Review Article

Microneedles in Oncology: Revolutionizing Cancer Therapy and Diagnosis

Manasi M. Chogale*, Nandini D. Banerjee
Department of Pharmaceutics, Saraswathi Vidya Bhawan's College of Pharmacy, Dombivali-421204, Thane, Maharashtra, India.
***Corresponding author's E-mail:** manasimanoharchogale@gmail.com

Received: 08-05-2025; **Revised:** 23-07-2025; **Accepted:** 02-08-2025; **Published online:** 20-08-2025.

ABSTRACT

Microneedles, an emerging technology in the biomedical field, holds significant promise for advancing cancer therapy. This review article examines the uses of different types of microneedles being explored in the field of oncology. The use of microneedles for chemotherapy is highlighted, showcasing their potential for localized drug delivery, which enhances efficacy and reduces systemic side effects. The article also delves into the development of cancer vaccines administered via microneedles, emphasizing their ability to improve immune responses and patient compliance. Additionally, it covers the innovative ways in which microneedles can work in gene therapy, facilitating targeted delivery of genetic material to tumor sites. Furthermore, the potential of microneedles in cancer diagnosis is examined, focusing on their minimally invasive nature and ability to provide rapid and accurate biomarker detection. Through these diverse applications, microneedles present a versatile and minimally invasive platform that could revolutionize cancer treatment and diagnosis, offering new avenues for personalized and effective therapeutic strategies.

Keywords: Microneedles, Cancer therapy, Cancer diagnosis, Vaccine delivery, Gene therapy, Transdermal route.

INTRODUCTION

The oral route is often considered the most favored method for drug delivery because of its convenient dosing and commercial advantages over other administration routes [1]. However, numerous drawbacks associated with this route, such as difficulty in ingestion, slower onset of action, lower bioavailability due to first-pass metabolism, and unpredictability in the absorption pattern, limit their application for the delivery of newer drug molecules that belong to BCS Class II and IV [2, 3]. An obvious alternative to the oral route of administration is the more expensive and invasive parenteral route. This route also suffers from numerous other drawbacks, such as the formation of thrombus at the application site and an allergic reaction [4]. To address the drawbacks associated with both these routes of drug delivery, researchers have shifted their focus to novel approaches for drug delivery. One such approach is the 'Transdermal' route, which implies applying the dosage form on the surface of the skin through which the drug reaches the systemic circulation by penetrating various layers of the skin. Various modes of transdermal delivery currently in practice include transdermal patches, iontophoresis, penetration enhancers, and nano/micro systems [5, 6].

Cancer continues to remain one of the leading health concerns facing the world despite extensive research efforts being taken towards its eradication. Both conventional and novel drug delivery systems present sub-optimal results in terms of their clinical efficacy. Even the highly promising 'nano' therapies fail to translate clinically due to complexities in the manufacturing process, difficulties in scale-up, and lack of therapeutic reproducibility. The efficiency of an API for cancer therapy can be elevated by ensuring its delivery in the right quantity, at the right site, and at the right time. Microneedles, which function as a combination of a transdermal patch and a hypodermic needle, can help offer customized delivery. Microneedles commonly function by penetrating the surface of the epidermis to form microchannels via which the active ingredient can be administered directly to the tumor site. Use of microneedles may be restricted only to the tumors in the breast, prostate, cervix, and skin. Besides facilitating site-specific delivery and avoiding side effects in patients suffering from chemotherapy, microneedles are almost painless compared to hypodermic needles and localise drug delivery. The scope of this article includes a brief review of the history and development of microneedles, including their types, materials, and methods of fabrication, followed by a detailed account of the application of microneedles for cancer diagnosis and therapy. The detailed account includes literature consisting of research reports and clinical /pre-clinical case studies detailing the use of microneedles for the treatment and diagnosis of tumors [5].

MICRONEEDLES: HISTORY AND DEVELOPMENT

Harvey Kravitz and Norman Letvinn were the first set of US inventors who conceived the idea of microneedles as a reliable approach for delivering vaccines through multiple layers of the skin. Gastrel and Place of Alza Corporation further developed this concept in 1971. The principles and approaches developed by Kravitz and Letvinn and Alza Corporation feature in the microneedles being developed and studied to date [5]. Structurally, microneedles, consist of micron-sized needles, which are assembled on a small patch or as an array. These needles are capable of penetrating through the stratum corneum and delivering the active ingredient systemically with minimal patient discomfort. The microneedles have a height ranging from 25 microns to 2000 microns, a breadth of 50-250 microns, and a tip thickness of 1-25 microns that is sufficient to penetrate the skin up to the epidermis, which has a thickness of 1500µm.

The microneedle tips may be fabricated in numerous configurations i.e., sharp, triangular, cylindrical, or octagonal. Microneedles can be fabricated in different sizes depending on their type and the excipient utilised for their fabrication [7]. The dimensions of microneedles depend on the control parameters such as penetration depth and, minimal force required for effective penetration. Microneedles facilitate the delivery of even hydrophilic high molecular weight drugs through the stratum corneum layer to reach systemic circulation [8]. Based on their mechanism, microneedles can be classified as: Solid Microneedles, Coated Microneedles, Dissolving Microneedles, Hollow Microneedles, and Hydrogel-based Microneedles as depicted in Figure 1.

