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Nanoemulsion-Based Strategies for Improving Solubility, Bioavailability, And Therapeutic Applications of Poorly Soluble Drugs: A Review

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ABSTRACT:

Introduction: Poor aqueous solubility is a persistent challenge in pharmaceutical research, with a large proportion of newly developed drug molecules classified as Biopharmaceutics Classification System (BCS) class II and IV compounds. Poor solubility often results in low and variable bioavailability, delayed onset of action, and suboptimal therapeutic outcomes, leading to formulation failure and increased development costs. Nano-emulsion-based drug delivery systems have gained considerable attention as an effective approach to overcome these limitations. Nanoemulsions are kinetically stable, isotropic dispersions of oil and water stabilised by suitable surfactants and co-surfactants, with droplet sizes typically in the range of 20–200 nm. The nanoscale droplet size provides a markedly increased interfacial surface area, which enhances drug solubilization, dissolution rate, and permeability across biological membranes. Additionally, nanoemulsions can protect drugs from chemical and enzymatic degradation, promote lymphatic uptake, and partially bypass hepatic first-pass metabolism, thereby improving systemic bioavailability. This review summarises nanoemulsion composition, formulation strategies, and preparation methods, marketed products, and case studies relevant to pharmaceutical applications. Furthermore, the mechanisms responsible for solubility and bioavailability enhancement are outlined, along with recent therapeutic applications via oral, parenteral, topical, ocular, and nasal routes. Overall, nanoemulsion-based delivery systems represent a platform for improving the therapeutic performance of poorly water-soluble drugs.

1. INTRODUCTION

The absorption, bioavailability, and overall therapeutic efficacy of an active pharmaceutical platform for improving the therapeutic performance of a poorly water-soluble drug ingredient (API) depend crucially on its aqueous solubility.[1,2] All of which results in low water solubility, drug discovery has created a growing number of chemicals with great lipophilicity, complex chemical structures, and strong crystal lattices.[3] As a result, the Biopharmaceutics Classification System (BCS) classifies many new drugs as either class II (low solubility, high permeability) or class IV (low solubility, low permeability). The dissolution of these molecules in physiological or gastrointestinal fluids is the primary rate-limiting factor in absorption, resulting in low and variable bioavailability, and ultimately lower therapeutic efficacy.[4, 5] These challenges are particularly relevant when treating central nervous system diseases, infectious diseases, cardiovascular problems, and malignancies—that is, chronic and life-threatening conditions—where the best possible therapeutic outcome calls for controlled and constant drug exposure. Increasing medication solubility and bioavailability is, therefore, not just a formulation goal but also a critical need for enhancing patient adherence and therapeutic efficacy.[6]

Traditional formulation methods such as salt formation, particle size reduction, solid dispersions, cyclodextrin inclusion complexes, co-solvents, and surfactants have all been utilised to solve problems related to drug solubility.[7] While these methods

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can provide some benefits, they are often limited by several disadvantages, including physical and/or chemical instability, drug precipitation when diluted, limited drug loading ability, difficulty in scaling up to commercial production, and inconsistent relationships between *in vivo* and *in vitro* results. Because of these disadvantages, there has been increased interest in the use of advanced and innovative methods of delivering poorly soluble drugs that overcome the biopharmaceutical barriers to these types of drugs.[8]

Lipid-based drug delivery systems are among those methods receiving the most interest for their ability to solubilise lipophilic drugs and increase their permeability through biological membranes.[9] Within this category of systems, nanoemulsions are one of the most promising types. Nanoemulsions are normally isotropic dispersions of droplets of sizes ranging from 20 to 200 nm, which can be made stable by using surfactants to keep them suspended; they contain oil, water, surfactant, and sometimes a cosurfactant.[10] The small size of the droplets increases the surface area available for absorption, thereby enhancing the rate of drug dissolution in solution and allowing a larger surface area for contact with biological membranes, thereby enhancing absorption.[10, 11]

