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Microemulsions in Pharmaceutical Applications: A Comprehensive Review of Formulation, Stability, And Delivery Systems

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Abstract: ***Micro emulsions are intricate liquids of great technological significance. They often need to incorporate functional additives like drugs, polymers, and nano particles, which adds to their complexity. Understanding and managing micro emulsions requires a variety of complementary techniques. These systems are transparent, stable, and uniform mixtures of oil, water, and surfactant, sometimes including a co - surfactant. They are particularly interesting to pharmaceutical researchers because of their potential as drug delivery systems, capable of integrating a wide array of drug molecules. This commentary provides a thorough overview of micro emulsions, including their formation, the factors influencing their stability, and their recent applications. The exploration of micro emulsions for drug delivery continues to be a compelling area of study due to their numerous potential benefits and unique properties.***

Keywords: Micro emulsion, Surfactant, Delivery system, Co - surfactant, oil phase.

1. Introduction

Microemulsions are transparent, stable, and uniform liquid mixtures of oil, water, and surfactant, often combined with a co - surfactant. The aqueous phase may include salts or other additives, while the "oil" component can be a complex blend of hydrocarbons and olefins. Unlike traditional emulsions, which require high shear to form, micro emulsions can be created simply by mixing the components. There are two main types of micro emulsions: direct (where oil is dispersed in water, o/w) and reversed (where water is dispersed in oil, w/o). The concept of micro emulsions was first introduced in the 1940s by Hoar and Schulman, who achieved a clear, single - phase solution by mixing a milky emulsion with hexanol. They produced the first microemulsion by dispersing oil in an aqueous surfactant solution and adding an alcohol as a co - surfactant, resulting in a transparent and stable formulation. Microemulsions are defined as clear, thermodynamically stable dispersions of oil and water, stabilized by an interfacial film of surfactant, often with a co - surfactant. [(1)]

They are sometimes referred to by alternative names such as swollen micelle, transparent emulsion, solubilized oil, or micellar solution. These systems are bi - continuous, consisting of bulk water and oil phases separated by a surfactant/co - surfactant rich interfacial region. A microemulsion requires at least three components: an oil phase, an aqueous phase, and surfactants. Occasionally, a fourth component, the co - surfactant, is necessary. Depending on the component ratios, the microstructure of micro emulsions can vary significantly, from tiny water droplets dispersed in oil (w/o micro emulsions) to oil droplets dispersed in water (o/w micro emulsions). [(2)]

Difference between micro emulsion and emulsion:
The primary differences between micro emulsions and conventional emulsions lie in the size and appearance of their dispersed phases. Microemulsions have much smaller droplets, ranging from 10 to 200 nm, compared to the larger droplets of conventional emulsions, which range from 1 to 20 µm. Additionally, micro emulsions are typically clear or translucent, while conventional emulsions are often cloudy. Another key distinction is in their preparation: emulsions require significant energy input to form, whereas micro emulsions do not. [(12)]

Types of micro emulsion: [(3, 19, 20)]
Microemulsions are primarily categorized into three types based on the proportions of oil and water used:

Oil - in - Water (o/w) Microemulsions (Winsor I):
In this type, oil droplets are dispersed within a continuous aqueous phase. The surfactant, and sometimes a co - surfactant, form a film around the oil droplets, which are distributed throughout the water. This type of microemulsion generally offers a higher interaction volume compared to water - in - oil (w/o) micro emulsions. The surfactant forms a "positive" curvature around the droplets, with the hydrophilic head - groups oriented towards the water and the hydrophobic tails directed into the oil droplets. This configuration is advantageous for increasing the solubility of hydrophobic drugs in aqueous systems, as the drugs dissolve in the internal oil droplets. The o/w micro emulsions are usually stable and retain their structure even when diluted with biological fluids.

