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Microneedle-Based Transdermal Drug Delivery: A Comprehensive Overview

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Abstract

Microneedle-based drug delivery systems offer a convenient alternative to traditional hypodermic injections, addressing concerns related to patient acceptance and injection safety. Unlike conventional transdermal methods, which rely on drug diffusion through the skin barrier, microneedles enable the delivery of macromolecular drugs like insulins and vaccines by creating microscale pathways into the body. These tiny needles penetrate only the outer layers of the skin, avoiding contact with nerve receptors in the deeper skin, resulting in painless insertions. This comprehensive review provides an overview of microneedle technology, discussing its advantages, disadvantages, various types, and applications in drug delivery.

1. Transdermal Drug Delivery

Transdermal drug delivery refers to the process of administering a medicinal substance through the skin, allowing it to be distributed throughout the body[1] However, this also includes conventional subcutaneous injection with a hypodermic needle and syringe, in addition to the "patch" that is more widely known. This implies that, the drug is transported into the body through an artificial route.[2]

The primary benefit of this approach lies in the direct entry of the drug into the body without being subject to the body's natural defense mechanisms, ensuring that there are no changes. Unlike oral administration, which is considered the most convenient method of drug delivery, the transdermal route offers distinct advantages. It eliminates the risk of drug degradation in the gastrointestinal tract and diminished effectiveness due to first-pass metabolism in the liver. Furthermore, it helps prevent oral-specific side effects such as liver damage, commonly associated with certain medications.[3, 4]

2. Conventional Needle-Based Administration

The utilization of a hypodermic needle as the established approach for parenteral administration proves to be an effective and efficient means of drug delivery. For instance, a drug can be swiftly administered as a bolus within a minute using disposable needles, incurring minimal cost. However, despite its effectiveness, this method of administration does possess significant limitations.

Firstly, the use of regular needles is linked to discomfort, leading to issues with acceptance and compliance. Secondly, employing needles raises concerns regarding device safety and the well-being of healthcare providers, as it can contribute to the transmission of hepatitis B, hepatitis C, and HIV. Thirdly, due to safety considerations, the use of needles necessitates trained personnel for administration and handling. Although patients can receive education on self-injections, as observed with individuals managing diabetes or requiring daily anticoagulant medication, this practice presents a hurdle for the accessibility of potent drugs such as nicotine conjugate vaccines in over-the-counter (OTC) settings. Moreover, apart from the increased cost of administration, the requirement for trained personnel poses a challenge, particularly when immunizing large populations, such as during a pandemic influenza or in response to bioterror threats.[5, 6]

Microneedles

Lately, focus has shifted towards a novel approach to drug delivery involving arrays of tiny needles that penetrate the skin. These miniature needles are of short length, preventing them from reaching the nerve-dense areas deeper within the skin. Consequently, the sensation caused by the insertion of these microneedles into the skin is mild, resulting in a painless experience. [7-9]

The large-scale production of these microneedles can be accomplished by utilizing batch-fabrication methods commonly employed in the microelectronics industry. This approach not only enables cost-effective manufacturing but also ensures a high level of precision. By integrating microneedles into a patch-like structure, it becomes possible to create a system that possesses all the advantageous characteristics of a conventional transdermal patch. These include continuous drug release, user-friendly application, inconspicuousness, and a painless experience.

In contrast to a conventional patch, a patch utilizing microneedles allows for the delivery of a wide range of macromolecular drugs, including insulin and vaccines. This type of patch not only provides a discreet and user-friendly method of drug administration but also offers an effective and potentially safe approach for administering drugs with minimal reliance on healthcare professionals.[10, 11]

Microneedles - Minimally invasive systems

The successful implementation of the microneedle technique has facilitated the transdermal delivery of diverse substances, encompassing macromolecules and hydrophilic drugs. By circumventing the formidable barrier imposed by the stratum corneum, the microneedle system has manifested a substantial enhancement in permeability, achieving a noteworthy amplification ranging from two to four orders of magnitude.

This significant augmentation holds true for both diminutive molecules like calcein and more substantial compounds such as proteins and nanoparticles. The essence of this technology lies in the utilization of microneedles possessing the ideal length and robustness to penetrate the stratum corneum layer, while simultaneously preserving a concise stature that mitigates the risk of provoking nerve stimulation. The ultimate objective driving the advancement of microneedle technology is to harmoniously amalgamate the efficacy demonstrated by hypodermic needles with the unparalleled convenience offered by transdermal patches, ultimately elevating the overall efficiency of drug delivery through the integumentary system.

