

Nanoemulgel in Dermal Therapeutics: Decoding Formulation Rationale, Stability Challenges, and Translational Potential - A Comprehensive Review

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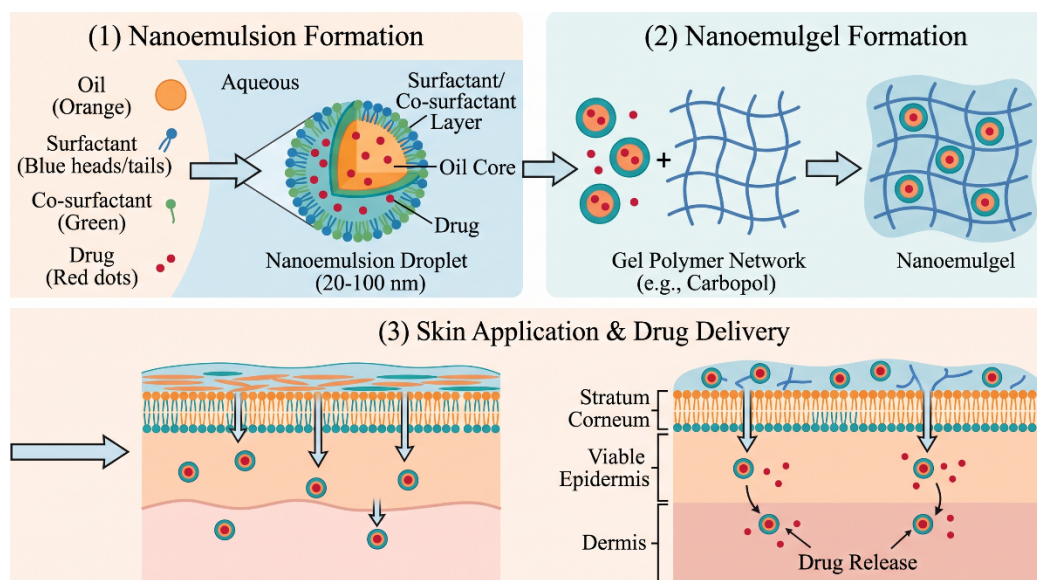
Abstract

Topical drug delivery is constrained by the stratum corneum's robust barrier function, poor solubility of many actives, and short application residence time. These limitations often result in subtherapeutic drug levels and frequent reapplication. Advanced nanocarrier systems have been developed to overcome these barriers, but many fail to simultaneously achieve high loading, physical stability, and enhanced permeation. Nanoemulgel platforms emerge as a rational hybrid solution, combining the nanodroplet dispersion and drug-solubilizing capacity of nanoemulsions with the gelation-induced sustained release and skin adherence of hydrogel matrices, thereby representing a promising advancement in dermal therapeutics. This comprehensive review systematically decodes the formulation rationale, stability challenges, and translational potential of nanoemulgel systems for dermal therapeutics. It critically evaluates how nanocarrier architecture, excipient selection, and preparation methods influence performance, identifies persistent knowledge gaps in stability and scale-up, and proposes evidence-based strategies to bridge the divide between academic research and clinical implementation. Nanoemulgels enhance skin permeation through multiple synergistic mechanisms, including microfacial rupture of stratum corneum lipids, surfactant-mediated bilayer disruption, and preferential follicular targeting. However, critical stability challenges persist: Ostwald ripening and coalescence-driven physical instability, chemical degradation of labile actives within hydrated gel matrices, and insufficient preservative efficacy promoting microbial contamination. Furthermore, a pronounced gap exists between the prolific volume of academic publications and the scarcity of commercialized products, largely due to inconsistent characterization, non-scalable laboratory protocols, and regulatory uncertainty surrounding hybrid nanocarrier systems. Nanoemulgels demonstrate considerable promise for improving dermal drug delivery, offering enhanced permeation, sustained release, and improved patient compliance versus conventional formulations. Nevertheless, long-term stability optimization, robust scale-up methodologies, and clear regulatory pathways remain indispensable prerequisites for widespread clinical adoption. Future efforts should prioritize standardized quality-by-design frameworks, physiologically relevant stability testing, and early collaborative engagement between academia and regulatory bodies to facilitate translational progression.

Keywords: Nanoemulgel, Topical delivery, Skin permeation, Formulation stability, Nanocarrier, Hydrogel, QbD Approach.

