MICRONEEDLES IN PAIN MANAGEMENT OF CANCER

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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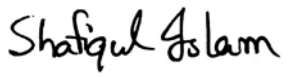

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Approval

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Ethics Statement

No living organism were harmed during this project.

Abstract

Pain management is an integral part of treatment in cancer. Researchers are constantly trying to find effective and efficient ways to manage pain, particularly in cancer patients, as well as devices to administer the drugs without further causing pain to the patient. Microneedles (MNs) are small needle-like devices, used to distribute drugs across the skin's membranes, are non-invasive and cause little or no discomfort at the site of administration to the skin. They can be considered to be used in the delivery of medications for managing pain in cancer patients, efficiently and effectively with minimal discomfort. The aim of this review is to compile current ideas and treatment methods for cancer patients' pain management in order to spur further progress.

Keywords: Microneedle; types of microneedle; cancer; mechanism of pain; cancer treatment options; application of microneedle in cancer pain management.

Dedication

Dedicated to my parents

Acknowledgement

Firstly, I am grateful to almighty Allah for making me able to choose this field and study Pharmacy. Without His blessings, I would not be able to continue this project paper and submit it for passing my Bachelor's degree in Pharmacy.

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List of Acronyms

MN	Microneedle
MNA	Microneedle Array
5-FU	5-fluorouracil
SC	Stratum Corneum
TDDS	Transdermal Drug Delivery Systems
PC	Prostate Cancer
DALY	Disability-Adjusted Life Year
NMSC	Non Melanoma Skin Cancer
5-ALA	5-aminolevelunic acid
CBD	Cannabidiol
AM	Additive Manufacturing
BMS	Burning Mouth Syndrome
DCF	Diclofenac
NMDA	N-methyl-D-aspartate
MITP	Microneedle Integrated Transdermal Patch
TMJ	Temporomandibular Joint

Chapter 1

Introduction

1.1 Cancer

In spite of every efforts, cancer remains one of the most serious health issues which affects the global population extensively. Cancer is a disease that develops as a result of changes at the cellular level, resulting in uncontrollable cell growth and division. The incidence of cancer has clearly increased in recent decades, according to recent data. In 2003, about 10 million people were identified with cancer, with 6.2 million dying as a result. In 2015, 17.5 million new cases of cancer were diagnosed and 8.7 million deaths were found. As a result, fewer cancer-related deaths were found however the number of cancer survivors has increased proportionally. In 2018 worldwide, an estimated 43.8 million people were found with cancer. Cancer can start almost anywhere in the cells of human body. The most common cancers in 2018 are breast cancer, colon cancer, lung cancer and prostate cancer, among others (Magee et al., 2019) According to recent projections for the global cancer burden in 2020, about 19.3 million new cases and 10 million cancer deaths can possibly found. Breast cancer affects one out of every four women worldwide, with 2.26 million cases registered. Women are more likely than men to develop colorectal, lung, cervical, and thyroid cancers. Lung cancer and prostate cancer, on the other hand, are the most prevalent cancers in male, accounting for about one-third of cancers of men. In 2020, 1.43 million new cases of lung cancer and 1.41 million new cases of prostate cancer were registered, respectively (*GLOBOCAN 2020: New Global Cancer Data | UICC*, 2020).

1.2 Pain Management

Cancer patients experience pain which is a very common and inconvenient symptoms, mostly those in later stages of the disease, with an occurrence of higher than 70%. As a result, pain relief is a crucial clinical goal in the care of cancer patients. “An emotional experience and unpleasant sensory associated with real or possible tissue damage or defined in case of same damage,” according to one definition. Psychogenic, neuropathic (non-nociceptive), or nociceptive pain (Zielińska et al., 2021) are the three forms of pain that follow the description above.

Cancer patients may experience pain as a result of the tumor itself, diagnostic or surgical procedures, or treatment-related adverse effects. The majority of cancer patients experience neuropathic and nociceptive pain. Lack of adequate pain management can provide negative influence on patient outcomes and lifestyle, and cancer-related pain places a significant financial strain on healthcare systems. According to the existing National Comprehensive Cancer Network (NCCN) recommendations for the management of pain observed in adult cancer patients, extreme untreated pain is a medical emergency that requires urgent evaluation and care. Opioids are prescribed for the treatment of cancer-related pain, perhaps in conjunction with other analgesics, NSAIDs, or acetaminophen, according to existing NCCN recommendations (Neufeld et al., 2017).

1.3 Transdermal Drug Delivery

Transdermal delivery is achieving popularity as a method of drug administration that can also be used to relieve pain. The medication enters in the systemic circulation within the skin without being lost along the way, improving physiological and pharmacological response, improving sustained drug release, increasing bioavailability and reducing unwanted side

effects,. Nonetheless, the chemical properties of drugs have a noteworthy effect on the delivery of drug through the transdermal administration path, which affects absorption via the SC. Microneedles (MNs) and other minimally invasive techniques circumvent the stratum corneum (SC) barrier, allowing the drug to reach the viable epidermis directly. As a result, only a few medications can be administered in clinical quantities through this path. The drugs delivered by the transdermal drug delivery system must travel a winding route to enter the systemic circulation, passing through several layers of skin that contain both aqueous and lipid domains (Ahmed Saeed AL-Japairai et al., 2020).

1.4 Microneedle

Microneedles (MNs) are tiny needle-like structures that deliver drugs through the skin's layers. They are non-invasive and have little or no discomfort at the site of application to the skin. Strong, hollow, coated, dissolving, and hydrogel-forming microneedles are divided into five classes based on their design. Fentanyl (Kornick et al., 2003), meloxicam (Castilla-Casadiego et al., 2021), lidocaine (Kathuria et al., 2016), calcitonin (Xie et al., 2017a), and prostaglandin analogues are among the analgesics and anesthetics currently administered through microneedle (Macedo et al., 2017). Cancer patients are already in excruciating discomfort as a result of their care or the disease. In this case, using conventional needles to administer painkillers can aggravate the situation. MNs are particularly good at supplying both large and small molecules in order to reduce pain. There are many drug delivery methods that use MNs, each with its own set of benefits and drawbacks. This research resulted in the production and commercialization of a product for medical purpose. Numerous drugs that are given by MN, also being tested in clinical trials to determine their effectiveness, tolerability and safety (Seetharam et al., 2020).

Pressure is experienced by a large number of cancer patients as a result of their diagnosis or treatment, which obstructs recovery and lowers their quality of life. In this scenario, a painless transdermal microneedle for analgesic might be an excellent option instead of a traditional injection.

1.5 Rational of the Study

A substantial number of cancer patients feel pain as a result of their illness or treatment, which obstructs recovery and has a negative effect on their quality of life. In the case of palliative care, improving the quality of life is significantly more focused than the management of disease itself and applies a holistic approach to meeting the physical, practical, functional, social, emotional and spiritual needs of patients. Whereas the conventional injection can cause more pain to cancer patients, we can opt for ways that can be painless or less painful than the conventional ways and are equally effective. Transdermal microneedles are such a method/technique which are less invasive and won't cause much pain to the already aching patients. It will help them to take their medications without the additional pain of invasive methods. Transdermal microneedles can be an impressive addition to the palliative treatment process, making the patients less anxious about the pain and sufferings of the traditional treatments and also improving their quality of life. In conclusion, transdermal microneedles should be considered as an important method to be included in the pain management of cancer and palliative patients so that the cancer/terminal patients can lead a life with comparably less pain and sufferings.

1.6 Aim of the Study

This review aims to compile both existing ideas and treatment strategies for the pain management of cancer patients in order to help promote further developments. It also briefly represents the applications of microneedles in the field of cancer pain management.

Chapter 2

Cancer

2.1 Statistics

As per the International Agency for Research on Cancer, 1 out of every 5 people will experience cancer at some point in their life, with one out of every 8 men and one out of every 11 women dying from it. According to the most recent statistics, more than 50 million people remain alive five years after being diagnosed with cancer. Globally, aging inhabitants and socioeconomic risk factors continue to be the key drivers of the growth. Breast cancer is one of every four malignancies diagnosed in women around the world. Women are more likely than men to develop colorectal, lung, cervical, and thyroid malignancies. The most frequent malignancies in males are lung cancer and prostate cancer, which together account for about one-third of all male cancers. Breast cancer of female has exceeded lung cancer as the most frequently observed cancer for the first time, owing to its high incidence low- and middle-income countries (LMICs). Not just in various LMICs, also in maximum high income provinces such as North America, Europe, and Australia, lung cancer remains the top cause of cancer death (*GLOBOCAN 2020: New Global Cancer Data | UICC*, 2020).

A thorough understanding of the epidemiology of cancer gives critical data on likely reasons and population patterns, allowing for the development of well-timed and effective healthcare involvements targeted at implementing effective preventive, screening, and diagnostic programs. Generally, cancer has the largest social, clinical and economic cost of all human diseases in cases of cause-specific Disability-Adjusted Life Years (DALYs). Cancer risk for people from 0 to 74 years old is 20.2%. Cancer causes the highest global load (244.6 million DALYs), both in women (107.1 million DALYs) and men (137.4 million DALYs), according

to the WHO. In 2018, about 18 million different instances of cancer were identified, with breast (2.09 million cases), prostate (1.28 million cases) and lung (2.09 million cases) being the most prevalent. Except for sex-specific cancers, the male-to-female cancer ratio is greater than one for all types of cancer other than thyroid cancer (i.e., 0.30). Second leading reason of death globally (8.97 million deaths) is cancer, after ischemic heart disease, but it is expected to overtake ischemic heart disease as the leading cause of death in 2060 (~18.63 million fatalities). Lung, liver, and stomach cancers are the three most fatal cancers in the overall population, however lung and breast cancers are the major causes of cancer-related mortality in men and women, respectively. The best prognosis is for prostate and thyroid cancers, which have a ~100% 5-year survival rate, while the worst prognosis is for esophageal, liver, and notably pancreatic tumors, which have a <20% 5-year survival rate. Colorectal (2.71%), lung (3.80%), and prostate (3.73%) cancers in men and cervix uteri (1.36%), lung and colorectal (both 1.77%), and breast (5.03%) cancers in women have the highest chance of acquiring cancer. All malignancies, with the exception of sex-specific cancers, have a male-to-female cancer ratio larger than one (i.e., 0.30%). The intrahepatic bile ducts (2.44%), liver and bladder (3.38%), and esophagus (2.32%) have the greatest men/women ratios (Mattiuzzi & Lippi, 2019).

