

A Review on Design of Nanoemulgel-Based Transdermal Drug Delivery Systems in Pharmaceuticals: Current Challenges and Future Prospects

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Abstract Newly synthesized pharmaceuticals and some active phytoconstituents often possess a highly lipophilic nature, which presents challenges such as poor solubility, low oral bioavailability, and others. Emulsions provide a promising solution for incorporating both hydrophilic and lipophilic compounds. As well, the addition of thixotropic agents or colloidal polymers imparts the necessary viscosity to these preparations. This nanoemulgel approach introduces a novel transdermal drug delivery system that improves the therapeutic efficacy of BCS Class II and IV drugs. Therefore, this review provides a comprehensive overview of the latest research in transdermal nanoemulgel delivery. This review also includes a meta-analysis of studies demonstrating the superiority of nanoemulgel formulations over conventional products. In brief, the primary aim of nanoemulgels, which integrate multiple systems, is to overcome the limitations associated with individual components. While drugs are often limited by their physicochemical properties, emulsions can suffer from stability issues and reduced skin retention, whereas gels may have insufficient drug-loading capacity. Nanoemulgel formulations address these challenges by incorporating nanoemulsions into gels, thereby enhancing stability, prolonging skin contact time, and enabling rapid and controlled drug release. Nanoemulgels excel in targeted drug delivery due to their

ease of application, avoidance of first-pass metabolism and gastrointestinal degradation, favorable safety profile, and stability. In conclusion, these advantages have led to growing interest in nanoemulgels as a promising transdermal drug delivery system.

Keywords Nanoemulgel, Transdermal Drug Delivery, Formulation, Drug Delivery

1. Introduction

Despite plenty of development in pharmaceuticals, poor solubility, low permeability, and poor bioavailability are the major problems for drugs. From its inception, various techniques have been developed to address the challenges associated with it. These methods include both chemical and physical modifications of pharmacologically active molecules. Herein, extensive studies have focused on strategies such as salt formation, solid dispersion, particle size reduction, crystal engineering, and complexation [1]. A particularly effective approach is the use of lipid-based formulations, which have gained significant attention due to their ability to enhance the solubility of both lipophilic and hydrophilic drugs. In this case, this approach involves

creating formulations with carrier systems such as macroemulsions, nanoemulsions, liposomes, niosomes, solid lipid nanoparticles, and nanostructured lipid carriers, among others. In short, liposomes are vesicular carriers composed of a phospholipid and cholesterol bilayer that encapsulates the active ingredient. However, liposomes face limitations, including poor permeability across the intestinal epithelium and stability issues within the gastrointestinal tract [2]. Niosomes are vesicles made from non-ionic surfactants. It also presents challenges, such as high production costs, vesicle agglomeration, drug leakage, and hydrolysis of encapsulated drugs [3]. Additionally, lipid nanoparticles, such as solid lipid nanoparticles and nanostructured lipid carriers, suffer from low drug-loading capacities, a lack of reliable controlled-release mechanisms, and limited efficacy in transdermal drug delivery. Recent advancements in the pharmaceutical industry have focused on improving drug delivery systems to enhance the bioavailability of various medications.

In this context, nanoemulsion emerges as a modern drug delivery system, demonstrating significant potential for enhancing drug bioavailability and targeting. Their versatility makes them an effective tool for developing new pharmaceutical formulations and improving drug delivery, stability, and solubility. As research in this area progresses, nanoemulsions are expected to play a crucial role in enhancing drug delivery and improving patient outcomes. Nanoemulsions are typically transparent or translucent, which might be because of their small droplet size. It is stabilized against creaming or sedimentation. Moreover, surfactants and co-surfactants stabilize oil and water to form stable nanocarrier systems known as nanoemulsions. There are two main types of nanoemulsion systems: water-in-oil (W/O) and oil-in-water (O/W) [4]. Recent studies have shown that nanoemulsions, as colloidal carrier systems, are effective in enhancing the bioavailability of topically administered drugs. Due to their ability to penetrate skin and ocular barriers, nanoemulsions are being explored as a potential alternative to traditional topical dosage forms. Incorporating drugs into nanoemulsions can improve their effectiveness by enabling targeted drug delivery, reducing non-specific toxicity, enhancing therapeutic efficacy, reducing dosage requirements, and improving penetration rates. This review highlights the latest advancements in transdermal drug delivery research using nanoemulsions as a delivery system. In contrast to traditional emulsion-based formulations, the applications of nanoemulsions showed significant advantages in addressing issues related to low solubility and bioavailability [5]. Importantly, nanoemulsions represent a promising alternative for delivering lipophilic drugs and are already utilized in established drug delivery systems. By enhancing drug absorption through the skin, nanoemulsions improve the permeability and bioavailability of pharmaceuticals [6]. Therefore, this review covers the most recent research on nanoemulgels, emphasizing their commercial potential and applications. It

also demonstrates the superiority of drug-loaded nanoemulgels in terms of bioavailability compared to conventional dosage forms.