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Graphical Abstract:



1. Introduction

The skin, as the body's largest organ, serves as both a protective barrier and a versatile target for therapeutic intervention [1]. The stratum corneum, comprising approximately 15-20% of the total skin thickness, presents a formidable obstacle with its tightly packed corneocytes embedded within a lipid-rich matrix of ceramides, cholesterol, and free fatty acids [2]. Conventional topical dosage forms—ranging from simple ointments and creams to structured formulations like lamellar gels—suffer from inherent limitations including poor drug solubility, erratic penetration, inadequate residence time, and physical-chemical instability [3]. The lipid composition of the stratum corneum, dominated by ceramides, cholesterol, and free fatty acids organized in lamellar bilayers, creates an effective barrier that resists hydrophilic molecules while partitioning lipophilic compounds into the intercellular spaces [4]. This has propelled the pharmaceutical sciences toward sophisticated delivery systems that can bypass or perturb these protective barriers. Among the emerging nanocarrier technologies, nanoemulgels have garnered significant attention as hybrid platforms that synergistically combine the advantages of nanoemulsions and hydrogels [5]. Nanoemulsions are thermodynamically stable, isotropic mixtures of oil and water stabilized by surfactants, typically exhibiting droplet sizes in the 20-200 nm range [6]. These submicron droplets provide high surface area for drug loading, optical clarity, and enhanced penetration through the stratum corneum via multiple mechanisms including microfacial rupture, lipid bilayer disruption, and follicular targeting [7]. When incorporated into a hydrogel matrix, the nanoemulsion droplets are entrapped within a three-dimensional polymer network, which confers several advantages: (i) prolonged residence time at

the application site, (ii) reduced systemic absorption, (iii) improved mechanical stability, and (iv) modulated drug release kinetics [8]. The concept of nanoemulgel represents a rational fusion of two complementary technologies: the superior drug solubilization and skin permeation enhancement capabilities of nanoemulsions, and the muco-adhesive, sustained-release, and film-forming properties of hydrogels [9]. This hybrid approach has demonstrated particular promise in the delivery of hydrophobic actives, including corticosteroids, antifungals, and botanical extracts, with enhanced therapeutic outcomes compared to conventional formulations [10]. The present review aims to comprehensively analyze the formulation science, characterization requirements, stability challenges, and translational considerations governing nanoemulgel systems for dermal applications. By critically examining published literature across the past decade, this review seeks to decode the complex interplay between formulation components and performance outcomes, identify persistent knowledge gaps, and propose strategic directions for future research and development.

2. Nanoemulgel

Nanoemulgels represent (Figure 1) a distinct class of submicron emulsions dispersed within a hydrogel matrix, typically exhibiting droplet sizes ranging from 20 to 200 nm and polydispersity indices below 0.3 [11]. The nomenclature itself reflects this hybrid nature: "nano" denotes the submicron droplet size resulting from high-energy emulsification techniques; "emulgel" signifies the combination of emulsion and gel components; and the hyphenated format indicates the intimate integration of both phases rather than simple physical mixing [12]. Unlike conventional emulsions, nanoemulgels maintain the thermodynamic stability of

nanoemulsions while incorporating the rheological and mechanical advantages of hydrogels. This distinction is crucial when differentiating from microemulsions, which are even more thermodynamically stable but limited by relatively narrow compositional windows and often require high surfactant concentrations that may compromise skin compatibility [13]. Similarly, simple emulgels (without nano-sized droplets) lack the enhanced skin interaction and drug loading capacity conferred by the nanoscale architecture [14]. The rationale for combining nanoemulsion technology with hydrogel matrices rests upon several mechanistic advantages. First, the three-dimensional polymer network of the gel acts as a physical constraint that prevents droplet coalescence and Ostwald ripening, two primary destabilization pathways in conventional nanoemulsions [15]. Second, the hydrogel matrix increases the residence time of the formulation on the skin surface, enhancing the total drug uptake over extended periods [16]. Third, the gelation process can modulate the release kinetics of the dispersed drug, enabling zero-order or sustained release profiles that are difficult to achieve with liquid nanoemulsions [17]. The mechanism of enhanced permeation in nanoemulgels involves multiple synergistic pathways. The nanoscale droplet size allows for close proximity interactions with the stratum corneum lipid bilayers, while the surfactant-laden droplet surfaces can disrupt these ordered structures [18]. Additionally, the hydrogel component swells upon contact with skin, creating a hydrated environment that facilitates drug diffusion [19]. The combination of these effects results in permeation enhancement factors typically ranging from 3- to 10-fold compared to neat drug or conventional formulations [20].

