Journal of Research in Pharmacy

Research Article

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The role of microemulsion technology in psoriasis treatment: an evaluation in light of clinical and preclinical findings

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Received: 14 August 2025 / Revised: 10 October 2025 / Accepted: 27 October 2025

ABSTRACT: Psoriasis is a chronic, inflammatory, and immune mediated dermatological diseases that adversely affects the quality of life of millions of individuals worldwide. Due to its heterogeneous nature, which varies from patient to patient, and its systemic manifestations, current treatment approaches are often insufficient and make disease management challenging. This complex pathophysiology has increasingly highlighted the need for more targeted and effective drug delivery systems beyond conventional therapeutic strategies. In recent years, nanotechnology-based drug delivery strategies have attracted attention in psoriasis treatment due to their potential to offer more effective pharmacodynamic profiles and reduce undesirable systemic effects. Among these, microemulsion systems are considered innovative delivery platforms thanks to their high stability, ability to penetrate biological barriers, and controlled release properties. Recent preclinical studies have demonstrated that these formulations can significantly enhance anti-inflammatory, immunomodulatory, and antiproliferative effects. This review aims to evaluate therapeutic potential, formulation techniques, pharmaceutical performance, and translational possibilities of microemulsion-based delivery systems considering preclinical and clinical studies published between 2019 and 2024.

KEYWORDS: Psoriasis; microemulsion; topical; treatment; clinical; preclinical.

1. INTRODUCTION

Psoriasis is a chronic, autoimmune, inflammatory disease characterized by sharply demarcated, erythematous plaques covered with silvery scales, significantly impairing quality of life [1]. Although primarily presenting with visible cutaneous lesions, psoriasis is associated with systemic inflammatory responses that can affect multiple organs and physiological systems [2]. According to data from the Global Psoriasis Atlas, more than 60 million people worldwide are estimated to be diagnosed with psoriasis [3]. While the disease can occur at any age, its prevalence is higher among adults. Moreover, an increased incidence has been reported in high-income countries with aging populations [4]. Various internal and external factors contribute to the pathogenesis of psoriasis. External triggers include agents causing mechanical stress on the skin such as radiotherapy and ultraviolet B (UVB) exposure, air pollution, medications (e.g., beta-blockers, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, antimalarials), vaccinations, infections (e.g., Streptococcus pyogenes, Staphylococcus aureus), and personal habits such as tobacco and alcohol use, psychological stress, and high body mass index [5]. Genetic studies have identified approximately 40 gene loci associated with psoriasis [6]. There are several subtypes of psoriasis, including plaque psoriasis (psoriasis vulgaris), guttate psoriasis, inverse psoriasis, pustular (generalized) psoriasis, and

How to cite this article: Saylam N, Gün E, Çoban Ö, Yener G. The role of microemulsion technology in psoriasis treatment: an evaluation in light of clinical and preclinical findings. J Res Pharm. 2026; 30(3): 882-894.

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ISSN: 2630-6344

https://doi.org/10.12991/jrespharm.1763606

erythrodermic psoriasis [7]. Plaque psoriasis accounts for approximately 90% of all cases[8]. In addition to affecting the skin, joints, and nails, psoriasis is associated with various comorbidities. Patients diagnosed with psoriasis have an increased incidence of hypertension, type 2 diabetes, obesity, non-alcoholic fatty liver disease, dyslipidemia, metabolic syndrome, cerebrovascular and peripheral arterial diseases [9,10]. In the United States, more than 3% of the population is diagnosed with psoriasis, making it the most common autoimmune disease among adults [11]. In Türkiye, psoriasis accounts for approximately 1.3% of all dermatological diseases, with a prevalence rate similar to that in North America and Europe. The condition is reported to be nearly twice as common in women as in men in the Turkish population [12].

