Microemulsions: A potential novel drug delivery system

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ABSTRACT

Microemulsions are defined as clear, transparent, thermodynamically stable, isotropic mixtures of oil and water, frequently in combination with a co-surfactant. Recently microemulsion formulations are widely used for the delivery of hydrophilic as well as lipophilic drug as drug carriers due to their improved drug solubilisation capacity, long shelf life, ease of preparation and improvement of bioavailability. In this present review, we will discuss about the various advantages of microemulsion in pharmaceuticals, along with its preparation, classification, evaluation parameters and research work carried out on microemulsions.

1. Introduction

The term "microemulsion" refers to a thermodynamically stable, isotropically clear dispersion of two immiscible liquids, such as oil and water, which is stabilized by an interfacial film of surfactant molecules. Surfactant molecules contain both a polar as well as an apolar group. So they exhibit a very peculiar behavior, firstly, they get adsorbed at the interface, where they can fulfill their dual affinity with hydrophilic groups located in aqueous phase and hydrophobic groups in oil or air. Secondly, they reduce mismatching with solvent by Micellization Process [1-5]. The dispersed phase typically comprises of 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. The concept of microemulsion was first introduced by Hoar and Schulman in 1943[1]; 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. The existence of this theoretical structure was later confirmed by use of various technologies, and today we can 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”[6].

1.1 Difference between emulsions and microemulsions

The main difference between emulsions and microemulsions lies in the size and shape of the particles that are dispersed in the continuous phase: these are at least an order of magnitude smaller in the case of microemulsions (10–200 nm) than those of conventional emulsions (1–20 µm). 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. Also, whereas emulsions consist of roughly spherical droplets of one phase dispersed into the other, microemulsions constantly evolve between various structures ranging from droplet-like swollen micelles to bicontinuous structures, making the usual “oil in water” and “water in oil” distinction sometimes irrelevant[7].

1.2 Advantages of microemulsions over other dosage forms[8,9]
Microemulsions are potential drug carrier system for various routes of administration. These are having advantages when compared to the other dosage forms:

- The rate of absorption is increased.
- Eliminates variability in absorption.
- Helps to solubilize lipophilic drugs.
- Provides an aqueous dosage form for water insoluble drugs.
- Increases bioavailability of drug.
- 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.

1.3 Components of microemulsion

The various components of microemulsions are:

**Oil phase**

The selection of oil is based on the nature of the drug as well as the route of administration. The screened oil should have solubilization potential for the drug. The oil influences the curvature and has the capability to swell the tail group of surfactant. Saturated and unsaturated fatty acids have penetration enhancing activity of their own. The fatty acids increase the permeability by disrupting densely packed lipids and filled up in extracellular spaces of stratum corneum. Amongst unsaturated fatty acids, oleic acid is an effective skin penetration enhancer. Also penetrating effect of fatty acids is selective of individual drug. Out of fatty acid esters, isopropyl palmitate is popular.

Recent trend is towards use of semisynthetic oils that are more stable than their natural counterparts. Poorly aqueous soluble drugs need to have solubility in dispersed oil phase to form efficient o/w microemulsion system. Even with increase in oil content in o/w microemulsions leads to increase in droplet size[8].

**Surfactant**

Surfactants are the molecules which when present in low concentration will adsorb to the surface of interfaces of a system and alter the interfacial energies of the system. The interfacial energy is the work required to create unit area of an interface. The actual purpose of surfactant is to lower the interfacial tension to negligible value that facilitates the process of dispersion during preparation of microemulsion. It presents the microemulsion with pertinent lipophilic character to furnish accurate curvature. This adsorption behavior can be attributed to solvent nature and to the chemical nature of surfactant that combines both polar and non-polar group in a single molecule. Due to their dual nature these amphiphiles “sit” at interfaces so that their hydrophobic moiety is repelled from strong solvent interactions. Surfactant screening can be done with help of HLB (Hydrophilic lipophilic balance) value. The HLB provides a numerical value that suggests whether o/w or w/o emulsion will form. It relates molecular structure to interfacial packing and film curvature[9,10].

<table>
<thead>
<tr>
<th>HLB Value</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3.5</td>
<td>Antifoams</td>
</tr>
<tr>
<td>3.5-8</td>
<td>Water in oil emulsion</td>
</tr>
<tr>
<td>7-9</td>
<td>Wetting and spreading agents</td>
</tr>
<tr>
<td>8-16</td>
<td>Oil in water emulsions</td>
</tr>
<tr>
<td>13-16</td>
<td>Detergents</td>
</tr>
<tr>
<td>15-40</td>
<td>Solubilizers</td>
</tr>
</tbody>
</table>

**Co-surfactants**

In most of the cases, single chain surfactants alone are incapable to reduce o/w interfacial tension sufficiently to form microemulsion. Owing to its amphiphilic nature, a co-surfactant accumulates substantially at interfacial layer, increasing the fluidity of interfacial film by penetrating into surfactant layer. Short to medium chain length alcohols are generally added as co-surfactants helping in to increase the fluidity of interface[12]. Amongst short chain alkanols, ethanol is widely used as permeation enhancer. In medium chain alcohols 1-butanol was reported to be most effective enhancer. The surfactant and co-surfactant ratio is a key factor for phase properties.

