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Review Paper

Nanotechnology-Driven Topical Drug Delivery Systems: Advances, Challenges, and Clinical Perspectives

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ABSTRACT

Topical drug delivery is a non-invasive and patient-friendly approach for local and systemic therapy; however, its effectiveness is limited by the strong barrier function of the skin, particularly the stratum corneum. Conventional formulations such as creams, gels, and ointments often show inadequate penetration, low drug retention, instability of active ingredients, and the need for frequent application. Nanotechnology has emerged as a promising strategy to overcome these limitations through the development of nanoscale delivery systems with enhanced physicochemical and biological properties. Nanocarriers including liposomes, niosomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, polymeric nanoparticles, and metallic nanoparticles improve drug solubility, protect labile molecules from degradation, and enable controlled and sustained drug release.Due to their small size and modifiable surface characteristics, nanosystems enhance drug permeation via transcellular, intercellular, and follicular pathways while minimizing systemic exposure and adverse effects. This review outlines the structural features of the skin barrier, challenges associated with conventional topical therapy, and the role of nanotechnology in modulating drug–skin interactions. Various nanocarrier systems, mechanisms of skin penetration, physicochemical characterization, stability assessment, and evaluation methods are discussed. Therapeutic applications in psoriasis, acne, fungal infections, inflammatory disorders, wound healing, and skin cancers are highlighted. Safety aspects, including irritation, cytotoxicity, systemic absorption, and long-term toxicity, are also addressed. Overall, nanotechnology-driven topical systems represent a rapidly advancing platform with significant potential to improve dermatological therapy and clinical outcomes.

INTRODUCTION

Topical drug delivery has gained considerable attention as a non-invasive and patient-friendly

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route of administration for both local and systemic therapy. The skin, being the largest organ of the human body, offers a large surface area for drug application; however, its highly efficient barrier function limits drug penetration. The outermost layer of the skin, the stratum corneum, consists of keratin-filled corneocytes embedded in a lipid matrix, often described as a "brick-and-mortar" structure[1]. This compact organization severely restricts the permeation of most therapeutic molecules, particularly hydrophilic drugs and high-molecular-weight compounds. Conventional topical formulations such as creams, ointments, and gels often suffer from poor penetration, low drug retention at the target site, instability of active ingredients, and frequent dosing requirements. These limitations have driven the exploration of advanced delivery approaches[2]. Nanotechnology has emerged as a transformative tool in topical drug delivery by enabling the design of nanosystems that can effectively interact with the skin barrier. Nanocarriers, typically in the size range of 1–1000 nm, possess unique physicochemical properties such as high surface area, tunable surface charge, and the ability to encapsulate both hydrophilic and lipophilic drugs[3]. These characteristics allow nanosystems to enhance drug solubility, improve penetration into deeper skin layers, and provide controlled or sustained drug release. As a result, nanotechnology-driven topical systems are being actively investigated for the treatment of dermatological disorders including psoriasis, acne, fungal infections, inflammatory conditions, and skin cancers. This review discusses the types, mechanisms, characterization, therapeutic applications, and future prospects of nanotechnology-based topical drug delivery systems[4].

2. Skin Barrier and Challenges in Conventional Topical Delivery

The skin is a complex, multilayered organ composed of the epidermis, dermis, and hypodermis, each contributing to its protective function. The epidermis, particularly the stratum corneum, acts as the primary barrier to drug permeation. This layer is composed of dead keratinized cells surrounded by a lipid matrix containing ceramides, cholesterol, and fatty acids. The highly ordered lipid domains create a formidable barrier that restricts the diffusion of most molecules. Only small, moderately lipophilic drugs with suitable partition coefficients can effectively cross this barrier, which significantly narrows the range of drugs suitable for conventional topical therapy. Traditional topical formulations rely primarily on passive diffusion for drug penetration, which often leads to suboptimal therapeutic outcomes. Drugs may remain on the skin surface, undergo degradation, or be removed by washing or sweating. Furthermore, frequent application may cause skin irritation and reduce patient compliance. Variability in skin hydration, thickness, and integrity among individuals also affects drug absorption. These challenges underscore the need for advanced delivery systems capable of overcoming the limitations of the stratum corneum and providing targeted and sustained drug action[5].

