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A Brief Review on Microemulsion its Concepts and Applications

Abstract

Microemulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. Microemulsions act as potential drug carrier systems for oral, topical, and parenteral administration. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, and improved drug solubilization and bioavailability. One can understand easily the structure, phase behavior, factors leading to thermodynamic stability and the potential uses and limitations of the microemulsion system while preparing a pharmaceutically acceptable dosage . Knowledge of the various methods available to thoroughly characterize a microemulsion system is essential. Application of microemulsion is more & more in our daily life & in several fields; in this review the pharmaceutical applications are emphasized.

Keywords : Microemulsion,Surfactant,Cosurfactant & Oil

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Introduction

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

In ternary systems such as microemulsions, where two immiscible phases (water and 'oil') are present with a surfactant, the surfactant molecules may form a monolayer at the interface between the oil and water, with the hydrophobic tails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase.

As in the binary systems (water/surfactant or oil/surfactant), self-assembled structures of different types can be formed, ranging, for example, from (inverted) spherical and cylindrical micelles to lamellar phases and bi-continuous microemulsions, which may coexist.

Microemulsions improve the transdermal delivery of several drugs over the conventional topical preparations such as emulsions [4, 5] and gels [6, 7]. Mobility of drugs in microemulsions is more facile [8], as compared to the microemulsion with gel former which will increase its viscosity and further decrease the permeation in the skin [9]. The superior transdermal flux from microemulsions has been shown to be mainly due to their high solubilization potential for lipophilic and hydrophilic drugs. This generates an increased thermodynamic activity towards the skin. Microemulsions may affect the permeability of drug in the skin. In this case, the components of microemulsions serve as permeation enhancers [10-12]. Several compounds used in microemulsions have been reported to improve the transdermal permeation by altering the structure of the stratum corneum [13-15]. For example, short chain alkanols are widely used

as permeation [16] enhancers. It is known that oleic acid, a fatty acid with one double bond in the chain structure, perturbs the lipid barrier in the stratum corneum by forming separate domains which interfere with the continuity of the multilamellar stratum corneum and may induce highly permeable pathways in the stratum corneum.

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

Theory

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

Historical Background

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

Type I

Surfactant-rich water phase (lower phase) coexists with surfactant-poor oil phase (Winsor I).

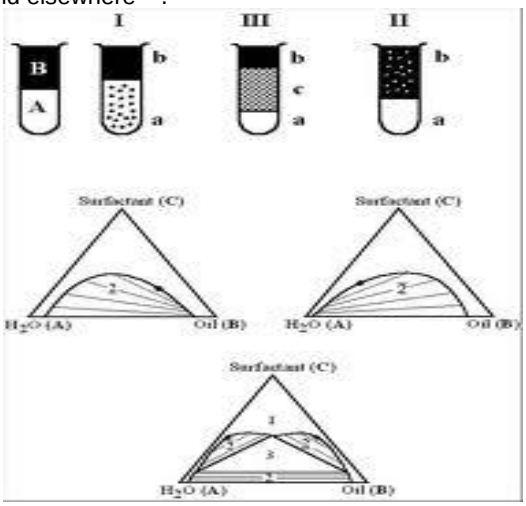
Type II

Surfactant-rich oil phase (the upper phase) coexists with surfactant-poor water phase (Winsor II).

Type III

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

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



Phase Diagrams

The microemulsion region is usually characterized by constructing ternary-phase diagrams. Three components are the basic requirement to form a microemulsion: an oil phase, an aqueous phase and a surfactant. If a cosurfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single "pseudo-component". The relative amounts of these three components can be represented in a ternary phase diagram. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behavior of the system. The three components composing the system are each found at an apex of the triangle, where their corresponding volume fraction is 100%. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist (ideally, according to the Gibbs' phase rule) of one, two or three phases. These points combine to form regions with boundaries between them, which represent the "phase behavior" of the system at constant temperature and pressure.

