Targeted Skin Delivery Using Nanotechnology: Emerging Trends in Cosmetic Formulation

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Abstract

The stratum corneum acts as a formidable barrier against the penetration of exogenous substances, limiting the efficacy of conventional cosmetic formulations. Over the past five years, nanotechnology has revolutionized the cosmetic landscape by offering sophisticated delivery systems capable of protecting active ingredients, enhancing skin permeation, and achieving targeted delivery to specific skin layers or appendages. This review provides a comprehensive analysis of the state-of-the-art nanocarriers employed in modern dermocosmetics, including lipid nanoparticles (SLN, NLC), vesicular systems (ethosomes, transfersomes), and emerging platforms such as exosomes and nanocrystals. We critically examine the mechanisms of permeation enhancement, ranging from follicular targeting to occlusion effects. Furthermore, the review addresses the specific applications of these systems in anti-aging, pigmentation control, and acne treatment. Finally, we discuss the pressing regulatory, safety, and ethical challenges associated with nanocosmetics, providing a forward-looking perspective on sustainable "green" nanotechnology and AI-driven formulation design.

Keywords: Nanocosmetics, Dermal Delivery, Lipid Nanoparticles, Stratum Corneum, Targeted Delivery, Anti-aging, Exosomes, Green Nanotechnology.

1. Introduction

1.1 Overview of Cosmetic Formulations and Challenges in Skin Delivery

The global cosmetic sector is experiencing a notable shift from conventional products that primarily enhance surface appearance to advanced formulations known as *dermocosmetics* or *cosmeceuticals*, which are intended to produce measurable biological effects within the skin [1]. The nanotechnology segment within the cosmetic industry alone was estimated to be worth approximately USD 9.23 billion in 2023 and is expected to exceed USD 37 billion by 2032, largely due to increasing consumer demand for high-performance anti-aging and therapeutic skincare solutions [2]. Despite this growth, the clinical effectiveness of many potent cosmetic actives including retinoids, bioactive peptides, antioxidants, and plant-derived extracts remains limited because of their inherent physicochemical instability and inadequate skin penetration.

A major obstacle to successful topical delivery is the protective barrier function of the skin. The stratum corneum (SC), which forms the outermost layer of the epidermis, is biologically designed to restrict the entry of foreign substances while simultaneously reducing transepidermal water loss (TEWL) [3]. As a result, this barrier severely limits the passive diffusion of hydrophilic molecules and compounds with molecular weights exceeding 500 Daltons, a concept commonly referred to as the “500 Dalton rule” [4]. Consequently, many traditional cosmetic formulations fail to deliver active ingredients beyond the skin surface, preventing them from reaching intended targets within the viable epidermis or dermis.

1.2 Importance of Targeted Delivery in Cosmetic Applications

In contemporary cosmetic research, the concept of “delivery” extends well beyond simple permeation through the skin. A dominant trend emerging during 2024–2025 is the emphasis on targeted delivery systems. The primary goal is to localize active ingredients at their specific sites of action while minimizing systemic exposure. For example, depigmenting agents must effectively reach melanocytes located in the basal layer of the epidermis, anti-acne compounds need to concentrate within the pilosebaceous unit, and anti-aging peptides are required to access dermal fibroblasts to exert their effects [5]. Non-selective permeation not only reduces therapeutic efficiency but may also increase the risk of irritation or systemic absorption. In contrast, targeted nanotechnological approaches aim to enhance local bioavailability and improve the overall therapeutic index of cosmetic actives.

1.3 Barriers in Dermal and Transdermal Delivery

The stratum corneum is structurally composed of flattened corneocytes embedded within a lipid-rich extracellular matrix, a configuration widely described as the “brick and mortar” model. Recent investigations conducted during 2024–2025 have further refined this

understanding by identifying *corneoptosis* a specialized form of programmed cell death responsible for transforming granular keratinocytes into corneocytes as a key determinant of the complex and tortuous pathways encountered by permeating substances [3]. The intercellular lipid matrix, primarily consisting of ceramides, cholesterol, and free fatty acids, forms highly ordered lamellar structures that strongly resist the penetration of hydrophilic compounds. Additionally, the "outside-in" hypothesis suggests that disruptions to the skin barrier, such as those observed in aged or xerotic skin, can significantly alter permeation dynamics, underscoring the importance of controlled delivery to prevent irritation from highly potent actives [3,6].

1.4 Role of Nanotechnology in Overcoming Limitations

Nanotechnology provides a powerful strategy to address the challenges associated with poor bioavailability of cosmetic actives. By engineering materials at the nanoscale typically within the range of 1–100 nm, though particles up to 500 nm are often considered in cosmetic applications delivery systems can be designed to encapsulate and transport active ingredients more effectively [7]. These nanocarriers offer several key advantages:

1. **Protection:** They protect chemically unstable actives, such as vitamin C and retinol, from oxidative and enzymatic degradation.
2. **Enhanced Permeation:** Their small size and high surface area promote close interaction with the stratum corneum and facilitate deeper skin penetration.
3. **Controlled Release:** Nanocarriers can function as reservoirs, enabling sustained release of active compounds, thereby minimizing irritation and prolonging therapeutic effects.
4. **Targeting:** Through size optimization or surface modification, nanocarriers can be directed toward specific skin appendages, including hair follicles [8].

