Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 103-115 | ISSN:2251-6727

Nanoemulgel Based Drug Delivery System: Advances in Formulation Design, Skin Penetration Mechanism and Therapeutic Applications

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(Received: 16 March 2026 Revised: 14 April 2026 Accepted: 01 May 2026)

KEYWORDS
Topical drug delivery, Transdermal delivery, Nanoemulsion, Skin penetration, Nanotechnology

ABSTRACT:
Topical and transdermal drug delivery systems are widely utilized for treating localized and chronic skin conditions due to their non-invasive nature, which enhances patient adherence and minimize systemic side effects. However traditional topical formulations like creams, ointments, and gels often encounter significant challenges including poor drug solubility, limited skin penetration, formulation instability, and low retention at the application site. These issue can ultimately compromise therapeutic effectiveness. The advent of nanotechnology based delivery systems has provided promising solutions, with nanoemulgel emerging as a noteworthy hybrid formulation. Nanoemulgel are semi-solid systems are created by embedding a nanoemulsion within a gel matrix, thus leveraging the benefits of both components. The nanoemulsion improves drug solubility, increases surface area, and facilitates better skin penetration, while the gel base contributes favorable rheological characteristics, enhanced spreadability, and extended residence time on the skin. The review addresses skin structure, barrier properties, and drug penetration mechanisms to elucidate the improved dermal and transdermal delivery provided by nanoemulgel. Essential physicochemical and evaluation metrics, such as droplet size, polydispersity index, zeta potential, pH, viscosity, drug content, and stability. Additionally, the potential pharmaceutical applications of nanoemulgel in areas such as antimicrobial, anti-inflammatory, wound healing, and natural product therapies are examined. In conclusion, nanoemulgels offer a versatile and innovative approach with significant promise for future clinical and commercial use in topical and transdermal drug delivery.

1. INTRODUCTION

Topical drug delivery is a highly preferred method for treating localized skin disorders because it is non-invasive, easy to administer, and allows for high concentrations of the medication at the targeted area while reducing systemic exposure. Nonetheless, the effectiveness of traditional topical forms like creams, ointments, lotions, and gels is often hindered by poor drug absorption through the skin barrier, insufficient drug solubilization, and formulation instability. The stratum corneum, made up of corneocytes within a lipid matrix, acts as the main barrier to drug penetration, limiting the movement of both hydrophilic and lipophilic substances. To overcome this challenge, various strategies have been developed to improve skin permeability, frequently by momentarily disrupting the skin's protective layer. These methods include chemical penetration enhancers, ultrasound, iontophoresis, sonophoresis, electroporation, and microneedle, although prolonged use can lead to irritation or damage. In comparison, nanocarrier-based delivery systems have emerged as a safer and more effective alternative to penetrate the SC barrier while minimizing skin damage. These nanocarriers promote drug movement through intracellular and intercellular pathways, interact with skin elements to enhance penetration, and can create drug reservoirs within the skin for sustained or responsive release.[1] The effectiveness of traditional topical formulations like creams, ointments, lotions, and gels is often hampered by poor drug penetration, insufficient solubilization, and formulation instability. Among the nanotechnology-based systems, nanoemulsion have garnered significant attention. These are kinetically

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 103-115 | ISSN:2251-6727

stable colloidal dispersions of immiscible liquids, commonly oil-in-water (o/w) or water-in-oil (w/o) systems, with droplet sizes typically between 20 to 200 nm. Unlike standard emulsions, which are milky, nanoemulsion appear clear or translucent due to their tiny droplet sizes. They are stabilized by appropriate surfactants and co-surfactants, sometimes referred to as mini-emulsions. Their small droplet size allows for a larger surface area, improved drug solubilization, and enhanced interaction with the skin, resulting in better permeability and bioavailability[2] .Despite their benefits, nanoemulsion have challenges such as low viscosity and reduced skin retention, which can cause them to quickly wash away from the application site and diminish therapeutic effectiveness. To address these issues, researchers have incorporated nanoemulsion into gel matrices, resulting in the creation of nanoemulgel. These hybrid systems merge the permeability-enhancing qualities of nanoemulsion with the physical advantages of gels. Nanoemulgel provide numerous benefits, such as enhanced drug penetration, controlled and sustained release, improved physical stability, longer duration on the skin, and higher patient compliance. Recent research has highlighted their potential for delivering synthetic drugs, antibiotics, antioxidants, and natural bioactive compounds for various skin conditions and wound healing applications [3].

