Bull. Pharm. Sci., Assiut University, Vol. 47, Issue 1, 2024, pp. 119-140.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/

SKIN CANCER ADVANCED TOPICAL TREATMENT WITH IMIQUIMOD LOADED NANOCARRIERS: AN IN-DEPTH REVIEW

Huda Mustafa Abdel-Ghaffar[1*], Hend Mohamed Abdel-Bar[2], Abdulaziz Mohsen Al-mahallawi[3,4], Omaima Naim El Gazayerly[3]

[1]*Central Administration of Drug Control, Egyptian Drug Authority, El Mansoria, Egypt*
[2]*Department of Pharmaceutics, Faculty of Pharmacy, University of Sadat City, Sadat City, Egypt*
[3]*Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo, 11562, Egypt*
[4]*School of Life and Medical Sciences, University of Hertfordshire Hosted by Global Academic Foundation, New Administrative Capital, Cairo, Egypt*

This review explores the significant advancements in topical skin cancer treatments, particularly focusing on the revolutionary role of nanotechnology in addressing the limitations found in traditional therapeutic methods. This comprehensive evaluation delves into the innovative development and clinical efficacy of cutting-edge nanocarrier platforms, notably those encapsulating Imiquimod. These platforms are specifically designed to enhance the delivery and performance of topical agents in the fight against nonmelanoma skin cancers, a prevalent concern in dermatological oncology.

The analysis methodically confronts the obstacles inherent to conventional skin cancer treatments by providing an in-depth examination of how nanotechnology-based platforms improve drug bioavailability, facilitate deeper skin penetration, and boost patient compliance with treatment protocols. This shift towards nanotechnology signifies a paradigm shift towards more patient-oriented and efficacious treatment modalities, offering a precise, targeted, and minimally invasive approach.

Moreover, the review illustrate the potential transformative of nanotechnology in dermatological applications and heralds a significant progression in the topical oncological treatments field. By highlighting the advancements facilitated by nanocarrier systems.

This shows that, with such enhanced treatments of skin cancer, there shall be a shift from a patient-centered approach that minimizes interruptions to the regimen and hence reduces recurrence rates, which marks the first foremost goal. In this way, not only will more easily accessible and effective therapies be facilitated, but also, in proportion to a better quality of life, that is kept to the minimum of patient distress.

Key words: *Imiquimod; Skin Cancer; Basal cell carcinoma; Nanoplatform; Skin delivery system*

INTRODUCTION

Skin carcinoma has emerged as a prominent health issue, with its roots traced back to the early studies by Laennec about melanoma[1], Jacob about basal cell carcinoma [2], and Bowen about squamous cell carcinoma[3] in the 19th and 20th centuries, evolving into the fifth most prevalent cancer worldwide by 2020, according to the World Health Organization[4]. The American Academy of Dermatology's 2022 statistics reveal a distressing reality: approximately 9,500 Americans receive a skin cancer diagnosis each day, translating to one in five Americans facing this affliction in their lifetime[5]. This concerning trend is not isolated to the United States; countries like Australia,

Received : 11/3/2024 & Accepted : 3/4/2024

*Corresponding author: Huda Mustafa Abdel-Ghaffar, E-mail: dr.hudaabdelghaffar@gmail.com

New Zealand, Norway, and Denmark also report significant incidence rates[46].

Skin cancer development is attributed to a variety of factors, including exposure to ultraviolet radiation[7], chemical carcinogens[8], genetic predispositions[9], having fair skin[10], and immunosuppressive states[11]. It is mainly classified into melanoma, originating from melanocytes, and non-melanoma skin cancers, which are derived from keratinocytes and include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Although BCC and SCC account for the majority of skin cancer cases[12], melanoma is notorious for being the deadliest, leading to the majority of skin cancer-related deaths[13].

The conventional spectrum of skin cancer treatments includes surgical interventions[14], Mohs surgery[15], radiation, and cryotherapy[16], primarily effective in the early stages. Advanced stages, however, often necessitate more aggressive treatments like immunotherapy[17], targeted therapy[18], and chemotherapy[19], which unfortunately are plagued by issues such as drug resistance, low bioavailability, and severe adverse effects, highlighting the critical demand for more effective therapeutic strategies[20].

Amidst these challenges, nanotechnology represents a groundbreaking stride in cancer treatment[21], exploiting nanoscale material properties to significantly enhance the efficacy of cancer therapeutics. Despite their proven potential in improving drug delivery systems, nanoparticles' application in skin cancer therapy remains relatively uncharted in comparison to other types of cancer. Current scientific and pharmaceutical endeavors are dedicated to harnessing nanoparticles' unique attributes to surmount existing treatment hurdles, igniting new hope for more efficient and impactful skin cancer treatments[22].

This detailed review navigates through the complex terrain of skin cancer, emphasizing the imperative for innovative therapeutic approaches. Through an examination of recent imiquimod (IMQ) loaded nanoplatforms, it aims to illuminate the promising intersection of nanotechnology in advancing skin cancer therapy. Delving into the capabilities of nanotechnology in skin cancer treatment transcends mere scientific inquiry; it represents a crucial shift in oncological approaches, striving to significantly enhance patient survival rates and improve overall quality of life.

Causes and Risk Factors of Skin Cancer

The skin serves as an essential shield, safeguarding our body against external adversities such as toxins, pollutants, and the harmful effects of ultraviolet (UV) radiation[23]. These external factors can lead to the production of free radicals or reactive oxygen species (ROS)[7], surpassing the body's natural antioxidant defenses and leading to oxidative stress as shown in **Fig. 1**. This stress, especially when intensified by environmental pollutants, chemicals, and prolonged exposure to UV rays, significantly heightens the risk of initiating skin cancer. A notable consequence of oxidative stress is the oxidative damage to DNA bases, specifically resulting in the formation of 8-oxo-G, a recognized marker of oxidative DNA damage[24].

The genesis of skin cancer is frequently linked to mutations within the DNA of skin cells, often stemming from the oxidative stress. Central to this process is the disruption of cellular signaling pathways, which can occur due to mutations or the elimination of genes responsible for encoding vital proteins in these pathways. Such disruptions can result in malfunctioning or absence of proteins impacted by radiation, altering cellular communication and potentially leading to cancerous growths[25].

Within the realm of skin cancer, two types of genes are pivotal: oncogenes and tumor suppressor genes. Oncogenes may lead to cancer through a dominant gain of function that fosters unchecked cellular growth and proliferation. On the other hand, tumor suppressor genes act as regulators of cell division; their deactivation or loss can dismantle this regulatory mechanism, further propelling the development of cancer[25]. Understanding these mechanisms is crucial for developing targeted treatments and preventive measures against skin cancer, highlighting the intricate interplay between our environment and genetic makeup in the onset of this disease.

We can classify risk factors of skin cancer into two main categories[26] **(Fig.2)**: biological, which are inherent and immutable, and non-biological, which encompass external and alterable influences[27]. The skin serves as a

crucial barrier, mediating interactions between external environmental factors and internal physiological mechanisms. It provides protection against a variety of dangers, including pathogens, ultraviolet (UV) radiation, and chemical insults, while also fulfilling critical functions in sensation, thermoregulation, and immune response[28].

From a biological perspective, innate factors play a significant role in skin cancer's onset by altering cellular protein synthesis, leading to uncontrolled cell growth. This dysregulation can manifest as melanoma and non-melanoma skin cancers (NMSC)[29]. People with compromised immune systems, such as those experiencing immunosuppression[30] or living with diseases like AIDS[31], are particularly vulnerable to skin cancer. Specifically, individuals infected with HIV are more likely to develop basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) in these patients is associated with an elevated risk of metastasis and mortality[32].Conversely, on the non-biological spectrum, environmental factors such as air pollution, excessive noise, and artificial lighting have been implicated in the rising rates of skin cancers by disturbing normal cellular processes and promoting skin aging[33]. Notably, UV radiation from the sun is the primary external trigger for skin cancer, initiating harmful molecular alterations including DNA damage[34], inflammatory reactions, and immunosuppressive effects[35], which together create a fertile ground for cancerous changes. Lifestyle factors like diet[36,37], and exposure to environmental toxins, such as arsenic and selenium, have also been associated with increased skin cancer risks, although these connections warrant further investigation[38].

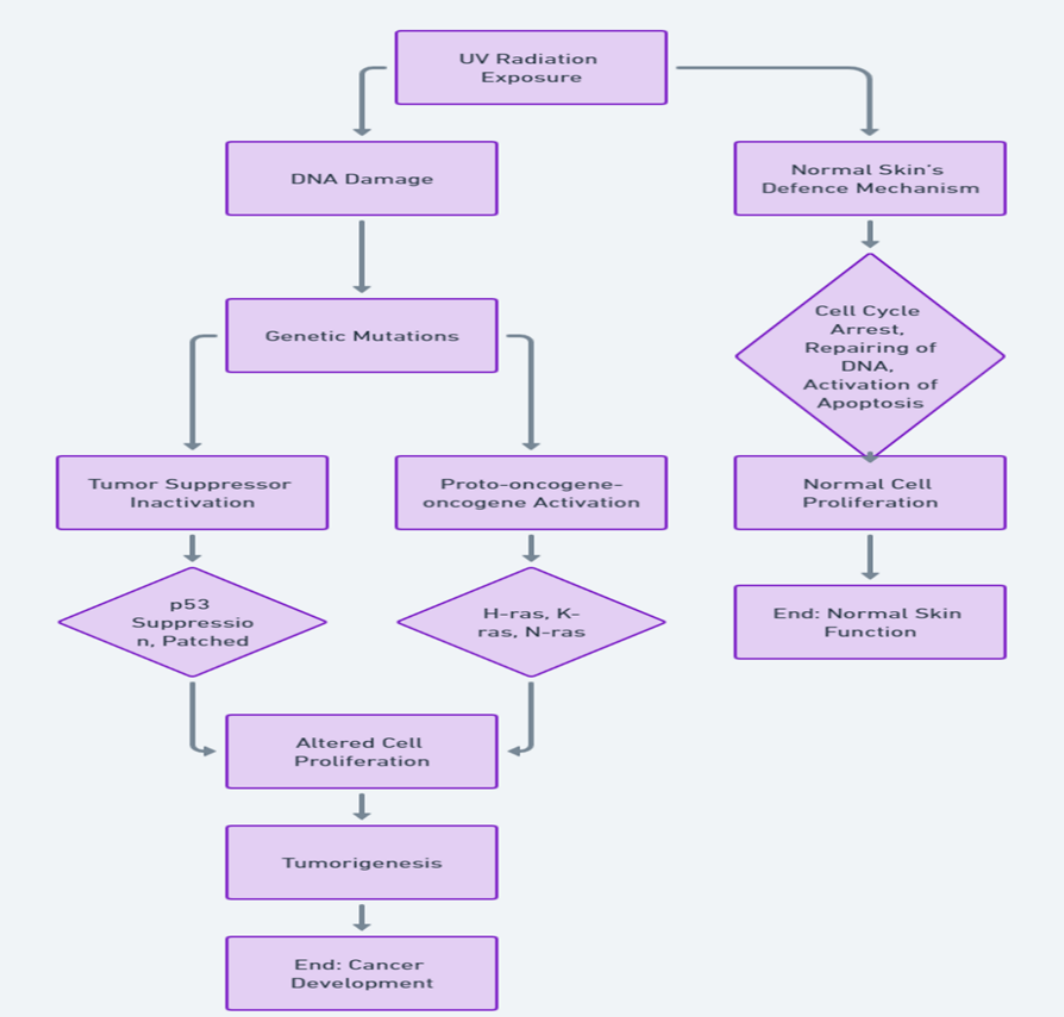

Fig. 1: Diagrammatic representation of UV-induced tumorigenesis mechanism.

