring their effectiveness in resource-poor settings. Some microneedle products are currently undergoing testing and commercialization. This shows that microneedles are becoming increasingly important within the pharmaceutical and biomedical industries. Thus, microneedle-enhanced transdermal drug delivery is being acknowledged as an innovative and non-invasive treatment approach for future use.[4]

STRUCTURE OF HUMAN SKIN

Human skin is an advanced multi-functional organ responsible for protecting the organism from different external environmental elements. The skin occupies about 1.5 – 2.0 sq.m. of the body's surface and constitutes up to 15% of body weight. In addition, the skin performs multiple physiological roles such as protecting, regulating temperature, sensing, immunological protection, and retention of excessive fluid losses. The skin structure consists of three major layers: epidermis, dermis, and hypodermis. Each layer features specific properties and responsibilities ensuring proper functioning of the skin.

Epidermis: The epidermis is the most superficial layer of skin, functioning as the primary barrier of protection. It is primarily made up of keratinocytes that make up different layers such as the stratum basale, stratum spinosum, stratum granulosum, stratum lucidum (only found in thick skin) and the stratum corneum. Of all these layers, the stratum corneum stands out in terms of its ability to impede the passage of drugs into the skin. The stratum corneum is characterized by dead, flattened corneocytes surrounded by lipids; this layer is referred to as the "brick and mortar" layer.[5]

Dermis: Beneath the epidermis lies a layer known as the dermis, which is composed of connective tissue and helps give strength and flexibility to the skin. The dermis contains collagen and elastin fibers within an extracellular matrix. The dermis is further classified into the papillary dermis and reticular dermis, and includes blood and lymph vessels, nerves, hair follicles, sweat glands, and sebaceous glands. In addition, this layer of the skin plays a critical role in nourishing the epidermis, regulating body temperature, and wound repair. For transdermal delivery systems, the dermis is of great importance because when medications reach this layer, they can pass into the bloodstream via its rich vascular supply.[6]

Hypodermis (Subcutaneous Tissue): The hypodermis, which is sometimes called subcutaneous tissue, is the deepest layer of the skin. The hypodermis consists mainly of fatty tissue, connective tissue, blood vessels, and nerves. Its main function is to store energy, provide insulation, and serve as a shock-absorbing layer to protect muscles and internal organs. While the hypodermis is not a primary barrier against drug penetration into the skin, it plays a role in drug distribution and absorption from other skin layers.[7]

FACTORS AFFECTING TRANSDERMAL DRUG PERMEATION

Successful transdermal administration requires penetration of the skin barrier by the drug for reaching the target site. There are multiple factors that can affect the process of drug penetration through the skin. The knowledge of these factors allows designing transdermal drug delivery systems properly.

Physicochemical Properties of the Drug: Drug properties play an important role in the permeability through the skin barrier. Drugs characterized by low molecular weight (<500 Da), moderate lipophilicity, and proper solubility demonstrate good permeability. Excessive lipophilicity and high hydrophilicity are not advantageous because drugs with high lipophilicity can be accumulated in the lipids of the skin barrier, while highly hydrophilic drugs cannot enter the stratum corneum.

Skin Hydration: An increase in skin hydration is very beneficial for enhancing drug permeability. High hydration levels cause swelling of the corneocytes and loosen the lipids, thus making room for drug molecules to pass through. Moisturizers and occlusive dressings have been commonly used to enhance hydration for effective absorption of drugs.

Skin Thickness and Anatomical Site: There is an obvious variation in the thickness of the skin in different parts of the body. There are certain sites such as around the eyes and behind the ear where the skin is thinner and therefore more permeable. In contrast, the skin in areas like the palm is thicker and relatively impermeable.[8]

Age and Physiological Conditions: Age influences permeability because the physiology of the skin differs from one age group to another. Infants and the elderly have different characteristics in their skins compared to other adults. Some factors influencing drug absorption include hydration of the skin, lipid content, and thickness of the epidermis.

Skin Diseases and Damage: Conditions like eczema, psoriasis, dermatitis, burns, and injuries to the skin alter the structure of the stratum corneum and increase the permeability of drugs. Although injured skin increases drug permeation, the skin can become irritated, experience toxic effects, and even result in an unpredictable flow of medication.

Drug Concentration and Dose: High drug concentration is associated with high rates of permeation due to creation of a concentration gradient. Excessive drug concentration can, however, lead to skin irritation or clog the pathway of skin absorption.[9]

Formulation Factors: Properties of the formulation play an important role in determining the permeation properties of drugs. These include the pH of the formulation, viscosity, type of vehicle, inclusion of permeation enhancers, and drug release from the formulation.

Environmental Factors: Environmental factors like temperature, humidity, and occlusion can also influence the skin's permeability. For instance, increased temperatures lead to increased blood flow in the skin and increased molecular activity within the skin leading to increased absorption. Increased humidity levels will also increase skin hydration hence increased permeability.

