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Review Article

# Step-by-Step Industrial Development of Microemulsion for Topical Application

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ABSTRACT

Microemulsions are stable nanoscale drug delivery systems formed from oil, water, surfactants, and cosurfactants, with droplet sizes of 10 to 200 nm. They offer high solubility, easy preparation, stability, and the ability to incorporate both lipophilic and hydrophilic molecules. Their nanoscale droplets increase skin contact, while SFs temporarily disrupt the barrier to improve absorption. Higher stability of microemulsions can be achieved by using Pseudo-ternary phase diagrams. Non-ionic SFs like tween and span, along with short-chain alcohol CSFs, are common. The oil phase includes fatty acid esters and vegetable or natural oils with penetration-enhancing properties. A quality target product profile is quintessential to defining the desired microemulsion properties. Critical quality attributes define the physicochemical properties of microemulsions, their target values, and significance. Evaluation involves droplet size, pH, viscosity, zeta potential, conductivity, stability, and in vitro release. Studies show drugs like cyclosporine, methotrexate, and tacrolimus in microemulsions improve skin retention, reduce systemic absorption and toxicity, and produce positive histopathological effects. Microemulsions can be formulated as gels, offering high permeability, spreadability, and sustained release. The manuscript systematically presents a sequential, logical workflow that mirrors actual industrial development processes. It systematically reviews advances in research, preparation methods, and evaluation techniques for microemulsions used in transdermal drug delivery, especially for psoriasis treatment. The article lacks original experimental data; all information and conclusions are based on published literature to support formulation development and industrial application in this area.

## Introduction

A Microemulsion (ME) is a transparent liquid comprised of oil and water, thermodynamically stable and stabilized by an interfacial film of a mixture of Surfactant (SF) and Cosurfactant (CSF) in a suitable proportion, with droplet sizes ranging from 10 to 200 nm. ME is characterized by higher stability and smaller liquid droplet size at the microscale (r<100 μm). Various fabrication methods can alter the ME's composition, structure, droplet size, and surface attributes.[1,2] The key difference between an ME and a nanoemulsion (NE) is their thermodynamic stability. ME is thermodynamically stable, whereas a NE is not.[3] Compared with traditional creams, ointments, and other dosage forms, MEs offer advantages such as strong solubilization, thermodynamic stability, and ease of preparation. Importantly, MEs can significantly enhance drug permeation through the skin barrier, thereby improving topical treatment outcomes.[4]

In recent years, ME formulations have attracted considerable attention as drug carriers for delivering both lipophilic and hydrophilic active moieties, owing to their excellent drug solubility, longer shelf-life, simple

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and economic method of preparation, and enhanced bioavailability. ME typically consists of four components: an oil phase (OP), an Aqueous phase (AP), an SF, and a CSF. Although MEs are macroscopically homogeneous, they are microscopically heterogeneous because an SF monolayer separates water- and oil-rich domains.[5]

This paper aims to provide a systematic review of MEs as thermodynamically stable nanoscale drug delivery systems, covering their formulation strategies, characterization methods, and potential applications in transdermal psoriasis treatment. The analysis will focus on the composition and microstructure of ME, the construction of pseudo-ternary phase diagrams, key quality attributes, and the effects of various ME types (single or multiple) on drug transdermal behavior. Furthermore, the review will explore the advantages of MEs and their gel formulations in improving drug retention in the skin, reducing systemic toxicity, and enhancing patient compliance. It will also highlight shortcomings in existing research regarding safety evaluation, clinical translation, and standardized preparation, with a view to providing a technical and conceptual reference for the subsequent development and application of ME formulations in the treatment of skin diseases.

Psoriasis is a long-term, recurrent, immune-driven inflammatory skin condition characterized by excessive keratinocyte growth and abnormal differentiation, along with infiltration of inflammatory cells into the dermis. Current topical treatments for psoriasis face several challenges: traditional formulations such as ointments and creams have limited ability to penetrate hyperkeratotic skin, making it difficult to achieve effective drug levels in both the epidermis and the dermis. Additionally, many standard therapies, including corticosteroids, retinoids, and vitamin D3 derivatives, are hindered by poor water solubility, irritancy, or high systemic absorption, restricting their use.[6] MEs, as thermodynamically stable nanoscale drug-delivery systems, offer a promising platform for overcoming these obstacles.[7]

MEs significantly enhance the anti-psoriatic efficacy of drugs through their unique microstructure and composition. Many anti-psoriatic drugs (such as cyclosporine, methotrexate, and glucocorticoids) have poor water solubility. The oil phase of MEs can efficiently dissolve lipophilic drugs, whilst the aqueous phase can carry hydrophilic drugs, significantly increasing the total drug loading capacity and thereby enhancing delivery efficiency.[8] MEs can be designed to rapidly form a high-concentration gradient on the skin surface, driving the drug into hair follicles and intercellular channels. At the same time, their nanostructure reduces rapid drug clearance by capillaries, prolonging its retention time at the lesion site and enabling sustained local release. MEs have substantially increased the solubility of poorly soluble drugs (e.g., calcipotriol, tacrolimus, dianthrone), forming high-concentration gradients that drive transdermal penetration. [9] The ultra-small particle size and low interfacial tension of MEs allow them to adhere closely to the skin's stratum corneum. This reversibly reduces barrier function, facilitating drug penetration through the thickened squamous layer to achieve targeted accumulation in the epidermal basal layer and dermis, the primary sites of action for the disease.[10] ME components (such as SFs and CSFs) can temporarily disrupt the lipid arrangement of the stratum corneum, reducing its barrier function and facilitating the drug's easier penetration into deeper layers of the skin, thereby enabling it to reach the sites of psoriatic lesions (the epidermis and dermis). Studies indicate that ME formulations containing cyclosporine, methotrexate, or glucocorticoids demonstrate superior drug retention and more pronounced histopathological improvements, e.g., reduced epidermal thickness and alleviated parakeratosis, in psoriasis animal models compared to conventional creams, whilst concurrently reducing systemic drug absorption and potential hepatotoxicity or nephrotoxicity. The composition of the ME (e.g., selection of oil phases or SFs with anti-inflammatory activity) can synergistically inhibit psoriasis-related inflammatory factors (e.g., TNF-α and IL-17). Their microstructure also facilitates drug interaction with skin immune cells (such as Langerhans cells), thereby modulating local immune responses. [11] Through multiple mechanisms—including drug solubilization, enhanced transdermal delivery, targeted retention, reduced toxicity, drug stabilization, and immune modulation- MEs significantly improve the efficacy of anti-psoriasis drugs. Their microstructure and flexible composition make them highly effective delivery systems for treating psoriasis.

Furthermore, MEs can be further developed into ME gel formulations, combining the high permeability of nanocarriers with the excellent application properties of gels.[12] ME gels not only alleviate the difficulty in spreading medication caused by dry, cracked, and desquamating psoriatic lesions but also form a local drug reservoir for sustained release, reducing the frequency of application.[13] More significantly, the oil phase and SFs of the ME may inherently possess keratolytic and moisturizing properties, aiding in the restoration of the compromised skin barrier function in psoriasis and thereby exerting adjunctive therapeutic effects. By rationally designing ME components (e.g., selecting oil phases with anti-inflammatory activity), synergistic effects between drug delivery and intrinsic therapeutic efficacy can be achieved, offering novel approaches for the comprehensive management of psoriasis.[14]

The microstructure of ME is depicted in Fig. 1 and varies with component ratios, ranging from small water or AP droplets dispersed in the OP (w/o ME) to OP droplets dispersed in the water or AP (o/w ME). This structure

transitions smoothly from a spherical shape to a cylindrical shape, then to a tubular shape, and finally to interconnected, continuous OP and AP. These phases are separated by a thin layer of SF and CSF molecules, forming a bicontinuous ME.[15]

Emulsions and MEs exhibit fundamental differences in thermodynamic stability, droplet size, and formation mechanisms. Emulsions are thermodynamically unstable systems with globule sizes typically ranging in the micrometer range. Consequently, they are prone to OP and AP isolation, flocculation, or coalescence during storage, necessitating the application of external mechanical forces (such as high-speed stirring or homogenization) and thermal energy for their formation. In contrast, MEs constitute thermodynamically stable systems—their microstructure forms spontaneously through SF-CSF interactions, requiring minimal external energy input. MEs exhibit extremely small droplet sizes, typically 5-100 nanometers. This results in a transparent or translucent appearance, coupled with exceptionally low interfacial tension and highly effective solubilization capabilities. These properties confer superior stability, enhanced transdermal delivery potential, and higher drug-loading efficiency than conventional emulsions.[16]

Three key mechanisms make MEs beneficial for transdermal drug delivery: solubilizing drugs, potentially increasing their thermodynamic activity at the skin surface, and weakening the stratum corneum's structure, thereby facilitating greater drug flux through the skin. Additionally, drug release from MEs can be enhanced because the drug's affinity for the internal phase can be easily adjusted. The ME formulation typically includes an SF, a CSF, an OP, and an AP. [17]

The industrial development of MEs for topical administration requires a step-by-step technical approach, as shown in Fig. 2. The first step involves screening suitable OP, SF, CSF, and AP components and determining the proportions of each component via a pseudo-ternary phase diagram to form a thermodynamically stable, transparent system. The second step involves optimizing formulation parameters, such as adjusting the SF-to-CSF ratio (typically 1:1-3:1) and controlling the OP content (5–20%), to ensure particle sizes within the 10 to 100 nm range and good skin permeability. The third step involves scale-up using low-energy emulsification methods, such as gradually diluting the oil-SF mixture with water to avoid foaming or degradation issues caused by high-energy agitation. The fourth step is pilot-scale production validation, controlling mixing temperature, stirring rate, and feed sequence to maintain consistency in particle size and drug loading between batches. The fifth step involves conducting quality control tests, including pH, conductivity, centrifugation stability, drug release profiles, and skin irritation assessments. Finally, commercial production is carried out in strict compliance with GMP conditions, and packaging compatibility and accelerated stability studies are completed to ensure the safety, efficacy, and quality control of the ME product for topical application.