1.1. Pathogenesis of Psoriasis

Although the pathogenesis of psoriasis has not yet been fully elucidated, it is thought to involve a complex interplay of immune, genetic, and environmental factors. Early studies on psoriasis pathogenesis primarily focused on keratinocyte hyperproliferation; however, subsequent research has highlighted the infiltration of immune cells into the skin and the role of immune and inflammatory responses [13]. Psoriatic lesions exhibit epidermal hyperproliferation, impaired differentiation, dilation of the dermal vascular plexus, and infiltration of $CD4^+$ and $CD8^+$ T cells into both the epidermal and dermal layers of the skin[14]. In healthy epidermis, basal keratinocytes divide approximately every 13 days, spending most of the time in the G1 phase, and complete their maturation and desquamation in about 26 days. In contrast, psoriatic keratinocytes complete this process nearly five times faster, in approximately 4 days[15]. Hyperproliferative keratinocytes release various cytokines and immune and inflammatory mediators. Although initial inflammatory responses in psoriasis were predominantly associated with T helper 1 (Th1) pathways, recent studies have emphasized the role of Th17 cytokines. Upon exposure to irritants, keratinocytes release antimicrobial peptides (AMPs) such as β-defensins, S-100 proteins, LL-37, and neutrophil gelatinase-associated lipocalin. LL-37 has been shown to promote keratinocyte proliferation and upregulate the expression of IL-36 and alarmin cytokines, both of which are implicated in the pathogenesis of psoriasis [16]. LL-37 forms complexes with DNA or RNA, stimulating various subtypes of Toll-like receptors (TLRs) on plasmacytoid dendritic cells (pDCs). Upon activation, pDCs secrete type I interferons (primarily IFN-γ), which, together with TNF-α and IL-1β directly released by keratinocytes, stimulate conventional dendritic cells. These in turn drive the maturation and differentiation of T cells into Th1 and Th17 subsets. Th1 cytokines (e.g., IFN-γ, IL-12, TNF-α) and Th17 cytokines (e.g., IL-17, IL-22, IL-23, TNF-α) activate keratinocytes, leading to a cascade of immune responses [17]. IL-23 is critical in promoting the proliferation, activation, and differentiation of Th17 cells, stimulating the release of IL-17A and IL-22 [18,19]. TNF-α and IL-17 have been shown to act synergistically, and recent studies have observed that IL-17A increases the expression of IL-36, a member of the IL-1 cytokine family, in psoriatic lesions [20] (Figure 1). In addition to T cell-mediated immune responses, cytokines and AMPs also contribute to the infiltration of neutrophils and macrophages into the skin [21].

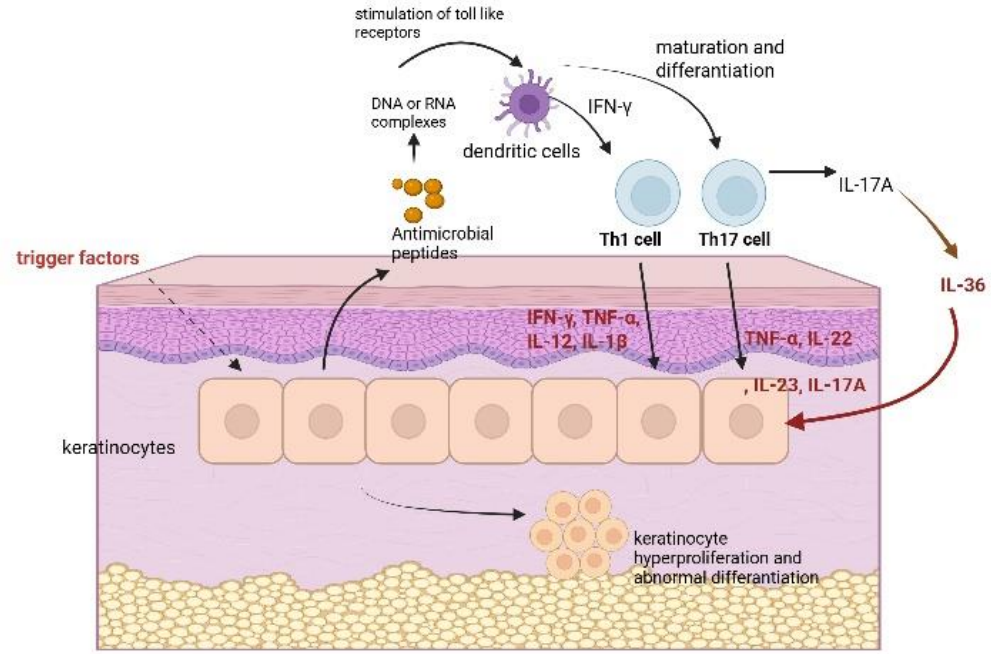


Figure 1. Pathogenesis of psoriasis (Created by Biorender)

