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Review

Innovative Approaches in Vitiligo Treatment: The Role of Nano-Drug Delivery Systems in Enhancing Therapeutic Efficacy

Nitish Nagdev*, Jiyaul Hak, Deeksha

Department of Pharmacy, IIMT College of medical sciences, IIMT University, O-Pocket, Ganganagar, Meerut, 250001, (U.P.), India

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Abstract:

Vitiligo is a condition characterized by the loss of pigmentation in the skin, which has a profound influence on the physical health, emotional state, and overall quality of life of those afflicted. The main objective of therapy is to regulate the immunological response by reducing oxidative stress. Nevertheless, the skin's cuticle acts as a barrier and the absence of specific drug accumulation leads to inadequate therapeutic results and adverse consequences. Nanotechnology has intriguing opportunities for the development of novel therapeutic approaches for vitiligo, while research in this field is currently constrained. This review provides a concise and thorough analysis of current research conducted on nano-drug delivery methods used in the treatment of vitiligo. Specifically, it focusses on liposomes, niosomes, Nano hydrogels, and nanoparticles. These investigations have achieved notable advancements by raising the effectiveness of drug loading and improving the ability of drugs to penetrate the skin. These results suggest three important concepts for topical nano-drug delivery systems in the treatment of vitiligo: boosting the penetration of drugs through the skin, improving the retention of drugs, and aiding the regeneration of melanin. The purpose of these approaches is to stimulate the development of topical medication delivery methods that can efficiently target and perhaps overcome vitiligo.

Keywords: *Nanoemulsion, Microemulsion, Therapeutic Approach, Vitiligo etc.*

***Corresponding Author**

Nitish Nagdev

Department of Pharmacy, IIMT College of medical sciences, IIMT University, O-Pocket, Ganganagar, Meerut, 250001, (U.P.), India

Email: nitishnagdev@gmail.com

Introduction:

Vitiligo is a dermatological condition that is both acquired and idiopathic in nature. It is characterised by the formation and presence of white patches that are linked to the programmed cell death or targeted damage of melanocytes. Vitiligo affects about 0.5–1% of the population. India has the highest documented incidence rate, reaching up to 8.8% [1].

Japan has a population growth rate of 1.68%, whereas Mexico's population growth rate ranges between 2.6% to 4%. Depigmentation usually appears in areas of the body that are often exposed, such as the face, neck, and limbs. Patients suffering with vitiligo can endure a substantial psychological load due to the terrible impact of the condition. Despite the similar prevalence of vitiligo in both males and females, women are more inclined to actively

seek treatment and publicly express their concerns about the condition's aesthetic effects. Reports indicate that 20% of individuals with vitiligo have family members who have also been diagnosed with the illness. Additionally, vitiligo often appears in certain family groups, indicating a strong familial clustering. Individuals with a positive family history of the illness often have a longer duration and an earlier age of onset compared to those without such a family history [2].

The aetiology of vitiligo is now believed to be multifactorial and remains incompletely understood. In the 1950s, Lerner performed a study involving 600 individuals diagnosed with vitiligo. The findings revealed that a significant number of patients with segmental vitiligo had emotional disturbances or excessive sweating, known as hyperhidrosis. This finding finally resulted in the progress of the neural theory. Vitiligo has been linked to several variables, including stress, autoimmune illnesses, melanocyterrhage, and auto inflammation, as scientific study has progressed [3]. The ideas of autoimmune illness, auto inflammation, and oxidative stress, together with their interconnections, are widely recognized as major contributing causes to the disease. Antigen-presenting cells in the illness deliver melanocyte antigens, leading to the subsequent activation of T lymphocytes, which then directly kill the melanocytes. Reports indicate that people with vitiligo have hyperactivity in their endogenous killer and inflammatory dendritic cells. Furthermore, cells that are naturally present in the body release a diverse range of cytokines, including IFN-γ, CXCL10, TNF-α, IL-6, and IL-17, as a component of an immune response against one's own tissues [4].

In addition to the autoinflammation idea, oxidative stress is also a prominent contributing cause for vitiligo. Melanin, synthesized by melanocytes, exhibits toxicity and triggers the cellular stress signaling pathway inside these cells. In addition, there is an excessive accumulation of reactive oxygen species (ROS) in the mitochondria due to the high level of energy metabolism. Additionally, this leads to the emergence of vitiligo [5].

To summarize, the body produces chemicals linked with epidermal damage and experiences increased levels of oxidative stress when microscopic lesions occur due to sunlight, viral infection, or physical trauma. Inflammasome are triggered by the release and generation of molecular and oxidative stress substances, resulting in the detachment of melanocytes. Immune-mediated destruction of melanocytes ultimately happens due to the buildup of particular cytotoxic T cells on the epidermis, the decrease in regulatory T cell function, and the release of inflammatory cytokines and autoantibodies after a series of immune responses (Figure 1).Oxidative stress has a role in the development of depigmentation, and the evolution of vitiligo is then aided by unwanted autoimmune reactions.26 to 30 The purpose of this study is to provide helpful materials and stimulate future research on novel therapies for vitiligo. More precisely, we analyses all nano-drug delivery methods that might be used for this objective [6].

