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Dr. Amul Mishra
Department of Pharmaceutics, B.N. Institute of Pharmaceutical Sciences, Udaipur-313002, Rajasthan, India

Ridhi Panola
Department of Pharmaceutics, B.N. Institute of Pharmaceutical Sciences, Udaipur-313002, Rajasthan, India

Dr. A.C. Rana
Director, Institute of Pharmacy, Kruksheta University, Kruksheta-136119, Haryana, India

Correspondence:
Dr. Amul Mishra
Department of Pharmaceutics, B.N. Institute of Pharmaceutical Sciences, Udaipur-313002, Rajasthan, India
Tel: +91 9414738107
E-mail:
amulmishra27@yahoo.co.in

Microemulsions: As drug delivery system

Amul Mishra, Ridhi Panola, A.C. Rana*

Abstract

Microemulsions are excellent candidates as potential drug delivery systems because of their improved drug solubilization, long shelf life, and ease of preparation and administration. The formulation of microemulsion for pharmaceutical use requires a thorough understanding of the properties, uses, and limitations of microemulsion. Three distinct microemulsions – oil external, water external and middle phase can be used for drug delivery, depending upon the type of drug delivery upon the type of drug and the site of action. In this article, Since the term 'microemulsion' was first coined almost fifty years ago to describe clear, isotropic, thermodynamically stable systems composed of oil, water, surfactant and cosurfactant, numerous and varied reports of the applications of microemulsions have appeared in the literature. Reports of the use of microemulsions in separation science began to appear in the literature in the early 1990's when they were first used as mobile phases for HPLC and as carrier electrolytes for CE separations, particularly for pharmaceutical applications.

Keywords: Micelle, Thermodynamics, Co-solvents, Transparent, Coarse.

Introduction

The term "microemulsion" refers to a thermodynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules. A microemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, microemulsions are transparent. The microemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases a cosurfactant or cosolvent is used in addition to the surfactant, the oil phase and the water phase.

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

- Oil in water microemulsions wherein oil droplets are dispersed in the continuos aqueous phase
- Water in oil microemulsions wherein water droplets are dispersed in the continuous oil phase;
- Bi-continuous microemulsions wherein microdomains of oil and water are interdispersed within the system.

In all three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

History

The concept of microemulsion 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 a transparent, stable formulation.[1]

The existence of this theoretical structure was later confirmed by use of various technologies, and we can today adopt the definition given by Attwood: "a microemulsion is a system of water, oil, and amphiphilic compounds (surfactant and co-surfactant) which is a transparent, single optically isotropic, and thermodynamically stable liquid".[2]

Objectives

The overall objective of this thesis was to develop stable salt-containing w/o microemulsions for possible release applications. The specific objectives were:

1. To prepare and optimise w/o microemulsions using combinations of surfactants, organic and aqueous phases and to characterise the resulting microemulsions along two dilution lines within the monophasic region in ternary phase diagrams.

2. To incorporate a model hydrophilic guest molecule (sodium chloride) into the water domains of oil-continuous microemulsions and to characterise these salt containing microemulsions along the two dilution lines within the monophasic region in the developed ternary phase diagrams.

3. To test the efficiency of selected salt-containing microemulsion compositions for salt-release using conductivity and establish the mechanism of release.

Formulation

Microemulsions are colloidal dispersions composed of an oil phase, aqueous phase, surfactant and cosurfactant at appropriate ratios.

Unlike coarse emulsions micronized with external energy microemulsions are based on low interfacial tension. This is achieved by adding a cosurfactant, which leads to spontaneous formation of a thermodynamically stable microemulsion.

The droplet size in the dispersed phase is very small, usually below 140 nm in diameter, which makes the microemulsions transparent liquids.[3] In principle, microemulsions can be used to deliver drugs to the patients via several routes, but the topical application of microemulsions has gained increasing interest.

A unique attempt was made[4] 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.

The surfactants used to stabilise such systems may be:

(i) Non-ionic
(ii) Zwitterionic
(iii) Cationic
(iv) Anionic surfactants

A combinations of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the microemulsion region.

i. Non-ionics include polyoxyethylene surfactants such as Brij 35 (C12E35) or a sugar esters such as sorbitan monooleate (Span 80). Phospholipids are a notable.

ii. Zwitterionic 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.[5-8]

iii. Cationic surfactants: Quaternary ammonium alkyl salts form with hexadecyltrimethyl ammonium bromide (CTAB), and the twin-tailed surfactant didodcecylammonium bromide (DDAB) are amongst the most well known.

iv. Anionic surfactan: The most widely studied is probably sodium bis-2-ethylhexylsulphosuccinate (AOT) which is twin-tailed and is a particularly effective stabiliser of w/o microemulsions.[9]

Attempts have been made to rationalise surfactant behaviour in terms of the hydrophile–lipophile balance (HLB) [10], as well as the critical packing parameter (CPP).[11,12] 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

favoured 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 cosurfactant 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.

