






ORIGINAL RESEARCH ARTICLE

Nanoemulsion Drug Delivery Systems for Dermatological Disorders: A Review of Mechanisms, Clinical Applications and Commercial Advances

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ABSTRACT

Objective: This review explores recent developments in nanoemulsion systems for both superficial and deep-skin applications, uniquely synthesizing clinical translation barriers, regulatory gaps, and emerging trends like nanoemulgels. **Methods:** A comprehensive narrative review was conducted using multiple complementary approaches across primary databases (PubMed, ScienceDirect) and secondary sources (Google Scholar). Enhanced search capabilities through Elicit and Research Rabbit were utilized to map relevant literature connections. Primary search terms included "nanoemulsion drug delivery," "dermatological applications," "skin penetration enhancement," and "topical nanoemulsions." The review focused on literature from 2019-2024 with strategic inclusion of foundational papers, encompassing original research, clinical studies, and review articles. **Results:** Nanoemulsions enhance drug permeability with improvements ranging from several-fold to over 39-fold compared to conventional creams through fluidizing or altering the stratum corneum's lipid matrix, improving solubility, stability, and bioavailability. Critical characteristics such as droplet size and zeta potential determine stability and skin absorptivity, enabling targeted delivery of anti-inflammatory agents and active ingredients while reducing systemic side effects compared to conventional treatments. Despite showing a favourable safety and non-irritant profile, the analysis revealed significant clinical translation barriers and regulatory gaps that limit widespread adoption. **Conclusion:** Further clinical studies remain necessary to confirm long-term safety. Future integration with wearables and smart delivery systems may revolutionize dermatological treatment paradigms, positioning nanoemulsions as a transformative technology in topical therapeutics.

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INTRODUCTION

Dermatological conditions like psoriasis, eczema, and acne can significantly impact people's physical and mental health. This leads to discomfort, psychological stress, and long-term damage to the skin. Remedies for such an issue must adopt approaches whereby the local symptoms are managed with as few systemic effects as possible, one of the challenges faced by conventional therapy (Akinsipo et al., 2021; Ujiie et al., 2022). These topical preparations, available in a variety of ointments and creams, seldom produce the anticipated therapeutic outcome owing to poor penetration and low bioavailability of the drug. Active deep delivery within the skin layers is a requisite factor for the effective handling of severe cases such as psoriasis and dermatitis (Ramanunny et al., 2020; Tapfumaneyi et al., 2022).

The natural barrier provided by the skin, consisting notably of the stratum corneum (SC), offers another restriction where topical absorption is thwarted,

preventing effective topical therapy (Farjami et al., 2021). Advances in diagnostics, as well as personalized treatment strategies, would have been made, but it still persists in ensuring that drug delivery is ever to be maximized, as well as minimizing side effects while having an actual targeted therapy at the pathological site (Luger et al., 2020; Singh et al., 2021).

Recently, advances in nanotechnology introduced nanoemulsions (NEs) as promising nanoscale delivery systems consisting of an oil phase and an aqueous phase stabilized by surfactants. Their chemical and physical dual capacity for both hydrophilic and lipophilic drugs, combined with their ability to solubilize materials of various types, offers a highly efficient carrier for dermatological use. They also show better dissolution, bioavailability, and longer sustained release (Eqbal et al., 2021; Qu et al., 2022). Unlike standard topical formulations, NEs allow better penetration through the

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stratum corneum into deeper skin levels, which is very much needed in conditions like psoriasis and dermatitis (Souto et al., 2022).

NEs not only increase the solubility of poorly water-soluble drugs but also stabilize the active agents, which will finally lead to an increase in the concentration of drug at the action site (Rauf et al., 2021; Waghule et al., 2020). The controlled and sustained release reduces the need for frequent applications and systemic side effects, thereby improving therapeutic effects concerning anti-inflammatory and anti-acne (Sghier et al., 2024). NEs show much higher penetration depth- diffusion local applications due to the presence of droplet sizes in the range of 20-200 nm upon irradiation (Rai et al., 2022; Tapfumaneyi et al., 2022). Besides symptom relief, NEs can transport natural active compounds like neem and curcumin with anti-inflammatory, antibacterial, and antioxidant properties-naturally providing potential therapeutic coping mechanisms for skin diseases.

This adaptability of nanoemulsions makes them viable routes for topical application and transdermal penetration (Eqbal et al., 2021; Parveen et al., 2023), further extending their utility in dermatological therapy. Such innovations include nanoemulgels, that is, a combination of gels and nanoemulsions, and self-nano-emulsifying drug delivery systems (SNEDDS), which are expected to provide better stability and controlled drug release necessary for chronic skin disorders that often require prolonged treatment. Additional aids to such formulations include ultrasound-assisted preparation of nanoemulsions with natural oils such as avocado oil, which has proven highly effective in anti-aging therapy through promoting collagen synthesis and alleviating signs of skin aging (Kiattisin et al., 2024).

Challenges in nanoemulsion development include the optimal selection of surfactants, control of production costs, and ensuring complete safety compliance with regulations for clinical applications (Rai et al., 2022). Nevertheless, the exciting promise of NEs in dermatology—in terms of superior stability, solubilization, and targeted delivery—lends credence to the notion that their use could potentially create new treatment paradigms.

While nanoemulsions have gained considerable attention, existing reviews such as those by Souto et al. (2022), Rai et al. (2022), Yousefpoor et al. (2024), Preeti et al. (2023), Sharma et al. (2023), and Singh et al. (2023) primarily focus on the general applications, advantages, and formulation aspects of nanoemulsions in skin drug delivery. Souto et al. (2022) provide a comprehensive overview of microemulsions and nanoemulsions, discussing their differences, composition, production processes, and applications in both pharmaceutical and cosmetic industries. Rai et al. (2022) highlight recent advancements and applications of transdermal nanoemulsions, summarizing their utilities, characteristics, clinical pertinence, and regulatory status. While Yousefpoor et al. (2024) review topical micro- and nanoemulsions for common skin diseases, and Preeti et al. (2023) examine nanoemulsions as emerging technology for improving

drug bioavailability. Sharma et al. (2023) provide comprehensive overviews of nanoemulsions for enhanced drug delivery, while Singh et al. (2023) focus on their role in various dermatological conditions. However, these reviews lack a comprehensive evaluation of the critical role of zeta potential manipulation in optimizing nanoemulsion performance and the intricacies of their commercial integration.

