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Review Paper

Nanoemulgels for Topical Drug Delivery: Formulation and Characterization

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ABSTRACT

Topical drug delivery has gained considerable attention over the past two decades owing to its ability to circumvent the hepatic first-pass effect, improve patient compliance, and provide localized as well as systemic therapeutic effects. Among the diverse nanocarrier systems explored for transdermal and topical applications, nanoemulgels have emerged as one of the most versatile and clinically promising platforms. A nanoemulgel is essentially a hybrid system that combines the drug-solubilizing and permeation-enhancing attributes of a nanoemulsion with the spread ability, bio adhesiveness, and ease of application offered by a hydrogel matrix. This dual nature allows nanoemulgels to overcome the limitations associated with both conventional emulsions and plain gel formulations.This review provides a comprehensive and critical examination of nanoemulgels intended for topical drug delivery. Beginning with a discussion of the anatomy and barrier function of human skin, the article explores the theoretical underpinnings of enhanced drug permeation through nanoscale carriers. It then systematically addresses the selection of excipients including oils, surfactants, co-surfactants, and gelling polymers and discusses both spontaneous emulsification and high-energy preparation methods. An extensive section on physicochemical, rheological, and biological characterization follows, covering particle size analysis, zeta potential measurement, rheological profiling, in vitro drug release testing, and ex vivo skin permeation studies. The review also highlights recent applications of nanoemulgels in the delivery of anti-inflammatory agents, antifungals, analgesics, and cosmeceuticals. Finally, regulatory perspectives, stability challenges, and future research directions are addressed. The goal is to provide formulators, pharmacists, and researchers with a well-grounded and practically useful synthesis of the current state of the art..

INTRODUCTION

The skin is the largest organ of the human body, covering approximately 1.7–2.0 m² in an average

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adult, and it serves as a formidable physical and biochemical barrier between the internal milieu and the external environment [1]. For pharmaceutical scientists, this barrier function is both an asset and a challenge. On one hand, the stratum corneum the outermost cornified layer of the epidermis protects the body from microbial invasion, dehydration, and the penetration of potentially toxic substances. On the other hand, this same barrier severely restricts the permeation of most therapeutic molecules applied topically, limiting the utility of conventional topical formulations to superficial skin conditions or to drugs with highly specific physicochemical properties [2].

Historically, topical formulations have included ointments, creams, lotions, gels, and pastes, each with distinct advantages related to their physical state and patient acceptability. Gels, in particular, have been favoured for their non-greasy texture, ease of spreading, transparency, and compatibility with hydrophilic active pharmaceutical ingredients (APIs). However, conventional gels suffer from a significant limitation, they are predominantly aqueous systems, and therefore show poor solubility for lipophilic drugs, which constitute a large fraction of the pharmacological compounds in current clinical use. This incompatibility often leads to inadequate drug loading, precipitation upon storage, and insufficient permeation across the lipid-rich stratum corneum [3].

The emergence of nanotechnology in pharmaceutical sciences offered a transformative solution to these challenges. Nanoparticulate delivery systems including polymeric nanoparticles, solid lipid nanoparticles, liposomes, noisome, nanostructured lipid carriers, and nanoemulsions—have been extensively explored for their ability to improve drug solubility, protect labile molecules from degradation, modify drug release kinetics, and enhance skin permeation [4]. Among these, nanoemulsions have attracted particular interest because of their thermodynamic metastability, optical translucency, small globule size (typically 20–500 nm), and ability to accommodate both hydrophilic and lipophilic drugs within a single system [5].

Despite these merits, nanoemulsions in their liquid form present practical challenges for topical application, including poor spread ability, runoff from the application site, and difficulty in maintaining adequate contact time with the skin surface. To address these limitations, formulators have combined nanoemulsions with polymeric hydrogel matrices to produce what is now widely referred to as a nanoemulgel a semisolid topical formulation in which nanodroplets are uniformly dispersed within a three-dimensional gel network [6]. This hybrid architecture confers the permeation-enhancing and solubilizing benefits of the nanoemulsion while lending the rheological properties, bio adhesiveness, and cosmetic elegance of the gel base.

Since the early 2000s, nanoemulgels have been investigated for a remarkably diverse range of therapeutic applications, including the delivery of nonsteroidal anti-inflammatory drugs (NSAIDs), antifungal agents, corticosteroids, analgesics, antibiotics, and various natural or botanical actives [7,8]. The growing number of publications in this area reflects both the scientific promise of the platform and the increasing clinical demand for effective, patient-friendly topical therapies.

The purpose of this review is to provide a thorough, well-referenced account of the current state of knowledge on nanoemulgels for topical drug delivery. Specifically, it aims to:

- outline the structural and functional properties of skin as they pertain to topical drug delivery.
- describe the composition, preparation, and physicochemical characteristics of nanoemulsions and nanoemulgels.

- review the methodologies used to characterize these systems.
- survey published applications in various therapeutic categories.
- identify regulatory considerations and future directions for the field.

2. Structure of the Skin and Barriers to Drug Permeation

2.1 Anatomy of the Skin

The skin is composed of three primary layers: the epidermis, dermis, and hypodermis (subcutaneous tissue). The epidermis is further subdivided into five strata stratum Basale, stratum spinosum, stratum granulosum, stratum lucidum (present only in palmar and plantar skin), and stratum corneum [9]. The outermost stratum corneum, approximately 10–20 μm thick in its dry state, consists of 15–20 layers of flattened, anucleate corneocytes embedded in a lipid-enriched extracellular matrix composed predominantly of ceramides, free fatty acids, and cholesterol. This so called 'brick and mortar' structure is the primary physical barrier to the permeation of topically applied drugs.

The dermis lies beneath the epidermis and is composed of a dense collagenous connective tissue matrix rich in blood vessels, lymphatics, nerve endings, sweat glands, and hair follicles. The rich vascular supply of the dermis is a critical target in transdermal drug delivery, as drugs that successfully traverse the epidermis can enter systemic circulation via dermal capillaries, thereby avoiding first-pass hepatic metabolism [10]. Hair follicles and sweat ducts represent alternative 'shunt routes' for drug permeation, accounting for less than 0.1% of the total skin surface area but potentially contributing disproportionately to the flux of certain macromolecules and nanoparticulate carriers.

