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Nanoemulsion-Based Transdermal Drug Delivery Systems

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ABSTRACT

Nanoemulsions (NEs)—kinetically stable colloidal dispersions of oil and water stabilized by surfactants/co-surfactants—have emerged as promising vehicles to enhance transdermal drug delivery by improving solubility, increasing thermodynamic activity, and acting as permeation enhancers. This review synthesizes recent developments (2020–2025) in NE design for transdermal applications, including formulation composition and example recipes, preparation methods, characterization techniques, mechanisms of skin permeation, representative case studies (e.g., diclofenac, ketoprofen, tadalafil), safety and regulatory considerations, and future directions for translation. Quantitative data on droplet size, component ratios, skin flux improvements, and stability testing are summarized to provide practical guidance.

KEYWORDS : Nanoemulsion; Transdermal system; Nanotechnology; Skin permeation; Oil-in-water nanoemulsion; Water-in-oil nanoemulsion.

INTRODUCTION

Transdermal drug delivery (TDD) offers advantages over oral and parenteral routes—bypassing first-pass metabolism, enabling sustained release, and improving patient compliance. However, the stratum corneum (SC) functions as a strong barrier, limiting passage to small, lipophilic molecules. Nanoemulsions (O/W or W/O, droplet sizes 20–200 nm) facilitate solubilization of poorly soluble actives, and provide inherent permeation-enhancing effects through oils, surfactants, and co-solvents, and can be converted into gels (nanoemulgels) or patches. Recent literature demonstrates significant permeability and flux enhancements in animal models across multiple drugs [1,2].

RATIONALE & CORE ADVANTAGES

1. Enhanced solubilization and drug loading: Oil phases dissolve lipophilic drugs and raise thermodynamic activity, aiding skin partitioning [3].

2. Permeation enhancement: Oils (oleic acid, IPM), surfactants (Tween 80, Span 80), and cosolvents (ethanol, Transcutol®) fluidize SC lipids or extract them, increasing diffusion [3].

3. Small droplet size → large interfacial area: Droplets (20–200 nm, often targeting 50–150 nm) improve contact with skin and drive concentration gradients [3].