FUNDAMENTALS OF MICRONEEDLE TECHNOLOGY

Microneedle technology stands out as among the greatest achievements in drug delivery system technology. As their name suggests, microneedles refer to tiny needle-like structures that are used to puncture the outermost layer of the skin known as the stratum corneum. They do not reach into the lower layers of skin rich in nerves hence they cause no pain, bleeding, and discomfort that would otherwise result from using hypodermic needles. Therefore, microneedle technology combines features of transdermal patches and injectable preparations to provide an effective method of administering drugs without causing any complications.

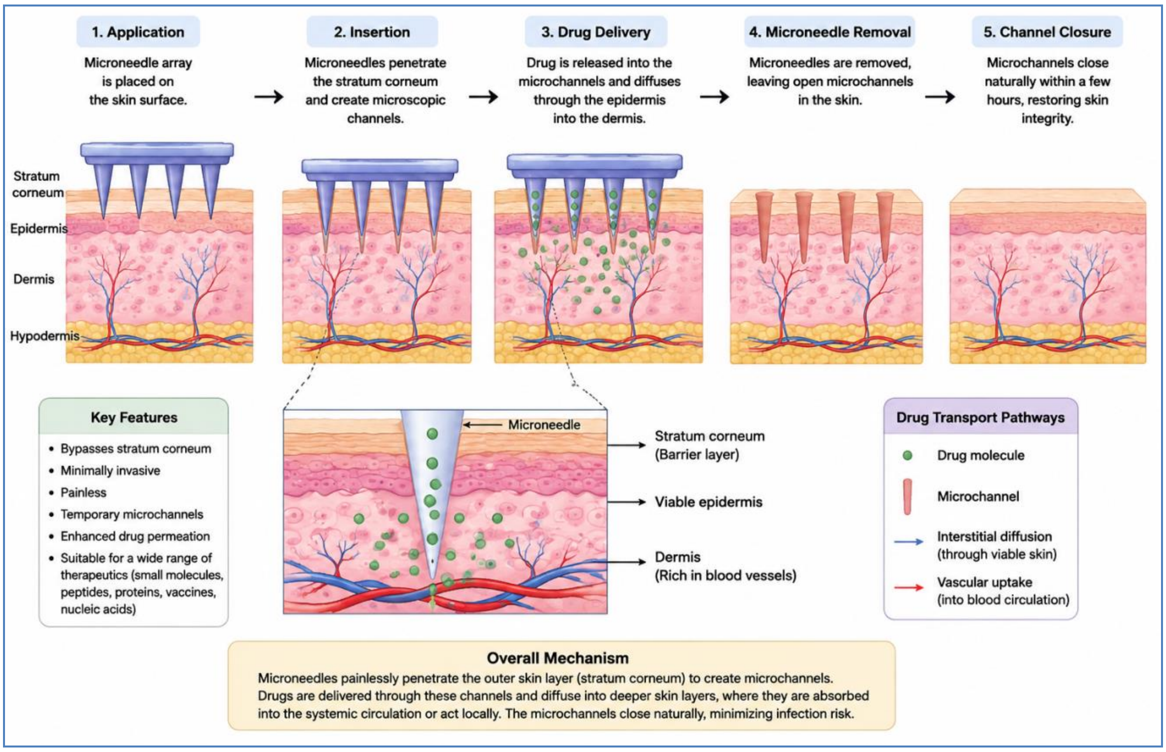
Microneedles are small needles measuring anywhere between 25 µm and 2000 µm in length and are configured into needle arrays made up of numerous projections. Microneedles work by piercing the skin and creating microchannels that temporarily affect the barrier activity of the stratum corneum. Using such microchannels, drugs will have the ability to reach the viable epidermis and dermis through the microchannels. Unlike conventional needles, microneedles are normally painless as they do not pierce deep enough to stimulate the pain nerves or the blood vessels. Depending on the specific type of microneedles used, drugs may be diffused, applied, injected, or released from dissolvable microneedles.[10]

HISTORICAL DEVELOPMENT OF MICRONEEDLES

Microneedle technology was introduced in the latter part of the twentieth century following advancements in the fields of microelectronics and microfabrication. Initial studies were directed toward designing micro-devices that were able to penetrate biological tissues without being highly invasive. It was not until the 1990s that the first successful fabrication of silicon microneedles was achieved using methods that had evolved from the semiconductor industry. Since then, a lot of development work has been done in the area of microneedles regarding their design, fabrication, and implementation. Different types of materials such as metal, plastic, ceramic, and biodegradable components have been used to enhance their performance.[11]