Water - in - Oil (w/o) Microemulsions (Winsor II):
Here, water droplets are dispersed in a continuous oil phase. These systems, often called "reverse micelles, " have surfactant molecules with their hydrophilic head - groups

facing inward towards the water droplets, and their hydrophobic tails extending into the oil phase. This type of microemulsion is commonly used when the volume of water is low. However, w/o micro emulsions can destabilize when exposed to an aqueous biological environment, potentially leading to phase separation or inversion. They are useful for oral peptide delivery, where the hydrophilic peptides are better protected from enzymatic degradation by the continuous oil phase. W/o micro emulsions are also suited for situations where the product is unlikely to be diluted by aqueous phases, such as in intramuscular injections or transdermal applications.

Bicontinuous Microemulsions (Winsor III):
These systems have both water and oil phases that are continuous, creating a structure with interlaced networks of oil and water resembling a "sponge - phase. " This type of microemulsion is characterized by having equal volumes of oil and aqueous phases. Bicontinuous micro emulsions can transition between o/w and w/o states, and they may exhibit non - Newtonian flow and plasticity. These properties make them particularly useful for topical drug delivery or intravenous administration, as they form stable o/w micro emulsions upon dilution with biological fluids.

In summary, micro emulsions can be classified into o/w (Winsor I), w/o (Winsor II), and bicontinuous (Winsor III) based on their composition and structure. Each type has specific applications and advantages depending on the required stability and drug delivery method.

Components of micro emulsion: [4]
The key components of a microemulsion system include:

Oil phase:
The oil phase is crucial for solubilizing lipophilic drugs and enhancing their absorption through the body's lipid layers. Examples of oil phase components include: Saturated fatty acids, such as lauric, myristic, and capric acids. Unsaturated fatty acids, like oleic, linoleic, and linolenic acids. Fatty acid esters, including ethyl or methyl esters of lauric, myristic, and oleic acids.

Surfactants:
Surfactants are essential for reducing the interfacial tension between oil and water, facilitating the dispersion of the components. They can be categorized as: Nonionic, Anionic, Cationic, Zwitterionic

Examples include:
Polyoxyl 35 castor oil (Cremophor EL)
Polyoxyl 40 hydrogenated castor oil (Cremophor RH)

Co - Surfactants:
Co - surfactants are used to lower the interfacial tension further, aiding in the spontaneous Formation of micro emulsions. High concentrations of single - chain surfactants are often required for this purpose. Examples include: Short - chain alcohols, such as ethanol and butanol.

Co - solvent:
Co - solvents, like ethanol, propylene glycol (PG), and polyethylene glycol (PEG), are organic solvents used to dissolve substances at higher concentrations.

Types of method of preparation of micro emulsion
Here are the methods for preparing micro emulsions:

High Energy Emulsification:
This involves techniques such as ultrasonication and high - pressure homogenization, which use intense energy to create micro emulsions.

Low Energy Emulsification:
Methods like the phase inversion temperature method, solvent displacement method, and phase inversion composition method use less energy and rely on changes in conditions to form micro emulsions.

High - Pressure Homogenization:
This technique utilizes specialized equipment to force oil and water phases through a small orifice at high pressures (500 to 5000 psi), creating nano - sized particles through turbulence and shear. It requires high temperature and energy, with particle size being influenced by pressure and homogenization cycles.

Micro fluidization:
This method uses a microfluidizer to create high pressure (500 to 20, 000 psi). A coarse emulsion is forced through micro channels in the device, resulting in nano - sized particles through impingement and subsequent filtration.

Ultrasonication:
By applying ultrasonic waves to a coarse emulsion, this method increases cavitation thresholds under high external pressure, leading to the formation of fine, nano - sized particles.

Phase Inversion Method:
This technique utilizes the phase inversion temperature, where temperature changes cause a transition between oil - in - water (O/W) and water - in - oil (W/O) emulsions. By rapidly cycling between high and low temperatures, fine particles are produced. Non - ionic surfactants like poly oxy ethylene switch from lipophilic at high temperatures to hydrophilic at low temperatures due to polymer chain dehydration.