3. Role of Nanotechnology in Topical Drug Delivery

Nanotechnology offers innovative solutions to enhance the efficiency of topical drug delivery by modifying drug–skin interactions at the nanoscale. Nanosystems can improve drug solubility, protect labile drugs from degradation, and modulate drug release profiles. Due to their small size, nanocarriers can closely interact with the stratum corneum, enhancing drug partitioning into the skin. Some nanosystems disrupt the lipid organization of the stratum corneum, while others

exploit appendageal pathways such as hair follicles and sweat glands to facilitate drug entry[6-8]. Another important advantage of nanosystems is their ability to provide targeted delivery within different skin layers. For instance, certain nanocarriers can localize drugs within the epidermis or dermis, minimizing systemic absorption and reducing side effects. Surface modification of nanoparticles with ligands or polymers further enhances adhesion, retention, and penetration. Controlled and sustained drug release from nanocarriers maintains therapeutic drug levels at the site of action, reducing dosing frequency. Thus, nanotechnology significantly improves the therapeutic performance of topical formulations[9,10].

4. Types of Nanotechnology-Driven Topical Systems

4.1 Lipid-Based Nanocarriers

Lipid-based nanocarriers are among the most extensively studied nanosystems for topical drug delivery due to their biocompatibility and structural similarity to skin lipids. Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic drugs. They enhance drug penetration by fusing with skin lipids and increasing hydration of the stratum corneum. Niosomes, formed from nonionic surfactants, offer improved stability and cost-effectiveness while providing similar benefits[11,12]. Solid Lipid Nanoparticles (SLN) consist of solid lipids stabilized by surfactants and provide controlled drug release and occlusive effects, enhancing skin hydration and drug penetration. However, their drug loading capacity may be limited due to lipid crystallization. Nanostructured Lipid Carriers (NLC) overcome this limitation by combining solid and liquid lipids, creating imperfections in the lipid matrix that allow higher drug loading and improved stability. These lipid nanosystems are widely used for anti-inflammatory, antifungal, and anticancer drugs[13,14].

4.2 Polymeric Nanoparticles

Polymeric nanoparticles are prepared using biodegradable polymers and offer precise control over drug release kinetics. PLGA nanoparticles are widely used due to their safety and controlled degradation into lactic and glycolic acids. These systems provide sustained drug release and protection of sensitive drugs. Chitosan nanoparticles, derived from natural polysaccharides, exhibit bioadhesive properties and enhance drug retention on the skin surface while facilitating penetration through electrostatic interactions with negatively charged skin components[15,16].

4.3 Nanoemulsions and Microemulsions

Nanoemulsions and microemulsions are colloidal dispersions of oil and water stabilized by surfactants and co-surfactants. Their small droplet size and high surface area enhance the solubilization of poorly soluble drugs and promote skin permeation. These systems can disrupt stratum corneum lipids and improve drug partitioning into the skin. They are particularly useful for lipophilic drugs and are commonly used in antifungal and anti-inflammatory formulations[17-19].

4.4 Metallic Nanoparticles

Metallic nanoparticles possess unique optical and antimicrobial properties. Silver nanoparticles are extensively used in wound healing due to their strong antibacterial activity. Gold nanoparticles have anti-inflammatory and photothermal properties useful in dermatological therapy. Zinc

oxide nanoparticles are widely used in sunscreens for UV protection and skin care products[20-22].

