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# A REVIEW BASED ON TOPICAL MICROEMULSIONS

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**ABSTRACT**

Topical microemulsion is principally supposed to be applied over the skin to produce target drug delivery. Microemulsions unit of measurement wonderful candidates as potential drug delivery system due to their improved drug solubilisation, long amount of your time and simple preparation and administration. Microemulsions have emerged as novel vehicles for drug delivery which permit sustained or controlled unleash for tissue, topical, stratum, ocular and channel administration of medicaments. Topical microemulsion supply the advantage of spontaneous formation, simple producing, natural philosophy stability, improved drug solubilisation of hydrophobic medication and increase bioavailability.

**KEYWORDS**

Microemulsion, Topical delivery and Surfactant.

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## INTRODUCTION

Microemulsions play a key role in many of the Drug delivery and cosmetics we use today. Topical microemulsions are applied to the surface of a part of the body and have effects only in a specific area of the body. Microemulsions are formulated in such a manner that the systemic absorption of the medicament is minimal. The concept of microemulsions or Micellaremulsion was first introduced by Hoar and Schulman in 1943[1]. They ready the primary microemulsions by dispersing oil in associate degree liquid wetting agent resolution

associate degreed adding an alcohol as a co wetting agent, leading to transparent stable formulation (Hoar T. P. and Schulman J. H., 1943)[1]. These systems supply a good deal of singularity not solely thanks to their novel transparency however additionally thanks to the little phase, usually having a droplet diameter between 10 to 140nm (Attwood D. and Kreuter J, 1994)[2]. Investigation for the utilization of microemulsion systems in a variety of chemical and industrial processes has increased in 70's. Microemulsions have shown a good vary of applications beginning with increased oil recovery within the 70's, expanding to a wide range of chemicals and entering in the pharmaceutical and cosmetic formulation area a decade ago (Bidyut K. P. and Satya P. M., 2001)[3]. Microemulsions will have characteristic properties like ultralow surface tension, large interfacial area and capacity to solubilise both aqueous and oil-soluble compounds (Solans C. and Kunieda H., 1997[4], Patel A. R. and Vavia P. R., 2007)[5]. Microemulsions are thermodynamically stable isotropic systems in which two immiscible liquids (water and oil) are mixed to form a single phase by means of an appropriate surfactant or its mixture. The short to medium chain alcohols ar usually thought of as co-surfactants within the microemulsion system. The presence of wetting agent and cosurfactant within the system makes the surface tension terribly low. Thermodynamic stability of the microemulsions has been proposed by Ruckenstein and Chi2. Microemulsions can be applied as liquid membrane carriers to transport lipophilic substance through an aqueous medium or to carry hydrophilic substances across lipoidal medium (Maibach H. I., 2005)[6]. As the size of the particle is much smaller than the wavelength of visible light, microemulsions are transparent and structure cannot be observed through an optical microscope (Sumedha Nadkar and Chandrakant Lokhand, 2010)[7]. Microemulsions are liquid behave as a newtonian liquid. They are not very viscous (Vandamme Th. F., 2002)[8]. The main difference between macroemulsions and emulsions lies in the size and shape of the particles dispersed in the continuous phase: these are at least an order of magnitude smaller in the case of microemulsions (10-140nm) than those of conventional emulsions (1-20μm).

**Advantage**

1. Increase bioavailability of poorly water soluble drug.
2. Good thermodynamically stable and inexpensive.
3. Direct target ability of the drug to affected area of the skin.
4. Direct delivery of the drug to affected area of the skin.
5. Microemulsions are used in pharmaceuticals and cosmetics formulation.
6. It is used as a vehicle for topical, oral, nasal, parenteral and transdermal applications.
7. It acts as a penetration enhancers and 'supersolvents' of drug.
8. Long shelf life.
9. Avoidance of hepatic first pass metabolism of the drug.
10. Avoidance of drug from its toxicity.

**Types of Microemulsion**

There are mainly three type of microemulsion. Classification of microemulsion is done on the basis of amount of oil and water used.

1. Oil in water (o/w) Winsor I,
2. Water in oil (w/o) Winsor II,
3. Bicontinuous microemulsions or Winsor III

Microemulsions are thermodynamically stable, but are only found under carefully defined conditions (Ghosh P. K. and Murthy R. S, 2006[9], Giustini M. *et al*, 2004)[10]. One way to characterize these systems is by whether the domains are in droplets or continuous (Giustini M., 1996)[11]. Characterizing the systems in this way results in three types of microemulsions: oil-in-water (o/w), water-in-oil (w/o), and bicontinuous. Generally, one would assume that whichever part was a bigger volume would be the continual part, but this is not always the case. Oil-in-water microemulsions are droplets of oil surrounded by a surfactant (and possibly co-surfactant) film that forms the internal phase distributed in water, which is the continuous phase.

