EAS Journal of Pharmacy and Pharmacology
Abbreviated Key Title: EAS J Pharm Pharmacol
ISSN: 2663-0990 (Print) & ISSN: 2663-6719 (Online)
Published By East African Scholars Publisher, Kenya

Volume-2 | Issue-2 | Mar-Apr:2020 | DOI: 10.36349/easjpp.2020.v02i02.07

OPEN ACCESS

Review Article

Topical Micro emulsions and it's Application - A Review

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Article History
Received: 14.04.2020
Accepted: 25.04.2020
Published: 27.04.2020

Journal homepage:
https://www.easpublisher.com/easjpp

Quick Response Code

Abstract: Microemulsions are one of the best candidates as novel drug delivery system because of their long shelf life, improved drug solubilization with ease of preparation and administration. Microemulsions are thermodynamically stable and optically isotropic liquid solutions of oil, water and amphiphile. They have emerged as novel vehicles for drug delivery which allow controlled or sustained release for ocular, percutaneous, topical, transdermal, and parenteral administration of medicaments. Microemulsions can be easily distinguished from normal emulsions by their low viscosity, transparency and more accurately their thermodynamic stability. Microemulsions have great range of applications and uses such as in pharmaceuticals, agrochemicals, cutting oils, biotechnology, food, cosmetics, analytical applications, environmental detoxification etc. The main objective of this review paper is to discuss microemulsions as drug carrier system with other possible applications. Microemulsions have emerged as novel vehicles for drug delivery which allow sustained or controlled release for percutaneous, topical, transdermal, ocular and parenteral administration of medicaments. Topical microemulsion offer the advantage of spontaneous formation, ease of manufacturing, thermodynamic stability, improved drug solubilization of hydrophobic drugs and increase bioavailability.

Keywords: Microemulsion, topical delivery, surfactant, amphiphile, solubilization.

INTRODUCTION

Microemulsions are liquid behave as a newtonian liquid .They are not very viscous (Vandamme Th. F., 2002). 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 (10-140 nm) than those of conventional emulsions (1-20µm). Microemulsions play a key role in many of the Drug delivery and cosmetics we use today. 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 are generally considered as co-surfactants in the microemulsion system. The presence of surfactant and cosurfactant in the system makes the interfacial tension very low. Thermodynamic stability of the microemulsions has been proposed by Ruckenstein and Chi[2].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). 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). 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 Micellar emulsion was first introduced by Hoar and Schulman in 1943. They prepared the first microemulsions by dispersing oil in an aqueous surfactant solution and adding an alcohol as a co surfactant, leading to transparent stable formulation (Hoar T. P. and Schulman J. H., 1943). These systems offer a great deal of uniqueness not only because of their novel transparency but also because of the small dispersed phase, usually having a droplet diameter between 10 to 140 nm (Attwood D. and Kreuter J., 1994). Investigation for the utilization of microemulsion systems in a variety of chemical and industrial processes has increased in 70's. Microemulsions have shown a wide range of

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applications starting with enhanced oil recovery in 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). Microemulsions can have characteristic properties such as ultralow interfacial tension, large interfacial area and capacity to solubilise both aqueous and oil-soluble compounds (Solans C. and Kunieda H., 1997, Patel A. R. and Vavia P. R., 2007).

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.

- Oil in water (o/w) Winsor I,
- Water in oil (w/o) Winsor II,
- Bicontinuous microemulsions or Winsor III

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 phase was a larger volume would be the continuous phase, 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).

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). 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 drugs tend to favour small or medium molecular volume oils as opposed to hydrocarbon oils due to the polarity of the poorly water-soluble drugs. 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). Water-in-oil microemulsions are made up of droplets of water surrounded by an oil continuous phase. 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). A w/o microemulsion used orally or parenterally may be destabilized by the aqueous biological system. The biological system increases the phase volume of the internal phase, eventually leading to a "percolation phenomenon" where phase separation or phase inversion occurs (Lawrence M. J. and G. D. Rees, 2000). Oral peptide delivery in w/o microemulsions is still used. However the hydrophilic peptides can be easily incorporated into the water internal phase and are more protected from enzymatic proteolysis by the continuous oil phase than other oral dosage forms (Lee V. H., 1988). 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, M. R. F. Pattarino and F. Lattanzi, 1990). 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). Transitions from o/w to w/o microemulsions may pass through this bicontinuous state. Bicontinuous microemulsions, as mentioned before, may show non- Newtonian flow and plasticity. 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). 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.

