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REVIEW ARTICLE

Microemulsion – A Potential Carrier for Improved Bioavailability

Priyanka Goswami*, Ananta Choudhury, Biplab Kumar Dey

Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences, Assam Down Town University, Guwahati, Assam, India

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ABSTRACT

Microemulsion (ME) are one of the potential and emerging drug carrier systems that help to improve the drug release and enhance the bioavailability of poorly aqueous soluble drugs. These are considered as thermodynamically stable system which mainly consists of three to five components such as aqueous phase, an oil phase, surfactant, cosurfactant, and in some cases electrolyte. Microemulsion became more popular as a drug delivery system, due to some of its unique features such as its capacity to increase the bioavailability, long shelf life and ease of preparation, and huge scope of application. The delivery system is widely used in different filed such as pharmaceutical, food industries, and cosmetics industries. As per literature, around 40% of the newly arrived drug molecules are poorly water-soluble in nature and results in poor bioavailability. Therefore, ME drug delivery system may play a key role to overcome the mentioned issue. Hence, the review has been written with an aim to address the capacity of ME drug delivery system to overcome the solubility issue of poor water-insoluble drugs and to provide adequate information's about its possible application.

Keywords: Amphiphile, application, evaluation of microemulsion, formulation of microemulsion, microemulsion

INTRODUCTION

The history of drug development and design of dosage form reflect the fact that the design of suitable dosage form plays an important role and enhances the bioavailability of the drug. Selection of a suitable dosage form is very important as dosage form with poor drug delivery capacity can make an efficient drug into an insignificant performer. Literature states that around 40% of new drug candidate are poorly soluble in water which results in the poor dissolution of the drug after oral administration and leading to poor bioavailability. Thus, the selection of an efficient drug delivery system to deliver the drugs through oral route is always a challenge. However, some researchers have suggested that solubility of poorly soluble drug can be enhanced by microemulsion (ME) formulation. For instance, Patel *et al.* 2010 suggested 80.66-folds enhancement in the solubility of poorly soluble drug clopidogrel compared to that of distilled water.[1] Furthermore, Hu *et al.,* 2011, suggested 1.9-fold increase in bioavailability of ibuprofen in ME when compared to its granule form.[7] Similarly, Ghosh *et al.,* 2006, suggested 12.78 times increase in bioavailability of acyclovir oral ME as compared with the commercially available tablets.[35] Thus, from the above citation, it can be concluded that ME plays an important role in enhancing solubility as well as bioavailability of the poorly soluble drug. However, the need of acceptable ingredient for preparation limits the use of ME at the same time ratio of surfactant and cosurfactant should be kept minimum due to GI irritation and toxicological reason.[14] Many formulation approaches such as nanoparticle, permeation enhancer, and solid dispersion have been utilized to improve the oral bioavailability of the poorly water-soluble drug. In recent time, the lipid-based formulation such as ME, liposomes, and self-microemulsifying formulation has fascinated considerable attention to improve oral bioavailability. Still, the most suitable formulation and their metabolic products are yet worth to be further explored. Some of the approaches to improve oral bioavailability

***Corresponding Author:**
Priyanka Goswami,
E-mail: priyankagoswami2812@gmail.com

are shown in Figure 1. ME due to its solubility of a broad range of drug and thermodynamically stability has turned its attention for their use of a novel vehicle for drug delivery.[2]

The arrival of impulsive ME was introduced by Hoar and Schulman in the year 1943 during the study of emulsion formation with the addition of a surfactant (strong amphiphilic) to oil and water system. In the year 1959, professor Schulman from Columbia University along with his coworker coined the term "ME."[3] However, the definition of ME was given by Danielsson and Lindman in the year 1981[4] as "the transparent, homogenous optically isotropic solution which acquires thermodynamic stability."[5,6] The droplet size of ME ranges from 10 to 100 nm.[7]

The ME can enhance the oral bioavailability due to its aptitude to increase permeability and solubility of the drug in the whole area of gastrointestinal tract. It also enhances the delivery of the drug through dermal transport in case of topical delivery due to its better permeation rate due to the appearance of surfactant and its lipophilicity. Advantages of ME have been highlighted in table.[8]

Depending on the proportion of the constituent, MEs are of three different types, namely: swollen micellar which is also known as oil in water ME, reverse micellar also known as water in oil (w/o) ME, and bicontinuous system.[9] Oil-in-water (o/w) ME is the approach that improves the oral bioavailability and solubility of the hydrophobic drug, whereas w/o emulsion is the approach that sustains the release and enhances the bioavailability of the hydrophilic drug across the intestinal mucosa.[10]

