International Journal of Pharmaceutics and Drug Research
ISSN: 2347-6346
Available online at http://ijpdr.com

Review Article

MICROEMULGEL: AS A NOVEL VEHICLE FOR ANTIMICROBIAL DRUGS

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***Article History:**

Received: 18/07/2023
Revised: 02/08/2023
Accepted: 23/08/2023

ABSTRACT

For local dermatological activity, topical drug administration is usually preferred. Preparations' topical activity is limited by drug solubility, residence time, lipophilicity, and permeability. Creams, ointments, and other traditional dosage forms have limitations such as poor stability, stickiness, absorption, and penetration, particularly in the case of big molecules. To address this, the development of emulgels, which primarily focus on the delivery of hydrophobic medicines, occurred. Thus, the current review focuses on microemulgel features, preparation, benefits, and antibacterial mode of action, as well as applications.

Keywords: Topical drug delivery, Micremulgel, Emulsion, Antimicrobial activity, Pseudo-ternary phase diagram.

INTRODUCTION

Microbial infections are increasingly a big concern for society. Because of the ease of transmission from person to person, the number of people suffering from bacterial, viral, and fungal infections disorders rises each year. A few hazardous germs, such as less than 1% of bacteria, can enter human body (the host) and cause illness. Infectious diseases caused by microbes include the flu and measles. There is also compelling evidence that bacteria play a role in many non-infectious chronic diseases, including several types of cancer and coronary heart disease. Microorganisms of many sorts cause various diseases. Pathogens are microbes that cause disease (Friedman *et al*., 2003; Cundell, 2018; Rosenthal *et al*., 2011).

Infection and sickness are caused by a variety of circumstances. To begin, an organism's infectivity defines the number of people who will become infected in comparison to the number of people that are susceptible and exposed. Second, pathogenicity is a measure of an infectious organism's ability to cause disease. Pathogenic bacteria have traits that allow them to bypass the body's defences and utilise its resources to cause disease. Finally, virulence characterises an organism's proclivity to cause disease through characteristics such as invasiveness and toxin production. Host variables play an important role in deciding whether disease develops once a bacterial pathogen is transmitted. These variables include genetic make-up, dietary state, age, duration of organism exposure, and associated illnesses. The environment also influences host susceptibility. Environmental pollutants such as air pollution and chemicals decrease the body's defences against bacterial illness (Morse; 2001; Delogu *et al*., 2011).

A topical drug delivery system is a localised drug delivery system that contains drug formulations for the skin to treat skin problems. The skin is the largest organ of the

integumentary system, accounting for 12-15% of body weight and covering an area of 1 - 2m^2. The skin is made up of seven layers of ectodermal tissue and protects the muscles, bones, ligaments, and internal organs beneath. The molecules enter the skin primarily through three routes: intact stratum corneum, sweat ducts, and sebaceous follicles. As a result, a topical formulation is critical for the treatment of fungal disease on the skin. The topical medicine can be delivered anywhere in the body via ocular, rectal, vaginal, or cutaneous routes. This medicine delivery technique is often useful when other potent routes of administration such as oral, sublingual, rectal, and paternal fail or are not practical, such as fungal infection. Skin-related or dermatological products vary in composition and consistency from liquid to semisolid to solid, but semisolid preparations are the most common and acceptable. The usage of aqueous gels in cosmetics and medicinal preparations has increased within the principal group of semisolid preparations (Tadwee *et al*., 2012; Tan *et al*., 2012).

Because of its dual action via emulsion and gel, microemulgel is regarded as one of the most promising new drug delivery systems. Furthermore, it was discovered that combining emulsion with gel boosted its stability.

Hoar and Schulman (1943) identified microemulsions as a type of colloidal dispersion for the first time. Lewis (1954) coined the term "microemulsions." However, they were most likely discovered by chance prior to that. Since the early twentieth century, Australian housewives have washed wool with a mixture of water, eucalyptus oil, soap flakes, and white spirit (Langevin 1988), which it has been proposed generated natural microemulsions afterwards utilised as cleaning agents. It wasn't until the 1970s that researchers discovered that microemulsions may be utilised to improve oil recovery (Madhav and Gupta, 2011). Microemulsions reside in a phase inversion region, with a spontaneous radius of curvature near to zero between the oil and water microdomains. As a result, the structure is lamellar. De Gennes and Taupin (1982) showed why the system is not macroscopically organised. Because the surfactant film's bending elasticity is low and heat fluctuations roughen the film, the lamellar order is swiftly destroyed. The dynamic properties of microemulsions have also been extensively explored, but they remain mostly unknown. Because of their propensity to solubilize both hydrophilic and lipophilic molecules, these liquids have piqued the interest of many industries, including pharmaceuticals, oil recovery, and household cleaning goods (De Gennes and Taupin, 1982).

