POTENTIAL OF NANOPARTICLES AS A TOPICAL DRUG DELIVERY SYSTEM FOR SKIN CANCER: A REVIEW

By

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Declaration

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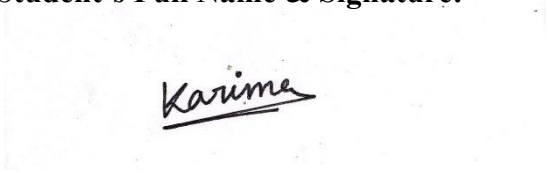

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Approval

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Ethics Statement

This project does not involve any clinical trial or human participants and no animals were used or harmed.

Abstract

Skin cancer is among the most widespread and challenging forms of cancer, with high death rates globally, the seventeenth most prevalent cancer in the world. Conventional treatment options for skin cancer, including surgical procedures, immunotherapy, radiation therapy, chemical peels, photodynamic therapy, chemotherapy, topical therapy, curettage and electrodesiccation, and cryotherapy, have many limitations which could be surpassed by the use of nanoparticle-based drug delivery systems. In addition to providing targeted treatment for skin cancer, nanoparticle-based drug carriers have the ability to improve the bioavailability, specificity, and therapeutic effectiveness of anti-cancer drugs and increase patient adherence. The present review summarizes the potential of different categories of nanoparticles that are currently being explored in order to treat and diagnose skin cancer. A brief introduction about the different types of skin cancer has also been included, followed by the application of nanoparticles-based therapy for the treatment of these different types of skin cancer. In the end, the challenges related to the formulation and development of nanoparticles for skin cancer and the current progress of use of this specialized drug delivery system have been highlighted with a direction towards ways to overcome these challenges.

Keywords: Nanoparticle; Skin cancer; Nanotechnology; Melanoma

Dedication

It is dedicated to my parents.

Acknowledgment

I would like to express my heartfelt gratitude to my supervisor, Dr. Zara Sheikh, for her unwavering support and guidance as well as for encouraging me, proofreading my paper, and correcting my numerous mistakes. My special thanks to all the faculty members, Deputy Chair, and Dean of the School of Pharmacy for their support throughout my Bachelor's journey. I am extremely grateful for the guidance provided by the School of Pharmacy.

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List of Acronyms

SC	Skin Cancer
NP	Nanoparticle
SCC	Squamous Cell Carcinoma
BCC	Basal Cell Carcinoma
NMSC	Non-Melanoma Skin Cancer
cSCC	Cutaneous Squamous Cell Carcinoma
PDT	Photodynamic Therapy
PTX	Paclitaxel
ROS	Reactive Oxygen Species
FU	Fluorouracil
UV	Ultraviolet
MCPyV	Merkel Cell Polyomavirus
AK	Actinic Keratosis
ALA	Aminolevulinic Acid
MAL	Methyl Aminolevulinate
IL	Interleukin
INF	Interferon
CTLA-4	Cytotoxic T-Lymphocyte Antigen-4

EGFR	Epidermal Growth Factor Receptor
DNA	Deoxyribonucleic Acid
EPR	Enhanced Permeability and Retention
DOX	Doxorubicin
siRNA	Small Inhibitor Ribonucleic Acid
API	Active Pharmaceutical Ingredient
BL	Bromelain
TEWL	Transepidermal Water Loss
CNTs	Carbon Nanotubes
Cur	Curcumin
BSAO	Bovine Serum Amine Oxidase
NHs	Nano Hydrogels
HA-CH	Cholesterol-graft-Hyaluronic Acid
AgNPs	Silver Nanoparticles
AuNPs	Gold Nanoparticles
HaCaT	Human Epidermal Keratinocyte
JNK	c-Jun N-terminal kinase
PLGA	Poly (lactic-co-glycolic acid)
PS	Photosensitizer

SLNs	Solid Lipid Nanoparticles
QDs	Quantum Dots
PCR	Polymerase Chain Reaction
NMR	Nuclear Magnetic Resonance
As	Arsenic
NE	Nanoemulsion

Chapter 1

The Introduction

1.1 Background

Skin malignancies are among the most widespread and challenging types of cancer, with extremely high death rates globally. Skin melanoma is the seventeenth most common cancer. (Skin Cancer Statistics, 2020) According to the most recent WHO data published in 2020, there were 853 skin cancer deaths in Bangladesh, or 0.12% of all deaths. In 2020, there were more than 150,000 new instances of cutaneous melanoma worldwide. Radiation exposure, drugs used to suppress the immune system following organ donation, infection with human papillomavirus, exposure to polychlorinated biphenyls, genetics and family history, and skin pigmentation are all linked with a high risk of skin cancer. Arsenic in drinking water raises the risk of lung cancer, bladder cancer, and skin cancer (Skin Cancer Statistics, 2022). Arsenic is a very well-known carcinogen that has been linked to skin cancer and a variety of internal tumors (Tondel et al., 1999). Approximately 100 million individuals are exposed to arsenic globally, most notably in Bangladesh, China, India, Chile, Taiwan, Mexico, and the United States of America (Yu et al., 2018). Epidemiologic research indicates that the elevated cancer risk associated with prolonged arsenic exposure may remain for many years after the source of exposure has ceased (Argos et al., 2013). Chemotherapy, surgery, and radiation are only a few current skin cancer (SC) therapies. Generally, the treatment choices for SC are determined by the patient's health as well as the form of carcinoma. SC therapy's success is still limited due to the poor penetration of drugs into the lesions or stratum corneum, its ineffectiveness, and the requirement for a more significant quantity of active pharmaceutical ingredient (API) to provide a therapeutic impact (R. Jain et al., 2020). Apart from limited bioavailability at the action site, the greater amount of dose needed results in skin irritation, which considerably

impairs the absorption of drugs into the skin. In this context, the use of nanocarriers could circumvent the limitations of traditional anticancer drug delivery methods. Nanotechnology-based therapy has demonstrated significant potential in treating and diagnosing skin cancer, and it may be utilized to increase the efficiency of drug delivery systems for cancer treatment. (R. Jain et al., 2020).

1.2 Rationale

Conventional methods of skin cancer treatment include surgery, photodynamic therapy, radiation therapy, chemical peeling, immunotherapy, chemotherapy, and cryotherapy. Simple excision, shave excision, Mohs micrographic surgery, dermabrasion, laser surgery, curettage, and electrodesiccation are all invasive treatments that might result in secondary infection and scarring. On the other hand, chemotherapy, radiation therapy, and immunotherapy, do not provide targeted treatment, resulting in higher toxicity. Nanotechnology has transformed the administration of drugs via topical, oral, and systemic routes. Nanoparticles based drug mediators can boost drugs' bioavailability, therapeutic effectiveness, and specificity and increases compliance of the patient (Krishnan & Mitragotri, 2020). In this context, nanoparticles (NPs) based therapy have the potential to treat SC by avoiding first-pass metabolism, enhancing absorption via skin, providing targeted drug delivery to the action site while lowering unwanted adverse effects.

1.3 Aims of the review

The review focuses on the potential of nanoparticles (NPs) to treat skin cancer along with the challenges associated in development of nanoparticles for the treatment of skin cancer. The different types of NPs currently explored for diagnostic and therapeutic purposes of skin cancer treatment has been discussed with a direction towards future application of NPs in the field of skin cancer.

Chapter 2

Literature Search

A thorough review of the current literature on use of nanoparticles-based technology on skin cancer diagnosis and treatment was undertaken using PubMed, Google Scholar, Elsevier, Science Direct, Springer, and Cancer Registry webpages. The key words/phrases to search the papers used were skin cancer, nanoparticles, melanoma skin cancer, non-melanoma skin cancer, squamous cell carcinoma, basal cell carcinoma diagnosis, cancer prevention, and skin cancer therapy. Approximately 50 papers were selected for the review, to include pertinent data and information, with appropriate citation using Mendeley Library to present a comprehensive review on nanoparticle for skin cancer therapy. The review provides information on the current scenario of the use of nanoparticles (NPs) and therapeutic implications of NPs in the management of SC.