1.5 Objectives and Scope of the Review

This review summarizes and critically examines recent developments in cosmetic nanocarrier systems reported between 2020 and 2025. It explores the fundamental principles governing skin permeation, systematically categorizes major nanocarrier platforms including lipid-based, polymeric, inorganic, and emerging systems and evaluates their mechanisms of action. Furthermore, the review addresses safety considerations, regulatory frameworks, and ethical concerns, with particular emphasis on the growing transition toward environmentally sustainable and "green" nanotechnological approaches in cosmetic formulation.

2. Fundamentals of Skin Structure and Delivery Mechanisms

2.1 Structure and Function of Skin Layers Relevant to Delivery

The performance of any dermocosmetic formulation is largely determined by how effectively it interacts with the anatomical structure of the skin. The skin is a highly specialized, multilayered organ whose primary role is protection. For nanocarrier-based systems to achieve targeted delivery, they must successfully traverse three principal layers: the epidermis, dermis, and hypodermis.

The Stratum Corneum (SC): The Primary Barrier

The stratum corneum (SC), which forms the outermost region of the epidermis, constitutes the main rate-limiting barrier for the penetration of topically applied substances. This layer is commonly described using the "brick and mortar" model, wherein 10–20 layers of flattened corneocytes ("bricks") are embedded within a highly ordered intercellular lipid matrix ("mortar") [9].

Corneocytes: These cells are terminally differentiated, anucleated keratinocytes primarily composed of keratin filaments and surrounded by a cross-linked protein envelope. Owing to their hydrophilic nature, corneocytes are largely impermeable to lipophilic compounds.

Lipid Matrix: The intercellular lipid domain consists predominantly of ceramides (approximately 50%), cholesterol (around 25%), and free fatty acids (10–20%), arranged in multilamellar bilayer structures [10]. This lipid organization is essential for maintaining barrier integrity. Recent investigations (2024–2025) have demonstrated that variations in the relative proportions of these lipids influence crystalline packing patterns (orthorhombic versus hexagonal), which in turn directly affect skin permeability [11].

The Viable Epidermis and Dermis

Located beneath the stratum corneum, the viable epidermis contains metabolically active cells, including keratinocytes, melanocytes, and Langerhans cells. Effective delivery to this layer is particularly important for cosmetic products targeting pigmentation disorders or immune-related skin responses. Below the epidermis lies the dermis, a connective tissue matrix rich in collagen and elastin fibers, which serves as the primary target for anti-aging formulations aimed at wrinkle reduction and skin firming. However, achieving dermal delivery while avoiding systemic absorption into the hypodermis and underlying vasculature remains a major challenge, as excessive penetration may lead to regulatory reclassification of cosmetic products as drugs [12].

2.2 Routes of Skin Penetration

Nanocarrier-based systems can access the skin through three main penetration pathways:

1. **Intercellular Route:** This pathway represents the most common route for both small molecules and lipid-based nanocarriers. Transport occurs through the continuous lipid matrix located between corneocytes. Delivery systems such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are specifically

engineered to interact with skin lipids, producing an occlusive effect that enhances skin hydration. This increased hydration disrupts lipid packing within the SC, thereby facilitating deeper penetration [13].

2. **Transcellular Route:** The transcellular pathway involves direct passage through corneocytes. Passive diffusion via this route is generally unfavorable, as permeants must repeatedly transition between the hydrophilic intracellular environment and the surrounding lipophilic lipid matrix. Nevertheless, certain polymeric nanoparticles and highly deformable vesicular systems, such as ethosomes, can promote this route by increasing membrane fluidity and altering corneocyte permeability [14].

3. **Transappendageal (Follicular) Route:** Although previously considered insignificant due to its limited surface area coverage (approximately 0.1%), the follicular route has gained substantial attention in 2023–2024 as an effective target for nanotechnological delivery systems. Hair follicles and associated sebaceous glands function as anatomical invaginations that partially bypass the stratum corneum.

4. **Depot Effect:** Experimental studies have shown that relatively rigid nanoparticles, including silica-based and metal oxide particles, as well as lipid carriers with sizes ranging from 200 to 600 nm, tend to accumulate deep within the follicular duct [15]. This reservoir-like behavior is particularly advantageous for localized treatment of acne, where the sebaceous gland is the primary target, and for conditions such as androgenetic alopecia, which require delivery to the hair bulb.

2.3 Factors Affecting Skin Permeability

Skin permeation is traditionally governed by physicochemical principles, most notably Fick's First Law of Diffusion. However, nanocarrier systems can significantly modify these conventional diffusion dynamics.

