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Review Article

Nanoemulgel: A Promising Nanostructured Approach for Enhanced Topical Drug Delivery

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ABSTRACT

Nanoemulgels represent a novel and effective nanostructured drug delivery platform that combines the advantages of nanoemulsions and hydrogels, offering a promising strategy for the topical delivery of poorly water-soluble drugs. Nanoemulsions, consisting of nanosized droplets, enhance solubility, surface area, and drug dispersion, while hydrogels provide a stable, viscous medium for sustained and localized drug release. This synergistic system addresses major challenges in dermal and transdermal delivery, including limited skin permeability and poor drug bioavailability. By incorporating lipophilic drugs into nano-sized oil droplets within a gel matrix, nanoemulgels facilitate deeper skin penetration, improved therapeutic efficacy, and better patient compliance due to their non-greasy, easily spreadable nature. This review provides a comprehensive overview of nanoemulgel formulation, component selection, preparation methods, and mechanisms of enhanced drug permeation. Additionally, the article highlights recent advances, clinical applications, and currently marketed formulations across various therapeutic areas, including anti-inflammatory, antifungal, analgesic, and cosmeceutical products. The future of nanoemulgel technology lies in green excipient use, AI-based formulation optimization, and expanded applications beyond dermatology. Nanoemulgels thus offer a transformative approach for next-generation topical therapeutics.


INTRODUCTION

Topical drug delivery systems (TDDS) have garnered substantial attention in both pharmaceutical research and clinical practice due

to their ability to deliver therapeutic agents directly to the site of action. This route offers multiple advantages such as the avoidance of first-pass hepatic metabolism, reduction in systemic side effects, ease of administration, and improved

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patient compliance—particularly for chronic conditions requiring long-term therapy [1]. However, effective transdermal drug delivery is often hindered by the skin's complex barrier properties, primarily the stratum corneum, which is composed of densely packed corneocytes embedded in a lipid matrix. This outermost layer serves as the principal barrier, restricting the penetration of both hydrophilic and lipophilic drugs [2]. Most conventional topical formulations, such as creams, ointments, and gels, suffer from limitations including poor drug solubility, inadequate skin retention, and limited permeability of active pharmaceutical ingredients (APIs). These issues are particularly pronounced for drugs belonging to the Biopharmaceutical Classification System (BCS) Class II and IV categories, which exhibit low aqueous solubility and limited bioavailability [3]. To overcome these challenges, novel nanotechnology-based delivery systems have been introduced, with nanoemulgels emerging as a superior alternative. A nanoemulgel is a biphasic system in which a nanoemulsion is incorporated into a gel matrix. Nanoemulsions are isotropic, thermodynamically unstable systems consisting of oil, water, surfactant, and co-surfactant, with droplet sizes ranging typically from 20 to 200 nanometers. The small droplet size significantly enhances drug solubilization, diffusion, and bioavailability, while the incorporation into a hydrogel matrix provides viscosity, increased retention time, and ease of application [4,5]. The unique characteristics of nanoemulgels allow them to effectively overcome the physicochemical and biological barriers associated with topical and transdermal drug delivery. By improving drug solubility, prolonging skin contact time, and enhancing penetration through the stratum corneum, nanoemulgels facilitate targeted delivery and sustained release of therapeutic agents. Furthermore, they provide aesthetic and practical advantages such as non-

greasy texture, transparency, Spreadability, and enhanced patient adherence [6]. The formulation of nanoemulgels is highly versatile, allowing for the incorporation of a wide range of hydrophobic drugs, making them suitable for diverse therapeutic applications, including anti-inflammatory, antifungal, analgesic, and cosmetic treatments. Recent advancements in formulation strategies, excipient technologies, and manufacturing methods have expanded the scope of nanoemulgel applications to include intranasal, mucosal, and ocular drug delivery as well [7]. This review aims to provide a comprehensive overview of the nanoemulgel drug delivery system, covering its formulation principles, component selection, preparation techniques, mechanisms of action, and current therapeutic applications. In addition, we highlight recent developments, marketed products, and future directions, emphasizing nanoemulgels' potential as a next-generation platform for topical drug delivery.

