

Review

The Prospects of Microneedle Drug Delivery Technology in Cancer Pain and Analgesia Fields

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Abstract

Cancer pain significantly impairs the quality of life of patients, yet conventional analgesic approaches—such as oral, rectal, subcutaneous, and intrathecal administration—are often limited by systemic side effects and poor compliance. Microneedle (MN) technology, an innovative transdermal drug delivery platform, offers a promising alternative by painlessly penetrating the stratum corneum to enable precise, controlled drug release. This review systematically examines recent advances in MN-based analgesic strategies, highlighting its applications across diverse pain conditions, including local anesthesia, rheumatoid arthritis, neuropathic pain, migraines, and post-operative pain. We further explore the translational potential of MNs for cancer pain analgesia, emphasizing their ability to enhance therapeutic efficacy while minimizing adverse effects. Looking forward, the development of smart-responsive MNs and multifunctional combination platforms is poised to advance personalized pain management. With its favorable safety profile and patient-friendly design, MN technology holds substantial promise for overcoming the limitations of traditional cancer pain therapies.

Keywords: Analgesia, cancer pain, drug delivery, microneedle, pain management.

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Introduction

Pain is a complex and diverse perceptual event, a subjective sensation caused by tissue damage or potential injury, characterized by its unpleasant or distressing nature [1]. Recognized as the “fifth vital sign,” pain significantly impairs patients’ quality of life, making its active treatment clinically significant [2]. Based on duration, pain can be classified as acute (e.g., postoperative or traumatic pain) or chronic (e.g., osteoarthritis pain or neuropathic pain) [3,4]. Etiologically, pain can be categorized into inflammatory pain [1] and cancer pain [5]. The mechanisms of pain involve intricate physiological and pathological processes, broadly divided into nociceptive pain (resulting from tissue damage or inflammation, such as arthritis) and neuropathic pain (caused by damage to the peripheral or central nervous system, such as diabetic neuropathy) [6]. Noxious stimuli trigger the release of various pain-inducing substances, such as prostaglandins and bradykinin, which activate spe-

cific receptors on nociceptors, depolarizing them and generating nerve impulses [7,8]. Pain signals are transmitted via afferent nerve fibers to the dorsal horn of the spinal cord, where they are preliminarily integrated before ascending through the spinothalamic tract to the cerebral cortex, forming the perception of pain. In chronic pain states, the nervous system undergoes plastic changes, such as central sensitization, where non-noxious stimuli can also elicit pain. Additionally, pro-inflammatory factors like prostaglandins, TNF- α , and IL-6, released during inflammatory responses, exacerbate local tissue damage and increase nociceptor sensitivity, lowering their threshold and leading to hyperalgesia and allodynia [9,10]. Furthermore, study on axonal retraction compounds in rat models of discogenic low back pain have provided new insights into the mechanisms and treatment of chronic pain [11].

Cancer is one of the most severe threats to human health, constituting a major public health crisis [12]. Cancer

pain, experienced by diagnosed patients due to the tumor itself or its treatment, is one of the most feared symptoms, affecting over half of patients during disease progression [2]. By adversely impacting emotional state, cognitive function, daily activities, and social relationships, cancer pain significantly impairs physical and mental health, reducing overall quality of life [13].

However, managing cancer pain poses significant challenges for clinicians. The World Health Organization (WHO) three-step analgesic ladder is the dominant approach, advocating a stepwise selection of analgesics based on pain severity [14,15]. The first step involves non-opioid analgesics like acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) for mild pain; the second step introduces weak opioids such as codeine; and the third step employs strong opioids like morphine. For moderate to severe cancer pain, opioids are irreplaceable [16]. With pharmacotherapy, over 80% of cancer patients achieve satisfactory pain relief. Adjuvant analgesics, minimally invasive interventions, radiotherapy, chemotherapy, hormone therapy, and non-pharmacological measures (e.g., cognitive, psychosocial, and spiritual interventions) serve as valuable complements [17,18].

Opioids can be administered via oral, sublingual, intramuscular, subcutaneous, transdermal, or rectal routes. Following WHO guidelines, oral and transdermal routes are most common. Oral administration is convenient but suffers from first-pass metabolism, gastrointestinal side effects, and slow absorption. Transdermal drug delivery systems (TDDS), where drugs permeate the skin to achieve local or systemic effects, are widely used due to their safety and efficacy [19,20]. Drugs penetrate through the stratum corneum of the skin to achieve both localized therapeutic effects and systemic therapeutic effects by crossing the epidermis and dermis and entering the bloodstream via the capillaries. However, the stratum corneum constitutes a natural barrier to molecular penetration, limiting the action of many therapeutic agents and making it difficult for them to successfully reach their targets.

Microneedle (MN) technology, a novel transdermal delivery method, enhances drug permeation physically [21]. MNs are neatly aligned arrays of micron-sized needles that penetrate the stratum corneum to create micron-sized channels, allowing the drug to be delivered directly to superficial areas of the epidermis or dermis. Through these channels, the drug can bypass the barrier and enter the body's circulation directly, thus improving delivery efficiency and overcoming various problems associated with conventional formulations [22].

MN patches are non-invasive, convenient, and avoid the first-pass metabolism. MNs also allow for termination at any time, prolong the duration of action, reduce dosing frequency, and improve patient compliance, making them widely used in controlled-release and sustained-release drug research [23]. In recent years, it has been found

that MN technology has demonstrated excellent therapeutic potential in a variety of biomedical fields, such as disease diagnosis and monitoring, vaccine delivery, biosensing, and cell therapy [24,25].

Therefore, this review systematically examines the remarkable efficacy of microneedle technology across multiple applications in pain management, with a particular focus on the unique demands of the complex clinical setting of cancer pain. It aims to critically evaluate the potential and challenges of existing MN designs in achieving sustained-release stability, rapid relief for breakthrough pain, and high-dose opioid delivery, thereby providing new perspectives for developing next-generation precision analgesic solutions for cancer pain.

Current Status of Cancer Pain Treatment

Cancer Pain

Cancer is one of the most serious diseases threatening human health [12]. Cancer pain, which is caused by the tumor itself or by the treatment of the tumor in a patient diagnosed with cancer, is often felt during the course of treatment, and its main symptoms include constant or intermittent episodes of burning, pins and needles, tearing, and knifing pain [26]. A literature review summarizing the prevalence and severity of pain among cancer patients during the period 2014–2021 concluded that the overall prevalence of pain was 44.5%. 30.6% of patients experienced moderate to severe pain [27]. Cancer pain causes profound suffering at both the mental and physical levels, making it one of the most difficult challenges for patients to tolerate and manage, and greatly reducing their quality of life.

The occurrence of pain involves two pathophysiological mechanisms, namely, injury sensory and neuropathic. Cancer pain is often mixed, with both injury-sensing pain [28] and neuropathic pain [26]. Cancer pain is the result of the interaction between cancer cells, the central nervous system, peripheral tissues, and the immune system, and the formation process is complex, involving multiple pathophysiological processes such as sensitization of peripheral injury receptors, central sensitization, acidification of the tumor microenvironment, nerve compression injury, and altered neuroplasticity, etc. [29,30]. The causes of cancer pain are varied and can be categorized into three main groups:

(1) Tumor-related pain

As the growth of malignant tumors is extremely fast and uncontrollable, when the volume of malignant tumors exceeds the range of normal tissues, the tissue envelope can not withstand the load, which results in the stretching of the tissue envelope and triggers severe pain. When the malignant tumor grows beyond the capacity of the normal tissue, the overstretched tissue capsule can trigger severe pain. Tumor cells have a tendency to infiltrate and metastasize to surrounding tissues, including but not limited to soft tissues, skin, bones, nervous system, vascular structures,

and internal organs. At the same time, fast-growing tumors compress or wrap around nerve fibers, which can lead to ischemia and mechanical damage [30]. In addition, perforation or obstruction of cavity organs, as well as abnormal increase of intracranial pressure caused by brain metastasis, are also important causes of pain.

(2) Tumor treatment-related pain

At present, the main cancer treatments include surgical resection, radiotherapy, radiofrequency ablation technology, interventional therapy, molecular targeted therapy, and immunotherapy, etc. Although there are certain therapeutic effects on the lesions, pain may also occur during the process of receiving anti-tumor treatment. For example, after chemotherapy, patients may develop mucositis, venous embolic inflammation, peripheral neuropathy, etc., which may lead to the appearance of pain symptoms. After surgery, it may induce a series of complications, including nerve damage, residual limb pain, and phantom limb pain, which is the phenomenon of adhesion between the organs caused by pain.

(3) Other causes of pain

Pain may also arise from a variety of comorbidities associated with the tumor, as well as the psychosocial aspects of the patient. For example, herpes zoster neuralgia and pressure sores are common in cancer patients, or other disease states that coexist with pain, such as diabetes-induced peripheral neuropathy and primary trigeminal nerve pain. In addition, psychiatric conditions such as fear and anxiety may also trigger or exacerbate pain.

Based on the duration of pain, cancer pain can be categorized into acute pain and chronic pain. In addition, there is a kind of intractable pain called breakthrough cancer pain (BTcP), which has a rapid onset, severe degree, and short duration, and can occur in both acute pain and chronic pain in patients with tumors. Cancer breakthrough pain occurs in approximately 60% of cancer patients [31]. Patients with burst pain suffer significantly more pain-related functional impairment and psychological trauma (depression and anxiety) and have a reduced quality of life compared to patients without burst pain.

The definition of BTcP proposed by the British and Irish Association for Palliative Care (APM) in 2009 is still widely respected and used as a reference. The APM proposes that BTcP is a transient exacerbation of pain that occurs spontaneously or suddenly, triggered by some predictable or unpredictable factor, in the context of relatively stable background pain control and adequate application of analgesic medication. Typical eruptive pain episodes are moderate to severe in intensity, occur rapidly (within minutes), and are of relatively short duration (median duration of 30 minutes) [32].

The diagnostic criteria for cancerous eruptive pain are as follows: (1) whether the patient has experienced persistent pain (i.e., background pain) in the past week; (2) whether the patient's background pain has been effectively

controlled in the past week (digitized pain score ≤ 3); and (3) whether the patient has experienced transient worsening of pain (digitized pain score ≥ 4). Only when all the above three conditions are met can the diagnosis of cancerous eruptive pain be made [33].

BTcP is characterized by a lag in pain relief, the possibility that the pain may have resolved on its own by the time treatment is effective, and an increase in the incidence of adverse effects with increased opioid dosage, making effective control of BTcP a therapeutic challenge.

Cancer Pain Treatment

Pain relief is a basic human right, and the rational use of medications in cancer pain management is particularly important to ensure clinical benefits and improve the quality of life of cancer pain patients. The three-step principle of pharmacotherapy advocated by the WHO has played a key role in guiding the management of cancer pain as a guideline and educational tool for cancer pain management, which has been promoted and applied globally for more than 40 years. This principle has also contributed significantly to the increase in the use of opioid analgesics [14].

The main mode of cancer pain treatment is oral medication according to the three-step principle. Oral medication is still the most important mode of medication because it is convenient to use, easy to obtain, simple to manage, and enables patients to have a high degree of adherence. In addition to the classic three-step approach, a two-step method has emerged as a validated alternative for cancer pain management, simplifying the transition from non-opioids to strong opioids [34]. The use of weak opioids in the second step of the WHO's three-step principle is controversial because low-dose strong opioids may be better, especially in low- and middle-income countries where low-dose opioids are expensive.

More than 80% of patients with cancer pain can be relieved more satisfactorily with medication. In addition, adjuvant analgesics, minimally invasive interventions, radiotherapy, chemotherapy, hormone therapy, radiofrequency ablation, and other therapies may be useful [35]. Non-pharmacological interventions such as cognitive, psychosocial, and spiritual interventions can be a valuable complement to pharmacological interventions [17,18].

