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Research Article

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Advances in Nanocarrier Systems for Dermatologic Transdermal Drug Delivery: A Chemical and Molecular Review

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Abstract

Background: *Transdermal drug delivery faces significant barriers due to the physicochemical properties of the stratum corneum, limiting the passive diffusion of therapeutic agents. Nanocarrier systems, including liposomes, ethosomes, niosomes, and polymeric nanoparticles, are being extensively investigated as innovative platforms to overcome these limitations in dermatologic applications.*

Objective: *This review synthesizes recent advances in the molecular design of nanocarrier systems engineered for enhanced transdermal drug delivery, emphasizing critical chemical principles that underpin their development and optimization.*

Methods/Discussion: *A targeted literature review was conducted using PubMed, Scopus, and Web of Science databases, identifying studies published between January 2023 and April 2025. A total of 64 peer-reviewed papers were selected based on relevance to nanocarrier-based dermatologic delivery systems. The included studies were analyzed for trends in particle size optimization, surface charge modulation (zeta potential), lipid phase behavior, PEGylation, surfactant composition, and pH-responsive or enzyme-cleavable linker strategies. Applications covered include nanocarrier-mediated delivery of tacrolimus and vitamin D3 for atopic dermatitis; methotrexate, calcipotriol, and siRNA for psoriasis; 5-fluorouracil and imiquimod for actinic keratosis and superficial basal cell carcinoma; spironolactone, chloramphenicol, and clindamycin for acne and rosacea; platinum nanozymes and nitric oxide donors for alopecia; and CpG-functionalized nanoparticles and photodynamic agents for melanoma and cutaneous malignancies.*

Conclusion: *Nanocarrier technologies exemplify the intersection of colloid chemistry, polymer science, and clinical dermatology. Although formulation stability, batch reproducibility, and translational scalability remain ongoing challenges, emerging innovations, including smart, AI-guided, and hybrid-responsive platforms, offer promising avenues for precision therapy.*

Significance Statement: *By integrating recent advances in nanochemistry with dermatologic pharmacotherapy, this review provides a comprehensive framework for developing next-generation transdermal delivery systems tailored to specific skin diseases. The interdisciplinary progress highlighted here underscores the translational potential of nanocarriers in reshaping dermatologic care.*

Keywords: Nanocarriers, Transdermal Drug Delivery, Dermatologic Therapeutics, Liposomes, Polymeric Nanoparticles, Solid Lipid Nanoparticles, Stimuli-Responsive Delivery, Psoriasis, Melanoma

1. Introduction

Transdermal drug delivery (TDD) has emerged as a critical approach in dermatology, offering localized treatment while minimizing systemic exposure and first-pass metabolism. The ability to deliver therapeutics directly to or across the skin holds particular promise for managing chronic inflammatory conditions, infections, neoplastic lesions, and pigmentary disorders. However, despite its clinical potential, conventional transdermal methods often fall short due to the barrier properties of the stratum corneum, the outermost layer of the epidermis designed to resist foreign molecule entry [1,2]. Passive diffusion is largely limited to small, lipophilic molecules with molecular weights under 500 Da, rendering it inadequate for many dermatologic drugs, particularly hydrophilic agents, peptides, and nucleic acid-based

therapeutics [3,4]. These limitations have spurred the development of nanocarrier-based strategies to bypass or transiently disrupt the skin barrier and enable enhanced drug delivery. Nanocarrier systems, such as liposomes, ethosomes, niosomes, nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and dissolvable microneedles, have rapidly advanced in the past decade. These platforms offer tunable properties including particle size, surface charge, lipid composition, and chemical responsiveness, allowing them to overcome skin barrier resistance and achieve targeted, sustained, or stimuli-responsive drug release [5-7]. For instance, elastic liposomes have demonstrated superior skin penetration in treating inflammatory and neoplastic skin conditions, while microneedles have enabled transcutaneous delivery of otherwise impermeable macromolecules. The growth of this field reflects a convergence of disciplines. Advances in colloid chemistry have enabled the stabilization of deformable and hybrid vesicles [8-13]. Polymer science has facilitated the design of hydrogels, microneedles, and stimuli-responsive matrices with controlled drug release [14,15]. Concurrently, dermatologic therapeutics continues to benefit from these innovations, with nanocarrier systems being applied to conditions ranging from acne to melanoma to alopecia [16-21]. This review synthesizes recent advances in nanocarrier-mediated transdermal drug delivery for dermatologic applications, with particular emphasis on the underlying chemical principles guiding their development. By examining the intersection of colloidal design, polymer engineering, and therapeutic translation, we aim to provide a comprehensive overview of a rapidly evolving interdisciplinary landscape.

2. Skin Barrier Chemistry and Challenges

The skin's protective barrier is primarily attributed to the stratum corneum (SC), a 10-20 µm-thick layer composed of dead, flattened keratinocytes (corneocytes) embedded in a matrix of intercellular lipids. This "brick-and-mortar" model describes corneocytes as the bricks and lipid bilayers as the mortar, forming a highly organized and formidable barrier to foreign agents, including therapeutic molecules [1,2]. The lipid matrix, primarily composed of ceramides, cholesterol, and free fatty acids, is organized into lamellar structures that restrict the diffusion of both hydrophilic and hydrophobic compounds. These lipid lamellae, along with tight junctions and a low pH, contribute to the skin's selective permeability and antimicrobial defense [20,22]. The aqueous gradient from the hydrated viable epidermis to the dry surface of the SC further influences drug absorption and stability, creating a challenging physicochemical environment for transdermal delivery.