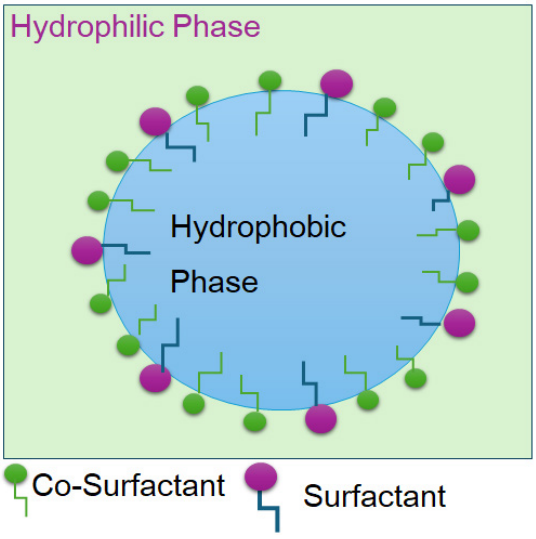



**Fig. 1:** Microstructure of ME

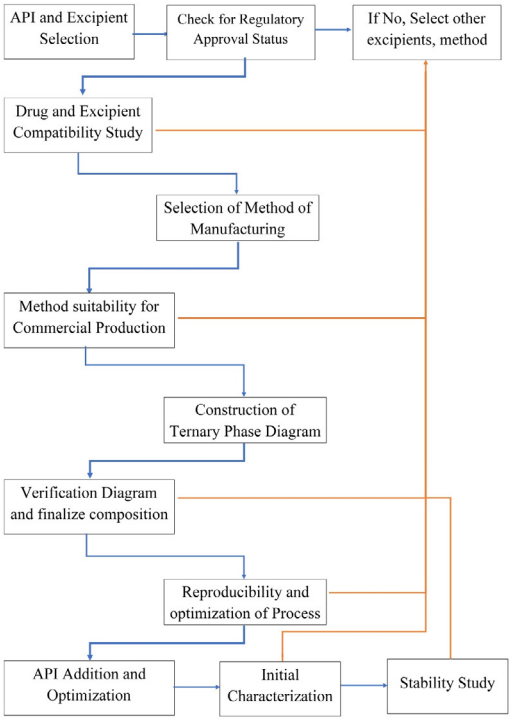



**Fig. 2:** Step-by-Step Flow-Chart ME Product Development

## ME Types

According to Winsor's theory, there are four types of ME phase states that exist in equilibrium, as shown in Fig. 3; these are known as Winsor phases. Winsor I is a two-phase system in which the upper OP coexists in equilibrium with the lower water-in-oil ME phase; Winsor II is also a two-

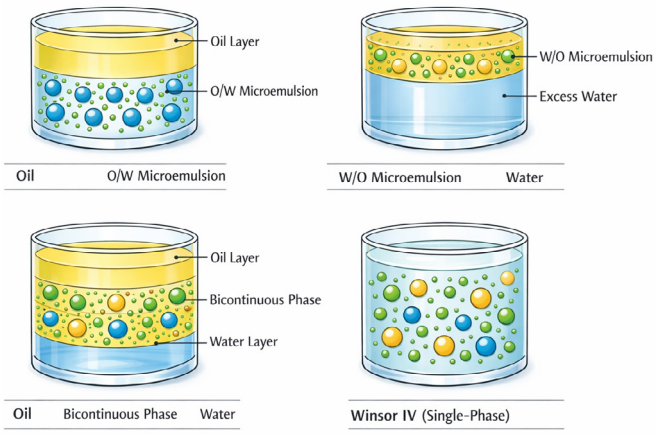



**Fig. 3:** Types of MEs

phase system in which the upper oil-in-water ME coexists in equilibrium with the lower excess water phase; Winsor III is a three-phase system, with an intermediate phase comprising a double-continuous ME of oil-in-water and water-in-oil, coexisting in equilibrium with the upper oil phase and the lower water phase respectively; Winsor IV, on the other hand, is a single-phase system, formed by a homogeneous mixture of OP, AP, SF, and CSF.[18]

The R-Ratio, introduced by Peter Winsor, describes how SFs, oil, and water interact, affecting behavior and microstructure. It compares SF affinities: R > 1 favors oil and results in inverted MEs; R < 1 favors water and results in normal MEs; R ≈ 1 results in straight interfaces and Winsor Type III MEs. The Ratio predicts phase behavior and guides industries such as oil recovery, detergents, and cosmetics by adjusting SF or salinity levels. While conceptually a ratio, R isn't directly measurable; rather, it serves as a theoretical framework. Researchers manipulate variables- like increasing hydrophobic chain length or altering oil phase- to alter R. Longer chains or polar oils increase lipophilicity, raising R. Adding SFs or salts influences interface bending and interfacial tension. Adjusting head groups in SFs improves hydrophilicity, lowering R. Temperature also affects R, stabilizing or dehydrating hydrogen bonds. Increasing salinity shifts R from below 1 to above 1, passing through the Winsor I, III, and II phases. Observing mesophase changes helps identify optimal conditions for solubilization and low interfacial tension, emphasizing the importance of molecular interactions in controlling interface curvature and stability. [19]

## Quality Target Product Profile [20]

Table 1 illustrates a generic template for quality target product profile (QTPP) and is not derived from a single experimental product. It could be employed as a reference for ME development.

## Critical Quality Attributes [21]

Table 2 illustrates a generic template for critical quality attributes (CQAs) and is not derived from a single experimental product. It could be employed as a reference for ME development.

**Table 1:** Example of QTPP for ME

| *QTPP Elements* | *Target* | *Justification* |
|---|---|---|
| Dosage form | ME | Better efficacy & safety profile |
| Dosage design | Oil-in-water or water-in-oil ME | Better efficacy & safety profile |
| Route of administration | Topical- Scalp Application | Hair Growth by using a local application |
| Dosage strength | 2, 5, 10 % w/w | Better safety & efficacy than the existing marketed drug product. |
| Pharmacokinetics | Effective permeation in the scalp and respective dermal layers. | Better safety & efficacy than the existing marketed drug product. |
| Pharmacodynamic | Clinical endpoint | Better safety & efficacy than the existing marketed drug product. |
| Stability | Minimum twenty-four-month shelf life at specified storage conditions. | Better safety and efficacy over time |
| Drug product quality attributes | This includes visual appearance, identification, potency, impurity, active ingredient uniformity, pH, apparent viscosity, globule size distribution, zeta potential, conductivity, refractive index, dye staining test, coalescence time, rheology, specific gravity, minimum fill, microbial limit test, residual solvents, elemental impurities, in vitro release test, packaging integrity, and leakage test. | To maintain the product quality & efficacy throughout the shelf life. |
| Container Closure System | A bottle with a suitable spray | A compatible device to secure the desired shelf life & maintain finished product integrity during transport and usage. |
| Administration | Twice-a-day application | To achieve the desired efficacy |

