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Review Article

Nanoemulsion-Based Drug Delivery Systems: Formulation Strategies, Characterization, Therapeutic Applications, and Translational Challenges

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ABSTRACT

Nanoemulsions are kinetically stable dispersions of two immiscible liquid phases, generally stabilized by surfactants and sometimes co-surfactants. Their small droplets and adaptable interfacial chemistry have made them candidates for delivering poorly water-soluble drugs, protecting selected labile compounds, and tailoring drug presentation across oral, dermal, ocular, nasal, and parenteral routes. This review examines formulation components, high- and low-energy preparation, self-emulsifying systems, quality-by-design (QbD), physicochemical characterization, stability, therapeutic applications, and barriers to translation. The discussion synthesizes the supplied draft and selected traceable literature, including recent reviews and regulatory guidance. It emphasizes that nanoemulsions are not universally superior carriers: outcomes depend on drug properties, excipient tolerability, digestion and release behavior, administration route, and study quality. Droplet size alone cannot establish quality or clinical benefit. Important gaps include inconsistent terminology, short stability studies, overreliance on in-vitro endpoints, incomplete reporting, limited head-to-head comparisons, and insufficient clinical evidence for many advanced systems. Future development should connect critical quality attributes to pharmacokinetic and therapeutic outcomes, apply route-appropriate safety testing, report reproducible manufacturing parameters, and assess scale-up and regulatory requirements early. This article is a narrative review and does not claim to be a systematic review or meta-analysis. The discussion synthesizes foundational publications, selected primary studies,

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recent reviews, and regulatory guidance relevant to formulation design, characterization, route-specific performance, safety, and translation. Because no protocol-driven screening or quantitative synthesis was undertaken, the conclusions should be interpreted as a critical narrative synthesis rather than an exhaustive ranking of all available evidence.

INTRODUCTION

Poor aqueous solubility is a recurring challenge in pharmaceutical development because dissolution can limit the rate and extent of drug absorption. Lipid-based formulations provide one strategy for presenting lipophilic molecules in a solubilized or finely dispersed state. Depending on composition, these systems can influence digestion, membrane partitioning, and drug transport.

Nanoemulsions (NEs) are attractive because their interfacial area and composition can be adjusted to suit different active pharmaceutical ingredients (APIs) and administration routes [1–5].

A formulation should not be judged solely by its initial appearance or a single nanoscale size measurement. The drug must remain acceptably stable, be released or transferred at a useful rate, and avoid unacceptable toxicity. A carrier that performs well in one route or with one molecule may perform poorly with another. A strong review therefore needs to separate formulation feasibility from evidence of pharmacokinetic improvement and from evidence of therapeutic benefit [1–4].

This article focuses on the formulation and evaluation of nanoemulsion-based drug delivery systems. It covers terminology, composition, preparation, optimization, analytical characterization, stability, route-specific applications, translational challenges, and future research needs. The emphasis is on critical interpretation: which findings are broadly useful, which are formulation-specific, and which remain too preliminary to support clinical conclusions.

1.2 Review scope and approach

The present manuscript expands the previously supplied draft and uses its core organization: fundamentals, formulation, preparation, characterization, stability, therapeutic applications, scale-up, and future directions. Selected peer-reviewed publications and regulatory guidance provide additional context. The approach is narrative; no protocol was registered, no formal duplicate screening was performed, and no statistical meta-analysis was undertaken. It should not be described as a systematic review unless a reproducible database search and selection process is subsequently completed.

For a stronger final submission, the author should document databases searched, search dates,

keywords, inclusion and exclusion criteria, and how the evidence was screened. Primary research should be distinguished from review articles. Where possible, the manuscript should report the formulation composition, comparator, model, endpoints, principal findings, and limitations of individual studies rather than relying only on broad claims from reviews.

1. Fundamentals and terminology

Nanoemulsions are dispersions in which one immiscible liquid is distributed as droplets within another liquid, with surfactants or other interfacial agents helping to maintain the dispersed structure. Oil-in-water (O/W) systems contain oil droplets in a continuous aqueous phase; water-in-oil (W/O) systems contain water droplets in a continuous oil phase. Multiple emulsions contain nested dispersed phases and can provide additional compartmentalization, but their structure is more complex and often harder to stabilize.