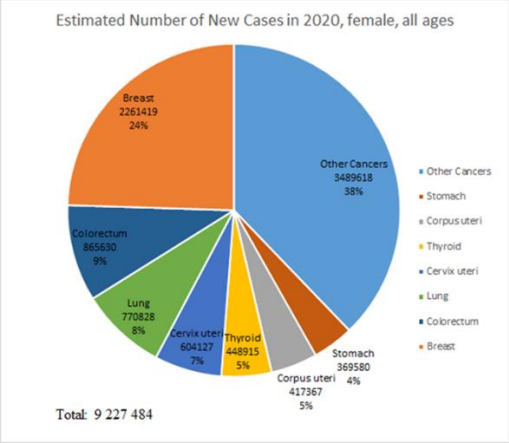

Figure 1: Estimated number of new cancer cases in 2020, female, all ages (GLOBOCAN 2020: New Global Cancer Data | UICC, 2020).

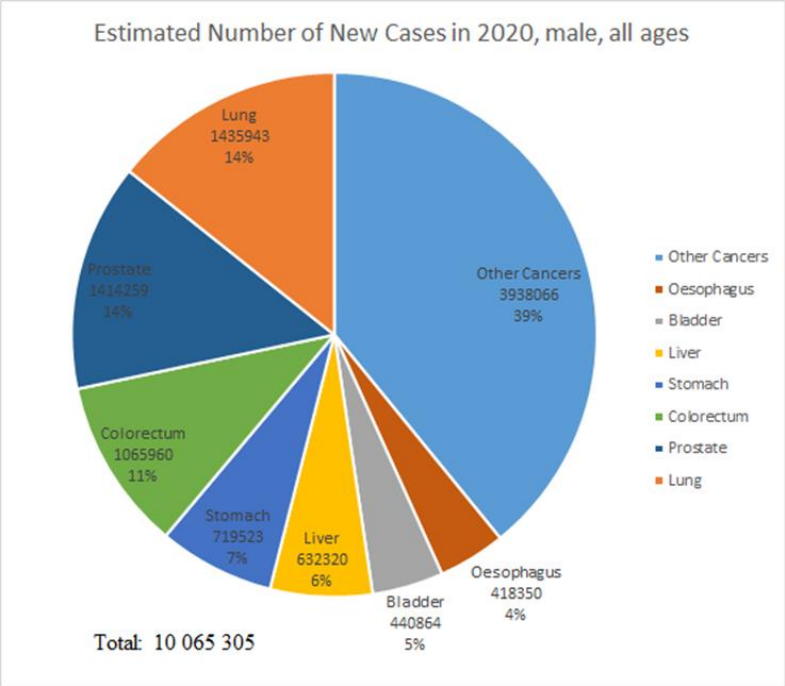

Figure 2: Estimated number of new cancer cases in 2020, male, all ages (GLOBOCAN 2020: New Global Cancer Data | UICC, 2020).

In the United States, about 1,806,590 cancer cases will be identified in 2020, equating to around 4,950 new cases within a day. Furthermore, women will be reported with 48,530 new cases of ductal carcinoma of the breast and 95,710 new cases of melanoma of the skin. An approximate 606,520 Americans will have died of cancer by 2020, amounting to nearly 1,600 deaths each day. Colorectal, prostate, and lung cancers kill the most men, while colorectal, breast, and lung cancers kill the most women. Lung cancer accounts for nearly a quarter of all cancer fatalities (Siegel et al., 2020). Furthermore, according to a study conducted in Canada, 225 800 additional cancer cases are predicted to be detected in 2020. With an estimated 29,800 cases, lung and bronchus cancer is expected to be the most often diagnosed malignancy, followed by breast (27,400), colorectal (26,900), and prostate (23,300). In 2020, these four tumors are predicted to account for roughly half of all cancer diagnoses (48 percent). Cancer will kill approximately 83,300 Canadians by 2020. Lung cancer is expected to be the leading cause

of cancer death, with 21,200 fatalities, compared to colorectal, pancreatic, and breast cancer, which are the three major causes. These five malignancies, and including prostate cancer, represent more than half of all cancer fatalities in Canada (55 %) (Brenner et al., 2020).

The current epidemiologic statistics, as well as the incremental increase in cancer mortality, incidence, and prevalence predicted over the following 40 years, show that the incidence of malignant diseases has reached epidemic proportions and will continue to do so for a long period of time. Malignant diseases are the primary and foremost public health concern, posing a significant clinical burden, disrupting societal norms, and depleting vast financial resources. As a result, it appears that supranational organizations and national governments will start on historic efforts to build or strengthen present cancer prevention, screening, diagnostic, and management measures (Mattiuzzi & Lippi, 2019).

2.2 Types of Cancer

There are more than 100 types of cancer. Cancers are often named after the organs or tissues that they originate in. Lung cancer, for example, develops in the cells of the lungs, but brain cancer occurs in the cells of the brain. Cancers can also be defined by the type of cell responsible for their development, such as squamous or epithelial cells. The following are examples of cancers:

2.2.1 Non-melanoma Skin Cancer

Non-melanoma skin cancer is a kind of skin cancer that begins gradually in the upper layers of the skin. Non-melanoma skin cancer is distinguishable from melanoma, which is a more deadly type of skin cancer. Each year, around 147,000 new cases of non-melanoma skin cancer are detected in the United Kingdom. It is more common in the elderly and affects more males than women. A lump or darkened patch on the skin that remains after a few weeks and spreads

slowly across months or years is usually the first sign of non-melanoma skin cancer. This can be a tumor, or cancer (*Non-Melanoma Skin Cancer - NHS*, 2020).

2.2.2 Sarcoma

Sarcomas are cancerous tumors that can develop in the soft tissues of our body, for example muscles, fat, blood vessels, lymph vessels, and fibrous tissue (such as tendons and ligaments). There are many type of bone malignancy but osteosarcoma is the most common one. The most prevalent soft tissue sarcomas among all of them are leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, Kaposi sarcoma, and dermatofibrosarcoma protuberans (*What Is Cancer? - National Cancer Institute*, 2015).

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2.2.3 Carcinoma

Carcinoma is a form of malignant solid tumor that arises in epithelial cells, which line the outside and inside surfaces of organs. Carcinoma is responsible for 80% to 90% of all cancer diagnosis. Epithelial cells coat the skin's outer surface, as well as the lining and covering of organs and inner passageways like the gastrointestinal system. Carcinoma cells proliferate quickly and clump together to create a tumor. The disease progresses in phases, while the features of the cells, described in grades, determine whether the cancer will be indolent (slow-growing) or aggressive (Paul, 2021).

2.2.4 Lymphoma

Lymphoma is a form of cancer that harms the lymphatic system. Lymphocytes, a type of white blood cell, are where it develops. These cells aid in the battle against disease and play a crucial part in the body's immunological defenses. Because this type of cancer is found in the lymphatic system, it can rapidly spread to other tissues and organs throughout the body. The liver, bone marrow, and lungs are the most common sites for lymphoma to spread. Lymphoma

can strike anyone at any age, but it is one of the most frequent cancers in children and young adults aged 15 to 24. It's usually curable (Felman, 2019).

2.2.5 Leukemia

Leukemias are malignancies that begin in the blood-forming tissue of the bone marrow. These cancers do not produce solid tumors. Huge numbers of abnormal white blood cells (leukemia cells and leukemic blast cells) form in the blood and bone marrow, pushing out normal blood cells. Leukemia cells cannot fight with infection, although normal white blood cells can. Because there are so many of them, they begin to influence how organs function. Some people may run out of white blood cells, platelets, or normal red blood cells over time, making it difficult to fight infection (Robinson, 2019).

2.2.6 Melanoma

Melanoma is a type of skin cancer that arises when pigment-producing cells, called melanocytes, change and begin to divide uncontrollably. The majority of pigment cells are formed in the skin. Melanomas can occur everywhere on the skin, although they are more prevalent in certain areas. It most commonly affects the chest and back in men. Legs are the most common place in women. Melanoma is also commonly found on the face. Melanoma can, however, occur in the eyes and other parts of the body, including the intestines on rare instances. People with darker skin are more likely to develop melanoma (Macgill, 2019).

2.3 Cancer Treatment option – current (approved) and in trial

Iquimod (Aldara®) and 5-fluorouracil (Efudix®) are two medicines commonly applied to the treatment of non-melanoma skin cancer (NMSC) topically. These medicines' topical therapy has side effects and limits, including local irritation and ulceration erosion. A lot of effort has gone into developing microneedle devices that will improve the distribution of these chemicals, allowing them to spread deeper tumor wounds with fewer doses and fewer systemic side effects (Coyle & Takwale, 2017).

Following Donnelly et al's pioneering research in using microneedles to deliver therapies for the treatment of skin malignancies in 2008, numerous groups have investigated alternative designs of microneedle to transport a variety of anticancer medicines to the skin. 5-fluorouracil methyl aminolevulinic acid (MAL), itraconazole, and meso-tetra N-methyl-4-pyridyl porphinetetratosylate (TMP) are examples of such medications (Sabri et al., 2019).