According to Winsor classification, the ME is classified into four classes, namely:

1. Type I or (o/w) ME, this type of ME is formed by solubilizing the surfactant in the water phase.
2. Type II or (w/o) ME, where the surfactant is solubilized in the oil phase to form w/o ME.
3. Type III ME is the formulation, where the surfactant is loaded in the middle phase which combines with both oil phase and the aqueous phase in this formulation both oil phase and aqueous phase are surfactant-deficient as a result it forms three phase ME.
4. Type IV is an extension of type III where at higher concentration of surfactant the middle phase becomes a single phase.[11,12]

The basic difference between emulsion and microemulsion are being cited in Table 1 and the

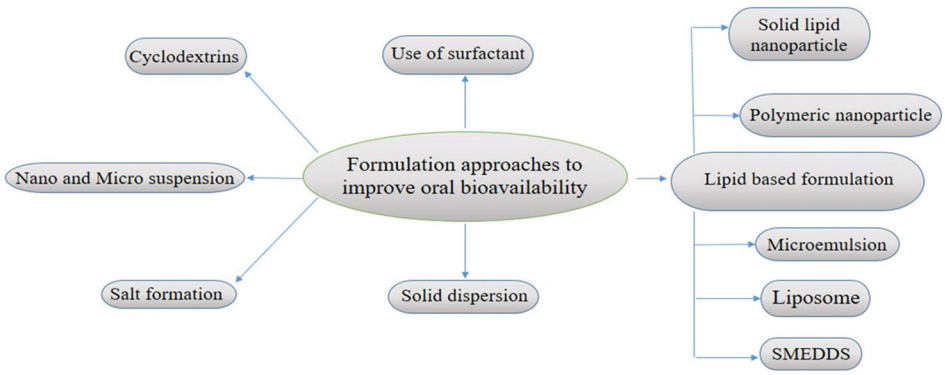

Figure 1: Some of the approaches to enhance the oral bioavailability of the poorly water-soluble drug

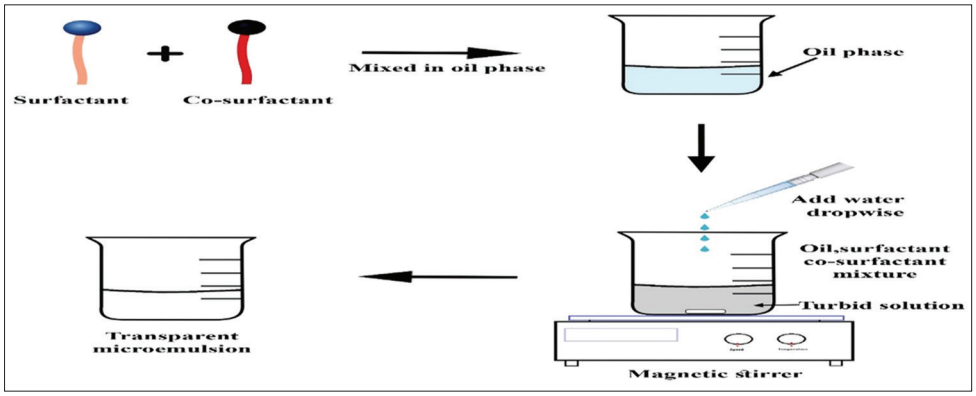

Figure 2: Preparation of microemulsion

advantages and disadvantages are being cited in Table 2.

FACTORS AFFECTING FORMATION AND PHASE BEHAVIOR OF ME[17]

Property of surfactant, oil-phase, and temperature

The concentration of surfactant is one of the factors responsible for phase behavior, as the concentration of surfactant increases the degree of dissociation of polar group decreases; as a result, it forms w/o type of emulsion. However, diluting it with water may increase the dissociation which may result in o/w system. Similarly, the oil phase is also a factor responsible for formation ME, oil phase due to its ability of penetration may influence the curvature which may result in the swelling of the tail group of surfactant. Furthermore, temperature also plays an important role increase in temperature may result in w/o system and the decrease in temperature may result in o/w system whereas at an intermediate temperature where it has an excess amount of oil as well as water a bicontinuous structure is formed.

The chain length, type, and nature of cosurfactant

Addition of short-chain cosurfactant may result in positive curvature; as a result, o/w ME is formed further on the addition of long-chain cosurfactant may result in negative curvature, which may result in w/o ME.

Nature of oil

As the aromaticity of the oil increases, a phase transition occurs from o/w to w/o.