The Opioids

Opioid analgesics are the most effective medications for the treatment of acute and chronic pain by acting on the central nervous system to provide significant pain relief or reduction, as well as eliminating pain-induced emotional reactions. Structurally, most opioids are derived from the extraction of alkaloids and their derivatives from the resin of the opium poppy [36]. Natural alkaloids include morphine, the classic opioid, and the semi-synthetic codeine. Synthetic derivatives include fentanyl, heroin, buprenorphine, hydromorphone, and methadone. Opioids act by engaging

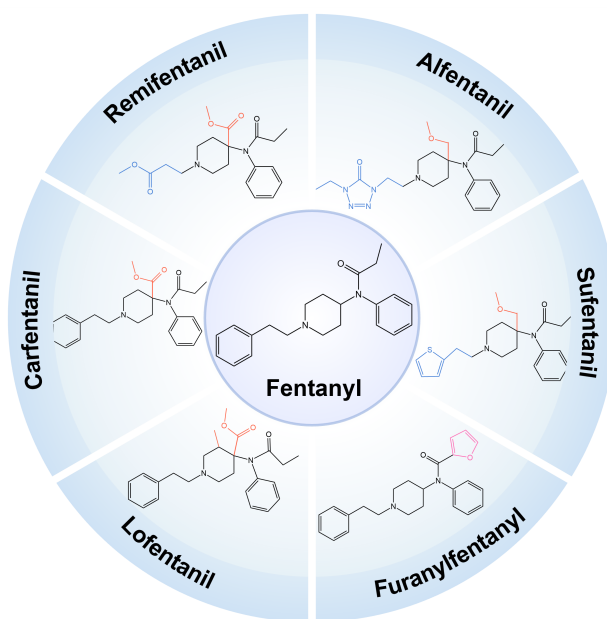


Fig. 1. Chemical structure of fentanyl and some of its analogs. The schematic was created with Microsoft PowerPoint.

specific cell surface receptors: μ , κ , and δ receptors, respectively [37]. These receptors are found primarily in the central nervous system, brain, and spine, but also in blood vessels, heart, lungs, intestines, and even peripheral blood mononuclear cells [38]. Opioids are widely used as analgesics for general anesthesia for surgical procedures, long-term analgesia, and sedation for intensive care patients [39]. Opioids have an irreplaceable role for patients with moderate to high cancer pain [40].

Classic Opioids

Morphine is the classic opioid, a natural product derived from the opium poppy plant. Morphine has a potent analgesic effect, significantly raising the pain threshold, and is accompanied by sedative and respiratory depressant effects. Morphine is widely used clinically for the relief of moderate to severe pain, but should be used with caution due to its addictive properties and potential respiratory depressant side effects [41].

The fentanyl family of drugs is also a common and potent opioid (Fig. 1), and since its development in the early 1960s by Dr. Paul Janssen of Janssen Pharmaceuticals in Belgium, this class of drugs has occupied an important place in clinical anesthesia and pain management [36]. The fentanyl family includes fentanyl, alfentanil, sufentanil, remifentanyl, carfentanyl, lofentanyl, and so on [37,39]. Fentanyl and its derivatives have demonstrated highly potent analgesic activity through structural modification and conformational studies, and have a similar mechanism of action to morphine but with significantly enhanced analgesic potency, often tens to hundreds of times that of morphine. New opioids have also been introduced in recent years, including hydrocodone and hydromorphone [42].

Sufentanil is a potent opioid analgesic [43] and is currently the most potent analgesic of the fentanyl family. Sufentanil has a stronger affinity for opioid receptors than fentanyl, so as a highly selective agonist for μ -opioid receptors, sufentanil has a 7–10 times stronger affinity for μ -opioid receptors than fentanyl, and the analgesic potency is approximately 5–10 times stronger than that of fentanyl, with a longer maintenance time than that of fentanyl. It is also superior to fentanyl in maintaining hemodynamic stability and regulating stress hormone secretion, and can ensure adequate myocardial oxygen supply [39].

In addition, the respiratory depression of sufentanil is less than that of fentanyl, which is less toxic and safer than fentanyl and morphine. With high-fat solubility, it can be rapidly diffused and distributed to all tissues in the body, and it is very easy to cross the cell membrane and the blood-brain barrier, so sufentanil has a higher binding rate to plasma proteins, and the onset of analgesia is rapid [39]. Therefore, sufentanil is a possible focus for better control of cancer eruption pain.

Although fentanyl family drugs have demonstrated significant analgesic effects in clinical applications, their potential adverse effects, such as respiratory depression, nausea and vomiting, and somatic dependence, should not be ignored. Therefore, when using these drugs, it is important to follow strict medical protocols and ensure that they are used under strict medical supervision to avoid possible serious side effects and dependence. Meanwhile, with the advancement of science and technology and the development of medicine, researchers are continuously exploring the structural modification and modification of fentanyl analogs to develop new analgesic drugs that are more efficient and safer, and provide better pain management pro-

grams for patients [44].

Opioid Delivery Modalities

According to the WHO's basic principles of pain medication, the most common routes of administration for opioids are oral and transdermal. In addition, there are many other routes of administration, such as subcutaneous injection, intrathecal injection, intramuscular injection, sublingual injection, rectal injection, etc.

Oral analgesic drugs are easy to use, simple to administer, and effective, but have the disadvantages of first-pass elimination effect and slow absorption [2]. When intravenously injected preparations such as sufentanil, remifentanyl, etc., have the advantages of immediate effect, suitable for unconscious patients and emergencies, avoiding first-pass elimination, and predictable blood concentration. However, intravenous drugs need to be used under the guidance of specialized doctors in clinical practice, and injection is often accompanied by injection pain, which makes it inconvenient for patients to use the drug and leads to poor compliance.

In the transdermal delivery of opioids, the fentanyl extended-release transdermal patch is widely used in the clinic, and its analgesic strength is 50–100 times that of morphine. It is easy to use, non-invasive, absorbed through the skin; not metabolized by the liver, no first elimination; fewer adverse reactions, and good patient compliance, especially for patients who can not be taken orally [45].

Transdermal Drug Delivery System

The TDDS is a drug delivery system in which drugs are administered through the skin and enter the body's circulation to produce systemic or local therapeutic effects, and is widely used in clinical practice because of its safety and effectiveness [19,20]. The drug penetrates through the stratum corneum to achieve a local therapeutic effect, or after crossing the stratum corneum, it further penetrates the epidermis and dermis, and enters the blood circulation through the capillaries to achieve a systemic therapeutic effect. TDDS has the unique advantages of: (1) avoiding the first-pass effect; (2) no needles are required to administer the drugs, which is convenient to administer the drugs; (3) painless or mild pain, which makes the patient's compliance good; (4) reducing the probability of the drug's enzymatic degradation, and maintaining a higher activity; (5) maintaining a stable blood concentration for a long time, which ensures the stability of the drug effect and improves the safety of the drug administration. (6) Reducing the probability of enzymatic degradation of drugs and maintaining high drug activity; (7) Maintaining stable blood concentration for a long time to ensure the stability of drug efficacy and enhance the safety of drug administration [20].

However, the stratum corneum of the skin is the biggest barrier limiting the application of TDDSs. The stratum corneum constitutes a barrier to the passage of

molecules, limiting the efficacy of most therapeutic agents and allowing only a few molecules to reach their targets. Drugs that can be delivered transdermally must meet the following conditions: a relative molecular mass of no more than 500; high activity with pharmacological effects at low doses; fewer than 5 hydrogen-bonded donors and 10 hydrogen-bonded acceptors; and a moderate oil-water partition coefficient. These conditions limit the applicability of this delivery system, as only lipophilic and low molecular weight drugs can be absorbed transdermally, whereas large molecules such as peptides and proteins cannot be delivered transdermally.

The unique physiological structure of the skin is an obstacle to transdermal drug delivery while ensuring human safety. To overcome this challenge, existing physical and chemical permeation enhancers can facilitate the transdermal absorption of drugs by reducing the resistance of the stratum corneum or enhancing the permeability of the skin, depending on the mechanism of permeation enhancement. The chemical approach focuses on the use of chemical permeation enhancers to modulate the physiological characteristics of the skin and to break the lipid tightness, thus increasing the acceptance of the drug by the stratum corneum. Physical means, on the other hand, focus on physically altering the physical morphology and physiological properties of the stratum corneum to enhance transdermal drug delivery. With the development of drug delivery technologies, such as liposomal [46], micelles [47], and emulsions [48], they have also been used for transdermal drug delivery. These new delivery techniques can improve the efficiency of transdermal drug delivery to a certain extent, and improve the therapeutic effect by prolonging the local retention time of the drug, but due to the existence of the natural barrier of the skin, the new drug delivery techniques can not essentially improve the efficiency of transdermal drug delivery. Currently, the commonly used techniques are still adjunctive therapies, such as electroporation, ultrasound, iontophoresis, magnetic field, thermal pore introduction, and laser introduction [19,49].

However, the development of novel TDDS, including MN technology, laser thermal ablation technology, ultrasound technology, and electroporation technology, can break the stratum corneum barrier to improve transdermal efficiency [19]. These technologies are capable of delivering macromolecular drugs by penetrating the stratum corneum at the nanoscale and microscale levels, which not only enhances the drug delivery efficiency of drug action but also expands the range of pharmaceutical and clinical applications of TDDS (Fig. 2).

Microneedle

MN consists of several micron-sized needle-like structures. Typical MN tips are 150–1500 μm in length, 50–250 μm in width, and 1–25 μm in tip thickness [22]. Studies have shown that MN, a novel transdermal drug delivery

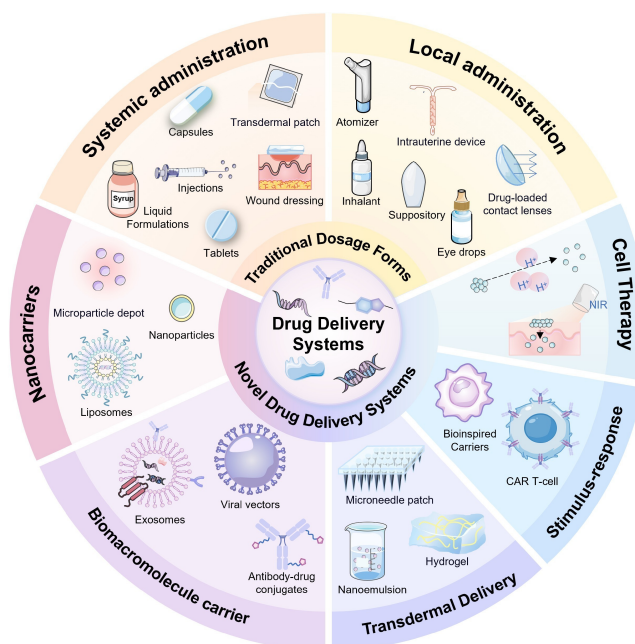


Fig. 2. Drug delivery systems. The schematic was created with Microsoft PowerPoint.

modality, enhances drug delivery and overcomes the problems associated with conventional formulations. The skin consists of the epidermis, dermis, and subcutaneous tissue [50]. The MN creates a micron-sized pathway that directs the drug to the epidermis or upper dermis, smoothly bypassing the stratum corneum (the strongest barrier of the skin) and entering the dermal microcirculation without having to face the barrier. MN is able to avoid activation of dermal nerves, without triggering pain receptors, and is able to efficiently deliver large molecules to the target site with little or no pain, as compared to needles used for hypodermic injections. Compared with subcutaneous needles, it can deliver macromolecular drugs to the target site with minimal pain or near painlessness, showing excellent drug penetration performance. In the process of applying a microneedle, controlling the length of the MN can avoid touching capillaries and nerve endings, reducing or eliminating pain; transdermal drug delivery can allow the drug to be continuously transported to the bloodstream, with stable plasma concentration of the drug, but also avoid the first pass metabolism by the liver, reducing the damaging effect of the drug on the liver and kidneys. MN patch has the advantages of minimally invasive, painless, convenient drug delivery, self-administration, good patient compliance, prolonging the duration of action, reducing the number of times the drug is used, and can be terminated at any time [51]. Therefore, MN not only leads a new trend in the field of cosmetology but also has a broad research, development, and application prospect in the field of biomedical transdermal drug delivery [21].

