International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 1644-1654 www.ijprajournal.com ISSN: 2456-4494

A Review on Formulation and Evaluation of Microemulsion

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Submitted: 10-12-2022 Accepted: 23-12-2022

ABSTRACT:
Microemulsions are one of the best candidates as novel drug delivery system because of their long shelf life, improved drug solubilization with ease of preparation and administration. Microemulsions are thermodynamically stable and optically isotropic liquid solutions of oil, water and amphiphile. They have emerged as novel vehicles for drug delivery which allow controlled or sustained release for ocular, percutaneous, topical, transdermal, and parenteral administration of medicaments. Microemulsions can be easily distinguished from normal emulsions by their low viscosity, transparency and more accurately their thermodynamic stability. Microemulsions have great range of applications and uses such as in pharmaceuticals, agrochemicals, cutting oils, biotechnology, food, cosmetics, analytical applications, environmental detoxification etc. The main objective of this review paper is to discuss microemulsions as drug carrier system with other possible applications.

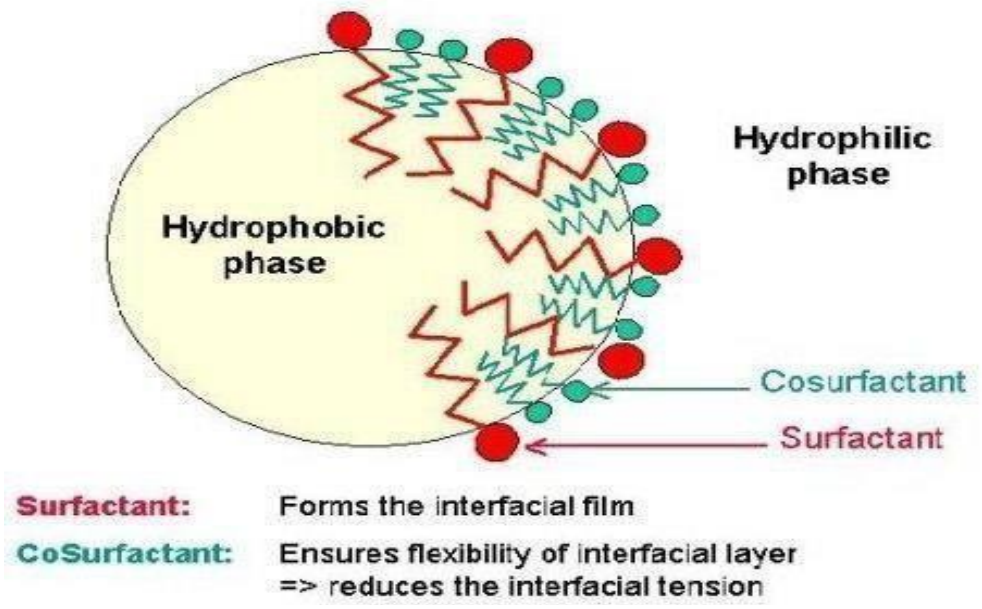
Key words: Microemulsions, thermodynamically stable, amphiphile, solubilization

I. DEFINITION

- The term micro emulsion introduced by Schulman and co works.

The term "micro emulsion" refers to a thermodynamically stable Iso-tropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules.

- A micro-emulsion 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 particle size of micro-emulsion range about 10 nm to 300 nm .because of the small particle sizes of micro-emulsion appears as clear or translucent solution.