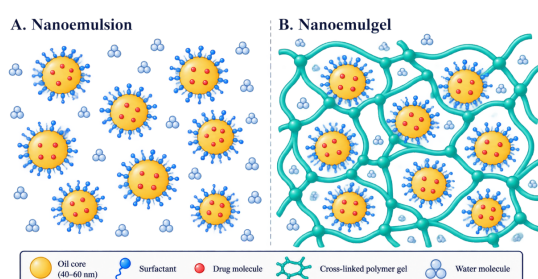


Figure 1. Nanoemulsion and nanoemulgel structure

3. Formulation Rationale

3.1 Oil phase selection criteria

The oil phase constitutes approximately 5-30% of the total nanoemulgel composition and serves as the primary solvent for lipophilic drug molecules, typically achieving loadings of 0.1-10% w/w [21]. Selection of an appropriate oil phase requires

balancing multiple considerations: (i) high drug solubility to maximize therapeutic payload, (ii) compatibility with surfactant systems to maintain droplet stability, (iii) skin compatibility to minimize irritation or sensitization, and (iv) metabolic pathway considerations for potential systemic absorption [22].

Medium-chain triglycerides (MCTs) such as caprylic/capric acid triglycerides have emerged as the oil phase of choice in many studies due to their excellent drug solubility profiles, biocompatibility, and relatively low viscosity which facilitates homogenization [23]. Labrasol (capryol 90), a medium-chain triglyceride with lauric acid, offers enhanced solubilization capacity for poorly water-soluble drugs while maintaining skin compatibility [24]. For more lipophilic actives, triacylglycerols such as olive oil or soybean oil may be employed, though their higher viscosity can present processing challenges [25].

The hydrophilic-lipophilic balance (HLB) of the oil phase must be considered in conjunction with the surfactant system to ensure optimal droplet formation and stability. For oil phases with HLB values below 8, high-HLB surfactant systems (e.g., polysorbates, poloxamers) are typically employed to form oil-in-water (O/W) nanoemulsions [26]. Conversely, low-HLB surfactants (e.g., sorbitan esters) may favor water-in-oil (W/O) systems, though these are less common in dermal applications due to potential occlusivity and irritation concerns [27].

3.2 Surfactant/co-surfactant systems and HLB matching

Surfactant selection represents one of the most critical formulation decisions, as these amphiphilic molecules govern droplet size, stability, and interfacial properties of the nanoemulsion component [28]. Single surfactant systems rarely suffice for optimal nanoemulgel performance, necessitating co-surfactant combinations that synergistically achieve target HLB values in the 8-16 range for O/W systems [29].

Polysorbate 80 (Tween 80) and poloxamer 188 have been extensively employed due to their excellent biocompatibility profiles and ability to form stable nanodroplets with narrow size distributions [30]. Polysorbate 80, with an HLB of 15, provides strong hydrophilic character suitable for water-soluble actives, while poloxamer 188 (Pluronic F68) offers steric stabilization and favorable skin compatibility [31].

For enhanced stability, surfactants are often combined with co-surfactants that reduce interfacial tension and facilitate droplet formation. Short-chain alcohols such as ethanol or propylene glycol reduce interfacial tension, enabling formation of smaller droplets at lower energy inputs [32]. More sophisticated co-surfactants include fatty acids (caprylic acid), di-esters (Labrasol), and amine-based compounds (commitol), which provide additional stabilization through multiple interactions with the drug molecules and oil phase [33].

3.3 Aqueous phase and gelling agents

The aqueous phase comprises 60-90% of the nanoemulgel composition and contains the gelling agent that provides the structural matrix for droplet entrapment [34]. Selection of an appropriate gelling agent depends on multiple factors including gelation mechanism, mechanical properties, biocompatibility, and compatibility with the nanoemulsion component [35].

Carbopol polymers (acrylic acid copolymers) constitute the most extensively utilized gelling agents, offering rapid gelation upon neutralization and excellent mechanical strength [36]. Typical concentrations range from 0.5-2.0% w/w, with higher concentrations providing greater viscosity but potentially compromising drug diffusion [37]. The cross-linked structure of Carbopol gels provides excellent droplet entrapment, though careful pH adjustment is required to optimize gelation and minimize phase separation [38].