**Aqueous phase**

Water is most commonly used as aqueous phase. The pH of aqueous phase always needs to be adjusted due to its considerable impact on phase behavior of microemulsions[12,13]. As in case of microemulsions used for parenteral administration aqueous phase should be isoosmotic to blood which is adjusted by sodium chloride, glycerol, dextrose and sorbitol.

2. Classification of microemulsion

Three types of microemulsions are most likely to be formed depending on the composition:
i. **Oil in water microemulsions** wherein oil droplets are dispersed in the continuous aqueous phase.

ii. **Water in oil microemulsions** wherein water droplets are dispersed in the continuous oil phase.

iii. **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.

### 3. Winsor classification of microemulsions

Four different types of situations may arise by mixing oil, water, amphiphiles as shown by Winsor[14,15].

**Type – I System**

It consists of O/W microemulsions in equilibrium with excess oil phase. The surfactant is preferentially soluble in water and oil-in-water (O/W) microemulsions form (Winsor I). The surfactant-rich water phase coexists with the oil phase where surfactant is only present as monomers at small concentration.

**Type – II**

It consists of W/O microemulsions in equilibrium with excess water phase. The surfactant is mainly in the oil phase and water-in-oil (W/O) microemulsions form. The surfactant-rich oil phase coexists with the surfactant-poor aqueous phase (Winsor II).

**Type – III**

It consists of microemulsion phase in equilibrium with both excess water and excess oil phase. A three-phase system where a surfactant-rich middle-phase coexists with both excess water and oil surfactant-poor phases (Winsor III or middle-phase microemulsion).

**Type – IV**

A single-phase (isotropic) micellar solution, that forms upon addition of a sufficient quantity of amphiphile (surfactant plus alcohol).

### 4. Theories of microemulsion formation

Historically, three approaches have been used to explain microemulsion formation and stability. They are as follows-

i. Interfacial or mixed film theories.

ii. Solubilization theories.

iii. Thermodynamic treatments.

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 change in entropy of the system such that,

$$G_f = \gamma a - T S$$

Where, $G_f =$ free energy of formation

$A =$ change in interfacial area of microemulsion

$S =$ change in entropy of the system

$T =$ temperature

$\gamma =$ surface tension of oil-water interphase

It should be noted that when a microemulsion is formed the change in $A$ is very large due to the large number of very small droplets formed. In order for a microemulsion to be formed (transient) negative value of was required, it is recognized that while value of is positive at all times, it is very small and it is offset by the entropic component. The dominant favorable entropic contribution is very large dispersion entropy arising from the mixing of one phase in the other in the form of large number of small droplets. However there are also expected to be favorable entropic contributions arising 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, microemulsion is spontaneous and the resulting dispersion is thermodynamically stable[16,17].

### 5. Method of preparation

#### 5.1 Phase titration method

Microemulsions are prepared by spontaneous emulsification method[18] which is illustrated with help of phase diagrams. Phase diagram construction is practical approach to study complex series of interaction which occurs when different components are mixed. The aspect of the phase diagram is phase equilibrium and demarcation of phase boundaries. Most often pseudo-ternary phase diagrams are constructed to figure out microemulsion zone as quaternary phase diagram is time consuming and difficult to interpret[19].

#### 5.2 Phase inversion method

Phase inversion of microemulsion happens upon addition of excess of dispersed phase. Phase inversion leads to radical physical changes as change in particle size that alters drug release[18]. During cooling, this system crosses the point of zero spontaneous curvature and minimal surface tension, prompting the formation of finely dispersed oil droplets[14]. Microemulsions can be prepared by controlled addition of lower alkanols (butanol, pentanol and hexanol) to milky emulsions to produce transparent solutions comprising dispersions of either o/w or w/o or colloidal dispersions. The lower alkanols are called co-surfactants. They lower the interfacial tension between oil and water sufficiently low for almost spontaneous formation[8].

### 6. Characterization of microemulsion

The droplet size, viscosity, density, turbidity, refractive index, phase separation and pH measurements shall be performed to characterize the microemulsion. This technique has been
advocated as the best method for predicting microemulsion stability.

6.1 Droplet size measurements

Size analysis of microemulsion was carried out by dynamic light scattering experiments or electron microscopy. The polydispersity index of the formulation was determined by the same instrument\cite{8, 20}.

6.2 Zeta potential measurements

Zeta potential for microemulsion was determined using zetasizer. Dilution test: It is confirmatory test of microemulsion to know which type of microemulsion was formed. The prepared optimized microemulsion was diluted with water (as external phase)\cite{20}.