From a molecular standpoint, successful transdermal delivery is generally restricted to drugs with (Table 1):

- **Molecular weight:**
  - <500 Da (5x100)
- **Lipophilicity:**
  - Log P (cLogP) values <5 (5x1)
- **Low hydrogen bonding potential:**
  - <10 hydrogen-bond acceptors (5x2)
  - <5 H-bond donors (5x1)

Parameter	Criterion	Implication for TDD
Molecular weight	< 500 Da	Facilitates passive diffusion
Log P (Lipophilicity)	< 5	Optimal for skin partitioning
H-bond acceptors	< 10	Enhances permeability
H-bond donors	< 5	Reduces polar interactions

Table 1: Lipinski's Rule of Five and Transdermal Suitability

These parameters are collectively referred to as Lipinski's "Rule of Five" and exclude many promising dermatologic agents such as peptides, nucleic acids, hydrophilic antimicrobials, and cytokine inhibitors [3,4]. For instance, delivery of siRNA or hydrophilic anti-psoriatic drugs like methotrexate typically fails without penetration enhancement [15,23]. Furthermore, electrostatic interactions between negatively charged SC lipids and charged drug molecules can hinder partitioning into the skin. This challenge is particularly evident in delivering ionic drugs such as tolterodine or cationic immunotherapeutics like CpG-adjuvanted nanoliposomes [7,24]. Given these limitations, innovative nanocarrier systems are essential to transiently disrupt or bypass the stratum corneum, enabling the controlled delivery of molecules with otherwise unfavorable properties. These strategies often exploit lipid-fluidizing agents, vesicular deformability, hydration-mediated delivery, or microneedle-induced bypass, all of which will be addressed in subsequent sections.

3. Overview of Nanocarrier Platforms in Dermatology

Nanocarrier-based systems have revolutionized transdermal drug delivery by circumventing the physicochemical limitations posed by the stratum corneum. Each platform, tailored in composition, architecture, and mechanism, addresses specific challenges in drug stability, skin penetration, and controlled release. This section provides an in-depth analysis of the major nanocarrier systems used in dermatologic applications, emphasizing their molecular composition and functional performance (Table 2).

Carrier Type	Key Materials	Advantages	Representative Drugs
Liposomes	Phospholipids, cholesterol	Biocompatible, flexible, targeted	Tacrolimus, Clobetasol
Ethosomes	Phospholipids + ethanol	Enhanced permeation via SC disruption	Gossypin, Vitamin D3

Niosomes	Nonionic surfactants (Span, Tween)	Chemically stable, cost-effective	Spironolactone, Arbutin
Polymeric Nanoparticles	PLGA, PEG, chitosan, dendrimers	Tunable release, nucleic acid delivery	siRNA, Methotrexate
SLNs/NLCs	Stearic acid, oleic acid, triglycerides	Controlled release, improved stability	Curcumin, Luliconazole, Caffeic Acid

Table 2: Summary of Nanocarrier Platforms in Dermatologic Applications

3.1. Liposomes

Liposomes are colloidal vesicles formed by one or more concentric phospholipid bilayers surrounding an aqueous core. Their amphiphilic architecture allows simultaneous loading of hydrophilic molecules (within the aqueous core) and lipophilic drugs (within the bilayer membrane), offering a highly adaptable platform for transdermal and topical drug delivery [1,4]. From a chemical perspective, the physical behavior of liposomes is governed by lipid composition, bilayer fluidity, and thermodynamic phase behavior. The phase transition temperature (Tm) of the constituent phospholipids, defined as the point at which the bilayer transitions from a gel to a liquid-crystalline phase, plays a pivotal role in dictating membrane permeability, drug release rates, and vesicle deformability [5]. For example, dioleoylphosphatidylcholine (DOPC) with a low Tm promotes bilayer flexibility and skin fusion, while dipalmitoylphosphatidylcholine (DPPC) or hydrogenated soy phosphatidylcholine (HSPC) confer higher rigidity and resistance to premature release [25]. Liposome size also directly influences transdermal performance: small unilamellar vesicles (SUVs) (~50–100 nm) are better suited for intercellular penetration, while large multilamellar vesicles (MLVs) offer higher drug loading and depot formation [15,26].

In dermatology, tacrolimus-loaded liposomes have been shown to enhance follicular uptake, prolong drug residence in the viable epidermis, and reduce systemic exposure in models of atopic dermatitis. The addition of hydrogel matrices such as poloxamer or chitosan improves adherence and release kinetics [27]. Similarly, clobetasol liposomes modified with hyaluronic acid target CD44 receptors, achieving enhanced site-specific uptake in hyperproliferative psoriatic plaques [28]. Surface engineering of liposomes, such as PEGylation, cationic lipid inclusion, or ligand conjugation, further modulates their skin interaction. Cationic liposomes, for example, enhance dermal penetration by electrostatically interacting with the negatively charged lipid headgroups in the stratum corneum, facilitating deeper drug transport and endosomal escape for gene therapies [8,15]. These strategies have been particularly useful in delivering microRNA, siRNA, and other nucleic acid-based agents for melanoma prevention and inflammatory disease modulation [29-31]. Innovations in thermosensitive liposomes, targeted liposomal gels, and pH-responsive lipid formulations are increasingly being explored to align drug release profiles with disease-specific pathophysiology, for example, releasing anti-angiogenic compounds in acidic tumor environments [23]. Taken together, liposomes exemplify the synergy between colloid chemistry, biomedical targeting, and cutaneous pharmacokinetics. Their versatility continues to drive innovation in treating dermatologic diseases where precision delivery, minimal systemic exposure, and barrier modulation are critical.