Vitiligo is a condition characterised by a deficiency or absence of melanocytes, leading to a decreased synthesis of melanin in the skin. Melanocytes are situated in the basal layer of the epidermis of human skin, where they are organized in a 1:16 proportion with keratinocytes to create functional units called epidermal melanin units. The control of melanocyte proliferation and the transfer of melanosomes to keratinocytes are governed by the balance between these entities [7].

Although the exact cause of vitiligo is not fully understood, scientists have suggested that it may be due to hereditary factors, cellular autoimmune factors, or a mix of both. Additional investigation is necessary to ascertain the aetiology of vitiligo, given the variability in its presentation between people [8].

Topically applying furanocoumarins is a recent therapy approach for vitiligo that might potentially enhance the production of melanin in regions of the skin affected by pigment loss. Brosimum gaudichaudii has the ability to synthesize a large amount of furanocoumarins, including bergapten and psoralen. The use of the decoction of Brosimum gaudichaudii stems and root casings, its alcoholic extract, and the infusion of its leaves has been a longstanding practice in traditional medicine for the treatment of vitiligo [9].

Although plant material extracts are widely used in the production of phytocosmetics and herbal remedies, there is a lack of evidence regarding the stability of natural substances and the ideal quantity needed to achieve safe, effective, and consistent therapeutic effects. Consequently, the presence of bioactive substances in these formulations requires a thorough examination to assess the quantity of plant extract components that enter the outer layer of the skin and the durability of the formulations during toxicity testing. Data on these parameters may guide the assessment of the

safety profile of the formulations and the ideal site of action of such compounds when applied to the epidermis. Researchers have highlighted the crucial need for improved delivery methods for melanocytes, as shown by the harmful effects of isolated bergapten and psoralen in vitro, which vary depending on the dosage and duration of exposure [10].

Microemulsions provide compelling options for the application of plant extracts on the skin in this particular situation. Surfactants are often used in conjunction with cosurfactants to enhance the stability of Microemulsions. These Microemulsions are liquid and transparent systems consisting of water and oil that remain thermodynamically stable. Consequently, these systems may improve the stability of unstable medications and control their release by include both hydrophilic and lipophilic molecules, leading to a usually non-toxic profile. Considering the information described above, we suggested assessing the stimulating impact of two extracts from Brosimum gaudichaudii on melanocyte growth in a controlled environment, as well as creating and analysing Microemulsions that include these extracts. The formulations were evaluated for their stability, skin penetration, and irritating potential, demonstrating the possibility of topical treatments to treat vitiligo [11].

Therapeutic approach:

Developing an efficacious therapy for vitiligo has been challenging owing to the limited comprehension of the underlying mechanisms and dynamics of the disorder. The primary goals of vitiligo therapy are to halt the progression of current depigmented areas on the skin, stimulate the restoration of pigmentation, and reduce the psychological distress associated with the condition. The main approaches now used to treat vitiligo include drug treatment and phototherapy. Corticosteroids, such as betamethasone dipropionate, clobetasol dipropionate, and methotrexate, are often used as the main therapy for vitiligo because of their ability to inhibit the immune system and reduce inflammation [12]. Tacrolimus and pimecrolimus, which are calcineurin inhibitors, were suggested as the primary therapy for vitiligo in newly issued recommendations. Several clinical studies have shown that calcineurin inhibitors have a similar impact to glucocorticoids, especially when it comes to treating face leukomas. The numbers are 35 and 36. Moreover, the buildup of oxidative chemicals in the outermost layer of the skin is a major component that causes dysfunction in melanocytes. Thus, to rejuvenate the skin's oxidation-antioxidant system, a range of antioxidants have been used to remove surplus ROS and hydrogen peroxide from the epidermis of skin affected by vitiligo [13]. Vitiligo is managed with the use of oral antioxidants, such as polypodium leucotomos, vitamin E, vitamin C, and minocycline, as a component of an antioxidant therapeutic approach. Phototherapy, including narrow-band ultraviolet (NB-UVA) and psoralen ultraviolet A (PUVA), is a safe physical-based treatment that is different from medication therapy. The range is from 38 to 40. These techniques have been extensively used in clinical practice because of their remarkable effectiveness in promoting repigmentation, both on their own and when used along with the stated drugs [14].

Vitiligo is characterised by a prolonged and gradual development, advancement, and treatment process that may extend over many months or even years. Hence, the prolonged use of certain drugs or treatment methods will unavoidably result in a wide range of undesirable consequences. For example, the prolonged use of glucocorticoids may lead to skin thinning, the development of acne, and inflammation of hair follicles. The extensive use of corticosteroids is impractical and may lead to a substantial occurrence of undesirable effects. Therefore, corticosteroids are considered unsuitable for treating generalized vitiligo [15].