1.2. Conventional Treatment in Psoriasis

The current management of psoriasis aims to suppress patients' symptoms, slow disease progression, and improve quality of life [22]. Treatment agents are selected based on the location and severity of psoriatic lesions, the presence of comorbidities, and patient adherence [23]. Although current treatment guidelines include topical agents, systemic conventional and biological therapies, as well as phototherapy options, no curative treatment exists to date [24]. While the use of biological agents has improved treatment success rates, there remains insufficient data on their long-term tolerability and safety profiles, especially with prolonged use [25]. Due to the adverse effects associated with systemic and biological agents, the development of effective topical agents capable of eliciting strong therapeutic responses in psoriasis is of significant importance [26].

Topical agents are the first-line treatment choice for localized and mild psoriasis. Topical corticosteroids, vitamin D analogs, calcineurin inhibitors, retinoic acid derivatives, and keratolytics are suitable for topical administration as antipsoriatic drugs. Among these, vitamin D analogs and corticosteroids are the most frequently used topical agents [26]. Topical treatments offer several advantages in localized psoriasis, including direct application to lesions, avoidance of metabolic reactions that reduce systemic bioavailability, and a lower incidence of serious side effects. However, the stratum corneum (SC) acts as a rate-limiting barrier for transdermal diffusion of active compounds. Once this barrier is surpassed, pharmacologically active agents rapidly penetrate deeper dermal layers and enter systemic circulation. Additionally, topical therapies may cause adverse effects such as hyperpigmentation and burning sensations in both healthy and diseased tissues, which can reduce patient compliance. Systemic therapies are also limited by poor water solubility, insufficient bioavailability, and irregular pharmacokinetic profiles, which may reduce therapeutic efficacy [27].

1.3. Nanotechnology-Based Drug Delivery Systems in Psoriasis

Nanotechnology-based drug delivery systems developed in recent years present a promising approach to overcome these limitations. These systems enhance drug diffusion, penetration, and targeting, enabling greater and prolonged accumulation within the skin. As a result, the duration of drug action is extended, improving therapeutic outcomes. Moreover, such innovative formulations can optimize dosages of conventional drugs, thereby minimizing systemic toxicity as well as local side effects such as burning, irritation, and necrosis during topical application. Given the high costs and lengthy timelines of new drug discovery, enhancing the efficacy and safety profiles of existing drugs through novel drug carrier systems has become a major focus in pharmaceutical research.

1.4. Microemulsions

Microemulsions are thermodynamically stable, transparent systems composed of oil phase, water phase, surfactants, and cosurfactants with droplet sizes ranging from 10 to 100 nm [28]. Due to their biphasic structure, they are capable of carrying both hydrophilic and lipophilic drugs, providing controlled drug release, delayed degradation, and targeted delivery [29,30]. Although the concept of microemulsions was first introduced by Hoar and Schulman in the early 1940s, it has been redefined over time [31]. In practice, oil and water phases are immiscible but can be combined with amphiphilic molecules. According to the definition by Danielsson and Lindman in 1981, microemulsions are optically clear, thermodynamically stable, single-phase, low-viscosity liquids consisting of water, oil, and amphiphilic systems [32]. Surfactants are amphiphilic molecules composed of a polar head and a nonpolar tail. Their hydrophilic and lipophilic parts enable them to stabilize both aqueous and oily phases, thereby forming emulsions. Microemulsions can be classified into three types: oil-in-water (O/W), water-in-oil (W/O), and bicontinuous structures [33]. In W/O systems, the external phase is oil, and the hydrophilic parts of the amphiphiles are oriented toward water droplets, while the hydrophobic tails face the oil molecules of the continuous phase. Conversely, in O/W systems, where water is the continuous phase, the hydrophobic parts of surfactants are directed towards the oil droplets and the hydrophilic parts face the external aqueous phase [33] (Figure 2). Conventional emulsions initially exhibit favorable kinetics but subsequently undergo phase separation. They appear turbid and are thermodynamically unstable, requiring high energy input during preparation [34]. In contrast, microemulsions possess droplet sizes ranging between 10 and 200 nm [35],which are well below the wavelength of visible light, resulting in transparency. Their structure cannot be observed with optical microscopy [19,36]. They have low viscosity, exhibit Newtonian flow behavior, and are thermodynamically stable, requiring low energy for preparation. Surfactants reduce the interfacial tension by penetrating oil and water phases. The combined use of surfactants and cosurfactants drastically lowers interfacial tension, allowing microemulsions to form spontaneously [33,37]. Despite their name, microemulsions are actually nanoscale carrier systems [37]. Microemulsions are structurally and compositionally similar to nanoemulsions; however, they differ in preparation methods and surfactant concentrations. Microemulsions contain higher proportions of surfactant-cosurfactant mixtures and form spontaneously, whereas nanoemulsions require high-energy emulsification methods [38]. The distinction between nanoemulsions and microemulsions is a frequently debated topic. Both systems offer significant advantages as colloidal carriers due to their small droplet size. Specifically, their adequate Brownian motion prevents undesirable phenomena such as creaming, phase separation, coalescence, or sedimentation during storage, thereby enhancing formulation stability. Additionally, nano/microemulsion systems exhibit fluidic properties owing to their large surface area and low interfacial tension.