The Gibbs phase diagram, however, is an empirical visual observation of the state of the system and may, or may not express the true number of phases within a given composition. Apparently clear single phase formulations can still consist of multiple iso-tropic

phases (e.g. the apparently clear heptane/AOT/water microemulsions consist multiple phases). Since these systems can be in equilibrium with other phases, many systems, especially those with high volume fractions of both the two immiscible phases, can be easily destabilized by anything that changes this equilibrium e.g. high or low temperature or addition of surface tension modifying agents. However, examples of relatively stable microemulsions can be found. It is believed that the mechanism for removing acid build up in car engine oils involves low water phase volume, water-in-oil (w/o) microemulsions. Theoretically, transport of the aqueous acid droplets through the engine oil to micro-dispersed calcium carbonate particles in the oil should be most efficient when the droplets are small enough to transport a single hydrogen ion (the smaller the droplets, the greater the number of droplets, the faster the neutralization). Such microemulsions are probably very stable across a reasonably wide range of elevated temperatures.

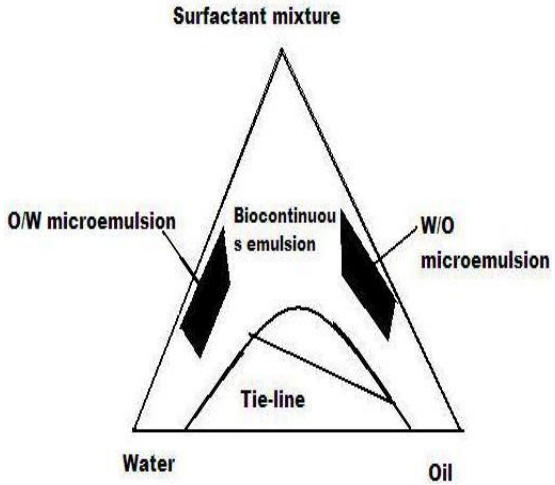


Figure 1 Schematic Representation of Pseudo Ternary Phase Diagram Showing Microemulsion Region

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

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

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

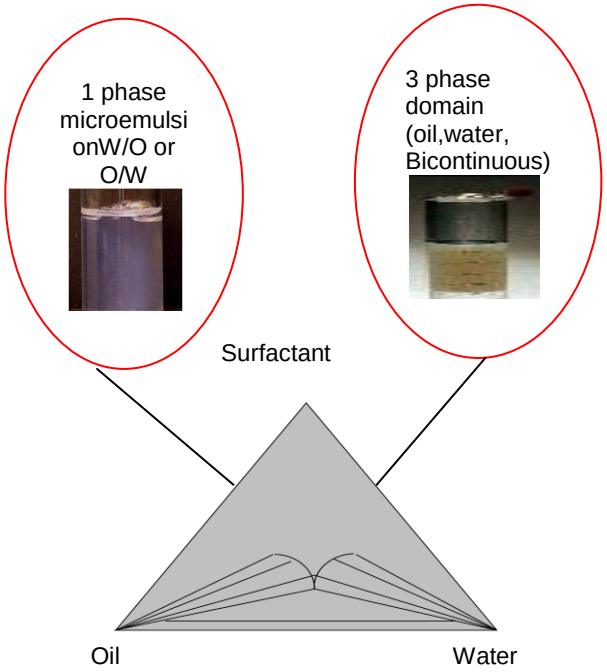


Figure 2 Formulating Microemulsion

Theory of Microemulsion Formulation

Microemulsion formation and stability can be explained on the basis of a simplified thermodynamic rationalization. The free energy of microemulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil–water interface and the change in entropy of the system such that,

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

Where, DG f =free energy of formation, γ = Surface tension of the oil–water interface, DA =Change in interfacial area on microemulsification, DS = Change in entropy of the system which is effectively the dispersion entropy, and T = Temperature. It should be noted that when a microemulsion is formed, the change in DA is very large due to the large number of nanodroplets are formed. It is seen that while the value of γ is positive at all times, it is very small (of the order of fractions of mN/m), and is offset by the entropic component. The dominant favorable entropic contribution is the very large dispersion entropy arising from the mixing of one phase in the other in the form of large numbers of nanodroplets. However, favorable entropic contributions also arise from other dynamic processes such as surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange. Thus, a negative free energy of formation is achieved when large reductions in surface tension are accompanied by significant favorable entropic change. In such cases, microemulsification is spontaneous and the resulting dispersion is thermodynamically stable. Though, it has been know that several factors determine whether a w/o or o/w microemulsion system will be formed but in general it could be summarized that the most likely microemulsion would be that in which the phase with the smaller volume fraction forms.