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.[13-17] Medium chain length alcohols which are commonly added as cosurfactants, have the effect of further reducing the interfacial tension, whilst increasing the fluidity of the interface thereby increasing the entropy of the system.[14, 15] Medium chain length alcohols also increase the mobility of the hydrocarbon tail and also allow greater penetration of the oil into this region.

Various pharmaceutically acceptable excipients available that can be used in microemulsion formulation are:

Long chain or high molecular weight (>1000) surfactants include:

Gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, microcrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidene (PVP).

The low molecular weight (<1000) surfactants include Stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, and sorbitan esters.

Preparation of Microemulsion

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 a cosurfactant is then added at slow rate with gradual 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 shall be determined with the help of pseudo-ternary phase diagram. Ultrasonicator can finally be used so to achieve the desired size range for dispersed globules. It is then be 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 shall be 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 shall be considered as biphasic. In case monophasic, clear and transparent mixtures are visualized after stirring, the samples shall be marked as points in the phase diagram. The area covered by these points is considered as the microemulsion region of existence.

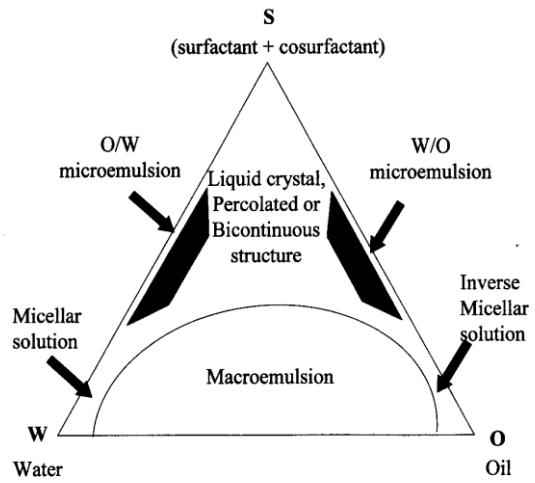


Figure 1: Hypothetical phase regions of microemulsion system of oil (O), water (W), and surfactant + cosurfactant (S)

Characterization of Microemulsion

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

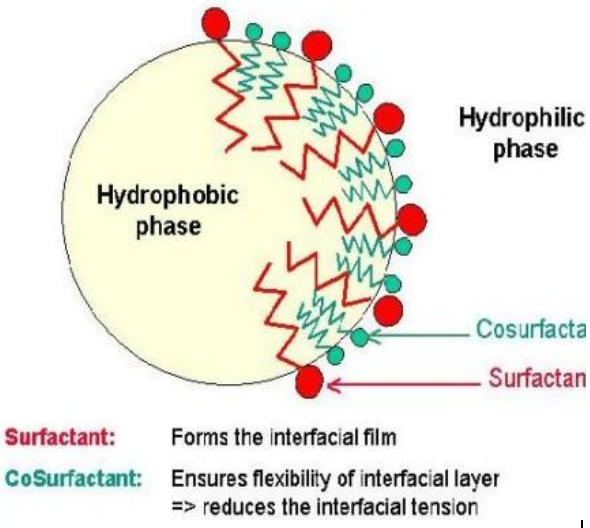
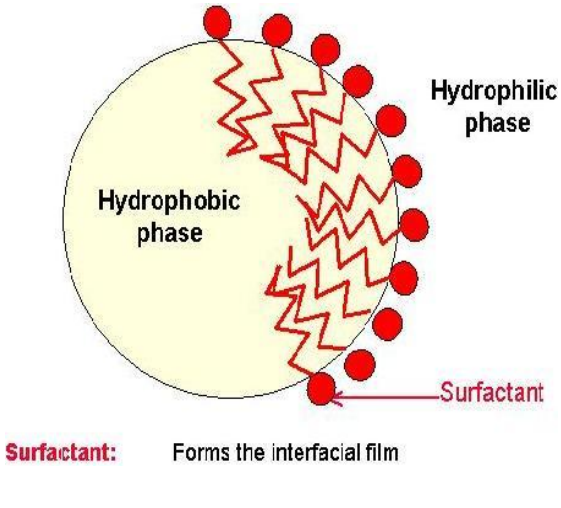
The droplet size distribution of microemulsion vesicles can be determined by either light scattering technique or electron microscopy. This technique has been advocated as the best method for predicting microemulsion stability.