Recent research highlighted that tacrolimus did not provide any discernible therapeutic benefits in the management of segmental vitiligo, despite the clinical synergy and comparable therapeutic effects of glucocorticoids and calcineurin. During the first two weeks of therapy, the most common side effect of calcineurin inhibitors is a burning feeling. Moreover, the financial costs linked to calcineurin inhibitors are much greater than those of corticosteroids, resulting in a major economic strain on patients [16].

When compared to these other therapies, antioxidant drugs are less strong and do not show any noticeable negative effects. However, established consensus recommendations do not support using topical antioxidants as the exclusive therapy for vitiligo. This is because most research on this issue was limited by a small sample size. Regarding non-pharmacological treatment, phototherapy for vitiligo requires many sessions (two or three times per week), resulting in annoyance for patients. Although the treatments for repigmentation have improved success rates, the recurrence rates remain elevated. Within the first year after discontinuing treatment, almost 50% of individuals are prone to

have recurring white patches on their regulated skin. Furthermore, phototherapy treatment may lead to kidney toxicity, vertigo, headaches, and ocular complaints. Furthermore, these medicines are associated with a heightened susceptibility to cutaneous cancer. Therefore, the NHS only advises the use of phototherapy when other substantial treatments have been shown to be futile [17.

The progress of nanotechnology has led to the development of large-scale nano-drug delivery systems that have been used to enhance medication penetration through the epidermis. These systems, such as Microemulsions, nanoemulsion, nanoparticles, lipid carriers, and several other Nano vesicles, exhibit notable benefits compared to conventional techniques. There is a limited amount of research available on the use of nanomedicine for treating vitiligo [18].

It serves as a physical barrier and performs activities such as aiding in immunological defence, regulating temperature, protecting against UV radiation, and retaining moisture.

The skin consists of three layers: the epidermis, which encompasses the corneum, dermis, and hypodermis. The outermost layer and the outermost layer of the skin are mostly made up of 70-90% protein and 5-15% lipids. These components play a crucial role in protecting the body from external factors such as stressors and toxins from the environment. Transdermal administration poses a major obstacle in treating conditions such as vitiligo due to the limited number of therapeutic agents that possess ideal penetration properties. Currently, the most cutting-edge technology allows medications with a molecular mass of 100 Da and high lipophilicity to effectively permeate the skin [19]. In addition, the existing dosage forms, such as creams, ointments, moisturizers, lubricants, and other carriers, are not successful in achieving the necessary therapeutic results. Overall, the problems related to traditional topical treatments highlight the pressing requirement for reformation and advancement in transdermal drug delivery for vitiligo treatment. This is crucial for better comprehension of the condition and to enhance the chances of achieving better results for patients [20].

Nano drug delivery used in vitiligo:

The human epidermis, being the biggest organ in the body, performs many vital roles such as immunological defence, temperature control, moisture retention, UV protection, and acting as a physical barrier. The skin consists of three layers: the epidermis, which comprises the stratum corneum, dermis, and hypodermis. The outermost layer and the outermost layer of the skin are mostly made up of 70-90% protein and 5-15% lipids. These components play a crucial role in protecting the body from external factors such as stressors and toxins from the environment. Transdermal administration poses a major difficulty, especially when treating conditions like vitiligo, since only a limited number of medicinal chemicals have the ideal ability to penetrate the skin effectively [21]. Currently, the most cutting-edge technology allows medications with a molecular mass of 100 Da and high lipophilicity to effectively permeate the skin. In addition, the existing dosage forms, such as creams, ointments, moisturizers, lubricants, and other carriers, are not successful in achieving the necessary therapeutic results. Overall, the problems related to traditional topical treatments highlight the pressing requirement for reform and innovation in transdermal drug delivery for vitiligo treatment. This is crucial for better comprehension of the condition and to enhance the chances of achieving better patient results [22].

The latest advancements in state-of-the-art nanotechnology provide an exceptional chance to tackle the shortcomings linked to conventional techniques.

The use of a nano-drug delivery system has the potential to enhance the transdermal penetration of medications and amplify their therapeutic benefits. This may be achieved by exploiting certain attributes of the stratum corneum. Several advanced nano-drug delivery technologies are now being developed, such as liposomes, polymeric nanoparticles, microspheres, solid lipid nanoparticles, and Nano fibrous structures. These systems are specifically designed to administer medicinal substances [23].