Types of Microneedles

Depending on the mode of delivery and mechanism of action, common types of MN include: solid MNs, coated MNs [52], hollow MNs, dissolvable MNs and hydrogel MNs [53] (Fig. 3). In recent years, new types of MNs such as cryo-MNs, isolated MNs and shaped MNs have been developed in response to the demand for individualization, which is highly valued in the field of biomedicine [21]. Depending on their structural design and function, MNs can also be categorized as integrated MNs [54], detachable MNs [55], bio-inspired MNs [56], and responsive MNs [57].

Different types of MNs can deliver drugs through different mechanisms (Fig. 4). Dissolving microneedle technology has received increasing attention in recent years [58]. Dissolvable MNs are made of biodegradable polymer materials and drugs prepared into MNs. After piercing the skin, the needles made of biodegradable materials will be gradually degraded in the microenvironment, and the drugs will be released synchronously, and the drug molecules will pass through the barrier of the stratum corneum and be absorbed into the human body through the subcutaneous tissues. In contrast to coated MNs, dissolvable MNs dissolve completely in the skin, thus leaving no biohazardous waste of sharp objects after use. Dissolvable MNs also greatly improve patient compliance by eliminating the need to remove the needles for drug delivery and reducing the risk of cross-contamination by not reusing MNs [59]. The preparation of MNs has evolved from chemical etching and micro-electromechanical systems (MEMS) processing to laser and mold injection molding [60]. The main preparation techniques for polymer dissolvable MNs include casting, hot

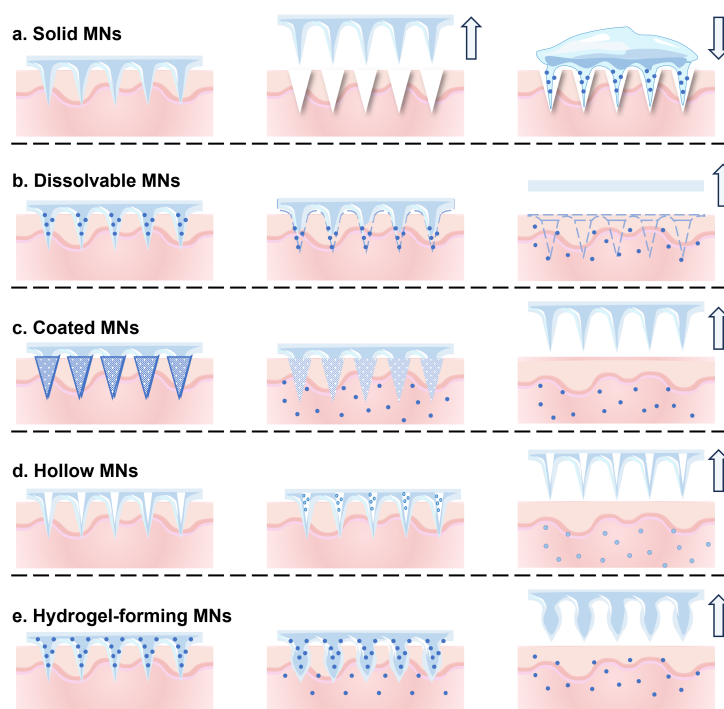


Fig. 3. The schematic illustrations of common microneedle (MN) types for transdermal delivery. (a) Solid; (b) Dissolvable; (c) Coated; (d) Hollow; and (e) Hydrogel-forming MNs. The schematic was created with Microsoft PowerPoint.

pressing, and injection molding, which greatly reduce production costs compared to other MNs.

Injection molding refers to the preparation of a mold, commonly made of monocrystalline silicon, stainless steel, and ceramics, which is then used to prepare the MN from the polymer material. The process involves injecting the polymer material into the mold, which is then vacuumed or centrifuged [61].

For dissolvable MNs, the tip matrix material is the key to development and needs to be able to be degraded or have good water solubility. Commonly used polymeric materials include hyaluronic acid (HA), sodium alginate, polyvinyl alcohol, dextran, chitosan, polyvinylpyrrolidone, chondroitin sulfate, etc., as well as materials for preparing microspheres such as polylactic acid and polylactic acid-hydroxyacetic acid copolymers [21,57,62]. HA was initially found in the vitreous tissues of the eyes of rabbits and cattle. As a key extracellular matrix component, HA is usually found as a sodium salt and is widely distributed in the human body, especially in tissues such as articular cartilage. HA is a common material for the preparation of dissolvable MNs due to its excellent water-absorbing and moisturizing properties, non-immunogenicity, resorbability, and excellent biocompatibility [63,64]. HA, with its exceptional hydrophilicity and biocompatibility, dissolves rapidly to enable immediate drug release, making it suitable for analgesic scenarios requiring a fast onset of action. Synthetic polyester materials like polylactic-polyhydroxyacetic acid copolymers allow precise control of degradation rates through molecular weight and monomer

ratios, enabling sustained drug release over weeks or even months. This provides an ideal solution for chronic pain management requiring long-term, stable dosing. Biocompatibility and degradation safety are paramount for clinical translation. These natural and synthetic polymers typically exhibit favorable tissue compatibility, with degradation products like lactic acid and glycolic acid participating in normal metabolic processes. Furthermore, the hydrophilicity and hydrophobicity of the material, its crystallinity, and its interactions with drug molecules directly determine the MN's drug loading efficiency, storage stability, and ultimate release kinetics [53,59].

Dissolvable MNs can realize efficient drug delivery, precise control of drug loading, and microneedle morphology can realize the controlled release of drugs; the production process conditions are mild, to ensure the stability of the drug in the production process; the use of biodegradable and biocompatible materials, to avoid wound infection, and high safety. The main obstacle to the development of dissolvable MNs is the preparation of materials that can meet the requirements of the material, in addition to being biodegradable and biocompatible, but also must have sufficient mechanical strength, otherwise the microneedle can not be used to puncture the skin for drug delivery. It is believed that with the development of modern material technology, these problems can be properly solved [59].

Research Status

With the development of material science and manufacturing technology, MN transdermal drug delivery tech-

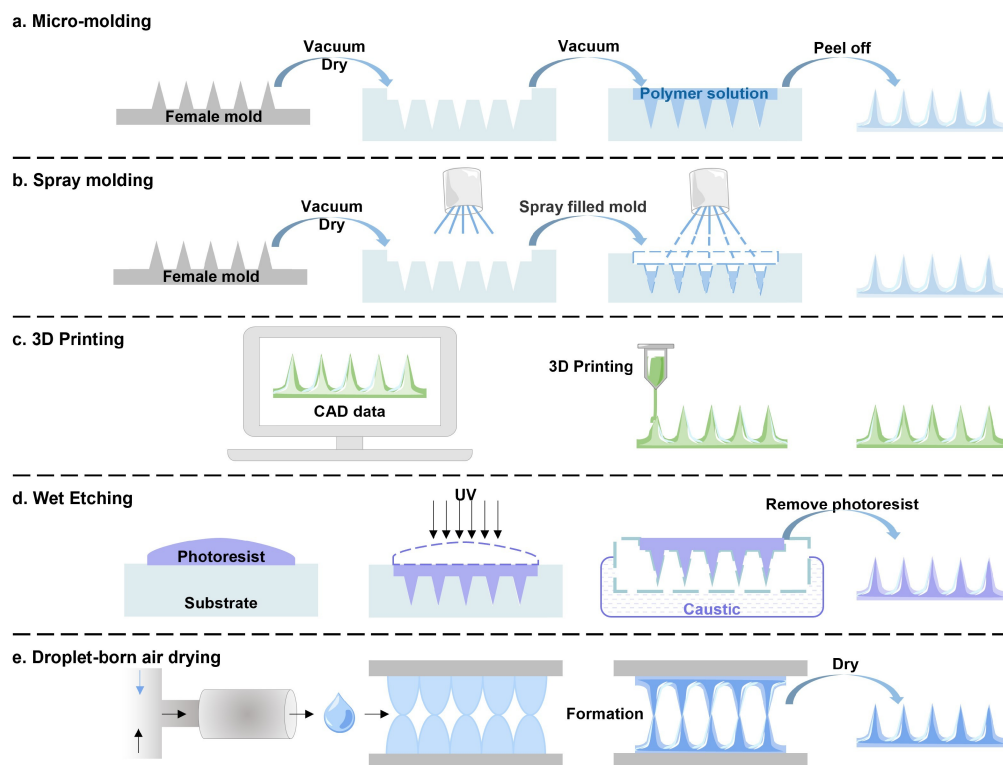


Fig. 4. Schematic illustrations of common microneedle fabrication methods. (a) Micro-molding; (b) Spray molding; (c) 3D Printing; (d) Wet Etching; (e) Droplet-born air drying. The schematic was created with Microsoft PowerPoint.

nology, in addition to drug delivery, can also realize the extraction of body fluids, biosensing, and mediating cellular delivery of cell therapy [65,66].

The application and implementation of MN in multiple fields, such as chronic diseases, such as arthritis or diabetes [67], cancer, skin aesthetics, family planning, prevention of infectious diseases, disease diagnosis and monitoring [24], and vaccine delivery [68], are becoming more and more widespread and have achieved remarkable results [23,25]. It shows the great potential of MN as a form of clinical treatment and has a broad application prospect in various biomedical fields.

MN technology is widely used in wound healing and tissue regeneration. In a variety of tissues such as skin, heart, bone, tendon, eye, blood vessels, mouth, hair, spinal cord, and uterus, it can promote wound healing and tissue regeneration [51,69] as well as exert antimicrobial effects [70]. It has shown favorable therapeutic effects in acne scarring [71], psoriasis [72], and alopecia areata [73].

MNs are a promising vehicle for applications in minimally invasive wearable technology, such as study that have found that deep melanoma treatment can be enhanced by wearable self-energizing MN patches [74]. In addition, MN is capable of extracting interstitial fluid (ISF) after passing through the skin barrier, making it valuable for applications in transdermal sensing and drug delivery [75]. For this reason, minimally invasive skin-worn devices with advanced integration of ISF sampling and target molecule sensing

have also been developed, allowing simultaneous detection of cortisol levels by MN-based sensors, with high sensitivity, excellent efficiency, and outstanding reproducibility [76].

Diverse Applications of MNs in Pain Management

Local Anesthesia and Acute Pain Management

The use of MN patches to deliver macromolecules in anesthesia and analgesia management can improve the efficiency of drug administration. Local anesthetics (LAs) include lidocaine, ropivacaine, and bupivacaine. Local anesthetics provide analgesia by binding to ion channels in the cell membrane and blocking nerve pathways. The anesthesiologist can adjust the dose, concentration, and location of the drug to achieve the desired anesthesia effect during surgery [77].

Using MN technology in delivering LAs can act directly on the skin or submucosal layer to achieve local anesthesia in a painless, minimally invasive, safe, and highly effective manner [78]. Due to the small volume of MNs and the superior water solubility of dissolvable MNs, dissolvable MNs loaded with LAs can take effect in a short period of time, e.g., loaded with local anesthetics such as lidocaine and ropivacaine [79].

Lidocaine, as a commonly used local anesthetic, can achieve rapid onset and long-lasting analgesia through microneedle delivery. Dissolvable MNs of lidocaine hy-

drochloride, prepared using dissolvable microneedle technology, can be used for rapid and efficient local anesthesia and are a possible alternative method of local anesthetic delivery [80], which meets the clinical requirements while overcoming the drawbacks of other traditional lidocaine delivery methods [81]. In different studies, the polymeric materials used in the preparation of lidocaine MN patches, including HA, polyvinyl alcohol, sodium carboxymethylcellulose, and polylactic acid [82], can be used for local anesthesia of the oral mucosa [80], indicating the potential of MNs in local anesthesia [83,84].