**Table 2:** Example of CQAs for ME

| *Quality attributes of drug product* | *Target* | *Is this a CQA?* | *Justification* |
|---|---|---|---|
| Physical attributes | | | |
| Visual appearance | Clear transparent Solution | Yes | Visual appearance in MEs is directly correlated to efficacy & safety, as changes in appearance indicate destabilization and cracking. Therefore, we will evaluate visual appearance throughout product & process development. |
| Apparent viscosity | Optimum viscosity spreads and sprays easily. For generic products, it should be similar to the innovator products. | Yes | Apparent Viscosity is directly linked to safety and efficacy, as it impacts not only drug release but also the uniformity of the active in bulk. Lower viscosity may increase drug release and the likelihood of phase separation, and vice versa. Both the formulation and process variables may affect the apparent viscosity. Thus, apparent viscosity should be evaluated throughout formulation & process development. |
| Globule/Droplet size distribution | $D_{10}$: NMT 10 nm<br>$D_{50}$: NMT 70 nm<br>$D_{90}$: NMT 100 nm | Yes | The globule/droplet size distribution of the drug product is linked to efficacy. The globule size may impact drug product uniformity, product microstructure, viscosity, rheology, and drug release. Not only formulation but also process variables impact the droplet/globule size distribution of finished products. Thus, the finished product's droplet/globule size should be evaluated throughout formulation and process development. The target is set based on RLD characterization and understanding of the drug product. |
| Microscopy | Microscopic appearance should include tiny droplets in the matrix, while the visual appearance is clear. | Yes | The change in the ME's microscopic structure demonstrates its instability, which can affect not only safety but also efficacy. It could be affected by both formulation variables & process variables. Advanced microscopic techniques are required for ME evaluation. |
| Optical transparency | True MEs scatter light minimally and are clear. MEs typically exhibit >90% transmittance at 500–600 nm. | Yes | MEs are optically transparent. Because MEs are optically transparent and isotropic, it is relatively straightforward to study them using light-scattering techniques. This facilitates the measurement of molecular diffusion behavior and particle size under highly dilute conditions. Hence, changes in optical transparency affect the quality. |
| Refractive index | The refractive index of the MEs ranged from 1.2 to 1.5. | Yes | The refractive index varies with changes in the ME composition. Hence, it could be a good tool for controlling the quality of the ME. Both the composition and process can impact the refractive index. |
| Specific gravity | *~0.95* | No | Specific gravity is not directly correlated to efficacy & safety. However, it is required to determine the appropriate volume of drug product in packaging containers. Hence, it is neither critical nor monitored throughout product and process development. |
| Minimum Fill | USP general chapter <755> *Minimum Fill* | Yes | Minimum fill is not directly linked to efficacy & safety. However, it is essential to ensure the drug product's appropriately filled weight meets the label claim. Minimum fill is critical and will be monitored during the filling operation and release of pilot-scale exhibit batches. Limits are set in accordance with USP General Chapter <755> Minimum Fill. |
| Packaging integrity | Upon visual inspection, the tube should be tightly closed without any leakage. The printed label information on the bottle and the carton box should be legible, with no stains on the carton box. | Yes | Packaging integrity is not directly linked to efficacy & safety. However, it will impact patient acceptability. Therefore, it will be monitored during packaging operations and during the stability program for the Exhibit batches. This target has been set to ensure patients can accept it. Needs to be monitored only in commercial batches. |

Cont…

| *Quality attributes of drug product* | *Target* | *Is this a CQA?* | *Justification* |
|---|---|---|---|
| Leakage# Testing (during filling operation) | No Leakage | Yes | Product leakage is not directly linked to efficacy & safety. However, it will impact the minimum fill and patient acceptability. Leakage Testing is performed during the filling operation. The target is set to ensure patient acceptance. |
| **Chemical attributes** | | | |
| Identification | Positive for API | Yes* | Although identification is crucial to efficacy and safety, this critical quality attribute can be effectively controlled through the quality management system and monitored at the time of finished product release. Neither formulation nor process variables affect identification. |
| pH | 4.0~6.0 | Yes | pH variability is directly linked not only to efficacy but also to safety. Higher or lower pH values may destabilize MEs, cause skin irritation, and trigger allergic reactions. In general, formulation variables affect pH, whereas process variables may not. Thus, pH will be evaluated throughout product development. The target is set based on RLD characterization |
| Zeta potential | For a topical ME, an ideal zeta potential is typically above ±30 mV for electrostatic stability. However, values of ±5 mV to ±20 mV can be acceptable if steric stabilization is present. | Yes | The significance of the zeta potential lies in the fact that its value is closely related to the short-term and long-term stability of an emulsion. Emulsions with a high zeta potential (whether negative or positive) exhibit electrical stability, whereas those with a low zeta potential are prone to coalescence or flocculation, which may result in poor physical stability. Generally speaking, when the zeta potential of an emulsion is high, repulsive forces outweigh attractive forces, thereby forming a relatively stable system. |
| Conductivity | O/W MEs usually exhibit high conductivity, typically around 300 μS/cm or higher, because the continuous external phase is conductive water, which helps with skin permeation. W/O MEs, on the other hand, have very low or nearly zero conductivity, typically less than 0.05 mS/cm, as their continuous external phase is non-conductive oil. | Yes | Conductivity measurements help to determine whether the ME system formed is oil-in-water or water-in-oil. By measuring conductivity, the dissolution of the aqueous phase in the selected oil mixture is quantitatively monitored. A conductivity meter was used to determine the conductivity of the optimized ME. |
| Assay | NLT 90.0% and NMT 110.0% of the label claim | Yes | Differences assay can affect the safety and effectiveness of medicinal products, while various manufacturing variables can also influence the analytical outcomes of drug formulations. Consequently, it is crucial to continually assess analytical methods during the product's development and manufacturing stages. |
| Bulk Uniformity # | All individual bulk uniformity sample test results should be within 90.0% – 110.0% w/w of the mean, and the RSD of those results should be NMT 5.0% | Yes | Variability in the uniformity of the bulk finished product can affect both the safety and effectiveness of the drug product. Manufacturing unit process variables may affect bulk uniformity, which, in turn, may affect tube uniformity. Therefore, bulk uniformity should be evaluated during the manufacturing process optimization. The target is set to produce a homogeneous bulk of the drug product. |
| Uniformity of API in Container | Meets the requirements of current USP <3> | Yes | Variability in the uniformity of the container's contents will affect the efficacy & safety of the medicinal product. Not only formulation but also process variables can influence content uniformity; therefore, this critical quality attribute (CQA) will be evaluated throughout the product and process development. |

Cont…

| *Quality attributes of drug product* | *Target* | *Is this a CQA?* | *Justification* |
|---|---|---|---|
| Degradation Products | Product-specific impurities | Yes | Degradation products from the drug substance may affect patients' vital conditions and must be controlled in accordance with ICH Q3B(R2). The limit for the total impurity limit, specified and unspecified, should be set in accordance with the ICH identification, qualification, and reporting threshold for this drug product. |
| Preservative content | NLT 90.0% and NMT 110.0% of the label claim | Yes | Variations in preservative content may affect efficacy & safety by promoting microbial proliferation in the finished product. Preservative content can be impacted primarily by process; however, formulation variables may interfere with preservative activity. Consequently, the preservative content should be assessed throughout the entire formulation and process development cycle. |
| Antioxidant content | NLT 90.0% and NMT 110.0% of the label claim | Yes | Antioxidant content may affect the efficacy & safety of the finished product by degrading active ingredients. Formulation & process can impact antioxidant content; consequently, the antioxidant content should be assessed throughout the entire formulation and process development cycle. |
| Chelating agent content | NLT 90.0% and NMT 110.0% of the label claim | Yes | Chelating agent content may affect efficacy & safety of the finished product by degrading active ingredients. Formulation & process can impact the chelating agent; consequently, the chelating agent should be assessed throughout the entire formulation and process development cycle. |
| ***Elemental impurity*** | Meet USP <232> and ICH Q3D Option 2b. No testing is required. | Yes* | Compliance with USP <232>/ICH Q3D Option 2b. It is therefore unlikely that formulation and process variables will affect Elemental Impurity. |
| Residual solvent | As per USP <467> Class 3 requirement | Yes* | Residual solvents in finished drug products may affect patients' safety. The manufacturing process and the medicinal product should comply with the Class 3 standard of the United States Pharmacopeia <467>. Therefore, there must be a lower chance that formulation and process variables impact residual solvent. |
| Microbial Enumeration Test and Test for specified microorganisms | Must meet the USP general chapters <61> and <62> requirements. | Yes* | Microbial limits should be strictly controlled, and any Non-compliance with them in finished products will impact patient safety. However, the raw materials are tested for microbial limits, and the process is conducted in a controlled environment, which is unlikely to affect the microbial enumeration test and the test for specified microorganisms. This CQA should be evaluated in batches of manufactured exhibits from the cGMP facility. |

*Drug, excipients, and process variables are unlikely to affect the critical quality attribute. Consequently, this critical quality attribute will not be further investigated or discussed in subsequent risk assessments or during drug development. However, as this critical quality attribute remains a target element in the product characteristics, it should be treated accordingly.

## Selection of Excipients

### *Surfactants (SFs) and Co-Surfactants (CSFs)*

Choosing the right combination of SFs and CSFs is vital for optimizing ME formulations, maintaining stability, and meeting desired application needs. This selection depends on numerous factors, including the attributes of the dispersed phases, target specifications, and industry standards. SFs and CSFs are essential for forming and stabilizing MEs by lowering the interfacial tension between incompatible phases. These amphiphilic molecules facilitate the creation of a stable colloidal system. MEs form spontaneously when SFs and CSFs reduce interfacial tension, allowing immiscible phases to disperse.[22] Examples of oils, SFs, and CSFs are tabulated in Table 3.