The term nanoemulsion is used inconsistently across pharmaceutical, food, cosmetic, and materials research. Some publications define systems by a particular droplet-size interval, while others emphasize optical appearance or preparation method. Since measurement depends on the analytical technique and sample conditions, manuscripts should report the size distribution and method rather than rely on the label alone [1,2,6].

Nanoemulsions are generally kinetically stable, not thermodynamically stable. They can remain dispersed for useful periods, but their free energy and interfacial structure mean that physical changes may occur over time. This distinction is central to interpreting stability data and to avoiding inaccurate comparisons with microemulsions [1,2].

1.1 Nanoemulsions, microemulsions, and SNEDDS

Microemulsions are thermodynamically stable, isotropic systems formed within suitable composition regions. Nanoemulsions are typically kinetically stabilized dispersions and may eventually undergo droplet growth or separation. Although both can appear clear or translucent and can improve the apparent solubilization of lipophilic compounds, their phase behavior and formulation requirements differ. The terms should not be used interchangeably [1,2,7].

Self-nanoemulsifying drug delivery systems (SNEDDS) are usually anhydrous preconcentrates containing oil, surfactant, and often a co-solvent or co-surfactant. When exposed to aqueous media and agitation, they form fine dispersions. Their performance depends on dilution, composition, digestion, and the drug's propensity to precipitate. Thus, an SNEDDS formulation should be characterized after dispersion under relevant conditions rather than solely as a concentrate [7–10].

These distinctions matter for experimental design. A preconcentrate that forms small droplets immediately after dilution may later show precipitation or a changed size distribution. A thermodynamically stable microemulsion has different expectations for phase behavior. A conventional nanoemulsion may require more extensive physical-stability testing. Clear definitions make evidence synthesis and regulatory communication more reliable.

1.2 Physicochemical basis of delivery

Reducing droplet diameter increases the interfacial area available for interactions between oil, water, surfactant, and drug. This may improve dispersion and can influence drug transfer during digestion or contact with biological membranes. However, droplet size does not independently determine drug release, absorption, tissue distribution, or therapeutic response. Drug partitioning, interfacial composition, viscosity, and the surrounding biological environment also matter [3,11–14].

For oral formulations, digestion of the oil phase can produce colloidal structures that maintain some lipophilic drugs in a solubilized state. Other drugs may precipitate as the formulation is diluted or digested. For topical systems, the drug must partition from the formulation into the skin; increased permeation may be useful for systemic delivery but may not be the desired endpoint for local therapy. Ocular and nasal products must also account for clearance, residence time, and tissue tolerability.

Mechanistic explanations should be tested rather than inferred from a favorable size result. If a study claims improved absorption, it should include an appropriate comparator and pharmacokinetic endpoint. If it claims local targeting, tissue distribution or local pharmacodynamic data are more persuasive than droplet size alone.

2. Formulation components

The oil phase influences drug solubility, digestion, interfacial behavior, and stability. Candidate materials can include medium-chain or long-chain lipids and pharmaceutically acceptable oil-like excipients. Selection should be based on the API's solubility and stability, the intended dose, route, and the possibility of drug precipitation after dilution or digestion. The oil should not be chosen only because it produces the smallest initial droplets [2,7,9].

Surfactants reduce interfacial tension and help create and maintain droplets. Non-ionic surfactants are common in some formulations, but the appropriate choice depends on route, concentration, compatibility, and safety. A surfactant concentration sufficient to form a small droplet may still be

undesirable if it causes irritation, alters biological membranes, or creates a high excipient burden. Co-surfactants and co-solvents can widen the formulation region, but may also change drug precipitation after dilution.

The aqueous phase may include buffers, preservatives, antioxidants, viscosity modifiers, or tonicity-adjusting agents. Each additional ingredient can affect pH, ionic strength, interfacial behavior, drug degradation, and biological tolerability. For products intended for sensitive routes, such as ocular or parenteral administration, excipient selection requires route-specific justification rather than extrapolation from oral or topical use [15,16].

2.1 Drug and excipient screening

An efficient screening workflow begins by measuring the drug's solubility in candidate oils, surfactants, and co-solvents. Chemical compatibility and degradation risk should be considered early. A high apparent solubility value is useful only if the drug remains stable and does not precipitate when the formulation encounters aqueous media. Screening should include the expected dose and the amount of excipient that would be administered at that dose.