This type of microemulsion generally has a larger interaction volume than the w/o microemulsions (Lawrence M. J. and G. D. Rees, 2000)[12]. The monolayer of surfactant forms the interfacial film that is oriented in a "positive" curve, where the polar head-groups face the continuous water phase and the lipophilic tails face into the oil droplets (Gelbart W. M. and A. Ben Shau, 1996)[13]. The o/w systems are interesting because they enable a hydrophobic drug to be more soluble in an aqueous based system, by solubilizing it in the internal oil droplets. Most medication tend to favour little or medium molecular volume oils as against organic compound oils thanks to the polarity of the poorly soluble medication. An o/w drug delivery tends to be straightforward when compared to w/o microemulsions. This is the result of the droplet structure of o/w microemulsions being retained on dilution with the biological aqueous phase (Lee V. H., 1998)[14]. Water-in-oil microemulsions area unit created from droplets of water encircled by Associate in nursing oil continuous part. These are generally known as "reverse-micelles", where the polar head groups of the surfactant are facing into the droplets of water, with the fatty acid tails facing into the oil phase. This type of droplet is usually seen when the volume fraction of water is low, although the type of surfactant also impacts this as well (Lawrence M. J. and G. D. Rees, 2000)[12]. A w/o microemulsion used orally or parenterally is also destabilized by the binary compound biological system. The biological system will increase the part volume of the inner part, eventually leading to a "percolation phenomenon" where phase separation or phase inversion occurs (Lawrence M. J. and G. D. Rees, 2000)[12]. Oral peptide delivery in w/o microemulsions is still used. However the hydrophilic peptides are often simply incorporated into the water internal part and area unit a lot of protected against accelerator chemical process by the continual oil part than alternative oral indefinite quantity forms (Lee V. H., 1988)[14]. A w/o microemulsion is best employed, though in situations where dilution by the aqueous phase is unlikely, such as intramuscular injection or transdermal delivery (Lawrence M. J. and G. D. Rees, 2000[12], M. R. F. Pattarino and F. Lattanzi, 1990)[15]. When the amount of water and oil present are similar, a bicontinuous microemulsion system may result. In this case, both water and oil exist as a continuous phase. Irregular channels of oil and water are intertwined, resulting in what looks like a "sponge-phase" (Scriven L. E., 1976)[16]. Transitions from o/w to w/o microemulsions may pass through this bicontinuous state. Bicontinuous microemulsions, as mentioned before, could show non- Newtonian flow and physical property. These properties make them especially useful for topical delivery of drugs or for intravenous administration, where upon dilution with aqueous biological fluids, form an o/w microemulsion (Lawrence M. J. and G. D. Rees, 2000)[12]. Winsor-I has more amount of aqueous phase as compared to Winsor II where as in bicontinuous microemulsions (Winsor-III) there is a equal volume of oil and aqueous phase is used.

**Factors to be considered during Microemulsion formulation**

(Jain N. K., 2004)[17], It is important to determine a system that must be non-toxic, non-irritating, non comedogenic and non-sensitizing.

Formulating elegant microemulsion.

The microemulsion formed should not show any allergic response over the skin should have high drug loading capacity and must have good physiological compatibility. The component selected for the formulation of topical microemulsion should be under GRAS (Generally regarded as safe).

**Components of microemulsion:**

- An oil phase
- An aqueous phase
- A primary surfactant (anionic, non ionic or amphoteric)
- A secondary surfactant or Co surfactant.

The surfactant chosen must have good Cutaneous tolerance, least irritation and hence it is recommended to choose non-ionic surfactants. Single chain or double chain surfactant can be used, single chain surfactant dose not lower oil water interfacial tension and cosurfactant is required.

Double chained surfactants like sulfosuccinate can form microemulsions in the absence of Cosurfactants but are tootoxic for general pharmaceutical applications (Jain N. K., 2004)[18]. Microemulsions prepared from phospholipids are preferred.

**Surfactant**

Surfactants are molecules that usually contain a polar head group and apolar tail. They are Surface-active and microstructure-forming molecules with a strong chemical dipole (Holmberg K., 2002)[19]. They can be ionic (cationic or anionic), nonionic, or zwitterionic. Surfactant molecules self-associate due to various inter- and intra-molecular forces as well as entropy considerations. All of these serves to optimize the free-energy overall. For example, when surfactant is mixed with oil and water, they accumulate at the oil/water interface, because it is thermodynamically favourable (Lawrence M. J. and G. D. Rees, 2000)[12]. The surfactant molecules can arrange themselves in a variety of shapes. At low concentrations of dispersed (internal) phase, spherical, isolated droplets are present in the microemulsions. At higher dispersed phase concentrations, the final structures depend on the interaction between droplets. If they are repulsive, no droplet overlap will be produced due to colliding droplets. If attractive interactions are present, multiple droplets may collide and for mother structures. The hydrophilic-lipophilic balance (HLB) of the surfactant can be taken into account to try to rationalize the surfactant's behaviour. It is generally accepted that a surfactant with HLB from 3-6 will favour the formation of water-in-oil (w/o) microemulsions, whereas surfactants with HLB from 8-18 are preferred for oil-in-water (o/w) microemulsions (Lawrence M. J. and G. D. Rees, 2000)[12]. Another method used to relate the type of surfactant to the structures it forms is through the critical packing parameter (CPP). This, like HLB, is an empirical approach since the reare many other factors that impact the final structures found in microemulsions. The CPP is a measure of the surfactant's preferred geometry, and therefore can be used to predict the type of structure that possibly will be formed. The CPP can be calculated by dividing the partial molar volume of the hydrophobic part of the surfactant by the product of the optimal head group area and length of the surfactant tail[14]. Surfactants that are "cone shaped" where the tail group or head group is much larger than the other will tend to accumulate at curved interfaces resulting in micelles. Surfactants that are more "block shaped" where tail group and head group are similar in size and the CPP values are close to one tends to form worm-like micelles or lamellar structures. Values of CPP greater than one indicate that the head groups are much larger, resulting in w/o microemulsion systems. The opposite is true for CPP values less than one. They generally produce o/w micro emulsion systems. Values for CPP around one indicate the possible formation of lamellar phases (Lawrence M. J. and G. D. Rees, 2000)[12]. Regardless of the surfactant chosen for the microemulsion formulation; it must be able to lower the interfacial tension to an extremely small value. This aids the dispersion process, providing a flexible film that readily surrounds droplets of the internal phase while still having appropriate lipophilic character to provide a curvature at the interfacial region (Shafiq-un-Nabi S., 2007)[20].