Advantages of emulsion over microemulsion

Conventional emulsion	**Microemulsion**
Large energy input for preparation technique	There is no significant energy input for the method of preparation.
Poor long-term storage stability, with a proclivity to coalesce, creaming/sedimentation, or phase separation.	Improved long-term storage stability (Holmberg *et al*., 2010)
A two-phase system is thermodynamically unstable.	The single phase system makes it thermodynamically

	stable.
Globule diameter more than 500 nm	Micelle sizes range from 5-500 nm.
Lipophilic transport is somewhat less prevalent.	Lipids promote lymphatic movement.
Bioavailability is lower in comparison.	Dose reduction due to increased bioavailability
Manufacturing is difficult, and scaling up is difficult.	Simple to produce and scale up

Formulation considerations

Oil

Oil has a high solubility for BCS class II medicines. In a microemulsion-based medication delivery method, the oil also works as a penetration booster. Short chain oil enters the tail group region more than long chain oil, resulting in tail group swelling and an increase in negative curvature, which reduces the effect of HLB balancing. Oils also influence the area of the microemulsion region; for example, Muhammad Asri Abd Sisak et al. 2017, successfully constructed 18 phase diagrams for both oleic acid and IPM. Each formulation had a substantial effect on the area of the microemulsion zone; however, the oleic acid-based method was unable to produce large microemulsion regions. IPM was the best option for obtaining a larger microemulsions zone with a higher concentration of water during the transition phase from w/o to o/w. The size of the droplet grows in proportion to the concentration of oil. The oils with enhanced drug solubility also have larger droplet size. The oil's molecular volume also demonstrates its effect on the microemulsion. For example, an IPM (molecular volume 528.2 g/cm^3)-based microemulsion system had a smaller area of microemulsion than an oleic acid-based system (molecular volume 523.9 g/cm^3)-based system (Abd *et al*., 2017).

Surfactant

Surfactant is the second factor to consider when preparing a microemulsion, and it should be chosen in such a way that it provides the best solubility for the medicine. During the emulsification process, the surfactant should immediately absorb within the interface and inhibit the droplets aggregation. There are four types of surfactants that stabilise the systems: non-ionic, zwitterionic, cationic, or anionic surfactants. Surfactants, both ionic and nonionic, have the ability to extend the microemulsion region. Brij-35, tween 20/80, and span 80 are examples of non-ionic surfactants. The influence of surfactant on medication solubility is demonstrated. The ratio or HLB values of the surfactant mixture also affect microemulsion penetration. The presence of a mixed surfactant proved advantageous in the preparation of microemulsions (Chen *et al*., 2018).

Co-surfactant

In the manufacture of microemulsions, the cosurfactant is usually combined with the surfactant, which reduces the interfacial tension between the two immiscible liquids to a transitory negative value. Fine droplets form due to interphase expansion at this negative value, and much surfactant/cosurfactant is absorbed on the surface until the bulk condition is sufficient to make the interracial tension positive again. As the interaction between primary surfactant molecules decreases both polar head group interaction

and hydrocarbon chain interaction, cosurfactant of short medium chain length alcohols ensures that the interfacial layer is flexible enough to misshape easily around droplets. According to the research of Muhammad asriabdsisak et al. 2017, the effect of a co-surfactant is dependent on its chain length, and only a suitable chain length is suited for good microemulsion creation. In his work, he used PEG400 (long chain), Transcutol (mid chain), and propylene glycol (short chain) to analyse the influence of co-surfactant on the manufacture of microemulsion. In his research, he concluded that medium chain length surfactant is the best co-surfactant to use in conjunction with single chain surfactant. Surfactants with HLB values greater than 20 frequently necessitate the addition of a cosurfactant to reduce surfactant effective HLB value within the range of required microemulsion formulation (Golwala *et al*., 2020).

