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Research Article

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Lipid Nanocarriers for Targeted Repigmentation in Vitiligo: Advances in Melanocyte Modulation and Topical Delivery

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Abstract

Background: *Vitiligo is a chronic autoimmune depigmenting disorder characterized by the loss of functional melanocytes. Current treatments, including corticosteroids, calcineurin inhibitors, and Janus kinase inhibitors, often fail to induce complete or sustained repigmentation due to poor skin penetration and inadequate targeting of melanocyte reservoirs. There is a growing need for precision delivery systems that address the multifactorial pathophysiology of vitiligo, including immune-mediated destruction, oxidative stress, and melanocyte stem cell depletion.*

Objective: *To evaluate the therapeutic potential of lipid-based nanocarriers, such as liposomes, ethosomes, solid lipid nanoparticles, and nanostructured lipid carriers, for targeted delivery of agents that modulate melanocyte survival and promote pigment restoration in vitiligo.*

Methods: *A structured literature review was conducted using PubMed, Embase, Scopus, and Google Scholar. Peer-reviewed articles published between 2016 and April 2025 were screened based on inclusion criteria: (1) focus on lipid-based nanocarriers, (2) topical or transdermal delivery relevant to vitiligo, and (3) measurable in vitro or in vivo outcomes. Key data points extracted included nanocarrier type, particle size, surface charge, encapsulation efficiency, release kinetics, and therapeutic agent class. Mechanistic targets (e.g., IFN-γ/CXCL10 axis, oxidative stress, p38 MAPK) and delivery optimization strategies (e.g., microneedle assistance, PEGylation, pH-sensitivity) were thematically analyzed.*

Results: *Lipid-based nanocarriers demonstrated enhanced skin penetration, follicular targeting, and drug stability. Notable outcomes included: 65% gene silencing and 45% repigmentation with siRNA-loaded lipid nanoparticles targeting p38 MAPK. 60% pigmentation restoration in tacrolimus liposomal human trial versus 35% with standard formulation. Baicalein-loaded liposomes and co-encapsulated NLCs (e.g., methotrexate + resveratrol) showed synergistic effects on melanogenesis, antioxidant response, and immune modulation in preclinical models. Surface modifications (e.g., chitosan-coating, PEGylation) improved nanocarrier retention and bioavailability, while microneedle-assisted delivery increased follicular deposition by greater than 300%.*

Conclusion: *Lipid-based nanocarriers represent a promising platform for repigmentation therapies in vitiligo. By facilitating targeted, sustained, and patient-tolerable delivery of immunomodulators, antioxidants, and melanogenic agents, they address critical limitations of conventional topical therapies. Further clinical trials, regulatory standardization, and personalized formulation design are needed to fully realize their translational potential in vitiligo care.*

Keywords: Vitiligo, Lipid Nanocarriers, Repigmentation, Melanocyte Modulation, Topical Drug Delivery, Nanostructured Lipid Carriers, Sirna Therapy, Targeted Dermatologic Treatment

1. Introduction

Vitiligo is a chronic autoimmune skin disorder characterized by the progressive destruction of melanocytes, leading to depigmented macules and patches across the skin. Affecting approximately 0.5–2% of the global population, the condition is mediated by CD8+ T cell–driven immune responses, primarily orchestrated through the interferon-γ (IFN-γ)/CXCL10 axis and accompanied by oxidative stress and melanocyte stem cell depletion [1,2]. In addition to immune dysregulation, decreased antioxidant defense via the Nrf2/ARE pathway and dysfunctional Wnt/β-catenin signaling have also been implicated in melanocyte apoptosis and impaired repopulation [3,4]. Despite multiple treatment options, including topical corticosteroids, calcineurin inhibitors, phototherapy, and JAK inhibitors, relapse and incomplete repigmentation remain common challenges [5,6]. To address these limitations, there is a growing need for therapeutic strategies that can both modulate melanocyte survival and promote pigment restoration in a site-specific, sustained, and minimally invasive manner. Topical drug delivery systems often fail due to the barrier posed by the stratum corneum, which limits the penetration of both hydrophilic and large molecular weight compounds [7,8]. This limitation is particularly problematic in vitiligo, where deeper epidermal and follicular reservoirs of melanocyte precursors must be targeted for effective repigmentation [9].

Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), ethosomes, and transfersomes, have emerged as promising vehicles for dermal drug delivery. These nanocarriers enhance drug solubility, provide sustained release, and enable follicular and epidermal targeting while minimizing systemic toxicity [10-12]. For example, ethosomal tacrolimus gels, liposomal JAK inhibitors, and NLCs co-loaded with antioxidants and immunomodulators have all demonstrated improved skin retention, melanocyte survival, and repigmentation in preclinical models [13-15]. The objective of this review is to comprehensively evaluate the potential of lipid-based nanocarrier systems in the treatment of vitiligo. We discuss the underlying pathophysiology of melanocyte loss, current challenges in treatment, types of lipid nanocarriers, and their advantages for cutaneous delivery. The review also synthesizes recent advances in formulation design, preclinical outcomes, and future translational directions with the goal of informing the development of more effective, targeted therapies for pigmentary restoration in vitiligo.

2. Materials and Methods

This narrative review was conducted to synthesize current evidence on lipid-based nanocarriers for melanocyte modulation and pigmentary restoration in vitiligo. A structured literature search was performed using PubMed, Scopus, Embase, and Google Scholar to identify relevant peer-reviewed studies published from 2016 to April 2025. Search terms included combinations of “vitiligo,” “lipid-based nanocarriers,” “liposomes,” “NLCs,” “SLNs,” “ethosomes,” “niosomes,” “transdermal delivery,” “melanocyte,” “repigmentation,” and “siRNA therapy.” Boolean operators and filters were applied to limit results to English-language articles related to dermatologic applications. Inclusion criteria comprised experimental, preclinical, and clinical studies investigating lipid nanocarriers for topical delivery of agents relevant to vitiligo. Excluded were studies focused on non-lipid vehicles, unrelated dermatologic diseases, or lacking topical/transdermal delivery data. Key data points extracted from eligible studies included nanocarrier type, particle size, zeta potential, encapsulation efficiency, release kinetics, and the therapeutic agents delivered (e.g., tacrolimus, JAK inhibitors, antioxidants, psoralens, siRNA). Outcomes were classified by model type. In vitro results included melanin production, tyrosinase activity, and cytotoxicity. In vivo data focused on repigmentation, melanocyte recovery, and histological outcomes. Delivery optimization strategies—such as microneedle assistance, surface modifications (e.g., PEGylation, chitosan-coating), and pH-sensitive release—were also catalogued. Emphasis was placed on mechanistic targeting of IFN-γ signaling, oxidative stress, and stem cell niche preservation.

All included studies were reviewed for scientific rigor and relevance to clinical translation. Findings were synthesized thematically across categories to evaluate therapeutic potential, limitations, and future directions of nanocarrier platforms in vitiligo management.

3. Mechanisms of Melanocyte Dysfunction in Vitiligo

Vitiligo is a multifactorial skin disorder characterized by progressive depigmentation due to the selective loss or dysfunction of melanocytes (Table 1). Understanding its pathogenesis is critical for developing targeted therapies that aim not only to halt disease progression but also to restore pigment.

Pathogenic Mechanism	Description	Key Molecular Targets	Therapeutic Relevance
Autoimmune-mediated destruction	CD8+ T cells target melanocytes via IFN-γ/ CXCL10	IFN-γ, CXCL10, JAK-STAT	Targeted by JAK inhibitors, immunosuppressants
Oxidative stress	ROS accumulation impairs mitochondria, induces apoptosis	Nrf2, ROS, H2O2	Addressed by antioxidant-loaded nanocarriers
Defective melanosome function	Impaired biogenesis and pigment transfer to keratinocytes	Wnt/β-catenin, MITF, tyrosinase	Modulated by natural compounds (e.g., baicalein)
Melanocyte stem cell depletion	p38 MAPK activation leads to McSC exhaustion	p38 MAPK	Silenced via siRNA-loaded lipid nanoparticles

Table 1: Mechanisms of Melanocyte Dysfunction in Vitiligo

3.1. Autoimmune Targeting and the IFN-γ/CXCL10 Axis

The autoimmune hypothesis remains central to vitiligo pathophysiology. Cytotoxic CD8+ T lymphocytes recognize melanocyte-specific antigens and initiate cell-mediated destruction, guided in part by the chemokine CXCL10 and its receptor CXCR3. These chemokines are upregulated in response to interferon-gamma (IFN-γ), promoting a feed-forward inflammatory loop within lesional skin [1,2]. The JAK-STAT signaling pathway plays a pivotal role in this immune cascade, ultimately resulting in melanocyte apoptosis and local immune memory. As such, therapies targeting this axis have gained interest not only for their immunomodulatory effects but also for their ability to promote durable repigmentation when combined with phototherapy.

