

MICROEMULSIONS AS A POTENTIAL CARRIER FOR IMPROVED DRUG DELIVERY

Miss. Tejaswini Pardeshi¹, Miss. Karuna P. Joshi², Mrs. Rushikesh Pardeshi³

¹Department Of Pharmaceutics Sumantai Institute Of Pharmacy, Bambrud Kh. Pachora, Dist Jalgaon, Maharashtra, India.

^{2,3}Asst. Prof Department Of Pharmaceutics Sumantai Institute Of Pharmacy, Bambrud kh. Pachora, Dist. Jalgaon, Maharashtra, India.

Corresponding Author Email Id : tejaswinip005@gmail.com

DOI: <https://www.doi.org/10.58257/IJPREMS38806>

ABSTRACT

Microemulsions are thermodynamically stable colloidal dispersions formed in an oil-water environment with the help of surfactants. They are transparent or translucent, isotropic, and have a small droplet size, typically 10 to 100 nanometers. In the pharmaceutical industry, microemulsions are often used to enhance the solubility of poorly soluble drugs. Many drugs have low aqueous solubility, leading to poor bioavailability and reduced therapeutic efficacy. However, when formulated as microemulsions, these drugs can be solubilized in the oil-water interface of the microemulsion system, resulting in a significant increase in their apparent solubility. The small droplet size and large interfacial area of microemulsions provide an ideal environment for incorporating hydrophobic drugs, as the drug molecules can be accommodated in the hydrophobic core of the micelles or droplets. This solubilization makes the drug more readily available for absorption in the body, thereby improving its bioavailability. As thermodynamically stable colloidal dispersions, microemulsions have gained significant attention due to their unique properties and versatile applications. This review paper aims to provide a comprehensive overview of microemulsions with respect to its patentability arena, delving into nuanced aspects that have not been extensively covered in prior review articles. We address key unanswered questions in the existing literature, offering fresh perspectives and insights. Our analysis encompasses the latest advancements in microemulsion research, highlighting novel applications, formulation strategies, emerging trends, market potential of microemulsion as well as its future scope in the pharmaceutical industry.

Keywords: Microemulsion; Ternary phase; solubilization; applications; co-solvents.

1. INTRODUCTION

A microemulsion-based drug delivery system is a sophisticated formulation technique that uses microemulsions to enhance the bioavailability, stability, and controlled release of drugs, particularly for hydrophobic or poorly water-soluble drugs. Microemulsions are thermodynamically stable, transparent, and isotropic mixtures of oil, water, surfactant, and co-surfactant, which form droplets typically ranging from 10 to 200 nm in size. These systems can improve drug solubility, protect drugs from degradation, and facilitate better absorption across biological membranes. The fundamentals lie in hosting the drug in carefully designed carriers to bring favorable change(s) in its surrounding microenvironment, and consequently, its delivery. It is the modification(s) in physicochemical characteristics of the molecules and in the barrier properties of the biological membranes at various locations, which lead to improved transportation of drugs toward the diseased locations. Further, it improves the chances of the availability of the drug at the specific receptor site and enhances drug receptor interaction through medication of specialized composition and design of the carrier systems. All these factors tend to potentiate the degree of pharmacodynamic response.

2. HISTORY

The concept of microemulsion was first introduced by Hoar and Schulman in 1943; they prepared the first microemulsions by dispersing oil in an aqueous surfactant solution and adding an alcohol as a co-surfactant, leading to a transparent, stable formulation. The existence of his theoretical structure was later confirmed by use of various technologies, and we can today adopt the definition given by Attwood: "a microemulsion is a system of water, oil, and amphiphilic compounds (surfactant and co-surfactant) which is a and transparent, single optically isotropic, and thermodynamically stable liquid".

3. COMPONENT OF MICROEMULSION

1. Oil phase: Usually a non-polar liquid (e.g., triglycerides, medium-chain triglycerides) that can dissolve lipophilic drugs.
2. Surfactants: Amphiphilic molecules (e.g., polysorbates, lecithin) that lower the interfacial tension between oil and water, stabilizing the emulsion.

3. Co-surfactants: Smaller molecules (e.g., alcohols) that assist in improving the flexibility of surfactants and enhancing the stability of the system.