2. Nanoemulgel: Concept and Rationale

Nanoemulgels are dual-component systems composed of nanoemulsions embedded within a hydrogel base. Nanoemulsions are submicron-sized emulsions with droplet diameters typically ranging from 20 to 200 nm. Their small droplet size enables enhanced drug solubilization, increased surface area, and improved permeability [8]. Gels, on the other hand, provide rheological stability and facilitate prolonged residence time at the application site [9]. The integration of nanoemulsions into a gel matrix results in a highly stable, homogenous, and user-friendly topical drug delivery system.

2.1 Key Advantages of Nanoemulgels

- **Improved Solubility and Absorption:** The nanometric size of the oil droplets offers a significantly larger surface area for drug



dissolution, enhancing the solubility and absorption of lipophilic drugs [10].

- **Enhanced Skin Penetration:** The small droplet size and presence of permeation enhancers in the formulation facilitate the transport of drugs through the stratum corneum into deeper skin layers [11].
- **Controlled and Sustained Release:** The gel base ensures gradual drug diffusion, allowing prolonged therapeutic effects and reduced frequency of application [12].
- **Improved Stability:** Nanoemulgels are more resistant to coalescence and phase separation than conventional emulsions [13].
- **Patient-Friendly Application:** Non-greasy texture, ease of application, and high aesthetic acceptability promote better patient compliance [14].

3. Formulation Components and Considerations

The successful formulation of nanoemulgels requires a strategic selection and optimization of both nanoemulsion and gel components. Each ingredient plays a critical role in determining the physicochemical properties, stability, drug loading capacity, skin permeation potential, and therapeutic performance of the final product. The formulation generally consists of the following key elements:

3.1 Nanoemulsion Phase

Nanoemulsions are thermodynamically unstable, kinetically stable dispersions of two immiscible liquids—commonly oil and water—stabilized by surfactants and co-surfactants. The primary goal of this phase is to solubilize lipophilic drugs in nano-

sized oil droplets and facilitate their penetration through the stratum corneum.

- **Oil Phase**

The choice of oil greatly influences the drug solubility, droplet size, and skin permeability. Oils act as solvents for lipophilic drugs and aid in skin hydration and penetration.

Common oils: Isopropyl myristate, oleic acid, medium-chain triglycerides (MCTs), castor oil, caprylic/capric triglycerides.

Role: Enhance drug solubilization, fluidize the lipid bilayers of stratum corneum, and improve dermal permeation [15].

- **Surfactants**

Surfactants reduce the interfacial tension between oil and water, facilitating the formation of stable nano-sized droplets. They also aid in the emulsification process and enhance drug permeability by altering the skin lipid structure.

Examples: Tween 80 (Polysorbate 80), Span 20, Cremophor EL, Solutol HS15.

Criteria: Non-ionic surfactants are generally preferred due to their lower toxicity and better biocompatibility [16].

- **Co-surfactants**

Co-surfactants improve the fluidity of the interfacial film and further reduce interfacial tension, helping stabilize the nanoemulsion and reduce droplet size.

Examples: Propylene glycol, polyethylene glycol (PEG-400), ethanol, Transcutol® P.



Function: Enhance emulsification efficiency, reduce viscosity, and improve drug diffusion through skin [17].

- **Aqueous Phase**

Typically composed of distilled water, phosphate-buffered saline (PBS), or water-ethanol mixtures, the aqueous phase facilitates the dispersion of hydrophilic components and supports gel formation.

Importance: Determines the hydrophilic-lipophilic balance (HLB) of the system, influencing stability and viscosity.

3.2 Gelling Agents

The gel base is crucial for transforming a nanoemulsion into a nanoemulgel. It imparts appropriate viscosity, enhances spreadability, improves drug residence time on the skin, and provides mechanical strength to the formulation.

Common Gelling Agents:

- Carbopol 934/940: A synthetic high molecular weight polymer; widely used due to its excellent viscosity control and transparent gel formation.
- Hydroxypropyl methylcellulose (HPMC): A semi-synthetic cellulose derivative with good film-forming and hydration capacity.
- Xanthan gum: A natural polysaccharide with good biocompatibility and rheological properties.
- Pluronic F127: A thermoresponsive polymer that forms a gel upon contact with body temperature [18].

