Microneedles in Cancer Therapy and Diagnosis

Subjects: Oncology

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The tumor is an uncontrolled growth of tissue that can be localized (benign) or possesses the capability of metastasis (malignant). The conventional methods of tumor diagnosis, such as acupuncture, endoscopy, and histopathology, and treatment methods, such as injections, chemotherapy, surgery, and radiotherapy, are invasive, expensive, and pose severe safety and management issues for the patients. Microneedle technology is minimally invasive, self-administrable, bypasses the first-pass effect, effectively delivers chemotherapeutics and drugs at low doses, and provides drug diffusion into the tumor areas, thus, overcoming the drawbacks of conventional delivery systems.

microneedles tumor therapy tumor diagnosis

1. Introduction

As per the American Cancer Society, cancer is defined as a set of diseases categorized by unrestrained proliferation and propagation of abnormal cells that left untreated may lead to fatality. The uncontrolled growth of new tissue is termed neoplasia and results in tumor formation. A tumor can be localized (benign) or possesses the capability of metastasis (malignant tumors) [1]. As per the latest estimations by GLOBOCAN2020 and WHO, there were 19.3 million cases of cancer and 10 million deaths worldwide for the year 2020. GLOBOCAN2020 also predicts that by the year 2040, there will be a rise in cancer cases to 30.2 million [2][3].

The existing methods of chemotherapy (injections, surgery, chemotherapy, radiotherapy) and diagnosis (acupuncture, endoscopy, and histopathology) pose severe safety and management issues for the patients and are also very expensive [4]. The oral delivery of anticancer agents is associated with the first-pass effect and low bioavailability problems [5]. To avoid these issues, chemotherapeutic agents are given by the IV route, as it provides advantages such as higher drug plasma levels, quicker onset of action, and prevents gastrointestinal side effects; however, this route is associated with a risk of infection, thrombus formation, pain, and hypersensitivity, and its administration requires trained personnel [6]. Even novel therapies such as nanomedicines cause sub-optimal efficacies. They are encumbered by their low capacity to accrue within the tumor tissue, i.e., no more than 0.7% of the dose that is administered reaches the tumor site. Moreover, the synthesis process, scale-up, and reproducibility of the therapeutics outcome are complicated due to high complexity [1][7][8]. The transdermal delivery system is being explored as an alternative route to oral and IV routes to deliver chemotherapeutic agents to the tumor site, as it is relatively less invasive and prevents systemic side effects and high first-pass metabolism [6]. Conventional transdermal delivery systems such as patches and ointments show limited bioavailability due to the major barrier of

the skin, the stratum corneum [9]. Moreover, the stratum corneum only allows the diffusion of drugs with a low molecular weight (<600 Da). Therefore, many strategies are employed to enhance the permeation of chemotherapeutic agents via the stratum corneum, such as electroporation, sonophoresis, iontophoresis, needleless jet injector, thermal ablation, and microneedles (MNs) array [6]. MNs are a novel transdermal delivery technology with unique micron-sized needles which easily penetrate the stratum corneum without coming into contact with painful nerves below the dermis region, and they have high efficiency, painless penetration, and sufficient convenience [9].

2. Microneedles in Cancer Therapy and Diagnosis

MNs technology is a form of active transdermal drug delivery and could be used as a substitute for conventional syringe injections. The direct injections of therapeutic agents into the tumor can cause leakage of the drugs to the surrounding healthy tissues, thereby decreasing safety and effectiveness. The basic mechanism of MNs-assisted drug delivery involves the disruption of skin layers by forming micron-sized pathways to directly deliver the drug to the epidermal or upper dermis region [10]; thus, the drug enters systemic circulation without obstructions from the stratum corneum barrier. The MNs array penetrates the stratum corneum, delivers the drug with a minimally invasive action, and provides drug diffusion into the tumor areas [11]. The MNs are available in various shapes and are sized with a height ranging from 150 to 1500 µm and a width ranging from 50 to 250 µm [12][13][14].