Table-1: Nanocarriers for topical drug delivery systems

Nanocarrier Type	Composition	Structure Nature	Examples of Drugs Delivered
Liposomes	Phospholipids + cholesterol	Spherical vesicles with bilayer	Diclofenac, Corticosteroids, Tretinoin
Niosomes	Non-ionic surfactants + cholesterol	Vesicular system	Ketoconazole, Acyclovir
Solid Lipid Nanoparticles (SLN)	Solid lipids	Solid lipid core	Ibuprofen, Clotrimazole
Nanostructured Lipid Carriers (NLC)	Solid + liquid lipids	Imperfect lipid matrix	Tacrolimus, Curcumin
Nanoemulsions	Oil + water + surfactant	Droplet size 20–200 nm	Luliconazole, NSAIDs
Polymeric Nanoparticles	Biodegradable polymers (PLGA, chitosan)	Matrix or reservoir type	5-Fluorouracil, Antifungals
Nanogels	Crosslinked polymer networks	Hydrogel nanoparticles	Lidocaine, Diclofenac
Dendrimers	Branched synthetic polymers	Tree-like structure	Antimicrobials, Anti-inflammatory drugs
Cubosomes	Lipid cubic phase (glyceryl monooleate)	Bicontinuous cubic structure	Indomethacin
Transfersomes	Phospholipids + edge activator	Ultra-deformable vesicles	Insulin, Diclofenac
Ethosomes	Phospholipids + high ethanol	Soft vesicles	Minoxidil, Acyclovir
Metal Nanoparticles	Gold, silver, zinc oxide	Smetallic particles	Silver (wound healing)

5. Mechanisms of Skin Penetration by Nanocarriers

Nanocarrier-mediated drug transport across the skin occurs through multiple complementary pathways, each influenced by carrier size, surface charge, lipid composition, deformability, and interaction with skin components. Unlike conventional formulations that rely mainly on passive diffusion of free drug molecules, nanosystems actively modify the microenvironment of the stratum corneum and exploit structural features of the skin to enhance penetration.

5.1. Transcellular (Intracellular) Pathway

The transcellular route involves transport through corneocytes, the keratin-filled cells of the stratum corneum. Although corneocytes are relatively hydrated compared to intercellular lipids, they are surrounded by a tough protein envelope and keratin network that restricts direct drug passage. Nanocarriers enhance transport through this pathway primarily by facilitating drug partitioning into the aqueous domains of corneocytes. Hydrophilic drugs encapsulated within vesicular carriers such as liposomes and niosomes can be delivered into corneocytes following fusion or adsorption of the vesicle membrane with the corneocyte surface. Additionally, deformable

nanocarriers (e.g., transfersomes) can squeeze through intracellular spaces under the influence of the skin's hydration gradient. These systems undergo reversible shape changes, allowing them to cross barriers smaller than their own diameter. The presence of edge activators (surfactants) in such systems destabilizes lipid packing and increases membrane elasticity, improving transcellular passage[23,24].

5.2. Intercellular (Paracellular) Lipid Pathway

The intercellular route is considered the primary pathway for penetration of most lipophilic drugs. It involves diffusion through the continuous lipid matrix between corneocytes, composed mainly of ceramides, cholesterol, and free fatty acids arranged in lamellar structures. This lipid network is highly ordered and presents the major resistance to permeation. Nanocarriers enhance intercellular transport by interacting with and altering the organization of these lipids. Lipid-based nanosystems such as SLNs and NLCs can merge with the skin's lipid bilayers, causing temporary lipid fluidization and increasing membrane permeability. Surfactants present in nanoemulsions or vesicular systems can extract lipids or disrupt hydrogen bonding within the lipid domains, reducing barrier rigidity. The increased fluidity creates transient pathways that facilitate deeper drug diffusion[24,25].

5.3. Follicular (Appendageal) Pathway

Hair follicles and associated sebaceous glands represent an important shunt pathway for nanoparticle penetration. Although they occupy only a small fraction of the skin surface, follicles can act as long-term reservoirs for nanosystems. Particles in the size range of 200–600 nm show preferential accumulation in hair follicles due to mechanical movement of hair shafts and sebum flow. This pathway is particularly useful for targeted therapy of follicle-associated conditions such as acne, alopecia, and folliculitis. Nanocarriers deposited in follicles gradually release drug into surrounding tissues, prolonging therapeutic action. The follicular route also bypasses the densely packed stratum corneum lipids, making it a favorable pathway for both hydrophilic and hydrophobic drugs[23-27].