**Nonionic Surfactants**

Most nonionic surfactants are structurally similar to ionic surfactants, except for the fact that with ionic surfactants, the head group is uncharged. Because there are no electrostatic charges from the head groups, the interactions between these nonionic head groups are dominated by steric and osmotic forces (Lange K.R., 1999)[21]. Cosurfactants are generally not needed to form microemulsions with nonionic. This is due to the fact that pure specimens of nonionic usually are made up of mixtures of slightly varying chain length (Lawrence M. J. and G. D. Rees, 2000)[12]. Ethoxylated alcohols are the most common nonionic surfactants. These alcohols contain a wide-ranging degree of ethoxylation, where ethylene oxide is added to fatty acids to make them more water-soluble. They are considered "amphiphiles", with oil having hydrocarbon tail

group and a water loving ethoxylated alcohol group. Non ionic surfactants show good biological acceptance (Kibbe A. H., 2000)[22]. They are able to form microemulsions that are insensitive to pH and electrolyte concentration. Examples of nonionic surfactants include polyoxyethylene surfactants such as Brij 35 or sugar esters such as sorbitan monooleate (Span 80). Polyoxyethylene sorbitan monooleate (Tween 80) and polyoxyethylene sorbitan monolaurate (Tween 20) appear safe and acceptable for oral and parenteral use (Lawrence M. J. and G. D. Rees, 2000)[12]. Polysorbate are partial carboxylic acid esters of sorbitol and its anhydrides copolymerized with close to twenty, five or four moles of ethene chemical compound for every mole of sorbitol and its anhydrides. These vary in size due to a mixture of molecules and are considered hydrophilic nonionic surfactants. Sorbitan are partial esters of sorbitol and its mono and dianhydrides with fatty acids. These are considered lipophilic nonionic surfactants.

**Ionic Surfactants**

The use of ionic surfactants can be fairly limited in general pharmaceutical dosage forms. A large majority of ionic surfactants do not form balanced microemulsions without the addition of another component. These additives are required because the head group of the ionic surfactants are generally substantially more hydrophilic than poly (ethylene oxide) moieties. The salts or co-surfactants shift the overall HLB into the optimal range for microemulsion formulation (Trotta M., 1999)[23].

Alkyl ammonium halides are excellent hydrogen bond donors and interact strongly with water. The most well known examples from the cationic surfactant class are hexadecyltrimethyl-ammonium bromide (CTAB) and didodcecylammonium bromide (DDAB). Although less numerous, phosphorous can be quaternarized with alkyl groups to create alkyl phosphonium cationic surfactants as well (Lange K.R., 1999)[21].

Alkali alkanoates, also known as soaps, are the most common anionic surfactants. The anionic charge in these surfactants comes from the ionized carboxyl group. This type is the most well understood surfactant when it comes to their structure and function (Lange K.R, 1999)[21]. Dioctyl sodium sulfosuccinate (DOSS) is the most widely studied anionic surfactant. It has twin tails and is a particularly good stabilizer of w/o microemulsions (Singh H. N, 1983)[24]. Other important classes of anionic surfactants include alkyl sulphates, alkyl ether sulphates, alkyl sulfonates, aryl sulfonates, methyl ester sulfonates, α-olefinsulfonates, and sulfonates of alkylsuccinates. The three most important anionic groups in all of these surfactants being the carboxylate, sulphate and sulfonates groups (Singh H. N., 1983)[24].

**Zwitterionic surfactants**

Zwitter ionic surfactants contain both negatively and positively charged groups, form microemulsions upon the addition of co-surfactants. Phospholipids, such as lecithin, are common zwitterionic surfactants. Unlike other ionic surfactants, which are somewhat toxic, these show excellent biocompatibility. This is most likely due to the fact that lecithin is obtained naturally from soybean or egg, which contains diacylphosphatidylcholine the major constituent (Shinoda K. and H. Kunieda, 1973)[25]. Another important class of zwitterionic surfactants to note is the betaines, such as alkyl betaines, amidoalkylbetaines and heterocyclic betaines.

**Surfactant Mixtures and Co-Surfactants**

One surfactant, whether nonionic or ionic, is not sufficient to form a microemulsion or does not result in an optimal microemulsion-forming region. The term “co-surfactant” will describe any part that aids the first wetter in microemulsion formulation. “Co-surfactant” will see a second wetter getting used, but may also refer to a low-molecular-weight amphiphile such as an alcohol (Bidyut K. P. and Satya P. M., 2001)[3]. Two different nonionic surfactants can be mixed together. Mixing a more lipophilic nonionic surfactant with a more hydrophilic nonionic surfactant can result in the exact HLB needed to form a microemulsion. The two surfactants can be mixed in varying ratios to determine the ideal combination of the two, which results in the largest microemulsion-forming region.