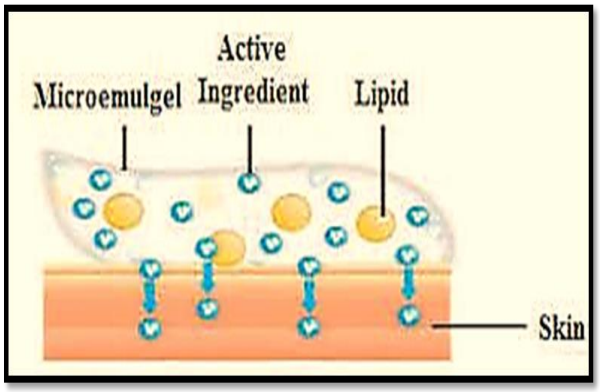

Figure 1: Pictorial presentation of microemulgel

Method of preparation of microemulgel

Phase inversion method

Phase inversion of microemulsions is formed either by adding excess of dispersed phase (Phase Inversion Concentration) or in response to temperature (Phase Inversion Temperature). The phase inversion method makes drastic physical changes in the system such as changes in particle size. In phase inversion temperature (PIT) method, the interfacial tension is the key factor. On cooling, the interfacial tension get lowered and can be found in the phase inversion region from water-in-oil (W/O) microemulsion to an oil-in-water (O/W) microemulsion. This low interfacial tension aids in the spontaneous creation of finely dispersed, blue-shining O/W PIT microemulsion in the phase inversion zone. Because the hydrophobicity of nonionic ethoxylated surfactants increases dramatically with temperature, all practical applications of PIT microemulsions rely on the use of ethoxylated surfactants. Changing the water volume fraction also produces a change in the spontaneous radius of curvature. Initially, water droplets are formed in a continuous oil phase by continually adding water to oil. As the water volume increases, changes in the spontaneous curvature of the surfactant lead the inversion point to convert from a W/O microemulsion to an O/W microemulsion. The resulting emulsion is known as phase inversion concentration (PIC) microemulsion because the phase inversion occurs at a certain water concentration within the intermediate microemulsion-like phase. Because of the flexible monolayer of short chain surfactants at the O/W interface, a bicontinuous microemulsion forms at the inversion spots (Kushwah *et al*., 2021).

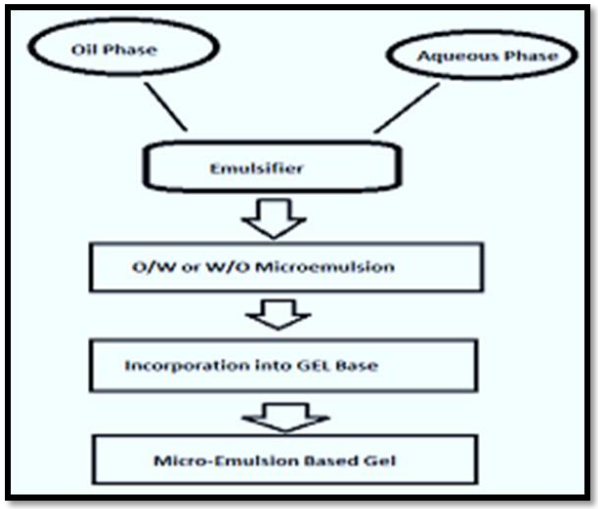

Figure 2: Micoemulgel preparation flow chart

Phase titration method

Microemulsions are created using the spontaneous emulsification method (Phase titration) and can be represented using phase diagrams. The use of phase diagrams to explore the complex series of interactions that might occur when different components are blended is a useful method. Depending on the chemical content and concentration of each component, microemulsions are generated along with various association structures (including emulsions, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion). Understanding their phase equilibrium and delineating the phase borders are critical components of the research. Because quaternary phase diagrams (four component systems) are time consuming and difficult to comprehend, pseudo ternary phase diagrams (four corners of the figure signify 100% of the particular component) are frequently used to locate the different zones, including the Microemulsion zone. The region can be classified as w/o or o/w Microemulsion based on its composition, that is, whether it is oil-rich or water-rich. It is important to make thorough observations so that metastable systems are not included (Vanti *et al*., 2021).

Phase diagrams associated with microemulsion

Pseudo-ternary phase diagram:

The water titration method is used to create phase diagrams in order to identify the type of structure that resulted in the subsequent emulsification and to characterise the behaviour of mixtures during dilution. At a constant weight ratio of surfactant/cosurfactant, a pseudo-ternary phase diagram of oil, water, and surfactant/cosurfactant combination is produced. By combining substances in the vial and titrating with water, the emulsification region is formed. Visual inspection confirms the formation of monophasic and biphasic systems. After stirring in a monophasic system, clean and transparent mixtures are visible, whereas in a biphasic system, turbidity appears followed by phase separation. Only the area where clear microemulsion was considered. The particle size and polydispersity index of the prepared microemulsion were then determined (PDI) (Nandgude *et al*., 2020).