4. Versatility: NEs can be applied as liquids, gels, patches, or loaded into microneedles for enhanced delivery [4,5].

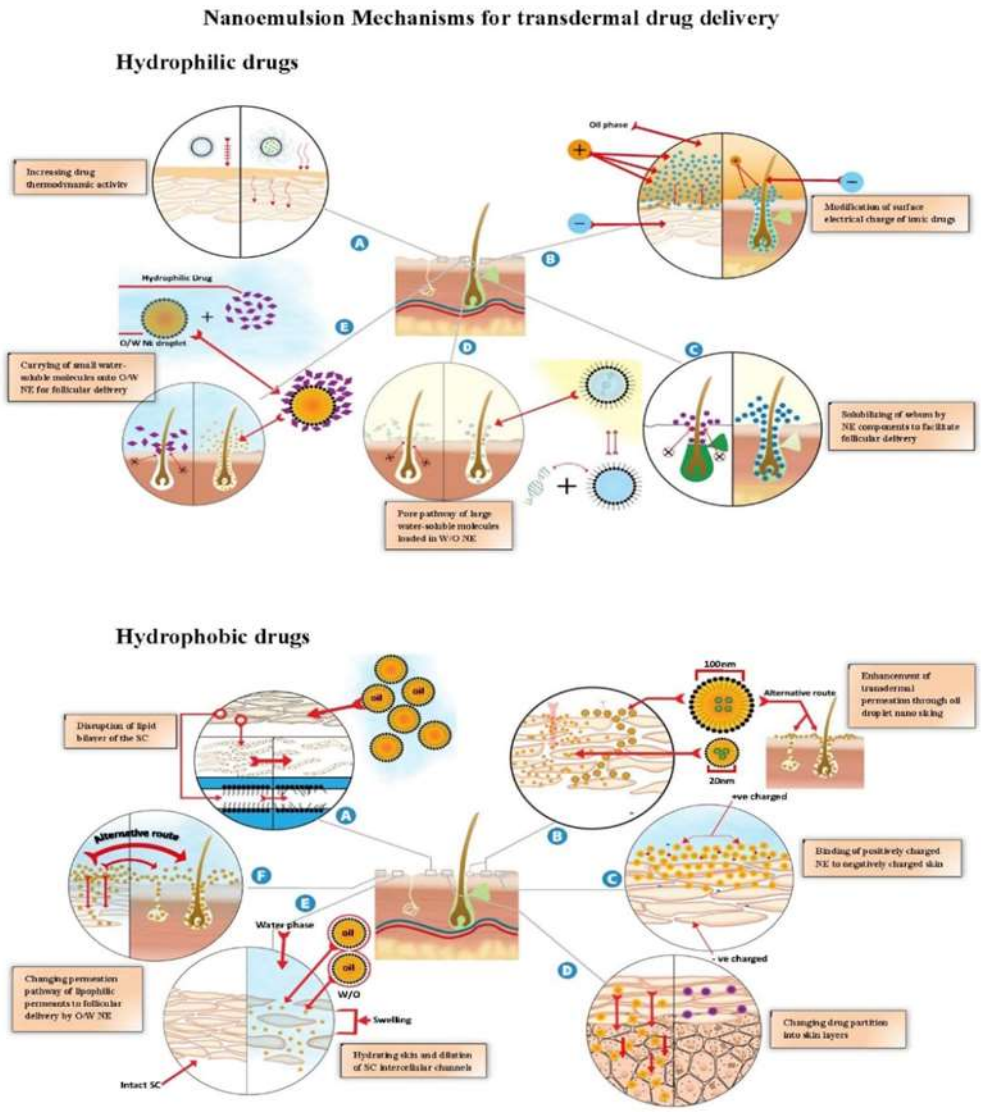

Fig. 1[29] : Mechanisms of Nanoemulsion-enhanced transdermal delivery pathways for hydrophilic and hydrophobic drugs.

The mechanistic pathways by which nanoemulsions enhance transdermal drug delivery for both hydrophilic and hydrophobic drugs, highlighting their distinct interactions with skin structure and function.

For hydrophilic drugs (upper panel):

Nanoemulsions (NEs) increase the thermodynamic activity of the drug, driving diffusion across the skin.

Modification of surface electrical charge enhances the delivery of ionic drugs.

Solubilization of sebum by NE components facilitates drug entry through the follicular route.

O/W nanoemulsions carry small water-soluble molecules for targeted follicular delivery.

W/O nanoemulsions allow penetration of larger water-soluble molecules through aqueous pore pathways.

For hydrophobic drugs (lower panel):

NEs disrupt the lipid bilayer of the stratum corneum (SC), enhancing permeation.

Hydrating the skin leads to swelling and dilation of intercellular channels, improving drug movement.

Positively charged NEs bind to negatively charged skin, aiding in drug retention and absorption.

W/O NEs alter the permeation pathway, enabling follicular delivery of lipophilic drugs.

Oil droplets in NEs facilitate enhanced partitioning of drugs into the skin layers.

Overall, the diagram emphasizes how nanoemulsion composition, droplet size, charge, and phase type (O/W or W/O) are tailored to optimize skin penetration routes, targeting both the intercellular lipid matrix and appendageal pathways for effective transdermal delivery.

TYPICAL COMPOSITION & QUANTITATIVE RANGES

Literature-reported ranges (w/w) include:

- Oil phase (5–30 %) — MCT, oleic acid, IPM, squalene; some systems use up to 37 % squalene [3,6].
- Surfactant (10–60 %) — Typically non-ionic (Tween 80, Span 80); S_mix often ranges 40–55 % for high solubilization [3,7].
- Co-surfactant/cosolvent (0–30 %) — Ethanol, propylene glycol, Transcutol® P; these reduce interfacial tension and expand NE region [3].
- Water — QS to 100 %, often 40–90 % depending on oil/surfactant content [3].
- Drug load — Usually 0.1–5 % (w/w); 0.5–2 % is common for maintaining clarity and stability [7,8].
- Representative formulation: Diclofenac diethylamine NE—1 % drug, ~15 % oleic acid oil, ~55 % surfactant/cosurfactant (polysorbate/ethanol 1:2 v/v), remainder water—yielded droplet size ~80–120 nm and improved skin flux vs. control [7,9].