Emulsification screening can then compare candidate combinations under standardized mixing and dilution conditions. Pseudo-ternary phase diagrams can identify composition regions where fine dispersions form, but these diagrams do not prove long-term stability or clinical suitability. The selected formulation should be checked for size distribution, drug content, physical appearance, chemical integrity, and performance after dilution.

For oral products, in-vitro lipolysis and precipitation testing may provide useful insight. For topical products, drug partitioning and skin compatibility should be examined. For parenteral products, sterility, endotoxin, hemocompatibility, and particle-related risks are central. The same excipient system cannot be assumed acceptable across all routes [7,9,15,16].

2.2 Interfacial chemistry and composition

The interfacial layer is not simply a passive boundary. Surfactant type, concentration, packing, and interactions with co-surfactants can influence droplet formation, surface charge, and response to environmental changes. Ionic strength and pH may alter the behavior of charged surfactants, while steric stabilization can remain important even when the measured zeta potential is modest.

Accordingly, zeta potential should not be treated as a universal predictor of stability.

Changing oil composition may alter both the drug's location within the droplet and the rate at which the oil phase is digested or exchanged. These changes can influence release and biological fate. A rational formulation study should avoid changing several composition variables at once without a design that can distinguish their effects. Factorial or response-surface designs can help reveal interactions that single-factor optimization may miss [17–20].

3. Preparation methods

Preparation methods are commonly grouped into high-energy and low-energy approaches. High-energy methods apply mechanical input to break larger droplets into smaller ones. High-pressure homogenization and microfluidization can be suitable for scale-up when pressure, number of passes, temperature, and feed composition are controlled. Ultrasonication is widely used at laboratory scale but can produce local heating and may be difficult to translate directly to larger batches [2,6,17].

The resulting size distribution is influenced by the balance between droplet disruption and recoalescence. Greater energy input does not guarantee a proportionate improvement: energy demand, heating, process time, and equipment wear may increase. The optimum process is the one that consistently meets the target quality attributes with acceptable cost and manufacturing control, not necessarily the one that achieves the smallest reported mean diameter.

Method descriptions should include equipment type, batch volume, pressure or amplitude, pass number, processing time, temperature control, and order of addition. Without these details, reproducibility is difficult to assess and comparisons between studies can be misleading.

3.1 High-pressure homogenization and microfluidization

High-pressure homogenization forces a coarse emulsion through a narrow valve or interaction region, where intense shear, turbulence, and pressure changes disrupt droplets. Microfluidization uses defined interaction chambers to generate high-energy mixing. Both methods can produce small droplets, but the outcome depends on formulation viscosity, oil fraction, surfactant coverage, and processing conditions.

Repeated passes may reduce droplet size up to a point, after which further processing may yield diminishing returns or increase temperature and degradation risk. The number of passes should therefore be optimized

together with product temperature and drug stability. Scale-up should consider throughput, energy density, cooling capacity, and equipment-specific differences rather than assuming that the same nominal pressure will produce an identical product at every scale.

3.2 Ultrasonication

Ultrasonication can be convenient for laboratory preparation because cavitation produces intense local mixing and droplet disruption. It can be useful for screening, small batches, and proof-of-concept studies. Nevertheless, the delivered energy depends on probe geometry, immersion depth, vessel dimensions, amplitude, pulse pattern, sample volume, and cooling.

Local heating can accelerate drug degradation or change the interfacial behavior of surfactants. Probe erosion or contamination may also be relevant. A reproducible report should specify the sonicator, amplitude or power setting, duration, pulse mode, sample volume, and temperature control. Direct scale-up from a small probe system should not be assumed feasible without process development.

3.3 Low-energy emulsification

Low-energy methods use changes in composition or temperature to promote interfacial curvature changes and spontaneous formation of fine droplets. Phase-inversion composition and phase-

inversion temperature methods are examples. Their appeal is that they may reduce mechanical energy requirements, but success depends on the oil, surfactant system, temperature, and path through composition space [2,6,18].

A narrow operating window can make these methods sensitive to ingredient variation and temperature history. The sequence of addition and the point at which water or oil is introduced may influence the final product. Reports should describe the composition path, temperature profile, mixing conditions, equilibration time, and final dilution conditions. Claims of easy scale-up require actual process evidence.

