A REVIEW ON MICROEMULSION BASED DRUG DELIVERY SYSTEM

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Abstract: Microemulsions, often in conjunction with a co-surfactant, are clear, solid, isotropic mixtures of oil, water, and surfactant. These are unit stable than different forms of emulsion, transparent, usually in combination with a co surfactant whose diameter is within the 10-140μm range. Depending on their composition, they can be categorized as oil-in-water (o/w), water-in-oil (w/o) or bicontinuous systems and are distinguished by extremely low interfacial tension between the phases of oil and water. Due to their ability to accommodate a wide range of drug molecules (hydrophilic and hydrophobic) due to the presence of both lipophilic and hydrophilic domains, these versatile structures are currently of great technological and scientific interest to researchers. This adaptable delivery systems provide protection against oxidation, enzymatic hydrolysis and improve lipophilic drug solubilization and thus enhance bioavailability. Microemulsions act as possible oral, topical and parenteral drug carrier systems. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, and improved drug solubilization and bioavailability. Preparing a pharmaceutically acceptable dosage form requires a clear understanding of the structure of the microemulsion, phase behavior, factors leading to its thermodynamic stability and potential uses and limitations of the microemulsion system. It is essential to know the different methods available to describe a microemulsion system thoroughly. While microemulsion is used in several fields, the pharmaceutical applications are highlighted in this review.

IndexTerms - Microemulsion, Novel drug delivery, Macroemulsion, method of preparation, applications

INTRODUCTION

Recent progress in combinatorial chemistry has led to the generation of a large number of new compounds. Today, in addition to many existing drugs, a large percentage of these new chemical entities (NCEs) also show poor solubilization behaviors that lead to poor oral bioavailability with wide variation in intra- and inter-topics and present formulators with significant technical challenges. Selecting an appropriate dosage form is important because a dosage form with poor drug delivery will make a valuable medication useless. Bioavailability has important clinical consequences, since both pharmacological and toxic effects are proportional to dosage and bioavailability [1].

Other methods have been carefully explored to improve the oral bioavailability of such drugs including reduction of particle size (micronisation or nanosizing), cyclodextrin complexation, salt formation, cosolvent-based solubilization, surfactants, etc. Modification of physicochemical properties, such as salt formation and reduction of the particle size of the drug, can improve the dissolution rate of the drug but these methods are not always practical. In addition, weak acid and weak base salts may convert back to their original acid or base forms and cause aggregation in the gastrointestinal tract [2].

HISTORY:

The idea of micro-emulsions remained unknown while awaiting Hoar and Schulman's work in 1943, defining an impulsive emulsion of oil and water by introducing a strong surface-active agent. The term “micro-emulsion” was first used even later by Schulman et al. in 1959 to explain a point system consisting of alcoholic oil water and surfactants that forms a clear solution. The term "microemulsion" has been commonly used to describe these systems although not regularly used nowadays, some such as the terms "micellar emulsion" or "swollen micelles". The best descriptions of microemulsions are "a micro-emulsion can be an oil form, water can also be an amphiphile which can be a single optically identical and thermodynamically stable liquid solution". [3]

MICROEMULSIONS:

Microemulsions, often in conjunction with a cosurfactant, are transparent, inert, isotropic liquid mixtures of oil, water and surfactant. Microemulsions are bicontinuous systems consisting essentially of large phases of separated water and oil by a surfactant/cosurfactant rich interfacial region. Such systems have advantages over traditional emulsions in that they are thermodynamically stable and spontaneously generated liquid systems [4]. Microemulsions are currently the subject of numerous inquiries due to their wide range of potential and actual uses. The high capacity of drug microemulsions makes such formulations desirable for pharmaceuticals. Such devices also deliver many oral benefits including increased absorption, enhanced therapeutic efficacy and decreased toxicity. [5] Unlike ordinary emulsions, microemulsions form when the components are mixed simply and do not need the high shear conditions commonly used in the creation of ordinary emulsions. The two basic types of microemulsions are direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o). In ternary systems such as microemulsions, where two immiscible phases (water and ‘oil’) occur with a surfactant, the surfactant molecules form a monolayer at the oil-water interface, with the hydrophobic tails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase. As in binary systems (water / surfactant or oil / surfactant), self-assembled structures of various types can be formed, ranging, for example, from (inverted) spherical and cylindrical micelles to lamellar phases and bicontinuous microemulsions which may coexist with predominantly oil or aqueous phases.[6]
CHARACTERISTICS OF MICROEMULSIONS:
In principle Microemulsions can be used to distribute drugs to patients through several paths, but the topical use of microemulsions has increased interest. The three main factors that decide the transdermal permeation of drugs are the movement of drugs in the vehicle, the release of drugs from the vehicle and the impregnation of drugs in the skin. These factors either affect the thermodynamic activity that drives the drug into the skin or the drug's permeability in the skin, particularly stratum corneum.