SFs play a crucial role in ME formation, with their selection greatly impacting stability. At low concentrations, SFs exist as monomers, making monomer and SF concentrations equal. These monomers accumulate at the phase boundary, forming a monolayer at the interface of water and oil. When the SF concentration reaches a specific level, micelle formation begins, a phenomenon called the critical micelle concentration (CMC). The structure of SFs influences the CMC; generally, higher hydrophobicity lowers it. Different SF types—anionic, cationic, zwitterionic, and nonionic—

show different CMC values in the presence of electrolytes. Temperature also significantly impacts the CMC. Choose SFs that effectively minimize interfacial tension between OP and AP, and combine lipophilic and hydrophilic SFs to stabilize the ME.[23]

Nonionic SFs include the Tween (polysorbates), Span, and Brij series. Tweens (polyoxyethylene sorbitan esters), such as Tween 20, 60, & 80, are widely used for their compatibility with various OP and APs. The Span (sorbitan fatty acid esters) series, including Span 20, 60, & 80, is often combined with Tween SFs to create stable MEs. The Brij (polyoxyethylene alkyl ethers) series (such as Brij 30 & 58) is a family of effective nonionic SFs with varying lipophilic attributes. Cationic SFs include benzalkonium chloride (BKC) and cetyltrimethylammonium bromide (CTAB). Cationic SFs are used in certain cases despite being less common in MEs due to potential toxicity. Anionic SFs are less frequently employed because they can destabilize MEs, but they are useful in certain formulations. Examples of anionic SFs include sodium lauryl ether sulfate (SLES) and sodium dodecyl sulfate (SDS).[24]

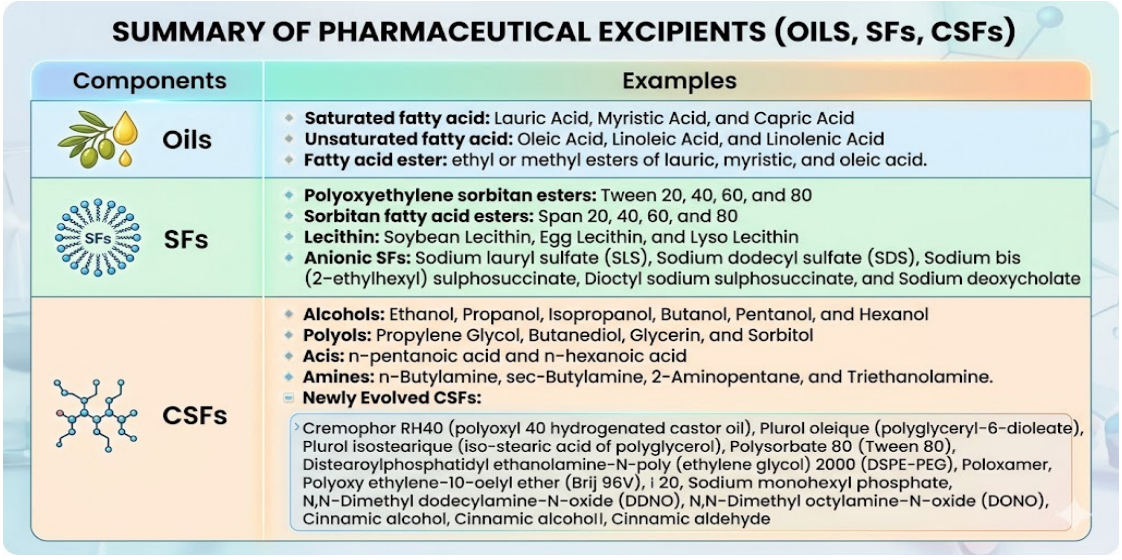
CSFs help SFs stabilize MEs. Common options include alcohols, polyols, and fatty acids. Short-chain alcohols, including ethyl, isopropyl, and n-butyl alcohols, enhance solubilization and stability. Meanwhile, long-chain alcohols such as decyl, hexyl, and dodecyl alcohols adjust the hydrophilic-lipophilic balance (HLB) and enhance stability. Polyols such as propylene glycol (PG) and glycerol act as CSFs as well as humectants, often used in cosmetics, thereby improving viscosity, water-holding capacity, and stability. Fatty acids and esters, such as oleic acid (OA) and isopropyl myristate (IPM), also serve as CSFs. Oleic acid's amphiphilic nature supports ME stability, while IPM serves as both an OP and a CSF, and is frequently used in medicated and non-medicated cosmetics products. Amines such as triethanolamine also serve as CSFs and pH adjusters, helping enhance stability in certain formulations.[25,26]

## Oil Phase (OP)

The selection of the OP depends on numerous factors, such as the target ME attributes, the drug's compatibility with other excipients, and the intended application. It is crucial to also evaluate toxicity, biodegradability, and regulatory approvals, particularly in sectors such as pharmaceuticals and cosmetics. The oil phase plays a crucial role in determining the colloidal system's stability, characteristics, and applications. Selecting the right oil depends on the particular needs of the application, as there are many oils to choose from. Opt for an oil that matches the desired ME characteristics and application needs, while considering solubility, biocompatibility, and stability.[27,28]

Saturated hydrocarbons such as decane and dodecane, along with isoparaffinic oils, are often chosen for their low polarity and excellent solubilizing properties. Mineral oils, derived from petroleum, are stable, low in toxicity, and commonly used in cosmetics and pharmaceuticals. Vegetable oils, such as sunflower and soybean oil, are biodegradable and suitable for biocompatible applications. However, their higher polarity can restrict their use in some formulations. Ester-based oils, such as IPM and ethyl oleate, are frequently used as oil phases in MEs because they can solubilize both hydrophobic and lipophobic compounds. These substances are often used in medicated pharmaceutical and non-medicinal cosmetic products. Silicone oils like Dimethicone and cyclomethicone are appreciated for their non-greasy texture, enhanced stability, and cosmetically appealing spreadability, making them common in cosmetic and personal care products. Natural oils, including Limonene and d-limonene, are extracted from herbs, trees, and plants. They are being

**Table 3:** Examples of Oils, SFs, and CSFs



employed more frequently as eco-friendly options in ME formulations, especially in pharmaceuticals and cosmetics. Fluorinated oils are stable and find applications in specialized fields such as drug delivery and imaging because of their distinctive properties. [29,30]

## Aqueous Phase (AP)

The selection of the AP depends on the site of application and the target indication. It can include distilled or purified water or any kind of aqueous solutions containing additives, such as salts, buffers, or other ingredients. Selecting the aqueous phase in ME systems is essential because it directly impacts the formation, stability, and performance for specific applications. It acts not just as a dispersing medium; its composition and properties significantly influence the system's phase behavior, interfacial characteristics, and solubilization ability. Proper selection of factors, including pH, polarity, and ionic strength, influences SF behavior at the interface of oil and water and determines whether the ME is O/W, W/O, or bi-continuous. For uses such as drug delivery and cosmetics, biocompatibility and stability are critical, necessitating appropriate pH, osmotic pressure, and compatibility with other formulation components. Understanding the purpose of the ME guides the choice, focusing on phase type, ionic strength, pH, and component compatibility to ensure stability and avoid precipitation or hydrolysis. [31]

Practical applications utilize various aqueous phases, including Purified or distilled water, Buffered solutions, Isotonic solutions, Salt-containing solutions, and Polyol aqueous solutions. Purified or distilled water is the most basic and commonly used type, suitable for model systems or fundamental research without specific ionic-strength needs. Buffered solutions, such as phosphate-buffered saline (PBS) or acetate-buffered saline, are frequently used in pharmaceutical MEs to stabilize pH, preserve drug effectiveness, and reduce irritation of biological mucosa. Isotonic solutions such as 5% glucose or 0.9% sodium chloride (physiological saline) are often used in MEs for injection or ocular applications to match body fluid osmolarity and prevent tissue damage.[32] Salt-containing solutions, including sodium chloride or potassium chloride at particular concentrations, primarily modify ionic strength, influence SF solubility, affect phase behavior, or enhance drug solubilization. Polyol aqueous solutions containing glycerol, propylene glycol, or polyethylene glycol adjust system viscosity and can act as CSF. These solutions may also increase the surface area of ME droplets, boosting moisturizing properties or improving drug penetration through the skin.[33]

## Construction Of Pseudo-Ternary Phase Diagram (TPD)

A TPD plot visually shows the phases of an ME with three components: OP, AP, and SF/CSF. It helps identify the concentration makeup for each component at specific points on the diagram. In ME systems, these diagrams are called pseudo-ternary phase diagrams (PTPD). They are equilateral triangles where each corner often represents a mixture of two or more components, such as SF/CSF, drug/water, or drug/oil, especially when more than three formulation components are involved. Each point on the diagram represents a specific combination of the three components, with their mass fractions indicated along the triangle's sides. [34,35]

Constructing phase diagrams is essential for identifying the best ratios of oil, water, SF, and CSF to achieve thermodynamic stability. These analyses are key to characterizing and understanding ME systems, especially when used alongside structural analysis methods. A comprehensive phase diagram detailing the experimental conditions for component mixing is critical for ME evaluation. Usually, the phase composition includes oil, water, and SF/CSF, as shown in a pseudo-ternary phase diagram in Fig. 4. This triangular diagram, with each vertex representing 100% of a component, illustrates the isothermal distribution of structural regions within its interior.

