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Microneedles: A materializing approach for Cancer treatment

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ABSTRACT

Conventional therapies for cancer were effective, there are several shortcomings, such as undesirable side effects, problems in the bioavailability of some drugs, due to which several advancements have been endeavored for curing cancer.
Nano-based advanced drug delivery systems possess tumor targeting ability, reduced side effects, high bioavailability, and controlled release of a drug, and thus, became a research hotspot for cancer too. Apart from the nano-based delivery system, micro-based delivery system, transdermal patches, microneedles have similarly been well-thought-out strategies.
Microneedle transdermal approach enhanced drug delivery, there are 4 types of microneedles such as solid, hollow, dissolving and coated. Different materials are used for manufacturing of microneedles.

KEYWORDS: Microneedle, cancer, transdermal.

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INTRODUCTION

As per WHO report "In 2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer. There are more lost disability-adjusted life years (DALYs) by women to breast cancer globally than any other type of cancer. Breast cancer occurs in every country of the world in women at any age after puberty but with increasing rates in later life". Currently, conventional therapies are used to treat breast cancer, but they have numerous shortcomings such as low bioavailability, short circulation time, and off-target toxicity. To address these challenges, Nano medicines are preferred and are being extensively investigated for breast cancer treatment. Nano medicines are novel drug delivery systems that can improve drug stability, aqueous solubility, blood circulation time, controlled release, and targeted delivery at the tumoral site and enhance therapeutic safety and effectiveness. Nanoparticles (NPs) can be administered through different routes. Although the injectable route is less preferred than the oral route for drug administration, it has its advantages: it helps tailor drugs with targeted moiety, boosts payload, avoids first-pass metabolism, and improves the pharmacokinetic parameters of the active pharmaceutical ingredients. Targeted delivery of nanomedicine, closer to organelles such as the mitochondria and nuclei in breast cancer, reduces the dosage requirements and the toxic effects of chemotherapeutics.

The largest organ of the body is the skin making it potentially a highly accessible organ of the human beings. But the stratum corneum (SC) represents the main barrier of the skin and its penetration is very difficult (Alkhiro and Ghareeb, 2020).

To address limitations of oral delivery and hypodermic injection, arrays of micron-scale needles have been developed to painlessly pierce skin's outer barrier of stratum corneum with the goal to deliver drugs with the efficacy of a needle and the convenience of a transdermal patch. This approach has demonstrated increased transdermal delivery of small-molecule drugs, proteins, DNA, and vaccines. One approach involves pre-treatment of skin with microneedles, followed by application of a transdermal patch for extended drug delivery through the permeabilized skin. Another approach involves coating or encapsulating drug onto or within microneedles. Upon dissolution of the coating or the needle itself, the drug cargo is released within the skin as a bolus or possible controlled-release delivery. Microfabrication tools have been leveraged to make microneedles using methods suitable for low-cost, high-volume manufacturing, which is critical to impacting medicine as a disposable device. Microneedles suitable for piercing skin to increase skin permeability or for carrying drug into the skin as a coating have been fabricated from silicon and metal. Microneedles that encapsulate drug and subsequently dissolve or degrade in the skin have been fabricated from polymers, such as slow-degrading polylactic-co-glycolic acid and rapidly-dissolving sugar (Lee, Park and Prausnitz, 2008).

Types of Microneedles:
Microneedles are classified on the basis material used for fabrication and release.

1. Based on release profile:
   Based on release profile microneedle are divied into 4 type
   i. Solid Microneedle
   ii. Hollow microneedle
   iii. Dissolving microneedle
   iv. Coted microneedle
2. Based on fabrication technique and material used
   i. Photo Lithography

ii. Laser cutting/ablation
iii. Micro-moulding /Micro milling
iv. 3D Printing
v. Solvent casting
vi. Electroforming

Based on release profile:
The choice of fabrication method depends on factors like material properties, desired microneedle geometry, and production scale. Advancements in these techniques continue to enhance the functionality and applicability of microneedles in various biomedical fields.

1.1. Solid Microneedles

Solid microneedles are used primarily for drug delivery through the skin or for the collection of interstitial fluid. These microneedles do not contain any drug or solution but rely on their mechanical properties to create transient pores in the skin.

- **Materials**: Typically made from stainless steel, silicon, or polymeric materials.
- **Applications**: Drug delivery, diagnostics, and micro-therapy. (Aldawood et al., 2021)

1.2 Hollow Microneedles

Hollow microneedles are equipped with a small lumen that can be used to inject drugs directly into the skin or to withdraw fluids from the skin. The major advantage of hollow microneedles is their ability to provide real-time drug infusion.(Wang et al., 2023)

- **Materials**: Often fabricated from metal, glass, or polymer.
- **Applications**: Drug delivery, vaccine administration, and fluid extraction.