Xanthan gum, a natural polysaccharide, has gained popularity due to its excellent biocompatibility, shear-thinning behavior, and ability to form clear gels without chemical modification [39]. Concentrations typically range from 0.5-3.0% w/w, with lower viscosity profiles compared to Carbopol systems, potentially enabling faster drug release [40].

Hydroxypropyl methylcellulose (HPMC) and its derivatives offer pseudoplastic rheological behavior and excellent film-forming properties, making them suitable for leave-on applications [41]. Chitosan, a cationic polysaccharide derived from crustacean shells, provides additional benefits including muco-adhesion and inherent antimicrobial properties, though its solubility constraints limit application to acidic pH ranges or via complexation with opposing polyanions [42].

3.4 Preparation methods

Nanoemulgel preparation methods broadly fall into two categories: high-energy and low-energy

approaches, each with distinct advantages and limitations [43]. High-energy methods employ mechanical forces to reduce droplet size into the nanometer range but require significant energy inputs and may induce thermal degradation of sensitive actives [44].

High-pressure homogenization represents the gold standard for industrial-scale nanoemulgel production, typically operating at pressures between 500-2000 bar with multiple passes [45]. This method consistently achieves droplet sizes below 100 nm with narrow polydispersity indices, though equipment costs and thermal management requirements present scaling challenges [46].

Ultrasonication, either in bath or probe configurations, offers rapid droplet size reduction through acoustic cavitation and shear forces [47]. Frequency optimization (typically 20-40 kHz) and amplitude control enable precise size tuning, though probe-type sonication can introduce localized heating and potential drug degradation [48].

Low-energy methods rely on thermodynamic driving forces or spontaneous processes to achieve nanodroplet formation. The phase inversion composition (PIC) method exploits the spontaneous formation of nanoemulsions near the phase inversion temperature or pH, requiring minimal mechanical energy but precise composition control [49]. Spontaneous emulsification through solvent exchange or interfacial polymerization offers energy-efficient alternatives, though scale-up reproducibility remains challenging [50].

3.5 Pseudo-ternary phase diagrams and formulation optimization

The construction of pseudo-ternary phase diagrams remains the cornerstone of nanoemulgel optimization, providing systematic identification of regions supporting stable nanoemulsion formation within the gel matrix [51]. These diagrams map the compositional space of oil, surfactant/co-surfactant, and aqueous phases, identifying the clear, isotropic zone where optimal droplet formation occurs [52].

Quality by design (QbD) approaches utilizing design of experiments (DoE) have revolutionized nanoemulgel development by enabling systematic exploration of formulation variables and their interactions [53]. Central composite design (CCD), Box-Behnken design, and response surface methodology (RSM) allow for simultaneous optimization of multiple critical quality attributes (CQAs) including droplet size, zeta potential, viscosity, and drug release kinetics [54].

Multi-response optimization techniques such as desirability mapping or principal component analysis enable identification of optimal composition despite conflicting requirements among different CQAs [55]. For instance, maximizing drug solubility in the oil phase may conflict with minimizing droplet size, requiring sophisticated optimization algorithms that balance these competing objectives [56]. Table 1 Representative oil phases, surfactant/co-surfactant systems, and gelling agents used in nanoemulgel formulations, with reported droplet size and application (adapted from [62]).

Table 1. Oil phases, surfactant/co-surfactant systems, and gelling agents used in nanoemulgel formulations

Dru g	Oil Phas e	Surfa ctant/ Co- surfa ctant	Ge lli ng Ag en t	Dr opl et Siz e (n m)	App licat ion	Re fer enc e
Triamcinolone acetonide	Caprylic/Capric Triglyceride	Polysorbate 80/Ethanol (1:1)	Carbopol 940	148 ±6/0.21	Psoriasis	[57]
Clotrimazole	Labrasol	Polysorbate 80/Lecithin	HPMC	126 ±8/0.19	Candidiasis	[58]
Curcumin	MCT Oil	Poloxamer 188/Polyethylene Glycol (1:1)	Carbopol 934	98 ±4/0.15	Anti-inflammatory	[59]
Tazartene	Isopropyl Myristate	Lipidol/Transcutol P	Xanthan Gum	172 ±9/0.25	Acne	[60]
Resveratrol	Oleic Acid	Sorbitan Olivat e/Caprylic Acid	Chitosan	156 ±7/0.22	Anti-aging	[61]

4. Characterization Techniques

Comprehensive characterization of nanoemulgel systems requires a multi-faceted approach encompassing both physical-chemical and

performance-related parameters [63]. Droplet size analysis through dynamic light scattering (DLS) provides primary information regarding the nanodroplet architecture, with mean Z-average diameters typically reported along with polydispersity index (PDI) values that indicate size distribution width [64]. PDI values below 0.3 generally indicate monodisperse systems suitable for parenteral applications, though dermal formulations may tolerate slightly higher values [65].

