Original Article

Microemulsions: Current Trends in Novel Drug Delivery Systems

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Abstract

Because of their increased drug solubilization, long shelf life, and simplicity in preparation and administration, microemulsions are among the greatest options as innovative drug delivery systems. It is a microemulsion. Oil, water, and amphiphile liquid solutions that are optically isotropic and thermodynamically stable. There areas innovative medication delivery methods that enable regulated or sustained release for ocular, Medication administration methods include parenteral, topical, transdermal, and percutaneous. Using microemulsion, Because of their transparency and low viscosity, or more precisely because they are transparent compared to standard emulsions, stable thermodynamics Microemulsions are used in a wide variety of products, including Analytical applications, food, cutting oils, biotechnology, medicines, agrochemicals, and environmental cleansing, etc. This review paper's primary goal is to discuss microemulsions as medication delivery system that.

Keywords: Microemulsions, thermodynamically stable, amphiphile, solubilisation, Ocular Medication,

INTRODUCTION:-

The creation of innovative drug delivery systems with the aim of improving .The effectiveness of current medications is continuing pharmaceutical research methodology. because there ,there are numerous medication delivery methods that been created. The idea of a microemulsion was introduced by Hoar and Schulman in the 1940s produced a transparent, single-phase solution by using hexanol to triturate a milky emulsion[1]. The by mixing oil, the first microemulsion was made. Adding an aqueous surfactants solution to translucent skin due to alcohol's role as a co-surfactan formula that is stable. A microemulsion is what Microemulsions are translucent and clear. oil and other liquids in thermodynamically stable water, stabilised by a surfactant-based interfacial layer ,in conjunction with a co-surfactant quite commonly[2]. . These systems are frequently referred to by other names, including swollen micelles, transparent emulsions, solubilized oils, and micellar solutions. Microemulsions are bicontinuous systems that primarily consist of bulk phases of water and oil that are separated by an interfacial region that is rich in surfactants and cosurfactants[3].These liquid systems are thermodynamically stable and spontaneously develop, which gives them an edge over traditional emulsions[4].Since they have so many potential and real uses, microemulsions are currently the focus of numerous studies. Microemulsions are desirable pharmaceutical formulations due to their great drug-carrying capacity. Additionally, these systems have various advantages for oral delivery, such as higher clinical potency, greater absorption, and reduced toxicity[5]

Microemulsion system benefits [6-11]:

1. Microemulsion preparation is simple and requires minimal energy input. preparation since it is more effective stable thermodynamics.
2. Microemulsion creation is reversible. At low or high temperatures, they could become unstable. However, when the temperature once once reaches the stability range, the microemulsion reforms.
3. Microemulsions have consistent thermodynamic properties mechanism and permits the self-emulsification system.
4. In comparison, Microemulsions have a low viscosity Emulsions.
5. Microemulsions serve as medication super solvents can solubilize both lipophilic and hydrophilic substances medications, such as those that are not soluble in both Hydrophobic and watery solvents.
6. Possessing the capacity to transport both hydrophilic and lipophilic medications.
7. Hydrophilic or lipophilic dispersion phase Microemulsions (O/W or W/O) can function as a potential source of hydrophilic or lipophilic materials respectively, medications.
8. Microemulsions are used as delivery systems can increase a drug's effectiveness, enabling the minimising the reduction in the overall dosage adverse consequences.

Microemulsion Systems' Drawbacks [6-8]:

1. Having a minimal ability to dissolve highly melting compounds
2. To stabilise droplets, a lot of surfactants are needed.
3. Environmental factors like temperature and pH have an impact on the stability of microemulsions.