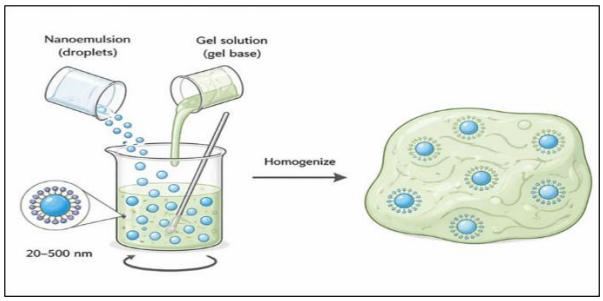

Figure 1. Nanoemulgel-Based Topical Delivery

2. RATIONALE FOR NANOEMULGEL BASED TOPICAL DELIVERY

The creation of nanoemulgel is primarily motivated by the need to address the traditional topical dosage forms. Many active pharmaceutical ingredients including synthetic medications and plant-derived compounds often suffer from poor water solubility, limited skin penetration, and low bioavailability, leading to diminished effectiveness in topical and transdermal delivery. serve as an effective delivery system to mitigate these issues by enhancing the solubilization of lipophilic drugs within their oil phase. Nanoemulsion low viscosity and inadequate skin retention, which lead to swift runoff from the application site and diminished therapeutic impact. To alleviate these challenges, nanoemulsion can be incorporated into gel matrices, resulting in the creation of nanoemulgel. This gel network boosts viscosity and forms a three-dimensional structure that traps nanoemulsion droplets, providing extended residence on the skin, enhanced adherence, and prolonged drug release. Moreover, nanoemulgel merge the excellent drug-loading and permeability-enhancing qualities of nanoemulsion with the desirable rheological and spreadability properties of gels. The high water content in gel bases makes them particularly well-suited for

emulgel systems, while maintaining droplet sizes under 500 nm significantly enhances physical stability and lowers the likelihood of phase separation. Nanoemulgel are generally compatible with skin and effectively deliver both hydrophilic and hydrophobic drugs, improving stability, solubility, and therapeutic efficacy.[4,5]

3. NEED FOR NOVEL TOPICAL DRUG DELIVERY SYSTEMS

The increasing incidence of chronic skin conditions like psoriasis, fungal infections, eczema has highlighted the pressing demand for more effective and user-friendly topical drug delivery systems. While nanoemulsion have demonstrated potential in improving drug solubility and skin penetration, their effectiveness in clinical topical therapy is hampered by poor spreadability and insufficient skin retention due to low viscosity. To address these issues, integrating nanoemulsion into gelling systems has been suggested as a viable solution.[6] Gels are created by dispersing appropriate polymers in water or hydroalcoholic bases, forming a high-water-content three-dimensional network. This structure allows for quicker drug dissolution and release than standard creams or ointments, while also enhancing spreadability and residence time on the skin. Nanoemulgel offer a targeted and efficient method for enhancing drug localization within the skin while reducing systemic absorption.[7]

Journal of Chemical Health Risks
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JCHR (2026) 16(3), 103-115 | ISSN:2251-6727

4. COMPARATIVE EVALUATION OF EMULGEL AND NANOEMULGEL SYSTEMS

	Emulgel	Nanoemulgel
	Emulsion droplets generally remain in the micrometer range, which limits interfacial surface area	Incorporation of nanoemulsion results in droplet sizes typically below 200 nm, significantly increasing surface area
	Effective for moderately lipophilic drugs but limited for poorly soluble compounds	Enhanced solubilization of poorly water-soluble drugs due to nanoscale oil droplets
	Drug permeation is often restricted to superficial skin layers	Nanosized droplets facilitate improved interaction with the stratum corneum and deeper skin penetration
	Typically exhibits relatively rapid and less controlled drug release	Provides sustained and controlled drug release due to entrapment of nanoemulsion droplets within the gel matrix
	Partial localization with higher probability of systemic absorption	Enhanced drug localization within the skin, limiting systemic exposure

Table 1. Comparison of Emulgel vs. Nanoemulgel Systems

5. SKIN BARRIER STRUCTURE AND MECHANISMS OF TOPICAL DRUG PENETRATION

The skin is the human body's largest organ, covering approximately 2 m² in healthy adults. It serves as a complex, primary protective barrier. Since the 1960s, numerous researchers have focused on understanding the skin's structure, particularly its barrier function. [10] The skin has three main layers: the epidermis, the dermis, and the subcutaneous tissue. The epidermis, aside from the outermost stratum corneum, is a living tissue without blood vessels; nutrients are supplied through diffusion from the dermo-epidermal junction to sustain its health.[11] The epidermis comprises five distinct layers reflecting the stages of cell development: the non-viable stratum corneum, followed by the stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum. The cutaneous barrier provides mechanical protection, preventing both dehydration and the entry of harmful substances and microorganisms.[12] The stratum corneum comprises 15 to 20 layers of corneocytes, measuring 10 to 15 micrometers in thickness, which can expand to 40 micrometers when hydrated, indicating increased permeability.[13]