Chapter 3

The Skin and Skin Cancer

3.1 Anatomy and Physiology of the Skin

The largest organ in the body is the skin, accounting for roughly 16% of total body mass. The epidermis and dermis are the skin's two major layers composed of epithelial, mesenchymal, glandular, and neurovascular components (Simões et al., 2015).

The epidermis, which originates from ectodermal cells, is the outermost layer that comes into touch with the outside world, acting as a physical and chemical impediment to environmental stresses such as infections, chemicals, as well as ultraviolet radiation. This film, thus serves as the body's defense mechanism (Simões et al., 2015). Different types of cells are present in epidermis such as keratinocytes, defined by their cytokeratin expression and their proximity to one another via desmosomes and tight junctions. As epidermal keratinocytes migrate outwards through the skin's surface, they undergo planned differentiation, eventually creating corneocytes, densely linked deceased yet undamaged cells that constitute the epidermis's main barrier (Madison, 2003; Proksch et al., 2008).

Dermis originates from mesoderm and holds cutaneous structures such as hair follicles, sweat glands, sebaceous glands, and nerves. Additionally, the dermis anchors many cells of the immune system and fibroblasts, which are involved in various physiologic reactions of the skin (D'Orazio et al., 2013; Proksch et al., 2008).

3.2 Skin Cancer

3.2.1 Epidemiology of skin cancer

3.2.1.1 Skin cancer in Bangladesh

Arsenic (As) exposure is a significant public health issue in Bangladesh (Argos et al., 2013). Bangladesh happens to be one of the worst impacted places with widespread As poisoning: in 41 out of 64 districts, 30–70 million people may have been drinking arsenic-contaminated water having more than 50µg/L As (the present drinking water limit of As in a number of countries) for a long time as the polluted water in the ground is the country's key water source for drinking (Argos et al., 2013; Tondel et al., 1999). Skin Cancer Fatalities in Bangladesh reached 301 in 2018, accounting for 0.04 percent of total deaths, according to the most recent WHO statistics published in 2018. Long-term As exposure impairs the immune system of some vulnerable people. Skin lesions (malignant and non-malignant) are the most often reported adverse health rigorousness of prolonged As exposure in humans (Yu et al., 2018). The incidence and complexity of arsenic-induced physiological problems of the skin are dependent on the amount of As in drinking water and also the usage length. Additionally, starvation increases the toxicity of As (Maharjan et al., 2007; Mitra et al., 2004). In South Asia, underground water supplies the majority of drinking water, and subsequently skin lesions have been observed in Bangladesh, Myanmar, Nepal and India, due to As-contaminated groundwater (Chakraborti et al., 2003; Guha Mazumder et al., 1998). Numerous epidemiological investigations in humans have established that arsenic in municipal water supplies and air is carcinogenic, causing skin conditions, melanoma, and lung cancer (Y. Chen & Ahsan, 2004; Ferreccio et al., 2000; Rahman et al., 2006). While efforts to limit the arsenic exposure by contaminated water are continuing, research for finding ways to minimize the

health implications of this tragedy requires immediate attention and resources (Argos et al., 2013).

3.2.1.2 Skin Cancer Worldwide

Globally, skin malignancies have increased dramatically (Apalla, Lallas, et al., 2017; Katalinic et al., 2003; Leiter et al., 2014; Lomas et al., 2012; Rogers et al., 2015). Over the last three decades, the global incidence of squamous cell carcinoma (SCC) has increased by 3-10% a year. Over the similar time, basal cell carcinoma (BCC) has mounted by between 20% and 80% in the United States (Wadhera et al., 2006). SCC is geographically specific, with a greater prevalence rate in tropical locations (Qureshi, 2008). Additionally, there seems to be a link between SC and immunology since individuals who have had organ transplantation at an early age have a higher frequency of non-melanoma skin cancer (NMSC) (Moloney et al., 2006). Ninety-nine percent of all NMSCs are BCC or cutaneous squamous cell carcinoma (cSCC). Historically, cSCCs accounted for 20 percent of all skin malignancies, with BCCs accounting for the remainder. However, recent research assessed the anticoincidence ratio between BCC and SCC in the Medicare fee-for-service group to be 1:1 (Rogers et al., 2015). Additionally, a total rise of 263 percent in the prevalence rate of cSCC was seen between 1976-1984 as well as 2000-2010 (Muzic et al., 2017). Such an increase is linked to the aging population and advancements in diagnostic technologies (Kosmadaki, 2002). Skin lymphomas, Merkel cell carcinoma, Kaposi's sarcoma, dermatofibrosarcoma, and skin carcinosarcoma are less prevalent variants of NMSCs (Losquadro, 2017). In general, NMSCs are treatable. However, since their prevalence has grown globally and healthcare costs have skyrocketed, NMSCs have become a significant public health alarm (Guy et al., 2015; Krishnan & Mitragotri, 2020; Lewis & Weinstock, 2004). In the United States alone, around 70,000 new instances of melanoma (which accounts for the majority of skin cancer-related death) are recorded each year, and 1–

2% of the population will experience wounds that are chronic (those that do not heal by 12 weeks) over their entire life (Gottrup, 2004).

Owing to its ability to begin, develop, and accelerate the growth of skin cancer in humans, ultraviolet radiation is a lethal carcinogen. Parts of the skin excessively exposed to high levels of ultraviolet radiation, whether early in childhood or overtime as an accumulating dosage, may be predisposed to the establishment of skin cancer due to genetic changes in exposed skin (Jemec et al., 2010). In skin pigmentation illnesses such as vitiligo and albinism, the lack of functioning melanocytes leads to an increased vulnerability to the adverse action of ultraviolet light (Slominski et al., 2004).

3.2.2 Types of Skin Cancer

Skin cancer is a broad phrase that refers to various malignant skin tumors. It is classified into the two most prevalent types of skin cancer: keratinocyte cancer (non-melanoma skin cancer/NMSC) and melanoma skin cancer (MSC). Among them, the most frequently spotted kind of cancer globally is NMSC. By comparison, melanoma skin cancer is the deadliest kind (Esteva et al., 2017; Sabir et al., 2021). Types of skin cancers are discussed below:

3.2.2.1 Melanoma Skin Cancer

Melanomas are the most aggressive cancer type. Melanocytes cause symptoms such as a mole with altered size, shape, color, uneven borders, and occasionally itchiness or bleeding. Skin cancer has the potential to spread through tissues, lymphatic systems, and the bloodstream (NIH). Malignant melanomas are highly hazardous, and they are notoriously difficult to cure. Certain infectious organisms, such as viruses, bacteria, and parasites, have the potential to cause cancer or increase one's risk of acquiring it. MCPyV (Merkel Cell Polyomavirus) has the ability to cause Merkel cell carcinoma, a unique kind of SC transmitted among people by blood or other bodily fluids (Thanaraj et al., 2020). Melanoma, the most lethal type of SC, begins in

melanocytes (A. J. Miller & Mihm, 2006). Melanocytes are pigment cells that provide color to the skin and hair, and are located in the epidermis's stratum basale and hair follicles (Slominski et al., 2004). Healthy melanocytes produce melanin, which triggers the tanning response by absorbing UV radiation, and protects against skin cancer (Gray-Schopfer et al., 2007b). Suppressed immune system, sensitivity to sun, and UV ray exposure in the presence of a genetic susceptibility all affect the process of melanoma formation (A. J. ; M. M. C. Miller, 2006). Melanoma risk factors involve periodic solar radiation, fair skin tone, and geographical region. However, one kind, acral lentiginous melanoma, develops on the feet and hands of people of color (Dasari et al., 2020).