METHODS OF PREPARATION

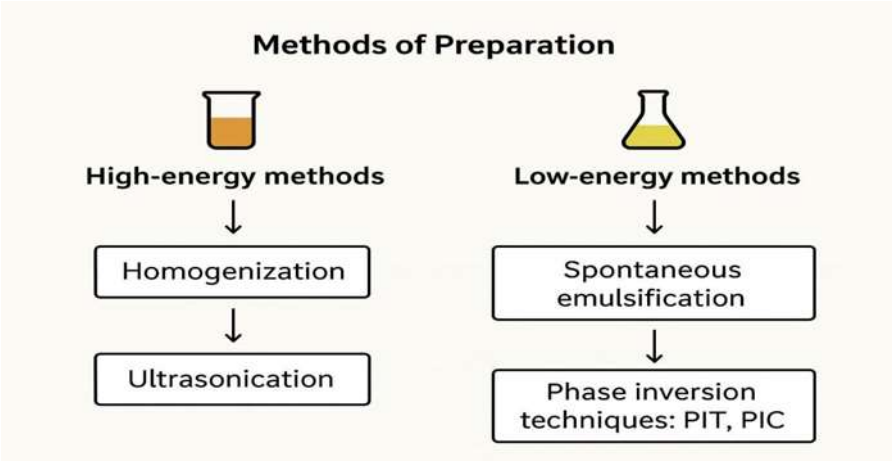

Fig. 2[29] : Schematic representation of Preparation Methods.

- High-energy methods (homogenization, ultrasonication) generate droplets in the tens of nanometers and are scalable [10].
- Low-energy methods (spontaneous emulsification, PIT, PIC) exploit interfacial chemistry and are common in lab-scale transdermal NE development [3,11].
- Key variables: Oil type, S_mix ratio, water titration rate, pressure/time in homogenization, sonication power/time; pseudo-ternary diagrams are standard for NE zone identification [11,12].

CHARACTERIZATION

- Droplet size & PDI (via DLS): Aim for size <150 nm, PDI <0.3 for uniformity and stability [3].
- Zeta potential: Monitors charge-mediated stability [3].
- Viscosity & rheology: Crucial for application; NE can be converted into nanoemulgels using Carbopol or Poloxamer [5].
- pH, drug content, entrapment efficiency: Standard quality control parameters [7].
- In vitro release & ex vivo Franz diffusion: Provide metrics like flux ($\mu g \cdot cm^{-2} \cdot h^{-1}$), and many NEs show 2–10 × higher flux vs. controls (up to ~39 × in specialized cases) [3,8].
- Morphology (TEM/SEM) & stability tests (centrifugation, freeze–thaw, heating–cooling, accelerated storage) are also routine [10].

MECHANISMS OF SKIN PERMEATION

Mechanisms include:

Lipid disruption/fluidization by penetration enhancers [3].

Increased thermodynamic activity from high drug solubility in oil [3].

Hydration of SC, loosening structure [3].

Enhanced contact & reservoir effect: High interfacial area facilitates a drug reservoir in the SC/epidermis [3].

Quantitatively, NE formulations typically show increased cumulative permeation and deposition compared to conventional gels; enhancement depends on oil/surfactant selection and drug properties [3].

The three primary pathways for transdermal drug delivery through the skin's structure. The skin is composed of multiple layers, beginning with the stratum corneum at the outermost surface, followed by the stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale, beneath which lies the dermis and the subcutaneous tissue.

The pathways shown are:

1. **Paracellular route** – Movement of drug molecules between adjacent skin cells, bypassing cell interiors and traveling through intercellular spaces. This pathway typically favors hydrophilic and small molecular weight compounds.

2. **Transfollicular route** – Drug penetration via hair follicles and associated sebaceous glands. This pathway can serve as a reservoir for drug deposition and is especially significant for larger molecules or particulate systems like nanoparticles.