5.4. Lipid Fluidization Mechanism

Many nanocarriers enhance penetration by modulating the physical state of stratum corneum lipids. Surfactants, phospholipids, and fatty acids in nanosystems insert into lipid bilayers, disturbing their crystalline arrangement. This transition from a highly ordered gel phase to a more fluid liquid-crystalline phase reduces diffusion resistance. Ethanol in ethosomes and certain nanoemulsions further enhances this effect by extracting lipids and increasing membrane flexibility[23-27].

5.5. Occlusion and Hydration Effect

Lipid nanoparticles, especially SLNs and NLCs, form an occlusive film on the skin surface after application. This film reduces transepidermal water loss (TEWL), leading to increased hydration of the stratum corneum. Hydrated corneocytes swell, expanding intercellular spaces and loosening lipid packing. The resulting increase in skin permeability enhances drug diffusion. This mechanism is particularly important for improving the delivery of hydrophilic drugs[23-27].

5.6. Nanocarrier–Skin Interaction and Adhesion

Surface charge plays a crucial role in nanoparticle adhesion to the skin. Positively charged nanoparticles interact electrostatically with negatively charged skin components, increasing

residence time. Bioadhesive polymers such as chitosan further promote intimate contact with the skin surface, enhancing drug penetration[23-27].

6. Characterization of Nano-Topical Systems

Comprehensive physicochemical characterization of nanocarriers is essential to ensure formulation performance, reproducibility, stability, and therapeutic efficacy. Because nanosystems interact with biological barriers at the molecular level, small variations in size, surface charge, morphology, and drug loading can significantly alter skin penetration, release behavior, and safety profile. Therefore, characterization is not merely analytical but predictive of in vivo performance[28-32].

6.1. Particle Size, Size Distribution and Polydispersity Index (PDI)

Particle size is one of the most critical parameters governing topical nanocarrier behavior. Nanosystems in the range of 10–300 nm typically show improved skin interaction and follicular targeting. Smaller particles provide a larger surface area, enhancing drug release and interaction with the stratum corneum lipids. However, excessively small particles may increase systemic absorption risk, while larger particles may remain on the skin surface. Size distribution is expressed through the polydispersity index (PDI), which reflects formulation homogeneity. A PDI value below 0.3 generally indicates a uniform population, while higher values suggest aggregation or instability. Dynamic Light Scattering (DLS) is widely used for determining hydrodynamic diameter and PDI. Consistent size distribution ensures predictable penetration and drug release. [28-32]

6.2. Zeta Potential and Surface Charge

Zeta potential indicates the electrical potential at the particle surface and reflects colloidal stability. High absolute zeta potential values ($\geq \pm 30$ mV) prevent aggregation due to electrostatic repulsion. In topical systems, surface charge also influences interaction with the negatively charged skin surface. Positively charged nanoparticles exhibit enhanced adhesion to skin through electrostatic attraction, increasing residence time and penetration. Conversely, neutral or slightly negative systems may show reduced irritation and better compatibility. Measurement is performed using electrophoretic light scattering, and it provides insight into both stability and biological interaction. [28-32]

6.3. Morphology and Structural Analysis

Particle shape and surface morphology significantly affect skin penetration and drug release. Spherical nanoparticles exhibit uniform distribution, while irregular shapes may influence aggregation behavior. Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) provide high-resolution images to confirm particle size, shape, surface smoothness, and structural integrity. Cryo-TEM is particularly useful for vesicular systems such as liposomes and niosomes, allowing visualization of bilayer structures. Morphological confirmation ensures that the intended nanostructure is successfully formed during formulation. [28-32]

6.4. Drug Loading and Encapsulation Efficiency

Encapsulation efficiency (EE%) determines how much drug is successfully incorporated into the carrier. High EE ensures sustained drug release and reduces the need for high surfactant concentrations. Drug loading capacity affects dose feasibility in topical application. These parameters are commonly measured using ultracentrifugation,

dialysis, or filtration followed by HPLC or UV analysis. [28-32]