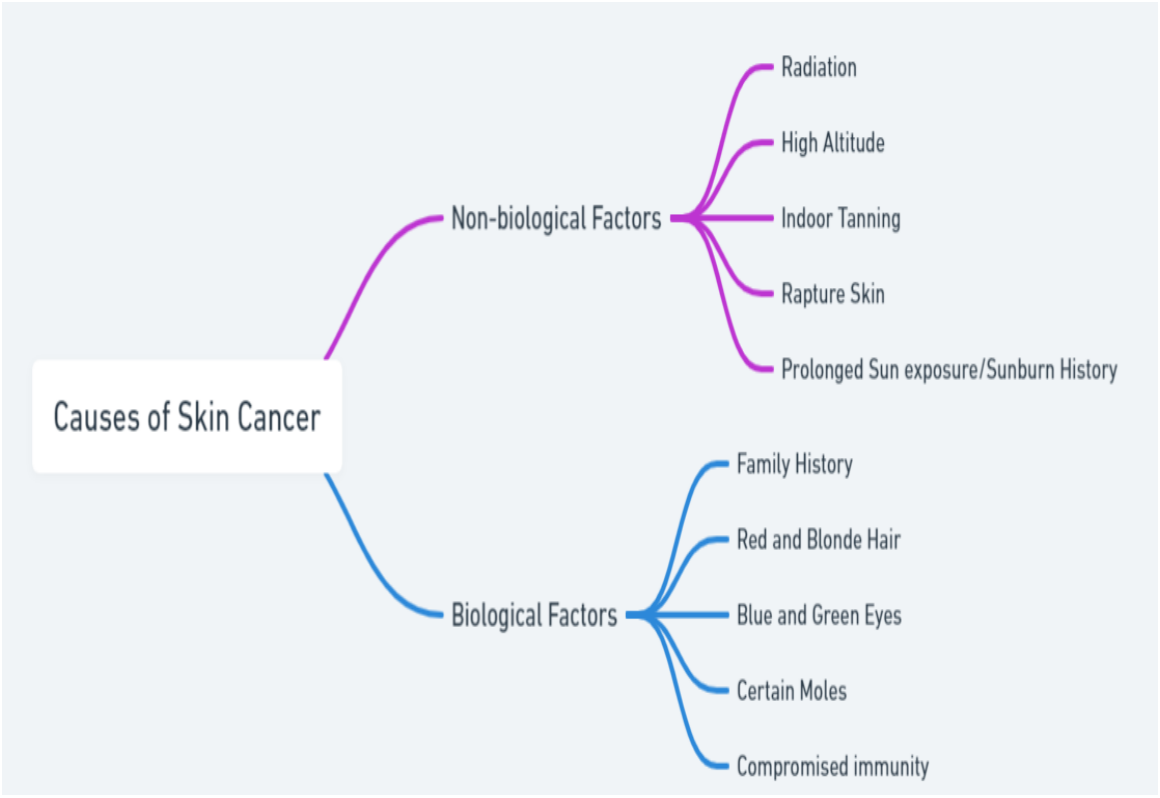

Fig. 2: Diagrammatic representation of non-biological and biological risk factors of skin cancer.

Significantly, skin cancer is the most prevalent post-transplant complication among organ transplant recipients[39], illustrating the complex interaction between genetic susceptibilities and environmental factors. These patients face a markedly higher likelihood of developing NMSC, accentuating the importance of regular surveillance and preventive measures.

In essence, the etiology of skin cancer is complex and multifactorial, involving both unchangeable biological elements and modifiable environmental factors[26]. Grasping these contributing factors is vital for crafting thorough approaches to prevention, monitoring, and management of this increasingly common ailment.

Types and Pathology of Skin Cancer

Skin cancer manifests primarily in two forms: melanoma and nonmelanoma (Basal Cell Carcinoma and Squamous Cell Carcinoma), each with distinct characteristics and pathological developments .

Melanoma

Melanoma accounts for about 5% of all skin cancers but is the most deadly, responsible for around 80% of deaths related to skin cancer[40,41]. It originates from melanin-producing cells, melanocytes, and is notorious for its aggressive proliferation and metastatic potential[42]. Melanoma typically begins as flat, pigmented lesions with indistinct edges, initially confined to the epidermis. As it progresses, it invades deeper into the dermal layer and eventually the subcutaneous tissue, forming more pronounced nodules and papules[40,43]. In the United States, advanced melanoma stages are associated with survival times of three to eleven months post-diagnosis, with metastatic melanoma patients having a less than 10% chance of surviving five years. However, early detection significantly improves prognosis, with five-year survival rates dropping from 99.4% at stages I and II to 68.0% and 29.4% at stages III and IV, respectively[44]. Major risk factors include exposure to ultraviolet radiation, genetic predisposition, fair skin, exposure to chemical carcinogens, immunosuppression, and the use of indoor tanning beds[27].

Nonmelanoma Skin Cancer (NMSC):

NMSC primarily encompasses Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC), differing markedly in prevalence and aggression[44].

- **Basal Cell Carcinoma (BCC)**

BCC is the most common form, representing 70% of NMSC cases, yet it is relatively less aggressive. Typically developing in areas exposed to the sun, such as the neck and head[44], it originates from cells in the basal layer of the epidermis. The primary cause is often ultraviolet B radiation, which leads to mutations and the inactivation of critical genes like the p53 tumor suppressor gene[45]. BCC's appearance can vary, with nodular, superficial, micronodular, and infiltrative subtypes impacting the risk of recurrence and treatment outcomes[46]. Risk factors include genetic syndromes like Gorlin-Goltz syndrome, age, gender, immunosuppression, and having a lighter skin type[47].

- **Squamous Cell Carcinoma (SCC)**

SCC is the second most common skin cancer, making up about 25% of cases, with greater invasiveness than BCC[48]. It frequently affects the cervicofacial region, particularly the ears and lower lip. The development of SCC is associated with the inactivation of E-cadherin protein and mutations in the p53 gene[49]. The aggressiveness of SCC can vary based on the lesion's location, size, depth, and differentiation level, with larger and deeper lesions posing higher risks of recurrence and metastasis. Additional risk factors include HPV infection, exposure to chemical carcinogens, chronic inflammatory conditions, and certain medications, like TNF-α inhibitors[50,51].

Understanding the types and pathology of skin cancer is crucial for effective prevention, early detection, and treatment, considering the varying behaviors, risk factors, and prognoses associated with each type.

Contemporary Strategies and Challenges in the Treatment of Skin Cancer

Skin cancer treatment strategies are highly dependent on factors such as the type, size, location, and stage of cancer[52]. For initial stage large skin cancers, treatments typically include excision surgery, Mohs surgery, or radiation therapy, which may be supplemented by immunotherapy or targeted therapy. Smaller lesions might be addressed with curettage and electrodesiccation, cryotherapy, laser therapy, or photodynamic therapy, followed by adjuvant treatments like immunotherapy or targeted therapy to minimize the risk of recurrence. For advanced-stage skin cancers, especially those with metastases, treatment often involves chemotherapy, which can be administered orally, intravenously, or topically[44].different Skin cancer treatment strategies and their limitations are shown in **Fig. 3**.

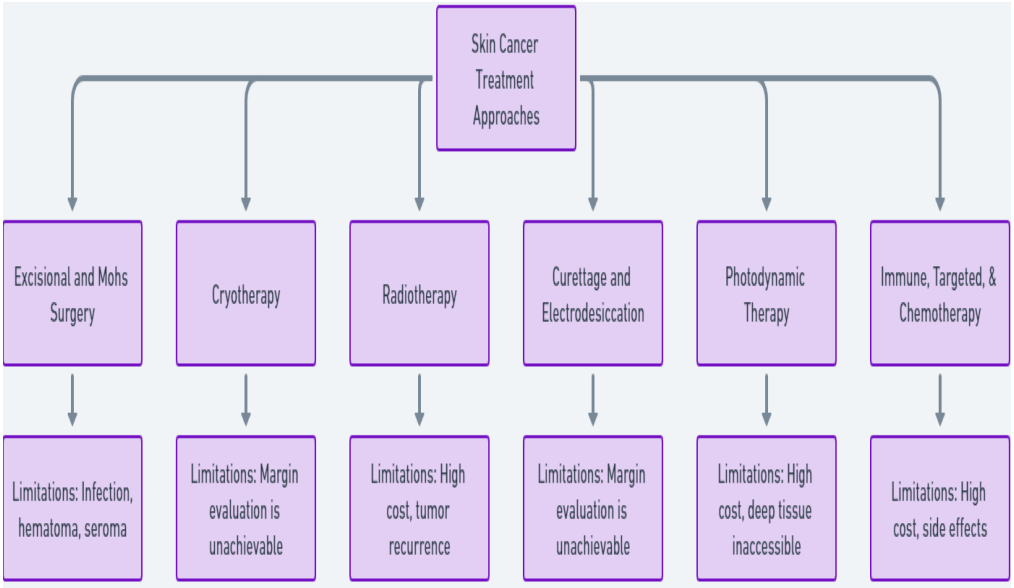

Fig. 3: Diagrammatic representation of different Skin cancer treatment strategies and their limitations.