2.2 Pathways of Transdermal Drug Permeation

Drug molecules can traverse the skin via three principal routes:

1. The transcellular pathway, in which molecules pass directly through corneocytes and the intervening lipid lamellae.
2. The intercellular pathway, which involves diffusion through the tortuous extracellular lipid bilayers surrounding corneocytes.
3. The appendageal or follicular pathway [11]. Of these, the intercellular lipid pathway is quantitatively most significant for small lipophilic molecules, while the follicular pathway may be important for larger molecules, charged species, and nanosized drug carriers.

The Fick's diffusion model describes passive drug permeation across the stratum corneum as a function of the concentration gradient, the diffusion coefficient within the membrane, and the membrane thickness. For a drug to achieve adequate flux through the skin, it generally needs to satisfy certain physicochemical criteria: a molecular weight below approximately 500 Da, adequate lipophilicity (log P between 1 and 4), low melting point, and the ability to exist in a unionized state at skin pH [12]. Nanoemulsions and nanoemulgels can circumvent many of these constraints through mechanisms discussed in the following sections.

2.3 Strategies to Enhance Skin Permeation

Numerous physical and chemical strategies have been developed to overcome the stratum corneum barrier. Chemical penetration enhancers such as alcohols, fatty acids, terpenes, and surfactants work by fluidizing or disrupting the lipid lamellae of the stratum corneum, thereby increasing the diffusivity of drug molecules [13]. Physical techniques include iontophoresis, microneedling, sonophoresis, and electroporation, all of which temporarily disrupt the barrier function to allow deeper penetration. Vesicular carriers such as

transferosomes (ultra-deformable liposomes) exploit the osmotic gradient between the skin surface and underlying dermis to squeeze through the intercellular channels [14].

Nanoemulsions occupy a unique position in this landscape: their nano-sized droplets can penetrate hair follicles and intercellular lipid channels more readily than conventional emulsion globules; the surfactants used in their preparation often function simultaneously as penetration enhancers; and the high surface area and thermodynamic activity of the dispersed nanodroplets promote drug partitioning into the stratum corneum [15]. When incorporated into a gel matrix to form a nanoemulgel, these permeation-enhancing properties are preserved while the rheological profile of the system is optimized for practical topical application.

3. Nanoemulsions: Foundation of the Nanoemulgel System

3.1 Definition and Classification

A nanoemulsion is a thermodynamically or kinetically stable colloidal dispersion consisting of two immiscible liquids typically oil and water stabilized by a surfactant or a surfactant/co-surfactant mixture, with a mean droplet diameter in the range of 20 to 500 nm (some authors use 20–200 nm as the defining range) [16]. Three structural types are recognized depending on the composition and preparation conditions: oil-in-water (O/W) nanoemulsions, in which oil droplets are dispersed in an aqueous continuous phase; water-in-oil (W/O) nanoemulsions, in which aqueous droplets are suspended in an oil phase; and bicontinuous or multiple emulsions for more complex systems [17]. For topical drug delivery, O/W nanoemulsions are most widely employed because of their pleasant cosmetic feel and ease of washing, although W/O systems are also used when a more occlusive effect is desired.

Nanoemulsions should be distinguished from microemulsions. Although both are optically clear or translucent systems with nano-scale droplet sizes, microemulsions are thermodynamically stable and form spontaneously upon mixing the appropriate components in the right proportions, whereas nanoemulsions are kinetically stable but thermodynamically metastable that is, they will eventually separate into their constituent phases given sufficient time or energy, but can remain physically stable for months to years if properly formulated [18].

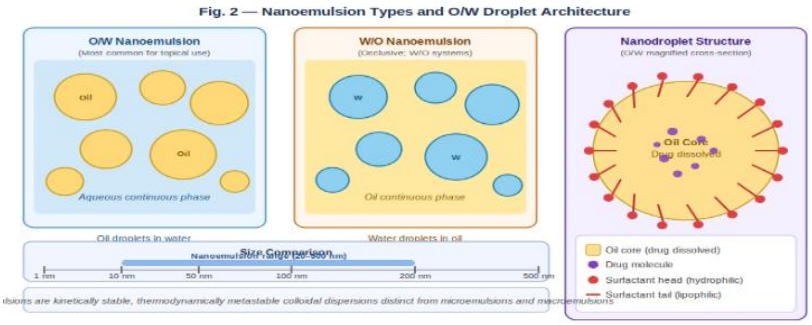

Figure 2 shows O/W and W/O nanoemulsions with nanodroplet structure and size range.

3.2 Components of Nanoemulsions

3.2.1 Oil Phase

The selection of the oil phase is one of the most critical decisions in nanoemulgel formulation, as it determines the drug's solubility within the internal phase, the system's toxicological profile, and, to a significant degree, its ability to enhance skin permeation. Oils can be broadly categorized as medium-chain triglycerides (MCTs), long-chain

triglycerides (LCTs), fatty acid esters, and natural vegetable or essential oils. MCTs derived from coconut or palm kernel oil such as Miglyol 812 (caprylic/capric triglyceride) are among the most commonly used oil phase components in pharmaceutical nanoemulsions because of their low viscosity, excellent spreading properties, GRAS (generally recognized as safe) regulatory status, and ability to solubilize a wide range of lipophilic drugs [19]. Other frequently employed oils include isopropyl myristate, ethyl oleate, oleic acid, soybean oil, castor oil, and various essential oils such as eucalyptus, clove, and peppermint oil, some of which also contribute to penetration enhancement through interaction with skin lipids [20].

Drug solubility screening in candidate oils is an essential early step, typically performed by adding an excess amount of drug to known volumes of each oil and agitating at 37°C to equilibrium, followed by centrifugation or filtration and quantification of dissolved drug by UV spectrophotometry or HPLC. The oil that achieves the highest drug solubility is generally selected, provided it is pharmaceutically acceptable and compatible with the other excipients.