While nanoemulsion efficacy is established, this review addresses unmet needs: clinical scalability, regulatory harmonization, and economic viability. Unlike prior reviews, we critically evaluate commercial nanoemulsion products and propose standardized safety assessment protocols for long-term clinical applications. This work uniquely positions nanoemulgel systems as the next evolutionary step in dermatological therapy and establishes a comprehensive framework for zeta potential manipulation as a controllable parameter for therapeutic optimization.

This review distinguishes itself by providing: (1) comprehensive evaluation of zeta potential manipulation as a pivotal optimization parameter; (2) detailed examination of commercial integration challenges and opportunities; (3) critical assessment of existing commercial nanoemulsion products; (4) standardized safety assessment protocols for clinical applications; and (5) positioning of nanoemulgel systems as advanced therapeutic platforms. Therefore, this review focuses on studying the potential of nanoemulsion-based drug delivery systems vis-à-vis their proposed design, synthesis, and special attributes, especially their enhancement of drug permeability, solubility, and stability, as well as the delivery of active pharmaceutical ingredients with improved bioavailability and therapeutic effects. A concise overview will be provided about their application in treating disorders such as psoriasis, eczema, alopecia, melanoma, and acne, reiterating these systems' versatility and the multifaceted need for additional research and development in this progressive area.

METHODOLOGY

Research Question Formulation

This narrative review was structured to address four main objectives:

- To analyze the present state of the art regarding nanoemulsion mechanisms in drug delivery to the skin
- To determine the critical appreciation of the role zeta potential manipulation plays in the performance optimization of a nanoemulsion.
- To appreciate the intricacies of these systems at the commercial level and evaluate regulatory hurdles in the way of the development of nanoemulsions
- To identify trends in nanoemulgel systems and their therapeutic applications.

Literature Search Strategy

To ensure the maximum coverage of this rapidly evolving multidisciplinary field, a comprehensive literature search was carried about using several complementary approaches. Primary databases included PubMed and Web of Science because of their biomedical and pharmaceutical research coverage. ScienceDirect and Google Scholar were secondary sources for the purposes of cross-reference and identifying additional relevant literature, especially in the commercial and regulatory domains. We also used search enhancements offered by Elicit and Research Rabbit, thereby mapping relevant literature associations and improving the identification of high-impact papers.

Search terms encompassed primary keywords ("nanoemulsion," "dermatological drug delivery," "transdermal delivery," "zeta potential," "commercial nanoemulsion") and secondary terms addressing specific conditions ("psoriasis," "eczema," "alopecia," "melanoma," "acne") and mechanisms ("skin penetration enhancement," "stratum corneum"). Combinatorial searches integrated these terms to capture interdisciplinary research, while specific therapeutic terms targeted anti-inflammatory and keratolytic agent delivery studies.

Inclusion and Exclusion Criteria

Studies reviewed principally covered the period during 2019-2024 to allow the very recent developments, and for well-established concepts. Included materials comprised peer-reviewed original research articles, clinical studies, review articles, patents, and commercial product documentation in English with clear methodology and quantitative data. Commercial data consisted of FDA-approved products, marketed formulations, and regulatory documentation.

Exclusion criteria included those references published in languages in which no reliable translation could be obtained or were unavailable in full-text mode, i.e., conference abstracts, poor-quality studies without proper controls or statistical analysis, duplicate publications, and articles in which the research was only related to oral or injectable nanoemulsions without any dermatological relevance.

Data Extraction and Analysis Framework

Data extraction considered mechanistic parameters that included droplet size measurement, zeta potential, penetration enhancement factors, and stability parameters. Clinical evidence was evaluated hierarchically from Level I (randomized controlled trial) through Level IV (clinically relevant in vitro studies). Commercial product assessment included the market analysis of FDA-approved nanoemulsion products, regulatory status, comparison of efficacy with conventional systems, and documentation of the safety profile.

The special focus was paid to studies on follicular targeting, showing mechanisms for enhanced penetration with droplet sizes below 100 nm, techniques to manipulate

zeta potential, including the incorporation of zwitterionic molecules and biopolymer modifications, and next-gen nanoemulgel systems encompassing formulation advantages, clinical applications, and commercial possibilities.

Quality Assessment and Limitations

No formal quality assessment tools were applied, in view of the narrative nature of this review; however, emphasis was placed on studies with solid methodological backgrounds holding clinical relevance, transparent data, and commercial validity. This approach acknowledges potential selection biases inherent in narrative reviews, the rapidly evolving nature of the field, limited commercial data availability due to proprietary restrictions, regional variations in regulatory information, and potential underrepresentation of historically significant foundational work due to the focus on recent literature.

NANOEMULSION TECHNOLOGY FOR DERMATOLOGICAL APPLICATIONS

Nanoemulsions are complex systems made up of two immiscible liquids—mostly oil and water—in a stable mixture with surfactants and cosurfactants (Ahire et al., 2021; Malode et al., 2021; Akinsipo et al., 2021). Such formulations have thermodynamically stable and homogenous characteristics and always have droplet sizes falling between 20 and 200 nm (Ahire et al., 2021; Malode et al., 2021). High-energy techniques like high-pressure homogenization and ultrasonication have been utilized to ensure an even distribution of droplet size and enhanced stability (Manickam et al., 2020; Tayal et al., 2024). The proper selection of surfactants, especially polysorbate-80 or oleth-20, is hence central to the stable formulations over time with the desired physicochemical properties (Pavoni et al., 2020). Figure 1 shows Oil-in-Water Nanoemulsion Structure.

Schematic representation of an O/W nanoemulsion structure showing nanoscale oil droplets (20–200 nm in diameter) dispersed in an aqueous continuous phase. The diagram illustrates: (A) surfactant molecules with hydrophilic head groups (purple spheres) oriented toward the aqueous phase and hydrophobic tails (white chains) extending into the oil core, stabilizing the oil–water interface; (B) hydrophobic drug molecules (green hexagons) solubilized within the oil phase; (C) the hydrophobic oil core (yellow) containing the encapsulated drug payload; and (D) the surrounding aqueous phase (blue), which serves as the continuous medium and supports colloidal stability. Scale bar = 100 nm. Original schematic inspired by Akinsipo et al. (2021) and Iskandar et al. (2024).

Fundamental Properties and Characteristic Zeta Potential

Due to large surface area, optical clarity, and rheological behavior changes, as well as many other parameters, nanoemulsions are relevant for dermal applications (Tayal et al., 2024). Droplet size, zeta potential, and overall

stability are the critical attributes by which drug delivery mechanisms and release profiles are ascertained (Rathee et al., 2023). Small droplet size aids in stratum corneum penetration, while positive or negative zeta potentials help improve formulation stability, drug bioavailability, and sustained release (Rai et al., 2022).