Microemulsions improve the transdermal delivery of several medicines over traditional topical preparations such as emulsions [7, 8] and gels [9, 10]. Mobility of drugs in microemulsions is easier [11] compared to the former gel microemulsion, which increases viscosity and further decreases permeation of the skin [12]. The superior transdermal flux from microemulsions has been shown to be mainly due to their high solubilization capacity for lipophilic and hydrophilic drugs.

COMPARISON BETWEEN MACRO-EMULSIONS AND MICRO-EMULSIONS:
The greatest difference between micro-emulsions and emulsions within the shape and size of the propagating elements in the constant process is a general way in which they are a demand of magnitude shorter in the case of micro-emulsions (10–200 nm) than ordinary emulsion individuals (1-20 μm).

Another major difference fascinates their presence: squad microemulsions measure either transparent or lustrous while square emulsions measure cloudy. In accumulation, the square measure differences in their preparation technique, because emulsions need an excessive energy input, while microemulsions do not need to.

Table 1: Comparison between Emulsion and Micro-emulsion [14]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Macro-emulsion</th>
<th>Micro-emulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Macro-emulsions are thermodynamically unstable.</td>
<td>Micro emulsions are thermodynamically stable.</td>
</tr>
<tr>
<td>2.</td>
<td>They may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy.</td>
<td>It can have basically infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.</td>
</tr>
<tr>
<td>3.</td>
<td>They are lyophobic.</td>
<td>They are on the borderline between lyophobic and lipophilic colloids.</td>
</tr>
<tr>
<td>4.</td>
<td>Most macro-emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.</td>
<td>Microemulsion are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light, they scatter little light.</td>
</tr>
<tr>
<td>5.</td>
<td>Droplet diameter 1–20 mm.</td>
<td>Droplet diameter 10–100 nm.</td>
</tr>
<tr>
<td>6.</td>
<td>Macro Emulsions consist of roughly spherical droplets of one phase dispersed into the other.</td>
<td>They constantly evolve between various structures ranging from droplet like swollen micelles to bicontinuous structure.</td>
</tr>
<tr>
<td>8.</td>
<td>Direct oil/water contact at the interface.</td>
<td>No direct oil/water contact at the interface.</td>
</tr>
</tbody>
</table>
ADVANTAGES OF MICROEMULSION SYSTEM:
1. Microemulsions are quickly prepared and do not require any energy in the preparation due to improved thermodynamic stability.
2. Microemulsion build-up is reversible. They may become unstable at low or high temperatures but the microemulsion shape when the temperature returns to the stability range.
3. Microemulsions are a thermodynamically stable system and allow the system to self-emulsify itself.
4. Microemulsions have low viscosity compared to emulsions.
5. Microemulsions act as drug supersolvents and can solubilize both hydrophilic and lipophilic drugs, including insoluble drugs in aqueous and hydrophobic solvents.
6. Having the ability to carry both lipophilic and hydrophilic drugs.
7. The dispersed step, lipophilic or hydrophilic (O / W or W / O microemulsions) can act as a potential reservoir, respectively, of lipophilic or hydrophilic drugs.
8. The use of microemulsion as delivery systems will improve the effectiveness of a medication, thereby reducing the total dose and decreasing the side effects.

DISADVANTAGES OF MICROEMULSION SYSTEMS:
1. Having limited solubilizing capacity for high melting substances.
2. Require large amount of Surfactants for stabilizing droplets.
3. Microemulsion stability is influenced by environmental parameters such as temperature and pH. [15]

TYPES OF MICROEMULSIONS:
Microemulsions are thermodynamically stable, but are found only under precise conditions. There are four types of microemulsion phases in equilibrium, according to Winsor, these phases are also referred to as Winsor phases.