Nanoemulsion-based drug delivery systems enhance bioavailability by many mechanisms, including improving wettability, accelerating diffusion rate, protecting medicines from enzymatic and chemical breakdown, promoting lymphatic transport, and partly avoiding hepatic first-pass metabolism, in addition to increasing solubility.[12] Further, more versatile nanoemulsions may be modified for a range of administration methods, including nasal, ocular, parenteral, transdermal, and oral delivery. [13-17] This flexibility has produced less frequent dosing, reduced systemic toxicity, and improved therapeutic efficacy in several preclinical and clinical studies.[15-17]

Nanoemulsions show promise as potential treatment options for multiple medical conditions. The system improves oncological treatments that use highly water-insoluble anticancer drugs by decreasing off-target harmful effects while increasing drug absorption.[18] Nanoemulsions enhance the effectiveness of antibacterial and antifungal treatments by facilitating the delivery of medicines to their target areas in the body.[19, 20] The use of nanoemulsion-based medicines has improved drug absorption and treatment outcomes in patients with inflammatory diseases, heart disease, and brain disorders.[21]

This review will cover nanoemulsion-based approaches to improving solubility, bioavailability, and therapeutic use of poorly soluble drugs so that current knowledge can be brought together and identified, as well as opportunities for rational design and future development of nanoemulsion-based delivery methods for medication.

2.METHODS

The nanoemulsion case studies and preparation methods were sourced from research and review articles accessed through Google Scholar, Scopus, Web of Science, and PubMed.

ADVANTAGES OF NANOEMULSIONS IN DRUG DELIVERY

Nanoemulsions increase the apparent solubility and improve the partition of BCS Class II/IV medicines by dissolving them in lipophilic oil-based nanodroplets with a very large surface area between oil and water. Because of this very high surface area, nanoemulsions allow an extremely high drug concentration without the risk of forming crystals or being supersaturated in an amorphous state (because of the turbulence and cavitation created during high-pressure homogenization, which stabilises the droplets). [22]

As described by the Noyes–Whitney equation, the dissolution rate is significantly increased by the extremely large interfacial area of the nanoemulsion; thus, the drugs are released quickly when they come in contact with the gastrointestinal fluids or at the absorption sites for the drugs.[23]

Surfactants included in the nanoemulsions increase the solubility of the oil phase, which minimises Ostwald ripening, weakens flocculation, and prevents coalescence of the droplets by forming elastic-plastic interfacial films.[23, 24]

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Unlike co-solvent systems, nanoemulsions keep drugs with low solubility in a dissolved condition during dilution, creating a brief supersaturation without precipitation. Through steric encapsulation, they protect enzymatic hydrolysis and presystemic metabolism (such as CYP3A4 and efflux transporters).[23- 25]

Nanoemulsions are versatile in terms of delivery methods: parenteral allows solvent-free IV delivery with less hemolysis (e.g., Cleviprex®.[23] while oral SNEDDS spontaneously create in GI fluids for lymphatic absorption and a 10-fold increase in bioavailability (e.g., paclitaxel).[25] Topical/transdermal disrupts the stratum corneum to allow permeation; ocular uses bioadhesion (e.g., Restasis®) to extend residence time; and nasal formulations facilitate nose-to-brain migration.[24]

With less systemic exposure and reduced toxicity with little use of surfactants (<10% vs. 50% of Cremophor), nanoemulsion technology enhances patient compliance by allowing lower dosages and a lower frequency of administration.[22] Because nanoemulsions can be manufactured as either liquid or semi-solid products, they are much easier to use and consume than other formulations, making nanoemulsions also suitable for pediatric and geriatric patients. [23, 24]

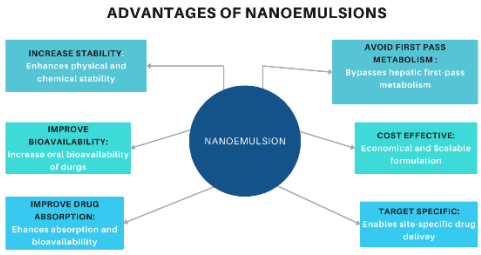

Figure 1: Advantages of nanoemulsion in drug delivery

FORMULATION COMPONENTS OF NANOEMULSIONS

To create colloidal systems that will be stable kinetically and have the best possible drug solubilization capacity, it is important to carefully choose and interrelate three series: the oils, the surfactants/ cosurfactants, and, finally, the aqueous phase containing the functional additives. Each component plays an essential role in the preparation of nanoemulsions, and the components of nanoemulsions are provided in Table 1.[26, 27].