3.2. Oxidative Stress and Melanocyte Apoptosis

In addition to immune dysregulation, melanocytes in vitiligo are particularly susceptible to oxidative stress. Elevated levels of reactive oxygen species (ROS) such as hydrogen peroxide disrupt mitochondrial integrity and induce apoptosis through multiple pathways. This redox imbalance is compounded by impaired antioxidant defense systems, including reduced activity of the Nrf2/ARE transcriptional pathway, which normally serves as a cellular buffer against oxidative insults [3]. Experimental models have shown that nanocarrier-based delivery of antioxidants like resveratrol can enhance melanocyte viability, underscoring the therapeutic potential of redox-targeted interventions [15]. Therefore, oxidative stress not only serves as a trigger but also as a perpetuator of disease.

3.3. Defective Melanosome Biogenesis and Transfer

Vitiligo also involves disturbances in the machinery responsible for melanin synthesis and transfer. Central to this are defects in melanosome biogenesis, organelles that synthesize, store, and transport melanin, and their impaired handoff to keratinocytes. These defects are linked to downregulation of Wnt/β-catenin signaling, which regulates MITF and other transcription factors critical for melanocyte function and survival [16,17]. As a result, even surviving melanocytes may fail to effectively produce or distribute pigment. Addressing these functional impairments is crucial for achieving complete and uniform repigmentation, especially in chronic or refractory cases.

3.4. Melanocyte Stem Cell Depletion and Niche Disruption

Hair follicle–associated melanocyte stem cells (McSCs) play a vital role in replenishing epidermal melanocytes during repigmentation. However, in vitiligo, chronic inflammation and stress signaling, particularly through the p38 MAPK pathway, lead to exhaustion or dysfunction of these stem cells [1]. Innovative strategies such as lipid-based delivery of p38 siRNA have shown promise in restoring melanocyte pools in preclinical models, with significant repigmentation and reduced inflammation observed following treatment [18]. Preserving the integrity of the follicular niche is increasingly recognized as a prerequisite for long-term therapeutic success.

Together, these mechanisms highlight the importance of a multipronged therapeutic approach. Strategies that modulate immunity, reduce oxidative damage, restore melanosome function, and reactivate melanocyte stem cells may work synergistically to reverse depigmentation in vitiligo.

4. Rationale for Lipid-Based Nanocarriers in Vitiligo

Topical therapy for vitiligo is frequently hampered by the skin's natural barrier function, particularly the stratum corneum, which limits the penetration of therapeutic agents into deeper epidermal and follicular compartments where melanocyte activity is centered [7,11]. This limitation is especially critical in vitiligo, where effective repigmentation relies on reaching melanocyte reservoirs located in the hair follicle bulge and basal layer of the epidermis. Moreover, depigmented skin has been found to possess altered permeability, further complicating drug delivery and increasing the risk of local irritation [6]. These challenges emphasize the need for drug delivery systems that can bypass or modulate the stratum corneum to achieve site-specific, sustained, and well-tolerated therapeutic effects. Lipid-based nanocarriers offer a robust solution to these challenges by enhancing dermal drug delivery through mechanisms such as lipid fusion, follicular targeting, and occlusion [8,19]. These nanosystems are capable of encapsulating both hydrophilic and lipophilic drugs, protecting them from enzymatic degradation and promoting deeper skin penetration through their

nanoscale size and lipid compatibility with the skin barrier. For example, NLCs and SLNs not only improve bioavailability but also offer controlled release, reduced systemic exposure, and improved patient compliance by minimizing dosing frequency [7]. Importantly, these delivery systems have shown strong safety profiles in preclinical studies, making them promising candidates for repurposing in vitiligo management [20].

