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A REVIEW ON MICROEMULSION BASED SYSTEM

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ABSTRACT

Microemulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. Microemulsions act as potential drug carrier systems for oral, topical, and parenteral administration. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, and improved drug solubilization and bioavailability. Preparing a pharmaceutically acceptable dosage form demands a clear understanding of the micro-emulsion structure, phase behavior, factors leading to its thermodynamic stability and the potential uses and limitations of the microemulsion system. Knowledge of the various methods available to thoroughly characterize a microemulsion system is essential. While microemulsion is used in several fields, in this review the pharmaceutical applications are emphasized. Several references are cited, but the list is by no means exhaustive. The review is written so that a newcomer to the field can easily grasp the important facts pertaining to this novel delivery system.

INTRODUCTION: Microemulsions are clear, stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. The aqueous phase may contain salt(s) and/or other ingredients, and the "oil" may actually be a complex mixture of different hydrocarbons and olefins. In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The two basic types of microemulsions are direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o) [1-3].

In ternary systems such as microemulsions, where two immiscible phases (water and 'oil') are present with a surfactant, the surfactant molecules may form a monolayer at the interface between the oil and water, with the hydrophobic tails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase. As in the binary systems (water/surfactant or oil/surfactant), self-assembled structures of different types can be formed, ranging, for example, from (inverted) spherical and cylindrical micelles to lamellar phases and bi-continuous microemulsions, which may coexist with predominantly oil or aqueous phases.

FIG. 1: MICROEMULSIONS.

In principle, microemulsions can be used to deliver drugs to the patients via several routes, but the topical application of microemulsions has gained increasing interest. The three main factors determining the transdermal permeation of drugs are the mobility of drug in the vehicle, release of drug from the vehicle, and permeation of drug into the skin. These factors affect either the thermodynamic activity that drives the drug into the skin or the permeability of drug in the skin, particularly stratum corneum.

Microemulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions [4, 5] and gels [6, 7]. Mobility of drugs in microemulsions is more facile [8], as compared to the microemulsion with gel former which will increase its viscosity and further decrease the permeation in the skin [9]. The superior transdermal flux from microemulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs.

This generates an increased thermodynamic activity towards the skin. Microemulsions may affect the permeability of drug in the skin. In this case, the components of microemulsions serve as permeation enhancers [10-12]. Several compounds used in microemulsions have been reported to improve the transdermal permeation by altering the structure of the stratum corneum [13-15]. For example, short chain alkanols are widely used as permeation [16] enhancers. It is known that oleic acid, a fatty acid with one double bond in the chain structure, perturbs the lipid barrier in the stratum corneum by forming separate domains which interfere with the continuity of the multilamellar stratum corneum and may induce highly permeable pathways in the stratum corneum.

Isopropyl myristate (IPM) is used as a permeation enhancer in transdermal formulations, but the mechanism of its action is poorly understood. Nonionic surfactants are widely used in topical formulations as solubilizing agents but some recent results indicate that they may affect also the skin barrier function[17]. It is of interest to explore the effects of these components in the organized microemulsion structures. The aim of the present study was to investigate the potential of several microemulsion formulations in transdermal delivery of lipophilic drugs. A unique attempt was made [18] to emulsify coconut oil with the help of polyoxyethylene 2-cetyl ether (Brij 52) and isopropanol or ethanol, forming stable isotropic dispersion thus paving way for use of plant and vegetable oil to be used as oil phase in microemulsion.

Theory: Various theories concerning microemulsion formation, stability and phase behavior have been proposed over the years. For example, one explanation for their thermodynamic stability is that the oil/water dispersion is stabilized by the surfactant present and their formation involves the elastic properties of the surfactant film at the oil/water interface, which involves as parameters, the curvature and the rigidity of the film. These parameters may have an assumed or measured pressure and/or temperature dependence (and/or the salinity of the aqueous phase), which may be used to infer the region of stability of the microemulsion, or to delineate the region where three coexisting phases occur, for example. Calculations of the interfacial tension of the microemulsion with a coexisting oil or aqueous phase are also often of special focus and may sometimes be used to guide their formulation.