MECHANISM OF MICRONEEDLE-ASSISTED DRUG DELIVERY

The use of microneedles increases effectiveness in transdermal drug administration since it bypasses the stratum corneum, which is the major hindrance for drug permeation. Microneedles perforate the uppermost layer of the skin and thus create aqueous microchannels in it. This allows for direct diffusion of drugs into the live epidermis and dermis layers where they can either be absorbed in the local tissue or circulate systemically via dermal blood vessels. Microneedles can deliver drug molecules into the skin through various processes, including passive diffusion, drug dissolution from coated needles, drug infusion in aqueous solutions, drug dissolution of polymers, or hydrogel swelling. The aqueous microchannels self-close after several hours once microneedles are detached, reducing the likelihood of infections.[12]



ADVANTAGES OF MICRONEEDLES OVER CONVENTIONAL NEEDLE-BASED ADMINISTRATION

1. Reduced Pain and Discomfort

The first advantage of microneedles is their capacity to administer drugs with almost no pain. Traditional needles pierce through multiple layers of body tissues that have numerous pain receptors and nerves causing pain. Conversely, microneedles pierce only the outer layers of the skin without causing damage to deeper layers. This implies that there is virtually no pain felt when using microneedles during drug administration.

2. Improved Patient Compliance

Needle phobia is another significant problem in administering treatments. Most people fear needles due to pain and possible injury from conventional needles. By introducing microneedles, the process becomes easier and more efficient, encouraging higher patient compliance. Patients who require frequent administration of drugs benefit the most from microneedles, especially diabetics.[13]

3. Minimal Risk of Bleeding and Tissue Damage

Traditional needle injection causes bleeding, bruises, and injury to underlying blood vessels and muscle tissues. On the other hand, microneedles create microscopic passages on the outer layer of the skin without any damage to the deeper structures and blood vessels. This means that there is a minimal possibility of bruising or bleeding.

4. Lower Risk of Needle-Stick Injuries

Injuries from needles pose considerable risks for health care practitioners and are linked with potential infectious disease transmission. As many microneedle-based systems have been designed to be completely dissolvable at the end of use or can be disposed of with no sharp parts, the chance of needle-stick injury becomes much smaller.

5. Potential for Self-Administration

Injection administration usually involves professional health care practitioners, thereby increasing the overall cost and restricting access to the therapy. Application of microneedle patches is relatively easy and allows for self-application. Thus, self-care opportunities become more prevalent due to this feature.[14]

6. Enhanced Delivery of Biologics and Vaccines

Therapeutic biologics such as peptides, proteins, vaccines, and nucleic acids cannot be delivered using oral administration due to their instability. With the help of microneedles, these substances can be delivered intradermally without any loss of biological properties. Furthermore, immunogenicity of vaccines may be increased when administered via microneedles, as skin consists of numerous antigen-presenting cells.

7. Improved Patient Safety

Some of the safety concerns that come with traditional injection needles such as infections, pain, and incorrect injection are lessened by the use of microneedles. In addition, the minute tunnels generated by microneedles are normally closed up after a few hours, preventing any possible microbial contamination.

8. Elimination of First-Pass Metabolism
While oral medication needs to pass through the gastrointestinal tract and undergo first pass metabolism, this is not the case when using microneedles to administer medication into the body. Such an effect enhances the efficiency of the drug since there will be no loss during administration.[15]

9. Controlled and Sustained Drug Release
Through careful design, advanced microneedles, specifically dissolving microneedles and hydrogel microneedles, can be manufactured to achieve either controlled or sustained release of drugs over prolonged periods of time, thus helping reduce the need for frequent doses and keeping drug levels constant.

10. Improved Stability and Ease of Transportation
Some microneedles are more stable under normal conditions than the conventional needle and syringe, including the vaccine-loaded dissolving microneedles, which may lead to easier transportation to less-developed areas.

11. Reduced Medical Waste
Regular syringes produce lots of biomedical waste that requires special handling, while dissolving microneedles do not produce any such waste upon insertion.

12. Cost-Effectiveness in Mass Healthcare Programs
Ease of use, reduced reliance on healthcare professionals, minimal refrigeration needs, as well as fewer disposal expenses make microneedles more efficient in mass healthcare initiatives.[16]

CLASSIFICATION OF MICRONEEDLES

Solid Microneedles: The simplest form of microneedles is solid microneedles. They are mainly used for the formation of microscopic holes on the skin surface. This technique is referred to as "poke-and-patch". The solid microneedles pierce into the skin, and thereafter, a drug formulation is applied to the area where the solid microneedles have been inserted. Solid microneedles are made of strong materials, which make their fabrication very simple. They find extensive use in the delivery of vaccines and drugs through the skin.

