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Microneedles: A New Frontier In Cancer Therapy

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Abstract*: Even though oncology has advanced throughout time, cancer remains the largest cause of mortality, a global burden that negatively affects patients' quality of life and the global economy. The present traditional cancer treatments, which include lengthy treatment periods and systemic drug exposure, cause early drug deterioration, excruciating pain, adverse effects, and cancer recurrence. In order to prevent further delays in cancer patient diagnosis or treatment which are crucial in lowering the worldwide mortality rate personalized and precision-based care are also desperately needed, particularly in light of the current pandemic. Recently, microneedles a patch with tiny, micron-sized needles attached have gained a lot of attention as a cutting-edge transdermal application technique for the diagnosis or treatment of a variety of diseases. Since microneedle patches provide a better treatment approach through self-administration, discomfort-free treatment, and an economical and environmentally friendly approach compared to other conventional methods, the use of microneedles in cancer therapies is also being thoroughly researched. The several kinds of microneedles, their materials and manufacturing processes, as well as the most current developments and prospects, are highlighted in this overview. Furthermore, this review discusses the difficulties and constraints associated with using microneedles in cancer treatment and offers solutions based on ongoing research and upcoming projects to support the clinical application of microneedles in cancer treatment...*

Keywords: Microneedles, Cancer, Cancer therapy, Drug Delivery, Chemotherapy

I. INTRODUCTION

Drug delivery via the oral route is the most preferred route of drug administration due to its simplicity and cost-effectiveness when compared to other routes. However, there are drawbacks to this route, including swallowing and prolong first pass metabolism that results in reduced bioavailability [1]

In order to overcome the drawbacks of the oral route, the parenteral route of administration is the most popular natural substitute. Drugs are traditionally given parenterally with a syringe and a hypodermic needle [2]

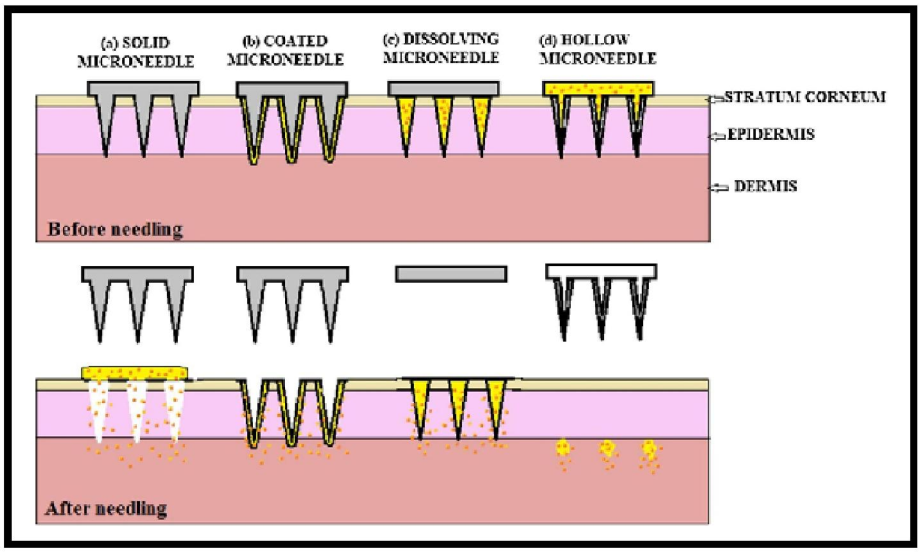
Even while the parenteral route was the natural costly choice, patients had to deal with a number of problems, including excruciating pain, thrombus formation at the administration site, and hypersensitivity. To get beyond the drawbacks of parenteral and oral route of administration [3].