DIFFERENTIATION:

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

S. No.	Macro-emulsion	Micro-emulsion
		
1.	Macro-emulsions are thermodynamically unstable.	Micro emulsions are Thermo dynamically stable.
2.	They may remain stable for long periods of time, will ultimately undergo phase separation on standing to attain a minimum in free energy.	It can have basically infinite lifetime assuming no change in composition, temperature and pressure, and do not tend to separate.
3.	They are lyophobic.	They are on the borderline between lyophobic and lipophilic colloids.
4.	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.	Microemulsion are transparent or translucent as their droplet diameter are less than ¼ of the wavelength of light, they scatter little light.
5.	Droplet diameter 1–20mm.	Droplet diameter 10–100nm.
6.	Macro Emulsions consist of roughly spherical droplets of one phase dispersed into the other.	They constantly evolve between various structures ranging from droplet like swollen micelles to bi-continuous structure.
7.	Inefficient molecular packing.	Efficient molecular packing.
8.	Direct oil/water contact at the interface.	No direct oil/water contact at the interface.

Advantages:

- Thermodynamically stable, long shelf life
- Micro-emulsion act as super solvent for drug
- Potential reservoir of liphophilic or hydrophilic drug
- Due small droplet size it has large interfacial area of globule so drug is rapidly released in external phase when absorption takes place
- Ability to carry both hydrophilic and liphophilic drug
- Easy to prepare require no significant energy
- Low viscosity
- Helpful in test masking

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Disadvantages:

- Require large amount of surfactant and co surfactant for stabilizing droplets
- Limited solubility for high melting substances
- Stability influenced by environmental parameter such as temperature and pH

Theories of Micro Emulsion Formation

Historically, three approaches have been used to explainmicro emulsion formation and stability. They are asfollows-

1- Interfacial or mixed film theories.
2- Solubilization theories.
3- Thermodynamic treatments.-0

The free energy of micro emulsion formation can be considered to depend on the extent to which surfactantlowers the surface tension of the oil water interface andchange in entropy of the system such that,

Gf = γ a - T S

Where,

Gf = free energy of formation

A = change in interfacial area of micro emulsion

S = change in entropy of the system T = temperature

γ = surface tension of oil water

interphase.

When micro emulsion is formed the change in A is verylarge due to the large number of very small dropletsformed. In order for a micro emulsion to be formed(transient) negative value was required, it is recognizedthat while value of A is positive at all times, it is very smalland it is offset by the entropic component. The dominantfavorable entropic contribution is very large dispersionentropy arising from the mixing of one phase in the otherin the form of large number of small droplets. Howeverthere are also expected to be favorable entropiccontributions arising from other dynamic processes suchas surfactant diffusion in the interfacial layer andmonomer-micelle surfactant exchange. Thus a negativefree energy of formation is achieved when largereductions in surface tension are accompanied bysignificant favorable entropic change. In such cases, microemulsion is spontaneous and the resulting dispersion isthermodynamically stable

Formulation of Micro-emulsion Composition:

The Major component in micro emulsion system are-

1) Oil phase
2) Surfactant (primary surfactant)
3) Co-surfactant (secondary surfactant)
4) Co-solvent

Component	**Example**
Oil	1)-saturated fatty acid- lauric acid, carpic acid 2)unsaturated fatty acid-oleic acid, linolic acid, linolenic acid 3)fatty acid ester-ethyl or methyl ester of lauric, oleic acid and myristic acid
Surfactant	1-polyoxyethylene/polysorbate/tween 20,40,60,80 2-sorbitan monolaurate, eggs lecithin 3-sodium dodecyl sulphate
Co-surfactant	1-ethanol, Propanol, butanol, isopropanol, Pentanol, hexanol 2-polyoxyethylene-10-oelyl ether 3-sodium monohexyl phosphate 4-cinnamic alcohol, cinamic alcohol

