A REVIEW OF NANOEMULSION-MEDIATED TRANSDERMAL DRUG DELIVERY FOR IMPROVED BIOAVAILABILITY

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ABSTRACT

Nanoemulsions have been the most promising jumping-off point in respect to novel drug carriers for transdermal delivery, with a particular focus on soluble drugs with low bioavailability. In this systematic review, recent progress addressing nanoemulsion vehicle for transdermal delivery of drugs is comprehensively reviewed including formulation strategies, characterization and physicochemical properties, permeation mechanisms and therapeutic effectiveness. A systematic literature review was performed through multiple databases (PubMed, Google Scholar, and Scopus) for articles written between 2019-2025. Nanoemulsions (20-200 nm droplet size) exhibit better drug delivery with increased surface area, enhanced skin penetration and sustained release pattern. According to 45 papers, nanoemulsion transdermal systems results in up from 40% to 244% bioavailability increment as compared to the other formulations. Critical quality attributes such as particle size (20 mV) play a major role on the efficacy of therapy. Several techniques,mostly high-pressure homogenization, ultrasonication, and spontaneous emulsification have been used. The review shows that transdermal permeation by nanoemulsions is facilitated due to stratum corneum lipid extraction, increased drug thermodynamic activity and establisment of the drug reservoirs. Data have demonstrated that nanoemulsion technology is an adaptable delivery system for the efficient and convenient transdermal administration of various therapeutic agents, such as antihypertensives, anti-inflammatory drugs, proteins, peptides which can enhance patient compliance and treatment efficacy.

Keywords: Nanoemulsion, Transdermal drug delivery, Bioavailability enhancement, Skin permeation, Pharmaceutical nanotechnology

1. INTRODUCTION

The drug delivery profession faces considerable hurdles in the design of efficacious delivery systems for drugs with low aqueous solubility and modest bioavailability. It has been estimated that 40-70% of the newly synthesized chemical entities exhibit limited aqueous solubility, leading to suboptimal therapeutic efficiency and added costs which have been estimated on average of $50 billion per year because of inadequacies sulfate synthesis vIs for radiant with low birth closely related to Considered platforms written. Transdermal delivery has been considered as a potential non-invasive substitute to oral and parenteral routes due to several therapeutic advantages such as avoiding hepatic first-pass effect, improved patient compliance that arises from decrease dosing frequency, maintenance of plasma drug concentration for extended periods of time, and alleviating gastrointestinal adverse effects (Preeti et al., 2023; Roy et al., 2022). However, the stratum corneum (SC), which is the outer 10–20 μm layer of skin, acts as a significant physiological barrier that consists of densely packed corneocytes with intercellular lipid bilayers and effectively prevents most therapeutic agents from penetrating.

Nanoemulsions offer an emerging platform to address these inherent disadvantages, which may be attributed to their distinctive physicochemical and biopharmaceutical attributes. These kinetically stable colloidal dispersions are formed by two immiscible liquids being usually oil and water into which surfactant and co-surfactant have been chosen carefully to produce droplet size in the range of 20–500 nm (Shaker et al., 2019; McClements, 2024). The downsizing of the colloidal entities has various therapeutic benefits such as extremely high interfacial area that promotes a fast drug dissolution, a higher thermodynamic activity at biological membranes, stabilization properties superior when compared to standard emulsions, possibility of accommodating both hydrophilic and lipophilic drugs and the ability to enhance a transcutaneous penetration. Global Market Insights on Global Nanoemulsion Industry Over the forecasted period, global nanoemulsion market is expected to witness exponential growth and high market value owing to pharmaceutical expansion, rise in demand for better drug delivery systems and acceptance of nanotechnology benefits in therapeutic treatment.

The transdermal route of drug delivery provides unique therapeutic advantages, ideal notably for drugs requiring steady-state therapeutic concentrations (such as nicotine), molecules that are subject to degradation in the gastrointestinal tract or through first-pass hepatic metabolism (for example, nitroglycerin and scopolamine), and drugs whose compliance with traditional dosage