Table 1: Components of Nanoemulsions [26, 27]

Component	Typical Concentration / Nature	Function in Nanoemulsion	Common Examples
Oil / Lipid Phase	Usually 5–20% in o/w nanoemulsions; can be up to 70% in special systems. Includes short-, medium-, and long-chain triglycerides; natural or synthetic lipids.	Solubilises lipophilic drugs; forms a dispersed phase; enhances oral absorption and bioavailability; affects droplet size and stability.	Coconut oil, sesame oil, rice bran oil, safflower oil, soybean oil, cottonseed oil, oleic acid, ethyl oleate, vitamin E (D-tocopherol), Miglyol® 812, Captex® 200/355/8000, Labrafil®, Maisine® 35-1, isopropyl myristate
Emulsifier (Surfactant)	Generally 1–10% w/w; amphiphilic molecules; selected based on HLB value (8–18 for o/w, 3–6 for w/o). Mostly non-ionic surfactants.	Reduces interfacial tension; stabilises droplets; prevents aggregation and coalescence; provides steric/electrostatic stabilisation.	Lecithin (phosphatidylcholine), Tween® 20/60/80, Span® 20/60/80, Cremophor® EL/RH40, Solutol® HS-15, Brij®-30, Labrasol®, TPGS

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Co-emulsifier / Cosolvent	Used in small amounts (0.5–5%); usually short- to medium-chain alcohols or glycols (C3–C8).	Further reduces interfacial tension; increases interfacial fluidity; enhances miscibility of oil and water phases; improves permeability.	Ethanol, propylene glycol, isopropyl alcohol, butanol, Transcutol® P, diethylene glycol monoethyl ether, Lauroglycol® 90
Aqueous Phase	Major continuous phase (up to 80–95%); purified water or buffers.	Acts as a dispersion medium; controls viscosity, pH, and stability; ensures compatibility with the route of administration.	Purified water, phosphate buffer, citrate buffer
Additives (Optional)	Low concentrations; formulation-dependent.	Improve stability, palatability, safety, or shelf life.	Antioxidants (BHT, tocopherol), preservatives (parabens), tonicity agents (glycerol), flavouring agents

METHODS OF PREPARATION OF NANOEMULSIONS

There are five methods for the preparation of nanoemulsions: high-pressure homogenization, microfluidization, and ultrasonication, the phase Inversion Temperature Method, and the phase inversion composition method.

High-Pressure Homogenization (HPH)

HPH is a commonly employed technique for producing nanoemulsions, typically by forcing a coarse emulsion through small holes under high pressure. This produces high shear and turbulent forces together with cavitation, all of which work to decrease the size of the droplets and typically produce a nanoemulsion with a narrow size distribution and droplet sizes of 40 to 150 nm. HPH is often used for both parenteral, oral, and ophthalmic formulations and can be used in aseptic, large-scale manufacturing. The disadvantages of HPH include high-energy requirements, expensive equipment, the need for low viscosity in pre-emulsions, multiple homogenization cycles, and a potential for thermal stress, which could adversely affect the safety of heat-sensitive drugs.[28]

Microfluidizations

When microfluidizing, two high-velocity fluid streams collide with each other in a fixed geometry interaction chamber to form very strong shear and impact forces. This process yields extremely homogeneous nanoemulsions with very low polydispersity, with droplet sizes typically ranging from 30 to 100 nm in diameter. Because the microfluidization process creates good homogeneity of droplet sizes and sterility, microfluidization would greatly benefit topical and ophthalmic nanoemulsions. However, there are some issues with scaling up the process because the technique requires formulations to have relatively low viscosity and ideally corresponding amounts of surfactants to avoid clogging. [29]