In contemporary medical contexts, there exists a requirement for the production of cost-effective hypodermic needles that possess extremely small dimensions. Presently, the smallest commercially accessible needles, measuring 30 gauge, exhibit an outer diameter of 305 µm along with a wall thickness of 76 µm. However, conventional machining techniques render the fabrication of needles with a diameter below 300 µm impractical.[11, 12]

Microneedles, in contrast, can be fabricated in various sizes and shapes through lithographic techniques. These microneedles are specifically engineered as efficient and minimally invasive channels for the delivery of drug solutions into the body. Their design aims to minimize invasiveness

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by keeping the needles as small as possible. Additionally, the needles are crafted to be exceptionally sharp, featuring submicron tip radii, enabling successful insertion into the skin. The application of force on the skin is inversely correlated with the area over which it is exerted, emphasizing the significance of a small and focused force application.[13, 14]

Hence, as the tip radii diminishes, the stress experienced by the skin at a consistent force intensifies, allowing for lower forces to be employed during needle insertion. Moreover, the reduced size of the needles results in less tissue compression upon insertion, which minimizes the compression of pain receptors and consequently decreases the discomfort associated with insertion. Additionally, the small dimensions of the microneedles reduce the likelihood of their proximity to pain receptors. This reduction in tissue damage also decreases the risk of infection at the insertion site. Furthermore, the internal features of the microneedle, such as in-line microfilters integrated during the lithography process, can effectively filter out foreign substances, including bacteria, from the injected fluid. This serves to lower the chances of inadvertently injecting a contaminated solution.

The cost and efficacy of technology production represent significant hurdles in its commercialization. However, the production of microneedles through a highly parallel batch process holds promising potential for reducing the individual cost per needle. By utilizing molded needles that do not compromise the integrity of the mold wafers, substantial cost savings can be achieved as the mold can be reused multiple times. This approach ensures the creation of high-quality, consistent devices that offer a viable solution for drug delivery applications with minimal financial and manufacturing obstacles hindering their adoption in the market.

3. Advantages

Microneedles offer a significant benefit over conventional needles in that they do not penetrate the outer layer of the skin known as the stratum corneum, which spans approximately 10-15 μm. Unlike traditional needles that pass through this skin layer, potentially causing pain and infection, microneedles can be designed to have sufficient length to penetrate the stratum corneum while remaining short enough to avoid nerve endings. This design characteristic greatly reduces the likelihood of experiencing pain, infection, or injury during the microneedle insertion process.[15]

In regards to the manufacturing process, there are numerous advantages associated with microneedles. Utilizing a silicon substrate allows for the fabrication of thousands of needles on a single wafer due to their small size. This approach results in high precision, excellent reproducibility, and a reasonably moderate fabrication cost.[16, 17]

Microneedles possess a notable edge compared to alternative methods like electroporation or the use of chemical enhancers. These alternative methods depend on decreasing the resistance for substances to pass through the stratum corneum.[18]

Microneedles provide precise control over the depth of therapeutic injection beneath the stratum corneum, allowing for targeted delivery of concentrated drug solutions with the aim of effective absorption into the bloodstream or stimulation of specific cell clusters within or near the skin. As a result, drug delivery is not reliant on the temporary diffusion across the skin but rather on the subsequent absorption of the drug into the blood, which is quicker. This capability also allows for the administration of complex drug delivery profiles, as the dosage can be adjusted over time through active injection. Additionally, by employing multiple needles or implementing effective fluid control and solution mixing, it becomes possible to deliver multiple drugs simultaneously to cater to the personalized needs of individual patients. Furthermore, microneedles can be utilized for transdermal sampling of bodily fluids for analysis purposes.[19, 20]

The exceptional miniaturization of fluidic devices allows the development of portable systems for personalized medicine, facilitating continuous monitoring of metabolite levels and responsive drug delivery. They are not constrained by clinic visits for outpatient services that often involve bolus injections or limited therapy between treatments. The use of microneedles also enables the administration of lower drug dosages over an extended period to maintain a constant blood concentration. In contrast, bolus injections lead to rapid and often toxic substances increases in blood concentration. Such time-varying, high-concentration injections are frequently associated with numerous side effects of many therapeutics. As the concentration inside the therapeutic range is maintained, microneedles can potentially reduce side effects associated with bolus injections. Furthermore, the controlled and slow rate of therapeutic delivery by microneedles obviates the need for large bolus injections altogether.[21-23]

This approach allows therapeutics to be delivered to a depth just below the stratum corneum, while remaining above the nerve bed in the skin. Unlike bolus injections that require deep tissue penetration to prevent leakage, microneedles eliminate the need for this form of therapeutic delivery.