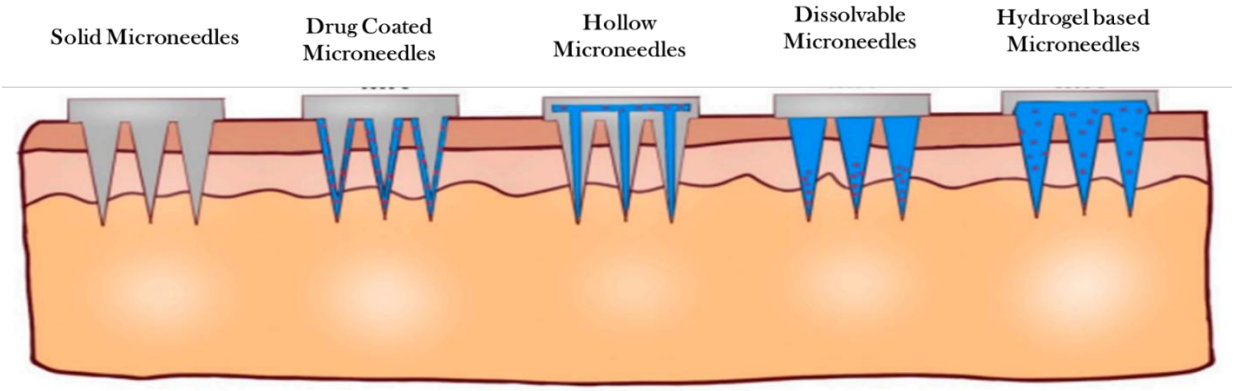

Figure 1: Different Types of Microneedles

Solid microneedles are inserted for a brief period and removed to form micron sized pores in the tissue. The formulation is then applied on the site of application of the microneedles, which allows the formulation to localise in the deeper regions of the tissue. Hollow microneedles are fabricated to enclose a drug reservoir, which flows into the skin driven by pressure through a small aperture at the tip of the microneedles. These devices function similarly to a hypodermic syringe, albeit they are almost painless. High molecular weight compounds such as polypeptides, immunization, and short single-stranded synthetic DNA or RNA are delivered by hollow microneedles. Coated microneedles are enclosed within a solution or suspension of the drug formulation. The coated drug diffuses from the surface of the microneedles into the layers of the skin. Drug-coated microneedles are used for the delivery of active molecules like proteins, small molecules, and vaccines, and for the simultaneous delivery of drugs. Dissolving microneedles, apropos of their name, dissolve after insertion and release their drug load. Biodegradable polymers are used for the fabrication of such microneedles, which contain the drug to be administered.

The mechanism of drug delivery using microneedles depends on the type of microneedle used. One approach is to form holes on the surface of the skin using microneedles, followed by removal of the microneedles and application of the drug-loaded patch over it. Another approach is to cover the microneedle surface with a drug-loaded layer and insert the entire system onto the skin. An alternate approach functions by dipping the microneedle in a drug-containing solution and scraping the surface of the skin with the needles. Finally, the drug may be incorporated into a biodegradable polymer matrix, which is then used to fabricate the microneedles. A hollow microneedle containing space to encapsulate the drug solution may also be fabricated [7].

The most employed methods for the manufacture of microneedles are micromoulding, solvent casting, pulling pipettes, etching, lithography, ceramic sintering, laser ablation, electropolishing, and microstereo lithography [8]. Multiple natural and synthetic materials have been explored for the synthesis of microneedles. The first microneedles were prepared in the 1990s from silicon. The flexibility of this material lent its application to the fabrication of microneedles in multiple shapes and sizes. Though solid microneedles made from silicon improved drug penetration, they were prone to fracture because of their brittle nature. Various biodegradable polymers such as polylactic acid, poly(methyl methacrylate) PMMA, polyglycolic acid (PGA), poly(carbonate), and PVA (polyvinyl alcohol) have also been used for designing microneedles. The micromoulding technique was used to prepare microneedles of hyaluronic acid and its derivatives. Hollow microneedles fabricated from glass have been reported, but show a major drawback of fragility. Biocompatible, sturdy metals such as titanium, stainless steel, nickel, palladium, and palladium cobalt alloys yield microneedles with good mechanical properties and are cost-effective [9]. Ceramic materials such as gypsum and brushite have also been used to fabricate hollow microneedles [10].

USE OF MICRONEEDLES FOR CANCER MANAGEMENT

Cancer is one of the most fatal diseases afflicting mankind with an ever-proliferating patient population. Conventional methods of cancer therapy, such as chemotherapy, surgery, and radiation, seldom yield clinical success due to their numerous drawbacks. Several chemotherapy drugs exhibit poor water-solubility, rapid clearance from the systemic circulation, accumulation in non-target organs, and poor bioavailability, which limit their therapeutic applications [11, 12]. Nanomedicines also fail to achieve clinical success due to their complicated fabrication procedure, difficulty and scale-up, and reproducibility, and inability of the drug to

accumulate in the tumor tissues. This has prompted the researchers to re-explore macro-scale drug delivery platforms for tumor therapy. Rapid and efficient delivery of such chemotherapeutic agents can be achieved with the help of microneedles. Microneedles combine the benefits of targeted drug delivery and the transdermal route of administration. Besides offering a safe, painless, and convenient mode of drug delivery, microneedles also offer the benefits of targeted administration, better uptake of the chemotherapeutic agent, and low extravasation to the non-tumorous tissue [13]. Microneedles are thus becoming a potential alternative to the oral and transdermal administration of chemotherapeutic drugs due to their specific advantages including, low occurrence of side effects, gradual administration of the drugs into the bloodstream at a controlled rate, better control of the therapeutic window, and patient compliance [14].

Microneedles have been studied at pre-clinical and clinical levels to enhance transdermal delivery of chemotherapeutic agents, assess the antigenicity of the vaccines, and assess altered protein pharmacokinetics and pharmacodynamics. Cancer therapy employs microneedles to stimulate anti-cancer immunologic response as well as to deliver anti-cancer drugs and delivery systems. Microneedle-based delivery of chemotherapeutic drugs may facilitate penetration of the drugs in the deeper areas of the tumours and prevent extravasation of the same in the adjacent tissues, preventing side effects. Microneedles may also be used for delivery of a single and/or a combination of multiple chemotherapeutic drugs, while also allowing temporally controlled release, which may serve as an important tool during the drug development phase [15-17].

MICRONEEDLE MEDIATED IMMUNE THERAPY

Cancer vaccines are receiving great importance as a robust method for a cancer-free population. Microneedles may offer a potential approach for the delivery of cancer vaccines (immune and gene-based therapies). The ability of the microneedles to traverse through the stratum corneum layer and deliver their contents in the interstitial fluid at a depth of greater than 200µ makes them a suitable tool. Cancer vaccines are delivered to prompt a host-induced immune response to eradicate the cancerous tissue. Delivery of these vaccines is preferred transdermally due to the skin being enriched with antigen-presenting cells (APCs), i.e. the macrophages, dendritic cells, Langerhans, etc., which then activate and stimulate the T and B cells to affect a systemic immune response [18].

Lee et al. developed an anti-tumour microneedle patch loaded with ovalbumin. When delivered to the mouse skin, these dissolving microneedles induced an immune response due to the antigenicity of ovalbumin via enhanced production and proliferation of cytokines by splenocytes and lymph nodes. A significant rise in the CD8+ T cell and CD4+ T cell population is unique to ovalbumin. The immunized mice also displayed a unique CD8+ T cell and CD4+ T cell population. Notably, suppression of tumor growth as well as preclusion of tumor formation was observed in the EG-7 tumor mouse model, justifying therapeutic and prophylactic use of the microneedle-based vaccine [19].

