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# NANOPARTICLE-BASED THERAPEUTICS FOR ATOPIC DERMATITIS: ADVANCES IN LIPID, POLYMERIC, INORGANIC, AND PHYTOCHEMICAL NANOCARRIERS

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## ABSTRACT

Background: Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder that imposes significant disease burden. Conventional therapies provide symptomatic relief but are associated with poor long-term efficacy, adverse effects, and low patient compliance. Objective: This review evaluates recent advances in nanoparticle-based therapeutics for AD, focusing on lipid, polymeric, inorganic, and phytochemical nanocarriers. Methods: A literature survey was conducted across PubMed, Scopus, and Web of Science (2010–2024) using keywords including nanoparticles, atopic dermatitis, lipid nanocarriers, and phytochemical nanocarriers. Emphasis was placed on therapeutic outcomes, mechanisms, and safety. Results: Lipid-based nanocarriers, such as liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, improve drug penetration, enhance hydration, and prolong drug retention. Polymeric nanoparticles (e.g., chitosan, PLGA) provide sustained release, skin targeting, and enhanced stability. Inorganic nanoparticles (ZnO, Au, mesoporous silica) demonstrate dual carrier and therapeutic functions but raise concerns of long-term safety. Phytochemical-loaded nanocarriers improve solubility, stability, and bioavailability of natural bioactives such as curcumin and quercetin. Innovative approaches, including functionalized textiles, hydrogels, and stimuli-responsive nanocarriers, show promise in overcoming limitations of conventional formulations. Conclusion: Nanoparticle-based systems represent a next-generation strategy for AD therapy by enhancing localized efficacy, minimizing systemic toxicity, and improving patient adherence. Future research should prioritize long-term safety, regulatory frameworks, and clinical translation.

**KEYWORDS:** Atopic dermatitis; Nanoparticle drug delivery; Lipid nanocarriers; Polymeric nanoparticles; Phytochemical nanocarriers; Targeted skin therapy.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder that represents one of the most prevalent dermatological conditions worldwide. It affects both children and adults and is characterized by intense pruritus, xerosis, and recurrent eczematous lesions, all of which significantly impair quality of life. Beyond its physical manifestations, AD is associated with sleep disturbance, anxiety, depression, and social stigma, contributing to a high overall disease burden. The global prevalence of AD has increased steadily in recent decades, reflecting complex interactions between genetics, lifestyle, environment, and urbanization.[1]

The pathogenesis of AD is multifactorial and involves a dynamic interplay between impaired skin barrier function, immune dysregulation, genetic susceptibility, microbial imbalance, and environmental triggers. Structural and functional defects in the epidermal barrier—often associated with mutations in proteins such as filaggrin—permit excessive trans epidermal water loss and increased penetration of allergens, irritants, and microbial products. This, in turn, activates type-2 immune pathways dominated by cytokines such as interleukin-4 and interleukin-13, which perpetuate inflammation, pruritus, and further compromise of the barrier. In addition, microbial dysbiosis, particularly colonization by Staphylococcus aureus, is strongly associated with disease severity and recurrent flare-ups.[2] The chronic relapsing course of AD and its heterogeneity across age groups make disease management especially challenging.

Current therapeutic options include emollients, topical corticosteroids, calcineurin inhibitors, phosphodiesterase-4 inhibitors, Janus kinase inhibitors, phototherapy, and systemic biologics. While these interventions provide symptomatic relief and have significantly improved disease outcomes, their limitations are evident. Long-term corticosteroid use is associated with skin thinning and tachyphylaxis; systemic immunosuppressants carry risks of organ toxicity; biologics and targeted small molecules are effective but costly, limiting accessibility for many patients. Furthermore, these approaches often fail to provide sustained remission, and adherence to long-term therapy is poor.[3] Collectively, these challenges highlight the need for innovative therapeutic strategies that offer efficacy, safety, and improved patient compliance.

Nanotechnology has emerged as a transformative platform to address these unmet needs in AD therapy. Nanoparticles are colloidal carriers, generally within the size range of 1–1000 nm, designed to encapsulate and deliver therapeutic agents. Their small size and tunable surface properties allow them to penetrate or interact closely with the skin barrier, improving drug delivery compared with conventional formulations. Importantly, the compromised epidermal barrier in AD facilitates greater nanoparticle accumulation in inflamed skin, offering a unique opportunity for targeted treatment. By enhancing drug solubility, protecting labile molecules from degradation, enabling controlled release, and improving skin retention, nanoparticle systems can achieve higher local concentrations at disease sites while minimizing systemic exposure.[4]