Microneedles offer several additional benefits, including the ability to precisely manipulate and transport fluid volumes with speed and efficiency. They enable the reduction of drug quantities required for therapy, facilitating more economical and resource-efficient treatment. Microneedles also allow for localized delivery of potent compounds, ensuring targeted administration to specific areas. Moreover, they enable the delivery of therapeutics that may be insoluble or prone to instability using conventional methods. By using microneedles, the risk of missing or incorrectly administering a dose can be minimized. These needles enable precise drug delivery at specific target sites, facilitating rapid onset of action. Additionally, there is potential for self-administration of medications using microneedles. The efficacy and safety of microneedle-based delivery systems can be comparable to approved injectable products. Furthermore, microneedles contribute to improved patient compliance with treatment regimens. Lastly, these devices offer good stability, ensuring the integrity and effectiveness of the delivered drugs.[24, 25]

Current Limitations of Microneedles

There exist several drawbacks associated with microneedles that necessitate further investigation. One crucial aspect is the biological response triggered by the presence of these needles. Upon insertion, an initial tissue reaction occurs, characterized by an inflammatory response at the site of insertion. This response may result in the constriction of capillaries, potentially impacting drug absorption. Concurrently, tissue edema may manifest, which could affect the fluid delivery through the needles. Furthermore, leukocytes tend to migrate towards the injury site during this phase. The adhesion of leukocytes to the needles is facilitated by protein adsorption onto the silicon surface. However, ongoing research is actively exploring surface modifications of silicon to mitigate protein adsorption. Promising approaches involve incorporating surface modifiers such as silicon carbide, polyethylene glycol (PEG) etc. These modifications aim to enhance the biocompatibility of the microneedles.[26-28]

As microneedles are primarily intended for brief intradermal drug delivery, the likelihood of fibrous encapsulation is minimal since the needles are not inserted for extended periods. Nonetheless, there is a possibility that the body may attempt to extrude the needle gradually by pushing it out. Consequently, it may be necessary to provide mechanical reinforcement to ensure the needle remains securely in place.

The compact dimensions of microneedles render strength and durability crucial in defining their potential applications. To be integrated into portable biomedical devices, these needles must withstand the forces involved during insertion, intact removal, and normal human movements. It is important to note that materials like silicon possess strength and are capable of effectively penetrating the skin. However, they are also brittle, making them prone to fracturing.[29, 30]

Metal and polymer needles offer contrasting characteristics in terms of stiffness, with each material exhibiting distinct advantages and challenges.[31] Polymer needles possess flexibility and can absorb greater stresses through plastic deformation. However, their flexibility also makes it more challenging to pierce the skin. On the other hand, metal needles, while stiffer, can be more difficult to insert due to their rigidity.[32, 33]

The parylene-coated silicon needle, which is a type of hybrid microneedle, offers a promising solution by integrating the advantages of both materials.[34] When inserted, the silicon tip provides rigidity initially, but it can later flex and transfer the associated stress to the polymer tube during movement. Due to its smaller size compared to a complete needle, the silicon tip experiences reduced stress levels and is less likely to

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break. Additionally, the presence of the polymer coating assists in holding the tip intact, even in the event of fracturing.[35]

Another approach involves the development of novel polymer processing techniques for needle fabrication. By utilizing a semi-crystalline polymer, it may be possible to achieve the necessary strength for needle insertion while maintaining a sufficient amount of the polymer in an amorphous phase to absorb mechanical stress.[36, 37]

Precise control over the stresses and forces experienced by the needle is another strategy to address material limitations. Microfabricated insertion actuators can be employed to regulate the insertion force with high precision.[12] These actuators can take the form of microfabricated linear stepper motors or piezoelectric actuators, enabling accurate positioning and axial needle insertion without imposing bending moments that could deform or fracture the needles. Piezoelectric actuators also have the capability to generate ultrasonic vibrations, which can reduce the amount of force required for insertion.[18, 38]

4. Applications in Drug Delivery

Diabetes

By combining microfluidic devices with microneedle-based sampling, a feedback loop can be established between a glucose sensor, responsible for monitoring the body's sugar levels, and a delivery module capable of dynamically administering insulin based on real-time requirements. This approach closely emulates the natural sugar regulation processes within the body, resulting in reduced complications associated with the treatment.[39-41]

Chemotherapy

In the context of chemotherapy, patients typically receive a fixed dose of medication during each session. However, by utilizing microneedles for continuous drug delivery, it becomes possible to administer the chemotherapeutic agents over an extended period. This approach offers several advantages. Firstly, it allows for a longer treatment duration, ensuring a sustained therapeutic effect. Secondly, it enables the administration of lower doses of the potent drugs, which would otherwise be required in a single injection. This reduction in dosage has the potential to decrease the severity of side effects associated with chemotherapy. By combining an extended treatment period with minimized side effects, it may be possible to reduce the overall number of treatment sessions and expedite the patient's recovery from the disease.[42]

Microneedles present potential benefits for the continuous administration of cell-based therapies, particularly in the context of targeting melanomas with antitumor effector cells. Extensive research has been conducted on these therapies, which have shown promising results in reducing the size of solid and hematologic tumors in humans. However, when these cells are administered intravenously, their localization to the tumors is not always effective, and a considerable proportion of the cells are eliminated by the liver and spleen. On the other hand, direct injection of the cells into or around the tumors (intralesional administration) ensures precise localization for targeted attack on the tumors.