The most important criteria in reference to nanoemulsion stability and performance is measuring the zeta potential, which refers to the electric potential at the shear plane of the droplet. High values of zeta potential (high than ± 30 mV) indicate that systems are stable under electrostatic repulsion of high strength, while relative low absolute values indicate a risk of aggregation or flocculation (Elsewedy et al., 2021; Wang et al., 2022). Besides stability influences, zeta potential also governs bioavailability and activity profiles in therapeutic formulations, thus affecting the behaviour of the droplet with the attached nanoemulsion and the drug release profiles (Rai et al., 2022; Rathee et al., 2023).

Manipulation of zeta potential through electroporatory techniques and electroacoustic tools can enhance

therapeutic performance (Elsewedy et al., 2021). Zwitterionic molecules such as phosphorylated tyramine dynamically change surface charge—from negative to positive—at the surface through interaction with alkaline phosphatase, thereby increasing mucus permeation and cellular uptake (Sharifi et al., 2021). Similarly, formulations containing polyoxyethylene nonylphenol monophosphate ester improved their uptake into cells through induced shifts in zeta potentials (Kurpiers et al., 2020).

Environmental conditions, especially ionic strength, also modify zeta potential. Increased NaCl concentration reduced absolute zeta potential values because ions screen the surface charge and further alter droplet sizes and viscosity parameters (Onaizi, 2022). Such techniques use positively charged biopolymer quaternized chitosan as modifiers of the surface, thus enhancing both stability and bioactivity of the contained agents. For example, nanoemulsions of Plai extract, modified with such biopolymers, shifted from -22.03 mV to +20.23 mV, thus enhancing therapeutic performance while holding the stability threshold near ± 30 mV (Luesakul et al., 2019). Therefore, understanding manipulation of zeta potential is necessary to prepare stable nanoemulsion formulations for pharmaceutical, cosmeceutical, and nutraceutical applications (Sneha & Kumar, 2021).

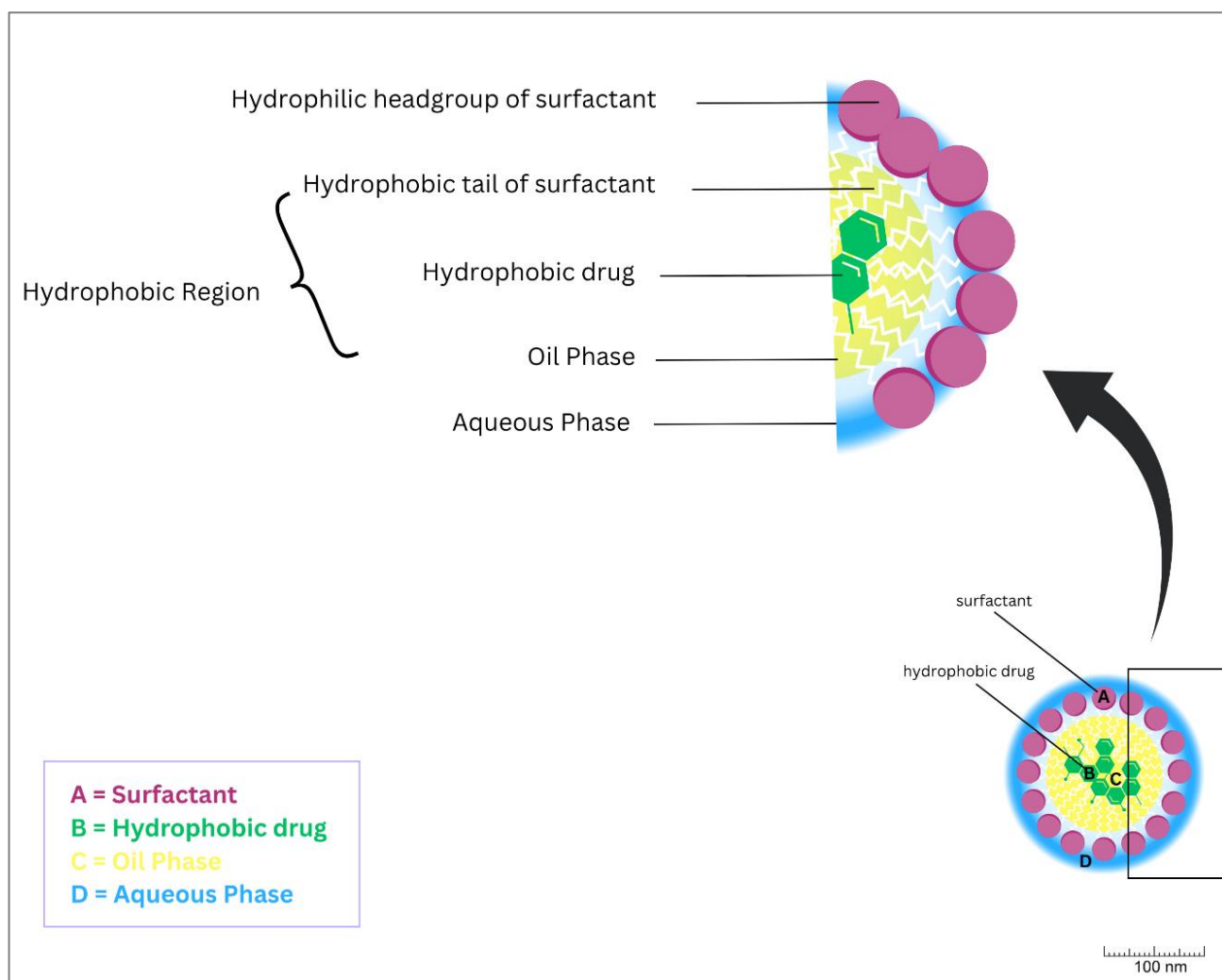


Figure 1: Oil-in-Water Nanoemulsion Structure

Enhanced Mechanisms of Skin Penetration and Bioavailability

Targeted disruption of the stratum corneum lipid matrix by nanoemulsions enhances permeability to active ingredients (Ramanunny et al., 2020b; Schmitt & Neubert, 2020). The effects of such disruption are concentrated reservoirs of drugs within the skin and, thus, release profiles that are controlled and sustained for longer periods (Zoabi et al., 2021).

This endogenous delivery system effectively targets skin appendages, especially hair follicles and the associated sebaceous glands (Costa et al., 2021; Harun et al., 2021). Other surface modifications such as PEGylation favor the targeting of these appendages and thus are beneficial for the treatment of acne and alopecia (Al Mahrooqi et al., 2021). This means that minoxidil-loaded nanoemulsions can penetrate the hair follicle well and release the drug for an extended period of time (up to six hours) (Cardoso & Barradas, 2020).