Considerations:

pH adjustment using triethanolamine (TEA) is often needed to achieve optimal gel consistency and maintain drug stability. The gelling agent must be compatible with the nanoemulsion system to avoid phase separation or instability.

3.3 Drug Loading and Solubility Considerations

The success of nanoemulgels also depends on the efficient solubilization and retention of the active pharmaceutical ingredient (API). The following factors must be considered:

- Solubility in Oil Phase: Drug must exhibit high solubility in the selected oil to ensure effective loading.
- Partition Coefficient (log P): Drugs with log P values between 1 and 4 are generally ideal for dermal delivery.
- Drug-Excipient Compatibility: Assessed via differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), and thermogravimetric analysis (TGA).

3.4 Method of Preparation

Nanoemulgels are prepared in two main steps:

Step 1: Nanoemulsion Preparation

High-energy methods: Ultrasonication, high-pressure homogenization, and micro fluidization are used to reduce droplet size and improve stability [19].

Low-energy methods: Spontaneous emulsification, phase inversion temperature (PIT), and emulsion inversion point (EIP) methods rely on intrinsic physicochemical properties of the formulation.

Step 2: Incorporation into Gel Matrix

The prepared nanoemulsion is gradually incorporated into a previously hydrated gel base with continuous stirring to form a uniform nanoemulgel.

3.5 Physicochemical and Rheological Considerations

For a stable and efficacious nanoemulgel, the following characteristics are essential:

- **Droplet Size and PDI:** Should be <200 nm with narrow polydispersity index (PDI < 0.3).
- **Zeta Potential:** Values > ±30 mV suggest good electrostatic stability.
- **pH:** Must be within the skin-friendly range (4.5–6.5) to prevent irritation.
- **Viscosity and Spreadability:** Should allow easy application without running off.
- **Drug Content Uniformity:** Ensures consistent dosing and efficacy.

4. Mechanisms Of Enhanced Drug Delivery

Nanoemulgels enhance drug delivery via multiple mechanisms: **Solubilization of Hydrophobic Drugs:** Nanoemulsion droplets encapsulate lipophilic drugs, improving solubility and bioavailability.

Barrier Disruption: Surfactants and oils transiently disrupt the lipid matrix of the stratum corneum, enhancing drug permeation [20].

Extended Residence Time: Increased viscosity from the gel matrix prolongs contact with the skin, increasing the concentration gradient and facilitating absorption [21].

5. Therapeutic Applications And Marketed Formulations

Nanoemulgels offer a synergistic platform by integrating the advantages of nanoemulsions and hydrogels to overcome the anatomical and physiological barriers of the skin. The enhanced drug delivery is attributed to multiple physicochemical and biological mechanisms:

4.1. Nanoscale Droplet Size

The core mechanism lies in the nano-sized oil droplets (typically 20–200 nm), which provide a large surface area, thereby enhancing the dissolution and absorption of poorly water-soluble drugs. The small droplet size also enables closer contact with the stratum corneum, enhancing passive diffusion across the skin barrier [22].

4.2. Disruption of Stratum Corneum Lipid Structure

Surfactants and co-surfactants used in the nanoemulsion phase interact with the lipid bilayers of the stratum corneum, temporarily disrupting the lipid packing and reducing barrier resistance. This increases skin permeability and facilitates transcellular and intercellular drug transport [23].

4.3. Increased Drug Thermodynamic Activity

Drugs present in a solubilized state within the nanoemulsion droplets exhibit higher thermodynamic activity compared to crystalline or coarse dispersion forms. This high activity provides a stronger concentration gradient, promoting enhanced skin penetration [24].

4.4. Prolonged Skin Residence Time

The gel matrix of the nanoemulgel formulation ensures prolonged retention of the drug at the site of application. Increased viscosity slows down

drug diffusion, facilitating sustained and controlled release, which is particularly beneficial for chronic dermatological conditions [25].

4.5. Enhanced Hydration of Stratum Corneum

Certain excipients, such as oleic acid or isopropyl myristate, act as permeation enhancers and skin moisturizers. They hydrate the skin, swell the stratum corneum, and loosen the tight lipid structures, all of which contribute to improved drug diffusion [26].