3. **Transcellular route** – Direct passage of drug molecules through the keratinized cells of the stratum corneum, requiring partitioning into and diffusion across both lipid and aqueous domains within cells. This route is generally more favorable for lipophilic molecules.

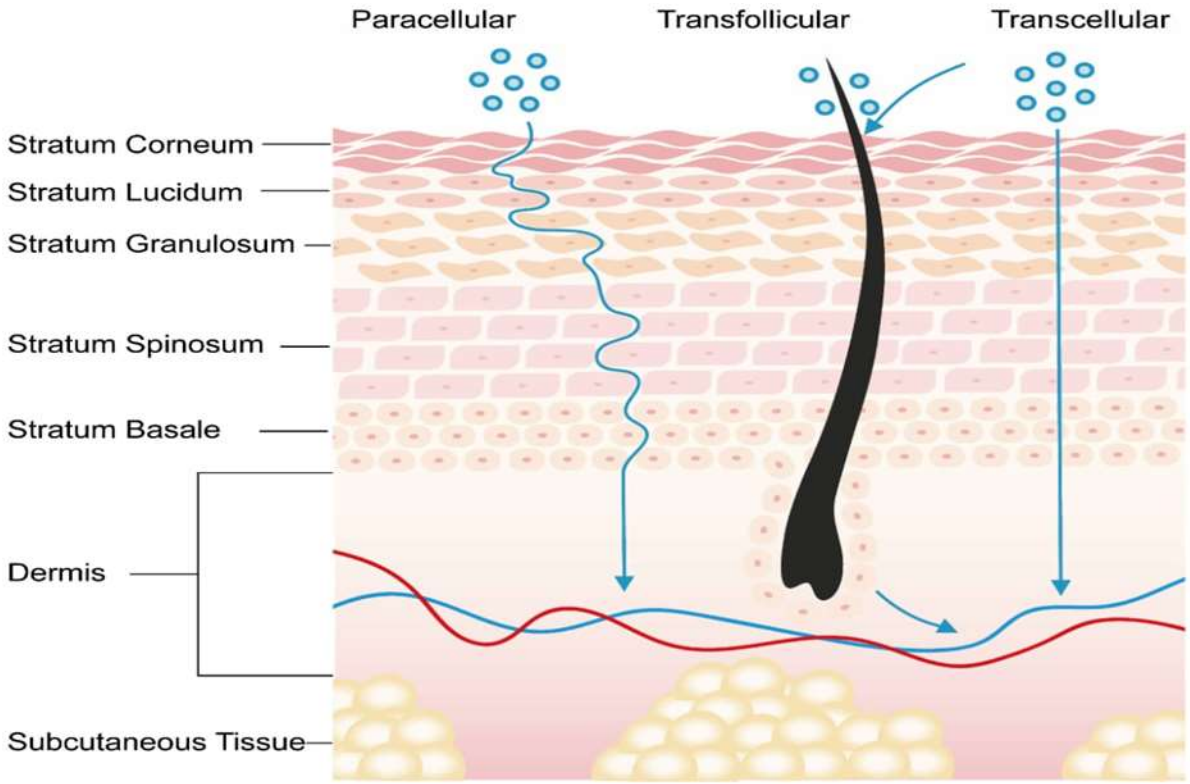

Fig. 3[29] : Schematic of Transdermal Penetration Routes Relevant to Nanocarrier-Based Delivery Systems.

FORMULATION TYPES AND SKIN DELIVERY PATHWAYS OF MICRO/NANOEMULSIONS-

Below figure depicts the formulation types, structural composition, and skin delivery pathway of micro/nanoemulsions for transdermal drug delivery.

At the top, the schematic shows the initial phase components—oil, water, surfactant (S), and co-surfactant (Co-S)—which, upon appropriate mixing, yield two primary nanoemulsion types:

Oil-in-water (O/W) micro/nanoemulsions, where hydrophobic drugs are solubilized within the oil droplets dispersed in a continuous aqueous phase, and hydrophilic drugs remain in the surrounding aqueous medium.

Water-in-oil (W/O) micro/nanoemulsions, where hydrophilic drugs are encapsulated within internal aqueous droplets dispersed in a continuous oil phase, while lipophilic drugs dissolve in the oil phase.