Apart from the above, another important merit of transdermal drug delivery systems based on nanoemulsions is that they can be easily administered by bypassing the hepatic first-pass metabolism. Hepatic metabolism of conventional drugs takes place when they are given orally before they enter the systemic circulation, which greatly reduces the effective concentration at the target (Eqbal et al., 2021; Ghasemiyeh & Mohammadi-Samani, 2020). By bypassing this pathway, systemic availability and overall therapeutic effect increase, with some studies suggesting dosage reduction accordingly (Akinsipo et al., 2021).

The lipid-based composition further facilitates enhanced drug permeation through the skin, supporting controlled release profiles while minimizing systemic side effects (Akinsipo et al., 2021; Souto et al., 2022). Recent study by Harde and Mallya (2024) emphasizes that self-emulsifying drug delivery systems (SEDDS), including nanoemulsions, effectively maintain sustained drug levels through this metabolic bypass mechanism.

Enhanced Solubility, Stability, and Release Characteristics

Nanoemulsions exhibit improved therapeutic performance and patient compliance by enhancing solubility, stability, and controlled release over conventional topical formulations (Fernandes, 2022). Such characteristics of small droplet size and enhanced surface area would facilitate effective solubilization of lipophilic drugs with higher encapsulation efficiency and sustained release profiles (Schafer et al., 2023; Tapfumaneyi et al., 2022).

These systems present extremely high bioavailability and stability as opposed to conventional topical preparations because of accurate droplet sizing and stable structural characteristics (Sharma & Saiyed, 2023; Souto et al., 2022).

The reduced frequency of application through controlled release mechanisms prolongs therapeutic effects and increases adherence to therapy (Tapfumaneyi et al., 2022). With recent advancements, nanoemulsions have gained importance for their penetrating ability and site-specific delivery capabilities toward various skin conditions like acne and alopecia. In addition, with more circulation, targeted tissue delivery, and better efficacy, other therapeutic fields like oncology, transdermal vaccines, and advanced drug delivery will also benefit from this technology (Milligan & Saha, 2022; Nguyen et al., 2021). Natural absorption enhancers, such as terpenes and fatty acids, may help in skin penetration without causing major irritation (Schafer et al., 2023).

KEY ACTIVE INGREDIENTS IN NANOEMULSION DELIVERY

Due to the encapsulation of various bioactive agents-antioxidants, anti-inflammatories, and keratolytics-and the subsequent increase in stability, enhanced skin penetration, and better therapeutic performance, nanoemulsions are one of the latest contenders in dermatological products (Choi & McClements, 2020; Rachman et al., 2023). The bioavailability of the active ingredients is enhanced and allows selective treatment with negligible intervention systemically by nanoemulsions.

Through their ability to boost the bioavailability of active ingredients, nanoemulsions facilitate targeted treatment while minimizing systemic effects (Table 1).

Anti-inflammatory Agents:

Topically delivered by nanoemulsions are anti-inflammatory drugs. One such agent is niacinamide, which greatly decreases skin inflammation while almost completely avoiding systemic absorption. Sustained release and enhanced penetration make it very potent in treating inflammatory conditions such as eczema and psoriasis (Lal et al., 2023; Placha & Jampilek, 2021).

Antioxidants:

Encapsulation of antioxidants, particularly ascorbic acid, protects these agents against degradation, thus ensuring that their full abilities to neutralize reactive oxygen species (ROS) and oxidative stress remain intact. Encapsulation acts as protection against environmental damage, bestowing rejuvenation and anti-aging effects on the skin (Hassan et al., 2022; Palma & Seiquer, 2020; Rathee et al., 2023).

Keratolytic Agents:

Nanoemulsion systems greatly facilitate the delivery of keratolytic agents in the skin, allowing salicylic acid to move deeper into the skin layers to cause effective exfoliation. Such a cleansing process in deep pores is beneficial in treating hyperkeratotic conditions like acnes (Patel & Patel, 2021; Patnaik et al., 2022).

Table 1: Active ingredients delivered through nanoemulsion-based formulations for treating dermatological disorders

Active Ingredient	Nanoemulsion-Based Formulation	Mechanism and Outcomes	Year of Publication
Azelaic Acid	Azelaic acid-loaded nanoemulsion with nanostructured lipid carriers (NLCs)	Increases transfollicular penetration, enhancing bioavailability and reducing irritation. Effective for acne and rosacea with minimized side effects compared to traditional formulations.	(Malik & Kaur, 2020; Salimi et al., 2020)
Niacinamide/ Ferulic Acid	Niacinamide combined with ferulic acid in nanoemulsion formulations	Demonstrates enhanced skin penetration, improved stability, and superior efficacy for treating hyperpigmentation, reducing sebum production, and providing antioxidant protection.	(Basto et al., 2021; Das et al., 2020)
Ascorbic (Vitamin C)	Acid Nanoemulsion patches with ascorbic acid	Stabilizes against oxidation, enhances skin absorption, and provides prolonged release for anti-aging and antioxidant benefits. Effective in preventing photo-aging due to UV exposure.	(Zaid Alkilani et al., 2022)
Salicylic Acid	Salicylic acid in nanoemulsion gel with Carbopol base	Improves solubility and provides sustained delivery for keratolytic effects, targeting acne and hyperkeratotic conditions with enhanced anti-inflammatory action.	(Souto et al., 2022)
Curcumin	Curcumin-loaded nanoemulsion gel with resveratrol and thymoquinone	Potent anti-inflammatory and antioxidant properties. Nanoemulsions improve skin permeability and stability, showing effectiveness in psoriasis treatment.	(Khatoon et al., 2021)
Kojic Acid	Kojic acid ester-based nanoemulsion for skin brightening	Enhances skin permeability and provides a controlled release profile, reducing pigmentation and inhibiting melanin production with less irritation.	(Syed Azhar et al., 2020)
Retinol (Vitamin A)	Retinol nanoemulsion stabilized with halloysite nanotubes	Increases stability and absorption for anti-aging benefits, boosting collagen production and reducing fine lines and wrinkles. Nanoemulsion delivery reduces irritation commonly associated with retinol.	(Borrego-Sánchez et al., 2021)

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Table 1 continued

Active Ingredient	Nanoemulsion-Based Formulation	Mechanism and Outcomes	Reference
Thymoquinone	Thymoquinone-curcumin-resveratrol nanoemulsion for psoriasis	Provides potent anti-inflammatory effects, enhancing psoriatic lesion improvement. Nanoemulsions facilitate deeper penetration and improve stability of bioactives.	(Khatoon et al., 2021)
Resveratrol	Resveratrol nanoemulsion with curcumin and thymoquinone	Enhances skin antioxidant defence, reduces inflammation, and supports skin rejuvenation. Nanoemulsion stabilizes resveratrol and enhances its penetration for improved therapeutic outcomes.	(Khatoon et al., 2021)

NANOEMULSION-BASED TREATMENTS

The use of nanoemulsion formulations in dermatotherapy has been on an advance because of their enhanced ability to increase the bioavailability and permeability of active molecules. For active agent delivery, successful performance over conventional topical preparations is provided by nano-scaled emulsions carefully designed

using engineering principles (Table 2). Nanoemulsions are increasingly thought to be valuable tools in treating chronic and complicated dermatological conditions, including psoriasis, eczema, alopecia, melanoma, and acne, due to their stability, penetration characteristics, and controlled release mechanisms (Patel & Patel, 2021; Rashid et al., 2021).

