

Nanoemulgel: A Promising Next-Generation Carrier for Topical Drug Delivery.

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Abstract

The topical route serves as a natural protective barrier that restricts the penetration of particulate drug delivery systems; however, it also represents a valuable and clinically relevant pathway for therapeutic delivery, particularly in diseased skin and through appendageal routes such as hair follicles. Recent advances in dermatological research have highlighted the potential of nanocarrier-based topical systems, including nanoemulsions and nanoemulgels, to overcome these barrier limitations by enhancing drug localization, penetration, and sustained release at the target site. Nanoemulsions, characterized by uniformly dispersed nanosized droplets typically ranging from 20 to 200 nm, can be formulated as oil-in-water or water-in-oil systems and offer advantages such as high drug-loading capacity for both hydrophilic and lipophilic drugs, improved stability, and cost-effective production. However, their low viscosity and limited skin retention restrict direct topical application. Incorporation of nanoemulsions into hydrogel matrices leads to the formation of nanoemulgels, which function as drug reservoirs, providing improved rheological properties, controlled and sustained drug release, enhanced skin permeation, and prolonged residence time. This review comprehensively discusses the formulation components, preparation methods, mechanisms of skin permeation, characterization parameters, therapeutic applications, current challenges, and future prospects of nanoemulgels. Owing to their superior stability, patient acceptability, and broad dermatological applicability, nanoemulgels represent a promising next-generation carrier for topical drug delivery.

Keywords: Nanoemulgel; Nanoemulsion; Topical drug delivery; Skin permeation; Controlled drug release

I. INTRODUCTION

Nanoemulsions

Nanoemulsions are colloidal particulate systems within the submicron size range, typically between 10 and 1,000 nm. They serve as carriers for drug molecules and consist of solid, spherical particles with an amorphous, lipophilic surface that usually carries a negative charge.

Nanoparticles can be incorporated into these systems to improve site-specific drug delivery, thereby enhancing therapeutic efficacy while reducing adverse effects and toxic reactions¹. Nanoemulsions are further classified as oil-in-water (O/W) emulsions, water forms the continuous phase with oil as the dispersed phase, whereas in water-in-oil (W/O) emulsions, the arrangement is reversed. Due to their small droplet size, nanoemulsions enable uniform deposition and deeper penetration of active ingredients through the skin. Their large surface area and low surface tension contribute to better ingredient absorption and bioavailability². However, nanoemulsions possess inherent drawbacks such as low viscosity, poor spreadability, and limited skin retention, which limit their direct topical application. Incorporating nanoemulsions into gel matrices can overcome these challenges by improving consistency, enhancing drug dissolution, and promoting controlled release³. The structure of nanoemulsion as shown below Fig 1,

Structure of a Nanoemulsion.

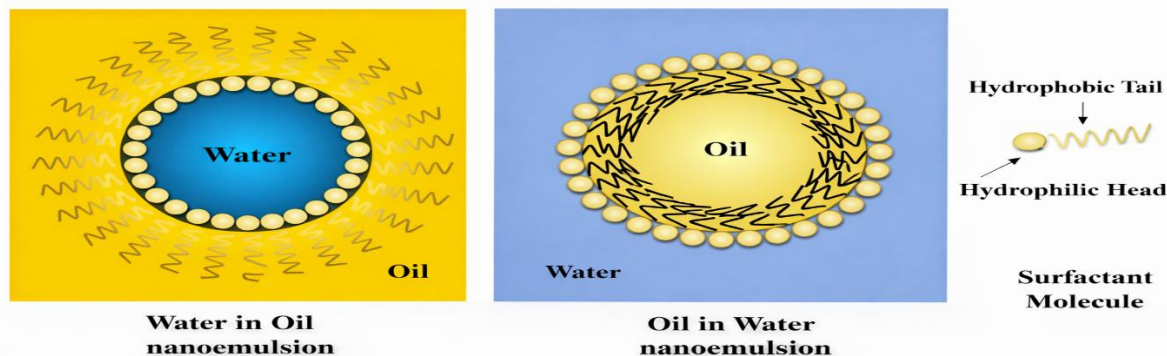


Figure 1: Structure of a Nanoemulsion

Nano-Emulgel:

Nanoemulsions are efficient carriers for drug delivery; however, their low viscosity and limited retention on the skin restrict their application in topical formulations. These limitations can be overcome by converting nanoemulsions into nanoemulgels through the incorporation of suitable gelling agents such as carbomers, xanthan gum, and Pluronics. The addition of a gel matrix enhances viscosity, thermodynamic stability, and residence time on the skin, thereby enabling controlled and sustained drug release. This hybrid delivery system combines the high permeation efficiency and small droplet size of nanoemulsions with the favorable rheological properties and patient acceptability of gels. As a result, nanoemulgels exhibit improved drug loading, enhanced skin penetration, reduced irritation potential, and superior bioavailability when compared with conventional emulgels and other nanocarrier systems⁴.

Nanoemulgel has emerged as an advanced topical drug delivery system due to its ease of application, improved patient compliance, and suitability for delivering lipophilic drugs. The presence of nano-sized droplets facilitates drug transport across the stratum corneum through intercellular and intracellular pathways. Formulation components, including the oil phase, surfactants, co-surfactants, and gelling agents, play a critical role in determining permeation enhancement, viscosity, and skin retention. Nanoemulgels have demonstrated therapeutic potential in the management of inflammatory conditions, arthritis, wound healing, and microbial skin infections⁵.