Coated Microneedles: In coated microneedles, drug formulations are coated on the surface of solid microneedles. Once the microneedles penetrate the skin, they dissolve quickly in the interstitial fluid and release the drug formulation into the dermis and epidermis. This technology ensures accurate dosage and rapid administration of the drug formulation to the skin. However, the quantity of the drug formulation that can be loaded in coated microneedles is very small. They are extensively used in protein, peptide, and vaccine formulations.[17]

Hollow Microneedles: The hollow microneedles refer to tiny needle devices featuring a central hollow structure through which fluid medications are administered in the dermal layer of the skin. Hollow microneedles work in a similar fashion to standard hypodermic needles but differ in size and invasiveness. The hollow microneedles enable controlled medication administration and also can be used for larger drug dosages compared to other types of microneedles. However, the process of microneedle fabrication is more complicated and lumen clogging is possible. These types of microneedles are intensively researched for the administration of insulin, vaccines, and biological drugs.

Dissolving Microneedles: The dissolving microneedles consist of biodegradable and water-soluble polymers, in which pharmaceuticals are loaded as an integral part of the needle material. When dissolving microneedles are inserted into the skin, they dissolve due to interaction with the interstitial fluid and release the drug. The dissolving microneedles are considered to be safer due to the lack of production of sharp medical waste. This type of microneedle is especially promising for the application in self-medication and mass vaccination campaigns.

Hydrogel-Forming Microneedles: The hydrogel-forming microneedles are made up of crosslinked polymer material that absorbs the interstitial fluid from the body and swells upon contact with the skin tissue. In contrast to dissolving microneedles, these microneedles do not dissolve. Rather, the swelling process causes the formation of hydrated networks through which the drugs in attached reservoirs are delivered. This mode of operation allows for the controlled and continuous delivery of drugs for longer periods. The advantages of using hydrogel-forming microneedles include biocompatibility and capacity for large drug loading.

Bio-Responsive (Smart) Microneedles: Bio-responsive or smart microneedles belong to the next level of microneedle technology. They are able to respond to physiological stimuli like glucose concentrations, pH changes, enzymes, temperatures, or disease biomarkers. This type of microneedles releases the drugs only upon recognizing certain bio-stimuli. Such microneedles allow for personalized delivery of drugs to the targeted site. Smart microneedles have already found practical application in managing diabetes, cancers, and other disorders. Currently, bio-responsive microneedles remain the subject of extensive research and have great potential in revolutionizing drug delivery systems.[18]

MATERIALS USED IN MICRONEEDLE FABRICATION

Fabrication is defined as the manufacturing process by which various structures with defined geometric, mechanical and delivery properties are designed and produced. Choosing the right method for fabricating microneedles affects the effectiveness and safety of microneedle technology and transdermal drug delivery.

Metals: Materials like stainless steel, titanium, nickel, and palladium are frequently used for making microneedles because of their superior strength and durability. Such needles have the ability to pierce the skin without getting damaged. They find application in solid, coated, and hollow microneedle systems but require special disposal post use.

Silicon: Silicon is one of the early discovered materials that are compatible with micro-fabrication technology and thus have been used for making microneedles. They provide superior dimensional accuracy and allow easy manufacturing of complex geometrical features. Silicon is, however, relatively brittle and can easily get fractured at application site.

Ceramics: Ceramic microneedles include materials like alumina and calcium phosphate. Such materials possess good biocompatibility, chemical stability, and corrosion resistance properties. They are, however, relatively brittle and thus more likely to crack on application.[19]

Biodegradable Polymers: Polymers like PLA, PGA, and PLGA are common in making dissolvable microneedles. The materials degrade easily within the body once drug delivery occurs. The polymers have the benefit of being biocompatible, allowing controlled drug release, without producing any sharp medical wastes.

Synthetic Water-Soluble Polymers: Water-soluble synthetic polymers, such as PVA, PVP, and carboxymethyl cellulose, are commonly used in dissolving microneedle fabrication. These materials are readily soluble once inserted in the skin, promoting effective drug delivery. The mechanical and other favorable properties of water-soluble synthetic polymers make them ideal in pharmaceutical uses.

Natural Polymers: Hyaluronic acid, chitosan, gelatin, and alginate are natural polymers increasingly applied in microneedles production. Such polymers exhibit good biocompatibility, degradation properties, and minimal toxicity levels. The natural polymers are capable of encapsulating various drugs while promoting skin compatibility.

Carbohydrates and Sugars: Carbohydrates like maltose, trehalose, dextran, and sucrose have been considered as materials for microneedles owing to their biocompatibility and potential to stabilize fragile drugs. These carbohydrates dissolve very quickly once inserted into the skin and aid in drug release. However, they may have inferior mechanical properties compared to other types of microneedles made of polymers.

Composite Materials: Composite microneedles refer to those that utilize more than one type of materials for fabrication, such as polymers, metal, ceramic, or nanoparticles. Composite microneedles can enhance mechanical properties, drug loading and release properties, among others.[20]

FABRICATION TECHNIQUES OF MICRONEEDLES

Photolithography: This is among the oldest processes employed in the fabrication of microneedles. It entails the use of light-sensitive resists to project a pre-defined pattern into the substrate using ultraviolet light. Photolithography allows for high accuracy and dimensional control, making it suitable for fabricating silicon microneedles with complex shapes. Nevertheless, photolithography requires costly equipment and special cleanroom environments.

