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MICROEMULSIONS AS A NOVEL DRUG DELIVERY SYSTEM: A COMPREHENSIVE REVIEW

***Pawan Kumari, Kapil Kumar, Aparna Joshi, Dipti Khairiya and Deepak Teotia**

Department of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Kashipur- 244713, Uttarakhand, India.

Corresponding Author: Pawan Kumari
Department of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Kashipur- 244713, Uttarakhand, India.

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ABSTRACT

Microemulsions are appear as novel vehicles for drug delivery system, microemulsions are clear, stable, isotropic mixtures of oil, water and surfactants, and in combination with co-surfactants. Microemulsions are ore, topical and parenteral administration. Microemulsions are thermodynamically stable. Microemulsions are clear, thermodynamically 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. In this review article different aspects of microemulsions are discussed that will be helpful for many researchers for their work.

KEYWORDS: Co-surfactants, Microemulsion, Surfactants, Thermodynamically stable.

INTRODUCTION

In formulation and development of novel drug delivery system with the nature of enhancing the effectiveness of existing drug is an ongoing process in pharmaceutical research. Microemulsions are clear, stable isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a co-surfactant. The aqueous phase may contain salt (s) and other ingredients, and an "oil" may actually be a complex mixture of hydrocarbons and olefins. The two types of microemulsions are direct (oil dispersed in water o/w) & reversed (water dispersed in oil, w/o).[1-5]

Various techniques have been published in the scientific literature to enhance the dissolution profile and also the absorption efficiency and bioavailability of water-insoluble and liquid lipoptilic drugs.[6-10]

- Reduction of partical size via micro-nization.
- Co-grinding
- Adsorption on porous structures
- Solid dispersion
- Self-emulsification
- Microencapsulation

1. Structure of Microemulsion

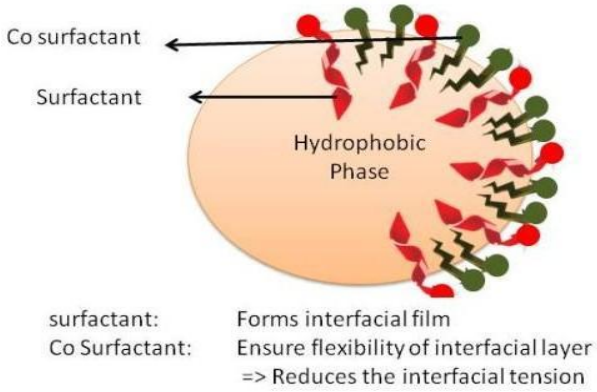

Figure 1: Microemulsion Structure.

Microemulsions or Micellar emulsion are dynamic system in which the interface is continuously and spontaneously fluctuating.[11-13] Structurally, they are divided in to oil in water (o/w), water in oil (w/o) and bi-continuous microemulsions. In w/o microemulsions, water droplets are dispersed in the continuous oil phase while o/w microemulsions are formed when oil droplets are dispersed in the continuous aqueous phase. In system where the amounts of water and oil are similar, the bi-continuous microemulsions may result.[14-18] The mixture oil water and surfactants are able to form a wide variety of structure and phase depending upon the proportions of component.

2. Advantages of Microemulsion Based Systems[19,20]

Microemulsions exhibit several advantages as a drug delivery system

- Microemulsions are thermodynamically stable systems and allows self-medications of this system.
- Microemulsions are both solvebilised in hydrophilic and lipophilic drugs.
- 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 hydrophilic or lipophilic drugs.
- Microemulsions have low viscosity compared to, primary and multiple emulsions.

3. Disadvantages of Microemulsions Based Systems[21,22]

1. Require large amount of S/Cs for stabilizing droplets.
2. The surfactant should be nontoxic for use in pharmaceutical applications.
3. Microemulsion stability is influenced by environmental parameters such as temperature and pH.

4. Limitations[23,24]

Factors which limit the use of microemulsion in pharmaceutical applications

- The concentration of surfactants and co-surfactants used must be kept low for toxicological reasons.
- Microemulsion also suffers from limitations of phase separation.
- For intravenous use, the demand of toxicity on the formulation is rigorous and very few studies have been reported so far.

5. Types of Microemulsion[25,26]

Microemulsions are thermodynamically stable, but are only found under carefully defined conditions. According to Winsor, there are four types of microemulsion.

6.1. Oil-in-water microemulsion or winsor I.
6.2. Water-in-oil microemulsion or winsor II.
6.3. Biocontinuous microemulsion or winsor III.
6.4. Single phase homogeneous mixture or winsor IV.

Winsor I: With two phases the lower with two phases, the lower (o/w) microemulsion phases in equilibrium with the upper excess oil.

Winsor II: With two phases, the upper microemulsion phase (w/o) microemulsion phases in equilibrium with lower excess water.

Winsor III: With three phases, middle microemulsion phase (o/w plus w/o, called bi-continuous) in equilibrium with upper excess oil and lower excess water.

Winsor IV: In single phase, with oil, water and surfactant homogenously mixed.

6. Methods of preparation of Microemulsion[27,28]

Two different methods are utilized to prepared microemulsion.