A variety of nanocarrier systems have been investigated for their potential in AD management. Lipid- based nanoparticles such as liposomes, ethosomes, solid lipid nanoparticles, and nanostructured lipid carriers can merge with skin lipids, improve penetration, and exert occlusive and moisturizing effects that support barrier repair. They have been employed to enhance the delivery of corticosteroids, calcineurin inhibitors, and natural compounds with favourable outcomes. Polymeric nanoparticles, prepared from biodegradable polymers like PLGA, PCL, chitosan, or alginate, offer versatile encapsulation options and enable sustained or stimuli-responsive drug release. Their

mucoadhesive properties also promote prolonged contact with diseased skin. Inorganic nanoparticles such as zinc oxide, silver, and gold not only serve as drug carriers but also possess inherent antimicrobial, antioxidant, or anti-inflammatory activities that are relevant in AD, where microbial colonization and oxidative stress contribute to pathogenesis. Finally, phytochemical-based nanoparticle systems have been developed to improve the delivery of natural agents such as curcumin, quercetin, and resveratrol, which otherwise suffer from poor solubility and stability. By overcoming these limitations, nanocarriers significantly expand the therapeutic potential of plant- derived compounds.

In addition to conventional drugs, nanotechnology also holds promise for advanced therapies, including nucleic acid-based treatments. Lipid nanoparticles are being explored for the delivery of siRNA or CRISPR-based systems directly into the skin, with the goal of modifying immune pathways or correcting barrier defects at the molecular level. Such "gene creams" represent an exciting step toward disease-modifying interventions rather than symptomatic management. While these approaches remain at an experimental stage, they illustrate the broad potential of nanotechnology in reshaping the therapeutic landscape of AD.

Despite the encouraging advances, important challenges remain. Variability in nanoparticle design, differences in physicochemical properties such as size, charge, and polydispersity, and lack of standardized testing protocols hinder direct comparison across studies. Concerns about long-term safety, potential cytotoxicity, immunogenicity, and the impact of chronic nanoparticle exposure on skin and systemic health also require thorough investigation. Moreover, scaling up production to achieve reproducibility, stability, and cost-effectiveness suitable for clinical use continues to be a hurdle. Nonetheless, the growing body of evidence strongly supports the role of nanoparticle-based therapeutics as a next-generation strategy in atopic dermatitis management.

This review aims to provide a comprehensive overview of the application of nanotechnology in AD, with a particular focus on lipid, polymeric, inorganic, and phytochemical nanocarriers. By analysing their design strategies, mechanisms of action, therapeutic outcomes, and limitations, this work highlights how nanoparticle-based approaches can address unmet needs in AD treatment and pave the way for safer, more effective, and targeted interventions for patients.

**Conventional therapy drawbacks**

Topical therapy techniques are plagued by a number of problems. Drug permeability through the stratum corneum is impacted by the damaged, inflammatory skin seen in dermal diseases. Drugs cannot penetrate deeply into the skin if there is a lack of normal skin hydration, low ceramide levels, excessive cholesterol, and the formation of dense, scaly plaques, which are common in conditions like psoriasis. The overall effectiveness of treatment is further harmed by inability to penetrate tightly packed epithelium and endothelial layers, difficulties delivering targeted drugs to specific tissues, and trouble reaching the intracellular arena in adequate concentration. Poor oral bioavailability, hepatic pass metabolism, poor skin distribution, quick clearance, and a higher frequency of severe side effects are common problems with older systemic medicines.[5]

**Principles of Nanotechnological Design**

Nanotechnology-based formulations are developed to overcome the drawbacks of conventional therapies for atopic dermatitis (AD). Their main purpose is to improve drug penetration into the skin, maintain drug stability, and ensure sustained release for better therapeutic outcomes.[6]

**Key considerations in nanocarrier design include**

1. **Size and Surface Properties** – Nanoscale carriers, generally ranging from 10–200 nm, can traverse intercellular lipid pathways of the stratum corneum. Adjusting particle charge and hydrophobicity enhances retention in skin layers.
2. **Drug Encapsulation and Release** – Nanocarriers allow higher drug loading and controlled release, which prolongs the therapeutic effect and decreases the need for frequent application.
3. **Biocompatibility and Safety** – Using safe materials such as phospholipids, biodegradable polymers, or natural polysaccharides reduces the risk of irritation and toxicity.
4. **Targeted Delivery** – Functionalization with ligands or antibodies enables selective delivery to inflamed or immune-active skin regions, increasing treatment efficiency.
5. **Stability and Shelf-Life** – Encapsulation shields sensitive compounds (e.g., phytochemicals) from degradation, extends shelf stability, and enhances clinical usefulness.

By integrating these principles, nanocarrier systems provide site-specific, sustained, and patient- friendly drug delivery. They represent a promising frontier in the management of AD by improving efficacy while minimizing side effects.