3.2. Ethosomes

Ethosomes are a subclass of lipid-based nanocarriers structurally similar to liposomes but uniquely characterized by their high ethanol content (20–45%), which serves as a membrane fluidizer and permeation enhancer. This ethanol-rich environment disrupts the ordered lipid packing of the stratum corneum, increasing bilayer fluidity, vesicle deformability, and percutaneous penetration, even for large or hydrophilic drug molecules [31,32]. From a molecular standpoint, ethanol lowers the phase transition temperature Tm of vesicle lipids, shifting the bilayer from a gel to a more flexible liquid-crystalline phase. This increased fluidity not only enhances fusion with skin lipids but also allows interlamellar diffusion and transient lipid extraction, forming a "softened" stratum corneum microenvironment [2]. In addition, ethanol increases the intervesicular negative surface charge, reducing vesicle aggregation and promoting dermal dispersion [33]. The physicochemical design of ethosomes often involves phosphatidylcholine, ethanol, and a small percentage of water, with or without cholesterol to modulate rigidity. Formulations may also incorporate bioadhesive polymers such as chitosan or hyaluronic acid to enhance residence time and target skin appendages [26]. In dermatologic applications, ethosomes have demonstrated therapeutic superiority in several disease states:

- **Melanoma:** Ethosomal delivery of gossypin, a flavonoid with anti-angiogenic properties, has shown improved intracellular uptake, antioxidant capacity, and inhibition of cancer cell migration [9]. The fluidity of ethosomes aids in delivering the drug past the tumor-affected epidermis, enhancing its cytostatic effect.
- **Psoriasis:** Vitamin D3-loaded ethosomal gels exhibit higher entrapment efficiency and prolonged dermal retention in comparison to conventional liposomal or emulsion formulations. This results in more efficient inhibition of keratinocyte hyperproliferation, a hallmark of psoriatic lesions [34].

- **Fungal infections:** Farnesol-loaded ethosomes disrupt biofilms of Candida albicans and penetrate through infected epidermis more effectively than standard farnesol formulations. The vesicles not only increase antifungal activity but also enhance barrier repair via anti-inflammatory effects [35].
- **Skin Whitening:** In zebrafish and murine models, ethosomes encapsulating ginsenosides (Rg1, Re, R1) have inhibited melanogenesis and suppressed tyrosinase activity more effectively than aqueous suspensions, underscoring their role in depigmenting cosmeceutical therapies [36].

Importantly, ethosomal systems are especially well-suited for poorly water-soluble or thermolabile compounds, offering a stable delivery matrix that protects the payload and ensures bioavailability at lower dosages. The integration of ethosomes with gels, patches, or microneedle systems represents a growing frontier in combining

passive and active delivery modalities for skin-targeted treatment [1,37]. In sum, ethosomes exemplify a successful translation of colloidal chemistry principles into dermatologic drug delivery by leveraging ethanol's physicochemical properties to breach the skin barrier and facilitate therapeutic penetration.

3.3. Niosomes

Niosomes are vesicular nanocarriers formed from non-ionic surfactants, often combined with cholesterol or other stabilizing lipids to form a bilayer structure analogous to liposomes. However, unlike phospholipid-based liposomes, niosomes are constructed using synthetic surfactants, such as Span (sorbitan esters), Tween (polysorbates), or Brij (polyoxyethylene ethers), which confer greater chemical stability, lower cost, and improved shelf life [38,39]. The bilayer assembly arises from the amphiphilic nature of these surfactants, which self-assemble in aqueous environments into unilamellar or multilamellar vesicles. The addition of cholesterol improves membrane rigidity and reduces leakage of hydrophilic contents, while also modulating phase behavior and vesicle elasticity [26]. Niosomes are particularly suitable for drugs that are sensitive to hydrolysis or oxidation, offering a more chemically resilient platform compared to conventional liposomes. One of the most tunable parameters in niosome design is the hydrophilic-lipophilic balance (HLB) of the surfactants used. Low HLB surfactants (e.g., Span 60) promote tight bilayer packing and slow drug release, whereas higher HLB agents (e.g., Tween 80) result in looser structures with enhanced deformability and faster release profiles [40]. This tunability makes niosomes highly versatile in matching delivery kinetics to specific dermatologic diseases. Recent innovations include ball milling and microfluidization, which yield uniform vesicle populations with narrow polydispersity and improved colloidal stability [39]. These methods are especially critical for scaling up formulations intended for commercial cosmeceutical or clinical dermatologic use. In dermatology, niosomes have been successfully applied to a wide range of agents, including:

• Anti-acne therapies, where niosomes facilitate follicular targeting and reduce sebaceous gland inflammation. Enhanced penetration of spironolactone and chloramphenicol-loaded vesicles has been observed in ex vivo and in vivo rat models [17,41].

• Skin-lightening and anti-melasma formulations, utilizing agents like kojic acid or arbutin, have demonstrated improved epidermal delivery and reduced post-treatment rebound pigmentation compared to traditional creams [40].

• Cosmeceutical delivery of vitamins, antioxidants, and peptides has leveraged niosomes' ability to cross the stratum corneum while maintaining drug stability in storage, particularly useful in formulations targeting photoaging, dryness, and dyschromia [38,42].

Moreover, niosomes may be co-formulated with gels or film-forming agents to enhance retention at the application site and improve patient compliance. When combined with temperature- or pH-sensitive polymers, niosomes can function as part of smart delivery platforms, releasing active agents in response to the skin's microenvironment [43]. Overall, niosomes represent a robust and adaptable vesicular system. Their surfactant-based architecture, ease of functionalization, and compatibility with a broad range of drugs and cosmetic actives make them a cornerstone of nanocarrier innovation in dermatology.

