International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 836-846 www.ijprajournal.com ISSN: 2249-7781

A Review On: Microemulsion

Aditi Nitin Sonawane
Dr. Vedprakash Patil Pharmacy College, Aurangabad

Submitted: 10-01-2023 Accepted: 21-01-2023

ABSTRACT:
Micro-emulsions are unit optically and macroscopically isotropous mixtures of a minimum of a hydrophilic associated, a hydrophobic and an ampiphilic half. These are unit stable than different emulsion forms, clear, usually conjoint with a co surfactant their diameter is within the parameter of 10-140µm. These days, the micro-emulsion formulations are unit accepted everywhere to deliver the hydrophilic yet because the lipophilic medications as drug carriers as a result they need lots of additional wonderful drug solubilizing ability, long time period, better bioavailability, the comfort of preparations, ultra-low surface tension and enormous surface space. Microemulsions are one of the pleasant applicants as novel drug delivery device due to their long shelf life, advanced drug solubilization with no trouble of preparation and administration. Microemulsions are thermodynamically stable solutions of oil, water and amphiphile. they have emerged as novel automobiles for drug transport which allow controlled or sustained release for ocular, percutaneous, topical, transdermal, and parenteral administration of medicaments. Microemulsions can be easily prominent from ordinary emulsions by means of their low viscosity, transparency and extra correctly their thermodynamic stability.

Key words: Thermodynamically stable, Amphiphile, Solubilization, Microemulsions,

I. INTRODUCTION:

Microemulsions comprise a special class of "dispersion" that may be transparent or translucent in appearance. They were first discovered by Hoar and Schulman (1943) in their experimental study of titration of long-chain fatty acids (soapy milky emulsions) with medium-/short-chain alcohols producing translucent or transparent system of emulsions.The formulation and development of novel drug delivery system with the nature of improving the effectiveness of existing of drug is an ongoing process in pharmaceutical studies. since there are numerous forms of drug delivery systems which have been developed. The microemulsion idea was introduced in 1940s by using Hoar and Schulman who generated a clear single-phase solution by triturating a milky emulsion with hexanol [1]. They prepared the first microemulsion via dispersing oil in an aqueous surfactants solution and adding an alcohol as a co-surfactant, leading to transparent stable formulation. Microemulsion is described as microemulsion are clear, transparent, thermodynamically stable dispersions of oil and water, stabilized by way of an interfacial film of surfactant frequently in combination with a co-surfactant. [2]

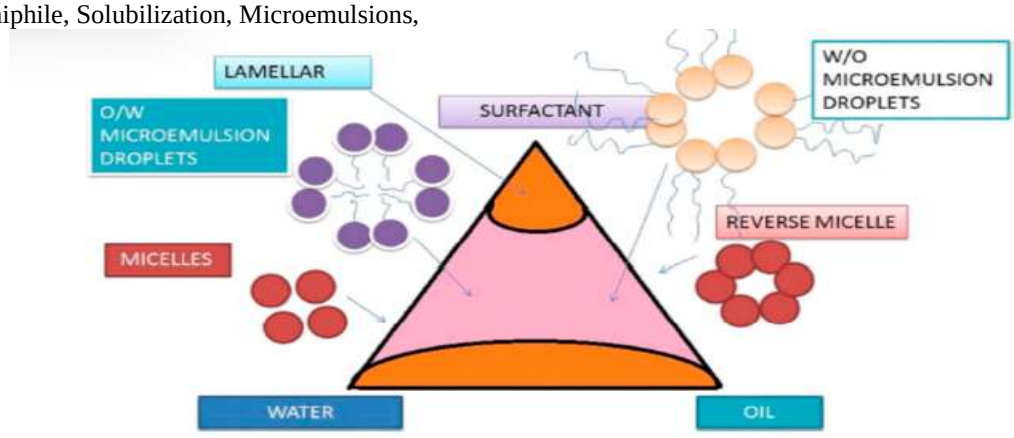

Fig No. 1 Phase diagram of a microemulsion system.