3.2.2.2 Nonmelanoma (keratinocyte cancer)

NMSC vastly exceed melanomas in occurrence, nevertheless most of them are far more treatable and have a significantly better prognosis. The SCC and BCC, the two primary types, are produced from keratinocytes on the epidermis. They are much less lethal than melanoma mostly because they tend to remain restricted to the site of infection, which simplifies therapy significantly. (Simões et al., 2015).

3.2.2.2.1 Basal Cell Carcinoma (BCC)

Although basal-cell cancer develops slowly and may cause harm to surrounding tissue, it is less capable of spreading to distant locations or causing mortality. It frequently presents as a painless elevated region of skin that is glossy and has several trivial veins running through it or as an inflamed elevated area (Thanaraj et al., 2020). BCC can destroy local tissues and frequently reappears following partial excision. It hardly ever keeps spreading, which is beneficial. The major modifiable risk factor for BCC formation is ultraviolet ray exposure from natural sources and tanning parlors. This explains why males with outdoor vocations and

elderly individuals have a greater prevalence of this malignancy. Genetic predispositions may also be involved (Apalla, Nashan, et al., 2017).

3.2.2.2.2 Squamous Cell Carcinoma (SCC)

SCC has a greater predisposition for metastasis. It often takes the form of a hard mass with a crusty surface, although it can potentially develop into an ulcer (Thanaraj et al., 2020). The second most frequent kind of skin cancer is SCC, having more than doubled occurrence during the last 30 years (Rogers et al., 2010). Chromosomal abnormalities, both quantitative and morphological, in epithelial keratinocytes are generated by UV exposure and play a role to the start of SCC. Additionally, chemical exposure, smoking tobacco, and infection with the human papillomavirus are risk factors (Dasari et al., 2020). Premalignant keratinocytes exposed to UV undergo clonal proliferation and evolve into actinic keratosis (AK) (Care et al., 2001).

Chapter 4

Conventional Therapies for Skin Cancer

Early identification and treatment of malignancy can dramatically enhance the survivability of melanoma patients. Cancer can be treated in various ways, including surgery, chemotherapy, radiation treatment, immunotherapy, photodynamic therapy, targeted therapy, and chemical peels (Thanaraj et al., 2020). The most crucial factor affecting skin cancer (SC) prognosis is early diagnosis and treatment. Treatment options for precancerous and cancerous skin lesions include surgical and non-surgical procedures (Amini et al., 2010; Fahradyan et al., 2017). Treatment for NMSCs is mainly determined by the number, thickness, and location of lesions and the patient's medical history and reappearance. Additionally, patient choice is addressed, particularly accessibility, tolerability, and insurance coverage (Goldenberg & Perl, 2014). When tumors are widespread, and the treatment area is big, non-surgical techniques are often explored for patients who are ineligible for surgery. Field-directed treatment has the potential to remove both medically visible and preclinical lesions and prevent their development in distant areas in certain instances (Goldenberg & Perl, 2014). This category comprises radiation treatment, topical chemotherapeutic or immune modulator medications, and photodynamic therapy, which are employed independently or with other techniques (Bray et al., 2016). The best treatment approach for SC is determined by the tumor's size, location, and developmental stage. Excision, radiation therapy or Mohs surgery are standard treatments for bigger SCs, whereas curettage and electrodesiccation, cryotherapy, laser therapy, or photodynamic therapy (PDT) are adequate for smaller SCs (Martinez & Otley, 2001).

4.1 Surgery

The surgical treatments used to treat BCC, SCC or actinic keratosis, are simple excision, curettage, electrodesiccation, Mohs micrographic surgery, and cryotherapy (Thanaraj et al.,

2020). These surgical methods are successful for single and visible lesions only. The benefits of surgical treatment are histological confirmation of tumor margins, fast healing, and an aesthetically acceptable bruise in most patients. Unfortunately, these invasive treatment procedures come with significant disadvantages such as the possibility of hematoma, seroma, infection, and dehiscence of the wound (Alam & Ratner, 2001), as well as discomfort, severe disfigurement, edema, gastrointestinal bleeding, development of persistent ulcers, hypopigmentation, blisters, hair loss, and scarring and also radiodermatitis with nonhealing ulcerations (Bray et al., 2016; Fahradyan et al., 2017; Garcia-Serra et al., 2003; Kimyai-Asadi et al., 2005).

4.2 Radiation Therapy

This treatment is employed to destroy or slow down the development of tumor cells by using X-rays of high energy or some other kinds of radiation (Thanaraj et al., 2020). Radiation treatment is used to treat older adults with bulky, hostile, or recurring SC who are unable to undergo surgery or in areas where surgery is unfeasible (Drake et al., 1993). It is frequently used in addition to alternative methods of therapy. Radiotherapy has several downsides, including high treatment costs, the requirement for several sessions, and the possibility of returning aggressive (Cook & Zitelli, 1998).

4.3 Photodynamic Therapy (PDT)

This procedure begins with the application to the skin of a photosensitizing compound (aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), accompanied by the activation of the compound with a particular wavelength, generating cytotoxic reactive oxygen species (ROS) capable of oxidizing the tumor's organelles. PDT offers considerably greater therapy and aesthetic benefits to skin cancer excision methods (Peng et al., 1997; Soler et al., 2001). The active component - hematoporphyrin ether – absorbs light, forming singlet oxygen

and toxic properties (Sacchini et al., 1987). In combination with other topical treatments, PDT is helpful in the treatment of superficial SCs (Kessel, 1982). Unfortunately, when a laser beam is shone on the skin, the medicine is activated and begins killing cancer cells while inflicting mild harm to healthy tissues (Thanaraj et al., 2020). At the moment, this is not a feasible therapy option due to more established alternatives (Jemec et al., 2010)

4.4 Immunotherapy

Immunotherapy is used to combat cancer by harnessing the patient's immune system. Substances synthesized in the body or in the laboratory are used to supplement, control, or reestablish the anti-cancer defense system of the body (Thanaraj et al., 2020). The most often utilized adjuvant immunotherapies for advanced melanoma include interleukin (IL)-2, carmustine, interferon (INF), paclitaxel (taxol), dacarbazine, cisplatin, and temozolomide (A. J. Miller & Mihm, 2006). As specific therapeutics for SC patients, ipilimumab as well as MAPK inhibitors trametinib, dabrafenib, and vemurafenib are available (Gray-Schopfer et al., 2007a). Ipilimumab is a medicine that has been licensed by the Food and Drug Administration (FDA) for people of age with metastatic melanoma. It functions as an immunoglobulin against cytotoxic T-lymphocyte antigen-4 (CTLA-4). It inhibits CTLA-4, permitting the suitable T cells to be activated. These mechanisms reestablish T-cell multiplication whilst simultaneously increasing the patient's potential of survival due to the anticancer immune reaction (Olszanski, 2014). Recent investigations have established that epidermal growth factor receptor (EGFR) inhibitors commonly cause cutaneous medication responses that impair life expectancy and necessitate treatment termination (Lupu et al., 2015). Additionally, it is observed that treatment for more extensive BCC lesions is less fruitful since the concentration on surface sections of the tumor masked the presence of a deeper component (Marzuka & Book, 2015).

4.5 Chemotherapy

Chemotherapy is a systemic treatment. This implies it circulates throughout the body via the bloodstream. Chemotherapy can harm normal tissue when they go through its natural cell cycle since it travels throughout the body. As a result, chemotherapy can induce adverse effects such as hair loss and nausea (What Is Chemotherapy, 2022). Chemotherapy is advantageous for avoiding and curing various superficial lesions, including superficial BCC and SCC in situ. Even, systemic chemotherapy might be necessary to treat more widespread and bigger tumors (Chakrabarty & Geisse, 2004). By triggering apoptosis, retinoids like 13-cis retinoic acid have exhibited favorable outcomes when applied regularly to superficial BCC and actinic keratoses (Niles, 2000). Cytotoxic retinoids inhibit tumor cells' proliferation and development (Lippman et al., 1987). Additionally, they increase the magnitude of gap junctions among tumor cells by doubling it and reduce desmosome density by 35% (S. J. Miller, 1991). Chemotherapy that is not aimed at advanced SC is related with various organ toxicity. This paved the way for innovative targeted medicines to be developed (Dasari et al., 2020). Traditionally to treat skin cancer, the drug which is used intravenously is paclitaxel (PTX). However, because PTX was unable to distinguish between cancerous and healthy cells, it caused a number of undesired side effects, including death in some cases. To limit cytotoxicity and side effects, it is necessary to design a method for delivering PTX to malignant cells while avoiding healthy cells (Ta et al., 2008). In this context, nanoparticles-based drug delivery system serves as promising option to deliver anti-cancer drugs for skin cancer treatment and also for diagnostic purposes of skin cancer.