Laser Cutting and Laser Ablation: This process involves the use of focused laser beams for cutting, shaping, or removing parts of the substrate to fabricate microneedles. Some benefits associated with laser fabrication include its capacity for rapid fabrication, accuracy, and ease of modifying designs. Nonetheless, excessive laser use can negatively affect the material properties, leading to increased costs.

Micromolding: Micromolding is considered among the most common methods for manufacturing polymeric and dissolving microneedles. In micromolding, the liquid form of the polymer-drug combination is introduced into the microneedle molds. The formed microneedles are extracted from the molds. Micromolding is economical, scalable, and feasible for the mass production of drug-loaded microneedle arrays.

Injection Molding: Injection molding is a process wherein the melted forms of polymer are injected into specifically designed molds and left to cool and harden before being taken out from the mold. Injection molding is effective for the quick mass production of microneedles of high quality and consistency.[21]

Wet and Dry Etching: Etching techniques mainly focus on making microneedles by using silicon as a base material. While wet etching uses chemical substances to remove unwanted material from silicon, dry etching uses plasma or other reactive gases for the same purpose. They offer high accuracy and surface finish. The etching process is popular in the manufacture of MEMS and can be used to make very precise microneedles.

Drawing Lithography: This approach relies on stretching a liquid polymer between two surfaces to achieve elongation in microneedles. Upon solidifying, the microneedles formed have sharp ends with proper dimensions to allow penetration through the skin. The method is cheap but may lack precision and control compared to other sophisticated techniques of microfabrication.

Hot Embossing: It refers to a manufacturing process where a heated mold is pressed against a sheet made of thermoplastic polymer material to form microneedle structures. Once cooled down, the material will retain the shape. It is a convenient method that enables mass production and accurate shapes for microneedles.

3D Printing: The advent of 3D printing technology has revolutionized the approach to microneedle fabrication. 3D printing facilitates the development of customized microneedles with intricate design features and fast prototyping capabilities. Stereolithography, digital light processing, and two-photon polymerization techniques are frequently used. This technology allows personalized treatment and minimizes time spent on manufacturing and material wastage.

Electroforming: Electroforming refers to an electrochemical method of fabricating metallic objects using the deposition of metal ions onto a conductive template. Electroformed metallic needles are distinguished by a high degree of accuracy and outstanding mechanical properties. Electroforming is applicable to the production of metallic microneedles and master molds for further use in micromolding.[22]

MECHANISMS ENHANCING TRANSDERMAL DRUG DELIVERY

Creation of Microchannels: There are two approaches to drug delivery through microneedles. First, upon piercing the skin layer, microneedles make micro-channels through which drugs have access to the subcutaneous skin tissue without passing through the skin layer. With the formation of micro-channels, the risks of infection become very small due to natural closing of the micro-channels within a few hours. In the second case, microneedles are utilized in conjunction with topical drug therapy.

Bypassing the Stratum Corneum Barrier: The stratum corneum layer constitutes the primary barrier to drug transdermal delivery. Using microneedles, the stratum corneum barrier is physically bypassed without damaging other parts of skin tissue. The use of microneedles for the transdermal delivery of drugs allows penetration through the stratum corneum and delivery to the inner skin tissue.[23]

Enhanced Drug Diffusion: The microchannels formed via the use of microneedles provide direct routes for diffusion of drugs. Once the barrier is breached, the drug molecules diffuse through aqueous channels into deeper layers of skin along the concentration gradient. The improvement in the diffusion process results in an increase in the rate and efficiency of drug diffusion when compared with normal transdermal patches.

Increased Permeability of Large Molecules: Biologics like peptides, proteins, vaccines, antibodies, and nucleic acids have large molecular weights which cannot penetrate intact skin passively. This problem is addressed through microneedles, where the physical routes are used to facilitate diffusion of such molecules. Hence, the drugs which otherwise required an invasive procedure for delivery can now be administered via the skin.[24]

Delivery to Highly Vascularized Skin Layers: The microneedles provide an easy way for the drugs to penetrate into the viable epidermal and dermal layers where there is a high degree of vascularization (blood vessels and lymphatic vessels). After penetration into these layers, the drugs can be immediately absorbed into the systemic circulation.

Controlled and Sustained Drug Release: In some cases, the microneedles, especially dissolving and hydrogel forming microneedles, may be designed in such a way that it leads to controlled or sustained drug delivery. This happens due to the slow dissolution of the drug-loaded microneedles, which slowly releases the drug molecules by diffusion through the hydrogel matrix.

Enhanced Immune Response for Vaccination: The skin layer consists of antigen-presenting cells such as Langerhans and Dendritic cells. The vaccine delivery using microneedles results in targeting these immune cells effectively; therefore, vaccines can cause increased immune responses and have received much attention for vaccination applications.