Surfactant hydrophobic chain length

Increase in hydrophobic chain length may result in the formation of o/w–w/o ME through bicontinuous phase.

MATERIALS AND METHODS

A number of oil and surfactant are used as a constituent of microemulsion system, but their unclear mechanism of action, irritation, and toxicity limit the use. The component used for the formulation of ME must be non-toxic, biocompatible, and clinically acceptable. Most commonly used material for ME preparation are as follows:

Oil phase

Oil is an important component in the formulation of ME. In general, short chain, oil perforate the tail group region to a great extent than a long chain which result in the swelling of the tail group and hence increase the negative curvature (minimize the effectual hydrophile/lipophile balance [HLB]). Solubilization of the drug in the oil phase is the main criteria for the selection of drug in ME formulation. In general, lipophilic drug get dissolve in o/w ME. Some examples of the oil phase for the formulation of ME are as follows:

- Saturated fatty acid: Capric acid and myristic acid.
- Unsaturated fatty acid: Linolenic acid.
- Fatty acid ester: Oleic acid and myristic acid.[18,19]

Aqueous phase

Water is the most preferably used aqueous phase in the preparation of ME. However, some researcher also used buffer solution. In the preparation of ME for parenteral use, the aqueous phase should be isoosmotic to blood which can be adjusted with dextrose, sodium chloride, sorbitol, and glycerol.[20]

Surfactant

Surfactant is the combination of a hydrophilic and lipophilic group in a molecule. The percentage weight of these two groups determines the behavior of the surfactant. However, the concentration of surfactant is essential to decrease the interface tension between the oily phase and the aqueous phase.[21] The HLB value of a surfactant is important to visualize the action of surfactant. For instance, if the HLB value is <10 (hydrophobic) would be preferable for w/o ME. However, the HLB value >10 (hydrophilic) is suitable for o/w ME.[22] The surfactant is generally classified into four groups, namely, anionic surfactant, a

Table 1: Basic difference between emulsion and ME[13,14]

Emulsion	ME
The diameter of the droplet is > 500 nm	The diameter of the droplet is 10–100 nm.
Emulsion is turbid	ME is transparent
The emulsion is thermodynamically unstable	The ME is thermodynamically stable
Direct o/w contact at the interface	No direct o/w contact at the interface
An emulsion is obtained by intense agitation for their formation	ME generally requires gentle mixing of ingredients
Emulsion is lyophobic	A ME is a borderline between lyophilic and lyophobic
Emulsion is biphasic	ME is monophasic

o/w: Oil-in-water, w/o: Water-in-oil

cationic surfactant, a non-ionic surfactant, and a Zwitterionic surfactant.

- Anionic surfactant: These are negatively charged surfactant and are the most widely used surfactant which accounts for about 50% of the world production.
- Cationic surfactant: These are positively charged surfactant and are more expensive when compared with an anionic surfactant. Didodecyl ammonium and hexatrimethyl ammonium are the examples of a cationic surfactant.
- Non-ionic surfactant: This is stabilized by dipole and hydrogen bond interaction by hydration layer to its hydrophilic surface. As the hydrophilic group of non-ionic surfactant is non-dissociable type, they do get ionize in aqueous solution. Phenol and alcohol are some of the examples of non-ionic surfactant.
- Zwitterionic: This are both positively charged and negatively charged and they form ME on the addition of cosurfactant. Lecithin is the most commonly used Zwitterionic surfactant.[23]

Cosurfactant

Alcohol is mainly used as cosurfactant. Cosurfactant helps to reduce the interfacial tension between two immiscible phases and increases the fluidity of the interface. Cosurfactant is used to destroy the gel structure and liquid crystalline that is formed in place of ME.[24]

Commonly applied method for the preparation of ME is as follows:

Selection of oil, surfactant, and cosurfactant

Selection of suitable oil, surfactant, and cosurfactant is done on the basis of solubility of drug by shake flask method.[25] Excess quantity of drug was added to 10 ml of various oil, surfactant, and cosurfactant separately and was shaken for 20°C for 24 h and the excess of insoluble drug was discarded by filtration. The concentration of drug is then determined in each oil, surfactant, and cosurfactant using ultraviolet (UV)-spectrophotometer at specific wavelength.[26]

Table 2: Advantage and disadvantage of ME[15,16]