Naguib et al., for example, established the viability of utilizing solid microneedles that increase the administration of 5-FU intradermally in skin cancer treatment of a mouse model. In vitro, the researchers found that by applying 5-FU cream to microneedle-perforated murine skin enhanced 5-FU flux by 4.5-fold compared to applying cream to intact skin. Application of 5-FU cream topically (5 %) on skin that is microneedle-perforated, revealed considerable tumor reduction compared to intact skin in an in vivo study employing a mouse model with the B16-F10 melanoma tumor (Naguib et al., 2014).

Other options include anti-cancer vaccinations, such as prostate cancer (PC) DNA vaccines, which can be applied in targeting cells that express immunogenic tumor-associated antigens (TAAs). Current PROSTVAC clinical trial outcomes, however, have cast doubt on the efficacy of a PC DNA vaccination alone. Using a good drug delivery mechanism, such as MNs, could

boost the efficiency of a PC DNA vaccination. MNs have the benefit of being able to deliver medicine to the tumor of tumor through the skin stratums to Antigen Presenting Cells (APCs) in the dermis and epidermis (Seetharam et al., 2020).

Bhatnagar and colleagues created a polyvinylpyrrolidone microneedle patch for docetaxel and doxorubicin administration to treat breast cancer tumors in combination. Chemotherapeutics such as docetaxel and doxorubicin are routinely given to treat this cancer. Doxorubicin is a non-selective anthracycline that induces cell death by binding with DNA and inhibits macromolecule synthesis. Docetaxel, on the other contrary, affects cytoskeleton flexibility and cell mitosis by interfering with the regular function of microtubule development. The medications were integrated on the microneedles tips using this method, which involved dissolving them in a polyvinylpyrrolidone solution. The patch was then put on a polydimethylsiloxane (PDMS) pyramidal needle mold and covered with a polyvinylpyrrolidone/polyvinyl alcohol mixture to improve its mechanical robustness (Moreira et al., 2019).

Eirion Therapeutics has reported two worldwide patent uses for transdermal delivery of big molecular weight compounds utilized in skin cancer treatment. A technique for transporting an emulsion formulation of botulinum toxin (molecular weight 100,000 KDa) with a physiologically active ingredient was claimed in the invention (hydrocortisone, retin A, lidocaine, and others). The procedure included skin conditioning with MNs and then the application of the formulation. By delivering botulinum toxin which is a big molecular agent, they combined emulsion technology (oil-in-water and water-in-oil nanoemulsions) with microneedle technology. The innovation also revealed the use of biologically active drugs with a high molecular weight, such as infliximab, golimumab, adalimumab, certolizumabpegol, siplizumab, and others, either alone or in combination (Seetharam et al., 2020).

For the treatment of melanoma in xenograft mice, Ahmed et al. applied an MNs-based device and a Dermaroller that is typically utilized for the applications of cosmetics, in combination with celecoxib co-loaded liposomes and doxorubicin (DOX). When compared to passive delivery pathways, this technique resulted in a two-fold increase in permeability of the skin and increased inhibition of tumor (Ahmed et al., 2019).

This method was also used to successfully treat the skin with metal MNs before micro particulate vaccination for breast cancer, which resulted in significantly higher serum levels of IgG, T cell (CD4+ and CD8+), B, and IgG2 in the vaccinated animals as compared to the untreated controls. The use of MNs resulted in a 5-fold increase in suppression of tumor (Chablani et al., 2019).

Jain et al., on the other hand, created a 5-aminolevelunic acid (5-ALA) coated microneedle to increase photosensitizer distribution to skin cancers. In contrast to application of 5-ALA cream topically, the researchers found that the microneedle patch which is coated by 5-ALA, allowed for better transfer of 5-ALA deeper into the tumor abrasion. Interestingly, while giving a lower dose than topical cream administration, the coated microneedle showed greater efficiency in the in vivo murine skin tumor model (Jain et al., 2016)

Furthermore, Jain et al. coated microneedle patches encompassing 57 microneedles with 5-aminolevulinic acid (5-ALA) for the photodynamic treatment of the skin cancers. A microprecision dip coater was used to make the 5-ALA microneedles. The 5-ALA coated microneedles group had good delivery efficiency in porcine skin and could considerably decrease tumor development when compared to the control group, which was treated with a topical 5-ALA cream formulation (Jain et al., 2016).

Alternatively, some researchers have investigated the use of microneedle devices for the high-throughput drug sensitivity in the screening of malignancies. These methods aim to asses a

variety of therapies on an in-vivo tumor while also determining a patient's particular reaction to a certain therapeutic agent. Jonas and colleagues designed a microneedle with numerous reservoirs of drug, each with a distinct drug combination or single agent that may be placed inside the lump for short-term drug sensitivity testing. This cylindrical device, with a diameter of 820 μm and a length of 4 mm, had up to 16 reservoirs of drug on its surface and could be inserted into lumps using a biopsy needle. Then the medications can diffuse into distinct lump locations of 200–300 μm, and diffusion of drug can be regulated (i.e. preferred or delayed) by varying reservoir size, and the use of expansive hydrogels and polymer matrices (Moreira et al., 2018).

The authors hypothesized that by encapsulating multiple chemicals in the same reservoir, this device might limit release of drug from each reservoir to specific tumor locations, and therapeutic combinations may be created. Furthermore, the scientists stated that this resistor over therapeutic release might go with the intratumoral concentration of drug reached by the systemic therapeutic treatment (Hao et al., 2018).

Chapter 3

Pain Management in Cancer

3.1 Types of pain

Cancer pain is still a prevalent complaint, despite recent breakthroughs in treatment. Actual or potential tissue damage is linked to the subjective feeling of pain. Regardless of actual damage, which is reported by 50 percent to 90 percent of persons diagnosed with cancer, this response to tissue-threatening stimuli is unavoidably unpleasant (Russo & Sundaramurthi, 2019). There are two forms of pain: acute and chronic, based on the duration and severity of the pain. Acute pain is defined as "pain that appears suddenly and lasts for a short period of time." It usually has a clear temporal and causal link to an injury or sickness (Hay & Nesbitt, 2019). Chronic pain, on the other hand, is defined as "pain with no obvious biological significance that persists beyond typical tissue healing time." In the United States, chronic pain harms greater individuals than diabetes, cancer and coronary heart disease combined. Around 3–4.5 % of the global population struggles from persistent neuropathic pain as they get older (Kochhar et al., 2019).

On the other hand, there are three forms of pain: nociceptive, neuropathic (non-nociceptive), and psychogenic, depending on the pathophysiology. The stimulation of pain receptors or nociceptors at nerve terminals causes nociceptive pain. It's a "natural" discomfort that we've all felt and can simply express to others. This form of discomfort is usually associated with a visible damage or mass. Visceral nociceptive pain and somatic nociceptive pain are two types of nociceptive pain. The somatic nociceptive pain is persistent and well-localized that frequently involves the body wall. The pain connected with bone metastases is a good example. In contrast, visceral nociceptive pain affects the visceral organ and is often paroxysmal and localized poorly. It could be a symptom of pancreatic cancer. Nociceptive pain, regardless of

its kind, involves the nociceptors and is responsive to nociceptive blockers for instance opioids (Zielińska et al., 2021).

Since neuropathic (non-nociceptive) pain is characterized by sensations that are not generally associated with pain, hence it is hard to explain. Many people experience a sense of "pins and needles," a burning sensation, or shooting pain. Chemotherapy-induced peripheral neuropathy is a prominent example of this sort of discomfort. Neuropathic pain (NP) is a type of pain caused by a malfunction of the central or peripheral nervous systems. It's best described as a neural system "short circuit" that handles pain impulses. Anticonvulsants and antidepressants, which try to reduce little circuiting, are common first line treatments. Psychogenic pain is real pain in the sense of an "unpleasant emotional experience," but it does not cause visible tissue damage. Psychogenic pain is neither neuropathic nor nociceptive, therefore identifying it is a process of eliminating other sorts of pain. It is a relatively infrequent source of discomfort in cancer patients (Zielińska et al., 2021). Therapy is based on psychological treatment rather than analgesic treatment.

Finally, breakthrough pain is described as a brief worsening of pain in cancer patients who are otherwise suffering from persistent pain that is managed with long-acting opioid medication (Fine et al., 2010). Up to 50% of cancer patients experience numerous, intense episodes of breakthrough pain, with exacerbations starting within minutes but lasting only 30 minutes on average (Deandrea et al., 2014). Because of worries about the negative effects of opioids, they are frequently undertreated.

Pain is fairly prevalent in everyday life and during internal clinical procedures such as surgeries, injections and other operations, and it is frequently managed with local anesthetics and painkillers in the form of injections, creams, patches, gels, oral dosage forms, and other methods. Although injections are quick and effective, they are inconvenient due to pain, and

oral administration is challenging for geriatric and pediatric patients due to swallowing issues. Due to the delayed entry of medications into the skin as a result of protective epithelial barriers, pain alleviation from creams, gels, and patches takes a long time. The microneedle (MN) patch is a patch with very small needles filled with pain-relieving compounds that penetrate deep enough into the skin to release the drugs, allowing for a faster, more effective, and painless pain management solution. (Kathuria, 2017).

3.2 Mechanism of cancer pain

The exact physiological factors underlying cancer discomfort are yet unknown. Depending on the tumor kind and location, several mechanisms are likely to be involved. A malignant lesion and its surroundings have a complex relationship; a tumor does not exist in isolation and has a dynamic association with host cells. Both release a variety of mediators involved in pain, peripheral sensitization, and angiogenesis (Magee et al., 2019).