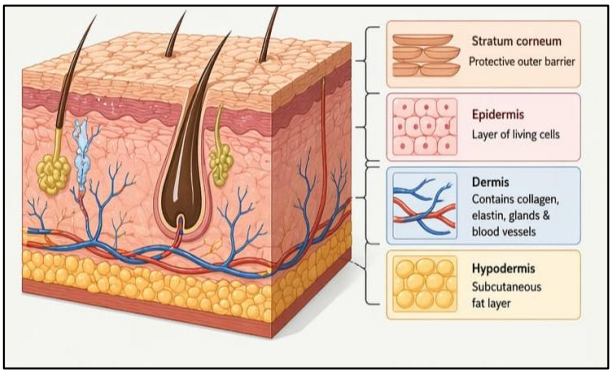

Figure 2. skin penetration Route

5.1. PATHWAY OF SKIN PENETRATION

[Topical Drug Application]
↓
[Skin Surface]
↓
┌──┐
│Transepidermal Pathway (Major Route)
└──┘
↓
[Stratum Corneum]
↓
Intracellular route (between corneocytes lipophilic)
Transcellular route (through corneocytes , partitioning acrosslipid and aqueous)
↓
[Viable Epidermis]
↓[Dermis]
↓

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 103-115 | ISSN:2251-6727

[Systemic Circulation]

┌──────────────────────────────────────┐

Transappendageal Pathway (Shunt Route)

└──────────────────────────────────────┘

↓

[Hair follicles / Sebaceous glands / Sweat glands]

↓

Bypasses Stratum Corneum

↓

Suitable for polar drugs, large molecules

and nanocarriers (liposomes, ethosomes, nanoparticles)

↓

[Viable Epidermis]

↓[Dermis]

↓

[Systemic Circulation] [14,15,16,17]MECHANISM OF DRUG TRANSPORT ACROSS SKIN LAYERS

Drug transport across the skin occurs primarily via three pathways. The intercellular pathway involves diffusion between corneocytes through the lipid-rich extracellular matrix of the stratum corneum, favoring lipophilic and amphiphilic molecules and representing the major barrier-controlled route [18] The transcellular pathway allows drugs to pass directly through corneocytes, crossing alternating hydrophilic and lipophilic domains, which is suitable for small molecules but is slower due to the dense keratin network. [19] The appendageal pathway utilizes skin appendages such as hair follicles and sweat glands to bypass the stratum corneum, providing a route for hydrophilic drugs nanocarrier-based formulations like Nanoemulgel. After crossing the stratum corneum, drugs diffuse through the viable epidermis, basal membrane,and dermis to reach local targets or systemic circulation.[20]

6. COMPOSITION OF NANOEMULGEL

The effectiveness of a nanoemulgel system hinges on the precise selection of its components, as each element significantly affects stability, drug loading, permeation efficiency, and overall therapeutic efficacy.

1. Oil Phase

The oil phase serves as the main solubilizing medium for lipophilic drugs and bioactive substances. The choice of oil is influenced by the drug's solubility, compatibility with surfactants, and the desired therapeutic effects. Both synthetic oils (like isopropyl myristate and medium-chain triglycerides) and natural oils (such as clove oil, tea tree oil, oregano oil) are commonly used.[21] Natural oils are particularly appealing because of their inherent antimicrobial, anti-inflammatory, and antioxidant properties, which can collaboratively enhance therapeutic results.

2. Surfactant and Co-surfactant

Surfactants minimize interfacial tension between oil and water, aiding in the creation of stable nano-sized droplets. Non-ionic surfactants like Tween 80, Tween 20, and the Span series are preferred due to their low toxicity and skin compatibility. Co-surfactants, which can include ethanol, propylene glycol, polyethylene glycol, bolster the flexibility of the interfacial film and help further reduce droplet size. Together, surfactants and co-surfactants not only stabilize nanoemulsion but also enhance penetration by disrupting the lipid structure of the stratum corneum.[22]

Aqueous Phase

The aqueous phase typically consists of purified water or buffered solutions that maintain a physiological pH and formulation stability.[23] It is crucial to control the pH to prevent skin irritation and ensure drug stability. Additionally, the aqueous phase affects the viscosity and release properties of the final nanoemulgel.