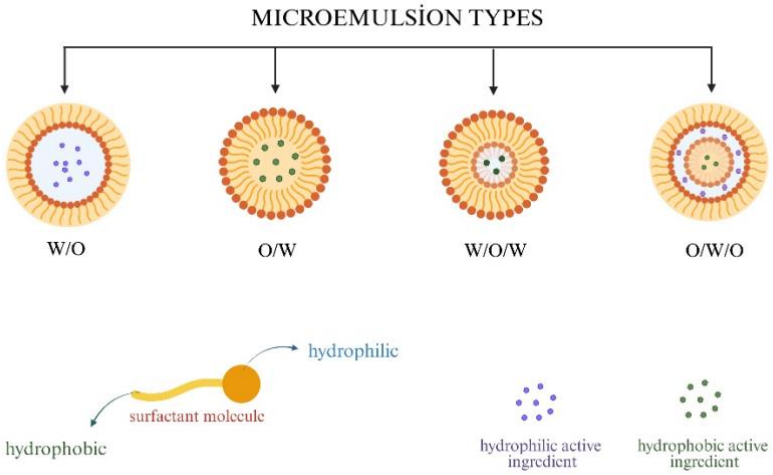


Figure 2. Schematic Diagram of Microemulsion Types (Created by Biorender)

1.4.1. Advantages of Microemulsions

Microemulsions have garnered significant interest in recent years as potential drug delivery systems. One of the main reasons for this is their ability to enhance solubility of drug by facilitating the transport of both hydrophilic and lipophilic active substances. Owing to their multilayered structure they allow the incorporation of water-soluble drugs into oil-based carriers and the delivery of lipophilic drugs within hydrophilic environments. Additionally, their preparation requires low energy input, simplifying the manufacturing process, and their thermodynamic stability contributes to long-term system integrity [35,39,40]. The surfactants present in their structure increase membrane fluidity, thereby enhancing permeability and contributing to improved drug absorption [33]. When lipophilic drugs are administered, their strong interaction with the lipid structure of the cell membrane significantly facilitates drug uptake [35]. Microemulsion systems offer a broad solubilization capacity for both hydrophilic and lipophilic drugs, enabling higher drug loading. This feature helps maintain the concentration gradient across the skin surface for a prolonged period. The internal phase within the system acts as a reservoir, supporting the sustained and controlled release of the drug via the external phase. Since the drug diffuses only from the external phase, the internal phase continuously supplies it, maintaining system saturation and prolonging therapeutic efficacy [35,41].

1.4.2. Routes of Administration

In recent years, microemulsions have been investigated for various applications, including topical, oral, parenteral, and cosmetic use. Their unique structure offers a wide range of applications, from drug delivery systems and cosmetic formulations to food technology and chemical synthesis. The benefits provided by these systems are increasingly drawing attention in many industries that require innovative solutions, and their usage potential continues to grow steadily [37,42]. The versatile nature of microemulsions enables drug administration through different routes, and extensive research has been conducted particularly on their topical applications [36]. As topical delivery systems, microemulsions can enhance the local or systemic absorption of drugs through various mechanisms. Additionally, gel-forming agents have been incorporated into microemulsions to increase their viscosity and develop microemulsion-based gels. The inclusion of a hydrogel matrix has led to the formation of microemulsion-based hydrogels, which are considered more suitable for topical applications compared to conventional microemulsions [40]. Microemulsions offer several advantages over traditional creams and lotions for topical drug delivery. By incorporating moisturizing agents, they can improve both the rate and depth of skin penetration. It has also been suggested that microemulsions may disrupt the organized structure of SC lipids, potentially compromising the skin's barrier properties [43].