In nanoemulgel systems, the dispersed nanoemulsion droplets act as drug reservoirs, regulating diffusion from the internal oil phase into the external gel matrix. Upon topical application, the gel network enables gradual release of the droplets, which subsequently penetrate the skin and deliver the drug to the target site. The strong adhesiveness of the formulation and efficient solubilization of the drug within the oil phase create a concentration gradient toward the skin, resulting in enhanced transdermal penetration. Improved spreadability and ease of application further contribute to better patient compliance⁶.

Mechanism of skin permeation by nanoemulgel.

Upon topical application, the nanoemulgel spreads on the skin surface, where nanosized emulsion droplets are dispersed within the gel matrix. These nanosized droplets enhance the contact area with the skin and prolong the residence time of the formulation, ensuring sustained interaction with the stratum corneum. Once the drug is released from the gel, surfactants and co-surfactants in the formulation disrupt the lipid bilayer of the stratum corneum, increasing membrane fluidity and reducing the barrier resistance of this outermost skin layer. This facilitates drug permeation through two main pathways: the **transcellular route**, where the drug passes directly through the cells, and the **paracellular route**, where the drug moves between adjacent cells. As a result, the active moiety penetrates deeper into the epidermis and dermis, leading to enhanced bioavailability at the target site and improved therapeutic efficacy⁷.

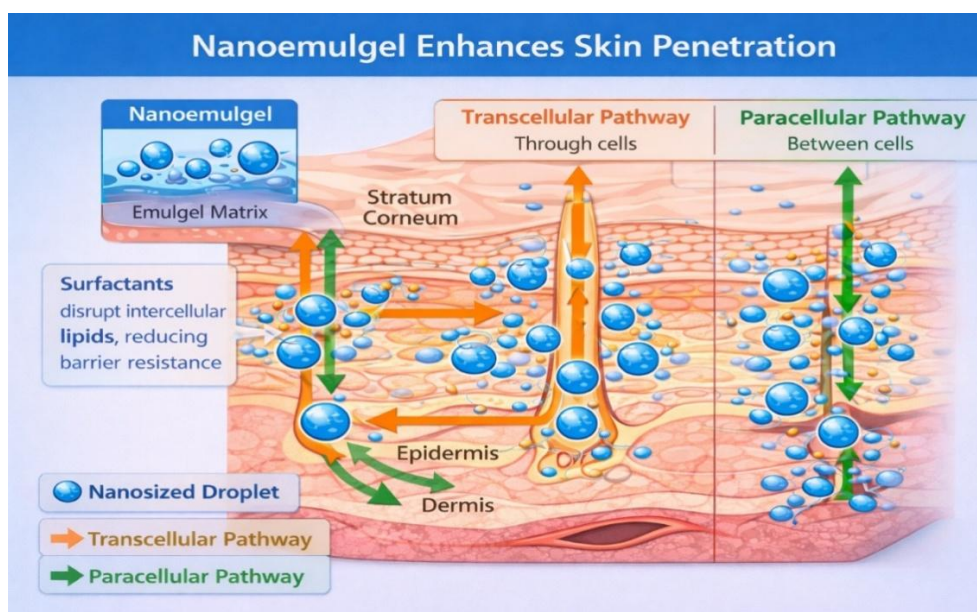


Figure2: Mechanism of skin permeation by nanoemulgel.

Advantages

- Helps avoid first-pass metabolism.
- Well accepted by patients.
- Suitable for self-administration of medications.
- Allows easy discontinuation of therapy whenever needed.
- Adapts well to the skin's physiological environment.
- Demonstrates strong effectiveness for controlled and sustained drug release.
- Generally non-irritant and non-toxic.
- Allows higher drug-loading capacity than many other formulations.
- Enhances drug deposition and improves skin permeability.

- Provides better spreadability compared to conventional creams⁸.

Disadvantage

- A high concentration of surfactant and co-surfactant is often required to achieve adequate stabilization of nanodroplets.
- Nanoemulsions exhibit limited solubilizing capacity for substances with high melting points.
- The surfactants employed must be biocompatible and non-toxic to ensure their suitability for pharmaceutical applications.
- The stability of nanoemulsions is strongly influenced by environmental factors such as temperature and pH, which may vary upon administration to patients⁹.

Components	Example
oil	Clove oil, olive oil, castor oil, coconut oil
surfactants	Tween 80, Span 80, Polyethylene glycol.
Co-surfactants	Lecithin, Propylene glycol, Propanolol, Transcutol P, Polyethylene glycol Butanol
Gelling agents	Carbapol 934, Carbapol 940, and hydroxypropyl methylcellulose
Penetration enhancers	Alcohols., Polyols., Alkanes., Ester., Terpenes., Surface active agent

Table 1: Components of Nanoemulgel

Components:

The main components of nanoemulgel are as follows:

Oils:

The oil phase in nanoemulgels acts as the dispersed medium for dissolving lipophilic drugs, enhancing solubility, bioavailability, and membrane permeability. Its selection depends on solubility, viscosity, and compatibility with formulation components. It also influences stability, texture, and drug release, making it a critical factor in achieving effective and stable nanoemulsion systems¹⁰.