2. Nanoemulsion

A nanoemulsion is an isotropic biphasic system composed of two components, water, and oil, where one phase is dispersed as nanoscale droplets within the other. These droplets are stabilized by an interfacial layer of surfactants [7]. Compared to conventional emulsions, nanoemulsions exhibit a lower tendency for phase separation [8]. The droplet size in nanoemulsions typically ranges from 20 to 200 nanometers, often below 500 nanometers [9]. In concisely, this small droplet size significantly enhances the interfacial area, improving the solubility and bioavailability of poorly water-soluble drugs. Nanoemulsions are also versatile platforms for drug delivery across various therapeutic contexts, capable of encapsulating both hydrophilic and hydrophobic drugs.

Although nanoemulsions and microemulsions share similarities in appearance, composition, and preparation methods, they differ in stability. Nanoemulsions are kinetically stable but thermodynamically metastable, while microemulsions are both kinetically and thermodynamically stable. Here, the choice of co-surfactants, particularly medium-chain alcohols, plays a crucial role in forming stable oil droplets and influencing the viscosity of the nanoemulsion. This underscores the importance of component selection in optimizing the kinetic stability and properties of nanoemulsions. Also, nanoemulsions are gaining significant interest as drug carriers due to their ease of preparation and scalability, wide range of compatible components, and potential to enhance drug delivery [10]. The choice of oil in a nanoemulsion can significantly influence its ability to penetrate the skin. For instance, oleic acid (OA) is commonly used for its ability to enhance permeability by increasing water absorption in the stratum corneum and disrupting its structural components. Other oils frequently used in transdermal nanoemulsions include Capryol 90, isopropyl myristate, and α -tocopherol [11]. Surfactants play a critical role in stabilizing the nanoemulsion and can also impact drug penetration. Importantly, non-ionic surfactants are often preferred for transdermal applications due to their low toxicity and minimal interference with the skin. They enhance drug absorption by fluidizing the stratum corneum lipids, either by interacting with the intercellular lipids or the keratin filaments within corneocytes [10]. Co-surfactants are employed to further reduce interfacial tension and improve the stability of the nanoemulsion. They also influence drug penetration, particularly in formulations where the drug, especially hydrophilic drugs, is contained within this phase. Nanoemulsions can be formulated with lower surfactant concentrations (3-10%) compared to microemulsions,

which typically require higher concentrations (around 20%). Nanoemulsions facilitate the efficient delivery of active compounds across semipermeable barriers. Their broad surface area enhances penetration, making them effective in transdermal drug delivery. Nanoemulsions prevent the coalescence of tiny droplets, ensuring the system remains stable and undivided. The nanosized globules in a nanoemulsion experience reduced Brownian motion and minimal gravitational forces, preventing cream separation or particle settling during storage. Nanoemulsions are easily produced and require low energy input. Their formulations also enhance the consistency of the plasma concentration profile. Due to their ability to incorporate both hydrophobic and hydrophilic drugs, nanoemulsions serve as highly effective solvents. When the active component is encapsulated within a nanoemulsion, it is shielded from environmental factors such as pH changes, hydrolysis, and oxidation [12]. It can be formulated in various forms, including gels, creams, foams, aerosols, and sprays, and can be administered via multiple routes, such as oral, topical, intravenous, intrapulmonary, intranasal, and intramuscular. They offer greater solubilization capacity and stronger thermokinetic stability compared to micellar dispersions. The oil/lipid-based delivery approach of nanoemulsions helps to bypass hepatic first-pass metabolism [13]. Nanoemulsions can effectively mask the bitter taste of drugs, reducing undesirable side effects such as nausea and vomiting [14]. Nanoemulsions can serve as viable alternatives to liposomes and vesicles, which often suffer from stability issues. When taken orally, the tiny droplets of nanoemulsions enhance the dissolution and absorption rates of highly hydrophobic drugs [15]. The release of drugs from nanoemulsions occurs via partitioning, where the drug moves from the inner oil phase to the surfactant

layer and finally into the continuous aqueous phase. Once solubilized, the drug diffuses out of the oil and undergoes nanoprecipitation upon contact with the surrounding water. This significantly increases the drug's surface area, leading to faster dissolution as described by the Noyes-Whitney equation. The dynamics of drug release can be adjusted by modifying the composition of the nanoemulsion, allowing for prolonged and controlled release [16]. Additional factors, such as direct paracellular/transcellular transport [17] and extended gastric retention due to mucosal entrapment [18], further enhance oral administration. Despite their many advantages, including reduced interfacial tension, nanosized droplets, and improved skin penetration, nanoemulsions face limitations in clinical applications due to issues with skin retention, viscosity, and spreadability [19]. **Figure 1** shows the nanoemulsion fabrication methods. Preparation methods significantly influence droplet size distribution, which in turn impacts the stability of nanoemulsions [20]. High-energy methods involve the use of mechanical devices to reduce droplet size and create a uniform distribution. While these methods are effective, they may not be suitable for heat-sensitive drugs [21]. Examples include high-pressure homogenization and ultrasonication [20]. Low-energy methods are generally simpler and rely on the spontaneous formation of nanoemulsions through phase transitions or gentle mixing [7]. Examples include the Phase Inversion Temperature (PIT) method and spontaneous emulsification [22]. The spontaneous emulsification method is particularly advantageous due to its simplicity and lack of reliance on specialized equipment [19]. However, this method requires a careful selection of ingredients to ensure the stability of the nanoemulsion and achieve a small droplet size.