3.4. Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) represent a diverse and modular class of nanocarriers engineered from natural, synthetic, or semi-synthetic polymers. Their unique advantage lies in the ability to finely tune particle size, surface chemistry, degradation rate, and drug release kinetics, enabling targeted and sustained delivery across the skin barrier. Key polymers include PLGA (polylactic-co-glycolic acid), polyethylene glycol (PEG), chitosan, polycaprolactone, and dendritic peptides, all of which exhibit favorable biodegradability and biocompatibility [14,44]. From a physicochemical perspective, polymeric nanoparticles are typically stabilized by hydrophobic–hydrophilic self-assembly, ionic interactions, or emulsion-based synthesis techniques such as nanoprecipitation and solvent evaporation. These allow for incorporation of hydrophobic drugs into the polymer core, while hydrophilic surface groups can be PEGylated or modified with ligands to control pharmacokinetics and enhance dermal targeting [6,45]. Chitosan-based nanoparticles are of particular interest in dermatology due to their cationic surface charge, which promotes electrostatic interactions with the negatively charged stratum corneum and epidermal keratinocytes. This electrostatic attraction enhances dermal penetration and drug retention. In one study, linoleic acid-coated chitosan nanoparticles significantly enhanced dermal diffusion of a model fluorophore, while PEG-modified analogs improved penetration depth and reduced aggregation in ex vivo skin [14]. The mucoadhesive and antimicrobial properties of chitosan further support its application in infected wounds, acne, and barrier-deficient inflammatory conditions [46]. PLGA nanoparticles, known for their predictable hydrolytic degradation into lactic and glycolic acids, are widely applied in transdermal drug delivery. These systems can achieve zero-order kinetics and multi-day sustained release, critical for managing chronic dermatoses. Surface PEGylation of PLGA particles improves colloidal stability and extends dermal residence, especially when co-formulated in gels or patches for localized delivery [46]. Dendritic lipopeptides (DLPs) have emerged as specialized carriers for nucleic acid therapeutics, particularly in inflammatory skin disease. Their branched architecture allows high-density loading of siRNA or antisense oligonucleotides. In a psoriatic mouse model, STAT3-targeted siRNA encapsulated in DLPs suppressed epidermal hyperplasia and inflammatory cytokine expression by modulating T-cell function [15]. The use of DLPs circumvents enzymatic degradation and enhances endosomal escape, a key limitation in topical nucleic acid therapy. In the context of oncodermatology, polymeric nanoparticles are increasingly employed in transcutaneous nanovaccine platforms. For instance, PLGA-based nanocarriers loaded with OVA antigen and CpG adjuvants stimulated robust CD8+ and CD103+ T-cell responses, leading to significant regression of cutaneous tumors in murine models [46]. These systems demonstrate how polymer science can bridge the gap between immunotherapy and dermatologic oncology via minimally invasive delivery routes.

Emerging trends include redox-responsive, pH-sensitive, and thermoresponsive polymeric systems, which trigger drug release in response to the inflamed or tumor-altered skin microenvironment. Additionally, graphene-enhanced polymer microneedles are under investigation for synergistic delivery and biosensing capabilities [47]. Overall, polymeric nanoparticles embody the intersection of macromolecular chemistry, cutaneous pharmacology, and immune modulation, offering a customizable toolkit for advanced dermatologic therapy.

3.5. Solid Lipid Nanoparticles (SLNs) & Nanostructured Lipid Carriers (NLCs)

Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) are lipid-based colloidal carriers designed to deliver therapeutic agents in a controlled, biocompatible, and dermally stable format. These systems harness the structural advantages of lipids in maintaining skin compatibility while enabling efficient encapsulation and sustained drug release. SLNs are composed of solid lipids such as glyceryl behenate, stearic acid, or tripalmitin, which remain solid at both room and body temperatures. Their matrix structure is formed through high-pressure homogenization or microemulsion techniques, resulting in nanospheres that encapsulate lipophilic drugs within a crystalline lipid core [5,31]. However, SLNs often face challenges related to lipid polymorphism and crystalline restructuring, which can lead to drug expulsion during storage. This occurs as the lipid matrix transitions from an amorphous or α-form to a more thermodynamically stable β-form, reducing the available space for drug accommodation and destabilizing payload retention [48]. To overcome this limitation, Nanostructured Lipid Carriers (NLCs) were developed by incorporating liquid lipids (e.g., oleic acid, medium-chain triglycerides) into the solid lipid matrix. This leads to a less-ordered, amorphous internal structure, increasing drug solubility, preventing recrystallization, and significantly improving entrapment efficiency for hydrophobic and amphiphilic molecules [49,50]. NLCs have demonstrated strong dermatologic utility:

• Curcumin-loaded NLCs have exhibited potent anti-inflammatory and antioxidant effects in melanoma and psoriasis models, outperforming conventional creams by sustaining epidermal drug levels and reducing cytokine expression [19,50].
• Luliconazole-loaded NLCs demonstrated enhanced follicular targeting and residence time in Trichophyton-infected guinea pig skin, offering superior outcomes over standard topical antifungal formulations [5].
• Caffeic acid-loaded SLNs displayed protective effects against UVB-induced oxidative stress by enhancing fibroblast migration and modulating reactive oxygen species (ROS) levels [51].

Beyond drug loading, these systems enable physicochemical customization:

• The melting point and polymorphic form of lipid mixtures can be optimized to modulate release rates.
• The zeta potential and surface charge can be tuned to control cutaneous deposition and systemic absorption.
• Hybridization with surfactants or polymers, such as in nanoemulgels, combines the colloidal stability of emulsions with the skin adherence and viscosity of hydrogels. This approach improves rheological properties, patient compliance, and localized therapeutic efficacy, especially in chronic dermatoses [52].