Avoidance of First-Pass Metabolism: With medications that are administered using microneedles, there is no need for them to be subjected to first pass effect as they reach the bloodstream directly and do not go through the gastrointestinal tract and liver. This helps to enhance drug effectiveness and reduce the dose that needs to be administered.

Improved Patient Compliance: The less invasive nature of microneedles plays an indirect role in better drug delivery because of increased compliance from patients. This can happen because of reduced pain during administration, simplicity in the method, and even allowing self-administration in certain cases.[25]

THERAPEUTIC APPLICATIONS OF MICRONEEDLE TECHNOLOGY

The advent of microneedle technology has revolutionized the drug and vaccine delivery industry. Due to the penetration through the stratum corneum barrier, microneedles can be used effectively for the administration of various medications such as small-molecule drugs, peptides, proteins, vaccines, and nucleic acids. The minimally invasive characteristics and high compliance of microneedles, together with the capability of drug controlled release, allow for the use of microneedle technology in many clinical fields.

Therapeutic uses of microneedle technology are reviewed as follows.

Vaccine Delivery: One of the main areas of application for microneedles is the delivery of vaccines. Being rich in antigen-presenting cells like Langerhans cells and dendritic cells, the skin can serve as an excellent target tissue for vaccinations. Vaccines can be administered into the antigen-presenting cells, allowing the effective stimulation of the body's immune system. Several microneedle-based vaccinations against influenza, COVID-19, hepatitis, measles, and HPV viruses were successfully tested in animal experiments.

Diabetes Management: The use of microneedles has exhibited a lot of potential for the management of diabetes due to their applicability in insulin therapy. Traditional insulin administration methods involve needles that are quite painful to patients, hence poor compliance by many individuals with diabetes. Microneedles can deliver insulin into the body without any pain, ensuring efficient glycemic regulation. Efforts are ongoing to develop glucose-responsive microneedles which would be used to release insulin in response to high blood sugar levels.

Cancer Therapy: Microneedles provide a more targeted mechanism of anticancer drug administration since they enable direct delivery of anticancer medicines into the targeted tissues. This method ensures high local concentration of the drug with reduced side effects. Anticancer drugs, immunotherapeutic drugs, and gene therapies have been delivered using microneedles. In cases involving skin tumors like melanoma, microneedles can be employed for the direct delivery of anticancer drugs.[26]

Dermatological Disorders: Microneedle technology has gained considerable attention in dermatology for the treatment of various skin disorders. Therapeutic agents can be delivered effectively for conditions such as psoriasis, acne vulgaris, atopic dermatitis, fungal infections, and vitiligo. Microneedles improve drug penetration into affected skin layers, leading to enhanced therapeutic outcomes. Their minimally invasive nature also reduces the need for repeated injections or high-dose topical treatments, improving patient comfort and adherence.

Hormone Replacement Therapy: Many hormonal preparations are required to be taken for prolonged periods of time, and there may be some issues with their oral absorption or injections. Microneedles offer a convenient means of delivery for many hormonal medicines, including such hormones as estrogen, progesterone, testosterone, and human growth hormone. Controlled-release microneedle delivery could result in the maintenance of steady hormone levels within the body for quite a long time, thereby minimizing the number of doses to be delivered.[27]

Pain Management: Analgesic and anesthetic drugs were studied in connection with their ability to be delivered via microneedle system directly into the bloodstream bypassing the digestive tract, thus providing a more rapid relief from pain, but excluding any possible adverse effects that arise with the use of oral medicines. Such an approach to pain medication could be beneficial for patients suffering from acute and chronic pain conditions.

Cardiovascular Diseases: There have been numerous cardiovascular medications including antihypertensives and antianginals whose transdermal delivery has been tested using microneedles. Microneedles can be helpful because through them there is no first pass effect and hence the bioavailability of the drugs can be maintained along with proper drug level control. Therefore, using the above technique can be more advantageous for patients taking medicines for hypertension, heart failure and other cardiovascular diseases.

Infectious Diseases: Antimicrobial and antiviral drugs and vaccines which can help prevent and cure infectious diseases have been found to be administered through microneedles successfully. The reason for the success of such administration methods is their capability to deliver the drugs either locally or even systemically without much inconvenience to the patients. Examples of some infectious diseases include influenza, tuberculosis, HIV and COVID-19.[28]

Gene and Nucleic Acid Delivery: Genetic materials like DNA, RNA, siRNA, mRNA, and CRISPR-based treatments pose a great difficulty in terms of delivery since they are very unstable due to their enormous size. Microneedles serve as an ideal tool for resolving these issues by allowing genetic materials to be delivered directly inside the tissue layer of the skin. The use of microneedles is growing significantly in the areas of gene therapy, genetic vaccinations, and personalized medicine.