MNs, such as solid MNs, coated MNs, hollow MNs, dissolving MNs, and hydrogel-forming MNs, are explored for therapeutic delivery and the diagnosis of disease conditions. Each type has its own set of attributes: solid MNs are useful in generating pores in the stratum corneum as pre-treatment, but there is also medication-coated MNs, dissolvable MNs for sustained release, or hollow MNs filled with drug solution. All types are employed in cancer diagnosis and therapeutics [13]. The different kinds of MNs and their approaches for transdermal delivery are shown in **Figure 1**.

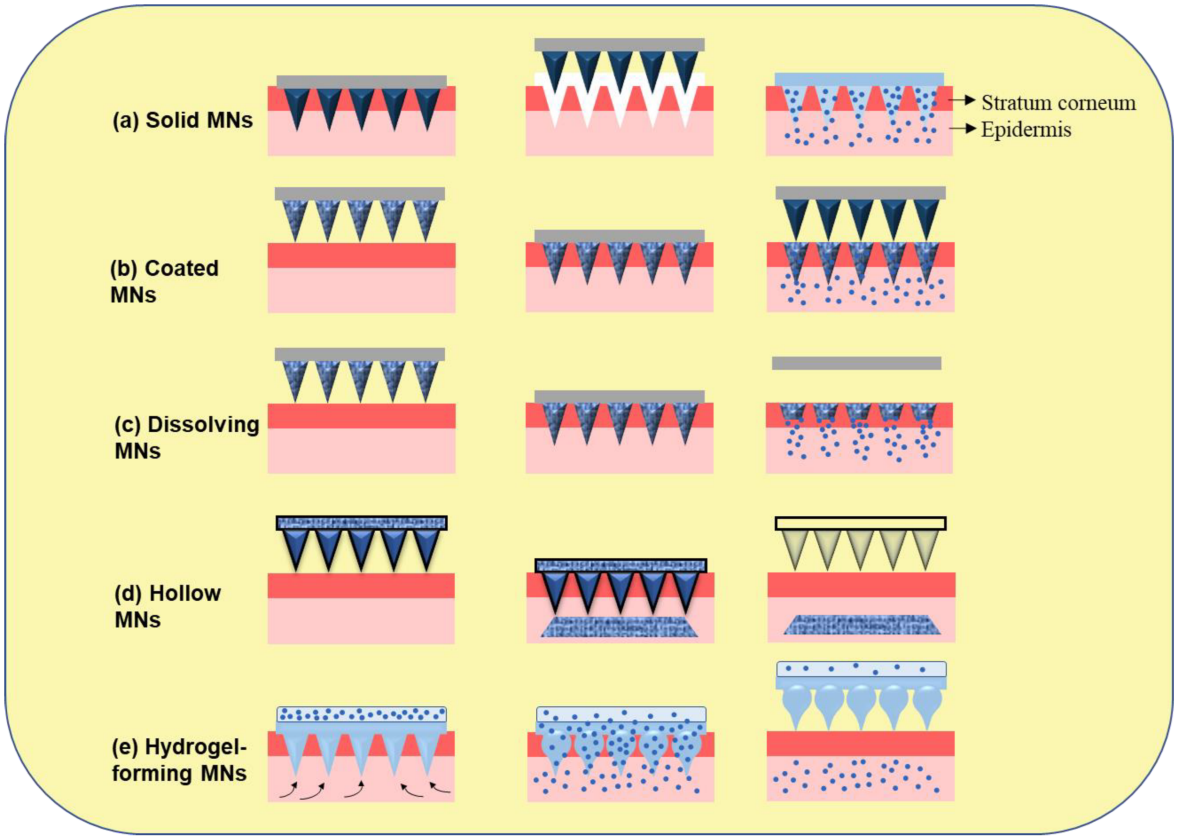

Figure 1. Different types of microneedles and their approaches for transdermal delivery. (**a**) Solid MNs (poke and patch); (**b**) coated MNs (coat and poke); (**c**) dissolving MNs (poke and dissolve); (**d**) hollow MNs (poke and flow); (**e**) hydrogel-forming MNs (poke and release).