Several types of lipid-based nanocarriers have been developed and tested in pigmentary disorders, each with unique advantages for cutaneous application (Table 2). Liposomes, composed of phospholipid bilayers, can deliver drugs directly into the epidermis and are especially suited for hydrophilic compounds [21]. Flexible variants such as transfersomes exhibit high deformability, enabling them to squeeze through intercellular spaces and access deeper skin layers [22]. Ethosomes, which incorporate ethanol into their lipid bilayer, further enhance dermal permeation by disrupting the lipid packing of the stratum corneum [13]. These properties make ethosomes particularly effective for delivering tacrolimus and antioxidants to vitiliginous skin, with studies showing improved skin retention and repigmentation outcomes. Niosomes, non-ionic surfactant-based vesicles, offer an economical alternative to liposomes and have demonstrated high entrapment efficiency and stability, especially for drugs like tacrolimus and pimecrolimus used in immunomodulatory therapy [23]. In a similar vein, NLCs, which blend solid and liquid lipids, have emerged as second-generation carriers with higher drug loading capacities and enhanced physical stability compared to SLNs. These systems have been effectively employed to co-deliver immunosuppressants and antioxidants, such as tacrolimus and resveratrol, demonstrating synergistic effects on melanocyte protection and immune modulation [12,15]. Lipid nanocarriers are also being explored for delivering genetic materials and signaling modulators. Cationic lipid nanoparticles, for instance, have been used to deliver p38 MAPK siRNA topically, resulting in significant melanocyte regeneration and repigmentation in mouse models of vitiligo [18]. This highlights their potential not only for passive drug delivery but also for active modulation of key pathogenic pathways. Such versatility positions lipid-based nanocarriers as a foundational technology in the future of vitiligo treatment strategies. Taken together, the physicochemical adaptability, biocompatibility, and mechanistic targeting afforded by lipid-based nanocarriers make them uniquely suited for addressing the multifactorial challenges of vitiligo therapy. Their integration into clinical practice could transform the delivery of repigmenting agents, especially when combined with phototherapy or immunomodulators in tailored, patient-specific regimens.

Nanocarrier Type	Key Features	Advantages for Vitiligo Therapy	Examples of Agents Delivered
Liposomes	Phospholipid bilayers	Hydrophilic drug loading, epidermal delivery	Tacrolimus, baicalein
Ethosomes	Ethanol-enriched liposomes	Enhanced penetration, follicular targeting	Tacrolimus, afamelanotide
Niosomes	Surfactant-based vesicles	Cost-effective, high entrapment efficiency	Tacrolimus, pimecrolimus
SLNs	Solid lipid matrix	Controlled release, stability	Methotrexate, resveratrol
NLCs	Solid-liquid lipid hybrid	Higher loading, better bioavailability	siRNA, methotrexate + resveratrol
Transfersomes	Highly deformable lipid vesicles	Deep dermal penetration	Psoralens, resveratrol

Table 2: Types and Features of Lipid-Based Nanocarriers

5. Agents for Melanocyte Modulation and Pigmentary Restoration

Repigmentation in vitiligo hinges on two therapeutic objectives: halting melanocyte destruction and reactivating pigment production from surviving or follicular melanocyte precursors. A range of pharmacologic and natural agents have been investigated for their ability to modulate these pathways, often in tandem with phototherapy. Lipid-based nanocarriers offer an advanced means of delivering these compounds directly to depigmented skin with improved targeting, stability, and patient tolerability.

5.1. Topical Corticosteroids and Calcineurin Inhibitors

Topical corticosteroids remain a first-line option in vitiligo, primarily through their suppression of pro-inflammatory cytokines and cytotoxic T-cell activity. However, their long-term use risks dermal atrophy and tachyphylaxis. Calcineurin inhibitors like tacrolimus and pimecrolimus offer a steroid-sparing alternative, particularly for facial and intertriginous areas. Their immunomodulatory effect is centered on blocking IL-2 and IFN-γ production, critical mediators in melanocyte-directed autoimmunity. Encapsulation in liposomes, niosomes, and NLCs significantly enhances their dermal bioavailability while minimizing systemic exposure and irritation [20,21,23].

5.2. Psoralens and Photochemotherapy

Psoralens, such as 8-methoxypsoralen (8-MOP), are melanogenic

agents used in conjunction with UVA exposure (PUVA therapy). These compounds intercalate DNA and, upon activation by UV-A light, stimulate tyrosinase activity and melanocyte proliferation. Liposomal formulations of psoralens have demonstrated improved skin retention and reduced phototoxicity, enhancing the safety and efficacy of PUVA in localized disease [24].

5.3. Melanocortin Agonists

Afamelanotide and melanotan analogs act as melanocortin 1 receptor (MC1R) agonists, promoting melanin synthesis through cAMP-mediated upregulation of MITF and tyrosinase. When encapsulated in ethosomes or liposomes, these agents exhibit increased melanosome formation and deeper dermal penetration, showing promise in restoring pigment in UV-damaged or vitiliginous skin [14].

5.4. Janus Kinase (JAK) Inhibitors

JAK inhibitors, including ruxolitinib and tofacitinib, have emerged as highly targeted therapies for vitiligo by disrupting IFN-γ signaling and downstream chemokines like CXCL10. While topical ruxolitinib is now FDA-approved, its incorporation into lipid nanocarriers such as ethosomes, liposomes, or NLCs allows for enhanced penetration, controlled release, and improved follicular targeting [5,14,17]. These systems aim to deliver JAK inhibitors precisely where memory T cells persist around hair follicles and basal epidermal layers.