1.4.3. Mechanisms of Skin Penetration

The mechanism by which microemulsions enhance skin permeability is thought to involve the loosening of ceramide components within the SC, as well as the disruption of the lipid bilayer in the skin caused by the oil/surfactant/co-surfactant content of the microemulsion [44]. Microemulsions can primarily enhance topical and transdermal drug delivery by increasing the solubility capacity for both hydrophilic and lipophilic compounds, providing a constant drug supply from the internal to the external phase, thereby maintaining saturation in the external phase and facilitating skin absorption. Formulation components such as oils, surfactants, co-surfactants, and penetration enhancers can promote drug diffusion by enhancing drug partitioning from the vehicle into the skin. In addition, the low interfacial tension required for microemulsion formation may be responsible for their excellent wetting properties, which facilitate intimate surface contact between the carrier and the membrane [45]. These penetration enhancers are thought to disturb the organization of SC lipids, thereby increasing lipid fluidity and reducing the diffusion resistance against solubilized substances. Enhanced solubility and permeability of active compounds within the SC are also considered key mechanisms [45]. Notably, the high concentration of oil phase can create permeable pores in the lipid domains, forming an environment with reduced resistance to the passage of transdermal drugs. Moreover, microemulsions possess ultra-low interfacial tension, allowing excellent contact with the skin and facilitating accumulation in fine wrinkles and microscopic skin crevices. This characteristic further improves the efficiency of transdermal drug transport [40,42].

2. RESULTS and DISCUSSION

2.1. Preclinical and Clinical Studies on the Investigation of Microemulsions in the Treatment of Psoriasis

Within the scope of this study, *in vitro, in vivo* (Table 1) and clinical studies (Table 2) investigating the topical use of various active substances with microemulsion technology in the treatment of psoriasis were reviewed. The literature search was conducted using the PubMed® and Clinical Trials® databases covering the period between 2019 and 2024. The search period for clinical studies was also extended. The keywords used during the search were psoriasis, microemulsion, and topical treatment.

Table 1. Preclinical Studies Investigating the Efficacy of Topical Microemulsions in the Treatment of Psoriasis

ME preparation method	Active substance / Concentration (%) / Route of administration	Oil phase (ratio) /Smix (ratio)/ Water phase	ME characterization test results	*In vitro*	*In vivo*	Reference
Pseudo-ternary phase diagram &aqueous ttitration method	Salvianolic Acid B/ 300 µg/mL/ topical	silicon:squalene:TG= 10:1:3 / RH40:Tween 80:PEG 400: 1,2PG=10:1:1:1 / 50% sorbitol and 15% glycerol in PBS	The droplet size, PDI, zeta potential, viscosity, and electronic conductivity were 696.2 nm, 0.435, –14.95 mV, 3112.3 cp, and 24.15 µS/cm, respectively.	Significantly increased flux, permeability, and skin deposition of Salvianolic Acid B vs. EtOH.	In the IMQ-induced psoriasis model in Balb/c mice, significant decreases (↓) were observed in Th17 cytokine and TNF-α levels, while skin irritation tests showed results comparable to the control group.	[46]
Pseudo-ternary phase diagram & aqueous titration method	Cyclosporine A/ 0.05% w/w / topical	15% IPM / 60% Smix (Tween 80 :isopropyl alcohol= 2:1) / 25% water	The droplet size, PDI, zeta potential, viscosity, pH, surface tension, and drug content of the optimized ME were 98.32 nm, 0.234, –11.8 mV, 89.7 cP, 5.5, 32.2 dyn/cm, and 98.4%, respectively.	Improved cyclosporine permeation and skin retention (38.9%) over 24 h compared to suspension; gel form showed slightly reduced penetration due to higher viscosity.	In the skin irritation test conducted on New Zealand rabbits, no erythema or irritation was observed on the skin.	[47]
Spontaneous emulsification method	Lithospermic acid / 0.1% (w/w) / topical	silicon:squalene:TG= 10:1:3 / RH40:Tween 80:PEG 400: 1,2PG=10:1:1:1 / 50% sorbitol and 15% glycerol in PBS	N/A	N/A	In the IMQ-induced psoriasis model in Balb/c mice, significant decreases (↓) were observed in PASI scores, as well as in Th17 and IL-6 cytokine levels, while proinflammatory cytokine levels in spleen homogenates showed no significant change (.)	[48]
Pseudo-ternary phase	Indurubin / N/A/ topical	castor oil/ polyoxyethylene ether: PEG-	The average particle size is 84.37 nm, PDI <	ME increased drug permeation (47.3 µg/cm², 24 h) — 2.1×	In the IMQ-induced psoriasis model in Balb/c mice,	[49]