**Atopic dermatitis dermopharmaceutical formulations based on nanocarriers**

Nanoemulsions (NEs), liposomes (LIPs), ethosomes (ETOs), transfersomes (TRAs), solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanocrystals, polymeric nanoparticles (NPs), and polymeric micelles (PMs) are among the NCs that have been the subject of numerous studies to develop for the topical delivery of medications for the treatment of AD. Table 1 lists formulations based on nanotechnology that are used to apply medications topically to treat AD.[6]

**Nanocarriers for topical drug delivery in the treatment of atopic dermatitis**

**Liposomes**

Phospholipid bilayers that resemble cell membranes make up LIPs, which are drug delivery systems. These systems are spherical vesicles that have an aqueous phase surrounded by one or more concentric bilayers. Another common ingredient in LIPs is cholesterol (Chol), which promotes membrane fluidity and prevents phospholipid aggregation. Since LIPs can trap water-soluble medications in their core and low water-soluble ones in the membrane, the combination of a hydrophilic aqueous core and a hydrophobic phospholipid layer is quite advantageous. Because LIPs can simultaneously encapsulate drugs with different natures and molecular weights—that is, hydrophilic drugs in the aqueous phase and hydrophobic drugs in the lipid bilayer—they have been highlighted as useful drug delivery systems for topical drug delivery. Furthermore, because of their enhanced pharmacokinetic qualities, target-specific delivery, biodegradability, and biocompatibility, LIPs have been thoroughly investigated as drug delivery systems that are well tolerated by the skin. Their lipid makeup is similar to that of SC constituents, which improves penetration and permeationthrough the SC and enhances cutaneous drug delivery. Accordingly, LIPs that are topically administered to the skin have a tendency to gather in the SC's higher layers, where they serve as a reservoir and have a localized effect. Another application for LIPs is as a transdermal medication delivery method. Indeed, by altering the composition of LIPs, the skin penetration efficacy can be improved, making them adaptable drug delivery vehicles. To enhance topical or transdermal medication delivery, for instance, a new generation of flexible or deformable vesicles, such as ETOs and TRAs, has been created. The findings of studies on LIPs as potential NCs of medications for the treatment of

dermatological conditions (such as vitiligo, psoriasis, acne, and AD) have confirmed their therapeutic usefulness. Antibiotics, corticosteroids, TAC, and antihistamines are only a few of the medications used to treat AD that have been encapsulated in LIPs.[6]

**Ethosomes**

Ethosome technology, which started to be commercialized in 2000, is a quickly developing field.[7] A state-of-the-art medication delivery method, ethersomes provide notable improvements in topical and transdermal applications. Hydrophilic and lipophilic medications can be delivered through the skin thanks to these vesicular carriers, which are made of phospholipids, ethanol, and water. Ethosomes address the drawbacks of traditional delivery methods by improving permeability and stability, which makes them very useful in the treatment of systemic diseases, fungal infections, and skin conditions. This review highlights the revolutionary potential of ethosomes in pharmaceutical sciences by offering a thorough examination of their structure, methods of preparation, mechanisms, applications, and future prospects.[14]

High concentrations of ethanol (20–45%) in phospholipid-based nanocarriers called ethersomes increase skin permeability by rupturing the lipid matrix of the stratum corneum.[15] Ethosomes have better deformability than traditional liposomes, which enables them to enter the skin more deeply and enable topical and systemic drug delivery.[16]

**Ethosomes: Composition and Structure**

Three main components make up ethosomes:

- **Phospholipids:** Create the bilayer of the vesicle and offer biocompatibility.
- **Ethanol (20-45%):** increases the flexibility of vesicles and breaks down lipids in the skin to make it easier for drugs to enter.
- **Water:** serves as ethosomal vesicle stabilizer and solvent.[17]

Ethosomes are adaptable carriers for transdermal and dermatological applications because of their composition, which enables them to encapsulate hydrophilic, lipophilic, and amphiphilic medications.[18]

Ethosomes are adaptable carriers for a variety of therapeutic applications because of their composition, which enables them to encapsulate a broad range of medications, including hydrophilic, lipophilic, and amphiphilic compounds.[19]

Ethosomes improve transdermal medication distribution in two ways:

1. **Ethanol Effect:** By upsetting the stratum corneum's intercellular lipid structure, ethanol causes an increase in skin permeability.[20]
2. **Flexible Vesicular System:** Drugs are delivered to deeper tissues by the flexible ethosomes, which pierce the skin's layers.[8]

**Advantages of Ethosomal Drug Delivery**

Compared to alternative dermal and transdermal delivery methods,

- Ethosomes improve the drug's penetration through cutaneous and transdermal administration.
- Large and varied drug groups (peptides, protein molecules) can be delivered via ethersomes.