When the AP and OP are mixed with an SF that forms a standard opaque emulsion, and the dispersion is then titrated with a CSF to form an optically transparent system, the SF/CSF ratio can be determined to achieve a thermodynamically stable system. The system's components and composition influence the formation of various microstructures and bi-continuous structures. Typically, a pseudo-ternary phase diagram is used for systems involving an SF blend, an SF with CSF, an OP from animal, natural, or chemical sources, and an AP, usually a water-based solution. The phase diagram's domain regions illustrate several critical transitions between the mixture's different states. These transitions include shifts from gel-emulsion (GEM) phases to gel-microemulsion (GME), as well as movements from gel-microemulsion (GME) and gel-emulsion (GEM) states into liquid-microemulsion (LME). Furthermore, the diagram captures the transition from gel-emulsion (GEM) to liquid-emulsion (LEM) and the subsequently transition from the liquid-emulsion (LEM) phase to a liquid-microemulsion (LME).[36]

Each phase has a significant impact on the physicochemical attributes of the ME microstructure, emphasizing the importance of detailing the TPD. Additionally, it is well established that MEs stabilized with nonionic SFs are heat-sensitive, often operating over a narrow temperature range. ME is characterized by a specific phase inversion temperature (PIT) where the curvature of the film reverses from positive to negative. Shinoda and colleagues established critical points for ME formation based on this temperature: when the temperature is lower than the PIT (T < PIT), an oil-in-water (O/W) ME known as Winsor I is formed. Conversely, if the temperature exceeds the PIT (T > PIT), the system shifts to a water-in-oil (W/O) ME

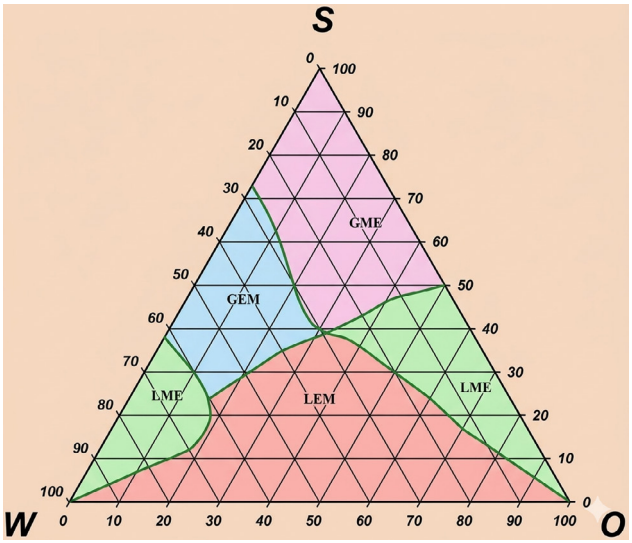



**Fig. 4:** PTPD for a system containing SF/CSF blend, OP, and AP.

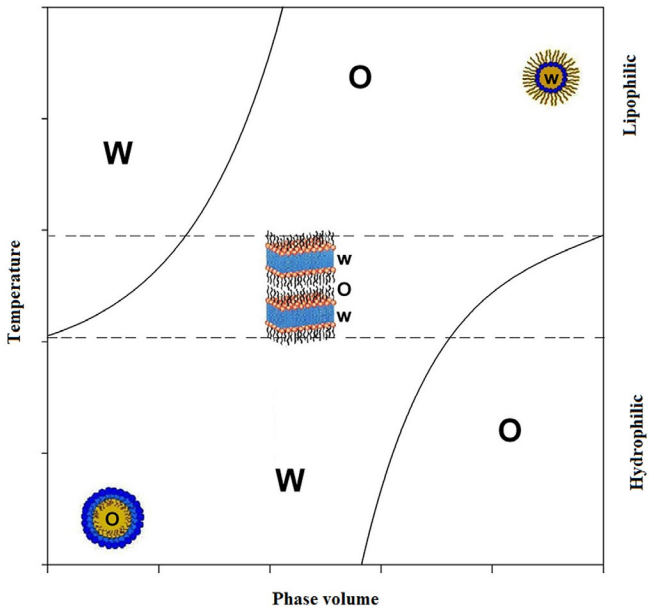



**Fig. 5:** Transition from O/W to W/O non-ionic ME systems

referred to as Winsor II. Finally, when the temperature equals the PIT (T = PIT), the system reaches a middle phase ME designated as Winsor III.

The diagram shows the transition from an oil-in-water ME at low temperatures with higher water concentration, to a bi-continuous ME near the phase inversion temperature (PIT), and finally to a water-in-oil ME at higher temperatures. It also helps clarify the structures of MEs, as discussed earlier in this review. The regions of the PTPD provide a quantitative understanding of the boundaries between different structural transition zones. For example, a gel ME appears in a small region where the AP (60–70%) dominates over the OP (up to 10%). When the AP exceeds 70%, and OP is minimal, a fully transparent liquid ME (LME) forms, which, at infinite water dilution, is demonstrated by swollen micelles. The systems on the PTPD can be analyzed and characterized using techniques such as small-angle X-ray scattering, X-ray diffraction, polarized light microscopy, and photon correlation spectroscopy to determine their microstructures. Since characterizing MEs is crucial, these analytical methods will be discussed in more detail.[37]

A PTPD was constructed to pinpoint the ME region. In brief, SF 1 and SF 2 were mixed in equal weight ratios and integrated into the oil phase. Beakers were filled with 10 grams of oil and SF blends with weight ratios ranging from 1.0:9.0 to 9.0:1.0. Ultrapure water was gradually added dropwise to each mixture while stirring at 200 rpm at room temperature (25 ± 1°C). Water was added until the mixture became turbid, marking a shift from ME to coarse emulsion. The volume of water causing slight turbidity was recorded. Subsequently, samples were left to equilibrate at 25±1°C for at least 24 hours, with transparent samples indicating monophasic regions within the phase diagram. [38,39]

## Formulation Examples

Studies cited in Table 4 primarily focused on enhancing the transdermal permeation and bioavailability of poorly soluble drugs using ME technology. They extensively explored its applications across multiple dermatological fields, including acne, fungal infections, psoriasis, skin cancer, and wound healing. In formulation design, studies predominantly employed oil phases (such as oleic acid and IPM), SFs (primarily Tween 80), and CSFs (e.g., Transcutol, ethanol, and PG) to construct the systems. Key findings indicate that MEs not only control drug particle size to the nanometer scale (some below 20 nm), significantly increasing drug retention and penetration rates within the skin, but also function as multifunctional carriers. For instance, the oil phase itself (e.g., peppermint oil, tea tree oil) can serve as a penetration enhancer or active ingredient, or the ME can be further gelled to prolong the duration of action. These optimized formulations consistently demonstrated superior therapeutic efficacy and favorable stability in animal models compared to conventional creams or gels. Recent formulations are shown in Table 4, along with key treatment indications, active ingredients, SFs, CSFs, and oils.

## Preparation Methods

The phase titration method involved preparing the ME by dispersing the required amount of active ingredient in a defined oil volume to ensure solubilization. The mixture must be stirred, and an accurately measured concentration of the SF-CSF blend must be added gradually under stirring. The blend should be thoroughly mixed employing a suitable stirrer, and purified water should be added dropwise while stirring continuously for about 10 minutes. The stirring and homogenization speed should

**Table 4:** Examples of ME formulation from recent research work

| *Treatment* | *Active Ingredient* | *Oil Phase* | *SF(s)* | *CSF / Other Components* | *Key Findings* |
|---|---|---|---|---|---|
| Anti-psoriatic | Apremilast | Captex 300 | TPGS, Tween 80 (3:1 ratio) | Water (to induce liquid crystal phase transition) | Formed a lyotropic liquid crystal system upon hydration, providing sustained drug release (>72h) and enhanced skin retention.[40] |
| | Methotrexate | IPM | Tween 80 | Ethanol / Propylene Glycol | Achieved a droplet size of $15.4 \pm 0.5$ nm, significantly increasing drug deposition in the dermis compared to commercial gels.[41] |
| Atopic dermatitis | Doxepin | Oleic acid | Tween 80, Labrazol | Propylene glycol (PG) | Droplet sizes 9.8-61.6 nm. Optimized formulation (ME-DX-8) showed an eightfold increase in skin permeation parameters and remained stable for 6 months.[42] |
| | Tacrolimus | Safflower oil, Miglyol 812 | Cremophor EL, PEG 400 | Transcutol P | ME was developed and scaled up to 600 mL.[43] |
| Antiacne | Dapsone | IPM | Tween 80 | Transcutol, Ethanol | An optimized ME containing 5% menthol significantly increased the skin permeation of dapsone compared to the control gel.[44] |
| | Azelaic Acid | IPM | Cremophor EL, PEG 400 | Transcutol HP | With the ME carrier, the permeability of azelaic acid was remarkably improved.[45] |
| | Tea Tree Oil | Tea Tree Oil (Active Oil) | Tween 80 | Span 80 / Glycerol | Optimized via Pseudo-ternary phase diagrams; showed 99.9% inhibition of *P. acnes* in vitro within 24 hours. [27] |
| Antifungal | Miconazole nitrate | oleic acid | Tween 80 | ethanol, 2-(2-ethoxyethoxy) ethanol, or 2-propanol | A topical ME formulation containing miconazole nitrate has been efficiently delivered, thereby enhancing miconazole nitrate bioavailability.[46] |
| | Clotrimazole | Peceol (Glycerol monooleate) | Kolliphor EL and Labrasol | Transcutol P | An optimized SF ratio of 3:1 provided the highest skin permeability and the greatest stability against phase separation.[47] |
| | Terbinafine HCl | Olive Oil | Tween 80 | Isopropyl Alcohol | Developed as a "U-type" ME (water-in-oil), which improved the solubility of the lipophilic drug by 15-fold.[48] |
| | Terbinafine HCl | Oleic acid | Labrasol S | Transcutol P | Microbiological studies showed greater antifungal activity than the currently marketed product ($P < 0.05$) when tested against *Aspergillus flavus* and *Candida albicans*. [49] |
| | LysM-C14 protein | Ionic liquid-in-oil bazed | (Part of an ionic liquid-based system) | Lauric (C12), Myristic (C14), or Palmitic (C16) acids (for lipidating the protein) | Novel ionic liquid ME effectively delivered antifungal proteins through the stratum corneum, retaining activity after 28 days of storage.[50] |
| Antibacterial | Azithromycin | vitamin E acetate | Labrasol® | Transcutol® P | A higher concentration of Azithromycin was found in pig skin compared to the control.[51] |
| Antiviral | Acyclovir | Labrafil M 1944 CS | Labrasol | Transcutol P | Used an SF and CSF ratio of 2:1 and showed a 3-fold increase in skin permeation flux compared to standard marketed creams.[52] |
| Anti-inflammatory effect | Benjakul | IPM | Labrasol®, Plurol® Oleique | Transcutol® | Benjakul ME demonstrated in vitro anti-inflammatory effects, significantly enhanced skin permeation, and good stability for 2 years at room temperature.[53] |