Mixtures of nonionic surfactants can be seen in commercial products and can sometimes be regarded as a single component (a pseudo component) in the microemulsion system and #40; Bidyut K. P. and Satya P. M., 2001[3] and #41;. Ionic surfactants can be combined with nonionic surfactants, or higher molecular weight ethoxylated alcohols. These mixtures have synergistic effects, which allow them to be applied to many things. The most popular advantage to these mixtures is the fact that they result in temperature insensitive microemulsions (Bidyut K. P. and Satya P. M., 2001)[3]. Generally, ionic and non ionic surfactants react oppositely with increasing temperature. Ionic surfactants show a hydrophilic shift with increasing temperature, while nonionic surfactants exhibit a lipophilic shift. Therefore, once mixed along during a explicit quantitative relation, the two will cancel each other out, resulting in a temperature insensitive microemulsion formulation. Frequently, single chain surfactants are not able to reduce the surface tension to the ultra low levels required for microemulsion formulation. Short and medium chain alcohols like alcohol, pentanol, ethanol, isopropanol or propylene glycol are commonly added as "co-surfactants". These co-surfactants help to further reduce the surface tension and fluidize the surfactant film, which increases the entropy of the system leading to its thermodynamic stability. Co-surfactants increase the pliability of the wetter film round the microemulsion driblet. The co-surfactant molecules distribute themselves between the oil, water and oil/water interface. The relatively small co-surfactant molecules ultimately get mixed in with the surfactant molecules at the oil/water interface. This releases the bending stress and allows for easier dispersion (Hait S. K. and S. P. Moulik, 2002)[26].

These alcohols increase the fluidity of the hydrocarbon tails of the surfactant. This allows greater penetration of the oil into the surfactant monolayer. As the chain length of the alcohol increases, the flexibility of the film decreases. Alkanol introduce more disorder into the interfacial film since their chain length is much different from the surfactant molecules. Molecules move laterally as the interfacial film spontaneously fluctuates (Moulik S. P. and B. K. Paul, 1998)[27]. As an added benefit, Alkanol added to ionic surfactants serve to reduce the repulsive forces between the charged head groups of the surfactant molecules. In the case of lecithin microemulsions, an alcohol must be added as a co-surfactant to disrupt the lamellar structures, which characterize its biological behaviour allowing for the formation of a microemulsion (Lawrence M. J. and G. D. Rees, 2000)[12]. Incorporation of co-surfactants can expand the microemulsion-forming region, but this may come at a cost. The requirement of a medium-chain alcohol as a co-surfactant may cause other problems. Many of these alcohols can be irritating to the biological system, especially with chronic use. There are significant toxicity issues with these chemicals, which may prevent microemulsions containing them from being, used pharmaceutically (Lawrence M. J. and G. D. Rees, 2000)[12]. Solubility of the alcohols in microemulsion formulations becomes an issue as well. Most alcohols tend to be more soluble in the aqueous phase of o/w systems than the primary surfactant. Because of this, as the system is diluted, the cosurfactant partitions more in the water-phase and reduces the amount of co-surfactant present at the interface. This destabilizes the droplets, and ultimately the microemulsion system itself. Short chain amines and alkanoic acids are also suitable co-surfactants, but these prove to have similar toxicity issues to the alcohols (Lawrence M. J. and G. D. Rees, 2000)[12].

**Factors Affecting Formation and Phase Behavior of Microemulsions**

**Factor affecting formation of Microemulsion system**

(Kumar P. and Mittal K. L., 1999[29], Rao Y. S. *et al*, 2009)[30], The formation of oil or water swollen microemulsion depends on the packing ratio, property of surfactant, oil phase, temperature, the chain length, type and nature of co-surfactant.

**Packing ratio**

The HLB (Hydrophilic Lipophilic Balance) of surfactant determines the type of microemulsion

through its influence on molecular packing and film curvature. The analysis of film curvature for surfactant associations leading to microemulsion formation has been explained by Israclachvili *et al* (1976)[31] and Mitchell and Ninham (1977)[32] in terms of packing ratio, also called as critical packing parameter.

Critical Packing Parameter (CPP) = v/a * l **----------(4)**

Where,

v is the partial molar volume of the hydrophobic portion of the surfactant,

a is the optimal head group area and

l is the length of the surfactant tail.

If CPP has value between 0 and 1 interface curves towards water (positive curvature) and o/w systems are favored but when CPP is greater than 1, interface curves spontaneously towards oil (negative curvature) so w/o microemulsions are favored. At zero curvature, when the HLB is balanced (p is equivalent to 1), then either bi continuous or lamellar structures may form according to the rigidity of the film (zero curvature).

**Property of Surfactant, Oil Phase and Temperature**

The type of microemulsion depends on the character of chemical agent. Surfactant contains hydrophilic head cluster and lipotropic tail cluster. The areas of these groups, which are a measure of the differential tendency of water to swell head group and oil to swell the tail area, are important for specific formulation once estimating the chemical agent HLB in an exceedingly specific system. When a high concentration of the chemical agent is employed or once the chemical agent is in presence of salt, degree of dissociation of polar teams becomes lesser and ensuing system may be w/o type. Diluting with water might increase dissociation and results in an o/w system. Ionic surfactants are strongly influenced by temperature. It mainly causes increased surfactant counter-ion dissociation. The oil element additionally influences curvature by its ability to penetrate and therefore swell the tail cluster region of the chemical agent monolayer. Short chains oils penetrate the lipotropic cluster region to a good extent and ends up in increased negative curvature. Temperature is very necessary in decisive the effective head cluster size of nonionic surfactants. At vasoconstrictor, they're hydrophilic and kind traditional o/w system. At higher temperature, they're lipotropic and kind w/o systems. At AN intermediate temperature, microemulsion coexists with excess water and oil phases and forms bicontinuous structure.

**The Chain Length, Type and Nature of Co-Surfactant**

Alcohols square measure wide used as a co-surfactant in microemulsions. Addition of shorter chain co-surfactant gives positive curvature effect as alcohol swells the head region more than tail region so, it becomes more hydrophilic and o/w type is favored, while longer chain co-surfactant favours w/o sort w/o sort by alcohol swelling a lot of in chain region than head region.