- In terms of both quantity and depth, ethosomal systems are far more effective at delivering a fluorescent probe (quantum dots) to the skin.
- Low risk profile: Because the toxicological profiles of the ethosome components are well- established in the scientific literature, there is no risk of large-scale drug development using this technology.
- High patient compliance is achieved by administering the ethosome medications in a semisolid form, such as gel or cream. On the other hand, patient compliance will be impacted by the relative complexity of iontophoresis and phonophoresis.
- High market appeal for goods using in-house technologies. Ethosomes are very easy to produce and do not require any complex technical inputs.
- The ethosomes system may be commercialized right away and is both passive and non- passive.
- Several uses in the veterinary, cosmetic, and pharmaceutical industries.[7]

**Transferosomes**

One kind of lipid-based drug delivery device called a transferosome is intended to improve the passage of medications across biological barriers like the skin. Phospholipids, surfactants, and occasionally cholesterol make up their bilayer structure, which envelopes the medication. Furthermore, transferosomes can be engineered to target particular tissues or cells, increasing the effectiveness of medications while lowering the possibility of adverse effects. Since their first introduction as a new drug delivery system in the 1990s, transferosomes have been the subject of intense research into their potential medicinal uses. The capacity of transferosomes to increase the bioavailability of medications with low water solubility, which may restrict their efficacy when given via conventional means, is one of its main benefits.

All things considered, transferosomes are a promising drug delivery method that may find use in a variety of therapeutic fields. The goal of ongoing research is to increase the stability, effectiveness, and safety of transferosomes while also investigating novel applications for them in clinical settings.[7]

**Advantages of Transferosomes**

Enhanced Penetration: Transferosomes may squeeze through small holes and get deep into the skin or mucosal tissues because of their great elasticity and deformability. This characteristic makes it easier to distribute medications effectively to target locations that are otherwise challenging to reach, such as deeper skin layers or systemic circulation. Increased Drug Bioavailability: By encouraging drug absorption through the skin or mucosal membranes, transferosomes' deformability increases the bioavailability of medications. This is especially advantageous for medications that need targeted distribution or have low oral bioavailability.

**Enhanced Stability:** By protecting encapsulated medications from enzyme breakdown, pH changes, and other environmental influences, transferosomes enhance their stability. This keeps the medicine active and intact while it is being transported and stored.

**Tailored Drug Delivery:** Transferosomes can be surface-modified with targeting ligands to accomplish tailored drug delivery, just like invasomes. These ligands minimize off-target effects while enabling precise and localized drug administration by recognizing particular receptors or molecules on the target cells.

**Flexible Formulation:** A variety of medications, including both hydrophilic and hydrophobic substances, can be encapsulated in transferosomes. Because of their adaptability, they can be used with a variety of medications, providing for flexibility in both drug composition and delivery.

When a lipid suspension, called transferosomes, is applied to the skin's surface, water evaporation creates a "osmotic gradient" that is the mechanism of transport. Concentration has no bearing on the movement of these elastic vesicles. Trans-epidermal hydration serves as the process's primary vesicle transport driver. The vesicles' flexibility allows them to flow through the corneum's pores, despite the holes' smaller diameter than the vesicles. To ensure adequate hydration, transferosomes tend to cross the barrier and move into the deeper, water-rich layers when applied to an open biological surface, such as non-occluded skin.[10,11]

The bilayer undergoes reversible distortion during penetration through the corneum. For the underlying hydration affinity, it is imperative to make sure that the gradient, barrier, and vesicle integrity are not jeopardized during this deformation.

Transferosomes must locate and create their own route into the organ because they are too big to diffuse through the skin. The capacity of transferosomes to enlarge and penetrate the skin's hydrophilic pores is essential to their efficacy in drug administration. Similar to normal endocytosis, which involves the diffusion of vesicles through the cytomembrane, intracellular drug transport may entail the diffusion of the lipid bilayer of the vesicles with the skin. The mechanism is complex and combines material transport, hydration/osmotic forces, and sophisticated elasto-mechanics concepts.[9]

**Solid Lipid Nanoparticles**

The unique size-dependent properties of lipid nanoparticles offer an opportunity to develop new treatments. The capacity to integrate medications into nanocarriers provides a novel drug delivery approach and enables therapeutic targeting. As a result, researchers are particularly interested in solid lipid nanoparticles because of their great potential to accomplish the objective of controlled and site-specific drug delivery. The pharmaceutical industry is using lipid nanocarriers more and more to transport and deliver a range of therapeutic agents, from small drug molecules to biotechnology goods. Phospholipids' many qualities, including as their amphiphilia, biocompatibility, and multifunctionality, make them an essential part of lipids and lipid-based drug delivery systems. Nevertheless, the creation of the SLN delivery system has been prompted by the complicated manufacturing process, low percentage Entrapment Efficiency (% EE), and difficult large-scale manufacturing of liposomes, lipospheres, and microsimulation carrier systems, among other drawbacks. SLNs usually have a diameter of 50–1000 nm and a spherical shape. The primary ingredients of SLN formulations are lipids, which are solid at room temperature, emulsifiers, and sometimes a combination of both, Active Pharmaceutical Ingredients (APIs), and an appropriate solvent system. Nanocarrier-based drug delivery systems can be categorized depending on many parameters, such as the degree of degradation and the manner of administration.