3.2.2 Surfactants and Co-surfactants

Surfactants stabilize the oil - water interface by reducing interfacial tension and providing a mechanical or electrostatic barrier against droplet coalescence. For pharmaceutical nanoemulsions, the choice of surfactant is constrained by biocompatibility, regulatory acceptability, and the ability to produce an emulsion with sufficiently small droplet size and adequate physical stability. Non-ionic surfactants are generally preferred over ionic species because of their lower irritancy, broader compatibility with drug molecules, and insensitivity to ionic strength and pH changes [21]. Polysorbates (Tween 20, Tween 80), and polyoxyethylene castor oil derivatives (Cremophor EL, Cremophor RH40) are among the most widely used surfactants in topical nanoemulsion systems.

Co-surfactants short-chain amphiphiles such as propylene glycol, polyethylene glycol 400, Transcutol P (diethylene glycol monoethyl ether), glycerol, and ethanol are employed in conjunction with primary surfactants to reduce interfacial tension to near-zero values, increase interfacial film flexibility, and allow the formation of droplets in the nanometer range [22]. The ratio of surfactant to co-surfactant (Smix ratio) is a critically important formulation variable and is typically optimized empirically using pseudo-ternary phase diagrams, which map the compositional space in which emulsification occurs spontaneously or with minimal energy input.

3.2.3 Aqueous Phase

Purified water is the standard aqueous phase component, but various additives may be incorporated to enhance drug solubility, adjust pH, preserve the formulation, or modify viscosity. Buffering agents (citrate, phosphate) are used when the drug's stability or ionization state is pH-sensitive. Humectants such as glycerol or propylene glycol, in addition to their role as co-surfactants, can improve skin hydration and reduce trans epidermal water loss [23]. Preservatives typically methyl paraben, propyl paraben, phenoxyethanol, or benzalkonium chloride are required in aqueous nanoemulsions to prevent microbial growth, though their compatibility with the surfactant system and potential for skin sensitization must be carefully evaluated.

4. Formulation and Preparation of Nanoemulgels

4.1 Gelling Agents Used in Nanoemulgels

The transformation of a nanoemulsion into a nanoemulgel requires incorporation of the liquid nanoemulsion into an appropriate polymeric gel

matrix. The gelling agent must be compatible with the nanoemulsion components, must not destabilize the nanodroplets upon mixing, and must impart suitable rheological properties to the final semisolid product. Several classes of polymeric gelling agents have been employed:

Carbopol (carbomer) polymers acrylic acid polymers cross-linked with allyl sucrose or allyl pentaerythritol are the most widely used gelling agents in pharmaceutical topical formulations [24]. Upon neutralization with a base (triethanolamine or sodium hydroxide), Carbopol dispersions form transparent, highly viscous gels with excellent bio adhesive properties and broad compatibility with various excipients. Carbopol 934, 940, 971, and 974 have all been employed in nanoemulgel formulations. The concentration of Carbopol typically ranges from 0.5% to 2.0% w/w, with the precise amount determined during optimization to achieve the desired consistency and spread ability.

Hydroxypropyl methylcellulose (HPMC) and carboxymethylcellulose (CMC) are cellulosic polymers that form hydrogels in aqueous media and are widely used as viscosity-imparting agents in ophthalmic and topical preparations [25]. Xanthan gum, a naturally derived polysaccharide with pseudoplastic rheology, has also been employed in nanoemulgel formulations targeting wound care and cosmeceutical applications. More recently, natural polymers such as chitosan, aloe vera gel, and Carbopol - chitosan combinations have been explored as biodegradable, biocompatible alternatives with additional biological activities.

4.2 Preparation of Nanoemulsions: Energy-Based Methods

4.2.1 High-Pressure Homogenization

High-pressure homogenization (HPH) is one of the most widely employed high-energy methods for the production of nanoemulsions at both laboratory and industrial scale [26]. In HPH, a coarse pre-emulsion is forced at pressures of 100–1500 bar through a narrow gap or valve, generating intense shear, cavitation, and turbulent forces that disrupt large emulsion droplets into nanometer-sized ones. Multiple passes (typically 3–10) through the homogenizer are often required to achieve the target droplet size. Equipment such as the Microfluidizer (Microfluidics Corp.) and the APV Gaulin homogenizer operates on this principle. HPH is scalable and capable of producing nanoemulsions with droplet sizes as low as 20–50 nm, but it requires specialized equipment and generates heat that may be problematic for thermolabile drugs.

4.2.2 Ultrasonication

Ultrasonic homogenization (sonication) uses high-frequency sound waves (typically 20–100 kHz) to generate cavitation in the liquid medium [27]. The violent collapse of cavitation bubbles produces intense local pressure and temperature fluctuations that disrupt emulsion droplets into the nanoscale range. Probe-type sonicators are commonly used at laboratory scale for preparing nanoemulsions in volumes of 10–500 ml. Process parameters including sonication time, amplitude, pulse duty cycle, and temperature must be optimized. A limitation of probe sonication is the risk of metal contamination from the titanium probe tip and the generation of heat, necessitating cooling during processing.

4.2.3 Micro fluidization

Microfluidizers process emulsions by forcing them through geometrically defined interaction chambers at high velocities (up to several hundred meters per second), generating intense shear, impingement, and cavitation [28]. Droplet sizes below 100 nm can be routinely achieved with micro fluidization, and the technique has been employed in the production of pharmaceutical-

grade nanoemulsions for parenteral as well as topical applications. The process is scalable and produces relatively uniform droplet size distributions, though energy consumption is high.

4.3 Preparation of Nanoemulsions: Low-Energy Methods

4.3.1 Spontaneous Emulsification (Self-Emulsification)

Spontaneous emulsification exploits the diffusion of water-soluble components (co-surfactants, co-solvents) from the oil phase into the aqueous phase upon dilution, generating intense interfacial turbulence that leads to spontaneous formation of fine droplets without the need for external energy input [29]. This method is simple, inexpensive, and easily scalable. The drug is dissolved in the oil phase or the surfactant blend, and the mixture is then added to the aqueous phase under gentle stirring. The system's emulsification efficiency is highly dependent on the type and concentration of surfactant and co-surfactant, the Smix ratio, and the oil phase composition.