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Alternative names for those systems are regularly used, inclusive of swollen micelle, transparent emulsion, solubilized oil and micellar solution. Microemulsions are bicontinuous systems which might be essentially composed of bulk phases of water and oil separated by means of a surfactant/cosurfactant rich interfacial region [3]. these systems have benefits over conventional emulsions in that they may be thermodynamically stable liquid systems and are spontaneously formed [4].

DIFFERENCE BETWEEN MICRO-EMULSIONS AND EMULSIONS

The greatest difference between micro-emulsions and emulsions exist within the form and size of the elements that are propagate within the constant phase is a general way these are a demand of magnitude shorter within the circumstance of micro-emulsions (10-200nm) than individuals of ordinary emulsions (1-20µm). One more main difference fascinates their presence;
micro-emulsions squad measure clear or lustrous whereas emulsions square measure cloudy. In accumulation, there square measure distinct variations in their methodology of preparation, since emulsions need an oversized input of energy whereas micro-emulsions don't.

Advantages of Microemulsionsystem[6-11]

1. Microemulsions are easily prepared and need no energy contribution during preparation this is due to their good thermodynamic stability.
2. Microemulsion is reversible. They may become unstable at low or high temperature but when the temperature returns to the stability range, the microemulsion reforms.
3. Microemulsions are thermodynamically stable system and allows self-emulsification of the system.
4. Microemulsions have low viscosity as compared to emulsions.
5. Microemulsions act as supersolvents for drug, can solubilise both hydrophilic and hydrophobic [lipophilic] drugs including drugs that are insoluble in both aqueous and hydrophobic solvents.
6. Having the tendency to carry both lipophilic and hydrophilic drugs.
7. The dispersed phase, lipophilic or hydrophilic (O/W or W/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively.
8. The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimize side effects.

Disadvantages of Microemulsion Systems[6-9]

1. Having narrow solubilizing capacity for high melting point substances.
2. Require a large amount of Surfactants for stabilizing droplets.
3. Microemulsion stability is affected by environmental parameters such as temperature and pH.

Limitations of the micro-emulsion system 15-17

There are certain reasons which limit the utilization of the micro-emulsion systems within the medicinal submissions:

• There is a common problem of phase separation seen in the case of micro-emulsions.
• For toxicity reasons, the concentrations of the co-surfactants and the surfactants must be kept low.
• The micro-emulsion systems are not that much suitable for the intravenous use due to the toxicity of the formulation and till now only a very few studies have been reported on them.
• To reduce the toxicity of the micro-emulsion systems, the surfactants which are to be used are to be of "Generally-Regarded-as-Safe" (GRAS) class.

TYPES OF MICROEMULSIONS[15-18]

Microemulsions are thermodynamically stable but are only found under carefully some conditions. According to Winsor, there are 4 types of microemulsion phases that exist in equilibrium, 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

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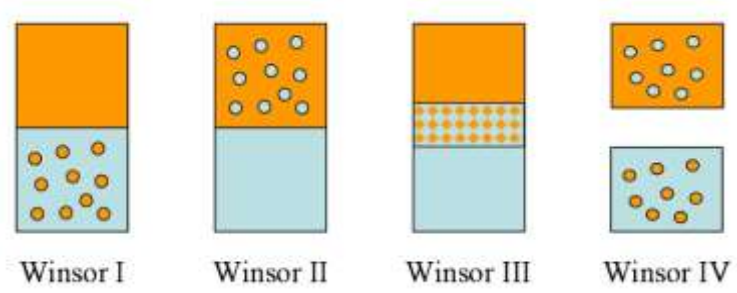

Fig No. 2

Oil- in- water microemulsion or Winsor I

In the Oil-in-water type of microemulsions droplets of oil is surrounded by a surfactant film that forms the internal phase dispersed in water, which is the continuous phase. This type of microemulsion has a larger interaction volume than the water-in-oil microemulsions.