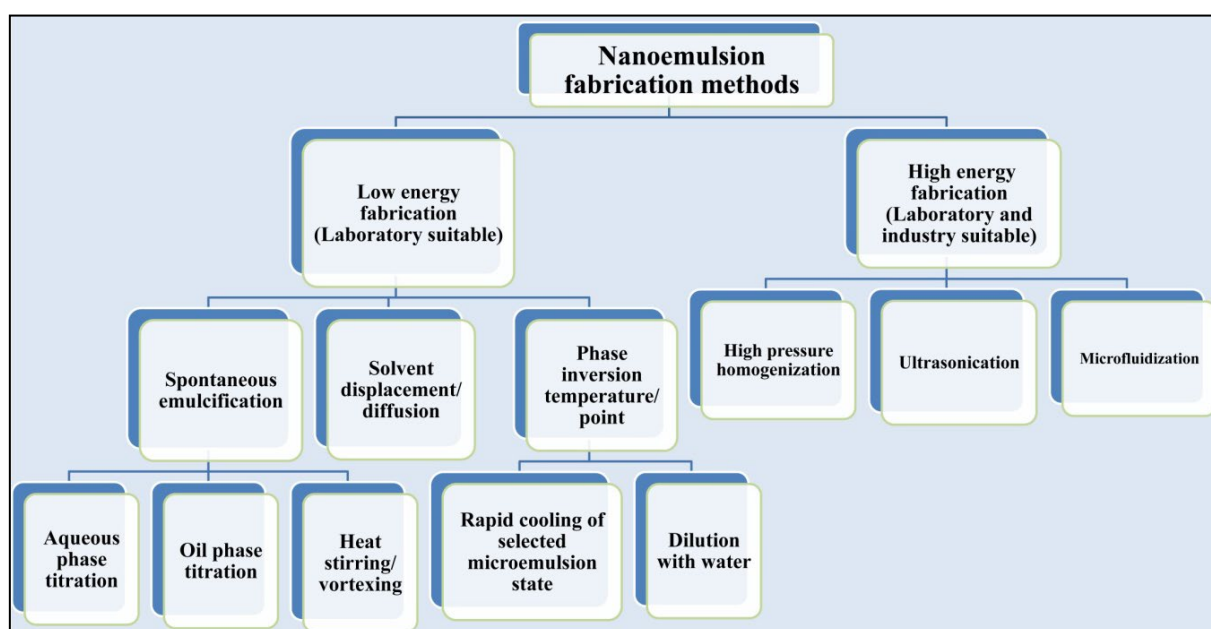


Figure 1. Nanoemulsion fabrication methods

3. Nanoemulgel

Although nanoemulsions offer several benefits, their low viscosity poses challenges in application, leading to poor retention on the skin [7]. This limitation hinders their therapeutic potential [22]. However, incorporating a gelling agent into nanoemulsions to create a nanoemulgel can address this issue [19]. Nanoemulgels, which combine nanosized emulsions (either water-in-oil or oil-in-water) with a gel-based system, exhibit unique properties. These systems transform nanoemulsions into a thicker, more stable, and non-oily formulation by using hydroalcoholic or aqueous bases in a colloidal particle system [7]. Each component of nanoemulgel has its limitations: gels may not effectively absorb hydrophobic molecules [23], while nanoemulsions suffer from poor skin retention due to low viscosity and spreadability and challenges in scalability [24]. Nanoemulgels, an amalgam of nanoemulsion and gel, can overcome the drawbacks of both systems. They allow the lipophilic component to dissolve in the oil droplets of the nanoemulsion, with the addition of a gelling agent or by incorporating the emulsion into the gel, thus increasing the consistency of the nanoemulsion and facilitating the incorporation of lipophilic drugs into a hydrogel [25].

The nanoemulsion component of the nanoemulgel protects the drug from enzymatic and hydrolytic degradation, while the gel component enhances viscosity and spreadability, reducing surface and interfacial tension to stabilize the system thermodynamically [26]. Lipophilic compounds are efficiently encapsulated into nanoemulsion droplets, potentially enhancing drug permeability and facilitating passage through skin layers. The widespread distribution of nanoemulsion droplets on the skin surface leads to significant improvements in the pharmacokinetics and pharmacodynamics of the drugs [27]. Conventional topical formulations often suffer from drawbacks such as sticky textures, unstable formulations like phase inversion or breaking in creams, and hygroscopic powders, leading to patient noncompliance. Nanoemulgel formulations, however, do not exhibit these negative effects [28].