Liu *et al.* [85] developed curved MNs patches inspired by mosquito beaks to provide rapid and painless local anesthesia for ophthalmic local anesthesia, overcoming the limitations of traditional local anesthetics delivery methods, thus opening up new possibilities for the treatment of ophthalmic diseases. Multiple clinical trials confirm that microneedle pretreatment significantly enhances surface anesthesia [86]. In addition, the use of percutaneous maltose-based MN patches to enhance surface anesthesia prior to intravenous cannulation in pediatric patients has also demonstrated a good safety and efficacy profile [87].

Chronic Pain and Inflammatory Disease Management

The application of microneedling in chronic pain management covers a wide range of chronic pain disorders such as rheumatoid arthritis, osteoarthritis, psoriatic arthritis, and atopic dermatitis. The use of MN technology to deliver NSAIDs has a wide range of applications. For example, diclofenac nanoparticle-loaded MN patches are effective in relieving arthritis pain through local and systemic delivery [88]. Meloxicam microneedle patches, on the other hand, have been designed for pain management in cattle, demonstrating their potential in veterinary medicine [89].

A composite MN patch loaded with Cucumaria frondosa polysaccharides (CFP) and 3-acetylaconitine (AA) was developed for the treatment of osteoarthritis of the knee. In OA model rats, this MN patch significantly reduced joint swelling and pain behavior scores and improved cartilage tissue morphology damage [90]. Feng *et al.* [91] developed a microneedle patch using poly-L-lysine (PLP) as a matrix and loaded with sinomenine hydrochloride (SH) for the synergistic treatment of rheumatoid arthritis (RA). The transdermal MN delivery system circumvented the oral first-pass effect of SH, enhancing its bioavailability. Additionally, PLP, as a natural polysaccharide matrix, strengthened the MNs' mechanical integrity and sustained-release properties. Pan *et al.* [92] developed a functional hydrogel MN patch for atopic dermatitis (AD) based on a phenylboronic acid-modified hyaluronic acid (HA-PBA) matrix crosslinked with tannic acid/silver nanoparticles (TA/Ag NPs), enabling precise transdermal delivery of cyclosporine. This MN-mediated transdermal delivery achieved superior therapeutic effects in an AD mouse model using only 29% of the oral dose.

Gout is a recurrent metabolic inflammatory disease caused by abnormal purine metabolism in the body, leading to excessive production or decreased excretion of uric acid, which in turn leads to elevated blood levels of uric acid and deposition of urate crystals in synovial membranes, bursae, cartilage, and other tissues of the joints. Rapid separation of dissolvable MNs for slow release of colchicine and stabilization of uricase to simplify long-term gout management Mei and colleagues achieved rapid separation of dissolvable MNs for slow release of colchicine and stabilization of uricase to simplify long-term gout management by co-loading colchicine (Col) and liposomes of uricase (UAO-LPO) in a dissolvable MN system with chitosan as a slow-release material [93].

Liu *et al.* [94] also developed colchicine microneedle arrays and demonstrated excellent analgesic and anti-inflammatory effects in a rat model of acute gout. The results of the study showed that the colchicine microneedle treatment group exhibited a significant analgesic effect within 6 hours after administration, the mechanical pain threshold was increased by about 2.5-fold compared with that of the model group ($p < 0.01$), and the analgesic effect lasted for more than 24 hours. In terms of anti-inflammatory effects, MN-delivered colchicine showed excellent therapeutic effects. These findings provide an important experimental basis for the development of safer and more effective therapeutic regimens for gout and demonstrate the broad application prospects of MN technology in the treatment of inflammatory joint diseases.

In addition, ziconotide can be used in patients with severe chronic pain requiring intrathecal therapy and intolerant or ineffective to other pain treatments such as morphine. A study developed MNs fused with exosomes of ziconotide liposomes, which demonstrated excellent analgesic efficacy, providing a safe and effective delivery modality for the treatment of chronic pain and further expanding the application of MN technology in pain management [95].

Neuropathic Pain

Neuropathic pain is a type of chronic pain caused by injury or lesions of the nervous system, and its pathogenesis involves complex pathological changes in the peripheral and central nervous systems. Studies have shown that neuropathic pain involves multiple complex mechanisms, including peripheral sensitization, central sensitization, and neuroimmune interactions [6,10].

Following nerve injury, peripheral nerve fibers undergo abnormal regeneration and upregulate voltage-gated sodium channels (e.g., Nav1.7) and sensitized transient receptor potential channels (e.g., TRPV1), collectively leading to neuronal hyperexcitability and hyperalgesia [10,96]. At the spinal cord level, nerve injury induces synaptic plasticity changes by enhancing NMDA and AMPA receptor function while weakening GABAergic inhibition, thereby amplifying and sustaining pain signals [10]. Fur-

thermore, activated microglia and astrocytes disrupt neuronal inhibitory balance and maintain neuroinflammation by releasing BDNF and proinflammatory cytokines (e.g., TNF- α , IL-1 β , and IL-6), serving as a key component of central sensitization [9]. Neuroimmune interactions, such as infiltrating Th17 cells, M1 macrophages, and epigenetic modifications, also contribute to the chronicity of neuropathic pain by regulating the expression of pain-related genes, including BDNF and Nav1.7 [97].

Therapeutic strategies for neuropathic pain require multi-targeted interventions. Modulation of ion channel activity (e.g., Nav1.7 inhibitors [98] and TRPV1 antagonists [99]), targeting glial cell activation (e.g., inhibition of microglia by minocycline [100]), modulation of immune responses (e.g., anti-TNF- α antibodies [101]), and intervention in epigenetic modifications (e.g., HDAC inhibitors [102]) are all potential therapeutic directions. Future studies should further explore the interactions of these mechanisms to develop more effective combination therapeutic regimens and provide more precise clinical interventions for neuropathic pain patients [103].

Calcitonin gene-related peptide (CGRP) released from sensory nerve endings plays an important role in chronic neuropathic pain. A research team has designed and developed an analgesic MN patch, which utilizes dissolvable MN technology to achieve painless transdermal delivery of selective CGRP antagonist peptides, opening up new avenues for the treatment of localized neuropathic pain [104].

As mentioned earlier, sensitization of transient receptor potential channels (e.g., TRPV1 [99] and TRPA1 [105]) can exacerbate nociceptive sensitization. Han *et al.* [106] found that MNs containing buprenorphine or 3-acetylphephedrine exerted sustained analgesic effects against neuropathic pain by blocking pain signaling pathways such as TRPV1. This experience is directly relevant to cancer pain, as advanced cancer pain often contains a significant neuropathic component, suggesting that similar MN-targeted delivery strategies could be adapted for managing refractory cancerous neuropathic pain.

Innovative Treatments for Other Pain Types

Postoperative pain is a protective response after tissue injury, which can promote wound healing but also brings adverse effects requiring close attention. For example, postoperative pain can cause adverse cardiovascular effects in the short term, including increased heart rate, increased blood pressure, and may even cause myocardial infarction, etc.; cause respiratory function to be weakened, which may lead to postoperative pulmonary complications; and also reduce gastrointestinal peristalsis, which is not conducive to the recovery of intestinal function. Therefore, postoperative analgesia can not only reduce the patient's pain but also be more favorable to the patient's recovery [107]. A study used a unique pH-responsive core-shell MN design to load ropivacaine, and successfully validated the long-

lasting analgesic effect and safety of this pH-responsive self-monitoring MN in an animal model of postoperative incisional pain [108].

Chemotherapy-induced neuropathic pain (CINP) is a common adverse effect of antineoplastic agents, which usually leads to dose reduction, treatment delay, or discontinuation of chemotherapy. Paclitaxel-induced peripheral neuropathy (PIPN) is a common dose-limiting adverse effect of oncologic chemotherapy, and its pathogenesis involves multiple pathophysiological processes. Studies have shown that paclitaxel causes microtubule structural disorders in sensory neurons of the dorsal root ganglion (DRG) by interfering with microtubule dynamics, triggering axonal transport disorders, and mitochondrial dysfunction. At the molecular level, paclitaxel activates injury receptor channels such as TRPV1 and TRPA1, increasing neuronal excitability, while promoting the release of proinflammatory cytokines (e.g., TNF- α , IL-6) and inducing neuroinflammatory responses [109]. In animal models, paclitaxel treatment leads to mechanical nociceptive hypersensitivity and thermal nociceptive hypersensitivity accompanied by decreased nerve fiber density and demyelination changes [109,110].

From a therapeutic point of view, current intervention strategies for PIPN mainly include pharmacological modulation and neuroprotection. Studies have shown that modulation of ion channel activity (e.g., Nav1.7/1.8 inhibitors [98]), inhibition of neuroinflammation [111], and the use of neurotrophic factors (e.g., NGF [112], BDNF [113]) can alleviate the symptoms of PIPN to varying degrees. Notably, novel drug delivery systems such as slow-release microneedle arrays may improve drug targeting and reduce systemic side effects. In addition, non-pharmacological therapies such as photobiomodulation therapy have also demonstrated some neuroprotective effects. Future studies should focus on elucidating the precise molecular mechanisms of paclitaxel neurotoxicity and developing multi-targeted combination therapies to better combat this clinical challenge [98].

In response to paclitaxel-induced peripheral neuropathy, a bilayer MN patch containing HA-PBA-QCT developed by Kong *et al.* [114] could significantly reduce pain through synergistic effects. Quercetin (QCT), known for its anti-inflammatory, antioxidant, and neuroprotective properties, has been investigated for the treatment of various neurological disorders. The study combined phenylboronic acid-modified hyaluronic acid (HA-pba) gels with doped QCT and prepared bilayered MN patches in needles using HA-PBA-QCT complexes and HA/polyvinyl alcohol (PVA) as a substrate. The cross-linking between PVA and HA-PBA-QCT allows for the control of the sustained release of QCT upon application. This work applied these QCT-loaded microneedle (QMN) patches to the dorsal skin of the feet of ptx-treated mice, which exhibited mechanically abnormal pain and cold nociceptive hypersensitivity.

Application of the QMN patch every two weeks significantly reduced the pain response. This analgesic effect was associated with modulation of satellite glial cell activity, reduction of macrophage infiltration, and reduction of TNF- α and IL-6 levels in dorsal root ganglia (DRGs). In addition, the treatment increased cellular antioxidant capacity through upregulation of Nrf2 and catalase in DRGs. Overall, these findings suggest that the bilayer QMN patch has long-term anti-inflammatory and antioxidant effects and reduces chemotherapy-induced neuropathic pain in patients. This strategy holds dual significance for cancer pain management: it can directly alleviate treatment-related pain, thereby improving patient tolerance to anticancer therapy, and its mechanism of targeting neuroinflammation and oxidative stress also offers a novel approach for treating cancerous neuropathic pain caused by tumor invasion or compression.

In addition, MN technology has demonstrated unique benefits in migraine pain. The zolmitriptan intradermal MN system (QtryptaTM) provides highly effective treatment for acute migraine headaches through rapid drug delivery [115]. Photochemical 3D printing technology has further advanced the development of programmable MNs, such as dexamethasone MN arrays for on-demand drug release [116].

New Perspectives on Microneedle for Cancer Pain Relief

Cancer pain seriously affects the quality of life of cancer patients, and there is still a need for continuous exploration and research on better pain management methods. The principle of three-step drug therapy proposed by WHO is the current mainstream therapy, in which opioids have an important role in effectively relieving the symptoms of moderate-to-severe cancer pain. MN patch is a new type of TDDS, which is minimally invasive, painless, and can pass through the barrier of skin stratum corneum to avoid the first pass elimination, solving the technical problem of low efficiency of drug transdermal in the traditional way of drug delivery. Its convenient way of drug delivery, no needles to give drugs, no pain, improves patient compliance characteristics, and can avoid the intramuscular injection or intravenous injection of needle operation to the patient's adverse psychological effects.