Solid Lipid Nanoparticles (SLNs), the initial generation of lipid-based nanocarriers, are composed of lipids, which are solid at body temperature and stabilized by emulsifiers. SLNs are submicron (less than 1000 nm) in size. Among their many advantages are their ability to shield medications from harsh environmental factors, enable large-scale synthesis through the use of the high pressure homogenization process, and be both biocompatible and biodegradable.

**Advantages of solid-lipid nanoparticles**

The benefits of various colloidal systems including liposomes, nanoemulsions, and polymeric nanoparticles are all combined in SLNs. The following succinctly describes the main benefits of SLNs:

- Because the lipids used are biocompatible and biodegradable, SLNs are not biotoxic.
- SLNs can be produced without the use of organic solvents.
- SLNs have a high level of physical stability.
- Both drug targeting and controlled drug release can be accomplished with SLNs.
- Adding active ingredients to SLNs can increase their stability.
- SLNs can be used to encapsulate hydrophilic and lipophilic drugs.
- Large-scale production of SLNs is easy.
- Sterilizing SLNs is possible.[9]

**Phytochemical- Loaded Nanocarriers**

Phytochemicals, also known as plant-derived bioactive compounds, have gained significant attention in the cosmetic industry due to their antioxidant, anti-inflammatory, anti-aging, skin-whitening, and antimicrobial properties.[12] These include polyphenols, flavonoids, terpenoids, alkaloids, and tannins extracted from various herbs, fruits, and plant sources. However, the practical application of phytochemicals in cosmetic formulations faces several challenges, such as poor aqueous solubility, low skin permeability, high instability under light and oxygen, and rapid degradation.[13]

To overcome these limitations, the use of **nanocarrier-based delivery systems** has emerged as a promising approach. Nanocarriers—such as liposomes, nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanoparticles—can encapsulate and protect sensitive phytochemicals, improve their bioavailability, and ensure sustained and targeted delivery to specific skin layers.[14,15].

The nanoscale size allows enhanced penetration through the stratum corneum, increasing the efficacy of cosmetic agents and reducing the need for high doses. Additionally, nanocarriers can improve formulation aesthetics and stability, offering innovative solutions for the delivery of natural compounds in modern skincare and cosmetic products.[16]

**Advantages of Phytochemical-Loaded Nanocarriers in Cosmetic Formulations**

1. **Enhanced Skin Penetration**: Nanocarriers improve dermal and transdermal delivery of poorly permeable phytochemicals.[17]
2. **Protection from Degradation:** They shield phytochemicals from oxidation, UV degradation, and enzymatic breakdown.[18]
3. **Sustained and Controlled Release**: Allows prolonged activity, reducing application frequency and enhancing efficacy.[19]
4. **Improved Solubility and Stability**: Phytochemicals with poor water solubility (e.g., curcumin, resveratrol) show improved formulation compatibility.[20]
5. **Biocompatibility and Safety**: Most phytochemical nanocarriers use natural, biodegradable materials ideal for cosmetic use.[21]
6. **Multifunctional Effects**: Enables delivery of multiple bioactives in one formulation for synergistic effects (e.g., anti-aging + photoprotection).[22]

**Inorganic NPs**

Inorganic nanoparticles (NPs) have emerged as a transformative innovation in cosmetic science due to their unique physicochemical properties and functional versatility. These NPs, typically composed of metal or metal oxide materials such as **titanium dioxide ($TiO_2$)**, **zinc oxide (ZnO)**, **gold (Au)**, **silver (Ag)**, **silica ($SiO_2$)**, and **iron oxide ($Fe_3O_4$)**, exhibit nanoscale dimensions (1–100 nm) that confer distinct characteristics like increased surface area, enhanced optical activity, and high stability under various environmental conditions.[23,24]

In cosmetic applications, inorganic nanoparticles serve multiple roles—as **UV filters**, **antimicrobial agents**, **skin whitening agents**, **coloring pigments**, and **delivery vehicles for active compounds**. For instance, $TiO_2$ and ZnO nanoparticles are extensively used in sunscreens due to their efficient UV- scattering and absorbing abilities while being less opaque than their bulk counterparts, providing better aesthetic appeal without compromising protection.[25] Silver and gold nanoparticles are incorporated for their **antibacterial**, **anti-inflammatory**, and **anti-aging** properties.[26,27]

Despite regulatory and safety concerns, the controlled design and surface modification of inorganic NPs have enabled their safe and targeted application in cosmeceuticals. Their physicochemical tunability allows the formulation of **multifunctional and long-lasting** cosmetic products that outperform conventional formulations in stability, performance, and skin compatibility.[28]