A microneedle patch for the sustained release of tumor antigen peptide ($OVA_{257–264}$: SIINFEKL) was prepared using biodegradable polymers. The peptide was linked with hepatitis B core (HBc) protein virus-like particles to form (OVA-HBc VLPs) to potentiate the immunogenicity of the tumor antigen. Mesoporous silica nanoparticles (MSNs) were employed as a vaccine adjuvant. Microneedles loaded with OVA-HBc VLPs and MSNs could stimulate the maturation of dendritic cells. The microneedle patch proved to be effective in inhibiting tumour formation by stimulating antigen-specific anti-tumor response. Inclusion of CpG-DNA can improve the clinical efficacy of this microneedle patch in distant tumours and facilitate a long-term immune memory effect [20].

Dissolving microneedles based on amphiphilic triblock co-polymers were fabricated by Kim et al., which formed in situ nanomicelles after cutaneous administration to facilitate encapsulation and delivery of hydrophilic antigens and water-soluble Toll like Receptors 7/8 agonist (R848). Application of these microneedles loaded with R848 and ovalbumin to the skin of EG7-OVA tumor-afflicted mice resulted in an elevated extent of antigen-specific humoral and cellular immunity, leading to substantial antitumor effects [21].

Microneedles can also be fabricated to deliver antibody based immune therapy to respond to/ bypass the immune-suppressant signals of tumour cells. Ye et al. developed hyaluronic acid-based microneedles for delivering anti-PD1 antibody (aPD1) and 1-methyl-DL-tryptophan (1-MT) to B16F10 melanoma tumors. The aPD1 targets the PD-1 receptors expressed by T cells and therefore can avoid the cancer cells inhibitory signaling that suppresses the T cells' activation. It was observed that the 1-MT and aPD1 release occurred in response to the HAase-triggered degradation of the microneedles and micelles. When administered to mice bearing B16F10 melanoma cells, the microneedles increased the retention of 1-MT and aPD1 at the tumor tissue. In fact, the accumulation of 1-MT on melanoma was 3-fold higher at day 1 and 5-fold higher at day 2 and 3 in the group treated with the microneedles than in that treated with free 1-MT. Moreover, the simultaneous delivery of aPD1 and 1-MT by the microneedles restrained the tumor progression (tumor area inferior to 50 mm2, whereas in the control group the area was superior to 300mm^2) and showed a higher mouse survival rate [11].

Besides using microneedles for the delivery of immunity mediators, these delivery systems are also used for the delivery of antitumoral gene therapy. Ali and coworkers developed a polyvinylpyrrolidone patch loaded with E6/E7 pDNA RALA particles for the treatment of cervical cancer. Developed by the micro molding method, following dermal application, the microneedle tips dissolved within 15 minutes. The levels of antibodies were found to be two times higher compared to the control, and the T-cells were

more sensitive to the HPV-16 oncogenic antigen expressing cells (TC-1). This elevated immune response prevented the occurrence of cervical tumors on forty percent of the mice treated with microneedles. Administration of microneedles to tumor-bearing mice resulted in regression of the tumor area [15]. In another report, Pan and colleagues fabricated microneedle patches developed from a combination of dextran/hyaluronic acid/polyvinylpyrrolidone for delivering polyethyleneimine/STAT3 siRNA complexes to skin melanoma tumors. It was observed that the topical application of these microneedles could reduce the STAT3 mRNA expression in 30% as well as induce the necrosis of 40% of the tumor cells. This effect suppressed melanoma tumor growth, resulting in a tumor weight 5 times lower than the control group [22].

MICRONEEDLE MEDIATED DELIVERY OF ANTICANCER DRUGS

Recently, microneedles have been explored as a potential alternative to systemic chemotherapy. Microneedles ensure a decrease in interaction with the healthy tissues, and provide better spatiotemporal control over the release of the drugs, thereby preventing extravasation of the drugs into the adjacent tissues. Besides, single drug therapy, microneedles can also be employed for the coadministration of two or more chemotherapeutic agents [23]. In one such report, Bhatnagar and colleagues developed a polyvinyl alcohol/ polyvinyl pyrrolidone microneedle patch for the simultaneous delivery of docetaxel and doxorubicin to breast cancer cells. The drugs were first dissolved in polyvinyl pyrrolidone solution, which was then deposited on a PDMS mould and coated with a solution blend of polyvinyl alcohol and polyvinyl pyrrolidone to further elevate the mechanical robustness of the patch. The microneedles completely dissolved within 30 minutes, releasing 90% docetaxel in the first 15 minutes. *In vivo* assessment performed on 4T1 breast tumor-bearing mice revealed that the synergistic action of docetaxel and doxorubicin was more efficient compared to a single drug therapy in terms of tumor growth. Furthermore, relative to free drug administration, mice treated with microneedles displayed an increased survival rate and a long-term retention of mouse weight, thereby proving a reduced drug's non-specific toxicity [24]. Another report by Bhatnagar dealt with the use of microneedles for concomitant administration of two other anti-breast cancer drugs i.e. Gemcitabine and Tamoxifen [17].

Dong et. al. developed hyaluronic acid dissolving microneedles loaded with Doxorubicin and gold nanocages for tumor treatment. The gold nanocages were incorporated to strengthen the mechanical strength of the microneedles, as well as enable photothermal therapy. The micromolding process was used for the fabrication of these microneedles, and the Young's moduli of the same was found to be sufficient for skin penetration. Photothermal activity of gold nanocages innaddition ot the chemotherapeutic potential of Doxorubin synergistically functioned to destroy tumors [25]. Lu and colleagues developed Dacarbazine loaded microneedles for therapy in skin carcinoma. The microneedles were loaded with poly (propylene fumarate) and diethyl fumarate as rate-controlling polymer and viscosity building polymer, respectively. Microstereolithography was used as the method of fabrication of these microneedles having a cylindrical base and a conical tip that with excellent skin insertion capacity. The microneedles showed a controlled delivery of the drug over 5 weeks [26]. Androgen Deprivation Therapy (ADT) is a unique approach for the treatment of prostate cancer. Goserelin is a Luteinizing Hormone Releasing Hormone (LHRH) analogue used for ADT. Hydrophilic polymeric nanoparticles of Goserelin using polymers like chitosan and polyvinyl alcohol/ polyvinyl pyrrolidone as the base support were developed by Chen and co-workers. The serum LHRH levels spiked initially after administration, followed by a lower value by the 7th day. The testosterone levels, on the other hand, peaked by the 14th day and significantly diminished by the 21st day[27].