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Surfactants, Co-Surfactants and Oil Used in Microemulsion Formulation

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

Attempts have been made to rationalize surfactant behavior in terms of the hydrophilic- lipophilic balance (HLB), as well as the critical packing parameter (CPP). Both approaches are fairly empirical but can be a useful guide to surfactant selection. The HLB takes into account the relative contribution of hydrophilic and hydrophobic fragments of the surfactant molecule. It is generally accepted that low HLB (3-6) surfactants are favored for the formation of w/o microemulsions whereas surfactants with high HLBs (8-18) are preferred for the formation of o/w microemulsion systems. Ionic surfactants such as sodium dodecyl sulphate which have HLBs greater than 20, often require the presence of a co-surfactant to reduce their effective HLB to a value within the range required for microemulsion formation. In contrast, the CPP relates the ability of surfactant to form particular aggregates to the geometry of the molecule itself. A combination of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the microemulsion region. Examples of non-Ionics include polyoxyethylene surfactants such as Brij 35(C12E35) or sugar esters such as sorbitan monooleate (Span 80). Phospholipids are a notable example of zwitter ionic surfactants and exhibit excellent biocompatibility. Lecithin preparations from a variety of sources including soybean and egg are available commercially and contain diacylphosphatidylcholine as its major constituent.[38-41] Quaternary ammonium alkyl salts form one of the best known classes of cationic surfactants, with hexadecyltrimethyl ammonium bromide (CTAB) (Rees et al., 1995), and the twin-tailed surfactant didodcecylammonium bromide (DDAB) are amongst the most well known (Olla et al., 1999). The most widely studied anionic surfactant is probably sodium bis-2-ethylhexylsulphosuccinate (AOT) which is twin-tailed and is a particularly effective stabiliser of w/o microemulsions.[42] In most cases, single-chain surfactants alone are unable to reduce the oil /water interfacial tension sufficiently to enable a microemulsion to form, a point made in a number of pertinent microemulsions reviews.[43-47] Medium chain length alcohols which are commonly added as co-surfactants have the effect of further reducing the interfacial tension, whilst increasing the fluidity of the interface thereby increasing the entropy of the system. Medium chain length alcohols also increase the mobility of the hydrocarbon tail and also allow greater[44,45]

Tab. 1 Common Excipients Used To Formulate Microemulsions

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

Advantages of Microemulsion Based Systems[33]

Microemulsions exhibits several advantages as a drug delivery system:

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

Disadvantages of Microemulsion Based Systems:[48]

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

Limitations

Some factors limit the use of microemulsion in pharmaceutical applications.

1. The need of pharmaceutically acceptable ingredients limits the choice of microemulsion components (e.g., oil, surfactant and cosurfactants) leading to difficulties in formulation.

2. The concentration of surfactants and co-surfactants used must be kept low for toxicological reasons.
3. Microemulsion also suffers from limitations of phase separation.
4. For intravenous use, the demand of toxicity on the formulation is rigorous and very few studies have been reported so far.
5. The major limitation is the toxicity of excipients i.e. surfactant/ co-surfactants. Exploration of safe excipients and evaluation of the toxicity parameters of available excipients may help in further expansion of research in this field.

Preparation of Microemulsion System

The drug is be dissolved in the lipophilic part of the microemulsion i.e. oil and the water phases can be combined with surfactant and then cosurfactant is added at slow rate with constant stirring until the system is transparent. The amount of surfactant and cosurfactant to be added and the percent of oil phase that can be incorporated is determined with the help of pseudo ternary phase diagram discussed in figure 3. Available online on www.ijpsr.com 1894) ternary phase diagram. Ultrasonicator can finally be used so to achieve the desired size range for dispersed globules. It is then allowed to equilibrate. Gel may be prepared by adding a gelling agent to the above microemulsion. Carbomers (crosslinked polyacrylic acid polymers) are the most widely used gelling agent.

