MICROEMULSIONS

MİKROEMÜLSİYONLAR

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SUMMARY

During the past few years, much attention has been given to the design of new dosage forms that increase the effectiveness of existing drugs. The use of this approach has the potential not only to improve the therapeutic efficacy of a drug but also to allow a reduction in the total dose needed, minimizing toxic side effects.

Some of this activity has focused on the development of microemulsions.

The present article provides a general overview of definition, properties, advantages, preparations, some application areas and recent researches on microemulsions.

Key words : Drug delivery systems, microemulsions

ÖZET

Son yıllarda mevcut etken maddelerin etkisini artıracak yeni dozaj formlarının tasarımına önem verilmeye başlanmıştır. Bu yaklaşımın yararı, sadece etken maddenin terapötik etkisinin artırılması değil, aynı zamanda gerekli total dozun azaltılmasını ve toksik yan etkilerin minimuma indirilmesini sağlamasıdır.

Bu konudaki çalışmaların bir kısmı da mikroemülsiyonlar üzerinde yoğunlaşmaktadır.

Bu makalede mikroemülsiyonların tanımı, özellikleri, avantajları, hazırlanma yöntemleri, bazı uygulama alanları ve bu konuda son yıllarda yapılan araştırmalar özetlenmiştir.

Anahtar kelimeler: İlaç taşıyıcı sistemler, mikroemülsiyonlar

INTRODUCTION

Microemulsions are stable dispersions of one liquid in another in the form of spherical droplets, of which the diameters are in the range of 50 - 1400 A^0 (1 - 27). The average diameter of the droplets is estimated at 300 A^0 (5). They appear to represent a state intermediate between thermodinamically stable solubilized solutions and emulsions, which are relatively unstable (28). Microemulsions have some interesting characteristics that differ them from macroemulsions such as

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transparency, high stability and optical isotropicy as shown in Table 1 (1-6, 11, 12, 15, 19, 22, 24, 25, 35, 37). Transparency is based on the fact that if the diameter of particles in a colloidal system is less than 1/4 of the wavelength of the incident light, the particles will not scatter light thereby resulting in a transparent system **(4).**

Table 1 . Distinctions between macroemulsions and microemulsions (35, 37).

Emulsion type Properties	Macroemulsions	Microemulsions
Appearence	opaque	transparent, translucent (opalescent)
Particle size	>~ 500 nm	≈ 5 -140 nm
Stability	thermodinamically unstable	thermodinamically stable
Formation	need vigorous mixing	form spontaneously
Composition	usually need three components : water, oil, surfactant	usually need four components : water, oil, surfactant, cosurfactant

The pioneering work on microemulsions started in 1943 (2). In 1959, Schulman and Hoar coined the word "microemulsion" for these clear, transparent dispersions (1 - 4, 6). They obtained a microemulsion by first preparing a normal emulsion of soap, water and hydrocarbon and then adding a medium chain alcohol (1, 3).

Today, it is known that microemulsions have four components; water, oil and a surfactant; in combination with a cosurfactant, typically a short or medium chain alcohol (18, 19, 22, 24).

Formation mechanism of microemulsions

The primary surfactant is mainly absorbed at the oil/water interface determines the initial curvature of the dispersed phase (2). The cosurfactant also interacts with oil, water and primer surfactant at the interface to form a mixed duplex film. The cosurfactant appears to act in a dynamic state. Initially it causes a transitory lowering of the interfacial tension necessary during the formation of the dispersion. Secondly, as the cosurfactant distribution reaches equilibrium, it further distributes at the interface to become part of the interfacial film (oil / water / surfactant molecules) with the primary surfactant. At this point, the system can be thermodinamically stable swollen mixed micelle (o/w) or inverse mixed micelle (w/o) system (2, 5).