3. Gelling Agents

Gelling agents transform the low-viscosity nanoemulsion into a semi-solid nanoemulgel that is suitable for topical use. Commonly utilized polymers include Carbopol 934/940, hydroxypropyl methylcellulose, chitosan, and xanthan gum. These polymers improve spreadability, prolong residence time, and enhance patient compliance, while simultaneously preserving the integrity of the nanoemulsion droplets within the gel matrix.[24]

7. FORMULATION DESIGN OF NANOEMULGEL

Nanoemulgel are advanced topical drug delivery systems that merge the advantages of nanoemulsion and hydrogels, enhancing drug solubility, stability, and skin absorption. The formulation of nanoemulgel follows a systematic approach to achieve the best physicochemical

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JCHR (2026) 16(3), 103-115 | ISSN:2251-6727

properties and therapeutic efficacy. The first stage in this formulation involves pre-formulation screening, which assesses the solubility of the active pharmaceutical ingredient in various oils, surfactants, and co-surfactants. Oils like medium-chain triglycerides, caprylic/capric oils are typically selected for their excellent solubilization abilities. Surfactants such as Tween 20, Tween 80, and Span 20, along with co-surfactants like polyethylene glycol 400 and propylene glycol, are chosen based on their emulsification effectiveness.[25] The ideal combinations and ratios of these materials are determined using pseudoternary phase diagrams, which help identify the stable nanoemulsion region and reduce the risk of phase separation.

Once the components are selected, the nanoemulsion is prepared through methods such as high-shear homogenization, ultrasonication. The goal is to optimize the formulation to achieve a droplet size typically between 120–180 nm and a low polydispersity index (< 0.3) to ensure uniformity, stability, and improved permeation.[26] Key factors like the oil-to-surfactant/co-surfactant ratio, homogenization speed, and sonication duration are fine-tuned to create a stable nanoemulsion with an appropriate zeta potential that supports long-term stability and prevents droplet coalescence.[27]

The gel base acts as a carrier for the nanoemulsion, offering viscosity, spreadability, and skin retention. Common gelling agents include Carbopol 934, Carbopol 940, and hydroxypropyl methylcellulose, which are typically used at concentrations of 0.5% to 2% w/w. The nanoemulsion is then mixed into the gel matrix while stirring gently to create a consistent nanoemulgel, ensuring even droplet distribution and preventing clumping. The final formulation's pH is adjusted to 5–6.5 for skin compatibility.[28]

To confirm the effectiveness of the prepared nanoemulgel for topical delivery, it is crucial to evaluate various parameters such as droplet size, zeta potential, viscosity, spreadability, drug content and stability. Well-optimized formulations typically show droplet sizes of 120–180 nm, zeta potential values between −20 to −35 mV, viscosities from 2500–4500 cP, and prolonged drug release over several hours. These attributes are vital for facilitating the effective delivery of therapeutic agents while minimizing side effects. [29]

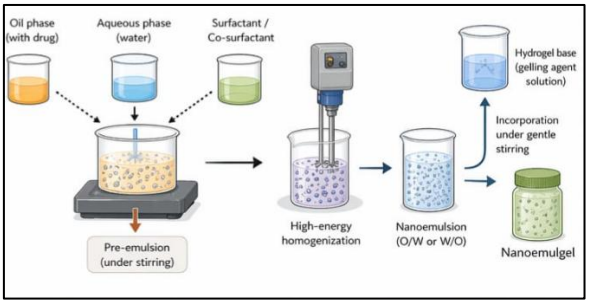

Figure 3. Formulation of Nanoemulgel

PSEUDO-TERNARY PHASE DIAGRAM

Pseudo-ternary phase diagrams are essential for the strategic design of nanoemulgel systems, facilitating the systematic selection of nanoemulsion compositions before integrating them into a gel. These diagrams depict the phase behavior of three primary components: oil, a mixture of surfactant and co-surfactant (Smix), and the aqueous phase. [30]