Table 2: Nanoemulsion-Based Formulations for Dermatological Conditions

Condition	Formulation & Active Agents	Mechanism & Outcomes	Year of Publication
Psoriasis	Methotrexate and curcumin-loaded nanoemulsions	Enhanced skin retention, deeper penetration, and stability lead to reduced Psoriasis Area and Severity Index (PASI) scores. Modulates immune response for effective lesion management.	(Akinsipo et al., 2021; Algahtani et al., 2020; Rapalli et al., 2021; Rashid et al., 2021; Rathee et al., 2023)
Eczema	α -Tocopherol and γ -tocotrienol nanoemulsions with microwave technology	Delivers antioxidants directly to the stratum corneum, promoting anti-inflammatory action and skin barrier repair. Biocompatible and non-irritating, unlike steroidal treatments.	(Harun et al., 2021; Lal et al., 2023; Rathee et al., 2023)
Alopecia	Minoxidil nanoemulsions with clove/garlic oil	Increases follicular penetration and localizes action for enhanced hair regrowth, reducing systemic side effects. Improved bioavailability and minimized irritation.	(Cardoso & Barradas, 2020; Giacone et al., 2020; Rizg et al., 2021)
Melanoma	Chrysin and norcantharidin nanoemulgels	Targeted delivery improves drug bioavailability and retention, inducing apoptosis in melanoma cells and minimizing healthy cell damage. Reduces systemic toxicity for safer treatment.	(Fard et al., 2022; Imran et al., 2020; Martínez-Razo et al., 2023; Nagarajan et al., 2021)
Acne	13-cis-retinoic acid and salicylic acid nanoemulsions	Enhanced penetration and sustained release target sebaceous glands effectively, reducing inflammation and side effects. Promotes patient adherence due to fewer applications.	(Patel & Patel, 2021; Rai et al., 2022; Sevinç Özakar et al., 2022; Tapfumaneyi et al., 2022b)

Psoriasis Management

The nanoemulsion formulation of methotrexate and curcumin shows great promise in psoriasis management. Clinical investigations showed that these formulations improve drug permeation and retention, significantly changing PASI (Psoriasis Area and Severity Index) scores in animal models (Algahtani et al., 2020). In addition, the olive oil gel system and sophisticated lipid carriers enhance delivery efficiency and stability, indicating the development of useful human therapeutics (Rapalli et al., 2021).

Treatment for Eczema and Atopic Dermatitis

Formulations with linseed oil-based nanoemulsions for eczema and atopic dermatitis have strong anti-inflammatory effects and sustained release for barrier restoration and symptom alleviation without the associated side effects of steroids (Kildaci et al., 2021; Lal et al., 2023). The use of microwave-assisted technology in formulations containing α -tocopherol and γ -tocotrienol further augments epidermal absorption and therapeutic efficacy (Harun et al., 2021).

Alopecia Treatment

The nanoemulsion applications contribute to improved protocols in the treatment of alopecia, namely in the minoxidil formulations. They provide targeted follicular penetration to boost efficacy in hair growth with minimum side effects, as experienced with oral administration. The incorporation of naturally occurring oils like clove and garlic enhances penetration and stability, adding to the therapeutic outcomes (Cardoso & Barradas, 2020; Rizg et al., 2021).

Melanoma Therapy

In melanoma treatment, nanoemulsion systems facilitate targeted delivery of anticancer agents, notably miconazole and norcantharidin, achieving localized therapeutic action while reducing systemic toxicity. This approach enhances bioavailability and demonstrates significant potential in inducing apoptosis in cancer cells, a crucial factor in early-stage treatment protocols (Martínez-Razo et al., 2023).

Acne Management

Acne treatment has also experienced substantial advancement through nanoemulsion formulations containing 13-cis-retinoic and salicylic acid. These sophisticated delivery systems enhance skin penetration while providing controlled, sustained release targeting sebaceous glands, effectively reducing inflammation and side effects while promoting improved patient compliance (Sevinç Özakar et al., 2022; Tapfumaneyi et al., 2022).

EVALUATION AND CHARACTERIZATION OF NANOEMULSION FORMULATIONS

A full characterization of nanoemulsion systems may be performed only by following standard characterization procedures with respect to particle size distribution, zeta potential, and various spectroscopic detailing, all of which

are vital for ensuring formulation consistency and robustness (Barradas & de Holanda e Silva, 2020; Wang et al., 2022). More so, advanced analytical methods, such as small-angle X-ray scattering and lipophilic fluorescent probe techniques, provide a comprehensive understanding of droplet behaviour, stability parameters, and bio-distribution patterns (Wang et al., 2022).

In Vitro Evaluations

The in vitro evaluation of nanoemulsion formulations is essential for determining parameters such as skin penetration efficiency, release kinetics, and stability profiles. This evaluation employs established techniques, including Franz diffusion cells and high-performance liquid chromatography (HPLC), which are primary methods used to appraise skin absorption behaviors and controlled release mechanisms that facilitate therapeutic optimization (Farooq et al., 2021; Martínez-Razo et al., 2023). Findings have consistently established that nanoemulsion systems provide better skin penetration than conventional formulation systems. Some specific composition systems have been proposed for sustained release to achieve prolonged therapeutic action (Malik et al., 2023; Martínez-Razo et al., 2023). Emphasis is given to the use of specific excipients—particularly terpenes—which affect different release mechanisms and disrupt the stratum corneum lipid matrix, thus allowing more accurate and deeper delivery of the compound (Miastkowska & Śliwa, 2020).