**Advantages of Inorganic Nanoparticles in Cosmetic Formulations**

1. **Effective UV Protection**: $TiO_2$ and ZnO NPs provide broad-spectrum UV protection with better transparency and stability.[29]
2. **Antimicrobial Activity**: Silver (AgNPs) and zinc oxide NPs exhibit strong antimicrobial effects, useful in acne treatment and deodorants.[30]
3. **Enhanced Skin Penetration**: Their nanosize facilitates better skin deposition of active ingredients without irritation.[31]
4. **Improved Stability**: Inorganic NPs are more photostable and resistant to oxidation than organic compounds, prolonging product shelf life.[32]
5. **Aesthetic Appeal**: Nano-sized particles are transparent on the skin, avoiding the white-cast effect seen with traditional UV filters.[25]
6. **Controlled Release and Targeting**: Modified surfaces enable controlled release and targeted delivery of actives for anti-aging and skin-brightening effects.[33]

**Efficacy and safety profiles**

Nanoparticle-based delivery systems have emerged as promising therapeutic strategies for atopic dermatitis (AD), offering enhanced targeting, prolonged drug retention in the skin, and reduced systemic side effects. Lipid-based carriers such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes are particularly effective due to their biocompatibility and occlusive properties, which improve skin hydration, restore the barrier function, and provide controlled drug release. Lipid nanocarriers, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes, are widely used due to their physiological compatibility and ability to enhance dermal delivery. These carriers form occlusive films that reduce transepidermal water loss (TEWL), improve skin hydration, and restore the stratum corneum barrier. Studies have shown that tacrolimus-loaded NLCs (T-

MNLCs) significantly enhance drug retention in inflamed skin and demonstrate superior therapeutic efficacy with reduced irritation compared to commercial formulations.[34] Similarly, betamethasone-loaded NLCs (BD-NLCs) showed enhanced local drug accumulation and controlled release without causing systemic side effects in animal models.[35]Liposomes have also been used to deliver corticosteroids, such as triamcinolone acetonide, resulting in higher drug retention in the epidermis and dermis than conventional creams. Polymeric nanoparticles—often based on chitosan or PLGA, sometimes decorated with hyaluronic acid (HA)—provide versatile platforms for improved stability, sustained drug release, and enhanced skin targeting. Hyaluronic acid-decorated tacrolimus-loaded chitosan nanoparticles (HA-TCS-CS-NPs) demonstrated sustained release, efficient skin retention, and superior anti-dermatitis efficacy with restored skin integrity in lesion models.[36] Chitosan nanoparticles co-loaded with hydrocortisone and the antioxidant hydroxytyrosol (HC-HT-CSNPs) demonstrated excellent safety in both animal and human studies: no irritation, stable formulation over one year, normal TEWL and erythema after 28- day application on healthy skin, and no systemic toxicity based on biochemical and hormonal parameters.[37] These findings underscore the dual utility of polymeric nanoparticles in improving therapeutic delivery while maintaining robust safety.

Inorganic nanoparticles, such as mesoporous silica nanoparticles (MSNs), offer unique advantages in terms of structural tunability, high surface area, and ability to solubilize poorly water-soluble drugs. Functionalized MSNs loaded with tacrolimus showed a seven-fold increase in solubility, sustained drug release, and deeper skin penetration compared to conventional creams. These particles effectively delivered therapeutic agents into lesional skin while maintaining low systemic exposure. However, the safety of inorganic carriers must be carefully assessed, as long-term accumulation and immunogenicity are concerns. Studies suggest that functionalization of MSNs (e.g., with phosphonate groups) can mitigate immune activation and enhance biocompatibility, especially in disrupted skin barriers, though comprehensive toxicity studies remain necessary.[38]

Phytochemical nanocarriers leverage natural bioactives for their antioxidant, anti-inflammatory, and antimicrobial properties, but face unique formulation challenges. While specific AD-oriented phytochemical nanoparticle studies are fewer, general concerns include particle aggregation, inconsistent biodegradation, and manufacturing scalability. Chitosan-based systems have been used to deliver natural actives: for example, the delivery of eugenol via Eudragit® nanocapsules reduced ear swelling and inflammation in murine AD models without cytotoxicity.[39] Chitosan itself possesses antimicrobial and immunomodulatory properties—such as reduction of S. aureus colonization and modulation of inflammatory responses—that can provide therapeutic benefit in AD when engineered appropriately.[40] Though promising, phytochemical carriers require further detailed studies to ensure controlled release, stability, biodegradability, and safety in both intact and compromised skin. Across all categories, nanoparticle efficacy in AD often stems from improved retention and penetration through the disrupted skin barrier, while their safety profiles remain favorable. Lipid and polymeric carriers localize drugs effectively in both intact and lesional skin with minimal systemic absorption, as demonstrated in multiple animal and human studies. Inorganic MSNs, when functionalized, also deliver controlled and deep retention with minimal immune reactivity. However, disrupted skin may allow deeper penetration of nanoparticles—raising potential systemic exposure risks for poorly biodegradable materials—highlighting the importance of using biodegradable, biocompatible polymers. Meanwhile, phytochemical systems hold theoretical advantages but require further validation in disrupted skin contexts.