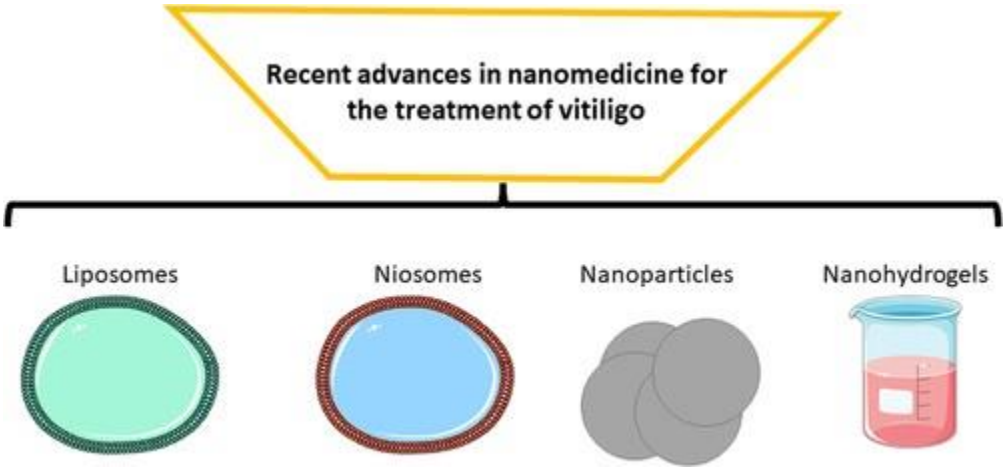

Figure 1: A scheme of the nano-drug delivery systems for vitiligo therapy.

Microemulsion:

Microemulsions are clear colloidal entities that exhibit thermodynamic stability. Surfactants are used to stabilise water and oil in the traditional composition of Microemulsions, which may also contain a Cosurfactants. The microstructures of Microemulsions can vary depending on the physical and chemical properties of the surfactants and constituents used in their formation. The advantages of Microemulsions as transdermal delivered drugs demonstrate their potential as a technological platform for the development of innovative pharmaceutical formulations. A research team discovered a gel containing clobetasol propionate that was formulated as a microemulsion. This gel successfully overcame the issue of clobetasol propionate's low solubility [24]. The effectiveness of the preparation was proven by the enlargement of the stratum corneum due to water retention caused by the gel formulation. This enlargement facilitated the penetration of clobetasol propionate into the epidermis. A clinical study found that patients treated with a clobetasol propionate-loaded microemulsion-based gel showed faster and more extensive repigmentation compared to control groups. Numerous studies and literatures have demonstrated that Microemulsions can substantially increase the percutaneous permeability of medications, although the precise mechanisms involved are not yet completely understood. The permeability of microemulsion is greatly affected by the composition or internal phase structure, as well as the internal microstructure. Microemulsions have shown a promising method for delivering anti-inflammatory medications (NSAIDs) through the skin, leading to a significant improvement in the rate at which the medication is absorbed [25].

Nanoemulsion: Nanoemulsion is increasingly being explored for the treatment of vitiligo due to their ability to enhance the delivery and efficacy of therapeutic agents. Their small droplet size allows for improved penetration through the skin barrier, ensuring that active ingredients, such as corticosteroids, calcineurin inhibitors, or herbal extracts, reach the targeted melanocytes more effectively. Additionally, nanoemulsion offer controlled and sustained release, enhancing the bioavailability of the drugs while reducing application frequency and minimizing side effects. This innovative approach holds promise for more efficient and patient-friendly management of vitiligo, potentially leading to better repigmentation outcomes [26].

Nanoemulgel: Nanoemulgel, which combine the properties of nanoemulsion and hydrogels, are being investigated for the treatment of vitiligo due to their enhanced drug delivery capabilities and improved patient compliance. These formulations offer the benefits of nanoemulsion, such as small droplet size for better skin penetration and controlled release of active ingredients, while also providing the soothing and moisturizing properties of hydrogels. This dual action facilitates effective delivery of therapeutic agents like corticosteroids or immunomodulatory to the depigmented areas, promoting repigmentation with reduced frequency of application and minimized side effects. The gel matrix also enhances the stability and retention of the formulation on the skin, making nanoemulgel a promising option for vitiligo management [26].