1.3 Coated Microneedles

Coated microneedles are microneedles that are coated with a drug or vaccine formulation. The coating dissolves after insertion into the skin, releasing the drug at the target site.

Materials: Commonly made of biodegradable materials such as polymers or sugars.
Applications: Controlled drug delivery, vaccination.

1.4 Dissolving Microneedles

Dissolving microneedles are made of materials that dissolve in the skin, releasing the drug in a controlled manner. They provide a simple and minimally invasive solution for drug delivery.

Materials: Typically made from biocompatible materials like poly(lactic-co-glycolic acid) (PLGA) or other biodegradable polymers.
Applications: Vaccination, gene delivery.(Alkhiro and Ghareeb, 2020; Ghazi and Al-Mayahy, 2022; Lee et al., 2008)

BASED ON FABRICATION TECHNIQUE:

2.1. Photolithography

Photolithography is one of the most widely used methods for preparing microneedle molds. It involves the use of light to pattern a photosensitive material, which is then developed to create the microneedle mold. Photolithography involves patterning a photoresist layer on a substrate, followed by etching to create microneedle structures. This method offers high precision and is widely used in semiconductor fabrication.

Procedure: The photosensitive material is exposed to ultraviolet light through a mask, and the unwanted material is removed to create the desired pattern.

Advantages: High precision, scalability.
Limitations: Requires expensive equipment and cleanroom facilities.(Handrea-Dragan, I.M., et al., 2022, Faraji Rad, M., et al., 2021 Kathuria, H., et al., 2020 , Lee, K., et al., 2012)

2.2. Laser Ablation

Laser ablation utilizes focused laser beams to remove material from a substrate, forming microneedles. This technique allows for rapid prototyping and is suitable for materials like silicon and metals.Laser ablation is used to etch or pattern microneedle molds by using a focused laser beam to remove material from a surface. This technique is particularly useful for creating high-precision molds.

Procedure: A laser beam is directed at a substrate to selectively vaporize or melt the material.
Advantages: High precision, capable of creating complex geometries.
Limitations: High cost, slower processing time. (Gattass and Mazur, 2008)

2.3. Micro-Milling & molding:

Molding techniques such as micro-molding or injection molding are employed to create microneedle molds. These methods involve injecting a material into a mold cavity that is shaped like a microneedle array.
Procedure: A microneedle mold is created by pouring or injecting materials such as metal, polymers, or silicon into pre-designed molds.

Advantages: High production rate and low cost.

Limitations: Limited to certain materials and sizes.
Micro-milling employs rotating tools to mechanically carve out microneedle shapes from solid materials. It is effective for producing complex geometries but may have limitations in achieving sharp tips. (Balázs et al., 2020, Zhu, D.D., et al., 2022)

2.4. 3D Printing
3D printing or additive manufacturing is an emerging method for creating microneedle molds. This technique allows the fabrication of complex microneedle structures layer by layer.

3D printing, including stereolithography (SLA) and two-photon polymerization, enables the layer-by-layer construction of microneedles. This additive manufacturing approach offers flexibility in design and material selection.(Detamornrat et al., 2022) It covers various 3D printing techniques, including stereolithography (SLA), selective laser sintering (SLS), and fused deposition modeling (FDM), highlighting their advantages and limitations in microneedle production. The article also explores the materials used, such as biocompatible polymers and hydrogels, and examines the challenges related to mechanical strength, drug loading, and regulatory considerations. Furthermore, it delves into the future prospects of integrating artificial intelligence and 4D printing technologies to enhance the functionality and personalization of microneedle-based drug delivery systems.(Olowe et al., 2022)
Procedure: A 3D printer is used to print the mold layer by layer, usually with photopolymers or other suitable materials.
Advantages: Customizability, ability to create complex shapes.
Limitations: Limited material selection, slower production speed.

2.5. Solvent casting:
Microneedles produce by pouring polymer solution. On previously available mold. Silicon mold available in market. . A liquid polymeric solution is poured into prepared molds, and then, air voids are removed with vacuum or centrifuge. Subsequently, the molds are dried in the oven, and MNs are removed after cooling. The advantages of this method lie in the relatively simple, cost-effective MN production at an ambient temperature. Also, the production of biodegradable polymer MNs, consisting of both natural and synthetic materials, with an appropriate geometry and sufficient strength to penetrate the skin, is reported. Interestingly, micromolding has even been used for the production of ceramic MNs. (Tucak A et.al.2020, Oliveira et.al.2024, Qi zong et.al.2024)

2.6 Electroforming
Electroforming involves the deposition of a metal layer onto a substrate to create a mold. It is particularly suitable for the fabrication of metal microneedles.
Procedure: A conductive substrate is coated with a thin layer of metal by applying an electric current.
Advantages: High precision, suitability for creating metal microneedles.
Limitations: Expensive, limited to conductive materials.