Advantages	Disadvantage
It enhances the solubility of the poorly water-soluble drug, has a long shelf life	A large concentration of surfactant and cosurfactant is necessary to stabilize the droplet of the ME
Easy to prepare and has high diffusion and absorption rates when compared with another solvent system without surfactant	The surfactant should be non-toxic for use in pharmaceutical application
The ME is inexpensive and thermodynamically stable	The stability of the ME is influenced by pharmaceutical parameter
The ME is used as a vehicle for topical, oral, transdermal, and nasal application	Stability of ME is influenced by the environment
ME acts as a penetration enhancer and helps to mask the taste	

Construction of pseudoternary phase diagram

The pseudoternary phase diagram of oil, water, surfactant, and co-surfactant was constructed using the water titration method to determine the concentration and possibility for the preparation of ME. Surfactant and cosurfactant are blended together at a fixed ratio. The mixture of surfactant and cosurfactant (S_{mix}) was then mixed with the oil phase in different ratio. Water is added dropwise with constant stirring with a magnetic stirrer until a homogeneous solution is obtained. Each system was visually observed for transparency. However, no heat is applied during the preparation. The endpoint of the titration was identified when the solution became turbid. The quantity of the aqueous phase required to make the mixture turbid was noted.[27,28] The schematic diagram of pseudo-ternary phase diagram is shown in Figure 2.

Phase titration method

In this method, the appropriate amount of oil and surfactant: cosurfactant mixture is taken in a beaker; it was then mixed with the help of sonication until the surfactant get solubilized and a clear solution is formed. The appropriate amount of drug is then incorporated (amount of drug is determined by solubility study) in the oil and surfactant mixture and dissolved with the help of magnetic stirrer. Later on, the aqueous phase is added dropwise until the system becomes transparent. Thus, the ME is formed.[28,29]

Phase inversion method

Phase inversion of ME means conversion of o/w to w/o or vice versa. Preparation of ME by phase inversion is the result of the addition of excess amount of dispersed phase with response to temperature. This process result is drastic physical change along with particle size which affects the drug both *in vitro* as well as *in vivo*.[30,31]

EVALUATION

Measurement of percentage transmittance

The percentage transmittance of the diluted ME can be measured at a specific wavelength using UV spectrophotometer against continuous phase as blank.[32,33]

Droplet size

Measurement of droplet size may be considered as an important parameter for pharmaceutical dosage form like ME. Formulation with larger droplet size is more susceptible to creaming or aggregation as compared to formulation with smaller droplet size which is more stable. Droplet size of the ME can be determined by diluting the formulation in distilled water at 37°C and mixing it gently with magnetic stir. It may be measured using Malvern Zetasizer at 90° angle and temperature of 25°C.[34,35]

Dilutability

The dilutability study of the formulation is also one of the important parameters to know the type of ME. It can be performed by diluting the sample with a continuous phase at the different ratio for 48 h and checked for any phase separation. The o/w ME is dilutable with water but w/o is not as a result phase separation occur. However, the w/o ME is dilutable with oil only.[36]

Turbidity measurement

Turbidity of the ME can be determined by measuring the absorbance with the help of UV-Spectrophotometer. The value of transparent ME is < 1%. It can be calculated using the following equation: [37]

$$\text{Turbidity \%} = 2.303 \times \text{absorbance/width cuvette (cm)}$$

Measurement of pH

The pH of the formulation is an important parameter as a change in the pH may result in the instability of the formulation. The pH of the product can be measured using a digital pH meter which is calibrated with a standard buffer solution of pH 4 and 7. The measurement of pH is done in triplicate and the average value is calculated.[37,38]

Electrical conductivity

The electro conductivity is utilized to identify the nature of the continuous phase. This can be measured using electro conductometer, which will help to identify whether the ME has oil or water as continuous phase as well as it will identify the phase inversion phenomenon.[39] For conductivity measurement, an electrode pair is attached to a lamp and a power source is attached to the formulation. If the formulation is o/w the water will conduct current and the lamp will glow, if the formulation is w/o lamp will not glow as oil in the external phase does not conduct the current.[40]

Drug content

Drug content of ME can be measured by dissolving a known amount of formulation in a solvent and then placing it in a dark place for 24 h. The absorbance is measured after its suitable dilution at a specific wavelength. The drug content can be determined using the following relationship.[41,42]

$$\text{Drug content} = (\text{experimental drug content/theoretical drug content}) \times 100$$

Viscosity

It is the important parameter which helps to determine the type of the system. If the formulation is low viscous then it is an o/w ME and if the system is more viscous then it is a w/o type of ME. Brookfield viscometer is generally used to determine the viscosity of the ME formulation. The trial is carried out in triplicate manner and a mean viscosity reading is noted.[42-44]