The lower section illustrates the targeted skin delivery of these nanoemulsions, showing penetration via both the stratum corneum and appendageal pathways (hair follicles and sebaceous glands). The delivery efficiency depends on droplet size, composition, and physicochemical properties of the formulation.

The characterization parameters listed—pseudo-ternary phase diagrams, particle size, polydispersity index (PDI), zeta potential, viscosity, and electrical conductivity—are critical in optimizing formulation stability, drug loading, and penetration performance.

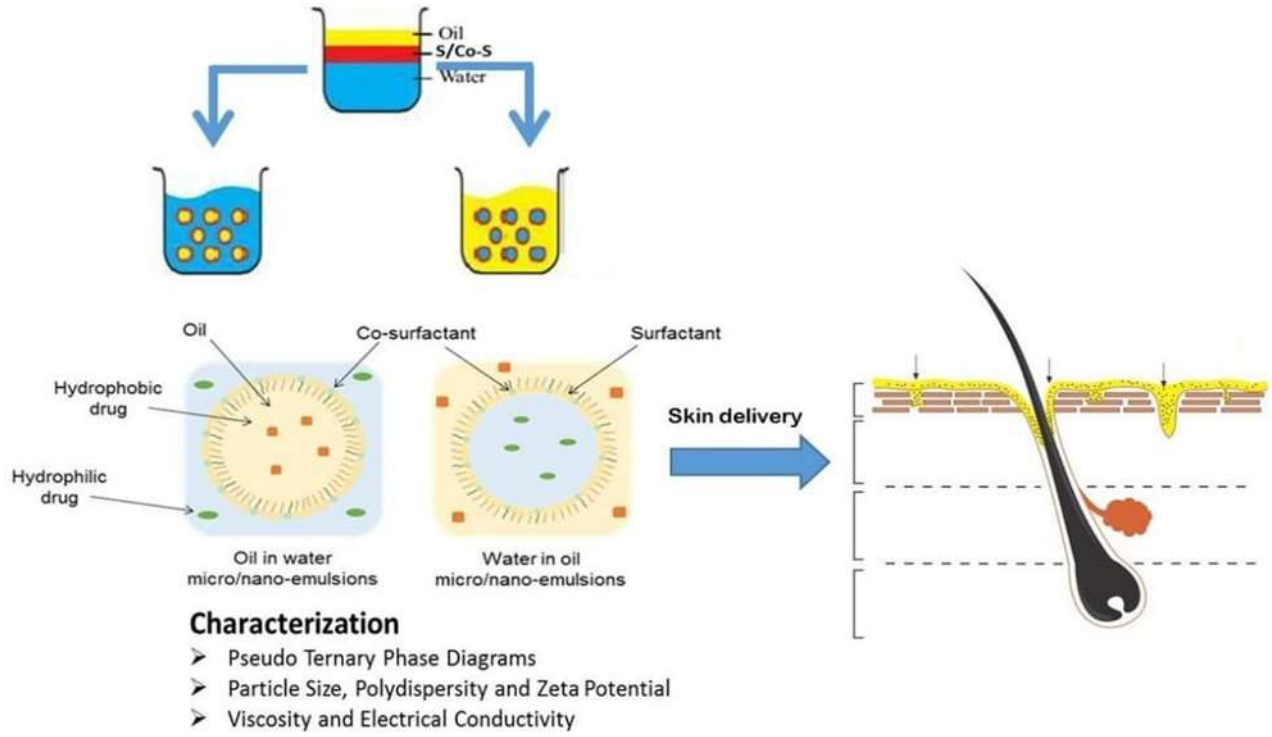

Fig. 4[29]: Graphical Abstract of Nanoemulsion Skin Pathways

CASE STUDIES

Diclofenac/NSAIDs: Nanoemulgels prepared via low-energy methods (droplet size ~50–200 nm, drug content 85–98 %) showed improved ex vivo flux and in vivo analgesic activity vs. marketed gels. Oil phase (5–20 % oleic acid or castor oil), surfactant (20–55 % Tween 80), cosolvent (propylene glycol/ethanol); drug load 0.5–1 % [7,8,9].