Solid tumors require supply of blood to grow fewer millimeters in size, hence angiogenesis is difficult for tumor growth and metastatic dissemination. Tumors can possibly cause this blood supply to form by sending chemical signals that promote angiogenesis. Tumors also can induce surrounding normal cells to produce angiogenesis signaling molecules. Following basement membrane disruption, tissue hypoxia, and the release of angiogenic factors, this process begins. Angiogenesis occurs when these factors cause endothelial cells to proliferate and solidify. The new blood vessels that develop provide oxygen and nutrition to growing tumors, letting the tumor to develop and the cancer cells to enter neighboring tissue, move all over the body, and create new cancer clusters known as metastases (*Angiogenesis Inhibitors - National Cancer Institute*, n.d.). IL-8, TNF-α, vascular endothelial growth factor (VEGF), prostaglandin E, IL-6, and endothelin are some of the mediators involved in this process. IL-10, IL-12, and angiotensin, on the other hand, have inhibitory effects. Protons, endothelin, adenosine

triphosphate, neurotrophic factors, and cytokines are among the mediators linked to cancer pain. neurturin, NGF, and brain-derived neurotrophic factor (BDNF) are examples of neurotrophic factors that have been involved (Magee et al., 2019).

3.2.1 Peripheral Sensitization

Nociceptive sensations are converted into action potentials in sensory neurons, although the exact methods by which this happens after mechanical nociceptor stimulation are unknown. Despite the fact that nociceptors have high activation thresholds, repetitive stimulation increases nociceptor excitability. Excitatory receptors are increased as inflammatory chemicals, such as bradykinin, prostaglandins, and substance P, are produced from a site of damaged tissue (Voscopoulos & Lema, 2010).

As a result, patients' pain sensitivity is heightened (hyperalgesia). Elevated voltage-gated sodium channel expression and lower potassium channel expression in neurons may also help in peripheral sensitization in chronic pain disorders. Peripheral sensitization causes receptors and ion channels to undergo transcriptional and translational changes, resulting in a lower threshold for neural activation and a larger magnitude of response. The mediators and mechanisms involved in the development of cancer and non-cancer pain appear to be comparable (Magee et al., 2019).

3.2.2 Central Sensitization

Increased membrane excitability and synaptic transmission, as well as decreased descending inhibition, cause central sensitization, resulting in states of facilitation, potentiation, or amplification. Excitatory sensory neuropeptides glutamate and like substance P interact with neuronal G protein-coupled receptors to decreased second-order neurons' action potential thresholds in the dorsal horn. Ascending neuron excitability is increased even more when

glycine-mediated and descending GABA inhibitory signals are reduced. The N-methyl-D-aspartate (NMDA) receptors are also important in central sensitization (D.J. et al., 2018).

Under normal physiological settings, Mg2+ ion blocks the receptor, which is expelled after persistent afferent input, enabling Ca2+ to pass. These receptors upregulate in persistent pain states which then allows rising pain signals to be sent with typically subthreshold stimuli, resulting in a "wind-up" effect. Depending on the underlying pain state, in the dorsal horn neurochemical alterations occurs and spinal cord that cause central sensitization in persistent pain states differ. When comparing wide dynamic range (WDR) neurons to nociceptive specific (NS) neurons electrophysiological investigations in cancer pain have revealed a larger percentage of WDR neurons, showing that NS cells have been sensitized and behave functionally as WDR cells. WDR neurons have higher spontaneous activity as well as greater sensitivity to and mechanical stimuli and temperature. Non-painful stimuli, such as light, pressure and touch can also elicit agonizing sensations (allodynia) (Magee et al., 2019).

3.3 Treatment Options - current (approved) and in trial

Pain is perceived by the body through a complex network of connecting channels. Pharmacologic medicines that target different parts of the nerve system depending on the etiology of the pain have the greatest results in treating both chronic and acute pain.

Anticonvulsants, antidepressants, anesthetics, and analgesics are some of the medications that can help with sensory hyper excitability. Calcium channels, G-protein–coupled membrane receptors monoamine absorption pathways, and sodium channels are the most common targets. Different drugs may work better for different types of pain. Tricyclic antidepressants, anticonvulsants, norepinephrine reuptake inhibitors (SNRIs), and serotonin, for example, may be the best treatments for neuropathic pain. Acetaminophen which is a nonsteroidal anti-

inflammatory medications (NSAIDs), or tramadol may be the Grade A treatments for osteoarthritis. In addition to tramadol, tricyclic antidepressants, anticonvulsants, selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors or serotonin and muscle relaxants may help in fibromyalgia. NSAIDs, acetaminophen, muscle relaxants, and tramadol may be the best treatments for low back pain (Dinakar & Stillman, 2016).

Multiple receptors, including the NMDA receptor, are activated in the spinal cord when glutamate and peptides are released. As a result, glutamate is released, which might lead to spinal hypersensitivity. There are some medications that can block excitability, as well as they promote inhibition in the spinal cord. The NMDA receptor–driven excitement is modulated by ketamine. Opioids like fentanyl, codeine, morphine, and oxycodone, for example, target the descending pain modulatory system via postsynaptic and presynaptic inhibitory actions on spinal neurons, peripheral and central C-fiber terminals, and supraspinal processes. Non-pharmaceutical therapies, such as cognitive behavioral therapy (CBT) and mindfulness practices, help to alleviate pain by addressing these top-down processes(Gilron et al., 2013).

There is no such thing as a perfect analgesic medicine, hence alternative treatments are needed to give more targeted and safer analgesia for neuropathic pain without the drawbacks.

A group of researchers recently looked into the effect of full-spectrum cannabis extract ‘cannador' in the treatment of neuropathic pain and discovered that it is effective (Maayah et al., 2020).

On rat models, many groups of researchers assessed the analgesic efficacy of Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), and their combination. Sativex® (Nabiximols), which contains the 2.5 mg and 2.7 mg doses of CBD and Δ9-THC, respectively, is one of the well-studied CBD-containing registered products. CBD and THC co-administration has been presented to be efficacious in decreasing pain in a variety of conditions

in clinical tests. It has been presented to reduce neuropathic pain and enhance quality of life in patients with a variety of illnesses, including multiple sclerosis, cancer, and rheumatoid arthritis (Hoggart et al., 2015).

Another group of researchers focused solely on CBD's clinical usefulness. CBD was discovered to be a well-tolerated and safe natural chemical with analgesic benefits in animal models of pain and clinical research. In both pre-clinical and clinical trials, the research cited show that CBD has a positive impact on the treatment of numerous disorders. CBD has been shown to have analgesic effects in the majority of animal investigations, reducing hyperalgesia and mechanical/thermal allodynia by multiple methods of administration (Mlost et al., 2020).

Another study looked at the analgesic properties of Rubimaillin (Rub) in mouse models. Rub lowered the amount of acetic acid-induced writhing in mice, decreased formalin-induced biphasic pain response, and lowered nitric oxide generation, according to tests (NO). The suppression of cyclooxygenase-2 (COX-2), endogenous inflammatory mediators, and a decrease in the content of pain-induced mediators may be involved in the analgesic and anti-inflammatory actions of Rub (Yan et al., 2020).

Another study looked into the analgesic effects of chewing gum in the treatment of burning mouth condition (BMS). BMS patients have greater plasma adrenaline levels, according to the findings. Adrenaline plays a role in the growth of BMS pain. The analgesic effect of gum chewing is generated by the prospective benefits of anxiety reduction rather than the gum chewing motion, according to the findings (Sekine et al., 2020).

In rat models, a tramadol-coated microneedle was tested as a platform for pain reduction. The final findings show that tramadol delivered via coated microneedles has a longer-lasting anti-nociceptive effect. It lasted up to two days after tramadol delivery, compared to an anti-

nociceptive effect lasting less than two hours after tramadol injection into the TMJ (Abdalla et al., 2019).

A clinical trial involving transdermal zolmitriptan was done to relieve migraine pain. Absorption was shown to be 2-hours faster and higher than oral delivery. More than 75% of test patients were satisfied with the treatment, according to clinical data (Rapoport et al., 2020).

Chapter 4

Microneedle

4.1 Brief History

The microneedle was initially demonstrated in 1976, and an American patent for the microneedle for transdermal distribution was issued at the same time. MNs (an array of MN) are a drug delivery device comprising a number of branches emerging from a drug reservoir and meant to perfuse for local or systemic drug delivery, according to the Gerstel and Place patent. The patent detailed both solid and hollow MNs (Bhatnagar et al., 2017). Gerstel and Place first proposed the concept of MNs, but it was Henry et al. that coined the name "microneedle" in 1998 (Henry et al., 1998). Following then, the rapid development of the high-precision microelectronics industry has accelerated microneedle manufacture and application (Yang et al., 2019).

4.2 Routes of administration

The largest human organ and a powerful natural shield that has developed to protect the human body, is the skin. The epidermis, dermis, and subcutaneous layers are the three histological layers of the skin that are usually depicted in relation to tissue layers (figure 3). The epidermis is branched into five layers: the stratum lucidum, the stratum spinosum, the stratum granulosum, the stratum corneum (SC), and the stratum basal. The stratum corneum (SC), is the epidermis' out most layer and is primarily accountable for the barrier properties of skin due to its "brick and mortar" construction. SC is made up of 15–20 stratified, lipid-depleted, and protein-rich corneocyte layers. The hypodermis, also known as the subcutaneous layer, is the skin's deepest layer, which lies beneath the dermis and is primarily composed of adipose tissue (fat). Underneath the epidermis is the dermis, which is significantly thicker than the epidermis (usually 2-4 mm). The hypodermis contains immunologically active cells, blood, connective

tissues, collagen (70 percent), and lymphatic arteries, glands, hair follicles, and nerve terminals. For transdermal systemic distribution, the intricate capillary network in the dermis and hypodermis is essential (Bhatnagar et al., 2017; Duarah et al., 2019).