MICRONEEDLES IN BREAST CANCER TREATMENT

3.1. Localized Drug Delivery
One of the most significant advantages of microneedles is their ability to deliver drugs directly to the tumor site, minimizing systemic exposure and reducing side effects commonly associated with chemotherapy. This targeted delivery can potentially enhance the efficacy of treatments while reducing harmful effects on healthy tissues.

For example, **paclitaxel**, a chemotherapy drug, has been successfully delivered via microneedles in animal models, resulting in improved tumor shrinkage with reduced toxicity (Sharifi-Rad, J et al., 2021). Additionally, microneedles could be used for the controlled delivery of **biologics** such as **monoclonal antibodies** or **immunotherapy agents** to improve the precision of cancer treatments.

3.2.Combination Therapies
Microneedles also hold promise for **combination therapies**, where different drugs can be delivered simultaneously or sequentially at the tumor site. For instance, studies are investigating the use of **microneedles for delivering chemotherapy drugs alongside immune checkpoint inhibitors** to activate the immune system and enhance anti-tumor effects (Ganeson, K. et al., 2023).

MICRONEEDLES FOR BREAST CANCER DIAGNOSIS

4.1. Minimally Invasive Biopsy
Microneedles offer an alternative to traditional **fine-needle aspiration biopsies**, which require inserting larger needles into the tumor to extract tissue samples. Microneedles, due to their small size, can collect tissue or fluid samples with minimal invasiveness, reducing patient discomfort and the risks associated with conventional biopsy methods(Desai et al., 2022, Oliveira et al.2024)

These minimally invasive procedures are crucial for improving the accessibility of biopsies in early-stage breast cancer detection, as well as for repeated testing to monitor tumor progression or response to treatment.

4.2. Tumor Marker Detection
Microneedles also hold potential for detecting **tumor markers** in the interstitial fluid surrounding breast tumors. This could enable the early detection of cancer, even before visible tumors form, by sampling for **circulating tumor DNA** or other molecular

markers (Tang et al., 2018).
The use of microneedles to extract biological samples offers the possibility of **non-invasive or minimally invasive** diagnostic approaches that could complement existing methods like mammography, providing a faster and more cost-effective way to diagnose breast cancer.

CURRENT RESEARCH AND CLINICAL TRIALS

Research on the application of microneedles for breast cancer is still in the preclinical and early clinical stages. A study conducted by **Wang et al. (2019)** demonstrated the effectiveness of microneedles in delivering paclitaxel directly to breast tumor tissues in animal models, achieving significantly better therapeutic outcomes than intravenous administration.

Another study by **Kim et al. (2017)** investigated the use of **dissolving microneedles** to deliver **doxorubicin**, a chemotherapy drug, to breast cancer cells. The study concluded that this method could potentially overcome the limitations of current delivery techniques, offering improved patient outcomes with fewer side effects.

In addition, **clinical trials** focusing on **microneedles for vaccine delivery** (Cui et al., 2018) could provide insight into how these devices might be adapted for **cancer immunotherapy**, an area of growing interest in breast cancer treatment.

CHALLENGES AND LIMITATIONS

While the potential of microneedles in breast cancer treatment and diagnosis is clear, several challenges need to be addressed before widespread clinical adoption can occur:

Penetration Depth: Microneedles may struggle to reach deeper tissues or tumors, limiting their application to superficial or accessible tumors. Overcoming this barrier requires further advancements in microneedle design and technology (Prausnitz & Langer, 2008).

Safety and Biocompatibility: The materials used in microneedles must be biocompatible and cause no adverse effects when inserted into the body. Biocompatibility testing is crucial to ensure that the device does not induce inflammation, tissue damage, or immune reactions (Vrdoljak et al., 2020).

Regulatory Approval: Microneedles must pass rigorous regulatory reviews, including clinical trials and safety assessments, before they can be approved for medical use. This process may take several years and significant investment (McHugh et al., 2020).

Cost and Accessibility: While microneedles may offer long-term cost savings through more efficient drug delivery, the initial investment and production costs could limit their widespread accessibility in low-resource settings.

CONCLUSION

Microneedles represent a promising new approach in the fight against breast cancer, offering potential improvements in both diagnosis and treatment. By enabling **localized drug delivery**, reducing the invasiveness of **biopsy procedures**, and improving the accuracy of **early cancer detection**, microneedles could play a pivotal role in transforming how breast cancer is managed.
While challenges remain, particularly with penetration depth, safety, and regulatory approval, continued research and technological innovation could pave the way for microneedles to become a mainstream tool in oncology, offering patients a more **personalized, efficient**, and **less painful** alternative to traditional methods.

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