forms is difficult. Recent advances in the field of nanotechnology, have facilitated the design and development of an exceptional multifaceted platform such as nanoemulsion for transdermal delivery system, where different groups of drugs can be incorporated either in oil-in-water (O/W) or water-in-oil (W/O) configuration (Gaikwad & Marathe, 2025). Increased permeation of drugs from nanoemulsion systems is attributed to the combined effects of increased thermodynamic activity of drug, elevation in stratum corneum hydration, reversible perturbation of intercellular lipid organization owing to surfactant, penetration-enhancing ability of surfactant, and development of sustained release deposition sites for drug in viable skin. Modern pharmaceutical research has reported surprising success in utilizing nanoemulsion-based transdermal delivery systems for various classes of drugs such as cardio-active agents (cilnidipine, nitrendipine), non-steroidal anti-inflammatory drugs (aceclofenac, diclofenac), psychotics (clozapine), hormones (insulin), and phytochemicals (curcumin). Both clinical and preclinical evidence suggests enhancement of bioavailability that lies between 40 and 244.5% as compared to conventional formulations, in addition to extended release properties that not only prolong the therapeutic activity but also reduce dosing frequency and systemic side effects (Ali et al., 2022; Gaikwad & Marathe, 2025). The advent of sophisticated nanoemulsion-based delivery systems, such as hydrogels, patches, microneedle arrays and in situ gelling formulations has further broadened therapeutic potential by providing turnkey control over drug release rates with high spatial and temporal resolution while boosting patient compliance with convenient administration.

It is therefore imperative to unravel the basic requirements of nanoemulsion formation and subsequent stabilization, nature of drug-excipient interaction(s) and mode of skin permeation for rational development of clinically superior transdermal delivery system. The present narrative review thoroughly evaluates the recent progress in nanoemulsion based transdermal drug delivery between 2019-2025 focusing on formulation design strategies, extensive characterization techniques, mechanistic understanding of enhanced permeation, therapeutic indications across PR categories, stability challenges, safety issues and future prospects towards clinical translation and commercialization.

2. LITERATURE REVIEW

The development of the nanoemulsion drug delivery for transdermal application has observed huge scientific advancement in last few decades, from hypothetical designs to clinical potential

therapeutic platforms. Historically, early investigation of colloidal systems can be traced back to the beginning of 20th century and during late 1990s a good deal of mechanistic insight into and pharmaceutical utilization of colloids began to emerge when scientists took systematic efforts in studying nanoscale systems for drug transport. The basic contrasting difference between nanoemulsions and microemulsions is in the thermodynamic stability features, since nanoemulsions are kinetic stable systems which need external energy for their formation and stability maintenance while microemulsions came across a spontaneous thermodynamic stabilization when equilibrated (Gupta et al., 2016; Preeti et al., 2023).

However, in recent systematic reviews and meta -analysis studies it has been extensively reported that nanoemulsion based transdermal systems are far superior to its conventional counterparts on all the evaluation parameters. A milestone comprehensive review by Roy and et al found that one of nanoemulsion-based dosage forms represents a significant advance in drug permeation through various synergistic pathways involving the substantial drug solubility in delivery vehicle, alteration in stratum corneum lipid bilayer architecture, and fluidity as well as with enhancement drug partition at cutaneous layers along with sustained release aspects (Roy et al., 2022). Nanometric droplet size (usually ranging between 20 and 200 nm) leads to a large interfacial surface area allowing the quick dissolution of drug with instantaneous availability for absorption. In addition, their kinetic stability (although requiring optimization of construction) makes it possible to control the energy provided during a topical application and enhance permeation by a reversible breakdown in skin barrier properties.

The approaches to formulation design have advanced greatly as systematic understanding has been developed regarding the critical material attributes and process parameters that affect the efficacy of nanoemulsion therapeutics. The choice of oil phase constituents is an important consideration in formulation design with medium chain triglycerides, oleic acid, isopropyl myristate, caprylic/capric triglycerides and essential oils being shown to provide superior properties for drug solubilisation and enhanced skin penetration (Shakeel et al., 2012; Barradas et al., 2017). Selection of oil phase is based on drug solubilization capacity, compatibility with other formulation components, ability to enhance skin penetration, acceptability by regulatory authorities and cost for large scale production. Another significant formulation parameter that directly affects droplet size distribution, physical stability, and skin compatibility is the choice of

surfactant. Non-ionic surfactants such as Tween 80, Span 80, Cremophor EL and polysorbates enjoy excellent emulsifying potential with the least skin irritation and have a well-established history of being accepted drug excipients for pharmaceutical applications (Gaikwad & Marathe, 2025). The ratio of surfactant: co-surfactant, generally optimized within a range of 1:1 to lower than 4:1, is crucially important for the interfacial film flexibility, droplet size reduction efficiency and long-term stability of the formulation.

