Microemulgels as Next-Generation Topical Delivery Platforms: Innovations, Optimization, and Therapeutic Potential

A Critical Analysis of Formulation Strategies, Performance Attributes, and Emerging Advances in Microemulgel Technology

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Abstract- Microemulgels are one of the advanced, hybrid drug-delivery systems that incorporate the excellent solubilization, permeation-enhancing, and nanometric properties of microemulsions with the structural stability and user-friendly aspects of gels. Such a dual system serves to balance and overcome the limitations pertaining to low viscosity and poor retention of microemulsions, with enhanced spreadability, consistency, and controlled-release profiles. Due to their ability to accommodate both hydrophilic and lipophilic drugs, microemulgels improve drug bioavailability, enable site-specific delivery, avoid first-pass metabolism, and decrease systemic side effects. This review describes the composition, preparation methods, optimization strategies, and parameters of evaluation necessary for microemulgel formulation. The low- and high-energy emulsification methods, phase inversion techniques, pseudo-ternary phase diagram construction, and statistical optimization methods such as Box–Behnken design are specially emphasized. The mechanisms of drug release, factors affecting skin permeability, and kinetic models representing diffusion behavior are discussed in detail to illustrate their performance attributes. Recent applications of microemulgels in dermatological, anti-inflammatory, antifungal, antibacterial, and cosmeceutical therapy are critically presented along with innovations such as nanocarrier integration, 3D-printed self-emulsifying systems, and stimuli-responsive gels. Developmental considerations at the key level inclusive of scalability, stability, regulatory challenges, and safety issues are also highlighted. Microemulgels exhibit tremendous potential for personalized, efficient, and patient-compliant topical therapy. Emphasized here, future developments will be performed by integrating smart polymers, AI-assisted formulation models, greener excipients, and improved in vitro–in vivo

correlations to advance microemulgel technology toward routine clinical and commercial use.

Index-Terms- Microemulgel, Topical drug delivery, Nanoemulsion, Skin permeation, Controlled release

I. INTRODUCTION

Microemulgels are a novel hybrid drug-delivery strategy that combines the high solubilizing capacity and permeation-enhancing properties of microemulsions with the rheological stability and patient acceptability of topical gels. With the topical and transdermal delivery routes gaining increased importance for both local and systemic therapy, microemulgels have recently assumed greater significance because of their ability to overcome disadvantages of conventional semisolid dosage forms. Their biphasic structure, consisting of a microemulsion dispersed into a gel matrix, allows superior drug penetration, prolongs its release, and gives better spreadability than that of creams, ointments, or simple gels [1-3]. Microemulsions are isotropic and thermodynamically stable systems consisting of oil, water, surfactant, and co-surfactant, possessing ultrafine droplet size normally below 100 nm. Their nanosized droplets provide a high interfacial surface area allowing improved drug solubilization and, therefore, superior diffusional transit through the barrier membrane. Low viscosity and poor skin retention impede direct topical application [4]; hence, microemulsions are incorporated into a three-dimensional network of a gel matrix constituted by gelling agents such as carbopol, HPMC, or xanthan gum. Such a combination preserves the permeation advantages of the former while conferring on the product structural integrity and aesthetic acceptability required for topical application. The various modes by which microemulgels enhance therapeutic performance include the following. Enhanced drug loading is possible, especially for poorly water-soluble drugs, in the microemulsion phase, ensuring better bioavailability. Surfactants and co-surfactants perturb the lipid packing of the stratum corneum, allowing deeper penetration. Simultaneously, the gel matrix provides stability to the formulation and regulates drug release, permitting residence time extension on the skin. These features make microemulgels ideal carriers for drugs requiring controlled release, local targeting, or improved dermal retention [5-6]. Their clinical utility spans dermatological, transdermal, and cosmeceutical applications. A large number of therapeutic molecules, including antifungals, corticosteroids, anti-inflammatory drugs, analgesics, and antibiotics, exhibit poor aqueous solubility or extensive first-pass metabolism on oral administration. Microemulsions overcome these challenges through the enhancement of solubility, circumvention of first-pass metabolism, and minimization of systemic exposure. Improved drug permeation and superior therapeutic response are reported in cases of drugs containing diclofenac, ketoconazole, clobetasol propionate, and various natural bioactives. [7-12]