Such considerations led to the mechanical model shown in Figure 1. This scheme illustrates how the tenants of an interphase can physically interact to effect microemulsification (6). The stress provided by different pressures at the oil and water sides of the interphase causes the absorbed tenants to occupy different areas being determined by the magnitude of $-\gamma_\phi$. Without the stress of these pressures there can be no curvature and hence no emulsion. Only the flat interphase is duplex in nature i. e., has different pressures at each side; curvature makes the final pressures on both sides equal. The direction of curvature depends on the relative value of the original pressures, and whether the system is macro or micro is determined by the magnitude of the pressure gradient Π_G relative to $(\gamma\ o/w)_a$. In accordance with Figure 1, if $\Pi_G > (o/w)_a$, microemulsion will form spontaneously; if $\gamma(0/w)_a > \Pi_G$ work will have to be done on the system to effect macroemulsification.
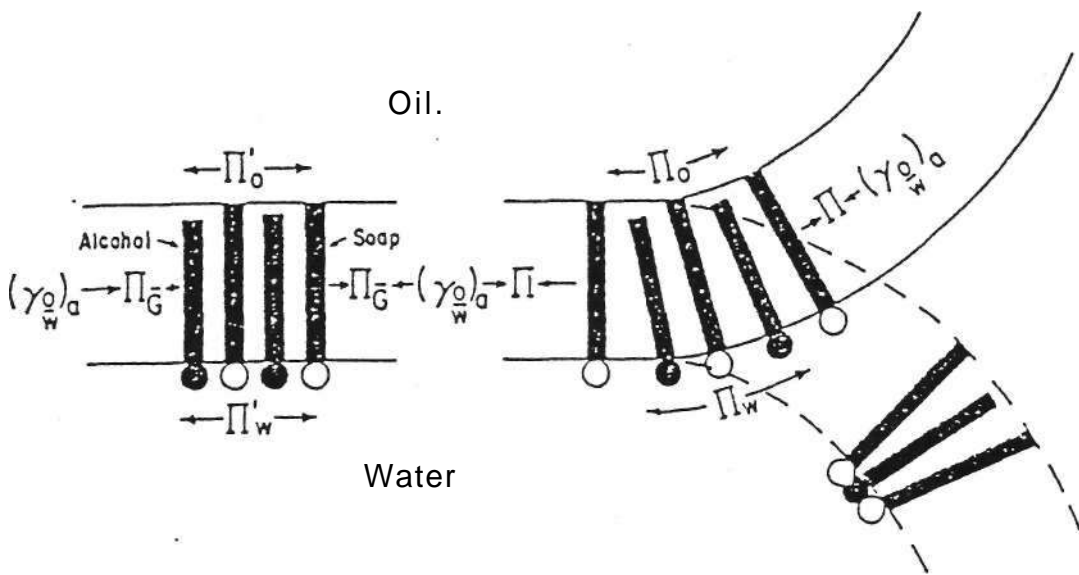

Figure 1. Diagram illustrating the mechanism of curvature of a microemulsion
film. The sum of the pressures at the sides of the flat film is Π_G, and the sum of the pressures at the sides of the curved film is Π. The stress of the pressure gradient due tΠ_O and Π_W is relieved by bending until $\Pi_O = \Pi_W$ or $\Pi = (\gamma\ o/w)_a$ The direction of curvature is determined by the relative magnitudes of Π_O and Π_W.
The degree of curvature is dependent on $\Pi_G \sim (\gamma o/w)a = -\gamma_\phi$ (6).

Advantages of microemulsions

Microemulsions are expected to have a variety of uses in oral and transdermal delivery (7, 17-20, 22, 26, 28-30). Along with the usual advantages of improved drug stability and availability afforded by surfactant solubilization, a microemulsion system has the added advantage of a very small disperse phase diameter and thermodynamic stability (10). Microemulsions can be used to prepare oral dosage forms of drugs whose bioavailability is lowered due to its hydrophobic nature and low aqueous stability and solubility. They can also be used to deliver a combination of drugs of varying lipophilicity in an aesthetically appealing dosage form (3, 10).

There are several other advantages of formulating drugs in microemulsions. For example, a drug administered in microemulsion will be immediately available for absorption and in most cases, is more rapidly and more efficiently absorbed than the same amount of drug administered in a tablet or capsule (3). Microemulsions are therefore ideal for delivery of drugs such as peptids, proteins, steroids, hormones, diuretics and antibiotics (8, 16, 20-22, 29, 31, 38, 39, 40).