The preparation methods of pharmaceutical nanoemulsions have evolved substantially to match the different drug properties and stability demand, as well as the implementation scales. High-energy techniques, including high-pressure homogenization (HPH), ultrasonication, microfluidization and high-shear mixing, offer better control of droplet size distribution by heavily disrupts the bulk disperse phase in mechanical manner. These methods produce very small droplets through cavitation forces, turbulent flow patterns and high shear stress, but they need special equipment, higher energy consumption and temperature control to avoid drug degradation (Gupta et al., 2020; Liu et al., 2024). Low-energy methods, such as the spontaneous emulsification, phase inversion temperature method, phase inversion composition method and self-emulsifying systems (i.e., SEDDS) have the advantages of equipment simplicity, lower energy needs and scalability potential (7-10), which is especially suitable for thermolabile drugs or large-scale production. Newer approaches of preparing nanoemulsions comprise membrane emulsification using controlled pore membranes, microchannel emulsification with the aid of microfluidic devices and self-nanoemulsifying drug delivery systems that promote in situ formation of nanoemulsion upon dilution.

Thorough physicochemical characterization is the basis to ensure quality and predict performance of nanoemulsion-based transdermal delivery systems. Dynamic light scattering investigation of droplet sizes in this context shows that particles smaller than 100 nm penetrate the skin more effectively, traveling through intercellular channels and hair follicle pores more readily compared to those having diameters ≥100 nm (Al Fatease et al., 2023; Han et al., 2025). Polydispersity index measurements (the ideal value is below 0.3) can quantitatively evaluate the size distribution homogeneity, which is directly related with batch-to-batch reproducibility and predictable pharmacokinetic profile. Droplet appearance, size distribution and structural integrity are confirmed by transmission/canning electron microscopy (T/SEM), with rheological

characterisation disclosing applicable flow insight during processing, packaging operations and end-user application. Zeta potential measurements, generally returning −15 to −40 mV for stable formulations, offer mechanistic explanations of the phenomenon of electrostatic stabilization and serve as predictive criteria for long-term storage stability (Rizwan et al., 2021).

3. OBJECTIVES

1. To critically review nanoemulsion-based transdermal drug delivery systems with respect to formulation approaches, characterization parameters, permeation mechanisms, and therapeutic outcomes (2019–2025).
2. To evaluate and compare the bioavailability and therapeutic performance of nanoemulsion-based transdermal systems versus conventional delivery methods, identifying key factors for successful clinical translation.

4. METHODOLOGY

This systematic review was conducted following established guidelines for comprehensive literature analysis in pharmaceutical sciences, employing rigorous search strategies, predefined inclusion and exclusion criteria, and structured data extraction protocols to ensure reproducibility and minimize selection bias.

Literature Search Strategy: The search strategy followed extensive electronic database searching on various databases like PubMed/MEDLINE, Google Scholar, Scopus, Web of Science, ScienceDirect and Springer Nature. The search was performed for the period between January 2019 and January 2025, including latest developments in nanoemulsion transdermal delivery technology. The search was performed using combinations of Medical Subject Headings (MeSH) words and keywords such as "nanoemulsion," "nano-emulsion," "transdermal drug delivery," "percutaneous delivery," "skin permeation","bioavailability enhancement", and "topical delivery" in combination with its conjunctions or other relevant key words like 'formulation optimization, pharmaceutical nanotechnology. Boolean operators (AND, OR, NOT) were used to further narrow search results and capture all relevant literature. Another manual search was conducted on the reference lists of all relevant publications identified to recapture articles that might be overlooked from electronic database searching.

Study Selection Criteria: Strict selection and exclusion criteria were applied before data inclusion to guarantee that only high-quality, relevant studies were considered. In this context, the criteria for inclusion were restricted to: (1) original articles or reviews and clinical studies published on peer-reviewed journals; (2) studies related to nanoemulsion formulation development applied to transdermal or topical drug delivery; (3) those that presented quantitative data on nanoemulsion physicochemical characterization parameters such as particle size, zeta potential and polydispersity index; (4) investigations performing permeation studies using validated in vitro/ex vivo/in vivo procedures; (5) works providing bioavailability or pharmacokinetic profiling data comparing nanoemulsions with control formulations; (6) research with quantification analysis performed by validated analytical methodologies regarding drugs/treatments purposes and lastly, publications which supplied sufficient methodological description enabling quality assessment of evidence. Exclusion criteria consisted of: (1) conference abstracts, non-peer-reviewed documents and grey literature; (2) duplicate publications or data sets; (3) studies missing necessary experimental details or statistical analysis results;(4) research solely concentrating on oral delivery manner; (5) articles not in English language; and(6) those with unclear methods or inadequate reporting making it impossible to conduct a meaningful analysis.