Moreover, patient acceptability is significantly enhanced because of the nongreasy nature, easy application, and elegance of the microemulgels[13]. Such features make these systems more suitable for the chronic dermatological conditions like psoriasis, eczema, fungal infections, and acne, where long-term application is usually needed. More recent advances have expanded their utility toward ocular, mucosal, and rectal drug delivery, too, supported by innovations like 3D printing of self-emulsifying systems and mucoadhesive microemulgels' development. Despite their several advantages, development of microemulgels remains complex [14-15]. Success of formulation requires careful selection of oils, surfactants, cosurfactants, and gelling agents. It further requires optimization techniques such as pseudo-ternary phase diagrams and DoE for the identification of stable microemulsion regions and prediction of the performance of formulation. Detailed investigations regarding problems of component interactions, thermodynamic stability, and scalability should be performed to ensure commercial feasibility [16]. Microemulgels thus represent a potentially next-generation platform for topical and transdermal drug delivery. Their capability of combining enhanced solubility, permeation, controlled release, and improved patient experience positions the microemulgels as a versatile carrier for a wide range of therapeutic and cosmetic applications.

II. METHODOLOGY

1. Composition of Microemulgels

The two major components of microemulgels include: 1) a microemulsion system comprising oil, water, surfactant, and co-surfactant; and 2) a gel base comprising suitable gelling agents such as carbopol or HPMC. The oil phase acts to solubilize lipophilic drugs and influences droplet size and skin penetration. Various commonly employed oils include oleic acid, isopropyl myristate, MCTs, and capryol 90, which can further interact with surfactants to provide effective interfacial tension and induce spontaneous droplet formation [17]. Surfactants act to promote microemulsion formation by reducing interfacial tension. For instance, Tween 80, Span 80, lecithin, and sodium lauryl sulfate are common surfactants, and among them, nonionic surfactants exhibit low irritation potential and stability across pH range [18]. Co-surfactants include propylene glycol, ethanol, PEG-400, and Transcutol P, acting to improve the interfacial flexibility and enhance stability of the microemulsion region. The pseudoternary phase diagram was a simple method to optimize their ratios [19-20]. The aqueous phase in general comprises purified water or buffers whose pH can be adjusted to effect on the polarity and dissolution of drugs incorporated. Gelling agents convert the optimum microemulsion into a structured semisolid system with improved viscosity, spreadability, and release control. Generally, carbopol 934/940, HPMC, NaCMC, and xanthan gum are predominantly used. In general, gels are prepared using the dispersion of polymers, followed by neutralization of the resulting dispersed gels, which were mixed with the dispersed microemulsion.

2. Preparation Techniques

Two major steps are involved in microemulgel preparation: (1) formulating a stable microemulsion; and (2) incorporating it into a gel matrix (Fig 1). Preparation techniques include low-energy emulsification, high-energy emulsification, and phase inversion methods [21].