Nanoemulgels offer numerous advantages, including continuous drug delivery, site-specificity, and reduced dosage and administration frequency, enhancing the overall efficacy of topical drug delivery. Unlike niosomes or liposomes, nanoemulgels do not experience drug-leaching or degradation issues, making them more effective at drug-loading. The ability of nanoemulgels to control drug release over an extended period is particularly beneficial for drugs with a short half-life. The release occurs in two stages: first from the gel, and then from the nanoemulsion. Their superior skin adhesion and drug solubilization properties enhance skin penetration, providing a larger concentration gradient. Nanoemulgels also bypass the gastrointestinal tract, avoiding associated side effects, and they have excellent safety and therapeutic profiles. Furthermore, they are easy to apply without

requiring specialized skills or practitioners, improving patient compliance over time [27]. As a carrier system, nanoemulgels are effective in treating inflammation-related skin disorders such as psoriasis, acne, fungal infections, osteoarthritis, and inflammation associated with rheumatoid arthritis. Lipid-based nano-formulations have made significant strides in enhancing the delivery of lipophilic drugs. Among these innovations, nanoemulgels have emerged as a notable advancement in topical and transdermal drug delivery systems, offering several key benefits. These include improved therapeutic effects, ease of administration, and enhanced patient compliance. Nanoemulgels deliver hydrophobic drugs non-invasively and without the need for penetration enhancers, which has spurred increased research interest despite the variety of available formulations [29]. Numerous *in vivo* studies have confirmed the potential and feasibility of topical micro- and nano-emulsions, with additional support from *in vitro* studies [30]. Nanoemulsions typically appear transparent or translucent and are known for their higher thermodynamic stability compared to other lipid carriers. They also demonstrate a greater solubilization capacity than simple micellar solutions [31]. The nanoscale size of the oil droplets and their increased surface area enable these formulations to solubilize and incorporate significant quantities of active pharmaceutical compounds [32]. Common challenges associated with emulsions, such as creaming or sedimentation, are effectively addressed in nanoemulsions. The reduced Brownian motion at the nanoscale, and minimal gravitational forces acting on the particles, contribute to the enhanced stability of nanoemulsions, preventing sedimentation and creaming [33]. Research has shown that drugs delivered via nanoemulsion systems can achieve deeper skin penetration and more thorough absorption compared to traditional formulations such as emulsions, creams, or ointment gels [34]. This improved delivery is attributed to the nanoemulsion's ability to penetrate the tightly bound lipid bilayers of the skin, enabling effective delivery of the drug into the systemic circulation. Moreover, the smaller dispersed droplets facilitate both transcellular and paracellular transport [20].

3.1. Nanoemulgel Components

Nanoemulgels offer several advantages, including enhanced epidermal penetration, increased drug-carrying capacity, reduced skin irritation, prolonged skin adherence, improved spreadability, and greater patient compliance. These benefits become particularly evident when compared to other nanocarriers such as liposomes and solid lipid nanoparticles. The increased viscosity provided by the gel component makes nanoemulsions suitable for topical application. Various skin-friendly gelling agents, such as carbomer 934, carbomer 980, xanthan gum, Pluronic, and carrageenan, are commonly used to achieve

this effect [35]. **Figure 2** shows the nanoemulgel components, their role, and their examples. Nanoemulsions ensure sufficient percutaneous absorption, enabling the drug to be appropriately localized and dispersed across the skin. This enhances the therapeutic efficacy both at the application site and systemically by penetrating the skin barrier. Furthermore, when administered via the nasal route, nanoemulgels have the potential to target drugs to the central nervous system by crossing the blood-brain barrier [36]. The non-greasy and non-irritating nature of nanoemulgels further improves patient compliance [26]. Additionally, these formulations exhibit favorable pharmacokinetic properties, such as reduced side effects and increased drug absorption [37]. The hydrogel matrix's consistency and uniformity have garnered significant attention towards nanoemulgels. Research has shown that the reduced movement of oil droplets within the gel matrix leads to a decrease in Ostwald ripening, thereby enhancing the stability of nanoemulgels [38]. Unlike other dosage forms, nanoemulgels are free from stability issues such as destabilization in conventional emulgels, moisture entrapment in powders, cake formation in suspensions, oil globule coalescence, and poor adherence or excessive

spreadability in nanoemulsions [39]. These factors contribute to the perception that nanoemulgels represent a superior and unique method for topical drug delivery compared to commercially available conventional dosage forms. The growing interest in nanoemulgels is driving research into their permeation properties for various skin conditions, diseases, and local or systemic drug delivery. In the realm of topical delivery, nanoemulgels are poised to become a popular alternative to traditional formulations. The effectiveness of nanoemulsions is further enhanced by the use of appropriate surfactants and co-surfactants that act as permeation enhancers, improving the capacity of nanosized globules to penetrate and disperse [26]. Additionally, the high water content of the gel effectively hydrates the outermost layer of the skin (stratum corneum), disrupting its tightly arranged structure and facilitating the penetration of active ingredients [39]. The drug in the nanoemulsion serves as a reservoir, moving from the inner phase (nanoemulsion) to the peripheral phase (gel) before reaching the skin's surface. Upon topical application, the greasy globules separate from the hydrogel and deeply penetrate the stratum corneum, delivering the medication component [40].