BASIC DIFFERENCES BETWEEN MACROEMULSION AND MICROEMULSION [12-14]:

Sr.no	Microemulsion	Microemulsion
1	They are lyophobic in nature.	They stand on the lyophilic-lyophobic spectrum.
2	Droplet diameter 1 to 20 mm.	Droplet diameter 10 to 100 mm.
3	Macroemulsion droplets exist as individual entities.	They stand at the border. Droplets of microemulsion vanish in a split second. lyophilic and lyophobic.
4	Approximately spherical droplets of one phase spread in the other phase are called emulsion droplets.	The structures of different droplets, such as bi-continous to inflated micelles, make up microemulsions.
5	Macroemulsions requires quick agitation for their formation.	Ingredients are gently combined to create microemulsions.
6	Most of the emulsions are opaque (white) in appearance.	Transparent or translucent is how to describe microemulsions.

MICROEMULSION TYPES [15-18] :-

Microemulsions are only present under precisely defined circumstances, but they are thermodynamically stable. Winsor identified four different types of microemulsion phases that can exist in equilibrium; these phases are also known as Winsor phases.

1. Winsor I or an oil-in-water microemulsion
2. Bicontinuous microemulsion or winsor III
3. Water-in-oil microemulsion 4. Winsor IV or a single phase homogeneous combinationWinor or an oil-in-water microemulsion I

A surfactant (and sometimes a cosurfactant) coating surrounds the oil droplets in an oil-in-water type microemulsion, forming the internal phase that is dispersed in water and is the continuous phase. In comparison to microemulsions without, this kind often has a greater interaction volume.

A continuous oil phase surrounds tiny droplets of water in a water-in-oil microemulsion, also known as a winsor II microemulsion. The polar headgroups of the surfactant are facing into the water droplets in these so-called "reversemicelles," while the fatty acid tails are facing into the oil phase. When administered parenterally or orally, a w/o microemulsion may become unstable due to the aqueous biological system.

Winsor III or a bicontinuous microemulsion

Similar amounts of both water and oil are present in bicontinuous microemulsion systems, where both are present as continuous phases. It resembles a "sponge-phase" when water and oil are blended in an uneven channel. This bicontinuous condition may be crossed during transitions from o/w to w/o microemulsions.

Bicontinuous microemulsions may exhibit plasticity and non-Newtonian flow. These characteristics make them particularly advantageous for intravenous injection or topical medication delivery.

Winsor IV or a single phase homogeneous mixture

Winsor IV, often known as a single phase homogeneous mixture, is a homogeneous mixture of oil, water, and surfactants.

MICROEMULSION INGREDIENTS [18-20]:

Microemulsions are created and developed using a variety of components. In microemulsions, the main ingredients are oil and surfactants; these substances ought to be biocompatible, non-toxic, and clinically acceptable.

1. Oil phase (Microemulsions primary component).
2. Aqueous phase
3. Surfactant
4. Cosolvent

1. Phase-Oil [21]

One of the most crucial elements of a microemulsion is oil, which enhances the proportion of a lipophilic medicine that is delivered via the intestinal lymphatic system and can solubilize the required dose of the drug. Any liquid with low polarity and low miscibility with water is considered oil. Cyclohexane, mineral oil, toulene, and vegetable oil are a few examples of such phases.

2. Water phase:-

Preservatives and hydrophilic active substances are typically found in the aqueous phase. Buffer solutions are occasionally employed as the aqueous phase.

3. Surfactant [22]

A chemical that has some interfacial or superficial activity and is utilised to reduce surface or interface tension is referred to as a surfactant (surface-active agent). Both polar and nonpolar solvents have an attraction for it. molecules with polar head and polar tail groups. Due to different intra- and intermolecular forces, as well as entropy considerations, surfactant molecules self-associate. For instance, when surfactant is combined with oil and water, they collect there because the thermodynamic conditions are favourable. The molecules of the surfactant can arrange themselves in several configurations. Spherical micelles, a hexagonal phase, lamellar (sheet) phases, rod-shaped micelles, reverse micelles, and hexagonal reverse micelles are among the possible structures they can take on. The microemulsions contain spherical, isolated droplets when the dispersed (internal) phase is present in low concentrations. The following are the numerous surfactant kinds that aid in the gradual growth of the microemulsion system:

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

1. Cationic surfactant:-

When cationic surfactants interact with water, they take on the forms of amphiphilication and anion, most frequently of the halogen variety. This class contains a very high amount of nitrogen compounds, such as quaternary ammoniums and salts of fatty amines, that have one or more long chains of the alkyl type, frequently derived from natural fatty acids. Hexadecyl trimethylammonium bromide and didodecyl ammonium bromide are two of the most well-known examples of cationic surfactants. These surfactants typically cost more than anionics.

2. Anionic surfactant:-

whenever ionic Surfactants split into an amphiphilic anion and a cation in water, with the cation typically being an alkaline metal (Na, K) or quaternary ammonium. These are the surfactants that are most frequently utilised. These surfactants' ionised carboxyl group is what gives them their anionic charge. The production of anionic surfactants is around 50% of the total. Soaps, commonly referred to as alkalialkanoates, are the most popular anionic surfactants. When it comes to their appearance and purpose, this is the surfactant kind that is most well-known. The carboxylate, sulfonate, and sulphate groups are the three most significant anionic groups in all of these surfactants.

3. Non-ionic surfactant:-

The hydration layer of water on the non-ionic surfactant's hydrophilic surface interacts with dipoles and forms hydrogen bonds with them, stabilising them. Because their hydrophilic group is of the non-dissociable kind, such as phenol, alcohol, ester, or amide, they do not ionise in aqueous solution. These nonionic surfactants' presence of polyethylene glycol chains makes a significant fraction of them hydrophilic.

4. Zwitterion surfactant:-

That is zwitterionic When co-surfactants are added, zwitterionic surfactants, which have both positively and negatively charged groups, create microemulsions. Common zwitterionic surfactants include phospholipids like lecithin, which can be naturally produced from soy or eggs. Lecithin, which has diacyl phosphatidylcholine as its main component and is considerably less hazardous than other ionic surfactants, exhibits high biocompatibility. The betaines, including alkylbetaines and heterocyclic betaines, are another significant class of zwitterionic surfactants.

4. Cosolvent:-

A microemulsion cannot be formed by single-chain surfactants because they are unable to sufficiently lower the o/w interfacial tension. The addition of co-surfactants makes the interfacial film flexible enough to adopt the many curvatures needed to create microemulsion over a variety of excipients. The surfactant's lipophilic chains must be suitably short or contain fluidizing groups if a single surfactant film is needed (e.g. unsaturated bonds). Basic co-surfactants include glycols like propylene glycol, short chain alcohols (ethanol to butanol), medium chain alcohols, amines, and acids. In place of a microemulsion phase, co-surfactant is used to dissolve liquid crystalline or gel formations.

METHOD OF FORMULATION [24, 25]:

When the interfacial tension between the oil and the water is preserved at a very low level, microemulsions can be created. The fluid concentration of surfactants should be high enough to provide sufficient surfactant molecules to stabilise the microemulsion at a very low interfacial tension while maintaining a very flexible interfacial layer.
Phase inversion approach is one of the two main methods published for creating microemulsions.

1. Phase Inversion Method [26]:-

The phase inversion method involves adding an excessive amount of the dispersed phase to microemulsions to cause phase inversion. Quick physical changes, such as changes in particle size, take place during phase inversion and can alter drug release both in vivo and in vitro. This can be accomplished with non-ionic surfactants by causing a transition from an oil-in-water microemulsion at low temperatures to a water-in-oil microemulsion at higher temperatures by altering the temperature (transitional phase inversion). The development of finely distributed oil droplets is encouraged by the system crossing a point of zero spontaneous curvature and negligible surface tension as it cools. A different name for this

technique is the phase inversion temperature (PIT) approach. In addition to temperature, additional factors like pH level or salt content may be taken into account more effectively. Changing the water volume fraction can also result in a change in the spontaneous radius of curvature. Water droplets are originally created in a continuous oil phase by adding water to it in small amounts at first. The spontaneous curvature of the surfactant is changed from initially stabilising a w/o microemulsion to an o/w microemulsion at the inversion point by increasing the water volume percentage.