A report on Cisplatin loaded microneedles for the treatment of skin tumors prepared by 3D printing was published by Uddin *et al.* in 2020. These cross-shaped microneedles featuring dimensions of 1000µ x 1000µ were 430µ long and were fabricated using a Form 2 SLA printer by Formlabs. The structures were cured under UV radiation to improve the mechanical properties of the MN patches. Inkjet printing was employed to apply a coating of Cisplatin and other excipients using a piezoelectric dispenser. The 3D printed MNs produced uniform and reproducible penetration onto neonatal porcine skin with a penetration depth of more than 80% of their length as revealed by the optical coherence tomographic studies. The cross-shaped MNs could efficiently penetrate the stratum corneum by applying a force of only 3N. Franz cell studies revealed the presence of almost 100% of the dose of Cisplatin in the receptor compartment after 4 hours, even at higher dose loading. The rapid release rates could be attributed to the presence of SOL, an amphiphilic molecule known to promote the dissolution rates of hydrophobic drugs. When evaluated in Balb/c nude mice injected with A431-human squamous carcinoma cells, no evident signs of toxicity or weight loss were observed. Surprisingly, a slight regression in the tumors was also seen in some animals treated with the MNs compared to the control group. This could be owing to the possible dislodgement of the MNs from the site of application or incomplete penetration. Another possible explanation of this occurrence could be the presence of a meager amount of interstitial fluid at the tumor site that may delay the dissolution and release of Cisplatin. However, when applied on a non-tumor site, a significant anti-cancer effect with complete tumor regression was seen. This could be due to the systemic delivery of the drugs that destroyed the tumor by accessing it through the systemic circulation. Thus, the drug-loaded 3D printed MNs could open newer avenues to transdermal delivery of chemotherapeutic drugs [28].

An emerging field is the integration of microneedles with microelectronic sensors. Sensor-based microneedles

possess the ability to transform non-electrical inputs, such as pressure or temperature, from their surrounding environment into electrical signals that can be read by microcomputers [29]. Currently, colorimetric microneedle sensors, the immunosensors, are widely studied with promising *in vivo* results [30]. Also, according to Zandi and colleagues, microbubbles were produced using microneedles of electrochemical probes colored by zinc-oxide nanostructures [31]. Following their implantation into the interstitial fluid of the tumor, these microneedles were used in sonoporation to create microbubbles using electrolysis that would later release paclitaxel

Microneedles can enter the SC and administer the medication to the dermal area using the acanthocyte and basal cell layers. The microneedles were created using micro stereolithography and poly (propylene fumarate) as a polymer, with diethyl fumarate added to adjust the polymer's viscosity [26]. Multiple studies demonstrated that the microneedles had good mechanical strength for insertion into the skin layers, 5mm down the skin, for the treatment of nodular skin carcinomas. For this reason, it is recommended to use polymeric microneedles (a copolymer of maleic acid and methyl vinyl ether) in photodynamic therapy for deep skin lesions. It is possible that various analytes could be targeted for microneedle-based cancer detection. Drug distribution to the tumour site will be disrupted by localized drug delivery employing microneedles [32].

Nanoformulation-based drug delivery systems have gained significant prominence due to their unique advantages, including targeted drug delivery, lower incidence of side effects, lower dose requirement, and less frequent dosage regimen. Nanoformulations of anticancer drugs may also be loaded onto MNs to potentiate the effect of chemotherapeutic drugs further. Gadag et al. developed Resveratrol based NLCs coupled with MN arrays, which were then evaluated for breast cancer therapy. The NLCs were prepared by the melt-emulsification method. Cytotoxicity, cellular uptake, and cell migration studies of the optimized NLCs were performed on MDAMB-231 breast cancer cell line. Preclinical and biodistribution studies were performed on female Sprague-Dawley rats. The IC_{50} value of the NLCs was found to be lower than that of the pure drug suggesting potency of the formulation. Cellular uptake studies revealed significant uptake of FITC NLCs after 4 hours. Minimum cell migration was observed for drug-loaded NLCs and pure drug compared to the placebo NLCs. In vivo pharmacokinetic studies revealed a significantly elevated C_{max}, AUC, and breast tissue distribution of resveratrol were administered via a microneedle array against per-oral administration of the pure drug. Thus NLC formulations of Resveratrol could be administered by local transdermal delivery via a microneedle array system to the breast tissue [33].

MICRONEEDLE MEDIATED PHOTOTHERMAL THERAPY

Light source functions as a stimulator for photothermal therapy (PTT). PTT employs photothermal materials with high photothermal conversion efficiency to ensure targeted delivery to the tumor cells. Wei and co-workers developed a dissolvable microneedle loaded with NIR 950 (an aggregation induced emission luminogen) for PTT of melanoma. pH-sensitive micelles containing NIR950 were prepared by a nanoprecipitation method, which were then loaded on a PVA/PVP base via a molding process. The microneedles were found to have excellent photothermal stability compared to those by intratumor or intravenous injection. A significant elimination in tumors was seen in a single PTT therapy, indicating excellent antitumor effect [12]. Another research group developed novel Nb2c nanosheets as a photothermal agent for tumour ablation. Owing to its strong NIR absorption, the Nb2c-based microneedle system was fabricated by the casting process. In vivo studies revealed the timely release of Nb2c in the skin, resulting in a rise in tumor temperature and significant suppression of tumor growth while also improving the survival of the mice.

A combination of chemotherapy and PTT was attempted by Moreira et al. by developing a layered PVP-based MN system with Doxorubicin as the drug and gold-core silica shell (AuMSS) nanorods developed by alternately electrospraying chitosan and polyvinyl alcohol (PVA). The beveled-tip microneedles were developed by the micromolding technique with 425 µm, 1,420 µm, and 1,740 µm of width, height, and length, respectively. The gold core dimensions influence the conversion of NIR light to heat, with aspect ratios between 3 and 4 found to be optimal. The in vitro chemotherapeutic potential of these MNs was evaluated against HeLa cancer cells by incubating the MNs with these cells for 48 hours in the presence or absence of NIR irradiation. While standalone chemotherapies reduced the cell viability only to an extent of 46.87%, the combination of drug and PTT therapy reduced the viability of these cancer cells to 3.8%. Literature claims support that the local increase in temperature due to irradiation hastens the release of Doxorubicin, while also sensitizing the cancer cells to the effect of the drug [34].