Surgical and Non-Surgical Treatments:

- **Excisional Surgery**

This minimally invasive method has a high success rate for removing skin cancer, offering quick recovery and minimal scarring. However, it carries risks such as infection and the potential for substantial wound formation[53,54].

- **Mohs Micrographic Surgery**

This technique is exceptional at preserving healthy tissue while removing cancer cells, providing a cost-effective solution with lower recurrence rates. The main drawback is the potential need for additional reconstructive surgeries[55,56].

- **Curettage and Electrodessication**

This quick method is effective for removing small cancers but does not provide precise margin evaluation, rendering it unsuitable for high-risk or poorly defined tumors[57,58].

- **Cryotherapy**

This approach is efficient for treating small BCCs or SCCs and does not result in bleeding or linear scars. However, it lacks margin evaluation and requires significant expertise for effective execution[59].

- **Radiation Therapy**

It offers a viable option for tumors that are inoperable or for patients who are not candidates for surgery, using advanced techniques to minimize damage to healthy tissue. The disadvantages include its high cost and the need for multiple treatment sessions[60].

- **Photodynamic Therapy (PDT)**

A non-invasive treatment that uses photosensitizers and light, PDT is a unique approach to treating cancer without surgery[61,62].The limitation of the technique is that it is costly and not effective in completely eliminating deep-seated tumors[63].

Adjuvant Therapies

- **Immunotherapy, Targeted Therapy, and Chemotherapy**

These are leading adjuvant treatments that improve survival rates and effectively manage BCC, SCC, and melanoma following surgery, radiation, or PDT. While offering significant benefits, they come with challenges such as high costs, issues with patient compliance, and adverse effects[64].

While these treatments provide a range of benefits, they also possess limitations that underline the need for developing more sophisticated, patient-friendly methods. Nanotechnology is emerging as a promising field, offering potential innovations for more effective and less invasive skin cancer treatments[65,66].

Expanding Role of Topical Therapies in Nonmelanoma Skin Cancer Management

As the incidence of nonmelanoma skin cancer (NMSC) climbs, the role of topical therapies in their management is becoming more pronounced. These treatments are carving out a niche both as independent options and as complements to traditional surgical methods[67]. While Mohs Micrographic Surgery (MMS) remains a primary method for tumor removal[56], topical therapies offer an alternative, particularly for patients facing significant surgical risks. They enhance NMSC management by treating underlying subclinical disease and outlining the extent of NMSC lesions, thus providing a broader, more holistic approach to care.

Topical treatments are especially beneficial for patients like organ transplant recipients, who may experience numerous NMSC lesions due to immunosuppression. These less invasive options reduce the likelihood of surgical scars and complications, presenting a gentler approach for managing multiple lesions[67].

Key topical agents include imiquimod (IMQ)[68], 5-fluorouracil (5-FU)[69], and diclofenac, each with distinct actions and applications. These medications serve various roles from being used in conjunction with surgery to addressing NMSC in high-risk patient groups, such as those who have undergone organ transplants[67].

Topical therapies represent a shift towards more patient centered NMSC care, offering convenience and reduced invasiveness.

Skinas Drug Delivery Systems

Anatomy of the Skin: A Multilayered Barrier

The skin, the largest organ of the human body, is intricately structured into three main layers: the epidermis, dermis, and hypodermis.Its total thickness is less than 2 mm. The stratum corneum (SC) is the epidermis's uppermost layer. It is rich in lipids, including ceramides, triglycerides, fatty acids, and cholesterol. Itacts as a critical barrier against the entry of most molecular entities, especially hydrophilicmolecules.but this barrier is not impervious, it enables specific substances to pass into the deeper skin layers. This selectivity permeation leads to extensive research aimed at understanding substance penetration through the skin layers for therapeutic purposes[70].

The Skin as a Versatile Delivery System

Many molecules with established pharmacological efficacyhave drawbacks like poor solubility, permeability, and severe adverse effects. That prompts research into alternative delivery systems and routes. the skin emerges as a pivotal medium, offering a path for both local (dermal) and systemic (transdermal) drug delivery[71]. The utilization of the skin bypasses common drawbacks associated with traditional routes, such as the first pass effect, and introduces benefits like controlled drug release and enhanced patient compliance. The skin provides a noninvasiveroute,also avoids the variabilities impacting oral drug absorption, including pH, gastrointestinal motility, and dietary factors, presenting a promising alternative for drug administration.[70]

Navigating the Barriers of Skin Drug Delivery

Many studies are directed towards identifying strategies to facilitate substance transport through the formidable permeability barrier presented by the skin, mainly due to the SC. The quest to enhance skin permeability has led to the development of various approaches to improve the delivery of therapeutic agents across this barrier. Despite the natural defense mechanisms of the skin, advancements in pharmaceutical sciences seek to identify methodologies that permit effective transdermal transport of drugs, thereby unlocking new realms of therapeutic interventions.

Approaches to Overcome Skin Barriers

In response to the skin's permeability challenges, extensive efforts have been devoted to devising both chemical and physical modalities. Chemical enhancers like Azone and terpenes aim to reorganize the SC's lipid matrix or enhance drug solubility, easing the drug's journey across the skin[72]. On the other hand, physical techniques such as sonophoresis and microneedling bypass or penetrate the SC, facilitating targeted drug administration[73–77]. While these methods have shown promise in drug delivery, their application is not without drawbacks, including potential discomfort and damage from physical methods and skin irritation from chemical enhancers that leads to the third approachof drug loaded nanocarrier system.

Revolutionizing Delivery through Nanocarrier system

Nanocarrier systems represent a revolutionary stride in skin drug delivery, addressing the shortcomings of conventional methods. These platforms, ranging from liposomes and ethosomes to solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have exhibited profound capabilities in improving drug solubility, enhancing cutaneous distribution, and ensuring deeper penetration. The evolution of lipid-based carriers since the late 20th century underscores the transformative potential of these NanoSystems in both local and systemic applications[78]. Unlike traditional approaches, nanocarriers can deeply infiltrate the skin or enter systemic circulation, utilizing mechanisms like vesicle fusion or acting as penetration enhancers to alter the SC's structure for more effective drug transport[79,80].

Nanocarriers revolutionize pharmaceutical delivery by transcending the skin’s innate barriers, marking a significant advance in the application of nanotechnology in medical treatments. These systems not only facilitate improved administration of existing medications but also herald new strategies for treating chronic diseases and dermatological conditions. With ongoing research, the fusion

of nanotechnology with dermatological and systemic therapy continues to unfold, presenting innovative solutions to drug delivery challenges and enhancing patient outcomes in the HealthCare landscape[81].

Imiquimod as Topical Agents in Skin Cancer Treatment

Imiquimod is a drug that modulates the immune system (immunomodulating drug), approved by the United States Food and Drug Administration (FDA)[82] for treating superficial basal cell carcinoma, actinic keratosis, external genital warts, and perianal warts. Its therapeutic scope, however, extends beyond this FDA-approved use, with ongoing clinical research uncovering its potential against a range of precancerous conditions such as lentigo maligna[83], hemangiomas[84], and even skin metastases from breast cancer[85]. The foundation of Imiquimod effectiveness against cancer stems from its ability to orchestrate a robust immune response, highlighting its role as a pivotal player in the realm of dermatological oncology treatments.

Mechanism of action of Imiquimod in Skin Cancer Treatment

Imiquimod, part of the imidazoquinolinone family, its chemical structure is shown in **Fig. 4**[86], acts as an immunomodulator, igniting a series of immune responses through its interaction with toll-like receptors (TLRs) present on macrophages, Langerhans cells, and dendritic cells. This interaction stimulates the production of cytokines known for their antiviral and antitumor effects, thereby activating both the body's innate and adaptive immune systems. The resultant immune response involves a wide spectrum of molecular and cellular activities contributing to the therapeutic effects of imiquimod in treating conditions like superficial basal cell carcinoma and actinic keratosis. For a detailed exploration of imiquimod's mechanisms and its broad immunological impacts, extensive academic and clinical research materials are recommended[87].

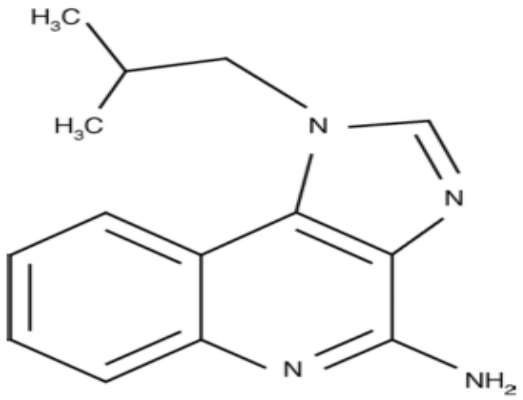

Fig. 4: Chemical structure of Imiquimod.

Obstacles and Advances in Topical Application of Imiquimod

Imiquimod (IMQ), commercially available in Aldara® cream, faces challenges in topical application, primarily due to limited skin penetration. The effectiveness of IMQ is significantly hampered by the protective barrier function of the skin's outermost layer, the stratum corneum[88]. The chemical structure of IMQ, marked by four amine groups, tends to bind with the polar components of the stratum corneum, such as keratinocytes, leading to its accumulation and the creation of a drug reservoir within this layer[88]. However, this does not facilitate its action in the underlying dermal layers, where more invasive skin cancer cells may reside[88,89]. This issue is compounded by IMQ's low solubility in water (18 µg/mL), which impedes its migration to the dermis's more aqueous environment.

Additionally, the accumulation of IMQ in the epidermal layers can trigger adverse reactions, like psoriasis[90], in some patients. The commercial cream's application process, requiring specific methods and protective gear, along with its frequent dosing schedule, poses practical challenges that may affect patient compliance[91].

Approaches to Increase Imiquimod Bioavailability and Decrease Side Effects

In this review, we delve into the advanced developments and applications of nanotechnology platforms designed to enhance the bioavailability and skin permeation of imiquimod. While existing strategies to boost the efficacy of imiquimod include its

formulation into microemulsions[92], amalgamation with fish oil[93,94], and the utilization of physical promoters like microneedles for pre-application[88,95], our analysis primarily focuses on the intricate exploration and meticulous assessment of nanotechnology platforms.

The advent of nanoformulations for imiquimod represents a critical milestone in addressing delivery inefficiencies. nanocarriers offer a sustained release mechanism, extending the duration of drug activity and reducing the frequency of applications, thus transforming traditional treatment protocols and boosting patient adherence.