The "500 Dalton Rule": According to this rule, molecules with molecular weights greater than 500 Da are generally unable to penetrate the stratum corneum. Nanotechnology overcomes this limitation by encapsulating high-molecular-weight actives, such as hyaluronic acid and collagen, within carriers that promote transport through mechanisms including endocytosis and lipid fusion [16].

Lipophilicity (Log P): Optimal skin penetration typically occurs when the log P value lies between 1 and 3. Nanocarriers can effectively conceal the extreme hydrophilic or lipophilic characteristics of the encapsulated active ingredient, allowing the physicochemical properties of the carrier itself to dominate interactions with the skin surface.

Surface Charge (Zeta Potential): At physiological pH, the skin surface possesses an overall negative charge. As a result, positively charged (cationic) nanoparticles exhibit enhanced

electrostatic interactions with the skin, leading to improved bioadhesion and prolonged residence time when compared with neutral or negatively charged systems [17].

3. Types of Nanocarriers Used in Cosmetic Formulations

Nanocarriers employed in cosmetic formulations are commonly classified based on their material composition such as lipid-based, polymeric, or inorganic systems as well as their physical form, including solid particles or vesicular structures.

3.1 Lipid-Based Nanocarriers

Lipid-based delivery systems represent the most widely commercialized class of nanocarriers in cosmetics due to their excellent biocompatibility, biodegradability, and close resemblance to endogenous skin lipids.

- **Liposomes:**
  As first-generation nanocarriers, liposomes are spherical vesicles composed of one or more phospholipid bilayers. While they are highly effective in enhancing skin hydration and improving sensory properties, conventional liposomes typically exhibit limited penetration and tend to remain on the skin surface.
- **Deformable Vesicles (Transfersomes and Ethosomes):**
  - **Transfersomes** are characterized by the presence of "edge activators," such as surfactants (e.g., sodium cholate), which impart high elasticity to the vesicle membrane. This flexibility enables transfersomes to pass through skin pores that are significantly smaller up to one-tenth of their own diameter thereby facilitating enhanced penetration [18].
  - **Ethosomes** contain relatively high concentrations of ethanol (20–45%), which increases the fluidity of both the vesicular lipid bilayer and the lipids within the stratum corneum, resulting in improved deep skin permeation.
- **Solid Lipid Nanoparticles (SLN):** Solid lipid nanoparticles were developed to address the stability limitations associated with conventional liposomes. SLNs are formulated using lipids that remain solid at room temperature, such as glyceryl behenate and stearic acid. These lipids form a highly ordered crystalline matrix that effectively protects sensitive active ingredients, including retinol and vitamin E, from chemical degradation. One of the principal mechanisms underlying SLN performance is the formation of an occlusive film on the skin surface, which reduces transepidermal water loss (TEWL) and enhances hydration of the stratum corneum [13,19].
- **Nanostructured Lipid Carriers (NLC):** Nanostructured lipid carriers represent the second generation of lipid-based nanocarriers and are produced by blending solid

lipids with liquid lipids or oils, such as almond oil or capric triglycerides. This combination results in a less-ordered crystal lattice, conferring two major advantages over SLNs:

1. Increased Drug Loading: Structural imperfections within the lipid matrix create additional space for accommodating active compounds.

2. Improved Stability: The irregular lattice minimizes the risk of active ingredient expulsion during storage, thereby enhancing formulation stability [20].

3.2 Polymeric Nanocarriers

Polymeric nanocarriers are available as nanospheres, in which the active ingredient is uniformly dispersed throughout a polymeric matrix, or as nanocapsules, where the active is confined within a central core surrounded by a polymer shell. These systems are particularly valued for their structural stability and ability to provide controlled and sustained release.

- **Chitosan Nanoparticles:** Chitosan, a natural polymer derived from chitin, has gained increasing attention between 2022 and 2024 due to its inherent antimicrobial activity and strong mucoadhesive properties. Chitosan nanoparticles are especially suitable for delivering anti-acne agents, as the polymer's positive charge promotes electrostatic interactions with negatively charged bacterial cell membranes as well as the skin surface [21].
- **PLGA (Poly (lactic-co-glycolic acid)):** PLGA is a biodegradable synthetic polymer frequently employed for the prolonged and controlled release of anti-aging peptides in cosmetic formulations.

3.3 Inorganic and Metallic Nanoparticles

Inorganic and metallic nanoparticles are primarily incorporated into cosmetic products for their unique physical and optical properties, although hybrid systems that combine carrier and functional roles are also being explored.

- **Titanium Dioxide (TiO_2) and Zinc Oxide (ZnO):** These materials are extensively used as physical ultraviolet (UV) filters in sunscreen formulations. The use of nanosized particles, typically in the range of 10–50 nm, effectively eliminates the undesirable "white cast" associated with conventional sunscreens while preserving broad-spectrum UV protection. To reduce photocatalytic activity and prevent the generation of free radicals, surface coating with materials such as silica or alumina is essential [22].
- **Gold Nanoparticles (AuNPs):** Gold nanoparticles are commonly incorporated into premium anti-aging products, where they are claimed to improve microcirculation and serve as carriers for antioxidant compounds.