4.3.2 Phase Inversion Methods

The phase inversion temperature (PIT) method and the phase inversion composition (PIC) method both exploit changes in the curvature and physicochemical properties of the surfactant interfacial film to spontaneously generate nanoemulsions [30]. In the PIT method, the emulsion is heated above the phase inversion temperature of the non-ionic surfactant (where it transitions from an O/W to a W/O emulsion), then rapidly cooled to below the PIT, trapping the oil in nanoscale droplets within the aqueous phase. The PIC method achieves the same phase inversion by changing composition (typically by progressive addition of water to an oil-surfactant mixture) rather than temperature.

4.4 Incorporation of Nanoemulsion into Gel Matrix

Once the nanoemulsion is prepared and its particle size characterized, it is incorporated into the polymeric gel matrix to form the nanoemulgel. The most common approach involves separately preparing the nanoemulsion and the hydrogel, then combining them under gentle mixing to avoid disruption of the nanodroplets [31]. The order of addition and the intensity of mixing are critical process variables. Excessive shear during mixing can cause droplet coalescence and aggregation, leading to an increase in particle size and loss of the desired nanostructure. The mixture is typically stirred with a propeller or magnetic stirrer at moderate speed (200–400 rpm) until a homogeneous semisolid product is obtained. pH adjustment (typically to 6.0–7.5 for Carbopol-based gels) is performed at this stage by dropwise addition of triethanolamine or sodium hydroxide.

An alternative approach involves direct preparation of the gel base using the aqueous phase of the nanoemulsion as the dispersion medium for the gelling agent [32]. In this technique, the gelling polymer (e.g., Carbopol) is dispersed in water, the oil and surfactant mixture containing the drug is added in defined proportions, and the resulting mixture is subjected to homogenization or sonication to achieve the nanoemulgel in a single step. While simpler in concept, this approach requires careful optimization to ensure simultaneous nanoemulsion formation and gel network development.

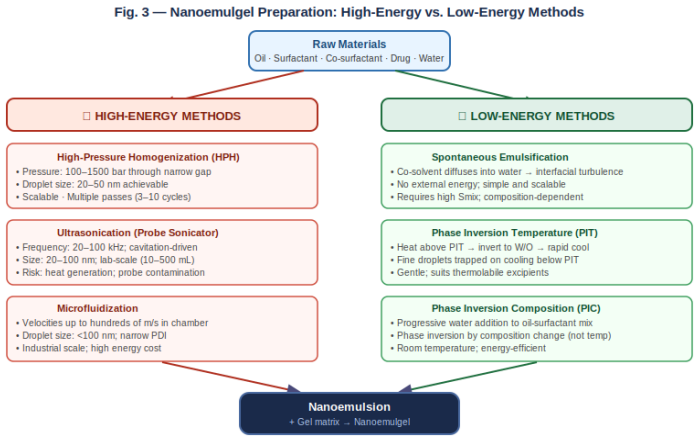

Figure 3 compares high- and low-energy nanoemulsion methods leading to nanoemulgel formation.

5. Characterization of Nanoemulgels

5.1 Physicochemical Characterization

5.1.1 Particle Size, Polydispersity Index, and Droplet Size Distribution

Particle size is arguably the most critical quality attribute of a nanoemulgel, as it influences skin permeation efficiency, physical stability, and drug release behaviour [33]. Dynamic light scattering (DLS), also known as photon correlation spectroscopy (PCS), is the most widely used technique for determining the mean droplet size and polydispersity index (PDI) of nanoemulgels. In DLS, the intensity fluctuations of laser light scattered by Brownian motion of the nanodroplets are analysed to yield hydrodynamic diameter and PDI. Values of PDI below 0.2 are generally considered indicative of a monodisperse system, while PDI values above 0.5 suggest a heterogeneous or poorly controlled size distribution.

For nanoemulgels prepared for topical application, mean droplet sizes typically fall in the range of 50 – 400 nm, with smaller sizes generally favouring follicular penetration and larger sizes associated with increased drug loading capacity. The Malvern Zetasizer series, Brookhaven 90Plus, and Horiba LA-960 instruments are among the most frequently used platforms for DLS-based particle sizing. For more detailed size distribution analysis, especially for polydisperse samples, laser diffraction (for particles > 100 nm) or nanoparticle tracking analysis (NTA) may be employed as complementary techniques [34].

5.1.2 Zeta Potential

The zeta potential is a measure of the electrostatic charge at the hydrodynamic shear plane of the nanodroplet and provides important information about the physical stability of the colloidal system [35]. Nanoemulsions with zeta potential values more negative than −30 mV or more positive than +30 mV are generally considered electrostatically stable, as the repulsive forces between similarly charged droplets resist aggregation. However, for non-ionic nanoemulsions stabilized by PEGylated surfactants, steric rather than electrostatic stabilization dominates, and zeta potential values closer to zero do not necessarily imply instability. Zeta potential measurements are performed on diluted samples using the same DLS instruments equipped with electrophoretic light scattering capability. It is important to note that the gel matrix may alter the measured zeta potential of the incorporated nanodroplets due to changes in the ionic environment and viscosity.

5.1.3 Refractive Index and Optical Properties

Nanoemulsions are typically translucent to transparent owing to the small size of their droplets (< the wavelength of visible light ~400 – 700 nm), whereas conventional emulsions appear white and opaque [36]. The optical clarity of the nanoemulsion before and after gel incorporation can be assessed by measuring turbidity (using a nephelometer or UV spectrophotometer at a non-absorbing wavelength) or by visual inspection. A high degree of optical clarity is often cited as a quality indicator, though it should be noted that some nanoemulgels with droplet sizes at the upper end of the nanoscale range will appear milky despite technically qualifying as nanoemulsions.

5.1.4 pH Measurement

The pH of a topical nanoemulgel is an important parameter both for stability of the drug and for biocompatibility with the skin surface. Human skin maintains a slightly acidic pH of approximately 4.5–5.5 (the acid mantle), which plays a role in controlling microbial colonization and regulating stratum corneum enzyme activity [37]. Nanoemulgels intended for topical use are generally formulated to a pH of 5.0–7.5, depending on the drug's stability profile and the condition being treated. pH measurement is routinely performed using a calibrated pH meter with a glass electrode, with the probe inserted directly into the semisolid formulation or into an aqueous dilution thereof.