Historical Background: The combination of water and oil, made into a single-phase system with the aid of a third component (surfactant), was patented in mid 1930's [19]. However, it was not until 1943 when the first academic studies were performed [20]. Hoar and Schulman showed, with the help of a strong surface-active agent, it is possible to induce spontaneous emulsification. This is now attributed to microemulsion formation, owing to very low interfacial tensions promoted by the surfactants. Five years later, Winsor [21]studied the phase behaviour of water-oil-surfactant mixtures in the presence of different additives and classified four types of phase equilibria:

Type I: Surfactant-rich water phase (lower phase) coexists with surfactant-poor oil phase (Winsor I).
Type II: Surfactant-rich oil phase (the upper phase) coexists with surfactant-poor water phase (Winsor II).
Type III: Surfactant rich middle-phase coexists with both water (lower) and oil (upper) surfactant-poor phases (Winsor III).

Type IV: Single phase homogeneous mixture.

In 1959, Schulman *et al*., [22] titrated a multiphase system (consisting of water, oil and surfactant) with alcohol and obtained a transparent solution which they termed 'a microemulsion'. At that early stage some researchers preferred to identify these systems with 'swollen micelles' [23], others used the term 'micellar emulsion' [24]. Nevertheless, the term 'microemulsion' is a commonly used name nowadays. A detailed historical background of microemulsions can be found elsewhere [25].

Phase Diagrams: The microemulsion region is usually characterized by constructing ternary-phase diagrams. Three components are the basic requirement to form a microemulsion: an oil phase, an aqueous phase and a surfactant. If a cosurfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single "pseudo-component". The relative amounts of these three components can be represented in a ternary phase diagram. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behavior of the system [26].

The three components composing the system are each found at an apex of the triangle, where their corresponding volume fraction is 100%. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist (ideally, according to the Gibbs' phase rule) of one, two or three phases. These points combine to form regions with boundaries between them, which represent the "phase behavior" of the system at constant temperature and pressure.

The Gibbs phase diagram, however, is an empirical visual observation of the state of the system and may, or may not express the true number of phases within a given composition. Apparently clear single phase formulations can still consist of multiple iso-tropic phases (e.g. the apparently clear heptane/AOT/water microemulsions consist multiple phases). Since these systems can be in equilibrium with other phases, many systems, especially those with high volume fractions of both the two immiscible phases, can be easily destabilized by anything that changes this equilibrium e.g. high or low temperature or addition of surface tension modifying agents.

However, examples of relatively stable microemulsions can be found. It is believed that the mechanism for removing acid build up in car engine oils involves low water phase volume, water-in-oil (w/o) microemulsions. Theoretically, transport of the aqueous acid droplets through the engine oil to micro-dispersed calcium carbonate particles in the oil should be most efficient when the droplets are small enough to transport a single hydrogen ion (the smaller the droplets, the greater the number of droplets, the faster the neutralization). Such microemulsions are probably very stable across a reasonably wide range of elevated temperatures.

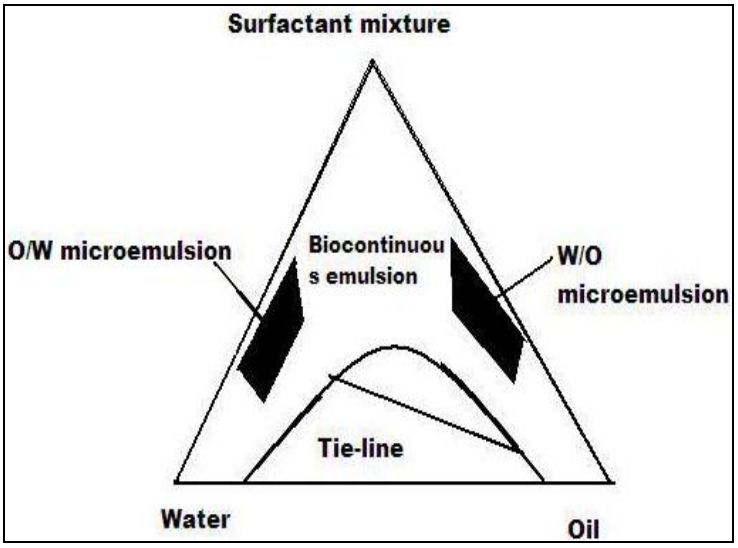


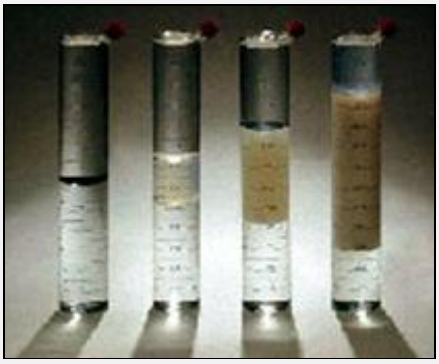
FIG. 2: SCHEMATIC REPRESENTATION OF PSEUDO TERNARY PHASE DIAGRAM SHOWING MICROEMULSION REGION [27]