Water - in - oil microemulsion or Winsor II

In the Water-in-oil type of microemulsions droplets of water are surrounded by a continuous oil phase. These are known as "reverse micelles", where the polar head groups of the surfactant are facing the droplets of water, with the fatty acid tails facing into the oil phase. A water-in-oil microemulsion used orally or parenterally may be de-stabilized by the aqueous biological system.

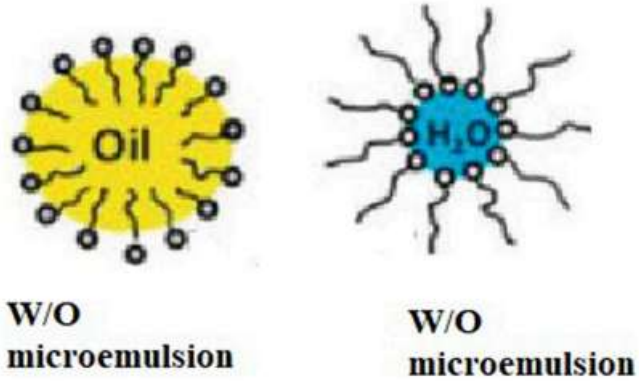

Fig No. 2

Bicontinuous microemulsion or Winsor III

In a bi-continuous microemulsion system the amount of water and oil present is similar, In this case, both water and oil are in a continuous phase. An irregular channel of oil and water is combined, and looks like a "sponge phase." Transitions from oil-in-water to w/o microemulsions may pass through this bicontinuous state. Bicontinuous microemulsion may show non-Newtonian flow and plasticity. These properties make them useful for the topical delivery of drugs.

Single-phase homogeneous mixture or Winsor IV

In a single phase, homogeneous mixture or Winsor IV the oil, water, and surfactants are homogeneously mixed.

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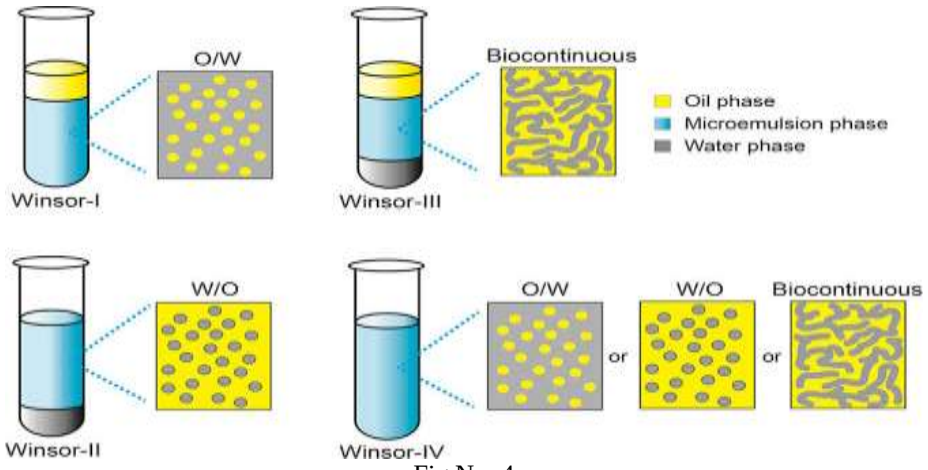

Fig No. 4

COMPONENTS OF MICROEMULSION [18-20]

Various components are used in the formulation and development of microemulsions. Mainly oil and surfactants are used in microemulsions they should be biocompatible, non-toxic, and clinically acceptable.

The main components of microemulsion are

1. Oil phase
2. Aqueous phase
3. Surfactant
4. cosolvent

Oil phase [21]

Oil is one of the most important units of microemulsion because it can solubilize the required dose of the lipophilic drug and it increases the amount of lipophilic drug transported by the intestinal lymphatic system. Oil is described as any liquid having low polarity and low miscibility with water. The e.g., of such phases, are cyclohexane, mineral oil, toluene, & vegetable oil, etc.