A variety of biomaterials, such as silicon, biodegradable and non-biodegradable polymers, metals, carbohydrates, and ceramics, are used to fabricate MNs for specific applications [13][15]. Various fabrication techniques for manufacturing theranostic MNs involve cutting, etching, photolithography, micro moldings, and 3D printing. Cutting is a process where computer-aided design software uses a laser to cut solid MNs from a stainless steel sheet into the desired shape and size. Etching involves the utilization of a powerful liquid acid or a gas to cut layers from the MNs surface to obtain the required dimensions. Photolithography utilizes light sources such as UV radiation to form thin, minutely patterned films by the spin-coating of a liquid photosensitive polymer on a substrate, which on hardening is used to replicate the substrate design. Micro molding produces MNs of silicon by pouring the hot polymer into micro- or nano-sized molds, followed by centrifugation, drying, and cooling. Three-dimensional printing is a newer technique that enables MNs fabrication in a single step, as well as specific customizations. This technique also utilizes a computer-aided design model that precisely place the material in a layer-by-layer pattern to produce MNs with the desired shape and geometry [13][14]. The general characteristics of MNs are shown in **Figure 2**.

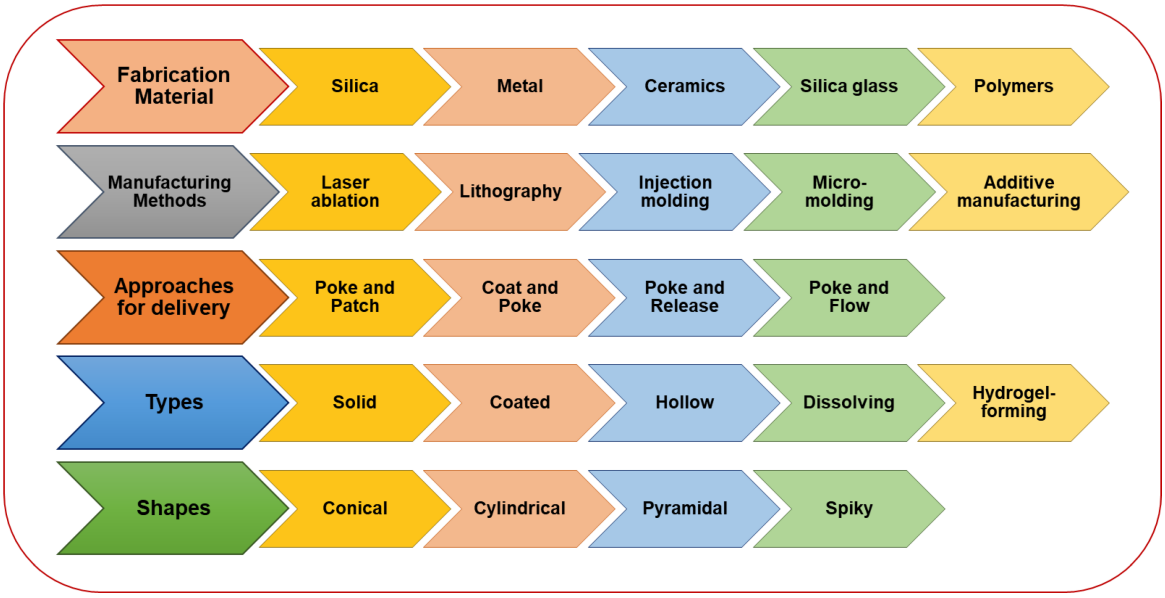

Figure 2. An overview of major aspects of microneedles.

MNs have a synergistic combination of the transdermal patch with hypodermic needles, wherein a drug is directly delivered via the micro-channels to the site of the tumor, especially in breast, prostate, cervical, and skin tumors. MNs provide controlled site-specific delivery, thereby preventing the destruction of healthy cells [5]. To achieve effective topical tumor treatment, MNs are incorporated with many therapies such as chemotherapy, gene therapy, photothermal therapy (PTT), immunotherapy, and photodynamic therapy (PDT) (**Figure 3**).