5.2 Rheological Characterization

Rheology the science of flow and deformation of matter is central to understanding the application behaviour, stability, and drug release characteristics of semisolid topical formulations [38]. Nanoemulgels are typically viscoelastic systems that exhibit non-Newtonian, pseudoplastic (shear-thinning) behaviour: their apparent viscosity decreases as the applied shear rate increases, which facilitates ease of spreading upon application while ensuring that the formulation does not flow under its own weight during storage.

Rheological characterization is performed using rotational rheometers (cone-and-plate or parallel plate geometry) in two primary modes:

(i) Steady-state flow testing, in which viscosity is measured as a function of shear rate to determine flow behaviour (Newtonian, pseudoplastic, thixotropic); and

(ii) Oscillatory testing, in which small-amplitude sinusoidal strains are applied to determine the storage modulus (G'), loss modulus (G"), and loss tangent (tan δ). A predominantly elastic response (G' > G") indicates a gel-like, structured material, while a viscous-dominant response (G" > G') indicates a more liquid-like system [39].

Most well-formulated nanoemulgels exhibit G' > G" across a range of frequencies, confirming their semisolid gel character. Thixotropy—the time-dependent recovery of viscosity after shear is another important parameter, as formulations with rapid structural recovery will resist drainage after application.

5.3 Microscopic Characterization

Transmission electron microscopy (TEM) and cryo-TEM are gold-standard techniques for directly visualizing nanoemulsion droplets within the gel matrix [40]. In conventional TEM, samples are negatively stained with phosphotungstic acid or uranyl acetate and examined under vacuum; the technique provides high-resolution images (sub-nanometer) of droplet morphology and internal structure. Cryo-TEM, in which samples are vitrified in liquid ethane before imaging, preserves the native hydrated state of the nanodroplets and is particularly valuable for characterizing temperature-sensitive systems.

Atomic force microscopy (AFM) provides three-dimensional topographic information about nanoemulgel surface architecture with sub-

nanometer resolution in both contact and tapping modes. Optical microscopy with polarized light can be used to confirm the amorphous (isotropic) nature of nanoemulsion droplets and to detect any crystalline drug particles or lipid aggregates that may have formed during storage [41]. Scanning electron microscopy (SEM) of lyophilized or chemically fixed samples provides additional morphological information, though sample preparation artifacts must be carefully controlled.

5.4 Drug Content and Encapsulation Efficiency

Accurate determination of drug content is essential to confirm that the formulation contains the labelled amount of drug and that no degradation or sorption losses have occurred during preparation [42]. Drug content is typically determined by dissolving a weighed amount of the nanoemulgel in an appropriate solvent system (which may involve disruption of the emulsion structure with alcohol or acetonitrile), followed by filtration or centrifugation and quantification by UV spectrophotometry or, preferably, HPLC with UV, fluorescence, or mass spectrometric detection.

Encapsulation efficiency (EE%) expresses the proportion of the total drug that has been successfully incorporated into the nanodroplets versus the free drug remaining in the aqueous phase. EE% can be determined by ultracentrifugation (to sediment the nanodroplets and collect the supernatant for free drug measurement), ultrafiltration using centrifugal devices with appropriate molecular weight cutoffs, or dialysis. High EE% (>80%) is generally desirable, as it indicates effective drug entrapment and reduces the risk of precipitation of free drug from the aqueous phase [43].

5.5 In Vitro Drug Release Studies

In vitro drug release testing provides a predictive assessment of the rate and extent of drug release from the nanoemulgel under controlled conditions, allowing comparison between formulations and supporting optimization efforts [44]. Several dissolution apparatus configurations are used for semisolid topical formulations. The Franz diffusion cell is the most widely employed setup: the formulation is placed in the donor compartment, separated from the receptor compartment by a synthetic membrane (cellulose acetate, polysulfone, Strat-M™) or excised biological membrane, and drug that permeates into the receptor fluid (usually phosphate-buffered saline, pH 7.4, or a hydroalcoholic mixture) is sampled at defined intervals and quantified. The USP paddle-over-disk (Apparatus 5) and membrane-less dissolution models are also described in the literature.

Drug release data are fitted to mathematical models zero-order, first-order, Higuchi matrix, Hixson-Crowell, Korsmeyer-Peppas, and Weibull models to elucidate the release mechanism (diffusion-controlled, erosion-controlled, anomalous transport) [45]. For nanoemulgels, drug release is often biphasic: an initial burst release attributable to drug present at or near the droplet surface or in the aqueous gel phase, followed by a sustained phase governed by diffusion from the nanodroplet core through the gel matrix and membrane.

5.6 Ex Vivo and In Vivo Skin Permeation Studies

Ex vivo skin permeation studies using excised skin (human cadaver skin, porcine ear skin, rat abdominal skin, or shed snake skin) mounted in Franz diffusion cells represent the closest in vitro surrogate for in vivo topical drug delivery [46]. Porcine ear skin is the most widely accepted surrogate for human skin due to its similar thickness, lipid composition, and hair follicle density. After application of the nanoemulgel formulation to the donor side, receptor fluid samples are collected and analyzed for drug

content over 8–24 hours. The cumulative amount of drug permeated per unit area is plotted against time, and the steady-state flux (μg/cm²/h), permeability coefficient (Kp), and enhancement ratio (compared to a reference formulation) are calculated from the linear portion of the profile.

Following permeation experiments, tape stripping of the epidermis allows depth profiling of drug concentration within the stratum corneum, providing information about drug localization versus transdermal transport [47]. Confocal laser scanning microscopy (CLSM) using fluorescently labelled drug or fluorescent marker lipids can provide detailed information about the depth and distribution of drug penetration within the skin layers.

In vivo studies in animal models (typically rats or rabbits with IACUC approval) and ultimately in human clinical trials provide the definitive assessment of a nanoemulgel's pharmacokinetic and pharmacodynamic performance. Pharmacodynamic endpoints relevant to in vivo evaluation include carrageenan-induced rat paw edema (for anti-inflammatory formulations), excision wound healing models, and drug plasma concentration monitoring for systemically absorbed drugs [48].