To create the phase diagram, oil, Smix mixtures are prepared in differing weight ratios and gradually combined with the aqueous phase while stirring continuously. The formulations are then visually

assessed for clarity, homogeneity, and phase separation. Systems that are clear, homogeneous, and have low viscosity are classified as nanoemulsion, while turbid or separated systems denote instability.[31] The results are plotted on a triangular diagram delineating the nanoemulsion region.In the development of nanoemulgel, the pseudo-ternary phase diagram is crucial for identifying compositions that produce stable nanoemulsion characterized by small droplet sizes and low polydispersity index.[32] A larger nanoemulsion area within the diagram reflects a more effective surfactant system and enhances formulation stability. Nanoemulsion from this region are optimal precursors for creating nanoemulgel, providing better physical stability, enhanced drug loading, and improved skin permeation when incorporated into a gelling matrix. Therefore, pseudo-ternary phase diagrams are vital for constructing efficient and reproducible nanoemulgel formulations.[33]

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JCHR (2026) 16(3), 103-115 | ISSN:2251-6727

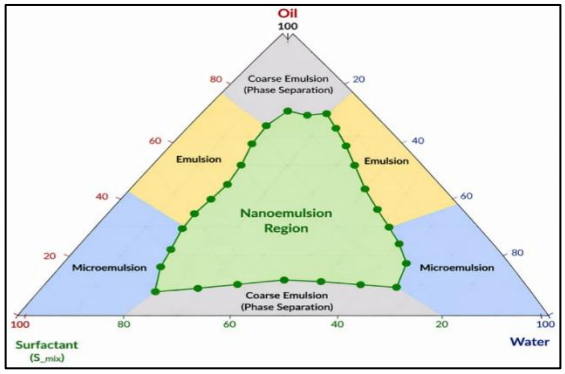

Figure 4. Pseudo- Ternary Phase Diagram

8. METHODS OF NANOEMULSION PREPARATION.

- High-Energy Methods

High-energy methods employ external mechanical force to reduce coarse emulsions to nano-sized droplets. Techniques like high-pressure homogenization, microfluidization, ultrasonication, and rotor-stator homogenization create significant shear and turbulence, allowing for precise control over droplet size and stable nanoemulsion, though they demand considerable energy and specialized equipment.[34]

- Low-Energy Methods

Low-energy approaches leverage the internal physicochemical traits of the system instead of external forces. Techniques like phase inversion composition (PIC) and phase inversion temperature (PIT) facilitate spontaneous emulsification by modifying formulation parameters or temperature.[35] These methods are energy-efficient and cost-effective, making them ideal for thermosensitive drugs, but they require careful optimization of formulation conditions.

1. **High-Pressure Homogenization (HPH):** A coarse emulsion is forced through a narrow valve under high pressure, creating high shear and cavitation that minimize droplet size to the nanometer range, offering scalability and uniformity.

2. **2 High-Pressure Microfluidization:** The emulsion flows through micro-channels where opposing streams collide, resulting in highly uniform nano-sized droplets with a narrow size distribution and enhanced stability.

3. **Ultrasonic Homogenization (Ultrasonication):** High-frequency ultrasonic waves generate cavitation bubbles that collapse to break down droplets into nano-sized particles; effective for lab-scale preparation, but potential heating can occur.

4. **Phase Inversion Composition (PIC) Method:** Nanoemulsions are generated by gradually changing the system's composition, typically by incrementally adding water, which leads to the inversion from water-in-oil (W/O) to oil-in-water (O/W) emulsions featuring fine droplets.

5. **Phase Inversion Temperature (PIT) Method:** This technique utilizes temperature-induced variations in surfactant affinity, resulting in emulsion inversion at a specific temperature and formation of nano-sized droplets upon cooling.[36,37,38]

9. CONVERSION OF NANOEMULSION INTO NANOEMULGEL

Transforming a nanoemulsion into a nanoemulgel is a critical step that affects the formulation's final physical and chemical attributes, stability, and overall efficacy. Incorporating the nanoemulsion into a gel matrix addresses these shortcomings, resulting in a semisolid form ideal for topical use.[39] The process typically starts with preparing a gel base using suitable gelling agents like Carbopol, hydroxypropyl methylcellulose, chitosan. The gelling agent is blended into the

aqueous phase and allowed to hydrate completely to create a uniform gel. In the case of Carbopol gels, neutralization may be required to achieve the target viscosity and pH. Following this, the optimized nanoemulsion is gradually added to the gel base while gently stirring to avoid disrupting the nanoemulsion droplets. It is essential to ensure that the nanoemulsion droplets are evenly distributed throughout the gel matrix to maintain their integrity and guarantee effective drug delivery.[40]

Poor mixing can lead to clumping of droplets or phase separation, which can compromise stability and therapeutic performance. Studies have demonstrated that well-formulated nanoemulgel preserve the nanoscale droplet size characteristic of the original nanoemulsion, indicating that the incorporation into the gel matrix does not adversely affect the internal structure of the system.[41]