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 too toxic for general pharmaceutical applications (Jain N. K., 2004). Microemulsions prepared from phospholipids are preferred.

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" can describe any component that aids the primary surfactant in microemulsion formulation. "Co-surfactant" can refer to a second surfactant being used, but may also refer to a low-molecular-weight amphiphile such as an alcohol

(Bidyut K. P. and Satya P. M., 2001).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 (Bidyut K. P. and Satya P. M., 2001).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). 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, when mixed together in a particular ratio, 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 lowlevels required for microemulsion formulation. Short and medium chain alcohols such as butanol, 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 flexibility of the surfactant film around the microemulsion droplet. 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). 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). 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). 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). 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).

Surfactant

Surfactants are molecules that usually contain a polar head group and a polar tail. They are Surface-active and microstructure-forming molecules with a strong chemical dipole (Holmberg K., 2002). 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). 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, where as surfactants with HLB from 8-18 are preferred for oil-in-water (o/w) microemulsions (Lawrence M. J. and G. D. Rees, 2000). 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 there are 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 microemulsion systems. Values for CPP around one indicate the possible formation of lamellar phases (Lawrence M. J. and G. D. Rees, 2000).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).

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). 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). 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). 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). 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).

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). Another important class of zwitterionic surfactants to note is the betaines, such as alkyl betaines, amidoalkylbetaines and heterocyclic betaines.

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). 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). 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). 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). Polysorbate are partial fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20, 5 or 4 moles of ethylene oxide for each 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.

Applications of Topical Microemulsions

Microemulsions are promising delivery systems (Kumar P. and Mittal K. L., 1999, Solans C. and Kunieda H., 1997) that allows sustained or controlled drug release for percutaneous, peroral, topical, transdermal, ocular and parenteral

administration. Enhanced absorption of drugs, modulation of the kinetics of the drug release and decreased toxicity are several advantages in the delivery process. The following is 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 itraconazole being lipophilic in nature have been formulated as microemulsions to impart to them the advantages like ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability compared to conventional dosage forms (Tenjarla S. N., 1999, Lieberman H. A. *et al*., 1996) 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) 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 water-soluble antifungal agents were successfully developed with *in vitro* release rates comparable to that of the gel formulation. The results of the work done on miconazole nitrate formulated as positively charged microemulsions indicate optimized drug targeting without a concomitant increase in systemic absorption. Lalanine benzyl ester, an ester of a natural amino acid, is an appropriate ionic charge-inducing agent (Peira E. *et al*., 2008). 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, Yogeshwar B. and Vandana P., 2009).

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 hydrogel stored at 4°C for 3 months had no significant change in physicochemical 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). Acyclovir containing microemulsion-based formulations for topical delivery were developed using isopropyl Myristate/Captex 355/Labara as an oil phase, Tween 20 as surfactant, Span 20 as cosurfactant, and water : dimethyl sulfoxide(1:3) as an aqueous phase. Transcutol, eucalyptus oil, and peppermint oil were used as permeation enhancers. *In vitro* permeation studies through mice skin were performed using Franz diffusion cells. The optimum formulation containing 2.5% 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 female mice against induced herpes simplex virus I infection indicated that a single application of microemulsion formulation containing 2.5% Transcutol, 24 hours post-injection resulted in complete suppression of development of herpetic skin lesions (Shishu Sunita Rajan and Kamalpreet, 2009).

Anti acne

Novel drug delivery strategies like microemulsions can play a pivotal role in improving the topical delivery of anti acne agents by enhancing their dermal localization with a concomitant reduction in their side effects (Date A. A. *et al*., 2006). Microemulsions of azelaic acid, a bioactive molecule used in many skin disorders, prepared using 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). To increase the solubility of azelaic acid in the dispersed oil phase of microemulsion containing polysorbate 20, butanol, decanol: dodecanol (2/1) and water, the pH of aqueous phase was lowered and propylene glycol was added. An increased partitioning into the lipophilic phase was noted as propylene glycol concentration was increased. Microemulsion thus provided a vehicle in which azelaic acid was dissolved rather than suspended as in a cream. Moreover, reservoir effect achieved by partitioning into the oil could prolong its release over several hours. It showed a 10 fold increase in the amount of drug released (upto 27-30% of initial amount) from the microemulsion when compared to a cream clinically used in treatment of skin disorders (Gallarate M. R. *et al*., 1990).