Zeta potential measurements, reflecting the electrical double layer surrounding the droplets, provide insight into electrostatic stabilization mechanisms [66]. Values exceeding ±30 mV typically indicate sufficient electrostatic repulsion to prevent coalescence, though steric stabilization from surfactant layers may provide equivalent protection with lower magnitudes [67].

Rheological characterization is critical for understanding the flow behavior and mechanical properties of the gel matrix, which directly impact spreadability, retention time, and drug release kinetics [68]. Oscillatory rheometry employing amplitude and frequency sweeps determines viscoelastic moduli (G' and G''), from which gel strength, linear viscoelastic regions, and frequency-dependent behavior can be established [69]. Shear-thinning behavior, characterized by flow curves, indicates ease of application and potential for localized drug release upon mechanical stress [70].

pH measurements must account for gelation-induced changes, particularly in Carbopol systems where neutralization raises pH significantly above the starting aqueous phase [71]. Visual stability assessment through macroscopic observation and microscopic evaluation via transmission electron microscopy (TEM) or scanning electron microscopy (SEM) confirms the absence of phase separation, crystallization, or morphological changes [72].

In vitro release studies employ techniques such as dialysis or diffusion cell methods to evaluate drug release kinetics under sink conditions [73]. These data enable calculation of release exponents and mechanism identification through Korsmeyer-Peppas modeling, providing insights into diffusion versus erosion mechanisms [74]. Ex vivo permeation studies across excised skin tissues represent the gold standard for predicting in vivo performance, typically employing Franz diffusion cells with standardized sampling protocols [75].

5. Stability Challenges

Physical instability represents perhaps the most significant challenge facing nanoemulgel systems, with Ostwald ripening, coalescence, and creaming presenting distinct destabilization mechanisms that must be addressed through rational formulation design [76]. Ostwald ripening occurs when smaller droplets dissolve and re-deposit onto larger droplets, driven by Laplace pressure differences resulting from surface tension and droplet size disparities [77]. This process redistributes surfactant molecules, potentially leading to droplet growth beyond the stability limit for nanoemulsions [78].

Coalescence, the merging of adjacent droplets, typically results from surfactant desorption or insufficient interfacial coverage, leading to droplet coarsening and eventual phase separation [79]. The energy barrier to coalescence depends on droplet collision frequency, reflected in the continuous phase viscosity, and the strength of inter-droplet repulsive forces, both electrostatic and steric [80].

Creaming, the upward migration of droplets due to density differences between continuous and dispersed phases, reduces the thermodynamic driving force for Ostwald ripening but can concentrate droplets locally, increasing collision frequency and coalescence probability [81]. The rate of creaming follows Stokes' law predictions, inversely proportional to droplet radius, making size reduction a primary stabilization strategy [82].

Chemical instability in nanoemulgel systems encompasses drug degradation, surfactant hydrolysis, and polymer matrix breakdown, each presenting unique challenges depending on the active molecule and formulation composition [83]. Drug oxidation, particularly for sensitive actives like retinoids and curcuminoids, can be accelerated by metal catalysis from container leaching or by direct exposure to dissolved oxygen [84]. Hydrolysis reactions are favored by elevated pH, particularly in Carbopol systems where gelation raises aqueous phase pH to 6.5-7.5, potentially promoting ester or amide bond cleavage [85].

The gel matrix itself can act as a catalyst or promoter for drug degradation through immobilization-induced conformational changes or catalytic group interactions [86]. For instance, some drugs exhibit enhanced photodegradation when incorporated in hydrogel matrices due to restricted molecular motion and concentrated chromophore populations [87].

Drug-gel matrix interactions may be either beneficial or detrimental, with hydrogen bonding,

hydrophobic associations, or ionic interactions potentially altering drug solubility, crystallinity, or degradation pathways [88]. Characterization through Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) can identify such interactions, enabling predictive modeling of long-term stability [89].