Currently, MN technology has been widely used in a variety of pain management applications, and studies have shown that the analgesic mechanism of drug delivery has significant commonalities with the pathways of cancer pain onset and inhibition [99,104,114]. Recently, MNs have also found applications in cancer treatment. Zhang *et al.* [117] designed a MN patch based on an oxygen vacancy-rich CoSn(OH)6/FeS₂ heterostructure. This system can responsively release H₂S gas in the tumor microenvironment to promote apoptosis, while simultaneously driving ferroptosis via the Fenton reaction, thereby achieving a synergistic

therapy pathway combining both apoptosis and ferroptosis. This work provides a novel strategy for overcoming tumor drug resistance and achieving precise, efficient, and localized combination therapy. Although MN technology in the field of oncology is currently focused on the delivery of anticancer drugs, its potential application in the analgesia of cancer pain is also worthy of expectation.

Translating MN technology into effective cancer pain management solutions requires a systematic evaluation of the delivery efficacy of different analgesic drugs. Although direct pharmacokinetic studies of MNs in cancer pain models remain limited, recent research on key opioids has yielded valuable data. For instance, fentanyl studies have advanced beyond mere delivery to integrated sensing applications; polymer-based microneedle sensing platforms have achieved highly sensitive detection of fentanyl in biological fluids, indirectly confirming the excellent compatibility and stability of this technology platform when combined with fentanyl [118]. More importantly, as an extremely potent opioid, sufentanil polymer-soluble MNs have demonstrated precise analgesic effects in mouse models. This study provides direct potency and safety references for developing MN formulations of such highly active drugs [119]. In contrast, for hydrophilic local anesthetics (such as ropivacaine), pH-responsive hydrogel MNs achieved on-demand sustained release (>72 hours) in inflammatory environments through smart materials, demonstrating high local delivery efficiency [108]. For easily degraded peptide drugs such as Ziconotide (ZIC), encapsulation within lipid or exosome-based nanocarriers followed by loading onto MNs serves as a key strategy to preserve activity and significantly enhance transdermal permeation efficiency [95]. These examples demonstrate that a drug's molecular properties—size, polarity, and stability—fundamentally dictate the design philosophy for microneedle formulations: from stable loading and controlled release of small-molecule opioids to nanoscale encapsulation and enhanced delivery of large-molecule biologics.

However, for morphine—the more commonly used clinical agent—systematic evaluation of its high drug loading capacity, long-term stability, and release kinetics within soluble MNs remains a critical gap that future research must address. Building upon existing work, future studies should further quantify and compare the encapsulation efficiency, in vitro release kinetics, and in vivo transdermal delivery efficiency of conventional cancer pain medications within optimized MN systems to accelerate their clinical translation.

Despite the promising prospects of MN technology in cancer pain management, its clinical translation faces multidimensional challenges. Firstly, achieving scalable production requires resolving issues such as material consistency, needle body structural precision, and uniform drug loading to ensure batch-to-batch quality control. As an invasive medical device, sterilization processes must guar-

antee sterility and safety without compromising microneedle structure, drug potency, or biocompatibility. This necessitates developing specialized solutions tailored to microneedle characteristics [120]. Moreover, significant individual variations in patient skin conditions—influenced by age, treatment toxicity, or malnutrition—manifest in differences such as stratum corneum thickness, hydration levels, and pathological alterations. These variations may compromise the consistency of transdermal penetration and the predictability of analgesic efficacy [121,122]. Additionally, long-term safety data for repeated use remain unavailable for chronic cancer pain requiring extended management. Finally, achieving safe and effective patient self-administration relies not only on intuitive and user-friendly patch design but also requires comprehensive patient education, clear instructions, and potential remote monitoring support to ensure treatment adherence and safety.

The future development direction can be centered on three core areas. First, the development of smart responsive MNs (such as light- or pH-responsive types). These MNs transform drug delivery from passive release to active regulation, providing a precise tool to address the complex dynamic demands of managing cancer pain, where background pain and breakthrough pain intertwine. For instance, Yu *et al.* [123] developed a near-infrared-responsive MN patch loaded with asymmetric Fe-N-S-C nanoenzymes and a radical initiator. This system induces ferroptosis through dual-enzyme-catalyzed (mimicking peroxidase/glutathione oxidase activity) to induce ferroptosis. Laser activation synergistically generates photothermal and radical-mediated killing effects, demonstrating significant antitumor and anti-metastatic efficacy both *in vivo* and *in vitro*. Near-infrared light-responsive MNs can be triggered by a portable light source applied by the patient at the specific skin site during an episode of breakthrough pain, enabling rapid, on-demand drug release within minutes [106]. This offers a revolutionary tool for the immediate, patient-controlled management of breakthrough pain. On the other hand, pH-responsive MNs can sense the characteristically acidic microenvironment of tumor tissues or inflammatory sites and intelligently accelerate drug release under these conditions [108]. This characteristic enables the drug to accumulate more extensively at the site of pain, achieving targeted sustained analgesia for cancerous lesions while minimizing systemic exposure and side effects. Furthermore, Hu *et al.* [124] developed a bismuth-based dissolvable MN platform integrating Bi/Bi₂SiO₅@SiO₂-x nanocomposites with gaseous prodrugs. This system not only enables CT imaging guidance but also achieves controlled release of NO and H₂ in response to multiple stimuli (pH, NIR light, and ultrasound), thereby synergistically enhancing photothermal, photodynamic, sonodynamic, and gas therapies.

Second, the construction of multifunctional platforms, the integration of the analgesic-antitumor drug delivery

(e.g., MN patches of chemotherapeutic agents combined with analgesic drugs [125]), or the integration of biosensors for real-time monitoring of pain markers and the dynamic modulation of drug delivery. The potential of MNs as a multifunctional platform has been preliminarily validated across diverse applications. In tissue engineering, MN-mediated cell implantation technology combined with decellularized scaffolds has successfully been used to construct bionic skin models and promote chronic wound healing [126]. This demonstrates MNs' capability to precisely deliver bioactive components (such as cells) while synergizing with biomaterial microenvironments. It provides crucial proof-of-concept and technical insights for developing multifunctional cancer pain management strategies integrating analgesia, tissue repair, and even immunomodulation. Another exemplary work is the smart MN system developed by Hu *et al.*, which innovatively integrates tumor CT imaging, starvation therapy (via glucose oxidase), and gas therapy (releasing H₂S) into a single platform, synergistically enhancing photothermal/sonodynamic therapy [127]. This integrated “diagnosis-multimodal therapy” design provides an inspiring technical blueprint and proof-of-concept for future development of integrated MN platforms capable of both anticancer and potential analgesic functions.

Third, promoting personalized medicine by customizing MN formulations based on patients' genotypic or phenotypic characteristics (e.g., CYP450 enzyme polymorphisms [128]). With its unique advantages of high efficiency, safety, and customizability, MN technology is expected to break through the bottleneck of traditional cancer pain management, and interdisciplinary synergistic innovation of material science, pharmacy, and clinical medicine will be the key to realizing the transformation of the intelligent MN system and promoting precise analgesia. In the future, safer and simpler cancer pain management may be realized through MN technology, which opens up a new way of thinking about cancer pain treatment and is expected to bring benefits to cancer patients.

Conclusions

This review systematically summarizes the innovative prospects of MN technology in cancer pain management. Its core innovation lies in creatively applying this physical penetration technique to the complex clinical scenario of cancer pain, offering a new paradigm to overcome the limitations of traditional drug delivery methods. By overcoming skin barriers to achieve painless, efficient drug delivery, MN systems demonstrate clear advantages in enhancing the local delivery efficiency of analgesics like opioids, enabling on-demand drug release to manage breakthrough pain, and improving patient compliance. Future development of smart, responsive MNs targeting the acidic microenvironment or abnormal biomarkers associated with cancer pain, alongside the creation of composite platforms

combining analgesic and antitumor functions, will be key directions for advancing this technology's clinical translation. MN technology holds promise for breakthroughs in achieving more precise, personalized, and patient-friendly cancer pain management.

List of Abbreviations

APM, Association for Palliative Medicine; BDNF, Brain-Derived Neurotrophic Factor; BTcP, Breakthrough Cancer Pain; CFP, *Cucumaria frondosa* Polysaccharides; CGRP, Calcitonin Gene-Related Peptide; CINP, Chemotherapy-Induced Neuropathic Pain; Col, Colchicine; DRG, Dorsal Root Ganglion; HA, Hyaluronic Acid; HDAC, Histone Deacetylase; ISF, Interstitial Fluid; LA, Local Anesthetic; MEMS, Microelectromechanical Systems; MN, Microneedle; NGF, Nerve Growth Factor; NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; OA, Osteoarthritis; PIPN, Paclitaxel-Induced Peripheral Neuropathy; PLP, Poly-L-lysine; PVA, Polyvinyl Alcohol; QCT, Quercetin; RA, Rheumatoid Arthritis; SH, Sinomenine Hydrochloride; TDDS, Transdermal Drug Delivery System; TRPV1, Transient Receptor Potential Vanilloid 1; WHO, World Health Organization.

Availability of Data and Materials

Not applicable.

Author Contributions

AYZ and YYG contributed equally to the conception and design of the work and drafted the manuscript. YTR and GBF contributed to the acquisition of data (literature search in the field of analgesia). AZ contributed to the creation of graphical materials (figures). XZ contributed to the acquisition of data (literature search in the field of microneedles). RX revised the work critically for important intellectual content. LCH and SHQ contributed equally to the supervision and critical guidance of the work's direction.

All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet* (London, England). 2021; 397: 2082–2097. [https://doi.org/10.1016/S0140-6736\(21\)00393-7](https://doi.org/10.1016/S0140-6736(21)00393-7).
- [2] Pozza DH, Azevedo LF, Castro Lopes JM. Pain as the fifth vital sign-A comparison between public and private healthcare systems. *PLoS One*. 2021; 16: e0259535. <https://doi.org/10.1371/journal.pone.0259535>.
- [3] Fernandez Rojas R, Brown N, Waddington G, Goecke R. A systematic review of neurophysiological sensing for the assessment of acute pain. *NPJ digital medicine*. 2023; 6: 76. <https://doi.org/10.1038/s41746-023-00810-1>.
- [4] Vase L, Wager TD, Eccleston C. Opportunities for chronic pain self-management: core psychological principles and neurobiological underpinnings. *Lancet* (London, England). 2025; 405: 1781–1790. [https://doi.org/10.1016/S0140-6736\(25\)00404-0](https://doi.org/10.1016/S0140-6736(25)00404-0).
- [5] Bhatt K, Palomares AC, Forget P, Ryan D, Societal Impact of Pain (SIP) platform. Importance of pain management in cancer patients and survivors. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2024; 35: 473–474. <https://doi.org/10.1016/j.annonc.2024.01.006>.
- [6] Petroianu GA, Aloum L, Adem A. Neuropathic pain: Mechanisms and therapeutic strategies. *Frontiers in cell and developmental biology*. 2023; 11: 1072629. <https://doi.org/10.3389/fcell.2023.1072629>.
- [7] Yin YL, Ye C, Zhou F, Wang J, Yang D, Yin W, *et al.* Molecular basis for kinin selectivity and activation of the human bradykinin receptors. *Nature structural & molecular biology*. 2021; 28: 755–761. <https://doi.org/10.1038/s41594-021-00645-y>.
- [8] Ghitani N, von Buchholtz LJ, MacDonald DI, Falgairolle M, Nguyen MQ, Licholai JA, *et al.* A distributed coding logic for thermosensation and inflammatory pain. *Nature*. 2025; 642: 1016–1023. <https://doi.org/10.1038/s41586-025-08875-6>.
- [9] Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. *Nature neuroscience*. 2007; 10: 1361–1368. <https://doi.org/10.1038/nn1992>.
- [10] Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: From Mechanisms to Treatment. *Physiological reviews*. 2021; 101: 259–301. <https://doi.org/10.1152/physrev.00045.2019>.
- [11] Lee F, Caparaso SMC, Cruz CJ, Barnett EC, Allen KD, Wachs RA. Investigation of the safety and therapeutic efficacy of axonal dieback compounds in a rat model of disc-associated low back pain. *European Cells & Materials*. 2025; 51: 1–30. <https://doi.org/10.22203/eCM.v051a01>.
- [12] Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA: a cancer journal for clinicians*. 2024; 74: 203. <https://doi.org/10.3322/caac.21820>.
- [13] Jeong Y, Im Y, Lee H, Park Y. Cancer pain experiences in adult patients with cancer: A qualitative meta-ethnography. *European journal of oncology nursing: the official journal of European Oncology Nursing Society*. 2025; 78: 102978. <https://doi.org/10.1016/j.ejon.2025.102978>.
- [14] Twycross R, Lickiss N. Pain control and the World Health Organization analgesic ladder. *JAMA*. 1996; 275: 835. <https://doi.org/10.1001/jama.1996.03530350017013>.
- [15] Azevedo São Leão Ferreira K, Kimura M, Jacobsen Teixeira M.