Cont...

| *Treatment* | *Active Ingredient* | *Oil Phase* | *SF(s)* | *CSF / Other Components* | *Key Findings* |
|---|---|---|---|---|---|
| | Herbal Extracts | IPM | Tween 80 | Propylene Glycol | Demonstrated non-irritant profile in skin sensitivity tests while maintaining a droplet size below 100 nm.[54] |
| | Naproxen | Oleic Acid | Tween 20 | Isopropanol | OA acted as both the OP and a chemical permeation enhancer, doubling the flux of Naproxen across the stratum corneum.[55] |
| | Lidocaine HCl and Ketorolac | Jojoba oil | Brij 97 | hexanol | The skin permeation rates of Lidocaine HCl and Ketorolac have been significantly increased by formulating as ME in the presence of hexanol.[56] |
| Skin brightening | Genistein | Capryol 90, Peceol, Oleic acid | Tween 80, Cremophor EL, Brij 30 | Labrasol, Transcutol HP, PEG 400 | The bioavailability of Genistein was enhanced 10-fold after the ME formulation was designed.[57] |
| | Methimazole | oleic acid-transcutol p at a 1:10 ratio | Tween 80 and Span 20 | Propylene glycol | The ME formulation demonstrates significant improvements in the physicochemical attributes and permeability of Methimazole in rat skin.[58] |
| Anti-aging | Passiflora setacea Oil | Passiflora setacea seed oil (10%) | PEG-30 Castor Oil | Span 80 | Using the active oil itself as the internal phase showed superior wound-healing and anti-inflammatory properties.[59] |
| | Acmella oleracea Extract | Caprylic/ Capric Triglycerides | Polysorbate 80 | Sorbitan Monooleate / Carbopol 940 (Gelling agent) | Successful conversion to a "microemulgel", which increased skin residence time and controlled release of botanical actives.[60] |
| Antioxidant | Curcumin | Medium-chain triglycerides (MCT) | Tween 80 | Ethanol (High concentration for solubilization) | High drug loading (7.7 g oil phase) and significantly enhanced dermal penetration compared to conventional creams.[61] |
| Anesthetic | Lidocaine | Eucalyptus Oil | Tween 80 | PEG 400 | Eucalyptus oil served as both the oil phase and a natural permeation enhancer, resulting in a faster onset of anesthesia.[62] |
| Chronic Wound Healing | Lycopene | Ethyl oleate | Tween 80 | PEG 400, Konjac glucomannan (KGM), Carbopol 940 | ME incorporated gel containing Lycopene exhibited complete wound healing and closure by day 14 in a diabetic rat model.[63] |
| Hair Growth | Minoxidil | Oleic acid | Tween 80 | Polyethylene glycol 200 | ME resulted in more than 5% of the drug remaining in the skin, which is almost 1.5 times the amount in the reference gel.[64] |
| Age-Related Macular Degeneration | Sirolimus / Axitinib / Fenofibrate | α-Linolenic acid (ALA) | Cremophor RH 40, Span 80 | Transcutol P | An ocular ME demonstrated sustained drug release for up to 240h. Sirolimus ME demonstrated strong antiangiogenic activity in the HET-CAM assay.[65] |
| Melanoma | Diacetyl Boldine | MCT | Solutol HS 15 | Lecithin/ Propylene Glycol | The DAB accumulation in intact skin for ME under infinite dose conditions was sufficient to suppress B16BL6 cell proliferation.[66] |

be adjusted based on the desired droplet size. The PIT method involves transforming MEs from o/w to w/o by either adding excess volume of non-continuous phase or enhancing the temperature, depending on the SF type. This process changes the SF's spontaneous curvature, bringing the system close to zero or minimal surface tension and producing the finest, dispersed OP globules. Such a process results in a significant reduction in droplet size, which can further affect drug release patterns both in vitro and vivo. [67, 68]

## Evaluation of ME

### *Visual Appearance*

The systems were visually inspected for uniformity, optical clarity, and fluidity. Appearance refers to the dispensed product's look, feel, and smell. Observations should describe the color, clarity, or opaqueness, texture, odor, and other product characteristics, such as being free from particulate matter or particles of the active ingredient.[69]

## Phase Behavior

Phase diagrams are extensively employed in researching emulsions and MEs. They offer detailed insights into identifying the domains of MEs and other systems, like liquid crystals and coarse emulsions. However, in many cases, it was difficult or impossible to distinguish between an ME and an ultrafine-emulsion clearly. They offer insights into the boundaries of different phases based on composition, structural organization, and temperature. Moreover, phase behavior studies allow for comparing how effective different SFs are for particular applications. The boundaries of one-phase regions can be directly observed by examining samples of known composition. Careful planning and execution of experiments are crucial for preparing a phase diagram, especially for systems prone to being supersaturated. The slow approach to equilibrium across multiple regions can make these procedures time-consuming, tedious, and subjective, particularly when liquid crystalline phases are involved.[70]

## Globule Size Analysis

Globule size distributions are notably influenced by the type and concentration of SFs used in MEs and by the methods of preparation. Biologically, MEs enhance drug absorption through the skin by facilitating quick release and expanding the contact surface between the internal phase and the skin.[71]

## Viscosity

Low viscosity characterizes MEs, providing cosmetic appeal and easy handling and packaging. The viscosity of the ME can be measured manually using a glass apparatus or with modern digital instruments. An appropriate spindle should be used for the measurement.[72]

## Rheology

Various factors affect the rheological characteristics of MEs, including the types of continuous and non-continuous phases, the phase volume ratio, and, to some extent, the droplet size distribution. Variation in the dispersed-phase volume or adjustments in SF type and concentration can create different products, including liquids that flow easily. In MEs with a low internal-phase volume, the overall consistency typically mirrors that of the continuous phase. Structural transitions, like sphere-to-rod or discontinuous-to-bicontinuous changes, affect rheology. Bi-continuous MEs usually behave as Newtonian fluids with persistent apparent viscosity at low to medium shear rates but show shear thinning at higher shear rates, likely because of structural breakdown. Discontinuous MEs often behave as Newtonian fluids over a broader shear rate range. Choosing the right spindle for the liquid or solution is essential during rheological tests. [73,74]

## Zeta Potential (ZP)

ZP assesses the stability of MEs and their o/w solubilization capacity. It represents the electric potential at the interface of a dispersed droplet relative to a point in the surrounding continuous phase away from the interface. In essence, it is the voltage difference between the moving dispersion medium and the stationary layer on the particle. Factors such as pH, ionic strength, additive concentration, and temperature significantly influence zeta potential. Its importance lies in predicting emulsion stability over various time frames. Emulsions with high absolute ZP (positive or negative) are electrically stabilized, whereas those with low zeta potential tend to coagulate or flocculate, risking physical instability. Generally, a high ZP indicates a predominance of repulsive forces, leading to a more stable system. [75]

## Conductivity

Electrical conductivity (EC) is an easy, simple, and affordable method for characterizing MEs. It determines whether the system is OP- or AP-continuous and helps estimate phase boundaries caused by compositional or temperature changes. Conductivity measurements provide a quantitative assessment of water solubilization in the chosen oily mixture. The optimized ME's conductivity was determined with a conductivity meter. EC measurements are essential for characterizing ME systems and understanding their microstructures. Studies indicate that the conductivity of MEs directly correlates with their internal organization: w/o MEs feature nanoscale water globules dispersed in a continuous oil phase. Their conductivity mainly depends on droplet collisions and transient coalescence, leading to lower conductivity. Conversely, o/w or bicontinuous systems, in which water forms the continuous phase or channels, exhibit considerably higher conductivity. In this research, all ME samples had conductivities below 5 µS/cm, confirming their classification as typical W/O MEs through additional methods. Results also demonstrated that, at fixed water content, increasing SF concentration increased conductivity, likely because SFs gather at the oil–water interface, stabilizing droplets and increasing collision rates, thereby enhancing charge transfer. Excess SF can introduce free molecules into the continuous phase, altering interfacial structure and droplet behavior and thereby influencing conductivity patterns. Therefore, conductivity not only helps distinguish ME types but also provides insights into system evolution and interfacial properties. During ME template optimization, conductivity measurements help select systems with the desired structural features for nanogel formation. As a rapid, non-destructive technique, conductivity offers valuable guidance for future nanogel synthesis using ME templates. [76]