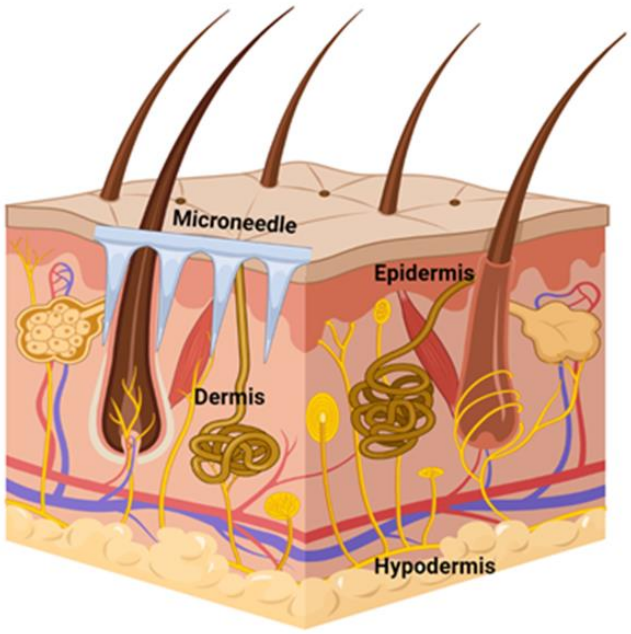

Figure 3: Layers of the human skin depicting a MN patch application (Duarah et al., 2019)

Parenteral administration, which is considered a natural alternative to oral administration, involves injecting medications into the body by a needle, which eliminates any of the aforesaid drawbacks. However, it has several disadvantages, including the necessity for aseptic materials and processes, discomfort, medical issues like hypersensitivity reactions or thrombus formation and greater expenses because of the need for experienced personnel to perform the procedure (Bruce & Wong, 2001). These microscopic devices transmit active pharmaceutical ingredients and vaccines, as well as genetic material such as RNA and DNA (W. Chen et al., 2016). The drug ingredient is delivered into the dermis via the stratum corneum, and MNs can breach the skin without producing discomfort. When delivered in a minimally invasive method, MNs have been proven to improve systemic medication adsorption and consequently bioavailability (Wermeling et al., 2008). Other penetration-enhancing techniques, such as iontophoresis,

electrophoresis, and sonophoresis, primarily harmed the stratum corneum's structure (Prausnitz, 2004). Over the last 50 years, transdermal drug delivery systems (TDDS) have been intensively explored as one of the most dependable ways for drug delivery (Ma et al., 2018; Q. Zhang et al., 2018)

The parenteral route, which uses hypodermic needles to deliver therapeutic biologics and medicines into the human body, is the most common method. Transdermal medication administration is intriguing because it can give continuous distribution over hours or days, allowing the drug level in the body to remain relatively constant. This is especially useful for medications with a narrow therapeutic window or short half-lives that would otherwise necessitate frequent dosage (Donnelly et al., 2010).

Hypodermic delivery, on the other hand, is linked to rapid degradation of delivered biologics, lowering the bioavailability of administered drugs/vaccines and needing higher doses to get the intended effect. Microneedles have recently gained a lot of recognition for cutaneous vaccination. MNs are needle-like microstructures with a length of up to 1 mm (Van Der Maaden et al., 2012), which are normally arranged in varying numbers on a patch. They pierce the stratum corneum and underlying tissue to transfer the antigen into the epidermis or dermis while remaining short enough to avoid pain receptors, resulting in the absence of pain feeling (Hegde et al., 2011).

4.3 Classification of Microneedle

MN arrays are a collection of micron-sized projections spanning in length from 25 µm to 2000 µm that are built on the one side of an associate base or patch (Tuan-Mahmood et al., 2013). Since 1990, the microelectronics sector has made significant progress, which is particularly advantageous for microneedle microfabrication. The numerous types of microneedles include solid microneedles for skin preparation, dissolving microneedles without remaining fragments, hollow microneedles for liquid formulations, coated microneedles with water-soluble pharmaceutical formulations, and swellable microneedles (figure 4) (Yang et al., 2019).

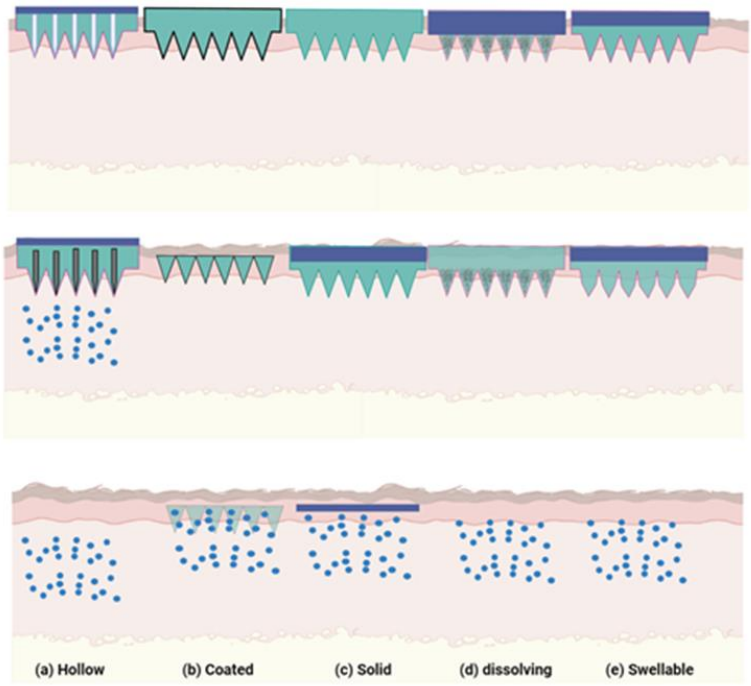

Figure 4: Schematic representation of five different MN modalities (Mccrudden et al., 2015)

Aside from that, MN can be classed based on a variety of factors like as composition, applications, manufacturing methods, and design. A general taxonomy of MNs is shown in (figure 5). The designs and applications of MNs are explored in this review.

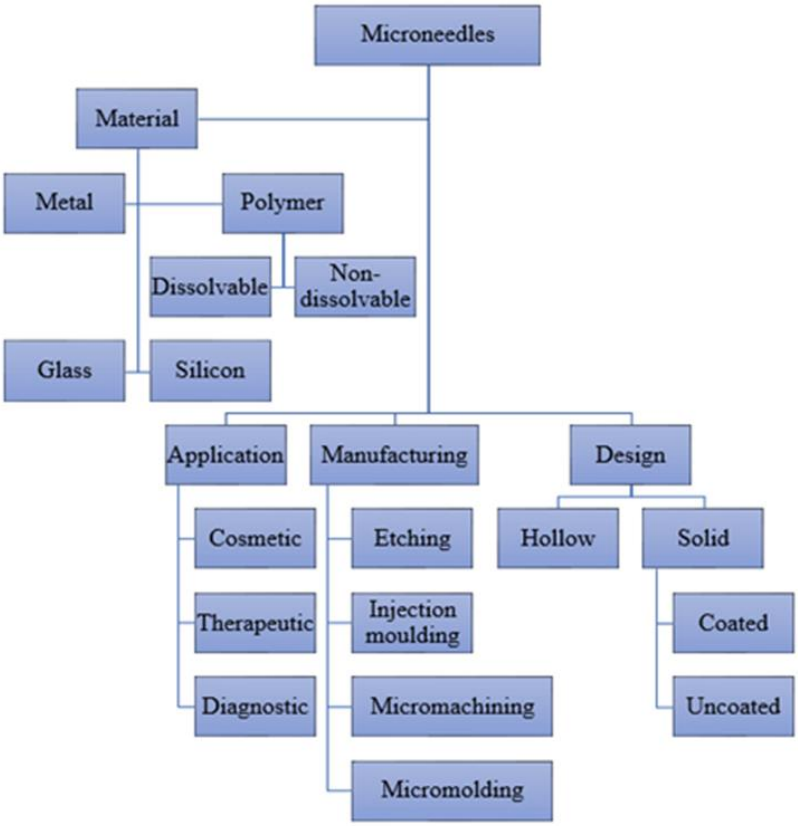

Figure 5: Broad Classification of microneedles

4.3.1 Solid microneedles

Solid microneedles for the delivery of drug were first proposed in the 1970s, but it wasn't until the 1990s that technological advances in the micromachining industry made solid MN manufacture easier (Bhatnagar et al., 2017). The "poke and patch" method involves perforating the skin with solid MNA and producing micro channels that penetrate the epidermis' innermost layers. This is it. After the pores have evolved, topical formulations (ointment, gel, and lotion) applied in the treatment of skin that can be transported into the dermis through them. After that they can be transported throughout the body via systemic circulation (Blagus et al., 2013).

Figure 6 shows how solid microneedles work in two steps: first, the micro channels in the skin are made by inserting the microneedle, then the drug formulation is allowed to pass through

the established micro channels (Kaur et al., 2014). One of the major disadvantages is that the micro holes are only open for a small time interval, potentially halting the transportation of active chemical. However, it is essential for the skin to retract and close the micro-channels after the MN patch is withdrawn from the skin. This will prevent hazardous compounds from entering the system or pathogenic organisms from infecting it (Gupta et al., 2011).

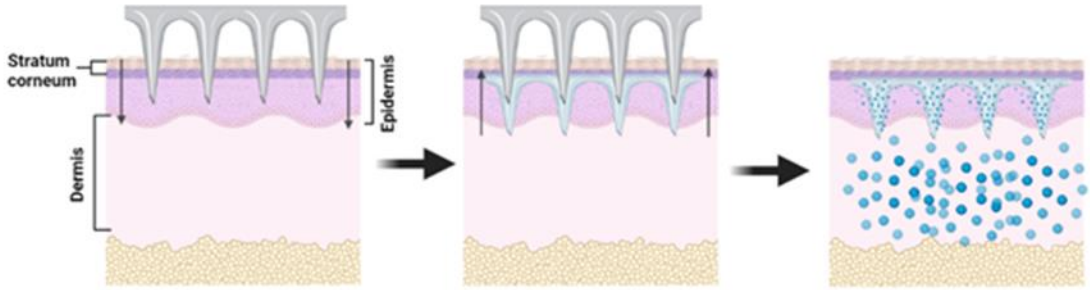

Figure 6: Schematic representation of the "poke and patch" approach with solid microneedle arrays (MNA)(Guillot et al., 2020).