5.7 Stability Studies

Physical and chemical stability assessment is essential to characterize the shelf life and storage requirements of nanoemulgel formulations. Accelerated stability studies following ICH Q1A guidelines involve storage at 40°C/75% relative humidity (RH) for 6 months, alongside long-term samples stored at 25°C/60% RH or the intended refrigerated temperature [49]. At defined intervals (0, 1, 3, and 6 months), samples are evaluated for changes in macroscopic appearance (phase separation, syneresis, color), droplet size (DLS), zeta potential, pH, drug content, viscosity, and in vitro drug release. The Turbiscan instrument, which measures backscattered and transmitted light across the sample height, is particularly useful for detecting early signs of creaming, sedimentation, or flocculation in a non-invasive manner.

Thermodynamic stability—the tendency of the nanoemulsion to resist phase separation under temperature stress—is commonly assessed through freeze-thaw cycling tests (typically 3–6 cycles between -20°C and +25°C) and centrifugation stress testing at 3,000–15,000 rpm. Nanoemulsions that survive these stress tests without significant changes in droplet size or macroscopic appearance are considered physically stable [50].

Fig. 4 — Characterization Methods for Nanoemulgel Formulations

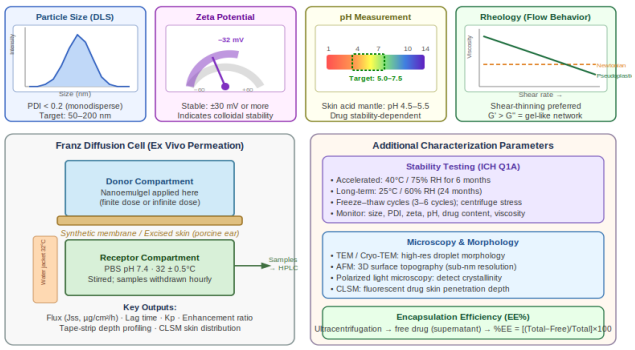

Figure 4: outlines key nanoemulgel characterization parameters and evaluation methods.

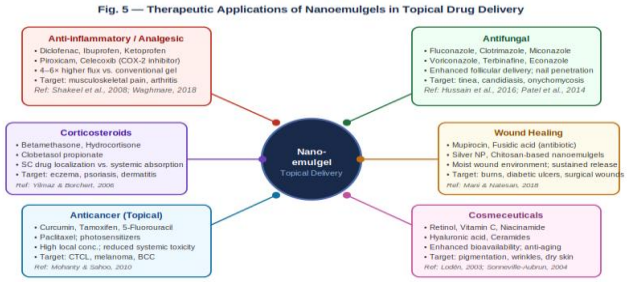

Figure 5: summarizes therapeutic applications of topical nanoemulgel systems with representative drugs and conditions.

6. Therapeutic Applications of Nanoemulgels

6.1 Anti-Inflammatory and Analgesic Applications

NSAIDs represent perhaps the most extensively studied class of drugs for nanoemulgel-based topical delivery. Drugs such as diclofenac, ibuprofen, ketoprofen, piroxicam, and lornoxicam are highly lipophilic (moderate to high log P), which renders them amenable to inclusion in nanoemulsion oil phases, while their pharmacological activity in musculoskeletal pain and inflammation makes topical delivery clinically attractive [51]. Multiple studies have demonstrated that nanoemulgel formulations of these drugs achieve significantly higher skin permeation fluxes compared to commercially available gel preparations (e.g., Voltaren for diclofenac), attributable to the enhanced solubility in the oil phase, the surfactant-mediated penetration enhancement, and the increased thermodynamic activity of the drug in nanodroplets.

Ketoprofen nanoemulgels incorporating Miglyol 812 as oil phase and Tween 80/Transcutol P as the surfactant blend have been shown to achieve 4–6 fold higher ex vivo permeation compared to conventional gel formulations in porcine skin models [52]. Diclofenac nanoemulgels prepared with oleic acid as the oil phase and Carbopol 940 as the gelling agent demonstrated superior anti-inflammatory effects in the carrageenan-induced rat paw edema model, with edema inhibition rates exceeding those of the reference cream at equivalent doses. Similar results have been reported for celecoxib, a selective COX-2 inhibitor with very low aqueous solubility, where nanoemulgel formulations improved both solubility and skin permeation substantially [53].

6.2 Antifungal Applications

Fungal infections of the skin and nails including tinea pedis, tinea corporis, onychomycosis, and Candida-related intertrigo represent a significant burden in dermatology practice. Many antifungal agents used to treat these conditions, such as fluconazole, clotrimazole, miconazole, voriconazole, and terbinafine, are poorly water-soluble and exhibit limited penetration into the deeper layers of the stratum corneum and the nail plate when formulated as conventional creams or gels [54].

Nanoemulgels have been explored as vehicles to enhance the localization of antifungals at the site of infection while minimizing systemic absorption. Fluconazole-loaded nanoemulgels incorporating cinnamon oil (which also possesses intrinsic antifungal activity) as the oil phase and Carbopol 934 as the gelling agent have demonstrated significant improvement in antifungal activity against Candida albicans compared to plain fluconazole gel in zone-of-inhibition assays [55]. Econazole and miconazole nanoemulgels have similarly shown enhanced ex vivo nail permeation compared to lacquer

formulations, suggesting utility in the challenging treatment of onychomycosis.

6.3 Corticosteroid and Dermatological Applications

Corticosteroids such as hydrocortisone, betamethasone, and clobetasol are cornerstones of treatment for inflammatory skin conditions including eczema, psoriasis, and contact dermatitis. The chronic nature of these conditions and the adverse effects associated with prolonged systemic corticosteroid use make targeted topical delivery highly desirable [56]. Nanoemulgels containing low doses of betamethasone dipropionate or hydrocortisone acetate have been developed to improve drug localization in the epidermis while minimizing systemic absorption. Skin deposition studies using tape-stripping have confirmed that nanoemulgel formulations achieve greater corticosteroid concentrations within the stratum corneum and viable epidermis compared to marketed cream formulations at equivalent nominal doses.