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 vitamin E delivered the vitamin predominantly to the epidermis avoiding accumulation in organs other than 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).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) have developed a temperature-sensitive microemulsion gel as an effective and safe delivery system suitable for simultaneous topical application of a hydrophilic vitamin C and a lipophilic vitamin E. 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 release studies have shown that the vitamin release at skin temperature from gel like microemulsion were comparable to those from o/w microemulsion and were much faster and more complete than from o/w microemulsion conventionally thickened with polymer (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 when vitamins were in the inner phase. Addition of thickener enhanced the deposition of vitamins E and C in the RHE (Branka R. *et al*., 2009). Various delivery systems of alpha-tocopherol (1%) were formulated, which included simple solution, 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). 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 appropriate for topical application, their viscosity was increased by adding thickening agents. Colloidal silica 4% (w/w) was chosen as a suitable thickening agent for w/o microemulsions and 0.5% (w/w) xanthan gum for the o/w microemulsions. The presence of thickening agent and the location of sodium ascorbyl phosphate in the microemulsion influenced the *in vitro* drug release 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, Spiclin P. *et al*., 2001). 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 derivative ascorbyl palmitate was tested under different conditions to evaluate 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 contrast, sodium ascorbyl phosphate was stable in both types of microemulsion and was shown to be convenient as an active 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). When applied on the skin, ascorbyl palmitate decreased the level of formation of free radicals. Its effectiveness depended significantly 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 significantly better than water in oil microemulsions. In both types 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) evaluated microemulsions as delivery vehicles. Oil in water and water in oil microemulsion formulations were prepared using 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 which are naturally occurring whitening 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).

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 identify the formulation variables for microemulsion formation. The effect of these variables on skin permeation of celecoxib was evaluated. Topical anti-inflammatory effect of celecoxib was assessed and it showed higher permeation rate and significant anti-inflammatory 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). **Baroli**[38] developed and evaluated alternative microemulsion formulations for topical administration of 8-Methoxsalen and related furocumarins for the treatment of hyper proliferative skin diseases in association with long wavelength UVA light 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). 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). Temozolomide acid hexyl ester used in the treatment of skin cancer 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 isopropyl alcohol (IPA) as a co-surfactant significantly increased permeation of temozolomide acid hexyl ester through silicon 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). 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). A microemulsion gel-based system of babchi oil (*Psoralea corylifolia*) 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 which reduces cell proliferation. Moreover, babchi oil, in addition to providing psoralen also acts as an oily phase for microemulsion system. The presence of surfactant and cosurfactant increases the permeation. Eight marketed samples of babchi oil were used for the preparation of microemulsions which were subjected to different thermodynamic stability tests and characterized for droplet size, viscosity and refractive index. In vitro skin permeation of babchi oil through rat abdominal skin was determined by the Franz diffusion cell. The *in vitro* skin permeation profile of a formulation consisting of 1.67% 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 distilled water was significant when compared with other microemulsion formulations. This formulation was converted into microemulsion gel by adding 1%Carbopol-940 and was tested for its *in vivo* anti-inflammatory effects determined by footpad edema. The results suggested that microemulsion gel is a potential vehicle for improved topical delivery of psoralen and that microemulsion gels are potential vehicles for improved topical delivery of babchi oil (Ali J. *et al*., 2008). 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).

CONCLUSION

Microemulsions can also be used to achieve drug targeting however challenges remain, primarily because of the layers of barriers that these systems need to overcome to reach to the target. Microemulsion has been shown to be able to protect labile drug, control drug release, and reduce patient variability. Furthermore

it has proven possible to formulate preparations suitable for most routes of administration. In today's world Microemulsion is accepted as full of potential for novel drug delivery systems. Current research work is focused on the preparation of safe, efficient and more compatible microemulsion constituents which will further enhance the utility of these novel vehicles. Microemulsion system provides viscous consistency for the topical application which delivered the drug in sustained or controlled manner and prolonged delivery as compared to conventional dosage form. 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. They can be used to optimize drug targeting without a concomitant increase in systemic absorption. The role of microemulsion 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.