4.3.2 Hollow Microneedle

Another method, known as poke and flow, consists of first penetrating hollow microneedles into the skin and delivering drugs into the dermis via the inner lumens of the MN, like SC injections (Jin et al., 2018). The goal behind the "poke and flow" method was to put a therapeutic solution in the skin, similar to hypodermic injections, while avoiding the disadvantages (Norman et al., 2013).

Hollow microneedles, unlike others, cannot be contained with a low dose, resulting in a poor therapeutic effect (Yang et al., 2019). Hollow MNs offer continuous infusion of larger medicinal components compared to solid or coated MNs that are capable of providing only a small and definite amount of medicines (figure 7) (Roxhed et al., 2008).

Their process of manufacturing is complicated and very much costly due to their micrometric size, requiring great technological resources. The usual patient accepting this technique with

smaller needles is higher than that of normal injections (Guillot et al., 2020). To distribute molecules through the skin, hollow MNs use diffusion, pressure, or electrically powered flow. A lot of extensive investigations show that flow rates can be modified through modifications in infusion parameters, like pressure of infusion, retrieval depths and tip sizes of MN (Martanto et al., 2006). The drug flow rate was found to be proportional to the internal diameter of MN and inverse to the length of the MN (Bodhale et al., 2010). The efficiency of hollow magnets can be restricted by the tissue blockage during skin insertion of the needle bore opening (Gardeniers et al., 2003).

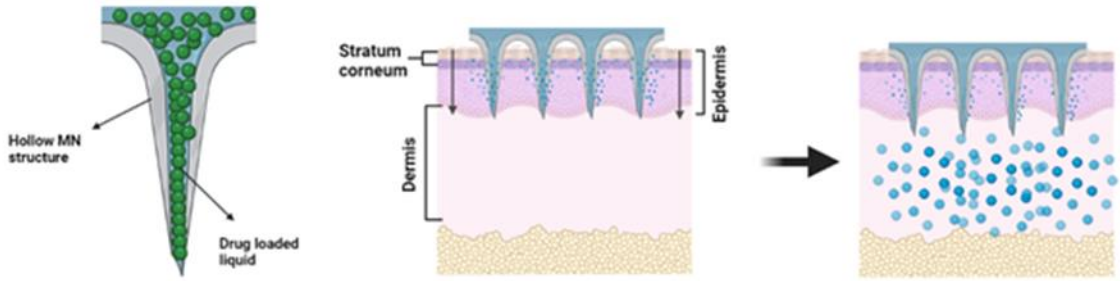

Figure 7: Schematic representation of "poke and flow" approach (Guillot et al., 2020).

4.3.3 Dissolving Microneedles

Following application to the skin, dissolving MN dissolves, allowing the encapsulated medicine to be released into the skin. The medications can be released and loaded as the MN dissolves after the insertion, and it can be prepared by a variety of biodegradable and water-soluble materials (figure 8) (Lee et al., 2019; Rodgers et al., 2018).

Dissolving microneedles consisting of safe materials such as biologically degradable polymers and natural polymers which can control the release of medicines or vaccine in the polymer. Dissolving microneedles that regulate the discharge of encapsulated therapeutic products are painless and efficient for the disease diagnosis purpose and treatment (Martin et al., 2012). This approach benefits from the dissolvement of micro-needles through adjusting the dissolution rate of the MNA matrix formulation, which allows the management of medication release for

a substantial amount of time. When the reservoir-based swelling MNs are inserted, they quickly absorb interstitial fluid and swell to form continuous, unblockable micro channels for drug administration (Donnelly et al., 2012). Because the MNA can enter the skin and remain attached until complete breakdown, it streamlines the medication administration process to a single step. Bulk micromachining and prototyping customized needle topologies, on the other hand, are still considered to be costly and time intensive (Yang et al., 2019).

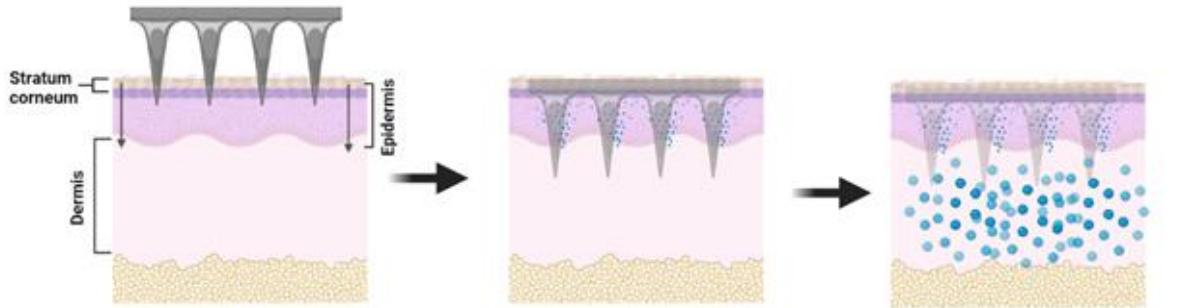

Figure 8: Schematic representation of "poke and release" approach (Guillot et al., 2020).

4.3.4 Coated Microneedle

The "coat and poke" method is another method for employing solid MNA, which entails covering with a medicine or vaccine-loft mixture the surface of the solid microneedles (Y. Chen et al., 2017). Coated MNs are covered with a dispersion that is drug-containing and are perfect to quickly bolus the production of highly molecular substances such as vaccines, proteins, peptides and DNA (Duarah et al., 2019). In the case of the coated MN method, medicines are deposited on the tip or shaft of the solid MNs, and after injection into the skin, the medicines that are covered with the MN are released inside of the tissue. After MNA implantation, this technique permits diffusion of drug from the coated surface to the deeper epidermal layers (figure 9) (Li et al., 2018).

Microneedles with a coating serve two purposes. The first is to puncture the skin, and the second is to add desired medications to the microneedle's surface. Over solid MNs, coated MNs

offer benefits such as one-step self-administration, regulated drug dose and fast cutaneous drug delivery. Chen and colleagues coated PLA microneedles with sulforhodamine B and discovered that the drug delivery effectiveness was around 90%. The continuous drug delivery was confirmed in mice in vitro tests (Y. Chen et al., 2017). Furthermore, even at room temperature, medication placed onto MNs in a solid phase holds its activity for a longer period of time (Jin et al., 2018). Lidocaine was loaded onto poly L-lactide (PLLA) microneedle arrays by Baek et al. In phosphate buffer saline, the loaded lidocaine re-released quickly and was found to be stable for poly L-lactide (PLLA) microneedle arrays. In phosphate buffer saline, the loaded lidocaine re-released quickly and was shown to remain stable for three weeks (J. Chen et al., 2018). Finally, because the needed antigen dose is usually within the range of nanograms to micrograms, the coated MNA have demonstrated an excellent immunization effectiveness.

The maximal medication dose is, however, less than 1 mg. This is why the creation of coated microneedles is restricted. Furthermore, there are concerns about the MN coating materials' consistency, homogeneity, reproducibility, and stability. Furthermore, it is important to verify that throughout the coating process or before being inserted into the skin no dangerous substances from the MN area are eliminated (Harvinder S. Gill & Prausnitz, 2007). The coating thickness could also decrease the sharpness and the perforation ability of the microneedles (Guillot et al., 2020).

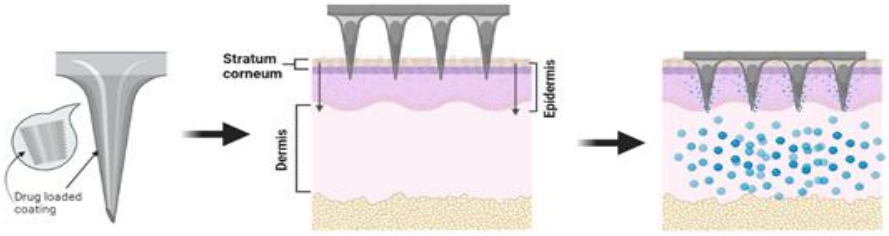

Figure 9: Schematic representation of "coat and poke" approach (Guillot et al., 2020).

4.3.5 Hydrogel-forming Microneedles

Recently, various creative approaches were developed to solve the difficulties of biocompatibility and the potential of incorrect reuse of silicon or metal MNs (Donnelly et al., 2013). As replacements to "plate and patch" procedures, hydrogel-forming MNA or swellable MNA have been created. Super-swelling polymers are formed of microneedles. Donnelly et al. were the first to apply 'super swelling' polymers to build an ensemble of hydrogel-forming MN with a drug reservoir-like patch (Donnelly et al., 2014). The hydrophilic structure of the polymers allows them to absorb a huge amount of water into their three-dimensional polymeric network (Waghule et al., 2019). The arrays do not contain any drugs, but when they penetrate the skin, they quickly absorb interstitial fluid of the skin and build routes between the reservoir of drug and the dermal microcirculation (Donnelly et al., 2014). These devices are designed to absorb skin interstitial fluid and produce continuous, unlocked micro channels among dermal capillaries upon insertion (figure 10). These microneedles are only used to disturb the epidermal barrier prior to needling. They act as a rate-controlling membrane as they swell (Waghule et al., 2019).This method allows for the release of less potent medications from a drug reservoir coupled to a patch (Donnelly et al., 2012; Raj Singh et al., 2012).

The fundamental advantage of hydrogel forming MNs in comparison with typical polymer MNs is that the pharmaceuticals provided are no longer conducted solely on the needle. They are adaptable in terms of size and shape. Microneedles with such features as easy sterilization and intact removal from the skin are rare. Hydrogel-forming MNs are especially advantageous in that they can be produced in a variety of shapes, are easily sterilizable, and can be eliminated completely from the skin (Donnelly et al., 2013).