5.5. Antioxidants and Natural Compounds

Oxidative stress is a well-established cofactor in melanocyte loss. Agents like catalase, glutathione (GSH), coenzyme Q10, and resveratrol exhibit free radical–scavenging properties and promote melanocyte survival. Their encapsulation in NLCs or ultradeformable liposomes improves stability and epidermal delivery [15,22]. Piperine, baicalein, and psoralen-derived compounds, often delivered via ethosomes or transfersomes, also stimulate melanogenesis via tyrosinase activation or Wnt/β-catenin signaling [16,25,26]. Baicalein-loaded liposomes, for instance, were shown to increase melanin deposition and melanocyte survival in oxidative stress models.

5.6. Co-Encapsulated and Dual-Action Systems

Innovative co-loaded nanocarriers that combine immunosuppressive and antioxidant agents represent a powerful emerging strategy. For instance, methotrexate and resveratrol co-encapsulated in NLCs showed enhanced epidermal retention and potential synergistic effects on melanocyte recovery and inflammation suppression [15]. Similarly, siRNA-loaded lipid nanoparticles targeting p38 MAPK, a suppressor of melanocyte stem cell activation, demonstrated robust repigmentation in preclinical vitiligo models, with up to 65% gene knockdown and 45% pigment recovery [18].

6. Lipid-Based Nanocarrier Systems in Vitiligo Models

Preclinical investigations using lipid-based nanocarriers have provided compelling evidence supporting their use in vitiligo therapy (Table 3). These systems not only enhance drug stability and dermal penetration but also allow precise targeting of melanocytes within the basal layer and follicular niches, critical sites for repigmentation. Key pharmacologic classes explored in these studies include immunomodulators, antioxidants, melanin-inducing compounds, and RNA-based therapies.

Study (Author, Year)	Nanocarrier System	Agent(s) Delivered	Model Used	Key Findings
Akombaetwa et al., 2023 [15]	NLC	Methotrexate + Resveratrol	Mouse, in vitro	↑ Epidermal retention, ↓ inflammation
Ghani et al., 2020 [13]	Ethosome	Tacrolimus	Mouse	Near-complete repigmentation
Atapour-Mashhad et al., 2024 [18]	Lipid NP	siRNA targeting p38 MAPK	Mouse	65% knockdown, 45% repigmentation
Li et al., 2025 [26]	Liposome	Baicalein	Guinea pig	40% repigmentation in 3 weeks
Doppalapudi et al., 2017 [22]	Ultradeformable liposome	Psoralen + Resveratrol	In vitro	↑ Tyrosinase activity, ↑ melanogenesis
Faizatun et al., 2023 [28]	NLC	Morus alba extract	Zebrafish	Dose-dependent melanin recovery

Table 3: Summary of Preclinical Outcomes with Lipid Nanocarriers in Vitiligo Models

6.1. Drug Classes Studied in Nanocarrier Systems

Numerous therapeutic agents have been encapsulated into lipid-based nanocarriers to improve outcomes in vitiligo models:

- **Immunomodulators:** Tacrolimus and methotrexate have been formulated into liposomes, niosomes, ethosomes, and NLCs, enhancing dermal retention and reducing systemic toxicity [13,20,23].
- **Antioxidants:** Resveratrol, glutathione, and catalase have demonstrated superior stability and melanocyte-protective activity when delivered via ultradeformable liposomes or NLCs [15,22].
- **JAK Inhibitors:** Ruxolitinib and tofacitinib encapsulated

in ethosomes or NLCs achieved higher follicular targeting, suppression of CXCL10, and superior repigmentation in murine models [14,17].

- **Melanin-Inducing Agents:** Compounds such as psoralens, baicalein, and afamelanotide were successfully delivered using liposomes or transfersomes, with enhanced tyrosinase activity and melanin synthesis [22,25,26].

6.2. Key Nanocarrier Parameters

The effectiveness of these delivery systems depends on several physicochemical and formulation characteristics:

- **Carrier Type and Composition:** NLCs combine solid and liquid lipids for improved drug loading, while transfersomes and ethosomes offer deformability for deep skin penetration [11,19].
- **Particle Size and Zeta Potential:** Most systems achieve particle diameters under 200 nm with negative surface charges (~−30 to −40 mV), favoring dermal interaction and formulation stability [7,27].
- **Encapsulation Efficiency:** Drug entrapment frequently exceeds 75–90%, as demonstrated in baicalein, tacrolimus, and co-loaded formulations [21,26].
- **Release Kinetics:** Sustained or biphasic drug release (up to 72 hours) ensures prolonged local activity with minimal systemic exposure [15,24].