Chapter 5

Nanoparticles and their Potential Therapeutic Applications in Skin Cancer

5.1 Nanoparticles and their advantages in the topical treatment of skin cancer

Considering the unpleasant effects generated by traditional treatments in individuals with melanoma, a new area of study, vehicle-based drug delivery systems, has evolved which targets the malignant cells without affecting the normal, healthy cells and circumvents the unwanted adverse effects (Bajpai, 2012; Dragu et al., 2015). Drug carriers such as nanoparticles (Cho et al., 2008), dendrimers (GILLIES & FRECHET, 2005), cyclodextrins (Challa et al., 2005), liposomes (Schmid & Korting, 1994), and hydrogels (Hoare & Kohane, 2008) are used in these sorts of drug delivery systems which include the bioactive anticancer drug within the core/pocket/scaffold. The practice of using nanoparticles in order to deliver drugs to specific areas in skin melanoma is generally predicted to alter the landscape of cancer therapies shortly. These nanoparticles can attach the polymer to the membrane of a malignant cell or nuclear or cytoplasmic receptor sites, increasing the concentration of the polymer at the targeted region while decreasing the cytotoxicity of the polymer (Sabir et al., 2021). Nanoparticle-delivered medications might have a longer biological half-life because of package protection. They might have a greater concentration at the cancer site because of the EPR (Enhanced Permeability and Retention) consequence (Prabhakar et al., 2013). The leakiness and insufficient lymphatic drainage of tumor vasculature induces EPR (Gabizon et al., 1994). As a result, nanotechnology improves therapy efficacy while minimizing adverse effects. Secondly, as nanoparticles can encompass numerous medications, it enables combination treatment. It is well established that combining immunotherapy with chemotherapy or targeted therapy results in significantly

improved treatment outcomes (Bei et al., 2010). Thirdly, nanoparticles can shield medications consisting of delicate siRNA (small interfering RNA) or proteins from a biochemical breakdown in the body because they possess stealth-like properties (Moghimi & Hunter, 2001). Finally, nanoparticles continuously discharge the medications they contain. Additionally, nanoparticles may be engineered to perform various roles, such as cancer cell targeting and image contrast (Prabhu & Patravale, 2012). Numerous nanoparticles, including liposomes, polymersomes, dendrimers, inorganic nanoparticles, carbon and protein based nanoparticles have been explored to treat melanoma (Bei et al., 2010; Liao et al., 2012; Sharifi et al., 2012). Drugs applied to the surface of the skin prevent the significant changes in plasma levels associated with the frequent administration of rapidly disappearing pharmacological components. Additionally, it enables API to evade the liver's first-pass metabolism following intestinal absorption.

There are various advantages in employing encapsulated anticancer medicines, including higher solubility of drug, increased bioavailability and stability, controlled release of drug, longer half-life, targeted distribution in the tissues or organs, with decreased dosage needed. All of the advantages described work in conjunction to help avoid unwanted side effects (Dikmen, 2011; R. Singh & Lillard, 2009).

Nanoparticles are particularly advantageous for skin-related disorders, enhancing chemical penetration and minimizing unwanted responses. Topical medication delivery via the skin enables the drug to be localized on the skin for targeted therapy while bypassing the first-pass metabolism after oral administration (Palmer & DeLouise, 2016). Additionally, topical medications are advantageous for treating clinical and sub-clinical lesions that cover a considerable portion of the body's surface area (Costa et al., 2015; Micali et al., 2014). Nanotechnology has transformed the administration of drugs via topical, oral, and parenteral routes. Nanoparticles based drug carriers can boost drugs' bioavailability, specificity, and

therapeutic effectiveness and increases compliance of the patient (Krishnan & Mitragotri, 2020). These nanostructures can overcome biological barriers and transport chemotherapeutic medications specifically to the tumor microenvironment, enabling to overcome biological barriers and transport chemotherapeutic medications specifically to the microenvironment of the tumor using a low dose thus avoiding adverse effects associated with high doses resulting in increased treatment effectiveness (Bilal & Iqbal, 2020; Sparreboom et al., 2005; R. Wang et al., 2013; M. Zhao et al., 2017). Nanoparticles provide significant advancements in skin cancer treatment through efficient transport, better cellular specificity, bioavailability, higher therapeutic effectiveness and opposition to multi-drug (Anselmo & Mitragotri, 2016; Nguyen et al., 2016; Z. Zhao et al., 2019). Furthermore, drug delivery by nanoparticles can boost drug absorption and customizable release at the intended affected region within the skin. Many applications have made use of nanoparticulate technology, including drug delivery, bioimaging, tumor targeting, and image-directed tumor elimination (Ain et al., 2020; Munir et al., 2020; Rasheed et al., 2019). Nanoparticles can pass through the skin and deliver drugs to particular tumor sites via surface modification. Numerous studies have been conducted to obtain better and new NPs with potential drug delivery efficiency to address skin cancer in recent years. Apart from the obvious benefits of nanoparticles for cancer therapy, majority of nanotechnology-based treatments are still in the early stages of research. However, certain nanoformulations have already entered clinical trials and are on the market to treat different types of cancer. Doxil® (Janssen Biotech, Horsham, PA, USA), a formulation of Dox (doxorubicin) within liposomes containing PEG (polyethylene glycol), is used in the treatment of ovarian and breast cancer, Kaposi sarcoma, and multiple myeloma (M. Zhao et al., 2017). Doxil® possesses 100 times longer half-life in the blood and a 7 times reduction in cardiocytotoxicity compared to free Dox (Gabizon et al., 1994). Another nanoformulation authorized by the FDA in the year of 2005 is Abraxane®, an albumin-bound paclitaxel

nanoparticle. It is utilized to treat a wide range of malignancies, most notably lung cancer and metastatic breast cancer (Sabir et al., 2021; Sparreboom et al., 2005; R. Wang et al., 2013). Nanotechnology is a burgeoning field for maintaining skin health and diagnosing and treating cutaneous illnesses. Nanotechnology is based on subatomic interactions with skin tissue (Gupta et al., 2013). By prolonging the stability of active compounds on the skin, it is possible to modify drug permeation/penetration (Hadgraft, 2001) and contact the stratum corneum and skin appendages directly (Guterres et al., 2007), and safeguard the medication against chemical or physical deterioration. NPs give therapeutic alternatives with significant efficacy, precision, and cost-effectiveness (Gupta et al., 2013). The scientific proof based on recent advancements in the domains of drug delivery via improved penetration via skin by NPs is quite intriguing (Knorr et al., 2009). Therapeutic applications of nanoparticles to treat and diagnos skin cancer is discussed in the next section.

5.3 Types of Nanoparticles Used for Skin Cancer Treatment

5.3.1 Lipid Nanoparticles

Lipid NPs are one of the greatest compatible NPs researched to use on the skin. These drug delivery methods have been adopted due to their favorable qualities, such as occlusive properties, improved skin perforation, and changes in release pattern associated with less adverse effects (Huber et al., 2015). One novel form of a liposome, known as the elastic type can control capillary flow via microscopic skin pores. This lipid formulation is capable of deeply penetrating and transporting the substance into the skin (Sabir et al., 2021).