- **Silica Nanoparticles:** Silica-based nanoparticles are frequently utilized to enhance the sensory attributes of cosmetic creams by improving spreadability and imparting a smooth texture. They are also employed in controlled-release systems for fragrances.

3.4 Emerging Nanocarriers (2020–2025 Trends)

- **Exosomes (Extracellular Vesicles):** Exosomes represent one of the most prominent emerging trends in cosmetic nanotechnology during 2024–2025. These naturally occurring nanosized vesicles (30–150 nm) are secreted by cells and contain a complex cargo of proteins, lipids, and nucleic acids. In cosmetic applications, exosomes derived from plant sources, such as *Centella asiatica* and *Rosa damascena*, are increasingly being commercialized for their powerful cell-signaling properties, which promote skin regeneration and collagen synthesis while avoiding the regulatory challenges associated with human-derived materials [23].
- **Nanocrystals:** Nanocrystals are carrier-free nanosystems composed entirely of the active ingredient, stabilized by appropriate surfactants. They are particularly effective in enhancing the saturation solubility of poorly water-soluble antioxidants, including rutin, hesperidin, and curcumin. Reduction of particle size to the nanoscale markedly increases the dissolution rate in accordance with the Noyes Whitney equation, thereby generating higher concentration gradients and improving passive diffusion through the skin [24].
- **Nanosponges:** Nanosponges are highly porous polymeric structures capable of encapsulating a broad range of substances. These systems are especially useful for absorbing excess sebum in matte-finish cosmetic products or for the controlled, prolonged release of volatile fragrance compounds.
- **Fibrous Clays (Halloysite Nanotubes):** Halloysite nanotubes are naturally occurring hollow aluminosilicate structures that are emerging as environmentally friendly nanocarriers. They are increasingly investigated for the sustained delivery of essential oils and antimicrobial agents, offering a sustainable and “green” alternative to conventional synthetic polymer-based systems [25].

4. Mechanisms of Targeted Skin Delivery

Targeted skin delivery defined as the precise localization of active ingredients within specific skin layers or appendageal structures while avoiding significant systemic absorption forms the foundation of modern dermocosmetic science. Nanocarrier-based systems employ a range of physicochemical strategies to overcome the stratum corneum (SC) barrier and efficiently deliver their encapsulated payloads to their intended sites of action.

4.1 Role of Particle Size, Surface Charge, and Deformability

The ultimate behavior and localization of nanoparticles following topical application are largely governed by their size and surface charge.

- **Size-Dependent Localization:** Numerous studies have demonstrated a clear relationship between particle size and penetration depth. Nanoparticles smaller than 100 nm preferentially penetrate into deeper epidermal layers via transcellular and intercellular pathways, whereas particles with sizes ranging from 200 to 600 nm are ideally suited for entry into hair follicles, where they tend to accumulate [26].
- **Surface Charge (Zeta Potential):** At physiological conditions, the skin surface exhibits a net negative charge, typically within a pH range of approximately 4.2–5.6. As a result, positively charged (cationic) nanocarriers experience strong electrostatic attraction to the skin, leading to prolonged residence time and enhanced interaction with the stratum corneum. For instance, lipid nanoparticles coated with chitosan display significantly greater bioadhesive properties than neutral formulations, thereby improving the cutaneous delivery of hydrophilic actives such as vitamin C [27].

4.2 Hair Follicle Targeting (The “Gear Pump” Effect)

The transfollicular pathway is now recognized as a primary route for targeted dermal delivery rather than merely a secondary shunt.

- **Mechanism:** The cuticular scales present on hair shafts function as a mechanical “gear pump.” Movement of the hair induced by arrector pili muscle activity or external massage generates a pumping action that actively drives nanoparticles deeper into the follicular canal.
- **Reservoir Effect:** Once deposited within the follicular infundibulum, nanoparticles can form a localized reservoir from which the active ingredient is released gradually over time. This mechanism is particularly beneficial for acne treatments, where delivery to the sebaceous gland is required, as well as for hair growth formulations targeting the hair bulb. Studies involving minoxidil-loaded nanostructured lipid carriers (NLCs) have demonstrated approximately tenfold greater follicular accumulation compared with conventional hydroalcoholic formulations [28].

4.3 Controlled Release and Depot Formation

One of the major advantages of nanocarrier systems is their ability to avoid the rapid and uncontrolled release commonly observed with conventional topical gels and creams.

- **Depot Formation:** Following penetration into the stratum corneum or follicular structures, lipid-based nanoparticles may aggregate to form microscopic depots within the skin. These depots enable sustained, near zero-order release of the encapsulated active ingredient. Such controlled release is particularly important for highly potent compounds, including retinol and tretinoin, as it significantly reduces adverse effects

such as erythema, peeling, and irritation that are frequently associated with conventional retinoid formulations [29].