Spontaneous Emulsification:
A straightforward method involving the use of a volatile organic solvent mix containing oil, water, and both lipophilic and hydrophilic surfactants. The mixture is homogenized by magnetic stirring, and the water - miscible solvent is then evaporated under vacuum to yield a nano emulsion.

Solvent Evaporation Technique:
This process involves dissolving a drug in an organic solvent with a surfactant to create an oil - in - water (O/W) emulsion. The organic solvent is then evaporated under vacuum, heating, or atmospheric conditions, resulting in drug - loaded microspheres, which are subsequently collected through centrifugation or filtration.

Hydrogel Method:
Similar to the solvent evaporation technique, this method uses

high shear forces to create a nano emulsion of the drug and solvent, which is then mixed with a drug anti – solvent to form a hydrogel.

Important characteristics of micro emulsion: [1, 13]

- **Particle Size**: Ranges from 10 to 100 nm.
- **Thermodynamic Stability**: Exhibits long shelf - life and remains stable under varying conditions.
- **Optical Clarity**: Appears clear and transparent.
- **High Surface Area**: Provides a large surface area for solubilization.
- **Small Droplet Size**: Ensures a fine dispersion.
- **Enhanced Drug Solubilization:** Improves the solubility of drugs.
- **Ease of Formation:** Forms spontaneously with zero interfacial tension.
- **Sterilization Capability:** Can be sterilized through filtration.
- **Long - Term Stability:** Maintains stability over extended periods.
- **High Solubilization Capacity:** Effective for both hydrophilic and lipophilic drugs.
- **Improved Drug Delivery:** Facilitates better drug delivery mechanisms.

Advantages of micro emulsion: [13]

- Thermodynamic Stability: Requires minimal energy for formation and remains stable without external energy.
- Enhanced Absorption: Increases the cutaneous absorption of both lipophilic and hydrophilic drugs compared to conventional formulations.
- Ease of Preparation: Simple to prepare with high diffusion and absorption rates.
- Reversible Formation: Can reform upon returning to stability temperature ranges if disrupted.
- Thermo - Labile Drug Incorporation: Suitable for drugs sensitive to heat, minimizing degradation risks.
- Super solvent Capability: Solubilizes both hydrophilic and lipophilic drugs, including those insoluble in other solvents.
- Wide Applications: Useful in drug targeting and controlled release systems.
- High Drug Loading: Allows significant amounts of drug incorporation, potentially enhancing skin activity.
- Penetration Enhancement: Surfactants and co - surfactants may reduce the skin's diffusional barrier.
- Low Surface Tension: Ensures good skin contact and maintains a steady drug concentration gradient.

Disadvantages of micro emulsion: [1]

- High Surfactant Concentration: Requires large amounts of surfactants and co - surfactants for stability.
- Limited Capacity for High - Melting Substances: Less effective for substances with high melting points.
- Surfactant Toxicity: Surfactants must be nontoxic for pharmaceutical use.
- Environmental Sensitivity: Stability can be affected by changes in temperature and pH during patient application.

Factors affecting the microemulsion system: [5]

Property of Surfactant:
Surfactants with hydrophilic single chains typically produce oil - in - water (o/w)
micro emulsions and dissociate in dilute solutions. The degree of dissociation of the polar groups can be reduced in the presence of salts or high surfactant concentrations, potentially leading to atypical microemulsion systems.

Property of Oil Phase:
The oil phase's ability to penetrate and interact with the surfactant monolayer affects the system's curvature. This interaction influences whether the microemulsion forms and its stability.

Packing Ratio:
The type of microemulsion formed is determined by the surfactant's hydrophilic -
lipophilic balance (HLB), which impacts the packing and curvature of the surfactant film. This influences the structure and stability of the microemulsion.