3.4 Self-emulsifying formulations

Self-emulsifying systems can simplify administration of lipophilic drugs by generating fine dispersions after contact with aqueous fluids. Their preconcentrates may contain substantial surfactant or co-solvent levels, so the excipient burden should be calculated at the intended dose. Dispersion behavior also depends on the aqueous medium and mixing conditions.

Testing should include dispersion time, droplet-size distribution after dilution, precipitation, and behavior under physiologically relevant pH and digestion conditions. A formulation that performs well in purified water may behave differently in gastrointestinal media. In-vitro dispersion alone is therefore not sufficient to demonstrate improved oral bioavailability [7–10].

4. Quality-by-design and optimization

Quality-by-design (QbD) connects the target product profile with material attributes, process parameters, and critical quality attributes (CQAs). It encourages developers to identify what must be controlled to achieve consistent performance, rather than relying on a single optimized batch. For nanoemulsions, potential CQAs include droplet size and distribution, drug content, free-drug fraction, pH, viscosity, chemical impurities, microbial quality, and stability.

Potential critical process parameters include homogenization pressure, pass number, sonication energy, temperature, mixing time, order of addition, and cooling profile. Risk assessment can prioritize variables likely to affect product quality. Factorial designs and response-surface methods can estimate main effects and interactions, but model predictions must be confirmed with independent batches [5,19].

Optimization targets should be justified scientifically. For example, minimizing droplet size at all costs may increase surfactant concentration or processing energy without improving the drug's release or bioavailability. A multi-response design may instead balance size distribution, drug loading, stability, safety, and process practicality. The final design space should be supported by data, not only by statistical fit.

4.1 Critical quality attributes

Droplet size and distribution are important because they describe the dispersed structure, but they are only part of the quality profile. Drug content and degradants establish dose accuracy and chemical stability. pH,

viscosity, osmolality, and appearance may be important depending on route. Sterility and endotoxin are essential for products intended for parenteral use. A CQA list should be tailored to the dosage form and intended clinical use.

4.2 In-vitro release and permeation

In-vitro release tests can compare formulations under defined conditions, but the setup can influence the result. Membrane binding, sink conditions, receptor-medium composition, surfactant effects, and the membrane's resistance may become rate-limiting. A dialysis-based test can measure release through the apparatus as much as release from the carrier if the method is not appropriately designed.

For oral systems, lipolysis and precipitation tests may better represent some aspects of digestion and drug transfer. For topical systems, skin retention should be distinguished from passage into the receptor compartment. The test model, exposed area, donor concentration, receptor conditions, sampling, and mass balance should be reported. In-vitro performance should not be presented as proof of in-vivo efficacy without supporting evidence [3,11–14,21].

4.3 Biological fate and pharmacokinetics

The biological fate of a nanoemulsion depends on composition, droplet attributes, route, and the behavior of the drug after administration. Lipid digestion, protein adsorption, uptake by cells, and distribution to tissues may change the formulation after it enters a biological environment. For parenteral products, particle size can affect distribution and clearance, but such relationships must be interpreted in the context of the particular formulation and animal or human model [32,33].

Pharmacokinetic studies should include appropriate comparators, a justified sampling schedule, validated analytical methods, and clear reporting of dose and route. Relevant endpoints may include maximum concentration, time to maximum concentration, area under the concentration-time curve, and half-life, but these parameters do not automatically establish therapeutic superiority. Changes in exposure must be interpreted alongside safety and pharmacodynamic outcomes.

The target range for each attribute should be set before final validation. If acceptance criteria are chosen only after results are observed, there is a risk of bias. Batch-to-batch variability should be assessed using independent preparations, and analytical methods should be suitable for the sample matrix. The chosen CQAs should ultimately be linked to product performance and safety.

5. Characterization

Dynamic light scattering (DLS) is commonly used to estimate hydrodynamic diameter and polydispersity index (PDI). However, results can be influenced by dilution, viscosity, refractive-index assumptions, concentration, and a small number of larger droplets. Authors should report

sample preparation and instrument conditions and should avoid treating a single DLS value as a complete description of the dispersion [2,6,19,20].

Zeta potential describes electrokinetic behavior under stated measurement conditions. It may provide useful information for charged systems, but a low absolute value does not necessarily mean instability when steric stabilization dominates. Electron microscopy can show morphology, although drying, staining, freezing, or other sample-preparation steps may alter the observed structure. Orthogonal methods can strengthen interpretation when the claim depends on detailed morphology or distribution.