4.4 Energy-Assisted Delivery

Between 2022 and 2025, hybrid strategies combining nanocarriers with physical enhancement techniques have emerged as highly effective approaches for improving targeted skin delivery.

- **Microneedles (MNs):** Dissolving microneedles fabricated from materials such as hyaluronic acid can be loaded with nanoparticle-based formulations. Upon application, the microneedles painlessly penetrate the stratum corneum, creating transient microchannels, and subsequently dissolve to release nanoparticles directly into the dermal layer. This approach effectively bypasses the skin barrier and has been adopted in advanced anti-aging treatments involving bioactive molecules such as growth factors [30].
- **Iontophoresis:** Iontophoresis involves the application of a low-intensity electrical current to enhance the transport of charged nanocarriers through the skin. This technique increases penetration depth by promoting electrorepulsion and electroosmotic flow, making it particularly effective for the delivery of charged systems such as ionic liposomes [31].

5. Applications in Cosmetic and Dermo-Cosmetic Products

5.1 Anti-Aging and Wrinkle Reduction

The anti-aging segment represents the largest share of the nanocosmetic market, with formulations primarily aimed at restoring structural proteins such as collagen and elastin while mitigating oxidative stress caused by free radicals.

- **Antioxidant Delivery:** Potent antioxidants, including vitamin C (ascorbic acid) and resveratrol, are inherently unstable and prone to degradation. In this context, fullerene (C_{60}) nanoparticles have attracted considerable attention in 2023 due to their exceptional “radical sponge” capacity. When incorporated into squalane-based carrier systems, these nanoparticles demonstrate enhanced chemical stability and significantly greater reductions in wrinkle depth compared with their non-encapsulated counterparts [32].
- **Peptide Delivery:** Bioactive signal peptides, such as palmitoyl pentapeptide, possess high molecular weights that limit their ability to penetrate the skin via passive diffusion. Encapsulation within elastic nanoliposomal systems markedly improves their transport into the dermis, where they activate fibroblasts and stimulate the synthesis of extracellular matrix components [33].

5.2 Skin Whitening and Pigmentation Control

Effective management of hyperpigmentation requires precise delivery of active compounds to melanocytes located within the basal layer of the epidermis.

- **Tyrosinase Inhibition:** Common depigmenting agents, including kojic acid and glabridin, are often compromised by oxidative instability and insufficient skin penetration. Ethosomal formulations loaded with glabridin have been shown to achieve approximately twofold higher skin deposition and significantly stronger inhibition of melanin synthesis in melanoma cell models when compared with conventional cream-based formulations [34].
- **Targeted Release:** Recently developed "smart" delivery platforms employ pH-responsive polymers that trigger the release of whitening agents only upon exposure to the slightly acidic microenvironment of melanosomes, thereby enhancing selectivity and therapeutic efficiency [35].

5.3 UV Protection (Sunscreens)

Nanotechnology has substantially advanced sunscreen formulation by simultaneously improving photoprotective performance and cosmetic elegance.

- **The "Sunglass Effect":** Nanostructured lipid carriers (NLCs) can function as physical UV-shielding systems. When organic UV filters are encapsulated within NLCs, the lipid matrix reflects incident ultraviolet radiation, leading to an enhancement in sun protection factor (SPF). This phenomenon, commonly referred to as the "sunglass effect," enables the use of lower concentrations of chemical filters, thereby reducing the likelihood of contact dermatitis and skin irritation [36].
- **Inorganic Filters:** Nanosized titanium dioxide (TiO_2) and zinc oxide (ZnO), when surface-coated with materials such as silica or alumina, provide broad-spectrum UV protection without imparting the undesirable whitening effect seen with conventional formulations. This advancement allows the development of high-SPF sunscreens suitable for a wide range of skin tones [37].

5.4 Anti-Acne and Sebum Control

Effective acne management requires a balanced approach that combines antimicrobial activity with sebum regulation while maintaining skin barrier integrity.

- **Sebum Targeting:** Chitosan-based nanoparticles are particularly effective in anti-acne applications due to their positive surface charge, which facilitates strong interactions with the negatively charged cell walls of *Cutibacterium acnes*, leading to membrane disruption. In addition, the encapsulation of essential oils, such as tea tree

oil and thyme oil, within nanocapsules minimizes volatility and skin irritation while preserving their potent anti-inflammatory and antimicrobial properties [38].

5.5 Hair Growth and Scalp Care

- **Alopecia Treatment:** Conventional delivery of minoxidil and finasteride often relies on alcohol-rich vehicles, which can cause scalp dryness and irritation. Advanced systems such as cholesterol-based niosomes and nanostructured lipid carriers have demonstrated enhanced follicular retention of minoxidil, resulting in improved hair regrowth outcomes in murine models. These systems also enable reduced dosing frequency, improving patient compliance [28,39].