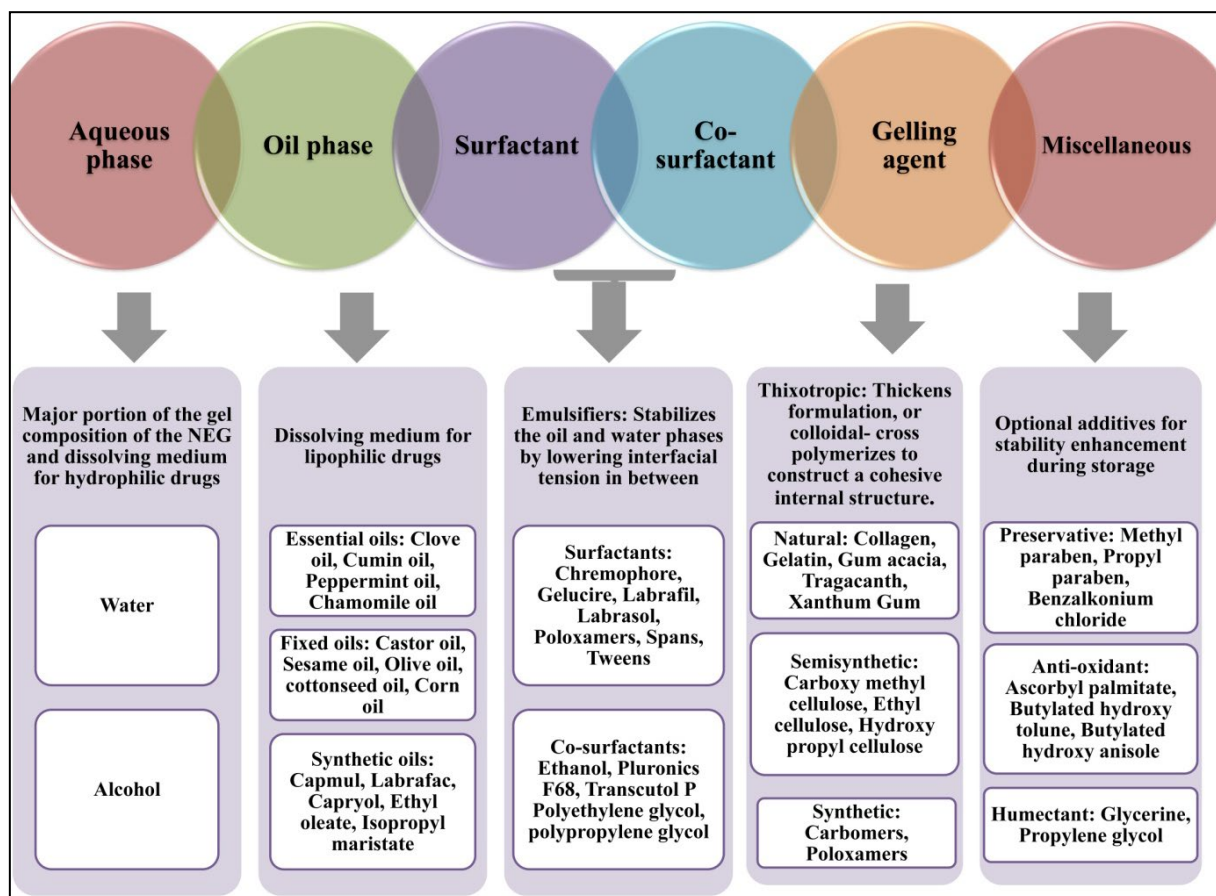


Figure 2. Nanoemulgel components, role, and their examples

3.2. Permeation of Nanoemulgel through the Skin

The stratum corneum, the outermost layer of the skin, is the primary barrier regulating the entry of foreign substances. When skin disorders or permeation enhancers disrupt the subcutaneous layer, the close-fitting junctions serve as an additional barrier [41]. Drug molecules can penetrate the skin through three main pathways: paracellular, transcellular, and transappendageal routes. In the paracellular pathway, drug molecules diffuse through the lipid matrix between corneocytes. Small, lipophilic molecules with a molecular mass of less than 500 Daltons can traverse the tightly packed lipid junctions in a winding and indirect manner [42]. In the transcellular pathway, molecules pass directly through corneocytes and the layers of the stratum corneum, potentially reaching the dermis. To achieve this, a molecule must partition and diffuse through corneocytes, which are separated by up to 20 layers of lipid lamellae. Effective transcellular transport requires the molecule or carrier to exhibit both hydrophilic and hydrophobic properties. While this route restricts the movement of highly lipophilic compounds, it enables the passage of small hydrophilic or moderately lipophilic substances with a log P value between 1 and 5 [43]. The transappendageal pathway involves the transport of substances via hair follicles, sebaceous glands, and sweat glands. However, hair follicles and associated glands have the minimal impact on skin permeation as they constitute only a small fraction of the skin's surface [44]. The specific mechanisms of nanoemulsion permeation can vary depending on factors such as the type (oil-in-water or water-in-oil), the physicochemical properties of the drug, and components (e.g., oil type, surfactant, co-surfactant), and the characteristics of the skin being treated [45]. Caffeine, a hydrophilic drug, was detected in the blood of healthy participants within 5 minutes for open follicles and 20 minutes for closed follicles. This highlights the importance of the pore route in hydrophilic drug delivery. Sebum can significantly impede the transport of hydrophilic drugs within hair follicles [46]. The transport of hydrophilic drugs from a water-in-oil (w/o) nanoemulsion differs from that of hydrophobic substances. Hydrophilic drugs require enhanced lipophilicity for effective skin penetration. For w/o nanoemulsions, the particle size of the active drug and droplet size are critical factors. Formulating hydrophilic drugs in a w/o nanoemulsion can increase their thermodynamic activity, raising the concentration gradient and enhancing permeation. The viscosity and concentration of the surfactant/co-surfactant mixture (S_{mix}) affect this process. Reduced S_{mix} content may lower viscosity and improve drug mobility [47]. The surface charge of nanoemulsions can be adjusted to impact the permeation of ionic drugs. For example, ropinirole hydrochloride, despite its low molecular weight, has limited permeability in aqueous solutions [48]. W/o nanoemulsions, particularly those