6.3. In Vitro and In Vivo Outcomes

A consistent theme across studies is enhanced melanocyte viability and function with lipid-based delivery systems:

In Vitro Models:

- Niosomal and NLC-encapsulated tacrolimus increased drug penetration into melanocyte-rich basal layers and demonstrated sustained immunomodulatory effects [20,23].
- Baicalein-loaded liposomes induced significant increases in melanin content and tyrosinase activity in stressed melanocytes [25].
- Doppalapudi et al. (2017) showed that psoralen + resveratrol ultradeformable liposomes triggered synergistic increases in melanogenesis and oxidative defense [22].

In Vivo Models:

- Atapour-Mashhad et al. (2024) demonstrated that lipid nanoparticle-mediated delivery of siRNA targeting p38 MAPK resulted in 65% gene silencing and 45% repigmentation in a murine model [18].
- Ghani et al. (2020) reported near-complete repigmentation in monobenzone-induced vitiligo mice treated with ethosomal tacrolimus gels [13].
- Baicalein-loaded flexible liposomes restored pigmentation by 40% in guinea pigs within 3 weeks [26].
- Faizatun et al. (2023) used zebrafish models to confirm dose-dependent melanin recovery from Morus alba NLC gels [28].

These findings demonstrate that lipid-based nanocarriers provide a multifunctional platform, optimizing drug delivery, targeting, and pharmacodynamics, all while minimizing irritation and systemic burden. Their adaptability to co-encapsulation strategies (e.g., antioxidant + immunosuppressant) further positions them as leading candidates for next-generation, patient-friendly vitiligo therapies.

7. Targeting Strategies and Delivery Optimization

Achieving efficient, localized delivery of repigmentation agents to melanocyte reservoirs remains a major challenge in vitiligo therapy. Lipid-based nanocarriers offer innovative solutions by enhancing penetration, retention, and specificity in targeted skin compartments, particularly the basal epidermis and hair follicle units (Table 4).

Strategy	Mechanism of Action	Effect on Delivery
Microneedle-assisted delivery	Bypasses stratum corneum	↑ Follicular deposition, ↑ penetration
PEGylation	Extends half-life, enhances stability	↑ Bioavailability, ↓ clearance
pH-sensitive formulations	Responds to lesion-specific pH changes	Targeted payload release in inflamed areas
Chitosan coating	Enhances mucoadhesion and retention	↑ Residence time in lesional skin
Charge modulation	Improves epidermal interaction	Better targeting, minimal irritation

Table 4: Delivery Optimization Strategies and Their Effects

7.1. Hair Follicle Targeting and Reservoir-Based Delivery

The outer root sheath and bulge region of hair follicles harbor melanocyte stem cells essential for durable repigmentation. Lipid-based systems such as transfersomes, ethosomes, and PEGylated NLCs have demonstrated enhanced follicular uptake compared to conventional creams. Studies by Atapour-Mashhad et al. (2024) and Zheng et al. (2024) reported significant repigmentation and melanocyte localization following follicular delivery of siRNA and JAK inhibitors, respectively [14,18]. Microneedle-assisted nanocarrier systems further enhance transfollicular targeting. Sun et al. (2023) and Vaziri et al. (2023) reported that microneedle pretreatment improved follicular drug deposition 3.4 times greater than topical alone, without systemic exposure [9,29]. This method enables precise deposition of nanocarriers into deeper follicular niches where melanocyte precursors reside.

7.2. Transfollicular vs. Intercellular Penetration Pathways

Two dominant cutaneous drug delivery routes are exploited in vitiligo: transfollicular and intercellular. Transfollicular pathways enable direct access to melanocyte stem cells but are

often underutilized in conventional treatments. Lipid-based nanocarriers, especially those under 300 nm with elastic or deformable membranes (e.g., transfersomes), facilitate deeper penetration via both routes. Stefanov et al. (2021) and Vocetkova et al. (2020) confirmed enhanced dermal accumulation of NLCs and SLNs through both pathways in in vitro and ex vivo models [7,10]. Importantly, vitiliginous skin may exhibit increased permeability due to inflammation and barrier disruption, allowing better intercellular diffusion. This supports the rationale for combining lipid-based delivery with anti-inflammatory agents to improve both penetration and efficacy [6].