6.4 Antimicrobial and Wound Healing Applications

Bacterial skin infections, chronic non-healing wounds, and post-surgical wound management represent important therapeutic targets for topically applied antimicrobials. Nanoemulgels containing antibiotics such as erythromycin, tetracycline, mupirocin, and fusidic acid, as well as natural antimicrobials such as tea tree oil, thymol, and eugenol, have been formulated and characterized [57]. The nanoemulgel platform is particularly appealing in this context because it can simultaneously provide antimicrobial efficacy (via the drug itself), moisturizing and barrier-restoring properties (via the oil phase), and a moist wound healing environment (via the hydrogel matrix). Nanoemulgels incorporating silver nanoparticles and antimicrobial essential oils have been reported to exhibit synergistic antibacterial and antifungal activity against multidrug-resistant strains.

For wound healing specifically, the moist environment provided by the gel phase is itself beneficial, and the delivery of growth-factor-like components (e.g., allantoin, aloe vera extract, vitamin E) via the nanoemulgel has been shown to accelerate wound closure in excision wound models in rats [58]. Chitosan-based nanoemulgels have attracted particular interest for wound applications because chitosan itself possesses hemostatic, antimicrobial, and cell-adhesion-promoting properties.

6.5 Cosmeceutical and Nutraceutical Applications

The cosmeceutical market has enthusiastically adopted nanoemulgel technology for the delivery of active ingredients such as vitamins (C, E, A, K), coenzyme Q10, retinoids, phytosterols, polyphenols (resveratrol, quercetin, curcumin), and peptides that would otherwise exhibit limited skin penetration due to their physicochemical properties or instability [59]. Vitamin C (ascorbic acid) is a particularly challenging cosmeceutical ingredient because of its hydrophilicity, rapid oxidation, and poor stratum corneum penetration; nanoemulgel formulations using ascorbyl palmitate (a lipophilic derivative) in MCT-based oil phases have shown significantly improved stability and skin delivery compared to conventional vitamin C serums.

Curcumin, the principal bioactive polyphenol of turmeric, has attracted intense research interest for its anti-inflammatory, antioxidant, and wound-healing properties, but its clinical utility is limited by extremely low aqueous solubility (< 1 µg/mL), rapid degradation, and poor bioavailability [60]. Curcumin nanoemulgels prepared with sesame oil or black seed oil and stabilized with Tween 80/Span 80 mixtures have demonstrated

substantially improved photostability and ex vivo skin permeation compared to plain curcumin suspensions, opening new avenues for its use in dermatological conditions such as psoriasis and atopic dermatitis.

7. Recent Advances and Emerging Trends

7.1 Smart and Stimuli-Responsive Nanoemulgels

An exciting frontier in nanoemulgel research involves the development of stimuli-responsive systems that modulate drug release or gel properties in response to specific triggers present in the skin or wound microenvironment [61]. pH-responsive nanoemulgels incorporating polyacrylic acid derivatives have been designed to release drug preferentially at the slightly acidic pH of healthy skin or the more alkaline pH of infected or inflamed wounds. Temperature-responsive systems based on poly(N-isopropylacrylamide) (PNIPA) or Pluronic F127 undergo sol-gel transitions near physiological skin temperature (33–37°C), providing liquid-state application ease followed by in situ gelation upon contact with the skin surface.

7.2 Combination Nanoemulgels

Fixed-dose combination therapy is well established in systemic pharmacology, and this concept is increasingly being applied to topical nanoemulgels [62]. Formulations combining a corticosteroid with an antifungal agent (e.g., betamethasone + clotrimazole), an NSAID with a local anesthetic, or an antibiotic with an anti-inflammatory are being developed as nanoemulgels to exploit the solubilizing capacity of the nanoemulsion oil phase for multiple lipophilic components and the potential for synergistic pharmacological effects.

7.3 Biopolymer-Based and Green Nanoemulgels

Growing awareness of the environmental impact of synthetic excipients and increasing consumer demand for 'clean label' cosmetic and pharmaceutical products have stimulated interest in nanoemulgels formulated entirely with natural, biodegradable, and sustainably sourced components [63]. Essential oils as both the oil phase and penetration enhancers, plant-derived surfactants (saponins, lecithins), and natural polysaccharide gelling agents (guar gum, locust bean gum, hyaluronic acid) are being explored in green nanoemulgel formulations. Hyaluronic acid-based nanoemulgels, in particular, have attracted attention for wound healing applications because hyaluronic acid promotes cell migration and proliferation in addition to providing the gel matrix.

7.4 3D Printing and Personalized Topical Dosage Forms

Additive manufacturing (3D printing) technologies—including semi-solid extrusion, inkjet printing, and stereolithography—are beginning to be applied to the fabrication of personalized topical dosage forms with precisely controlled composition, dose, and geometry [64]. Nanoemulgels are, in principle, well-suited for extrusion-based 3D printing given their semisolid, shear-thinning rheology. Patient-specific patches or wound dressings containing nanoemulgel-based drug-laden layers could be fabricated on demand, enabling personalized dosing for patients with unusual wound geometries or specific drug requirements.

8. Regulatory Considerations and Safety Profile

Regulatory classification of nanoemulgels for topical drug delivery falls under the broader

framework governing topical semisolid drug products. In the United States, the FDA's Center for Drug Evaluation and Research (CDER) classifies topical drug products as either prescription or OTC drugs, with guidance documents addressing manufacturing quality, bioequivalence testing, and specification setting [65]. The FDA's 2018 guidance for industry on 'Nonsterile Semisolid Dosage Forms' provides detailed requirements for process validation, in-process testing, and finished product specifications applicable to nanoemulgel products.

The use of nanomaterials in pharmaceutical and cosmetic products is subject to increasing regulatory scrutiny globally. The European Medicines Agency (EMA) and the Scientific Committee on Consumer Safety (SCCS) have published guidelines on the safety assessment of nanomaterials in cosmetics, requiring characterization of particle size, surface chemistry, and potential for systemic absorption [66]. For drug products, nanotechnology-based formulations are expected to undergo standard preclinical safety testing (acute, subacute, and chronic toxicity; dermal irritation and sensitization studies; genotoxicity assays) alongside specialized studies addressing nanoparticle-specific endpoints such as phototoxicity, phagocytosis, and biodistribution.