In Vivo Studies and Clinical Efficacy

Evidence for the efficacy of nanoemulsions is further consolidated by exhaustive in vivo studies, particularly from a dermatological perspective where maximum drug retention and improved therapeutic outcomes are crucial. For instance, α -tocopherol-loaded nanoemulsions have demonstrated remarkable enhancement in skin delivery and retention capabilities. Harun et al. (2021) reported that water-rich α -tocopherol nanoemulsions achieved exceptional skin permeation ($87.41 \pm 7.17\%$) and retention ($11.71 \pm 0.20\%$) at 24 hours, significantly outperforming neat α -tocopherol samples which showed minimal permeation ($0.09 \pm 0.00\%$) and retention ($0.07 \pm 0.00\%$) (ANOVA, $p = 0.000$). The water-rich formulation also demonstrated superior performance compared to water-poor nanoemulsions, which achieved $35.99 \pm 4.99\%$ permeation and $2.44 \pm 0.01\%$ retention. FTIR imaging analysis confirmed successful penetration of the nanoemulsion into both epidermis and dermis layers, indicating enhanced transdermal delivery through intercellular pathways.

In animal studies, advanced formulations containing collagen and vitamin C have provided conclusive evidence of stimulating wound healing and preventing UV damage to skin. Yousry et al. (2022) demonstrated that collagen-loaded nanoemulsions exhibited superior cell viability in fibroblast cell lines, with surviving fractions reaching approximately 1.4 for both HFB4 and BHK cells at optimal concentrations. Most significantly, in vivo histopathological investigations revealed that the

combination of collagen and vitamin C-loaded nanoemulsions reduced UVB-induced skin damage to an extent where the skin was free from any detectable alterations, compared to control groups that showed characteristic hyperkeratosis and acanthosis following UVB exposure (Yousry et al., 2022).

Furthermore, glucocorticoid-infused tea tree oil nanoemulsions have shown markedly improved anti-inflammatory responses in preclinical studies. Alam et al. (2019) reported that optimized drug-loaded nanoemulsions achieved 84.51% inhibition of carrageenan-induced paw edema at 12 hours, significantly outperforming placebo nanoemulsions (33.9% inhibition) and marketed preparations (46.03% inhibition) ($p < 0.05$). The enhanced NTPDase activity observed in lymphocytes treated with CP-loaded nanoemulsions (approximately 200 nmol Pi/min/mg protein for both ATP and ADP hydrolysis) was significantly higher compared to control groups, indicating superior anti-inflammatory efficacy through modulation of purinergic signaling pathways.

Additionally, skin irritation studies confirmed the safety profile of these formulations, with mean irritation scores remaining below 2.0 for optimized nanoemulsion gels (1.66 ± 1.03) over a 14-day observation period, falling well within the acceptable range for topical applications. Acute and repeated dose dermal toxicity studies showed no mortality or abnormal histopathological changes in major organs, with only mild keratosis observed at application sites during prolonged exposure (Alam et al., 2019).

These findings prove the efficacy of nanoemulsion systems in the targeted delivery of active ingredients where penetration and retention remain the major therapeutic concerns—especially pronounced in dermatological conditions (Espinoza et al., 2020). The quantitative evidence demonstrates superior therapeutic outcomes through enhanced bioavailability, prolonged retention, and reduced systemic toxicity compared to conventional formulations.

Formulation Optimization

Progressing from the laboratory to application requires a meticulous optimization and scale-up protocol for production. Statistical designs, especially the Box-Behnken design, facilitate the development of formulations within specified parameters of droplet diameter, stability, and bioavailability (Sharma et al., 2019). Crucial aspects of formulation—the surfactant-to-oil ratio and the selected emulsification method—significantly influence both the product quality and the production scalability. Quality assurance protocols, comprising dynamic light scattering and zeta potential measurement, ensure that production is carried out to consistent standards (Gawin-Mikolajewicz et al., 2021; Leibtag & Peshkovsky, 2020).

SAFETY AND TOXICOLOGICAL CONSIDERATIONS

Safety evaluation protocols for nanoemulsion formulations include biocompatibility assessments and

irritation evaluations resulting from long-term topical application. It is currently known that formulations with natural excipients are less toxic and exhibit better skin tolerance than their synthetic counterparts, making them particularly suitable for sensitive applications (Vlaia et al., 2020). For example, terbinafine-loaded nanoemulsions cause minimal skin irritation and have more favourable toxicity profiles, which are thought to be beneficial for chronic disease management (Gul et al., 2022). Additionally, propolis nanoemulsion systems show very good in vitro cytotoxicity profiles, confirming their use in wound healing and skin medicinal applications (Sevinç Özakar et al., 2022). Repeated short-term trials indicate that most nanoemulsions enhance drug delivery and bioavailability; however, very few long-term studies are available, and their effects remain under investigation. Studies suggest that drug accumulation in the body system is very low, though long-term studies are necessary to confirm safety over prolonged use (Eqbal et al., 2021).

REGULATORY AND ETHICAL CONSIDERATIONS

Regulatory frameworks warrant robust protocols for testing nanoemulsion-based products' stability, toxicity, and biocompatibility for human use. The main regulatory requirements include assuring ingredient safety, consistently maintaining production standards, and systematically assessing systemic absorption patterns. These requirements necessitate a comprehensive menu of labelling requirements alongside comprehensive clinical trials (Yousefpoor et al., 2023).

Regulatory and Economic Implications in Commercial Contexts

European Regulatory Framework

The European Union's stringent regulatory approach significantly impacts nanoemulsion commercialization. European Regulation (EC) 1223/2009 establishes comprehensive rules for cosmetic products containing nanomaterials, requiring responsible persons to ensure compliance with safety assessments and labeling requirements (Ferreira et al., 2023). The European Commission maintains a catalogue of authorized nanomaterials, with the Scientific Committee on Consumer Safety (SCCS) providing critical safety opinions.

Specific provisions apply to nanomaterials used as colorants, UV-filters, or preservatives, requiring notification and comprehensive safety assessments before market entry (Ferreira et al., 2023). This regulatory complexity creates significant barriers to commercialization, particularly for smaller companies lacking extensive regulatory expertise.

United States Regulatory Considerations

The FDA's approach differs substantially from European regulations. While the FDA governs nanotechnology in cosmetics through the Federal Food, Drug, and Cosmetic Act (FFDCA), it employs a "risk management" framework

rather than premarket approval requirements (Bilal & Iqbal, 2020). Notably, the United States does not require explicit labeling of nanomaterials, creating potential consumer awareness issues.

The FDA has issued specific guidance on nanomaterial safety in cosmetics, but Bilal & Iqbal (2020) noted that up to 13% of registered cosmetic products contain nanomaterials, highlighting the widespread yet potentially under-regulated use of these technologies.