Tadalafil: Nanoemulgels with optimized S_mix, droplet sizes <150 nm, exhibited enhanced permeation, suggesting potential for non-invasive transdermal therapy [13].

Analgesics (ibuprofen, ketoprofen): NE and nanoemulgel systems showed significantly higher skin flux and deposition than conventional creams, with sustained effects in animal inflammation models [8,14].

Novel platforms: NE-loaded dissolvable microneedles and patches showed promise for localized, sustained delivery with improved penetration and lower systemic exposure [5,15].

RECENT ADVANCES (2020–2025)

1. Nanoemulgels & rheology tuning—Improved retention and acceptability via conversion of NEs into gels (with Carbopol, HPMC) while balancing release/permeation [5].

2. NE–microneedle hybrids—Combining mechanical disruption with solubilized payload for controlled release [15].

3. Green, bioactive oils—Use of plant-derived oils (cumin, babassu) offering additional permeation or bioactivity; quantitative formulations reported in 2023–2025 [8,6].

4. Surfactant role mapping—Systematic studies correlating surfactant type/S_mix to droplet size and flux for rational design [5,16].

5. Translation & regulation focus—Emerging interest in scalable GMP production and toxicity profiling for clinical advancement [1,17].

SAFETY, TOXICITY & REGULATORY CONSIDERATIONS

Irritation & sensitization: Surfactant and penetration enhancer selection must minimize skin irritation; in vitro and in vivo testing are required [3].

Systemic exposure: Increased transdermal flux may raise systemic absorption; pharmacokinetic evaluation is essential.

Excipient safety and regulatory limits: Use pharmacopeial-grade excipients and justify high surfactant content with safety data. Marketed NE transdermal products remain rare due to regulatory caution [1,18].

CHALLENGES & GAPS

1. High surfactant loads—Potential irritation/toxicity and regulatory hurdles [5].

2. Long-term stability & phase changes—NEs are kinetically but not necessarily thermodynamically stable; stability studies under stress conditions are critical [10].

3. Scale-up variability—Shear differences between lab ultrasonicators and industrial homogenizers may alter droplet size; process transfer studies needed [10].

4. Lack of clinical comparative data—More head-to-head clinical trials vs. marketed topicals are necessary [17].

PRACTICAL FORMULATION WORKFLOW

1. Preformulation: Solubility screening in oils, surfactants, and cosolvents [3].

2. Phase diagram construction: Map oil : S_mix : water; select S_mix (1:1 to 3:1 surfactant:cosurfactant) ratios yielding broad NE zones [12].

3. Lab batch preparation: Aim for droplet size <150 nm, PDI <0.3; monitor pH and content [10].

4. Characterization: DLS, zeta, viscosity, TEM; in vitro release and ex vivo Franz diffusion (measure flux, lag time, deposition after 24 h) [3].

5. Formulation refinement: Convert to nanoemulgels (e.g., with 1 % Carbopol); re-evaluate rheology and permeation [5].

6. Stability and irritation tests: Centrifugation, freeze–thaw, accelerated storage (e.g., 40 °C/75 % RH), and in vitro skin irritation assays [10].

FUTURE PERSPECTIVES

Rational design of safer excipients to reduce surfactant load while keeping efficacy (e.g., natural enhancers) [6].

Hybrid systems combining NEs with microneedles and patches for controlled, localized delivery [15].

Standardised translational pipelines linking lab data to human PK/PD and establishing GMP manufacturing methods [17].

Clinical trials comparing NE systems to marketed topicals in chronic pain or dermatologic areas to support efficacy claims.

CONCLUSION

Nanoemulsions and nanoemulgels offer a flexible, scientifically grounded approach to enhance transdermal delivery of poorly soluble drugs. From 2020 to 2025, advances in formulation mapping, NE–microneedle hybrids, green oil excipients, and systematic surfactant studies, as well as preclinical efficacy in several APIs, underscore their potential. Remaining hurdles include excipient safety (especially surfactant load), long-term stability, scalable manufacturing, and robust clinical data. Focused efforts to develop safer excipient systems, scalable processes, and clinical studies will accelerate their translation.

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