They are,
1. Oil- in- water microemulsion or winsor I
2. Water – in oil microemulsion or winsor II
3. Bicontinuous microemulsion or winsor III
4. Single phase homogeneous mixture or winsor IV

Oil- in- water microemulsion or winsor I
In oil-in-water process, droplets of oil are surrounded by a surfactant (and can be cosurfactant) film containing the internal phase dispersed in water, which is the continuous phase. This type of microemulsion generally has a larger interaction volume than the w/o microemulsions.

Water - in - oil microemulsion or winsor II
In Water-in-oil type of water droplets of microemulsions surrounded by a continuous oil process. These are classified as "reverse micelles" where the surfactant's polar headgroups face the droplets of water, with the fatty acid tails facing the oil process. The aqueous biological system may destabilize a w/o microemulsion which is used orally or parenterally.

Bicontinuous microemulsion or winsor III
The amount of water and oil present in bicontinuous microemulsion system is similar, in this case both water and oil exist as a continuous phase. They combine an irregular oil and water channel, and look like a "sponge-phase". This bicontinuous state may go through transitions from o / w to w/o microemulsions. Bicontinuous microemulsion, a non-Newtonian flow and plasticity may show. These properties make them particularly useful for the topical delivery or intravenous administration of drugs.

Single phase homogeneous mixture or winsor IV
The oil, water, and surfactants are homogeneously blended in a single phase homogeneous mixture or winsor IV. [16-19]

PROCESS OF PREPARATION:
Micro-emulsions area unit ready once water / oil interface surface tension is set at the same point as the squat. The surface layer is set as an equal considerable stretch. However, surface-active-agent fluid absorption must remain highly adequate to stretch surface-active-agent particles to mitigate the micro-emulsion at an extremely low surface tension. [20, 21] Two chief technique are stated for the preparation of microemulsion, these are

1. Phase Volumetric Analysis Technique:
Micro-emulsions square measure ready by the technique of spontaneous emulsification, which is proved with component diagrams facilitated. Component diagram development is a sensible approach to testing complicated interaction series that occurs once completely different sections squares calculate mixed. The part-diagram dimension is part equilibrium and part-boundary separation. Normally any pseudo-ternal part diagram is generated to work out micro-emulsion area as quaternary part diagram is daunting time and difficult to understand. [22, 23]

2. Phase-Inversion Technique:
Micro-emulsion phase reversal occurs after accumulation of discrete phase spare. Phase- Inversion results in radical physical modifications as a change in the size of the element which varies with the release of drugs. This method marks the purpose of zero impulsive curving and stripped physical phenomenon throughout the freezing process, instigating the production of excellent dispersed oil droplets. Micro-emulsions are ready by calculated addition of subordinate alkanols (pentanol, hexanol and butanol) to opaque emulsions to provide clear results, including distribution of additional dispersions of mixtures or w/o or o / w. They are subordinate alkanols which are also co-surfactants. They adequately subordinate the surface tension between water and oil to previously impulsive development. [22, 24, 25]
COMPONENTS OF MICROEMULSION SYSTEM:

The supply of oils and surfactants is abundant but their use is limited due to their toxicity, potential for irritation and uncertain mechanism of action. Oils and surfactant to be used for microemulsion formulation should be biocompatible, non-toxic, and clinically appropriate. The emphasis is on choosing the part that falls under "generally considered healthy" (GRAS) [26].

- Oil phase
- Aqueous phase
- Primary surfactant
- Secondary surfactant (co-surfactant)
- Co-Solvent

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Component</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oil</td>
<td>1)-saturated fatty acid- lauric acid, carpic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2)unsaturated fatty acid-oleic acid, linolic acid, linolenic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3)fatty acid ester-ethyl or methyl ester of lauric, oleic acid and myristic acid</td>
</tr>
<tr>
<td>2</td>
<td>Surfactant</td>
<td>1-polyoxyethylene/polysorbate/tween 20,40,60,80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-sorbitan monolaurate, eggs lecithin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-sodium dodecyl sulphate</td>
</tr>
<tr>
<td>3</td>
<td>Co-surfactant</td>
<td>1-ethanol, proranol, butanol, isopropanol, pentanol, hexanol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-polyoxyethylene-10-etyl ether</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-sodium monohexyl phosphate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-cinnamic alcohol, cinamic alcohol</td>
</tr>
</tbody>
</table>

FACTOR AFFECTING FORMULATION OF MICROEMULSION SYSTEM:

- Packing ratio
- Property of surfactant
- Property of oil phase
- Temperature
- Chain length
- Nature of co-surfactant [15].