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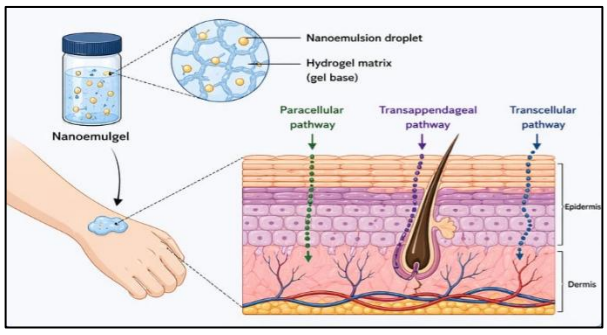

Figure 5. Representation of entry of nanoemulgel into Skin

10. PHYSICOCHEMICAL CHARACTERIZATION OF NANOEMULGEL

Thorough physicochemical characterization is crucial for assessing the quality, stability, and efficacy of nanoemulgel. These characteristics not only guarantee consistency across batches but also inform how the formulation behaves during storage and usage.

1. Droplet Size and Polydispersity Index

Analyzing droplet size is vital as it directly affects drug release, skin penetration. Nanoemulgel generally have droplet sizes under 200 nm with a low polydispersity index, indicating a uniform size distribution.[42] Smaller droplet sizes increase surface area and enhance interaction with the skin barrier, leading to better permeation.

2. Zeta Potential

Zeta potential indicates the surface charge of nanoemulsion droplets and serves as a measure of colloidal stability. High absolute zeta potential values help prevent droplet aggregation through electrostatic repulsion. [43]

3. pH Determination

The pH of nanoemulgel must align with skin physiology, usually ranging from 5.0 to 7.0. Maintaining the appropriate pH is vital to prevent skin irritation and preserve drug stability. pH levels are monitored throughout the storage period to examine formulation stability.

4. Viscosity and Rheological Behavior

Rheological analysis assesses the flow characteristics and consistency of nanoemulgel. Most display pseudoplastic or shear-thinning properties, which facilitate easy application and spreadability while retaining sufficient viscosity at rest. These rheological attributes significantly affect patient satisfaction and the duration of the product on the skin. [44]

5. Drug Content and Uniformity

Analyzing drug content ensures that the drug is evenly distributed throughout the formulation. High uniformity in drug content indicates efficient integration of the nanoemulsion into the gel matrix.[45]

11.1 STABILITY STUDIES

Stability studies play a crucial role in verifying the physical, chemical, and microbiological stability of nanoemulgel during their shelf life. These assessments are performed under various storage conditions, including room temperature, accelerated settings, and refrigeration, in line with regulatory standards. Compared to standard nanoemulsion, nanoemulgel exhibit enhanced stability, thanks to the protective gel matrix that reduces droplet movement and merging. Research has shown that the physicochemical parameters of nanoemulgel change minimally over time, demonstrating the durability of these systems.[46]

11. PHARMACEUTICAL APPLICATIONS OF NANOEMULGELS

Nanoemulgel are increasingly recognized as sophisticated systems for topical and transdermal drug delivery, attributed to their capacity for improving drug solubility, skin penetration, and localized bioavailability. This hybrid system, which integrates nanoemulsion with a gel matrix, efficiently accommodates both hydrophilic and lipophilic drugs, providing extended residence time at the application site. Such features render nanoemulgel suitable for a diverse array of pharmaceutical and cosmeceutical uses.[47]

1. Wound Healing and Dermatological Applications

In the realms of wound healing and dermatological treatment, nanoemulgel have demonstrated considerable promise. Their enhanced delivery of active ingredients accelerates epithelialization, stimulates collagen production, and offers effective antimicrobial defense at wound sites. Formulations incorporating curcumin, thymoquinone, and various essential oils have been proven to expedite wound healing, diminish inflammation, and enhance tissue regeneration in both in

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JCHR (2026) 16(3), 103-115 | ISSN:2251-6727

vitro and in vivo settings.[48]

2. Antimicrobial and Antibacterial Applications

Nanoemulgel formulated with antibiotics and essential oils exhibit enhanced antimicrobial effectiveness against a broad range of Gram-positive and Gram-negative bacteria. The nanoscale droplet size increases surface area, facilitating closer interactions with microbial membranes, while surfactants assist in membrane destabilization, thereby boosting antibacterial action. Essential oil-based nanoemulgel containing compounds like tea tree oil, clove oil have demonstrated significantly greater antibacterial effects compared to traditional gels and emulsions.[49]

3. Anti-Inflammatory and Analgesic Applications

Nanoemulgel serve as effective carriers for anti-inflammatory and analgesic drugs, enabling targeted drug delivery to inflamed areas while reducing systemic exposure. Formulations containing non-steroidal anti-inflammatory drugs and natural anti-inflammatory agents have shown improved dermal permeability, longer drug retention, and better pain relief outcomes.[50]The gel matrix contributes to sustained drug release and promotes better patient compliance, positioning nanoemulgel as a promising option for the treatment of inflammatory conditions and pain management.