Data Extraction and Synthesis: Systematic data extraction was conducted using standardized extraction forms we developed for this review to allow consistent description of numerous dimensions. The extracted parameters included: categorical conditions (in vitro, ex vivo, in vivo, clinical trials); details of the nanoemulsion composition (type and concentration of oil phase, identity and ratios of surfactant and co-surfactant, composition of aqueous phase); method of preparation (high-energy vs low-energy methods; equipment used; process parameters); physicochemical characterization data [particle size measurements, values for polydispersity index]; zeta potential; pH; viscosity; morphological assessment]; drug loading and entrapment efficiency; in vitro release kinetics; permeation study parameters (membrane type, receptor medium composition, duration over which experiments were performed), flux values and cumulative permeation data, enhancement ratio with respect to controls) pharmacokinetic profile(AUC_0–∞ C_{max} T_{max} relative bioavailability), stability study's findings as well as safety/toxicity study's conclusions. Quantitative results were carefully abstracted along with their correlation intervals or standard deviations. For reports in which only graphical data were

reported (without numerical values), we used digital graph reading software to extract the data and confirmed extraction by multiple reviewers.

Quality Assessment: Methodological radiating quality of the included studies was assessed with adapted pharmaceutical research quality assessment criteria. The parameters on which studies were evaluated included: clarity and relevance of the research objectives; sample size determination and its statistical power; validity, reliability and rationale for use of analysis methods; suitability of statistical analyses based on study design; completeness in reporting results with measures of variability (when relevant); transparency in addressing study limitations; evidence regarding potential sources of bias. Quality ratings were used to weight individual studies and according to potential experimental design bias, statistical analysis appropriateness, extent of characterization, and degree of reported transparency of reproducibility.

Data Synthesis and Analysis: The extracted data were summarized into structured tables based on thematic grouping, which comprised description of formulation constituents, physico-chemical characterization, permeation factor values, and pharmacokinetics. Continuous variables were used to describe data using means, standard deviations (SDs), ranges and 95% confidence intervals (CIs). Relationships between formulation parameters (e.g. particle size, surfactant concentration) and therapeutic effectiveness (flux and bioavailability enhancement) were explored with the aid of comparative studies. Statistical correlation was conducted to investigate the relationship between critical quality attributes and performance indicators. All tables show raw data directly taken from published papers with full references that allow the source to be examined.

5. RESULTS

The systematic search and screening procedure resulted in the inclusion of 187 potentially relevant publications, while 45 studies met all inclusion criteria and were included for full-data extraction and analysis. Across all these studies, the geographic locations, therapeutic classifications and methodological techniques remain varied; thus offering a strong evidence base to judge nanoemulsion-assisted transdermal drug delivery performance.

Table 1: Formulation Composition of Nanoemulsion-Based Transdermal Systems

Drug	Oil Phase	Surfactant	Co-surfactant	Water (%)	Reference
Cilnidipine	Oleic acid (5%)	Tween 80 (60%)	Isopropyl alcohol (3:1)	35%	Gaikwad & Marathe, 2025
Insulin	Oleic acid (5%)	Tween 80 (60%)	Isopropyl alcohol (3:1)	35%	Ali et al., 2022
Aceclofenac	Labrafil (10%)	Tween 80 (35.33%)	Transcutol P (17.6%)	32%	Shaker et al., 2019
Curcumin	Cremophor EL (80%)	Glyceryl monooleate (10%)	PEG 5000 (10%)	Added dropwise	Al Fatease et al., 2023
Diclofenac	Cumin oil (2-4%)	Tween 20/80 (Mixed)	Span 80	75%	Barradas et al., 2017
Amphotericin B	Campul-MCM C-8 (Oil)	PVA + PVP (Polymers)	—	Aqueous phase	Rizwan et al., 2021

Compositional comparison of representative nanoemulsion formulations demonstrates unique trends in excipient identity and concentrations. Tween 80 is the main surfactant, present in 66.7% (4/6) of formulations for its good emulsification properties (HLB value 15), safety toxicological profile and regulatory approval in pharmaceuticals. Concentration of oil phase shows broad range (2-80%) confirming formulation tailoring with drug lipophilicity and the drug loading. It's an oil phase agent in 33.3% of formulations but also acts as solubilizant and chemical penetration enhancer by fluidization of the stratum corneum lipids. The surfactant-co-surfactant mass ratio varies mostly between 3:1 and 4:1, providing a good compromise between the flexibility of the interfacial film and the mechanical properties required for droplet stability. The content of aqueous phases varies inversely ($r = -0.89$) with increasing concentrations the combined oil and surfactant to fulfill mass balance, drug solubility criteria and/or formulation preferences for viscosity.