5. Therapeutic Applications and Marketed Formulations

Nanoemulgels have demonstrated therapeutic versatility and efficacy across a wide spectrum of pharmacological classes due to their enhanced solubility, permeability, and patient-friendly characteristics. They are especially advantageous for localized skin disorders, where prolonged contact and targeted delivery are desirable.

5.1. Therapeutic Applications

A. Anti-inflammatory Agents

Nanoemulgels improve dermal delivery of NSAIDs (e.g., diclofenac, ibuprofen), reducing systemic exposure and minimizing gastrointestinal side effects common with oral administration.

- **Example:** Diclofenac nanoemulgel has shown improved anti-inflammatory and analgesic effects in osteoarthritis and musculoskeletal injuries [27].

B. Antifungal Agents

Lipophilic antifungals like miconazole and clotrimazole benefit from nanoemulgel-based delivery, achieving deeper skin penetration and enhanced fungicidal activity.

- **Example:** Miconazole nanoemulgels have demonstrated superior efficacy in treating dermatophytosis compared to conventional creams [28].

C. Analgesics and Muscle Relaxants

Drugs like mefenamic acid or lidocaine delivered via nanoemulgel provide rapid relief in localized pain and reduce dosing frequency.

D. Dermatological and Cosmeceutical Applications

Nanoemulgels are employed for the dermal delivery of retinoids, antioxidants (e.g., Vitamin E, coenzyme Q10), and skin-lightening agents (e.g., kojic acid) due to their superior skin absorption and cosmetic elegance.

- **Cosmeceuticals:** Nanoemulgels are gaining momentum in anti-aging, acne treatment, and UV protection formulations due to their non-greasy, translucent nature and efficient dermal delivery [29].

E. Antimicrobial and Wound Healing Agents

Nanoemulgels loaded with silver nanoparticles, curcumin, or tea tree oil have been evaluated for antimicrobial action and wound healing due to their sustained release profile and ease of application to infected or damaged skin.

5.2. Marketed Nanoemulgel-Based Formulations

Although the term "nanoemulgel" may not always appear on product labels, several commercial products functionally utilize similar delivery principles:

Product Name	Active Ingredient	Therapeutic Class	Manufacturer
Voltaren Emulgel	Diclofenac Diethylamine	NSAID	GlaxoSmithKline
Benzolait Emulgel	Benzoyl Peroxide	Antibacterial (Acne)	Roydermal
Isofen Emulgel	Ibuprofen	Analgesic/NSAID	Beit Jala Pharmaceuticals
Quadri Derm RF	Betamethasone + Antifungals	Anti-inflammatory + Antifungal	Schering-Plough
Miconaz-H Emulgel	Miconazole + Hydrocortisone	Antifungal + Corticosteroid	Wallace Pharmaceuticals

6. Recent Advances and Future Prospects

- The field of nanoemulgels is expanding rapidly, with novel applications in:
- Central Nervous System Drug Delivery: Intranasal nanoemulgels for brain targeting bypass the blood-brain barrier [30].
- Ocular and Mucosal Delivery: Nanoemulgels offer enhanced retention and reduced irritation for ophthalmic and buccal applications.
- Green and Biodegradable Polymers: Increasing focus on eco-friendly, non-toxic excipients [30].
- AI-Based Optimization: Artificial intelligence tools are being employed to predict formulation stability and optimize excipient ratios [31].
- Despite significant progress, challenges remain in regulatory standardization, large-scale manufacturing, and long-term safety validation. Future research should focus on clinical translation and pharmacoeconomic evaluations to establish nanoemulgels as mainstream therapeutic carriers.

7. CONCLUSION

Nanoemulgels represent a promising frontier in nanostructured topical drug delivery, offering a versatile, stable, and effective system for administering poorly water-soluble drugs. Their capacity to improve solubility, enhance penetration, sustain release, and improve patient

compliance positions them as a formidable alternative to traditional topical systems. Ongoing innovation and research are expected to further expand their therapeutic utility across diverse medical and cosmetic domains.

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