Ultrasonication

Ultrasonication is a laboratory method for breaking down emulsion droplets using high-frequency sound waves and cavitation forces to produce nano-sized droplets. This method has been found to produce very small droplet sizes efficiently and is simple to perform; however, the production of heat from using a metal probe, the erosion of the metal probe, the fact that this is a batch process, and that ultrasonication is not scalable prevent this method from being a viable option for mass pharmaceutical manufacturing.[28, 30]

Phase Inversion Temperature (PIT) Method

The basis for the PIT technique is the temperature-dependent changes in the hydrophilic-lipophilic balance of the non-ionic surfactants. Phase inversion occurs from the dehydration of the surfactant during the heating process, and stable

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formation of oil-in-water nano-emulsions with droplet sizes that will typically lie between 50 and 200 nm is formed upon cooling in a controlled manner. The energy used in this technique is very low; however, the method is limited by the temperature sensitivity of the formulation's components and surfactant specificity.[31]

Phase Inversion Composition (PIC) Method

Using the PIC technique to prepare nanoemulsions involves adding water to an aqueous/surfactant/oil mixture and varying the amount of water until a phase transition in the curvature occurs, triggering spontaneous emulsification. The PIC method can be performed at room temperature and is particularly valuable for self-nanoemulsifying drug delivery systems. However, changes in pH, ionic strength, or composition have the potential to affect the stability of the formulations; therefore, you will need to adjust the formulations carefully.[32]

NANOEMULSION-BASED STRATEGIES FOR IMPROVING SOLUBILITY AND BIOAVAILABILITY

Nanoemulsion-based strategies for improving solubility and bioavailability of poorly soluble drugs are clearly illustrated in Table 2.

Table 2: Nanoemulsion-Based Strategies for Improving Solubility and Bioavailability [22-27]

Strategy	Impact on Solubility and Bioavailability
Increased Interfacial Surface Area	Nano-sized droplets provide a large oil–water interface, enhancing dissolution rate and absorption of BCS class II/IV drugs.
Enhanced Dissolution Kinetics	Reduced diffusion distance and improved wettability promote rapid drug dissolution and higher systemic exposure.
Maintenance of Supersaturation	Steric and electrostatic stabilization prevents precipitation, ensuring consistent drug absorption.
Improved Wettability and Dispersion	Surfactants enhance interaction with gastrointestinal fluids, increasing the fraction of the drug available for absorption.
Lymphatic Transport	Long-chain lipid nanoemulsions bypass hepatic first-pass metabolism, leading to significant bioavailability enhancement.
Protection from Degradation	Oil droplets protect drugs from acidic and enzymatic degradation, increasing the amount of intact drug reaching circulation.
Surfactant-Mediated Permeation Enhancement	Surfactants improve membrane permeability, enhancing transcellular transport and absorption rate.
Route-Specific Advantages	Adaptability to multiple administration routes increases AUC and Cmax, reduces dose requirements, and minimises variability.

THERAPEUTIC APPLICATIONS OF NANOEMULSIONS

Nanoemulsions have shown great versatility as adaptable platforms in numerous therapeutic areas because of their nanoscale architecture, the ability to load large amounts of lipophilic molecules, and their unique modifications (based on route) to enhance the drug's toxicity and efficacy through increased systemic/local exposure with decreased toxicity and improved patient outcome of poorly soluble compounds [33-37] and therapeutic applications are provided in Table 3.