5.6 Moisturizing and Rejuvenation

- **Occlusion:** Formulations based on solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) form a continuous, adhesive film on the skin surface. This occlusive layer significantly reduces transepidermal water loss (TEWL) compared with conventional emulsions, leading to both immediate and sustained improvements in skin hydration and overall rejuvenation [40].

6. Evaluation and Characterization Techniques

Successful translation of nanocosmetic formulations from laboratory research to commercial products requires comprehensive characterization to confirm their stability, performance, and safety. Regulatory authorities, including the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), increasingly require detailed information not only on the finished formulation but also on the intrinsic physicochemical properties of the nanomaterials involved.

6.1 Physicochemical Characterization

- **Particle Size and Polydispersity Index (PDI):** Particle size and size distribution are among the most critical quality attributes of nanocosmetic systems. Dynamic Light Scattering (DLS) is the most widely employed technique for determining hydrodynamic particle diameter. For cosmetic applications, achieving a narrow size distribution is essential, with a polydispersity index (PDI) below 0.3 indicating a monodisperse system. Such uniformity ensures consistent skin penetration behavior and minimizes instability phenomena such as Ostwald ripening, wherein smaller particles dissolve and redeposit onto larger ones, leading to particle growth and formulation destabilization.
    - **Target ranges:** particles smaller than 100 nm are preferred for deep epidermal delivery, whereas sizes between 200 and 400 nm are optimal for follicular targeting [41].

- **Zeta Potential (Surface Charge):** Zeta potential, typically measured through electrophoretic mobility analysis, serves as a predictor of colloidal stability. Absolute values greater than ±30 mV generally indicate sufficient electrostatic repulsion to prevent particle aggregation. As discussed in Section 4, cationic surface charges in the range of +20 to +40 mV are often intentionally engineered to enhance electrostatic interactions with the negatively charged skin surface, thereby improving bioadhesion and residence time [42].
- **Encapsulation Efficiency (EE) and Drug Loading (DL):** Encapsulation efficiency and drug loading capacity are determined by separating unencapsulated active ingredients from the nanocarrier system, commonly using techniques such as ultracentrifugation or dialysis. The concentration of free drug in the supernatant is subsequently quantified using high-performance liquid chromatography (HPLC). High encapsulation efficiency values, typically exceeding 80%, are crucial for economically viable manufacturing, particularly when formulating costly active compounds such as bioactive peptides or highly purified retinol.

6.2 In Vitro and Ex Vivo Permeation Studies

- **Franz Diffusion Cells:** Franz diffusion cell systems remain the gold standard for assessing drug release and permeation profiles from topical formulations. Synthetic membranes, such as Strat-M®, are routinely employed for formulation screening and quality control, whereas excised human skin obtained from abdominoplasty procedures or porcine ear skin is used for ex vivo permeation studies to more closely mimic in vivo conditions.
- **Recent Trend:** Between 2023 and 2024, the adoption of three-dimensional bioprinted skin models, including EpiDerm™, has increased substantially. These models offer reproducible, ethically acceptable, and animal-free alternatives that align with the European Union’s ban on animal testing for cosmetic products [43].
- **Tape Stripping:** Tape stripping is a minimally invasive method in which adhesive tapes are sequentially applied to the skin surface to remove successive layers of the stratum corneum. Quantification of the active ingredient extracted from each tape allows the construction of depth-dependent concentration profiles, providing valuable insights into penetration behavior.

6.3 Advanced Imaging and Visualization

Demonstrating true “targeted delivery” requires direct visualization of nanoparticle localization within the skin.

- **Confocal Laser Scanning Microscopy (CLSM):** CLSM enables non-invasive optical sectioning of skin tissues with high spatial resolution. By labeling nanocarriers with fluorescent probes such as rhodamine B or Nile red, researchers can monitor

nanoparticle distribution and movement through intercellular lipid domains or into hair follicles in real time [44].

- **RamanSpectroscopy:**
  Raman spectroscopy is a label-free imaging technique that has gained considerable traction in 2024. This method simultaneously maps the molecular signatures of both the active ingredient and skin lipids, allowing confirmation of nanocarrier-induced lipid matrix fluidization and providing mechanistic insights into enhanced permeation [45].

7. Safety, Regulatory, and Ethical Aspects

As nanocosmetic formulations become increasingly potent and sophisticated, concerns related to their safety have intensified accordingly. In parallel, the regulatory environment surrounding nanomaterials has undergone substantial tightening in 2024, reflecting heightened scrutiny from both regulatory authorities and consumers.

7.1 Toxicity and Nano–Bio Interactions

The principal safety challenges associated with nanocosmetics arise from the exceptionally high surface-area-to-volume ratio of nanoparticles, which can amplify their chemical and biological reactivity.

