Volume 10, Issue 7, July– 2025 International Journal of Innovative Science and Research Technology
ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25jul845

Microemulsions in Modern Drug Delivery

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Publication Date: 2025/07/25

Abstract: Microemulsions are thermodynamically stable, optically clear, and isotropic dispersions of oil and water stabilized by a combination of surfactants and co-surfactants. Due to their unique physicochemical properties such as nanoscale droplet size (10–300 nm), enhanced solubilization potential for hydrophobic drugs, and ease of preparation, microemulsions have gained significant attention as promising carriers for drug delivery. This review systematically explores the fundamentals of microemulsion systems, including their types, mechanism of formation, composition, and various preparation techniques like phase titration and phase inversion temperature methods. A detailed discussion is presented on the evaluation parameters crucial for ensuring their stability and performance. Special emphasis is laid on the use of different oils and surfactants, expanding the applicability of microemulsions in multiple routes of administration such as oral, topical, parenteral, and nasal drug delivery. Recent research advances and real-time examples highlight their role in enhancing bioavailability, improving targeted delivery, and overcoming solubility challenges of poorly water-soluble drugs. With increasing demand for patient-centric, non-invasive, and effective drug delivery systems, microemulsions stand out as a versatile and innovative platform, warranting further research and clinical translation.

Keywords: *Microemulsions; Drug Delivery Systems; Ternary Phase Diagram;, Emulsions; Surfactants.*

How to Cite: Vaishnavi Kasha; Amreen Begum; Mohammed Muzaffar Ali; Anu Pravallika Janipalli; Dr. Venna R Surya Anusha; Koppala RVS Chaitanya (2025), Microemulsions in Modern Drug Delivery. *International Journal of Innovative Science and Research Technology*, 10(7), 1970-1975. https://doi.org/10.38124/ijisrt/25jul845

I. INTRODUCTION

Emulsions are biphasic dispersions of two immiscible liquids in which one phase (discontinuous) is subdivided as fine globules within the other (continuous) with the aid of surface-active agents [1]. By selecting appropriate oils, surfactants and co-surfactants, formulators can tailor droplet size, interfacial curvature and drug-release kinetics to meet route specific objectives ie., oral, topical, ophthalmic, pulmonary and parenteral [2]. For example, nanoemulsion eye drops improve precorneal residence of cyclosporine [3], and oil-in-water vaccine emulsions prolong intramuscular antigen release [4]. Microemulsions are thermodynamically (or kinetically) stable, isotropic dispersions with droplet diameters between 10 nm and 300 nm [6]. Their optical clarity, high drug-solubilising capacity and ease of manufacture make them attractive carriers for poorly water-soluble drugs.

II. ADVANTAGES AND LIMITATIONS

Microemulsions are thermodynamic stability and can form spontaneously with minimal energy. The manufacturing process can be scalable with simple mixing equipment. Microemulsions improves oral or dermal bioavailability of BCS class II drugs by Superior solubilisation. Due to their versatility they are applicable to oral, parenteral, topical and ocular delivery [7]. However, they require relatively high surfactant/co-surfactant load and provide limited solubilisation of high melting drugs. Microemulsions are also sensitive to environmental changes such as pH and temperature.

III. PREPARATION METHODS

The key ingredients of microemulsions are oil phase, aqueous phase, surfactant, co-surfatant. Mostly aqueous phase

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25jul845

comprise water or buffer, which may include co-solvents, electrolytes and preservatives [8]. Fatty acids, triglycerides or essential oils that dissolve lipophilic APIs and modulate interfacial curvature are employed as oil phase [9]. Ionic or non-ionic agents are employed as surfactants. Surfactant with HLB value of 8–18 favours O/W systems [8]. Co-surfactants are short-chain alcohols or amines that fluidise the interfacial film and further reduce tension [8]. Microemulsions can be prepared by phase titration method or phase inversion method.

➢ *Phase-Titration Method*

The phase-titration method is a widely used and straightforward technique for developing microemulsions. It involves the gradual addition of the aqueous phase (usually water or buffer) into a pre-mixed blend of oil, surfactant, and co-surfactant under gentle magnetic or mechanical stirring. The addition is typically carried out dropwise to allow the components to interact progressively and form a thermodynamically stable, isotropic, and transparent microemulsion [10].

This method allows for the construction of pseudo-ternary phase diagrams, which help map out the microemulsion region by varying the proportions of oil, surfactant/co-surfactant mixture, and water. Various ratios of oil to surfactant were prepared at each S_{mix} ratio i.e., weight ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9 (w/w). These diagrams are instrumental in identifying the most stable region for formulating the drug delivery system. Importantly, no high energy input (like sonication or homogenization) is necessary, making this method scalable and cost-effective.