Zeta potential measurement

Zeta potential measurement is analog to surface charge of the ME and is highly dependent on the surfactant used. Zeta potential is used to check the stability of the formulation. It can be measured using Zetasizer nano series equipment which can measure the size between 0.6 and 6000 nm. It is analyzed in triplicate at 25°C and the mean value is calculated.[45,46]

Drug-excipient compatibility study

It is used to determine the compatibility of drug and excipients. Compatibility study of drug and excipient can be measured by Fourier-transform infrared spectrophotometer. In this study, the samples are dried under vacuum to avoid the influence of residual moisture. And then, it was scanned at a specific frequency.[47]

Table 3: Commercially available ME[23]

Composition	Manufactured By	Brand Name
Cyclosporine A	Novartis	Sandimmune Neoral®
Saquinavir	Roche laboratories	Fortovase®
Ritonavir	Roche laboratories	Norvir®
Mulberry extract	Lotus Herbals	White Glow

In vitro drug release

The drug release of the formulation can be carried out using modified Franz diffusion cell in which the receptor compartment is consist of buffer solution and the donor compartment is fixed with the cellophane membrane which consists of the ME formulation. At a specific interval of time, the sample is withdrawn from the receptor compartment and the same amount of fresh solution was added to the receptor compartment. The drug content is checked with the help of UV spectrophotometer at a specific wavelength.[48,49]

Stability test

The stability study of the ME can be performed by long-term stability study and accelerated stability studies. For long-term study, the formulation is kept at three different storage conditions, i.e. room temperature, refrigeration temperature (4–8°C), elevated temperature (50 ± 2°C), and over a period of time it is evaluated. Accelerated studies can be done by centrifugation, freeze/thaw cycle, and heating/cooling for thermodynamic stability of the formulation.[50,51]

Table 4: Patent ME[54-60]

Patent	Inventor	Patent no./patent date	Reference no.
ME and sub-micron emulsion process and compositions (United States Patent)	Maria Graziella Larm, Ronald Harding, Michael Johnston, Albert Zorko Abram, Prema Viyayakumar, Phoebe Sun	US8,962,000 B2/February 24, 2015	54
ME formulation (United States Patent)	Keith R. Rowley, Mark Trimmer, Thomas J. Richard, Clara Leung	US 2007/0078057 A1/April 5, 2007	55
Cyclodextrin-based MEs, and dermatological uses thereof (United States Patent)	Pinaki Ranjan Majhi, Sharon, Mark W. Trumbore	US 2013/0251644 A1/September 26, 2013	56
Miocroemulsions and uses thereof to displace oil in heterogeneous porous media (United States Patent)	Lamia Goual, Tianzhu Qin, Gina Javanbakht, Mohammad Piri	US 2018/0155610 A1/June 7 2018	57
Cleaning composition containing polymer ME (United States Patent)	Claudia E. Britton	US 8,569,218 B2/October 29, 2013	58
Fragrance ME compositions (United States Patent)	Stuart Fraser, Jonathan Warr, Catherine Regniez	US 8.461,099 B2/June 11, 2013	59
Massively parallel on-chip coalescence of ME (United States Patent)	Paul Blainey, Anthony Kulesa, Jared Kehe	US 2018/0071738 A1/March 15, 2018	60

APPLICATION[17,52,53]

- Parenteral: ME is more advantageous due to its small particle size and its longer residence time in the body.
- Oral: Formulation of oral ME has several benefits over conventional oral formulation which include decreased drug toxicity, and increased absorption.
- Topical: Topical administration of the drug has several advantages over another method due to several factors one of which is a direct application of the drug to the target site and avoidance of hepatic first-pass metabolism and its related toxicity.
- Ocular and pulmonary delivery: Delivery of drug through ocular can be done by o/w ME to attain the prolong release profile and increase the absorption.
- Intranasal drug delivery system: Administration of ME formulation through intranasal help in overcoming the first-pass hepatic metabolism of the labile drug.

Some of the commercially available marketed formulation are given in Table 3 however few patent microemulsion formulation are given in Table 4

CONCLUSION

ME may be considered as an innovative technology in the field of Pharmaceutical formulation development. The effective solubilization capacity and easy formulation process make it a versatile drug delivery. It can play a key role to enhance drug targeting with an increased drug concentration in systemic absorption. Extensive researches are being carried out to overcome the existing limitation of ME drug delivery system. Considering the above statements it may be consider as a potent drug delivery system with wide scope of applicability for near future.

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