7.1. Phase Titration Method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method). Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depend on the chemical composition and concentration of each component.) The region can be separated into w/o or o/w microemulsion by simply considering the composition it is oil rich or water rich.[29]

7.2.2 Phase Inversion Method

Phase inversion of microemulsion method, physical changes can occur, also changes in particle size, these can be ultimately affected drug release in in-vitro and in-vivo for non ionic surfactants can be accomplish by the changing the temperature of the system, in these processes an o/w microemulsion at low temperature changes to w/o microemulsion. This is also called as transitional phase inversion method. During the cooling, the system cross the zero-point spontaneous shape and maintaining the surface tension, and increasing the formation of oil droplet dispersion.[30]

In this phase inversion method, transition in the radius can be occur by changing in the water volume fraction. Water volume fraction can be increased, surfactants from stabilizing a w/o microemuslion to an o/w microemulsion using temperature.

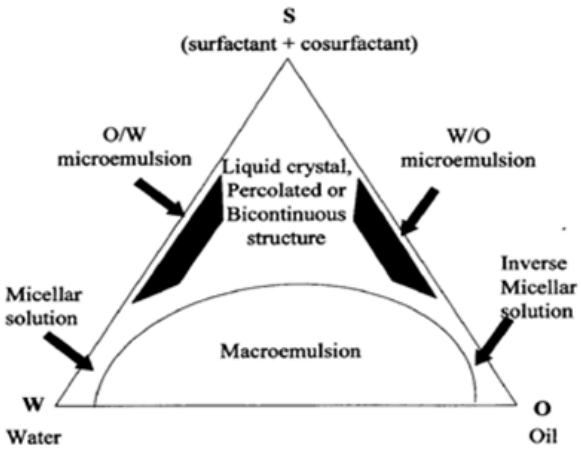

Figure 2: Hypothetical phase regions of microemulsion system of oil (O), water (W), and surfactant + cosurfactant (S).

7. Evaluation of Microemulsion.[31,32,33]

- Visual Inspection
- Thermodynamic stability
- Measurement of p^H
- Viscosity measurements
- Zeta potential determination
- Particle size determination
- Drug content estimation

- **Visual Inspection**

Visual inspection was made after each addition of water to the oil and surfactant and co-surfactant mixture. The samples were identified as microemulsion, emulsion or gel formation by visual observation.

- **Thermodynamic stability**

To overcome the problem of metastable formulation, thermo-dynamic stability tests were performed.

a) Centrifugation

The formulation was centrifuged at 3500 rpm for 30 min to ensure physical stability.

b) Stress test

These tests were done to optimize the best microemulsion formulation under extreme conditions. Stress was carried out at 4 °C and 45 °C for 48 h each for a period of six cycles, followed by 25 °C and 21 °C for 48 h for about three cycles. The samples were checked for coalescence, cracking or phase separation.

- **Measurement of p^H**

The pH values of the optimized formulation were measured by immersing the electrode directly into the dispersion using a calibrated pH meter (Digital Potentiometer Model EQ-601 Equip-Tronics).

- **Viscosity measurements**

The viscosity of the optimized formulation was determined as such without dilution using Brookfield Viscometer (DV-E Brookfield Viscometer Model-LVDVE).

- **Zeta potential determination**

Zeta potential of samples was measured by Zeta sizer. Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with methanol and rinsed using the sample to be measured before each experiment.

- **Particle size determination**

The mean particle size and particle size distribution of drug loaded microemulsion were determined by Horiba SZ-100 nanoparticle analyzer, at 28°C. It measures the fluctuation of the intensity of the scattered light which is caused by particle movement. Each sample was measured in triplicate.

- **Drug content estimation**

Microemulsion containing 100 mg drug was dissolved in 100 ml 0.1N HCl taken in volumetric flask. Then the solvent was filtered, 1 ml was taken in 50 ml volumetric solution and diluted up to the mark with 0.1N HCl and analyzed spectrometrically at 295 nm. The concentration of drug in mg/ml was obtained by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each formulation batch.

8. Marketed formulation of Microemulsion

Ascabiol emulsion, Noreva Sebodiane DS, Winsor ointment etc.

9. Application of Microemulsion

These are some applications of microemulsions in delivery of drug.

During the last two decades, microemulsions are used as drug delivery system, they are offer the advantages like thermodynamic stability, optical clarity, easy of penetration.