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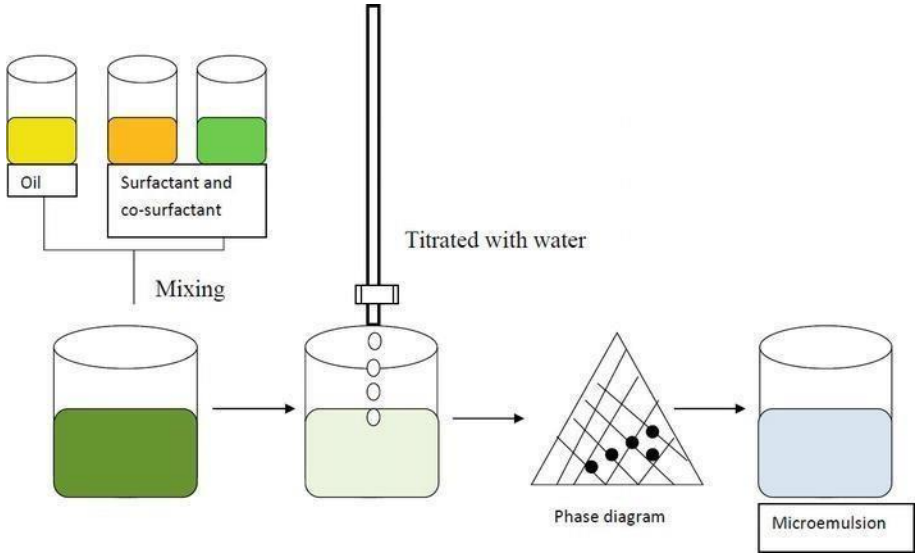
Preparation Method of Micro-Emulsion:
Following are the method used for the preparation of themicro emulsion:

1) Phase titration method
2) Phase inversion method

Phase Titration Method:

Micro emulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. Micro emulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depending on thechemical composition and concentration of each component. The understanding of their phase equilibriumand demarcation of the phase boundaries are essentialaspects of the study. As quaternary phase diagram (fourcomponent system) is time consuming and difficult tointerpret, pseudo ternary phase diagram is oftenconstructed to find the different zones including microemulsion zone, in which each corner of the diagramrepresents 100% of the particular component. The regioncan be separated into w/o or o/w micro emulsion bysimply considering the composition that is whether it isoil rich or water rich.

Observations should be madecarefully so that the metastable systems are not included.



Phase Inversion Method:

Phase inversion of micro emulsions occurs as a result ofaddition of excess of the dispersed phase or in responseto temperature. During phase inversion drastic physicalchanges occur including changes in particle size that canaffect drug release both in vivo and in vitro. Thesemethods make use of changing the spontaneouscurvature of the surfactant. For non-ionic surfactants, thiscan be achieved by changing the temperature of thesystem, forcing a transition from an o/w micro emulsionat low temperatures to a w/o micro emulsion at highertemperatures (transitional phase inversion). Duringcooling, the system crosses a point of zero spontaneouscurvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method isreferred to as phase inversion temperature (PIT) method.Instead of the temperature, other parameters such as saltconcentration or pH value may be considered as wellinstead of the temperature alone. Additionally, atransition in the spontaneous radius of curvature can beobtained by changing the water volume fraction. Bysuccessively adding water into oil, initially water dropletsare formed in a continuous oil phase. Increasing thewater volume fraction changes the spontaneouscurvature of the surfactant