Three types of microemulsions are most likely to be formed depending on the composition:

- Oil in water microemulsions wherein oil droplets are dispersed in the continuous aqueous phase
- Water in oil microemulsions wherein water droplets are dispersed in the continuous oil phase;
- Bi-continuous microemulsions wherein micro-domains of oil and water are inter-dispersed within the system.

In all three types of microemulsions, the interface is stabilized by an appropriate combination of the surfactants and/or co-surfactants. The key difference between emulsions and microemulsions are that the former, whilst they may exhibit excellent kinetic stability, are fundamentally thermodynamically unstable and will eventually phase separate [1]. Another important difference concerns their appearance; emulsions are cloudy while microemulsions are clear or translucent. In addition, there are distinct differences in their method of preparation, since emulsions require a large input of energy while microemulsions do not. The latter point has obvious implications when considering the relative cost of commercial production of the two types of system.

TABLE 1: COMPARISON WITH EMULSIONS (MACROEMULSIONS) [28-33]

Emulsions (Macroemulsions)	Microemulsions
	
FIG. 3: EMULSIONS	**FIG. 4: MICROEMULSIONS**
Emulsions consist of roughly spherical droplets of one phase dispersed into the other.	They constantly evolve between various structures ranging from droplet like swollen micelles to bi-continuous structure.
Droplet diameter: 1 – 20 mm.	10 – 100 nm
Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	Microemulsions are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light, they scatter little light.
Ordinary emulsion droplets, however small exist as individual entities until coalescence or ostwald ripening occurs.	Microemulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system.
They may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy. They are kinetically stable thermodynamically unstable.	More thermodynamically stable than macroemulsions and can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
They are lyophobic.	They are on the borderline between lyophobic and lipophilic colloids.
Require intense agitation for their formation.	Generally obtained by gentle mixing of ingredients.

Theory of microemulsion formulation: Microemulsion formation and stability can be explained on the basis of a simplified thermodynamic rationalization. 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 the change in entropy of the system such that [34],

$$DG_f = \gamma DA - T\,DS$$

Where, DG_f =free energy of formation, γ = Surface tension of the oil–water interface, DA =Change in

interfacial area on microemulsification, DS = Change in entropy of the system which is effectively the dispersion entropy, and T = Temperature.

It should be noted that when a microemulsion is formed, the change in DA is very large due to the large number of nanodroplets are formed. It is seen that while the value of γ is positive at all times, it is very small (of the order of fractions of mN/m), and is offset by the entropic component. The dominant favorable entropic contribution is the very large dispersion entropy arising from the mixing of one phase in the other in the form of large numbers of nanodroplets. However, favorable entropic contributions also arise from other dynamic processes such as surfactant diffusion in the interfacial layer and monomer-micelle 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, microemulsification is spontaneous and the resulting dispersion is thermodynamically stable.

Though, it has been know that several factors determine whether a w/o or o/w microemulsion system will be formed but in general it could be summarized that the most likely microemulsion would be that in which the phase with the smaller volume fraction forms.

Surfactants, co-surfactants and oil used in microemulsion formulation:

- Surfactants- used to stabilize the system; -non-ionic, zwitter ion, cationic or anionic.
- Co-surfactant- decrease the interfacial tension; -and increase the microemulsion region; -alcohols, amines, and cholesterol
- Oils- hydrocarbon oils such as heptane or -cyclic oils like cyclohexane the droplets i.e., internal phase.

Attempts have been made to rationalize surfactant behavior in terms of the hydrophilic- lipophilic balance (HLB) [35], as well as the critical packing parameter (CPP) [36, 37]. Both approaches are fairly empirical but can be a useful guide to surfactant selection. The HLB takes into account the relative contribution of hydrophilic and hydrophobic fragments of the surfactant molecule. It is generally accepted that low HLB (3-6) surfactants are favored for the formation of w/o microemulsions whereas surfactants with high HLBs (8-18) are preferred for the formation of o/w microemulsion systems. Ionic surfactants such as sodium dodecyl sulphate which have HLBs greater than 20, often require the presence of a co-surfactant to reduce their effective HLB to a value within the range required for microemulsion formation. In contrast, the CPP relates the ability of surfactant to form particular aggregates to the geometry of the molecule itself.