Parenteral Delivery

The formulation of parenteral dosage form of lipophilic and hydrophilic drugs has proven to be difficult. The formulation of w/o microemulsions are beneficial in the parenteral delivery of sparingly soluble drugs where the administration of suspensions is not required. For frequent administration of drugs requires high concentration. They are existing the higher physical stability in plasma than liposomes or other vehicles and the internal oil phase is more resistant against drug leaching. Several sparingly soluble drugs have been formulated in to o/w microemulsions for parenteral delivery. Von Corsewant and Thoren was taken the alternate approach in which C3- C4 alcohols were replaced with parenterally acceptable co- surfactants, poly ethylene glycol (400)/ poly ethanol glycol (600) 12-hydroxy stearate/ ethanol will maintaining a flexible surfactant film, these are forming the spontaneous curvature near zero, in the microemulsions obtaining the almost balanced middle phase.[34]

Oral Delivery

The development of effective oral delivery systems has been challenging because drug efficiency can be restricted by instability or poor solubility in gastrointestinal fluid. The solubilization of poorly soluble drugs (particularly BCS class II/class IV) are enhanced by the microemulsions. Also overcome the dissolution related bioavailability problems. The presence of polar, non-polar and interfacial domains, hydrophilic drugs are encapsulated with varying solubility of macromolecules. These systems have been protecting the incorporated drugs agonist oxidation, enzymatic degradation and enhance membrane permeability. Commercially available microemulsions for formulation of oral delivery are Sandimmune Neoral® (Cyclosporine A), Fortovase® (Saquinavir), Norvir® (Ritonavir) etc. Improving the oral bioavailability of poorly water-soluble drugs can be enhanced their solubility in gastrointestinal fluids are potential useful in the formulation of microemulsions.[35]

Topical Delivery

Topical administration of drugs having the advantages like avoidance of hepatic first-pass metabolism of drug and related toxicity effects. These are having the direct delivery and targetability of the drug to affected areas of the skin and eyes. The area of drug penetration into the

skin having the number of studies. In these drug penetration studies they are incorporate both hydrophilic (5-fluroracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, methotrexate) and lipophilic drugs (oestradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide) and enhance their penetration. In the formulation of microemulsions requires high surfactant concentration. Skin irritating aspects must be considered specially when they are intended to be applied for a long period.[36]

Nasal Delivery

Recently, microemulsions are being studied as a delivery system to enhance uptake of drug through nasal mucosa. Mucoadhesive polymers helps in prolonging residence time on the mucosa. Lianly et al. investigating the effect of diazepam on the emergency treatment of status epilepticus. They found that the nasal absorption of diazepam fairly rapid at 2 mg kg-1 dose with maximum drug plasma concentration reached within 2-3 min.[37]

Current and Future Developments

During the last two decades lot of research work has been carried out on microemulsion system **(Table 1, 2)** for providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide reproducible bioavailability. Industrial point of view, it can be easily scaled up with considering relative cost of commercial production. Microemulsion can also be used for cosmetic purpose and drug targeting. Now a day, researcher work is focused on the production of safe, efficient and more compatible microemulsion constituents whichwill further enhance the utility of this novel delivery system.

Table 1: Research work carried out on microemulsions.[38-40]

S. No.	Drug	Category	Route
1.	Fluconazole	Antifungal	Topical
2.	Piroxicam	NSAID	Topical
3.	Acyclovir	Antiviral	Topical
4.	Aceclofenac	NSAID	Percutaneous
5.	Ketorolac tromethamine	NSAID	Topical
6.	Celecoxib	NSAID	Topical
7.	Fluconazole	Antifungal	Topical
8.	Sertaconazole	Antifungal	Topical
9.	Diclofenac Sodium	NSAID	Transdermal
10.	Clotrimazole	Antifungal	Vaginal
11.	Fexofenadine	Antihistamines	Oral
12.	Lorazepam	Antiepileptic	Parenteral
13.	Clopidogrel	Antiplatelet	Oral
14.	Flurbiprofen	Analgesics	Parenteral
15.	Apomorphine Hcl	Antiparkinson	Transdermal
16.	Ketoprofen	Analgesics	Transdermal
17.	Fenofibrate	Antihyperlipidemic	Self micro emulsifying
18.	Estradiol	Anticholesteremic	Transdermal
19.	Timolol	Antihypertensive	Opthalmic
20.	Ibuprofen	Analgesic	Parenteral
21.	Piroxicam	Cyclooxygenase Inhibitors	Oral
22.	Progesterone	Hormones	Dermal
23.	Ibuprofen	Analgesic	Topical
24.	Terbinafine	Antifungal	Transdermal
25.	Amphotericin	Antifungal	Parenteral
26.	Dexamethasone	Glucocorticoids	Topical ocular
27.	Itraconazole	Antifungal	Parenteral
28.	Prilocaine Hcl	Local Anesthetics	Transdermal
29.	Chloramphenicol	Antibacterial	Ocular

Table 2: Microemulsionsbased marketed product.[21,33]

S. No.	Brand name	Composition	Manufactured by
1.	Sandimmune Neoral®	Cyclosporin A	Novartis
2.	Norvir ®	Ritonavir	Roche laboratories
3.	Fortovase ®	Saquinavir	Roche laboratories
4.	White Glow	Mulberry Extract	Lotus Herbals

CONCLUSION

Microemulsions are commercially simple and convenient vehicle for delivery of medicaments which can enhance drug absorption with reduced systemic side effect. They can be used to optimise drug targeting without a concomitant increase in systemic absorption. Appropriate excipients selection and safety evaluation especially of the cosurfactants is crucial in the formulation of microemulsions. They can be potential drug delivery systems for the delivery of more than one medicament simultaneously.

Compliance with ethical standards

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Disclosure of conflict of interest
No conflict of interest is associated.

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