## pH

Topically applied drug products should be tested for pH, as pH changes can influence the physicochemical characteristics of the drug moiety in the final finished

product. Significant shifts in pH may affect drug ionization and permeability. This requirement does not apply to non-aqueous formulations. In MEs, pH affects SF charge and stability. The pH conditions should be selected that are compatible with the formulation ingredients and intended use. The direct testing method involves placing about 5 to 10 g of the sample in a suitable container, immersing the electrode, and recording the stable pH reading. For the dilution method (10%), accurately weigh 1 g of the product, add 9 g of purified or demineralized water, mix thoroughly, and measure the pH until a stable reading is obtained.[77]

## Electron Microscopy (EM)

Transmission EM (TEM) and scanning EM (SEM) are employed to investigate the internal and surface mesophase nanostructures. Typically, TEM involves preparing a thin-film sample that allows electrons to pass through, with contrast arising from differences in electron absorption and scattering across regions. As with all electron microscopy methods, artifacts from sample preparation and dehydration are significant concerns, leading to the development of cryogenic TEM and freeze-fracture TEM techniques. Cryogenic TEM combines rapid vitrification of the sample into a thin film, preserving it in a frozen, hydrated state very close to its natural condition without ice formation or crystallization. A recent review discusses cryogenic TEM techniques and their applications in colloidal systems, including MEs and sponge phases. Freeze-fracture TEM entails splitting samples under a vacuum, usually along the inner (lipophilic) regions of membrane-like structures. This method offers a "face-on" perspective that distinctly displays network structures of bicontinuous or droplet MEs. This method complements cryo-TEM for ME characterization. SEM offers direct surface mapping of MEs, but it is less common due to preparation issues similar to those encountered in non-cryogenic TEM. Field-emission SEM, which uses narrower electron beams at not only low but also high energies, enhances resolution. Cryogenic Field-emission SEM has also been used to analyze the surface morphology of various MEs. [78, 79]

## Refractive Index

Isotropic materials, like MEs, possess a single refractive index (RI) and enable light to vibrate in any direction as it passes through. This results in uniform optical properties regardless of light direction. For example, MEs with a low OP-to-SF ratio exhibit isotropic behavior, as confirmed by employing dark-field microscopy and the absence of a Maltese cross in PLM microscopy. The RI of the formulated ME was determined by placing a single drop on a slide and measuring it with a digital refractometer.

The RI is an essential parameter that defines the optical properties of MEs; it directly affects the system's transparency, uniformity, and internal structure. In ME studies, measuring the RI helps confirm the system's homogeneity and distinguishes MEs from conventional emulsions. Typically, MEs are transparent or translucent because the dispersed-phase particles are much smaller than visible wavelengths. Their RI generally lies between those of the oil and water phases, reflecting the system's composition. The RI of the prepared ME was measured at 1.45 ± 0.01 at room temperature. This slightly exceeds water's 1.333, due to the OP and SFs affecting its optical properties. The value supports the ME's transparent look, suggesting a uniform nanoscale dispersion without phase separation or droplet aggregation. These results are consistent with refractive indices reported for similar transparent MEs, confirming the system's optical clarity and structural uniformity. Measuring the RI is valuable for quality control of MEs. Being highly sensitive to compositional changes, it provides a fast, non-destructive method to ensure batch consistency and physical stability. During formulation development, in addition to particle size analysis and conductivity tests, the RI provides additional information on ME type, structural modifications, and long-term stability. The RI is a key physicochemical parameter for ME formulations. It not only confirms the system's homogeneity and transparency but also acts as an additional metric for quality assessment, playing a crucial role in the formulation, development, and functional use of ME systems.[80]

The RI is generally measured with an Abbe refractometer at room temperature. A suitable amount of sample is placed on the prism surface, spread evenly, and free of bubbles. The RI of ME typically lies between those of the oil and aqueous phases, exhibiting regular fluctuations with changes in the composition ratio of the system. In the ME developed in this study, the measured RI was consistent with the system's transparent appearance, indicating the formation of a uniform nanoscale-dispersed structure. RI can also help make a preliminary judgment about the type of emulsion: o/w ME typically has a lower RI, close to that of water. In comparison, w/o systems tend to have a higher RI. Furthermore, RI stability can serve as an auxiliary indicator of the formulation's physical stability; if it changes significantly during storage, it may indicate phase separation or structural evolution within the system. The RI is a key parameter for evaluating ME. Its measurement reveals homogeneity, transparency, and emulsion type, and supports stability studies. Combining it with other methods during nanodrug development allows a comprehensive physicochemical assessment, aiding further application.[81]

In the ME formulations developed, optical transparency was assessed using RI measurements. The RI value of all ME formulations remained stable between 1.07 and 1.08, indicating optical isotropy, i.e., the formation of thermodynamically stable, transparent ME systems. This consistency reflects the uniform composition of the formulations and the successful construction of ME systems with stable phase behavior. Furthermore,

in characterizing the physicochemical properties of the ME gels, the preparations were all white, smooth, and possessed a characteristic essential oil odor; no mention was made of turbidity or phase separation, further supporting their macroscopic homogeneity and transparency.[82]

## Dilution Test

The dilution test is a confirmatory procedure used to investigate the type of ME formed. The optimized ME should be diluted with water or oil to determine whether separation occurs in either solvent. Dilution testing is a common method to assess ME stability. In this study, the optimized ME was diluted with purified water and phosphate-buffered saline (pH 5.8) at ratios of 1:10 and 1:100. After thorough mixing, samples were examined for phase separation, turbidity, or stratification to evaluate stability under dilution conditions. This simple test quickly indicates the ME's capacity to maintain its structure in physiological environments such as the gastrointestinal tract or on the skin surface. Results showed the ME remained clear and stable in both media, with no phase separation, turbidity, or stratification. Some samples appeared pale blue and milky, characteristic of nanoscale droplets. These outcomes suggest good dilution stability and the ability to preserve a uniform nanostructure upon dilution. Proper selection of SFs is essential for stability; an optimal SF/CSF ratio forms a dense interfacial film, providing steric and electrostatic barriers that prevent droplet aggregation or phase changes during dilution. Additionally, dilution tests can help identify emulsion type: o/w ME tend to stay transparent or semi-transparent after dilution, while w/o systems may phase-separate or become turbid with excess water. Overall, the dilution test is a critical indicator of ME stability, reflecting its structural integrity under diluted conditions such as those in body fluids. It aids in identifying formulations with strong stability, ensuring quality for oral or topical applications. Including this test alongside particle size and conductivity measurements offers a comprehensive assessment of the formulation's physicochemical properties and suitability.[83]

The dilution test assesses the type and stability of a ME by diluting it with water and oil, then observing its dispersion. In this study, the optimized ivermectin ME was tested by adding excess water and oil separately. When diluted with water, it formed a clear, uniform, transparent dispersion without phase separation or cloudiness. However, dilution with excess oil did not produce a homogeneous mixture. These results indicated that the ME is of the w/o type. This method, based on the ME's spontaneous dispersion behavior in excess water or oil, is easy to perform and quickly distinguishes between w/o and o/w MEs, serving as a useful auxiliary for identifying ME types.[84]

## Dye Staining Test

The dye test is used to identify the type of ME by applying water or oil-soluble dyes. To do this, dissolve an oil-soluble dye in the oil phase and prepare the sample. Examine the final product under a microscope to observe the phase. For oil-soluble dyes: If the continuous phase is colored, it indicates a w/o emulsion; if the dispersed phase is colored, it indicates an o/w emulsion. For water-soluble dyes: If the continuous phase is colored, it suggests an oil-in-water emulsion; if the dispersed phase is colored, it suggests a water-in-oil emulsion.

This study employed three complementary methods to determine the emulsion type, including dye solubility testing. Sudan III (a fat-soluble red dye) and methyl orange (a water-soluble orange dye) were added separately to the samples, which were then observed under a stereomicroscope. If Sudan III stained the continuous phase, the emulsion was classified as o/w; if methyl orange did, it was classified as w/o. All eight probiotic-containing emulsions were identified as w/o, indicating that water was the continuous phase and the oil was dispersed. This emulsion type supports probiotic viability and provides good user comfort and washability. [85]

A scarlet dye was mixed with cream, placed on a slide, covered, and examined under a microscope. Red droplets against a clear background indicated an o/w emulsion; colorless droplets against a red background indicated a w/o emulsion. All three formulations showed features of an o/w emulsion: an aqueous continuous phase with dispersed oil droplets. This emulsion is lightweight, non-greasy, skin-absorbed, and suitable for cosmetic cream formulation.[86]

The cream's emulsion type was identified by adding Scarlet Red dye and observing the sample under a microscope. The dye distribution identified the emulsion type: if the continuous phase was stained while the dispersed phase remained unstained, it indicated an o/w emulsion. Results showed that all nine antifungal cream formulations were w/o emulsions. This type of emulsion helps extend the residence time of active ingredients on the skin surface and is ideal for topical antifungal treatments.[87]

A dye-dissolution test was performed to identify whether the ME was w/o or o/w. In this test, water-insoluble methyl red and water-soluble methylene blue dyes were added to the formulations. First, a 1% w/v ethanol solution of each dye was prepared. Then, 100 µL of these dye solutions was added to the MEs, and the dye dispersion was observed after 1 hour. The results showed that methyl red, which is water-insoluble, remained floating on the surface in a layered form, indicating it did not penetrate the ME interior. Conversely, methylene blue, which is water-soluble, quickly and evenly diffuses throughout the system, indicating water is the continuous phase and confirming that the ME is of the oil-in-water type.[88]

## Specific Gravity

Specific gravity, or relative density, is a dimensionless measure defined as the ratio of a material's density to that of water at a specific temperature and pressure. Variations in specific gravity can result from changes in composition, grades, or ME density. The viscosity of individual components affects the specific gravity of the final product. Consequently, significant fluctuations in specific gravity may reflect differences in the three-dimensional arrangements of topical product bases. Additionally, specific gravity analysis can detect air entrapment caused by process variations.