Aqueous Solvents:

Aqueous solvents form the continuous aqueous phase of nanoemulsions and represent a significant component of the gel matrix in nanoemulgels. Water is the most widely used solvent, often complemented by aqueous-compatible alcohols, which aid in solubilization and enhance formulation stability¹¹.

Surfactants:

Surfactants are essential in the preparation of nanoemulsions and nanoemulgels due to their ability to reduce interfacial tension and stabilize droplets formed between two immiscible phases. Their amphiphilic nature facilitates the formation of a flexible interfacial film around dispersed droplets, thereby preventing coalescence and contributing to long-term formulation stability. In topical delivery systems, surfactants also play a significant role in enhancing drug permeation by temporarily altering the structure of the stratum corneum, which improves drug penetration across the skin barrier.

Co-surfactants:

Co-surfactants work synergistically with surfactants by further reducing interfacial tension and improving droplet flexibility. Although they cannot stabilize emulsions on their own, they promote the formation of fine nano-sized droplets and enhance skin penetration. Short-chain alcohols and similar amphiphilic compounds are commonly used as co-surfactants. The optimal ratio of surfactant to co-surfactant is typically determined through **pseudo-ternary phase diagrams**, which help identify the most stable nanoemulsion region before incorporating it into a gel base¹².

Ternary Plot:

Pseudo-ternary phase diagrams of oil, water, and surfactant/co-surfactant mixtures are constructed at fixed surfactant-to-co-surfactant weight ratios to identify the nanoemulsion region. For phase diagram construction, accurately weighed components are mixed in glass vials and subsequently titrated with water under continuous stirring at room temperature. The resulting systems are visually examined to distinguish between monophasic and biphasic regions. Formulations exhibiting turbidity or phase separation are classified as biphasic, whereas clear and transparent systems observed after stirring are considered monophasic. Each formulation is plotted as a point on the ternary phase diagram, and the region encompassing the monophasic systems is designated as the nanoemulsion existence region¹³.

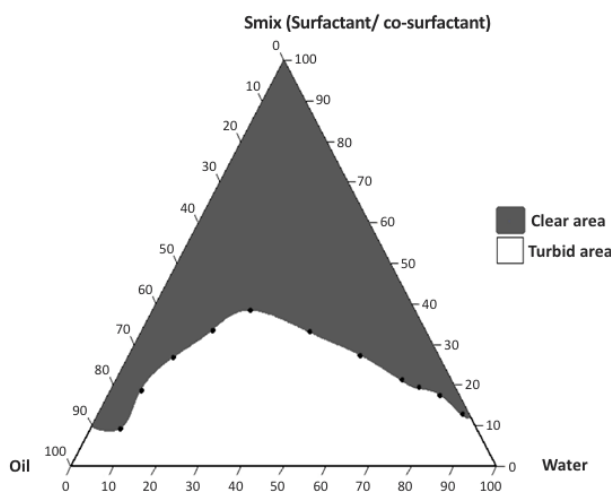


Figure 3: Schematic representation of pseudo-ternary phase diagram construction using the aqueous titration method. The shaded region indicates the transparent nanoemulsion zone, while the unshaded region represents turbidity.

Gelling Agents:

Gelling agents are incorporated into nanoemulgel formulations to impart appropriate viscosity, improve consistency, and enhance structural integrity. They function as thickening polymers that transform liquid nanoemulsions into semi-solid systems suitable for topical application. In addition to improving patient acceptability, gelling agents contribute to formulation stability, uniform drug distribution, and ease of application, while maintaining clarity and compatibility with other formulation components¹⁴.

Preservatives:

Preservatives are antimicrobial agents added to pharmaceutical formulations to inhibit microbial growth and contamination. Their primary function is to enhance shelf life and ensure the safety, stability, and efficacy of the product throughout storage and use. In topical nanoemulgels, preservatives are particularly important due to the presence of aqueous components that can support microbial proliferation¹⁵.

Penetration Enhancers:

Penetration enhancers are substances incorporated into topical formulations to improve the transport of drugs across the skin and underlying layers. In nanoemulgel systems, they play a crucial role in increasing drug absorption by temporarily and reversibly modifying the barrier properties of the skin. These agents generally act by interacting with components of the stratum corneum, leading to increased skin permeability without causing permanent damage, thereby enhancing the therapeutic efficacy of the formulation¹⁶.

Emulsifiers:

Emulsifiers are surface-active agents incorporated into nanoemulsion and nanoemulgel formulations to stabilize dispersed oil droplets formed during homogenization. They adsorb onto the droplet surface, reduce interfacial tension, and facilitate the formation of smaller droplet sizes. By forming a protective interfacial layer, emulsifiers prevent droplet aggregation and coalescence, thereby enhancing kinetic stability and extending shelf life. The selection and concentration of emulsifiers are critical, as adequate droplet surface coverage and strong interfacial adsorption are essential for maintaining formulation stability. Emulsifiers may be polymeric or low-molecular-weight amphiphilic compounds and can be classified based on their ionic nature, all of which influence droplet stabilization and overall performance of the nanoemulsion system¹⁷.