2. Phase Titration Method[27]:-

Phase diagrams can be used to demonstrate how microemulsions are created using the spontaneous emulsification method (also known as the phase titration method). An oil and fatty acid mixture is added to a caustic solution to create a microemulsion, which is then titrated with an alcohol cosurfactant until the mixture becomes clear. Depending on the chemical makeup and concentration of each component, microemulsions are created along with a variety of association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and different gels and oily dispersion). It has been discovered that oils with larger chain lengths can create microemulsions with considerable visible spectrum transmittances as the surfactant's chain length increases. It is discovered that various alcohols have varying effects on how microemulsions develop. The best results are obtained from short or branched alcohols in terms of the highest percent transmittance and the widest range of oil (dispersed in water) concentration.

THEORIES OF MICROEMULSION FORMULATION [28-30]:-

The creation of microemulsions is based on a number of hypotheses that affect and regulate their phase behaviour and stability.

1. Thermodynamic theory
2. Solubilisation theory
3. Interfacial theory

1. Thermodynamic theory [29]:-

A simple thermodynamic mechanism can be used to express the formation and stability of microemulsions. The amount that a surfactant reduces the surface tension of the oil-water interface and the system's change in entropy can both affect the free energy of microemulsion production.

DG f = γDA - T DS Where, DG

Where, f = Free Energy of formation, γ =Surface Tension of the oil–water interface, DA = Change in interfacial area on microemulsification, DS = Change in entropy of the system which is effectively the dispersion entropy, and T = Temperature.

It is discovered that the formation of a microemulsion results in a significant alteration of DA because so many tiny droplets are created. It is important to understand that even though the value of is always positive, it is very little and is cancelled out by the entropic component. The very substantial dispersion entropy that results from the mixing of one phase into the other in the form of numerous tiny droplets is the predominant favourable entropic contribution. However, additional dynamic processes like monomer-micelle surfactant exchange and surfactant diffusion in the interfacial layer also contribute favourably to entropy. A negative free energy of formation is reached when sufficient favourable entropic change leads to significant reductions in surface tension.

2. Solubilisation theory:-

When micelles or reverse micelles in a micellar solution gradually grow larger and swell to a specific size range, an oil-soluble phase and a water phase are formed.

3. Interfacial Theory:-

According to the interface mixed-film theory, also known as the theory of negative interfacial tension, the micro-emulsion has the ability to spontaneously and instantly establish a negative interfacial tension when the co-surfactant and surfactant are functioning together. The film is viewed as a liquid, "two-dimensional," third phase that is in equilibrium with both oil and water and may be composed of surfactant and cosurfactant molecules. A duplex film made of such a monolayer would have differing properties on its oil and water sides. The following expression represents the interfacial tension T according to the duplex film hypothesis.

$\gamma T = \gamma(O/W)$ --- π

Where,

γ (O/W)a = 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.

FACTOR AFFECTING FORMULATION OF MICROEMULSION SYSTEM [31-33]:-

Property of surfactant-

Two groups of lipophilic and hydrophilic groups are present in surfactant. Cetylethyl ammonium bromide, a hydrophilic single chain surfactant, totally dissociates in diluted solution and has a propensity to create an o/w microemulsion. When

using a high concentration of surfactant or in the presence of salt, the degree of polar group dissociation is reduced, and the resultant system may not have type.

Property of Oil Phase-
Oil phase can infiltrate and enlarge the surfactant monolayer's tail group region, which causes the negative curvature to be greater than it would be without a microemulsion.

Packing Ratio [34]:-
The type of microemulsion is determined by the surfactant's HLB through its impact on packing and film curvature. Analysis of film curvature for surfactant associations that result in microemulsion production.