Advantages of Microemulsion over other dosage forms:

- Increase the rate of absorption
- Eliminates variability in absorption
- Helps solublize lipophilic drug
- Provides a aqueous dosage form for water insoluble drugs
- Increases bioavailability
- Various routes like tropical, oral and intravenous can be used to deliver the product
- Rapid and efficient penetration of the drug moiety
- Helpful in taste masking
- Provides protection from hydrolysis and oxidation as drug in oil phase in O/W microemulsion is not exposed to attack by water and air.
- Liquid dosage form increases patient compliance.
- Less amount of energy requirement.

The key difference between emulsions and microemulsions[18]

Table 1: Key difference between emulsions and microemulsions

	
1. Emulsions consist of roughly spherical droplets of one phase dispersed into the other.	1. They constantly evolve between various structures ranging from droplet like swollen micelles to bicontinuous structure.
2.Droplet diameter: 1 – 20 mm.	2.10 – 100 nm.
3. Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	3. Microemulsions are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light, they scatter little light.
4 .Ordinary emulsion droplets, however small exist as individual entities until coalesance or Ostwald ripening occurs.	4. Microemulsion droplet may disappear within a fraction of a second whilst another droplet forms spontaneously elsewhere in the system.
5. They may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy. They are kinetically stable thermodynamically unstable.	5. More thermodynamically stable than macro emulsions and can have essentially infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
6. They are lyophobic.	6. They are on the borderline between lyophobic and lyophilic colloids.
7. Require intense agitation for their formation.	7. Generally obtained by gentle mixing of ingredients.

Microemulsion as drug carrier system and method of drug delivery system

Microemulsion as drug carrier system

Some of the important properties of microemulsions are that they improve therapeutic efficacy of the drug and allow reduction in the volume of the drug delivery vehicle, thus minimizing toxic side effects. The presence of surfactant raises the permeability of the cell membrane, which allows for easier absorption. In some cases, the capacity of the cell membrane to solubilize large amounts of lipophilic drugs at the same time can be advantages as well.

In addition to these advantages, microemulsions are expected to be administering to children and adults who have difficulty swallowing solid doses forms. They also offer several benefits for oral administration, including increased absorption, improved clinical potency, and decreased toxicity. Therefore, microemulsions have been reported to be ideal for oral delivery of drugs such as steroids, hormones, diuretics, and antibiotics.

Some factors limit the use of microemulsion in pharmaceutical applications. The need for pharmaceutically acceptable ingredients limits the choice of microemulsion components (e.g., oil, surfactant, and cosurfactant), leading to difficulties in formation.[19]

Method of drug delivery system

The use of microemulsions as drug delivery vehicle has been an exciting and attractive area of research because of its many potential and extraordinary benefits. Microemulsions offer an interesting and potentially quite powerful alternative carrier system for drug delivery because of their high solubilization capacity, transparency, thermodynamic stability, ease of preparation, and high diffusion and absorption rates when compared to solvent without the surfactant system. The oral efficacy of microemulsion has already been proved by cyclosporine formulation (Neoral), but apart from oral route, microemulsions for other routes like dermal, transdermal, ocular, vaginal, rectal, buccal, periodontal, parenteral, and nasal delivery routes have also been developed. The present review focuses on various applications of microemulsions through different above mentioned routes and also gives idea about new application of micro emulsion as oral solid dosage form, as microreactors and as blood substitute.[20]

Topical drug delivery

Topical drug delivery Microemulsions may enhance transdermal drug delivery primarily by the following effects: Micro emulsions can exhibit a high solubilization capacity for both lipophilic and hydrophilic drugs, thus more drug can be loaded into the microemulsion, which increases the concentration gradient across the skin without depletion. The reservoir effect of the internal phase maintains a constant driving force of drug from the external phase to the skin and prolongs absorption. Since the diffusion of the drug into the skin only occurs from the external phase of the micro emulsion, the internal phase continually supplies drug to the external phase so that it remains saturated with the drug.[21]

Applications of Topical Microemulsions

Microemulsions are promising delivery systems that allow sustained or controlled drug release for percutaneous, peroral, topical, and transdermal, 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 application of topical micro emulsions.-

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 or 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 between conventional dosage forms. .

Antiviral

A study was done to investigate and evaluate microemulsion and microemulsion-based hydrogel as a topical delivery system for penciclovir in comparison with a commercial cream.

Acyclovir containing microemulsion-based formulations for topical delivery were developed using isopropyl myristate/Captex 355/Labrafac as an oil phase, Tween 20

as surfactant , Span 20 as cosurfactant , and water dimethylsulfoxide (1:3) as an aqueous phase.