The field of nanotechnology introduces innovative solutions to surpass these challenges, particularly through the development of lipid-based nanocarriers[96]. Recent advancements have seen the formulation of imiquimod-infused lipid-based systems, including nanoemulsions[97], nano-lipidic capsules[98], and solid lipid nanoparticles (SLNs)[99]. These advanced delivery mechanisms provide structural benefits that enhance drug delivery efficiency.

Imiquimod Loaded Nanocarriers

In our review, we examine a variety of imiquimod (IMQ) loaded nanoplatforms, summarized in **Table 1**, designed to enhance the bioavailability of IMQ through topical application. These advancements aim to address the shortcomings of conventional formulations. The compilation reflects a spectrum of nanocarriers developed using different materials, preparation techniques, and formulation specifics, which in turn influence their distinct physicochemical attributes such as particle size, polydispersity index (PDI), and zeta potential. A consistent finding among these studies is the improved skin permeation and stability offered by these nano formulations compared to traditional IMQ creams and gels.

Table 1: Comparative Analysis of Nanoplatforms Loaded with Imiquimod for Enhanced Bioavailability.

Nanocarriers	Materials	Method of Preparation	Optimum Formula	Main Results	Conclusion
Imiquimod-loaded Nanostructured Lipid Carriers (IMQ-NLCs)	Precirol® ATO 5, Gelucire® 50/13, Compritol® 888 ATO, Stearyl Alcohol, Oleic Acid, Polysorbate 80, Stearoyl Polyoxyl-32 Glycerides, HPMC K4M, Propylene Glycol, Almond Oil, Sesame Oil	Hot melt homogenization followed by ultrasonication	Binary mixture of solid and liquid lipids (BM): 4.379%, Total Surfactant (50:50 Polysorbate 80 and Stearoyl Polyoxyl-32 Glycerides): 8.890%, Sonication Time: 5.099 minutes	Particle Size (PS): 75.6 ± 1.3 nm, Polydispersity Index (PDI): 0.235 ± 0.005, Zeta Potential (ZP): –30.9 ± 1.4 mV, Increased drug deposition in deeper skin layers compared to commercial cream, Stability at 4°C for 14 days, burst release of 64% in first 2 hours followed by sustained release	Suitable for skin penetration with improved treatment potential, enhanced skin permeation and deposition rates indicate effectiveness for skin cancer treatment.
TPGS Micelles	TPGS, Oleic Acid, Linoleic Acid, Isostearic Acid, Plurol® Oleique, Peceol™, Span® 80	Method 1: Direct dissolution and saturation; Method 2: Mixture of methanol and oleic acid under magnetic stirring; Method 3: Imiquimod first dissolved in oleic acid	TPGS 20 mM + Oleic Acid (TO20); Highest imiquimod solubility and stability	Imiquimod solubility: 1154.08 ± 112.78 µg/mL (TO20), Significant improvement in oleic acid solubility, Size (DLS): Approximately 14-16 nm, Higher skin accumulation compared to commercial cream	Enhances IMQ solubility and skin delivery, suggesting improved therapeutic outcomes and reduced side effects.

Table 1: Continued.

Hydrogel Formulations with TPGS Micelles	Xanthan Gum, Hydroxyethyl Cellulose, Sodium Hyaluronate, Carbopol® 934, Polyvinyl Alcohol	Hydration of polymers in high purity water or in IMQ-loaded TO20 micelles	XG (Xanthan Gum) and HA (Hyaluronic Acid) based on TO20 micelles	Nile Red-loaded micelle diffusion effective in XG and HA hydrogels, Stability in XG and HA gels without disrupting micelles	XG and HA hydrogels suitable for TPGS-based micelles, allowing for efficient drug delivery while maintaining stability and integrity of the micelles.
Polymeric Nanocapsules (NCimiq)	PCL, Span 60, Tween 80, Copaiba oil,	Self-assembling technique, solvent evaporation	PEC-NCimiq: Pectin hydrogel with NCimiq; Drug content: 0.47 ± 0.04 mg/g	Increased cytotoxicity against SK-MEL-28 cells over time, Sauter mean diameter: 168 ± 14 nm, Polydispersity: 1.58, Improved adhesiveness and skin permeation compared to PEC-imiq	Indicates potential for melanoma treatment with increased cytotoxicity, higher adhesiveness, and improved skin permeation and penetration.
Nanoemulgel System (IMQ and CUR)	Oleic acid, Curcumin, Cremophor EL, Isopropyl alcohol, Ethanol, Captex 355, Capmul MCM, Tween 80, Tween 20, PG, PEG 400	Heating–cooling and freeze–thaw cycles, vortex mixing for homogenous nanoemulsion formation	NE4: 10% Oleic acid, 40% Tween 20, 20% Transcutol HP, 30% Water; Drug loading: IMQ (10 mg/mL), CUR (15 mg/mL)	Solubility: Maximum in oleic acid, Thermodynamic Stability: Passed without phase separation, Viscosity: NE1 (55.26 cP) to NE4 (63.82 cP), Droplet Size: NE1 (197.1 nm) to NE4 (76.93 nm), Zeta Potential: NE1 (-10.9 mV) to NE4 (-35.8 mV), High in vitro and ex vivo skin permeation and deposition	Successful formulation for controlled delivery of IMQ and CUR through topical application, enhanced permeation and reduced skin irritation indicate potential for effective treatment of psoriasis-like conditions.
mPEG-hexPLA Micelles, Eudragit® L100 Nanoparticles	mPEG-hexPLA, solvents, Eudragit® L100, Span® 85, medium chain triglycerides, Poloxamer® 407	Solvent evaporation method then Nanoprecipitation of preformed polymer	0.05% IMQ in micelle formulation, 250 μg/mL IMQ in nanoparticle dispersion	Average Size 181 nm and 249 ± 12.6 nm (DLS), Polydispersity Index <0.2, Zeta Potential -40.1 mV ± 3.7, Encapsulation Efficiency= 92.5% ± 0.4, Significant reduction in papilloma multiplicity and size in murine skin cancer model, Similar skin permeation to commercial cream with 100-fold lower content	Enhanced skin permeation and potentially improved stability and efficacy at lower concentrations, indicating effective antiangiogenic and chemopreventive activity.

Table 1: Continued.

Imiquimod-loaded Nanoparticles (NPImq)	Polymethacrylate copolymer (Eudragit® L100), Medium chain triglycerides, Sorbitan trioleate, Polyoxyethylene-polyoxypropylene copolymer	Nanoprecipitation of preformed polymer	mq: 10 mg, Span® 85: 50 mg, Eudragit® L100: 75 mg, medium chain triglycerides: 100 mg, Poloxamer® 407: 50 mg in 70 mL of solvent	Encapsulation efficiency: 92.5% ± 0.4; Size: 249 ± 12.6 nm; Zeta potential: -40.1 mV ± 3.7; Improved skin permeation; Reduced tumor formation and size in vivo	Offers improved delivery, enhanced antiangiogenic and chemopreventive activities, and better skin penetration with lower toxicity.
Nanostructured Copaiba Capsules (NCCImq)	Poly(ε-caprolactone), Span 60®, Copaiba oil, Polysorbate 80	Interfacial deposition of pre-formed polymer	PCL (0.2502 g), Sorbitan monostearate (0.0962 g), Copaiba oil (835 µL), Imiquimod (0.025 g), Polysorbate 80 (0.1923 g)	pH: 6.2, Viscosity: 0.0013 Pa.s, Drug Content: 97%, Encapsulation Efficiency: 97.9%, Particle Size: 220 ± 24 nm, Stability with slight sedimentation, Higher retention in skin layers	Increased drug retention in skin layers, suitable for cutaneous use with potential for improved treatment efficacy.
Nanostructured Brazilian Lipids (NBLImq)	Cupuaçu butter, Copaiba oil, Sorbitan monooleate, Polysorbate 80	High-pressure homogenization	Cupuaçu seed butter (13.4 g), Copaiba oil (6.6 g), Sorbitan monooleate (3.0 g), Imiquimod (0.2 g), Polysorbate 80 (3.08 g)	pH: 6.0, Viscosity: 0.0015 Pa.s, Drug Content: 98%, Encapsulation Efficiency: 99.9%, Particle Size: 177 ± 5 nm, Stability with slight tendency for creaming, Increased permeation to receptor compartment	Efficient in skin permeation but less preferred due to higher systemic absorption, indicating suitability for cutaneous application but with caution regarding systemic effects.

Imiquimod-Loaded Nanostructured Lipid Carriers

The primary objective of this research is to formulate, optimize, and characterize Imiquimod-loaded Nanostructured Lipid Carriers (IMQ-NLCs) for the inaugural time, employing a combined Design of Experiments (DoE) methodology[99].

This study is dedicated to assessing the efficacy of these carriers as a novel topical delivery mechanism for the treatment of nonmelanoma skin cancers (NMSC). By integrating IMQ into a nanostructured lipid framework, the research seeks to enhance the drug's therapeutic performance, skin penetration, and patient adherence, addressing the challenges posed by standard IMQ formulations, notably inadequate skin absorption and pronounced local adverse effects. Additionally, the investigation intends to confirm the eco-friendliness of the production process, aiming to diminish the ecological footprint traditionally associated with pharmaceutical manufacturing[99].

The development of optimized Imiquimod-loaded Nanostructured Lipid Carriers (IMQ-NLCs) involved a detailed and precise formulation process. The selection of solid and liquid lipids, stearyl alcohol (STA) and oleic acid (OA) respectively, was based on their exceptional ability to solubilize IMQ, thereby ensuring significant drug loading and encapsulation efficiency within the lipid matrix. The optimal lipid ratio, established at 70% STA to 30% OA, was determined through methods such as differential scanning calorimetry and visual evaluation, ensuring an ideal balance between the structural integrity and fluidity of the NLCs. This balance is crucial for modulating the release rate of IMQ and enhancing its penetration through the skin.

The choice of surfactants is integral to the stability of lipid nanoparticles, as they help reduce particle size and prevent aggregation. The formulation utilized a synergistic

combination of polysorbate 80 and stearoyl polyoxyl-32 glycerides, selected for their superior emulsification properties and low skin irritation potential, contributing to the NLCs' enhanced stability and patient compatibility.

The manufacturing process comprised hot melt homogenization followed by ultrasonication, ensuring even particle distribution and size, which are vital for the stable formation of the nano-emulsion that subsequently transitions into NLCs upon cooling[100]. Integrating a lyophilization phase further bolstered the NLCs' stability, facilitating their conversion into a reconstitutable powder form, thus extending shelf life and simplifying application.