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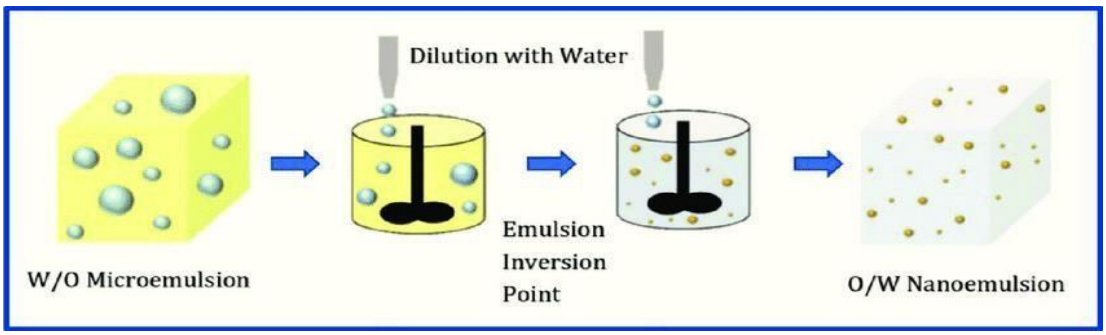
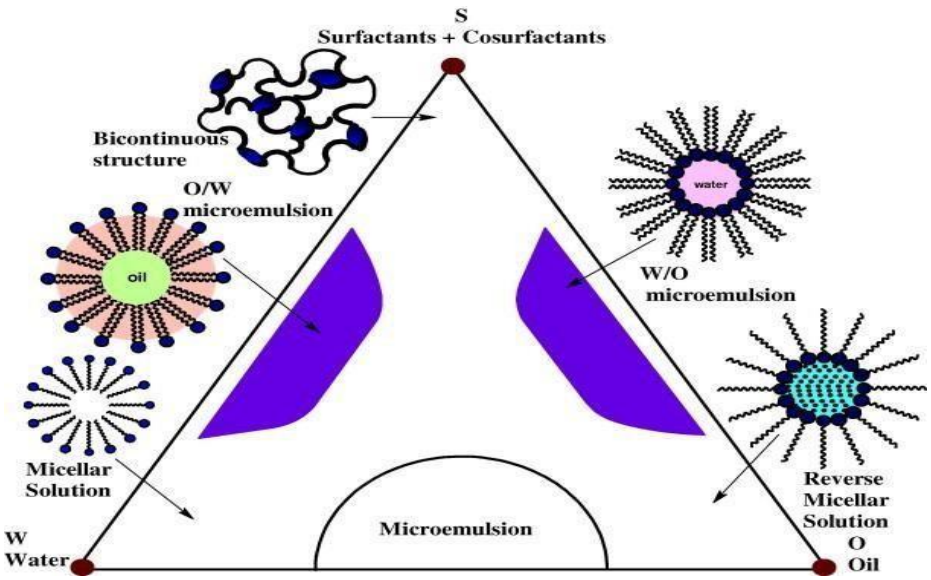
from initially stabilizing a w/omicro emulsion to an o/w micro emulsion at the inversionlocus. Shortchain surfactants form flexible monolayer atthe o/w interface resulting in a discontinuous microemulsion at the inversion.



Micro-emulsion as Nano-templates



EVALUATION OF MICROEMULSION

1. Phase behaviour
2. Size and shape
3. Rheology
4. Conductivity
5. Zeta potential
6. P^H
7. Drug release studies
8. Physical stability study

Phase behavior:

Lavender essential oil (LO) is widely used as a bioactive component in cosmetics. In this study, the pseudo ternary phase diagrams of micro-emulsions composed of oil phase (LO: short-chain alcohol = 1:1, w/w), nonionic surfactant (Tween 80) and water were constructed to evaluate the impact of co-surfactant type on the dilute ability of micro-emulsion systems. The solubilization of LO was improved in the presence of 1, 3-butylene glycol. For this reason, microstructural inversion of a water titration line D82 was investigated by dye diffusion, conductivity, viscosity and DSC. Micro-emulsions transition from W/O to bi-continuous occured at 20% water content, and then to O/W structure at 50% water content. In the bi-continuous phase, the viscosity reduced rapidly by the rise of temperature. The structure transition affected the free radical scavenging activity. The DPPH radical scavenging activity increased