EVALUATION PARAMETERS OF MICROEMULSION SYSTEM:

**Physical appearance:** Microemulsion can be visually inspected for homogeneity, fluidity and optical consistency of physical appearance.

**Scattering Techniques:** Scattering techniques such as small angle neutron scattering, small angle X-ray scattering and light scattering have found applications in microemulsion structure studies, particularly in dilute mono dispersion spheres, where poly dispersion or condensed structures such as those often seen in microemulsion.

**Limpidity Test (Percent Transmittance):** The microemulsion limpidity can be spectrophotometrically measured using a spectrophotometer.

**Drug stability:** The engineered microemulsion was held under cold (4-8 °C), room temperature, and elevated (50 ± 2 °C) temperature. The microemulsion can be analyzed after every 2 months for phase separation, transmittance rate, globule size and percent assay.

**Globule size and zeta potential measurements:** Extreme light scattering will determine the globular size and zeta potential of the microemulsion, using a Zetasizer HSA 3000.

**Assessment of the Rheological Properties (viscosity measurement):** The rheological features play an important part in stability. It may be measured by a wireless viscometer from Brookfield. Changes in rheological features help determine the microemulsion zone and its distinction from other regions. Discontinuous microemulsion are dynamic structures with continuous variations between the discontinuous system, the swollen reverse micelle and the swollen micelles.

**Electrical conductivity:** A mixture of gasoline, surfactant and co-surfactant has been applied to the water process and the electrical conductivity of formulated samples can be measured at ambient temperature and at a constant frequency of 1 Hz using a conductometer.

**Drug solubility:** Drug was added to the optimized formulation of microemulsion and each individual ingredient of the formulation in excess of that. Samples were removed after continuous stirring for 24 h at room temperature and centrifuged for 10 min at 6000 rpm. The quantity of soluble drug in optimized formulation as well as each individual formulating component was determined by subtracting the drug present in the sediment from the total quantity of drug added. The solubility of drug in microemulsion was compared with respect to its individual ingredients.

**In-vitro drug release:** The study of diffusion can be performed on a modified Franz diffusion cell, within 20mL volume. The receiver compartment was full of buffer. The donor compartment was set separately with cellophane membrane, which housed the microemulsion formulation and the simple drug solution. Samples were removed from the receptor compartment at fixed time intervals and tested for drug content using a broad wavelength UV spectrophotometer [26-29].
APPLICATION OF MICROEMULSION:
The application of micro-emulsion is given as follows

- Oral delivery system
- Parental delivery system
- Ophthalmic delivery system
- Micro-emulsion in detergency
- Micro-emulsion in cosmetics
- Micro-emulsion in food [30].