6.3 Phase analysis

To determine the type if microemulsion that has formed the phase system (o/w or w/o) of the microemulsions is determined by measuring the electrical conductivity using a conductometer. The measurement of electrical conductivity gives the quantitative idea of the solubilization of water phase in the selected mixture containing oil phase, surfactant and cosurfactant. It also gives the idea about the types of microemulsion\cite{21}.

6.4 Viscosity measurement

The viscosity of microemulsions of several compositions can be 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\cite{20}.

6.5 Drug content determination

Itraconazole content in microemulsion based gel was measured by dissolving known quantity of microemulsion based gel in solvent (methanol) by Sonication. Absorbance was measured after suitable dilution at 280 nm using UV/VIS spectrophotometer (UV-1700 CE, Shimadzu Corporation, Japan)\cite{20}.

6.5 In vitro drug permeation studies

Franz diffusion cells with a cellulose membrane are utilized to determine the Release rate of drug from different microemulsion formulations. The cellulose (molecular weight G12 000) membrane is first hydrated in the distilled water solution at 25 °C for 24 hours. The membrane is then clamped between the donor and receptor compartments of the cells Diffusion cell was filled with 25 ml of phosphate buffer (pH = 7.4) and methanol (1:2). The receptor fluid was constantly stirred by externally driven magnetic bars at 600 rpm throughout the experiment. The Microemulsion (5 g) is accurately weighted and placed in donor compartment. At 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h time intervals, 2 ml sample is removed from receptor for spectrophotometric determination and replaced immediately with an equal volume of fresh receptor solution. Samples are analyzed using UV visible spectrophotometer. The results are plotted as cumulative released drug percent versus time \cite{22}.

6.6 Stability studies

The physical stability of the microemulsion must be determined under different storage conditions (4, 25 and 40 °C) during 12 months. Fresh preparations as well as those that have been kept under various stress conditions for extended period of time were subjected to droplet size distribution analysis. Effect of surfactant and their concentration on size of droplet is also to be studied\cite{23}.

8. Research work on microemulsions

During the last one decade much research work has been carried out on microemulsions for various routes of drug administration. Research work on microemulsions is summarized in Table 2:

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Route</th>
<th>Purpose/Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurbiprofen\cite{24}</td>
<td>Parenteral</td>
<td>Increased the solubility</td>
</tr>
<tr>
<td>Apormorphine HCL\cite{25}</td>
<td>Transdermal</td>
<td>Increased the permeability</td>
</tr>
<tr>
<td>Ketoprofen\cite{26}</td>
<td>Transdermal</td>
<td>Enhancement of permeability</td>
</tr>
<tr>
<td>Prilocaine-HCL\cite{27}</td>
<td>Transdermal</td>
<td>Increased the solubility</td>
</tr>
<tr>
<td>Estradiol\cite{28}</td>
<td>Transdermal</td>
<td>Improvement in solubilization</td>
</tr>
<tr>
<td>Aceclofenac\cite{29}</td>
<td>Dermatological</td>
<td>Increased the solubility</td>
</tr>
<tr>
<td>Piroxicam\cite{30}</td>
<td>Oral</td>
<td>Increased the solubility</td>
</tr>
<tr>
<td>Diclofenac\cite{31}</td>
<td>Transdermal</td>
<td>Permeability enhancement</td>
</tr>
<tr>
<td>Dexamethasone\cite{32}</td>
<td>Topical Ocular</td>
<td>Enhanced the Bioavailability</td>
</tr>
<tr>
<td>Chloramphenicol\cite{33}</td>
<td>Ocular</td>
<td>Increased the solubility</td>
</tr>
<tr>
<td>Ibuprofen\cite{34}</td>
<td>Parenteral</td>
<td>Increased the solubility</td>
</tr>
<tr>
<td>Sumatriptan\cite{35}</td>
<td>Intranasal</td>
<td>Enhanced the Bioavailability</td>
</tr>
<tr>
<td>Ibuprofen\cite{36}</td>
<td>Topical</td>
<td>Increasing the solubility</td>
</tr>
<tr>
<td>Doxorubicin\cite{37}</td>
<td>Topical</td>
<td>Increasing the Stability</td>
</tr>
</tbody>
</table>
References


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9. Conclusion

Today microemulsions have been shown to be able to protect labile drug, control drug release, increase drug solubility, increase bioavailability, reduce patient variability increase the rate of absorption, helps solublize lipophilic drug, various routes like tropical, oral and intravenous can be used to deliver the product, helpful in taste masking, provides and increases patient compliance. So use of microemulsion drug delivery system is most attractive and suitable area of research, offering not only many challenges to overcome but also potential extra ordinary benefits. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration.


[38] Rhee Y.S., Park CW., Nam TY., Shin YS., Chi SC and Park ES., Formulation of parental microemulsion containing itraconazole, Arch Pharm. Res. 2007;30: 114-123.


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