MICRONEEDLE MEDIATED PHOTODYNAMIC THERAPY

Photodynamic therapy involves the use of photosensitizers that activate in response to light in an oxygen-rich environment, and generate reactive oxygen species (ROS) that facilitate antitumor effect. Photodynamic therapy has the advantages of being noninvasiveness, highly selective and reducing side-effects. A very commonly used photosensitizer is 5-aminolevulinic acid (5-ALA), which is known to accumulate in tumor cells and convert into protoporphyrin IX (PPIX). Typically, a hyaluronic acid-based microneedle patch loaded with 5-ALA was developed using a two-casting fabrication process. Following application, mild erythema was observed at the site that disappeared within few hours. *In vivo* assessment revealed high PDT efficiency. In another report, Zhu and co-workers, developed 5-ALA-Hyaluronic acid based dissolvable microneedles for PDT based tumor therapy. Hyaluronic acid not only functions as a matrix-forming agent, but also maintains the chemical and biological functionality of 5-ALA.

Significant anti-tumor activity was observed following irradiation at 635 nm. Contrastingly, when delivered sans microneedles, the tumor growth proliferated. Furthermore, the microneedles still responded to PDT despite being stored for over 9 months at room temperature, thereby providing excellent long term stability of microneedles for tumor therapy [35]. Research carried out by Jain et al. involved a microneedle patch coated with 5-ALA developed for the treatment of skin tumors. The microneedles were found to retain their needle-like structure despite being coated with the drug, facilitating both skin penetrability and drug delivery. The coated drugs could dissolve from the surface of the microneedles and deliver transdermally they transforming into PPIX [36].

MICRONEEDLE MEDIATED GENE THERAPY

Besides delivering single and/or combination of drugs, antigens, antibodies etc., microneedles have also been explored for the delivery of genetic materials. Gene delivery to the tumors has received wide recommendation as an effective module for cancer treatment. The therapy implies the introduction of genetic materials to the cancer cells to counteract or replace the dysfunctional genes in the cells. Li and co-workers developed a polycaprolactone-based microneedle array layered with a pH-responsive polyelectrolyte multilayer (PEM) for gene delivery. The PEM is composed of alternate layers composed of (PLL-DMA/PEI) and gene containing layers composed of p53 DNA PEI. The layers were pH responsive, which could dissolve in the weakly acidic microenvironment of tumors to release the genetic materials. In vivo studies showed that the group administered with the microneedles containing the pH-sensitive layer showed better site-specific gene release compared to the control group devoid of the pH sensitive layer. Tumor inhibition was also found to be more significant in the microneedle group compared to intravenous injections of the same [37]. Motivated by these results, Ruan et al. fabricated steel microneedles loaded with R8/siBRAF nanocomplexes for gene silencing therapy of melanoma. *In vivo* assessment proved that the microneedle based therapy successfully inhibited progression of the melanoma, and the BRAF genes were significantly silenced thereby furthermore proving the anti-tumor efficacy of microneedle based therapy [38]. Cole and colleagues proposed to combine the pDNA and RALA to form the combination nanoparticles. Further, the nanoparticles were lyophilized to improve their stability in the dissolvable microneedles. The microneedles could achieve enhanced gene expression and more significant tumour inhibition compared to intravenous injection [39].

MICRONEEDLE MEDIATED TUMOR DIAGNOSIS

Beyond the plethora of applications that microneedles find in tumor therapy, the use of this system for tumor diagnosis has also been extensively explored. Microneedles may be used as a medium for withdrawing biological samples such as interstitial fluid or capillary blood for the presence of tumor biomarkers. In one such report, Chang and colleagues fabricated a swellable microneedle patch for rapid and safe extraction of interstitial fluid for metabolic evaluation[40]. Blicharz and coworkers developed a microneedle based automatic capillary blood collection system for painless extraction of capillary blood for biochemical analysis. The efficacy of this system was evidenced by the hemoglobin A1c levels, which were almost equivalent in the blood collected by this device and venous blood samples [41]. Microneedles can also be potentially used for tumor diagnosis due to their piercing potential and rapid sampling ability. Microneedles have been proven to be a robust tool for sampling interstitial fluid, which can be further used for tumor diagnosis. Microneedles may function as a simple penetrating device that may result in overflow of the interstitial fluid, or the interstitial fluid may be captured by the microneedles.

In a report published by Chen et al., microneedles were used to collect tissue fluid for the early detection of breast tumors. The microneedles formed microporous channels on the surface of the mammary glands for the collection of tissue fluid containing the CEA (carcino-embryonic antigen) biomarker. In vivo studies showed a significant increase in the survival of mice due to the timely diagnosis. In another example, hybrid alginate PNA based microneedle patches would be developed for the collection of interstitial fluids. In addition to being tools for sample extraction micro needles complement with other devices to serve as biomarkers for disease diagnosis, including tumor detection [42]. A study by Ciui et al. proposed a microneedle based biosensor for rapid detection and diagnosis of skin cancer by detection of levels of tyrosinase enzyme, a tumor biomarker. The microneedle arrays were loaded with immobilized catechol, which would be converted to benzoquinone, which was detected by amperometry. The intensity of the current signal was directly proportional to the levels of tyrosinase enzyme, thereby offering a minimally invasive platform for tumor detection. The device can serve as a platform technology for the detection of a host of other biomarkers [43]. Another diagnostic system developed by Yang et al. was applied for the detection of nasopharyngeal carcinoma. The system consisted of a hydrogel based microneedle patch and a RPA (recombinase polymerase amplification) platform. The microneedle patch was capable of specifically collecting EBV Cf DNA in interstitial fluid, which is a biomarker associated with nasopharyngeal carcinoma [11].

ECONOMICS OF MICRONEEDLE IN CANCER THERAPY

The use of microneedles (MNs) in cancer therapy offers a promising approach in terms of cost, labor requirements, and energy efficiency. Economically, MNs can reduce healthcare expenses by minimizing hospital stays, lowering drug dosages due to localized delivery, and reducing the need for complex equipment used in traditional intravenous methods. However, there are initial costs tied to the development and manufacturing of microneedles, particularly because of the high-quality materials and advanced production techniques like micro-molding and laser cutting [44].

From a manpower perspective, MNs are advantageous as they require less specialized training for administration compared to intravenous cancer treatments, which must be administered by skilled healthcare professionals. MNs can be self-administered or handled with minimal training, reducing the burden on healthcare workers. Still, their development demands significant expertise, especially in the areas of material science and biomedical engineering.

Energy consumption during MN production can be substantial due to energy-intensive processes like laser cutting and sterilization. However, when considering the overall energy used in cancer treatment, including the infrastructure needed for traditional methods, MNs have the potential to be more energy-efficient in the long term. As the technology evolves, it's expected that production costs and energy consumption will decrease, further enhancing the economic and environmental benefits [45,46].