A combination of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the microemulsion region. Examples of non-Ionics include polyoxyethylene surfactants such as Brij 35($C_{12}E_{35}$) or sugar esters such as sorbitan monooleate (Span 80). Phospholipids are a notable example of zwitter ionic surfactants and exhibit excellent biocompatibility. Lecithin preparations from a variety of sources including soybean and egg are available commercially and contain diacylphosphatidylcholine as its major constituent [38-41].

Quaternary ammonium alkyl salts form one of the best known classes of cationic surfactants, with hexadecyltrimethyl ammonium bromide (CTAB) (Rees et al., 1995), and the twin-tailed surfactant didodcecylammonium bromide (DDAB) are amongst the most well known (Olla et al., 1999). The most widely studied anionic surfactant is probably sodium bis-2-ethylhexylsulphosuccinate (AOT) which is twin-tailed and is a particularly effective stabiliser of w/o microemulsions [42].

In most cases, single-chain surfactants alone are unable to reduce the oil /water interfacial tension sufficiently to enable a microemulsion to form, a point made in a number of pertinent microemulsions reviews[43-47]. Medium chain length alcohols which are commonly added as co-surfactants have the effect of further reducing the interfacial tension, whilst increasing the fluidity of the interface thereby increasing the entropy of the system. Medium chain length alcohols also increase the mobility of the hydrocarbon tail and also allow greater [44, 45].

TABLE 2: COMMON EXCIPIENTS USED TO FORMULATE MICROEMULSIONS

Oils	Surfactant	Co-surfactant
Oleic acid	polysorbate20	ethanol
Castor oil	polysorbate 80	Glycerine
Corn oil	polyoxyl 35 castor oil	PEG 300
Peanut oil	polyoxyl 60 castor oil	poloxamer 407
Sesame oil	PEG 300 caprylic	propylene glycol

Advantages of Microemulsion Based Systems [33]: Microemulsions exhibits several advantages as a drug delivery system:

1. Microemulsions are thermodynamically stable system and the stability allows self-emulsification of the system.
2. Microemulsions act as supersolvents for drug. They can solubilize both hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents.
3. The dispersed phase, lipophilic or hydrophilic (oil-in-water, O/W, or water-in-oil, W/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively. Drug release with pseudo-zero-order kinetics can be obtained, depending on the volume of the dispersed phase, the partition of the drug and the transport rate of the drug.
4. The mean diameter of droplets in microemulsion is below 0.22 mm. The small size of droplet in microemulsions e.g. below 100 nm, yields very large interfacial area, from which the drug is released rapidly into external phase when absorption (in vitro or in vivo) takes place, maintaining the concentration in the external phase close to initial levels.
5. Same microemulsions have the ability to carry both lipophilic and hydrophilic drugs.
6. Because of thermodynamic stability of microemulsions, they are easy to prepare and require no significant energy contribution during preparation. Microemulsions have low viscosity compared to primary and multiple emulsions.
7. The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.
8. The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms.

Disadvantages of Microemulsion Based Systems [48]:

1. Use of a large concentration of surfactant and co-surfactant is necessary for stabilizing the droplets of microemulsion.
2. Limited solubilizing capacity for high-melting substances used in the system.
3. The surfactant should be nontoxic for use in pharmaceutical applications.
4. Microemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change as microemulsion delivered to patients.

Limitations: Some factors limit the use of microemulsion in pharmaceutical applications.

1. The need of pharmaceutically acceptable ingredients limits the choice of microemulsion components (e.g., oil, surfactant and cosurfactants) leading to difficulties in formulation.
2. The concentration of surfactants and co-surfactants used must be kept low for toxicological reasons.
3. Microemulsion also suffers from limitations of phase separation.
4. For intravenous use, the demand of toxicity on the formulation is rigorous and very few studies have been reported so far.
5. The major limitation is the toxicity of excipients i.e. surfactant/ co-surfactants. Exploration of safe excipients and evaluation of the toxicity parameters of available excipients may help in further expansion of research in this field.