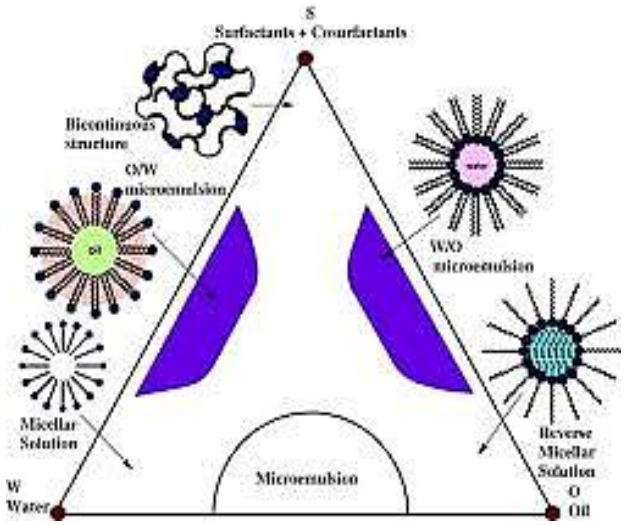

Figure 3: Pseudo-ternary phase diagram

Characterization of microemulgel

Physical Examination

The colour, appearance, consistency, grittiness, phase separation, and homogeneity of the created microemulgel formulations were visually assessed. Grittiness, consistency, and phase separation.

Extrudability test

It is a test used to determine the force needed to extrude material from a tube. The collapsible tubes were filled with the mixtures. The formulation's extrudability was assessed by the weight required to extrude a 0.5 cm ribbon of microemulgel in 10 seconds. Extrudability is thought to be improved when more material is extruded. The amount of gel that was extruded was calculated and recorded (Shrestha *et al*., 2017).

Syneresis Measurement

After visually inspecting the microemulgel, it was tested for any probable phase separation. Standing causes the gel to shrink and a small amount of liquid to be squeezed out. This is referred to as syneresis. It is given as a percentage of syneresis. A centrifuge machine is used in this test. The formulation was placed in a cylindrical tube with a perforated bottom and Whatman filter paper on top. The tube was inserted into the centrifuge and spun for 15 minutes. Weighing the tube and liquid separated from the microemulgel. The formula was used to compute the percentage syneresis.

pH

A pH metre (Digital pH metre) can be used to determine the pH value. Before use, the pH metre was calibrated with a standard buffer solution with pH values of 4 and 7. The produced Microemulgel can subsequently be converted into a 1% aqueous solution. The required amount of formulation was dissolved in distilled water and agitated until it formed a homogeneous suspension; it was then set aside for 2 hours. The digital pH metre can be used to measure the volume created up to 100 ml as well as the pH of the suspension. The pH levels of each formulation were measured in triplicate (Ashara *et al*., 2016).

Spreadability Test

To test the spreadability of microemulsion-based gel, 0.5 g of gel was deposited within a 1 cm diameter circle pre-marked on a glass plate, which was then covered with a second glass plate. For 5 minutes, a 500g weight was permitted to lie on the upper glass plate. The diameter increased as a result of gel spreading.

Rheological Study

Brookfield's viscometer was used to determine the viscosity of the microemulgel.

Drug content determination

The drug content of microemulgel will be determined by sonicating 1gm of microemulgel in solvent. Using a UV spectrophotometer, absorbance will be determined at max nm after appropriate dilution.

In-vitro Diffusion Study

For drug release experiments, a Franz diffusion cell (effective diffusion area 3.14 cm2 and cell volume 15.5ml) is used. The surface of the cellophane membrane is coated with microemulgel. The donor and receptor chambers of the diffusion cell are separated by a cellophane membrane. To solubilize the medication, the receptor chamber is filled with freshly made PBS (pH 5.5) solution. A magnetic stirrer is used to stir the receptor chamber. After proper dilutions, the samples are collected at appropriate time intervals and

analysed for drug content using a UV visible spectrophotometer at a respected wave length. To calculate the total amount of medication released at each time interval, cumulative adjustments are used. The total amount of medication released across the cellophane membrane over time is calculated (Sattar *et al*., 2023).

Release Kinetics:

The best fit model was used to evaluate drug release from all batches of microemulgel. Zero order, first order, Higuchi, and Korsmeyer Peppas are some kinetic models.

Stability study:

The improved batch underwent a stability investigation in accordance with ICH criteria. For three months, gel was tested for short-term accelerated stability at 40°C 2°C/75% 5% RH. At regular intervals, the microemulgel formulation was tested and examined for changes in physical appearance, consistency, pH, viscosity, spreadability, and drug content (Suharti and Putri, 2022).