containing surfactants, can solubilize sebum in hair follicles, facilitating drug delivery through the trans follicular pathway. This is especially relevant for hydrophilic drugs [49]. For large, water-soluble molecules, w/o nanoemulsions may enhance permeation through the pore pathway, which refers to the spaces between corneocytes in the stratum corneum [50]. Although less common, there is some evidence suggesting that oil-in-water (o/w) nanoemulsions containing small hydrophilic drugs might also utilize the follicular route for permeation. This is believed to be due to the accumulation of the nanoemulsion near hair follicles and the potential for the aqueous external phase to enhance drug partitioning into the follicles [51]. Components of nanoemulsions, such as oleic acid and certain surfactants, can interact with and disrupt the lipid bilayers of the stratum corneum. This disruption creates temporary pathways for drug molecules to permeate. The small droplet size of nanoemulsions increases their surface area, allowing for greater contact with the skin and potentially enhancing drug partitioning into the stratum corneum. Some studies suggest that positively charged nanoemulsions can bind to the negatively charged skin surface, potentially enhancing drug deposition and permeation. However, other studies argue that this mechanism primarily increases drug retention in the skin rather than deeper layer permeation. Low-viscosity nanoemulsions can facilitate drug diffusion through the skin. Nanoemulsions can alter the partitioning coefficient of drugs, making them more likely to enter and remain in the skin. The aqueous component of o/w nanoemulsions can hydrate the stratum corneum, leading to swelling and dilation of intercellular spaces. This increased hydration can facilitate the permeation of both hydrophilic and hydrophobic drugs. Although less intuitive, there is evidence that o/w nanoemulsions can deliver hydrophobic drugs to hair follicles. This may involve the accumulation of the nanoemulsion near follicles and interactions between the oil droplets and sebum.

4. Formulation Strategy for Nanoemulgel

Before formulating a nanoemulgel, preformulation experiments are essential to identify suitable oils, surfactants, co-surfactants, and gelling agents, and to determine their optimal quantities. These preliminary studies help establish the final composition of the nanoemulsion. The choice of oil phase is based on the solubility of the active pharmaceutical ingredient. This phase is crucial for ensuring that the drug is adequately dissolved and effectively incorporated into the nanoemulsion. The ratios of the surfactant and co-surfactant in the nanoemulsion are determined to stabilize the formulation. A pseudoternary phase diagram can be used to visualize the optimal ratios of oil, water, and

surfactant required to achieve a stable nanoemulsion [52]. The drug is dissolved in the oil phase, while the surfactant and co-surfactant are dissolved in the aqueous phase. The two phases are combined by gradually adding one to the other with continuous stirring until a clear, transparent, and homogeneous system is achieved. Nanoemulsions can be prepared using high-energy or low-energy methods: Techniques such as ultrasonication, microfluidization, and high-pressure homogenization fall under this category. These methods generate intense shear forces that reduce droplet size but may affect the stability and color of the emulsion. They also increase the temperature, which can destabilize heat-sensitive drugs [53]. To counteract this, refrigeration methods like ice baths are used during high-energy processing. Techniques such as self-nanoemulsification, phase inversion, and solvent diffusion are considered low-energy methods. They use the system's chemical potential to form nanoemulsions, which are gentler and avoid heat-related degradation of sensitive components [54]. To prepare the gel, polymers are dissolved in a water-based solution until fully swollen. This involves dispersing the selected polymer in clean water with vigorous stirring using a mechanical device for a specified duration. The gel base is adjusted to the required pH level to ensure effective skin transport and to prevent irritation [8]. The prepared nanoemulsion is