For instance, curcumin-EGCG-loaded NLC emulgels demonstrated significant SIRT1 activation, dermal retention, and anti-aging activity in in vitro antioxidant assays and skin models, highlighting the potential of these hybrid formats in cosmeceutical dermatology [52]. Emerging NLC formulations also incorporate responsive polymers or functionalized lipids, enabling release in response to pH, temperature, or redox gradients associated with inflammatory or neoplastic skin lesions. These innovations position SLNs and NLCs at the forefront of smart dermatologic drug delivery.

4. Physicochemical Modifications to Enhance Permeation

Overcoming the formidable barrier of the stratum corneum requires more than drug encapsulation, it demands strategic manipulation of nanocarrier physicochemical properties to enhance skin permeation, drug release, and site-specific retention. Multiple studies within the dermatologic nanocarrier field have converged on five key areas of molecular optimization: particle size, surface charge, PEGylation, membrane fluidizers (edge activators), and stimuli-responsive linkers (Table 3).

Modification	Mechanism	Effect on Delivery
Particle Size Reduction	Smaller vesicles (<300 nm)	Enhances follicular and intercellular access
Zeta Potential Tuning	Cationic surface (>+20 mV)	Improves SC interaction, uptake
PEGylation	Hydrophilic steric barrier	Extends dermal residence, reduces clearance
Edge Activators	Surfactants like Tween 80, Span 60	Improves vesicle deformability
pH-/Enzyme-Responsive Linkers	Acid-/protease-triggered release	Enables stimuli-specific drug release

Table 3: Physicochemical Modifications to Enhance Skin Permeation

4.1. Particle Size Optimization

Particle size is one of the most critical determinants of cutaneous penetration depth, follicular targeting, and systemic absorption avoidance. Nanocarriers under 300 nm have been shown to effectively traverse the intercellular lipid matrix and localize within the viable epidermis or pilosebaceous units [5,17]. For example, curcumin-loaded SLNs and NLCs ranging from 80–150 nm demonstrated superior antioxidant activity and dermal retention in both melanoma and psoriasis models, compared to their micron-sized counterparts [19,50]. Similarly, micelle-based carriers for 5-FU in skin cancer treatment showed size-dependent uptake, with smaller vesicles (~100 nm) achieving deeper diffusion [43]. In

hair follicle-targeted therapy, smaller cationic liposomes (~120–140 nm) showed improved deposition into sebaceous ducts and reduced systemic leakage [16,24].

4.2. Zeta Potential and Surface Charge

The zeta potential reflects the electrical potential at the shear plane of the nanoparticle and strongly influences vesicle stability, skin binding, and intercellular lipid interaction. Cationic nanocarriers (zeta potential > +20 mV) demonstrate enhanced attraction to the negatively charged stratum corneum, increasing permeation and cellular uptake [8,14]. Chitosan-coated nanoparticles with zeta potentials around +30 mV achieved significant dermal diffusion and retention in ex vivo human skin, outperforming neutral or anionic analogs [14]. Meanwhile, cationic elastic liposomes (OTEL1) enhanced transdermal delivery of tolterodine tartrate for bladder therapy by exploiting Hansen solubility matching and electrostatic attraction [24]. However, excessive positive charge can increase cytotoxicity and nonspecific interactions. Therefore, formulations often aim for a balance, achieving surface charges in the +20 to +40 mV range for optimal dermal targeting and colloidal stability [53].

4.3. PEGylation and Stealth Properties

PEGylation, the covalent attachment of polyethylene glycol (PEG) chains to nanocarriers, enhances their hydrophilicity, reduces opsonization, and prolongs skin residence by forming a steric barrier against protein adsorption [14,26]. In cutaneous delivery, PEGylation also reduces aggregation and improves penetration into hydrated dermal layers, especially in inflamed or barrier-disrupted skin [15]. Cyclodextrin-coated liposomal gels have used PEGylation to stabilize hydrophobic phytoconstituents like hederacoside C, enhancing epidermal penetration and modulating immune response in psoriasis [54]. PEGylated PLGA nanoparticles, when loaded with immunotherapeutic cargo, also increased lymph node drainage and CD8+ T-cell priming in dermal tumor models [46].

4.4. Edge Activators and Surfactants

Edge activators are typically single-chain surfactants added to lipid bilayers to increase membrane elasticity and vesicle deformability. These agents, such as Tween 80, Span 60, or sodium cholate, fluidize the bilayer and allow nanocarriers to squeeze through intercellular junctions of the stratum corneum [41,37]. For instance, transfersomes and ultradeformable liposomes incorporating Tween 80 achieved superior delivery of 5-FU and imperatorin into melanoma-bearing skin, inducing cell cycle arrest and apoptosis [55]. Span/Tween-based nanoemulsions also enhanced the flux of 5-ALA in photodynamic therapy, increasing fluorescence intensity and drug accumulation in Yucatan micropig models [56]. The hydrophilic-lipophilic balance (HLB) of these surfactants is crucial; higher HLB values (≥10) are associated with better skin permeability and aqueous dispersion, whereas low HLB systems tend to be occlusive and trap the formulation at the surface [39,48].

4.5. pH-Responsive or Enzyme-Cleavable Linkers

Stimuli-responsive systems exploit the diseased skin microenvironment, such as acidity, redox imbalance, or protease overexpression, to trigger targeted drug release. pH-sensitive hydrogels, enzyme-degradable peptides, and acid-labile linkers are now widely integrated into dermatologic nanocarrier design [23,28]. In psoriasis, methotrexate-loaded silk fibroin nanoparticles modified with hyaluronic acid demonstrated pH-dependent release, CD44 targeting, and improved disease resolution in mouse models [28]. Similarly, thermosensitive and pH-sensitive hydrogels carrying curcumin or caffeic acid improved antioxidant efficacy in UVB-irradiated fibroblast models and inflamed skin [6,51]. Advanced constructs such as gold nanorods within thermosensitive gels have also enabled near-infrared (NIR)-triggered release, exploiting phase transitions to release methotrexate only upon external stimulation [23]. These physicochemical modifications exemplify the critical role of rational chemical design in enhancing nanocarrier-skin interactions. By tuning these variables, researchers can tailor delivery systems for specific dermatologic pathologies, ensuring efficient permeation, targeted release, and improved patient outcomes.