In this study, the physicochemical parameters of Jatropha seed oil were evaluated using standard procedures, with the specific gravity measured at 25°C. The specific gravity results of Jatropha seed oil were found to be 0.933 ± 0.002. This value is one of the key indicators of seed oil quality control and, together with other physicochemical parameters, reflects its quality characteristics. This specific gravity value complies with the relevant standards, indicating that the oil possesses favorable physicochemical properties and providing a foundation for its further use in the preparation of nanoemulsions.[89]

## Centrifugal Stress

Centrifugal stress tests are used to evaluate the stability and deflocculation of the ME over time. A quick separation at lower RPMs within a short period suggests instability and potential separation over time. Conversely, the absence of separation at higher speeds and over extended durations indicates greater stability of the ME.

To evaluate the kinetic stability of ME formulations, four samples were tested by centrifugation. The samples of prepared ME were centrifuged for 15 min at 1000, 2000, & 3000 rpm (at room temperature, 25°C), and the formation of MEs, as well as any phase separation that occurred before and after centrifugation, was recorded. The results showed that only the AE2 ME remained stable at all three rotational speeds, whilst the remaining formulations exhibited instability, such as demulsification or phase separation, at different rotational speeds.[89]

In the thermodynamic stability study, centrifugation tests were conducted on the MEs. The samples were first subjected to a temperature cycle from 45°C to room temperature (24 hours at each temperature, for a total of six cycles), followed by centrifugation at 5000 rpm for 30 min, after which they were investigated for any signs of phase isolation, demulsification, or emulsion breakdown. The results showed that AE2 remained stable under these centrifugation conditions, whilst others failed the test. This series of centrifugation tests was used to screen for ME formulations with good physical stability, ensuring they can withstand mechanical stress during storage and transport. [90]

## Coalescence Time

The coalescence time is the duration it takes for a ME to coalesce when stored without agitation. This measurement can help understand the phase-separation behavior.

Nanoemulsions are thermodynamically unstable but kinetically stable; that is, over time, they can resist phase separation and coalescence, primarily due to the use of SFs and CSFs. The literature indicates that the mechanisms of physical instability in nanoemulsions mainly include Ostwald ripening, flocculation, and coalescence. Among these, coalescence is the process by which globules come into contact and merge to form larger globules, leading to structural disruption and decreased nanoemulsion stability. To prevent coalescence, a sufficient quantity of SF must be incorporated into the formulation to form a robust interfacial layer, thereby preventing droplets from approaching and merging through steric hindrance or electrostatic repulsion. Compared to conventional emulsions, nanoemulsions, due to their extremely small droplet size (typically 20–200 nm), are dominated by Brownian motion and are therefore more resistant to stratification or gravity-induced sedimentation. However, attention must still be paid to their long-term stability during storage, particularly under high-temperature or extreme conditions, where coalescence may be exacerbated. By optimizing the oil phase composition (e.g., by adding highly water-insoluble oils as Ostwald ripening inhibitors) and selecting a suitable SF system, the time to coalescence in nanoemulsions can be significantly prolonged, thereby maintaining their physical stability throughout their shelf life.[91]

Oil globule size and spacing significantly influence coalescence time under different conditions. When one of the three globules gradually enlarges, the coalescence time decreases— for example, increasing a globule's diameter from 4 to 8 mm shortens the coalescence time from 950 to 300 ms. Conversely, as a globule approaches nanoscale size, the coalescence time increases markedly. The globule positions also affect coalescence; when the third globule is near the centerline between the other two, coalescence time can be as low as 400 ms, but deviating from the centerline can extend it to 2500 ms. Fluid flow conditions further affect coalescence; in laminar flow, higher velocities reduce coalescence time, while in turbulent flow, it increases with velocity. For a flow speed range of 0.05~ 0.2 m/s, the time ranges from about 600 to 1000 ms. Gravity slightly accelerates coalescence compared to static conditions, as higher droplet velocities increase collisions between liquid films.[92]

## Recent Trends and Limitations

Based on the above research, two major trends in the application of ME transdermal delivery systems for the treatment of psoriasis can be identified: firstly, formulation strategies are evolving from single MEs towards diversified

approaches, such as ME gels, composite drug delivery systems and the delivery of natural active ingredients; secondly, characterization methods are becoming more systematic, encompassing the construction of PTPD and the comprehensive evaluation of CQAs such as particle size, zeta potential and electrical conductivity. However, existing research suffers from significant limitations: most reports remain confined to in vitro permeation research and validation in animal models, with a scarcity of clinical trial data, resulting in insufficient maturity for clinical translation; there is significant heterogeneity across studies in terms of animal models, dosing regimens and statistical methods, and a lack of systematic comparison and critical analysis of efficacy and safety; Furthermore, key issues such as the long-term cutaneous safety of high-concentration SFs, their thermodynamic stability under storage and dilution conditions, and the controllability of large-scale production processes remain inadequately addressed. These limitations suggest that future research must achieve breakthroughs in standardized evaluation systems, long-term safety monitoring, and industrial production technologies to facilitate the genuine clinical application of ME formulations in the treatment of psoriasis.

## Discussion

MEs face regulatory challenges in pharmaceuticals and cosmetics, including unclear definitions, classification issues, and confusion with nanoemulsions or self-emulsifying systems. Regulators need precise descriptions, full identification, and characterization studies to confirm stability. Challenges also arise from the regulatory status of excipients, as higher SF levels are often not approved for certain routes. Limited long-term safety data may delay approvals and increase costs. The lack of standardized characterization methods complicates filings, requiring independent validation without reference products. Stability testing is burdensome due to sensitivity to temperature, dilution, and composition changes, demanding extensive testing. For drug products, evidence must show that the ME structure doesn't affect safety or efficacy, often needing additional studies. It guides drug selection based on market potential, discusses SF combos and oil phases, and provides phase diagrams, enabling rapid screening and scale-up with insights into preparation and process parameters. Quality control, stability testing, and regulatory templates streamline approval. Ostwald ripening informs stability, and root cause analysis resolves storage or transport issues.

Drugs such as cyclosporine, methotrexate, and glucocorticoids in MEs improve skin retention, reduce toxicity, and show positive results in animal models, suggesting they may lower systemic side effects and enhance topical therapy. Despite promising research, challenges remain in moving from lab to commercial use. Sections on QTPP and CQAs detail indicators such as droplet size, pH, viscosity, zeta potential, conductivity, and refractive index, as well as content uniformity, degradation, and microbial limits.

Creating pseudoternary phase maps guides the formulation of oil, water, and SF ratios for stability and the target microstructure. Selecting excipients like SFs, coSFs, and oil phases is key to understanding ME properties. Nonionic SFs like Tween and Span are preferred for their low toxicity and biocompatibility. CoSFs, such as short-chain alcohols, reduce interfacial tension and stabilize systems. The oil phase affects drug solubility, release, and outcomes, and options such as peppermint and tea tree oil offer additional benefits. Various formulations targeting skin conditions like psoriasis, acne, and fungal infections demonstrate the platform's versatility.

Formulating multi-drug MEs offers synergistic effects and personalized therapy. Using them to deliver natural anti-inflammatory agents or traditional Chinese medicine is promising. A better understanding of interactions with lesions and of keratinocyte regulation can guide design improvements. Although MEs could improve psoriasis treatment, more research on stability, safety, and commercial-scale manufacturing is needed for clinical use.

## Conclusion

This review provides pharmaceutical and regulatory scientists with a practical framework covering formulation design, quality control, and industrial-scale preparation. It analyzes key ME aspects—component screening, pseudo-ternary phase diagrams, quality attribute evaluation, and large-scale manufacturing—to support rational development and standard assessment of transdermal psoriasis treatments. MEs, with stability, nanoscale droplets, solubilizing ability, and reversible skin barrier modification, overcome the challenge of penetrating the thick stratum corneum. This enhances drug delivery to the epidermis and dermis. Their stability depends on component ratios, making phase diagrams and behavior analysis crucial for reliable formulations. Choosing SFs, CSFs, and oils affects stability, penetration, and anti-inflammatory effects, creating synergy. Quality control uses droplet size, zeta potential, conductivity, and microscopy to ensure consistency. Animal research indicates MEs are more effective and safer than traditional formulations, with gels enhancing adherence and drug release. Challenges include safety concerns from high SF levels, limited clinical data, and manufacturing hurdles. Future research should explore molecular interactions, develop combination therapies, evaluate long-term safety, and improve production to meet GMP standards.

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