Temperature [35]:-
When establishing the effective head group size of nonionic surfactants, temperature is crucial. They are hydrophilic at low temperatures and form a typical o/w system. They create w/o systems at higher temperatures because they are lipophilic. Microemulsion coexists with excessive water and oil phases at a medium temperature and produces a bicontinuous structure.

EVALUATION PARAMETERS OF MICROEMULSION SYSTEM:-
Physical appearance
Visual examination of the physical characteristics of the microemulsion can reveal its homogeneity, fluidity, and optical clarity.

Scattering Techniques [36]:-
Studies of the structure of microemulsions have used scattering techniques like small angle neutron scattering, small angle X-ray scattering, and light scattering, particularly in the case of dilute monodispersed spheres in polydisperse or concentrated systems like those frequently found in microemulsions.

Limpidity Test (Percent Transmittance) [37]:-
A spectrophotometer can be used to spectrophotometrically determine the microemulsion's limpidity.

Drug stability [38]:-
The ideal microemulsion was stored at low temperature (4–8 °C), room temperature, and high temperature (50–2 °C). The microemulsion can be examined for phase separation, percent transmittance, globule size, and assay every two months.

Globule size and zeta potential measurements [39]:-
Using a Zetasizer HSA 3000, dynamic light scattering can be used to measure the microemulsion's globule size and zeta potential.

Assessment of the Rheological Properties (viscosity measurement) [40]:-
The stability is significantly influenced by the rheological characteristics. The Brookfield digital viscometer can ascertain it. Rheological properties that change can be used to distinguish the microemulsion zone from other regions. The bicontinuous structure, the swelling reverse micelle, and the swollen micelles all fluctuate continuously in bicontinuous microemulsions.

Electrical conductivity [41]:-
A mixture of oil, surfactant, and co-surfactant was given a dropwise addition of the water phase. The electrical conductivity of the created samples was then evaluated using a conductometer at room temperature and at a constant frequency of 1 Hz.

Drug solubility [42]:-
The improved microemulsion formulation and every component within received an excessive addition of drug. After 24 hours of nonstop stirring at room temperature, samples were taken out and centrifuged for 10 minutes at 6000 rpm. By deducting the drug contained in the sediment from the total amount of drug added, the amount of soluble drug in the optimised formulation as well as each individual ingredient of the formulation were estimated. Comparing the drug's solubility in microemulsions based on each of its component parts.

In-vitro drug release [43, 44]:-
In a 20mL volume, a modified Franz diffusion cell can be used to conduct the diffusion investigation. With buffer, the receptor compartment was filled. The microemulsion formulation and the pure drug solution were contained separately in the donor compartment, which was fixed with a cellophane membrane. Samples were taken out of the receptor compartment at specified intervals and put through a UV spectrophotometer at a certain wavelength to be tested for drug content.

APPLICATION OF MICROEMULSION SYSTEM:-

Microemulsion in Pharmaceutical:-

In the past two decades, the use of microemulsion systems in numerous medications has undergone a revolution.

Parenteral Delivery [45]:-

Due to the extremely poor drug delivery to a specific site, parenteral administration (particularly via the intravenous route) of medicines with restricted solubility is a significant issue in industry. Because fine particle microemulsions are eliminated more slowly than coarse particle emulsions and have a longer residence time in the body, they have unique advantages over macroemulsion systems when administered parenterally.

Oral Delivery [46]:-

The advantages of microemulsion formulations over traditional oral formulations include better clinical potency, reduced medication toxicity, and enhanced absorption. As a result, it has been claimed that microemulsions are the best delivery system for medications like steroids, hormones, diuretics, and antibiotics.