Temperature:
Temperature significantly affects the head group size of nonionic surfactants. At low temperatures, these surfactants favor the formation of o/w micro emulsions due to their hydrophilic nature. As temperature increases, surfactants may become more lipophilic, affecting the microemulsion's structure, which can shift towards a bicontinuous or other forms depending on the water - to - oil ratio.

Evaluation parameters of micro emulsion: [1, 13]

Physical Appearance:
Visual inspection assesses homogeneity, fluidity, and optical clarity.

Scattering Techniques:
Techniques such as small - angle neutron scattering, small - angle X - ray scattering, and light scattering are used to study the structure of micro emulsions, particularly in dilute or concentrated systems.

Limpidity Test (Percent Transmittance):
Using a spectrophotometer, the optical clarity of the microemulsion is measured to assess its limpidity.

Drug stability:
Stability is tested by storing micro emulsions at different temperatures (4–8 °C, room temperature, and 50–60 °C) and evaluating phase separation, percent transmittance, globule size, and drug assay every two months.

Globule Size and Zeta Potential Measurements:
Dynamic light scattering (e. g., using a Zetasizer HSA 3000) is used to determine globule size and zeta potential, which are critical for stability and performance.

Assessment of Rheological Properties:
Rheological properties are measured using a Brookfield digital viscometer to understand the stability and dynamic structure of micro emulsions.

Electrical Conductivity:
The electrical conductivity of micro emulsions is evaluated using a conductometer to assess the phase behavior and ionic

properties.

Drug Solubility:
Drug solubility in the microemulsion is determined by adding excess drug, stirring, centrifuging, and measuring the amount of soluble drug compared to the total added.

In - vitro Drug Release:
Drug release is studied using a modified Franz diffusion cell, with samples analyzed using UV spectrophotometry to determine the drug's release profile.

Application of micro emulsion: [5]

Parenteral Delivery:
Microemulsions improve drug delivery to specific sites compared to traditional parenteral formulations, offering prolonged circulation and reduced clearance rates.

Oral Delivery:
Microemulsions enhance clinical potency, reduce toxicity, and improve absorption of oral medications, making them suitable for drugs like steroids, hormones, diuretics, and antibiotics.

Topical Delivery:
Microemulsions bypass hepatic first - pass metabolism and degradation, delivering drugs directly to the skin or eyes. They improve penetration of both lipophilic and hydrophilic drugs, though high surfactant concentrations may cause skin irritation.

Ocular and Pulmonary Delivery:
Microemulsions are used in ocular treatments to enhance solubility and absorption of poorly soluble drugs, and in pulmonary delivery for effective drug administration and prolonged release.

Identification test of micro emulsion: [2]

Dilution Test:
Adding the continuous phase to a microemulsion should not cause phase separation or cracking. For oil - in - water (o/w) micro emulsions, the addition of water should not destabilize the system.

Staining Test:
A water - soluble dye, such as methylene blue or amaranth, is added to the aqueous phase of a microemulsion. Under a microscope, the background will appear blue or red, while the globules in the microemulsion will be colorless, confirming the type of microemulsion.

Dilute Ability Test:
The microemulsion is diluted in ratios of 1: 10 and 1: 100 with double - distilled water to check for signs of separation. A stable microemulsion will not separate upon dilution.

Zeta Potential Measurement:
The zeta potential should be negative or neutral, indicating that the droplets have little to no charge and the system is stable. Zeta potential is measured using a Zetasizer and is crucial for assessing flocculation, as the electrical charges on particles influence flocculation rates.

Polydispersity:
This property is evaluated using an Abbes refractometer to assess the uniformity of droplet sizes within the microemulsion.