Anup Jose et al. investigated the anti-melanoma efficacy of co-encapsulated curcumin and anti-STAT3 siRNA utilizing positive liposomes (Jose et al., 2018). The zeta potential, encapsulation efficiency, and particle size of the liposomes were measured. Cell line tests using viability assays on mouse melanoma cells revealed that co-encapsulation of both medicines suppressed

melanoma cell proliferation in comparison to alternative formulations. Using the iontophoretic approach, cationic liposomes containing curcumin were able to penetrate the skin to a certain depth. In mice, the *in vivo* investigations were carried out using the melanoma skin cancer cell model. Incorporating curcumin as well as STAT3 siRNA into liposomes inhibit tumor growth as shown by measuring tumor volume and weight with either curcumin or STAT3 siRNA. Furthermore, the curcumin-encapsulated liposomes-siRNA combination outperforms the intratumorally administered intervention to reduce cancer growth and STAT3 protein. It is suggested that cationic liposomes can be used topically to treat skin problems by iontophoretic co-encapsulation of small molecules and siRNA (Jose et al., 2018).

Carla Caddeo et al. examined liposome manufacturing to co-administrate natural polyphenols such as quercetin and resveratrol. When polyphenols were incorporated into liposomes, they displayed a much more efficient cellular absorption than a single drug. This study showed that fibroblasts had a greater capacity to remove ROS. Polyphenols incorporated into liposomes were tested for effectiveness in a model of mouse of cutaneous eruption. Topical treatment using liposomes significantly improves tissue damage by lowering edema and infiltration of leukocyte. As a result, the study indicated that encapsulation of polyphenol in liposomes aids the treatment of oxidative stress or inflammation associated with cancerous skin lesions (Caddeo et al., 2016).

According to Raquel Petrilli et al., SCC is a form of the tumor where the epidermal growth factor receptor (EGFR) is overexpressed (Petrilli et al., 2018). Cetuximab (an anti-EGFR antibody) is given in conjunction with chemotherapeutic medication to improve effectiveness in treating SCC. To target SCC cells, EGRF-targeted immuno-liposomes encapsulated with 5-fluorouracil (5-FU) were produced. Iontophoresis used in the SCC xenograft animal model for 5-FU-loaded immunoliposomes was to look into the impact of the intervention method on treatment effectiveness. The absorption of immunoliposomes containing cetuximab by EGFR

positive SCC cells was 3.5 times larger than the controlled uptake. According to the findings of this investigation, immuno-liposomes encapsulated 5-FU topical delivery through iontophoresis is practical for the targeted treatment of SCC (Petrilli et al., 2018). Overall, lipid nanoparticles are incredibly tolerable, stable, and preserve drugs from deterioration and allows extended drug release (Krishnan & Mitragotri, 2020).

5.3.1.1 Solid-Lipid Nanoparticles (SLNs)

A very extensively investigated NPs for topical medicine administration are solid-lipid NPs (SLNs) and polymeric NPs made of poly (lactic-co-glycolic acid) (PLGA), poly (D-lactic acid), and polycaprolactone (Rancan et al., 2009). Topical use of solid-lipid and polymeric nanoparticles increases continuous drug release and protects from worsening, resulting in distribution of drugs with precision (Dianzani et al., 2014). Application of drugs (doxorubicin) (Tupal et al., 2016), natural compounds (sesamol and resveratrol) (Geetha et al., 2015; Rigon et al., 2016), and photosensitizer (PS) (aluminum chloride phthalocyanine) (Goto et al., 2017) loaded with SLNs proves latent for the progress of effective treatments for SC (Dasari et al., 2020). SLNs are colloidal systems with diameters with a range of 50 to 1000 nm (H. Muller et al., 2011). They are synthesized using a high-pressure homogenization process from biocompatible and biodegradable solid lipids, emulsifiers, as well as water. Glycerides, triglycerides, waxes, and fatty acids are frequently utilized lipids (Mukherjee et al., 2009). SLNs can be used to encapsulate pharmaceuticals with high solubility in their lipid matrix. The drug is integrated within a solid lipophilic matrix, inhibiting early release and quick deterioration as well as a highly adaptive structure (Bhaskar et al., 2009; Y. Zhang et al., 2014). SLNs form a single layer on the skin that increases water retention within the skin resulting in enhanced absorption into the skin (S. Jain et al., 2017; Wissing & Müller, 2003). They are pretty straightforward to expand during manufacturing and sterilization while remaining cost-efficient and repeatable (Mukherjee et al., 2009).

5.3.2 Polymeric Nanoparticles

Polymeric Nano-capsules are NPs with a lipid center and an extremely thin polymeric external surface stabilized by a surfactant. Natural polymeric NPs such as albumin, chitosan, alginate, and gelatin are commonly employed for topical skin administration and targeting skin melanoma (Sabir et al., 2021).

Polymeric NPs enclosed with siRNA (small inhibitor ribonucleic acid) have the potential to precisely suppress expression of genes. Nano-encapsulation of siRNA has been used in human studies for the treatment of congenital pachyonychia and targeted administration to decrease the activation of a test gene in cancer (Sabir et al., 2021; Tan et al., 2011).

Bhatnagar et al. created a bromelain-encapsulated poly (lactic-co-glycolic acid) and investigated its anticancer properties in a skin tumorigenesis mouse model. The study findings indicated that NPs had a more significant antineoplastic impact in a skin cancer model stage II. When NPs loaded with BL was compared to free BL, tumor cells decreased, as did the % tumorigenesis and mortality. Histopathological examinations backed these findings. The evidence showed that the NPs were created to incease the efficacy of chemotherapy against cutaneous melanoma at low dosages (Bhatnagar et al., 2015).

Self-assembly of polymer chains can result in the formation of particles resembling micellar structures with a non-polar center and a polar exterior. The hydrophobic center can be utilized to include less soluble or insoluble medicines to boost bioavailability, while the outer polar exterior helps to stabilize the center in its hydrophilic environment (Torchilin, 2006). Additionally, the corona protects the drug from causing adverse effects on healthy cells and quick disintegration (Krishnan & Mitragotri, 2020).

5.3.3 Nanoemulsions (NE)

Nanoemulsions (NEs) are nanoscale thermodynamically stable emulsions of water in oil (w/o) or oil in water (o/w) that become stable via a surfactant interfacial film (W. Liu et al., 2006; Shakeel et al., 2007). They have a transparent appearance and distinct rheological properties. It is a frequently utilized delivery technique for the continuous release of APIs into the skin's deep layer. The benefit of nanoemulsions over other alternatives is that they are able to reduce transepidermal water loss (TEWL) by moisturizing the skin and thus are more permeable to APIs. They are an appealing formulation because of their higher solubilization and kinetic stability (Sabir et al., 2021).

Severino et al. studied SCC and BCC, two of the most frequent types of cancer. Chemotherapeutics employed demonstrated non-specific targeting and serious adverse effects, whereas dacarbazine nanoemulsions demonstrated sustained release and ensured chemical stability of encapsulated medicines. Nanoemulsion helps elevate drug intracellular concentrations while reducing toxicity (Severino et al., 2013).

NEs have an excellent capability for solubilizing hydrophobic drugs and transporting them with hydrophilic substances. As a result of its large surface area, it can form a tight occlusive contact with the skin, which aids in the permeation and delivery of medications into the skin's deep layers. The absorption of NEs into the skin is further boosted by surfactants and oil (e.g., oleic acid or eucalyptol), which alter the stratum corneum (Bouchemal et al., 2004; SOLANS et al., 2005).

5.3.4 Carbon Nanotubes (CNTs)

Carbon nanotubes (CNTs) are long carbon tubes that are capable of acting as biopermanent fibers (de Jong, 2008). CNTs like diamond, graphite, fullerenes, nanotubes, nanowires, graphene, and nanoribbons are the most persistent molecules with anti-oxidant and

cytoprotective properties. Initially, the conductivity of CNTs was used to build an effective biomarker sensor for skin melanoma detection and infections (Sabir et al., 2021).