The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. 2006; 14: 1086–1093. <https://doi.org/10.1007/s00520-006-0086-x>.

- [16] Paice JA, Bohlke K, Barton D, Craig DS, El-Jawahri A, Hershman DL, *et al.* Use of Opioids for Adults With Pain From Cancer or Cancer Treatment: ASCO Guideline. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2023; 41: 914–930. <https://doi.org/10.1200/JCO.22.02198>.
- [17] Mestdagh F, Steyaert A, Lavand'homme P. Cancer Pain Management: A Narrative Review of Current Concepts, Strategies, and Techniques. *Current oncology (Toronto, Ont.)*. 2023; 30: 6838–6858. <https://doi.org/10.3390/curroncol30070500>.
- [18] Bell BK, Cha J, Cavanaugh KA, O'Riordan DL, Rabow MW, Yang AK, *et al.* Integrative Management of Cancer Pain: A Scoping Review of the Literature. *Cancer medicine*. 2025; 14: e70833. <https://doi.org/10.1002/cam4.70833>.
- [19] Phatale V, Vaiphei KK, Jha S, Patil D, Agrawal M, Alexander A. Overcoming skin barriers through advanced transdermal drug delivery approaches. *Journal of controlled release: official journal of the Controlled Release Society*. 2022; 351: 361–380. <https://doi.org/10.1016/j.jconrel.2022.09.025>.
- [20] Sabbagh F, Kim BS. Recent advances in polymeric transdermal drug delivery systems. *Journal of controlled release: official journal of the Controlled Release Society*. 2022; 341: 132–146. <https://doi.org/10.1016/j.jconrel.2021.11.025>.
- [21] Ruan S, Zhang Y, Feng N. Microneedle-mediated transdermal nanodelivery systems: a review. *Biomaterials science*. 2021; 9: 8065–8089. <https://doi.org/10.1039/d1bm01249e>.
- [22] Zhang J, Li H, Albakr L, Zhang Y, Lu A, Chen W, *et al.* Microneedle-enabled therapeutics delivery and biosensing in clinical trials. *Journal of controlled release: official journal of the Controlled Release Society*. 2023; 360: 687–704. <https://doi.org/10.1016/j.jconrel.2023.07.023>.
- [23] Yang D, Chen M, Sun Y, Jin Y, Lu C, Pan X, *et al.* Microneedle-mediated transdermal drug delivery for treating diverse skin diseases. *Acta biomaterialia*. 2021; 121: 119–133. <https://doi.org/10.1016/j.actbio.2020.12.004>.
- [24] Hu Y, Chatzilakou E, Pan Z, Traverso G, Yetisen AK. Microneedle Sensors for Point-of-Care Diagnostics. *Advanced science (Weinheim, Baden-Württemberg, Germany)*. 2024; 11: e2306560. <https://doi.org/10.1002/adv.202306560>.
- [25] Zhang W, Zhang W, Li C, Zhang J, Qin L, Lai Y. Recent Advances of Microneedles and Their Application in Disease Treatment. *International journal of molecular sciences*. 2022; 23: 2401. <https://doi.org/10.3390/ijms23052401>.
- [26] Shkodra M, Brunelli C, Zecca E, Formaglio F, Bracchi P, Lo Dico S, *et al.* Neuropathic pain: clinical classification and assessment in patients with pain due to cancer. *Pain*. 2021; 162: 866–874. <https://doi.org/10.1097/j.pain.0000000000002076>.
- [27] Snijders RAH, Brom L, Theunissen M, van den Beuken-van Everdingen MHJ. Update on Prevalence of Pain in Patients with Cancer 2022: A Systematic Literature Review and Meta-Analysis. *Cancers (Basel)*. 2023; 15: 591. <https://doi.org/10.3390/cancer15030591>.
- [28] Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annual review of neuroscience*. 2009; 32: 1–32. <https://doi.org/10.1146/annurev.neuro.051508.135531>.
- [29] Mantyh PW, Clohisy DR, Koltzenburg M, Hunt SP. Molecular mechanisms of cancer pain. *Nature reviews. Cancer*. 2002; 2: 201–209. <https://doi.org/10.1038/nrc747>.
- [30] Zheng XQ, Wu YH, Huang JF, Wu AM. Neurophysiological mechanisms of cancer-induced bone pain. *Journal of advanced research*. 2021; 35: 117–127. <https://doi.org/10.1016/j.jare.2021.06.006>.
- [31] Mercadante S. Breakthrough cancer pain in the radiotherapy setting: a systematic and critical review. *Expert review of anticancer therapy*. 2023; 23: 229–234. <https://doi.org/10.1080/14737140.2023.2182773>.
- [32] Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G, Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain*. 2009; 13: 331–338. <https://doi.org/10.1016/j.ejpa.2008.06.014>.
- [33] Mercadante S, Portenoy RK. Understanding the Chameleonic Breakthrough Cancer Pain. *Drugs*. 2021; 81: 411–418. <https://doi.org/10.1007/s40265-021-01466-5>.
- [34] Fallon M, Dierberger K, Leng M, Hall PS, Allende S, Sabar R, *et al.* An international, open-label, randomised trial comparing a two-step approach versus the standard three-step approach of the WHO analgesic ladder in patients with cancer. *Ann Oncol*. 2022; 33: 1296–1303. <https://doi.org/10.1016/j.annonc.2022.08.083>.
- [35] Mercadante S, Schiavella A. Radiofrequency ablation for cancer pain with inadequate opioid response. *BMJ Support Palliat Care*. 2024. <https://doi.org/10.1136/spcare-2024-004795>.
- [36] Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clinical pharmacokinetics*. 1983; 8: 422–446. <https://doi.org/10.2165/00003088-198308050-00004>.
- [37] Zhuang Y, Wang Y, He B, He X, Zhou XE, Guo S, *et al.* Molecular recognition of morphine and fentanyl by the human mu-opioid receptor. *Cell*. 2022; 185: 4361–4375. e19. <https://doi.org/10.1016/j.cell.2022.09.041>.
- [38] Che T, Roth BL. Molecular basis of opioid receptor signaling. *Cell*. 2023; 186: 5203–5219. <https://doi.org/10.1016/j.cell.2023.10.029>.
- [39] Scholz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. *Clinical pharmacokinetics*. 1996; 31: 275–292. <https://doi.org/10.2165/00003088-199631040-00004>.
- [40] Chapman EJ, Edwards Z, Boland JW, Maddocks M, Fettes L, Malia C, *et al.* Practice review: Evidence-based and effective management of pain in patients with advanced cancer. *Palliative medicine*. 2020; 34: 444–453. <https://doi.org/10.1177/0269216319896955>.
- [41] Clark D, Graham F. Morphine, cocaine, and 19th century cancer care. *The Lancet. Oncology*. 2008; 9: 1018. [https://doi.org/10.1016/S1470-2045\(08\)70258-4](https://doi.org/10.1016/S1470-2045(08)70258-4).
- [42] Barrett JE, Shekarabi A, Inan S. Oxycodone: A Current Perspective on Its Pharmacology, Abuse, and Pharmacotherapeutic Developments. *Pharmacological reviews*. 2023; 75: 1062–1118. <https://doi.org/10.1124/pharmrev.121.000506>.
- [43] Koushik SS, Schwartz RH, Cherkalin D, Sankar V, Shaparin N, Viswanath O. A Review of Sublingual Sufentanil Tablet (SST) and its Utility as an Analgesic Agent for Pain Procedures. *Current pain and headache reports*. 2022; 26: 145–149. <https://doi.org/10.1007/s11916-022-01014-0>.
- [44] Macintyre PE, Quinlan J, Levy N, Lobo DN. Current Issues in the Use of Opioids for the Management of Postoperative Pain: A Review. *JAMA surgery*. 2022; 157: 158–166. <https://doi.org/10.1001/jamasurg.2021.6210>.
- [45] Fu Q, Han N, Li N, Gui L, Shi C, Rong P, *et al.* Guidelines for Rational Clinical Use of Fentanyl Transdermal Patch. *Drug design, development and therapy*. 2024; 18: 233–255. <https://doi.org/10.2147/DDDT.S414318>.
- [46] Tang S, Davoudi Z, Wang G, Xu Z, Rehman T, Prominski A, *et al.* Soft materials as biological and artificial membranes. *Chemical Society reviews*. 2021; 50: 12679–12701. <https://doi.org/10.1039/d1cs00029b>.
- [47] Kahana A, Lancet D. Self-reproducing catalytic micelles as nanoscopic protocell precursors. *Nature reviews. Chemistry*. 2021; 5: 870–878. <https://doi.org/10.1038/s41570-021-00329-7>.