**Factor Affecting Phase Behavior** (Sarkhejiya Naimish A. *et al*, 2007)[33]

**Salinity**

At low salinity, the droplet size of o/w microemulsion increases. This corresponds to extend within the solubilization of oil. As salinity further increases, the system becomes bi-continuous over an intermediate salinity range. Increase in salinity results in formation of continuous microemulsion with reduction in globe size. Further increase in salinity ultimately leads to complete phase change.

**Alcohol concentration**

Increasing the concentration of low molecular weight alcohol as a co surfactant leads to the phase transition from w/o to bi continuous and ultimately to o/w type microemulsion. Exactly opposite phase change is noticed just in case of high relative molecular mass alcohol.

**Surfactant Hydrophobic Chain Length**

The increase long of hydrophobic chain length of the chemical agent shows the amendment of o/w microemulsion to w/o via atomic number 83 continuous section.

**pH**

Change in pH influences the microemulsions containing pH sensitive surfactants. This impact is a lot of pronounced just in case of acidic or alkaline surfactants. Carboxylic acids and amines change the phase behavior from w/o to o/w by increasing the pH.

**Nature of Oil**

Increase within the aromaticity of oil results in phase change from o/w to w/o and is opposite thereto of increase within the oil paraffin carbon variety.

**Ionic Strength**

As the ionic strength will increase the system passes from o/w microemulsion in equilibrium with excess oil to the center section and eventually to w/o microemulsion in equilibrium with excess water.

**Construction of pseudo-ternary phase diagrams**

(Shaji J. and Reddy M. S., 2004)[34], Pseudo-ternary phase diagram is constructed by using titration method to obtain the appropriate components such as oil, surfactant, co-surfactant, and water and their concentration ranges that can result in large existence area of microemulsion. Once the appropriate microemulsion components are selected, ternary pseudo phase diagram is constructed to define the extent and nature of the microemulsion regions. To produce such diagrams, a large number of samples of different composition are prepared. Based on the solubility study the pseudo ternary phase diagrams of oil, surfactant, co-surfactant and distilled water were developed for the drug. The pseudo ternary phase diagrams were developed by the water titration method. The ratios of surfactant to co-surfactants were chosen to be 1:2, 1:1, 2:1, and 4:1, and such mixtures (Smix) were prepared. Then each surfactant and co-surfactant mixture (Smix) were mixed with the oil at ambient temperature to give the weight ratio of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9. Water was added drop wise to each oil- Smix mixture under vigorous stirring until a homogeneous dispersion/solution was obtained. After each addition, the samples were visually examined for the appearance, flow property and determined as being clear microemulsions. The end point of the titration was the point where the solution becomes cloudy or turbid. The quantity of the binary compound section needed to form the mixture murky, was noted. The percentages of the different incorporated pseudo phases were then calculated and the same procedure was followed for the other S/CoS ratios. No heating was done during the preparation. Phase diagrams were constructed using Chemix software. The area of the monophasic region was used as a tool for the selection of suitable surfactant to co-surfactant ratio for respective drug.

**Applications of Topical Microemulsions**

Microemulsions are promising delivery systems (Kumar P. and Mittal K. L., 1999[35], Solans C. and Kunieda H., 1997)[4] that allows sustained or controlled drug release for percutaneous, peroral, topical, transdermal, ocular and parenteral administration. Enhanced absorption of medicine, modulation of the kinetics of the drug release and decreased toxicity are several advantages in the delivery process. The following could be a compilation of reported literature for topical microemulsions.

**Antifungal**

Superficial mycoses usually respond to topical therapy. In the settling of eczema, topical antifungal agents such as ketoconazole are used to reduce the fungal infection caused by Pityrosporum ovale (Malassezia furfur). Antifungal agents e.g. miconazole, ketoconazole, and Sporanox being oleophilic in nature are developed as microemulsions to impart to them the benefits like easy preparation thanks to spontaneous formation, physical science stability, transparent and stylish look, accrued drug loading, increased penetration through the biological membranes, increased bioavailability compared to conventional dosage forms (Tenjarla S. N., 1999[36], Lieberman H. A. *et al*, 1996)[37] Microemulsions of poorly water soluble antifungal drugs miconazole, ketoconazole, and itraconazole were designed and developed by Puranajoti *et al* (Puranajoti P. R. *et al*, 2002)[38] using either mineral oil or olive oil as an oil phase.

Various combinations of surfactant and cosurfactant were used, including Labrafil M 1944 CS and Plurol Oleique (1:1); Labrafil M 1944 CS and Plurol Oleique (1:2); or Labrafil M 1944 CS, Capmul MCM C-8, Plurol Oleique, and dehydrated ethyl alcohol (3:3:1:1). Microemulsions of poorly soluble antifungal agents were with success developed with *in vitro* unharness rates such as that of the gel formulation. The results of the work done on antimycotic nitrate developed as charged microemulsions indicate optimized drug targeting while not a concomitant increase in general absorption. Lalanine benzyl ester, an ester of a natural amino acid, is an appropriate ionic charge-inducing agent (Peira E. *et al*, 2008)[39]. Microemulsion based gels for vaginal delivery of clotrimazole and fluconazole were developed and compared with the marketed clotrimazole gel (Candid-V gel) by *in vitro* methods. These microemulsion based gels showed significantly higher in vitro bioadhesion, antifungal activity as compared to that of Candid-V gel. Fluconazole microemulsion based gel did not exhibit vaginal irritation (Yogeshwar B. and Vandana P., 2009[40], Yogeshwar B. and Vandana P., 2009)[41].