Ophthalmic Applications: There have been many attempts at ocular drug delivery using microneedles in order to circumvent the shortcomings of topical drops or injections. Drugs can be delivered efficiently to ocular regions and minimize the absorption of substances into the rest of the body. Some of the disorders that can benefit from microneedle application are glaucoma, retinal diseases, macular degeneration, and other ocular infections.

Cosmetic and Aesthetic Applications: Apart from being used in treatments for medical problems, microneedles find wide applications in cosmetic and aesthetic medicine. In microneedling treatment, microneedles work towards boosting collagen and skin regeneration, leading to the enhancement of scarring, wrinkles, stretch marks, and other pigmentation issues. The microneedles can be used to boost the delivery of cosmetic ingredients including vitamins, peptides, and growth factors.[29]

SAFETY PROFILE OF MICRONEEDLE-ASSISTED TRANSDERMAL DRUG DELIVERY

Transdermal drug delivery using microneedles is often viewed as a technique that is both safe and minimally invasive for delivering medicines. As compared to traditional hypodermic needles, microneedles will not cause damage to tissues that contain nerves and major blood vessels as they will not go beyond superficial layers of the skin. Thus, there would be minimal discomfort, pain, bleeding, and skin irritation upon use. Several experiments carried out using pre-clinical and clinical models proved that the technique has been very well accepted by patients with only mild skin reactions such as redness, mild swelling, itching, or irritation of the skin. This can easily resolve itself after several hours or days and requires no further treatment.[30]

Even with the high level of safety offered by microneedle systems, there are several factors to consider when using them in practice. Improper handling of the microneedles, repeat applications at the same spot, or low-quality microneedles could result in irritation, inflammation, infection, and even poor skin penetration. Microneedles need to be made from materials that are biocompatible and non-toxic to avoid immune reactions or allergies in the patients. Studies conducted over a long period of time reveal that the tiny openings made in the skin by microneedles heal quickly, preventing bacteria from entering the body through the skin. When evaluating microneedles in terms of regulatory standards, sterility, mechanical strength, and the safety of the materials used should be considered before clinical application.[31]

CLINICAL STUDIES AND COMMERCIALLY AVAILABLE MICRONEEDLE PRODUCTS

Authors	Title	Conclusion
Rouphael NG, Paine M, Mosley R, Henry S, McAllister DV, Kalluri H, et al. (2017)	The Safety, Immunogenicity and Acceptability of Inactivated Influenza Vaccine Delivered by Microneedle Patch: A Randomized, Partially Blind, Placebo-Controlled Phase 1 Trial	Microneedle patch vaccination was safe, well tolerated, highly acceptable to participants, and generated immune responses comparable to conventional intramuscular vaccination while enabling potential self-administration.[32]
Jeong SY, Park JH, Lee YS, Kim YS, Park JY, Kim SY (2020)	The Current Status of Clinical Research Involving Microneedles: A Systematic Review	Analysis of 38 clinical studies demonstrated that microneedles are generally safe and effective, with most adverse events being mild and transient, supporting their potential in diverse therapeutic applications.[33]
Zhang J, Li H, Albakr L, Zhang Y, Lu A, Chen W, Shao T, Zhu L, Yuan H, Yang G, Wheate NJ, Kang L, Wu C (2023)	Microneedle-Enabled Therapeutics Delivery and Biosensing in Clinical Trials	Clinical evidence indicates that microneedles provide painless, self-administrable drug delivery and diagnostic capabilities, demonstrating strong potential for broader clinical translation and commercialization.[34]
Nguyen TT, Park JH (2018)	Human Studies with Microneedles for Evaluation of Their Efficacy and Safety	Human studies consistently showed improved patient acceptance, reduced pain, and favorable safety profiles, highlighting microneedles as promising alternatives to conventional injection-based drug delivery systems.[35]
Kim YC, Park JH, Prausnitz MR (2012)	Microneedles for Drug and Vaccine Delivery	Microneedle technology effectively enhances transdermal delivery of drugs and vaccines by overcoming skin barriers while minimizing pain, improving patient compliance, and enabling simplified administration.[36]

CHALLENGES AND LIMITATIONS

1. Mechanical Strength Limitations

The most important drawback in using microneedles as drug carriers is the ability to sustain sufficient mechanical strength during their application. The mechanical strength of materials used in making microneedles determines their ability to avoid bending, breaking, and distortion while inserting into the skin surface. Sufficient mechanical strength should be obtained to facilitate easy drug administration through microneedles.

2. Limited Drug Loading Capacity

Due to the small size of microneedles, it becomes difficult to load substantial amounts of drugs into each patch, especially drugs that require high amounts. Even though there have been innovations aimed at increasing the drug loading abilities, including using hydrogel-forming microneedles and hollow microneedles, it still poses a problem among researchers and manufacturers.[37]

3. Manufacturing and Scalability Challenges

The fabrication process of microneedles entails advanced techniques such as photolithography, micromolding, and three-dimensional printing. All these methods entail advanced and expensive pieces of equipment as well as stringent quality control standards. The scaling up from the laboratory stage to full-scale manufacturing has proven to be challenging, hence posing a hindrance to the uptake of microneedle-based drug delivery devices.