Structure of micro emulsion: [5]

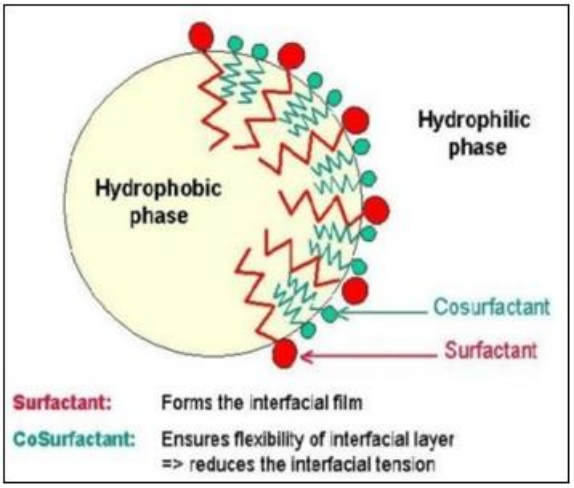

Figure 1: Structure of micro emulsion

Microemulsions or micellar emulsions are dynamic systems characterized by a constantly fluctuating interface. In an oil - in - water (o/w) microemulsion, water droplets are dispersed throughout a continuous oil phase, while in a water - in - oil (w/o) microemulsion, oil droplets are dispersed in a continuous aqueous phase. Bilateral micro emulsions can occur when water and oil are present in comparable quantities. The combination of oil, water, and surfactants can result in a diverse range of phases and structures, depending on the proportions of the components. [6 - 9]

Theories of micro emulsion: [5, 13]
Historically, three approaches have been used to explain microemulsion formation and stability.

a) Interfacial or mixed film theories.
b) Solubilization theories.
c) Thermodynamic treatments.

The free energy of microemulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil - water interface and changes in entropy of the system such that,

$$Gf = \gamma a - T S$$

Where Gf = free energy of formation
A = change in the interfacial area of microemulsion
S = change in entropy of the system
T = temperature
γ = surface tension of oil - water interphase It should be noted that when a microemulsion has formed the change in A is very large due to the large number of very small droplets formed. [9, 10]

To form a microemulsion, the interfacial tension between oil and water must approach zero. Microemulsions are characterized as biphasic liquid dosage forms, distinguishing them from molecular solutions of hydrocarbons and water

(Burrows and Miguel, 2001). The theories and approaches underlying microemulsion formation are as follows:

Thermodynamics of Microemulsion Formation
Microemulsions exhibit interdependent thermodynamic characteristics such as free energy, surface tension, and interfacial area, as described by the algebraic relationship below. A significant reduction in surface tension, combined with positive entropy changes, leads to negative free energy values. This results in a spontaneous and thermodynamically stable microemulsification process.

Mixed Film Theory of Microemulsion Formation
The mixed film theory posits that the interface between oil and water is covered by a dual film of surfactant and cosurfactant. The type of microemulsion formed depends on the curvature of this film (Schulman et al., 1959). The dual film at the interface greatly lowers oil - water tension, and the spreading pressure of this film exceeds the oil - water tension, leading to a reduction in droplet size. This adjustment results in interfacial tension reaching zero or a very low positive value at equilibrium (Figure 1).

Solubilization Theory of Microemulsion Formation
According to solubilization theory, there are two types of micelles: normal and inverse. Normal micelles solubilize oil, while inverse micelles solubilize water. Solubilization is closely linked to micelle concentration and is influenced by factors such as temperature. Generally, as temperature increases, so does solubilization. Alcohols and non - electrolytes, including electrolytes, can increase micelle size and solubilizing capacity. Microemulsion systems are often described either as expanded micelles or as modifications at the oil/water interface.

Microemulsion droplets are formed through two processes:
1) **Breakdown of Larger Droplets**: Reduction of interfacial tension causes the breakup of larger droplets.
2) **Swelling of Micelles:** The micelle's internal phase undergoes swelling due to molecular diffusion, contributing to the formation of microemulsion droplets. (13 - 18)

Construction of phase diagram: [5]
A pseudo - ternary phase diagram is a type of phase diagram used to represent the phase behavior of micro emulsions, which are mixtures of surfactants, co - surfactants, and oils (or other lipophilic substances) in a continuous aqueous phase.