Publisher focused on developing a novel drug delivery system that help in delivering the drug(s) through the layers of skin, also know as 'Transdermal Drug Delivery System' (TDDS) Cancer is still one of the most common health issues impacting people worldwide, despite all the efforts [4]. Indeed, it is evident from recent data that the incidence of cancer has been rising over the past few decades. However, both novel(Nano medicines) and traditional (chemotherapy and radiation) anticancer treatments have lessthanideal results[5]. Furthermore, the low ability of highly promising nanoparticle-based anticancer therapies to accumulate within the tumor tissue (less than 0.7% of the administered dose reach the tumor site) has significantly impeded their clinical translation. In addition, the high complexity of the nanomedicines makes it challenging to scale up the synthesis processes and replicate the therapeutics' results [6].

In particular, microneedle devices have demonstrated encouraging outcomes that lend credence to their use as anti-cancer treatments. The idea behind microneedle-based drug delivery devices was initially presented over 30 years ago, and in the last 15 years, there has been a significant push for its practical clinical use[7].
In cancer treatment, the drug performance could be significantly enhanced by at specific time and site, This can be over using Microneedles. Microneedles are superior to hypodermic needles because they help with localized, controlled medication distribution with better flux and cause little to no pain at the administration site [8].
When anticancer medications are administered parenterally, they frequently accumulate in many organs and have low bioavailability because they are quickly removed from the bloodstream, which reduces their therapeutic efficiency [9].
The concept of microneedle for use in drug delivery was initially considered a number of decades ago, with the first patent being filed by Gerstel and Place in 1976 [10].

II. TYPES OF MICRONEEDLES

Different types of microneedles fabricated and investigated for their application in drug delivery are solid, coated, dissolving, hollow, and hydrogel microneedles.



2.1 Solid microneedles

In order for the medicine to reach the lower layers of the skin, where diffusion is faster, solid microneedles are typically made to puncture the top layer of the skin[10,11].
Solid microneedles are tiny, needle-like devices that are usually composed of metals, polymers, or ceramics. They are intended to pass through the skin and administer medications, vaccinations, or other substances without requiring blood. These microneedles are “solid” since they don’t contain any liquid and aren’t hollow. In order to transfer chemicals directly into the dermal or epidermal layers, they make microscopic channels in the skin [12].

2.2 Coated microneedles

Tiny, needle-like devices called coated microneedles are used to inject medications, vaccinations, and other materials into the skin. The active component is applied to these microneedles in a coating that is released as soon as the needles pierce the skin [23]. A controlled release of the medication straight into the tissue or bloodstream is made possible by the coating’s frequent use of elements that dissolve or break down rapidly. Because of their low pain, simplicity of use, and possibility for precise dosing, coated microneedles are a prospective substitute for conventional injections in transdermal drug delivery systems[24].The “coat-and-poke” method of transdermal medication delivery is employed with coated Microneedles. In particular, drug-coated Microneedles are injected into the skin, after which the

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medications dissolve and penetrate the skin, and at last, the microneedle are removed from the skin [25]. In the treatment of cancer, coated microneedles are showing promise as a medication delivery technique. The following are some possible uses for them in oncology is.Targeted drug delivery, Immunotherapy, Pain Management, Chemotherapy and Minimally Invasive Delivery[26].

2.3 Dissolving Microneedles

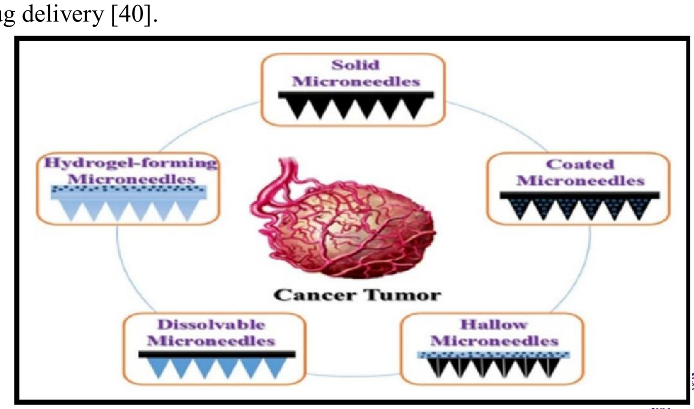
One kind of microneedle technology utilized for medication delivery and other medical purposes is dissolving microneedles [27].Usually composed of biocompatible and soluble materials, these microneedles dissolve when they come into touch with bodily fluids or the skin.These Microneedles have several benefits, including high drug loading, ease of use, and ease of manufacturing [28]. Used the thermal micromolding technology to create the dissolving Microneedles composed of polylactic acid (PLA) for insulin administration [29]. Discussions were held regarding the connections among Microneedles dimensions, drug concentration, drug viscosity, administration duration, and drug penetration into the skin[30]. It was determined that the longer Microneedles were better suited for drug penetration, whereas the shorter Microneedles exhibited superior mechanical stability [31]. The amount of drug permeation increased in response to an increase in drug concentration, while the rate of drug permeation remained unchanged[32]. However, the amount of drug permeation reduced as the drug’s viscosity increased. When the drug was administered to the skin for an additional hour, the amount of drug penetration reached a steady value and remained largely unchanged. It is in vivo investigation[33].