4. Water phase: Usually distilled water, which acts as the continuous phase.

4. ADVANTAGES

1. Because microemulsions have better thermodynamic stability, they can be made quickly and with no energy.
2. The accumulation of microemulsion can be reversed. Both low and high temperatures can cause them to become unstable, but once the temperature drops back into the stability range, the microemulsion will regain its shape.
3. Microemulsions enable self-emulsification and are a thermodynamically stable system.
4. In contrast to emulsions, microemulsions are less viscous.
5. As drug supersolvents, microemulsions can dissolve hydrophilic and lipophilic medications, including those that are insoluble in aqueous and hydrophobic solvents.
6. Being able to transport both hydrophilic and lipophilic medications.
7. The hydrophilic or lipophilic (O/W or W/O microemulsions) dispersed step may serve as a possible reservoir for hydrophilic or lipophilic medications, respectively.
8. The use of microemulsion as delivery systems will improve the effectiveness of a medication, thereby reducing the total dose and decreasing the side effects.

5. DISADVANTAGES

1. Microemulsions may pose challenges related to stability, with issues such as phase separation or droplet coalescence impacting their shelf life.
2. The ability of microemulsions to dissolve high-melting substances is limited, which can constrain their applicability for certain drugs or formulations.
3. A drawback of microemulsions is the requirement for a significant amount of surfactant, which may raise concerns regarding potential toxicity or formulation costs.
4. The stability of microemulsions is susceptible to variations in temperature and pH, necessitating careful storage conditions and potentially affecting their performance in different environments.



6. CHARACTERISTICS OF MICROEMULSION

Microemulsions are increasingly recognized as effective carriers for drug delivery due to their unique physicochemical properties. Here are the key characteristics that make microemulsions a promising option for improved drug delivery:

1. **Thermodynamic Stability -**
Microemulsions are thermodynamically stable, meaning they do not separate over time, unlike emulsions. This stability ensures consistent drug delivery and shelf life.
2. **Nano-sized Droplets -**
Microemulsions consist of nanoscale droplets (typically 10–100 nm), which enhance drug solubility and bioavailability. Their small size allows for better penetration through biological barriers.
3. **Improved Drug Solubility -**
Microemulsions can solubilize both hydrophilic and hydrophobic drugs due to their unique structure (oil, water, and surfactant). This is particularly beneficial for poorly water-soluble drugs.

4. **Enhanced Bioavailability -**
The small droplet size and improved solubility lead to better absorption and bioavailability of drugs, especially for oral, transdermal, and topical delivery systems.
5. **Low Viscosity -**
Microemulsions typically have low viscosity, making them easy to administer and suitable for various routes of delivery, including oral, topical, and parenteral.
6. **Transparency and Optical Clarity -**
Due to their small droplet size, microemulsions are often transparent and optically clear, which is advantageous for cosmetic and pharmaceutical formulations.
7. **Controlled and Targeted Drug Release -**
Microemulsions can be designed to provide controlled or sustained release of drugs, improving therapeutic efficacy and reducing side effects. They can also be tailored for targeted delivery to specific tissues or cells.
8. **Ease of Preparation -**
Microemulsions are relatively simple to prepare and do not require high-energy input, making them cost-effective and scalable for industrial production.
9. **Versatility in Drug Delivery Routes -**
Microemulsions can be adapted for various routes of administration, including oral, transdermal, ocular, nasal, and intravenous delivery.
10. **Biocompatibility and Safety -**
When formulated with biocompatible and FDA-approved components, microemulsions are generally safe and well-tolerated. However, the choice of surfactants and co-surfactants is critical to minimize toxicity.
11. **Enhanced Permeation -**
Microemulsions can improve drug permeation through skin or mucosal barriers, making them ideal for transdermal and topical drug delivery systems.
12. **Protection of Encapsulated Drugs -**
Microemulsions can protect drugs from degradation (e.g., enzymatic or oxidative degradation), enhancing their stability and efficacy.
13. **Customizable Formulations -**
The composition of microemulsions (oil, water, surfactant, and co-surfactant) can be tailored to suit specific drug properties and delivery requirements.
14. **Reduced Side Effects -**
By improving drug targeting and reducing systemic exposure, microemulsions can minimize side effects and improve patient compliance.