- [48] Heaton AR, Lechuga LM, Tangsangaksri M, Ludwig KD, Fain SB, Mecozzi S. A stable, highly concentrated fluoros nanoemulsion formulation for in vivo cancer imaging via (19)F-MRI. *NMR in biomedicine*. 2024; 37: e5100. <https://doi.org/10.1002/nbm.5100>.
- [49] Gao Y, Du L, Li Q, Li Q, Zhu L, Yang M, *et al.* How physical techniques improve the transdermal permeation of therapeutics: A review. *Medicine (Baltimore)*. 2022; 101: e29314. <https://doi.org/10.1097/MD.0000000000029314>.
- [50] Qi L, Zhang C, Wang B, Yin J, Yan S. Progress in Hydrogels for Skin Wound Repair. *Macromolecular bioscience*. 2022; 22: e2100475. <https://doi.org/10.1002/mabi.202100475>.
- [51] Lyu S, Dong Z, Xu X, Bei HP, Yuen HY, James Cheung CW, *et al.* Going below and beyond the surface: Microneedle structure, materials, drugs, fabrication, and applications for wound healing and tissue regeneration. *Bioactive materials*. 2023; 27: 303–326. <https://doi.org/10.1016/j.bioactmat.2023.04.003>.
- [52] Ingrole RSJ, Gill HS. Microneedle Coating Methods: A Review with a Perspective. *The Journal of pharmacology and experimental therapeutics*. 2019; 370: 555–569. <https://doi.org/10.1124/jpet.119.258707>.
- [53] Zhang L, Guo R, Wang S, Yang X, Ling G, Zhang P. Fabrication, evaluation and applications of dissolving microneedles. *International journal of pharmaceutics*. 2021; 604: 120749. <https://doi.org/10.1016/j.ijpharm.2021.120749>.
- [54] Yuan A, Xia F, Bian Q, Wu H, Gu Y, Wang T, *et al.* Ceria Nanozyme-Integrated Microneedles Reshape the Perifollicular Microenvironment for Androgenetic Alopecia Treatment. *ACS Nano*. 2021; 15: 13759–13769. <https://doi.org/10.1021/acsnano.1c05272>.
- [55] Hu S, Zhu D, Li Z, Cheng K. Detachable Microneedle Patches Deliver Mesenchymal Stromal Cell Factor-Loaded Nanoparticles for Cardiac Repair. *ACS Nano*. 2022; 16: 15935–15945. <https://doi.org/10.1021/acsnano.2c03060>.
- [56] Jeon EY, Lee J, Kim BJ, Joo KI, Kim KH, Lim G, *et al.* Bio-inspired swellable hydrogel-forming double-layered adhesive microneedle protein patch for regenerative internal/external surgical closure. *Biomaterials*. 2019; 222: 119439. <https://doi.org/10.1016/j.biomaterials.2019.119439>.
- [57] Ma Y, Wang W, He M, Liu Y, Li C, Zhong Y, *et al.* PVA-based bulk microneedles capable of high insulin loading and pH-triggered degradation for multi-responsive and sustained hypoglycemic therapy. *Biomaterials science*. 2024; 12: 507–517. <https://doi.org/10.1039/d3bm01760e>.
- [58] Lee BM, Lee C, Lahiji SF, Jung UW, Chung G, Jung H. Dissolving Microneedles for Rapid and Painless Local Anesthesia. *Pharmaceutics*. 2020; 12: 366. <https://doi.org/10.3390/pharmaceutics12040366>.
- [59] Sartawi Z, Blackshields C, Faisal W. Dissolving microneedles: Applications and growing therapeutic potential. *Journal of controlled release: official journal of the Controlled Release Society*. 2022; 348: 186–205. <https://doi.org/10.1016/j.jconrel.2022.05.045>.
- [60] Lammerding LC, Breikreutz J. Technical evaluation of precisely manufacturing customized microneedle array patches via inkjet drug printing. *International journal of pharmaceutics*. 2023; 642: 123173. <https://doi.org/10.1016/j.ijpharm.2023.123173>.
- [61] Qiang N, Liu Z, Lu M, Yang Y, Liao F, Feng Y, *et al.* Preparation and Properties of Polyvinylpyrrolidone/Sodium Carboxymethyl Cellulose Soluble Microneedles. *Materials (Basel)*. 2023; 16. <https://doi.org/10.3390/ma16093417>.
- [62] Liu Z, Wang Y, Zhang Y, Hu L, Chen B, Li Y, *et al.* Biguanide chitosan microneedles with cell-free DNA scavenging ability for psoriasis therapy. *Bioact Mater*. 2023; 33: 497–505. <https://doi.org/10.1016/j.bioactmat.2023.11.015>.
- [63] Graça MFP, Miguel SP, Cabral CSD, Correia IJ. Hyaluronic acid-Based wound dressings: A review. *Carbohydrate polymers*. 2020; 241: 116364. <https://doi.org/10.1016/j.carbpol.2020.116364>.
- [64] Rodella G, Preat V, Gallez B, Malfanti A. Design Strategies for Hyaluronic Acid-based Drug Delivery Systems in Cancer Immunotherapy. *Journal of controlled release: official journal of the Controlled Release Society*. 2025; 383: 113784. <https://doi.org/10.1016/j.jconrel.2025.113784>.
- [65] Mbituyimana B, Adhikari M, Qi F, Shi Z, Fu L, Yang G. Microneedle-based cell delivery and cell sampling for biomedical applications. *Journal of controlled release: official journal of the Controlled Release Society*. 2023; 362: 692–714. <https://doi.org/10.1016/j.jconrel.2023.09.013>.
- [66] Ertaş YN, Ertaş D, Erdem A, Següjja F, Dulchavsky S, Asham-makhi N. Diagnostic, Therapeutic, and Theranostic Multifunctional Microneedles. *Small*. 2024; 20: e2308479. <https://doi.org/10.1002/smll.202308479>.
- [67] Zhang X, Gan J, Fan L, Luo Z, Zhao Y. Bioinspired Adaptable Indwelling Microneedles for Treatment of Diabetic Ulcers. *Advanced materials (Deerfield Beach, Fla.)*. 2023; 35: e2210903. <https://doi.org/10.1002/adma.202210903>.
- [68] Creighton RL, Woodrow KA. Microneedle-Mediated Vaccine Delivery to the Oral Mucosa. *Advanced healthcare materials*. 2019; 8: e1801180. <https://doi.org/10.1002/adhm.201801180>.
- [69] Deng Y, Yang C, Zhu Y, Liu W, Li H, Wang L, *et al.* Lamprey-Teeth-Inspired Oriented Antibacterial Sericin Microneedles for Infected Wound Healing Improvement. *Nano letters*. 2022; 22: 2702–2711. <https://doi.org/10.1021/acs.nanolett.1c04573>.
- [70] Liang M, Shang L, Yu Y, Jiang Y, Bai Q, Ma J, *et al.* Ultrasound activatable microneedles for bilaterally augmented sono-chemodynamic and sonothermal antibacterial therapy. *Acta biomaterialia*. 2023; 158: 811–826. <https://doi.org/10.1016/j.actbio.2022.12.041>.
- [71] Shen YC, Chiu WK, Kang YN, Chen C. Microneedling Monotherapy for Acne Scar: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Aesthetic plastic surgery*. 2022; 46: 1913–1922. <https://doi.org/10.1007/s00266-022-02845-3>.
- [72] Qu F, Sun Y, Bi D, Peng S, Li M, Liu H, *et al.* Regulating Size and Charge of Liposomes in Microneedles to Enhance Intracellular Drug Delivery Efficiency in Skin for Psoriasis Therapy. *Advanced healthcare materials*. 2023; 12: e2302314. <https://doi.org/10.1002/adhm.202302314>.
- [73] Zhang S, Zhou H, Chen X, Zhu S, Chen D, Luo D, *et al.* Microneedle Delivery Platform Integrated with Codelivery Nanoliposomes for Effective and Safe Androgenetic Alopecia Treatment. *ACS applied materials & interfaces*. 2024; 16: 15701–15717. <https://doi.org/10.1021/acsmi.3c16608>.
- [74] Wang C, He G, Zhao H, Lu Y, Jiang P, Li W. Enhancing Deep-Seated Melanoma Therapy through Wearable Self-Powered Microneedle Patch. *Advanced materials (Deerfield Beach, Fla.)*. 2024; 36: e2311246. <https://doi.org/10.1002/adma.202311246>.
- [75] Wang X, Wang Z, Xiao M, Li Z, Zhu Z. Advances in biomedical systems based on microneedles: design, fabrication, and application. *Biomaterials science*. 2024; 12: 530–563. <https://doi.org/10.1039/d3bm01551c>.
- [76] Liu K, Wang H, Zhu F, Chang Z, Du R, Deng Y, *et al.* Lab on the Microneedles: A Wearable Metal-organic Frameworks-Based Sensor for Visual Monitoring of Stress Hormone. *ACS Nano*. 2024; 18: 14207–14217. <https://doi.org/10.1021/acsnano.3c11729>.
- [77] Zhao M, Zhou M, Lu P, Wang Y, Zeng R, Liu L, *et al.* Local anesthetic delivery systems for the management of postoperative pain. *Acta biomaterialia*. 2024; 181: 1–18. <https://doi.org/10.1016/j.actbio.2024.04.034>.
- [78] Daly S, Claydon NCA, Newcombe RG, Seong J, Addy M, West NX. Randomised controlled trial of a microneedle patch with a topical anaesthetic for relieving the pain of dental injections. *Journal of dentistry*. 2021; 107: 103617. <https://doi.org/10.1016/j.jdent.2021.103617>.
- [79] Ramadan D, Kam PR, Anjani QK, Kim MH, Cho DY, Hwang H, *et al.* Development of ropivacaine hydrochloride-loaded dissolving microneedles as a local anesthetic agent: A proof-of-concept.