The use of microneedles for such delivery holds promise due to their minimal tissue damage. Patients can receive continuous therapy without significant interruption. Additionally, the small size of the microneedles reduces the risk of causing tumor damage or promoting metastasis, unlike larger needles. This targeted and localized approach facilitated by microneedles allows for enhanced therapeutic efficacy while minimizing the potential for adverse effects. [43, 44]

Vaccinations, Pain Relievers and Antibiotics

At present, numerous medications, such as the Hepatitis B vaccine, necessitate multiple administrations spaced over a specific duration. Unfortunately, many individuals receive only the initial or second dose and neglect to follow up with subsequent injections. Similarly, patients often discontinue antibiotic usage once their symptoms diminish, disregarding the importance of completing the full course. Regrettably, this behavior contributes to a significant rise in antibiotic-resistant bacterial strains.[11, 45]

Certain analgesics like Sufanta (Sufentanil Citrate), Sublimaze (Fentanyl Citrate), and Dilaudid

(Hydromorphone) require dosages of less than 3 ml per hour. Continuous delivery of these pain relievers enables patients to benefit from the analgesic properties without being hindered by the need for an intravenous drip. Employing a continuous delivery approach simplifies the therapy process for these medications. A patch device could be applied once a day or every few days, providing the necessary medication for the designated time period.

Additionally, the drug itself could be in the form of a lyophilized powder. The powder would be reconstituted with water, accurately dosed, and administered by the patient as needed. This approach enhances convenience and adherence to the prescribed treatment regimen.[46, 47]

Catheterized Instrumentation

Microneedles have the potential to be attached to the tip of a catheter for intravascular delivery. This configuration allows the needle to puncture the walls of blood vessels, enabling precise administration of drug dosages to the surrounding tissue. For instance, microneedles can be utilized to directly inject clot-dissolving medications into a coronary arteriosclerosis. Examples of such drugs include alteplase, which is a genetically engineered form of the body's own plasminogen activator proteins, or Streptokinase, a plasminogen activator produced by streptococcus bacteria.[18, 48, 49]

Blood glucose measurements

In a recent advancement, a device has been developed that allows patients to insert a cartridge into an electric monitor and effortlessly place the monitor on their skin. Through this process, a minute microneedle punctures the skin to collect a minute quantity of blood (less than 100 nanoliters) into a disposable container. The chemicals present in the container react with the glucose in the blood, causing a noticeable change in color. The blood glucose concentration is subsequently measured using electrical or optical techniques, and the corresponding value is presented on the monitor.

Utilizing hollow microneedles enables the administration of medications, insulin, proteins, or nanoparticles that can carry drugs or facilitate viral delivery for vaccination purposes. These microneedles can be designed to penetrate the skin, similar to a nicotine patch used by individuals attempting to quit smoking, to deliver the desired drug. [50, 51]

Skin therapy

Microneedle skin therapy is currently undergoing testing and development, but it shows great potential. This therapy offers a way to rejuvenate the skin without causing damage to the outer layer, unlike laser treatment. Microneedles are used to penetrate the epidermis and break down old collagen fibers. The destruction of these collagen fibers stimulates the production of new collagen beneath the epidermis, resulting in a more youthful appearance.[52]

One drawback of this method is that it may cause minor bleeding, which is not typically seen in laser treatments. However, microneedle therapy has several advantages, including increased collagen production, no sensitivity to sunlight following treatment, no disruption of the epidermis, lower cost, and ease of application.[53, 54]

Eye Treatment

Microneedles have the potential to revolutionize the treatment of common eye conditions such as glaucoma, macular degeneration, and diabetic retinopathy by enabling the delivery of drugs through a minimally invasive procedure. These microneedles are designed to penetrate the eye tissue to a depth of only half a millimeter. This shallow penetration ensures that they cause significantly less damage compared to traditional needles. Consequently, local anesthesia is sufficient for applying these microneedles to the eye. This technique offers a promising approach for effectively treating various eye conditions, providing a less invasive and potentially game-changing method. [55, 56]

5. Conclusion

In conclusion, microneedle-based transdermal drug delivery holds great promise for transforming medication administration. Microneedles offer advantages such as enhanced drug absorption, minimized side effects, and patient-friendly alternatives to injections. They have the potential to revolutionize healthcare by improving compliance, expanding treatment options, and enabling targeted therapies. Microneedles can be particularly beneficial for pediatric and geriatric populations due to their non-invasive nature. The progress made in this field is encouraging, and further innovations are expected to enhance drug delivery and improve the quality of life for patients worldwide. Microneedle-based transdermal drug delivery represents a promising avenue for personalized medicine and optimized therapeutic outcomes.

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