7. PREPARATION

1.Phase titration method (Spontaneous emulsification method)

The creation of microemulsions uses the method of spontaneous emulsification, also known as the phase titration method, and can be visually illustrated through the use of phase diagrams. Developing a phase diagram can be an effective method for examining the intricate array of interchanges that may take place when various components are combined. Multiple association structures, such as emulsions, micelles, lamellar, hexagonal, cubic, and numerous kinds of gels and oily dispersion, are created through the chemical composition and concentration of each element, leading to the formation of microemulsions. It is crucial to comprehensively comprehend the phase equilibria and accurately classify the phase boundaries in this research. Because the quaternary phase diagram is challenging to read and takes a lot of time to create, the frequently utilized pseudo-ternary phase diagram identifies specific zones, like the microemulsion zone. Each corner of the diagram depicts 100% of a specific component. The separation of the region into either w/o or o/w microemulsion can be easily determined based on the composition, specifically if it contains rich oil or water. It is important to conduct observations with precision to avoid the incorporation of metastable system

2. Phase inversion method

The microemulsion leads to a phase inversion when the dispersed phase is excessively added or due to temperature changes. During phase inversion, significant physical transformations occur, resulting in modifications of particle size that may negatively affect drug release in both laboratory and living systems. These techniques involve modifying the innate curvature of the surfactant. To achieve this for non-ionic surfactants, the system's temperature can be modified, prompting a shift from a low-temperature oil-in-water microemulsion to a high-temperature water-in-oil microemulsion. As the system cools, it reaches a moment where spontaneous curvature becomes zero and surface tension becomes insignificant, allowing the formation of fine-distributed droplets of oil. The technique is commonly referred to as the

method of temperature inversion during the phase conversion process. Instead of focusing solely on temperature, other factors such as pH level or salt content could also be taken into account. Furthermore, modifying the proportion of water in the system can result in a change in the natural curvature radius transition. The addition of water into oil results in the creation of predominantly discrete water droplets within the ongoing oil phase. By altering the proportion of water, the natural curvature of surfactants shifts from primarily stabilizing microemulsions of water in oil to those of oil in water when reaching the inversion point. Surfactants with shorter chains create adaptable monolayers at the interface between o/w, leading to the formation of a bicontinuous microemulsion when the inversion point is reached.

8. EVALUATION

1. Dilutin test/miscibility test

In the miscibility test, an uninterrupted component, such as a continuous phase is introduced. If an o/w emulsion is exposed to continuous additions of water, it will remain stable but if unlimited amounts of oil are added, the emulsion will lose its stability and the oil will separate from the mixture. On the contrary, w/o emulsion is an opposite scenario.

2. Viscosity Measurement

At 25°C, a digital viscometer was utilized to determine the viscosities of the microemulsion.

3. pH

pH is a crucial factor when it comes to nanoemulsion. The pH of the final preparation and, accordingly, the mode of application is dependent on the excipients utilized in the formulation. A

modification in the pH level can impact the zeta potential of the mixture, potentially leading to an adverse impact on the formulation's stability. The pH level of the compositions was assessed using a digital pH meter. The data was collected three times and then an average of the results was considered.

4. Polarized light microscopy

A microscope made by Nikon Inc., specifically the Optiphot-Pol NIKON 144850 model. A camera equipped mic was utilized in Garden City, NY, for examining the different stages of the phase diagram and confirming the homogeneous behavior of microemulsions. Under polarized light, an examination was carried out by placing a small quantity of the specimen between a glass slide and a coverslip. Photographs were captured with a magnification of 10X and 20X.

5. Entrapment efficiency (EE)

The % EE was calculated by promptly centrifuging newly prepared w/o/w multiple emulsions at 4000 rpm for 10 minutes. Using a hypodermic syringe, an accurate amount of the aqueous phase (which is the lower layer) measuring 1ml was extracted and suitably mixed with phosphate buffer 6.8 after dilution. The millipore filter (0.22 mm) was used to filter the solution, and the drug content was examined with a UV spectrophotometer at 247.6 nm. To determine the encapsulation efficiency, equation 5 was utilized.

$$\% EE = \frac{[\text{Total drug incorporated} - \text{Free Drug}]}{\text{Total drug}} \times 100$$

Total drug

6. Particle size evaluation

The size and distribution of droplets in various Amphotericin B microemulsions were measured using photon correlation spectroscopy with the Malvern S zetamaster. To analyze the samples, the drugloaded microemulsions were diluted with the external aqueous phase at a 1:5 (v/v) ratio and filtered through 0.45 mm filters before being examined. All recorded values were taken at a temperature of 25°C. Each sample underwent 10 runs with a fixed detection angle of 90° to measure the intensity of scattered light.