SHORTCOMINGS IN THE APPLICATIONS OF MICRONEEDLES IN CANCER TREATMENT

The application of microneedles in cancer treatment, while promising, faces several shortcomings. A key limitation is the restricted drug-loading capacity of microneedles. Due to their small size, they can only carry a limited amount of therapeutic agents, which poses a challenge for cancer treatments requiring large doses. For instance, coated microneedles are typically used for potent molecules administered in small quantities, potentially reducing their efficacy in broader cancer therapies. While hollow microneedles can carry larger drug payloads, issues such as drug leakage, blockage, and mechanical weakness make them less reliable for repeated use in complex cancer treatments.

Another significant concern is the pain and skin reactions at the application site, particularly following repeated insertions. The use of microneedles could also increase the risk of infections and other skin complications, limiting their comfort and safety during long-term use. Manufacturing these devices on a larger scale presents challenges as well, with concerns over sterility, fabrication costs, and the materials used. Biocompatibility remains an issue, as certain materials may trigger immune responses, further complicating their use in clinical settings.

Regulatory hurdles add further complexity, as the integration of microneedles into cancer care requires adherence to stringent standards like Good Manufacturing Practice (GMP). The novel nature of microneedles means regulatory bodies are still developing specific guidelines, which could slow down their path to commercialization [47]. Despite these challenges, ongoing research demonstrates the potential of microneedles to become a transformative approach in cancer therapy, particularly for low-dose chemotherapeutic drugs. However, toxicity concerns, alongside the mentioned limitations, need to be addressed before microneedles can fully revolutionize cancer treatment [44, 48-49].

FUTURE DIRECTION OF MICRONEEDLES IN CANCER CARE

Microneedles represent a promising innovation in cancer treatment, offering the potential to revolutionize how therapies are administered. One of the key future directions for microneedles is improving their safety and effectiveness through rigorous preclinical and clinical investigations. Given that cancer treatment requires chronic care, understanding how microneedles perform in the human body, particularly in terms of mechanical strength, material durability, and immunogenic reactions, is critical for their success.

Moreover, scaling microneedles from laboratory research to commercial use presents challenges, such as managing production costs, ensuring quality control, and adhering to regulatory standards like Good Manufacturing Practice (GMP). Addressing these issues is crucial for the widespread use of microneedles in oncology [32].

Another promising avenue is the development of personalized and precision-based cancer care through microneedles. These devices are being designed to integrate diagnostic and therapeutic capabilities in a single platform, allowing for real-time monitoring of cancer progression and targeted treatment delivery. Such theranostic systems could enable localized treatment, minimizing damage to healthy tissues and offering a more customized approach to cancer therapy.

Smart microneedles embedded with biosensors could further enhance this approach by monitoring specific biomarkers in the tumor microenvironment and adjusting treatment in response to physiological changes. This data can be transmitted wirelessly to healthcare providers for continuous monitoring, enhancing patient outcomes through personalized treatment strategies [43].

However, for microneedles to be fully integrated into cancer care, several challenges must be addressed. These include optimizing manufacturing processes to meet sterile production requirements, ensuring patient safety during use, and resolving issues related to cost and waste management. Despite these hurdles, advances in microneedle technology hold the potential to significantly reduce cancer mortality by providing minimally invasive, efficient, and patient-friendly drug delivery systems [46].

CONCLUSION

Microneedle based drug delivery rests on the principle of facilitating an accurate and site-specific delivery via the transdermal route. Compared to other approaches of transdermal and parenteral delivery, microneedles possess the potential to be a principal route of drug delivery, especially in tumour therapy, owing to their suitability for a site-specific attack on cancerous cells and lowering systemic toxicity. Precision and personalized medicine, tailored to individual patient histories and genetic profiles, continues to advance significantly. There is considerable potential for future advancements in the design and fabrication of microneedles. However, it is crucial to acknowledge the