Aqueous phase

Generally, the aqueous phase contains hydrophilic active ingredients and preservatives. Sometimes Buffer solutions are used as an aqueous phase.

Surfactant [22]

The term surfactant denotes a substance that exhibits some superficial or interfacial activity & used to lower the surface or interface tension. It has an affinity for polar & nonpolar solvents. Surfactants are molecules that contain a polar head group and a polar tail. Surfactant molecules self-associate due to various inter- and intra-molecular forces as well as entropy considerations. For example, when a surfactant is mixed with oil and water, they accumulate at the oil/water interface, because it is thermodynamically favourable. The surfactant molecules can arrange themselves in a variety of shapes. They can form spherical micelles, a hexagonal phase, lamellar (sheet) phases, rod-shaped micelles, reverse micelles, or hexagonal reverse micelles. At low concentrations of dispersed phase, spherical, isolated droplets are present in the microemulsions.

The various types of surfactants that help in the progressive development of microemulsion systems are

1. Cationic
2. Anionic
3. Non-ionic
4. Zwitterionic surfactants.

Cationic surfactant

Cationic Surfactants when come in contact with water they come into amphiphilic cation and anion form, most often of halogen type. A very large quantity of this class corresponds to nitrogen compounds such as quaternary ammoniums and fatty amine salts, with one or several long chain of the alkyl type, often coming from natural fatty acids. The most well-known examples from the cationic surfactant class are hexadecyl trimethylammonium bromide and didodecyl ammonium bromide. These surfactants are in general more expensive than anionics.

Anionic surfactant

When anionic Surfactants are dissociated in water in an amphiphilic anion, and a cation, which is in general an alkaline metal (Na, K) or a quaternary ammonium. These are the most commonly used surfactants. The anionic charge in

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these surfactants comes from the ionized carboxyl group. Anionic surfactants account for about 50 % of the world production. Alkalialkanoates, also known as soaps, are the most common anionic surfactants. This is the most well-known type of surfactant when it comes to their shape and function. The three most important anionic groups in all of these surfactants are carboxylate, sulfonate and sulphate groups.

Non-ionic surfactant

Non-ionic surfactant is stabilized by dipole and hydrogen bond interactions with the hydration layer of water on its hydrophilic surface. They do not ionize in aqueous solution, because their hydrophilic group is of non-dissociable type, such as phenol, alcohol, ester, or amide. A large proportion of these non-ionic surfactants are made hydrophilic by the presence of a polyethylene glycol chain.

Zwitterionic surfactant

Zwitterionic surfactants contain both positively and negatively charged groups and form microemulsions by addition of co-surfactants. Phospholipids, such as lecithin, obtained naturally from soybean or egg are common zwitterionic surfactants. Unlike other ionic surfactants, which are somewhat toxic, lecithin which contains diacyl phosphatidylcholine as the major constituent show excellent biocompatibility. Other important class of zwitterionic surfactants is the betaines, such as alkyl betaines, and heterocyclic betaines.

Cosolvent [23]

It has been observed that single-chain surfactants are unable to reduce the o/w interfacial tension sufficiently to form a microemulsion. The addition of co-surfactants allows the interfacial film to be flexible to take up different curvatures required to form microemulsion over a wide range of excipients. If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short, or contain fluidizing groups (e.g., unsaturated bonds). Basic co-surfactants are short-chain alcohols (ethanol to butanol), glycols such as propylene glycol, medium-chain alcohols, amines or acids. The use of co-surfactant is to destroy liquid crystalline or gel structures that come in place of a microemulsion phase.

METHOD OF FORMULATION [24, 25]

Microemulsions are prepared when interfacial tension at the oil-in-water is kept at a very low level. The interfacial layer is kept very much flexible and the fluid concentration of surfactants should be high enough to give surfactant molecules to be stabilized the microemulsion at an extremely low interfacial tension.