diagram & aqueous titration method		400 (4:1) / 68% water	0.2, and zeta potential are in the range of 0~−20 mV.	vs. oil and 13.1× vs. aqueous; due to small particle size and SC interaction.	decreases (↓) were observed in spleen weight and PASI scores, as well as in proinflammatory cytokines and proliferation markers in the skin.	
Pseudo-ternary phase diagram & aqueous titration method	Desoximetasone/ %0.01 ve %0.05/topical	silicon:squalene:TG= 10:1:3 / RH40:Tween 80:PEG 400: 1,2PG=10:1:1:1 / 50% sorbitol and 15% glycerol in PBS	N/A	Esperson (0.25% desoximetasone) showed higher flux, permeation, and skin deposition than DXM, while DXM had shorter lag time and slightly higher permeability.	At both concentrations, significant decreases (↓) were observed in epidermal thickness and trans epidermal water loss, while skin hydration increased (↑). The reductions in Th17 cytokines and TNF-α levels were comparable to those achieved with the 0.05% desoximetasone commercial formulation. Additionally, the safety profile was similar to that of the control group.	[50]
Pseudo-ternary phase diagram & aqueous titration method	Tacrolimus /N/A/ /topikal	Stearic acid, Softisan® 601, Tefose® 63, Tefose® 1500, Monosteol®, Lauroglycol® 90, Capryol® 90, Brij® C20, Miglyol® 812, Capmul® PG12, Capmul® MCM, Capmul® PG8, Tween-20, Tween-80, Kolliphor® HS15, Transcutol® P, Plurol Oleique®, Labrasol®, Labrafil® M2125, carbomer polymers.	The droplet size is 320 nm, PDI < 0.3 and zeta potential is -19.4 mV. Entrapment efficiency is 60%.	Tacrolimus nanogel showed sustained 24 h release (~95%) vs. 56% for the marketed product. No transdermal permeation observed; nanogel had lower skin retention but ~3.5× higher epidermal deposition. Non-toxic to NIH-3T3 cells.	In the oxazolone-induced psoriasis model in Sprague Dawley rats, tacrolimus emulsion showed significant decreases (↓) in epidermal thickness and inflammatory cell infiltration compared to tacrolimus alone.	[51]

ME: Microemulsion, **Smix:** Surfactant:cosurfactant mixture, **PDI:** Polydispersity index, **RH40:** PEG-40 Hydrogenated Castor Oil, **1,2-PG:** 1,2-Propylene Glycol, **TG:** Triglyceride, **PBS:** Phosphate-Buffered Saline, **IPM:** Isopropyl Myristate, **PEG:** Polyethylene glycol, **PG**: Propylene glycol, **Th**: T helper, **TNF:** Tumor Necrosis Factor, **OA:** Oleic acid, **N/A:** Not available, **EtOH**: Ethanol, **DXM:** Desoximetasone

Table 2. Clinical Studies Investigating the Efficacy of Topical Microemulsions in the Treatment of Psoriasis