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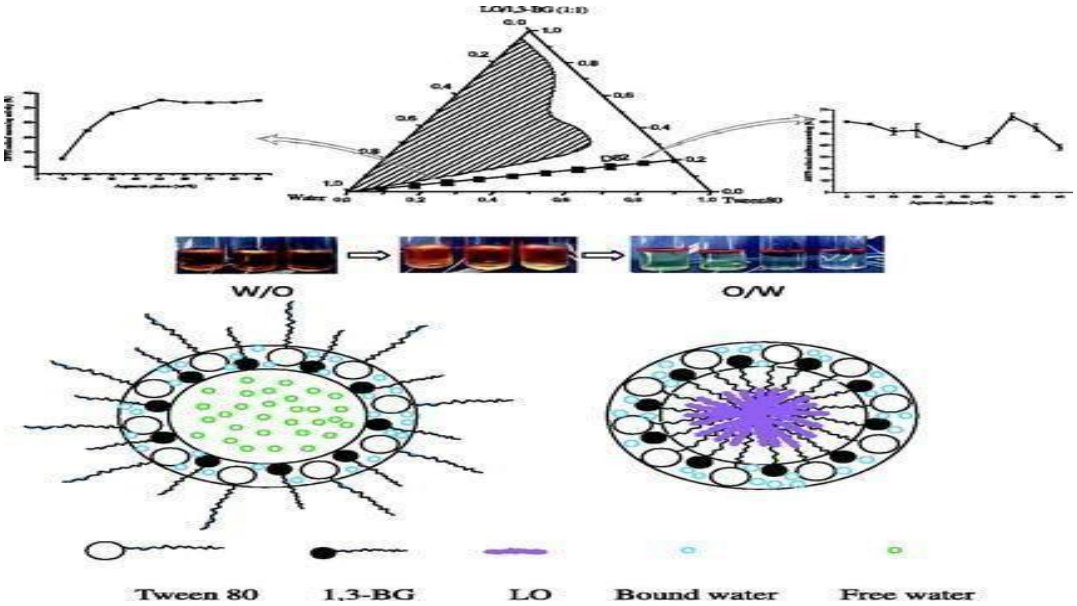
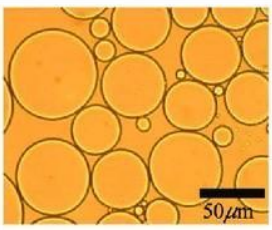
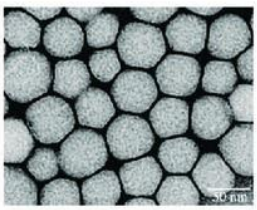
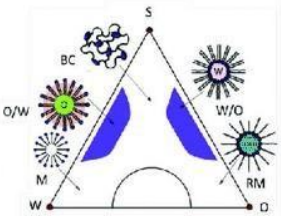
continuously with water content from 10% to 90%, indicating that increasing free water may accelerate the interaction between LO and DPPH radicals. The ABTS radical scavenging activity of W/O and bi-continuous formulations was concentration-dependent while increased again and peaked at 70% water content in O/W regions. The micro-emulsion techniques could be applied as potential delivery systems to improve the application of poorly water-soluble essential oils.



SIZE AND SHAPE:

	macroemulsions	nanoemulsions	microemulsions
			
size	1-100 μm	20-500 nm	10-100 nm
shape	spherical	spherical	spherical, lamellar
stability	thermodynamically unstable, weakly kinetically stable	thermodynamically unstable, kinetically stable	thermodynamically stable
method of preparation	high & low energy methods	high & low energy methods	low energy method
polydispersity	often high (>40%)	typically low (<10-20%)	typically low (<10%)