Two main methods are reported for the formulation of the microemulsion, these are

1. Phase Inversion Method
2. Phase Titration Method
3. Agitation method

Phase Inversion Method [26]

In the phase inversion method phase inversion of microemulsions occurs by the addition of excess amount of the dispersed phase. During phase inversion quick physical changes occur including changes in particle size that can affect drug release both in vivo and in vitro. For non-ionic surfactants, this can be completed by changing the temperature, forcing a transition from oil in water microemulsion at low temperatures to water in oil microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is also known as phase inversion temperature (PIT) method. Other than temperature, other parameters such as pH value or salt concentration may be considered more effectively instead of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. By increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion point.

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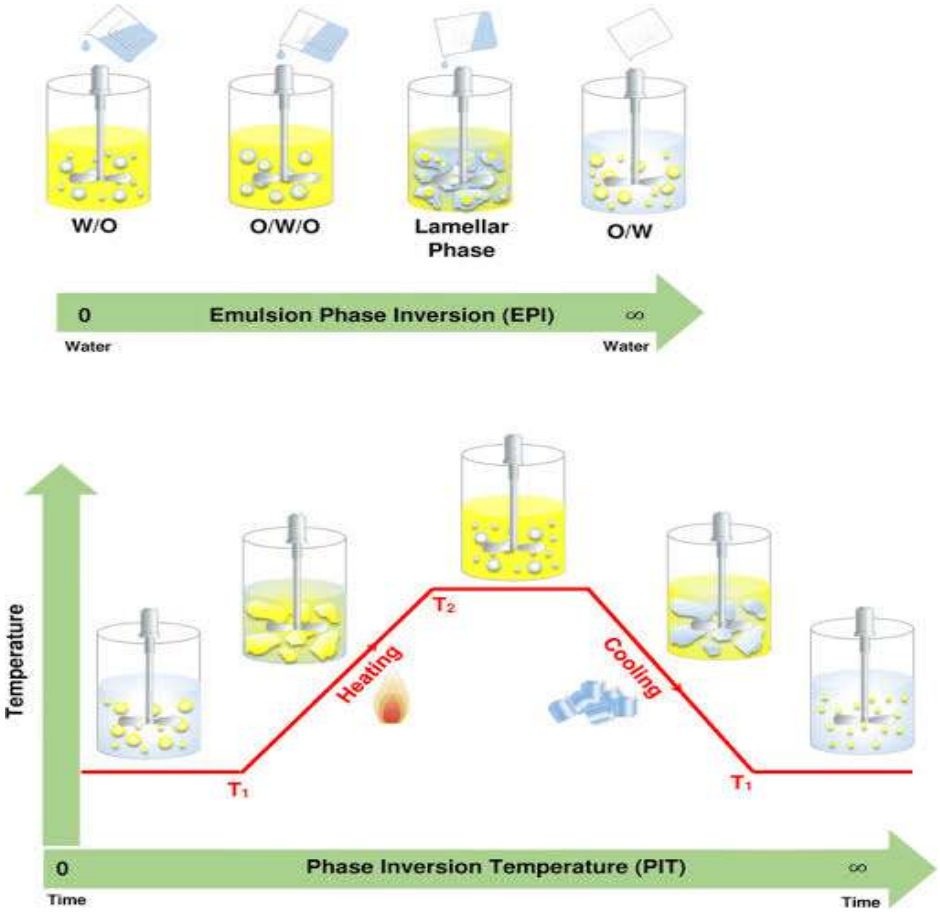

Fig No. 5

Phase Titration Method [27]