II. METHOD OF PREPARATION:

Preparation of Nanoemulsion:

The drug is initially dissolved in the lipophilic (oil) phase of the nanoemulsion. The oil and aqueous phases are then combined in the presence of a suitable surfactant, followed by the gradual addition of a co-surfactant under continuous stirring until a clear and transparent system is formed. The optimal concentrations of surfactant and co-surfactant, along with the maximum proportion of oil phase that can be incorporated, are determined using a pseudo-ternary phase diagram. Finally, high-pressure homogenization is applied to obtain nano-sized dispersed globules, after which the formulation is allowed to equilibrate¹⁸.

Preparation of Nanoemulgel:

Nanoemulgels are non-equilibrium, structured liquid systems formulated using energy input, surfactants, or a combination of both, and may be formed spontaneously by increasing the energy of the biphasic oil-water system or by reducing interfacial tension between the immiscible phases. Various nanoemulgel preparation methods have been reported in the literature, primarily differing in the sequence of mixing of the oil and aqueous phases¹⁹.

The preparation process involves the formation of a gelling medium by dispersing the selected polymer in an aqueous phase under continuous mechanical stirring until complete hydration and swelling are achieved, followed by adjustment of the gel base pH to ensure compatibility with topical delivery. An oil-in-water nanoemulsion, prepared using an appropriate technique, is then incorporated into the gel base, where the gelling agent imparts thixotropic properties, enabling reversible gel-sol transition under shear stress without volume change. The nanoemulsion and gel matrix are uniformly blended at a fixed ratio under continuous stirring to obtain a homogenous nanoemulgel formulation²⁰.

High-Pressure Homogenization method :

High-pressure homogenization is a widely employed technique for the preparation of nanoemulsions with extremely small droplet sizes, often reaching the nanometer range. This method utilizes a high-pressure piston homogenizer, wherein the emulsion is forced through a narrow gap under high pressure, generating intense hydraulic shear, turbulence, and cavitation forces that collectively reduce droplet size. The resulting formulation may be subjected to multiple homogenization cycles until the desired droplet size and polydispersity index are achieved. The formation of submicron droplets requires the application of high energy, and the efficiency of emulsification can be enhanced through various

approaches, such as preparing the emulsion at a high dispersed-phase volume fraction followed by dilution. However, excessively high phase volume ratios may promote coalescence, which can be minimized by increasing surfactant concentration to reduce effective interfacial tension. Additionally, the use of surfactant mixtures that provide greater

surface tension reduction than individual surfactants, or dissolving the surfactant in the dispersed phase rather than the continuous phase, can further facilitate droplet size reduction. Stepwise emulsification with progressively increasing intensity is also beneficial, particularly for systems containing highly viscous dispersed phases²¹.

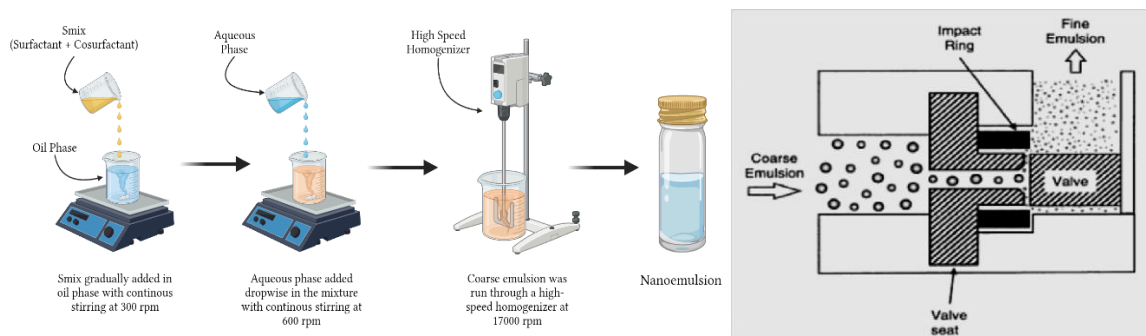


Figure 4: High-Pressure Homogenization & Schematic representation of high pressure valve homogenizer.

Microfluidization method :

Microfluidization is a widely utilized technique in the pharmaceutical industry for obtaining fine emulsions. In this method, a specialized device known as a microfluidizer operates under high pressure (as illustrated in Figure 5). The process involves forcing a macroemulsion through an interaction chamber, where intense mechanical forces transform it into a nanoemulsion with submicron-sized droplets. Uniform nanoemulsion formation can be achieved by repeating the process multiple times and adjusting the operating pressure to achieve the desired particle size. Within the

microfluidizer, two crude emulsion streams collide at high velocity from opposite channels in the nozzle region, known as the interaction chamber. The emulsion flow is driven by a pneumatically powered pump capable of compressing air to pressures ranging from 150 to 650 MPa. This high pressure propels the emulsion through microchannels, and the subsequent collision of jets generates extremely high shear forces. These intense shear and impact forces effectively reduce droplet size, resulting in the formation of finely dispersed and stable emulsions²².