The excipients employed in nanoemulgels—oils, surfactants, co-surfactants, and gelling agents—are generally of established safety profiles, but their use at concentrations or in combinations not previously evaluated may require additional safety data [67]. Surfactants such as Cremophor EL and Cremophor RH40 carry well-known risks of hypersensitivity reactions; while this is more significant for parenteral use, the potential for skin sensitization upon chronic topical exposure must also be assessed. GRAS-listed excipients and those with established dermal safety records (e.g., polysorbates, propylene glycol, MCTs) are generally preferred.

9. Challenges and Limitations

Despite the considerable promise of nanoemulgels for topical drug delivery, several challenges must be addressed before this platform can achieve its full clinical potential. Physical stability remains a persistent concern: nanoemulsions are thermodynamically metastable systems, and over time they are susceptible to Ostwald ripening (diffusion-driven growth of larger droplets at the expense of smaller ones), flocculation, coalescence, and phase separation [68]. Although incorporation into a gel matrix provides some protection against these degradation pathways by reducing droplet mobility, stability over the intended shelf life (typically 24 months) must be rigorously demonstrated.

Scale-up from laboratory-scale preparation (typically 50–200 g batches) to industrial-scale manufacturing presents significant engineering challenges. High-energy methods such as high-pressure homogenization and micro fluidization require capital-intensive equipment and careful process control to ensure reproducibility of droplet size and distribution across batches [69]. Low-energy methods, while simpler, may not always produce droplet sizes or stability characteristics comparable to high-energy methods, and their scale-up parameters are less well established.

The bioavailability and permeation enhancement achieved by nanoemulgels, while generally superior to conventional formulations, can be unpredictable across different skin types, body sites, disease states, and patient populations [70]. Diseased skin (e.g., in atopic dermatitis or psoriasis) has a compromised barrier function with altered permeability characteristics, which may lead to higher drug absorption than predicted from normal skin studies—potentially increasing the risk of systemic side effects. Conversely, very aged or photodamaged skin with reduced follicular density and altered lipid composition may respond

differently than the young adult skin used in preclinical studies.

There is also an ongoing need for robust in vitro–in vivo correlations (IVIVCs) for semisolid topical dosage forms. Unlike for oral solid dosage forms, where IVIVCs are relatively well established and regulatory frameworks for their use are mature, the correlation between in vitro drug release/permeation data and in vivo clinical efficacy for topical products remains incompletely understood and is an active area of regulatory and scientific research [71].

FUTURE PERSPECTIVES

The trajectory of nanoemulgel research points toward several promising directions that are likely to shape the field over the coming decade. First, the integration of active targeting ligands—such as antibodies, aptamers, peptides, or hyaluronic acid—on the surface of nanodroplets offers the possibility of receptor-mediated selective delivery to specific cell types in the skin (e.g., keratinocytes, Langerhans cells, melanocytes, fibroblasts), potentially enhancing efficacy and reducing off-target effects in complex skin disorders such as melanoma and other skin cancers [72].

Second, the combination of nanoemulgels with physical penetration enhancement technologies—particularly microneedle arrays—represents an exciting hybrid approach in which nanodroplets are deposited directly into the viable epidermis and upper dermis through micron-scale channels created by the microneedles, bypassing the stratum corneum barrier entirely [73]. Early proof-of-concept studies have demonstrated substantially enhanced drug deposition and systemic bioavailability compared to either technology used alone.

Third, advances in computational modelling and machine learning are beginning to be applied to the rational design of nanoemulgel formulations [74]. Quantitative structure-property relationship (QSPR) models relating excipient properties to emulsion stability, HPLC-MS-based metabolomic profiling of skin after nanoemulgel application, and molecular dynamics simulations of drug partitioning into lipid bilayers are all beginning to inform formulation design in a more hypothesis-driven and efficient manner than traditional trial-and-error approaches.

Fourth, the theranostic concept—combining therapeutic drug delivery with diagnostic imaging capability in a single platform—is being explored in some advanced nanoemulgel systems [75]. Incorporation of contrast agents (superparamagnetic iron oxide nanoparticles for MRI, quantum dots for fluorescence imaging) into nanoemulgel droplets could allow simultaneous drug delivery and real-time monitoring of skin drug distribution, which would be invaluable in optimizing treatment of localized skin conditions.

CONCLUSION

Nanoemulgels represent a sophisticated and versatile platform for topical drug delivery that elegantly addresses the complementary limitations of nanoemulsions (poor skin contact and retention) and conventional hydrogels (limited solubilization of lipophilic drugs and modest permeation enhancement). By combining the drug-solubilizing capacity, nano-scale droplet architecture, and surfactant-mediated penetration enhancement of a nanoemulsion with the bio adhesive, spreadable, and cosmetically elegant properties of a polymeric gel, nanoemulgels offer a therapeutically powerful and patient-friendly semisolid dosage form.

The formulation of a successful nanoemulgel requires systematic screening and optimization of the oil phase, surfactant, co-surfactant, and gelling agent, guided by solubility studies, pseudo-ternary phase diagrams, and design-of-experiment (DoE) approaches. Thorough characterization—

encompassing physicochemical properties, rheological behaviour, drug release kinetics, skin permeation performance, and long-term stability—is essential to establish the quality and performance attributes of the product. The growing body of published research demonstrates consistent advantages of nanoemulgels over conventional formulations across diverse therapeutic applications, including anti-inflammatory, antifungal, corticosteroid, antimicrobial, wound healing, and cosmeceutical drug delivery.

Looking ahead, the continued evolution of nanoemulgel technology will be driven by advances in stimuli-responsive materials, green formulation strategies, personalized manufacturing, and computational design tools. Regulatory frameworks for nanotechnology-based topical products are maturing, and with appropriate safety data generation and demonstration of robust manufacturing processes, nanoemulgels are well-positioned to make a meaningful impact on dermatological therapy in the years to come.

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