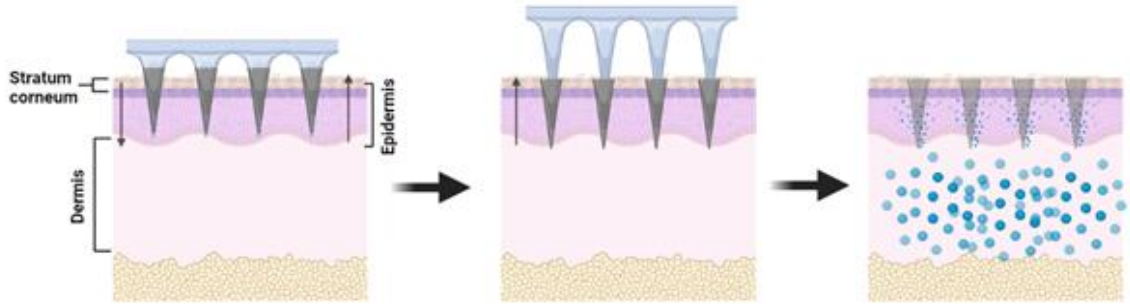

Figure 10: Schematic representation of hydrogel-forming or swelling MNA (Guillot et al., 2020).

4.4 Design of Microneedles

When designing and constructing microneedles, there are various critical design factors to consider (Krieger et al., 2019). Microneedle insertion can be made relatively painless by limiting the needle's height to the sub-millimeter range (H S Gill et al., 2008).

Despite the numerous benefits attributed to microneedle devices, more research into the elements that influence their efficacy is required (Zoudani & Soltani, 2020). However, the materials and manufacturing procedures used to make MNs have a number of drawbacks that prevent widespread implementation of such systems for transdermal drug administration. MNs' key qualities, like as toughness, flexibility, and permeability, are determined by the materials they are made of. MN devices are made from a variety of materials. The method selected must in any circumstances be exact, precise, repeatable and lasting. Laser ablation, lithography, electrodeposition, laser cutting, etching, and micro molding are among the most regularly utilized techniques (Table 1).

Table 1: Summary of advantages and disadvantages of the main materials and methods used to manufacture MNA (Guillot et al., 2020).

Fabrication Process	MNA Type	Material	Advantages	Disadvantages
Solvent casting or micro molding	Dissolving, Hydrogel-forming, Coated (coating)	Polymers	Optimal biocompatibility, biodegradation, and absence of waste after use	Mechanical properties are more difficult to achieve
Laser cutting, laser ablation, etching, electro polishing, lithography, and Micro stereolithography	Solid, Hollow, Coated (array)	Stainless steel, Titanium, Nickel, Gold	Desirable mechanical properties and high tensile strength	Desirable mechanical properties and high tensile strength

Solvent casting or micro molding	Solid, Dissolving	Sugars	Good biocompatibility	Mechanical properties are more difficult to achieve, stability problems, storage issues
Lithography and ceramic sintering	Ceramic Solid	Alumina, Zirconia, Calcium phosphate/Sulphate	Good biocompatibility	Fractures
Pulling pipettes	Hollow	Borosilicate (glass)	Good biocompatibility	Fractures
Etching, Lithography	Solid, Hollow, Coated (array	Silicone	Desirable mechanical properties	High material cost, long fabrication, and fractures

4.5 Manufacturing of Microneedles

4.5.1 3D & 4D Printing

3D print is also called additive manufacturing (AM). It produces structure in consecutive layers of material through accumulation, adhesion or polymerization until all materials, as opposed to classical subtractive and formative production, are formed (Prasad & Smyth, 2016). It is a set of technologies being used produce an additive physical object by layering it using the virtual computer aided design (CAD) model. It was first launched in the 1980s (Hull, 1984) and, because to its capacity to quick and cost-effectively prototype intricate structures, it has revolutionized pharmaceutical, biomedical, and material sciences (Pedde et al., 2017). 3D printing provides prototype and manufacturing process adaptation; objects with high complexity and reproducibility can be produced in a single phase (Pere et al., 2018). 3D printing is a term that refers to a group of technologies that use a variety of materials and physicochemical principles to generate a physical object from a virtual Computer Aided Designed (CAD) model through the creation of successive layers. Stereolithography (SLA) is a 3D printing technology that enables the fabrication of designed structures, by using a curative process called photo polymerisation, by layer polymerisation of UV-sensitive polymers (Uddin et al., 2020). The common use of medical fabrics, which is designed to support cells and produce a new tissue, has developed as 3D technology is interdisciplinary, pulling in polymer chemical science, pharmaceutical science, biology, fundamental and clinical medicine (Goole & Amighi, 2016). 3D printing is an excellent approach in the pharmaceutical sector to create simple, precise, low cost, organized and individualized systems for medication distribution. 3D structures may be printed with the necessary permeability, hydrophobicity and porosity on a functionalized surface (Sandler et al., 2011).

4D printing is the latest manufacturing technology for microneedles. The technique by which a 3D printed object is transformed into a different structure by additional energy input such as temperature, light, etc. is called 4D printing. As 4D printing is basically the same as 3D printing so it uses the same 3D printer as well as the same computer system to deposit materials in subsequent stages until a 3D structure is created. On the other hand, 4D printing makes a unique contribution to the structure, making it possible over time to modify its shape. In order for 3D printing to modify shape once activated with a certain stimulus like heat, water or light, the software requires exclusive materials and particular designs (Smith, 2020).

According to the researchers, 4D printing creates a finished product by using smart materials that change shape after printing in line with their programming. Microneedles, which are supposed to be minimally intrusive to lessen the pain and risk of infection associated with injections, were created using this technology. According to author Howon Lee, a 4D-printed microneedle array would enable more robust and long-term use of minimally invasive, pain-free, and simple-to-use microneedles for drug delivery, wound healing, biosensing, and other soft tissue applications (Balfour, 2020).

4.5.2 Advantages over traditional manufacturing

For pharmaceutical applications, there are numerous distinctions between traditional manufacturing and additive manufacturing. For starters, AM may create complicated geometries that allow pharmaceutical goods to perform several tasks, for instance a polypill with numerous kinetics of drug release in a particular tablet (K. Park, 2015). Second, AM enables customization like as printing of the anatomical components (Wu et al., 2009) in medicinal eluting implants or tailored dosages of medicinal products, for example theophylline, at a low therapeutic window (Vakili et al., 2015). Third, as suggested by Lim et al. (Lim et al., 2016) on-site manufacturing of patient pharmacotherapy may be

performed in pharmacies, where drugstores manufacture individualized tablets on-site and deliver them to patients, due to AM's quick prototype abilities and relatively easy utilization. AM is also known for being economically efficient because of its capacity to manufacture small amounts of tailored products at a low cost. The cost of AM also reduces, notably for modest production processes like standard implants, prosthesis, or personalized dosage tablets. The expiry of numerous significant AM patents exacerbates this low cost. These include stereolithography, selective laser sintering and fused deposition modeling (Santoso & Wicker, 2016).

Chapter 5

Application of Microneedle in Cancer Pain Management

When compared to orally taken analgesics, transdermal application for pain treatment has a lower risk of systemic side effects. As a result, a number of topical and transdermal medicines have been demonstrated to be effective in the treatment of acute and chronic pain.

5.1 Solid Microneedle

J. H. Park et al. produced solid polymer microneedle rollers to increase the ASA distribution. These microneedles formed micron-scale holes in the epidermis of both humans and swines, enabling the administration of acetylsalicylic acid. The quantity of acetylsalicylic acid administered increased by 1 to 2 magnitude holes in the skin, more than untreated skin, showing that the skin is more permeable to drugs (J. H. Park et al., 2010). Olatunji et al. conducted the experiment on the supply of ASA on porcine skin. For the pretreatment of porcine skin, solid metal microneedles are utilized. A patch is then placed with the ASA-loaded FSBP. The discharge of ASA from transdermal fish-scale biological polymer by the 'Poke-and Patch' method has significantly increased after treatment of the porcine skin with solid metal MNs (Olatunji et al., 2018).

Diclofenac (DCF) is a non-steroidal anti-inflammatory medicine that is both potent and economically successful (NSAID). DCF, like other medications in this family, is linked to gastrointestinal, cardiovascular, and renal damage that is dose-dependent. Pireddu et al. investigated the use of DCF nano suspensions (NS) in conjunction with a microneedle roller. In combination with a microneedles roller treatment, DCF nano suspensions were administered to the skin of newborn pigs. Final results demonstrate that when applied to undamaged skin, this formulation outperformed the control, resulting in a 3-fold larger level of DCF in the

stratum corneum. Unfortunately, regardless of needle lengths, the operation of the microneedles rollers does not improve DCF accumulation (Pireddu et al., 2020).

5.2 Dissolving Microneedle

Polydimethylsiloxane molds were used to make meloxicam-loaded dissolving microneedles. In-vitro penetration investigations revealed that approximately 100 percent of the medication was released in 60 minutes. The drug deposition was determined to be 63.37 percent, and the transdermal flux was improved to 1.60 g/cm2/hr. When compared to a free drug solution, penetration increased 2.58 times (Amodwala et al., 2017).

Another set of researchers created dissolving microneedles to distribute meloxicam in animal models to test its analgesic effectiveness. Meloxicam was delivered to the skin quickly and efficiently (79.18%) without causing skin irritation in the experiments. When compared to the control, the relative bioavailability was 122.3% , with strong anti-inflammatory and analgesic effects (J. Chen et al., 2018)

Xie et al. employ a dissolving microneedle for administration of a provincially selective, calcitonin gene-related peptide (CGRP) peptide antagonist which can induce peripheral anti-hypersensitivities through the antagonistic peripheral CGRP for the treatment of neuropathic pain Dissolvable MNs were used in this study to administer the anti-CGRP peptide directly to uncomfortable locations and alleviate localized neuropathic pain in a painless and convenient manner. There were no skin irritation or negative effects from the analgesic microneedle patch. On the application, about 75% of the microneedle dissolved in 20 minutes (Xie et al., 2017b).