Construction of Phase Diagram

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

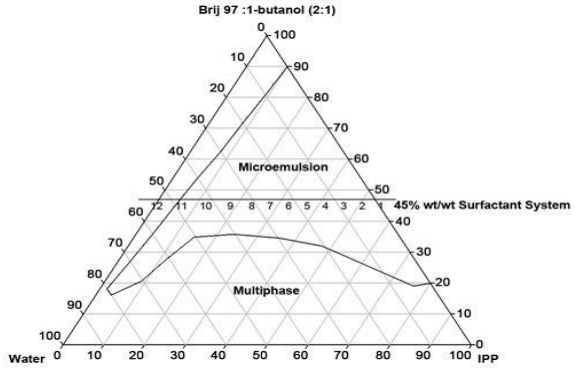

Figure 3 The Pseudoternary Phase Diagram of Ipp/Water/Brij 97:1-Butanol (2:1) and the Dilution Line for Investigation at 45% Wt/Wt Surfactant System[49]

Figure 3 shows the pseudoternary phase diagram with the area inside the frame assigned on the phase diagram showing the microemulsion region. The area outside the frame indicates a turbid region with multiphase systems. It could be noted that the area of microemulsion region was considerably large since 1-butanol acted as a cosurfactant and interacted with the surfactant monolayer to increase the flexibility of the interfacial film.

Characterization of Microemulsion

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

Droplet size

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

Dynamic Light-Scattering Measurements

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

Polydispersity

Polydispersity is studied using Abbe refractometer.

Phase Analysis

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

Viscosity Measurement

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

Applications of Microemulsions:

Pharmaceutical Applications

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

Parenteral Delivery

Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered to a targeted site. Microemulsion formulations have distinct advantages over macroemulsion systems when delivered parenterally because of the fine particle microemulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both o/w and w/o microemulsion are used for parenteral delivery. The literature contains the details of the many microemulsion systems, few of these can be used for the parenteral delivery because the toxicity of the surfactant and parenteral use. An alternative approach was taken by Von Corsewant and Thoren[50] in which C3-C4 alcohols were replaced with parenterally acceptable co-surfactants, polyethylene glycol (400) / polyethylene glycol (660) 12-hydroxystearate / ethanol, while maintaining a flexible surfactant film and spontaneous

curvature near zero to obtain and almost balanced middle phase microemulsion. The middle phase structure was preferred in this application, because it has been able to incorporate large volumes of oil and water with a minimal concentration of surfactant.

Oral Delivery

Microemulsion formulations offer the several benefits over conventional oral formulation for oral administration including increased absorption, improved clinical potency and decreased drug toxicity.[51]Therefore, microemulsion has been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics. Pharmaceutical drugs of peptides and proteins are highly potent and specific in their physiological functions. However, most are difficult to administer orally. With on oral bioavailability in conventional (i.e. non-microemulsion based) formulation of less than 10%, they are usually not therapeutically active by oral administration. Because of their low oral bioavailability, most protein drugs are only available as parenteral formulations. However, peptide drugs have an extremely short biological half life when administered parenterally, so require multiple dosing. A microemulsion formulation of cyclosporine, named Neoral has been introduced to replace Sandimmune, a crude oil-in-water emulsion of cyclosporine formulation. Neoral is formulated with a finer dispersion, giving it a more rapid and predictable absorption and less inter and intra patient variability.

Topical Delivery

Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects. Second is the direct delivery and targetability of the drug to affected area of the skin or eyes. Both O/W and W/O microemulsions have been evaluated in a hairless mouse model for the delivery of prostaglandin E1.The microemulsions were based on oleic acid or Gelucire 44/14 as the oil phase and were stabilized by a mixture of Labrasol (C8 and C10 polyglycolysed glycerides) and Plurol Oleique CC 497 as surfactant. Although enhanced delivery rates were observed in the case of the o/w microemulsion, the authors concluded that the penetration rates were inadequate for practical use from either system. The use of lecithin/IPP/water microemulsion for the transdermal transport of indomethacin and diclofenac has also been reported. Fourier transform infra red (FTIR) spectroscopy and differential scanning calorimetry (DSC) showed the IPP organogel had disrupted the lipid organisation in human stratum corneum after a 1 day incubation. The transdermal delivery of the hydrophilic drug diphenhydramine hydrochloride from a w/o microemulsion through the excised human skin has also been investigated. The formulation was based on combinations of Tween 80 and Span 20 (surfactants) with IPM. However two additional formulations were tested containing cholesterol and oleic acid, respectively. Cholesterol increased drug penetration whereas oleic acid had no measurable effect, but the authors clearly demonstrated that penetration characteristics can be modulated by compositional selection.