According to Hanabi et al., the synthesis of antitumor drugs as well as CNTs has been studied. These CNTs containing the medicines, aminolevulinic acid and tretinoin, were tested for the composites' stability. CNTs encapsulated in tretinoin are more stable than nanotubes encapsulated in aminolevulinic acid as suggested by the findings (Hesabi & Hesabi, 2013).

One of the primary advantages of carbon nanotubes is their ability to transport API directly to melanoma cells: various investigations *in vitro* and *in vivo* have been conducted recently, employing antibody-functionalized carbon nanotubes loaded with antineoplastic drugs for the treatment of SC (Simões et al., 2015).

5.3.5 Hydrogels

Among the several drug delivery techniques, creating hydrogels using naturally derived as well as manmade polymers in the form of drug mediators has garnered particular interest. These biomaterials provide a promising prospect for developing novel cancer treatment techniques (Vishnubhakthula et al., 2017).

Hydrogel NPs—also known as polymeric nanogels or macromolecular micelles—are gaining traction as therapeutic drug carriers (Gonçalves et al., 2010). Hydrogels are three-dimensional polymeric networks that are hydrophilic and can absorb vast volumes of biological fluids, water, or chemicals (Caló & Khutoryanskiy, 2015). The capacity of hydrogels to expand and dissolve in water is another critical characteristic (Yahia, 2015). These systems exhibit unique features that enhance the drugs' efficiency while minimizing side effects (Phan et al., 2016). Topical and transdermal use of anticancer drugs using a drug delivery system can help to minimize adverse impacts while increasing the drug's effectiveness (Bharadwaj et al., 2016). The skin is a frequently targeted tissue for hydrogel applications (Wiraja et al., 2020).

However, since these nanocarriers are solely deposited in hair follicles, they have certain limitations as they may not penetrate far into the skin layer. Emine Kahraman et al. produced nano-micelles containing terpenes to address these issues and examine the possibility of skin delivery. The tape stripping technique determined the drug's buildup and penetration into the skin. The results indicated that nano-micelles containing terpinolene might result in a higher degree of drug aggregation in the skin that is striped than the commercial product and micelles devoid of a terpene. Terpinolene incorporated into nanomicelles may be a more viable method of medication delivery (Kahraman et al., 2018).

Xu et al. created paclitaxel-loaded micelles and hydrogels to treat cutaneous melanoma. The composition was studied for skin penetration and absorption. Cell lines investigations demonstrated increased absorption by B16 melanoma cells, and in vivo experiments in B16 cells showed preferred antitumor efficacy to free taxol (H. Xu et al., 2020).

Several delivery mechanisms or vehicles for topical application have been devised, including aerosols, powders, creams, and emulsions. Nevertheless, hydrogels have several benefits over more traditional kinds of treatment. This is because of modifiable/tunable hydrogels, which allow for precise control of hydrogel features like degradation rate, long-term release, and pore size management (Tsou et al., 2016). Due to hydrogels' long-term viability based on the features listed above, it is beneficial to do extensive research to identify optimal hydrogel compositions with particular properties for treating skin cancer (Vishnubhakthula et al., 2017). Traditional pharmacology had to adjust to some drawbacks of anticancer drugs, including low hydrophobicity. Significant attempts have been made in this domain to address this issue through hydrogels. Curcumin (Cur), for example, is a hydrophobic polyphenol that has antineoplastic and antiproliferative properties. However, its low solubility in water and photochemical instability have been significant impediments to its formation. Cur has been encapsulated in in-situ-forming hydrogels supported by hydroxypropyl—cyclodextrin. Cur's

therapeutic impact on melanoma has been examined in vitro. By incorporating Cur in hydrogel scaffolds, stability under light, the solubility, in vitro release, erosion, cytotoxicity, and transdermal permeability efficiency of Cur inclusion complexes were enhanced. Thus, Cur encapsulated in a hydrogel is a potential solution to treat melanoma (Sun et al., 2014).

Recent investigations have been conducted to determine the efficacy of doxorubicin (DOX) release using a hydrogel preparation. Several research papers have conducted in-depth examinations of chemotherapy for melanoma. These experiments combined a natural silk protein called sericin with dextran to create hydrogels and then added DOX to develop a drug delivery system. Subcutaneous injection of a hydrogel containing DOX dramatically inhibited tumor development in male mice in an a vivo melanoma model. Additionally, this hydrogel is biocompatible and biodegradable (J. Liu et al., 2016).

Matricardi et al. featured a novel anticancer therapeutic technique based on enzymes. The researchers in this investigation used bovine serum amine oxidase (BSAO). BSAO transforms overexpressed polyamines in cancer cells into H_2O_2 and aldehyde(s), resulting in a significant level of cytotoxicity in malignant cells. To boost the efficiency of drug delivery, they devised a formulation in which the enzyme is immobilized in injectable nano hydrogels based on cholesterol-graft-hyaluronic acid (HA-CH). In aqueous solutions, this biocompatible conjugate instantly self-assembles. (Montanari et al., 2013). Agostinelli et al. presented a "novel BSAO delivery method" in which the enzyme is immobilized on other hydrogel polymers, namely alginate/chitosan. Although the findings of this specific technique were highly encouraging, further investigation is necessary before it can be a functional therapeutic for cancer (Agostinelli et al., 2010).

5.3.6 Metallic nanoparticles

Typically, metallic NPs are composed of silver, gold, and metallic oxides. They have been widely employed in a variety of skincare products. Drugs are either integrated into the metallic

NPs' core or bonded to their surface. (Krishnan & Mitragotri, 2020) Metallic nanoparticles have been demonstrated to collect externally or within the skin, based on the qualities of the substance on the surface. Adding skin-penetrating proteins to these technologies might be an extra benefit (Y. Chen et al., 2017; Leite-Silva et al., 2016; Mahmoud et al., 2019; Niu et al., 2017; Safwat et al., 2018; D. Zheng et al., 2012).

5.3.6.1 Gold Nanoparticles

A very widely utilized platform to diagnose, treat, and monitor skin disorders, including skin cancers, is gold nanoparticles (AuNPs). Limon et al. created AuNPs covered with thiolates that are very hydrophilic. Confocal fluorescence microscopy investigated the internalization and absorption of fluorophore-coated AuNPs in human keratinocytes (Sabir et al., 2021). The functionalized NPs suppressed intracellular activity of KLK5 and HaCaT and decreased IL-8 production in response to TLR-2 ligand stimulation. The following study showed that AuNPs had a substantial ability to transport medications and antibodies intracellularly to treat skin cancer and other disorders, including Rosacea (Limón et al., 2018).