Microemulsions can also be used to prepare oral liquid dosage forms of drugs. These dosage forms are easy to administer to children and to people who have difficulty swallowing solid dosage forms (3). Microemulsions have been proposed as liquid membrane carries to transport lipophilic substances through an aqueous medium or inversely to carry hydrophilic substances across a lipoidal medium (36).

Preparation of microemulsions

Once an appropriate microemulsion has been selected from a phase diagram, it can be produced spontaneously simply by blending oil, water, surfactant and cosurfactant with mild agitation (3, 6).The most common surfactants used in o/w or w/o microemulsions are shown in Table 2 (3). The surfactants which have a HLB range of 8 to 18 are used for the formation of o / w and 3 to 6 for the formation of w / o microemulsions respectively (3). The order in which the different components are added to the mixture does not affect the formation of the microemulsion in a properly selected system (1). A water in oil (w/o) microemulsion is generally much easier to produce than oil in water (o/w) microemulsion (3).

Table 2. HLB values of some emulsifiers (3).

Ionic Nature	Emulsifier	Approximate HBL
Nonionic	Propylene glycolmonostearate	3.4
	Triton X-15 ①	3.6
	Glycerylmonostearate ②	3.8
	Pluronic L122 ③	4.0
	Span 80 ②	4.3
	Span 60 ②	4.7
	Span 40 ②	6.5
	Volpo 3 ④	6.6
	Polychol 5 ④	7.3
	Amerchol L-101 ⑤	8.0
	Span 20 ②	8.6
	Triton X-45 ①	10.4
	Methylcellulose	10.5
	Glycerylmonostearate, self-emulsifying ②	11.0
	Solulan 98 ⑤	13.0
	Triton X-100 ①	13.5
	Polychol 20 ④	14.0
	Tween 60 ②	14.9
	Tween 80 ②	15.0
	Pluronic L64 ③	15.0
	Volpo 20 ④	15.4
	Tween 40 ②	15.6
	Tween 20 ②	16.7
	Myrj 52 ②	16.9
	Pluronic F68 ③	17.0
Anionic	Glycerymonostearate, self-emulsifying ②	11.0
	Triethonolamine oleate	12.0
	Trağacanth	13.0
		40.0
Cationic	Atlas G-3570 ②	4.5
	Atlas G-2090 ②	12.5
	Quaternary ammonium compounds	18-20
Amphoteric	Gelatin	10.0

① Rohm and Hass, Philedelphia. Pennsylvania

② ICI America, Wilmington. Delaware

③ BASF-Wyandotte Chemical Corporation. Parsippany. New Jersey

④ Croda. New York, New Yark

⑤ Amerchol Coporation. Edison. New Jersey

Rosano has described a simple four-step procedure for preparing microemulsions (1-3, 6, 11). The four-steps as follows:

* A primary surfactant that is only slightly soluble in the oil phase is selected.

 * Enough amount of this surfactant in the oil phase to yield an o/w microemulsion is dissolved (10-20 %).

* The oil phase, including the primary surfactant, to the water phase is added and stirred.

* The oil and water mixture with a cosurfactant that is more soluble in water than the primary surfactant is titrated to produce a clear o/w microemulsion (11).

On the other hand, Hoar and Schulman suggested the following method to prepare microemulsions (4).

Surfactant, oil and water are mixed together to form a lactecent emulsion and then titrated with the fourth component, the cosurfactant, until the mixture becomes clear. In the case of a w/o system, if more oil is added to the system will become milky again but addition of more cosurfactant will clear the system.

Another recognized and classical approach to microemulsion formulation is to utilize phase diagrams. Friberg and coworkers have been great supporters of this technique (2). A major drawback to this approach is the time it takes to develop the phase diagram, especially when one has a variety of surfactants and cosurfactants and oils at his disposal for use and evaluation.

After the preparation of microemulsions, several physical identification methods can be applied to determine the characteristics of the system such as conductivity, light scattering, optical birefringence, ultracentrifugation, rheology, nuclear magnetic resonance, infrared spectroscopy, low angle x - ray, electron microscopy and photon correlation spectroscopy (3).