ECONOMIC AND MARKET IMPLICATIONS

The lack of universally accepted nanomaterial definitions creates varying regulatory approaches globally, significantly impacting international commerce (Ferraris et al., 2021). Companies must navigate multiple regulatory frameworks simultaneously, increasing development costs and time-to-market periods.

Commercial success stories, such as La Prairie's Skin Caviar and Bayer Healthcare's Bepanthol Facial Cream Ultra Protect, demonstrate market acceptance despite regulatory challenges (Martel-Estrada et al., 2022). However, these products typically originate from well-resourced companies capable of meeting complex regulatory requirements.

The economic burden of regulatory compliance particularly affects nanoemulgel formulations, which show superior clinical performance but require extensive stability and safety documentation. Sghier et al. (2024) noted that while nanoemulgel systems offer excellent therapeutic potential, their commercialization faces significant regulatory hurdles due to their novelty and complex characterization requirements.

REGULATORY HARMONIZATION CHALLENGES

Current regulatory disparities between regions create significant compliance burdens for global nanoemulsion commercialization. The European REACH organization's expanding influence on nanoparticle regulation aims to protect human health and environmental safety, while potentially establishing global standards (Dhawan et al., 2020). Companies must increasingly comply with REACH standards for nanoparticle production and use, affecting global supply chains and manufacturing costs.

The regulatory landscape's complexity is compounded by Ferreira et al. (2023) identifying limited data availability and inconsistent regulatory definitions as primary challenges. These factors create uncertainty for commercial investment and extend product development timelines, particularly affecting innovative nanoemulgel formulations that require novel assessment protocols.

Personalized Dermatological Therapies and Innovative Applications

The integration of nanoemulsion technology into dermatological practice represents a fundamental shift toward personalized therapeutic approaches tailored to individual patient requirements. These advanced formulation systems provide the necessary precision for targeted therapy, improving drug delivery mechanisms and enhancing therapeutic outcomes across diverse dermatological conditions (Duarte et al., 2023; Ramanunni et al., 2020b). Continuous innovations in nanocarrier system development facilitate therapeutic approaches specific to various conditions, establishing nanoemulsions as promising interventions for chronic inflammatory conditions, dermatological infections, and oncological applications (Alhasso et al., 2024; Shree et al., 2022).

Advancements in Nanoemulsion Formulations

The development of nanoemulgel systems represents one of the most promising advances within nanoemulsion technology. These systems combine the bioavailability benefits of nanoemulsions with the ease of application characteristic of gels, resulting in excellent penetration and retention of active substances in dermatological tissues. Clinical evidence demonstrates significant improvements in therapeutic outcomes, with nanoemulgel formulations showing remarkable enhancements in drug delivery: flurbiprofen nano-emulsion achieved a 4.4-fold increment in bioavailability, while Nile red dye nano-emulsion demonstrated a 10-fold increase in penetration compared to conventional formulations (Donthi et al., 2023). Additionally, specific therapeutic applications have shown substantial improvements, including celecoxib nano-emulgel achieving 95.5% cumulative release versus 56.90% for commercial formulations, and ketoconazole nano-emulgel demonstrating a 53% increase in permeation compared to marketed cream (Donthi et al., 2023).

Further clinical studies support these findings, with telmisartan nanoemulgel showing a 51% increase in area under the curve (AUC) and higher peak plasma concentrations, while tenofovir nanoemulgel demonstrated a remarkable 39.65-fold enhancement in permeation (Malavi et al., 2022). Eprinomectin formulations exhibited permeability enhancements of 8.07-fold and 5.57-fold compared to suspension formulations (Malavi et al., 2022). This dual functionality enhances therapeutic efficacy and patient compliance across various dermatological applications. Nanoemulgel systems are characterized by their versatility in encapsulating active agents, ranging from conventional pharmaceuticals to repurposed therapeutic agents and natural compounds, with some formulations enhancing skin permeability "in several folds" for lipophilic drugs (Sghier et al., 2024).

Table 3: Commercial Products Utilizing Nanoemulsion Technology

Brand/Product Name	Company	Primary Function	Key Ingredients/Features	Therapeutic Outcomes	Formulation Outcomes	Year of Publication
Skincare Products						
Skin Caviar	La Prairie	Anti-aging	Caviar extract, marine proteins, peptides	Restores skin elasticity and tone; provides instant and lasting hydration; reduces fine lines and wrinkles; enhances skin firmness and brightness; visible lift in 15 minutes; jawline lift up to 1 cubic centimeter; supports skin architecture; targets wrinkle count, depth, and volume	Nanoemulsion technology enhances moisturizing properties and active ingredient penetration	(Martel-Estrada et al., 2022)
Bepanthol Facial Cream Ultra Protect	Bayer Healthcare	Facial care	5% provitamin B5, antioxidants	Effective for eczema, rashes, wounds, and psoriasis; maintains skin flexibility and moisture; protects against environmental factors and free radicals; prevents premature aging; nourishes dry and sensitive skin	Modern nanoemulsion formulation for enhanced daily facial care delivery	(Martel-Estrada et al., 2022)
Nanovital VITANICS Crystal Moisture Cream	Vitacos Cosmetics	Skin whitening & anti-aging	Niacinamide, arbutin, vitamin C, oriental herbs	Optimizes skin activity; provides UV protection; delivers anti-oxidative effects; achieves skin whitening and anti-aging benefits	100% true nanoemulsion cream formation for enhanced ingredient stability and penetration	(Martel-Estrada et al., 2022)
Nano Emulsion Multi-Peptide Moisturizer	Hanacure	Skin texture improvement	Multi-peptides, sodium hyaluronate, squalene, mushroom extract	Reduces fine lines and wrinkles; provides skin firming and tightening; improves skin tone, texture, and clarity; reduces inflammation and acne; delivers long-lasting hydration	Lightweight, ultra-hydrating formulation using specialized nanotechnology process	(Martel-Estrada et al., 2022)