12. NATURAL PRODUCT–BASED NANOEMULGEL

The integration of natural products into nanoemulgel is attracting more interest as the need for safer and more biocompatible topical treatments increases. Many natural compounds, like curcumin, essential oils, and plant extracts, often face challenges such as poor water solubility, instability, and limited skin absorption, which hinder their clinical application.[51]

Nanoemulgel systems enhance the solubility and stability of these natural compounds by trapping them in the oil phase of nanoemulsion. Furthermore, the small droplet size facilitates better skin penetration and bioavailability of the active ingredients.[52] Research has shown that curcumin-loaded nanoemulgel exhibit improved therapeutic effects in wound healing and inflammatory skin conditions compared to traditional formulations.

Nanoemulgel based on essential oils provide enhanced therapeutic benefits due to the combined effects of the oil's natural bioactivity and the advanced delivery system. Additionally, chitosan- coated nanoemulsion within gel matrices further boost antimicrobial effectiveness and stability, making them promising options for herbal and natural topical products.[53,54]

Figure 6. Herbal Nanoemulgel

14. REGULATORY CONSIDERATIONS OF NANOEMULGEL

1. Nanoemulgels are currently regulated under existing frameworks for topical semisolid dosage forms and nanotechnology-based drug delivery systems, as there are no dedicated regulatory pathways specifically for nanoemulgel formulations. This creates challenges in classification, as they possess both conventional and nanoscale characteristics.

2. Regulatory authorities such as the U.S. Food and Drug Administration and the European Medicines Agency emphasize comprehensive physicochemical characterization of nanocarriers, including particle size distribution, zeta potential, morphology, rheological properties, and long-term stability, to ensure product consistency and safety.[57,58]

3. The implementation of Quality by Design principles as described in ICH Q8(R2) is critical for nanoemulgel development. This involves identifying Critical Quality Attribut such as droplet size, polydispersity index, viscosity, and drug release profile, along with Critical Process Parameters like homogenization speed and surfactant ratio [59].

4. Risk management strategies based on ICH Q9 guidelines are necessary to evaluate formulation risks, including phase separation, aggregation, instability, and toxicity concerns, ensuring robust product development and lifecycle management .

5. Excipients used in nanoemulgel, particularly surfactants and co-surfactants, must comply with

Journal of Chemical Health Risks
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JCHR (2026) 16(3), 103-115 | ISSN:2251-6727

pharmacopeial standards and demonstrate dermal safety, non-toxicity, and compatibility with active pharmaceutical ingredients [60,61].

6. Evaluation of bioavailability for nanoemulgels is complex due to their localized action. Therefore, pharmacokinetic studies, in vitro permeation testing and tape-stripping techniques are recommended to assess drug distribution within skin layers

7. Stability testing must follow ICH guidelines under accelerated, intermediate, and long-term conditions, evaluating parameters such as phase separation, viscosity changes, and drug degradation [62].

8. Regulatory submissions increasingly require toxicological and environmental risk assessments, as nanomaterials may pose ecological hazards during manufacturing and disposal.

15. TOXICITY AND SAFETY OF NANOEMULGEL

1. The nanoscale droplet size (<200 nm) enhances skin permeation but may also increase systemic absorption, particularly for potent drugs, raising concerns about systemic toxicity.

2. Surfactants and co-surfactants used in nanoemulgels can disrupt the lipid bilayer of the stratum corneum, leading to irritation, erythema, and barrier dysfunction upon prolonged application [63,64]

3. Cytotoxicity evaluation using human keratinocyte and fibroblast cell lines is essential to determine the safety of nanoemulgel formulations at the cellular level.

4. Dermal toxicity studies such as the skin irritation test and sensitization studies are required to evaluate the potential of nanoemulgel to cause allergic reactions.

5. Nanocarriers may induce oxidative stress and inflammatory responses due to the generation of reactive oxygen species which can damage skin cells and tissues.

6. Natural product-based nanoemulgels often exhibit improved safety due to biocompatible phytoconstituent, but variability in plant extracts and possible allergenicity must be carefully evaluated [65].