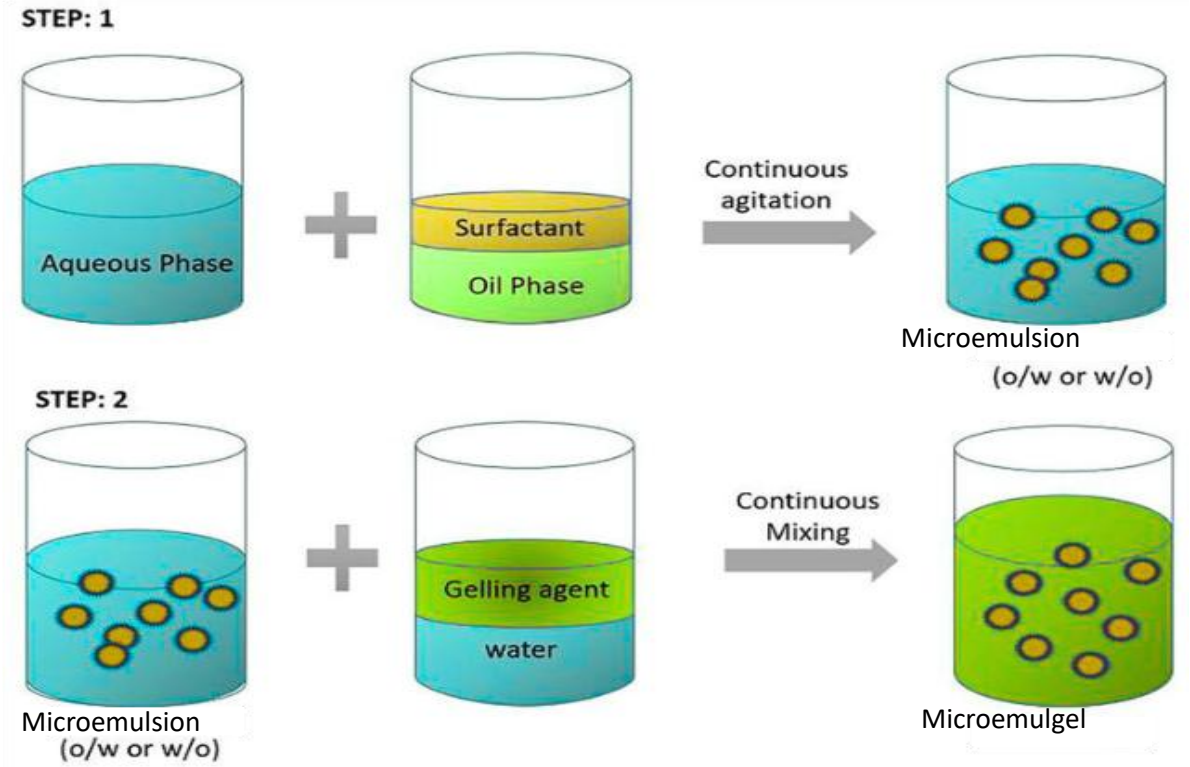

Fig 1: Schematic Representation of formulation of Microemulgel

a. Low-Energy Emulsification Techniques

In fact, these depend only on the intrinsic physicochemical properties of the formulation components. Another largely employed emulsification is the spontaneous emulsification, in which gentle addition of the aqueous phase into the oil/surfactant mixture causes nanoscale droplet self-formation without external mechanical force [22,23]. This method can be used effectively for thermolabile drugs and cost-effective scale-up. Solvent displacement methods are based on the injection of an organic solvent containing the dissolved oil components into water, leading to instantaneous formation of microemulsion droplets due to solvent diffusion [24]. Curcumin microemulsions prepared with isopropyl myristate and Tween 80 exemplify this method [25].

b. High-Energy Emulsification Techniques

When these spontaneous methods are not able to provide uniform nanoscale droplets, some high-energy techniques such as high-pressure homogenization, microfluidization, and ultrasonication are utilized. In high-pressure homogenization, coarse emulsion is forced to pass through narrow gaps with very high pressure (500–1500 bar) to generate uniform droplets [26-27]. Cavitation caused by high-frequency sound waves in ultrasonication (20–40 kHz) yields droplets of smaller

size and better homogeneity. Ultrasonicated clove oil microemulgels demonstrated better antibacterial activity and rheological performance [28-29].

c. Phase Inversion Techniques

Phase inversion temperature (PIT) and phase inversion composition (PIC) methods are based on temperature or composition changes in surfactant affinity for the production of fine emulsions. PIT utilizes temperature-mediated hydration changes of nonionic surfactants, while PIC gradually adjusts water content until inversion takes place [30–32]. The combined method of PIC with ultrasonication has been used successfully for preparing nanoemulsions of isoliquiritigenin [33].

3. Optimization Strategies

The complexity of microemulsion systems requires systematic optimization. There are mainly two commonly used tools:

a. Pseudo-ternary Phase Diagrams

These diagrams present the identification of regions of stable microemulsions by variation in the ratios of oil, water, surfactant, and co-surfactant. They help to determine component ratios, droplet size expectations, and ideal stability zones [34–35].

b. Statistical Optimization of the proposed surface treatment methods (DoE Methods)

Box–Behnken and response surface methodologies present the influence of variables such as surfactant level, polymer concentration, and oil ratio. These methods reduce trial numbers and improve reproducibility.

4. Evaluation Parameters

Evaluation comprises physicochemical, rheological, and performance-specific tests:

• Globule size and PDI: The smaller the globules, the better the permeation of drugs. PDI ≤ 0.3 is considered to show the uniformity of globules.

• Zeta potential: It is a measure of the electrostatic stability; a value of ±30 mV assures adequate repulsion. [36]

• pH: optimum 5.0–6.5 to avoid irritation [37].

• Viscosity: Tested using Brookfield viscometer for optimum spreadability and retention [38].

• Spreadability: Assessed by drag/slip method.

• Drug content: Analyzed with UV or HPLC.