Table 1: Vitiligo therapy using a nano-drug delivery system

Formulation	Name of drug	Results	Ref
Microemulsion-based gel	Clobetasol propionate	The therapeutic use of modified lipid carriers in vitiligo treatment has demonstrated promising results. These carriers showed better retention in the skin and less irritation potential, effectively permeating and retaining in the skin layers. They significantly enhanced skin permeation and accumulation, leading to improved therapeutic outcomes. Patients treated with modified lipid-based carriers (MBC) experienced faster repigmentation, highlighting the potential of these advanced delivery systems in vitiligo therapy.	[28]
Cationic niosomes	Tyrosinase plasmid pMEL34	The measured tyrosinase activity was fourfold greater than those of the unbound plasmid and the plasmid encapsulated in nonelastic niosomes. Display promise as a gene-based topical delivery method for vitiligo.	[28]
Deformable liposomes	Resveratrol and psoralen	The increased penetration rate greatly enhanced the activity of melanin and tyrosinase, leading to possible antioxidant effects. Additionally, it facilitated pigmentation and the restoration of redox equilibrium by effectively scavenging free radicals.	[29]
Cationic niosomes	Human tyrosinase plasmid in mouse melanoma cells by Tat peptide	Increased the activation of the human tyrosinase gene and the generation of melanin with little harm to cells; enhanced the durability of the plasmid contained inside the niosomes.	[30]
Nanosized ethosomes-based hydrogel	8-Methoxypsoralen	There was a notable increase in the penetration and buildup of the substance in the outermost layer of the skin (epidermis) and the layer underneath it (dermis). Demonstrated little phototoxicity and erythema in comparison to the traditional cream.	[31]
Nanoparticles	Palladium and platinum	Can activate AHR and NRF2 in human keratinocytes.	[32]
Nanoparticles	Polydopamine	Human epidermal keratinocytes internalized the melanin-like nanoparticles and exhibited similar characteristics to natural melanosomes.	[33]
Liposomes	8-Methoxypsoralen	In vitro studies show that 8-MOP has enhanced release and permeation-accumulation.	[34]
Deformable liposomes	Baicalin and berberine	Enhanced melanin synthesis and increased tyrosinase function. Demonstrated exceptional capacity to prevent oxidation and defend against the harmful effects of sunlight.	[35]

Liposome and noisomes:

Liposomes are lipid-based particles with a bilayer structure similar to the cell membrane, surrounding a watery centre. Liposomes are often regarded as the most favorable Nano carrier for delivering drugs to the skin's surface because of their ability to break down naturally and their lack of toxicity. The apparent efficacy of liposomes may be related to the fusion of lipid vesicles with the stratum corneum, allowing the therapeutic agent to permeate into

deeper layers of the skin.7Liposomes also improve the solubility of drugs on the skin and expedite their disintegration. In addition, liposomes are regarded as drug carriers that enable the controlled release of medications at a steady pace and minimize the need for repeated administrations. One group used a film hydration technique to create a liposomal therapy filled with 8-methoxypsoralen. Following a sequence of purges, it was concluded that the ultimate vehicle had exceptional penetration characteristics and had a diameter ranging from 100 to 500 nm, in comparison to controls treated with a hydroalcoholic solution [36]. All nano vehicles shown significant capabilities in sustaining the amounts of 8-MOP release and its permeation-accumulation into epidermal layers. Another group reported the effects of co-loading psoralen and resveratrol with ultradeformable liposomes (UDL) for the treatment of vitiligo. Psoralen, a naturally occurring furanocoumarin derivative, is used in combination with UV or PUVA therapy to treat several skin conditions. The presence of a surfactant causes changes in the shape of the vesicle in response to external environmental circumstances. Resveratrol has antioxidant properties and promotes mitogen-activated protein kinase signaling. Previous investigations by other organisations have performed optimization experiments, and the formula that best met the criteria of particle size, PDI, and zeta potential was selected. The drug loading efficiencies varied between 2.5% and 5%, whereas the liposome particle size was 120 nm [37]. Co-loaded liposomes were created using a modified film hydration method. The carrier's capacity to sustain the release of both drugs over prolonged durations was established by in vitro experiments and kinetics. Cellular experiments conducted in a laboratory setting showed that the carrier significantly enhanced the production of melanin and the activity of tyrosinase, while also preserving the antioxidant properties of psoralen and resveratrol. A group of researchers created samples of baicalin and berberine that were loaded along with ultradeformable vesicles. These samples showed promise as adjuvants for treating vitiligo. The therapeutic drugs selected were baicalin and berberine because to their antioxidant, anti-inflammatory, and proliferative characteristics. The range is from 76 to 78. Preparation was shown to enhance the penetration of antioxidants and medicines in laboratory experiments. The assessment of the photo protective impact revealed that the co-loaded vesicles enhanced the functions of melanin and tyrosinase. A cationic noisome with elastic properties has been developed by others to carry the human tyrosinase plasmid pMEL34. Gel electrophoresis and documentation confirmed that the maximum quantity of pMEL34 loaded onto the elastic vehicle was 150 mg per 16 mg of niosomal. Compared to pMEL34 loaded into nonelastic cationic niosomes, the amount of pMEL34 and the rate at which it passed through increased significantly after 6 hours of treatment with pMEL34, thanks to the elasticity-enhancing effects of ethanol on the vesicles [38]. The tyrosinase-associated activities were found to be four times more than the corresponding values seen for loose plasmid and plasmid put into nonelastic niosomes. These findings indicate that flexible positively charged niosomes have the ability to serve as efficient gene delivery vehicles for the treatment of vitiligo when applied topically. In 2012, a human tyrosinase plasmid called pMEL34 was identified and shown to enhance melanin synthesis by using the Tat peptide. The carrier stays within the stable dispersion range, as shown by the vesicular size and zeta potential. In vitro studies have shown that this method of preparation effectively enhances the expression of the tyrosinase gene and stimulates melanin formation, while causing little to no harmful effects on cells [39]. Another group used a central composite design (CCD) to generate 8-MOP ethosomes. Ethosomes improve the penetration and retention of medications in the layers of the skin, whereas traditional liposomes transport pharmaceuticals to the outermost layers of the skin. The use of this preparation resulted in improved effectiveness when applied to the skin, as well as an optimised formulation that included ethosomes. This led to a considerable increase in the accumulation of 8-MOP, likely due to the deformation of the ethosomes, as shown by the in vitro investigation on the penetration of this chemical through the skin. The findings from the experiments conducted outside a living organism were supported by the studies conducted within a living organism. The lipid nanocarrier is the most effective way for delivering drugs via the skin, because to its excellent compatibility with living tissues and its ability to efficiently encapsulate drugs. This approach surpasses all other complex methods in terms of its benefits. An increasing number of researchers in this sector are concentrating on several new vesicle delivery technologies that demonstrate improved therapeutic efficacy and percutaneous penetration [40].