Some application areas of microemulsions

Several physiological applications of microemulsions have been reported in the literature (3). Artificial blood composed of fluorocarbon oil in water is a unique example of a system in which microemulsions have an important role. The supply of human blood for transfusion and other medical applications is now faced with new exigencies of biocompatibility and sterility, as well as those inherent in the economics of the collection and storage of samples. Recent concern with AIDS has highlighted the well recognized problem of viral contamination of blood, especially due to the viral hepatitis. Because of these reasons certain fluorocarbon oils in microemulsion form are chosen in order to replace blood. They have the advantages of forming spontaneously, remaining stable for months or years, and have a range of particle sizes which are compatible with blood and being able to store oxygen and releasing it in the presence of carbon dioxide. Any hemolysis case has not been reported in the literature. Such systems could be employed as blood substitutes (32).

A recent work on microemulsions has been done by Halbert and coworkers, who have experimented with the incorporation of lipid soluble antineoplastic agents into a microemulsion. They mixed lipid soluble cytotoxic agents with low density lipoproteins (LDL's) and incorporated them into a microemulsion. LDL's have aroused interest as novel drug carries for cytotoxic agents; they have targetting potential because the dividing cells require large quantities of cholesterol for cell membrane synthesis. When cyctotoxic agents are incorporated into a system with LDL's it is thought that the system will deliver cytotoxin to cancer cells, providing a specific drug delivery system (33).

A different application area of microemulsions is topical delivery systems. Since microemulsions are thermodinamically stable, the properties of the formulation would not be dependent upon process, and the product will not phase - separate, provided temperature and pressure conditions remain reasonably constant. In addition to improved physical stability, microemulsions often function as "super solvents" for certain compounds. Thus, these clear, fluid liquids may drustically increase the solubility / solubilization of poorly soluble drugs but microemulsion compositions must be carefully optimized to achieve maximum percutaneous transport (28).

Another useful application field of microemulsions is cosmetics. In a recent work, Jachowicz and Berthiaume have focused on the performance aspects of the applications of macro and microemulsions in hair care products. Aside from the improved stability benefits, it has been demonstrated that microemulsions are more efficacious and substantive conditioners than macroemulsions. They are able to impart a conditioning effect to hair damaged by oxidative treatments, such as dyeing and bleaching. In addition to this, they can be used as treatments prior to chemical processing because of their high affinity to hair. Even a prolonged exposure to surfactants, solvents and high pH (usually associated with the oxidative formulations) does not completely nullify their ability to soften hair and reduce the combing forces. For semipermanently dyed hair, the application of a silicone microemulsion can significantly reduce color loss due to shampooing (11).

Some recent studies on microemulsions

A recent work which is done by Pattarino and coworkers is about topical drug delivery systems and the effect of the suspended drug in microemulsions. The model drug; azelaic acid, is a naturally occuring straight chained 9-carbon atom saturated dicarboxylic acid, possesses a variety of biological activities and was found to be active in both pigmentary and hyperpigmentary disorders (34). While the oral and systemic uses yield high absorption level of the diacid, the achieved serum level by topical administration is very low. By percutaneous administration the designed therapeutic effects can be obtained only for high concentrations of the drug at the side of the lesion and upon

administration for long periods of time. A viscozied o/w microemulsion has been proposed for the topical delivery of azelaic acid. The administration of this system to patients affected by lentigo maligna gave in 4-6 months complete remission of the disease in all the treated cases (29).