• In vitro release: Using Franz diffusion cells, the release patterns were analyzed according to the models of Higuchi, zero order, and Korsmeyer–Peppas.

• Stability studies: Performed under ICH guidelines in order to detect phase separation, viscosity/pH changes, and drug degradation.

5. Mechanism of Drug Release and Skin Penetration

The drug release from microemulgels occurs via the:

1. Diffusion from microemulsion droplets to gel matrix
2. Diffusion from gel network to skin surface

The release can follow a zero-order, first-order, Higuchi, or Korsmeyer–Peppas kinetics depending on the structure of the polymer and the solubility of the drug. Droplet size, surfactant type, oil penetration enhancers, viscosity of gel, and hydration effects are the major factors affecting skin permeation.

6. Pharmacological Applications
Microemulgels exhibit their effectiveness in:
• Dermatology: psoriasis, acné, fungal & bacterial infections.
• Anti-inflammatory therapy: diclofenac, piroxicam, ketoprofen, aceclofenac.
• Cosmeceutical applications: vitamin E, retinol, niacinamide, coenzyme.
Transdermal delivery: propranolol, lidocaine, nifedipine.

III. DISCUSSION

Microemulgels have emerged as one of the most versatile topical and transdermal drug-delivery systems because of their ability to combine the advantages of microemulsions with gels. Their nanoscale droplets provide superior solubilization and permeation, while the gel matrix will ensure better retention, ease of application, and controlled release. Their advantages over conventional semisolid formulations were strongly evidenced by the literature by improved bioavailability for a variety of hydrophilic and lipophilic drugs. The past decade has seen reasonable progress in formulation science, particularly with the adoption of pseudo-ternary phase diagrams and statistical optimization methods such as Box–Behnken design. These approaches diminished the empiricism in formulation and enhanced reproducibility. However, there is still an empirical lacuna regarding long-term thermodynamic stability, interfacial interactions, and the influence of large-scale manufacturing conditions. Applications of microemulgels have been expanded across dermatology, inflammation, pain management, antifungal therapy, and cosmetics. Their ability to confer sustained release and site-specific action allows them to be preferable for chronic skin diseases where high patient adherence is crucial. New innovations such as nanocarrier-integrated microemulgels, stimuli-responsive systems, and 3D-printed microemulsifying suppositories opened up newer therapeutic avenues.
Even today, despite all scientific advances, the regulatory and industrial translation is limited. For example, high concentrations of surfactant can provoke irritation, and the multi-component nature complicates scale-up and quality control. More importantly, skin physiology is a truly complex field; hence, the establishment of clear IVIVC is difficult to achieve. In summary, microemulgels represent a bright future in the area of personalized topical therapy. Most likely, their integration with artificial intelligence for predictive modeling, green excipient selection, and advanced nanotechnology could help to overcome such barriers and will pave the path toward commercial success.

IV. CONCLUSION

Microemulgels have emerged as a robust and innovative hybrid drug-delivery system that successfully combines the solubilizing potential of microemulsions with the stability and ease of application of gels. Their capacity to enhance drug permeation, provide controlled release, improve bioavailability, and reduce systemic side effects makes them a superior platform for topical and transdermal therapy. Over the past two decades, significant progress has been made in formulation strategies, optimization tools, and evaluation methodologies, demonstrating their ability to deliver both hydrophilic and lipophilic therapeutic agents effectively. Despite these promising advancements, several challenges prevent microemulgels from achieving widespread commercial use. These include formulation complexity, stringent regulatory requirements, variability in excipient quality, and the difficulty of achieving batch-to-batch uniformity during scale-up. Stability concerns, such as phase separation, viscosity variation, and microbial contamination, further complicate long-term storage and commercialization. Additionally, limited in vitro–in vivo correlation data continues to hinder regulatory acceptance and therapeutic predictability. Looking ahead, the future of microemulgels lies in adopting more advanced technological interventions. Integration of nanocarriers, biodegradable polymers, and smart delivery systems could enhance targeting precision and therapeutic outcomes. Artificial intelligence-assisted formulation design, machine learning models for prediction of stability/permeation, and green chemistry-based excipient selection represent key directions for future development. With continued collaboration between researchers, clinicians, regulatory authorities, and industry, microemulgels have the potential to transition from laboratory innovations to clinically established and commercially available delivery systems. Their adaptability, patient-friendly nature, and strong therapeutic promise position them as a next-generation platform for effective, safe, and personalized topical drug delivery.

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