5.1 Packaging and storage

Packaging can influence oxidation, evaporation, adsorption, and exposure to light. Headspace, container material, closure integrity, and compatibility with surfactants or oils should be considered. For products containing oxidation-sensitive lipids or drugs, oxygen control and suitable antioxidants may be useful, but their effectiveness must be demonstrated analytically.

Storage conditions should reflect intended distribution and use. A product that is stable in a laboratory vial may behave differently in its final packaging or after repeated opening. In-use stability and compatibility with administration devices may also matter. These issues should be addressed early enough to influence

formulation selection rather than being postponed until late development.

Drug assay, association or encapsulation efficiency, free-drug fraction, pH, viscosity, release, and stability should be included as appropriate. Method validation is particularly important where surfactants, oils, or excipients interfere with detection. A complete characterization package is route- and product-specific; it should be designed around the quality and performance claims being made.

6. Physical and chemical stability

Nanoemulsions may undergo Ostwald ripening, flocculation, coalescence, creaming, or sedimentation. Chemical changes may include drug degradation, lipid oxidation, pH drift, or loss of preservative effectiveness. These phenomena are distinct and may occur simultaneously. A visually unchanged sample may still have developed a broader size distribution or lost drug potency.

Ostwald ripening is driven by differences in pressure and solubility between droplets of different sizes. Oil selection and appropriate ripening inhibitors may reduce this process, although the candidate excipients must remain acceptable for the intended route. Recent research continues to examine how composition and interfacial properties affect resistance to ripening [22].

Stability claims should specify storage conditions, container closure, light and oxygen exposure, sampling schedule, analytical methods, and predefined acceptance criteria. Real-time and accelerated studies serve different purposes. Freeze–thaw and centrifugation tests may support early screening but do not replace appropriately designed stability studies. For sterile products, processing and sterilization can change droplet attributes and drug integrity and must be evaluated [20,23]

7. Therapeutic applications: overview

Nanoemulsions have been investigated for oral, dermal/transdermal, ocular, nasal, parenteral, and intra-articular delivery. Their potential varies by route, drug, and product objective. A carrier may be useful for solubilization but less useful for targeting; it may improve local retention but not systemic exposure. The level of evidence differs across applications, and preclinical proof-of-concept should be separated from established clinical utility [3,4,24].

The sections below summarize route-specific rationales and evaluation questions. Selected primary studies are summarized in Table 3 to distinguish reported preclinical findings from evidence of clinical benefit.

7.1 Oral delivery

Oral lipid-based formulations may improve the apparent solubility and absorption of selected lipophilic drugs. Digestion can move a drug into mixed colloidal structures, but dilution and digestion may also cause precipitation. Therefore, the formulation's behavior in water alone may not predict gastrointestinal performance.

An ibuprofen-loaded nanoemulsion study illustrates the use of formulation development and bioavailability assessment [25]. Work on oral hydrogel nanoemulsion co-delivery for inflammatory bowel disease illustrates a different strategy in which the carrier is combined with a local-delivery platform [26]. These examples should not be generalized to all poorly soluble drugs. Drug loading, food effects, dose, excipient tolerability, and comparative pharmacokinetics remain important.

A well-designed oral study should compare the nanoemulsion with a clinically relevant reference formulation. It should examine the drug's solubility and precipitation under biorelevant conditions,

use validated pharmacokinetic assays, and report variability. A statistically significant increase in exposure may still be insufficient if the dose, tolerability, or variability is unacceptable.

7.2 Dermal and transdermal delivery

Topical nanoemulsions have been explored to improve spreading, drug solubilization, skin deposition, and permeation. The oil phase, surfactant composition, drug partitioning, droplet characteristics, and viscosity all affect performance. A formulation intended for local skin treatment may need to retain drug in the skin rather than maximize transport into systemic circulation [11,12,27].

Evaluation should distinguish surface deposition, retention within skin layers, and passage into the receptor

compartment. A high permeation result may reflect barrier disruption, which could be undesirable or unsafe. Skin irritation, sensitization, barrier integrity, and repeated-dose effects should be assessed where relevant. The test model and mass balance should be clearly reported.