- **Oxidative Stress (Reactive Oxygen Species, ROS):** Certain inorganic nanoparticles, particularly unmodified titanium dioxide (TiO_2) and zinc oxide (ZnO), are capable of generating reactive oxygen species when exposed to ultraviolet radiation. This photocatalytic activity can induce oxidative damage, including lipid peroxidation and DNA damage, in cutaneous cells. To mitigate these risks, the use of surface-coated nanoparticles typically capped with silica or alumina has become mandatory in modern cosmetic formulations to suppress ROS generation [46].
- **Cytotoxicity:** Evaluation of cytotoxic effects using in vitro models, such as human keratinocyte (HaCaT) and dermal fibroblast cell lines, is now standard practice in nanocosmetic safety assessment. Recent evidence indicates that cationic lipid-based nanoparticles, although highly effective for enhancing skin delivery, may exhibit increased cytotoxicity relative to neutral systems due to their ability to disrupt cellular membranes. This underscores the importance of careful optimization of nanoparticle concentration and surface properties to balance efficacy and safety [47].

7.2 Regulatory Frameworks: The 2024 Shift

European Union (EU): The Global Benchmark for Regulation

The European Union continues to maintain the most stringent cosmetic regulatory framework worldwide under the EU Cosmetics Regulation (EC) No 1223/2009.

- **Major Update (March 2024):** The publication of Commission Regulation (EU) 2024/858 marked a significant regulatory shift. Based on assessments by the Scientific Committee on Consumer Safety (SCCS), the regulation prohibits the use of several nanomaterials previously permitted in cosmetic products, including styrene/ acrylates copolymer (nano), copper (nano), and colloidal silver and gold (nano), due to concerns related to potential genotoxicity and long-term accumulation in biological tissues.
- **Restrictions:** Hydroxyapatite (nano), widely used in "enamel repair" toothpaste formulations, is now subject to strict concentration limits (maximum 10% in toothpaste) and is prohibited in sprayable cosmetic products to minimize inhalation risks. These materials are subject to strict concentration limits and recent safety assessments highlighting potential toxicity concerns [48,49].
- **Labeling Requirements:** In accordance with EU regulations, all ingredients present in nanoform must be clearly identified in the ingredient list by appending the term "(nano)" following the substance name, for example, Titanium Dioxide (nano).

United States (FDA): Implementation of MoCRA

Historically, cosmetic regulation in the United States has been comparatively less stringent; however, this landscape has changed significantly following the implementation of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), which became fully operational during late 2023 and 2024.

- **Safety Substantiation:** Although MoCRA does not explicitly prohibit the use of nanomaterials, it requires that the designated "Responsible Person" maintain comprehensive records demonstrating the safety of each ingredient used in cosmetic formulations.
- **Facility and Product Registration:** Under MoCRA, cosmetic manufacturers are now obligated to register production facilities and submit product listings through the FDA's "Cosmetics Direct" portal. In 2024, the FDA issued additional guidance emphasizing that nanoparticle size, aggregation state, and physicochemical characteristics must be explicitly considered during safety evaluations [50,51].

7.3 Environmental Impact (The "Wash-Off" Effect)

Beyond human safety, growing ethical concerns focus on the environmental fate of nanomaterials following consumer use, particularly for rinse-off cosmetic products.

- **Aquatic Toxicity:** Nanoparticles such as TiO_2 and ZnO can enter wastewater streams during product wash-off and subsequently accumulate in aquatic ecosystems. Studies have demonstrated toxic effects on algae and coral reefs, contributing to phenomena

such as coral bleaching. These findings have driven the increasing popularity of "reef-safe" certification for sunscreen products.

- **Microplastic Pollution:** Non-biodegradable polymeric nanoparticles may contribute to microplastic contamination in the environment. This concern has accelerated a major shift within the cosmetic industry toward the use of biodegradable nanocarriers, including lipid-based systems and polysaccharide-derived materials such as chitosan and alginate, which offer improved environmental compatibility [52].

8. Challenges and Future Perspectives

Although nanotechnology has fundamentally transformed cosmetic formulation science, several critical challenges continue to limit the seamless transition from laboratory research to large-scale commercial products. The forthcoming decade (2025–2035) is expected to focus on resolving manufacturing constraints while incorporating advanced technologies such as Artificial Intelligence (AI) and principles of Green Chemistry to enhance efficiency, sustainability, and personalization.

8.1 Scale-Up and Manufacturing Stability

Scaling nanocosmetic formulations from laboratory quantities (milligrams) to industrial volumes (kilograms to tonnes) remains one of the most formidable obstacles.