The optimization phase was pivotal, utilizing a Design of Experiments (DoE) strategy to refine the formulation. This approach methodically examined the impacts of varying lipid mixture concentrations, surfactant levels, and IMQ amounts, as well as processing conditions like homogenization speed and sonication duration. The objective was to identify the best conditions for producing NLCs characterized by a small particle size, low polydispersity index, suitable zeta potential, and optimal entrapment efficiency. These parameters are critical for effective skin penetration and reduced systemic toxicity, ultimately boosting the IMQ-NLCs' therapeutic potential for treating skin-related ailments.

The development of optimized IMQ-NLCs resulted in a notably small particle size, pivotal for deep skin penetration and efficient drug delivery, enhancing therapeutic interaction with skin tissues.A low Polydispersity Index (PDI) was observed, reflecting a consistent and uniform particle size distribution, crucial for the reliability of drug delivery and performance.

The zeta potential values, being negative and within a desirable range, indicated commendable colloidal stability, minimizing the risk of particle aggregation and ensuring formulation stability during storage.

High levels of entrapment efficiency and drug loading were realized, signifying that a substantial quantity of IMQ was successfully encapsulated within the NLCs, critical for delivering adequate therapeutic levels to the target site.

The formulation exhibited robust colloidal stability over time, vital for preserving the therapeutic effectiveness of the IMQ-NLCs during storage and application.

Comparative studies indicated that the IMQ-NLC-Patch significantly surpassed the commercial cream in terms of skin permeation and deposition, suggesting superior delivery of IMQ into deeper skin layers, which could enhance treatment outcomes for skin cancers.

The enhanced drug deposition in deeper skin layers by the optimized patch, as opposed to the commercial formulation, underscores the potential of this novel approach for more effective treatment of skin-related conditions.

The utilization of nanostructured lipid carriers promotes deeper penetration and precise drug targeting, potentially enhancing therapeutic effects, where targeted delivery minimizes systemic absorption, thereby reducing potential side effects and improving safety profiles. NLCs offer a stable platform for IMQ, prolonging shelf life and simplifying topical application, which could lead to enhanced patient adherence. The efficient preparation process and use of lipid-based materials may offer a more affordable solution compared to other sophisticated drug delivery systems, and the adaptable and scalable nature of the manufacturing process makes the IMQ-NLC formulation suitable for broader commercial production.

The potential of IMQ-NLCs as a promising avenue for the topical treatment of nonmelanoma skin cancers, was studied, offering significant improvements in drug delivery, efficacy, and patient experience compared to conventional therapies.

Imiquimod Solubilization and Skin Retention via TPGS Micelles: Exploiting the Co-Solubilizing Effect of Oleic Acid

The primary objective of this study is to enhance IMQ's solubility and its dermal delivery by employing TPGS(d-α-tocopheryl polyethylene glycol 1000 succinate) based micelles, aiming to boost therapeutic efficiency while mitigating adverse effects associated with IMQ[101].

The study employed Imiquimod, TPGS, and a range of fatty acids including oleic, linoleic, and linolenic acids from reputable sources, chosen for their micelle-forming

capabilities and potential to improve drug solubility. High-Performance Liquid Chromatography (HPLC) was utilized for accurate IMQ concentration measurements, ensuring precise drug dosing in the formulations, in addition to determining the concentrations of fatty acids crucial for their role in enhancing IMQ's solubility. The developed blank and IMQ-loaded polymeric micelles using direct dissolution and saturation methods to identify the best conditions for stable and effective micellar systems.

TPGS-based micelles, particularly when combined with oleic acid, substantially increased IMQ's solubility. Various concentrations and mixtures were examined to pinpoint the most effective solubilization conditions. The study optimized fatty acid ratios and concentrations in the micellar formulations, identifying oleic acid as the most potent in enhancing drug solubility. Higher concentrations of TPGS improved solubility but not in a linear manner, suggesting a nuanced interaction affecting encapsulation efficiency. DLS confirmed the adjusted micellar formulations to ensure size stability over time, which is crucial for consistent drug delivery and long-term storage.

Ex vivo studies showed that the optimized micellar formulations enhanced skin penetration and retention compared to standard IMQ creams, highlighting the formulation's potential for superior therapeutic efficacy. The TO20 micellar formulation (TPGS 20 mM +oleic acid)displayed significant improvements such as heightened IMQ skin penetration at reduced concentrations, reducing potential side effects and boosting patient adherence. The addition of TPGS enhanced IMQ solubility and offered antioxidant benefits from vitamin E, potentially diminishing skin irritation linked with IMQ use. This novel formulation holds promise for enhanced therapeutic results and decreased side effects, representing a notable progression in treatment methodologies for skin conditions such as actinic keratosis and superficial basal cell carcinoma[101].

New pectin-based hydrogel containing imiquimod-loaded polymeric nanocapsules for melanoma treatment

The primary objective this study was to boost the bioavailability and skin penetration of imiquimod (IMQ) through a novel nanoencapsulation approach combined with a pectin-based hydrogel system, focusing on improved drug delivery, enhanced adhesion, and deeper skin penetration crucial for the effective management of melanoma[102].The formulation included Poly(ε-caprolactone) (PCL) as the core polymer matrix, sorbitan monostearate (Span 60), and polysorbate 80 (Tween 80) as surfactants to stabilize the system, and copaiba oil, which aids in the solubilization of the drug and formation of nanocapsules. The production involved a solvent displacement technique, beginning with an organic phase comprising PCL, Span 60, copaiba oil, and IMQ dissolved in acetone and ethanol. This phase was then introduced into an aqueous solution containing Tween 80 at 40°C, instigating the rapid diffusion of solvent and formation of nanocapsules. Adjustments were made to the concentrations of PCL, Span 60, copaiba oil, and IMQ to refine nanocapsule properties such as particle size, polydispersity index (PDI), and drug loading efficiency, achieving optimal encapsulation characteristics. IMQ was encapsulated within the nanocapsules concurrently with their formation, ensuring the drug was integrated within the polymeric matrix effectively[103].

Two hydrogel bases, pectin-based and Carbopol-based, were selected for their biocompatibility and gelation capabilities, serving as the medium for topical application. The IMQ-loaded nanocapsules were uniformly dispersed into a pectin matrix through gentle stirring, forming a consistent, homogenous hydrogel suitable for skin application. Similarly, the IMQ-loaded nanocapsules were incorporated into a Carbopol solution, which was then neutralized and homogenized, ensuring the nanocapsules were evenly distributed throughout the gel.

The nanocapsules showcased a Sauter mean diameter of approximately 168 nm along with a polydispersity index reflecting uniform size distribution, beneficial for consistent drug delivery and effective skin penetration. High drug content within the nanocapsules was observed, indicating a successful encapsulation process. Zeta potential measurements confirmed the stability of the nanocapsule suspensions, minimizing aggregation risk and enhancing shelf life.

Nanocapsule formulations exhibited increased cytotoxicity against melanoma cells over time compared to both free imiquimod and control nanocapsules, suggesting preserved biological activity of encapsulated imiquimod and potential for superior therapeutic effects at reduced concentrations, owing to enhanced cellular uptake.

Both pectin and Carbopol hydrogels were characterized by suitable pH and viscosity levels for topical use, promoting patient comfort and ease of application. Drug release from the hydrogels demonstrated a sustained pattern, advantageous for prolonged therapeutic imiquimod levels.

Pectin-based hydrogels outperformed Carbopol-based ones in terms of skin penetration and permeation of imiquimod, likely due to pectin's inherent properties enhancing drug release and absorption. Incorporation of nanoencapsulated imiquimod into hydrogels notably improved skin adhesion properties, especially in pectin-based hydrogels, leading to reduced drug wash-off and potentially enhanced treatment efficacy.

The nanoformulations displayed heightened cytotoxicity to melanoma cells while likely reducing systemic side effects, in contrast to traditional imiquimod formulations that may induce irritation or systemic side effects. The incorporation of nanocapsules into hydrogel matrices significantly improved the penetration of deeper skin layers, effectively reaching target cells more efficiently than conventional formulations. Optimized formulations ensured a controlled and extended imiquimod release, maintaining therapeutic levels for longer durations and reducing the necessity for frequent applications.

Hydrogels, particularly those based on pectin, exhibited superior adhesiveness, reducing the likelihood of removal by sweat or water, thus improving the treatment's convenience and efficacy.

This research showed that imiquimod-loaded polymeric nanocapsules integrated into hydrogel bases, especially those based on pectin, presented considerable improvements over traditional formulations. These advancements included enhanced drug delivery and skin penetration, sustained release, minimized systemic absorption for reduced side effects, and enhanced patient compliance due to improved application properties.

Co-Delivery of Imiquimod and Curcumin by Nanoemugel for Improved Topical Delivery and Reduced Psoriasis-Like Skin Lesions

Ananoemulsion-based gel (nanoemulgel) aiming at the topical administration of imiquimod (IMQ) to enhance penetration and minimize skin irritation, with the incorporation of curcumin (CUR) for synergistic benefits in treating conditions like psoriasis or skin cancer was investigated.

Components such as IMQ, oleic acid, CUR, cremophor EL, isopropyl alcohol (IPA), ethanol, Transcutol HP, Captex 355, capmul MCM, Tween 80, Tween 20, propylene glycol (PG), and polyethylene glycol (PEG) 400 were employed[97].

The optimized IMQ-NE and CUR-NE formulations displayed high drug content, appropriate viscosity, minimal droplet size, and suitable zeta potential, indicating their stability and potential efficacy in skin application. The nanoemulgel exhibited superior skin permeation, sustained drug release, and diminished irritation when contrasted with traditional IMQ creams. CUR's integration offered additional therapeutic benefits and mitigated IMQ-induced skin irritation, showing controlled drug release and enhanced IMQ and CUR penetration from the nanoemulgel, suggesting an improvement in therapeutic efficiency.

The alleviation of psoriasis-like symptoms and skin irritation in BALB/c mice, highlighting the formulation's capacity to deliver IMQ effectively while reducing adverse effects, augmented by CUR's anti-inflammatory attributes was proved by the *in vivo* study.

This research emphsized the nanoemulgel's potential in managing skin conditions while alleviating side effects, representing a considerable progression in topical drug delivery technologies. The synergistic combination of IMQ and CUR in this novel delivery system ensured a controlled release, improved penetration, and better treatment outcomes for skin disorders.