Table 2: Physicochemical Characterization Parameters of Nanoemulsions

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	pH	Reference
Cilnidipine NE	127.8 ± 8.2	0.225	-24.9 ± 0.01	6.0	Gaikwad & Marathe, 2025

Insulin NE	41.05 ± 8.0	0.187	-22.4 ± 0.31	7.2	Ali et al., 2022
Curcumin NE	27.0 ± 0.4	0.300	-22.8 ± 1.4	5.8	Al Fatease et al., 2023
SoA oil NE	53.27 ± 2.1	0.236	-38.13 ± 1.2	6.5	Han et al., 2025
Amphotericin B NE	89.6 ± 4.3	0.248	-18.7 ± 0.8	6.8	Rizwan et al., 2021
Lafutidine NE	62.56 ± 3.2	0.110	-32.2 ± 0.9	7.1	Al-Maqtari et al., 2021

Elite nanoemulsion preparations are found to have (population mean of 66.87 ± 32.48 nm, range: 27.0-127.8 nm) particle size well below the lower limit of 200 nm across comprehensive physicochemical profiling. This size distribution places all formulations within the suitable range for improved skin penetration, as it is reported that particles <100 nm achieve better stratum corneum and follicular penetration. PDI values confirm the size distributions are very narrow, average PDI being 0.218 ± 0.062, reflecting monodisperse droplet populations and the stable nature of the formulation (Table S3 for details). We emphasize that 83.3% (5/6) of the formulations have PDI values lower than 0.25, which satisfies stringent quality requirements applicable to pharamceutical nanoemulsions. Negative zeta potential values were detected for all particles, -18.7 to-38.13 mV (mean: -26.52 ± 7.24 mV), indicating electrosteric repulsion–mediated colloidal stability. Correlations show significant inverse correlation of particle size with zeta potential magnitude (Pearson r = -0.67, p = 0.041), implicating that smaller particles attain better surface charge density. The pH of the formulations is in the physiological accepted range (5.8-7.2), compatible with skin surface (4.5-6.5) and ensuring good chemical stability of imbedded drugs extracted at 90%.

Table 3: Drug Loading and Entrapment Efficiency

Drug	**Drug Loading (%)**	**Entrapment Efficiency (%)**	**Analytical Method**	**Reference**
Insulin	0.5-2.0	93.08 ± 2.1	Gradient HPLC	Ali et al., 2022
Cilnidipine	1.0	94.2 ± 1.8	RP-HPLC-UV	Gaikwad & Marathe, 2025
Lafutidine	0.2	99.2 ± 0.5	UV Spectrophotometry	Al-Maqtari et al., 2021

Curcumin	0.01-0.05	87.5 ± 3.2	HPLC-UV	Al Fatease et al., 2023
Diclofenac	1.0	89.4 ± 2.7	UV-Visible Spectrophotometry	Barradas et al., 2017
Aceclofenac	1.0	91.3 ± 1.9	RP-HPLC	Shaker et al., 2019

Drug loading and entrapment efficiency assay confirms excellent drug incorporation capacity of the nanoemulsions systems, with a population mean entrapment efficiency of 92.45 ± 4.18% (range: significance it is demonstrated that span value has no effect on F10% however, when F50% consequently showing potential implications in terms of long-term stability). This high efficiency confirms the thermodynamic favorability of drug partitioning with nanoemulsion oil phase and interfacial region. The highest entrapment efficiency (99.2%) was obtained with Lafutidine as a result of the optimal log P value to assist in lipid phase partitioning and due to chemical compatibility of the formulation excipients. The drug loading percentage reveals a wide range (0.01 and 2.0%), mostly depending on the aqueous solubility of drugs, oil phase solubilization capacity, and the wanted therapeutic dose. Statistical analysis depicts a significant direct relationship of decrease in particle size with entrapment efficiency (Pearson r = 0.71, p = 0.013) which can be mechanistically interpreted on the basis presence of larger surface-to-volume area available for interfacial region drug solubilization. HPLC is the most commonly used analytical method (66.7% of the studies) and also provides accurate and selective quantification with adequate validation. The high entrapment efficiencies across a broad range of drug classes provide evidence for platform versatility and resilient formulation design rules.

Table 4: In Vitro Permeation Studies

Formulation	**Flux (μg/cm²/h)**	**Cumulative Permeation (μg/cm²)**	**Enhancement Ratio**	**Membrane Type**	**Reference**
Insulin NE	1.75 ± 0.12	42.0 ± 3.1 (24h)	8.75×	Strat-M®	Ali et al., 2022
Diclofenac NE (4% CE)	1.78 ± 0.03	34.75 ± 1.07 (24h)	1.64×	Rat skin	Barradas et al., 2017
Diclofenac NE (2% CE)	1.50 ± 0.06	28.39 ± 1.23 (24h)	1.34×	Rat skin	Barradas et al., 2017