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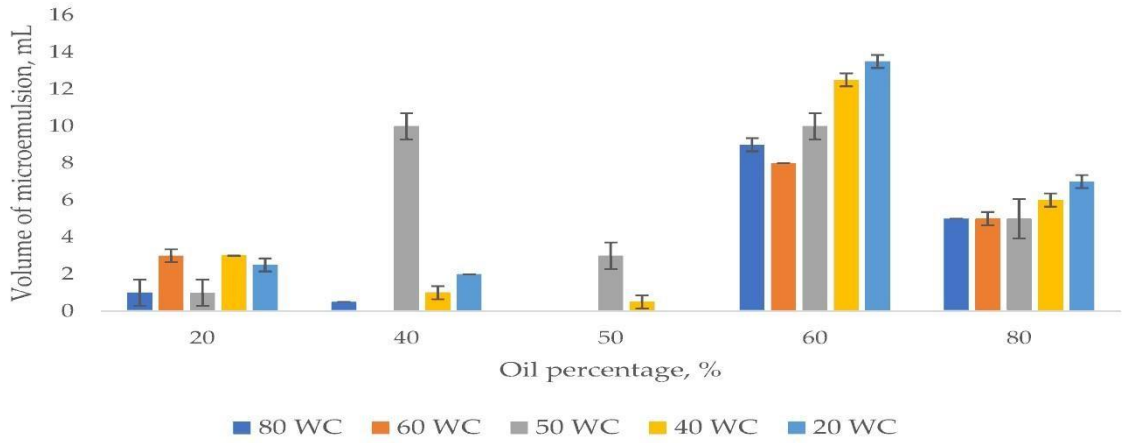
RHEOLOGY:

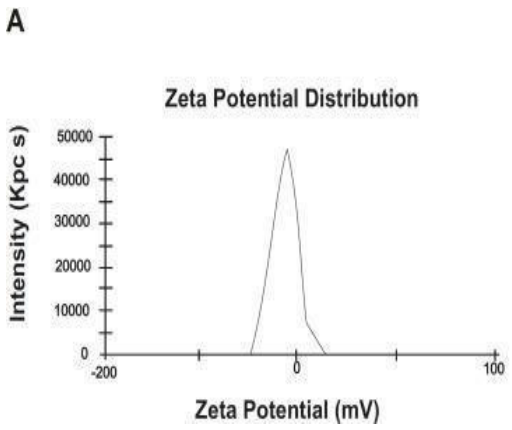


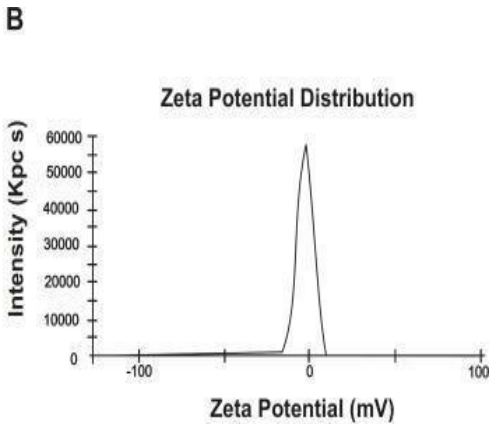
CONDUCTIVITY:

The conductivity measurements help in determining whether the micro-emulsion system formed is oil-continuous or water-continuous. The solubilization of water phase in the selected oily mixture was monitored quantitatively by measuring the electrical conductivity. The conductivity of the optimized micro-emulsion (B-9) as determined by the conductivity meter was found to be 0.283 σ. From electro conductivity study it can be concluded that the system is of o/w type.

ZETA POTENTIAL:

Zeta potential results of the optimized micro-emulsion and its diluted form (100 times diluted with 0.1N HCL) have been shown in Figure 3, and were found to be -6.34 mV and -3.02 mV, respectively. Aggregation is not expected to take place, due to the slightly negative charge of the droplets.





P$^{H:}$

The pH of 10% aqueous solution of the base was measured For SA ME systems, it was measured by direct immersion of the electrode of the pH meter (Hanna-213, Portugal) in the system. P^{H} 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-tonics).

DRUG RELEASE STUDIES:

The in vitro drug release studies were performed by using Franz diffusion cell with cellophane paper. The water jacketed recipient

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compartment had total capacity of 25 ml and it had 2 arms, one for sampling and another for thermometer. The donor compartment had internal diameter of 2 cm. The donor compartment was placed in such a way that it just touches the diffusion medium in receptor compartment. The receptor compartment contained phosphate buffer saline (PBS) that was maintained at 37°C ± 1°C. The membrane was equilibrated before application of the micro-emulsion equivalent to 10 mg of drug onto the donor side. Samples were periodically withdrawn from the receptor compartment, replacing with the same amount of fresh PBS solution, and assayed by using a spectrophotometer at 254 nm.