7. Long-term toxicity, bioaccumulation, and penetration into deeper tissues remain areas of concern, especially for chronic use formulations.

8. Comprehensive safety assessment requires integration of physicochemical characterization, in vitro cytotoxicity, in vivo dermal studies, and clinical safety evaluation to ensure safe therapeutic application [66].

16. INDUSTRIAL CHALLENGES AND SCALE-UP

1. Scaling up nanoemulgel formulations from laboratory to industrial level requires high-energy equipment such as high-pressure homogenizers and ultrasonication systems, which increases capital investment and operational complexity.

2. High-energy methods demand significant energy input and process optimization, making large-scale production costly and sometimes inefficient.[67]

3. Maintaining consistent droplet size distribution and low polydispersity index during large-scale manufacturing is challenging, affecting formulation stability and performance.

4. Minor variations in formulation composition, such as surfactant concentration or oil phase ratio, can lead to phase separation, coalescence, or instability, impacting product quality [68].

5. The incorporation of nanoemulsion into gel matrices must preserve nanostructural integrity, as improper mixing may lead to aggregation or loss of nano-characteristics.

6. Selection of excipients suitable for industrial production must consider regulatory approval, cost-effectiveness, and long-term stability, which limits formulation flexibility [69,70]

7. Packaging materials must protect nanoemulgels from light, temperature fluctuations, and oxidation, as these factors can degrade the formulation.

8. Lack of standardized industrial protocols and regulatory clarity for nanocarriers remains a major barrier to commercialization.

9. Ensuring batch-to-batch reproducibility and quality control is essential for industrial success, requiring advanced analytical and process monitoring techniques [71].

Journal of Chemical Health Risks
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17. CLINICAL APPLICATIONS OF NANOEMULGEL

1. Nanoemulgels are widely used in dermatology for treating acne, psoriasis, eczema, and fungal infections, due to their ability to enhance drug penetration through the stratum corneum.
2. They provide localized drug delivery, minimizing systemic side effects and improving therapeutic outcomes compared to conventional topical formulations
3. In wound healing, nanoemulgel promote epithelialization, collagen synthesis, and angiogenesis, leading to faster tissue regeneration [72.]
4. Antimicrobial nanoemulgele xhibit enhanced activity against Gram-positive and Gram-negative bacteria, due to increased surface interaction and membrane disruption.
5. Anti-inflammatory and analgesic nanoemulgel provide sustained drug release, improving pain management and reducing dosing frequency.
6. Nanoemulgel containing natural bioactive such as curcumin, essential oils, and plant extracts show improved bioavailability and therapeutic efficacy.
7. Clinical translation requires controlled clinical trials to establish safety, efficacy, and therapeutic equivalence with existing treatments [73.]
8. Despite promising research, the number of approved nanoemulgel products remains limited due to regulatory challenges and lack of long-term clinical data .

18. FUTURE PROSPECTS OF NANOEMULGEL

1. Nanoemulgel present a promising platform for drug delivery via topical and transdermal routes.

2. Current research focuses on improving the safety and therapeutic efficacy of nanoemulgel formulations.

3. The creation of environmentally friendly and biodegradable surfactants is anticipated to enhance the biocompatibility of formulations.

4. Utilizing natural polymers as gelling agents can decrease toxicity and enhance patient acceptance.

5. Stimuli-responsive nanoemulgel allow for controlled and site-targeted drug release.

6. These advanced systems are especially advantageous for treating chronic and localized skin conditions.[74,75]

CONCLUSION

Nanoemulgel are innovative drug delivery systems that blend the benefits of nanoemulsion and gel matrices to address the shortcomings of traditional topical formulations. They improve drug solubility, skin absorption, duration of effect, and controlled release, making them ideal for both topical and transdermal uses. The small droplet size enhances interaction with the stratum corneum, which boosts localized bioavailability while reducing systemic exposure. Thorough physicochemical characterization is crucial for verifying quality, safety, and performance. The addition of natural oils, herbal extracts, and biocompatible polymers can further enhance antimicrobial, anti-inflammatory, and wound-healing properties. However, challenges like large-scale production, long-term stability, regulatory hurdles, and limited clinical data still exist. Future innovations involving eco-friendly surfactants, natural polymers, systems responsive to stimuli, Quality-by-Design strategies. Overall, nanoemulgel present a flexible and promising approach for creating safer, more effective, and user-friendly topical and transdermal therapies.

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Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(3), 103-115 | ISSN:2251-6727

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