Experiments of azelaic acid transport through hairless mouse skin were performed for microemulsions containing different amounts of the drug, namely; 6.4, 10.0, 15.0 % (microemulsions no. 1,2 and 3 respectively). Azelaic acid in system no 1 was completely dissolved, while in the others (no.2 and 3), it was partly dissolved and partly suspended. It was reported that among the three formulations, the second one which had the azelaic acid partly suspended form gave the best result due to the transport area and the quantity of solid azelaic acid and the results can be seen in Figure 2 (29).
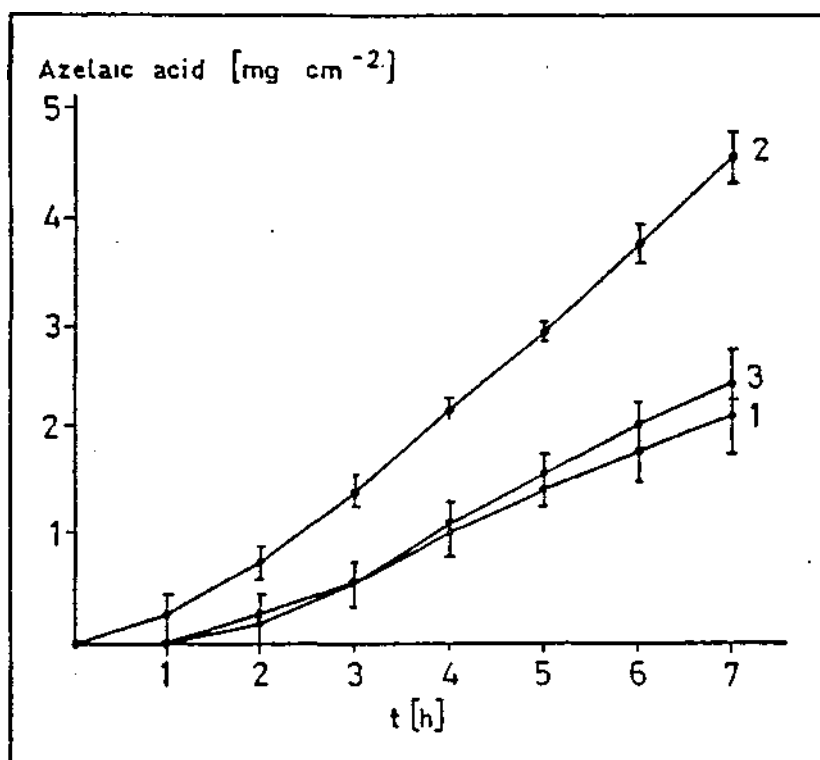

Figure 2 . Amount of azelaic acid transported through
hairless mouse skin from microemulsion no. 1,2 and 3
containing dissolved and / or suspended drug (29).

Another study was done by Trotta and Gasco. They investigated the release of five drugs (Nitrofurazone, phenylbutazone, prednisone, betamethasone and menadione) with different lipophilicities from oil/ water (o/w) microemulsions by determining mass transfer constants of the drugs.

It was indicated that the results of the permeation studies showed only the drug dissolved in the external aqueous phase is able to permeate through the hydrophilic membrane. From the results so far obtained it was concluded that the partition coefficients of a drug between oil, water and cosurfactant can be used to approximate its partition between the continuous and the disperse phase (including the interphase in the disperse phase) of a microemulsion (8).

Another interesting investigation was done by Attwood and coworkers.They examined the phase properties of an oil-in water microemulsion composed of lecithin (Ovothin 200/Epikuron 200-both egg and soya lecithin), n- butanol, isopropyl miristate (IPM) and water. The influence of the ratio of surfactant to cosurfactant on the area of existence of the oil - in - water microemulsion was investigated.

Figure 3 shows the influence of Ovothin 200 / butanol weight ratio on the phase properties. From a formulation viewpoint, it was reported that the increased oil content obtained with the 1: 0.33 ratio may provide a greater opportunity for the solubilization of poorly water-soluble compounds. The authors could not able to form oil - in - water microemulsions with ratios of 1:0.25 presumably because of insufficient cosurfactant to produce adequate lowering of the interfacial tension (15).

Primorac and his colloboraters investigated the rheological properties of o/w type microemulsions. They concluded that if the droplets are spherical, microemulsions exhibit flow properties of Newtonian systems (9).

In another study, that was done by Ritschel and co workers was about peroral absorption of the endekapeptide cyclosporine A. They prepared peroral formulations in the form of capsules and compared them with the commercially available peroral solution and intravenous solution. Among the three experimental capsule formulations, they noted that the one which was based on a microemulsion formulation had absolute and relative bioavailabilty results not different from that of the available peroral solution. They also mentioned the manipulation easiness of capsules rather than the solution (38).