5.3.6.2 Silver Nanoparticles

Due to their antibacterial characteristics, silver nanoparticles (AgNPs) are the most extensively utilized NPs (Burdușel et al., 2018). AgNPs have a wide range of possible therapeutic uses, as evidenced by research on their potential medicinal implications. AgNPs are extensively employed in the healthcare business, medical equipment, paints, the food industries, cosmetics, feminine hygiene products, sunscreen, clothes, biosensors, and electronics (J. Liu & Jiang, 2015). The cytotoxicity of AgNPs has been investigated experimentally in a range of various cancers such as cervical, lung, breast, hepatocellular, nasopharyngeal, colorectal adenocarcinoma, glioblastoma, and prostate carcinoma (L. Xu et al., 2020). AgNPs are mostly ingested by endocytosis via lysosomes (He et al., 2012). When AgNPs are exposed to the

lysosomes' low pH environment, they dissolve into Ag ions, generating hydroxyl radicals (T. Zhang et al., 2014). Internalized AgNPs compromise the cell membrane's stability, resulting in the enlargement of lysosomes and collapse of the membrane (Yang et al., 2012). Ag ions released into the mitochondrion's inner membranes, cell membrane, and, cytoplasm react with superoxide dismutase and reduced glutathione-S-transferase impairing membrane integrity. Additionally, mitochondrial dysfunction affects electron transport, slows ATP production, and induces oxidative stress via lipid peroxidation (Arora et al., 2008). AgNPs cause cell death via mitochondrial, intrinsic, and orp53-mediated mechanisms (Foldbjerg et al., 2011). These activities suppress cell development by interfering with the G2/M phase of the cell cycle (AshaRani et al., 2009). AgNP-induced phosphorylation of histone proteins stimulates the c-Jun N-terminal kinase (JNK) pathway (X. Zhao et al., 2017). Transmission electron imaging and elemental mapping of single cells have indicated that AgNPs may diffuse to the nucleus and induce mutations associated with DNA damage (T. Zhang et al., 2014). Effective therapy is dependent on the duration of exposure dosage, dosage, the size and form of the AgNP. Surface charge, shape, coating, dissolving rate, agglomeration, and LSPR are all physicochemical features of AgNPs (Wei et al., 2015) which significantly control their electromagnetic, optical, and catalytic characteristics. Their measurements, structure, and dispersion can frequently be altered by modifying the synthesis procedures, reducing agents, and stabilizing agents (Abou El-Nour et al., 2010). Cytotoxicity of AgNP is influenced by the charge and size of the molecule. The higher surface area of smaller particles generates more significant toxicity (Johnston et al., 2010). The charge of AgNPs' coatings influence how NPs interact with specific biomolecules at the site of action (Powers et al., 2011). Polymer-drug conjugates have the potential to decrease undesirable side effects while specifically targeting sick tissue (Capanema et al., 2019).

Due to AgNPs' toxicity to non-target organs, green production of AgNP has been presented as a viable strategy for SC treatment (Gurunathan et al., 2009). The environmentally friendly synthesis of AgNPs utilizes bacteria, fungus, algae, plant extracts, or yeasts as reducing agents and stabilizers (Akter et al., 2018). SC has made use of various AgNPs biosynthesized utilizing microbes and natural sources. This approach to generating environmentally friendly NPs minimizes harmful byproducts and the use of hazardous chemicals. NP biosynthesis has several advantages, including more straightforward techniques of processing, faster manufacturing periods, low toxicity, biocompatibility, and high yield (Kalimuthu, 2010). Numerous researches have been conducted to determine the anticarcinogenic impact of green AgNPs on SC. Globular AgNPs were lethal to Mus musculus cutaneous melanoma cells after being synthesized in a one-step synthesis using Carpesium cernuum entire plant extract and reduced Ag ions (Ahn et al., 2019). AgNPs of various forms biosynthesized from Moringa oleifera (leaves), Cucurbita maxima (petals), and Acorus calamus (rhizome) extracts have shown antitumor efficacy against cutaneous carcinoma (Nayak et al., 2015).

5.3.7 Liposomes

Liposomes are amongst the most extensively investigated nanocarriers for cancer therapy (Dianzani et al., 2014). They are tiny, rounded synthetic packets composed of cholesterol and harmless naturally occuring phospholipids. Due of their size and lipophilic and polar properties, liposomes are excellent vehicles for the delivery of drug (Akbarzadeh et al., 2013). A liposome is a bilayer of lipids enclosing an aqueous center for hydrophilic drugs (Prabhu & Patravale, 2012). Between the two layers, hydrophobic medicines can be retained. Liposomes were initially employed in treatment more than 50 years ago and were the first nanoparticles to be developed (BANGHAM, 1961). A liposome is formed by sonicating a lipid, an emulsification process. A 0.2 M membrane can be used to filter homogeneous nanosized liposomes (J. Chen et al., 2013). Additionally, particular ligands directed against cancer

antigens can be added to the surface of liposome, allowing the NPs to precisely aim tumor cells (Al-Jamal et al., 2008; Sawant & Torchilin, 2012). Liposomes are used to deliver anti-cancer drugs, immune cytokines, and siRNA to improve melanoma therapy effectiveness (Bei et al., 2010).

Liposomes containing doxorubicin (Barenholz, 2001; Lukyanov et al., 2004), cisplatin (Krieger et al., 2010; Lasic, 2019), oxaliplatin (Abu Lila et al., 2010), and camptothecin (Watanabe et al., 2008) have been employed systemically to maximize drug cytotoxicity with the fewest possible adverse consequences. Combinations of topical medications including tretinoin and diclofenac-loaded liposomes have exhibited increased drug penetration into the skin compared to non-liposomal formulations (el Zaafarany et al., 2010; Kitagawa & Yuasa, 2006).

5.3.8 Magnetic NP

Magnetic nanoparticles are advantageous for theranostics (the combination of therapeutic and diagnostic technologies) (Shubayev et al., 2009). Magnetic nanocomposite spheres filled with albumin and 5-FU have been utilized to treat NMSC (Misak et al., 2013). This increases the absorption of 5-FU and lowers the adverse effects associated with traditional topical medicines. Additionally, in vitro investigations on magnetic nanoemulsions containing zinc phthalocyanine showed significant SC therapy synergistic potential. (Primo et al., 2008). Thermosensitive liposomes coated with Cetuximab containing magnetic nanoparticles and doxorubicin have been evaluated for their effectiveness as an EGFR NP-liposome drug delivery system in breast cancer cells (Dorjsuren et al., 2020)

5.3.9 Quantum Dots

Quantum dots (QDs) are fluorescent colloidal semiconductor nanocrystals. They have a wide range of absorption and asymmetric, narrow range of emission, generally visible to near-

infrared (NIR) in wavelength (Idris et al., 2012). The center of QDs is typically made of elements from 2nd to 6th groups of the periodic table (for example: cadmium, zinc, tellurium, and selenium) or 3rd to 5th groups of the periodic table (such as arsenic and phosphorus) (Y. Wang & Chen, 2011), which are "overcoated" with a zinc sulfide layer. Quantum dots are photostable; hence, their optical features make them ideal for applications requiring high sensitivity, long-term imaging, and multitarget imaging (Alivisatos, 1996; H.-C. Huang et al., 2011).

Chapter 6

Diagnostic Applications of Nanoparticles for Skin Cancer

Nanoparticles are being explored to determine the presence of melanoma and its stage of development. Early detection is crucial for melanoma patients to have a reasonable survival probability. Besides naked eye inspection and histological examination, several novel diagnostic methods have been developed, including dermoscopy, whole-body photography, multispectral digital image analysis, reflectance confocal microscopy, and RNA microarray (Ahlgrimm-Siess et al., 2012; Ferris & Harris, 2012). In metastatic melanoma, molecular markers may be used to develop an effective therapy regimen. This is critical because molecular changes are connected with changes in intracellular signaling pathways, clinical characteristics, and responses to various therapy regimens. Molecular diagnostics may soon be included in regular melanoma diagnosis (Cooper et al., 2012). A growing number of recently discovered tools, including tissue arrays, proteomics, and DNA sequencing, are being applied in the melanoma molecular diagnosis (Joyce et al., 2012). Appropriate judgment is required during melanoma therapy to determine whether the technique taken is suitable and whether there is a more effective technique to boost the responsiveness of the patient to therapy. This diagnosis is made through imaging to identify the tumor's mass and structure (Joyce et al., 2012).

Nanotechnology has been demonstrated to be a beneficial technique in improving melanoma diagnosis. Quantum Dots (QDs) are employed for cancer detection at an early stage (Kim et al., 2012; Michalet et al., 2005). QDs can be coupled with compounds including folic acid or antibodies against overexpressed tumor cell antigens (Morosini et al., 2011). Zheng et al. detected CD146 overexpressed cancer cells in cultured and fixed cells using PEG-COOH capped greatly fluorescent CdSe/ZnS core/shell QDs linked with antibodies against CD146 (H. Zheng et al., 2010). Positive cells were shown to have a high level of brightness, photostability,

and specificity using flow cytometry and confocal imaging. Kim et al. established a coculture system combining cancer cells as well as healthy skin cells to examine QDs coupled with anti-melanoma antibodies (ab732 or Ab733) (Kim et al., 2012). Melanoma cells were demonstrated to be distinct from melanocytes.