Anti acne

Novel drug delivery strategies like microemulsions can play a pivotal role in improving the topical delivery of antiacne agents by enhancing their dermal localization with a 25 concomitant reduction in their side effects .Micro emulsions of azelaic acid, a bioactive molecule used in many skin disorders, prepared using the monosodium salt (AZA-Na) have been evaluated as delivery vehicles.

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 photoprotective effects by reducing the number of sunburn cells; UV B induced damage and inhibiting photocarcinogenesis. 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.[22]

Ocular drug delivery

"Ophthalmic drug delivery is one of the most interesting and challenging endeavours facing the pharmaceutical scientist. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. The primitive ophthalmic solutions, suspensions and ointment dosage forms are clearly no longer sufficient to combat some present virulent diseases." Eye is a unique and very valuable organ. This is considered a window hinge. We can enjoy it and look at the world body. There are many eye diseases that can affect the body and loss of vision as well. Therefore, many eyes in drug delivery systems are available. They are classified as traditional and new drug development system. Topical application of drugs to the eye is the most popular and well-accepted route of administration for the treatment of various eye disorders. The bioavailability of ophthalmic drugs is, however, very poor due to efficient protective mechanisms of the eye. Blinking, baseline and reflex lachrymation, and drainage remove rapidly foreign substances, including drugs, from the surface of the eye. Newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, intophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner.[23]

Self emulsifying drug delivery system

Self emulsifying system has gained exposure of their ability to increase solubility and bio availability of poorly soluble drug. SEDDS are isotropic mixture of oil, surfactant and co-solvent. SEDDS produce fine oil in water emulsion when introduced in aqueous media under gentle agitation.

There are two type of SELF system:

Self emulsifying drug delivery system [SEDDS]

Self micro-emulsifying drug delivery system [SMEDDS][24]

Parenteral drug delivery

Parenteral Drug Delivery Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem extremely low amount of drug actually delivered to a targeted site. Microemulsion formulations have distinct advantages over macro emulsion systems when delivered parenterally because of the fine particle micro emulsion 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 micro emulsion can be used for Parenteral delivery.

O/W as the carrier for lipophilic drug -IV, IM and SC. o/w emulsion as a vector for FC, Ca antagonist, steroids. The targeting potential of O/W ME containing lipophilic drug to RE system. Higher PC better will target of drug. W/O ME –hydrophilic drug prolong the release of drug by SC and IM.[25]

Research work on microemulsions

During the last one decay much research work has been done on microemulsions for various routes of drug administration. Due to their unique properties namely, ultraflow interfacial tension, large interfacial area, thermodynamic stability and the ability to solubilize otherwise immiscible liquids. Research work on microemulsions is summarized in Table 2.[26]

Table 2: Research Work carried out on Microemulsions

Drug Name	Route	Purpose/Result
Flurbiprofen	Parenteral	Increased the solubility
Apormorphine HCL	Transdermal	Increased the permeability
Ketoprofen	Transdermal	Enhancement of permeability
Prilocainne-HCL	Transdermal	Increased the solubility
Estradiol	Transdermal	Improvement in solubilization
Aceclofenac	Dermatological	Increased the solubility
Piroxicam	Oral	Increased the solubility
Diclofenac	Transdermal	Permeability enhancement
Dexamethasone	Topical Ocular	Enhanced the Bioavailability
Chloramphenicol	Ocular	Increased the solubility
Ibuprofen	Parenteral	Increased the solubility
Sumatriptan	Intranasal	Enhanced the Bioavailability
Ibuprofen	Topical	Increasing the solubility
Doxorubicin	-	Increasing the Stability
Itraconazole	Parenteral	For better absorption
Timolol	Ophthalmic	For better absorption
Terbinafine	Transdermal	Permeability enhancement
Fenofibrate	Self-Micro emulsifying	Increasing the solubility
Progesterone	Dermal	Increased the chemical Stability

Conclusion

Microemulsions are optically isotropic and thermodynamically stable liquid solutions of oil, water and amphiphile. Microemulsions are readily distinguished from normal emulsions by their transparency, low viscosity and more fundamentally their thermodynamic stability. Drug delivery through microemulsions is a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability and for drug targeting to various sites in the body.

To 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 behaviour of microemulsions that needs to be performed before they can live up to their potential as multipurpose drug delivery vehicles.

This lack of research in the field does not mean that that microemulsions offer any less potential as delivery systems than liposome's, indeed it is pertinent to note that it took considerably less time for a microemulsion product to get onto the market than the first liposomal drug delivery system.

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