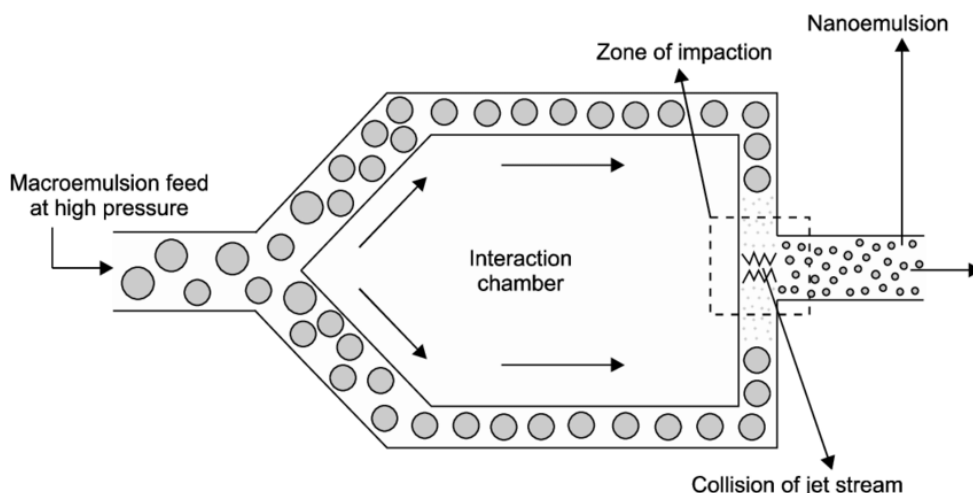


Figure 5: Schematic representation of microfluidizer

Ultrasonic emulsification method :

The ultrasonic homogenization (sonication) method is a high-energy technique used to prepare kinetically stable nanoemulsions by applying ultrasound waves above 20 kHz to induce cavitation, where the formation and collapse of microbubbles create intense shear forces that break larger droplets into nanosized ones. The process involves preparing separate oil and aqueous phases containing respective lipophilic and hydrophilic components, followed by forming a coarse pre-emulsion through mild stirring and then subjecting it to ultrasonication to achieve uniform droplet size and enhanced stability. The efficiency and characteristics of the resulting nanoemulsion depend on parameters such as ultrasound power or amplitude, sonication time, temperature, emulsifier concentration, and equipment configuration. Ultrasonication requires less energy compared to other high-energy methods and effectively produces fine emulsions, though limitations such as probe contamination and scalability issues exist. To address these challenges, continuous-flow ultrasonic homogenizers have been developed for large-scale production of uniform and stable nanoemulsions²³.

Solvent evaporation method:

In this approach, a water-miscible organic solvent is used to dissolve the oil phase, the drug, and the hydrophilic polymeric matrix, forming a homogeneous solution. The organic solvent is

subsequently removed under reduced pressure, often with gentle heating, leading to its gradual evaporation. As the solvent is eliminated, a nanoemulgel is formed, in which nanosized oil droplets become uniformly dispersed and immobilized within the three-dimensional gel matrix, resulting in a stable system suitable for drug delivery applications²⁴.

Self-nanoemulsification method:

The self-nanoemulsification method relies on the spontaneous formation of nanoemulsions without significant alteration of the surfactant's spontaneous curvature, wherein surfactant and co-solvent molecules rapidly diffuse from the dispersed phase into the continuous phase, creating local turbulence and interfacial disturbances that generate nanosized droplets. This process, often termed spontaneous emulsification, forms the basis of self-nanoemulsifying drug delivery systems (SNEDDS), which typically contain a higher proportion of hydrophilic surfactants and/or co-surfactants and a lower lipid content. SNEDDS are isotropic mixtures of oil, surfactant, co-surfactant, and drug that, upon dilution with gastrointestinal fluids and under the gentle agitation produced by gastric and intestinal motility, spontaneously form fine, optically clear oil-in-water nanoemulsions, thereby enhancing the solubilization, absorption, and bioavailability of poorly water-soluble drugs²⁵.

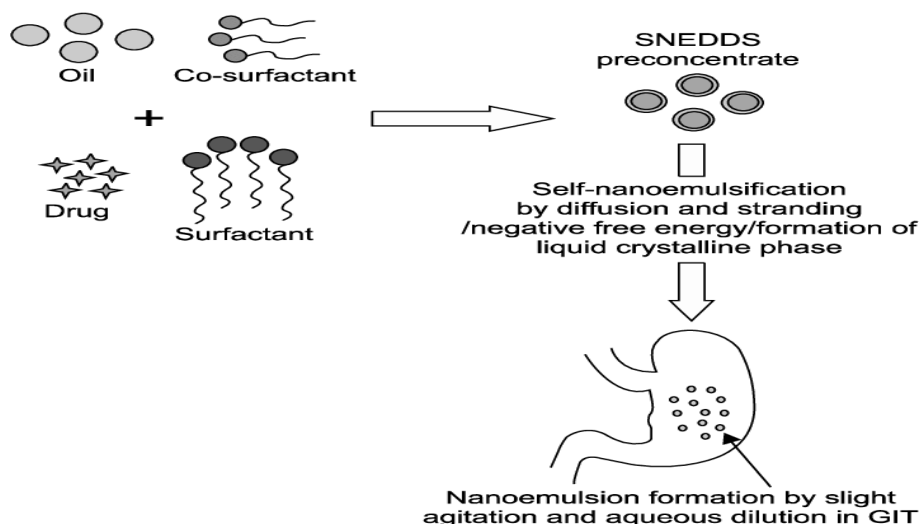


Figure 6: Self-nanoemulsification techniques, SNEDDS, self-nanoemulsifying drug delivery system; GIT, gastrointestinal tract.