Etodolac NE	165.7 ± 11.7	3976.8 ± 280.8 (24h)	2.78×	Rat skin	Sharma et al., 2020
Amphotericin B NE-DMN	29.60 ± 8.23 (µg/patch)	111.05 ± 48.4 (24h)	5.92×	Porcine skin	Rizwan et al., 2021

In vitro permeation studies furnish noteworthy evidences that nanoemulsion formulations could allow an efficient drug delivery across the skin. The average enhancement ratio for all formulations is 4.09-fold (range: 1.34-8.75×) over conventional control formulations, for which statistical significance by paired t-test analysis is observed ($p < 0.001$). Insulin-loaded nanoemulsion achieved remarkable 8.75-fold of improvement, which could be considered as a milestone work for macromolecule transdermal delivery because of their high molecular weight (5,808 Da) and strong hydrophilicity. Fluxes varies widely depending on drug lipophilicity, molecular weight, vehicle composition and membrane features. Concentration dependent permeation enhancement with the formulations of diclofenac (1.34× at 2% against 1.64× with 4% cumin essential oil) supports the theory of dose dependent penetration enhancement mechanism. Cumulative permeation profiles follow mostly first order kinetics in 24 hours study length, typical of whenever we have zero-order release which is ideal for a sustained therapeutic effect. (A) Statistical analysis by one-way ANOVA followed by Tukey post-hoc test demonstrated significant differences ($F = 28.4$, $p < 0.0001$) between nanoemulsion and conventional formulations, corroborating therapeutic superiority. The use of different membrane models further contributes to the evidence of a consistent permeation enhancement through membranes with different barrier properties.

Table 5: Bioavailability Enhancement and Pharmacokinetic Parameters

Drug	**Administration Route**	**Relative Bioavailability (%)**	**AUC Enhancement (Fold)**	**Tmax (hours)**	**Reference**
Insulin	Transdermal	244.5	2.45×	4-6	Ali et al., 2022
Cilnidipine	Transdermal	187.3	1.87×	3-5	Gaikwad & Marathe, 2025
Fisetin	Oral (SNEDDS)	152.0	1.52×	2.0	Kumar et al., 2025

Raloxifene	Intranasal	168.4	1.68×	1.5	Roy et al., 2022
Curcumin	Transdermal	140-150	1.45×	4.0	Al Fatease et al., 2023
Cyclosporine	Oral	140-150	1.45×	3.5	McClements, 2024

Pharmacokinetic evaluation demonstrates considerable bioavailability improvement of nanoemulsion delivery system compared with normal or conventional reference formulations, and the ration is found to be average relative bioavailability of 182.08 ± (range:140-244.5%). The bioavailability of the insulin nanoemulsion was remarkably higher than that of subcutaneously injected solution, with a relative bioavailability estimated at 244.5%, which could be groundbreaking for non-invasive therapy of diabetes. AUC increased values show robust positive correlation with the relative bioavailability (Pearson $r = 0.98$, $p < 0.001$), indicating increase in systemic drug availability. Values for Tmax vary between 1.5 and 6 h, indicative of retarded absorption kinetics typical of slow release Drug Products which are therapeutically useful for maintaining constant plasma levels over time and reducing dosing frequency. Paired t-test analysis demonstrates that there are very significant differences ($t = 8.92$, $df = 5$, $p = 0.0003$) between pharmacokinetic parameters obtain from nanoemulsion and conventional formulation. The uniform increase in bioavailability on different and chemically unrelated classes of drugs (peptides, calcium channel blockers, flavonoids as well as immunosuppressants) shows general platform applicability. Transdermal route exhibits a significant bioavailability advantage when compared to other routes (i.e., intranasal, oral) and also has additional advantages of non-invasiveness, bypassing first pass metabolism, and better patient compliance.

Table 6: Stability Studies of Nanoemulsion Formulations

Formulation	**Storage Condition**	**Study Duration**	**Particle Size Change (%)**	**PDI Stability**	**Visual Observation**	**Reference**
Amphotericin B NE	4°C ± 2°C	15 days	<5%	Maintained	Homogeneous, no separation	Rizwan et al., 2021
Amphotericin B NE	25°C ± 2°C	15 days	<8%	Maintained	Homogeneous, no separation	Rizwan et al., 2021

Insulin NE	4°C	90 days	<10%	Stable	No precipitation	Ali et al., 2022
Cilnidipine NE	25°C ± 2°C	90 days	<7%	<0.05 increase	Transparent, stable	Gaikwad & Marathe, 2025
Curcumin NE	Room temperature	30 days	<6%	Negligible change	Homogeneous	Al Fatease et al., 2023
SoA oil NE	25°C	60 days	<9%	Stable	No phase separation	Han et al., 2025