**Antiviral**

A study was done to investigate and evaluate microemulsion and microemulsion-based hydro gel as a topical delivery system for penciclovirin comparison with a commercial cream. The results of permeation test *in vivo* in mice showed that as compared with the commercial cream, microemulsion based hydro gel and microemulsion could significantly increase the permeation of penciclovir into both epidermis and dermis. Stability tests showed that microemulsion-based gel keep at 4°C for three months had no vital modification in chemical science properties. Skin irritation test in rabbits demonstrated that single application or multiple applications of microemulsion-based hydro gel did not cause any erythemaor edema. Thus, it can be concluded that microemulsion based hydro gel could be a promising vehicle for topical delivery of penciclovir (Weiwei Zhu *et al*, 2009)[42]. Acyclovir containing microemulsion-based formulations for topical delivery were developed victimisation isopropyl Myristate/Captex 355/Labara as associate oil part, Tween 20 as surfactant, Span 20 as cosurfactant, and water : dimethyl sulfoxide (1:3) as an aqueous phase. Transcutol, essential oil, and peppermint oil were used as permeation enhancers. In vitro permeation studies through mice skin were performed victimisation Franz diffusion cells. The optimum formulation containing two. 5% Transcutol as the penetration enhancer showed 1.7-fold enhancement in flux and permeation coefficient as compared to marketed cream and ointment formulation. In vivo antiviral studies performed in feminine mice against iatrogenic herpes simplex virus I infection indicated that one application of microemulsion formulation containing two.5% Transcutol, twenty four hours post-injection resulted in complete suppression of development of herpetic skin lesions (Shishu Sunita Rajan and Kamalpreet, 2009)[43].

**Anti acne**

Novel drug delivery methods like microemulsions will play a crucial role in up the topical delivery of opposed skin disorder agents by enhancing their dermal localization with a concomitant reduction in their side effects (Date A. A. *et al*, 2006)[44]. Microemulsions of azelaic acid, a bioactive molecule employed in several skin disorders, ready victimization the monosodium salt (AZA-Na) has been evaluated as delivery vehicles. Dialysis membrane experiments showed decreasing permeability to AZA-Na, and this was related to its partition at the microemulsion interface. The results suggested that microemulsions containing AZA-Na could be used to optimize drug targeting in acne treatment (Peira E. *et al*, 2006)[45]. To increase the solubility of azelaic acid within the distributed oil section of microemulsion containing polysorbate twenty, butanol, decanol: dodecanol (2/1) and water, the pH of aqueous phase was lowered and propylene glycol was added. An accumulated partitioning into the oleophilic section was noted as humectant concentration was accumulated. Microemulsion so provided a vehicle during which

azelaic acid was dissolved instead of suspended as during a cream. Moreover, reservoir result achieved by partitioning into the oil may prolong it's unleash over many hours. It showed a tenfold increase within the quantity of drug free (upto 27-30% of initial amount) from the microemulsion compared to a cream clinically employed in treatment of skin disorders (Gallarate M. R. *et al*, 1990)[46].

**Antioxidants**

Antioxidants have been used in dermatological and cosmetic products because of their property of scavenging and destroying aggressive oxidizing agents and free radicals that are involved in various skin conditions. In animals, topical application of alpha-tocopherol has shown to exert photo protective effects by reducing the number of sunburn cells; UV B induced damage and inhibiting photo carcinogenesis. An o/w or w/o microemulsion of aliment|antioxidant} delivered the vitamin preponderantly to the stratum avoiding accumulation in organs apart from the skin. The cream or lotion preparations of the same amount of vitamin results in excessive accumulation in the organs (Martini M. C. et al. 1984)[47]. Newer studies show that combined applications of various antioxidants can increase their potency as compared with a single antioxidant alone. Branka Rozman *et al* (Branka R. *et al*, 2009)[48] have developed a temperature-sensitive microemulsion gel as a good and safe delivery system appropriate for concurrent topical application of a hydrophilic antioxidant and a oleophilic fat-soluble vitamin. By changing water content of liquid o/w microemulsion, a gel like microemulsion with temperature sensitive rheological properties was formed. The temperature-driven changes in its microstructure were confirmed by rotational rheometry, viscosity measurements and droplet size determination. The unleash studies have shown that the aliment release at skin temperature from gel like microemulsion were resembling those from o/w microemulsion and were abundant quicker and a lot of complete than from o/w microemulsion conventionally thickened with compound (Carbomer). Non-thickened (o/w, w/o and gel-like) and thickened (with colloidal silica) microemulsions were studied as carriers for vitamin C and E using reconstructed human epidermis (RHE). The amounts of these vitamins accumulated in and permeated across the RHE were determined, together with factors affecting skin deposition and permeation. Notable differences were observed between formulations. The absorption of vitamins C and E in RHE layers was in general enhanced by microemulsions and the vitamins incorporated in the outer phase of the microemulsion exhibited greater absorption than that once vitamins were within the inner section. Addition of thickener enhanced the deposition of vitamins E and C in the RHE (Branka R. *et al*, 2009)[49]. Various delivery systems of alpha-tocopherol (1%) were developed, including easy resolution, gels, emulsions, and microemulsions. The hydro alcoholic gel delivered significantly higher amounts of alpha-tocopherol into the receptor than the other gels used. A microemulsion containing isopropyl myristate emerged as the best delivery system for alpha-tocopherol amongst all the systems studied (Rangarajan M. and Zatz J., 2003)[50]. Microemulsions of w/o and o/w type for topical application containing sodium ascorbyl phosphate (hydrophilic derivative of ascorbic acid) were formulated and compared with topical application of ascorbylpalmitate which is a lipophilic derivative of vitamin C. To obtain liquid microemulsions applicable for topical application, their viscosity was increased by adding thickening agents. Colloidal silicon oxide four-dimensional (w/w) was chosen as an acceptable thickening agent for w/o microemulsions and zero.5% (w/w) xanthan gum for the o/w microemulsions. The presence of thickening agent and also the location of metallic element ascorbyl phosphate within the microemulsion influenced the in vitro drug unharness profiles. When incorporated in the internal aqueous phase, sustained release profiles were observed. This study confirmed microemulsions as suitable carrier systems for topical application of sodium ascorbyl phosphate (Spiclin P. *et al*, 2003[51], Spiclin P. *et al*, 2001)[52]. Spiclin *et al* studied the stability of o/w and w/o