7. Partition coefficient (P)

The investigation on partition coefficient was carried out by utilizing n-octanol as the oil component and a saline phosphate buffer with a pH value of 7.4 as the aqueous phase. An equal quantity of both phases was combined and mechanically shaken in a water bath shaker for 24 hours before the experiment until saturation was achieved. The centrifugal force of 2000 rpm was utilized to isolate the saturated stages. 10 mL of each phase were measured and transferred into separate conical flasks to ensure equal volume. The experiment involved introducing 100 milligrams of precisely measured drug into a flask, which was then shaken for 6 hours at a temperature of 32°C and a speed of 100 rpm to ensure complete partitioning. After being subjected to centrifugation for 5 minutes at 1000 rpm, the two phases were separated. The spectrophotometric analysis was carried out on the buffer phase to determine the drug concentration. The drug's concentration in octanol was determined as the discrepancy between its initial and ultimate concentrations in the buffer phase. The formula for finding the partition coefficient (P) of the drug Ko/w involved determining the

concentration in octanol and concentration in phosphate buffer pH 7.4, and then plugging those values into the equation. The resulting P value was used to calculate Log P

8. Interfacial tension

One can gain insights into microemulsion creation and characteristics by calculating interfacial tension. The phase behavior in low ultra-values is associated with interfacial tension, which reveals the presence of a surfactant or middle-phase microemulsions in equilibrium with oil and aqueous phases. The measurement of ultra-low interfacial tension can be done utilizing the spinning-drop apparatus. These characteristics are obtained by analyzing the shape of a drop containing a low-density phase, which is rotated within a cylindrical capillary containing a high-density phase.

9. Staining test/dye-solubility test

A drop of methylene blue solution, which can dissolve in water, measuring 10 microliters was introduced into the emulsion. If the emulsion is water-based with an oil phase, the dye will smoothly dissolve in the whole structure. If the emulsion is oil-based with a water phase dispersed throughout, the dye will gather in a cluster on the surface of the mixture.

10. Differential scanning calorimetry (DSC)

The thermal analysis can be conducted using a mettler toledo DSC822. The specimens underwent a gradual cooling process from 25 to -50°C, decreasing at a rate of 5 °C per minute, and were maintained at -50°C for 3 minutes before being swiftly heated up to 50 °C at a rate of 10 °C per minute. The process of heating was executed in an environment that accommodated nitrogen gas flowing at a velocity of 50 ml/min.

11. Centrifuge stress test

The centrifuge was used to spin the systems at 1,073 times gravity (4,000 rpm) for a duration of 15 minutes. Following this, phase separation can be assessed.

12. Freeze thawing method

The stability of the formulations was assessed using the freeze-thaw method. The mixtures were exposed to 3-4 rounds of freeze-thaw cycles that consisted of being frozen at -4°C for 24 hours and then thawed at 40°C for 24 hours. The substances were also centrifuged for 5 minutes at 3000 rotations. The formulations that were chosen for further investigations were those that exhibited stability toward phase separation.

THEORIES

Historically, three approaches have been used to explain microemulsion formation and stability. They are as follows-

- Interfacial or mixed film theories.
- Solubilization theories.
- 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 change in entropy of the system such that,

$$G_f = \gamma \Delta A - T \Delta S$$

Where, G_f = free energy of formation

ΔA = change in interfacial area of microemulsion

ΔS = change in entropy of the system

T = temperature

γ = surface tension of oil water interphase

It should be noted that when a microemulsion is formed the change in ΔA is very large due to the large number of very small droplets formed. In order for a microemulsion to be formed (transient) negative value of G_f was required, it is recognized that while value of ΔS is positive at all times, it is very small and it is offset by the entropic component. The dominant favorable entropic contribution is very large dispersion entropy arising from the mixing of one phase in the other in the form of large number of small droplets. However there are also expected to be favorable entropic contributions arising from other dynamic processes such as surfactant diffusion in the interfacial layer and monomeric surfactant exchange. Thus a negative free energy of formation is achieved when large reductions in surface tension are accompanied by significant favorable entropic change. In such cases, microemulsion is spontaneous and the resulting dispersion is thermodynamically stable.

FACTOR AFFECTING

- ❖ Packing ratio
- ❖ Property of surfactant
- ❖ Property of oil phase
- ❖ Temperature
- ❖ Chain length
- ❖ Nature of co-surfactant.

APPLICATION

1. Oral applications

Consequently, microemulsion has been identified as an optimal channel for dispensing pharmaceuticals like steroids, hormones, diuretics, and antibiotics. While peptides and proteins are incredibly effective in their physiological abilities, administering them through the oral route can prove to be challenging. In traditional methods, the uptake of medication through the mouth is limited in its effectiveness. Typically, formulations without microemulsions that contain less than 10% of the active ingredient are not effective for oral consumption in terms of providing therapeutic benefits. The majority of protein drugs are solely accessible as parenteral formulations due to their limited ability to be absorbed orally. Peptide drugs necessitate multiple dosing due to their brief biological half-life when administered through a parenteral route. The administration of microemulsion formulations orally has numerous advantages in comparison to traditional oral formulations, such as enhanced absorption rate, improved therapeutic effectiveness, and reduced drug toxicity.