Ritschel and colloboraters were tried to improve the peroral absorption of cyclosporine A by microemulsions. They prepared peroral formulations in the form of microemulsions and compared the bioavailability results aganist the commercially available peroral solution which needs dilution before use and a solution for intravenous administration. They observed an extent and significant

bioavailability increasement in one of the microemulsion formulations when compared with the commercially available peroral solution (39).

In another study, Ritschel investigated the peptide absorption from the gastrointestinal tract (GI tract) when administered in the form of microemulsions as a drug delivery system. The author concluded that the systemic peptide uptake from microemulsion in the GI tract was dependent on the particle size, type of lipid phase of microemulsion, digestability of lipid used, presence of bile salts, lipase, type of surfactants in microemulsion, pH and shedding of enterocyte cells (40).

Samama and colloborators were studied on water-in-oil microemulsions which were containing enzymes (horse liver alcohol dehidrogenase). The results of their study showed that in the anionic microemulsions, the enzyme quickly lost its activity, but it was efficently protected by the coenzyme and some adenine nucleotids. But in the case of cationic microemulsions, they observed that the enzyme activity was much higher than that of anionic microemulsions and with higher alcohols, the enzyme was stable for at least 20 minutes (41).
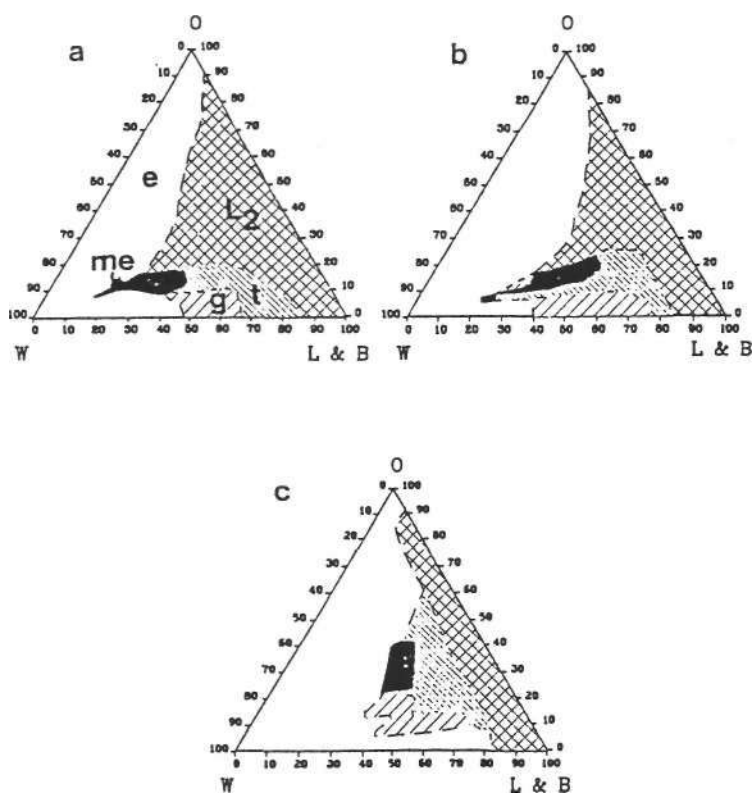

Figure 3: Partial phase diagrams of the system 0 200 / butanol / IPM / water
showing stable oil - in - water microemulsion (me), gel (g), monophasic turbid (t),
unstable emulsion (e) and isotropic (L₂) regions, for 0 200 / butanol weight ratios
(a) 1:0.6, (b) 1: 0.45, (c) 1: 0.33 0, IPM ; W, water ; L and B lecithin + butanol (15).

CONCLUSION

It is really a very hard task to summarize many years of extensive work done in the area of microemulsions. But it can be concluded that microemulsions promise to be excellent drug delivery systems and owing to their high stability, microemulsions ought to be considered as viable alternatives to classical macroemulsions. They offer several benefits for oral, topic and parenteral administration such as increased absorption, improved clinical potency and decreased toxicity.

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