5. Clinical Applications in Dermatologic Diseases

The therapeutic potential of nanocarrier systems in dermatology lies in their ability to address the heterogeneous biochemical environments of skin diseases. From inflammatory dermatoses to neoplastic lesions, each disorder presents distinct challenges in penetration depth, barrier integrity, immune dysregulation, and drug tolerability. Nanocarriers allow the precise tuning of drug release kinetics, cutaneous targeting, and co-delivery of synergistic agents, facilitating more effective and patient-tailored interventions (Table 4).

Condition	Drug	Nanocarrier Type	Delivery Benefit
Atopic Dermatitis	Tacrolimus, Vitamin D3	Liposomes, Ethosomes	Barrier penetration, CD44 targeting
Psoriasis	Methotrexate, siRNA	DLPs, SLNs/NLCs, hydrogels	CD44/pH targeting, immune modulation
Melanoma	Gossypin, 5-FU, CpG	Ethosomes, Transfersomes	Anti-migratory, ROS-mediated apoptosis
Acne & Rosacea	Spironolactone, Chloramphenicol	Niosomes, Ethosomes	Follicular targeting, anti-inflammatory effects
Alopecia	Minoxidil, Platinum nanozymes	Microneedles, liposomes	VEGF, Wnt pathway activation

Table 4: Disease-Specific Nanocarrier Applications in Dermatology

5.1. Atopic Dermatitis (AD)

Atopic dermatitis is defined by chronic inflammation, barrier dysfunction, and elevated skin pH, making it ideal for nanocarrier strategies that target epidermal penetration and immunomodulation without systemic side effects. Conventional therapies like tacrolimus and corticosteroids are limited by irritation and poor dermal uptake. Liposomes and ethosomes loaded with tacrolimus demonstrated markedly improved permeation and retention in skin, particularly when integrated into hyaluronic acid-based gels that promote hydration and CD44-mediated targeting [28,34]. Xia et al. used sodium alginate/chitosan hydrogels to stabilize tetramethylpyrazine-loaded liposomes, achieving anti-inflammatory, antibacterial, and barrier-repair effects, critical for managing the microbial dysbiosis and inflammation characteristic of AD [57]. Ethosomal gels also supported vitamin D3 delivery, enhancing its photoprotective and keratinocyte-differentiation effects without irritation [34]. These systems surpass traditional ointments by leveraging ethanol-induced SC disruption and vesicle deformability to penetrate thickened or inflamed skin.

5.2. Psoriasis

Psoriasis involves keratinocyte hyperproliferation, T-cell–driven cytokine release (IL-17, IL-23, TNF-α), and thickened plaques that block passive diffusion. Nanocarriers provide solutions through follicular targeting, pH-responsive release, and immune modulation. Methotrexate-loaded carriers, including HA-functionalized silk fibroin nanoparticles and thermosensitive hydrogels, enabled targeted delivery to inflamed plaques via CD44 receptors and acidic microenvironments, leading to reduced epidermal thickening and cytokine expression in vivo [23,28]. Calcipotriol and corticosteroid combinations delivered via NLCs and liposomal-in-gel systems improved therapeutic adherence and reduced local irritation, often seen with monotherapies [19,38]. Genetic nanotherapy is emerging with dendritic lipopeptides (DLPs) delivering STAT3-targeting siRNA, downregulating key inflammatory transcription factors and restoring epidermal homeostasis [15]. Curcumin-based SLNs and NLCs, especially those modified with α-linolenic acid or EGCG, suppressed keratinocyte-derived ROS and inhibited ferroptosis-related inflammatory pathways [50,52].

5.3. Actinic Keratosis (AK) and Superficial Basal Cell Carcinoma (BCC)

These lesions originate from chronic UV damage and require localized treatment to avoid surgical morbidity. 5-FU and imiquimod are mainstays of therapy but limited by surface irritation and poor retention. Niosomal and transfersomal 5-FU formulations have improved lesion targeting by penetrating deep into the epidermal proliferative zones while reducing off-target effects [37,55]. These carriers promote G2/M cell cycle arrest and enhance apoptosis in transformed keratinocytes. Imiquimod-loaded PLGA and cyclodextrin-polymer hybrids increased lymphatic trafficking, amplified Toll-like receptor (TLR7) activation, and induced cytotoxic T-cell responses in cutaneous tumor models [44,46]. For photodynamic therapy, ALA and chlorin e6 loaded into cubosomes and hexosomes showed superior phototoxicity, ROS generation, and encapsulation efficiency, while gold nanorods in temperature-sensitive hydrogels allowed NIR-triggered methotrexate release, offering light-controlled lesion ablation [23,58].

5.4. Acne and Rosacea

Acne and rosacea are chronic inflammatory dermatoses linked to dysregulated sebaceous activity, microbial overgrowth (notably Cutibacterium acnes), and cutaneous immune dysfunction. Conventional topical agents such as clindamycin and azelaic acid often face challenges in penetrating the follicular unit or cause barrier irritation. To overcome these limitations, ethosomes, SLNs, and NLCs have been employed to deliver spironolactone directly to pilosebaceous units, enabling follicular targeting while minimizing systemic hormone absorption [17,41]. These nanocarriers improved residence time in sebaceous-rich skin and reduced inflammatory lesions. Binary ethosomal hydrogels and silver nanoparticle–NLC hybrids enhanced the transcutaneous delivery of chloramphenicol and enrofloxacin, resulting in synergistic antimicrobial effects and improved wound healing in infected skin [17,45]. Additionally, niosomal formulations of azelaic acid and niacinamide demonstrated improved tolerability and erythema reduction in rosacea, surpassing conventional creams [39,40]. Emerging technologies such as skin-penetrating peptides (SKPs) offer promising solutions for large biomolecule and gene delivery in inflamed or barrier-deficient skin, expanding the therapeutic scope beyond antibiotics and retinoids [4].