inherent limitations in transdermal microneedle-based delivery. Despite challenges, recent years have seen substantial progress in cancer research, diagnosis, and treatment. Anticipated advancements, particularly in fields such as computer science, artificial intelligence, and virtual reality, are expected to further enhance these efforts. Microneedle technology holds promise in cancer therapy by aiming to maximize damage to cancer cells while minimizing adverse effects, signaling a promising future in this field.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. MacGregor RR, Graziani AL., Oral administration of antibiotics: a rational alternative to the parenteral route., Clin Infect Dis.,. 1997; 24(3):457-67. DOI: 10.1093/clinids/24.3.457, PMID: 9114201.
2. Maderuelo C, Lanao JM, Zarzuelo A., Enteric coating of oral solid dosage forms as a tool to improve drug bioavailability., Eur J Pharm Sci., 2019; 138: 105019. DOI: 10.1016/j.ejps.2019.105019, PMID:31374253.
3. Pišlar M, Brelih H, Mrhar A, Bogataj M., Analysis of small intestinal transit and colon arrival times of non-disintegrating tablets administered in the fasted state., Eur J Pharm Sci., 2015; 75: 131–41. DOI:10.1016/j.ejps.2015.03.001, PMID: 25769525.
4. Paudel KS, Milewski M, Swadley CL, Brogden NK, Ghosh P, Stinchcomb AL., Challenges and opportunities in dermal/transdermal delivery., Ther Deliv., 2010; 1(1): 109–31. DOI: 10.4155/tde.10.16, PMID: 21132122.
5. Seetharam AA, Choudhry H, Bakhrebah MA., Microneedles Drug Delivery Systems for Treatment of Cancer : A Recent Update., Pharmaceutics, 2020;1–27. DOI: 10.3390/pharmaceutics12111101, PMID: 33212921.
6. Singh R, Vyas SP., Topical liposomal system for localized and controlled drug delivery. J Dermatol Sci., 1996; 13(2): 107–11. DOI: 10.1016/s0923-1811(96)00508-7, PMID: 8953409
7. Waghule T, Singhvi G, Kumar Dubey S, Pandey M, Gupta G, Singh M, Dua K., Microneedles: A smart approach and increasing potential for transdermal drug delivery system., Biomedicine and Pharmacotherapy, 2018; 109: 1249-1258. DOI: https://doi.org/10.1016/j.biopha.2018.10.078.
8. Dharadhar S, Majumdar A, Dhoble S, Patravale V., Microneedles for transdermal drug delivery: a systematic review., Drug Dev Ind Pharm., 2019; 45(2): 188–201. DOI: 10.1080/03639045.2018.1539497, PMID: 30348022.
9. Wang M, Li X, Du W, Sun M, Ling G, Zhang P., Microneedle-mediated treatment for superficial tumors by combining multiple strategies., Drug Deliv Transl Res., 2023; 13(6): 1600–20. DOI: 10.1007/s13346-023-01297-9, PMID: 36735217.
10. Sartawi Z, Blackshields C, Faisal W., Dissolving microneedles: Applications and growing therapeutic potential., J Control Release., 2022; 348: 186-205. DOI: 10.1016/j.jconrel.2022.05.045, PMID: 35662577
11. Singh V, Kesharwani P., Recent advances in microneedles-based drug delivery device in the diagnosis and treatment of cancer., J Control Release., 2021; 338: 394–409. DOI:10.1016/j.jconrel.2021.08.054, PMID: 34481019
12. Moreira AF, Rodrigues CF, Jacinto TA, Miguel SP, Costa EC, Correia IJ., Microneedle-based delivery devices for cancer therapy: A review., Pharmacol Res., 2019; 148: 104438. DOI: https://doi.org/10.1016/j.phrs.2019.104438
13. Chen Y, Zhu J, Ding J, Zhou W., Recent progress of vaccines administration via microneedles for cancer immunotherapy., Chinese Chem Lett., 2024; 35(3): 108706. DOI: https://doi.org/10.1016/j.cclet.2023.108706.
14. Khan S, Hasan A, Attar F, Babadaei MMN, Zeinabad HA, Salehi M, Alizadeh M, Hassan M, Derakhshankhah H, Hamblin M,m Bai Q, Sharifi M, Falahati M, Hagen T, Diagnostic and drug release systems based on microneedle arrays in breast cancer therapy., J Control Release., 2021; 338: 341–57. DOI: 10.1016/j.jconrel.2021.08.036, PMID: 34428480.
15. Ali AA, McCrudden CM, McCaffrey J, McBride JW, Cole G, Dunne NJ, Robson T, Kissenpfenning A, Donnelly R, McCarthy H., DNA vaccination for cervical cancer; a novel technology platform of RALA mediated gene delivery via polymeric microneedles., Nanomedicine Nanotechnology, Biology and Medecine, 2017; 13(3): 921–32. DOI: https://doi.org/10.1016/j.nano.2016.11.019.
16. Duong HTT, Yin Y, Thambi T, Nguyen TL, Giang Phan VH, Lee MS, Lee JE, Kim J, Jeong JH, Lee DS., Smart vaccine delivery based on microneedle arrays decorated with ultra-pH-responsive copolymers for cancer immunotherapy., Biomaterials, 2018; 185: 13–24. DOI: 10.1016/j.biomaterials.2018.09.008. PMID: 30216806.
17. Bhatnagar S, Kumari P, Pattarabhiran SP, Venuganti VVK. Zein Microneedles for Localized Delivery of Chemotherapeutic Agents to Treat Breast Cancer: Drug Loading, Release Behavior, and Skin Permeation Studies. AAPS PharmSciTech., 2018; 19(4): 1818–26. DOI: 10.1208/s12249-018-1004-5, PMID: 29616489.
18. Kim JH, Shin JU, Kim SH, Noh JY, Kim HR, Lee J. Successful transdermal allergen delivery and allergen-specific immunotherapy using biodegradable microneedle patches. Biomaterials, 2018; 150: 38–48. DOI: 10.1016/j.biomaterials.2017.10.013, PMID: 29032329
19. Lee SJ, Lee HS, Hwang YH, Kim JJ, Kang KY, Kim SJ. Enhanced anti-tumor immunotherapy by dissolving microneedle patch loaded ovalbumin. PLoS One. 2019; 14(8): e0220382. DOI: 10.1371/journal.pone.0220382, PMID: 31386690.
20. Guo Q, Wang C, Zhang Q, Cheng K, Shan W, Wang X. Enhanced cancer immunotherapy by microneedle patch-assisted delivery of HBc VLPs based cancer vaccine. Appl Mater Today, 2021; 24: 101110. DOI: https://doi.org/10.1016/j.apmt.2021.101110.
21. Kim NW, Kim SY, Lee JE, Yin Y, Lee JH, Lim SY. Enhanced Cancer Vaccination by In Situ Nanomicelle-Generating Dissolving Microneedles. ACS, 2018; 12(10): 9702–13. DOI: 10.1021/acsnano.8b04146.
22. Pan J, Ruan W, Qin M, Long Y, Wan T, Yu K. Intradermal delivery of STAT3 siRNA to treat melanoma via dissolving microneedles. Sci Rep, 2018; 8(1): 1–11.
23. Indermun S, Luttge R, Choonara YE, Kumar P, Du Toit LC, Modi G. Current advances in the fabrication of microneedles for transdermal delivery. J Control Release 2014; 185(1): 130–8. DOI: 10.1016/j.jconrel.2014.04.052, PMID: 24806483.
24. Bhatnagar S, Bankar NG, Kulkarni MV, Venuganti VVK. Dissolvable microneedle patch containing doxorubicin and docetaxel is effective in 4T1 xenografted breast cancer mouse model. Int J Pharm., 2019; 556: 263–75. DOI: 10.1016/j.ijpharm.2018.12.022, PMID: 30557681.
25. Dong L, Li Y, Li Z, Xu N, Liu P, Du H. Au Nanocage-Strengthened Dissolving Microneedles for Chemo-Photothermal Combined Therapy of Superficial Skin Tumors. ACS Appl Mater Interfaces, 2018; 10(11): 9247–56. DOI: 10.1021/acsami.7b18293.
26. Lu Y, Mantha SN, Crowder DC, Chinchilla S, Shah KN, Yun YH. Microstereolithography and characterization of poly(propylene fumarate)-based drug-loaded microneedle arrays. Biofabrication, 2015; 7(4): 045001. DOI: 10.1088/1758-5090/7/4/045001. PMID: 26418306