Dendrimers have been used to monitor melanoma that has metastasized. A recent work sought to synthesize a dendrimer using arginine-glycine-aspartic acid along with fluorescence (Boswell et al., n.d.). The nanoparticle was supposed to aggregate within the lump and consequently be analyzed using fluorescence or nuclear magnetic resonance (NMR) spectroscopy to determine the vascular structure and size of the tumor. The particles, however, collected in the kidney and reticuloendothelial system, as previously reported. Additional research is necessary to accomplish the objective of employing dendrimers to diagnose metastatic melanoma.

NPs are activated by a halogen lamp's white light. Simultaneously, a darkfield condenser supplies and concentrates the light on the sample's top, creating a picture of a bright item against a dark backdrop with dazzling color depending on the particle's form and size. The nonspecific adsorption of NPs with antibodies significantly scatters signals, allowing for the identification of aberrant growth in the presence of a weak signal from normal tissue (X. Huang & El-Sayed, 2010).

Gold nanorods might potentially be employed as image contrast agents in conjunction with a standard optical microscope for cancer diagnosis. Due to the large scattering cross-sections and higher photostability of gold (Au) nanoparticles, anti-EGFR coupled AuNPs attach particularly to melanoma cells due to their overexpression on the malignant cells' cytoplasmic membrane (X. Huang et al., 2006; Sokolov et al., 2003). The nanoshell structure coated with AgNP is

utilized in cancer imaging and photothermal treatment for absorbing and destroying light via the photothermal effect (Loo et al., 2005).

Chapter 7

Challenges in development of nanoparticles for skin cancer

Utilizing metallic nanoparticles, nanomedicine is among the most rapidly growing and effective ways of combating cancer. Traditional cancer treatments, including chemotherapy and radiation therapy, have drawbacks because of unforeseen drug-related adverse effects, lower drug concentrations' lack of selectivity at the tumor specified location, and the emergence of resistance against drugs (Fanciullino et al., 2013; S. Singh et al., 2012). NP-mediated therapy is the optimal as well as innovative cancer treatment method. NPs are capable of targeting specific cancer cells or tissues passively or actively, and they've been utilized as drug delivery systems (Wicki et al., 2015). Even though the fact that numerous NP-mediated techniques have been established, the the tumor's complexity and associated stroma poses a substantial obstacle for nanotechnologists and doctors attempting to build formulations that specifically target individual cancerous cells. Using novel nanoparticles in system techniques to transcend the limits of traditional chemotherapy and achieve more specificity, reduced toxicity, biocompatibility, safety, and improved efficacy is another issue in cancer therapy. However, the problems and limits of employing NPs for cancer therapy must be addressed. These include physiological hurdles, confined loading capacity, EPR, nanoparticle diversity, and regulatory and production issues (Wicki et al., 2015).

Specifically targeting molecular alterations or immunological characteristics, new drugs against SC and melanoma cells are considerably better than traditional chemotherapy, but the greater toxicity as well as the development of resistance are the key constraints to their usage. Therefore, it is therapeutically important to create techniques that can improve drug efficacy, circumvent resistance, and lower adverse effects. In this respect, nanomedicine has provided a number of cues for enhancing drug delivery and release, as well as reducing therapeutic doses. Recently, nanotechnology has achieved noteworthy strides in the development of appropriate

targeted medicines as well as diagnostic markers. Several studies have indicated that few nanomaterials used to create NPs are therapeutically inactive; nevertheless, the loading of agents and ligands may alter the harmfulness of the particles. In addition, despite the fact that passive targeting based on the EPR effect promotes the concentration and retention of the NPs at the cancer site, physical characteristics such as mass, dimentions, and charge can influence their pharmacokinetic as well as pharmacodynamic profiles. Most NPs injected into the body eventually appear in liver, kidney, and spleen, despite the EPR effect (Bae & Park, 2011). This implies that every NP should undergo organ toxicity testing (Pizzimenti et al., 2016)

Another challenge is the absence of common guidelines for measuring the potent cytotoxicity of NPs as well as surfactants. Before the commercialization of NP, this problem is inevitable and must be considered. For the successful introduction of NPs into practices in the clinics, biodistribution, pharmacokinetics, metabolism, long-term toxicity, and degradation must be taken into account. Despite the need for additional research, nanotechnology may play an important function in the future of personalised medicine (Pizzimenti et al., 2016).

Numerous hurdles are linked with topical administration, such as the tight connection within the stratum corneum and the high turnover rate of tissue fluids in the eye, nose, and vagina. These barriers restrict the entrance of a drug to its target site, shorten the residence time, or lead to a quick washing of the formulation from its application site (Singh Malik et al., 2016).

Chapter 8

Current progress of Nanoparticles

Nanoparticle-based systems have not yet been authorized to treat skin malignancies on a topical basis. In 2007, the FDA approved a liposomal lotion composed of T4N5 (a bacterial DNA repair enzyme) for the treatment of photosensitivity in individuals with xeroderma pigmentosum. When administered topically for a year, the lotion reduced the emergence of new AK lesions in clinical studies (Yarosh et al., 2001). NB-001 (Nanobio Corporation) is a new topical antiviral emulsion now undergoing clinical investigation to treat recurring cold sores and Herpes Labialis (Kircik et al., 2012). BF-200 ALA (Ameluz®), a nanoparticle formulation of 5-aminolevulinic acid (5-ALA), is now undergoing clinical studies in combination with PDT to prevent AK and cure superficial BCC (Reinhold, 2017). Additionally, a clinical investigation is underway to determine the tolerability, safety, and effectiveness of a NP-based Paclitaxel formulation (NanoPac; Nanotax; SOR 007) for the topical treatment of NMSC.

Chapter 9

Conclusion and Future Directions

Drug delivery using nanoparticles serves to be a feasible technique to increase the efficacy of melanoma treatment as it offers various benefits over other drug delivery technologies and traditional therapy (Sabir et al., 2021). Nanotechnology provides an opportunity on a molecular level by explicitly interacting with and inhibiting the activity of cancer cells. In addition, it is non-invasive and provides targeted drug delivery while minimizing adverse side effects associated with conventional skin cancer treatment (Vishnubhakthula et al., 2017). SC is the most frequent kind of cancer in human populations and is associated with a high morbidity and death rate. Numerous nanoparticles based formulations have already found their path in the field of medicine and have established themselves as the gold standard of treatment of different kinds of SC (Simões et al., 2015b) and therefore nanoparticles are an attractive option for treatment of skin cancer. Although a number of oral as well as systemic NP-based drug delivery systems are used to treat skin cancer, topical based nanoparticles have not yet been used to treat skin malignancies and are currently undergoing different stages of clinical trials. Knowledge and information acquired from recent advances in the formulation science can serve as a guide for future topical nanoparticle-based medication delivery as it has the potential to push the frontiers of this fast-advancing technology well beyond imagination. It is important to select the correct drug (i,e., the specific anti-cancer drug for the specific type of skin cancer), carrier (e.g., the NP), and the formulation for cutaneous distribution based on the indication. Nanoparticles' capacity to aggregate inside hair follicles and the skin may be utilized to treat SC for topical treatment (Krishnan & Mitragotri, 2020). However, a few issues like the nanoformulation's toxicity, dosage determination, and cost-effectiveness needs to be resolved as it poses a barrier from bench to bedside translation. Nano-formulations have been approved for oral and parenteral routes, and it is envisaged that topical nanoformulations will be

marketed effectively in the future for skin cancer treatment and may prove to be cost-effective. To summarise, NP based drug delivery systems hold a great potential for treatment and diagnosis of SC.

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