5.5. Alopecia (Androgenetic & Telogen Effluvium)

Hair loss disorders, including androgenetic alopecia (AGA) and telogen effluvium, present challenges in delivering active agents to the base of the follicle and stimulating growth-related signaling pathways. Nanocarrier systems such as dissolvable microneedles, ionic liquids, and liposomal constructs have enabled deep follicular delivery of growth-promoting and anti-inflammatory agents. Platinum nanozyme-loaded microneedles improved hair regrowth by scavenging ROS and reactivating follicular stem cells, outperforming minoxidil in murine AGA models [59]. Xing et al. introduced HA-liposomes co-loaded with minoxidil and nitric oxide donors (HL@Mi/NONOate), which synergistically enhanced dermal vasodilation and follicle stem cell activation [60]. Similarly, Zhao et al. (2025) used tofacitinib-encapsulated dissolving microneedles to increase follicular density by modulating local JAK/STAT signaling. Ginsenoside Rg3 liposomes embedded into microneedles stimulated VEGF and Wnt/β-catenin expression, restoring hair cycling in both AGA and stress-induced effluvium [21]. Novel ionic liquid vehicles incorporating valproic acid further disrupted SC lipids and reactivated dormant follicles through β-catenin signaling [13].

5.6. Melanoma and Other Cutaneous Malignancies

Topical treatment of melanoma and cutaneous squamous cell carcinoma (cSCC) is limited by poor penetration of chemotherapeutic and immunomodulatory agents, as well as the need for localized action with minimal systemic toxicity. Transfersomes carrying 5-FU and imperatorin penetrated deeply into epidermal tumors and triggered G2/M cell cycle arrest and apoptosis in melanoma

models [55]. Ethosome-loaded gossypin showed potent anti-migratory and cytotoxic effects on melanoma cell lines, mediated by antioxidant and anti-angiogenic properties [9]. Camptothecin and CpG-loaded mesoporous silica nanoparticles triggered tumor regression in cSCC through combined chemotherapeutic and immunostimulatory mechanisms [61]. Photodynamic therapy has also benefited from nanocarrier innovation: ALA and chlorin e6 embedded in cubosomes or hexosomes improved ROS generation and lesion-specific toxicity, while gold nanorod-thermogels enabled NIR-triggered methotrexate release for targeted ablation [23,58]

5.7. Photoaging and UV-Induced Dermatoses

Photoaging involves cumulative UV-induced damage to dermal collagen, elastin, and skin immune surveillance, resulting in pigmentation changes, wrinkles, and thinning. Antioxidants and regenerative molecules often suffer from poor stability and penetration. Nanocarrier formulations offer targeted antioxidant delivery, fibroblast stimulation, and anti-inflammatory effects. Catechol chitosan-coated liposomes encapsulating resveratrol and carnosine reduced oxidative stress and restored fibroblast function in UV-damaged skin [33]. HA-liposomes encapsulating high molecular weight hyaluronic acid enhanced hydration and collagen regeneration in photodamaged models, while reducing inflammatory markers [60]. Nano-liposomes delivering recombinant human growth hormone (rhGH) mitigated UVB-induced collagen loss and hyperplasia in nude mice [22]. Ultrasound-assisted sonophoresis of rutin further enhanced intradermal retention and barrier recovery by increasing dermal penetration and scavenging ROS [62].

5.8. Wound Healing and Barrier Repair

Wound healing and chronic barrier disruption, common in post-inflammatory dermatoses and trauma, require bioactive delivery that enhances re-epithelialization, angiogenesis, and infection control. Nanocarrier-based systems such as nanoemulsions, hydrogels, and biopolymer conjugates have been developed to meet these multifactorial needs. Gong et al. formulated a PVA-modified NLC–silver nanoparticle hybrid, accelerating wound closure and demonstrating potent antimicrobial synergy [45]. Sugar ester-stabilized auraptene nanocarriers improved stratum corneum permeability and promoted antioxidant-mediated repair [26]. Chitosan nanoparticles coated with linoleic acid and PEG significantly enhanced dermal penetration and maintained stable drug fluorescence in wounded tissue models [14]. Curcumin + EGCG-loaded NLC emulgels activated SIRT1 pathways, promoting fibroblast migration and reducing oxidative damage, key events in chronic wound resolution [52].

5.9. Fungal and Yeast Infections

Topical fungal infections, including dermatophytosis and candidiasis, are complicated by keratinized tissue penetration barriers and microbial biofilm formation. Luliconazole-loaded NLCs achieved superior skin retention and therapeutic efficacy against T. indotineae in animal models, surpassing commercial antifungal creams [5]. Farnesol-loaded ethosomes significantly reduced fungal burden in Candida albicans infections by penetrating and disrupting biofilms [63]. A synergistic nanoemulgel composed of ketoconazole and eugenol exhibited deeper SC penetration and enhanced antifungal activity relative to monotherapy formulations, offering a promising solution for resistant or recurrent cutaneous fungal disease [44].