2.4 Hollow Microneedles

A wide range of medications have also been delivered via hollow Microneedles[34]. Hollow microneedles are tiny, needle-like objects having a hollow interior that usually range in size from a few micrometres to hundreds of micrometres. They are made for minimally invasive medical procedures like biological fluid sample, medication delivery, and vaccination administration. Fluids can travel through the hollow core, allowing the needles to inject or retrieve materials without seriously harming surrounding tissue[35]. They are frequently employed in procedures like transdermal drug delivery and blood sample where conventional needles could be excessively big or uncomfortable[36].

2.5 Hydrogel Microneedles

Made from hydrophilic (water-absorbing) polymers, hydrogel microneedles are tiny, needle-like structures that are frequently utilized in biomedical applications such as drug delivery and diagnostics[37]. Usually soft and pliable, these microneedles have the potential to enlarge in the presence of moisture, such as the skin's surface or internal fluids[38]. Because of this characteristic, they can pierce skin or tissue with little discomfort and deliver medications or other therapeutic agents straight into the body. The ability to dissolve or deteriorate in the body without the need for removal makes hydrogel microneedles an alluring substitute for conventional needles[39].The use of hydrogel microneedles in cancer treatment is being investigated more and more because of its special qualities, which allow for controlled, precise, and localized drug delivery [40].



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III. MECHANISM OF MICRONEEDLES DRUG DELIVERY

3.1 Local Drug Delivery to Tumor Sites

3.1.1 Direct Tumor Penetration

One of the most important steps in using nanomedicine to deliver medications to malignancies. However, the tumor microenvironment and the characteristics of the nanomedicine can make tumor penetration difficult. Several elements may make it challenging for nanomedicine to enter tumors, including-Compressed blood and lymphatic vessels,Dense extracellular matrix and high interstitial fluid pressure [41]. It is a cutting-edge method of treating cancer that uses microneedles to introduce therapeutic substances straight into the tissues of tumors. The drawbacks of traditional drug delivery techniques, such oral or intravenous administration, which can result in inadequate drug targeting, systemic side effects, and restricted penetration into solid tumors, are intended to be addressed by this approach[42].

The diffusion mechanism states that the concentration of nanocarriers In the tissue is what determines the penetration depth , hence these carriers also need to have a high transvascular velocity and a lengthy circulation duration [43].

3.1.2 Minimally Invasive

By establishing direct and localized distribution of medications, vaccinations, or other therapies to the targeted spot is made possible via microchannels or tiny punctures in the tissue (such as the skin or tumor surface). This improves drug efficacy and eliminates the need for systemic administration[44].As a less intrusive option to conventional needles and injections, minimally invasive microneedles are small needles made to pierce the skin or other biological tissues with little harm. These microneedles, which are used for cosmetic operations, drug delivery, and diagnostics, usually have a length of a few millimeters to hundreds of micrometers[45].

The following are the main advantages of "minimally invasive" microneedles.

- Reduced Pain and Discomfort
- Reduced Risk of Infection
- Precision and Controlled Delivery
- Improved Patient Compliance[46].