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Table 3. Therapeutic Applications of Nanoemulsions

Therapeutic Area	Outcomes	References
Oral Drug Delivery	Paclitaxel nanoemulsions (90-120 nm) showed significantly higher systemic concentrations and distribution in liver/kidneys/lungs in mice vs. aqueous solution, suggesting 5-15X bioavailability boost.	[33]
Parenteral Drug Delivery	Paclitaxel nanoemulsion has lower toxicokinetics vs. Taxol® in dogs.	[34]
Topical/Transdermal Delivery	Clotrimazole rapeseed oil nanoemulsion (with Span 80, Pluronic F-68) achieved high drug solubility and stability for vaginal/skin antifungal use, with enhanced penetration potential	[35]
Ocular/Nasal Delivery	Moxifloxacin (likely intended vs. oxifloxacin) nanoemulsion (MM3) doubled AUC_{0-8h} (1859 ng·h/mL) in aqueous humor vs. control ($p<0.0005$), improving ophthalmic bioavailabilit	[36]
Cancer/Targeted Therapy	Paclitaxel nanoemulsions showed superior anti-tumor efficacy vs. Taxol® in multi-drug resistant cell lines and xenograft models, with greater cellular uptake and tumor delivery .	[37]

CASE STUDIES OF NANOEMULSION FORMULATIONS FOR POORLY SOLUBLE DRUGS

The following table summarises exemplary case studies demonstrating nanoemulsion efficacy in enhancing solubility, bioavailability, and therapeutic indices for challenging BCS II/IV drugs across diverse indications and routes [Table 4].

Table 4: Case studies of nanoemulsion formulations for poorly soluble drugs

Drug	BCS Class	Preparation Method	Key Outcomes	Application	References
Itraconazole (ITZ)		Spontaneous emulsification	Globule size 157.5 ± 14.2 nm.	Topical ocular antifungal	[38]

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	BCS Class II		Thermodynamically stable; 7-fold higher in-vitro release vs. suspension after 24 h	delivery (keratitis)	
Paclitaxel (PTX)	BCS Class IV	High-pressure homogenization	Particle size <100 nm 100% encapsulation efficiency; 100-fold higher targeting to CD44+ cancer cells sustained release >6 days without burst; MTD >50 mg/kg (2.5× Taxol®) Prolonged circulation and increased tumor retention; enhanced antitumor efficacy with reduced toxicity	Targeted ovarian cancer therapy (CD44-mediated active targeting)	[39]
Clotrimazole	BCS Class II	Spontaneous nanoemulsification	Enhanced solubility up to 25 mg/mL; 100% drug release within 15 min in all media	Topical and antifungal therapy	[40]
Curcumin	BCS Class IV	PIT method	Droplet size 26–129 nm; PDI <0.3; Zeta potential = −26 mV; high drug loading (9.53 ± 0.49 mg/mL); photostability increased by 36–42%; Improved antioxidant activity after UV exposure; higher retention (11–57%) during simulated digestion; enhanced bioaccessibility and in vitro absorption vs. free curcumin.	Oral delivery of curcumin for anticancer and antioxidant therapy	[41]
Celecoxib (CXB)	BCS Class II	Nanoemulsion formulation for transdermal delivery	3.03-fold (nanoemulsion) and 2.65-fold (nanoemulsion gel)	Transdermal anti-inflammatory therapy and	[42]

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		(composition optimized for skin permeation)	increase in bioavailability vs. oral capsule	enhanced systemic bioavailability	

Cyclosporine A	BCS Class II	Phase IV Study	Significant improvement in corneal and conjunctival staining scores at 12 weeks; non-inferior to cyclosporine emulsion 0.05%; superior improvement in conjunctival staining vs. conventional emulsion; better TBUT and Schirmer test outcomes vs. diquafosol;	Ophthalmic therapy for dry eye disease	[43]
Difluprednate	BCS Class IV	Oil-free aqueous nano/micellar formulation using mixed surfactant system	Improved ocular absorption and patient compliance	Ophthalmic anti-inflammatory therapy (post-surgical inflammation)	[44]
Salidroside	BCS Class III	Water titration method	Stable nanosized spherical droplets; controlled drug release vs. aqueous solution. improved pharmacokinetics: t½ increased 2.11-fold, AUC_{0-48h} increased 1.75-fold, MRT increased 2.63-fold; reduced metabolism and enhanced oral absorption	Oral delivery of salidroside with improved bioavailability	[45]
Quetiapine fumarate	BCS Class II	Water titration method	Droplet size: 144 ± 0.5 nm >2-fold increase in drug release vs pure drug. Shorter Tmax after intranasal administration vs. IV; higher drug transport efficiency and direct nose-to-brain transport; improved brain targeting	Intranasal brain-targeted therapy for antipsychotic treatment	[46]

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CLINICAL TRANSLATION AND MARKETED NANOEMULSION PRODUCTS

MARKETED PRODUCTS

Marketed Nanoemulsion Products are illustrated in Table 5.