type of microemulsions for topical use containing ascorbyl Palmitate and sodium ascorbyl phosphate which are derivatives of ascorbic acid that differ in stability and hydrophilic and lipophilic properties. The stability of the less stable by-product ascorbyl palmitate was tested below totally different conditions to guage the influence of initial concentration, location in microemulsion, dissolved oxygen and storage conditions. High concentrations of ascorbyl palmitate reduced the extent of its degradation. In distinction, metallic element ascorbyl phosphate was stable in each forms of microemulsion and was shown to be convenient as a lively ingredient in topical preparations. In the case of ascorbyl palmitate, long-term stability in selected microemulsions was not adequate. Investigation on the amphiphilic antioxidant ascorbyl palmitate and its effectiveness against free radical formation was proven by Polona Jur kovic *et al* (Polona Jurkovic *et al*, 2003)[53]. When applied on the skin, ascorbyl palmitate decreased the level of formation of free radicals. Its effectiveness depended considerably on the carrier system, the type of microemulsion and its concentration while the time of application had no influence on its effectiveness. Oil in water microemulsions delivered ascorbyl palmitate to the skin considerably higher than water in oil microemulsions. In each forms of microemulsions, the effectiveness increased at higher concentrations of ascorbyl palmitate. In order to develop alternative formulations for topical administration of retinoic acid, Michele Trotta *et al* (Trotta M. *et al*. 2003)[54] evaluated microemulsions as delivery vehicles. Oil in water and water in oil microemulsion formulations were ready mistreatment water, isopropyl myristate, lecithin, caprylyl–caprylglucoside and ethanol or 1, 2-hexanediol. The result suggested that o/w microemulsions containing a counter ion can be used to optimize drug targeting without a concomitant increase in systemic absorption.

**Miscellaneous Skin Conditions**

The following are examples depicting the use of microemulsions in varied skin conditions: An o/w microemulsion formulated using lecithin and an alkyl glucoside as mild, non-irritant surfactants was proposed as a cosmetic vehicle for arbutin and kojic acid that area unit present change of color agents. The photo stability to UVB irradiation of both whitening agents was determined in aqueous solutions and in microemulsions, and also in the presence of the perfumed compositions. The stability of arbutin and kojic acid was higher in microemulsions than in aqueous solutions (Ghosh P. K. and Murthy R. S., 2006)[9]. Subramanian et al studied the topical delivery of celecoxib using microemulsion as the vehicle for the treatment of UVB induced skin cancer. Various oil to cosurfactant ratios were studied to spot the formulation variables for microemulsion formation. The effect of these variables on skin permeation of celecoxib was evaluated. Topical anti-inflammatory drug result of Celebrex was assessed and it showed higher permeation rate and important anti-inflammatory drug activity. The studied microemulsion formulations have a prospect for use as a potential vehicle for treatment of UV Binduced skin cancer (Subramanian N. *et al*, 2004)[55]. Baroli38 developed and evaluated various microemulsion formulations for topical administration of 8-Methoxsalen and connected furocumarins for the treatment of hyper proliferative skin diseases in association with long wavelength UVA light-weight using water, isopropyl Myristate (IPM) and Tween 80: Span 80: 1, 2-Octanediol (3:1:1.2 w/w) and results suggest that the studied microemulsion system is suitable (Baroli B. *et al*, 2000)[56]. A combination of inhibitors of cyclo-oxygenase-2 and 5-lipoxygenase applied via a microemulsion delivery system was proven to be effective in topically inhibiting skin carcinogenesis. The results clearly showed that topical treatment with microemulsions containing celecoxib alone or celecoxib plus zileuton significantly inhibited skin carcinogenesis and that a combination of both agents had the best results (Fegn L. and Wang Z., 2009)[57]. Temozolomide acid hexyl organic compound employed in the treatment of carcinoma has poor solubility and instability. Microemulsion systems