REFERENCES

1. Ali J., Akhtar N., Sultana Y., Baboota S. and Ahuja A.; Antipsoriatic microemulsion gel formulations for topical drug delivery of babchi oil (Psoraleacorylifolia); *Methods Find Exp. Clin. Pharmacol.*, 2008; Vol. 30(4), pp. 277-85.
2. Attwood D., Kreuter J.; Colloidal Drug Delivery Systems; New York: *Marcel Dekker*, 1994; pp. 31-71.
3. Baroli B., López-Quintela M. A., Delgado-Charro M. B., Fadda A. M. and Blanco-Méndez; Microemulsions for topical delivery of 8-methoxsalen, *Journal of Controlled Release*, 2000; Vol. 69(1), pp. 209-218.
4. Bidyut K. P., Satya P. M.; Uses and applications of microemulsions; *Current Science*, 2001; Vol. 80(8), pp. 990-1001.
5. Biruss B. and Valenta C; The advantage of polymer addition to a non-ionic oil in water microemulsion for the develop delivery of progesterone; *Int. J. Pharm.*, 2008; Vol. 349, pp. 269-273.
6. Branka R., Alenka Z., Francoise F. and Mirjana G.; Temperature-Sensitive Microemulsion Gel: An Effective Topical Delivery System for Simultaneous Delivery of Vitamins C and E; *AAPS Pharm. Sci. Tech*., 2009; Vol. 10(1), pp. 54- 61.
7. Branka R., Mirjana G., Estelle T., Fabrice P. and Francoise F.; Simultaneous absorption of vitamins C and E from topical microemulsions using reconstructed human epidermis as a skin model; *European Journal of Pharmaceutics and Biopharmaceutics*, 2009; Vol. 72(1), pp. 69-75.
8. Cannon J. B.; Lipid-based Formulation Approaches for Poorly Soluble drugs; *www.aapspharmaceutica.com/.../Lipid Based Formulation Cannon.pdf*, 2010.
9. Corswant C., Thoren P., Engstrom S.; Triglyceride-based Microemulsions for intravenous administration of sparingly soluble substances; *J. Pharm Sci.*, 1998; Vol. 87, pp. 200.
10. Date A. A., Naik B. and Nagarsenker M. S.; Novel Drug Delivery Systems: Potential in Improving Topical Delivery of Antiacne Agents; *Skin Pharmacology and Physiology*, 2006; Vol. 19, pp. 2-16.
11. Fegn L. and Wang Z.; Topical chemoprevention of skin cancer in mice, using combined inhibitors of 5-lipoxygenase and cyclo-oxygenase-2; *The Journal of Laryngology & Otology*, 2009; Vol. 123(8), pp. 880-884.
12. Gallarate M. R., Gasco M. R. and Rua G.; In vitro release of azelaic acid form oil in water microemulsions; *Acta. Pharm. Jugosla*, 1990; Vol. 40, pp. 533.
13. Gelbart W. M. and A. Ben Shaul, The new science of complex fluids; *Journal of Physical Chemistry*, 1996; Vol. 100(31), pp. 13169-13189.
14. Ghosh P. K. and Murthy R. S., Microemulsions: A potential drug delivery system, *Curr. Drug Delivery*, 2006; Vol. 3(2), pp. 167-180.
15. Ghosh P. K. and Murthy R. S.; Microemulsions: A potential drug delivery system; Current Drug Delivery, 2006; Vol. 3(2), pp. 167-180.
16. Giustini M., S. Murgia and G. Palazzo; Does the Schulman's titration of microemulsions really provide meaningful parameters?; *Langmuir*, 2004; Vol. 20(18), pp. 7381-4.
17. Giustini M.; Microstructure and dynamics of the water-in-oil CTAB/n-pentanol/ n-hexane/water microemulsion: A spectroscopic and conductivity study; *Journal of Physical Chemistry*, 1996; Vol. 100(8), pp. 3190-3198
18. Hait S. K. and S. P. Moulik; Interfacial composition and thermodynamics of formation of water/isopropyl myristate water-in-oil microemulsions stabilized by butan-1-ol and surfactants like cetyl pyridinium chloride, cetyl trimethyl ammonium bromide, and sodium dodecyl sulphate; *Langmuir*, 2002, Vol. 18(18), pp. 6736-6744.
19. Hoar T. P., Schulman J. H.; Transparent water in oil dispersions: the oleopathic hydromicelle; *Nature*, 1943; Vol. 152, pp. 102-103.
20. Holmberg K.; Handbook of applied surface and colloid chemistry; *Chichester, New York: Wiley*, 2002.
21. Hongzhuo L., Yongjun W., Yiyong L., Huimin Y., Yang D. and Sanming Li.; Bicontinuous Cyclosporin-a loaded Water -AOT/Tween 85 – isopropylmyristate microemulsion: Structural characterization and dermal pharmacokinetics in-

vivo; *J. Pharm. Sci*., 2009; Vol. 98, pp. 1167-1176.