For cancer or inflammatory skin applications, claims of improved therapeutic response should be supported by appropriate biological models and comparators. A favorable release profile is useful but does not establish that the drug reaches the target tissue at an effective and safe concentration. Formulation viscosity and patient acceptability may also influence use.

7.3 Ocular delivery

Ocular products must balance solubilization and residence time with comfort, transparency, sterility, and ocular-surface safety. Nanoemulsions have been explored for ophthalmic delivery, including systems intended to improve retention or deliver drugs and genetic material to ocular tissues [4,29]. However, a favorable droplet size or in-vitro release profile is not sufficient evidence of improved ocular bioavailability.

Important measurements may include pH, osmolality, visual clarity, droplet distribution, sterility, preservative effectiveness where applicable, and ocular tolerability. The formulation should be evaluated in a way that reflects the intended dosing route and tissue. For advanced delivery claims, in-vivo distribution and pharmacodynamic evidence are needed.

Ocular delivery also illustrates why excipient safety cannot be generalized across routes. Ingredients tolerated in oral products may not be suitable for repeated ocular exposure. The concentration, frequency of administration, and duration of use must be considered when selecting the surfactant and other excipients.

7.4 Nasal and nose-to-brain delivery

Nasal nanoemulsions have been studied for local treatment and potential delivery to the central nervous system. The nasal route is influenced by mucociliary clearance, epithelial integrity, residence time, drug permeability, and the balance between local absorption and systemic exposure. Claims of direct nose-to-brain delivery require evidence that distinguishes transport pathways and distribution patterns.

Clozapine nanoemulsion-based in-situ gels illustrate the combination of a nanoemulsion with a viscosity-changing platform [31]. Such approaches may increase residence time, but increased viscosity can also affect release and administration. Preclinical findings do not establish clinical effectiveness; tolerability and repeat-dose safety remain important.

Studies should specify the device, administered volume, dose, deposition model, and relevant tissue or pharmacokinetic endpoints. A useful study should also assess nasal irritation and mucosal integrity. Direct comparison with a suitable conventional formulation helps establish whether the carrier adds meaningful value.

7.5 Parenteral and oncology applications

Parenteral nanoemulsions must meet stringent requirements for sterility, endotoxin, particle characteristics, hemocompatibility, and excipient safety. The formulation must remain compatible with the intended administration route and avoid unacceptable changes during storage or administration. Sterilization and filtration can affect the product and therefore require validation.

Lipid nanoemulsions have been investigated as carriers for poorly soluble anticancer agents and drug combinations. Co-delivery of paclitaxel and docosahexaenoic acid is one example of a targeting-oriented strategy [35]. Research on particle size and pharmacokinetics highlights that physical attributes can influence distribution and exposure [32]. These findings require careful interpretation because the effect of size may depend on composition, surface properties, dose, and biological model.

A credible oncology study should include relevant controls, a clear dosing rationale, pharmacokinetic or

tissue-distribution data, efficacy endpoints, and toxicity assessment. Targeting claims should be supported by quantitative evidence rather than inferred from the presence of a targeting ligand. Clinical translation requires reproducible manufacturing and a favorable safety profile, not only tumor inhibition in a preclinical model.

7.6 Vaccines, theranostics, and emerging applications

Research has explored nanoemulsions for vaccine delivery, imaging-linked systems, and multifunctional formulations. These applications may require surface functionalization, nucleic-acid protection, immune-response characterization, or targeted tissue distribution. Intranasal mRNA vaccine carriers illustrate the interest in combining delivery and immunological functions [31,34].

A multifunctional formulation can also increase development complexity. Each added component may alter stability, biological fate, manufacturability, or regulatory classification. The design should therefore start from a specific unmet need and a measurable advantage, rather than adding features without a clear purpose.

Emerging applications should be described with appropriate evidence qualifiers. A preclinical platform is a research candidate, not an established therapy. Translation requires repeatable manufacture, characterization of biological fate, route-appropriate safety, and a practical clinical administration strategy.

8. Critical discussion of the evidence

The most defensible overall conclusion is that nanoemulsions are adaptable formulation tools rather than universally superior delivery systems. Benefits are most persuasive when a study uses a relevant comparator, provides adequate physicochemical characterization, tests a plausible mechanism, and measures pharmacokinetic or pharmacodynamic outcomes. Reviews are useful for mapping the field, but claims about a particular drug should be traced to primary studies whenever possible [1–4,6,7].