PHYSICAL STABILITY STUDY:

Selected formulations were centrifuged at 3000 rpm for 30 min. The formulations having no phase separations were taken for the heating and cooling cycle (freeze thaw cycle). Six cycles between the temperatures 4°C (refrigerator) and 45°C in a hot air oven with storage at each temperature for not less than 48 h were done. The formulations which were stable at these temperatures were selected for further studies.

The optimized micro-emulsion formulation was stored at 4°C, room temperature and 45°C for 3 months and samples were evaluated for physicochemical parameters like globule size and drug content at 1 month interval.

Application of micro-emulsion

Sr. No.	Delivery System	Drug	Category	Application
1.	Nasal Delivery	Diazepam	Anticonvulsant or antiepileptic drug	Nasal route for administration of diazepam is useful approach for the rapid onset of action during the emergency treatment of status epilepticus.
2.	Ophthalmic Delivery	Dexamethasone	Anti-allergic	It showed better tolerability and higher bioavailability. The formulation showed greater penetration in the eye which allowed the possibility of decreasing the number of applications per day.
3.	Parenteral Application	vitamins E, A, D, and K	Supplements	It suitable for fat soluble vitamins and hydrophobic drugs

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4.	Oral administration	Paclitaxel	Anticancer	Micro-emulsion permitted its rapid and efficient absorption resulting in improved oral bioavailability.
5.	Topical administration	miconazole, ketoconazole, itraconazole	Anti-ycotics	Micro-emulsions impart to them increased drug loading, enhanced penetration through the biological membrances, and increased bioavailability,
6.	Tumor targeting	Aclacino-mcycin	Antitumor agent	Folate-linked micro-emulsion is feasible for tumour targeted ACM delivery. The study showed that folate modification with a sufficiently long PEG chain on emulsions is an effective way of targeting tumour cells.
7.	Brain targeting	Clonazepam	Anticonvulsant or antiepileptic drug	Muco-adhesive micro-emulsion compared to iv. was found to be 2-fold higher indicating larger extent of distribution of the drug in the brain.
8.	Cosmetic	-	Moisturizing, soothing agents, sunscreens, antiperspirants, body cleansing agents.	They are now being widely investigated for preparing personal care products with superior features such as having improved product efficiency, stability.

Current and Future Developments: The full potential of micro-emulsion systems is yet to be realized. A lot of innovations

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are expected to come in the field of micro-emulsion technology. The role of micro-emulsion systems is of paramount importance in providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability. Furthermore, these formulations can be easily scaled up which is important from industrial standpoint considering the relative cost of commercial production. In addition to oral drug delivery, a lot of topical products employing the micro-emulsion technology are likely to emerge. This is significant not only from the view point of drug delivery but also from the huge and lucrative cosmetic market prospects. Micro-emulsions can also be used to achieve drug targeting however challenges remain, primarily because of the layers of barriers that these systems need to overcome to reach to the target. Recent research work is focused on the production of safe, efficient and more compatible micro-emulsion constituents which will further enhance the utility of these novel vehicles. A considerable amount of work still needs to be performed to characterize the physicochemical behavior of the microemulsions. Despite the caveat associated with this therapeutic system, the current scientific interest seems to be directed at recognizing its full potential as a novel drug delivery tool.

II. CONCLUSION:

Micro-emulsion is drug delivery systems for the delivery of more than one medicament simultaneously. Micro-emulsion protect labile drug, control drug release, increase drug solubility, increase bioavailability and reduce patient variability also it has proven possible to formulate preparations suitable for most routes of administration. The role of microemulsion in providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability. The drug delivery through the micro-emulsion is a promising area for the continued research with the aim of achieving the controlled release with enhanced bioavailability and for drug targeting to various sites of the body.

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