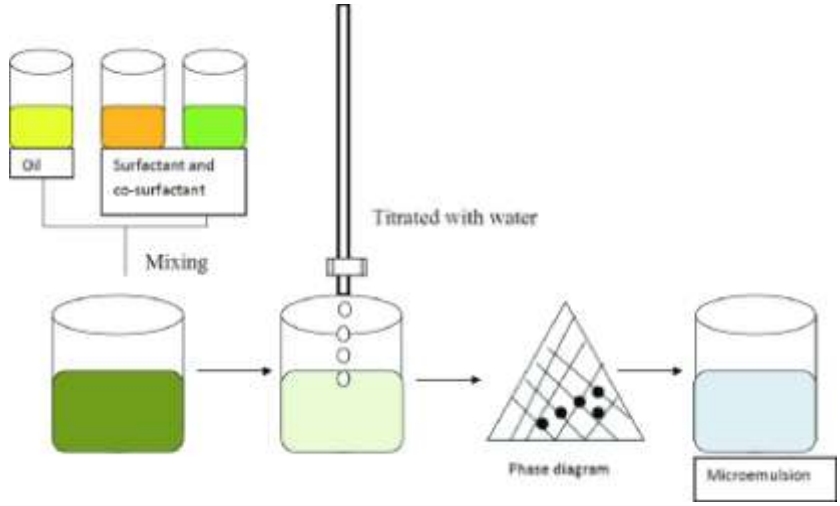

Fig No. 6

Microemulsions are formulated by the spontaneous emulsification method (phase titration method) and can be shown with the help of phase diagrams. A mixture of fatty acid and oil is added to a caustic solution to prepare a microemulsion, then after it is titrated with a cosurfactant, an alcohol, until the system turned clear. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various

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gels and oily dispersion) depending on the chemical composition and concentration of each component. It is found that as the chain length of the surfactant increased, microemulsions with significant transmittances by visible spectrum can be formed with oils of longer chain lengths. It is also found that different alcohols affect the formation of microemulsions in different ways. The best results, in terms of the greatest percent transmittance coupled with the widest range of oil (dispersed in water) concentration, are obtained from short or branched alcohols.

Agitation Method

The drug is dissolved in the lipophilic part of the microemulsion i.e. Oil and the water phases can be combined with surfactant and a cosurfactant is then added at slow rate with gradual stirring until the system is transparent. The amount of surfactant and cosurfactant to be added and the percent of oil phase that can be incorporated shall be determined with the help of pseudo-ternary phase diagram. Ultrasonicator can finally be used so to achieve the desired size range for dispersed globules .

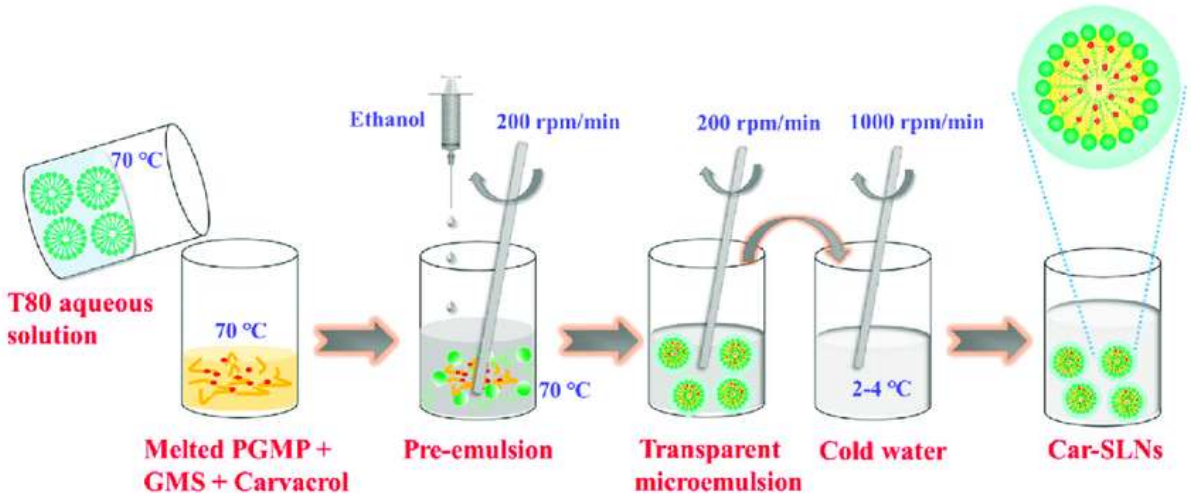

Fig No : 7

THEORIES OF MICROEMULSION FORMULATION [28-30]

The formulation of microemulsion is based on various theories that effect and control their stability and phase behaviour.