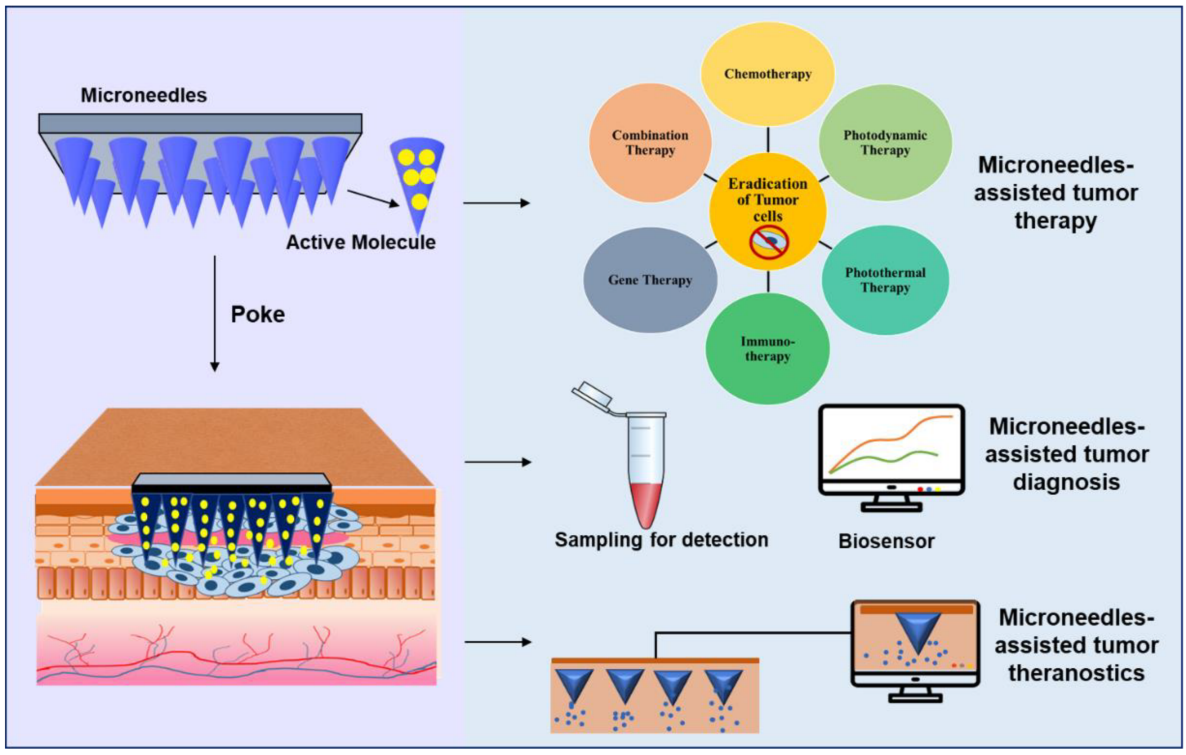

Figure 3. Microneedles-assisted tumor therapy, diagnosis, and theranostics.

3. Conclusion

MNs-assisted monotherapy and combination therapies for tumors overcome the majority of drawbacks, such as the effective and localized delivery of chemotherapeutic agents at low doses; site-specific delivery, preventing damage to healthy tissues; and the rapid and effective delivery of nanoparticles, liposomes, and other delivery agents, which are difficult to administer by conventional routes. MNs are also effectively used as diagnostic tools to bio-sample blood or Interstitial Fluid and biosensing various cancer biomarkers, enabling rapid and early detection which can allow the timely initiation of treatment. MNs are also applied as theranostic tools that combine therapy and diagnosis, such as tumor imaging-guided therapies, and are ideal for personalized tumor treatment. Nanocarrier systems with pH-responsive and enzyme-responsive properties were also successfully incorporated with MNs. To cater to the requirements of controlled release, MNs were designed as multi-layered or core-shell structures, which shows their practical and wide applicability with innovative designs [9]. Therefore, MNs are an emerging diagnostic and drug delivery system with unique features that contribute significantly to cancer and tumor therapy and diagnosis, which is challenging by conventional methods.

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