Table 5. Marketed Nanoemulsion Products and Pipeline Notables

Product Name	Indication/Route	Approval/ Status	References
Restasis® (cyclosporine 0.05% ophthalmic emulsion)	Chronic dry eye (keratoconjunctivitis sicca)/Ocular	FDA-approved 2003	[47]
Durezol® (difluprednate 0.05% ophthalmic emulsion)	Post-operative inflammation/ Ocular	FDA-approved 2008	[48]
Cleviprex® (clevidipine 0.5 mg/mL injectable emulsion)	Hypertension (perioperative)/Parenteral IV	FDA-approved 2008	[49]
Neoral®	Organ transplant rejection/Oral	FDA-approved 1995 (post-Sandimmune®)	[50]

FUTURE PERSPECTIVES

The future development of nanoemulsion-based drug delivery systems is expected to focus on improving formulation stability, scalability, safety, and therapeutic precision.[51] Advances in formulation science, materials engineering, and pharmaceutical technology are likely to play a crucial role in overcoming current limitations.[52] One important direction is the development of novel biocompatible and biodegradable surfactants and lipids that reduce toxicity while maintaining high drug-loading capacity and stability.[53]

Another key area is the integration of nanoemulsions with targeted and stimuli-responsive delivery strategies. Surface modification with ligands, polymers, or antibodies may enable site-specific drug delivery, particularly in cancer therapy and central nervous system disorders. Such targeted nanoemulsions can improve therapeutic outcomes by increasing drug concentration at the diseased site while minimizing systemic side effects.[52-56]

Technological advancements in manufacturing, such as continuous processing, microfluidics, and scalable low-energy methods, are expected to improve reproducibility and industrial feasibility. Additionally, the application of artificial intelligence and machine learning in formulation design may accelerate optimization of nanoemulsion compositions, stability prediction, and in vivo performance.[55] Overall, the continued evolution of nanoemulsion technology, combined with advances in materials science, process engineering, and personalized medicine, is expected to position nanoemulsions as a central platform for next-generation drug delivery systems.[57, 58]

CONCLUSION

Nanoemulsion-based drug delivery systems have emerged as a highly promising and versatile approach for addressing the long-standing challenge of poor aqueous solubility associated with many modern drug candidates, particularly BCS class II and IV compounds. By reducing droplet size to the nanometer range, nanoemulsions provide a significantly increased interfacial surface area that enhances drug solubilization, dissolution rate, and permeability across biological membranes. These systems not only improve oral bioavailability but also enable alternative routes of administration, including parenteral, topical, ocular, and nasal delivery, thereby expanding therapeutic possibilities. In addition to solubility enhancement, nanoemulsions offer multiple pharmacokinetic and pharmacodynamic advantages, such as protection of drugs from chemical and enzymatic degradation, promotion of lymphatic uptake, and partial avoidance of hepatic first-pass metabolism. These features result in improved therapeutic efficacy, reduced dose-related toxicity, and enhanced patient compliance. The availability of several approved

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nanoemulsion-based pharmaceutical products further validates their clinical relevance and translational potential. However, despite these advantages, certain limitations remain. Issues such as physical instability due to Ostwald ripening, high surfactant concentrations, long-term storage concerns, scale-up challenges, and regulatory complexities continue to restrict the broader industrial adoption of nanoemulsion systems. Addressing these challenges is essential to ensure consistent product quality, safety, and efficacy. Overall, nanoemulsions represent a robust and adaptable platform with significant potential to transform the delivery of poorly soluble drugs, bridging the gap between formulation research and clinical application.

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CONFLICTS OF INTEREST

The author declares that they have no conflicts of interest.

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