A recurring weakness is the use of droplet size as a surrogate for performance. Smaller droplets can increase interfacial area but do not guarantee drug retention, absorption, tissue targeting, stability, or safety. Another weakness is heterogeneous terminology: some papers use “nanoemulsion” for

systems that may instead be microemulsions, lipid nanoparticles, or self-emulsifying preconcentrates. These differences complicate cross-study comparisons.

Study design also varies substantially. Oil composition, surfactant concentration, drug loading, route, dosing conditions, animal model, and analytical method may all differ. A result from one model may not transfer to another. Narrative reviews should make these limits explicit rather than presenting all positive findings as equally strong evidence.

8.1 Contradictions and sources of variability

Reported outcomes can conflict because the formulations are not directly comparable. A high surfactant concentration may improve emulsification while worsening tolerability. Increased viscosity may improve residence time while slowing drug release. Stronger skin permeation may be beneficial for systemic delivery but undesirable for a local treatment. The same drug can behave differently in different oils because partitioning and digestion vary.

Variability also arises from analytical methods. DLS measurements can differ with dilution and sample conditions; release tests may be limited by membrane resistance; and different animal models can show different pharmacokinetics. A robust study should describe these methods in enough detail for replication and should avoid comparing numerical values generated by incompatible methods without qualification.

Publication bias is another concern. Optimized formulations with favorable results may be more likely to be reported than failed compositions or negative findings. Including unsuccessful formulations, batch variability, and adverse results would help the field identify which design rules are genuinely generalizable.

8.2 Limitations of the current literature base

The literature includes many narrative reviews and a large number of formulation-specific preclinical studies. These sources are useful for identifying methods and hypotheses but do not provide equivalent evidence

of clinical benefit. A review that relies too heavily on other reviews risks repeating broad claims without evaluating the original experiments.

A stronger final manuscript should include a table of selected primary studies, with columns for API, oil/surfactant composition, preparation method, size/PDI, comparator, model, key outcome, and major limitation. The table should not simply list favorable outcomes; it should reveal where methods and results disagree. The author should verify the full texts and bibliography before adding detailed numerical claims.

9. Translational and regulatory challenges

Translation requires more than successful laboratory preparation. Scale-up can alter energy density, temperature history, mixing, and droplet distribution. Sterilization or filtration may change product attributes or fail to address contaminants without altering the formulation. Packaging, oxygen exposure, extractables and leachables, microbial control, and long-term stability can become critical.

FDA guidance emphasizes careful characterization of drug products containing nanomaterials and evaluation of how material attributes relate to quality, safety, and efficacy [50]. The development plan should identify relevant CQAs and control strategies early. The specific requirements depend on product type, route, and regulatory pathway, so general statements should not replace consultation of current guidance.

Excipient safety must be considered at the administered dose and intended route. A surfactant with a history of use in one product may not be acceptable at the same concentration for a different route or duration. Developers should justify exposure, assess local and systemic toxicity as appropriate, and demonstrate that the formulation's benefit outweighs its risks [15,16,37].

9.1 Manufacturing and process control

Manufacturing control requires defined specifications for raw materials, mixing, temperature, energy input, and in-process measurements. Scale-up may change flow patterns and heat removal, even when nominal process settings are held constant. Pilot-scale studies should therefore verify that the critical quality attributes remain comparable and that the process is robust to realistic variation in raw materials.

A manufacturing control strategy can include raw-material specifications, in-process monitoring, finished-product tests, and stability trending. The control strategy should be linked to risk assessment and supported by data. Reproducibility should be assessed across independent batches rather than inferred from repeated measurements of a single batch.

10. Research gaps and future perspectives

Several research priorities emerge from the literature. First, more head-to-head comparisons are needed against clinically relevant conventional formulations. Second, studies should standardize reporting of composition, process conditions, size distribution, stability, and biological endpoints. Third, researchers should link CQAs to in-vivo exposure or therapeutic response rather than treating droplet size as a stand-alone success metric.

Fourth, route-appropriate safety and biological-fate studies should be performed early. Fifth, oral systems require better understanding of digestion, precipitation, and drug transfer. Sixth, scale-up and batch-to-batch variability should be reported transparently. Finally, clinical development should be planned with realistic manufacturing, packaging, and regulatory requirements in mind [3,19,23,36].