Ocular and Pulmonary Delivery

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

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

Microemulsions in Biotechnology

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

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

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

Other Applications

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

Conclusion

Till date, microemulsions have been shown to be able to protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration. There is still however a considerable amount of fundamental work characterizing the physico-chemical behavior of microemulsions that needs to be performed before they can live up to their potential as multipurpose drug delivery vehicles. Recently, several research papers have been published for the improvement of drug delivery, but still there is a need to put an emphasis on its characterization part including in vitro evaluation. Besides this, research papers shows higher percentage of surfactant (much higher than CMC level) used for the formation of microemulsion, irrespective of different routes of administration, but there is a lack of toxicological evaluation of the prepared microemulsion, which can be a broad research area in future.

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Declaration of Interest Section: None

References

1. Danielsson I, Lindman B: The definition of microemulsion. Colloid Surf 1981; 3: 391-392.
2. Narang AS, Delmarre D, Gao D: Stable drug encapsulation in micelles and microemulsions. Int J Pharm 2007; 345: 9-25.
3. Yuan Y, Li S-M, Mo F-K, D-F Zhong: Investigation of microemulsion system for transdermal delivery of meloxicam. Int J Pharm 2006; 321: 117-123.
4. Ktistis, G., Niopas, I., 1998: A study on the in-vitro percutaneous absorption of propranolol from disperse systems. J. Pharm. Pharmacol. 50, 413–418.
5. Kreilgaard, M., Pedersen, E.J., Jaroszewski, J.W: NMR characterization and transdermal drug delivery potential of microemulsion systems. J. Control. Release 69, 421–433.
6. Gasco, M.R., Gallarate, M., Pattarino, F., 1991: In vitro permeation of azelaic acid from viscosized microemulsions. Int. J. Pharm. 69, 193–196.
7. Kriwet, K., Müller-Goymann, C.C: Diclofenac release from phospholipid drug systems and permeation through excised human stratum corneum. Int. J. Pharm. 125, 231–242.
8. Trotta, M: Influence of phase transformation on indomethacin release from microemulsions. J. Control. Release 60, 399–405.
9. Alvarez-Figueroa, M.J., Blanco-Méndez, J: Transdermal delivery of methotrexate: iontophoretic delivery from hydrogels and passive delivery from microemulsions. Int. J. Pharm. 215, 57–65.
10. Pershing, L.K., Lambert, L.D., Knutson, K: Mechanism of ethanol-enhanced estradiol permeation across human skin in vivo. Pharm. Res. 7, 170–175.
11. Liu, P., Kurihara-Bergstrom, T., Good, W.R: Cotransport of estradiol and ethanol through human skin in vitro: understanding the permeant/enhancer flux relationship. Pharm. Res. 8, 938–944.
12. Kim, Y.-H., Ghanem, A.-H., Mahmoud, H., Higuchi, W.I: Short chain alkanols as transport enhancers for lipophilic and polar/ionic permeants in hairless mouse skin: mechanism(s) of action. Int. J. Pharm. 80, 17–31.
13. Pershing, L.K., Parry, G.E., Lambert, L.D: Disparity of in vitro and in vivo oleic acid-enhanced b-estradiol percutaneous absorption across human skin. Pharm. Res. 10, 1745– 1750.
14. Tanojo, H., Junginger, H.E., Boddé, H.E: In vivo human skin permeability enhancement by oleic acid: transepidermal water loss and Fourier-transform infrared spectroscopy studies. J. Control. Release 47, 31–39.
15. Hadgraft, J: Skin, the final frontier. Int. J. Pharm. 224, 1–18.
16. Goldberg-Cettina, M., Liu, P., Nightingale, J., Kurihara-Bergstrom, T: Enhanced transdermal delivery of estradiol in vitro using binary vehicles of isopropyl myristate and short-chain alkanols. Int. J. Pharm. 114, 237–245.
17. Fang, J.-Y., Yu, S.-Y., Wu, P.-C., Huang, Y.-B., Tsai, Y.-H: In vitro skin permeation of estradiol from various proniosome formulations. Int. J. Pharm. 215, 91–99.
18. Acharya, S. P., Moulik, S. K. Sanyal, Mishra, B. K. and Puri, P. M: Physicochemical Investigations of Microemulsification of Coconut Oil and Water Using Polyoxyethylene 2-Cetyl Ether (Brij 52) and Isopropanol or Ethanol, Journal of Colloid and Interface Science 245 , 163–170.
19. Winsor, P. A. Trans. Faraday Soc. 1948, 44, 376.
20. Schulman, J. H.; Stoeckenius, W.; Prince, M. J. Phys. Chem. 1959, 63, 1677.
21. Friberg, S. E.; Mandell, L.; Larsson, M. J: Colloid Interface Sci. 1969, 29, 155.
22. Adamson, A. W. J: Colloid Interface Sci. 1969, 29, 261.
23. Prince, L. M: Microemulsions, Theory and Practice; Prince, L. M., Ed.; Academic Press: New York, 1977.
24. Tadros, Th. F.; Vincent, B: Encyclopaedia of Emulsion Technology; Becher, P., Ed.; Vol 1; Marcel Dekker: New York, 1980.
25. Hunter, R. J: Introduction to Modern Colloid Science; 1st ed.; Oxford University Press: Oxford, 1994.
26. Martin, A: Coarse Dispersions In Physical Pharmacy, Fourth Edition; B.I. Waverly Pvt. Ltd., New Delhi, 1994; 495 – 496.
27. Shaji, J., Reddy, M.S: Microemulsions as drug delivery systems, Pharma Times, 2004, 36 (7); 17 – 24.
28. Kayes, F.B: Disperse systems In Pharmaceutics: The Science of Dosage Form Design, International Student Edition; Ed: Aulton, M.E.; Churchill Livingstone, 1999; 110.
29. Rieger, M.M: Emulsions In Theory and Practice of Industrial Pharmacy, Third Edition; Ed: Lachman,