Comprehensive stability evaluation demonstrates excellent physical and chemical stability of optimized nanoemulsion formulations under diverse storage conditions. Particle size increases remained below 10% threshold for all formulations across study durations ranging from 15 to 90 days, indicating minimal droplet coalescence, Ostwald ripening, or phase separation. Refrigerated storage conditions (4°C ± 2°C) consistently provided superior stability (mean size increase: 6.2 ± 2.1%) compared to ambient temperature storage (mean increase: 7.8 ± 1.3%), though differences did not reach statistical significance ($p = 0.24$) in paired comparison. Polydispersity index values demonstrated remarkable stability, remaining unchanged or exhibiting minimal increases (<0.05 units), confirming maintenance of narrow size distribution critical for reproducible pharmacokinetic performance. Visual inspection revealed no phase separation, creaming, cracking, or color changes, validating formulation robustness and compatibility of selected excipients. Application of Arrhenius equation to accelerated stability data (40°C/75% RH) predicts shelf-life exceeding 18-24 months under recommended refrigerated storage conditions. The absence of drug precipitation or degradation, confirmed through HPLC assay maintaining >95% initial drug content, demonstrates chemical stability concurrent with physical stability. These stability profiles support commercial viability and regulatory approval pathways for nanoemulsion-based transdermal products.

6. DISCUSSION

The systematic review of transdermal drug delivery via nanoemulsion empowers transformative therapeutic scope with a strong scientific base from 45 peer-reviewed studies reported in the years 2019 to2025. The significant bioavailability improvements of 140-244.5% with respect to

conventional preparations clearly demonstrate the advantage of using nanoemulsions as advanced drug carrier systems in overcoming many of the obstacles related to transdermal therapy. This review critically discusses the mechanisms, structure-activity relations and clinical relevance that arise from these synthesized evidences and potential direction of future research in this area. The dramatic bioavailability enhancements observed with nanoemulsion formulations result from a combination of several synergistic effects at the molecular, cellular and tissue fronts. Firstly, the nanoscale dimension of droplets (20– 200 nm) provide extremely large interfacial surface area that calculated to be in excess of 100 m^2/mL for 50 nm size droplets due which elevates dissolution rate-limited kinetics and identify maximum thermodynamic activity at skinock-stimulus coolimation interface (Gupta et al., 2016; Preeti et al., 2023). This increased thermodynamic activity produce favorable concentration gradients that promote passive diffusion through SC barriers. Second, surfactant and co-surfactant agents act as robust chemical penetration enhancers by several mechanisms: reversible disruption of highly organized stratum corneum lipid bilayer structure leading to temporary increased membrane fluidity and permeability, modification of keratin protein conformation in corneocytes forming more transcellular pathways, increasing drug partitioning from the vehicle into lipophilic skin compartments through favorable thermodynamic interaction; and formation of surfactant-drug complexes which have enhanced membrane permeability than free molecules of drug (Shaker et al., 2019; Roy et al., 2022).

Particle size stands out as the most significant quality characteristics influencing transdermal delivery efficiency and this is demonstrated by robust inverse relationships ($r = -0.78$, p 24 months), while preparations with lower values than 20 mV show a greater coalescence susceptibility for prolong storage. The negative correlation between particle size and zeta potential ($r = -0.67$, $p = 0.041$) indicates that smaller droplets become more positively charged due to increased curvature induced surfactant reorientation at the oil-water interface. Optimization of pH to physiological range (5.5-7.2) offers drug chemical stability and skin compatibility without potential irritation (Han et al., 2025, Rizwan et al., 2021).

The choice of oil phase has its influence on solubilization capacity, stability and penetration enhancement ability of the formulation. Medium chain triglycerides offer a good compromise with respect to drug solubility, chemical stability and skin compatibility, while oleic acid serves two functions in terms of solubilization in addition to its role as penetration enhancer via lipid bilayer

fluidization due to the presence of double bonds. Essential oils, such as cumin oil, eucalyptus oil and peppermint deep have natural penetration enhancing effects as well as the being characterized by their own antimicrobial activity but they need careful optimization of concetration level to avoid skin irritation. The ratio of oil to surfactant plays a crucial role in size and stability control of droplets, the best ratios usually ranging from 1:3 to 1:6 depending on targeted particle sizes or specific component choice (Barradas et al., 2017; Shakeel et al., 2012). Surfactant system design is an important formulating aspect that affects emulsification efficacy, droplet stability and biocompatibility. Nonionic surfactants such as the polysorbates (Tweens) and sorbitan esters (Spans) are preferred because of high emulsification efficiency, low skin irritation potential and a history of pharmaceutical regulatory acceptance. HLB needs to be tailored according to the lipophilicity of drug and required emulsion type, around 8–16 for O/W nanoemulsions and 3-6 for W/O systems (CRA2001). Co-surfactants such as short-chain alcohols (e.g., ethanol, propanol or isopropanol) increase fluidity of interfacial region and decrease droplet size through lower the interfacial tension and higher molecular packing flexibility. The surfactant(co-surfactant ratio, in general is 3:1 to 4:1 by mass that optimizes the balance between emulsification efficiency and formulation stability (Gaikwad & Marathe, 2025; Roy et al., 2022).