Self-assembled mPEG-hexPLA polymeric nanocarriers for the targeted cutaneous delivery of imiquimod

This study aimed to surmount the challenges presented by conventional imiquimod (IMQ) formulations, focusing on enhancing IMQ's solubility, stability, and skin delivery by formulating mPEG-hexPLA micelles loaded with IMQ and integrating them into a gel for improved topical application. The goal was to offer controlled release, superior skin penetration, and fewer side effects than existing treatments[89].

A novel approach involved creating IMQ-loaded micelles using the synthesized block copolymer mPEG-hexPLA. Adjustments were made to traditional solvent evaporation techniques to improve IMQ's poor solubility. A carboxymethyl cellulose (CMC) gel was developed as the base for topical application, chosen for its suitable textural and adhesive properties for skin use, while preserving the integrity and activity of the micelles and the encapsulated drug.

The micelles improved IMQ solubility and maintained stability over time. However, IMQ incorporation was partial, attributed to the acidic conditions for dissolution. A 2% CMC gel proved effective for micelle application, offering an optimal balance between application ease and skin adherence, thus enabling controlled IMQ release. When compared to traditional formulations like Aldara®, the micelle gel achieved more effective skin delivery of IMQ, despite lower drug content, suggesting enhanced efficiency due to the nanocarrier system.

The prepared gelachieved effective skin IMQ levels with lower concentrations, indicating a more efficient system than traditional creams. It also enabled precise delivery to necessary skin layers, reducing potential systemic side effects. The less irritating and easier-to-apply gel formulation is expected to lead to better adherence and outcomes.

The new mPEG-hexPLA micelle and CMC gel approach showed promise over traditional IMQ treatments in terms of drug solubility, stability, and skin delivery. While promising, further studies are needed to validate these findings in clinical scenarios and refine the formulation for commercial deployment. This advancement signifies a considerable progression in developing more effective, user-friendly dermatological treatments involving IMQ.

Imiquimod loaded polymeric nanoparticles

Imiquimod loaded polymeric nanoparticles (NPImq)[104], were utilized to augment the bioavailability and therapeutic effectiveness of imiquimod utilizing the nanoprecipitation technique[98].

The NPImq were crafted using Imiquimod, Eudragit® L100, medium-chain triglycerides, Span® 85, and Poloxamer® 407.

The formulation was optimized for effective delivery, selecting excipients for their biocompatibility, stability, and skin permeation enhancement. Eudragit® L100 was chosen for its biodegradability and protective properties, while Span® 85 and Poloxamer® 407 were incorporated for their surfactant qualities, aiding in nanoparticle suspension stability and skin penetration.

The NPImq exhibited an average size of 249 ± 12.6 nm and a zeta potential of -40.1 mV ± 3.7, signifying stable and uniformly distributed nanoparticles, crucial for consistent drug delivery and skin penetration.A high encapsulation efficiency of 92.5% ± 0.4 was achieved, ensuring that most of the active drug is delivered to the target site. NPImq demonstrated a controlled release, where about 25% of Imqwas released within the initial two hours, showcasing the nanoparticles' ability to moderate drug release. NPImq substantially inhibited blood vessel formation by 70.6% in the CAM assay compared to controls, indicating a significant antiangiogenic effect crucial for hindering tumor growth and spread.*In vivo* studies indicated higher drug levels in the dermis than in the epidermis, signifying efficient permeation and retention. Histological examinations confirmed minimal impacts on skin structure and cellular integrity, suggesting lower toxicity.

NPImq treatment markedly reduced papilloma multiplicity and size in murine models, exhibiting superior chemopreventive efficacy over conventional formulations. The study highlighted numerous benefits of NPImq, including enhanced skin permeation, deeper drug delivery, sustained drug release reducing application frequency, higher encapsulation

efficiency for stable and effective delivery, alongside diminished local and systemic side effects due to precise targeting and controlled release. Furthermore, significant antiangiogenic and chemopreventive effects underscore its therapeutic potential.

By integrating Imquimod into a tailored nanoparticle system, the study overcame typical limitations of conventional imiquimod applications, such as inadequate skin penetration and adverse reactions. The pronounced antiangiogenic and chemopreventive results affirm NPImq's potential as an effective and safer alternative for treating skin cancers and related conditions, setting a foundation for further clinical investigations and the application of nanotechnology in dermatological treatments.

Co-encapsulation of imiquimod and copaiba oil in novel nanostructured systems

This study developed and characterizedtwo distinct nanocarrier formulations for the cutaneous delivery of imiquimod (IMQ)[98].The research primarily centered on the formulation of nanostructured copaiba capsules (NCCImq) and nanostructured Brazilian lipids (NBLImq), incorporating unique components like copaiba oil and Brazilian native lipids to augment topical IMQ application. The objective was to improve skin retention and penetration of IMQ while diminishing its systemic absorption and the adverse effects commonly associated with its traditional applications.

NCCImqwere synthesized via the interfacial deposition method, whereas NBLImq wereformed through high-pressure homogenization.

Both NCCImq and NBLImq demonstrated suitable pH and viscosity for topical application, high encapsulation efficiency indicating effective IMQ delivery, and nanometric particle sizes conducive to enhanced skin penetration. The physical stability of both formulations, albeit with minor sedimentation or creaming, expected in such suspensions, was demonstrated.

Controlled release profiles was achieved and differing skin layer retention—NCCImq showed enhanced dermis retention, aligning with basal cell carcinoma treatment needs, whereas NBLImq exhibited increased drug permeation, potentially escalating systemic side effects.

The controlled release mechanism may enhance treatment adherence and diminish the need for frequent dosing.Formulations appeared to be less irritating and toxic to skin cells compared to conventional IMQ treatments.

The study posited that NCCImq holds superior promise for skin carcinoma therapy due to its skin layer retention and controlled release capabilities, unlike NBLImq, which presented a risk of increased systemic drug permeation. Integrating these nanocarriers into semi-solid bases may further optimize treatment application and efficacy.

Conclusion

The collective findings from these studies underscore significant progress in the development of nanocarrier systems for the delivery of imiquimod (IMQ). By tackling pivotal challenges such as IMQ's poor solubility, inadequate skin penetration, and the negative side effects linked with its traditional formulations, this body of research lays the groundwork for dermatological treatments that are more efficacious, safer, and more conducive to patient compliance. The array of nanocarrier designs explored—from lipid-based carriers and polymeric nanoparticles to hydrogels and nanoemulgels—highlights a wide range of inventive approaches designed to cater to distinct therapeutic requirements. Looking ahead, the field should direct its efforts towards further clinical assessments, fine-tuning of formulation specifics, and the enhancement of production scalability. The overarching aim is to improve patient outcomes and adherence in managing skin conditions, marking a pivotal stride forward in dermatological healthcare.

REFERENCES

1. V. W. Rebecca, V. K. Sondak and K. S. M. Smalley, "A brief history of melanoma: From mummies to mutations", ***Melanoma Res,*** 22(2), 114-122(2012).
2. M. Kasper, V. Jaks, D. Hohl and R. Toftgård, "Basal cell carcinoma - Molecular biology and potential new

therapies", ***J Clin Invest***, 122(2), 455-463(2012).
3. T. Neubert and P. Lehmann, "Bowen"s disease-a review of newer treatment options", (2008).
4. https://www.who.int/news-room/fact-sheets/detail/cancer.
5. https://www.aad.org/media/stats-skin-cancer.
6. H. T. Trinh, S. Mohanan, *D. Radhakrishnan, et al.,* "Silica-based nanomaterials as drug delivery tools for skin cancer (melanoma) treatment", ***Emergent Materials,*** 4(5), 1067-1092(2021).
7. J. D"Orazio, S. Jarrett, A. Amaro-Ortiz and T. Scott, "UV radiation and the skin", ***Int J Mol Sci,*** 14(6), 12222-12248(2013).
8. M. Neagu, C. Caruntu, C. Constantin, *et al.*, "Chemically induced skin carcinogenesis: Updates in experimental models (Review)", ***Oncol Rep,*** 35(5), 2516-2528 (2016).
9. https://www.cancer.gov/types/skin/hp/skin-genetics-pdq.
10. https://www.cancerresearchuk.org/about-cancer/skin-cancer/risks-causes.
11. C. F. Griffith, "Skin cancer in immunosupressed patients", J Am Acad Physician Assist, 35(2), 19-27(2022).
12. https://www.ncbi.nlm.nih.gov/books/NBK441949/.
13. https://www.cancer.net/cancer-types/melanoma/statistics.
14. S. J. Quazi, N. Aslam, H. Saleem, J. Rahman and S. Khan, "Surgical Margin of Excision in Basal Cell Carcinoma: A Systematic Review of Literature", ***Cureus,*** 12(7), e9211 (2020).
15. C. T. Lee, E. J. Lehrer, A. Aphale, M. Lango, T. J. Galloway, and N. G. Zaorsky, "Surgical excision, Mohs micrographic surgery, external-beam radiotherapy, or brachytherapy for indolent skin cancer: An international meta-analysis of 58 studies with 21,000 patients", ***Cancer,*** 125(20), 3582-3594(2019).
16. E. G. Kuflik, "Cryosurgery for Skin Cancer: 30-Year Experience and Cure Rates ,"Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.], 30(2), 297-300(2004).
17. K. G. Paulson, M. C. Lahman, A. G. Chapuis and I. Brownell, "Immunotherapy for skin cancer", ***Int Immunol,*** 31(7), 465-475(2019).
18. V. Singh, A. Sheikh, M. A. S. Abourehab and P. Kesharwani, "Dostarlimab as a Miracle Drug: Rising Hope against Cancer Treatment", ***Biosensors,*** 12(8), 617(2022).
19. J. J. Luke and G. K. Schwartz, "Chemotherapy in the management of advanced cutaneous malignant melanoma", ***Clin Dermatol,*** 31(3), 290-297(2013).
20. D. A. Worku and V. Hewitt, "The role and economics of immunotherapy in solid tumour management. Journal of oncology pharmacy practice: official publication of the International", ***J Oncol Pharm Pract,*** 26(8), 2020-2024 (2020).
21. H. Kaur and P. Kesharwani, "Advanced nanomedicine approaches applied for treatment of skin carcinoma", ***J Control Release,*** 337, 589-611(2021).
22. L. B. Naves, C. Dhand, J. R. Venugopal, L. Rajamani, S. Ramakrishna and L. Almeida, "Nanotechnology for the treatment of melanoma skin cancer", ***Prog Biomater,*** 6(1-2), 13-26 (2017).
23. G. J. T. P. (auth.), W. B. C. G. J. T. (eds.) William B. Coleman PhD, ***The Molecular Basis of Human Cancer***, (2002).
24. L. Tremmel, O. Rho, T. J. Slaga and J. DiGiovanni, "Inhibition of skin tumor promotion by TPA using a combination of topically alied ursolic acid and curcumin", ***Mol Carcinog,*** 58(2), 185-195(2019).
25. F. R. De Gruijl, H. J. Van Kranen and L. H. F. Mullenders, "UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer", ***J Photochem Photobiol B,*** 63(1-3), 19-27(2001).
26. N. H. Khan, *et al.*, "Skin cancer biology and barriers to treatment: Recent applications of polymeric micro/nanostructures", ***J Adv Res,*** 36, 223-247(2022).
27. S. Carr, C. Smith and J. Wernberg, "Epidemiology and Risk Factors of Melanoma", ***Surg Clin North Am,*** 100(1), 1-12(2020).
28. R. Goyal, L. K. Macri, H. M. Kaplan and J. Kohn, "Nanoparticles and nanofibers