Nanoparticles:

The emerging use of nanoparticles represents a transformative advancement in nanomedicine, leveraging their large surface-to-volume ratios to enhance drug-tissue interaction and enable controlled drug release. Recently, nanoparticles have been integrated into everyday products, demonstrating their potential in various applications. Their ability to penetrate the skin is influenced by size, charge, and structure. Metal nanoparticles like palladium (Pd) and platinum (Pt) have been shown to boost enzyme activity and exhibit anti-inflammatory effects in UV-treated HaCaT keratinocytes. Notably, cells pretreated with nano-Pt exhibited significantly reduced apoptosis rates compared to controls. A combination of Pd and Pt nanoparticles, known as PAPLAL, has been used to treat chronic conditions such as burns, gastric ulcers, and rheumatoid arthritis, demonstrating SOD catalase activity and reducing O2- generation in mouse skin tissue. Both in vivo and in vitro studies indicate that PAPLAL effectively suppresses endogenous superoxide levels via SOD and catalase activity through the AHR and NRF2 pathways. While further research into the use of Pd and Pt nanoparticles for vitiligo treatment is warranted, it must be approached cautiously due to potential allergenic properties of metals. By employing coating techniques or other modifications, nanoparticles can overcome their limitations, achieving efficient transdermal delivery and targeted drug release [41].

Concepts of Vitiligo Treatment-Specific Nano-Drug Delivery Systems:

Enhancing the Accumulation of Therapeutic Agents: Understanding the Mechanism of Receptor-Ligand Binding:

Melanocytes are dendritic cells located in the basal cell layer of the epidermis, responsible for synthesizing and secreting melanin. Despite numerous methods to breach the stratum corneum barrier for deeper skin penetration, effectively driving and accumulating therapeutic agents at the target site remains challenging. Active targeting, leveraging the affinity between receptors and ligands, is a promising strategy for specific retention. Melanocortin-1 receptor (MC1R), a G protein-coupled receptor found on melanocytes, is targeted by endogenous ligands such as α-MSH, β-MSH, γ-MSH, and ACTH, with α-MSH showing the highest affinity. The simple amino acid sequence of α-MSH makes it an ideal target for nano-drug delivery systems to aggregate near melanocytes. Another critical receptor is the endothelin receptor, which participates in various physiological activities and whose endothelin B receptor expression increases as melanocytes transform into melanoma cells. Studies have shown that Endothelin-1 (ET-1) promotes melanin synthesis and dendrite formation in normal human epidermal melanocytes. Additionally, the protease-activated receptor-2 (PAR-2) on keratinocytes plays a central role in melanosome transport, with peptides SLIGRL and SLIGKV activating PAR-2 without receptor cleavage. These targeting mechanisms offer potential pathways for developing more effective treatments for conditions like vitiligo and other pigmentary disorders [42].

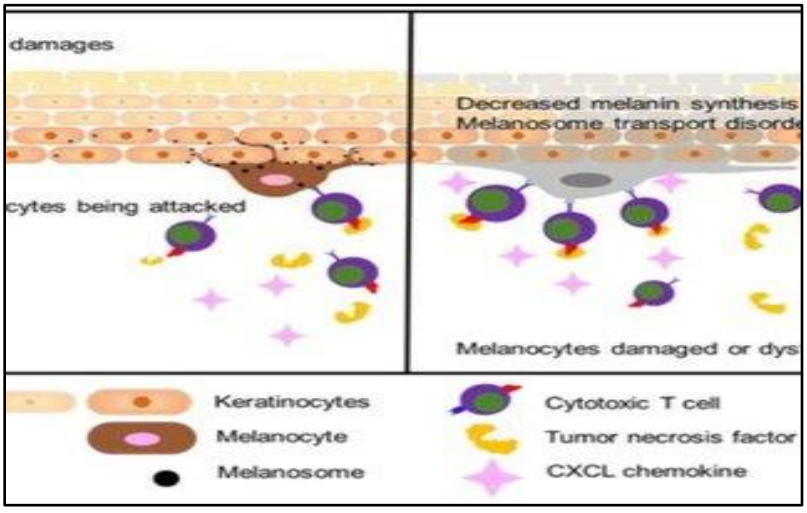

Figure 2: Diagram illustrating the function of MC1R in the production and release of melanin