Preparation of Microemulsion system: The drug is be dissolved in the lipophilic part of the microemulsion i.e. oil and the water phases can be combined with surfactant and then cosurfactant is added at slow rate with constant stirring until the system is transparent. The amount of surfactant and cosurfactant to be added and the percent of oil phase that can be incorporated is determined with the help of pseudo-

ternary phase diagram. Ultrasonicator can finally be used so to achieve the desired size range for dispersed globules. It is then allowed to equilibrate. Gel may be prepared by adding a gelling agent to the above microemulsion. Carbomers (crosslinked polyacrylic acid polymers) are the most widely used gelling agent.

Construction of Phase Diagram: Pseudo-ternary phase diagrams of oil, water, and co-surfactant/surfactants mixtures are constructed at fixed cosurfactant/ surfactant weight ratios. Phase diagrams are obtained by mixing of the ingredients, which are pre-weighed into glass vials and titrated with water and stirred well at room temperature. Formation of Monophasic/Biphasic system is confirmed by visual inspection. In case turbidity appears followed by a phase separation, the samples are considered as biphasic system. Monophasic, clear and transparent mixtures are visualized after stirring and the samples are marked as points in the phase diagram. The area covered by these points is considered as the microemulsion region of existence.

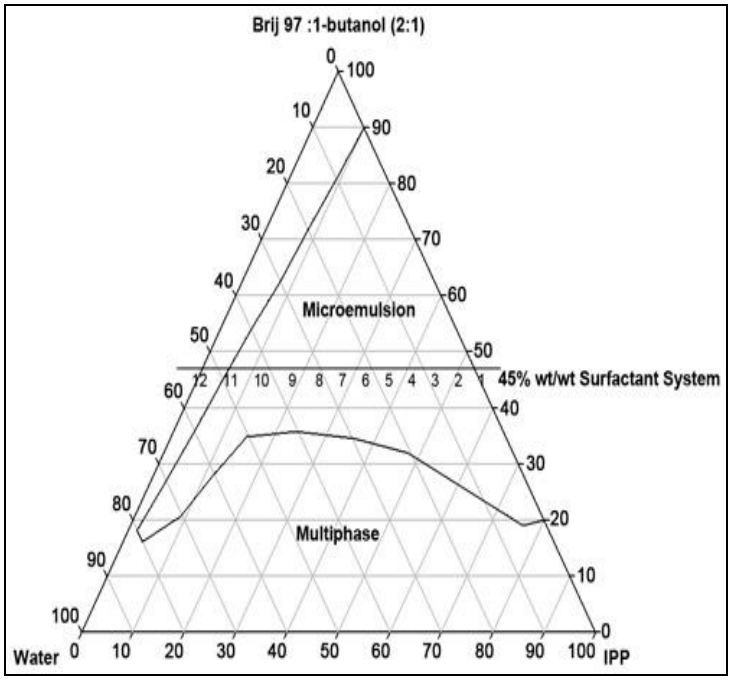


FIGURE 5: THE PSEUDOTERNARY PHASE DIAGRAM OF IPP/WATER/BRIJ 97:1-BUTANOL (2:1) AND THE DILUTION LINE FOR INVESTIGATION AT 45% WT/WT SURFACTANT SYSTEM [49]

Figure 5 shows the pseudoternary phase diagram with the area inside the frame assigned on the phase diagram showing the microemulsion region. The area outside the frame indicates a turbid region with multiphase systems. It could be noted that the area of microemulsion region was considerably large since 1-butanol acted as a cosurfactant and interacted with the surfactant monolayer to increase the flexibility of the interfacial film.

Characterization of Microemulsion: The droplet size, viscosity, density, turbidity, refractive index, phase separation and pH measurements shall be performed to characterize the microemulsion.

1. **Droplet size:** The droplet size distribution of microemulsion can be determined by either light scattering technique or electron microscopy. This technique has been suggested as the best method for predicting microemulsion stability.

   - **Dynamic Light-Scattering Measurements:** The DLS measurements are taken at 90° in a dynamic light-scattering spectrophotometer using a neon laser of wavelength 632 nm. The data is processed by the built-in computer with the instrument.

   - **Polydispersity:** Polydispersity is studied using Abbe refractometer.

   - **Phase analysis:** The type of microemulsion forming the phase system (o/w or w/o) is determined by measuring the electrical conductivity using a conductometer.

2. **Viscosity Measurement:** The viscosity of microemulsions of several compositions is measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 37 ± 0.2°C by a thermobath, and the samples for the measurement are to be immersed in it before testing.