3.2 Skin Barrier Disruptions

3.2.1 Micropores Formation

After being placed into the skin, the microneedles produce tiny, precisely regulated punctures or micropores that facilitate the easier passage of materials, including medications, through the skin.Elastic deformation skin experiences elastic deformation when the microneedles pierce the stratum corneum, momentarily stretching and forming microchannels. Usually, this distortion does not cause irreversible skin damage, but it is sufficient to permit the diffusion of molecules via the pores [47].Sometimes, especially in the lipid-rich stratum corneum, the use of microneedles can cause microscopic skin rips or fractures. This makes the passage of medications easier, especially for larger molecules that typically have trouble diffusing across the epidermal barrier [48].

3.3 Controlled and Sustained Release

3.3.1 Polymeric Microneedles

The main applications for polymeric microneedles, which are made of polymeric materials, include transdermal medication administration, diagnostics, and vaccinations. These microneedles are less intrusive than conventional hypodermic needles because they are made to pass through the epidermis without getting to the pain receptors. This is an explanation of polymeric microneedles.Once the microneedles are implanted into the skin, they might dissolve or release the therapeutic substances [49].Certain biodegradable materials, such as polymers, can be used to make microneedles that can hold anticancer medications. These microneedles release the medication gradually over time after dissolving or degrading in the skin or tumor. At the tumor location, this regulated release aids in preserving therapeutic medication concentrations [50].

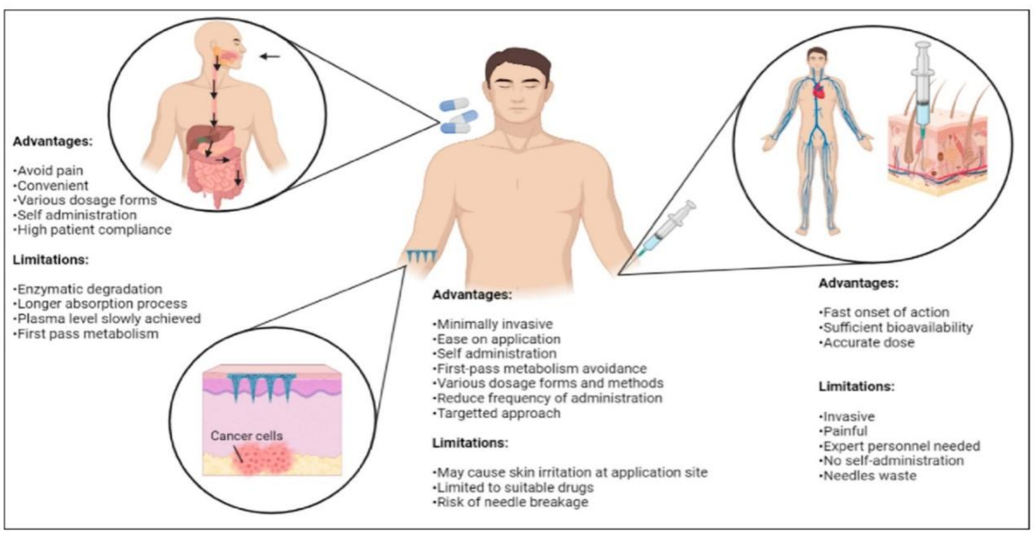
3.3.2 Minimized Side Effects

Drugs can be released from polymeric microneedles gradually and at a regulated rate. The peak concentrations of medications, which are frequently linked to adverse effects including toxicity or irritation, are reduced by this prolonged release. Adverse reactions are less likely when drug levels are kept within a therapeutic range. Since,medications are administered directly to the tumor, there is less systemic exposure and a lower chance of adverse consequences[51].