Improving the ability of therapeutic agents to penetrate:

Lipid particles share similarities with the stratum corneum, making liposomes excellent vectors for therapeutic delivery. While conventional liposomes are inadequate for transdermal delivery, advanced liposomes such as invasomes, transferosomes, ethosomes, and niosomes address these limitations. Invasomes, introduced in 2003, incorporate soy-phosphatidylcholine (SPC), ethanol, and terpenes to significantly enhance percutaneous permeability compared to traditional liposomes. For instance, invasomes loaded with ferulic acid have shown excellent skin permeation, making them ideal for transdermal delivery. Transferosomes, reported in 1992, utilize surfactants like sodium cholate, spans, and tweens to increase elasticity, demonstrating superior antiedema activity and penetration ability over traditional liposomes. For example, transferosomes encapsulating dexamethasone showed improved performance in a carrageenan-induced rat paw edema model, with Span-80 identified as the optimal edge activator. Microneedles (MN), ranging from 10–2000 μm in height and 10–50 μm in width, have been extensively studied for transdermal drug delivery, including combinations with nanocarriers for conditions like diabetes, cancer, and vitiligo [43]. Despite their potential, poor water dispersibility and weak percutaneous permeability of nanoparticles pose challenges. However, combining microneedles with nanoparticles shows promise for vitiligo therapy, as demonstrated by the successful delivery of gold nanoparticles into the hamster cheek at a depth of 100–200 μm. Frequent use of microneedles, however, can cause persistent skin damage and inflammation, highlighting the need for comprehensive strategies. Iontophoresis, using mild electrical currents to enhance transdermal delivery, has been combined with nano-drug delivery systems since 1996, though initial results were unsatisfactory. Subsequent research revealed that electrical stimulation through iontophoresis induced connexin43 phosphorylation, filamentous actin depolymerization, and Ca2+ inflow, enhancing liposome permeation by altering skin physiology. These insights suggest potential improvements in combining nano-drug delivery systems with iontophoresis for better therapeutic outcomes [44].

Encouraging the production of melanin:

The therapeutic goals for vitiligo treatment include inhibiting the inflammatory response and promoting melanin regeneration. Many current treatments primarily focus on reducing inflammation rather than repigmentation, driving the demand for drug delivery systems that can address both aspects [45. Tacrolimus, a calcineurin inhibitor, suppresses T cell activity and proinflammatory cytokine secretion, thereby promoting melanocyte migration and repigmentation. Despite its effectiveness, tacrolimus is limited by risks of lymphoproliferative disease, a narrow therapeutic index, and low solubility. To address these issues, a nanolipid carrier incorporating lipophilic solubilizes was developed, showing high entrapment efficiency (96.66%) and superior drug release in vitro and in vivo compared to commercial ointments, while also causing less skin irritation [46, 47].

Specific receptors on melanocytes and keratinocytes play crucial roles in controlling melanocyte proliferation, melanin synthesis, and migration. Endogenous ligands or their analogs can be used as peptide drugs to activate melanocyte-associated biochemical reactions. For instance, α-Melanocyte-stimulating hormone (α-MSH), derived from pro-opiomelanocortin (POMC), significantly stimulates melanogenic pigmentation in skin tissues by binding to the Melanocortin-1 receptor (MC1R), which increases cyclic adenosine monophosphate (cAMP) and exhibits strong anti-inflammatory effects [48, 49]. Short fragments of α-MSH or its derivatives, such as Lys-Pro-Val (KPV) and (CKPV)2, show similar or enhanced biological activity. Endothelin-1 (ET-1) also regulates melanin synthesis, promotes melanocyte proliferation, and aids dendrite formation. These molecules or their analogs can be integrated into transdermal delivery systems to enhance transdermal efficiency and promote melanin regeneration, providing a comprehensive approach to vitiligo treatment [50].