Active substance /Dose/ Frequency of administration	Microemulsion composition	Diagnosis	Phase	Period	Route of administration	Starting date	Status	Result	Clinical Trial ID/ References
Cyclosporine / 10, 25, 50, and 100 mg / Twice weekly	N/A	Plaque psoriasis	Phase III	24 weeks	Oral	2006	Completed	Compared to placebo, a significant increase in adverse effects was observed, while the improvement in psoriasis scores was positive.	NCT00438360 /[52]
Methotrexate / 0.1% / Three times per week	40% jojoba oil, 45% Tween-80 and Span-85 (3:1 ratio)%15 su	Plaque psoriasis	Phase IV	12 weeks	Topical	2021	Unknown	N/A	NCT04971239 /[53]
Oleuropein / 0.2% (compared with 0.05% clobetasol)	Etil oleat, Capryol 90, Transcutol	Plaque psoriasis	N/A	8 weeks	Topical	N/A	N/A	Treatment with oleuropein cream resulted in a 70.04% reduction in PASI scores, compared to a 45.6% reduction with clobetasol ($p < 0.05$). A decrease (↓) was also observed in epidermal thickness and keratinocyte hyperproliferation.	[54]
Ferulic acide 0.1% / Once daily (compared in combination with laser therapy)	77% water, 20% Tween-80:ethanol (2:1), 3% benzyl benzoate, and bergamot oil containing 1% benzyl alcohol, 0.2% sodium carboxymethylcellulose	Scalp psoriasis	N/A	2 weeks	Topical	N/A	N/A	Although reductions in psoriasis scores were observed in both treatment groups, a significant decrease (↓) was noted in the psoriasis scores with ferulic acide microemulsion combined with laser therapy.	[55]

Although our understanding of the pathogenesis of psoriasis has improved in recent years, the adverse effects of current treatment options, treatment resistance, and the safety and cost issues associated with the chronic nature of the disease—requiring long-term therapy—underscore the ongoing need for novel therapeutic approaches [23]. While topical agents offer ease of application and are considered first-line treatment options for mild to moderate psoriasis, their clinical effectiveness is often limited by structural barriers to skin absorption, which restrict optimal drug delivery to target sites [27]. To overcome these challenges, microemulsion formulations have been developed. These innovative systems enhance the percutaneous penetration and bioavailability of active ingredients, allowing for the effective topical application of various therapeutic compounds, some of which have historically been administered orally or faced challenges with skin permeation.

Cyclosporine, a calcineurin inhibitor, has demonstrated efficacy in moderate to severe psoriasis since 1985 through numerous preclinical and clinical studies [24,56]. Despite its rapid onset of action, which is advantageous for clinical management, its long-term use is restricted due to adverse effects such as nephrotoxicity and hypertension; treatment beyond two years is not recommended. Consequently, topical cyclosporine applications have been proposed to enhance safety profiles [57,58]. However, its low skin permeability has long hindered topical delivery [59]. To address this issue, cyclosporine-loaded microemulsions have been designed to enhance penetration and retention of the drug within the skin, thereby overcoming its limited permeability [47]. In the clinical trial registered as NCT00438360, oral cyclosporine microemulsions were administered for 24 weeks to patients with chronic plaque psoriasis, with monitoring of PASI scores and adverse events. While the treatment improved disease progression compared to placebo, adverse effects were more frequently reported. Redesigning such studies with direct comparisons to conventional cyclosporine formulations may provide clearer insights into the safety and therapeutic balance of oral microemulsion therapy.

Beyond cyclosporine, other active molecules have also shown improved efficacy when formulated into microemulsions. For instance, Indirubin-based microemulsions with an average particle size of 84.37 nm exhibited enhanced topical delivery, resulting in reductions in PASI scores, proinflammatory cytokines, and proliferation markers in the skin [49]. Desoximetasone microemulsions significantly reduced epidermal thickness, increased skin hydration, and demonstrated comparable decreases in Th17 cytokines and TNF-α levels relative to commercial formulations [50]. Similarly, lithospermic acid delivered via microemulsion induced marked reductions in PASI scores and inflammatory cytokine levels [48]. Collectively, these findings emphasize that microemulsions can enhance both the therapeutic efficacy and dermal delivery of a wide range of compounds for psoriasis therapy. By improving targeted drug delivery to affected skin layers, microemulsions represent a promising strategy to maximize local efficacy, minimize systemic exposure and adverse effects, and ultimately improve patient outcomes.

Tacrolimus, another calcineurin inhibitor acting through T-cell-mediated mechanisms, has also been extensively investigated for topical psoriasis treatment [60]. However, its efficacy is reduced in areas with thickened skin, such as psoriatic plaques [61]. In an *in vivo* psoriasis model, Kakade et al. demonstrated that the microemulsion formulation of tacrolimus achieved significantly better therapeutic outcomes than conventional topical formulations [51].