2. Topical applications

The topical application of medications can offer various benefits compared to other methods because it helps prevent the drug's hepatic first-pass metabolism and its resulting damaging effects. The second advantage pertains to the efficient administration and precise placement of medication directly to the impacted region of the dermis or ocular surface. The efficiency of both o/w and w/o microemulsions in administering prostaglandin E1 53 has been analyzed in a hairless mouse model [40]. Despite finding improvements in delivery rates with the o/w microemulsion, the authors ultimately deemed the penetration rates insufficient for pragmatic application with either system. It has been reported that lecithin/IPPP/water microemulsion has been utilized for transdermal transportation of indomethacin and diclofenac. The interruption of lipid organization in the stratum corneum of humans was observed after oneday incubation of utilizing IPP organogel, as indicated by Fourier transform infrared spectroscopy and DSC.

3. Parenteral applications

Developing injectable forms for both lipid and water-soluble medicines has been a challenging task. The use of w/o microemulsions is advantageous for delivering poorly soluble medications intravenously, eliminating the need for administering suspensions. Maintaining a high dosage is necessary for regular medication. Plasma has demonstrated superior physical stability compared to liposomes and other carriers, with the added advantage of increased resistance against drug leakage from the internal oil phase. Parenteral delivery of sparingly soluble drugs has been made possible through the development of o/w microemulsions. Von Corsewant and Thoren adopted a different method by substituting C3-C4 alcohols with co-surfactants that are suitable for parenteral use, such as polyethylene glycol (400)/polyethylene glycol (600) 12-hydroxy stearate/ethanol. This allowed for the maintenance of a flexible surfactant film and the formation of a spontaneous curvature close to zero, resulting in the generation of microemulsions with a nearly evenly balanced middle phase. Numerous literature sources have documented the application of water-in-oil (w/o) microemulsions as a vehicle for delivering water-soluble substances via intramuscular means. If the microemulsion is absent, undergoing phase inversion becomes a noteworthy characteristic that yields an o/w microemulsion that can serve as a viable option for delivering parenteral drugs.

4. Ophthalmic applications

The dexamethasone eye drop formulated with microemulsion is easily tolerated by the eye and provides improved bioavailability. The enhanced system displayed improved permeation into the eye, presenting the potential to reduce the frequency of eye drop usage per day. The study examined microemulsion systems containing retinol and its esters as the oil component, along with surfactants including tween 80, tween 60, and soybean lecithin, as well as cosurfactants like n-butanol, triacetin, and propylene glycol for delivery to the eye. The composition with the best ophthalmic properties, including refractive index, viscosity, pH, and osmotic tension, was determined to be the most effective for drug delivery. For a duration of 6 months at a temperature of 20°C, no visible alteration was noticed and the substance was well-tolerated by the body.

5. Nasal applications

Currently, microemulsions are being examined as a method of administering drugs more effectively through the nasal mucosa. Mucoadhesive polymers aid in increasing the duration of their stay on the mucosal surface. Lianly and her colleagues; explored the impact of diazepam on the immediate response to status epilepticus. They discovered that the uptake of diazepam through the nose was swift when administered at a dose of 2 mg kg⁻¹, with the highest level of the drug in the blood plasma achieved within 2 to 3 minutes.

9. CONCLUSION

Microemulsion is drug delivery systems for the delivery of more than one medicament simultaneously. Microemulsion prevents labile medications, monitors the release of pharmaceutical products, enhances drug solubility, improves bioavailability and decreases patient variability. The role of microemulsion in providing new solutions to the problems of poor water solubility of compounds of highly lipophilic drugs and providing strong, more stable and reproducible bioavailability. Drug delivery by microemulsion is a promising field for ongoing research to achieve controlled release with improved bioavailability and drug targeting at different body sites. Recently, several research papers have been published for the improvement of drug delivery, but still there is a need to put an emphasis on its characterization part including in vitro evaluation. Besides this, research papers shows higher percentage of surfactant (much higher than CMC level) used for the formation of microemulsion, irrespective of different routes of administration, but there is a lack of toxicological evaluation of the prepared microemulsion, which can be a broad research area in future.

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