In a rat model, McCrudden et al. developed and tested dissolving polymeric microneedle (MN) arrays for facilitating Ibuprofen sodium distribution. MNs were strong and pierced rat skin successfully, dissolving quickly to give the contained medication. Approximately 33 mg of the

medication primarily placed into the arrays was transported in the in vitro trials. Over the course of the 24-hour experiment, roughly 90% of the entire loaded medication was properly delivered (McCrudden et al., 2014).

Fentanyl is a powerful opioid that can be used to treat cancer pain. Fentanyl is a low-molecular-weight synthetic -opioid receptor agonist that is extremely lipid-soluble. For the management of chronic and acute pain, fentanyl is offered as an injection and a transdermal patch. Because of the potential for abuse, these items require strict regulatory restrictions and disposal label warnings (Schug & Ting, 2017).

To address this, Maurya et al investigated the anti-nociceptive efficacy of fentanyl given using soluble microneedles in a regional setting. Mold casting was used to create microneedles, with the casting material, hyaluronic acid (HA). In rats, the anti-nociceptivity of the microneedle patches has been examined by evaluation of paw retraction latency in contrast to patches for systemic distribution when subjected to a heat stimulation. The findings show that fentanyl delivered regionally using soluble microneedles has an anti-nociceptive impact. When it is differentiated from the adhesive dermal patch (6 h), the microneedle patch had a faster onset of analgesic action (0.5 h). Although more clinical research into this route of opioid delivery is needed, it reveals the efficiency of microneedle-mediated pain treatment for rapid pain alleviation (Maurya et al., 2019)

5.3 Coated Microneedle

Photolithography was employed by Kathuria et al to administer lidocaine into skin using MNs manufactured of PEGDA. MN may perpendicularly transport lidocain to the skin and release the active ingredient in an in vitro and in vivo trial to alleviate acute and chronic pain (Kathuria et al., 2016).

Zhang et al used injection to make the coated MNs. Dip-coating was utilized to apply the lidocaine to the MNs. Lidocaine was delivered into the skin of swine using the MN. The lidocaine quickly dissolved from MNs and caused local analgesics in vivo for about 1 minute, which simplified routine or emergency therapy (Y. Zhang et al., 2012).

Meanwhile, Kochhar et al. developed a microneedle patch to deliver lidocaine, a pain reliever that can be used for both acute and chronic pain. The high drug loading microneedle patch could transfer lidocaine into skin and disseminate the active component in the management acute and chronic pain (Kochhar et al., 2013).

A microneedle Integrated Transdermal Patch (MITP) for quick onset and persistent lidocain delivery has been developed lately by the same group of researchers. The distribution of MITP lidocaine was discovered more rapid than Lignopad in 5 minutes from the administration of MITP, compared with 45 minutes for Lignopad in lidocain penetrating rat-skin. It is meant to supply a reservoir with a large load of medication, swiftly release the first drug load, and then permanently release the active ingredient. This integrated patch could therefore be an excellent approach of drug administration for pediatric and chronic health care applications (Kochhar et al., 2019).

Chen et al. have developed a photolithographic integrated micronedle transdermal patch (MITP) process, in which microneedles can quickly produce lidocaine in a micrometer sized chaneel in the skin while the drug's bulk retaining reservoir patch allows greater drug loading and continues to release the drug for a long time. They also stated that the phototriggerable microneedle technology can deliver lidocaine to the skin when stimulated by near-infrared (NIR) light. A PCL-PLA supporting array and a PVA/PVP coating layer are used to make the microneedle patch. Light-induced heating might stimulate lidocaine release from the microneedle patch and reduce pain when it was put into the skin and exposed to NIR light

stimulation. It has a faster initial rate of lidocaine delivery and can permeate skin within 5 minutes of MITP application. Patients may experience faster pain alleviation as a result of the faster penetration. A greater amount of lidocaine penetrating through the skin can potentially shorten the patch application time, lowering the risk of skin irritation. The integrated patch has the potential to be a good clinical tool for pediatric applications for the management of perioperative and chronic pain in cancer patients, and it may be employed in home care settings because of its ease of use (M. C. Chen et al., 2017). A larger proportion of lidocaine that penetrates the skin can reduce the time required to apply the patch, minimizing the chances of skin irritation. It can be used in home-care environments due to its ease of use as the integrated patch is an excellent clinical instrument for pediatric applications to treat perioperative and chronic pain in cancer people (M. C. Chen et al., 2017). Greater penetration of lidocaine into the skin can reduce the time of application of the patch and the risk of skin irritation. The integrated patch could be an excellent therapeutic tool for pediatric applications for perioperative and chronic pain management in cancer patients and can be used easily in home treatment environments (M. C. Chen et al., 2017). Increased lidocaine across the skin may reduce the applied time of the patch and reduce the risk of skin irritation. The integrated patch has the potential to be an effective clinical tool for pediatric applications for the management of perioperative and chronic pain in cancer patients, and it may be implemented in home care settings for its convenience of use (M. C. Chen et al., 2017).(M. C. Chen et al., 2017).

15-deoxy-Δ12, 14-prostaglandin J2 (15d-PGJ2) is a naturally arising anti-inflammatory substance produced by the human body. To test the drug's efficacy in pain relief, Macedo et al. designed and incorporated coated MNs into rat models. In a rat model, the skin was prepared with microneedle without causing any discomfort. After MN therapy, topical administration of 100 μg of 15d-PGJ2 was not as efficacious as injection of 100 μg. They calculated that 15d-PGJ2 bioavailability through MN-treated skin is close to 50%. TNF-α and IL-1β levels were

observed to be greatly lowered after formalin challenge, and they remained at low levels for up to 8 hours after 15d-PGJ2 administration. These modest levels are linked to reduced nociception for up to 8 hours (Macedo et al., 2017).

Abdalla et al. proposed a unique technique to distribute tramadol with MNs, based on the safety profile of tramadol compared to other opioids. Microneedles coated with tramadol were tested as a platform for treating temporomandibular joint (TMJ) discomfort in rats in this study.

The findings indicate that tramadol delivered directly into the tissues may have an anti-inflammatory impact. Tramadol-coated MNs were found to be more efficacious than intra-TMJ injections. Overall, our findings support the use of MNs coated with tramadol in a direct therapeutic approach to pain management (Abdalla et al., 2019).

5.4 Hydrogel Microneedle

Indomethacin's usefulness in the treatment of acute pain and inflammation is well recognized. In a number of studies, indomethacin provided pain alleviation that was comparable to or better than that of other NSAIDs and opioids (Nalamachu & Wortmann, 2014). Indermun et al. used sodium indomethacin to manufacture and test an electro-modulated hydrogel microneedle array (EMHM) for the treatment of chronic pain in a rat model. The levels of sodium indomethacin in the plasma were lower than those achieved by traditional IV administration, but they were still within the therapeutic range. The medication delivery system was also well tolerated, with no symptoms of irritation (Indermun et al., 2017).

Hardy et al. later created ibuprofen-delivery microneedle arrays consisting of hydrogel-forming microneedles built of light-responsive polymers. With an optical device, up to three doses of ibuprofen 50 mg were given over a lengthy time, showing its potential for long-term medication management (Hardy et al., 2016). Ramöller et al. has developed a unique method for delivering

ibuprofen via a hydrogel that forms polymeric micro array patches (MAP). Industrial micro molds with a high needle density were used to make these patches. Both a newborn porcine skin and an artificial skin model can be transplanted effectively with MAPs. The amount of ibuprofen administered between the traditional and high-density patches was not different after 24 hours. The permeability profile seen with high-density MAPs, on the contrary, followed a linear zero-order kinetics and in 24 hours the plateau was not attained to emphasize its usefulness for the administration of long-term drugs (Ramöller et al., 2020).

Chapter 6

Conclusion & Future Aspects

Microneedles are now a very well-present and forward-looking resource in the area of transdermal drugs. Their tremendous potential is to disturb the barrier properties of the skin and hence to be less invasive than previous techniques. The injection of these equipment does not contact the nerve endings of the skin, which makes the distribution of drugs to cancer patients a practically painless procedure. Cancer patients suffer from agony and pain as a result of the disease itself and medications as well. In this situation the best solution is to administer potent and efficient analgesics without causing additional nerve pain to alleviate the pain sensation. The levels of anxiety created by MNA have been demonstrated to be far lower than those induced by conventional approaches such as injections, possibly improving levels of compliance, in particular amongst the cancer population. This paper provided a comprehensive evaluation of the therapeutic uses of MN-technology, with an emphasis on cancer pain management. MNs may be employed both to produce local and systemic effects when the drug is released at stratum corneal intersection and viable epidermis. It appears that MN-based delivery of analgesics are gaining popularity in management of different cancer pains. However, potent opioids such as morphine, codeine and buprenorphine which are already being used in the management of cancer pain via oral and topical routes are still needed to be investigated to utilize MN technology. The use of fentanyl patches and microneedle arrays are gaining popularity in the management of pain. Nevertheless, the efficacy and potency of transdermal fentanyl needs more research and evidence to be included in the clinical practice.

Even though many research using a variety of compounds to control pain effectively are currently in progress, the industrial interest in MNA as a result of favorable outcomes is lower

than we may have expected. Research should in this respect try to enhance the evidence of MNA use beyond immunization, to increase the spectrum of therapies feasible and other exciting options for the population. It is hoped that this review can serve as a foundation for the study of microneedle delivery systems and promote the clinical application of microneedles in the future.

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