These theories are;
1. Thermodynamic theory
2. Solubilisation theory
3. Interfacial theory

Thermodynamic theory[29]

Formulation and stability of microemulsion can be expressed based on a simplified thermodynamic mechanism. The free energy of microemulsion formation can be dependent on the extent to which surfactant lowers the surface tension of the oil-water interface and the change in entropy of the system, thus

$DG_f = \gamma DA - T\,DS$

Where, DG_f = Free Energy of formation, γ =Surface Tension of the oil–water interface, DA = Change in interfacial area on micro-emulsification, DS = Change in entropy of the system which is effectively the dispersion entropy, and T = Temperature. It is found that when a microemulsion is formed, DA is changed to a large extent due to the large number of very small droplets formed. It is a must to know that while the value of γ is always positive, it is very small, and is offset by the entropic component. The dominant favorable entropic contribution is the very large dispersion entropy arising from the mixing of one phase in the other in the form of large numbers of small droplets. However, favourable entropic contributions also come from other dynamic processes such as monomer-micelle surfactant exchange and surfactant diffusion in the interfacial layer. When large reductions in surface tension are found by significant favourable entropic change, a negative free energy of formation is achieved. In that case, micro-emulsification is spontaneous and the resulting dispersion is thermodynamically stable.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 836-846 www.ijprajournal.com ISSN: 2249-7781

Solubilisation theory

The formation of the microemulsion is oil soluble phase and water phase by micelles or reverse micelles in micellar gradually become larger and swell to a certain size range result.

Interfacial theory[30]

The interface mixed-film theory i.e., a negative interfacial tension theory, according to this theory the micro-emulsion has been capable to form instantaneous and spontaneously generate a negative interfacial tension in the surfactant and co-surfactant in working together. The film, which may consist of surfactant and cosurfactant molecules, is considered as a liquid ''two-dimensional'' third phase in equilibrium with both oil and water. Such a monolayer could be a duplex film, i.e. giving different properties on the water side and oil side. According to the duplex film theory, the interfacial tension γT is given by the following expression

$\gamma T = \gamma(O/W) --- \pi$

Where,

γ (O/W)a is Interfacial Tension(reduced by the presence of the alcohol).

γ (O/W)a is significantly lower than γ(O/W) in the absence of the alcohol.

EVALUATION PARAMETERS OF MICROEMULSION SYSTEM

Physical appearance

For Physical appearance microemulsion can be inspect visually for homogeneity, fluidity and optical clarity.

Scattering Techniques [36]

Scattering techniques such as small-angle neutron scattering, small-angle X-ray scattering and light scattering have found applications in studies of microemulsion structure, particularly in the case of dilute monodisperse spheres, when polydisperse or concentrated systems such as those frequently seen in microemulsions.

Limpidity Test (Percent Transmittance) [37]

The limpidity of the microemulsion can be analysed spectrophotometrically using a spectrophotometer.

Drug stability [38]

The optimized microemulsion is kept under cold conditions (4-8°C), room temperature, and at elevated temperature (50 ± 2 °C). After every two months, the microemulsion can be analysed for phase separation, percent transmittance, globule size, and percent assay.

Globule size and zeta potential measurements [39]

The globule size and zeta potential of the microemulsion can be identified by dynamic light scattering, using a Zetasizer HSA 3000.

Assessment of the Rheological Properties (viscosity measurement) [40]

The rheological properties play an important role in stability. It can be determined by Brookfield digital viscometer. Changes in the rheological characteristics help in identifying the microemulsion region and its separation from another region. Bicontinuous microemulsions are dynamic structures with continuous fluctuations occurring between the bicontinuous structure, swollen reverse micelle, and swollen micelles.