6.5. In Vitro Drug Release Studies

In vitro release testing provides information on release kinetics and mechanism (diffusion-controlled, erosion-controlled, or biphasic). Franz diffusion cells with synthetic membranes or dialysis bags are commonly used. Release data are fitted into kinetic models (zero-order, first-order, Higuchi, Korsmeyer–Peppas) to understand the release mechanism. Controlled release from nanosystems prevents burst effects and maintains therapeutic drug levels over prolonged periods, which is essential for chronic dermatological conditions. [28-32]

6.6. Ex Vivo Skin Permeation and Retention Studies

Ex vivo permeation studies using excised animal or human skin provide realistic information on penetration behavior. Franz diffusion cells are employed to measure permeation flux, permeability coefficient, and drug retention in skin layers. Tape stripping techniques quantify drug distribution in the stratum corneum. These studies demonstrate whether nanosystems enhance localized drug delivery while minimizing systemic absorption, which is critical for safety. [28-32]

6.7. Rheological and Texture Analysis (for Final Dosage Form)

When nanosystems are incorporated into gels or creams, viscosity, spreadability, and texture must be evaluated. Rheological behavior affects application, patient compliance, and residence time on the skin. Non-Newtonian pseudoplastic flow is usually preferred for topical formulations. [28-32]

7. Therapeutic Applications of Nanotechnology-Driven Topical Systems

Nanotechnology-based topical delivery systems have demonstrated remarkable potential in managing a variety of dermatological disorders by improving drug localization, enhancing penetration, prolonging retention, and minimizing systemic exposure.

7.1. Psoriasis: Psoriasis is characterized by keratinocyte hyperproliferation and chronic inflammation. Conventional therapies often suffer from poor penetration and irritation. Liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsions enhance delivery of corticosteroids, methotrexate, tacrolimus, and natural anti-inflammatory agents into deeper epidermal layers. Lipid nanoparticles also provide an occlusive effect, improving skin hydration and drug absorption while reducing systemic toxicity[38,39].

7.2. Acne Vulgaris: Nanoemulsions, liposomes, and polymeric nanoparticles improve follicular targeting of antibiotics (clindamycin), retinoids, and benzoyl peroxide. These systems enhance drug accumulation in sebaceous glands, reduce irritation, and provide sustained release, leading to better therapeutic outcomes[40,41].

7.3. Fungal Infections: Poor aqueous solubility of antifungal drugs limits conventional therapy. Nanoemulsions, SLNs, and NLCs enhance penetration into infected skin and nail beds, improving bioavailability and therapeutic efficacy[42,43].

7.4. Inflammatory Skin Disorders: Nanocarriers enable controlled delivery of NSAIDs, corticosteroids, and phytoconstituents such as curcumin, reducing systemic side effects and maintaining therapeutic levels locally[44-47].

7.5. Wound Healing: Silver nanoparticles and lipid-based nanosystems exhibit antimicrobial, anti-inflammatory, and collagen-promoting effects, accelerating wound repair and tissue regeneration[48-50].

7.6. Skin Cancer: Gold nanoparticles and lipid nanocarriers facilitate targeted delivery of anticancer drugs and photothermal therapy, improving tumor localization while minimizing damage to healthy tissues[51-54].

8. Stability Studies

Stability assessment is a critical component in the development of nanotechnology-based topical formulations because nanosystems are thermodynamically unstable and prone to physicochemical changes over time. Unlike conventional formulations, nanosystems possess high surface free energy due to their extremely small particle size, which increases the tendency for aggregation, drug leakage, or structural rearrangement. Therefore, stability testing ensures that the nanocarrier maintains its integrity, drug retention capacity, and therapeutic performance throughout its shelf life[33-37].