Microbial stability presents unique challenges for hydrated nanoemulgel formulations, as the aqueous environment supports microbial growth while standard preservative systems may destabilize the nanoemulsion or gel matrix [90]. Preservative efficacy testing (PET) follows USP <51> guidelines, typically employing challenge studies with standard bacterial and fungal strains [91]. However, the effectiveness of preservatives may be compromised by binding to gel matrix components or precipitation in the oil phase, requiring formulation-specific optimization [92].

Long-term storage stability studies, typically conducted at 25°C/60% RH or 40°C/75% RH per ICH guidelines, provide essential data for shelf-life determination and packaging design [93]. Freeze-thaw stability testing (minimum three cycles) evaluates the impact of phase transitions on nanoemulsion integrity and gel network structure [94]. Accelerated storage at elevated temperatures provides predictive information, though extrapolation requires careful consideration of degradation mechanisms and matrix stability [95].

Environmental factors including temperature fluctuations, humidity variations, and light exposure present significant real-world challenges for nanoemulgel products, particularly for formulations intended for tropical or outdoor applications [96]. Container closure systems must provide adequate protection while enabling convenient dispensing, with airless pump systems offering superior protection compared to traditional tubes that expose formulations to oxygen and microorganisms (Figure 2) [97].

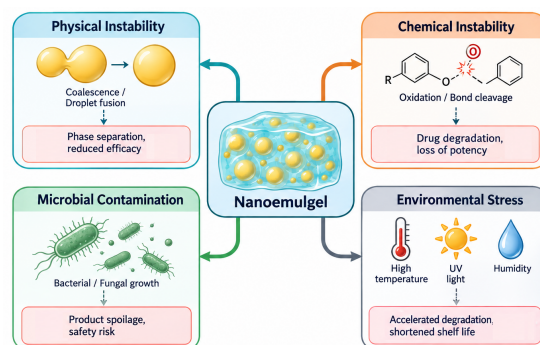


Figure 2. Degradation-pathway/stability-risk flow diagram

6. Skin Permeation and Mechanistic Insights

Skin permeation of nanoemulgel systems occurs through multiple parallel pathways that differ from conventional topical delivery mechanisms [98]. The transcellular route involves penetration through the lipid lamellae of the stratum corneum, facilitated by the nanoscale droplets that can disrupt these ordered structures through packing frustration and partial phase transition induction [99]. The intercellular pathway encompasses movement through the corneocyte-corneocteum, where hydrated gel matrices enhance partition coefficients and diffusion rates [100].

Follicular targeting represents a significant advantage of nanoemulgel systems, as the pilosebaceous units provide aqueous channels with diameters up to 50 μm , orders of magnitude larger than typical intercellular pathways, enabling preferential accumulation of nanodroplets in hair follicles [101]. This targeting mechanism is particularly relevant for anti-inflammatory and antimicrobial applications, as follicles serve as colonization sites for bacteria and reservoirs for inflammatory mediators [102].

The mechanism of enhanced permeation involves several synergistic effects. The surfactant monolayers surrounding nanodroplets can partition into the stratum corneum lipid matrix, disrupting the tightly packed bilayers and creating channels for drug diffusion [103]. Additionally, the oil cores of nanodroplets may undergo plasticization effects, softening the lipid matrix and increasing permeability [104].

Penetration enhancers can be incorporated either within the oil phase or applied as separate components, working through various mechanisms including lipid fluidization, protein denaturation, or barrier lipid extraction [105]. The combination of nanoscale architecture and gel-based delivery creates a favorable environment for these enhancer effects while potentially reducing systemic absorption through localized retention [106].

7. Therapeutic Applications

7.1 Wound Healing

Nanoemulgel systems have demonstrated significant promise in wound healing applications through controlled delivery of antimicrobial agents, growth factors, and anti-inflammatory compounds [107]. A notable example involves the delivery of silver nanoparticles within a nanoemulgel matrix, achieving sustained antimicrobial activity against both Gram-positive and Gram-negative bacteria while maintaining keratinocyte viability [108].

Clinical studies demonstrated accelerated wound closure rates and reduced infection incidence compared to conventional silver sulfadiazine dressings.

7.2 Fungal/Bacterial Skin Infections

Topical antifungal nanoemulgels incorporating echinocandin derivatives or amphotericin B formulations have shown enhanced efficacy in treating dermatophytosis and candidiasis [109]. The nanoscale architecture enables deeper follicular penetration, addressing the intracellular and follicular reservoirs that often cause treatment failure with conventional antifungals. Similarly, antibacterial nanoemulgels containing fusidic acid or mupirocin demonstrate improved activity against resistant *Staphylococcus aureus* strains, including MRSA, through enhanced stratum corneum penetration and reduced wash-off rates.