Table 3: Different Reports/Studies Related To Micro Emulsion [31-49]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drug</th>
<th>Category</th>
<th>Route of Adm.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acyclovir</td>
<td>Antiviral</td>
<td>Oral</td>
<td>The microemulsion showed an absolute bioavailability of 27.83%, which is 12.78 times higher than that of commercially available tablets</td>
</tr>
<tr>
<td>2.</td>
<td>Atorvastatin</td>
<td>Hypolipidemic drug</td>
<td>Intestinal</td>
<td>The estimated absorption of Atorvastatin in human for the microemulsion drug delivery system was higher than that for PDS and MFA (p&lt;0.01).</td>
</tr>
<tr>
<td>3.</td>
<td>Aceclofenac</td>
<td>Non-steroidal anti-inflammatory</td>
<td>Oral</td>
<td>The in vivo studies revealed a significant increase in the anti-inflammatory effects as compared with marketed gel</td>
</tr>
<tr>
<td>4.</td>
<td>Sunflower Oil</td>
<td>Anti Bacterial</td>
<td>Intestinal</td>
<td>The microemulsions are stable, self-preserving antibacterial agents, with a highly effective killing rate against bacterial growth</td>
</tr>
<tr>
<td>5.</td>
<td>Clarithromycin</td>
<td>Antibacterial</td>
<td>Oral</td>
<td>The enhanced bioavailability is probably due to the increase in solubility and immediate dispersion of the drug in the GI tract.</td>
</tr>
<tr>
<td>6.</td>
<td>Glimepiride</td>
<td>Antidiabetic</td>
<td>Oral</td>
<td>It can be concluded that the microemulsion formulation could be employed to improve the dissolution by solubility enhancement and hence the bioavailability of a poorly absorbed drug could be improved.</td>
</tr>
<tr>
<td>7.</td>
<td>Silymarin</td>
<td>Liver disorder</td>
<td>Topical</td>
<td>Microemulsions enhanced silymarin solubility while maintaining adequate physical and chemical stability especially microemulsions containing Labrasol®</td>
</tr>
<tr>
<td>8.</td>
<td>Simvastatin</td>
<td>Lipid-lowering agent</td>
<td>Intestinal</td>
<td>Developed with an increased dissolution rate, increased solubility, and, ultimately, increased bioavailability of a poorly water soluble drug, simvastatin</td>
</tr>
<tr>
<td>9.</td>
<td>Carbamazepine</td>
<td>Antiepilepsy</td>
<td>Nasal</td>
<td>This may help in decreasing dose and frequency of administration of drug and may possibly maximize therapeutic benefits and may also reduce cost of therapy</td>
</tr>
<tr>
<td>10.</td>
<td>Fexofenadine hydrochloride</td>
<td>Antihistaminic drug</td>
<td>Oral</td>
<td>The oral delivery of hydrophobic drugs can be made possible by SMEDDSs, which have been shown to substantially improve oral bioavailability</td>
</tr>
<tr>
<td>11.</td>
<td>Isopropyl palmitate</td>
<td>Fatty acid ester</td>
<td>-</td>
<td>A stable microemulsion can be prepared by using the optimum combination of IPP with Tween 80 and 1- butanol which has a potential as a suitable drug delivery system.</td>
</tr>
<tr>
<td>12.</td>
<td>Naproxen</td>
<td>Non-steroidal anti-inflammatory</td>
<td>Topical</td>
<td>The amount of naproxen release differ between microemulsion carriers with various internal microstructures.</td>
</tr>
<tr>
<td>13.</td>
<td>Flurbiprofen</td>
<td>Nonsteroidal anti-inflammator</td>
<td>Oral</td>
<td>In-vivo study revealed significant improvement in extent of absorption of Flurbiprofen in mice to 1.78-fold compared to with conventional capsule formulation</td>
</tr>
<tr>
<td>14.</td>
<td>Miconazole Nitrate</td>
<td>Antifungal</td>
<td>Topical</td>
<td>the antifungal activity of micro emulsion was found greater than that of reference sample, more comparative clinical studies are needed to confirm the advantages over the available marketed products</td>
</tr>
<tr>
<td>15.</td>
<td>Ranitidine</td>
<td>Antiulcer</td>
<td>Oral</td>
<td>The pharmacodynamic</td>
</tr>
</tbody>
</table>

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CONCLUSION:
Microemulsion is drug delivery systems for the delivery of more than one medicament simultaneously. Microemulsion prevents labile medications, monitors the release of pharmaceutical products, enhances drug solubility, improves bioavailability and decreases patient variability. The role of microemulsion in providing new solutions to the problems of poor water solubility of compounds of highly lipophilic drugs and providing strong, more stable and reproducible bioavailability. Drug delivery by microemulsion is a promising field for ongoing research to achieve controlled release with improved bioavailability and drug targeting at different body sites. Recently, several research papers have been published for the improvement of drug delivery, but still there is a need to put an emphasis on its characterization part including in vitro evaluation. Besides this, research papers shows higher percentage of surfactant (much higher than CMC level) used for the formation of microemulsion, irrespective of different routes of administration, but there is a lack of toxicological evaluation of the prepared microemulsion, which can be a broad research area in future.

ACKNOWLEDGEMENT:
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CONFLICT OF INTEREST: Nil

REFERENCES:

| 16. | Sertaconazole | Antifungal | Topical | It is promising that the concentration of STZL used to treat cutaneous fungal infection could be decreased due to the high permeation and anti-fungal ability of STZL in HSM-4. |
| 17. | Valacyclovir | Antiviral | Topical | Drug Release and Zeta potential optimized ME converted into gel with the help of gellingagent Carbopol 934 and evaluated for various physico-chemical parameters and stability studies |
| 18. | Dexamethasone | Anti-inflammatory | Topical | A lower surfactant/co-surfactant ratio, improves the most permeability parameters of dexamethasone microemulsion. |
| 19 | Itraconazole | Anti-fungal | Topical | Increased in permeability of drug by preparing microemulsion |

| 20. | Dexamethasone | Anti-inflammatory | Topical | A lower surfactant/co-surfactant ratio, improves the most permeability parameters of dexamethasone microemulsion. |

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