for topical drug delivery", ***J Control Release,*** 240, 77-92(2016).
29. W. Zhang, Z. Zhang and Y. Zhang, "The application of carbon nanotubes in target drug delivery systems for cancer therapies", ***Nanoscale Res Lett,*** 6(1), 555(2011).
30. A. Fahradyan, A. C. Howell, E. M. Wolfswinkel, M. Tsuha, P. Sheth and A. K. Wong, "Updates on the Management of Non-Melanoma Skin Cancer (NMSC)", ***Healthcare (Basel),*** 5(4), 82 (2017).
31. E. Venanzi Rullo, M. G. Maimone, F. Fiorica, *et al.*, "Non-Melanoma Skin Cancer in People Living With HIV: From Epidemiology to Clinical Management", ***Front Oncol,*** 11, 689789(2021).
32. N. Crum-Cianflone, et al., "Cutaneous malignancies among HIV-infected persons", ***Arch Intern Med,*** 169(12), 1130-1138(2009).
33. H. W. Rogers, "Is Mohs Surgery Cost-Effective versus Traditional Surgical Excision?", ***Curr Dermatol Rep,*** 3(2), 91-97(2014).
34. C. Potenza, N. Bernardini, V. Balduzzi, *et al.*, "A Review of the Literature of Surgical and Nonsurgical Treatments of Invasive Squamous Cells Carcinoma", ***Biomed Res Int,*** 2018, 9489163(2018).
35. T. N. Chinembiri, L. H. Du Plessis, M. Gerber, J. H. Hamman and J. Du Plessis, "Review of Natural Compounds for Potential Skin Cancer Treatment", ***Molecules,*** 19(8), 11679-11721(2014).
36. A. Sreedhar, J. Li, and Y. Zhao, Next-Gen Therapeutics for Skin Cancer: Nutraceuticals", ***Nutr Cancer,*** 70(5), 697-709(2018).
37. T. R. Su, J.-J. Lin, C.-C. Tsai, *et al.*, "Inhibition of Melanogenesis by Gallic Acid: Possible Invement of the PI3K/Akt, MEK/ERK and Wnt/β-Catenin Signaling Pathways in B16F10 Cells", ***Int J Mol Sci,*** 14(10), 20443-20458(2013).
38. J. Iqbal, B. A. Abbasi, R. Ahmad, *et al.*, "Potential phytochemicals in the fight against skin cancer: Current landscape and future perspectives", ***Biomed Pharmacother,*** 109, 1381-1393 (2019).
39. A. S. Choudhari, P. C. Mandave, M. Deshpande, P. Ranjekar and O. Prakash, "Phytochemicals in Cancer Treatment: From Preclinical Studies to Clinical Practice", ***Front Pharmacol,*** 10, 1614(2020).
40. I. Yeh and B. C. Bastian, "Melanoma pathology: new approaches and classification", ***Br J Dermatol,*** 185(2), 282-293(2021).
41. C. J. Cockerell, "The Pathology of Melanoma", ***Dermatol Clin,*** 30(3), 445-468(2012).
42. R. A. Scolyer, R. V. Rawson, J. E. Gershenwald, P. M. Ferguson and V. G. Prieto, "Melanoma pathology reporting and staging", ***Mod Pathol,*** 33(1), 15-24(2020).
43. R. J. Reed and P. Martin, "Variants of melanoma", ***Semin Cutan Med Surg,*** 16(2), 137-158(1997).
44. L. Zeng, B. H. Jaswanth Gowda, M. G. Ahmed, *et al.*, "Advancements in nanoparticle-based treatment approaches for skin cancer therapy", ***Mol Cancer,*** 22(1), 10(2023).
45. T. R. Correia De Sá, R. Silva and J. M. Lopes, "Basal cell carcinoma of the skin (part 1): epidemiology, pathology and genetic syndromes", ***Future Oncol,*** 11(22), 3011-3021(2015).
46. J. Roewert-Huber, B. Lange-Asschenfeldt, E. Stockfleth and H. Kerl, "Epidemiology and aetiology of basal cell carcinoma", ***Br J Dermatol,*** 157(2), 47-51(2007).
47. W. Lear, E. Dahlke and C. A. Murray, "Basal cell carcinoma: Review of epidemiology pathogenesis, and associated risk factors", ***J Cutan Med Surg,*** 11(1), 19-30(2007).
48. A. Waldman and C. Schmults, "Cutaneous Squamous Cell Carcinoma", ***Hematol Oncol Clin North Am,*** 33(1), 1-12(2019).
49. C. L. Kane, C. A. Keehn, E. Smithberger and L. F. Glass, "Histopathology of cutaneous squamous cell carcinoma and its variants", ***Semin Cutan Med Surg,*** 23(1), 54-61(2004).
50. A. S. Weinberg, C. A. Ogle and E. K. Shim, "Metastatic cutaneous squamous cell carcinoma: An update", ***Dermatol Surg,*** 33(8), 885-899(2007).
51. S. K. T. Que, F. O. Zwald and C. D. Schmults, "Cutaneous squamous cell carcinoma: Incidence, risk factors,

diagnosis, and staging", ***J Am Acad Dermatol,*** 78(2), 237-247(2018).
52. S. A. Gandhi and J. Kam, "Skin Cancer Epidemiology, Detection, and Management", ***Med Clin North Am,*** 99(6), 1323-1335(2015).
53. P. K. Dekker, M. D. Mishu, R. Youn and S. B. Baker, "Serial Excision for Treatment of Non-melanoma Skin Cancer", ***Plast Reconstr Surg Glob Open,*** 9(6), e3607(2021).
54. P. Salmon, N. Mortimer, M. Rademaker, L. Adams, A. Stanway and S. Hill, "Surgical excision of skin cancer: the importance of training", ***Br J Dermatol,*** 162(1), 117-122(2010).
55. "CADTH RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL A(RAISAL Mohs Surgery for the Treatment of Skin Cancer: A Review of Guidelines", 2019.
56. E. Van Loo, et al., "Surgical excision versus Mohs' micrographic surgery for basal cell carcinoma of the face: A randomised clinical trial with 10 year follow-up", ***Eur J Cancer,*** 50(17), 3011-3020(2014).
57. J. M. Knox, T. W. Lyles, E. M. Shapiro and R. D. Martin, "Curettage and Electrodesiccation in the Treatment of Skin Cancer", ***Arch Dermatol,*** 82(2), 197-204(1960).
58. E. Galles, R. Parvataneni, S. E. Stuart, E. Linos, S. Grewal and M. M. Chren, "Patient-reported outcomes of electrodessication and curettage for treatment of nonmelanoma skin cancer", ***J Am Acad Dermatol,*** 71(5), 1026-1028(2014).
59. P. J. A. Holt, "Cryotherapy for skin cancer: results over a 5-year period using liquid nitrogen spray cryosurgery", ***Br J Dermatol***, 119(2), 231-240(1988).
60. L. Tagliaferri, et al., "Immunotherapy and radiotherapy in melanoma: a multidisciplinary comprehensive review", ***Hum Vaccin Immunother,*** 18(3), 1903827(2022).
61. J. F. Algorri, M. Ochoa, P. Roldán-Varona, L. Rodríguez-Cobo and J. Miguel López-Higuera, "Photodynamic Therapy: A Compendium of Latest Reviews", ***Cancers,*** 13(17), 4447(2021).
62. M. R. Hamblin, "Photodynamic Therapy for Cancer: What"s Past is Prologue", ***Photochem Photobiol,*** 96(3), 506-516(2020).
63. J. Park, Y. K. Lee, I. K. Park and S. R. Hwang, "Current Limitations and Recent Progress in Nanomedicine for Clinically Available Photodynamic Therapy", Biomedicines, 9(1), 85(2021).
64. V. Verma, T. Sprave, W. Haque, *et al.*, "A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors", ***J Immunother Cancer,*** 6(1), 128(2018).
65. V. Krishnan and S. Mitragotri, "Nanoparticles for topical drug delivery: Potential for skin cancer treatment", ***Adv Drug Deliv Rev,*** 153, 87-108(2020).
66. S. A. Ahmed, M. Nur Hasan, D. Bagchi *et al.*, "Nano-MOFs as targeted drug delivery agents to combat antibiotic-resistant bacterial infections", ***R Soc Open Sci,*** 7(12), 200959(2020).
67. D. F. MacFarlane, "Skin cancer management: A practical approach. Springer New York", (2010).
68. C. A. Burns and M. D. Brown, "Imiquimod for the treatment of skin cancer", ***Dermatol Clin,*** 23(1), 151-164(2005).
69. M. K. Iqubal, A. Iqubal, K. Imtiya, *et al.*, "Combinatorial lipid-nanosystem for dermal delivery of 5-fluorouracil and resveratrol against skin cancer: Delineation of improved dermatokinetics and epidermal drug deposition enhancement analysis", ***Eur J Pharm Biopharm,*** 163, 223-239(2021).
70. A. Ahad, M. Aqil, K. Kohli, Y. Sultana, and M. Mujeeb, "Enhanced transdermal delivery of an anti-hypertensive agent via nanoethosomes: Statistical optimization, characterization and pharmacokinetic assessment", ***Int J Pharm,*** 443(1-2), 26-38(2013).
71. F. K. Akomeah, "Topical dermatological drug delivery: quo vadis?", ***Curr Drug Deliv,*** 7(4), 283-296(2010).
72. A. C. Williams and B. W. Barry, "Penetration enhancers", ***Adv Drug Deliv Rev,*** 56(5),603-18 (2004) .
73. Y. Shahzad, R. Louw, M. Gerber and J. Du Plessis, "Breaching the skin barrier