High-energy emulsification methods:

High-energy methods are widely employed for the formulation of nanoemulsions, wherein intense mechanical energy is used to generate strong disruptive forces that break coarse emulsion droplets into nanosized droplets, resulting in kinetically stable dispersions with narrow size distribution. These disruptive forces are typically produced using mechanical devices such as ultrasonicators, microfluidizers, and high-pressure homogenizers, which enable fine control over droplet size and distribution through adjustment of formulation composition and processing parameters. High-energy techniques also permit modulation of key product attributes, including physical stability, rheological behavior, and visual properties such as opacity or color, by tailoring both the energy input and the nature and ratio of formulation components. However, their application is limited in the case of thermolabile drugs and excipients, as the substantial energy dissipation often causes significant temperature elevations that may induce degradation of heat-sensitive materials²⁶.

Phase inversion temperature (PIT) method :

This process utilizes a thermosensitive non-ionic surfactant that transitions from hydrophilic to lipophilic character at a specific temperature due to polyoxyethylene dehydration. By heating the oil-surfactant-polymer mixture to the PIT or HLB point, interfacial tension minimizes to enable spontaneous emulsification with nanosized oil droplets; rapid cooling then traps the dispersed oil phase within the gelling matrix, forming a stable nanoemulgel structure²⁷.

Coacervation method:

The coacervation method involves the use of two or more polymers that undergo phase separation in response to changes in pH or the presence of an electrolyte, leading to the formation of a gel-like structure. The dispersed phase can subsequently be incorporated into this polymeric gel through techniques such as high-energy emulsification, enabling the development of stable encapsulated systems²⁸.

Sol-gel transition method:

The sol-gel transition method involves the transformation of a liquid sol into a semi-solid gel through the aggregation and crosslinking of particles or polymers within a solvent. This transition is typically triggered by adding a crosslinking agent or incorporating thermosensitive polymers that induce

gel formation under specific temperature or environmental conditions. The method is used to enhance the stability, viscosity, and controlled release properties of nanoemulsion-based systems²⁹.

Electrostatic Complexation Method :

The electrostatic complexation method utilizes oppositely charged polymers or surfactants to form a stable emulsion, which can subsequently be converted into a gel through the addition of a suitable crosslinking or gelling agent³⁰.

Characterization of Nanoemulgel

Physical Appearance

The physical appearance of the developed nanoemulgel formulations was assessed visually in terms of colour, homogeneity, consistency, and pH³¹.

Droplet size

Droplet size is a critical parameter influencing the performance, stability, and efficacy of nanoemulgel formulations. Nanoemulgels with droplet sizes below 200 nm are preferred due to their increased surface area, which enhances drug release and promotes deeper skin penetration by facilitating closer interaction with the stratum corneum. The concentration of surfactants and co-surfactants plays a key role in reducing interfacial tension and forming smaller, uniform droplets, thereby improving permeability. In contrast, increased water content may enlarge droplet size and reduce permeation efficiency. Droplet size also directly affects formulation stability, as larger droplets are more prone to creaming, sedimentation, and phase separation, while smaller droplets exhibit reduced gravitational movement and better viscosity characteristics. Therefore, precise control of droplet size is essential for optimizing drug delivery and maintaining the physical stability of nanoemulgel systems for pharmaceutical and cosmetic applications³².

Zeta Potential

Zeta potential is an important indicator of nanoemulgel stability, as it reflects the surface charge of dispersed droplets and the resulting electrostatic repulsive forces that prevent aggregation, flocculation, and coalescence. Adequate positive or negative zeta potential values contribute to improved physical stability and consistent in vivo performance. Zeta potential is commonly determined by diluting the nanoemulgel or its corresponding nanoemulsion with a suitable aqueous medium to avoid multiple scattering, followed by measurement using a zeta potential analyzer based on electrophoretic light scattering.

During analysis, an electric field is applied, and the velocity of charged droplets is measured to calculate their electrophoretic mobility, which is then converted into zeta potential values. This procedure provides reliable information on droplet surface charge and helps predict the long-term stability of nanoemulgel formulations used in pharmaceutical and cosmetic applications³³.

Viscosity

Viscosity represents a critical property for nanoemulgels, determining their effective skin application and spreadability. Assessing rheological behavior helps optimize the formulation for topical delivery. Viscosity refers to a fluid's resistance to flow, where higher values indicate greater opposition to movement. Fluids are categorized as Newtonian or non-Newtonian: Newtonian systems maintain constant viscosity across varying shear rates, requiring proportional increases in shear stress for higher shear rates, while non-Newtonian systems deviate from this, exhibiting shear-dependent viscosity changes³⁴. The viscosity of the nanoemulgel formulations was determined using a Brookfield viscometer. Spindle No. 5 was immersed centrally in the nanoemulgel sample contained in a beaker, ensuring that it did not touch the bottom during measurement and rotated at 10 rpm for 10 minutes. The resulting viscosity values, calculated from the dial readings, were averaged from three replicate measurements to ensure accuracy and reproducibility³⁵.