- **Methodological Constraints:** Many laboratory-scale preparation techniques, including sonication and solvent evaporation, are inherently difficult to translate to industrial manufacturing. Although High-Pressure Homogenization (HPH) is the preferred large-scale method for producing lipid-based nanoparticles, identifying optimal processing parameters such as homogenization pressure and number of cycles without inducing particle aggregation continues to be a significant challenge.
- **Physical Stability Issues:** Nanocarriers are thermodynamically unstable by nature. Over extended storage periods, instability phenomena such as Ostwald ripening where smaller particles dissolve and redeposit onto larger ones as well as sedimentation may occur. Achieving and maintaining a consistent particle size distribution throughout the typical cosmetic shelf life of approximately three years, without phase separation, requires meticulous design of the surfactant and stabilizer system [53].
- **Loading Capacity Limitations:** Another persistent challenge is achieving high active loading while preventing expulsion of the encapsulated ingredient during lipid crystallization, a problem commonly encountered with Solid Lipid Nanoparticles (SLNs). Improving drug retention within the carrier matrix remains a key formulation objective.

8.2 AI-Driven Formulation Design (Nanoinformatics)

Conventional formulation development relies heavily on iterative trial-and-error experimentation, which is both time-consuming and resource-intensive. The integration of Artificial Intelligence (AI) and Machine Learning (ML) has emerged as a transformative approach during 2024–2025.

- **Predictive Modeling:** Machine learning algorithms are increasingly capable of predicting critical physicochemical parameters such as particle size, polydispersity index (PDI), and encapsulation efficiency based on formulation inputs including lipid composition and surfactant concentration. Recent investigations have demonstrated that Random Forest and Neural Network models can successfully optimize nanostructured lipid carrier (NLC) formulations for anti-aging peptides, reducing formulation development timelines by more than 60%.
- **In Silico Skin Permeation:** The field of nanoinformatics is also advancing tools that computationally simulate interactions between nanomaterials and skin lipid matrices. These models enable prediction of penetration depth and distribution prior to experimental testing, thereby streamlining formulation screening and reducing experimental costs.

8.3 Green and Sustainable Nanotechnology

Growing consumer awareness and increasing regulatory pressure particularly under initiatives such as the EU Green Deal are accelerating the transition toward environmentally responsible nanotechnology.

- **Solvent-Free Manufacturing:** There is a marked shift away from the use of organic solvents, such as chloroform and dichloromethane, toward solvent-free or low-solvent techniques including High-Pressure Homogenization (HPH) and phase inversion temperature (PIT) methods.
- **Eco-Friendly Materials:** The replacement of synthetic polymers with biodegradable and renewable alternatives is gaining momentum. Nanocarriers derived from lignin (sourced from wood waste) and starch-based nanocapsules are emerging as sustainable options that also provide intrinsic antioxidant activity.
- **Energy-Efficient Processing:** The development of cold-processing strategies aims to minimize energy consumption and reduce the carbon footprint associated with conventional heated lipid emulsification processes.

8.4 Smart and Stimuli-Responsive Systems

Future nanocosmetic formulations are expected to rely heavily on “smart” delivery systems capable of responding dynamically to the skin’s microenvironment.

- **pH-Responsive Systems:** Polymeric nanocarriers can be engineered to swell or degrade selectively at specific pH conditions, such as the mildly acidic pH (~5.5) of the skin surface or the relatively alkaline environment of inflamed acne lesions, thereby enabling site-specific release of active compounds.
- **Enzyme-Triggered Release:** Enzyme-sensitive nanoparticles that degrade in response to skin enzymes such as esterases or proteases offer precise, on-demand release of active ingredients in regions of elevated metabolic activity [54,55].

9. Conclusion

The incorporation of nanotechnology into cosmetic science has brought about a fundamental transition from conventional surface-level application toward advanced, biologically targeted skin interventions. As outlined in this review, lipid-based nanocarriers such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) along with vesicular systems including ethosomes and transfersomes, have emerged as benchmark technologies. Their success is largely attributed to their excellent biocompatibility, ability to overcome the stratum corneum barrier, and effectiveness in stabilizing sensitive active ingredients such as retinoids and bioactive peptides.

Developments reported between 2020 and 2025 clearly indicate a strategic shift in formulation objectives. The emphasis has moved beyond achieving deeper skin penetration toward precise and controlled targeting of specific skin compartments. Whether addressing follicular delivery for acne management, directing depigmenting agents to melanocyte-rich basal layers, or ensuring dermal delivery of anti-aging actives, nanotechnology provides the necessary level of control to meet the evolving demands of modern dermocosmetic products.

Despite these advances, the expanding use of nanomaterials has raised legitimate safety and regulatory considerations. Recent regulatory reforms in the European Union during 2024 introducing stricter restrictions on certain nanomaterials and reinforcing the requirement for comprehensive safety substantiation reflect a more mature and responsible industry approach that balances innovation with consumer protection.

Looking ahead, the integration of Green Chemistry principles with Artificial Intelligence driven formulation strategies is expected to shape the future of nanocosmetics. Emerging products are likely to combine high therapeutic performance with environmental sustainability and personalized design tailored to individual biological characteristics. As understanding of the bio nano interface continues to deepen, nanocosmetics will increasingly bridge the gap between aesthetics and therapy, delivering measurable and meaningful benefits to skin health.

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