through temperature modulations", ***J Control Release,*** 202, 1-13(2015).
74. A. Nawaz and T. W. Wong, "Microwave as skin permeation enhancer for transdermal drug delivery of chitosan-5-fluorouracil nanoparticles", ***Carbohydr Polym,*** 157, 906-919(2017).
75. J. Hao, "Topical iontophoresis for local therapeutic effects", ***J Drug Deliv Sci Technol,*** 24(3) ***Editions de Sante,*** 255-258(2014).
76. T. Han and D. B. Das, "Potential of combined ultrasound and microneedles for enhanced transdermal drug permeation: A review", ***Eur J Pharm Biopharm,*** 89, 312-328(2015).
77. A. Azagury, L. Khoury, G. Enden and J. Kost, "Ultrasound mediated transdermal drug delivery", ***Adv Drug Deliv Rev,*** 72, 127-143(2014).
78. S. Jain, N. Patel, M. K. Shah, P. Khatri and N. Vora, "Recent Advances in Lipid-Based Vesicles and Particulate Carriers for Topical and Transdermal A(lication", ***J Pharm Sci,*** 106(2), 423-445(2017).
79. A. M. Al-Mahallawi, A. A. Abdelbary and M. H. Aburahma, "Investigating the potential of employing bilosomes as a novel vesicular carrier for transdermal delivery of tenoxicam", ***Int J Pharm,*** 485(1-2), 329-340(2015).
80. S. Barua and S. Mitragotri, "Challenges associated with penetration of nanoparticles across cell and tissue barriers: A review of current status and future prospects", ***Nano Today,*** 9(2), 223-243(2014).
81. M. G. Nava-Arzaluz, E. Piñón-Segundo and A. Ganem-Rondero, "Lipid nanocarriers as skin drug delivery systems", in Nanoparticles in Pharmacotherapy, 311-390(2019).
82. E. Marcet, S. De Macedo, R. C. Carneiro and S. Matayoshi, "Nova modalidade no tratamento do carcinoma basocelular periocular: Imiquimode New aproach to periocular basal cell carcinoma treatment: imiquimod ARTIGO DE REVISÃO", (2007).
83. M.A. Hyde, M. L. Hadley, P. Tristani-Firouzi, D. Goldgar and G.M. Bowen, "A randomized trial of the off-label use of imiquimod, 5%, cream with vs without tazarotene, 0.1%, gel for the treatment of lentigo maligna, followed by conservative staged excisions", ***Arch Dermatol,*** 148(5), 592-596(2012).
84. C. C. McCuaig, J. Dubois, J. Powell, *et al.*, "A phase II, open-label study of the efficacy and safety of imiquimod in the treatment of superficial and mixed infantile hemangioma", ***Pediatr Dermatol,*** 26(2), 203-212(2009).
85. S. Adams, L. Kozhaya, F. Martiniuk, *et al.*, "Topical TLR7 agonist imiquimod can induce immune-mediated rejection of skin metastases in patients with breast cancer", ***Clin Cancer Res,*** 18(24), 6748-6757(2012).
86. https://pubchem.ncbi.nlm.nih.gov/compound/Imiquimod.
87. A. A. Gaspari and D. N. sauder, "Immunotherapy of basal cell carcinoma: evolving approaches", ***Dermatol Surg,*** 29(10), 1027-1034(2003).
88. A. H. Sabri, Z. Cater, P. Gurnani , *et al.*, "Intradermal delivery of imiquimod using polymeric microneedles for basal cell carcinoma", ***Int J Pharm,*** 589, 119808(2020).
89. M. Lapteva, M. Mignot, K. Mondon, M. Möller, R. Gurny and Y. N. Kalia, "Self-assembled mPEG-hexPLA polymeric nanocarriers for the targeted cutaneous delivery of imiquimod", ***Eur J Pharm Biopharm,*** 142, 553-562(2019).
90. H. Jamshaid, F. Ud Din, M. Malik, *et al.*, "A cutback in Imiquimod cutaneous toxicity; comparative cutaneous toxicity analysis of Imiquimod nanotransethosomal gel with 5% marketed cream on the BALB/c mice", ***Sci Rep,*** 12(1), 14244(2022).
91. I. Telò, E. Del Favero, L. Cantù, *et al.*, "Gel-like TPGS-Based Microemulsions for Imiquimod Dermal Delivery: Role of Mesostructure on the Uptake and Distribution into the Skin", ***Mol Pharm,*** 14(10), 3281-3289(2017).
92. S. Pescina, G. Garrastazu, E. Del Favero, *et al.*, "Microemulsions based on TPGS and isostearic acid for imiquimod formulation and skin delivery", ***Eur J Pharm Sci,*** 125, 223-231(2018).
93. K. Rehman and M. H. Zulfakar, "Novel Fish Oil-based Bigel System for

Controlled Drug Delivery and its Influence on Immunomodulatory Activity of Imiquimod Against Skin Cancer", ***Pharm Res,*** 34(1), 36-48(2017).

94. K. Rehman, M. F. F. M. Aluwi, K. Rullah, L. K. Wai, M. C. I. Mohd Amin and M. H. Zulfakar, "Probing the effects of fish oil on the delivery and inflammation-inducing potential of imiquimod", ***Int J Pharm,*** 490(1-2), 131-141(2015).
95. M. H. Al-Mayahy, A. H Sabri ,C. S. Rutland, *et al.,* "Insight into imiquimod skin permeation and increased delivery using microneedle pre-treatment", ***Eur J Pharm Biopharm,*** 139, 33-43(2019).
96. S. Hua, "Lipid-based nano-delivery systems for skin delivery of drugs and bioactives", ***Front Pharmacol,*** 6, 219(2015).
97. M. S. Algahtani, M. Z. Ahmad, I. H. Nourein and J. Ahmad, "Co-delivery of imiquimod and curcumin by nanoemugel for improved topical delivery and reduced psoriasis-like skin lesions", ***Biomolecules,*** 10(7), 1-19(2020).
98. C. G. Venturini, F. A. Bruinsmann , R. V. Contri , *et al.,* "Co-encapsulation of imiquimod and copaiba oil in novel nanostructured systems: Promising formulations against skin carcinoma", ***Eur J Pharm Sci,*** 79, 36-43(2015).
99. S. Kim, et al., "Development and Optimization of Imiquimod-Loaded Nanostructured Lipid Carriers Using a Hybrid Design of Experiments Approach", ***Int J Nanomedicine,*** 18, 1007-1029(2023).
100. D. Sivadasan, M. H. Sultan, O. A. Madkhali, A. A. Alessa and S. H. Alsabei, "Stealth Liposomes (PEGylated) Containing an Anticancer Drug Camptothecin: In Vitro Characterization and In Vivo Pharmacokinetic and Tissue Distribution Study", ***Molecules,*** 27(3), 1086(2022).
101. M. Ghezzi, S. Pescina, A. Delledonne *et al.,* "Improvement of imiquimod solubilization and skin retention viatpgs micelles: Exploiting the co-solubilizing effect of oleic acid", ***Pharmaceutics,*** 13(9), 1476(2021).
102. R. P. Gazzi, L. A. Frank, G. Onzi, A. R. Pohlmann and S. S. Guterres, "New pectin-based hydrogel containing imiquimod-loaded polymeric nanocapsules for melanoma treatment", ***Drug Deliv Transl Res,*** 10(6), 1829-1840(2020).
103. L. A. Frank, P. S. Chaves, C. M. D'Amore, *et al.,* "The use of chitosan as cationic coating or gel vehicle for polymeric nanocapsules: Increasing penetration and adhesion of imiquimod in vaginal tissue", ***Eur J Pharm Biopharm,*** 114, 202-212(2017).
104. M. F. Dias, B. C. P. de Figueiredo, J. Teixeira-Neto, M. C. A. Guerra, S. L. Fialho and A. Silva Cunha, "In vivo evaluation of antitumoral and antiangiogenic effect of imiquimod-loaded polymeric nanoparticles", ***Biomed Pharmacother,*** 103, 1107-1114(2018).

Bull. Pharm. Sci., Assiut University, Vol. 47, Issue 1, 2024, pp.119-140.

نشرة العلوم الصيدليـــة
جامعة أسيوط

BULL. PHARM. SCI. Assiut Univ.

العلاج الموضعي المتطور لسرطان الجلد باستخدام نانوجزيئات محملة بعقار الايميكيمود : نظرة فاحصة

هدى مصطفى عبد الغفار[1*] – هند محمد عبد البر[2] – عبد العزيز محسن المحلاوي[3،4] – اميمة نعيم الجزايرلى[3]

[1] الإدارة المركزية لمكافحة المخدرات، هيئة الدواء المصرية، المنصورية، مصر

[2] قسم الصيدلانيات، كلية الصيدلة، جامعة مدينة السادات، مدينة السادات، مصر

[3] قسم الصيدلانيات والصيدلة الصناعية، كلية الصيدلة، جامعة القاهرة، القاهرة، ١١٥٦٢، مصر

[4] كلية الحياة والعلوم الطبية، جامعة هيرتفوردشاير تستضيفها المؤسسة الأكاديمية العالمية، العاصمة الإدارية الجديدة، القاهرة، مصر

يتناول هذا البحث المرجعيالتطورات البارزة في العلاج الموضعيلسرطان الجلد، مع التأكيد على الدور الهام الذي تلعبه التكنولوجيا النانوية في تخطي القيود المرتبطة بالعلاجات التقليدية. تُقـــيّم بعمـــق تطوير وكفاءة أنظمة الناقلات النانوية المبتكرة، مثل النانوجزيئات المحملة بالإميكويمود، التي صُممت لتحسين توصيل وفاعلية الدواء الموضعي ضد سرطانات الجلد غير الميلانينية. يغطي التقييم التحديات والحلول المتعلقة بالعلاجات الكلاسيكية، مع التركيز على التحسينات في التوافر البيولوجي ونفاذية الجلد وامتثال المرضى التي توفرها هذه المنصات النانوية. من خلال تقديم منهج موجه وأقل اجتياحًا، تشـــير هذه التطورات إلى تحول نحو علاجات موضعية أكثر فعالية وملائمة للمرضى. حيث يسلط هذا البحث المرجعيالضوء ليس فقط على إمكانيات التكنولوجيا النانوية في التطبيقات الجلدية ولكن أيضًا يبرز تقدمًا حاسمًا في علاجات الأورام الموضعية، مما يفتح الطريق أمام تحسين نتائج المرضى في مجال عـــلاج سرطان الجلد.