Mechanism action of antimicrobial action of microemulsions

The postulated mechanism of microemulsion antimicrobial activity is the irreversible breakdown of microbial membranes, resulting in cell lysis and death. This theory is founded on two phenomena:

i. i. The forces involved in the structure and energy preservation of microemulsions and bacterial membranes are identical. Both systems are created and maintained by a precise balance of interfacial hydrophobic forces that rely on a sensitive but consistent energy state. As a result, the physicochemical interaction of two similar systems, such as a microemulsion and a bacterial cell membrane, is predicted to have a negative influence on the forces that keep the cellular membrane together. Microemulsions have a higher level of kinetic activity than cell membranes because they have a substantial and continually changing diversity in particle size and structure, resulting in constant energetic shifts and fluid structural rearrangements. These modifications provide microemulsions with enough energy to interact with and significantly disrupt the typically fluid but stable bacterial membrane structure (Al-Adham *et al*., 2022; Pavoni *et al*., 2019).

ii. ii. The presence of surfactants and, in some cases, cosurfactants in the microemulsion structure will inevitably bring these molecules into close contact with bacterial membranes. Surfactants' capacity to disrupt and sometimes dissolve bacterial membranes is well established, and they are frequently utilised in the creation of bacterial membrane and protein solutions by experimental microbiologists (e.g.: for SDS-PAGE etc) (Shaaban and Edris, 2015; Costa *et al*., 2019).

Many researchers have investigated the incorporation of plant-extracted actives into microemulsions in attempt to increase antibacterial activity. Herbal microemulsions as anti-cariogenic biofilm agents are among them. Microemulsions made with thyme essential oil (Thymus vulgaris) have been found to be effective fruit disinfectants.

Microemulsions have also been employed to develop antiviral medicines and delivery methods (Ebenazer et al., 2020). Microencapsulation in a microemulsion method improved the inherent antibacterial activity of galangal (Alpinia galanga), an Asian ginger spice (Khumpirapang *et al*., 2021). Furthermore, the antibacterial activity of essential oils has been increased by entrapment in microemulsions. Microemulsions have been found to have anti-insect properties. Turmeric (Curcuma spp.) microemulsions, in particular, have been shown to have a considerable acaricidal action against the red spider mite. Microemulsions have exhibited significant preservation benefits in food production, in that they have been proven to improve the quality and safety of muscle-derived foods. Almasi et al. (2021b) have also used microemulsion biopolymers' antibacterial capabilities in food production and preservation. Strawberry edible coatings based on microemulsions have an antifungal effect against black-spot (produced by Colletotrichum acutatum) and so lengthen the fruit's shelf life (Almasi *et al*., 2021).

Microemulsions continue to pique the interest of the pharmaceutical industry, with recent developments including the incorporation of Amphotericin B into microemulsions for the treatment of fungal lung infections, the encapsulation of moxifloxacin into microemulsions for the treatment of skin conditions, and the development of a trans-dermal delivery system for the antispasmodic drug Eperisone Hydrochloride (Cardoso *et al*., 2022).

Some formulations of microemulgel

Name of drug/ Plant extact	**Uses**	**References**
Terbinafine	Athlete's foot	(Shrestha *et al*., 2017)
Voriconazole	Fungal skin infection	(Ashara *et al*., 2017)
benzoic and salicylic acid	Fungal infections	(Chandira *et al*., 2022)
triamcinolone	arthritis, eczema, psoriasis	(Jagdale and Chaudhari, 2017)
ketoconazole	onychomycosis	(Amra and Momin, 2019)
Cannabidiol	Skin diseases	(Vanti *et al*., 2021)
Carthamus tinctorius	Vehicle for cosmeceutical purposes	(Zaka *et al*., 2022)
Khellin	Skin care applications	(Vannucchi *et al*., 2022)
Musa paradisiaca	Antioxidant activity	(Sriarumtias *et al*., 2019)
Miconazole Nitrate	Topical infections	(Oza *et al*., 2021)
Pogostemon cablin	Bacterial infection	(Suharti and Putri, 2022)
Nigella sativa	Hypopigementation	(Badhe *et al*., 2022)
Calophyllum inophyllum extract	sunscreen	(Sari *et al*., 2023)
3,4-Dimethoxychalcone	Photoprotective Agent	(Maulana *et al*., 2021)
Luliconazole	Antifungal	(Dandagi *et al*., 2020)

CONCLUSION

Most medications are quite effective when administered orally or parenterally, but they have a slew of unpleasant side effects, necessitating additional routes of administration such as topical, ophthalmic, vaginal, and so on. Because most drugs are poorly water soluble, they have difficulty penetrating the skin. The selection of oil, emulsifiers, and co-emulsifiers for preparation is based on their solubility in them, so the problem of solubility is overcome. The oil part has some pharmacological activity and helps with penetration. Because microemulgel promotes the deposition of drug moieties at the site, therapeutic action is boosted. When compared to microemulsion, stability is higher.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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