8.1. Physical Stability

Physical stability focuses on maintaining the nanocarrier's structural properties. Particle size and polydispersity index (PDI) are monitored regularly because an increase in size indicates aggregation or fusion of particles. Aggregation may occur due to insufficient electrostatic or steric stabilization, leading to sedimentation or creaming in dispersions. Changes in zeta potential often precede aggregation; a decrease in absolute zeta potential reduces repulsive forces, allowing particles to come closer and stick together. In lipid-based systems such as SLNs and NLCs, polymorphic transitions of lipids during storage can cause particle growth and drug expulsion. Vesicular systems like liposomes may undergo bilayer fusion, leading to leakage of encapsulated drug. In nanoemulsions, instability may appear as flocculation, coalescence, or phase separation[33-37].

8.2. Chemical Stability

Chemical stability refers to the preservation of drug integrity and excipient compatibility. Drugs encapsulated in nanosystems may degrade due to oxidation, hydrolysis, or photodegradation. Lipid components are particularly susceptible to oxidative rancidity, which may compromise formulation quality. Drug content is periodically analyzed using HPLC or UV spectroscopy to detect degradation. pH monitoring is also important because changes in pH can accelerate drug hydrolysis or destabilize vesicular membranes. Buffer systems and antioxidants are often incorporated to improve chemical stability[33-37].

8.3. Drug Retention and Leakage

One of the major stability concerns in nanosystems is premature drug leakage. Over time, structural rearrangements in lipid matrices or polymeric carriers can reduce encapsulation efficiency. This leads to burst release, loss of controlled release properties, and reduced therapeutic efficacy. Drug leakage is assessed by measuring encapsulation efficiency at different storage intervals[33-37].

8.4. Rheological and Organoleptic Stability

When nanosystems are incorporated into semisolid dosage forms such as gels or creams, changes in viscosity, spreadability, and texture must be evaluated. Variations in rheology may indicate phase separation or polymer degradation. Organoleptic properties such as color, odor, and

appearance are also monitored, as these influence patient acceptability[33-37].

8.5. Storage Conditions According to ICH Guidelines

Stability studies are conducted under controlled temperature and humidity conditions to simulate real storage environments. Long-term studies typically involve storage at 25°C/60% RH, while accelerated conditions involve 40°C/75% RH. Intermediate conditions may be used if significant changes occur under accelerated testing. These studies follow the principles of International Council for Harmonisation (ICH) guidelines, which help predict shelf life and establish storage recommendations[33-37].

8.6. Accelerated Stability Studies

Accelerated testing exposes formulations to stress conditions to predict long-term stability in a shorter time. Elevated temperatures increase kinetic energy, accelerating processes such as aggregation, lipid crystallization, and drug degradation. Data from accelerated studies are used to estimate degradation kinetics and predict shelf life using Arrhenius equations. This approach is crucial for determining commercialization feasibility[33-37].

CONCLUSION

Nanotechnology has profoundly transformed topical drug delivery by overcoming the intrinsic barrier properties of the skin and enabling efficient drug transport to targeted sites. Nano-carriers such as liposomes, niosomes, solid lipid nanoparticles, nanoemulsions, nanostructured lipid carriers, dendrimers, and polymeric nanoparticles enhance drug penetration through transcellular, intercellular, and follicular pathways while improving drug solubility, stability, and controlled release behavior. These systems protect labile drugs from degradation, reduce dosing frequency, and minimize systemic side effects, thereby improving therapeutic efficacy and patient compliance. Furthermore, nanotechnology enables targeted delivery to specific skin layers, making it highly valuable in the management of dermatological disorders, inflammatory conditions, fungal infections, wound healing, and even localized cancer therapy.Despite these advantages, challenges remain regarding long-term safety, potential skin irritation, systemic absorption of nanoparticles, large-scale manufacturing, and regulatory standardization. Comprehensive toxicological evaluation, reproducible characterization methods, and alignment with regulatory frameworks are essential for successful clinical translation. Continued interdisciplinary research integrating pharmaceutical sciences, materials engineering, nanotoxicology, and regulatory science will accelerate the development of safe, effective, and commercially viable nano-based topical formulations, positioning nanotechnology as a cornerstone of next-generation dermatological therapy.

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