22. Jain N. K., Progress in controlled and novel drug delivery system I[st] ed; *CBS publisher and distributor New Delhi*, 2004; pp. 319-320.
23. Jain N. K.; Progress in controlled and novel drug delivery system; *CBS Publisher, New Delhi*, 2004; Vol. 1, pp. 309-340.
24. Kibbe A.H.; Handbook of Pharmaceutical Excipients. 3rd ed; *London: Pharmaceutical Press*, 2000.
25. Kumar P. and Mittal K. L.; Handbook of Microemulsion Science and Technology, 1[st] ed; *CRC Press, New York*, 1999; pp. 1.
26. Kumar P. and Mittal K. L.; Handbook of microemulsion science and technology; *New York Marcel Dekker Inc*., 1999; pp. 457-497, 549-603, 679-712, 755-77.
27. Lange K.R.; Surfactants : a practical handbook, Munich Cincinnati: Hanser Publishers; *Hanser Gardner Publications. xiii*, 1999; pp. 237.
28. Lawrence M. J. and G. D. Rees; Microemulsion-based media as novel drug delivery systems*; Adv Drug Delivery Rev*, 2000; Vol. 45(1),pp. 89-121.
29. Lee V. H.; Enzymatic barriers to peptide and protein absorption; *Crit Rev Ther Drug Carrier System*, 1988; Vol. 5(2), pp. 69-97.
30. Lieberman H. A., Rieger M. M. and Banker G. S.; Pharmaceutical Dosage Forms: Disperse Systems 2nd ed.; *New York : Marcel Dekker Inc*., 1996; Vol. 1, pp. 211-281, 315-370.
31. M. R. F. Pattarino and F. Lattanzi; Long acting delivery systems for peptides: reduced plasma testosterone levels in male rats after a single injection; *Int J Pharm*, 1990; Vol. 62, pp. 119-123.
32. Maibach H. I.; Elastic vesicles as topical/transdermal drug delivery systems via microemulsions; *Int. J. Cosmetic sci.*, 2005*;* Vol. 27, pp. 211-221.
33. Martini M.C., Bobin M. F., Flandin H., Caillaud F. and Cotte J.; Role of microemulsions in the percutaneous absorption of alpha-tocopherol; *J. Pharm. Belg.*, 1984; Vol. 39(6), pp. 348-54.
34. Moulik S. P. and B. K. Paul; Structure, dynamics and transport properties of microemulsions; *Advances in Colloid and Interface Science*, 1998; Vol. 78, pp. 99-195.
35. Patel A. R. and Vavia P. R.; Preparation and *in vivo* evaluation of SMEDDS containing fenofibrate; *AAPS J*., 2007; Vol. 9, pp.344.
36. Peira E., Carlotti M. E., Cavalli R. and Trotta M.; Azelaic acid sodium salt in the formulation of microemulsions for topical applications; *Journal of drug delivery science and technology*, 2006; Vol. 16(5), pp. 375-379.
37. Peira E., Carlotti M. E., Trotta C., Cavalli R. and Trotta M.; Positively charged microemulsions for topical application; *Int. J. Pharm*., 2008; Vol. 346(1-2), pp. 119-23.
38. Polona Jurkovic, Marjeta Sentjurc, Mirjana Gasperlin, Julijana Kristl and Slavko Pecar; Skin protection against ultraviolet induced free radicals with ascorbyl palmitatein microemulsions; *European J. Pharm. and Biopharm*aceutics, 2003; Vol. 56(1), pp. 59-66.
39. Puranajoti P. R., Patil T., Sheth P. D., Bommareddy G. P. and Egbaria D. K.; Design and Development of Topical Microemulsion for Poorly Water-Soluble Antifungal Agents; *The Journal of Applied Research*, 2002; Vol. 2(1).
40. Rangarajan M. and Zatz J.; Effect of formulation on the topical delivery of alpha-tocopherol; *Journal of Cosmetic Science*, 2003; Vol. 54(2), pp. 161-74.
41. Rao Y. S., Deepthi K. S. and Chowdary K. P; Microemulsions: A Novel Drug Carrier System; IJDDT, 2009; Vol. 1, pp. 39-41.
42. Sarkhejiya Naimish A., Nakum Mayur A., Patel Vipul P., Atara Samir A., Desai Thusarbindu R.; Emerging Trend Of Microemulsion In Formulation And Reserach; *International Bulletin of Drug Research*, 2007; Vol. 1(1), pp. 54-83.
43. Scriven L. E.; Equilibrium bicontinuous structures; *Nature (London)*, 1976; pp. 263
44. Shafiq-un-Nabi S., Formulation development and optimization using nanoemulsion technique: a technical note; *AAPS Pharm Sci Tech*, 2007; Vol. 8(2), pp. 28.
45. Shaji J., Reddy M. S.; Microemulsions as drug delivery systems; *Pharma Times*, 2004; Vol. 36 (7), pp. 17 – 24.
46. Shinoda K. and H. Kunieda; Conditions to produce so-called microemulsions: factors to increase the mutual solubility of oil and water by solubilizer; *Journal of Colloid and Interface Science*, 1973; pp.42.
47. Shishu Sunita Rajan and Kamalpreet; Development of novel microemulsion based topical formulations of Acyclovir for the treatment of cutaneous herpetic infections; *AAPS Pharm. Sci. Tech*., 2009; Vol. 10(2), pp. 559-565.
48. Singh H. N.; Structural description of water-in-oil microemulsions using electrical resistance; *Berichte der Bunsen-Gesellschaft*, 1983; Vol. 87(12), pp. 1115-1120.
49. Solans C. and Kunieda H.; Industrial Applications of Microemulsions, *Marcel Dekker, New York*, 1997.
50. Solans C. and Kunieda H.; Industrial applications of microemulsions; *New York Marcel Dekker Inc.*, 1997; Vol. 199, pp. 147-174, 97-122, 123-145, 69-95.
51. Spiclin P., Gasperlin M. and Kmetec V.; Stability of sodium ascorbyl phosphate in topical microemulsions; *Int. J. Pharm.*, 2001; Vol. 222(2), pp. 271-9.
52. Spiclin P., Homar M., Zupancic V. A. and Gasperlin M.; Sodiumascorbyl phosphate in topical