4. Stability and Storage Issues

Stability of drugs when incorporated into microneedles has proven to be one of the biggest challenges especially with biological agents like vaccines, peptides, and proteins. Environmental conditions such as temperature, moisture, and even exposure to light can influence both the efficacy of the drug as well as microneedle structure.

5. Regulatory and Approval Barriers

Microneedles, by nature, are a combination of pharmaceutical preparations and medical device. For any company wanting to manufacture microneedles, there is need for safety, effectiveness, sterility, biocompatibility and quality documentation to prove before an approval is issued. This could be exacerbated in cases where there exist no standard regulations guiding their use in certain regions.[38]

6. Patient-Related and Clinical Challenges

There are some challenges related to patients that might affect the efficacy of microneedle-based drug delivery. For instance, the varying thickness of skin, skin hydration level, patient's age and health condition may influence the efficiency of the method. Moreover, issues related to skin irritation, patient ability to apply microneedle patches independently and costs may be significant barriers to adoption.

RECENT ADVANCES AND EMERGING TRENDS

1. Smart and Stimuli-Responsive Microneedles

With current advancements in technology, stimuli-sensitive microneedles have been developed. These microneedles can respond to signals like glucose levels, pH levels, temperature, or particular biomarkers in the body. With the help of such microneedles, one can control and regulate the release of medication, which helps minimize side effects.

2. Wearable Microneedle Devices

The combination of microneedles with wearable technologies has led to novel applications that involve continuous drug delivery and monitoring of patients' physiological parameters. Such devices deliver medications for prolonged time spans and at the same time gather health information about the patient. Wearable microneedles enhance patients' comfort and enable remote medical treatment. They are used more often in the treatment of chronic diseases.

3. 3D Printing-Based Microneedle Fabrication

3D printing has proven to be an efficient method of fabricating microneedles with complex structures and precise dimensions. This approach enables faster prototyping and personalized design. 3D printing gives great opportunities for creating new microneedles and promoting transdermal drug delivery studies.

4. Nanotechnology-Integrated Microneedles

The use of nanotechnology along with microneedle systems has led to improvements in drug loading capacity, stability, efficiency, and release. The use of nanoparticles, liposomes, and nanocarriers loaded within microneedles is helpful in achieving efficient transport of drugs having low solubility, vaccines, and biological drugs. It provides better therapeutic results without any adverse effect on the body.[39]

5. Gene and Nucleic Acid Delivery

Various research studies have shown that microneedles could be used for delivering genetic material such as DNA, mRNA, siRNA, and other nucleic acids. The ability of microneedles to overcome the barriers of the skin easily is useful for gene delivery and vaccines based on nucleic acids.

6. Artificial Intelligence-Assisted Microneedle Design

AI is being employed for optimizing the design of microneedles, predicting drug delivery kinetics, and enhancing manufacturing processes. AI modeling helps in analyzing vast amounts of data and determining optimal conditions for effective drug delivery systems. The innovation plays an important role in developing highly effective microneedle based systems.

7. Multifunctional Microneedle Platforms

The current trend with microneedles is their development as multifunctional systems that can incorporate the ability to deliver drugs and monitor biosensors for diagnostic and disease monitoring in one platform. These multifunctional systems can offer real-time feedback and therapeutic action at the same time.[40]

CONCLUSION

Microneedle-mediated transdermal delivery is considered an innovative delivery approach that successfully addresses the shortcomings of traditional oral and parenteral delivery systems. By inducing temporary pathways into the skin, microneedles enable effective delivery of multiple drugs, including small molecules, peptides, proteins, vaccines, and nucleic acids, without any adverse effects on pain, tissue injury, and patient comfort levels. The use of microneedles with different structures, including solid needles, coated needles, hollow needles, dissolving microneedles, hydrogel forming microneedles, and biomimetic microneedles, allows for the application of microneedles in different medical applications. The evolution of material sciences, manufacturing processes, and drug delivery methods has enabled microneedle technologies to become more reliable and safer. The use of microneedles for vaccinating patients, treating diabetes, curing cancer, dealing with skin problems, hormone replacement treatment, and gene delivery is proof of their efficacy. Moreover, innovations such as smart microneedles, wearable devices, nanotechnology, and artificial intelligence have increased their potential and brought personalized treatment a step closer. Even though there are some concerns about manufacturing at a large scale, drug loading, stability, and regulatory issues, there is still extensive research being conducted on how to overcome such obstacles. However, with more advancement in technology and clinical acceptance of microneedles, microneedle-based transdermal delivery of drugs is set to become an important part of the future of medicine.

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