Rheological Properties

Rheological characterization is a critical parameter in assessing the quality, performance, and applicability of nanoemulgel formulations, as it is strongly influenced by the composition and interaction of key components such as the oil phase, surfactants, and gelling agents. Even slight variations in the physicochemical properties of these constituents can markedly alter viscosity and flow behavior, thereby affecting formulation stability, spreadability, drug release, and overall therapeutic efficacy. Since viscosity governs resistance to flow, it directly impacts patient acceptability and the biological performance of topical nanoemulgels. A comprehensive rheological evaluation therefore provides essential insight into the structural integrity, consistency, and predictability of in vivo behavior of the system. Rheological studies are typically conducted using a viscometer or rheometer by subjecting the nanoemulgel to controlled shear rates at a defined temperature, with viscosity

measurements used to determine flow behavior. Analysis of shear stress versus shear rate profiles allows classification of the formulation as Newtonian or non-Newtonian, including pseudoplastic or thixotropic systems, which is particularly desirable for topical applications due to improved spreadability, stability, and ease of administration³⁶.

pH Measurement

The pH of nanoemulgel formulations is determined by diluting 1 g of the sample in 10 ml of distilled water to achieve a homogeneous dispersion suitable for analysis. The pH meter is first calibrated using standard buffer solutions (pH 4.0 and 7.0), after which the electrode is immersed into the diluted nanoemulgel and stirred gently until a stable reading is obtained. This measurement, typically performed in triplicate, ensures the formulation's pH falls within the skin-compatible range (ideally 5.5–6.5) to minimize irritation and enhance stability³⁷.

Spreadability testing

Spreadability testing is an important evaluation parameter for nanoemulgels, as it is directly influenced by the viscosity of the formulation and determines ease of application and patient compliance. The parallel-plate method is most commonly employed to assess spreadability, using two glass slides of identical dimensions, where one slide is fixed on a wooden block and the other is attached to a pulley system. A measured quantity of nanoemulgel is placed on the stationary slide and compressed between the two slides. A known weight is gradually applied to the pulley until the upper slide moves or slips over the lower slide, and the time required for this movement is recorded. This test provides valuable insight into the consistency, applicability, and suitability of nanoemulgels for topical delivery³⁸.

Spreadability is then calculated using the formula:

$$S = M \cdot L / T$$

Where- s is Spreadability.

M- is weight bounded to the upper slide.

L- is the length of the slide.

T- is the time taken to detach the slide.

In Vitro Drug Release TEST (IVRT)

In vitro drug release from nanoemulgels is typically evaluated using Franz diffusion cells equipped with a dialysis membrane (molecular weight cut-off 12,000–14,000 Da) mounted between the donor and receptor compartments. The receptor chamber is filled with phosphate buffer (pH 6.4) as the diffusion medium and maintained at $37 \pm 0.5^\circ\text{C}$ on a

magnetic stirrer at 50 rpm. Approximately 1 g of nanoemulgel is uniformly applied to the donor chamber over the membrane, with samples withdrawn from the receptor at predefined intervals (1, 2, 3, 4, 5, 6, 7, 8, and 24 h), replaced with fresh buffer to maintain sink conditions, filtered, and analyzed spectrophotometrically for cumulative percent drug release³⁹.

Extrudability

Extrudability of nanoemulgels is assessed using a closed collapsible tube filled with the formulation to evaluate its ease of application and patient compliance. The tube cap is removed, and a measured force is applied using a texture analyzer or manual compression to extrude a specific quantity of nanoemulgel. The extrudability is quantified as the ratio of extruded gel weight to applied force, with higher values indicating superior spreadability and tube-filling efficiency⁴⁰.

Thermodynamic Stability Study

The selected nanoemulgel formulations were evaluated for thermodynamic stability using both long-term and accelerated stability studies to assess their physical robustness.

Long-Term Stability Studies

The formulations were stored for a period of three months at temperatures of 4 °C, 25 °C, and 40 °C. Viscosity measurements were performed in triplicate at monthly intervals, and the results were expressed as mean ± standard deviation (SD).

Accelerated Stability Studies

Accelerated stability testing was conducted through six heating-cooling cycles. Each involved storage at 4 °C followed by exposure to 40 °C for 48 h at each temperature. After completion of the cycles, the formulations were visually examined for any signs of physical instability. The samples that remained stable were further subjected to centrifugation at 3750 rpm for 5 h to simulate long-term gravitational stress equivalent to approximately one year of storage. Visual inspection was carried out to identify phase separation, cracking, or other instability phenomena⁴¹.

Skin Irritation Test (Patch Test)

The skin irritation potential of the formulation was evaluated using a patch test in rats. The preparation was applied to the properly shaved dorsal skin, and the treated area was observed for up to 24 h for any signs of irritation, including changes in skin color, erythema, edema, or alterations in skin morphology. The formulation was considered non-irritant if no visible adverse reactions were observed during the observation period⁴².

Factors Affecting Topical Drug Absorption

The absorption of drugs through the skin is influenced by both **physiological** and **physicochemical** factors. These parameters collectively determine the permeability of the skin and the extent to which a drug can penetrate into or across the topical site.