microemulsions; *Int. J. Pharm.,* 2003; Vol. 256(1-2), pp. 65-73.

53. Subramanian N., Ghosal S. K., Moulik S. P., Topical delivery of celecoxib using microemulsion; *Acta. Pol. Pharm.,* 2004; Vol. 61(5), pp. 335-41.
54. Tenjarla S. N.; Microemulsions: An overview and pharmaceutical applications Critical Reviews; *Therapeutic Drug Carrier Systems,* 1999; Vol. 16, pp. 461-521.
55. Trotta M., Ugazio E., Peira E. and Puritano C., Influence of ionpairing on topical delivery of retinoic acid from microemulsions; *Journal of Controlled Release*, 2003; Vol. 86(2-3), pp. 315-321.
56. Trotta M.; Influence of phase transformation on indomethacin release from microemulsions; *J. Control. Release,* 1999; Vol. 60, pp. 399-405.
57. Vandamme Th. F.; Microemulsions as ocular drug delivery systems: recent developments and future challenges; *Progress in retinal and eye research*, 2002; Vol. 21, pp. 15-34.
58. Weiwei Zhu, Chenyu Guo, Aihua Yu, Yan Gao, Fengliang Cao and Guang Xi Zhai; Microemulsion-based hydrogel formulation of penciclovir for topical delivery; *International Journal of Pharmaceutics*, 2009; Vol. 378(1- 2), pp. 152-158.
59. Yogeshwar B. and Vandana P.; Microemulsion based vaginal gel of fluconazole: formulation, in vitro and in vivo evaluation; *Int. J. Pharm.,* 2009; Vol. 365(1-2), pp. 175-179.
60. Yogeshwar B. and Vandana P.; Microemulsion-Based VaginalGel of Clotrimazole: Formulation: In vitro Evaluation and Stability Studies; *AAPS Pharm. Sci. Tech.,* 2009; Vol. 10(2), pp. 476-481.