Nanocarrier-based drug delivery systems offer a compelling strategy for enhancing both the efficacy and safety of topical treatments for atopic dermatitis. Their ability to improve drug retention, enable site-specific delivery, and provide controlled, sustained release ensures more consistent therapeutic outcomes, reduced flare-ups, and improved skin barrier restoration. Critically, these systems address longstanding challenges in AD management by minimizing systemic drug absorption, thereby significantly lowering the risk of adverse effects—particularly with potent agents like corticosteroids and immunosuppressants. Among the various platforms, lipid and polymeric nanocarriers emerge as the most effective and biocompatible options, demonstrating excellent tolerability in both intact and lesional skin, even with long-term use. In contrast, inorganic and phytochemical nanocarriers, while showing promise in terms of antioxidant and anti-inflammatory activity, still require more comprehensive safety evaluations, especially under conditions of barrier disruption. Overall, the balance of enhanced localized efficacy with a strong safety profile positions nanocarrier-based formulations as a next-generation therapeutic solution in AD care, with the potential to improve patient adherence, reduce systemic burden, and elevate the standard of treatment.

**Innovative Methods for the Treatment of Atopic Dermatitis**

Innovative delivery strategies for atopic dermatitis (AD) aim to overcome the limitations of conventional topical formulations by enhancing drug penetration, prolonging therapeutic action, and repairing the impaired skin barrier. One promising approach is functionalized textile-based therapy, where medical garments made from materials such as cotton or silk are impregnated or coated with active agents like anti-inflammatory drugs, ceramides, or antimicrobials. These textiles maintain constant contact with the skin, provide occlusion and hydration, and act as a physical barrier to reduce scratching. Examples include silver nanoparticle-coated fabrics that reduce Staphylococcus aureus colonization, ceramide-coated garments for replenishing the lipid barrier.[41], and microencapsulated fabrics that gradually release moisturizers or vitamins during wear.

Another emerging method is the use of hydrogel-based delivery systems, which are three- dimensional hydrophilic polymer networks capable of retaining large amounts of water. These formulations soothe inflamed skin, reduce dryness, and enable uniform drug distribution. Hydrogels can be loaded with corticosteroids, herbal extracts, or antimicrobial agents.[42] Advanced hydrogel systems include thermo-responsive hydrogels that gel at skin temperature[43], nanocomposite hydrogels incorporating silver nanoparticles for antimicrobial activity[44], and hydrogel patches for sustained drug release directly to affected lesions.[45]

Stimuli-responsive drug delivery systems provide a smart and targeted approach by releasing drugs in response to specific skin environmental changes. pH-responsive carriers target the slightly alkaline pH of atopic skin.[46], enzyme-responsive systems are activated by elevated protease activity in inflamed lesions.[47], temperature-sensitive carriers increase drug release during flare-ups.[48], and light-responsive systems use photothermal triggers to enhance skin penetration.[49] These systems reduce off-target effects and ensure drug release occurs only when needed.

Nanotechnology-enabled carriers offer further improvements in stability, targeting, and controlled drug release. Liposomes and niosomes can deliver both hydrophilic and lipophilic drugs.[50], while solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) assist in restoring the lipid barrier and providing sustained release.[51] Polymeric nanoparticles can offer prolonged anti- inflammatory action.[52], and nanoemulsions enhance the solubility and absorption of poorly water- soluble drugs.[53]

Alongside drug delivery, barrier-repair formulations are critical in AD therapy. Ceramide-loaded nanocarriers mimic the lipid arrangement of the stratum corneum, improving barrier integrity.[54] Phospholipid vesicles assist in reorganizing lipid lamellae, while natural oil-based formulations—such as those containing jojoba, sunflower, or coconut oil—supply essential fatty acids that restore skin hydration and reduce inflammation.[55] Emerging adjunctive methods include probiotic-infused dressings to rebalance the skin microbiota and reduce pathogenic bacterial growth, gene delivery approaches for correcting filaggrin mutations.[56], and personalized 3D-printed hydrogel patches for lesion-specific treatment. Electrospun nanofiber mats also provide breathable, flexible, and controlled-release delivery platforms suitable for long-term application.

**Future Perspectives**

One possible approach to improving the treatment of atopic dermatitis (AD) is through the use of nanoparticle-based therapies. Even though preclinical research has shown a great deal of promise, a few crucial advancements are needed to enable successful clinical translation.

One significant direction involves the development of stimuli-responsive or "smart" nanoparticles that release therapeutic agents in response to specific environmental triggers such as low pH, elevated reactive oxygen species (ROS), or disease-related enzymes present in eczematous skin.[57,58] These systems enable precise, on-demand drug delivery to inflamed areas, potentially enhancing therapeutic efficacy while reducing systemic exposure and adverse effects.