IV. APPLICATIONS OF MICRONEEDLE DRUG DELIVERY IN CANCER THERAPY

4.1 Transdermal route of administration

The transdermal mode of administration, which provides accurate and focused site-specific drug delivery, is the fundamental idea behind a microneedle-based medicinal system. Despite being extensively researched over the past 50 years, the transdermal mode of administrationwhich involves delivering active substances across the skin for a systemic distributionhas gained popularity once more with the microneedle system. In contrast to other drug delivery methods (such as oral, topical, parental, etc.), it is regarded as one of the most reliable, particularly for cancer therapies, since it has demonstrated significant promise in targeting tumor cells specifically and minimizing systemic harmful effects[52].
In transdermal drug delivery, the skin acts as a reservoir, allowing the penetrated drugs to diffuse to the deeper epidermis and dermis without continuously accumulating in the dermal layer over an extended period of time [53]. This allows for the controlled and sustained release of drug candidates with short biological half-lives that need frequent administration [54,55].



4.2 Self-Administration

Insufficient public health personnel, particularly in second and third world nations, and the prioritization and distribution of limited resources caused delays in a number of cancer therapies during the recent COVID-19 pandemic [56]. Microneedle-based self-administered, safe, economical, and convenient drug delivery systems are being researched due to the significance of personalized medicine and its advancements [57]. Because microneedles don't require aseptic materials, skilled personnel to perform the procedure, or the proper insertion technique, their self-administrative nature and ease of use may help cancer patients receive the appropriate treatments when they need them [58].
The self-administration of microneedles would be extremely advantageous for cancer patients in terms of cost, convenience, and safety [59]. This is because it lowers the risk of any additional hospital infections and may shorten the length of time spent in medical facilities waiting for the doctors to give the medications. Compared to a hypodermic needle, microneedles are easier to self-administer since they are painless and promote quicker healing at the injection

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site. Furthermore, a number of in vivo studies have demonstrated that, in comparison to hypodermic needles, microneedle penetration causes very little bleeding in both human and animal models [60].

4.3 Painless Treatment Approach

Subsequently 64% of patients with advanced or terminal cancer, 59% of cancer patients during treatment, and 33% of cancer patients who have been cured of the disease have pain, cancer pain is another major global issue that affects billions of people globally. The pain and needle anxiety that cancer patients experience, together with the negative effects of the therapies themselves, are the main reasons why they frequently fear them. In addition to being time and money-consuming, other non-invasive approaches include physical care such as massages, exercises, acupuncture, aromatherapy, and repositioning. These methods are safe and may help reduce pain, but there is little evidence that they are successful in treating persistent cancer pain [61].

In order to release medications into the eye, oral, vaginal, and circulatory tissues, among other biological barriers, microneedles are also being researched. Patients with ocular melanoma, cervical cancer, and many other conditions could benefit immensely from this by receiving effective and painless treatments in the designated areas [62]. Since cancer patients already have too much on their plates, painless treatment should be an option for all medical conditions. Therefore, alleviating cancer patients' suffering may be the greatest benefit to both the patients and the healthcare sector [63]

4.4 Economical

The prevalence of cancer is steadily rising worldwide, placing a significant burden on people's financial, emotional, and physical health as well as on health systems. Compared to high-income nations, which have higher survival rates because of factors like accessibility, prompt diagnosis, high-quality treatment, increased public awareness, dietary changes, lifestyle adjustments, financial security, and survivorship care, low- and middle-income nations are particularly finding it difficult to handle this burden [64].

Although the cost of producing, administering, transporting, and disposing of microneedles may appear to be one of the main obstacles, the advantages of using themsuch as fewer injections per patient, fewer dosages of medications or vaccines, and decreased painmay lower the overall cost of maintenance. In addition to reducing the need for preparation and sterilization for every treatment, the accuracy and effectiveness of microneedles in drug delivery can also prevent drug waste and side effects, making them more cost-effective than hypodermic needles used in cancer therapy [65].