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Table 3 continued

Brand/Product Name	Company	Primary Function	Key Ingredients/Features	Therapeutic Outcomes	Formulation Outcomes	Year of Publication
Skincare Products						
Phyto-Endorphin Hand Cream	Rhonda Allison	Revitalizing moisturizer	Vitex agnus-castus casticin extract, Bellis perennis flower extract, lecithin, cholesterol, corn oil, soybean oil	Provides radiant glow; softens and smooths skin; strengthens thinning skin; reduces pigmentation; mood-enhancing activity	Nanoemulsion system with potent antioxidants, moisturizing factors, and skin lighteners	(Mohd-Setapar et al., 2022)
Olivenol Anti Falten Pflegekonzentrat Cream	Dr. Theiss	Anti-aging	Olive oil (Olea europaea), Acacia senegal	Anti-aging effects; moisturizing; skin lightening properties	Nanoemulsion delivery system for enhanced olive oil bioavailability	(Mohd-Setapar et al., 2022)
Body Care Products						
Bruma De Leite	Natura	Body moisturizing	Moisturizing complex	Enhanced body hydration and moisturization	Nanoemulsion technology for improved skin penetration	(Martel-Estrada et al., 2022)
Coco Mademoiselle Fresh Moisture Mist	Chanel	Body moisturizing	Fragrance oils, moisturizing agents	Moisturizes skin; enhances fragrance longevity; reduces moisture loss; softens skin	Fresh body mist with airy texture through nanoemulsion formulation	(Martel-Estrada et al., 2022)
Hair Care Products						
Korres Red Vine Hair Sun Protection Spray	Korres	Hair protection	Red vine polyphenols, Helianthus annuus seed extract, aloe vera, provitamin B5, UV filters	Provides lightweight sun protection; nurtures sun-damaged hair; prevents hair color fading; protects from UV light and free radicals; revitalizes hair	Water-resistant UV filters in nanoemulsion delivery system	(Mohd-Setapar et al., 2022)
Pureology Colour Max	Pureology	Anti-fading	Color protection complex	Hair color protection; anti-fading effects; strengthens and repairs color-treated hair; renews softness and shine	Advanced delivery system for color protection actives	(Ferraris et al., 2021)

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Table 3 continued

Brand/Product Name	Company	Primary Function	Key Ingredients/Features	Therapeutic Outcomes	Formulation Outcomes	Year of Publication
Specialized Treatments						
Azelaic Acid Formulation	Not specified	Skin whitening/Acne treatment	Azelaic acid, hyaluronic acid	Enhanced topical delivery; reduces inflammatory and non-inflammatory acne lesions; treats comedonal, pustular, and nodular acne; anti-inflammatory and antibacterial effects; treats hyperpigmentation, melanoma, and rosacea	Nanoscale droplets for enhanced skin penetration and controlled drug release	(Martel-Estrada et al., 2022)
Citral Nanoemulsion	Health Sciences and Management Universities Consortium	Antimicrobial	Citral, deionized water, cosolvent	Antimicrobial activity against <i>Listeria monocytogenes</i> ; reduces biofilm formation; neuroprotective and antioxidant activity; anti-inflammatory effects; wound healing properties	Protects citral from degradation; penetrates bacterial lipid structure; increases delivery efficiency	(Martel-Estrada et al., 2022)
Commercial Nanoemulsion Base						
Nanocream	Sinerga	Emulsifier base	Vegetable-based substances, lipoaminoacids, palm glycerides	Serves as foundation for various therapeutic formulations	Enables production of stable oil/water nanoemulsions for cosmetic applications	(Martel-Estrada et al., 2022)
Precision Skincare						
Precision-Solution Destressante Solution	Chanel	Sensitive skin care	Specialized nanoemulsion complex	Targeted care for sensitive and reactive skin types	Nanoemulsion formulation optimized for sensitive skin tolerance	(Ferraris et al., 2021)
Coni Beauty Hyaluronic Acid & Nanoemulsion	Coni Beauty	Intensive hydration	Hyaluronic acid, hydration complex	Intensive skin hydration and moisture retention	Nanoemulsion toner for enhanced hyaluronic acid delivery	(Ferraris et al., 2021)
Marie Louise Vital Nanoemulsions A-VC	Marie Louise	Anti-aging	Vitamin A, Vitamin C complex	Anti-aging benefits through vitamin delivery	Vitamin-enriched nanoemulsion for enhanced stability and penetration	(Ferraris et al., 2021)

Integration with Advanced Monitoring Technologies

The evolution of seamless, real-time dermatological treatment may soon integrate wearable skin sensor technology with nanoemulsion-based therapeutic systems, enabling responsive dermatological care. Continuous monitoring of skin conditions could facilitate adaptive drug release mechanisms that respond to dynamic physiological conditions, potentially revolutionizing treatment efficiency and patient satisfaction (Harun et al., 2021).

Commercial Development

The commercialization of nanoemulsion-based dermatological formulations is experiencing rapid market expansion. Products targeting common dermatological conditions, such as acne and eczema, along with advanced applications in skin cancer, are increasingly entering the commercial market (Table 3). In every aspect, these products surpass traditional topical preparations in terms of bioavailability and stability. Moreover, they promise to capitalize on the growing market demand for novel dermatological products, aided by scalable production capabilities (Duarte et al., 2023; Tapfumaneyi et al., 2022).

Nanoemulsion systems offer myriad therapeutic possibilities yet face setbacks regarding clinical and commercial applications. Specific challenges include ensuring droplet stability, maintaining formulation consistency, and efficiently producing large batches according to established protocols without sacrificing treatment efficacy. Improvements in regulatory stipulations that address the unique features of nanoemulsion substances are necessary to guarantee safety and quality standards during mass manufacturing (Yousefpoor et al., 2023; Panthi et al., 2023). Ongoing research is critical to overcoming these challenges and enhancing the clinical applicability of nanoemulsions in therapeutic systems.

CONCLUSION

Drug delivery using nanoemulsions has opened up new avenues in dermatotherapy, since such advanced applications are able to bypass the limitations imposed by regular topical applications. With highly precise nano-engineering processes, parameters such as droplet size, zeta potential, and surface characteristics can be manipulated to allow for a fine-tuning of the drug-delivery kinetics, being able to target skin pathologies with minimal systemic effects. Nanoemulsion preparations are able to ensure stability and greater skin permeability, thus serving as effective systems capable of handling a variety of dermatological conditions, from psoriasis to even advanced melanoma.

However, the translation from laboratory success to clinical reality remains constrained by significant knowledge gaps. The question is not whether nanoemulsions will transform dermatological practice, but how quickly the scientific and regulatory communities can address the critical barriers that currently limit their widespread clinical adoption. These barriers encompass

the need for standardized safety assessment protocols, harmonized regulatory frameworks across international markets, and comprehensive long-term safety validation studies.

The future of precision dermatology depends on our immediate commitment to rigorous safety validation, regulatory innovation, and collaborative research excellence. Future research must prioritize optimizing zeta potential profiles for enhanced follicular delivery, establishing robust clinical trial frameworks for long-term safety assessment, and developing cost-effective manufacturing processes that ensure accessibility across diverse healthcare systems. Nanoemulsion technology can only fulfil its transformative potential in revolutionizing dermatological therapeutics through this comprehensive approach.

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