Personalized nano medicine represents another important future avenue. Advances in genomics, proteomics, and microbiome profiling have laid the groundwork for individualized treatment approaches. Nanoparticle formulations could be tailored based on a patient's genetic background, immune phenotype, and skin microbiota, thereby improving treatment specificity and minimizing variability in response.[59,60]

In addition, multifunctional nanoparticles capable of co-delivering anti-inflammatory, antimicrobial, and antioxidant agents, alongside skin barrier-restoring compounds such as ceramides, may offer comprehensive disease control. Such platforms could address multiple pathophysiological factors of AD simultaneously, reducing the need for polypharmacy and improving patient compliance.[61]

Another area of development lies in enhancing barrier repair. Nanoparticles encapsulating ceramide analogs, fatty acids, or growth factors could support stratum corneum regeneration, mitigate transepidermal water loss, and interrupt the itch–scratch cycle that exacerbates inflammation.[62]

Nanoparticles may also enhance cutaneous and transdermal drug penetration when combined with cutting-edge physical delivery technologies like microneedle arrays, iontophoresis, and ultrasound (sonophoresis), especially in persistent AD lesions marked by neurodermitis and thicker epidermis.[63,64]

Despite the progress, safety and tolerability remain central to future clinical adoption. Long-term toxicological studies, including immunogenicity and bioaccumulation assessments, are crucial for chronic-use formulations. Understanding nanoparticle–skin and nanoparticle–immune system interactions will be essential for evaluating their safety profile. [65]

Finally, broader implementation will require clear regulatory guidelines and scalable, cost-effective manufacturing strategies. Standardized protocols for quality control, biocompatibility assessment, and product stability must be established to facilitate approval processes and commercial production.[66]

In conclusion, nanoparticles offer significant potential to redefine AD therapy by enabling targeted, multifunctional, and patient-specific treatment modalities. Continued interdisciplinary research, supported by clinical trials and regulatory engagement, will be critical in translating these innovations from the laboratory into clinical practice.

## CONCLUSION

Atopic dermatitis (AD) is a chronic inflammatory skin disorder associated with significant patient burden due to persistent pruritus, relapsing flares, and impaired skin barrier function. Conventional topical therapies, such as corticosteroids and calcineurin inhibitors, though effective, often result in limited long-term adherence and adverse effects with prolonged use.[67,68] Nanoparticle-based drug delivery systems have emerged as a promising alternative, offering enhanced skin penetration, targeted delivery, sustained drug release, and reduced systemic toxicity.[69,70]

Various nanocarriers—including liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, and metallic systems—have demonstrated potential in delivering anti-inflammatory, antimicrobial, and immunomodulatory agents effectively across the stratum corneum.[71,72] Furthermore, smart nanomaterials responsive to pH, enzymes, or oxidative stress offer opportunities for site-specific and on-demand drug release.[73] These advances pave the way for more precise and patient-tailored therapies in AD.

Despite promising preclinical outcomes, the clinical translation of nanotechnology in dermatology remains limited. To harness its full therapeutic potential, several key research gaps must be addressed.

### Research Gaps

1. Limited Clinical Translation Most studies on nanoparticle formulations for AD remain at the in vitro or animal model stage. Only a few have progressed to early-phase human clinical trials, highlighting the need for robust, controlled clinical evaluations to establish efficacy, safety, and optimal dosing in real-world AD populations.[74,75]
2. Interindividual and Disease-State Variability The heterogeneity of skin barrier function in AD patients—affected by disease stage, anatomical location, and age—can alter nanoparticle penetration and performance. More research is needed to understand how skin condition impacts nanoparticle delivery efficiency [76].
3. Long-Term Safety and Toxicity Concerns Although many nanoparticle systems have demonstrated biocompatibility in short-term studies, the chronic use required in AD therapy raises questions regarding long-term toxicity, immune responses, and potential systemic absorption—especially for metallic and non- biodegradable nanoparticles.[77]
4. Regulatory and Manufacturing Barriers Standardized guidelines specific to nanoformulations for dermatological use are lacking. In addition, challenges in cost-effective large-scale manufacturing, reproducibility, and quality control continue to hinder commercialization and regulatory approval.[78]
5. Lack of Patient-Centered Evaluation Few studies have assessed patient satisfaction, cosmetic acceptability, and adherence to nanoparticle-based formulations. These factors are essential in chronic conditions like AD, where treatment adherence significantly influences outcomes.[79]

**Closing Remarks**

Nanoparticle-based delivery systems represent a promising frontier in the treatment of atopic dermatitis, offering novel strategies to overcome the limitations of conventional therapies. Addressing the above research gaps through interdisciplinary collaboration and translational research will be key to advancing nanoparticle technologies from bench to bedside.

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