7.3. Use of Penetration Enhancers and pH-Sensitive Formulations

Several studies incorporated chemical enhancers like oleic acid, Tween 80, and ethanol into nanocarrier systems. These agents disrupt stratum corneum lipid packing, improving percutaneous absorption. Akombaetwa et al. (2023) utilized Tween 80 and oleic acid in resveratrol-methotrexate NLCs, achieving sustained dermal drug retention and epidermal melanocyte targeting [15]. pH-sensitive formulations also present a promising delivery method in vitiligo, where local inflammation raises skin pH. Zheng et al. (2024) demonstrated that pH-triggered liposomes preferentially released their payload in vitiliginous lesions, increasing local drug availability and minimizing off-target effects [14].

7.4. Microneedle-Assisted Lipid Delivery

Microneedles represent a minimally invasive, precision-enhancing adjunct to nanocarrier therapy. Dissolving microneedles loaded with tacrolimus or JAK inhibitors have been shown to significantly enhance drug penetration into melanocyte-rich basal and follicular compartments [30]. These platforms bypass the stratum corneum entirely, improving bioavailability of hydrophilic or large-molecule drugs such as siRNA [18]. Studies also support combination therapies, microneedles followed by topical lipid nanocarrier application, which may act synergistically to prolong delivery and improve targeting efficiency [9,29].

7.5. Surface Modifications for Stability and Retention

Lipid nanocarriers can be functionally optimized using surface modifications that improve dermal adhesion, immune evasion, and drug retention:

- Chitosan-coated carriers: Improve mucoadhesion and prolong residence time in lesional skin; shown to enhance tacrolimus retention and stability [14].
- PEGylation: Adds stealth properties and extends circulation and half-life in dermal tissues; PEG-NLCs increased melanocyte repopulation in murine vitiligo models [9].
- Charge modulation: Slightly negative or near-neutral zeta potential (~−20 to −40 mV) favors epidermal accumulation without causing irritation [7].

Together, these strategies represent a shift toward personalized, lesion-specific delivery in vitiligo care, targeting melanocyte stem cell niches, minimizing systemic risk, and improving therapeutic durability.

8. Discussion

8.1. Clinical Translation and Limitations

LNCs have emerged as a promising transdermal strategy for repigmentation therapies in vitiligo, but their translation into clinical practice remains in its infancy. While several preclinical models demonstrate substantial benefits such as increased skin penetration, melanocyte targeting, and reduced systemic exposure, few have advanced to human clinical trials [18,20]. Notably, Bergqvist (2021) conducted a split-lesion human trial using liposomal tacrolimus and observed >60% repigmentation in treated lesions versus 35% in the control group, highlighting the comparative superiority of lipid-based formulations [31]. However, despite these early clinical successes, most studies remain in the preclinical or exploratory phase, limiting the ability to generalize findings across populations.

The safety, tolerability, and cosmetic acceptability of nanocarriers also remain critical concerns. While in vitro studies report minimal cytotoxicity and no dermal irritation, long-term biocompatibility has not been well characterized in vitiliginous skin, which often displays barrier abnormalities and heightened photosensitivity [13,20]. For instance, ethosomal formulations, despite their deep penetration abilities, can induce transient irritation due to high ethanol content [6]. Moreover, the cosmetic appeal of LNCs, such as transparent gel bases or lightweight cream formulations, is promising, yet patient preferences and adherence in real-world settings remain underexplored (Table 5).

Challenge in Conventional Therapy	Lipid Nanocarrier Solution	Examples
Poor skin penetration	Deformability, lipid fusion, microneedles	Transfersomes, ethosomes
Incomplete melanocyte targeting	Follicular delivery and niche targeting	Microneedle-assisted PEG-NLCs
Drug degradation	Encapsulation improves stability	SLNs, NLCs with antioxidants
Local irritation/systemic effects	Controlled release, reduced systemic exposure	Tacrolimus liposomes
Inconsistent adherence	Improved cosmetic feel, lower frequency dosing	Resveratrol gels, ethosomal tacrolimus

Table 5: Advantages of Lipid Nanocarriers Over Conventional Topical Therapies

Regulatory hurdles present additional limitations. The absence of FDA-approved LNC-based therapies for vitiligo is partly due to inconsistent standards for nanotoxicology assessment, challenges in scaling up manufacturing, and a lack of standardized characterization protocols [7,9]. Additionally, the high entrapment efficiencies (>90%) and occlusive delivery profiles observed in systems like SLNs and NLCs may not be universally replicable across diverse skin types or climatic conditions. The lack of standardized outcome metrics in nanocarrier studies, such as unified pigmentation scales, biomarker assessments, and immune profiling, also hampers inter-study comparisons and translational clarity.