➢ *Phase-Inversion Temperature (PIT) Method*

The phase-inversion temperature (PIT) method is particularly suitable for non-ionic surfactants, which exhibit temperature-dependent solubility. At low temperatures, these surfactants are more hydrophilic, favoring oil-in-water (O/W) emulsions. When the temperature increases, their hydrophilic-lipophilic balance (HLB) decreases, making them more lipophilic and reversing the emulsion type to water-in-oil (W/O) [11].

The inversion temperature is the specific temperature at which the surfactant's affinity switches from the aqueous phase to the oil phase, resulting in a transitional bicontinuous phase with very low interfacial tension. Upon cooling, the system stabilizes into a fine O/W microemulsion with nano-sized droplets, making this method suitable for enhancing drug solubilization and absorption. However, the method is unsuitable for **thermolabile drugs** due to the elevated temperatures involved.

IV. EVALUATION TESTS FOR MICROEMULSIONS

To ensure the performance, quality, and stability of emulsion and microemulsion-based drug delivery systems, a series of physicochemical and biopharmaceutical evaluations are essential. Visual examination is the initial step, where formulations are assessed for homogeneity, phase separation, color, and clarity. High optical clarity often indicates smaller droplet sizes in microemulsions [12]. Dynamic light scattering (DLS) techniques are employed to determine droplet size distribution, polydispersity index (PDI), and zeta potential, which are critical indicators of stability and uniformity. Zeta potential values exceeding ±30 mV generally suggest good electrostatic stabilization [13].

Advanced characterization techniques like small-angle X-ray scattering (SAXS), neutron scattering (SANS), or laser diffraction further provide insights into the internal structure and droplet morphology. Viscosity and rheological behavior, measured using instruments like the Brookfield viscometer, reveal flow characteristics and help predict the formulation's behavior during application or administration [14]. Drug solubility and partitioning within the microemulsion are evaluated using centrifugation methods, which separate unincorporated drug from the solubilized fraction [15].

Stability testing under accelerated conditions, including temperature cycling and centrifugation, helps predict long-term shelf stability and identify tendencies for creaming, coalescence, or cracking [16]. *In vitro* drug release studies, such as those performed using Franz diffusion cells, simulate the drug diffusion kinetics and assess membrane permeability [17,18]. Additionally, pH and osmolarity evaluations ensure that the formulation is suitable for the intended route of administration, particularly in sensitive sites like the eyes or bloodstream [19,20].

V. MICROEMULSIONS IN DIFFERENT DRUG-DELIVERY ROUTES

Emulsions and microemulsions have gained significant importance across various routes of drug delivery due to their ability to enhance solubility, improve bioavailability, and modulate release profiles of active pharmaceutical ingredients (APIs).

➢ *Oral Drug Delivery*

Microemulsions have demonstrated significant promise in improving the oral bioavailability of poorly water-soluble drugs by enhancing solubilization and protecting the active moiety from first-pass metabolism. For instance, Hu L et al. developed a microemulsion based oral formulation of ibuprofen, which showed enhanced dissolution and 1.9 fold increase in relative bioavailability compared to conventional granule [21].

➢ *Topical Drug Delivery*

Topical microemulsions offer superior drug penetration through the skin due to their small droplet size and surfactant-mediated lipid bilayer disruption. Amra K et al. formulated a ketoconazole-loaded microemulsion for topical antifungal application, achieving improved zone of inhibition and retention compared to cream formulations [22].

➢ *Intranasal Delivery*

Microemulsions are effective carriers for nose-to-brain delivery of CNS-active drugs, enabling rapid onset of action and bypassing hepatic metabolism. Patel RB et al. reported an

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25jul845

intranasal microemulsion of risperidone that demonstrated enhanced brain uptake and prolonged therapeutic effect [23].

➢ *Parenteral Administration*

Sterile microemulsions have been employed in parenteral formulations to deliver lipophilic drugs safely with controlled release. A study by Mas et al. developed a microemulsion formulation of docetaxel for intravenous administration that showed improved therapeutic activity with *Brucea javanica* oil [24].

➢ *Ophthalmic Delivery*

Microemulsions can overcome ocular barriers and prolong precorneal residence time. Kalam MA et al. prepared a gatifloxacin microemulsion for opthalmic drug delivery, which showed significantly improved adherebce to corneal surface and 2 times increase in drug ocular bioavailability [25].

Pulmonary delivery of emulsified drugs offers the advantage of generating respirable-sized droplets for deep lung deposition, improving onset of action, especially in conditions like asthma or COPD. Additionally, parenteral routes, including intravenous or intramuscular injection of have enabled the administration of drugs that otherwise suffer from solubility challenges, and have facilitated controlled release over extended periods, such as depot formulations, in case of nanoemulsions [26]. Intranasal emulsions have also shown potential in nose to brain delivery, bypassing the blood brain barrier for central nervous system targeting [27]. Each route demands careful formulation and excipient selection, ensuring that emulsions meet the physicochemical and biological requirements for optimal therapeutic outcomes.