- International journal of pharmaceutics. 2024; 660: 124347. <https://doi.org/10.1016/j.ijpharm.2024.124347>.
- [80] Zhu T, Yu X, Yi X, Guo X, Li L, Hao Y, *et al.* Lidocaine-Loaded Hyaluronic Acid Adhesive Microneedle Patch for Oral Mucosal Topical Anesthesia. *Pharmaceutics*. 2022; 14: 686. <https://doi.org/10.3390/pharmaceutics14040686>.
- [81] Yang H, Kang G, Jang M, Um DJ, Shin J, Kim H, *et al.* Development of Lidocaine-Loaded Dissolving Microneedle for Rapid and Efficient Local Anesthesia. *Pharmaceutics*. 2020; 12: 1067. <https://doi.org/10.3390/pharmaceutics12111067>.
- [82] Liu Y, Zhao ZQ, Liang L, Jing LY, Wang J, Dai Y, *et al.* Toward a solid microneedle patch for rapid and enhanced local analgesic action. *Drug delivery and translational research*. 2024; 14: 1810–1819. <https://doi.org/10.1007/s13346-023-01486-6>.
- [83] Li Q, Yu X, Zheng X, Yang J, Hui J, Fan D. Rapid dissolution microneedle based on polyvinyl alcohol/chitosan for local oral anesthesia. *International journal of biological macromolecules*. 2024; 257: 128629. <https://doi.org/10.1016/j.ijbiomac.2023.128629>.
- [84] Lee H, Min HS, Jang M, Kang G, Gong S, Lee C, *et al.* Lidocaine-loaded dissolving microneedle for safe local anesthesia on oral mucosa for dental procedure. *Expert opinion on drug delivery*. 2023; 20: 851–861. <https://doi.org/10.1080/17425247.2023.2216450>.
- [85] Liu X, Sun X, Zhu H, Yan R, Xu C, Zhu F, *et al.* A mosquito proboscis-inspired cambered microneedle patch for ophthalmic regional anaesthesia. *Journal of advanced research*. 2025; 72: 605–614. <https://doi.org/10.1016/j.jare.2024.07.020>.
- [86] Ornelas J, Foolad N, Shi V, Burney W, Sivamani RK. Effect of Microneedle Pretreatment on Topical Anesthesia: A Randomized Clinical Trial. *JAMA dermatology*. 2016; 152: 476–477. <https://doi.org/10.1001/jamadermatol.2015.5544>.
- [87] Abdul Jalal MI, Ooi KS, Foo KC, Hamzah AA, Goh CS, Dee CF, *et al.* Transdermal Maltose-Based Microneedle Patch as Adjunct to Enhance Topical Anesthetic before Intravenous Cannulation of Pediatric Thalassemic Patients Receiving Blood Transfusion: A Randomized Controlled Trial Protocol. *Journal of clinical medicine*. 2022; 11: 5291. <https://doi.org/10.3390/jcm11185291>.
- [88] Li M, Vora LK, Peng K, Sabri AHB, Qin N, Abbate M, *et al.* Novel nano-in-micro fabrication technique of diclofenac nanoparticles loaded microneedle patches for localised and systemic drug delivery. *Biomaterials advances*. 2024; 161: 213889. <https://doi.org/10.1016/j.bioadv.2024.213889>.
- [89] Castilla-Casadio DA, Miranda-Munoz KA, Roberts JL, Crowell AD, Gonzalez-Nino D, Choudhury D, *et al.* Biodegradable microneedle patch for delivery of meloxicam for managing pain in cattle. *PLoS One*. 2022; 17: e0272169. <https://doi.org/10.1371/journal.pone.0272169>.
- [90] Xiao M, Zhang J, Wu J, Yuan N, Liu T, Tang C, *et al.* Microneedles containing Cucumaria frondosa polysaccharides and 3-acetylaconitine exert analgesic, anti-inflammatory and chondroprotective activity for knee osteoarthritis. *International journal of biological macromolecules*. 2024; 281: 136204. <https://doi.org/10.1016/j.ijbiomac.2024.136204>.
- [91] Feng Y, Tang Y, Hu J, Chen C, Zhong G, Xiang C, *et al.* Phaseolus lunatusL. polysaccharide microneedles loaded with sinomenine hydrochloride for synergistic rheumatoid arthritis management and analgesia. *International journal of biological macromolecules*. 2025; 306: 141511. <https://doi.org/10.1016/j.ijbiomac.2025.141511>.
- [92] Pan J, Han X, Yuan P, Xu Y, Wang W, Zhang Z, *et al.* A Multifunctional Hydrogel Microneedle Patch for Treatment of Atopic Dermatitis. *ACS Appl Mater Interfaces*. 2025; 17: 29341–29351. <https://doi.org/10.1021/acsami.5c03594>.
- [93] Yang Y, Li Z, Huang P, Lin J, Li J, Shi K, *et al.* Rapidly separating dissolving microneedles with sustained-release colchicine and stabilized uricase for simplified long-term gout management. *Acta pharmaceutica Sinica. B*. 2023; 13: 3454–3470. <https://doi.org/10.1016/j.apsb.2023.02.011>.
- [94] Liu Y, Zhu X, Ji S, Huang Z, Zang Y, Ding Y, *et al.* Transdermal delivery of colchicine using dissolvable microneedle arrays for the treatment of acute gout in a rat model. *Drug delivery*. 2022; 29: 2984–2994. <https://doi.org/10.1080/10717544.2022.2122632>.
- [95] Song K, Hao Y, Tan X, Huang H, Wang L, Zheng W. Microneedle-mediated delivery of Ziconotide-loaded liposomes fused with exosomes for analgesia. *Journal of controlled release: official journal of the Controlled Release Society*. 2023; 356: 448–462. <https://doi.org/10.1016/j.jconrel.2023.03.007>.
- [96] Qu Y, Fu Y, Liu Y, Liu C, Xu B, Zhang Q, *et al.* The role of TRPV1 in RA pathogenesis: worthy of attention. *Frontiers in immunology*. 2023; 14: 1232013. <https://doi.org/10.3389/fimmu.2023.1232013>.
- [97] Calvo M, Dawes JM, Bennett DL. The role of the immune system in the generation of neuropathic pain. *The Lancet. Neurology*. 2012; 11: 629–642. [https://doi.org/10.1016/S1474-4422\(12\)70134-5](https://doi.org/10.1016/S1474-4422(12)70134-5).
- [98] Silagi ES, Segal RA. Uncomfortably numb: how Nav1.7 mediates paclitaxel-induced peripheral neuropathy. *Brain: a journal of neurology*. 2021; 144: 1621–1623. <https://doi.org/10.1093/brain/awab196>.
- [99] Rahman MM, Jo YY, Kim YH, Park CK. Current insights and therapeutic strategies for targeting TRPV1 in neuropathic pain management. *Life sciences*. 2024; 355: 122954. <https://doi.org/10.1016/j.lfs.2024.122954>.
- [100] Shin DA, Kim TU, Chang MC. Minocycline for Controlling Neuropathic Pain: A Systematic Narrative Review of Studies in Humans. *Journal of pain research*. 2021; 14: 139–145. <https://doi.org/10.2147/JPR.S292824>.
- [101] Garcia-Domínguez M. The Role of TNF-alpha in Neuropathic Pain: An Immunotherapeutic Perspective. *Life (Basel, Switzerland)*. 2025; 15: 785. <https://doi.org/10.3390/life15050785>.
- [102] Zhang W, Jiao B, Yu S, Zhang C, Zhang K, Liu B, *et al.* Histone deacetylase as emerging pharmacological therapeutic target for neuropathic pain: From epigenetic to selective drugs. *CNS neuroscience & therapeutics*. 2024; 30: e14745. <https://doi.org/10.1111/cns.14745>.
- [103] Soliman N, Moisset X, Ferraro MC, de Andrade DC, Baron R, Belton J, *et al.* Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: a systematic review and meta-analysis. *Lancet Neurol*. 2025; 24: 413–428. [https://doi.org/10.1016/S1474-4422\(25\)00068-7](https://doi.org/10.1016/S1474-4422(25)00068-7).
- [104] Zhang A, Wu W, Wang S, Liu X, Jiang X, Xiao Y, *et al.* Dissolving Microneedle Patch for Peripheral Delivery of Pregabalin in Neuropathic Pain Management. *Advanced healthcare materials*. 2025; 14: e2500316. <https://doi.org/10.1002/adhm.202500316>.
- [105] Puthumana EA, Muhamad L, Young LA, Chu XP. TRPA1, TRPV1, and Caffeine: Pain and Analgesia. *International journal of molecular sciences*. 2024; 25: 7903. <https://doi.org/10.3390/ijms25147903>.
- [106] Han H, Li B, Yang R, Guo HL, Li Q, Wang H, *et al.* NIR-Remote Selectively Triggered Buprenorphine Hydrochloride Release from Microneedle Patches for the Treatment of Neuropathic Pain. *ACS biomaterials science & engineering*. 2024; 10: 5001–5013. <https://doi.org/10.1021/acsbiomaterials.4c00733>.
- [107] Chen DX, Zhang YY, Liu J, Chen Y. Postoperative acute pain trajectory and chronic postsurgical pain after abdominal surgery: a prospective cohort study and mediation analysis. *International journal of surgery (London, England)*. 2025; 111: 1968–1976. <https://doi.org/10.1097/JS9.0000000000002218>.
- [108] Zhang A, Zeng Y, Xiong B, Jiang X, Jin Y, Wang S, *et al.* A pH-Responsive Core-Shell Microneedle Patch with Self-Monitoring Capability for Local Long-Lasting Analgesia. *Advanced Functional Materials*. 2024; 34: 2314048. <https://doi.org/10.1002/adfm.202314048>.
- [109] Mortensen C, Thomsen MT, Chua KC, Hammer HS, Nielsen F, Pötz O, *et al.* Modeling mechanisms of chemotherapy-induced peripheral neuropathy and chemotherapy transport using induced pluripotent stem cell-derived sensory neurons. *Neuropharmacology*. 2024; 258: 110062. <https://doi.org/10.1016/j.neuropharm.2024.110062>.

- [110] Klein I, Wiesen MHJ, Albert V, Bobylev I, Joshi AR, Muller C, *et al.* Impact of drug formulations on kinetics and toxicity in a preclinical model of paclitaxel-induced neuropathy. *Journal of the peripheral nervous system*: JPNS. 2021; 26: 216–226. <https://doi.org/10.1111/jns.12440>.
- [111] Kalynovska N, Diallo M, Sotakova-Kasparova D, Palecek J. Losartan attenuates neuroinflammation and neuropathic pain in paclitaxel-induced peripheral neuropathy. *Journal of cellular and molecular medicine*. 2020; 24: 7949–7958. <https://doi.org/10.1111/jcmm.15427>.
- [112] Abd Elaleem WS, Ghaiad HR, Abd Elmawla MA, Shaheen AA. Attenuation of p38 MAPK/NF-kappaB/TRPV1/CGRP is involved in the antinociceptive effect of hesperidin methyl chalcone and taxifolin in paclitaxel-induced peripheral neuropathy. *BioFactors* (Oxford, England). 2025; 51: e2125. <https://doi.org/10.1002/biof.2125>.
- [113] Kim SH, Kim KH, Hyun JW, Kim JH, Seo SS, Kim HJ, *et al.* Blood neurofilament light chain as a biomarker for monitoring and predicting paclitaxel-induced peripheral neuropathy in patients with gynecological cancers. *Frontiers in oncology*. 2022; 12: 942960. <https://doi.org/10.3389/fonc.2022.942960>.
- [114] Kong Y, Pan T, Liu B, Kuss M, Krishnan MA, Alimi OA, *et al.* Double-Layer Microneedle Patch Loaded with HA-PBA-QCT for Management of Paclitaxel-Induced Peripheral Neuropathic Pain. *Small*. 2025; 21: e2409748. <https://doi.org/10.1002/smll.202409748>.
- [115] Rapoport AM, Ameri M, Lewis H, Kellerman DJ. Development of a novel zolmitriptan intracutaneous microneedle system (Qtrypta™) for the acute treatment of migraine. *Pain management*. 2020; 10: 359–366. <https://doi.org/10.2217/pmt-2020-0041>.
- [116] Bahnick AJ, Dziewior CS, Li Y, Chou A, Segal M, Augustine EK, *et al.* Controlled Transdermal Delivery of Dexamethasone for Pain Management via Photochemically 3D-Printed Bioresorbable Microneedle Arrays. *Advanced healthcare materials*. 2024; 13: e2402113. <https://doi.org/10.1002/adhm.202402113>.
- [117] Zhang Q, Jiang J, Hu T, Xu M, Zhang X, Yang C, *et al.* Oxygen vacancy-rich CoSn(OH)(6)/FeS(2) heterostructure-based microneedles for combinatorial cancer therapy via activation of ferroptosis and apoptosis. *Journal of colloid and interface science*. 2025; 700: 138558. <https://doi.org/10.1016/j.jcis.2025.138558>.
- [118] Joshi P, Riley PR, Mishra R, Azizi Machekposhti S, Narayan R. Transdermal Polymeric Microneedle Sensing Platform for Fentanyl Detection in Biofluid. *Biosensors* (Basel). 2022; 12: 198. <https://doi.org/10.3390/bios12040198>.
- [119] Pourmansouri Z, Malekkhatabi A, Toolabi M, Akbari M, Shahbazi MA, Rostami A. Anti-Nociceptive Effect of Sufentanil Polymeric Dissolving Microneedle on Male Mice by Hot Plate Technique. *Iranian biomedical journal*. 2024; 28: 192–205. <https://doi.org/10.61186/ibj.4062>.
- [120] Edwards C, Shah SA, Gebhardt T, Jewell CM. Exploiting Unique Features of Microneedles to Modulate Immunity. *Advanced materials* (Deerfield Beach, Fla.). 2023; 35: e2302410. <https://doi.org/10.1002/adma.202302410>.
- [121] Kushwaha R, Palei NN. Transdermal Drug Delivery Systems: Different Generations and Dermatokinetic Assessment of Drug Concentration in Skin. *Pharmaceutical medicine*. 2024; 38: 407–427. <https://doi.org/10.1007/s40290-024-00537-8>.
- [122] Chaudhary M, Khan A, Gupta M. Skin Ageing: Pathophysiology and Current Market Treatment Approaches. *Current aging science*. 2020; 13: 22–30. <https://doi.org/10.2174/1567205016666190809161115>.
- [123] Yu J, Yang Z, Jiang J, Xu M, Yang C, Li Z, *et al.* Engineering asymmetric electronic structures in Fe-N-S-C nanozymes for dual enzyme-catalyzed-induced ferroptosis and enhanced antitumor efficacy. *Chinese Chemical Letters*. 2026; 37: 111693. <https://doi.org/10.1016/j.ccl.2025.111693>.
- [124] Hu T, Lin S, Yang Z, Li Y, Yang C, Xu M, *et al.* Bismuth-based dissolvable microneedle: A precision-targeted “surgical scalpel” for dual-gas synergistic tumor therapy. *Journal of Colloid and Interface Science*. 2026; 703: 139171. <https://doi.org/10.1016/j.jcis.2025.139171>.
- [125] Wang T, Liu H, Li M, Ji Z, Zhang X, Wang N, *et al.* Microneedle-based nanodrugs for tumor immunotherapy. *J Control Release*. 2025; 380: 539–562. <https://doi.org/10.1016/j.jconrel.2025.02.003>.
- [126] Wu ZF, Cheng W, Su JD. Progress in the application of microneedle-mediated cell implantation combined with artificial dermal scaffolds. *European Cells & Materials*. 2025; 53: 52–64. <https://doi.org/10.22203/eCM.v053a05>.
- [127] Hu T, Jia L, Li H, Yang C, Yan Y, Lin H, *et al.* An Intelligent and Soluble Microneedle Composed of Bi/BiVO₄ Schottky Heterojunction for Tumor Ct Imaging and Starvation/Gas Therapy-Promoted Synergistic Cancer Treatment. *Advanced healthcare materials*. 2024; 13: e2303147. <https://doi.org/10.1002/adhm.202303147>.
- [128] Zhao M, Ma J, Li M, Zhang Y, Jiang B, Zhao X, *et al.* Cytochrome P450 Enzymes and Drug Metabolism in Humans. *International journal of molecular sciences*. 2021; 22: 12808. <https://doi.org/10.3390/ijms222312808>.

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