27. Chen MY, Chen YY, Tsai HT, Tzai TS, Chen MC, Tsai YS. Transdermal Delivery of Luteinizing Hormone-releasing Hormone with Chitosan Microneedles: A promising tool for androgen deprivation therapy. Anticancer Res., 2017; 37(12): 6791–7.
28. Uddin MJ, Scoutaris N, Economidou SN, Giraud C, Chowdhry BZ, Donnelly RF. 3D printed microneedles for anticancer therapy of skin tumours. MSEB: C., 2020; 107: 110248. DOI: https://doi.org/10.1016/j.msec.2019.110248
29. Henning W. Semiconductor microelectronic sensors. In: Helbig R., Advances in Solid State Physics, Festkoerperprobleme, Springer Nature Link, 2007, 189-200.
30. Blake DA, McLean N V. A colorimetric assay for the measurement of D-glucose consumption by cultured cells. Anal Biochem, 1989; 177(1): 156–60. DOI: 10.1016/0003-2697(89)90031-6, PMID: 2742145
31. Zandi A, Khayamian MA, Saghafi M, Shalileh S, Katebi P, Assadi S, et al. Microneedle-Based Generation of Microbubbles in Cancer Tumors to Improve Ultrasound-Assisted Drug Delivery. Adv Healthc Mater., 2019; 8(17): 1900613. DOI: 10.1002/adhm.201900613, PMID: 31328442.
32. Hamdan IMN, Tekko IA, Matchett KB, Arnaut LG, Silva CS, McCarthy HO. Intradermal Delivery of a Near-Infrared Photosensitizer Using Dissolving Microneedle Arrays. J Pharm Sci., 2018; 107(9): 2439–50. DOI: 10.1016/j.xphs.2018.05.017, PMID: 29864428
33. Gadag S, Narayan R, Nayak AS, Ardila DC, Sant S, Nayak Y. Development and preclinical evaluation of microneedle-assisted resveratrol loaded nanostructured lipid carriers for localized delivery to breast cancer therapy. Int. J. Pharm., 2021; 606: 120877. DOI: 10.1016/j.ijpharm.2021.120877, PMID: 34252522.
34. Moreira AF, Rodrigues CF, Jacinto TA, Miguel SP, Costa EC, Correia IJ. Poly (vinyl alcohol)/chitosan layer-by-layer microneedles for cancer chemo-photothermal therapy. Int. J. Pharm., 2020; 576: 118907. DOI: 10.1016/j.ijpharm.2019.118907, PMID: 31870955
35. Zhu J, Dong L, Du H, Mao J, Xie Y, Wang H. 5-Aminolevulinic Acid-Loaded Hyaluronic Acid Dissolving Microneedles for Effective Photodynamic Therapy of Superficial Tumors with Enhanced Long-Term Stability. Adv Healthc Mater., 2019; 8(22): 1900896. DOI: 10.1002/adhm.201900896, PMID: 31638739
36. Jain AK, Lee CH, Gill HS. 5-Aminolevulinic acid coated microneedles for photodynamic therapy of skin tumors. J Control Release., 2016; 239: 72–81. DOI: 10.1016/j.jconrel.2016.08.015, PMID: 27543445.
37. Li X, Xu Q, Zhang P, Zhao X, Wang Y. Cutaneous microenvironment responsive microneedle patch for rapid gene release to treat subdermal tumor. J Control Release., 2019; 314: 72–80. DOI: 10.1016/j.jconrel.2019.10.016, PMID: 31629710.
38. Ruan W, Zhai Y, Yu K, Wu C, Xu Y. Coated microneedles mediated intradermal delivery of octaarginine/BRAF siRNA nanocomplexes for anti-melanoma treatment. Int J Pharm., 2018; 553(1–2): 298–309. DOI: 10.1016/j.ijpharm.2018.10.043, PMID: 30347273.
39. Cole G, Ali AA, McCrudden CM, McBride JW, McCaffrey J, Robson T. DNA vaccination for cervical cancer: Strategic optimisation of RALA mediated gene delivery from a biodegradable microneedle system. Eur J Pharm Biopharm., 2018; 127: 288–97. DOI: 10.1016/j.ejpb.2018.02.029, PMID: 29510205.
40. Chang H, Zheng M, Yu X, Than A, Seeni RZ, Kang R. A Swellable Microneedle Patch to Rapidly Extract Skin Interstitial Fluid for Timely Metabolic Analysis. Adv Mater., 2017; 29(37): 1–8. DOI: 10.1002/adma.201702243, PMID: 28714117.
41. Blicharz TM, Gong P, Bunner BM, Chu LL, Leonard KM, Wakefield JA. Microneedle-based device for the one-step painless collection of capillary blood samples. Nat Biomed Eng., 2018; 2(3): 151–7. DOI: 10.1038/s41551-018-0194-1, PMID: 31015714.
42. Chen L, Zhang C, Xiao J, You J, Zhang W, Liu Y. Local extraction and detection of early stage breast cancers through a microneedle and nano-Ag/MBL film based painless and blood-free strategy. Mater. Sci. Eng. C., 2019; 109: 110402. DOI: https://doi.org/10.1016/j.msec.2019.110402.
43. Ciui B, Martin A, Mishra RK, Brunetti B, Nakagawa T, Dawkins TJ. Wearable Wireless Tyrosinase Bandage and Microneedle Sensors: Toward Melanoma Screening. Adv Healthc Mater., 2018; 7(7): 1701264. DOI: 10.1002/adhm.201701264, PMID: 29345430.
44. Xu J, Xu D, Xuan X, He H. Advances of microneedles in biomedical applications. Molecules, 2021; 26(19): 5912. DOI: 10.3390/molecules26195912, PMID: 34641460.
45. Zhang W, Zhang W, Li C, Zhang J, Qin L, Lai Y. Recent advances of microneedles and their application in disease treatment. Int. J. Mol. Sci., 2022; 23(5): 2401. DOI: 10.3390/ijms23052401, PMID: 35269545.
46. Dugam S, Tade R, Dhole R, Nangare S. Emerging era of microneedle array for pharmaceutical and biomedical applications: recent advances and toxicological perspectives. Future Journal of Pharmaceutical Sciences, 2021; 7: 1-26. DOI: https://doi.org/10.1186/s43094-020-00176-1.
47. Umeyor CE, Shelke V, Pol A, Kolekar P, Jadhav S, Tiwari N, Anure A, Nayak A, Bairagi G, Agale A, Raut V. Biomimetic microneedles: Exploring the recent advances on a microfabricated system for precision delivery of drugs, peptides, and proteins. Future Journal of Pharmaceutical Sciences, 2023; 9(1): 103. DOI: https://doi.org/10.1186/s43094-023-00553-6.
48. Luo X, Yang L, Cui Y. Microneedles: materials, fabrication, and biomedical applications. Biomed. Microdevices, 2023; 25(3): 20. DOI: 10.1007/s10544-023-00658-y, PMID: 37278852.
49. Gill HS, Prausnitz MR. Does needle size matter? J Diabetes Sci Technol., 2007; 1(5): 725–9. DOI: 10.1177/193229680700100517, PMID: 19885141.