VI. CONCLUSION

Precisely engineered emulsions and microemulsions have become indispensable across oral, dermal, ocular, pulmonary and parenteral delivery platforms. Selection or modification of oils, surfactants and polymers, validated through comprehensive physicochemical and biopharmaceutical testing, enables customised solubility, stability and controlled-release performance while improving patient compliance.

ACKNOWLEDGMENT

None to acknowledge

Table 1 Evaluation of Emulsions

Test (Parameter)	Detailed Purpose & Method
Physical appearance & transmittance	Visual clarity, phase separation and % T (650 nm) indicate homogeneity and droplet size consistency
Small-angle scattering (SAXS/SANS/DLS)	Determines internal structure, droplet radius and polydispersity. SAXS confirms bicontinuous vs. swollen-micelle structures
Accelerated stability (centrifugation, freeze–thaw)	Samples spun at 10,000 rpm or cycled between 4 °C and 45 °C (6 cycles) to predict shelf stability
Droplet size, PDI, zeta potential	Dynamic light scattering (Malvern Zetasizer) measures intensity-weighted mean diameter; electrostatic repulsion >
Rheology (viscosity, shear-thinning)	Brookfield DV3T maps flow curve; viscoelastic gels minimise creaming and improve topical retention
Drug solubility capacity	Excess API incubated 24 h; supernatant assayed HPLC: distinguishes solubilised vs. precipitated fractions
In-vitro release & permeability	Franz cell across cellulose-ester or Strat-M® membrane; sink phase sampled over 24 h to compute flux & lag time
pH and osmolarity	Must match physiological site (e.g., pH 6.5–7.5 for ocular; 280–320 mOsm kg^{-1} for IV) to avoid irritation

Table 2 Microemulsions for Different Drug Delivery Routes and Their Composition

S. No	Drug & Route	Principal Oil / Surfactant (co-surf.) System*	Key Outcome(s) Reported	Ref.
1	Meloxicam – transdermal	Isopropyl myristate / Tween 80 : Span 80 (1:1) / propylene glycol	↑ skin flux 2.3-fold vs. saturated solution. It is stable for 90 days @ 25 °C	[28]
2	Methimazole – topical	Oleic acid-Transcutol P (1:10) / Tween 80 : Span 20 / propylene glycol	Mean droplet 7–28 nm; rat-skin permeation increased 3 times the control	[29]
3	Celecoxib – transdermal	Capryol PGMC / Tween 80 / Transcutol P	Selected microemulsion showed greater permeation and therapeutic effect for arthritis	[30]
4	Diclofenac sodium – foamable topical	Caprylic/capric triglyceride / Labrasol / Transcutol HP	Foamable ME ↑ release rate vs. commercial gel; physicochemically stable for 90 days	[31]
5	Linalool – dermal	Isopropyl myristate / Cremophor EL + Transcutol P	6.5-fold ↑ skin flux; no irritation after 3-month stability test	[32]
6	Sunitinib – ocular	Oleic acid / Cremophor RH40 / Transcutol P	19 nm ME; corneal AUC ↑ 2.5×;	[33]

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/25jul845

		(+ 0.3 % Na-hyaluronate)	inhibited alkali-burn CNV in mice	
7	Zotepine –intranasal (nose-to-brain)	Capmul MCM C8 / Labrasol / Transcutol HP	Brain AUC ↑ 4.3× (i.n.) vs. oral; safe on RPMI-2650 nasal cells	[34]
8	Valsartan – oral	Labrafac Lipophile / Tween 20 / PEG 400	Solubility ↑ 45-fold; 2.1× C_{max} in rats	[35]
9	Raloxifene – oral SMEDDS	Labrafil M 1944 CS / Kolliphor EL / PEG 400	Droplet 17 nm; rat bioavailability ↑ 3.8× vs. suspension	[36]
10	Azithromycin – topical anti-infective	Vitamin E acetate / Labrasol / Transcutol P	Sustained release & enhanced MRSA kill; non-cytotoxic to keratinocytes	[37]
11	Quercetin – ocular	Oleic acid + Transcutol P / Tween 80: Span 20	J_ss ↑; rabbit corneal permeation improved	[38]
12	Curcumin – i.v. (neuro-protective)	Coconut oil / Tween 80 / ethanol	Brain Cmax ↑ 1.96-fold; globule size is 20 nm; safe i.v.	[39]
13	Coenzyme Q10 – oral SMEDDS	ω-3 oil / Labrasol LG / Gelucire	AUC ↑ 4.2×; brain distribution enhanced in rats	[40]
14	α-Tocopherol – oral ME-gel	Mixed dietary lipids / lecithin / glycerol	Human AUC_0-12h ↑ significantly vs. tablet in crossover study	[41]
15	Linagliptin – oral	Nigella sativa oil / Labrasol / Transcutol P	Bioavailability ↑ 3.7×; improved glycaemic control in rats	[42]

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