A practical development sequence is to define the target product profile, choose route-appropriate excipients, identify CQAs, optimize using a planned experimental design, confirm the process with independent batches, perform stability-indicating tests, and evaluate relevant biological performance. Advanced targeting or functionalization should be pursued only when it addresses a clear limitation and its contribution can be measured reproducibly.

CONCLUSION

Nanoemulsions provide a flexible approach to solubilizing and delivering selected drugs, with research spanning oral, topical, ocular, nasal, parenteral, and emerging applications. Their practical value depends on drug-specific behavior, excipient safety, interfacial structure, preparation conditions, stability, and route-specific biological performance.

A strong development strategy should avoid equating nanoscale size with efficacy, distinguish nanoemulsions from related lipid-based systems, and use a QbD framework to connect material and process attributes to meaningful outcomes. More standardized comparative studies, complete reporting, reproducible scale-up, and carefully designed safety and clinical investigations are needed before many promising preclinical systems can be regarded as established therapeutic solutions.

12. Evidence synthesis tables

Table 1: Route-specific Rationale and Critical Evaluation Questions.

Route	Potential rationale	Key evaluation questions
Oral	Improve dispersion/solubilization of selected lipophilic drugs	Dilution, lipolysis, precipitation, food effects, excipient exposure
Dermal/transdermal	Increase drug solubilization, skin deposition or permeation	Skin retention vs receptor permeation, irritation, barrier integrity, mass balance
Ocular	Improve solubilization/residence for selected ophthalmic actives	Sterility, clarity, pH, osmolality, tolerability, in-vivo exposure
Nasal	Local delivery or investigation of nose-to-brain transport	Mucociliary clearance, epithelial safety, residence, biodistribution
Parenteral	Carry selected poorly water-soluble compounds	Sterility, endotoxin, hemocompatibility, droplet distribution, systemic safety

Table 2: Critical Quality Attributes and Interpretation Cautions.

Attribute	What it informs	Caution
Droplet size/distribution	Dispersed phase dimensions and distribution breadth	Method, dilution, viscosity and rare large droplets influence results
PDI	Relative breadth of size distribution in DLS	A single threshold is not universally valid
Zeta potential	Electrokinetic behavior under stated conditions	May not predict stability in sterically stabilized systems
Drug assay/degradants	Dose accuracy and chemical stability	Requires a stability-indicating analytical method
pH/viscosity/osmolality	Route-relevant product properties	Acceptance limits depend on dosage form and route
Release/permeation	Comparative transport under defined conditions	Test setup may not predict in-vivo performance
Stability	Resistance to droplet growth, separation and degradation	Stress tests do not replace real-time stability

Future studies should report a complete formulation composition, preparation settings, independent-batch reproducibility, validated characterization methods, a relevant comparator, prespecified endpoints, and both favorable and unfavorable findings.

13. Selected primary-study evidence

Study	Formulation / model	Reported finding	Interpretatio n / limitation
Anuar et al. (2020) [25]	Ibuprofen-loaded nanoemulsion; olive oil, sucrose ester L-1695 and glycerol; D-phase emulsification.	The study developed and characterized ibuprofen nanoemulsions and assessed oral bioavailability.	A formulation-specific study; conclusions should not be generalized to other drugs, excipients, or patients.
Lei et al. (2023) [26]	Oral hydrogel–nanoemulsion co-delivery system studied for inflammatory bowel disease.	The authors reported anti-inflammatory effects and improved intestinal mucosal repair in experimental models.	A combined hydrogel/nano emulsion platform; effects cannot be attributed to droplet size alone or assumed to establish clinical benefit.
Li et al. (2022) [35]	Folate-decorated lipid nanoemulsions co-delivering paclitaxel and docosahexaenoic acid; in-vitro and in-vivo breast-cancer models.	The formulation showed sustained release, increased cellular uptake/apoptos is in experimental models, and reduced tumor growth in the reported animal study.	Preclinical oncology evidence; receptor-mediated targeting and safety require independent replication and clinical evaluation.
Michels et al. (2023) [33]	Temozolomide -loaded thermorespons ive nanoemulsion for intranasal delivery; preclinical glioblastoma model.	The selected formulation increased measured brain delivery in rats and reduced tumor Growth compared with the reported control.	Preclinical model and formulation-specific result; it does not establish effectiveness or safety in humans.

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