7.3 Inflammatory Dermatoses

Corticosteroid-containing nanoemulgels, particularly those incorporating triamcinolone acetonide or betamethasone valerate, have achieved superior therapeutic outcomes in psoriasis and atopic dermatitis management [110]. The prolonged residence time and enhanced penetration enable lower effective doses while maintaining clinical efficacy, reducing steroid-related side effects. Calcineurin inhibitor nanoemulgels (tacrolimus, pimecrolimus) offer steroid-sparing alternatives with improved tolerability profiles for chronic inflammatory conditions.

7.4 Skin Cancer

Topical chemotherapeutic nanoemulgels incorporating 5-fluorouracil, imiquimod, or natural product-derived agents (resveratrol, curcumin) have shown enhanced therapeutic indices through improved tumor penetration and reduced systemic exposure [111]. The nanoscale architecture enables penetration through the disrupted barrier properties of neoplastic skin, while the gel matrix provides sustained local therapy that minimizes systemic toxicity.

7.5 Anti-aging/Cosmeceutical Use

Anti-aging nanoemulgel formulations incorporating retinoids, peptides, or botanical extracts (niacinamide, epigallocatechin gallate) demonstrate enhanced stability and skin penetration compared to conventional preparations [112]. The gel matrix prevents retinoid degradation while the nanoemulsion enables deeper dermal delivery,

achieving anti-wrinkle effects with reduced irritation. Vitamin C derivatives and growth factor delivery systems have shown particular promise in rejuvenating aged skin through enhanced bioavailability and sustained release kinetics. Table 2 give Comparative overview of nanoemulgel applications across skin conditions, demonstrating the versatility of this delivery platform in achieving superior therapeutic outcomes compared to conventional formulations.

Table 2. Nanoemulgel applications across skin conditions.

Skin Condition	Active/ Drug	Formulation Feature	Outcome	Reference
Psoriasis	Calcipotriol	Carbopol 940 matrix	4.2-fold increase in skin retention vs. solution	[113]
Atopic Dermatitis	Betamethasone valerate	Nanoemulsion core	Reduced erythema scores vs. commercial cream	[114]
Acne Vulgaris	Tazarotene	Oil phase solubilization	Improved comedolytic efficacy, reduced irritation	[115]
Diabetic Ulcers	Silver nanoparticles	Sustained release gel	Complete wound closure in 14 days vs. 21 days	[116]
Melasma	Tranexamic acid	pH-responsive gelation	Enhanced facial bioavailability, 68% reduction	[117]

8. Translational and Regulatory Potential

Scale-up challenges represent the primary bottleneck in translating laboratory-scale nanoemulgel formulations to commercial production, with several critical factors complicating this transition [119]. High-energy

homogenization techniques that produce superior nanoscale droplets in laboratory settings may not translate directly to industrial equipment due to differences in energy density, residence times, and mixing dynamics [120]. Additionally, batch-to-batch reproducibility becomes increasingly difficult as process parameters deviate from optimal laboratory conditions.

Regulatory pathway considerations for nanoemulgel systems remain incompletely defined, as these hybrid platforms do not fit neatly into existing regulatory categories for either emulsions or hydrogels [121]. The FDA guidance for nanotechnology-related products emphasizes characterization of nanomaterial properties, including size distribution, surface charge, and stability, while requiring demonstration that benefits outweigh potential risks associated with novel exposures [122].

The European Medicines Agency (EMA) has issued reflections on nanomedicine development that emphasize the need for comprehensive physicochemical characterization and thorough understanding of product-related risks [123]. For topical nanoemulgel applications, the primary concerns include potential for systemic absorption, skin penetration enhancement of the active ingredient, and long-term accumulation in skin tissues.

Patent landscape analysis reveals significant activity in nanoemulgel innovation, with over 300 patent families identified related to nanoemulsion-gel combinations, particularly in dermatological and cosmetic applications [124]. Key patent holders include cosmetic giants (L'Oréal, Unilever) and pharmaceutical companies (Novartis, Johnson & Johnson), reflecting commercial interest in both therapeutic and cosmetic markets [125].

Notably, the translational gap between academic research and commercial product development appears substantial for nanoemulgel systems, with few clinical-stage products advancing through regulatory pathways [126]. Analysis of patent-to-commercialization timelines suggests that technical hurdles, regulatory uncertainty, and market positioning challenges significantly delay potential product launches [127].