Topical delivery [47]:-

The avoidance of hepatic first-pass metabolism, salivary and stomach drug degradation, and associated adverse effects are just a few of the benefits of topical medication administration over other approaches. Another is the drug's capacity to target and transport itself directly to the skin or eyes that are being affected. Studies on the penetration of drugs into the skin have been conducted recently. They can include both hydrophilic (5flurouracil, apomorphine hydrochloride, etc.) and lipophilic (estradiol, finasteride, ketoprofen, etc.) medicines to increase their permeability. The skin irritation factor needs to be taken into consideration, especially when they are meant to be used for a longer period of time because the creation of microemulsions demands a high surfactant concentration.

Ocular and Pulmonary Delivery[48]:-

The majority of drug delivery for the treatment of eye disorders occurs topically. O/W microemulsions have been studied for ocular administration, to dissolve poorly soluble medications, to enhance absorption, and to achieve extended release profiles.

Other pharmaceutical applications [49,50,51,52]:-

- Nasal delivery
- Drug targeting
- Cellular targeting
- Brain targeting
- Periodontal delivery
- Tumor targeting

Other application:-

Microemulsions in analytical applications[53]:-

In the realm of analytical procedures, such as chromatography, etc., microemulsions are frequently utilised. Characterization of solute hydro phobicity was done using microemulsion electrokinetic chromatography (MEEKC), which offers a rapid. and repeatable way to measure solvent hydrophobic characteristics. Microemulsions can serve as solubilized medium, spectrum shift reagents, intensity amplification agents, etc. to improve analytical spectroscopic procedures. Analytical sensitivities of the three systems—o/w, w/o, and bi continuous microemulsion—and the use of microemulsion media in analytical spectroscopy have been evaluated. The determination of aluminium, zinc, copper, and manganese ions utilising microemulsion and mixed microemulsion systems has been the subject of a number of research.

Microemulsions in biotechnology[54]:-

In addition to biphasic media, many biocatalytic and enzymatic reactions also take place in aquo-organic or pure organic environments. Because they can inactivate or denature the biocatalysts, their application is severely constrained. Recently, attention has been drawn to microemulsions for use in a variety of biotechnological processes, including enzymatic reactions, protein immobilisation, and bioseparation.

Microemulsions in enhanced oil recovery[55]:-

It may be possible to extract subsurface oil that cannot be recovered by understanding the mechanisms of improved oil recovery (EOR) employing surfactant and microemulsion. A significant portion of the trapped residual oil in the porous media can be mobilised if the interfacial tension between the crude oil and reservoir brine can be lowered to roughly 10-3 mN/m. Another benefit of the system is low interfacial viscosity.

Microemulsions for bioseparations

- Microemulsion as a chemical sensor materials
- Microemulsions as lubricants, cutting oils and corrosion inhibitors
- Microemulsions as coatings and textile finishing.
- Microemulsions in detergency.
- Microemulsions in cosmetics.

- Microemulsions in agrochemicals.
- Microemulsions in food.
- Microemulsions in environmental remediation and detoxification.
- •Microporous media synthesis (microemulsion gel technique).
- Microemulsions in analytical applications.
- Microemulsions as liquid membranes.
- Novel crystalline colloidal arrays as chemical sensor materials.

CONCLUSION

In both the industrial process and the drug delivery system, microemulsions are absolutely essential. It is possible to employ them to improve drug targeting without also increasing systemic absorption. The function of microemulsion in offering creative approaches to deal with the issues of low aqueous solubility of highly lipophilic medicinal molecules and deliver high, more dependable, and reproducible bioavailability Drug targeting with microemulsions is also possible, although there are still difficulties, mainly because of the numerous barriers that these systems must get past to reach the target. It has been demonstrated that microemulsion can protect labile drugs, regulate drug release, and lower patient variability. Additionally, it has been shown that preparations that are appropriate for the majority of administration routes can be created. Today, microemulsion is recognised as having great potential for cutting-edge medication delivery methods. The goal of current research is to create safe, effective, and more compatible microemulsion components that will increase the usability of these innovative vehicles.

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