V. FUTURE DIRECTION OF MICRONEEDLES IN CANCER CARE

Microneedles have a bright future in cancer care because of their ability to improve patient monitoring, diagnosis, and treatment delivery. Microneedles are anticipated to have an impact on cancer care in the following important areas. The study of microneedle capabilities in the human setting is thought to be crucial, and since cancer is a chronic illness and the use of microneedles in cancer therapies is still a novel idea, the scope for the future direction of microneedles should first focus on safety and performance with more preclinical and clinical investigations[66].Since microneedles would provide patients with more individualized care with less pain and supervision, the future of microneedles in cancer therapy is likewise shifting toward a more precise and individualized approach. In the near future, when we have more sophisticated technology, this would be an excellent strategy [67].Recent years have seen the rise of theranostics, a technique that combines therapeutic and diagnostic capabilities into a single system to increase the personalization of medicines. This field is expanding and has the potential to enable minimally invasive illness monitoring, which will eventually integrate closed-loop devices that enable minimally invasive detection and therapy. With their focus on a localized, painless method of targeting tumors through dermal layers, microneedles in particular have provided a practical path for theranostic development [68].The design and construction of smart microneedle systems, such as a microneedle patch with biosensors integrated and wearable or tattoo-based applications, is another ongoing research endeavor. The multipurpose approach that this device may provide would elevate cancer treatment to a completely new level. Additionally, this could enable wireless transmission of individualized health data and enable tailored diagnostics via cloud medicine and telemedicine [69].In addition to lowering the amount of different metals and petrochemical compounds used in the manufacturing of syringes, intravenous bags, and injection tools, microneedles offer a more

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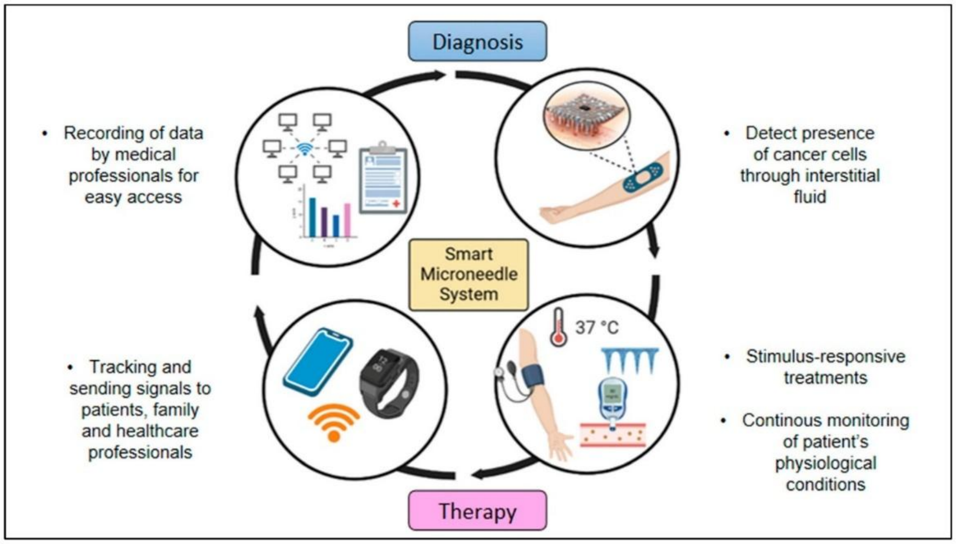
environmentally friendly option than hypodermic needles because they can be used to deliver multiple medications simultaneously [70,71].



VI. CONCLUSION

The use of microneedles in cancer treatment has raised expectations that patients could soon have access to a painless treatment option. As previously said, a number of elements of the microneedle-based delivery method for cancer therapies have been discovered, which may open the door to new therapeutic approaches. There may be a lot of advancements to be made in the design and manufacturing of microneedles to make it more remarkable in the near future. Precision and personalized medicine, which is tailored based on patients' history and DNA, is making tremendous progress. Nonetheless, it is important to take into account the inherent constraints of transdermal microneedle-based administration, and more research is required to fully comprehend the mechanisms underlying effective delivery. Despite the difficulties, there have been considerable advancements in the study, diagnosis, and treatment of cancer in recent years. These advancements are anticipated to continue to improve in the years to come, particularly with the developments in computer science, artificial intelligence, virtual reality, and the internet of things. We are already on the verge of a better era with the use of microneedles in cancer therapy, since the ultimate goal of the treatment is to maximize damage to the cancer cells while limiting the bad and undesired effects.

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