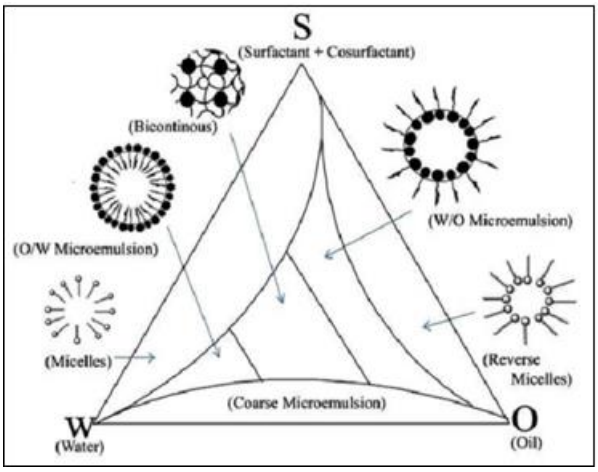

Figure 2: Phase diagram of microemulsion

To construct pseudo - ternary phase diagrams of oil, water, and surfactant/cosurfactant mixtures at fixed cosurfactant/surfactant weight ratios, follow these steps:
1) Prepare the Components: Weigh the oil, water, and surfactant/cosurfactant mixtures into separate glass vials according to the desired ratios.
2) Mix and Titrate: Add varying amounts of water to the oil and surfactant/cosurfactant mixtures, stirring well at room temperature to achieve thorough mixing.
3) Visual Inspection: After stirring, visually inspect the mixtures to determine the phase behavior:
   - Monophasic: If the mixture is clear and transparent, it is considered monophasic. Mark this point on the phase diagram.
   - Biphasic: If the mixture exhibits turbidity followed by phase separation, it is considered biphasic.
4) Plot the Phase Diagram: Record the observed behavior (monophasic or biphasic) at each combination of components and plot these results on the pseudo - ternary phase diagram.

By following these steps, a detailed pseudo - ternary phase diagram that illustrates the stability regions of micro emulsions in relation to varying concentrations of oil, water, and surfactant/cosurfactant mixtures. [12]

Table 1: Research work carried out on microemulsion

Drug Name	Route	Result
Flurbiprofen [21]	Parentral	Increased the solubility
Apormorphine hcl [22]	Transdermal	Increased the permeability
Ketoprofen [23]	Transdermal	Enhancement permeability
Prilocaine - hcl [24]	Transdermal	Increased the solubility
Estradiol [25]	Transdermal	Improvement in solubilization
Aceclofenac [26]	Dermatological	Increased the solubility
Piroxicam [27]	Oral	Increased the solubility
Diclofenac [28]	Transdermal	Permeability enhancement
Dexamethasone [29]	Topical ocular	Enhance the bioavailability
Chloramphenicol [30]	Ocular	Increased the solubility
Ibuprofen [31]	Topical	Increased the solubility
Itraconazole [32]	Parentral	For better absorption
Timodol [33]	Ophthalmic	For better absorption
Terbinafine [34]	Transdermal	Permeability enhancement
Progesterone [35]	Dermal	Increased chemical stability

2. Conclusion

Microemulsions are vital to both the industrial process and the medicine delivery mechanism. They can be used to enhance medication targeting without also boosting systemic absorption. The role of microemulsion in providing innovative solutions to address the low aqueous solubility of highly lipophilic pharmaceutical compounds and provide high, more consistent, and repeatable bioavailability Although there are still challenges, drug targeting with micro emulsions is also feasible. This is mostly due to the multiple obstacles that these systems must overcome in order to reach the target. Microemulsion has been shown to protect labile medications, control drug release, and reduce patient variability. Furthermore, it has been shown that it is possible to design preparations that are effective for the majority of administration techniques.

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