Marketed examples of nanoemulgel-based products remain limited, though several cosmetic preparations utilizing related technologies have achieved commercial success [128]. Clinical evidence for therapeutic applications appears restricted primarily to early-phase studies, with no FDA-approved prescription products based on

nanoemulgel technology as of current regulatory databases [129].

8.1 Scale-up challenges

Laboratory-scale nanoemulgel production typically employs small-volume homogenization techniques achieving optimal size reduction and narrow polydispersity [130]. Transition to pilot-scale manufacturing requires addressing several challenges: (i) scale-dependent changes in mixing dynamics that affect droplet size distribution, (ii) increased energy requirements for maintaining consistent nanoscale droplet formation, (iii) heat dissipation issues during high-shear processing, and (iv) batch uniformity concerns during gelation [131].

Industrial-scale production may require specialized equipment including high-pressure homogenizers capable of processing hundreds of liters per batch, inline mixing systems to ensure uniform surfactant distribution, and automated gelation control systems to maintain consistent viscosity profiles [132]. Process analytical technology (PAT) implementation becomes critical for real-time monitoring of critical quality attributes during scale-up [133].

8.2 Regulatory pathway considerations

The FDA guidance for topically applied nanomaterials emphasizes comprehensive characterization and risk assessment specific to the nanoconfiguration [134]. For nanoemulgels, regulators expect evidence that the nanoscale architecture contributes meaningfully to therapeutic benefit beyond what could be achieved with conventional formulations [135].

EMA's reflection paper on nanomedicine calls for thorough understanding of nanomaterial behavior in biological systems, including dissolution, distribution, metabolism, and excretion profiles [136]. Topical application complicates this assessment, as the primary route of absorption may be minimal, but enhanced skin penetration of both nanoemulgel components and active ingredients must be evaluated [137].

8.3 Patent landscape snapshot

Current patent activity in nanoemulgel technology spans dermatological, cosmetic, and pharmaceutical applications, with significant focus on formulation optimization and stabilization strategies [138]. Key patent areas include: (i) synergistic surfactant combinations that enable low-energy processing

while maintaining nanoscale droplets, (ii) gel matrix compositions that enhance droplet entrapment without compromising release kinetics, and (iii) novel applications in specific therapeutic areas such as psoriasis or acne [138].

9. Current Limitations and Future Perspectives

Despite promising therapeutic advances, current nanoemulgel research faces several limitations that constrain clinical translation. First, the lack of standardized characterization protocols hampers cross-study comparison and regulatory acceptance, necessitating consensus guidelines for critical quality attribute evaluation. Second, limited availability of biomarkers for assessing in vivo performance creates reliance on surrogate metrics that may not accurately predict therapeutic outcomes. Future research directions should prioritize: (i) development of predictive stability models that account for the complex interactions between nanoemulsion and gel components, (ii) establishment of physiologically relevant ex vivo and in vitro models that accurately reflect human skin properties, and (iii) integration of quality-by-design principles from early development to enable robust process understanding and control [139]. Advanced analytical techniques including machine learning-based formulation optimization and multi-scale modeling approaches offer promising avenues for accelerating development timelines and improving product outcomes. Additionally, personalized medicine approaches that tailor nanoemulgel properties to individual patient characteristics could unlock new therapeutic opportunities while improving safety profiles [140].

10. Conclusion

Nanoemulgel represents a sophisticated hybrid delivery platform that successfully merges the advantages of nanoemulsion technology with the functional benefits of hydrogel matrices for dermal therapeutics. The nanoscale architecture enables enhanced skin penetration through multiple mechanisms, while the gel matrix provides sustained release, prolonged residence time, and improved stability compared to conventional nanoemulsions alone. However, significant challenges persist in achieving clinical translation, particularly regarding long-term stability optimization, scalable manufacturing processes, and regulatory pathway clarification for hybrid nanocarrier systems. The substantial gap between academic research publication volume and commercial product development underscores the need for focused efforts in bridging this translational divide through early-stage regulatory engagement, standardized development protocols, and industry-academia

collaboration. Future success in nanoemulgel development will likely require multidisciplinary approaches that integrate formulation science, stability engineering, regulatory strategy, and commercial viability assessments throughout the development process. With appropriate focus and resources, nanoemulgel systems have the potential to transform topical drug delivery across multiple therapeutic areas, offering patients improved efficacy and safety compared to current standard-of-care formulations.

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