L., Lieberman, H.A., Kanig, J.L.; Varghese Publishing House, Bombay, 1987; 507 – 519.
30. Emsap, W.J., Siepmann, J., Paeratakul, O: Disperse Systems In Modern Pharmaceutics, Fourth Edition; Ed: Banker, G.S., Rhodes, C.T.; Marcel Dekker, Inc., New York, 2002, Vol-121; 260 – 261.
31. Eccleston, G.M: Emulsion and Microemulsions In Encyclopedia of Pharmaceutical Technology, Second Edition; Ed: Swarbrick, J., Boylan, J.C.; Marcel Dekker, Inc., New York, 2002, Vol-2; 1080 – 1085.
32. Betageri, G., Prabhu, S: Semisolid preparations In Encyclopaedia of Pharmaceutical Technology, Second Edition; Ed: Swarbrick, J., Boylan, J.C.; Marcel Dekker, Inc., New York, 2002, Vol-3; 2441 – 2442.
33. Ghosh, P.K., Murthy, R.S.R: Microemulsions: A Potential Drug Delivery System, C. Drug. Del., 2006, 3; 167-180.
34. Hoar, T.P., Schulman, J.H: Transparent water-in-oil dispersions: the oleopathic hydro-micelle, Nature, 1943, 152; 102-103.
35. Carlfors, J.,Blute, I. , Schmidt, V: Lidocaine in microemulsion — a dermal delivery system, J. Disp. Sci. Technol. 12, 467–482.
36. Israelachvilli, J.N., Mitchell, D.J., Ninham, B.W: Theory of self assembly of hydrocarbon amphiphiles into micelles and bilayers, J. Chem. Soc. Faraday Trans. II 72, 1525–1567.
37. Mitchell, D.J., Ninham, B.W: Micelles, vesicles and microemulsions, J. Chem. Soc. Faraday. Trans. II 77, 601–629.
38. Attwood, D., Mallon, C., Taylor, C.J: Phase studies of oil-in water phospholipid microemulsions, Int. J. Pharm. 84, R5–R8.
39. Aboofazeli, R., Lawrence, C.B., Wicks, S.R., Lawrence, M.J: Investigations into the formation and characterisation of phospholipid microemulsions. III. Pseudo-ternary phase diagrams of systems containing water–lecithin–isopropyl myristate and either an alkanoic acid, amine, alkanediol, polyethylene glycol alkyl ether or alcohol as cosurfactant, Int. J. Pharm. 111, 63–72.
40. Aboofazeli, R., Lawrence, M. J: Investigations into the formation and characterization of phospholipid microemulsions: I Pseudo-ternary phase diagrams of systems containing water–lecithin–alcohol–isopropyl myristate, Int. J. Pharm. 93, 161–175.
41. Shinoda, K., Araki, M., Sadaghiani, A., Khan, A., Lindman, B: Lecithin-Based Microemulsions: Phase Behaviour and Micro-Structure, J. Phys. Chem. 95, 989–93.
42. Angelo, M.D., Fioretto, D., Onori, G., Palmieri, L., Santucvelocity, A: Dynamics of water-containing sodium bis(2-ethylhex-yl)sulfosuccinate (AOT) reverse micelles: a high-frequency dielectric study, Phys. Rev. E 54, 993–996.