Electrical conductivity [41]

The water phase is added dropwise to a mixture of oil, surfactant, and co-surfactant and the electrical conductivity of formulated samples can be determined by using a conductometer at ambient temperature and at a constant frequency of 1 Hz.

Drug solubility [42]

The drug was added in excess to the optimized microemulsion formulation as well as each separate individual ingredient of the formulation. After continuous stirring for 24 hrs at room temperature, samples were withdrawn and centrifuged at 6000 rpm for 10 min. The amount of soluble drug in the optimized formulation as well as each individual ingredient of the formulation is calculated by removing the drug present in the sediment from the total amount of drug added. The solubility of the drug in microemulsion was compared with its individual ingredients.

In-vitro drug release [43, 45]

The diffusion study can be done on a modified Franz diffusion cell, within the volume of 20mL. The receptor compartment was filled with buffer. The donor compartment is fixed with a cellophane membrane, containing the microemulsion formulation and the plain drug solution, separately. At predetermined time intervals, samples were withdrawn from the

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receptor compartment and analysed for drug content, using a UV spectrophotometer at a specific wavelength.

II. CONCLUSION:

Microemulsions are highly important in the drug delivery system as well as in the industrial process. They can be used to optimize drug targeting without a concomitant increase in systemic absorption. The role of microemulsion in providing new solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent, and reproducible bioavailability. Microemulsions can also be used to get drug targeting however challenges remain, primarily because of the layers of barriers that these systems need to avoid to reach the target. Microemulsion has been shown to be able to protect labile drugs, control drug release, and reduce patient variability. Furthermore, it has proven possible to prepare formulations suitable for most routes of administration. In today's world Microemulsion is accepted as full of potential for novel drug delivery systems. Current research work is focused on the preparation of safe, efficient, and more compatible microemulsion constituents which will further improve the utility of these new vehicles.

Marketed Preparations

Drug	**Product name**	**Company**	**Therapeutic area**
Cyclosporine	Sandimmune oral	Novartis	Immunosuppressant
Cyclosporine	Neoral	Novartis	Immunosuppressant
Calcitrol	Rocaltrol	Roche	Calcium regulator
Clofazimine	Lamprene	Geigy	Leprosy
Doxercalciferol	Hectoral	Bone care	Calcium regulator
Dronabionol	Marinol	Roxane	Anoxeria
Dutasteride	Avodart	GSK	Benign Prostatic Hyperplasia (BPH)
Isotretionoin	Accutane	Roche	Acne
Ritonavir	Norvir	Abbott	AIDS
Ritonavir/lopinavir	Kaletra	Abbott	AIDS
Paricalcitol	Zemplar	Abbott	Calcium regulator
Progesterone	Prometrium	Solvay	Endometrial hyperplasia
Saquinavir	Fortovase	Roche	AIDS
Sirolimus	Rapumune	Wyeth-ayerst	Immunosuppressant
Tritionoin	Vesanoid	Roche	Acne
Tipranavir	Aptivus	Boehringer Ingelheim	AIDS
Valproic acid	Depakene	Abbott	Epilepsy
Cyclosporine A	Restasis	Allergan	Immunomodulation
Diazepam	Diazemuls	Braun Melsungen	Sedation
DexamethazonePalmitate	Limethason	Green Cross	Carticosteroid
Etomidate	Etomidat	Dumex (Denmark)	Anesthesia
Flurbiprofen	Lipfen	Green Cross	Analgesia

International Journal of Pharmaceutical Research and Applications
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Prostaglandin-El	Liple	Green Cross	Vasodilator
Propofol	Propofol	Baxter Anesthesia	Anesthesia
	Diprivan	AstraZeneca	Anesthesia
Perflurodecalin+Perflurotripropylamine	Fluosol-DA	Green Cross	Analgesia
Vitamins A, D, E and K	Vitalipid	Kabi	Nutrition

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