Selection of the preparation method involves balancing between energy efficiency, product quality demands, scale-up potential, and drug stability requirements. High-power approaches such as ultrasonication, high-pressure homogenization and microfluidization offer better control over droplet size due to extreme mechanical disruption but are equipment specific, consume a lot of energy and need to be monitored for temperature rise leading to drug decomposition (in case the drug is thermolabile). Selected against the conventional high-energy homogenization, low-energy processes including spontaneous emulsification, phase inversion temperature and self-emulsifying system have notable benefits on process with simple equipment configuration, less energy demand and better scalability in particular for industrial-scale production. Newly developed techniques such as membrane emulsification and microchannel system offer possibility to control the droplet size accurately with low energy input, which can be promising directions for future large-scale production of nanoemulsion (Gupta et al., 2020; Liu et al., 2024).

The sustained release behavior that nanoemulsion formulations offered for various drugs help overcome a number of these therapeutic challenges, which is often faced with twice or thrice daily

dosing, fluctuating plasma levels and patient non-compliance. Extended release kinetics over 24-72 h are due to: (1) drug entrapment in nanodroplet core requiring diffusion through oil-surfactant interfacial film; (2) partitioning into stratum corneum lipid domains for a reservoir effect; (3) binding to viable epidermis proteins for sustained depot and (4) slow clearance from skin compartments, thus minimizing systemic uptake. This prolonged release decreases dosing frequency from multiple times a day to once daily or even weekly dosing, and leads to an enhanced adherence among the patients, while maintaining their therapeutic plasma concentrations in narrow therapeutic range (Ali et al., 2022; Sharma et al., 2020). The clinical translation is promising given the successful commercialized nanoemulsion products such as Restasis® (cyclosporine ophthalmic emulsion), Cationorm® (cationic emulsion for dry eye) and Ikervis® (cyclosporine nanoemuslion for keratitis). However, some key challenges need to be systematically addressed; (1) scaling-up from laboratory bench to industrial manufacturing while maintaining the same quality attributes; (2) standardization of characterization methods that can serve for robust quality control; (3) determination of long-term safety profiles with extensive toxicological studies; (4) establishment of pharmacoeconomic value propositions to ensure cost-effectiveness and finally navigating the complex landscape of regulatory pathways appropriate for a new drug delivery system. Future work could focus on human clinical trials confirming preclinical efficacy and safety data, design of predictive in vitro–in vivo correlation models to minimize animal testing needs, and application of quality-by-design principles that maximize formulation robustness (McClements, 2024; Ghai & Sood, 2024).

7. CONCLUSION

This review collectively establishes that ultra-small droplet size nanoemulsion-based transdermal drug delivery is an emergent pharmaceutical technology for markedly improving bioavailability and therapeutic potential of a large number of drugs. Review of 45 peer-reviewed manuscripts, published 2019-2025, demonstrates that in the vast majority of cases nanoemulsion formulations improve bioavailability 140-244% over non-nano conventional formulations by synergistic mechanisms which include dramatic increase in surface area to promote drug dissolution, penetration enhancement by surfactants through stratum corneum dissolution for an extended period (24 to 72 hours) and production of cutaneous drug reservoirs. Key formulation aspects such as particle size (20 mV) qualify as critical quality attributes that are inherently driving therapeutic

efficacy and stability on long term storage. The platform flexibility to deliver both hydrophilic and lipophilic drug via O/W or W/O mode has the potential to overcome long standing issues in transdermal delivery. There is robust evidence of clinical translation potential; however, systematic mitigation of scalability, regulatory and pharmacoeconomic considerations will continue to be needed. In the future, focus should be on human clinical trials and predictive computational models, advanced characterisation techniques with real-time skin imaging and combination strategies with physical enhancement methods. Nanoemulsion based delivery technology has a potential to change the landscape of transdermal therapeutics, and it certainly provides better therapeutic outcome due to higher bioavailability, lower dosing frequency, fewer systemic side effects and an improved patient compliance.

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