Physiological Factors

1. **Skin thickness:** Variations in the thickness of the stratum corneum significantly influence drug permeation, with thinner skin allowing greater absorption.
2. **Lipid content:** The lipid composition of the stratum corneum plays a crucial role in regulating the diffusion of lipophilic drugs.
3. **Density of hair follicles:** Hair follicles provide shunt pathways that can facilitate enhanced drug penetration.
4. **Density of sweat glands:** Sweat ducts may contribute to percutaneous absorption by acting as alternative penetration routes.
5. **Skin pH:** The pH of the skin affects the ionization state of drugs, thereby influencing their permeability.
6. **Cutaneous blood flow:** Increased blood flow enhances systemic uptake by maintaining a concentration gradient at the site of absorption.
7. **Skin hydration:** Hydrated skin exhibits increased permeability due to swelling of the stratum corneum.
8. **Inflammation of the skin:** Inflammatory conditions can disrupt the skin barrier, leading to increased drug absorption⁴³.

Physicochemical Factors

1. **Partition coefficient:** An optimal balance between lipophilicity and hydrophilicity is essential for effective skin penetration.
2. **Molecular weight:** Drugs with a molecular weight below 400 Da generally exhibit better transdermal permeability.
3. **Degree of ionization:** Non-ionized forms of drugs penetrate the skin more readily than ionized forms.
4. **Effect of vehicles:** The formulation vehicle significantly influences drug solubility, release and subsequent skin penetration⁴⁴.

Scope of Nanoemulgels in Topical Drug Delivery

1. **Enhanced Absorption and Bioavailability:** Nanoemulgels improve drug absorption and pharmacokinetic behavior due to their

nanosized droplets, resulting in higher therapeutic efficacy compared to conventional lipophilic formulations.

2. **Improved Patient Compliance:**
Their non-greasy nature, reduced stickiness, and superior spreadability enhance patient acceptability over traditional topical dosage forms.
3. **Improved Stability and Drug Release:**
Incorporation of nanoemulsions into gel matrices overcomes problems such as creaming and phase separation associated with conventional emulsions, while improving drug release and spreadability.
4. **Efficient Delivery of Hydrophobic Drugs:**
Nanoemulgels effectively deliver hydrophobic drugs by solubilizing them in the oil phase of nanoemulsions prior to gel incorporation, making them suitable for treating skin infections and inflammatory conditions.
5. **Controlled and Sustained Release:**
The gel network acts as a drug reservoir, enabling controlled release and prolonged drug residence at the site of application.
6. **Broad Therapeutic and Cosmetic Applications:**
Nanoemulgels have shown enhanced efficacy in the treatment of acne, psoriasis, fungal infections, osteoarthritis, and rheumatoid arthritis, and are also used in cosmeceuticals such as UV-protective formulations⁴⁵.

Current Challenges and Future Prospects in Nanoemulgel

Based on reported studies, nanoemulgels have emerged as a promising novel topical drug delivery system designed to enhance the pharmacokinetic and pharmacodynamic performance of poorly bioavailable drugs while improving patient compliance. Several lipophilic drugs across diverse therapeutic categories have been successfully formulated as nanoemulgels, demonstrating improved solubility, enhanced skin permeation, controlled drug release, and superior localized therapeutic efficacy. Consequently, nanoemulgels are extensively investigated for the topical management of acute and chronic conditions such as fungal infections, inflammation, wound healing, psoriasis, alopecia, and other dermatological disorders. Owing to these advantages, nanoemulgels also offer potential for revitalizing drug candidates previously discontinued

due to poor bioavailability or inadequate clinical efficacy⁴⁶. Despite these benefits, the translation of nanoemulgels into commercial topical products remains limited due to challenges including dependence on high-energy emulsification techniques, thermodynamic instability, degradation of thermolabile drugs, and difficulties in achieving consistent batch-to-batch reproducibility, which complicate large-scale manufacturing and regulatory approval. Future prospects include the development of low-energy and scalable fabrication approaches, optimization of skin-compatible polymers, lipids, and surfactants, and the application of quality-by-design strategies and standardized evaluation protocols to enhance formulation robustness and facilitate regulatory acceptance⁴⁷.

III. CONCLUSION:

Nanoemulsions and nanoemulgels have emerged as promising platforms for topical drug delivery owing to their ability to enhance drug solubility, stability, skin penetration, and bioavailability. Nanoemulsions, characterized by nanosized droplets and a large interfacial surface area, facilitate uniform drug distribution and improved percutaneous absorption; however, their low viscosity, poor spreadability, and limited skin retention restrict direct topical application. Incorporation of nanoemulsions into gel matrices to form nanoemulgels effectively overcomes these limitations by improving rheological behavior, thermodynamic stability, adhesiveness, and skin residence time while enabling controlled and sustained drug release. The therapeutic performance of nanoemulgels is governed by formulation components, preparation techniques, and evaluation parameters, along with physiological and physicochemical factors influencing topical drug absorption. Overall, the synergistic combination of enhanced permeation from nanoemulsions and the patient-friendly properties of gels results in improved drug loading, better skin deposition, reduced irritation, and enhanced patient compliance, positioning nanoemulgels as a robust and versatile drug delivery system with significant potential for pharmaceutical and dermatological applications.

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