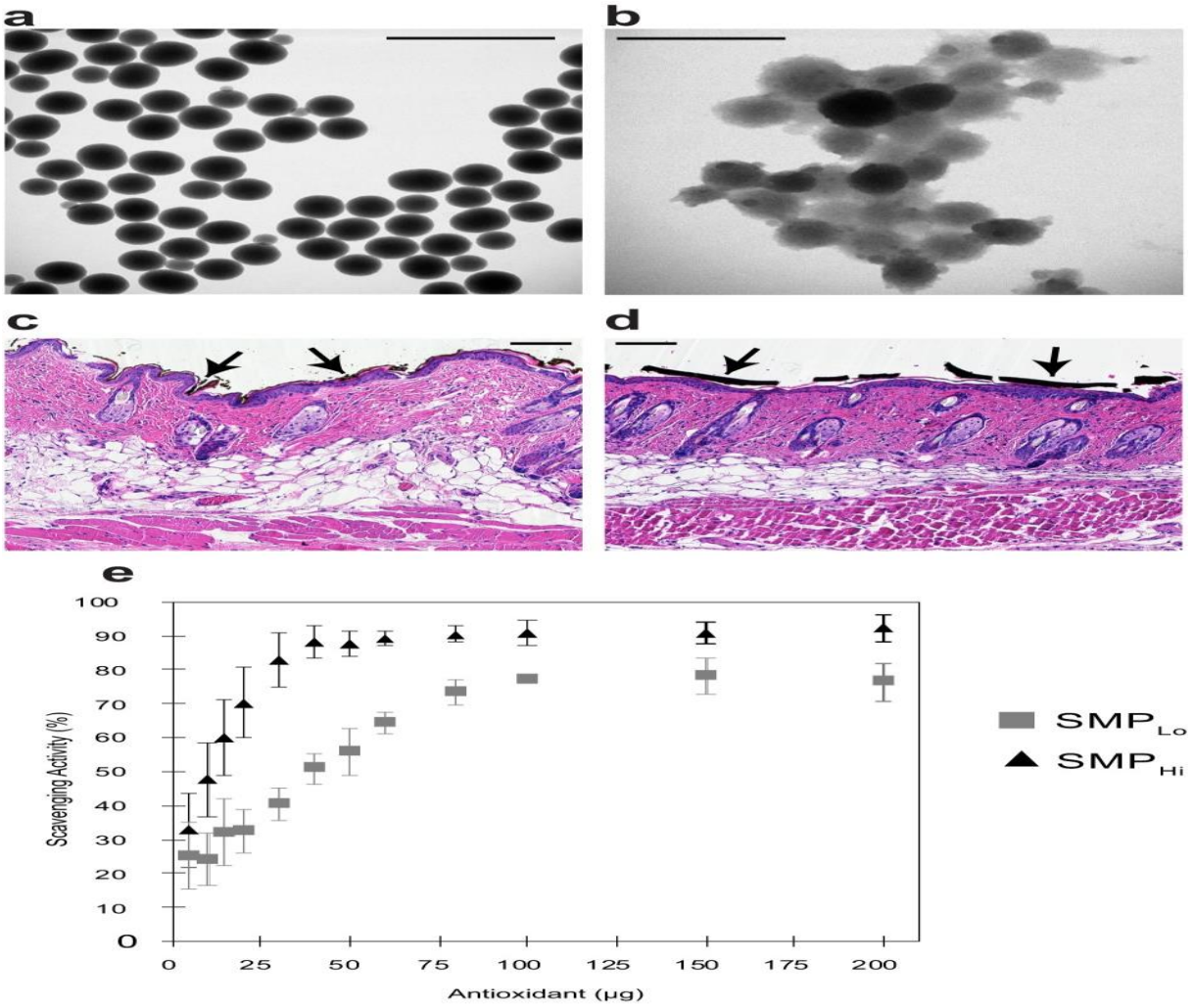

Figure 2: Promoting Melanin Regeneration

Conclusion:

Vitiligo is a prevalent condition that causes loss of pigmentation in the skin, affecting around 1% of the world's population. It has notable psychological and social consequences because of the obvious white patches it creates, which might be mistaken for leprosy in some areas. Scientists and dermatologists have persistent difficulties in efficiently treating and controlling vitiligo. Mounting data indicates that the development and progression of vitiligo are strongly linked to immunological responses in the skin and melanocytes. This justifies its designation as a chronic immune illness, rather than a problem only related to regenerative medicine. Nano-drug delivery systems have rapidly progressed, offering new opportunities for treating vitiligo. These methods allow for prolonged or regulated release of drugs, improving the effectiveness of therapy while minimizing adverse effects. Nevertheless, contemporary research often prioritises achieving minimum symptom management rather than achieving total elimination of the illness. Although there are challenges to overcome, it is expected that there will be ongoing improvements in the optimizations of nano-drug delivery systems. By focussing on receptors found on melanocytes and keratinocytes, such as granulocyte colony-stimulating factor receptors (G-CSFR) and melanocortin receptors (MC1R-MC5R), there is potential for effective therapies with minimal adverse effects, since the natural ligands or similar compounds of these receptors may be used. Furthermore, novel methods such as the use of ultrashort cysteine-containing peptides that spontaneously form hydrogels demonstrate excellent compatibility with living organisms and little risk of causing allergic reactions. Further investigation into peptide-based topical medication delivery methods has the potential to enhance the treatment of vitiligo in the future. This study is on the

development and potential of nano-drug delivery systems for treating vitiligo. It discusses the causes of the disease, present treatment approaches, and future possibilities. The review suggests that advancements in this field may lead to improved control, management, and even possible treatments for vitiligo.

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