were formulated with either oleic acid or isopropyl myristate as the oil phase and to co pheryl polyethylene glycol 1000 succinate as a surfactant. Topical formulations of oleic acid or isopropyl Myristate demonstrated beneficial solubilizing ability and provided a stable environment for the drug. In permeation studies, the isopropyl Myristate microemulsion systems with inclusion of isopropanol (IPA) as a co-surfactant considerably augmented permeation of temozolomide acid hexyl organic compound through chemical element membranes and rat skin resulting in less drug retention within the skin, while oleic acid microemulsion systems demonstrated higher solubilizing ability and a higher concentration of temozolomide acid hexyl ester retained within the skin (Suppasansatorn *et al*, 2007)[58]. The abilities of an o/w microemulsion of ethyl oleate with Tween 80 as emulsifier and n-pentanol as a co-emulsifier were investigated to inactivate suspensions of vegetative cells of Salmonella spp. *Escherichia coli Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Listeria monocytogenes* and were found to be effective against all five microorganisms. The abilities of these microemulsions to reduce preformed bio films of the five bacteria were also investigated and were found to be effective (Teixeira P. C. *et al*, 2007)[59]. A microemulsion gel-based system of babchi oil (*Psoraleacorylifolia*) was studied for the treatment of psoriasis which could provide improved permeation of the drug through the skin and increased patient compliance. The chief constituent of babchi oil is psoralen, a photoactive furocoumarin that reduces cell proliferation. Moreover, babchi oil, additionally to providing psoralen additionally acts as Associate in nursing oily part for microemulsion system. The presence of wetter and cosurfactant will increase the permeation. Eight marketed samples of babchi oil were used for the preparation of microemulsions that were subjected to totally different thermodynamical stability tests and characterised for drop size, viscosity and refractive index. *In vitro* skin permeation of babchi oil through rat abdominal skin made up our minds by the Franz diffusion cell. The *in vitro* skin permeation profile of a formulation consisting of one. 67% v/v of babchi oil, 8.33% v/v of oleic acid, 55% v/v of Tween 80: Transcutol-P (1:1) and 35% v/v of H2O was vital compared with different microemulsion formulations. This formulation was converted into microemulsion gel by adding 1Êrbopol-940 and was tested for its in vivo anti-inflammatory effects determined by footpad edema. The results prompt that microemulsion gel may be a potential vehicle for improved topical delivery of psoralen which microemulsion gels area unit potential vehicles for improved topical delivery of babchi oil (Ali J. *et al*, 2008)[60]. Microemulsions containing Aerosol OT, Tween 85, isopropyl myristate and water were observed to possess a potentially improved skin bioavailability of cyclosporine A for topical delivery against autoimmune skin disorders. In animal studies the amount of drug deposition into the skin and subcutaneous fat was respectively almost 30 and 15-fold higher than the concentrations compared with oral administration. The systemic distribution in blood, liver and kidney was much lower following topical administration as compared to oral administration. The study indicated that because of high local concentrations and minimal distribution to other organs via the circulation, topical microemulsion is a suitable vehicle for cyclosporine A (Hongzhuo L. *et al*, 2009)[61].

**Table No.1: Component used for microemulsion formulation** (Cannon J. B, 2010)[28]

| S.No | Components | Examples | |
|---|---|---|---|
| 1 | Oil | Oleic acid, Coconut oil, Safflower oil, Soyabean oil, Olive Oil, Sesame oil, Cotton seed oil, Ethyl oleate, Isopropyl myristate, Decanol, Mineral oil, Captex 355, Capmul MCM, Capmul GMO, Propylene glucolmonolaurate | |
| 2 | Surfactants | HLB<10 | Labrafil 2125, Sorbitanmonoplamitate (Spam 40), Sorbitalmonooleate (Spam 80), Phosphatidylcholine, Lauromacrogol 300, Decylpolyglucoside, Lecithins, Labrafil M 1944 LS, Dioctyl sodium sulfosuccinate, Aerosol OT, Polyglyceryl-6-dioleate, Plurololeique, |
| | | HLB>10 | Tween 20, Tween 80, PEG 8 caprylic/capric glyceride (Labrasol), Cremophor EL, Cremophor RH 40 etc. |
| 3 | Co-surfactants | Ethanol, Propylene glycol, Polyethylene glycol, Capryol 90, Transcutol P, Sorbitanmonooleate, Sorbitanmonostearate etc. | |

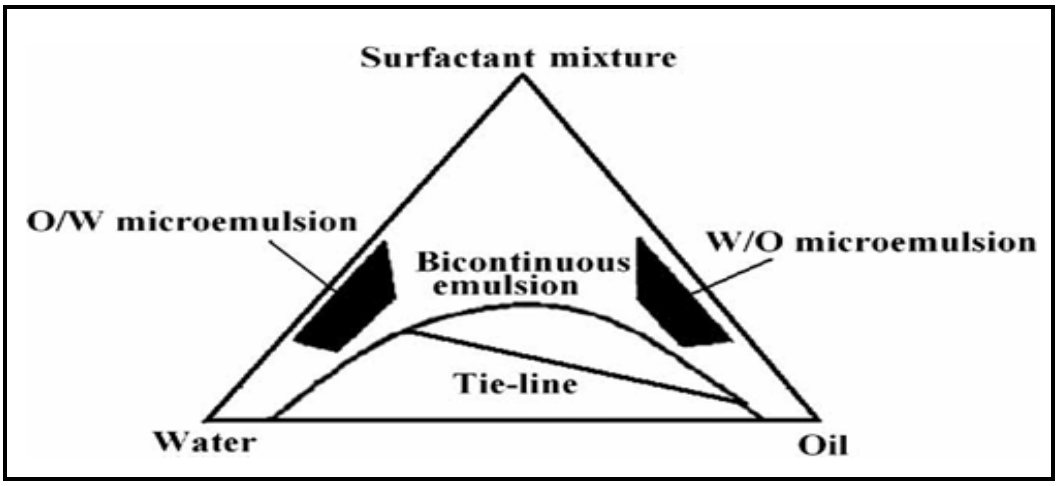


**Figure No.1: Microemulsion**

## CONCLUSION

Microemulsion system provides viscous consistency for the topical application that delivered the drug in sustained or controlled manner and prolonged delivery as compared to traditional indefinite quantity kind. The role of microemulsion systems is of paramount importance in providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability. The availability of efficient, non toxic surfactants and co-surfactant now makes them a very attractive and feasible option to overcome the bioavailability problems frequently encountered in the development of modern drugs.

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## CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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