43. Bhargava, H.N., Narurkar, A., Lieb, L. M: Using microemulsions for drug delivery, Pharm. Tech. 11, 46–52.
44. Attwood: Microemulsions, in: J. Kreuter (Ed.), Colloidal Drug Delivery Systems, Dekker , New York , 31–71.
45. Eccleston: Microemulsions, in: J. Swarbrick, J.C. Boylan (Eds.), Encyclopedia of Pharmaceutical Technology, Vol. 9, Marcel Dekker, New York, 375–421.
46. Lawrence, M.J: Surfactant systems: microemulsions and vesicles as vehicles for drug delivery, Eur. J. Drug Metab. Pharmacokinet. 3, 257-269.
47. Lawrence, M.J: Microemulsions as drug delivery vehicles, Curr. Opin. Colloid Interface Sci. 1, 826–832.
48. Vyas, S.P., Khar, R.K: Submicron emulsions in targeted and controlled drug delivery, Novel Carrier Systems; CBS Publishers and Distributors, New Delhi, 2002; 282 – 302.
49. Prapaporn Boonme et al., Mahidol University, Bangkok: Characterization of Microemulsion Structures in the Pseudoternary Phase Diagram of Isopropyl Palmitate/Water/Brij 97:1-Butanol. Published: May 12, 2006
50. Corswant, V.C., Thoren, P., Engstrom, S: Triglyceride – based microemulsion by Intravenous administration of sparingly soluble substances, J .Pharm. Sci., 1998, 87 (2); 200.
51. Ho, H.O., Hsiao, C.C., Sheu, M.T: Preparation of Microemulsions Using Polyglyceryl Fatty acid Esters as Surfactant for the Delivery of Protein Drugs, J.Pharm Sci, 1996, 85 (2) ; 138.
52. Kovarik, J.M., Muller, E.A., Van Bree, J.B., Tetzioff, W., Kutz, K: Reduced Inter and Intra Individual Variability in Cyclosporin Pharmacokinetics From Microemulsion Formulation, J. Pharm. Sci., 1994, 83 (3); 444.
53. Ho, H.O., Huang, M.C., Chen, L.C., Hsia, A., Chen, K.T., Chiang, H.S., Spur, B.W., Wong, P.Y.K., Sheu, M.Y: The percutaneous delivery of prostaglandin E1 and its alkyl esters by microemulsions, Chin. Pharm. J., 1998, 50; 257–266.
54. Schmalfun,U., Neubert, R., Wohlrab, W: Modification of drug penetration into human skin using microemulsions, J. Control. Rel., 1997, 46; 279–285.
55. Dreher, F., Walde, P., Walther, P., Wehrli, E: Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport, J. Control. Rel., 1997, 45; 131–140.
56. Hasse, A., Keipert, S: Development and characterisation of microemulsions for ocular application, Eur. J. Pharm. Biopharm., 1997, 43; -179–183.
57. Malmsten, M: Microemulsions in pharmaceuticals In Handbook of Microemulsion, Science and Technology; Ed : Kumar, P., Mittal, K.L.; Marcel Dekker, Inc., New York, 1999; 755 – 771.
58. Paul, B.K., Moulik, S.P: Uses and Applications of Microemulsions, Current Science, 2001, 80 (8); 990 – 1001.