Cost and scalability issues are equally pressing. While the ingredients in lipid nanocarriers (e.g., phospholipids, surfactants like Tween 80, and biocompatible solvents) are relatively affordable, the specialized equipment needed for high-pressure homogenization or ultrasonication can limit accessibility in lower-resource settings. In real-world contexts, cost-effective manufacturing, product shelf stability, and reproducible skin penetration across heterogeneous patient groups must be achieved for successful deployment. Patient adherence, a key determinant of long-term success in vitiligo therapy, may be influenced by dosing frequency, perceived benefit, skin feel, and ease of application. Despite promising pharmacologic performance, a topically applied nanocarrier that requires refrigeration or long application times may fail to achieve consistent real-world uptake.

8.2. Future Directions

To enhance therapeutic outcomes and bridge the translational divide, future efforts should focus on the personalization of nanocarrier-based therapies. Tailoring formulations based on patient-specific parameters such as Fitzpatrick skin type, lesional depth, and inflammatory profile may improve efficacy. For example, Atapour-Mashhad et al. (2024) demonstrated that p38 MAPK silencing via lipid nanoparticles facilitated ~45% repigmentation in lesional skin, yet such response may be modulated by regional immune activity or follicular reservoir density [18]. Incorporating immune biomarkers like CXCL10 or IFN-γ into patient selection criteria could further optimize outcomes. The combination of nanocarriers with other established or investigational modalities is a logical progression. Studies such as Bergqvist (2021) and Sun et al. (2023) have shown that combining liposomal or NLC-based tacrolimus with NB-UVB phototherapy yields synergistic outcomes, reducing time to initial repigmentation and increasing pigmentation durability [29,31]. The co-delivery of antioxidants (e.g., resveratrol) with immunomodulators or melanogenic agents within a single nanocarrier system offers another pathway to dual-targeted therapy, simultaneously mitigating oxidative damage and restoring melanocyte function [22]. Technological integration with AI-guided imaging and wearable delivery platforms is also on the horizon. Microneedle-assisted LNC patches, biosensors to monitor local cytokine levels, or even smartphone-connected drug release systems represent opportunities for patient-driven, precision dermatology [14,30]. The incorporation of smart polymers that respond to skin pH, temperature, or oxidative load may offer "on-demand" drug delivery that adapts to disease activity. Furthermore, leveraging AI to predict lesion-specific absorption rates based on histologic and imaging data could enable tailored application protocols. Longitudinal studies with robust design are urgently needed. Most existing data derive from short-term experiments (24–72 hours for in vitro release, 2–4 weeks for in vivo models). Establishing longer study durations will be essential to evaluate durability, relapse prevention, and side effect profiles. Metrics such as F-VASI75, melanocyte density via histology, and CXCL10 suppression via RT-PCR should be incorporated into future trials to ensure consistent and objective outcomes. Additionally, post-market surveillance mechanisms must be designed early to monitor unforeseen adverse events in patients with sensitive or barrier-compromised skin.

8.3. Conclusion

This review consolidates the growing body of evidence supporting lipid-based nanocarriers as transformative tools in vitiligo therapy. By enhancing drug penetration, enabling targeted melanocyte delivery, reducing systemic exposure, and supporting controlled release, these systems overcome several limitations of conventional topical and systemic treatments. Compounds such as tacrolimus, resveratrol, baicalein, and psoralens, delivered via liposomes, NLCs, ethosomes, and transfersomes, have demonstrated enhanced bioavailability, reduced toxicity, and promising repigmentation effects in both in vitro and in vivo models. Despite these advances, clinical translation remains limited by regulatory, technical, and implementation challenges. Safety data, long-term efficacy, scalable production, and patient-centered formulation design are areas in need of further exploration. Future research should focus on integrating nanocarrier platforms with adjunctive therapies, optimizing them for personalized immune and pigment profiles, and developing smart delivery systems capable of dynamic disease-responsive modulation. With continued innovation, collaborative research, and a commitment to addressing disparities in dermatologic care, lipid-based nanocarriers hold strong translational potential as a mainstay in the therapeutic armamentarium for vitiligo and other pigmentary disorders.

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