integrated into the gel matrix at the appropriate ratio while continuously agitating. An oil-in-water nanoemulsion undergoes thickening with a gelling agent, which forms the final gel [8]. Characterization involves analyzing both the nanoemulsion and the gel to assess their physicochemical properties (Figure 3). Characterization involves a comprehensive analysis of both the nanoemulsion and the gel to assess their physicochemical properties. The globule size determines the distribution of nanoemulsion droplets, while the zeta potential indicates the surface charge and stability of the nanoemulsion. The polydispersity index (PDI) reflects the range of droplet sizes within the formulation. pH measurements ensure that the formulation is suitable for skin application. Rheological properties measure the viscosity and flow behavior of the gel. Spreadability assesses how easily the gel can be applied to the skin, and adhesion evaluates how well it sticks to the skin. Dermal irritation tests check for potential irritation upon skin contact. *In vitro* drug release studies examine how the drug is released from the gel over time, whereas *ex vivo* permeation tests assess how effectively the drug penetrates the skin. Finally, *in vivo* performance evaluates the overall effectiveness of the nanoemulgel in clinical settings. These characterization steps are crucial for ensuring the efficacy, safety, and stability of the nanoemulgel formulation.

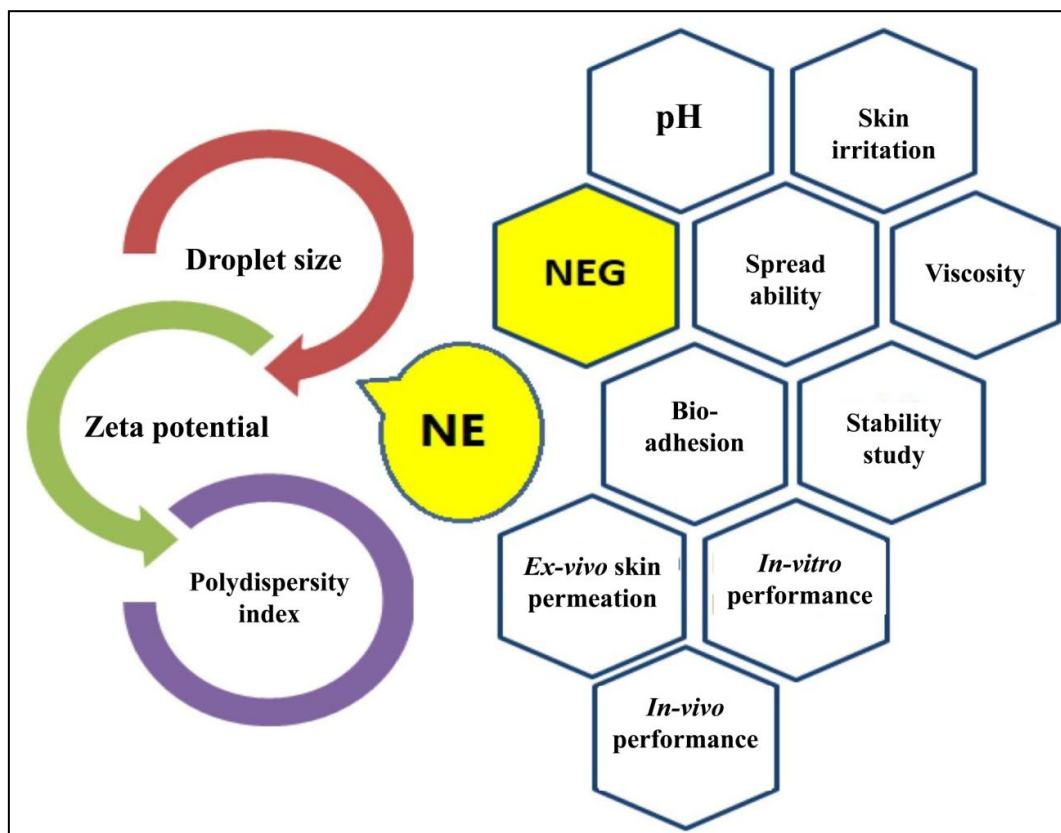


Figure 3. Characterization of nanoemulsion (NE) and nanoemulgel (NEG)