6. Discussion

While nanocarrier systems hold immense promise for transforming dermatologic therapeutics, several challenges continue to impede their seamless translation from bench to bedside. A primary concern is the long-term stability of these formulations. Vesicular systems such as liposomes and ethosomes are particularly prone to degradation, fusion, or drug leakage due to oxidation of unsaturated lipids or volatility of ethanol-rich matrices. Although solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) offer enhanced physical stability, they may undergo polymorphic transitions over time, leading to expulsion of the encapsulated drug and compromised efficacy. Stabilization strategies, including PEGylation, hydrogel encapsulation, and lyophilization, have been explored with varying success [5,14,19,25]. Another persistent limitation is batch-to-batch variability during formulation. Slight differences in surfactant composition, lipid-to-drug ratios, or homogenization conditions can lead to inconsistencies in particle size, zeta potential, and drug loading efficiency. These inconsistencies affect both therapeutic outcomes and regulatory compliance. Techniques such as quality-by-design (QbD) modeling and real-time process analytics are increasingly necessary to standardize nanoparticle synthesis, particularly for complex systems like co-loaded liposomes or microneedle-integrated platforms [39,64]. Scaling up production remains a formidable obstacle. Many research-grade nanocarriers are developed using solvent evaporation or sonication, which are not readily translatable to industrial manufacturing. Large-scale, GMP-compliant methods such as twin-screw processing, microfluidization, and high-pressure homogenization require optimization to preserve nanoparticle integrity, drug entrapment, and sterility, especially for thermolabile or multi-component formulations [26,43]. In parallel, regulatory frameworks have not yet fully adapted to the complexity of nanomedicine. Agencies such as the FDA and EMA demand extensive physicochemical characterization and biological safety data, including information on biodistribution, immunogenicity, and nanoparticle clearance. The lack of harmonized global standards further complicates the registration and commercialization of dermatologic nanocarriers. Systems that combine mechanical, chemical, or biological delivery mechanisms, such as AI-optimized microneedles or multifunctional liposomes, face even greater regulatory ambiguity due to their hybrid nature [3,37]. Finally, safety concerns persist regarding skin irritation, cytotoxicity, and immune activation. Cationic liposomes may interact strongly with negatively charged skin structures, potentially disrupting barrier function or causing localized irritation. Ethanol-based carriers, while effective at SC disruption, can also induce dryness or stinging with prolonged use. Silver nanoparticles and other metal-based carriers have demonstrated cytotoxic effects on keratinocytes

at higher concentrations, raising concerns about their long-term dermatologic application. Additionally, nanoparticle accumulation within follicles or uptake by antigen-presenting cells poses a risk of unwanted immunologic reactions, particularly in sensitized individuals [4,8,45]. These risks underscore the need for rigorous preclinical toxicology studies, careful excipient selection, and post-market surveillance to ensure both efficacy and patient safety (Table 5).

Challenge	Barrier Type	Mitigation Approach
Formulation Stability	Physical/Chemical	PEGylation, lyophilization, hybrid gels
Batch-to-Batch Variation	Manufacturing	QbD modeling, microfluidization, standardization
Regulatory Complexity	Approval Pathways	Comprehensive physicochemical & toxicologic data
Skin Irritation Potential	Safety	Surface charge balancing, excipient refinement
Scaling Production	Industrial	GMP-compliant twin-screw or high-pressure processing

Table 5: Summary of Barriers to Translation and Mitigation Strategies

6.1. Future Directions and Conclusion

The next frontier in nanocarrier-based dermatologic therapy lies in the fusion of precision medicine, artificial intelligence, and material science. Emerging research suggests that future transdermal delivery systems will be increasingly personalized, engineered to align with an individual's skin barrier properties, immune profile, and microbiome composition. By leveraging advances in skin omics and patient-specific biomarkers, these systems can be optimized for pharmacogenomic compatibility, minimizing side effects and maximizing therapeutic response. Artificial intelligence is poised to accelerate nanocarrier design and screening. Machine learning algorithms trained on large datasets of physicochemical parameters and biological performance metrics can predict optimal compositions, particle sizes, and surface modifications to achieve desired drug release profiles and skin penetration outcomes [64]. AI-guided in silico modeling may also aid in anticipating immune reactivity, formulation stability, and skin irritation potential before any benchwork begins, streamlining development timelines and enhancing regulatory readiness. Smart nanocarriers represent another major evolution. These stimulus-responsive systems are engineered to release their payloads in response to pH shifts, redox gradients, enzymes, or temperature changes associated with diseased skin microenvironments. For instance, redox-responsive microneedles using thiolated polymers can release drugs only in inflamed or infected skin, while pH-sensitive ethosomal gels or nanoemulsions can selectively unload actives in psoriatic lesions with acidic pH [11,23]. Such "on-demand" delivery minimizes off-target effects and enhances therapeutic precision. Hybrid nanosystems, combining lipid, polymer, dendrimer, or inorganic components, offer modularity, enhanced encapsulation, and controlled kinetics. Lipid-polymer hybrids enable co-delivery of hydrophilic and hydrophobic drugs with improved physical stability. Gold nanorod-hydrogel platforms allow NIR-triggered lesion-specific photothermal release, while exosome-liposome fusions are emerging as natural-mimetic systems for regenerative applications [23,30]. These multifunctional carriers could one day integrate diagnostics, feedback-controlled release, and regenerative cues into a single nanoscale entity. Ultimately, the field of dermatologic nanomedicine sits at the confluence of colloid chemistry, polymer physics, and clinical dermatology. The ability to rationally design nanoscale delivery vehicles based on molecular interactions, skin histology, and disease-specific targets reflects a profound shift toward integrated, systems-level thinking. As regulatory clarity improves and translational pipelines expand, nanocarriers will play an increasingly central role in treating chronic skin diseases, managing oncologic lesions, and supporting barrier repair and cosmetic rejuvenation.

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