3. ***In-vitro* Drug Permeation Studies**

   - **Determination of permeability coefficient and flux:** Excised human cadaver skin from the abdomen is used for permeation study. The skin is stored at 4^{o}C and the epidermis separated. The skin is first immersed in purified water at 60^{o}C for 2 min and the epidermis then peeled off. Dried skin samples can be kept at -

20^0C for later use. Alternatively the full thickness dorsal skin of male hairless mice may be used. The skin shall be excised, washed with normal saline and then used. The passive permeability of lipophilic drug through the skin is investigated using Franz diffusion cells with known effective diffusional area. The hydrated skin samples are used for the study. The receiver compartment contains a complexing agent like cyclodextrin in the receiver phase, which increases the solubility and allows the maintenance of sink conditions in the experiments. Samples are withdrawn at regular interval and analyzed for amount of drug released.

4. ***In- vivo* Studies:**

- **Bioavailability studies: Skin bioavailability of topical applied microemulsion on rats:** Male Sprague–Dawley rats (400–500 g) are needed to be anesthetized (15 mg/kg pentobarbital sodium i.p.) and placed on their back. The hair on abdominal skin is trimmed off and then bathed gently with distilled water. Anesthesia should be maintained with 0.1-ml pentobarbital (15 mg/ml) along the experiment. Microemulsions is applied on the skin surface (1.8 cm^2) and glued to the skin by a silicon rubber. After 10, 30 and 60 min of *invivo* study, the rats are killed by aspiration of ethyl ether. The drug exposed skin areas is swabbed three to four times with three layers of gauze pads, then bathed for 30 s with running water, wiped carefully, tape-stripped (X10 strips) and harvested from the animals.

- **Determination of residual drug remaining in the skin on tropical administration:** The skin in the above permeation studies can be used to determine the amount of drug in the skin. The skin cleaned with gauze soaked in 0.05% solution of sodium lauryl sulfate and is bathed with distilled water. The permeation area is cut and weighed and drug content is determined in the clear solution obtained after extracting with a suitable solvent and centrifuging.

Pharmacological Studies: Therapeutic effectiveness is evaluated for the specific pharmacological action that the drug purports to show as per stated guidelines.

Estimation of Skin Irritancy: As the formulation is intended for dermal application skin irritancy should be tested. The dorsal area of the trunk is shaved with clippers 24 hours before the experiment. The skin shall be scarred with a lancet. 0.5 ml of product is applied and then covered with gauze and a polyethylene film and fixed with hypoallergenic adhesive bandage. The test be removed after 24 hours and the exposed skin is graded for formation of edema and erythema. Scoring is repeated 72 hours later. Based on the scoring the formulation shall be graded as 'non-irritant', 'irritant' and 'highly irritant'.

Stability Studies: The physical stability of the microemulsion shall be determined under different storage conditions (4, 25 and 40°C) for 12 months.

Fresh preparations as well as those that have been kept under various stress conditions for extended period of time are subjected to droplet size distribution analysis. Effect of surfactant and their concentration on size of droplet are also studied.

Applications of Microemulsions:

- **Pharmaceutical Applications**

1. Parenteral delivery.
2. Oral drug delivery.
3. Topical drug delivery.
4. Ocular and pulmonary delivery.
5. Microemulsions in biotechnology.

Parenteral Delivery: Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered to a targeted site. Microemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle microemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body.

Both o/w and w/o microemulsion are used for parenteral delivery. The literature contains the details of the many microemulsion systems, few of these can be used for the parenteral delivery because the toxicity of the surfactant and parenteral use. An alternative approach was taken by Von Corsewant and Thoren [50] in which C3-C4 alcohols were replaced with parenterally acceptable co-surfactants, polyethylene glycol (400) / polyethylene glycol (660) 12-hydroxystearate / ethanol, while maintaining a flexible surfactant film and spontaneous curvature near zero to obtain and almost balanced middle phase microemulsion. The middle phase structure was preferred in this application, because it has been able to incorporate large volumes of oil and water with a minimal concentration of surfactant.

Oral Delivery: Microemulsion formulations offer the several benefits over conventional oral formulation for oral administration including increased absorption, improved clinical potency and decreased drug toxicity [51]. Therefore, microemulsion has been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics.

Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions. However, most are difficult to administer orally. With on oral bioavailability in conventional (i.e. non-microemulsion based) formulation of less than 10%, they are usually not therapeutically active by oral administration. Because of their low oral bioavailability, most protein drugs are only available as parenteral formulations. However, peptide drugs have an extremely short biological half life when administered parenterally, so require multiple dosing.

A microemulsion formulation of cyclosporine, named Neoral® has been introduced to replace Sandimmune®, a crude oil-in-water emulsion of cyclosporine formulation. Neoral® is formulated with a finer dispersion, giving it a more rapid and predictable absorption and less inter and intra patient variability[52].

Topical Delivery: Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects. Second is the direct delivery and targetability of the drug to affected area of the skin or eyes. Both O/W and W/O microemulsions have been evaluated in a hairless mouse model for the delivery of prostaglandin E1 [53].The microemulsions were based on oleic acid or Gelucire 44/14 as the oil phase and were stabilized by a mixture of Labrasol (C_8 and C_{10} polyglycolysed glycerides) and Plurol Oleique CC 497 as surfactant.

Although enhanced delivery rates were observed in the case of the o/w microemulsion, the authors concluded that the penetration rates were inadequate for practical use from either system. The use of lecithin/IPP/water microemulsion for the transdermal transport of indomethacin and diclofenac has also been reported. Fourier transform infra red (FTIR) spectroscopy and differential scanning calorimetry (DSC) showed the IPP organogel had disrupted the lipid organisation in human stratum corneum after a 1 day incubation [54].

The transdermal delivery of the hydrophilic drug diphenhydramine hydrochloride from a w/o microemulsion through the excised human skin has also been investigated. The formulation was based on combinations of Tween 80 and Span 20 (surfactants) with IPM. However two additional formulations were tested containing cholesterol and oleic acid, respectively. Cholesterol increased drug penetration whereas oleic acid had no measurable effect, but the authors clearly demonstrated that penetration characteristics can be modulated by compositional selection [55].

Ocular and Pulmonary Delivery: For the treatment of eye diseases, drugs are essentially delivered topically. O/W microemulsions have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

The microemulsions containing pilocarpine were formulated using lecithin, propylene glycol and PEG 200 as co-surfactant and IPM as the oil phase. The formulations were of low viscosity with a refractive index lending to ophthalmologic applications [56]. The formation of a water-in-HFA propellant microemulsion stabilized by fluorocarbon non-ionic surfactant and intended for pulmonary delivery has been described.

Microemulsions in Biotechnology: Many enzymatic and bio-catalytic reactions are conducted in pure organic or aqua-organic media. Biphasic media are also used for these types of reactions. The use of pure apolar media causes the denaturation of biocatalysts. The use of water-proof media is relatively advantageous. Enzymes in low water content display and have;

1. Increased solubility in non-polar reactants
2. Possibility of shifting thermodynamic equilibrium in favor of condensations
3. Improvement of thermal stability of the enzymes, enabling reactions to be carried out at higher temperatures.

Many enzymes, including lipases, esterases, dehydrogenases and oxidases often function in the cells in microenvironments that are hydrophobic in nature. In biological systems many enzymes operate at the interface between hydrophobic and hydrophilic domains and these usually interfaces are stabilized by polar lipids and other natural amphiphiles. Enzymatic catalysis in microemulsions has been used for a variety of reactions, such as synthesis of esters, peptides and sugar acetals transesterification; various hydrolysis reactions and steroid transformation. The most widely used class of enzymes in microemulsion-based reactions is of lipases [57].

Other Applications:

1. Microemulsions can improve skin penetration of lycopene.
2. Microemulsion as a vehicle for transdermal permeation of nimesulide
3. Microemulsion in enhanced oil recovery, detergency, cosmetics, agrochemicals, food. Microemulsions in environmental remediation and detoxification.
4. Microemulsions as fuels, as lubricants, cutting oils and corrosion inhibitors, coatings and textile finishing.
5. Microemulsions in microporous media synthesis (microemulsion gel technique) Microemulsions in analytical applications.
6. Microemulsions as liquid/membranes Novel crystalline colloidal arrays as chemical sensor materials [58].

CONCLUSION: Till date, microemulsions have been shown to be able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration. There is still however a considerable amount of fundamental work characterizing the physico-chemical behavior of microemulsions that needs to be performed before they can live up to their potential as multipurpose drug delivery vehicles.

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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