5. Toxicity Concerns

Surfactants and co-surfactants incorporated into nanoemulsions can potentially cause skin irritation, degradation, cell toxicity, and adverse or allergic reactions in some individuals. Anionic surfactants primarily affect the stratum corneum, damaging the lipid bilayer, altering proteins, and causing skin dryness, which may lead to dermatitis, especially in individuals with sensitive skin. Cationic surfactants, on the other hand, can induce more severe cytotoxic effects and apoptosis in both normal and malignant cells [55]. In contrast, non-ionic surfactants tend to have lower toxicity and cause less skin irritation, making them more suitable for topical applications. Co-surfactants, such as propylene glycol, may lead to increased osmotic pressure, lactic acidosis, and cardiac arrhythmias, potentially affecting the central nervous system. Therefore, careful selection of surfactants and co-surfactants is crucial to minimize adverse effects and ensure the safety and effectiveness of topical formulations [56]. Emulsifier selection plays a crucial role in the stability and safety of nanoemulsion formulations. Excessive use of surfactants can lead to skin irritation, discomfort, and potential adverse effects. Non-ionic surfactants are generally preferred over their ionic counterparts due to their lower toxicity, making them a safer choice for pharmaceutical and cosmetic applications [57]. It is essential to utilize these components in small amounts to reduce any potential harmful consequences. According to studies, nanoemulgels do not cause toxicity or skin irritation when prepared in the right quantities. In research on skin irritation, for example, Abdallah et al. administered a brucine-loaded nanoemulgel to rats' shaved skin before covering it with gauze. Even after 24 h, no erythema or edema symptoms were seen [58]. Similarly, after seven days of administration, Bhattacharya and Prajapati found that celecoxib-loaded nanoemulgel reduced irritation scores in rabbits by 1.6 times when compared to a normal irritant. Notwithstanding these encouraging results, it is impossible to rule out the potential for systemic adverse effects brought on by the improved skin penetration and nanoscale size of nanoemulgels [59]. These formulations' ability to penetrate the circulation and cause unforeseen biological interactions is still a worry. Furthermore, separate safety problems are displayed by various nanoformulations. For instance, rare-earth fluoride nanoparticles have shown the ability to stimulate tumor growth through electrical dipole interactions, which become more intense as particle size decreases; polymeric nanoparticles have been connected to oxidative stress and cytotoxicity; and lipid-based nanoparticles have been linked to hypersensitivity reactions and cardiopulmonary complications. Additional thorough research is required to fully comprehend and reduce these risks [58]. In concise, careful selection and controlled use of surfactants, co-surfactants, and nanoemulsions/nanoemulgels are crucial to minimizing

toxicity, ensuring skin compatibility, and maintaining the safety and effectiveness of topical formulations.

6. Current Challenges, Future Prospects, and Concluding Remark

Anti-inflammatory, anti-arthritic, antifungal, and so on category medications often encounter significant challenges when incorporated into traditional dosage forms such as tablets, capsules, and syrups. These challenges stem from the medications' tendency to aggregate and their poor dispersion in water, which can lead to inconsistent dosing and diminished therapeutic efficacy. Nanoemulgels have emerged as a promising solution to these issues, offering advancements in drug delivery systems. Despite these promising attributes, the large-scale commercial production of nanoemulgels remains problematic. The high-energy manufacturing methods commonly used can induce thermodynamic instability, especially with heat-sensitive drugs, and are associated with high energy consumption. To address these challenges, there is a need for more efficient and cost-effective manufacturing techniques. Overcoming these barriers could significantly improve the practicality and feasibility of nanoemulgels, making them a more viable alternative to traditional formulations. Although current production constraints may present temporary obstacles, the long-term benefits of nanoemulgels suggest they could provide a more effective and economical approach to drug delivery.

In conclusion, extensive research has demonstrated that nanoemulgels enhance the efficacy of both synthetic and natural anti-inflammatory drugs when applied topically. Their benefits include improved thermodynamic and kinetic stability, increased skin permeability, and controlled drug release, positioning them as a highly promising choice for drug delivery. Nanoemulgels stand out by eliminating the need for additional additives, such as penetration enhancers and stabilizers, thanks to their lipid-based components and nanoscale size. Their properties such as efficient spreading, prolonged skin adhesion, non-invasive application, and ease of use further support their suitability for transdermal administration. The nanoemulgel formulation significantly enhances drug bioavailability, demonstrating notable wound-healing activity and accelerating skin repair. Compared to traditional delivery methods, nanoemulgels offer greater transdermal potential, ensuring more efficient drug absorption. By incorporating appropriate texture and sensory properties, the formulation minimizes adverse reactions and maximizes effectiveness. This advanced delivery system leads to improved permeation and bioavailability of the active ingredient, reduced side effects, increased drug uptake, and enhanced cytotoxicity against targeted cells. The formulation also provides a rapid onset of action, delivering therapeutic benefits more swiftly than

conventional methods. Additionally, the advanced formulation aims to minimize systemic adverse drug reactions while ensuring effective drug delivery. The inclusion complex of the drug markedly enhances *in vitro* skin permeation, facilitating better absorption into target tissues. Furthermore, the new delivery system achieves an improved therapeutic index, allowing for reduced dose and frequency of administration. With enhanced skin permeation and a significant rise in therapeutic activity, this innovative treatment shows promise as a potential substitute for current medications used to treat diseases, offering improved efficacy and patient outcomes. Overall, the nanoemulgel formulation overcomes the limitations associated with traditional dosage forms and ensures more effective drug delivery.

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Conflict of Interest

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