Furthermore, cytochrome P450 (CYP) enzymes—key regulators in the metabolism of drugs and xenobiotics—are expressed in various keratinocyte subtypes. Studies have confirmed the expression of CYP1A1, CYP1A2, CYP1B1, CYP2A6/7, CYP2B6/7, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2C, CYP2E1, CYP3A4/7, and CYP3A5 at both mRNA and/or protein levels in keratinocytes [62]. Comparative studies have shown that excipients commonly used in topical formulations, such as Tween-20 and Tween-80, can disrupt CYP structure and inhibit enzyme activity [63]. Similarly, surface-active agents including Cremophor EL, Tween 80, and Solutol HS have been shown to influence microsomal enzyme activity, with Solutol HS dose-dependently decreasing hepatic clearance, and Cremophor EL and Tween 80 inhibiting enzymatic activity by 20–50% at 0.3% concentrations [64]. Such excipients, widely used in microemulsion systems, may help prolong the topical activity of drugs by preventing rapid metabolic inactivation by keratinocyte-expressed enzymes, as demonstrated in the study by Guo et al. [50]. Nonetheless, the impact of excipients on enzyme kinetics underscores the importance of considering drug metabolism during formulation design. Moreover, the appropriate selection of excipients is crucial not only for metabolic stability but also for minimizing skin irritation induced by keratolytic agents such as salicylic acid [46].

In light of these data, microemulsion technology demonstrates potential as an innovative and promising topical drug delivery system that enhances active ingredient penetration, reduces inflammation, and improves treatment safety in psoriasis therapy.

3. CONCLUSION

The persistent challenges in managing psoriasis, including the adverse effects of current therapies, treatment resistance, and the chronic nature of the disease necessitating long-term care, underscore an urgent need for innovative therapeutic strategies. While topical agents offer convenience and serve as a first-line treatment for mild to moderate cases, their efficacy is often hampered by the skin's formidable barrier, limiting optimal drug delivery. In this context, microemulsion technology emerges as a highly promising and transformative approach.

As elucidated throughout this review, microemulsion formulations address these critical limitations by significantly enhancing the percutaneous penetration and bioavailability of active ingredients. This allows for the effective topical application of a diverse range of therapeutic compounds, many of which traditionally faced hurdles with skin permeation or were limited to oral administration due to their physicochemical properties. The ability of microemulsions to carry both hydrophilic and lipophilic drugs, coupled with their thermodynamic stability, low energy preparation, and controlled release properties, positions them as superior delivery platforms.

Preclinical and clinical findings demonstrate the tangible benefits of microemulsion-based systems. For instance, cyclosporine-loaded microemulsions have been shown to overcome the drug's low skin permeability, increasing its retention in the skin and enabling topical use. Similarly, compounds like Indurubin, Desoximetasone, Lithospermic acid, and Tacrolimus, when formulated into microemulsions, exhibit improved topical delivery, leading to significant reductions in inflammatory markers, PASI scores, and epidermal thickness. These examples collectively highlight microemulsions' capacity to maximize therapeutic efficacy by ensuring better drug delivery to affected skin layers, thereby potentially reducing systemic exposure and associated side effects, and ultimately improving patient outcomes in psoriasis treatment.

Furthermore, the careful selection of excipients within microemulsion formulations holds additional importance, not only for optimizing drug metabolism by influencing CYP enzymes but also for mitigating skin irritation. This holistic approach to formulation development is crucial for developing safe and effective long-term treatments.

In summary, current evidence highlights microemulsion technology as an innovative and promising topical drug delivery platform that enhances the penetration of active ingredients, reduces inflammation, and improves both safety and therapeutic outcomes in psoriasis management.

Acknowledgements: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions: Concept – N.S.; Design – N.S., E.G..; Supervision – Ö.Ç., G.Y.; Resources – N.S., E.G., Ö.Ç., G.Y.; Materials – N.S., E.G., Ö.Ç., G.Y..; Data Collection and/or Processing – N.S., E.G.; Analysis and/or Interpretation – N.S., E.G., Ö.Ç., G.Y.; Literature Search – N.S., E.G.; Writing – N.S., E.G.; Critical Reviews –N.S., E.G., Ö.Ç., G.Y.

Conflict of interest statement: The authors declared no conflict of interest.

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